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

March 23, 2017

A Matter of Record (301) 890-4188

**Min-U-Script® with Word Index** 

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

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3	Introduction and Meeting Objectives		
4	Roy Freeman, MD 4	3	Introduction and Meeting Objectives
5	Introduction to ACTTION	4	DR. FREEMAN: Good morning. Welcome to the
6	Robert Dworkin, PhD 5		ACTTION meeting on chemotherapy-induced peripheral
7	Overview of CIPN		neuropathy. My name is Roy Freeman, and on behalf
		7	of my co-chair and myself, I'd like to welcome you.
8	Joanna Brell, MD 20	8	I see a lot of new faces, and it's great to
9	Predictors of CIPN	9	have new faces at this meeting. I also see a
10	Patrick Dougherty, PhD 50	10	number of familiar faces. I, of course, was not
11	Regulatory Perspective on CIPN - Division of	11	going to say old faces.
12	Oncology Products	12	For the new faces, as the meeting evolves, I
13	Lynn Howie, MD 81	13	will give you some sense of how these kinds of
14	Regulatory Perspective on CIPN - Division of		meetings go, and they are quite unique meetings
15	Anesthesia, Analgesia, and Addiction		where everybody is a participant, everybody is
16	Products		involved. This is not the kind of meeting where
17	Pamela Horn, MD 100		you slip out for an hour or two and pay your
18			
	Q&A and Panel Discussion		respects to the White House.
19	Moderator: Robert Dworkin 115	19	You are here throughout the meeting. You
20			contribute whether you're on the podium, whether
21		21	you're a panel member, whether you're a speaker, or
1			
22		22	whether you're in the audience, and everybody is

Inel	ropatny (CIPN) Trial Design Considerations		March 25, 2017
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1	involved in the final work product.	1	that generates the new idea for drug, biologic, or
2	I want to introduce Bob Dworkin, who is the	2	device."
3	president of ACTTION, who will give a brief	3	In general, NIH and academia do not perform
4	overview of ACTTION and its goals, role, and	4	research in this area of efficacy and safety,
5	contributions.	5	indicating the need to develop mechanisms and
6	Bob.	6	incentives to foster research directed in improving
7	Introduction to ACTTION	7	the scientific base for what came to be called "the
8	DR. DWORKIN: Thanks, Roy.	8	critical path." In fact, the examples she gives us
9	I do have to set the record straight,	9	is for analgesic drug development, which is one of
10	especially in Washington, D.C. I am not the	10	the emphases of ACTTION.
11	president of ACTTION. I'm the director.	11	So the mission of this public-private
12	I just want to spend a couple of minutes for	12	partnership is to identify, prioritize, sponsor,
13	those of you who aren't familiar with ACTTION,	13	coordinate, and promote innovative activities, and
14	saying just a few brief words about what it is.	14	this meeting exemplifies it, a particular interest
15	You can see from the slide what the acronym stands	15	in optimizing the design of clinical trials. That
16	for.	16	is across four different therapeutic areas: pain,
17	It's a public-private partnership that was	17	analgesia, anesthesia and sedation, treatment of
18	established by the FDA about six or seven years	18	various types of addiction, and disease
19	ago. At the University of Rochester, we've	19	modification if a peripheral neuropathy.
20	essentially been the coordinating center for	20	So ACTTION has a large portfolio of
21	ACTTION for the past six or seven years. So I'll	21	activities across those four different therapeutic
22	just give you an overview of it.	22	areas. And of course, this meeting today fits in
	Page 6		Page 8
1	Housekeeping, you can read this yourself. I	1	the peripheral neuropathy bucket.
2	assume that it says that the restrooms are outside	2	These activities of ACTTION are coordinated
3	in the hall somewhere, and please do silence your	3	by consortia and various collaborations, and this
4	cell phones.	4	one I highlighted on the slide is the Consortium on
5	The meeting and this is important, and if	5	Clinical Endpoints and Procedures for Peripheral
6	you don't like this, unfortunately, you have to	6	Neuropathy Trials. We like acronyms. The acronym
7	leave. The FDA has asked us to record all of these	7	is CONCEPPT. We have other acronyms, and also a
8	meetings that ACTTION sponsors and prepare	8	large number of working groups.
9	transcripts that are then posted on our website.	9	Because ACTTION originated with a focus on
10	Whatever you say will eventually appear on our	10	pain, there's been a greater amount of activity
11	website in a very detailed 600-page transcript.	11	involving analgesic treatments and methods for
12	We're not sure that anyone actually reads those		analgesic clinical trials. Sedation and
13	transcripts, but they're there.	13	anesthesia, addiction medicine, and disease
14	This is a quote from Dr. Janet Woodcock	14	modification in peripheral neuropathy were added
	from, as you can see, back in 2007 that I think is		after ACTTION was originally established, and so we
	really excellent in providing the overarching		just haven't had as much time to ramp up activities
17	rationale for public-private partnerships in	17	to the extent that we've done in pain. But that's
18	general and also ACTTION. And I think it's worth	18	
19	reading, and I'll read it.		example of that.
20	What Dr. Woodcock said back then is, "The	20	Overall, I think our research objective
	science base necessary to evaluate and predict		crosscutting those four different therapeutic areas
22	safety and efficacy is different from the science	22	has been to develop an evidence-based approach to

	Page 9		Page 11
1	design, execution, analysis, and interpretation of	1	(No response.)
2	clinical trials of analgesic, anesthetic, sedation,	2	DR. DWORKIN: Well, okay. Without further
3	peripheral neuropathy clinical trials.	3	ado, I'd like to turn this back over to Roy. Thank
4	I love the phrase "evidence-based approach	4	you.
5	to design of clinical trials," and I have to	5	DR. FREEMAN: Next set of slides.
6	acknowledge Nat Katz as being the source of that I	6	This meeting is in large part a consequence
7	think really felicitous phrase. I hadn't heard of	7	of success. Few would argue about the major
8	it until Nat exposed me to it, but I've used it	8	success of the treatment of cancer over the past
9	with abandon since learning this from Nat several	9	few decades. The number of cancer survivors are in
10	years ago.	10	the tens of millions, and this has necessitated a
11	We've got a bunch of partners reflecting	11	change in focus, that one now needs to focus not
	diverse professional societies, U.S. government	12	only on the treatment of cancer but on the quality
	agencies, and industry. There are multiple	13	of life of those surviving cancer.
	industry sponsors, supporters of ACTTION. The two	14	
	I've put on this slide are the two companies that		is one of the issues that is directly related to
	have provided support for this meeting and for the		quality of life. There is, unnecessary to say to
17	CONCEPPT peripheral neuropathy initiative.		this audience, a substantial prevalence,
18	So we all have to express our appreciation		disability, reduced quality of life of patients who
	to Mundipharma and Regenacy for supporting this		have received chemotherapy, had a peripheral
	meeting, and we really appreciate it. It goes		neuropathy, even years after treatment. The
	without saying, but I'll say it anyway, that		numbers are not well worked out. The predictors
22	ACTTION wouldn't be able to do the things it does	22	are not well worked out, but there is a substantial
	Page 10		Page 12
1	Page 10 without the support of industry and, of course, the	1	Page 12 prevalence.
		1 2	prevalence.
	without the support of industry and, of course, the	2	prevalence.
2 3	without the support of industry and, of course, the FDA.	2 3	prevalence. Chemotherapy-induced peripheral neuropathy
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2 3 4 5 6 7	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	2 3 4 5	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
2 3 4 5 6 7 8	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	2 3 4 5 6 7 8	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.
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1	publication, and again, as you heard all earlier,	1	DR. FREEMAN: Maybe one line, two lines if
2	every one of you, if you wish, will be involved in	2	you can.
3	the development of that publication.	3	(Laughter.)
4	The goal, and this is the ball upon which I	4	DR. DWORKIN: I just want to reiterate, in
5	want you to keep your eyes throughout the meeting	5	Washington, D.C. that I am not president of
6	despite the challenges, is to come up with	6	ACTTION. I'm on the faculty at the University of
7	something, which is I think in the long run going	7	Rochester School of Medicine.
8	to be a lot more simple than the challenges you	8	DR. GEWANDTER: I am an assistant professor
9	will hear will suggest.	9	at University of Rochester and an assistant
10	We want to establish what would be a	10	director of ACTTION, and CIPN is my main area of
11	clinical trial or what would be clinical trials to	11	clinical research interest.
12	evaluate disease modification of chemotherapy-	12	DR. FREEMAN: Simon?
13	induced peripheral neuropathy, that is, to prevent	13	DR. HAROUTOUNIAN: Simon Haroutounian. I'm
14	or delay the appearance or attenuate the features	14	from Washington University in St. Louis, Department
15	of chemotherapy peripheral neuropathy.	15	of Anesthesiology in Washington University Pain
16	We want to evaluate symptomatic treatment of	16	Center. CIPN is one of the areas of my clinical
17	chemotherapy peripheral neuropathy and design a	17	research.
18	clinical trial to do that. We want to attempt to	18	DR. KATZ: Nathaniel Katz. I'm a
19	design a clinical trial to evaluate chemotherapy	19	neurologist from Boston, and I actually am
20	disruption during the receipt of chemotherapy. And	20	president of a small company called Analgesic
21	there will, of course, many unknowns, and we want	21	Solutions. It's not in Washington, so I guess
22	to define a research agenda to deal with those	22	we're all okay.
	Page 14		Page 16
1	unknowns.	1	DR. BRELL: I'm Joanna Brell. I'm a medical
2	This is the ball that I want you to keep	2	oncologist formerly with the Division of Cancer
3	your eye on throughout the proceedings because what	3	Prevention at NCI, National Cancer Institute. And
4	we want to do at the end of this is come up with a	4	now I'm a medical oncologist at a safety net
5	product that will address these issues and allow us	5	hospital in Cleveland associated with Case Western
6	to go forward in this area.	6	Reserve University.
		1	

- As I mentioned earlier, this is a meeting in 7
- 8 which everybody is a participant. We purposefully
- 9 have a relatively small number of invitees so that
- 10 people, whether they are delivering a talk, on a
- 11 panel, or sitting in the audience, are
- 12 contributing.
- 13 I want just to set the tone for this -- and
- 14 the meeting is sort of in between, just a little 15 bit too big for a roundtable and perhaps a little
- 16 too small for an auditorium -- but to set the tone
- 17 of participation. I'd like to begin by having
- 18 everybody, starting on the right in the front row,
- 19 introduce themselves so that we know who each other 20 are.
- 21 DR. DWORKIN: Bob Dworkin.
- DR. GEWANDTER: Jennifer Gewandter. 22

7

13

14

18

20

22

19 to participate.

21 statistical reviewer at DAAAP.

DR. CAVALETTI: I'm Guido Cavaletti from

8 University of Milan, Italy. I'm the coordinator of

11 Europe, U.S., and Australia, and I'm the head of

12 the experimental neurology unit in my university.

DR. DASTROS-PITEI: I am Daniela

16 pain, and new products at Mundipharma in Europe.

17 We have a product, which we are very interested in

DR. ZHOU: I am Yan Zhou. I am a

developing in CIPN. So thank you for allowing me

15 Dastros-Pitei. I'm the head of medical science,

10 network of neurologists and oncologists from

DR. FREEMAN: Daniela?

9 the CI PeriNorms Study Group that is international

110	aropatily (CIIII) IIIai Design Considerations		March 25, 2017
	Page 17		Page 19
1	the MD Anderson Cancer Institute, and I do both	1	neurologist. I direct the neuro-oncology program
2	patient-based and animal-based CIPN research.	2	at Dana Farber.
3	DR. GAUTHIER: I'm Lynn Gauthier, an	3	DR. FREEMAN: Thank you for that.
4	assistant professor from Laval University in	4	I'd like to now hand back to Bob, who will
5	Quebec, Canada; professor and scientist in	5	begin the first session.
6	palliative care, and CIPN is one of my areas of	6	DR. DWORKIN: The format of the se meetings,
7	interest.	7	as you can see from the agenda, is we have
8	DR. WILTROUT: Hi. I'm Lisa Wiltrout. I'm	8	presentations. But the most important part of the
9	a medical officer in the Division of Anesthesia,	9	meeting is the discussion periods that follow the
10	Analgesia, and Addiction Products at the FDA.	10	presentations, so we try to have as much time for
11	DR. FIELDS: Good morning. I'm Ellen	11	discussion as possible at these meetings.
12	Fields, deputy director in the same division.	12	As a consequence, I think the best format,
13	DR. McDERMOTT: I'm Mike McDermott, a	13	at least for this morning's session that I'll be
14	professor of biostatistics at the University of	14	chairing, is we'll have a series of four
15	Rochester.	15	presentations. And after each one, maybe we should
16	DR. EVANS: Good morning. Scott Evans,	16	take just a couple of questions before the next
17	biostatistics at Harvard.	17	presentation. So if you don't get to ask your
18	DR. JARPE: I'm Matt Jarpe from Regenacy	18	question after the presentation, don't worry about
19	Pharmaceuticals, a company primarily focused on	19	it because we'll have lots of time during the Q&A
20	treatments for peripheral neuropathy.	20	period before lunch.
21	DR. G. SMITH: I'm Gordon Smith. I'm a	21	It's a great pleasure to introduce
22	neurologist at the University of Utah interested in	22	Dr. Joanna Brell, our first speaker, who is going
	Page 18		Page 20
1	peripheral neuropathy.	1	to be presenting an overview of chemotherapy-
2	DR. HOWIE: I'm Lynn Howie. I'm a medical		induced peripheral neuropathy. As you just heard,
	oncologist and a medical officer at the Food and		Joanna spent some time at the National Cancer
4			Institute and is now on the faculty at Case Western
	Products.		Reserve University School of Medicine in Cleveland.
6	DR. O'MARA: I'm Ann O'Mara. I'm a program	6	
7		7	DR. BRELL: Good morning. Thank you,
8	manage a portfolio of symptom management of which	8	
9		9	speak.
10	DR. LAVOIE SMITH: I'm Ellen Smith. I'm an	10	The title of my talk is An Overview, and
11	associate professor at the University of Michigan,	11	then we've had over 55 years of neuropathic
12		12	toxicity with the agents we use to treat patients
13	DR. LOPRINZI: Charles Loprinzi, medical	13	with, so if not now, when are we going to take
14	oncologist, Mayo Clinic, been involved with the	14	action? And I think it was outlined very clearly
15	cooperative groups, been involved with a number of	15	this morning that we are taking action.
16	treatment and/or prevention clinical trials with	16	What I am going to do is a 30,000-foot view.
17	chemotherapy-induced peripheral neuropathy.	17	There are a few people in here that may not be as
1		1	

- 17 chemotherapy-induced peripheral neuropathy.
- DR. CLEARY: I'm James Cleary. I'm a 18
- 19 medical oncologist at Dana Farber. I specialize in
- 20 gastrointestinal malignancies and give a lot of
- 21 oxaliplatin, which causes neuropathy.
- 22 DR. WEN: I'm Patrick Wen. I'm a

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22 approach to CIPN.

18 familiar with CIPN. I'm going to give a case

19 report, which will really help us understand the

20 impact and the significance of this and then talk

21 about the American Society of Clinical Oncology

	Page 21		Page 23
1	It's hard to define. You know it when you	1	that then depends on what treatment you're on.
2	see it. To describe CIPN, it's the most common	2	Some people may be on a clinical trial that's not
3	dose-limiting toxicity for chemotherapeutic agents.	3	known to cause peripheral neuropathy, but they
4	When I say chemotherapy, I mean any of the drug	4	develop it, so there's a cohort of patients with
5	agents, any of the anti-cancer agents.	5	the neuropathy that we don't really know about and
6	No FDA treatments or prevention and further	6	don't really count.
7	preclinical data is needed to help inform	7	If you had several lines of therapy already
8	development of treatments. As stated earlier, it's	8	with CIPN-inducing treatments, it's possible if you
9	a very serious unmet clinical need, and I think we	9	get another one that you may be a little more
10	really need to work at some point getting a	10	predisposed to having neuropathy. And it's been
11	definition of this condition, though you can take	11	shown that the dose, the route of administration,
12	any definition of sensory neuropathy right now.	12	and the infusion rate of some of these agents can
13	What is also needed is being on a typical	13	really make a difference on the development, and
14	chemotherapeutic agent that could cause neuropathy,		there are host risk factors.
15	and the onset of the disease and the symptoms are	15	We think it's under-reported just because we
	based on which type of chemotherapy one is		don't always have the best tools to diagnose it.
	receiving. And of course, the symptoms simply		What we can do to estimate the incidence is look at
	range from having sensory problems to having pain	18	the 2017 new cases of cancer, and you can see these
	to having both.		are the top 10 malignancies for men and women.
20	Of course, those symptoms really depend on	20	Within the purple circles, you can see agents that
21	which peripheral nerves are involved. You can see	21	are treated with CIPN-inducing drugs. That's
22	that sensory nerves are the A alpha, beta, larger	22	really 57 percent of the top 10 cancers in 2017
	Page 22		Page 24
1	Page 22 fibers, and the A delta and C fibers are smaller.	1	Page 24 that could potentially be exposed to these agents.
1 2	-		
2	fibers, and the A delta and C fibers are smaller.	2 3	that could potentially be exposed to these agents. That's almost 1 million patients. Of course, there's other malignancies. Many
2 3 4	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	2 3	that could potentially be exposed to these agents. That's almost 1 million patients.
2 3 4	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.	2 3 4 5	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
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2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21	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	2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21	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

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1	nerve fiber density studies, and germline mutations	1	about the questions or the scales, have some
2	are being assessed.	2	confusion about how to respond. Sometimes it's
3	This is a short list of the anti-cancer	3	difficult to discern on that spectrum between
4	therapies that are associated with CIPN. On the	4	sensory symptoms both in pain where their symptoms
5	left are the mechanisms or class, and the drugs	5	actually are.
6	themselves are on the right. The drugs themselves	6	Expectations of the patient can sometimes
7	are just examples because there are many others	7	influence what they say. My best example is a
8	that cause the disease but I don't have listed	8	patient of mine telling me he had severe, very
9	here.	9	painful well, numb, severe numbness peripheral
10	If you go towards the bottom, some of these	10	neuropathy. And he said he couldn't even button
11	newer therapies, some of them are approved, some of	11	his own clothes, yet he was putting his shirt back
12	them are still in testing. Targeted therapies,	12	on and expertly buttoning his shirt without any
13	crizotinib is a new targeted therapy for lung	13	difficulty, correctly, easily.
14	cancer. It's also being tested in other cancers,	14	So without talking to him, I would have said
15	and we're seeing peripheral neuropathy with that.	15	this is terrible. He's at 3. We have to dose
16	Then you need the patient report so the	16	reduce. But by observing him, I was able to see
17	patient can tell you what the symptoms are and what	17	that he was probably a grade 1. He was able to do
18	the issues are. You can grade in the office on a	18	the thing he said he couldn't do.
19	numeric rating scale.	19	Then of course, we talked about validation
20	Here's five other scales or instruments,	20	of instruments.
	tools that we use to assess CIPN. The most common	21	As far as clinician's assessment, what's
22	is the EORTC quality of life survey that has 20	22	been used in the past is the NCI common terminology
	Page 26		Page 28
1	-	1	Page 28 criteria for adverse events. There's multiple
	Page 26 questions on CIPN. As you can see, I didn't get my circles right there, but sensory, motor, and		
2	questions on CIPN. As you can see, I didn't get my	2	criteria for adverse events. There's multiple
2	questions on CIPN. As you can see, I didn't get my circles right there, but sensory, motor, and	2	criteria for adverse events. There's multiple versions. The name has changed from terminology to toxicity and back and forth.
2 3 4	questions on CIPN. As you can see, I didn't get my circles right there, but sensory, motor, and autonomic questions are assessed.	2 3 4	criteria for adverse events. There's multiple versions. The name has changed from terminology to toxicity and back and forth.
2 3 4 5	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	2 3 4 5	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
2 3 4 5 6	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	2 3 4 5 6	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
2 3 4 5 6 7	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	2 3 4 5 6 7	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
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11	curopadity (CIIII) Inal Design Considerations	Watch 25, 2017
	Page 29	Page 31
	1 amplitudes.	1 she gets parathesias. Patients have described this
	2 What will eventually need to happen is the	2 as feeling like there's glass, breaking glass in
	3 total neuropathy score can be used in research, and	3 their mouths and throat, so obviously not a good
	4 then eventually as time goes on, hopefully, we'll	4 sensation, obviously distressing again to the
	5 be able to find the couple points of this that will	5 patient.
	6 help us diagnose CIPN easily in the clinic.	6 She comes back for her cycles. These cold-
	7 I'm going to talk about a case study just to	7 induced symptoms that I just described, they're now
	8 illustrate what happens in the clinic. This is a	8 lasting instead of a couple days, over a week, and
	9 typical case, but it will bring up a couple of	9 she's beginning to feel some mild parathesias in
1	o points about oxaliplatin-induced peripheral	10 her toes.
1	1 neuropathy.	11 She comes back a couple cycles later, and
1	2 This is a 69-year-old African American woman	12 she's now having parathesias with a little bit of
1	3 who works part-time as a seamstress. She's	13 numbness in her fingers and toes, but it's still
1	4 sedentary, lives alone. She has type 2 diabetes	14 mild, according to her, and she's still functioning
1	5 for 5 years, has never been on insulin, and does	15 well. But by the time she comes for cycle 7, she's
1	6 not have any neuropathy.	16 dropping things. She cannot button her clothes
1	7 She was diagnosed with adenocarcinoma of the	17 very well. She can't pick up the needles to sew as
1	8 colon, and she underwent a complete resection	18 a seamstress.
1	9 hemicolectomy. She was found to have stage IIIB	19 This is more of a grade 2 because she can do
2	o disease. She's at high risk for recurrence of this	20 all of her other activities of daily living but
2	1 cancer, approximately 50 percent, and there are	21 she's not able to perform other things. This is a
2	2 even other factors in the tumor that make her even	22 distress to her. It's hard to know. Some grade 2s
	Page 30	Page 32
	1 a higher risk.	1 have to be dose reduced, and so we decided to dose
	2 Her priority is to extend her life, so she's	2 reduce her oxaliplatin. We don't have any disease-
	3 interested in adjuvant therapy. The standard	3 modifying agents, so there was nothing we can do at
	4 off-study adjuvant chemotherapy for colorectal	4 that time. She had no pain, so we did not start
	5 cancer in the United States is FOLFOX. This	5 any analgesics for her.
	6 includes oxaliplatin at 85 milligrams meters	6 When she comes back for subsequent cycles,
	7 squared. It's given every 2 weeks as a cycle, and	7 she says she's stable or improved with the dose
	8 it takes about 6 months to get through the total 12	8 reduction, and that's a red flag that she's not
	9 cycles.	9 reporting her symptoms because there's no
1		10 expectation that you would improve with a dose
	1 before she even leaves the cancer center, she's	11 reduction in chemotherapy. So you have to question
	2 complaining of shortness of breath, laryngospasm.	12 her more. You have to try to find out what's going
	3 She has some perioral sensations. She's	13 on.
	4 distressed. Even though she's short of breath,	14 She came back for her last cycles and says
1	-	
	5 she's not hypoxic, and we give her IV steroids.	15 she's stable. Later on, she admits that her
1	<ul><li>5 she's not hypoxic, and we give her IV steroids.</li><li>6 Whether the natural history of this was that she</li></ul>	16 symptoms had been worsening the whole time, but she
1 1	<ul> <li>5 she's not hypoxic, and we give her IV steroids.</li> <li>6 Whether the natural history of this was that she</li> <li>7 was going to get better or whether she responded to</li> </ul>	<ul><li>16 symptoms had been worsening the whole time, but she</li><li>17 feared dose reduction. So 6, 8 weeks later, she</li></ul>
1 1	<ul> <li>5 she's not hypoxic, and we give her IV steroids.</li> <li>6 Whether the natural history of this was that she</li> <li>7 was going to get better or whether she responded to</li> <li>8 the steroids is unclear.</li> </ul>	<ul> <li>16 symptoms had been worsening the whole time, but she</li> <li>17 feared dose reduction. So 6, 8 weeks later, she</li> <li>18 comes back with an abrupt worsening of her</li> </ul>
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1 1 1 2 2	<ul> <li>5 she's not hypoxic, and we give her IV steroids.</li> <li>6 Whether the natural history of this was that she</li> <li>7 was going to get better or whether she responded to</li> <li>8 the steroids is unclear.</li> <li>9 Then also after cycle 1, a couple hours</li> <li>0 later, she has cold-induced sensations. If she</li> <li>1 touches anything cold with her hands, she gets</li> </ul>	<ul> <li>16 symptoms had been worsening the whole time, but she</li> <li>17 feared dose reduction. So 6, 8 weeks later, she</li> <li>18 comes back with an abrupt worsening of her</li> <li>19 symptoms.</li> <li>20 Now, several months later, she has numbness</li> <li>21 in her fingers and toes. She's not able to return</li> </ul>
1 1 1 2 2	<ul> <li>5 she's not hypoxic, and we give her IV steroids.</li> <li>6 Whether the natural history of this was that she</li> <li>7 was going to get better or whether she responded to</li> <li>8 the steroids is unclear.</li> <li>9 Then also after cycle 1, a couple hours</li> <li>0 later, she has cold-induced sensations. If she</li> </ul>	<ul> <li>16 symptoms had been worsening the whole time, but she</li> <li>17 feared dose reduction. So 6, 8 weeks later, she</li> <li>18 comes back with an abrupt worsening of her</li> <li>19 symptoms.</li> <li>20 Now, several months later, she has numbness</li> </ul>

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	Page 33		Page 35
1	a diabetic foot ulcer on the first digit. She's	1	group of survivors is going to accumulate as well.
2	not able to feel her feet.	2	But look at the types of survivors, and she is this
3	This illustrates some of the risk factors	3	type. After treatment for many years, she has
4	that we think we know for CIPN: older age, history	4	chronic late conditions.
5	of diabetes. Her diabetes probably wasn't in as	5	Some of the consequences of having
6	good of control as she thought; obesity and being	6	peripheral neuropathy to simply state, we talked
7	female.	7	about dose reduction or dose continuation. And as
8	She also had symptoms of acute oxaliplatin	8	stated earlier, we don't really know the clinical
9	neurotoxicity, and these are experienced by almost	9	manifestation of what that really means. With some
10	every patient that has oxaliplatin. It can happen	10	drugs, that may not be as problematic. With other
11	right after the infusion. It can happen hours	11	agents, it really could be a serious problem. We
12	later, but it's particularly involving the head and	12	just don't know.
13	neck. Not sure exactly what causes it, whether	13	We mentioned that it takes a couple years to
14	it's a hypersensitive reaction where it's ion	14	recover. Some patients do not resolve at all.
15	channel dysfunction, but these patients will	15	There's certainly increased healthcare utilization,
16	experience this right away, again, very	16	and functional rate is diminished completely. So
17	distressing.	17	they need more support from family and friends if
18	They feel short of breath, but we know	18	they still have severe neuropathic pains.
19	they're not hypoxic, but the sensation is poor.	19	These are just a few references on multiple
20	And that's most likely related to the other	20	studies showing that chemotherapy-induced
21	symptoms that they're having such as laryngospasm.	21	peripheral neuropathy interferes with quality of
22	She has then developed the chronic sensory	22	life. If you look at the bottom one, this is very
	Page 34		Page 36
1	Page 34 peripheral neuropathy, and that's what we focus on.	1	Page 36 interesting, one we don't think of. This was
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2	peripheral neuropathy, and that's what we focus on.	2	interesting, one we don't think of. This was
2 3	peripheral neuropathy, and that's what we focus on. There are some reports in the literature saying it	2 3	interesting, one we don't think of. This was spiritual pain from patients in Japan, and a lot of
2 3 4 5	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	2 3 4 5	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,
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Ne	uropathy (CIPN) Trial Design Considerations		March 23, 2017
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1	caregivers. That was the biggest division of the	1	not surprisingly, has shown some benefit in
2	money. There was hardly any of this money that was	2	neuropathic pain.
3	spent on treatments, symptomatic treatments, or the	3	This ASCO group also put forward some
4	multiple clinic visits. That was about \$5,000 per	4	recommendations and a research agenda, and of
5	patient.	5	course, the goal was to develop a comprehensive and
6	In 2012, this study looked at not only	6	standardized approach to assessment of CIPN, for
7	outpatient visits and caregiver lost wages and time	7	obvious reasons, to help with data acquisition and
8	utilization, but it looked at inpatient and all	8	to also help the clinician in the clinic.
9	total healthcare utilization for these patients.	9	The research agenda is listed below. They
10	They looked at just some of the most common	10	believe that we can get more benefit from some
11	cancers, and they found about \$17,000 per patient	11	topical treatments for peripheral neuropathy. They
12	per year. About 8,000 of this was in outpatient,	12	thought that another phase 3 trial of gabapentin or
13	and this was a rough estimate of the total cost.	13	pregabalin was warranted. I'm not sure if this is
14	So we're talking about billions of dollars.	14	the right way to go or not, and I'm afraid that we
15	I'd like to switch gears a little bit and	15	won't get the FDA indication for peripheral
16	talk now about the American Society for Clinical	16	neuropathy just like we didn't get it for the
17	Oncology approach to CIPN, ASCO. That's our lead	17	duloxetine.
18	organization for medical oncologists. There was in	18	There's work on electrocutaneous nerve
19	2014 a publication. A group of experts met to	19	stimulation that's going on, and there's a lot of
20	ascertain best practices for CIPN and then provide	20	clinical trials going on that are looking at
21	some research guidance.	21	complementary and alternative therapies.
22	They did look at 48 eligible randomized	22	A lot of this information on CIPN and a lot
	Page 38		Page 40
1	trials from the time period of 1990 to 2013 and	1	of studies come from the NCI-sponsored Community
-			On coloring Decompts Dreaments collect the NCODD. These

2 Oncology Research Program called the NCORP. These

3 are peer-reviewed grants that go either to cancer

5 for developing clinical trials. And these trials

able to perform the clinical trials.

6 are performed out in the community with a very

large network of support of physicians that are

10 the community, and they have the time restrictions

11 that all of us have. There's competing interest

12 when a medical oncologist sees a patient. The

14 focus on the treatable toxicity. We can fix nausea

16 insufficiency. There's not too much to do for the 17 peripheral neuropathy, so there's less time to

20 complex clinical studies. I think when we get

21 closer to having better treatments, this is the

22 perfect network in which to study that.

This may not be the best environment for

13 patient has other toxicity. You really tend to

and vomiting. We can hydrate for renal

Of course, these medical oncologists are in

4 centers or academic centers, and they are the point

- 2 found what we know, that a lot of these clinical
- 3 trials with CIPN are small sample size. There's
- 4 different eligibility criteria, different
- 5 populations are used, multiple different outcomes
- 6 and instruments, different time points for when the
- 7 objectives are assessed. So it's hard to really
- 8 compare any of these trials, unfortunately.
- 9 They made some recommendations based on the
- 10 quality and quantity of evidence, and I don't want
- 11 to go through that slide. But there was no
- 12 recommendation for any agent that would be able to
- 13 prevent peripheral neuropathy. This is concordance
- 14 with another review that was published the same
- 15 year that also showed that there were no agents
- 16 that could prevent neuropathy.

Min-U-Script®

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

7

8

9

15

19

18 focus on that.

N	europathy (CIPN) Trial Design Considerations		March 23, 2017
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-	NCI has a major investment, of course, in	1	There's a study that's being assessed right
	2 NCORP, and that's where their CIPN investment is	2	now looking at oxaliplatin, the 12 cycles versus
	3 for the most part. Over the years, there's been		the 6 cycles, and we don't have the data back on
	L clinical trial planning meetings sponsored by NCI.		that. But even with 6 cycles using FOLFOX,
	5 The first one looked at clinical trial research and		oxaliplatin, that's still within the timeframe that
	5 knowledge gaps, and there was a CIPN workshop in	6	people develop peripheral neuropathy.
	2011. That was focused on mechanistic research	7	Of course, there's increasing interest.
8	recommendations, and that led to some translational	8	We're here. The NCI is gathering groups,
9	and basic science funding announcements to further	9	multidisciplinary, but we need to keep in mind that
1(	the science.	10	vincristine was FDA approved about 55 years ago, so
1:	Then just a few weeks ago, some of us in the	11	patients have been suffering at least 55 years with
1:	2 room were at another clinical trials planning	12	peripheral neuropathy.
1:	meeting, and this was focusing on developing novel	13	I think, as beautifully said by Dr. Freeman
14	trials incorporating translational research. We	14	and Dr. Dworkin, that now is the time, and we're
1!	5 had some excellent translational research talks	15	going to make some headway in this meeting and move
10	5 with this. We had a diverse group as we have here,	16	forward. Thank you.
1'	neurologists, PhD researchers, advocates, community	17	(Applause.)
18	members, community oncologists.	18	DR. DWORKIN: Just a few questions.
19	Then we broke into two groups, and one was	19	DR. FREEMAN: Maybe let me start with a
20	looking at longitudinal study recommendations.	20	question. I'm going to frame the question within
23	L There's a hope for a database with lots of	21	the context of the meeting and then ask the
23	2 information, mainly phenotype, any other	22	question.
	Page 42		Page 44
	-	1	
	assessments, a real focus on drug levels and dosing		The way I'm thinking about this meeting is
:	-	2	The way I'm thinking about this meeting is in a number of very specific boxes. The one is
:	assessments, a real focus on drug levels and dosing of drugs, and to really look at exactly what amount	2 3	The way I'm thinking about this meeting is
:	<ul> <li>assessments, a real focus on drug levels and dosing</li> <li>of drugs, and to really look at exactly what amount</li> <li>of drug the patient receives and how that relates</li> </ul>	2 3 4	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
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Net	ropathy (CIPN) Trial Design Considerations		March 23, 2017
	Page 45		Page 47
1	address that, somehow measure that, value that in	1	toxicity even though we have much less
2	terms of its long-term consequences, where should		neurotoxicity. So we're revisiting how can we
	we focus? Where is the area of		optimize dose and schedule around first in class
4	DR. BRELL: I think certainly not on	4	like bortezomib and second generation boronate
5	oxaliplatin because there was some data from Europe	5	
	showing that maybe we may get by with 6 cycles	6	area in our space, what you just asked.
	instead of 12 cycles. So the only way that's going	7	DR. BRELL: Dr. Richardson, could you
	to be used clinically is to make sure there's no	8	comment a little bit on the peripheral neuropathy
	difference in survival.		that's disease induced in myeloma?
10	So oxaliplatin may not be the best drug for	10	DR. RICHARDSON: Yes, it's a great question.
11	that, but certainly there's many people on	11	Thank you for asking that.
	paclitaxel for a lot of different reasons for	12	The incidence and it's great to be with
13	breast cancer. And I think that drug or that	13	Patrick right here because we did some of the
14	family of drugs would be the drugs we would want to	14	original work showing this clinically, it's
15	look at.	15	around 20, 25 percent clinical manifestation of
16	Of course, it's going to be a long-term	16	peripheral neuropathy that's typically small fiber
17	proposition. If you look at adjuvant therapy	17	from myeloma itself.
18	patients, you're going to have to wait a long time	18	When we do nerve conduction studies, we
19	to look at overall survival, and even disease	19	realized that the actual incidence is probably much
20	recurrence unless you look at those that are at	20	higher, and certainly in some preliminary work we
21	very high risk for disease recurrence. You could	21	did and published some years ago, if you looked at
22	look at a metastatic group of patients and look at	22	newly diagnosed patients and studied them
	Page 46		Page 48
1	Page 46 issues like disease progression, but we're going to	1	Page 48 carefully, the incidence of documentable
	-		-
2	issues like disease progression, but we're going to	2	carefully, the incidence of documentable
2	issues like disease progression, but we're going to have to really figure out which drug to use and the	2	carefully, the incidence of documentable neurotoxicity from the disease was probably approaching 50 percent.
2 3 4	issues like disease progression, but we're going to have to really figure out which drug to use and the timing of the outcomes.	2 3	carefully, the incidence of documentable neurotoxicity from the disease was probably approaching 50 percent.
2 3 4 5	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	2 3 4 5	carefully, the incidence of documentable neurotoxicity from the disease was probably approaching 50 percent. DR. BRELL: Thank you.
2 3 4 5 6	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	2 3 4 5	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
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1	never dose reduce. I don't have many patients with	1	of them.
	very much neuropathy. I see breast cancer, and	2	I will bring up a few, and one that I think
	taxane is what we use, paclitaxel. And the reason	3	is very surprising, it came from our own data, and
	why I say I never dose reduce is I either stop or		I had never really paid much attention to this in
	continue. This 20 percent dose reduce, you're		the past. But it opens up a whole new kettle of
	still getting more of this neurotoxic agent process		fish, I think, when we get into the predictors.
	in there.	7	We're all aware and familiar with this
8	I think we'll get data from the IDEA trial.	8	picture. And again, some of you may not have heard
9	All rumors are that it will come out at this year's	9	me talk in the past, so for those that are familiar
	ASCO. It will be very interesting from there.		with my work, I apologize for doing a little bit of
11	In practice, to help figure out, what I do		review, but I wanted to get everyone up to the
12	with my patients at the end of therapy, if they've		rationale of what we're doing.
13	had 8 doses of paclitaxel, I have to estimate how	13	I began a number of years ago looking at
14	much more benefit would be 12, which is our	14	CIPN patients, and we began with the chronic
15	standard versus the 8. And maybe it's a percentage	15	patients. One of the things I had them do, of
	point or so in terms of 10-year survival and that		course, was give me a drawing to show where their
17	sort of stuff. Then you put that up against the	17	symptoms were located.
18	bout of neuropathy they have, which can be	18	Here's the typical presentation. This is
19	long-term neuropathy for things, so you make	19	not surprising to anybody, but what we did is we
20	choices along those sorts of ways.	20	laid out then, as we did our psychophysical test,
21	DR. DWORKIN: Seems like we'll have no	21	trying to target in this particular patient where
22	trouble with that material for discussion. Thanks	22	they've colored solid is where they actually had
	Page 50		Page 52
1	very much.	1	ongoing pain. Then you notice there's a stripe in
2	DR. BRELL: Thank you.		their palm, and that's where they said they went
3	DR. DWORKIN: It's a pleasure to introduce		from overt pain to numbness and tingling. It was
4	our next speaker, Dr. Pat Dougherty from		bothersome but not necessarily painful.
5	MD Anderson Cancer Center in Houston. Pat's done	5	You notice how this patient in particular
6	really landmark studies, both preclinical and	6	was very interesting because they drew a line right
7	clinical, of chemotherapy-induced peripheral	7	at their ankles and their wrists saying that above
8	neuropathy. So it's a great pleasure to have him	8	that point, they're symptom free. The fact is, as
9	here, and he'll be speaking for the next half hour	9	you further talk to folks, they really complain
10	on predictors of CIPN.	10	about the glabrous surface of their hands being
11	Presentation – Patrick Dougherty	11	affected, not as much the hairy backside of the
12	DR. DOUGHERTY: Thank you for that	12	hands.
13	introduction, and thank you very much for the	13	So we set up then to do some psychophysical
14	invitation just to participate. As I commented to	14	studies directed at both the fingertip so that
15	a few folks, when I saw the list of participants, I	15	will be labeled the painful area this numbness,
16	was kind of surprised actually that I was included,	16	tingling area that's not necessarily painful but
17	so I'm very appreciative.	17	symptomatic, we call that the border area, and then
18	I knew I was coming after Joanna, and Bob	18	we picked an area outside the area of pain, up in
19	already told you that I do both clinical and		the volar forearm.
20	preclinical studies. So please don't be shocked	20	We did primarily hands just because it's
21	when I don't spend an entire half hour on the	21	easier for the patients, but we get very much the
22	predictors because again, Joanna has just hit some	22	same data if we target the feet. What we found,
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1	using again these sorts of tests and I'll get	1	chronicity is what led us initially to do skin
2	into that one with the little colored dots in a	2	biopsies. This picture here is a very nice pretty
3	second because I think that's a really intriguing	3	picture, and this was in collaboration with a guy
4	test. But each of these different tests are	4	named Bill Kennedy, who taught us how to do this
5	designed to get at the different subtypes of	5	sort of work on our own.
6	fibers.	6	The blue stain that you see there, that's
7	So touch is mediated by A beta fibers.	7	for the stratum basale keratinocytes. Then down
8	Pinprick is mediated by A delta fibers, and then	8	below, you can see the red. Those are the blood
9	overt pain is mediated by C fibers. And the	9	vessels down in the dermis, and then the green is a
10	different tools that we use are directed at those.	10	stain for what's called PGP 9.5. It's just a pan
11	I've also put this in just to remind you	11	neuronal marker.
12	that the dorsal root ganglion is where all those	12	The little squiggly lines that are going
	cell bodies live, and I'm going to come back at the	13	from the dermis up into the blue is the free nerve
	end with some new findings as to what we think is		endings, so those would either be C fibers or
	going on in the ganglia, or what we've observed		A delta fibers. And then the big swirly things
	going on in the ganglia, that I think may point		that you see, those are Meissner's corpuscles, so
17	future directions to potential therapies.		those are A-beta-type fibers.
18	The initial psychophysical test we did, and	18	There's your nice normal skin, and there's
19	the white bars, the open bars, that's data from you	19	your skin on chemotherapy. So the reason folks are
	or I, and then the colored bars, the black being		getting numb is because those fibers are becoming
	our initial test, then the gray being a test that		largely obliterated. Not all the fibers, you can
	we did a year after the first. It shows, number		still see there's some down there around the blood
	Page 54		Page 56
1	one, there's compromise of touch fiber, so A beta	1	vessels. But right in the center, just next to
2	fibers seem to get sick. There's some compromise	2	that blood vessel right in the center, you can see
3	of A delta fibers. The sharpness detection is	3	there's a sick Meissner's corpuscle, and then
4	increased in that pain area, marginally in some of	4	there's very few fibers going up past the blue
5	the other areas. Then there's variable changes in	5	line, showing that the A deltas and C in this
6	the percept for hot and cold.	6	little section at least are remarkably knocked out.
7	The gray tells you that once these folks get	7	I just thought the picture shows us a couple
8	to a chronic condition, we don't see them getting	8	of things. Number one, the fibers are gone, but
9	better. The idea that we're going to somehow put	9	number two, as I was looking at this, this picture
10	folks back together and cure them of CIPN is going	10	here, I was looking at this because we were
11	to be quite the challenge, which again then I think	11	counting these fibers. And it suddenly occurs to
12	pushes the emphasis to perhaps prevention as being	12	me that we've talked about die-back neuropathy. I
13	the key here ultimately.	13	thought, you know what, those free nerve endings
14	The other take-home message is that there is	14	are getting up into the stratum spinosum. That's
15	a sparing of sensibility. Folks don't go	15	where tight junctions form.
16	completely numb. So what that tells you is that	16	Does that mean then that that axon is
17	the treatments are not just uniformly neurotoxic.	17	trapped into the skin? Meaning that to keep this
18	There's some element of selectivity in the types of	18	innervation intact, the nervous system needs to be
19	nerves that are affected. That then gets to	19	constantly extending into that tissue. So these
20	important issues related to underlying mechanisms,	20	neurons are being renewed all the time.
21	which I won't get too much into that.	21	So it's not that the axons so much retract
22	That level of impairment that we saw in the	22	as what potentially is going on is that the axons
1		1	

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1	are failing to reextend for some period of time.	1 quantitatively what you just saw in the picture.
2	And if the tissue is sloughing, well, then that	2 In the areas of pain, those fibers dramatically
3	means that eventually those axons are going to get	3 depleted. As you move proximal, then the fiber
	cut off.	4 numbers start to recover.
5	In this particular slide here, there's just	5 When we looked at normal people and by
6	a little bit of a picture all the way down at the	6 the way, I'll tell you, if you want to do biopsies
	bottom and I guess it's on your right where	7 in patients, you're going to get one try, one
	you can see the dermal plexuses down there. And if	8 chance at doing that. Here, we had our normal
	you count those Gary Bennett actually went in	<ul><li>9 volunteers, and I asked a couple folks if they</li></ul>
	and did some counting of the dermal plexus down in	10 would do it again. Under no circumstances will
	there, and he could not find any change in axon	11 they do that again.
	content. We found the same thing.	12 The volar forearm is not a big deal. The
13	But the interesting thing about that then is	13 fingertips, particularly if they're still healthy,
	that if the C fibers are broken off, then somewhere	14 hurts like hell the next day. Don't tell anybody
	down in that dermal plexus is the original axon.	15 that as they're signing the form.
	Everyone remembers from their neuroembryology of	16 (Laughter.)
	course it's vivid in all of our imaginations	17 DR. DOUGHERTY: But they'll all remember you
	-	
	still a growing axon, if those axons eventually	18 the next time they're sitting in clinic and that
	try to regrow, they form growth cones on them.	19 guy comes in. Don't go with him. He's going to
20	Growth cones cause spontaneous discharges.	20 hurt you.
	So there's one substrate, then down potentially in	21 The interesting thing that came out of our
22	that dermal plexus of axons that are somehow trying	22 volunteer counts is you look through there, and the
	Page 58	Page 60
1	Page 58 to find their way back to mama, the growth factor	Page 60 1 number one thing that jumps out, ENF density, free
	-	
2	to find their way back to mama, the growth factor	1 number one thing that jumps out, ENF density, free
2 3	to find their way back to mama, the growth factor is being released by the keratinocytes. They're	<ol> <li>number one thing that jumps out, ENF density, free</li> <li>nerve endings are lowest in your fingertips and</li> </ol>
2 3 4	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	<ol> <li>number one thing that jumps out, ENF density, free</li> <li>nerve endings are lowest in your fingertips and</li> <li>then recover as you come proximal. If you're doing</li> </ol>
2 3 4 5	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	<ol> <li>number one thing that jumps out, ENF density, free</li> <li>nerve endings are lowest in your fingertips and</li> <li>then recover as you come proximal. If you're doing</li> <li>something that's depleting ENFs, essentially what</li> </ol>
2 3 4 5 6	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	<ol> <li>number one thing that jumps out, ENF density, free</li> <li>nerve endings are lowest in your fingertips and</li> <li>then recover as you come proximal. If you're doing</li> <li>something that's depleting ENFs, essentially what</li> <li>you're doing is we're built in, we're hard wired,</li> </ol>
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2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21	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,	<ol> <li>number one thing that jumps out, ENF density, free</li> <li>nerve endings are lowest in your fingertips and</li> <li>then recover as you come proximal. If you're doing</li> <li>something that's depleting ENFs, essentially what</li> <li>you're doing is we're built in, we're hard wired,</li> <li>for the clinical phenotype of CIPN. If you knock</li> <li>out those ENFs, you're going to knock them out down</li> <li>to zero in your fingertips first, and then you're</li> <li>going to have reserve as you move proximal.</li> <li>Now, as I presented that data in the past,</li> <li>people have said hold on, that's completely</li> <li>counterintuitive. My fingertips are most</li> <li>sensitive, and then I'm less sensitive. But that's</li> <li>for light touch.</li> <li>We all presumably took showers today. If</li> <li>you stick your hand in the hot water, it doesn't</li> <li>feel nearly as hot as when it hits your back,</li> <li>right? So you already know that this is actually</li> </ol>

	TTION - Chemotherapy-Induced Peripheral ropathy (CIPN) Trial Design Considerations		March 23, 201
	Page 61		Page 63
1	Some of those folks are walking in with very low	1	panicked me a little bit because I initially
2	ENF at baseline, which made me think immediately,	2	thought that all of our tools were simply out of
3	wow, this is cool. What we've got here is this is	3	calibration, so we quickly recruited some more
4	a clear risk factor, is that if folks are latently	4	healthy volunteers, and sure enough, the data came
5	put together with a low functional reserve, then	5	out consistent.
6	they're likely to be the ones that are going to	6	So this seemed to be a reliable data point
7	show symptoms when they go to therapy.	7	that, in fact, it really is true. There is
8	That's what we focused on. And that picture	8	something about the disease process of cancer
9	there, I'll get to it in a second why that picture	9	itself that seems to start to impact your ENF
0	is there. So that's what we decided to do, is	10	density and presumably then predisposes you to the
.1	initially we were just biopsy a whole bunch of	11	onset later then of treatment-related neuropathies.
2	folks, send them off to therapy, and then we'll	12	One of the big critiques of trying to do
.3	sort them out later.	13	QSTs is that it's too time consuming. It's going
.4	The table shows because again, I said how	14	to take too long to work up each patient. Well, in
.5	this hurts, so I knew we would have a heck of a	15	panel C, that's a slotted pegboard test. It takes
.6	time trying to recruit people if the entry criteria		roughly for any of us 70 seconds or so to do that
.7	was you got to give me a chunk of skin. But the		test. The patients, you see, take considerably
18	table showed that, in fact, the Meissner corpuscle	18	
9	density more or less parallels your ENF density.	19	done. So that's something that can be quickly
	What saved us is this because we could find a	20	done.
21	noninvasive way of counting Meissner corpuscles	21	In panel B is where we're showing this bumps
	using a confocal laser reflectance microscopy.	22	test. Now, that bumps test is here, and again,
	Page 62		Page 64
1	That's, in fact, my fingerprint there. You	1	it's something that can be done really quick. This
2	can see the bumps coming up at you, and then the	2	was developed by Bill Kennedy in Minnesota along
3	dark spots is the valleys going down. The little	3	with Don Simone at University of Minnesota. They
	arrows are all pointing at little Meissner		promised me they got this very close; actually they
5	corpuscles, so you can count those noninvasively.		can mass produce this.
6	That's what we did. We began in our	6	The test is basically you can see the
	psychophysical study. And as Paul was just	7	finger there is on one of the dots. Over one of
	mentioning, one of the things that came out when we		those dots is a little cylinder that I think is
	started doing these baseline studies is that lo and		550 microns in diameter, and then they vary from a
		10	half micron tall to 22 and a half microns tall.
	healthy volunteers, in fact, patients have		And the task is for each dot, tell me where is the
_			

- 13 Initially, I saw this in non-small cell lung
- 14 cancer patients, then we saw it in myeloma 15 patients, and I wasn't particularly surprised
- 16 because of the idea that there may be subclinical
- 17 paraneoplastic syndrome running around out there. 18 So that wasn't really surprising.
- 19 This slide, though, was surprising to me
- 20 because this comes from colorectal cancer patients.
- 21 Even in a group not associated with paraneoplastic,
- 22 we're finding these subclinical neuropathies. It

- 13 I'm actually terrible at this because I get 14 so competitive, I want to find that doggone dot,
- 15 that I end up just messing up. But you guys would
- 16 all probably perform at roughly 3 microns for your
- age. Kids can go all the way down to that half 17
- micron tall. Patients, though, they end up more or 18
- 19 less somewhere in double that. They're walking in
- 20 somewhere in the 7 to 8 micron range.
- 21 Again, this is something that can be done
- 22 relatively quickly. So if Bill can just push this

	Page 65		Page 67
1	out the door as a product, it's something again	1	reported outcome that we found was much more
2	that could be applied.	2	sensitive, in fact, than the rate at which folks
3	This then is showing you as we move	3	changed their QST function.
4	forward and now we're actually looking at going	4	I think the next slide I have that. Yes, I
5	out into the study where we're showing then this	5	have a little more QST data.
6	number of out-of-range measures. I'm going to	6	Here, you're showing touch gets worse over
7	actually skip that.	7	time slowly. The sharpness threshold doesn't
8	This is the picture I wanted to get to,	8	really change much. Similar with warm and cool,
9	where when we look at then the correlation of	9	they really don't change that fast. There is some
10	folks' ability to detect the bumps back to their	10	changes over time, but it's relatively slow.
	Meissner corpuscle counts, we find that those	11	This is, I thought, the more important
	things are correlated to one another. So the long		slide. So as you look at the total neuropathy
	and the short, you can use simple QST measures to		score, that does tend to build up over time.
	get at what those patients' underlying ENF and		That's just giving a score of 1 to each QST measure
15	density might be.	15	that changes over time, so that builds up.
16	Looking prospectively, this is again	16	But the center is what I thought was more
	colorectal cancer patients, and one of the		interesting. It gets to what Joanna was talking
	take-home messages I'd give you is that once you		about a little bit ago. On oxaliplatin, you can
	start doing these therapies so here we're		see that numbness builds up fairly rapidly over
	looking at again colorectal cancer patients,		time. And we ended up with roughly 80 percent of
	pegboard time, which we thought was very sensitive		our patients by the end of the trial showing some
22	to initially detect folks.	22	degree of numbness and tingling. Only about
	Page 66		Page 68
1	Page 66 As you go through therapy, it didn't tend to	1	Page 68 20 percent of patients started to show pain.
	-	1 2	20 percent of patients started to show pain.
2	As you go through therapy, it didn't tend to	2	20 percent of patients started to show pain.
2 3	As you go through therapy, it didn't tend to get worse, which is what I would have expected. In	2 3	20 percent of patients started to show pain. There's one measure of what the expected
2 3 4 5	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	2 3 4 5	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
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	Page 73		Page 75
1	forward to treat folks.	1	become spontaneously active. There are still other
2	The other thing and I'll leave this as		groups of neurons that aren't affected that
	the last tidbit we found preclinically, this is		treatment. So in fact, you may need combination
	dorsa root ganglia from animals treated with		treatments to actually get an effective block of
	paclitaxel, and they developed spontaneous activity		this activity.
	in the soma, in the ganglion cells themselves.	6	Then some data showing you some of the
7	This previously was in large cells using a	_	interventions that we've tried to suppress this
	sharp electrode preparation where we were able to		activity. I'm not going to get into that. Then as
	sample large cells. This is where we were using		well, we've been doing now some in vitro culture
	disassociated neurons so now we can better sample		work focusing on the mechanisms of this activity
	the small cells.		that I'm not going to get into.
12	So we're seeing activity in both large and	12	
	small neurons, and the shocker, we're able to get		right on time and potentially going to take a few
	dorsal root ganglia out of people at MD Anderson,		questions. Thank you.
	basically patients going in for vertebrectomies in	15	
	the thoracic dermatomes, so the dorsal root is		to the people that did all the work.
	often sacrificed, and we were able then to collect	17	
	those.	18	
19	We found spontaneous activity in ganglia of		questions.
20	patients but only in dermatomes where they had	20	·
	pain. If we got these ganglia out of dermatomes	21	interested in that immune observation that you
	where patients did not have pain, there was no		made. Could you just go over that? Because you
	Page 74		Page 76
1	Page 74 spontaneous activity. So exactly like we're seeing	1	Page 76 moved through it rather quickly. But what was the
	-		
2	spontaneous activity. So exactly like we're seeing	2	moved through it rather quickly. But what was the
2	spontaneous activity. So exactly like we're seeing in animals, we're getting the same type of	2	moved through it rather quickly. But what was the implication of the macrophage function that you talked about?
2 3 4	spontaneous activity. So exactly like we're seeing in animals, we're getting the same type of spontaneous activity occurring in patients.	2 3 4	moved through it rather quickly. But what was the implication of the macrophage function that you talked about?
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2 3 4 5 6 7 8	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	2 3 4 5 6	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
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1	in the British Journal of Hematology a	1	They'll shake your hand.
	meta-analysis from our bortezomib experience	2	Why do the animals move their paw quicker?
3	showing that you must partner dexamethasone on the	3	I'm not sure. One of the things that I can guess
4	day of bortezomib administration and the day after.	4	at is, again, this spontaneous activity that we see
5	Previous adaptations of the regimen had moved to a	5	and we think about what the patients tell us. A
6	weekly schedule dislocating steroid from	6	lot of folks have spontaneous pain. That's what
7	bortezomib, and we saw a spike in grade 3	7	they got. And if they walk or they use their
8	neuropathy in the meta-analysis.	8	hands, it makes their spontaneous pain worse, and
9	Your observation is extremely pertinent	9	then it lingers.
10	because it exactly correlates with what we see	10	The animals, I suspect, are learning to
11	clinically.	11	avoid a stimulus. Now, is that because they also
12	DR. DOUGHERTY: It'd be interesting, and	12	would have a spontaneous dysesthesia pain, that
13	I've given a lot of thought to that steroid	13	they know that if you touch them, you're going to
14	treatment because, again, the macrophages are	14	make it worse and it's going to linger? That's my
15	resistant to steroids.	15	interpretation.
16	DR. RICHARDSON: Right, but it's downstream.	16	I would say that we're preventing the onset
17	It's cytokines and	17	of the CIPN itself. Now, we have not done the
18	DR. DOUGHERTY: Your T cells would	18	nerve counts. We have not done the ENF counts,
19	potentially be sensitive to steroids. So it'd be	19	et cetera, other things that we could measure to
20	very interesting to see whether the T regs are less	20	look at, but that's my suspicion.
21	sensitive, say, than T helpers. And so you're	21	DR. DWORKIN: Last question from Ellen.
22	actually augmenting the activity of those T regs,	22	DR. LAVOIE SMITH: You mentioned that you
	Page 78		Page 80
1	so a lot of interesting immunology based on that	1	thought that a patient-reported outcome measure
	observation as well. Thank you.		would be more sensitive than the bumps test. Can
3	DR. CAVALETTI: Pat, may I ask a question?		you elaborate on why you think that's true?
	Guido Cavaletti. You mentioned that blocking	4	DR. DOUGHERTY: Just based on the rate of
	macrophages, killing macrophages, stops CIPN.		
		5	
6			change. So if you're going to use an objective
	Would it be more correct to say it stops pain?	6	change. So if you're going to use an objective functional measure to say, all right, we're
7	Would it be more correct to say it stops pain? Because we have the same data you provided us in	6 7	change. So if you're going to use an objective
7 8	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	6 7	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.
7 8 9	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.	6 7 8 9	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
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	Page 81		Page 83
1	about, I think that comes on faster than the	1	delivery of chemotherapy, many of which are given
2	deterioration in function.	2	with curative intent.
3	DR. DWORKIN: (Inaudible – off mic).	3	We have had lots of talk about the
4	DR. DOUGHERTY: That's my impression.	4	incidence. The numbers range greatly, as Dr. Brell
5	That's the result that we have is if you look at	5	had talked about. Platinums tend to be one of the
6	the PRO data and the patient's complaint of	6	highest rates of the incidence of chemotherapy-
7	numbness, tingling, and then later pain precedes an	7	induced peripheral neuropathy, and this can lead to
8	objective decline in sensory function.	8	dose reductions, delays, and/or early
9	DR. DWORKIN: (Inaudible – off mic).	9	discontinuation.
0	DR. DOUGHERTY: Haven't done that.	10	Manifestations are broad. It can be pain,
1	DR. DWORKIN: Thanks very much.	11	numbness. Some people end up having difficulty
2	Next speaker, before the coffee break, which	12	with proprioception and balance. There can be
3	will be in about a half hour, it's my pleasure to	13	difficulty with motor symptoms and then autonomic
4	introduce Dr. Lynn Howie. She's from the Division	14	symptoms as well. As was well described by
5	of Oncology Products at the Food and Drug	15	Dr. Brell in her description of her patient, these
6	Administration and will be giving an overview on	16	can be detrimental to function as well as quality
7	the regulatory perspective involving the	17	of life.
8	development of therapeutics for CIPN.	18	Moreover, we have little evidence of agents
9	Thanks very much for joining us.	19	that can actually prevent or even treat
b	Presentation – Lynn Howie	20	chemotherapy-induced peripheral neuropathy. As a
L	DR. HOWIE: Thank you, Dr. Dworkin. Thank	21	practicing physician, I find that there are few
2	you for allowing me to be here.	22	evidence-based options that I can offer to patients
	Page 82		Page 84
1	I'm actually going to give one regulatory	1	to prevent or treat CIPN, and this makes this an
2			unmet clinical need.
	two divisions. Dr. Horn will speak after the	3	Now I want to put my regulator hat on and
	coffee break, and she's the primary division that	-	talk about what's important to FDA oncology when
	these drugs are going through.		we're evaluating these products. First and
6	We primarily can serve as consultants, but		foremost, we need evidence that these therapies do
	up until 2015 were reviewing these products. So I		not attenuate or interfere with anti-cancer
	take a lot of this talk from the wisdom of one of		therapies. Sometimes the mechanism of action for
	our longtime reviewers, Dr. Schecter, in providing		the neurotoxicity is the mechanism of action that's
	the oncologist's perspective and the FDA oncology		treating the tumor, and so we need to figure out
	regulatory perspective on development of agents for		how to balance those two things.
	CIPN.	12	We also in clinical trials design want to
3	As a medical oncologist and a medical		have awareness of the variability of chemotherapy
	officer, I first want to just acknowledge how much		agents and various mechanisms of action of
	supportive care is crucial for cancer treatment,		causation of CIPN. And putting all of these
	and we have FDA-approved supportive care agents in		chemotherapy agents together in a basket to treat
	the area of antiemetics, growth factors, bone		in a trial to evaluate an agent is probably not
	health agents, agents to reduce mucositis, and		going to lead to much success because of these
8			variations.
	antidiarrheals		
9	antidiarrheals. These have beloed to reduce symptoms and		
8 9 0	These have helped to reduce symptoms and	20	We also want to encourage trial designs and
9 0 1		20 21	

	ropathy (CIPN) Trial Design Considerations		March 25, 2017
	Page 85		Page 87
1	prevent or treat CIPN as opposed to the myriad of	1	be associated with this in order to better evaluate
	factors that can affect the development and	2	the outcome of interest.
3	persistence of these symptoms.	3	Getting back to the cancer, we want
4	We want to also say that when you get an	4	preclinical data that shows that the agent would
5	approval for a drug, it's probably going to be	5	not interfere with the anti-tumor activity of the
6	chemotherapy specific. Because of these different	6	chemotherapy. So that includes data in the
	mechanisms of action, we want to be clear that	7	preclinical setting that gives a good and strong
8	approval for one chemotherapy type or chemotherapy	8	scientific rationale that the mechanism of action
9	regimen and potentially even in one tumor type may	9	will not interfere with the anti-cancer agent
10	not mean approval for use in all chemotherapies or	10	and/or pharmacologic studies that demonstrate that
11	chemotherapy regimens.		there is no evidence of detriment to the anti-tumor
12	We want to strongly encourage the	12	activity.
13	development process be focused on agents that are	13	As far as the clinical studies go, we
14	used to prevent or treat peripheral neuropathy for	14	strongly encourage that the initial clinical
15	common chemotherapies and common malignancies. So	15	studies be done in the metastatic setting. This
	as we've talked about already, the two that come to		would likely be in the first-line metastatic
17	mind most readily are breast cancer and colon	17	setting as we know that cumulative chemotherapy
18	cancer with the use of taxanes and platinums	18	increases the risk for CIPN. This is because we
19	respectively.	19	need to know that the agent does not have an effect
20	As Dr. Brell covered, there are multiple		on tumor-related endpoints such as survival or
21	agents that are associated with CIPN.	21	progression-free survival.
22	Interestingly and going back to Dr. Dougherty's	22	Well-designed, randomized placebo-controlled
	Page 86		Dece 99
			Page 88
1	-	1	-
	comments, immunotherapies, the pembrolizumab and		trials with a homogenous patient population,
2	comments, immunotherapies, the pembrolizumab and nivolumab, are also associated with the development	2	trials with a homogenous patient population, meaning the same tumor, the same stage of disease,
2 3	comments, immunotherapies, the pembrolizumab and nivolumab, are also associated with the development of autoimmune neuropathies. So all of these can	2 3	trials with a homogenous patient population, meaning the same tumor, the same stage of disease, and the same treatment with appropriate endpoints
2 3 4	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	2 3 4	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
2 3 4 5	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.	2 3 4 5	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
2 3 4 5 6	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.	2 3 4 5 6	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
2 3 4 5 6 7	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,	2 3 4 5 6 7	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.
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2 3 4 5 6 7 8 9	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	2 3 4 5 6 7 8 9	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,
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	Page 89		Page 91
1	development.	1	acute neuropathic syndromes and chronic syndromes,
2	For symptom measurement scales, we strongly	2	
3	encourage that the symptoms that are measured are	3	is a surrogate for the prevention of chronic
	validated in the disease studied and in the		chemotherapy-induced peripheral neuropathy, but it
	chemotherapy studied. In other words, if you are	5	
	concerned about pain, make sure that the primary	6	Then just to give a brief mention to the
	manifestation of peripheral neuropathy from that	7	
	agent is pain and not numbness, tingling, or other	8	
	things. If it is those other manifestations, make		Devices and Radiologic Health.
	sure that you have measures that account for that	10	
	because you're not going to show a change in a		been multiple devices that have been evaluated for
	symptom that is not the primary manifestation of		treatment. This is actually treatment of pain
	CIPN.		associated with chronic chemotherapy-induced
14	We recommend that you conduct focus groups		peripheral neuropathy, and to get labels for these
	of patients in the same disease and same stage that		particular things, you would go through the CDRH
	you intend to test the agent in as that can help		for the development and approval of those devices.
	inform what PRO measures are selected, and that can	17	
	be tested in a larger group to demonstrate whether		oncology perspective are safety first. We want
	the change in those symptoms occurs at a frequency		evidence that these agents do not attenuate
	great enough that that could be detected as an		anti-cancer therapy and do not negatively affect
	outcome measure for the study.		tumor-related outcomes. We recommend trials that
22	Additionally, we want to show that the drug	22	have patients with the same underlying malignancy,
	Page 90		Page 92
1	Page 90 can improve impacts on function. We are not	1	Page 92 the same anti-cancer therapy, and that we minimize
	-		
2	can improve impacts on function. We are not	2	the same anti-cancer therapy, and that we minimize
2 3	can improve impacts on function. We are not prescribing any particular measures per se, but	2 3	the same anti-cancer therapy, and that we minimize the number of patients who have comorbidities
2 3 4	can improve impacts on function. We are not prescribing any particular measures per se, but measures that will be sensitive enough to show a	2 3 4	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
2 3 4 5	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	2 3 4	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
2 3 4 5 6	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	2 3 4 5	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
2 3 4 5 6 7	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	2 3 4 5 6	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
2 3 4 5 6 7	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	2 3 4 5 6 7	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
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22 Then given the lack of relationship between

22 It was a wonderful talk. We appreciate it greatly.

	ropathy (CIPN) Trial Design Considerations		March 23, 2017
	Page 93		Page 95
1	Because I think what we really want to do is also	1	you are pretreating before a neuropathy develops
	get the perspective from the Division of Anesthesia		where your sample size might need to be very large.
	and Analgesia and Addiction Products, so we can see	3	
	overlaps and differences, but one or two questions.	_	your views on why you think you wish to exclude
5	DR. CLEARY: That was a good talk. One of		those patients at risk.
	the things I think holds back oncology drug	6	DR. HOWIE: It's not necessarily exclude
	development is the CTCAE with neuropathy. It's		them per se but to make sure that they're so for
	really vague, and it's really hard to score. I		diabetes, have patients who have a hemoglobin a1c
	think your emphasis on trying to come up with a		that's within below 8 per se and are well
	validated symptom and also functional assessment		controlled otherwise defined.
	for neuropathy is important. Maybe we can also	11	
	translate that over to oncology trials as well, but		was what was strongly encouraged by Dr. Schecter,
	I think that's going to be really important.		my mentor, is that when you're trying to tease out
14	DR. HOWIE: I agree, and I have actually		the effect of the drug, these patients actually,
	been working with patient-reported outcomes in		while they are efficient for accrual, are not very
	oncology as well, not from the COA perspective but		efficient for figuring out the change in the
	from the oncologist perspective. And one of the		endpoint. Because if you have people who have
	hard things about many of those are that there are		severe neuropathy in both arms, you're not able to
	item questions that include so many things, that		tease out what is the chemotherapy and also not
	you can't show a change in the overall score		necessarily able to show a difference in the end.
	because everything is gemisched together.	21	So that's the primary reason to minimize
22	So you want to be able to have things,		these patients. It's not to make it less
	Page 94		Page 96
1	particularly for neuropathy, that tease out the		
		1	generalizable. It's basically to try to help
	specific symptoms that are causing the most pain		generalizable. It's basically to try to help determine the effect of the drug as well as the
3	specific symptoms that are causing the most pain because if you can show a difference in those	2	determine the effect of the drug as well as the
	because if you can show a difference in those	2 3	determine the effect of the drug as well as the degree to which the chemotherapy and the treatment
4	because if you can show a difference in those symptoms, that would be what would be our measure	2 3	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.
4	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.	2 3 4 5	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
4 5 6	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	2 3 4 5	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
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- 22 actually include at-risk patients, particularly if
- 22 prevention of the acute neurotoxicity of

1 5 ( )	8	1	
	Page 97		Page S
1 oxaliplatin, your er	ndpoints could be shorter. But	1	keratinocyte growth factors are on
2 again, we would w	ant that primarily in a first-line	2	epithelial-derived tumors. And that is why FDA
3 metastatic setting	to be able to show that you were	3	approved it only in the hematologic malignancy
4 not also minimizin	g the anti-cancer effect of the	4	setting, is because we were concerned that because
5 drug.		5	it could potentially promote tumor growth, it would
6 DR. DWORK	IN: There's undoubtedly going to	6	be less safe in that patient population.
7 be a lot more disc	ussion of these issues.	7	DR. DWORKIN: Thank you.
8 DR. HOWIE:	Yes.	8	There's going to be lots more. Let's have a
9 DR. DWORK	(IN: So we hope you're going to	9	coffee break now. Please return promptly at 10:30
10 stay here through	tomorrow afternoon.	10	because we're going to have one more talk and then
11 Last question	n from Simon.	11	discussion at 11:00. Thank you all.
12 DR. HAROU	TOUNIAN: Thank you for a wonderful	12	(Whereupon, at 9:58 a.m., a recess was
13 talk. I just wanted	to ask about the preclinical	13	taken.)
14 safety data. My q	uestion is, how much confidence	14	DR. DWORKIN: Thank you all for returning
15 do you have in the	e translational value of data that	15	from the coffee break. It's a pleasure for me to
16 comes from in vitr	o experiments or maybe an animal	16	introduce our next speaker, Dr. Pamela Horn.
17 model of cancer, v	which have very little to do with	17	Dr. Horn is at the FDA's Division of Anesthesia,
18 a true cancer, with	n human immunological setting, et	18	Analgesia, and Addiction Products, and she'll be
19 cetera if your inf	tervention does not interfere	19	giving a second regulatory perspective on the
20 with oxaliplatin, et	cetera, in a mouse, or in	20	development of treatments for chemotherapy-induced
21 vitro, how much co	onfidence do you really have that	21	peripheral neuropathy.
22 it's a safety		22	Dr. Horn.
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1	DR. HOWIE: That's why we want our first	1	Presentation – Pamela Horn
2	clinical trials to be in patients with metastatic	2	DR. HORN: Good morning. Thank you,
3	disease. We don't have enough confidence to say go	3	Dr. Dworkin. It's a pleasure to be here.
4	out and take this agent and test it in all patients	4	I am going to pick up where Dr. Howie left
5	who are receiving adjuvant therapy.	5	off, around 2016 when we in the Division of
6	DR. HAROUTOUNIAN: A clinical study in a	6	Anesthesia, Analgesia, and Addiction Products took
7	metastatic setting where you have clear safety	7	over the primary responsibility for CIPN drug
8	outcomes would probably be a more clinically	8	development. I will start off with the outline of
9	relevant way for	9	what I'm going to cover.
10	DR. HOWIE: Exactly, that's where we would	10	First of all, I'm going to talk very quickly
11	recommend the first studies to be, yes.	11	about a patient-focused drug development meeting
12	DR. HAROUTOUNIAN: Thank you.	12	that we had last year where CIPN patients were very
13	DR. DWORKIN: But after some preclinical or	13	well represented, and we learned some interesting
14	in vitro	14	things from them.
15	DR. HOWIE: Exactly. One example is	15	Then I'm going to touch on drug approval
16	palifermin. Palifermin is an agent that reduces	16	standards, the approved therapies for peripheral
17	mucositis in patients who are receiving stem cell	17	neuropathic pain in other conditions, and a little
18	transplant. It was thought to be something that	18	bit about the division roles that we have, and then
19	could be used also in patients who were receiving	19	the rest of my talk I'm going to spend on different
20	combined chemo and radiation for head and neck	20	trial design issues that have come up in our work,
21	cancer. However, its mechanism of action is that	21	and really give you as much as I can about what
22	it is a keratinocyte growth factor stimulant, and	22	we've encountered in our division.

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1	This meeting is part of the last PDUFA	1	alternative routes of administration other than
2	legislation that was passed. FDA committed to	2	oral route were being used by some patients.
3	having a little more than 20 of these meetings	3	A lot of the patients were using additional
4	where patients had the opportunity to tell us about	4	therapies like massage, physical therapy,
5	their disease and the available treatments and	5	acupuncture. A lot of them were taking vitamin
6	their experience.	6	supplements and making lifestyle modifications
7	This one that we had on peripheral	7	through diet and exercise.
8	neuropathy was June 10, 2016. It was attended by	8	Now I'll shift gears and just talk briefly
9	37 patients in person, and then there were a few	9	about the drug approval standards, and highlight in
10	more that had a live webcast and were able to	10	our analgesic guidance for the peripheral
11	participate in real time. There were quite a few	11	neuropathic pain conditions, the general standard
12	CIPN patients, and they had a lot to offer. They	12	is for two adequate and well-controlled trials. So
13	contributed a lot, so it was very interesting for	13	that is consistent with what Dr. Howie talked about
14	me to learn about it. And anybody who's	14	in her talk.
15	interested, the summary report was posted last	15	The other thing is that if there are three
16	month.	16	successful trials in three separate neuropathic
17	I will just give you a little summary of	17	pain indications, there may be an opportunity for a
18	what was said. One interesting thing, the first	18	general neuropathic pain indication.
19	bullet there, that's not an error. People actually	19	In addition to the efficacy, there needs to
20	did even though we were asking, prompting for	20	be an adequate assessment of safety, and it needs
21	painful sensations and how to describe them,	21	to be in enough individuals to characterize the
22	numbness was described as well as burning and	22	safety and for adequate duration of exposure. Then
	Page 102		Page 104
	Page 102		Page 104
	stabbing. Most commonly, what was described was		we have to look at the risk-benefit balance and
2	stabbing. Most commonly, what was described was hands and feet, so similar to what we've heard	2	we have to look at the risk-benefit balance and determine that it's favorable.
2 3	stabbing. Most commonly, what was described was hands and feet, so similar to what we've heard already about CIPN in particular.	2 3	we have to look at the risk-benefit balance and determine that it's favorable. This is just a quick summary of the drugs
2 3 4	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	2 3 4	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.
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- 20 differences in the different drugs and when they
  - 21 cause neuropathy, and it affects when in the
  - $\ensuremath{\ensuremath{\text{22}}}$  process of receiving chemotherapy would be the

The other drug therapies that came up,

22 NSAIDs, opioids, and then also some of the

20 attention.

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	Page 105		Page 107
1	opportunity to initiate and measure the effective	1	important for defining the study population in the
2	drugs for prevention and treatment.	2	proposals that we see. Then the entry criteria for
3	The bottom left, there are some of these	3	treatment, so now we're looking at people who
4	chemotherapy agents that actually could cause the	4	already have a neuropathy; baseline pain scores
	neuropathy very early on with the first dose	5	defined by a 11-point NRS; NCI CTCAE criteria,
	perhaps of chemotherapy, and in that case, you	6	
	might be starting the preventative treatment before	7	
	chemotherapy, certainly by the first dose of	8	and then also clinical diagnosis based on symptoms
	chemotherapy. Then you could also have a situation		
	where you're trying to treat the acute	10	criteria, and the timing of the chemotherapy
	manifestations of the neuropathy and starting		regimen with respect to the treatment period.
	treatment very early and having it potentially be	12	Next, I'm going to sum up what has been
	concurrent with the chemotherapy.	13	
14	Then the other extreme would be that the		dosing. Some dosing considerations for dose
	symptoms could be appearing after the chemotherapy		selection, it may be that a drug has been tested as
	regimen is completed and maybe even delayed by a		a chemotherapy agent, and then it's possible that
	number of weeks after the end of chemotherapy in		the next step would be to test it at the same
	which case your treatment period wouldn't start	18	dosing as was used in the chemotherapy trials for
	until well after the chemotherapy is ended. Also,		CIPN.
	potentially if you're trying to target chronic	20	There also could be that we'll be seeing
	CIPN, which is very clinically important to		some phase 2 work for pain or neuropathy endpoint,
22	patients, then you also might be starting the	22	and that's what the dose selection is based on,
	Page 106		Page 108
1	-	1	Page 108 generally, placebo-controlled double-blind trials.
	Page 106 treatment period after the end of the chemotherapy regimen.	1	
	treatment period after the end of the chemotherapy	2	generally, placebo-controlled double-blind trials.
2 3	treatment period after the end of the chemotherapy regimen.	2 3	generally, placebo-controlled double-blind trials. And we know that there could be a flexible dosing
2 3 4	treatment period after the end of the chemotherapy regimen. Then the other aspect of the CIPN indication	2 3 4	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
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2 3 4 5 6	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	2 3 4 5	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
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	Page 109		Page 111
1	proprietary, wasn't publicly available. What it	1	DR. HORN: I'm summarizing, yes.
2	is, is a 3-domain scale, and it's a quality-of-life	2	DR. DOUGHERTY: not that are allowed.
3	questionnaire. Then of course, there could be	3	DR. HORN: Correct.
4	proposals for novel PRO development, and then	4	DR. DOUGHERTY: Oh, okay. Great.
5	there's the Sanofi NCI scale, which is clinician	5	DR. HORN: Right. So everything here that
6	reported.	6	I've presented is trying to give you a flavor for
7	This is the 11-point NPRS that we're very	7	what we see right now to allow you to have that
8	familiar with, the BPI short form. This is	8	context for your discussion. I have not presented
9	version 4 of this scale, which you can see is	9	anything in terms of what we're recommending.
10	definitely specific to neuropathy and has been used	10	DR. FIELDS: Hi. It's Ellen Fields from
11	in trials in this setting. Then this one comes	11	FDA. I also think we can talk about that during
12	from the eloxatin program and is a clinician-	12	the panel discussion, and Dr. Howie may have some
13	administered scale, and the setting that it was	13	input into some of those questions about single
14	used for was advanced colorectal cancer patients.	14	class versus multiple classes at the same time.
15	That is the breadth of what we can talk	15	DR. DWORKIN: Another question?
16	about in terms of what we have been seeing	16	DR. FREEMAN: You made it quite clear
17	proposed. So in summary, we know that the CIPN is	17	earlier on and then now, you're not saying what you
18	not being adequately managed for many patients and	18	are recommending, and you're not saying also what
19	that we need treatment options. There have been a	19	you're not recommending or recommending against.
20	range of proposals made that we've encountered, and	20	Do you intend to do that?
21	when we've seen the proposals, it's brought up some	21	(Laughter.)
22	unique study design issues that are unique to CIPN.	22	DR. HORN: In terms of when we're
	Page 110		Page 112
1	Page 110 Thank you.	1	Page 112 interacting with sponsors
1		1	interacting with sponsors
	Thank you.	2	interacting with sponsors
2 3	Thank you. (Applause.)	2 3	interacting with sponsors DR. FREEMAN: If I could maybe ask it much
2 3 4	Thank you. (Applause.) DR. DWORKIN: Let's follow our format and	2 3 4	interacting with sponsors DR. FREEMAN: If I could maybe ask it much more specifically. Can you give us some sense of
2 3 4	Thank you. (Applause.) DR. DWORKIN: Let's follow our format and take a couple of questions for Dr. Horn, and then	2 3 4 5	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
2 3 4 5 6	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?	2 3 4 5	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?
2 3 4 5 6 7	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	2 3 4 5 6 7	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?
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	Page 113		Page 115
1	So it would be nice to hear just some sense	1	put forward to make sure safety and potential
2	of your views on the kinds of things that you would		efficacy and all that stuff, makes a ton of sense
3	say this is acceptable even though there are risks	3	to me.
	involved and it may not be the perfect efficient	4	DR. DWORKIN: What I'd like to do is invite
5	trial design, or the kind of thing where you would	5	the other three presentation speakers from this
6	say, this is the kind of thing that we would find	6	morning up to the table, and also Daniela and
7	just totally unacceptable.	7	Dr. Fields, who will be substituting for Dr. Sharon
8	DR. HORN: Okay.	8	Hertz, who has to deal with a failure to resolve
9	DR. FREEMAN: I understand I'm asking not an	9	pain from oral surgery, is my understanding.
10	easy question.	10	DR. FIELDS: She's on her way.
11	DR. FIELDS: You want me to respond?	11	Q&A and Panel Discussion
12	DR. HORN: You can respond.	12	DR. DWORKIN: I thought a reasonable way to
13	DR. FIELDS: Appreciate the question. We're	13	begin this session, it's really Q&A and discussion,
14	very early in our regulatory experience with these	14	but to start by asking the two people who are up
15	products, and we base a lot of our recommendations	15	here who didn't present this morning if they have
16	on the science and what the sponsor comes to us	16	anything they would like to add to what they've
17	with. We look at the potential risk-benefit for an	17	heard.
18	individual product.	18	Could we start with Ellen. Is there
19	So there's not going to be a single we	19	anything else you'd like to add to what you heard
20	can't give you we'll definitely allow treatment	20	this morning, any thoughts you have, any questions
21	with all preventive chemotherapy-induced peripheral	21	for the four presenters, and then we'll give
22	neuropathy products starting prior to chemotherapy.	22	Daniela a chance, also.
	Dogo 114		Dogo 116
	Page 114		Page 116
	It's going to depend on the product, it's going to	1	DR. FIELDS: I think in my last comment, I
2	It's going to depend on the product, it's going to depend on the population, it's going to depend on	2	DR. FIELDS: I think in my last comment, I said our overall approach. I don't have anything
2 3	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.	2 3	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
2 3 4	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	2 3 4	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.
2 3 4 5	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	2 3 4 5	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.
2 3 4 5 6	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	2 3 4 5 6	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
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1	encompass both symptoms and functions. And we hear	1	and so some of our analyses have been looking at
2	from our oncologists that that's crucial in	2	what the patient is at baseline versus change
3	evaluating the PRO. The PROs need to be clinically	3	within that patient as one of the ways that we can
4	relevant. What's important to the patient? What		better understand what their symptom burden is over
	are their most disturbing symptoms?		time.
6	I don't want to over-speak because I'm not	6	DR. FIELDS: I don't know if you're actually
7	part of the CRO staff, and I don't want to say	7	asking also about the duration of follow-up in the
	something wrong. But there was a second part to		studies?
	your question about follow-up?	9	DR. DASTROS-PITEI: That's right, yes.
10	DR. DASTROS-PITEI: Yes. Perhaps the	10	
	oncology aspect because obviously this is a disease		think in a perfect world, you'd want years of
	which is so correlated with an oncology treatment		follow-up to see is the neuropathy being prevented,
	many times, right?		is it being delayed
14		14	
15	DR. DASTROS-PITEI: It's more how we assess	15	
	from a clinician perspective when to stop or to		with that, the outcomes of the cancer treatment, we
	delay and how would you be convinced that measuring		need to see both. So we're still working on how
18	clinical studies will enable the clinicians to make		long that follow-up should be in the clinical
	that decision.		studies.
20	So in the past, we used NCI CTCAE for	20	
	neuropathy as a decision making, perhaps for		progression of the disease, which is related to the
	oxaliplatin, it's on the label, but how would you		chemotherapy injury
	······································		
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1	see the future? Because we're focusing more on the	1	DR. FIELDS: Right, so
2	patient signs and function, but would we want to	2	DR. HOWIE: That's part of the reason too
3	see measures of oncology treatment?	3	that we encourage there to be homogeneity among the
4	I understand overall, this is perhaps much	4	patients who are in the initial clinical trials is
5	harder to achieve for a neurology drug, right? So	5	because with the known data about what the duration
6	how would you balance this? I think this is	6	of follow-up is as well as survival data, can help
7	probably where we're struggling a bit.	7	inform the duration of the study needed.
8	DR. HOWIE: I think those are all really	8	Because it's not likely to say I can't
9	great points because I think we don't know what the	9	say oh, if you follow the patient up for 2 years,
10	optimal timing is. I think part of the thing about	10	that's enough because that's going to be very
11	PROs and symptom-related issues in cancer patients	11	different in metastatic hormone receptor positive
12	is that they often wax and wane with time in and of	12	breast cancer versus metastatic triple negative
13	themselves.	13	breast cancer versus ovarian cancer.
14	So I think as we develop measures, it's	14	DR. DASTROS-PITEI: Yes, and I think many of
15	going to be important to understand not so natural	15	the drugs which were mentioned earlier, the
16	history as meaning kind of what are the effects	16	taxanes, oxaliplatin, and the platinums, which are
17	without the agent to better understand what the	17	the most often associated with CIPN, really these
18	and the set of the second s	1 9	days are used in an adjuvant setting. And that
	optimal time period for measure would be. Does	10	days are used in an adjuvant setting. The that
19	that make sense?		means the duration would be even longer for these
19 20			means the duration would be even longer for these
20	that make sense?	19	means the duration would be even longer for these patients in terms of disease progression.
20 21	that make sense? Then one of the things that we have done on	19 20	means the duration would be even longer for these patients in terms of disease progression. DR. HOWIE: Correct.

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1	find a way to learn when the difference occurs,	1 necessarily pain.	
	when it is important for the patients and for the	2 DR. DWORKIN: I'm corrected. So symptoms	
	agency.	3 and function.	
4	DR. HOWIE: I think that that's going to be	4 DR. LOPRINZI: You just come from your pain	
	disease specific. Does that help? At least in the	5 background. I know I've got to keep you honest	
	initial trials, I think it's going to be disease	6 there.	
	specific.	7 DR. DWORKIN: Yes, you do. Thank you.	
8	DR. FIELDS: There's also the option of	8 You're absolutely right. I meant symptoms, but I	
-	following the patient in the clinical trial for a	9 said pain.	
	certain period of time to get the drug out there	DR. DOUGHERTY: Let me just chime in. So	
	and have a postmarketing requirement after the drug	11 co-primaries is clearly not the way you want to go	
	is on the market to gain more information about the	12 because if you use a functional measure that's	
	product to learn more about its behavior.	13 going to be expressed at a year, you're going to	
	DR. DASTROS-PITEI: Which will make sense.		
14		14 end up being forced to stop early because nothing	
15	DR. FIELDS: Those are also options. DR. DWORKIN: I'm going to preempt into	<ul><li>15 is changing early on. You got to be really careful</li><li>16 of that part of the design.</li></ul>	
16	tomorrow's discussion, but it sounds like and		
		The other comment and so Joanna and I decided to talk off-line because she was surprised	
	this goes back to what Roy was asking for in terms of recommendations. It sounds like we've heard	•	
		<ul><li>19 by this opioid potential risk factor. So what that</li><li>20 means is that your definition of homogeneity in</li></ul>	
	from Drs. Horn, Howie, and Fields that one agency	20 means is that your definition of nonogeneity in 21 your population is, in fact, I think a lot more	
	recommendation perspective is for co-primary endpoints in clinical trials of pain and some	22 complex than what we might be actually trying to	
22		zz complex than what we might be actually trying to	
	Page 122	Pa	ge 124
1	Page 122 functional measure.	Pa 1 look at first blush.	ge 124
1	-		ge 124
2	functional measure.	1 look at first blush.	ge 124
2 3	functional measure. That seems like a very clear perspective	<ol> <li>look at first blush.</li> <li>Joanna and I started talking about, well,</li> </ol>	
2 3	functional measure. That seems like a very clear perspective we're hearing from the three speakers representing	<ol> <li>look at first blush.</li> <li>Joanna and I started talking about, well,</li> <li>what about the number of patients running around</li> </ol>	
2 3 4 5	functional measure. That seems like a very clear perspective we're hearing from the three speakers representing FDA; is that correct?	<ol> <li>look at first blush.</li> <li>Joanna and I started talking about, well,</li> <li>what about the number of patients running around</li> <li>with hyperglycemia? How many of our patients are</li> </ol>	
2 3 4 5 6	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	<ol> <li>look at first blush.</li> <li>Joanna and I started talking about, well,</li> <li>what about the number of patients running around</li> <li>with hyperglycemia? How many of our patients are</li> <li>running around with sugars of 200 all the time? Is</li> </ol>	
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	Page 125		Page 127
1	consideration.	1	are these symptoms so focused in glabrous skin.
2	DR. CAVALETTI: Pat, I think this is a very,	2	Clearly there, the autonomics are quite different
3	very good point. I saw a list of potential risk	3	than they are in hairy skin.
4	factors in one of the slides, and I think that	4	Another piece of QST data I didn't present
5	actually as a neurologist, the only way to stratify	5	is that in our experience, the areas of pain are
6	this population which is very, very non-homogenous	6	associated by markedly colder skin. The fingertips
7	by definition, is to stratify based on some	7	in a patient with painful CIPN are anywhere from at
8	neurological aspect, maybe bumps or maybe something	8	least 3 if not 5 degrees centigrade cooler than
	else.	9	their volar forearm where they're asymptomatic.
10	But I wouldn't care about the fact that one	10	I absolutely agree. I think the
11	is smoking or is not smoking because someone in one	11	microvasculature is a major contributor.
12	single trial showed that smoking is a risk factor	12	DR. RICHARDSON: That's a great point, Pat,
13	for most severe CIPN. I would like to understand	13	because in myeloma, we see this all the time, that
14	which is the biology of this kind of association,	14	the colder weather brings this.
15	so probably is not the true association. But if a	15	The other thing is we've had great success
16	patient has used innervation or is unable to feel	16	with very simple emollients, which I think is what
17	the same level of thickness or the bumps, probably	17	one of the FDA speakers was touching on with the
18	is more reasonable to me to stratify according to	18	therapeutic massage. We just recommend this
19	that point.	19	regular vigorous hand massage and feet massage
20	All the rest, obesity, age, who knows? We	20	using simply cocoa butter and coconut oil. I know
21	have patients older than me that is much better	21	it sounds slightly implausible, but it really does
22	than me in terms of peripheral nerves probably. So	22	seem to work anecdotally.
	Page 126		Page 128
1	I think that we should carefully consider the fact	1	Pat's had this experience from our
2	that they should stratify according to some	2	collaboration in myeloma, this simple therapeutic
-	neurological indicator because we are looking for a	2	
3		5	massage with an appropriate emollient that
	neurological side effect.		massage with an appropriate emollient that penetrates the skin. Patients anecdotally reported
		4	
4 5	neurological side effect.	4 5	penetrates the skin. Patients anecdotally reported
4 5 6	neurological side effect. DR. RICHARDSON: May I make a comment,	4 5 6	penetrates the skin. Patients anecdotally reported that for the soles of the feet, they find cocoa
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1	taking. They come in with polypharmacy, and we are	1	we not have the two arms adequately balanced to
2	not even looking to see what other medications		each other? That could be just an underlying
3	could cause neuropathy.	3	problem in the original study design.
4	So I think we're going to have to delve a	4	DR. DWORKIN: I'll give a simple-minded
5	lot deeper into patient characteristics and what	5	answer. I don't think there's been a high quality
6	their concomitant diseases are and what the	6	clinical trial of pregabalin in this condition, not
7	medications are.	7	that I know of. So I'm not sure that we really
8	DR. WEN: Can I ask Pat	8	know whether it works for pain in CIPN.
9	DR. DWORKIN: Gordon, yes?	9	I personally wouldn't expect it to work for
10	DR. G. SMITH: I think someone was ahead of	10	numbness, which is an issue we heard a lot about.
11	me.	11	The drugs that are efficacious for peripheral
12	DR. DWORKIN: Dr. Wen, then Gordon.	12	neuropathic pain may have zero efficacy for
13	DR. WEN: Pregabalin has been useful in a	13	numbness associated with peripheral neuropathy.
14	number of other neuropathies, but it hasn't been	14	But I think it would be a fascinating trial to do,
15	useful in chemotherapy-induced peripheral	15	to do a large well-designed clinical trial of
16	neuropathy. So what are the potential mechanistic	16	pregabalin in patients with chronic painful CIPN.
17	differences you think that might account for this?	17	DR. DOUGHERTY: Good point.
18	DR. DOUGHERTY: Between other neuropathies	18	DR. DWORKIN: Gordon?
19	and CIPN, I think that's part of the issues in	19	DR. G. SMITH: I have to congratulate you on
20	previous neuropathy studies. The etiologies for	20	having a neuropathy meeting where we're at 11:00
21	most of the neuropathies excluding PHN, clearly,	21	o'clock and no one's mentioned biomarkers. So I
22	the etiology there is pretty clear, but if you get	22	guess I'm going to ruin it by doing so.
	<b>D</b> 400		<b>D</b> 400
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1	Page 130 into any of the other and diabetic	1	Page 132 I work in the diabetes world primarily, and
			-
2	into any of the other and diabetic	2	I work in the diabetes world primarily, and
2 3 4	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	2 3 4	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
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1	with us.	1	the fingertip, and the forearm, you showed data,
2	DR. HORN: We have applied some of the same	2	and then you showed functional data, the pegboard.
3	advice that we've given for DPN to companies	3	DR. DOUGHERTY: Right, right.
4	interested in looking at CIPN in terms of looking	4	DR. FREEMAN: What I missed and maybe you
	at those objective measures for safety and to see	5	mentioned it and maybe you didn't was whether
	whether there's any deleterious effects going on,		there was any correlation between what
7	on the nerves.		you because this addresses the point that Bob is
8	Then also, we have to really consider		making. What is the relationship between the more
9		9	objective measures, the histopathology, and the
10	needs to be clinically meaningful, whatever you're	10	functional measures?
	looking at, your primary measure. The thing that	11	DR. DOUGHERTY: Yes, I did not address that
	you're going to try to demonstrate efficacy with	12	directly, but yes, each of our patients that were
	has to be correlated with or in itself be		biopsied had marked psychophysical deficits. We
14	clinically meaningful to the patients, and that, we		didn't line them up and try to correlate whether
	have not gotten very far with any of these with		the counts exactly matched because at the
	that.	16	
17	DR. DWORKIN: Let me ask a follow-up	17	They're just absent.
18	question. If I was a sponsor and I had a drug that	18	So as you get to that end of the graph for
	I thought could promote reinnervation of the		the function, it's not going to correlate because
	epidermis I'm thinking of Pat's wonderful		it's zero to whatever function that that patient
	slides. And let's say the drug did that versus		had. There is a variability in that. Some people
	placebo, is that an indication? It's a biomarker,		are profoundly impaired to the point where they
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1	I guess, right? We show on skin-punch biopsy	1	have a positive Romberg sign essentially in their
2	reinnervation. That's not feeling. That's not	2	hands. They can't tell where their fingers are.
3	function. It's not survival. Is it an indication?	3	Others have markedly elevated touch threshold,
4	DR. FIELDS: Well, the sponsor would have	4	et cetera, again in their fingertips, but they
5	to we'd have to have data that showed that	5	still have some sensibility.
6	reinnervation could be correlated with the actual	6	It will more or less correlate, but it may
7	clinical outcome.	7	not be a one-to-one correlation. You see what
8	DR. DWORKIN: So you'd have to validate the	8	DR. FREEMAN: I understand, yes. So
9	biomarker with a clinical outcome?	9	clearly, more data is needed to answer that
10	DR. FIELDS: Correct.	10	question.
11	DR. FREEMAN: Which may be a good time for	11	I do want to make one I think rather
12	me to ask a question. During Pat's talk, I may	12	important point. One of the issues always and
13	have missed it, but was there a link between your	13	this will come up in the symposium tomorrow, one of
14	functional measures and the skin biopsy data that	14	the late symposia, is the difficulty of recruiting
15	you acquired?	15	for these clinical trials. I think it's
16	DR. DOUGHERTY: Are you talking about what	16	probably of the neuropathy and neuropathic pain
17	we've done with preclinical models or clinical	17	trials, I think it's one of the most difficult
18	models?	18	trials to recruit for.
19	DR. FREEMAN: No, no, no. In the clinical	19	One of many reasons is that the oncologists
20	models don't let me leave the microphone without	20	are very protective of their patients and the
21	making another point you showed in your studies	21	discomfort that is involved in these assessments,
1			
22	of the glabrous skin biopsies, the thenar eminence,	22	and I want to very strongly make the point about

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	Page 137	Page 139
1	skin biopsy because this may one of the measures	1 DR. RICHARDSON: If I may echo, Pat, just
2	that is used.	2 echo your point, we did a prospective study.
1	Clearly, glabrous skin biopsy is	3 Patrick was a collaborator, and we published in the
4	uncomfortable, but skin biopsy in and of itself is	4 JCO in 2009 when we looked at bortezomib
5	onot. And if we are looking at non-glabrous skin,	5 monotherapy in newly diagnosed myeloma patients,
6	there are many patients and many controls and many	6 which is a very challenging population because
	members of my lab who have 5, 6, 7 biopsies and are	7 they're newly diagnosed. They obviously require
	quite willing to have more. And I'm not at this	8 treatment.
	point suggesting that this is of necessity a	9 We found excellent compliance with not only
	measure that we will be using or should be using in	10 nerve conduction testing but also the skin biopsy,
	a clinical trial, but skin biopsy is not a heart	11 to your point. And we required that it be just
	transplant. It's a benign procedure	12 these tiny little punctures done sequentially
13		13 across therapy. And we saw this neurite fallout
	the fingertips, these closed compartments, they're	14 with this microangiopathic 6th signal, didn't we,
	going to hurt, and patients I don't think will sign	15 from that analysis, which was quite intriguing, to
	up for that.	16 echo the feasibility on the one hand and on the
17	· · · · · · · · · · · · · · · · · · ·	17 other hand, the hypothesis around the small fiber
	we have not number one, let me address the issue	18 question.
	of the oncologists. Absolutely, I think that a	19 DR. DOUGHERTY: Actually, I wanted to follow
	breast oncologist, you're going to have to have	20 up on something with your cohort and your
	real convincing evidence that you're going to	21 experience because in the other cohorts that are
	improve his outcomes, and they have pretty good	22 susceptible to CIPN, all of those patients are
	Page 138	Page 140
1	Page 138 . outcomes, which is why I asked the question about	Page 140 1 having surgery. Myeloma stands out as one of the
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ropathy (CIPN) Trial Design Considerations		March 23, 2
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Page 141		Page 1
point.	1	minutes ago stimulated that as an important
I think from what we see as underlying risk	2	research agenda question.
factors, obviously, we see more African Americans	3	Gordon?
affected by this illness, which is interesting to	4	DR. G. SMITH: I have a very specific
learn about the risk of CIPN from African	5	question for you, but I want to echo what Roy said
Americans. We see obviously an older population.	6	about the challenges of recruitment and even
So there are all sorts of preexisting factors.	7	studying this patient population.
Also frankly, obesity is a risk factor	8	I think one of the things I've really
amongst women for myeloma, which is not I think a	9	learned from working with our oncologists is their
widely appreciated fact. So there are lots of	10	tremendous dedication to their patients, which is a
things which may drive this increased risk for	11	model for all of us. My father died of cancer, and
myeloma neuropathy that we see from our	12	I learned a lot about the care model in our cancer
	13	centers, which is something I often talk about in
The one thing that I missed in the		our neuroscience center as something we ought to
-		replicate. So I think working together is really
include in the list of neuropathic drugs the IMiDs,		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 142		Page 1
intended to be there if it was not.	1	technician has had, I think, about 150. He does
DR. RICHARDSON: Not an issue, just to say		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
		punches viral digit. They at least tell me their
		patients will actually come back for a second.
-		DR. DOUGHERTY: Yes. We've done biopsies
hope this doesn't preempt what you're going to say,		both in thenar and hyper-thenar eminence. Notably,
	1	the counts don't really come out all that
it seems to me that there is an emerging consensus	15	
it seems to me that there is an emerging consensus that if one of the tables in the article that we		-
that if one of the tables in the article that we	16	different. We did both index finger and the edge
that if one of the tables in the article that we are going to be preparing from this meeting is	16 17	different. We did both index finger and the edge of the pinkie finger, and again
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	16 17 18	different. We did both index finger and the edge of the pinkie finger, and again DR. G. SMITH: Like this?
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	16 17 18 19	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
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	16 17 18 19 20	different. We did both index finger and the edge of the pinkie finger, and again DR. G. SMITH: Like this?
	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	point. 1 I think from what we see as underlying risk factors, obviously, we see more African Americans 3 affected by this illness, which is interesting to 4 learn about the risk of CIPN from African 5 Americans. We see obviously an older population. 6 So there are all sorts of preexisting factors. 7 Also frankly, obesity is a risk factor 8 amongst women for myeloma, which is not I think a 9 widely appreciated fact. So there are lots of 10 things which may drive this increased risk for 11 myeloma neuropathy that we see from our 12 therapeutics. 13 The one thing that I missed in the 14 presentation from the FDA was the failure to 15 include in the list of neuropathic drugs the IMiDs, 16 the thalidomide classically. And also frankly, 17 Revlimid, lenalidomide, has its own neurotoxicity, 18 about 20 percent. I was just interested in why 19 that wasn't on the immunomodulatory section because 20 I thought that was really interesting. 21 DR. HOWIE: I think it was there. It was 22 Page 142 intended to be there if it was not. 1 DR. RICHARDSON: Not an issue, just to say 14 that it's obviously 3 DR. HOWIE: But to get back to the 4 combination 5 DR. RICHARDSON: thalidomide we see the 6 same as well 7 DR. HOWIE: Correct. 8 DR. RICHARDSON: And frankly, I thought what 9 was really interesting was to see the 10 immunotherapeutic size in the IOS having 11 neurotoxicity as well. 12

	Page 145		Page 147
1	least. So yes, you can move around.	1	DR. DOUGHERTY: We deliberately used the
2	Again, just from a grants perspective, I was	2	hands, the upper limb, because I was really worried
3	always really worried about just that question.	3	about wound healing issues as you get down in the
	Well, where exactly on the finger would you biopsy		lower limb. I have no basis other than I was
5	et cetera? That's why, again, I was attracted to	5	afraid of the idea, and so I didn't want to go that
6	this noninvasive method of measuring because you	6	way.
7	can use the fingerprint whirls as a modulus. You	7	But yes, the calf has been used a lot.
8	can come back to the same spot again and again and	8	Polydefkis at Hopkins has done that, so it should
9	get those repeat counts. So that was the built-in	9	be perfectly safe. We just didn't do it because I
10	strategy that I didn't comment about.	10	was worried that it would be a problem, and we
11	But again, it's not entirely clear to	11	would be shut down by the IRB or somebody. So
12	me and again, Roy brought up the issue of	12	that's why I picked the upper limb.
13	correlating between function.	13	But yes, there is data out there. Like I
14	What I don't have a good correlation to in	14	say, folks have done the lower limb. Again, you
15	function is once you move into hairy skin because	15	get down past the calf and down toward the ankle,
16	there, the numbers jump up quite quickly. And if I	16	and you're just getting into a more potentially
	use the volar surface forearm data, I would have no	17	problematic spot to put a biopsy at.
	correlation. So that now pushes this back to the	18	
19	glabrous skin biopsies.	19	5 5 5
20	I would proceed with caution pushing the	20	the enrollment issue. I think it is a real issue.
	ENFs necessarily because where you will have to go	21	5
22	to get repeat biopsies, as has been pointed out,	22	One is if after the chemotherapy, if after someone
	Page 146		Page 148
1	-	1	
	you're going to have to go up into glabrous skin.		develops neuropathy, I think patients will be
2	you're going to have to go up into glabrous skin. I agree, biopsying repeatedly in the forearm or	2	develops neuropathy, I think patients will be extremely motivated. I actually think it will be
2 3	you're going to have to go up into glabrous skin.	2 3	develops neuropathy, I think patients will be
2 3 4	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	2 3 4	develops neuropathy, I think patients will be extremely motivated. I actually think it will be an easy sell, and I think the biopsies, also
2 3 4 5	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	2 3 4	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.
2 3 4 5 6	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	2 3 4 5 6	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.
2 3 4 5 6	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	2 3 4 5 6	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
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	ropauly (CIFN) That Design Considerations		
	Page 149		Page 151
1	been done.	1	DR. RICHARDSON: I couldn't agree with you
2	DR. DWORKIN: Charles?	2	more. That's where the bortezomib neuropathy first
3	DR. LOPRINZI: A comment with regards to the	3	manifests itself. You're quite right.
4	skin biopsies. I think it's very interesting from	4	DR. DWORKIN: Roy and then Simon.
5	a scientific standpoint and all that sort of stuff,	5	DR. FREEMAN: I want to get away from skin
6	and I wouldn't discourage it in studies, in	6	biopsies I'm sure we'll come back to it
7	situations where patients want or laboratory	7	again and get back to predictors because I think
8	investigators or investigators want to do that.	8	predictors are of potential importance with
9	It's not something I would recommend for big	9	proof-of-concept trials if you want to recruit a
10	intergroup trials for multiple, those sort of	10	small number of subjects, you want to maximize the
11	things. I don't know that it adds to. If you see	11	likelihood of patients getting a chemotherapy-
12	something on that and there's symptoms or a	12	induced peripheral neuropathy.
13	function doesn't change, is that really going to	13	Picking up on the point that James Cleary
14	make a difference? It's really their function and	14	made about there being reluctance of patients to
15	their symptoms that really are the bottom line.	15	take preventative therapy, true preventative
16	I think it is interesting, and I could say	16	therapy before the emergence of a chemotherapy
17	the same thing about reflexes and neurological	17	peripheral neuropathy.
18	component of that. But I don't know want to get	18	If you want to do such a trial, where there
19	into the, oh, you have to do this in all situations	19	may be a greater likelihood of success, if you were
20	because I don't think it's really necessary.	20	to be before the toxin is given and exerts its
21	DR. RICHARDSON: Charles, if I could make	21	effect, one of the ways that one might be able to
22	one comment from our bortezomib experience. We had	22	do such a trial more efficiently would be to have
	Page 150		Page 152
1	a multicenter trial, and we enrolled a good phase 2	1	good strong predictors.
	a multicenter trial, and we enrolled a good phase 2 number, if my memory serves me right, about 50, 60		good strong predictors. Now, I vnn Howie mentioned that there's
2	number, if my memory serves me right, about 50, 60	2	Now, Lynn Howie mentioned that there's
2 3	number, if my memory serves me right, about 50, 60 patients. We were able to do the biopsies on a	2 3	Now, Lynn Howie mentioned that there's certain situations in which you, for example, don't
2 3 4	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	2 3 4	Now, Lynn Howie mentioned that there's certain situations in which you, for example, don't want to include those patients in the trial,
2 3 4	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.	2 3 4 5	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
2 3 4 5 6	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,	2 3 4 5 6	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
2 3 4 5 6 7	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	2 3 4 5 6 7	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
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ACTTION - Chemotherapy-Induced Peripheral Neuropathy (CIPN) Trial Design Considerations

A C Nei	TTION - Chemotherapy-Induced Peripheral uropathy (CIPN) Trial Design Considerations		March 23, 201
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1	The extent of that being a powerful predictor, I'd	1	going to have them, and that's how they develop
2	never seen before.	2	their cancer.
3	So I want you to talk a little bit about	3	DR. DWORKIN: Simon?
4	that, and then I want to hear from the rest of the	4	DR. HAROUTOUNIAN: I just wanted to make a
5	panel the views of Guido, who really said that one	5	note on the feasibility of the biomarker testing,
6	trial has smoking as a predictor, another doesn't,	6	especially skin biopsy in subsets of patients
7	that a lot of these psychosocial factors are much	7	because we're now doing a clinical trial in
8	softer than the biology.	8	pregabalin in chemotherapy-induced peripheral
9	So if we want to conduct an efficient trial,	9	neuropathy, and we do have an optional skin biopsy
L0	I think we need to know what are the predictors and	10	in the study.
L1	what are not the predictors.	11	About 50 percent of the patients and
L2	DR. DOUGHERTY: Right. To your first	12	these are patients who already have developed
L3	comment, the slotted pegboard test, that's simply a	13	CIPN they would not participate that's what
L4	crude measure of sensory motor function at	14	they're telling us. They would not participate in
L5	baseline. Again, that was only at baseline. As	15	the study if the biopsy was an absolute
L6	patients went on through the trial, in fact, they	16	requirement.
L7	get better from practice.	17	I think we might lose about 50 percent or
L8	As an initial screen, yes, the bumps test,	18	so, maybe depending on the setting, of patients if
L9	any one of these crude psychophysical tests, or	19	we make it as a just from a patient recruitment,
20	simple psychophysical tests, or the slotted	20	enrollment perspective.
21	pegboard seemed to be predictive of which group was	21	DR. DASTROS-PITEI: From a predictor's
22	more predisposed to develop CIPN. That's true.	22	perspective, in those CIPNs, which we know that
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1	The male and female thing, Joanna and I	1	they are occurring in 80 percent of the patients,
2	actually talked about this onside, she has made the	2	would you still need to preselect these patients in
3	same observation. She was asking me what I thought	3	some way, when we know that 80 to 90 percent of
4	the biology was. I don't think there's any biology	4	them will develop CIPN within hours of the
5	there at all. I think men are just better liars	5	chemotherapy start?
6	than women are.	6	DR. HOWIE: I think there's a difference
7	(Laughter.)	7	between thinking about a high-risk population for
8	DR. DOUGHERTY: They just aren't tell you	8	developing peripheral neuropathy and thinking about
9	that they have neuropathy because they know that if	9	trying to seek an indication for everyone who's
L0	they tell you, you're likely going to cut their	10	receiving that drug.
L1	dose back, so they're just going to lie.	11	So I think it depends on what your
12	DR. BRELL: I understand the need to have a	12	development strategy is as to how much you want to
13	very homogenous population. It makes complete	13	control for it or not because I think that you can
14	sense when doing clinical trials, and we certainly	14	have a strategy where you're saying, in patients
L5	need these predictors. But just about all of the	15	who are high risk as defined by X, Y, and Z, this
L6	predictors for CIPN are predictors for cancer. So	16	agent works to reduce the risk of chemotherapy-
L7	all the gastrointestinal cancers are associated	17	induced peripheral neuropathy. It's just how that
L8	with being overweight. Some African Americans are	18	development strategy is being pursued.
19	at higher risk, tobacco.	19	DR. DWORKIN: Charles, did you have a
20	So we won't be able to accrue very many	20	question?
21	patients if we don't figure out a way to control	21	DR. LOPRINZI: You do want a uniformed group
22	for these risk factors because the patients are	22	of patients. If you have a very small group, then

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1	you have to have them fairly uniform. If it's a	1	hundreds of patients.
	bigger group, it's a randomized design, that takes	2	DR. LOPRINZI: Well, this was one of 50
	care of most of the things. And I can give an	3	patients on this particular trial, but with a
	illustration of that in a moment. It depends on		couple of hundred patients, I think you could see
	how long I go for this part.		the same sorts of things in there. But the point
			is the randomization will take care of it. It
6	-		
	can stratify it because there are only so many		won't do it for a 5-patient study or 20-patient
	things the statistician will allow you to stratify		study or 30 or 40 or 50, but if you're going to do
	because of how many groups you have, then you pick		these sort of studies and you're going to do a
10	the most important of them.		placebo-controlled trial, you probably need 100,
11	Let me give this quick example. We had	11	200, 300, 400, 500 patients. If you need 3,000
12	patients with anorexia-cachexia years ago,	12	patients, then it's not enough of a difference to
13	450 patients on a clinical trial, all sorts of	13	make a difference there.
14	different cancers, all sorts of different stages of	14	DR. DOUGHERTY: No, my point being, you're
15	their disease. They had advanced they had at	15	making a trial now so ridiculously expensive, it
	least four months survival, and they had		can't be done. I mean, that's going to
	anorexia-cachexia. They were losing weight. And		cost well, we could add that to the national
	we randomized them to megestrol acetate versus		debt.
	placebo on them.	19	DR. LOPRINZI: I think if you're going to do
20	I wanted to see whether or not we could see		a randomized placebo-controlled trial for these
	in a situation like that whether the drug we're		things for prevention and whatnot, you're talking
	-		
22	looking at might affect survival. So I asked the	22	about 100, 200, 300 patients. I think that's
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1	statistician to take all these patients, regardless	1	ballpark. I'm not a statistician, but the
2	of what they were getting, and just break them up	2	experience has been you need that. You don't need
	into group A and B, and do that 20 times, and give		20 patients. You don't need a thousand patients.
	me survival curves for the apples and oranges and	4	DR. DOUGHERTY: But 100 is completely
	all that stuff, all sorts of different cancers.	_	differently powered than 2 or 3 or 400. As you're
6			quickly scaling, the dollar signs are ka-ching,
	curves were not statistically different in any of		ka-ching, ka-ching.
8		8	I think I would focus on a more homogenous
9			smaller trial than just and I do agree with you.
	okay, thank you, do that. And the number of times		If you have enough patients, you can control for
	these curves were statistically significantly		everything because it will all homogenize, but for
	different from each other with these varied groups		some sort of a potential therapeutic, it's going to
	of patients was 5 percent, p equals 0.05. That was		have to be a fairly focused, I think, very
14	without stratification.	14	homogenous group.
15	If we threw in the stratification factors	15	DR. LOPRINZI: If you go that route, you say
16	that we had figured out for these patients from the	16	this has got to be patients between the age of 30
17	study, it dropped it down to 4 percent. So if you	17	and 40 because older age have that, and they've got
18	got the randomized design, it takes care of it if	18	to be blond, and they got to be this and this and
19	you have reasonable numbers of patients, and then	19	this, then you've got this drug that fits for this
	adding your stratification helps a little bit more.		and doesn't fit for anything else. You got to use
21			
	DR. DOUGHERTY: Charles, the basic	21	some common sense in there.
	assumption there is that you're going to do	21 22	some common sense in there. What we've utilized in ours is no

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	1 neuropathy, no past neuropathy. On several of our	1 the sample of patients affects your assessment of	
	2 studies, we have allowed them to have diabetes as	2 what your primary endpoint is, which is CIPN.	
	3 long as they have no neuropathy from that, and then	3 DR. LAVOIE SMITH: We stratified because we	
	4 there are a bunch of other criteria in there, but	4 thought that that was going to be an important	
	5 it's not that hard to do that.	5 concern, that if we didn't think about diabetes,	
	6 DR. DWORKIN: Our next question or comment	6 then that might be a limitation, so that's why we	
	7 is from the only person who's done a successful	7 did it and found no difference.	
	8 trial in CIPN of that size, Ellen.	8 I guess what I'm saying is that it's an	
	9 DR. LAVOIE SMITH: I was just going to	9 argument that supports depending upon the design	
1	0 comment on, again, thinking about predictors and	10 and the outcome and the mechanism, that a	
1	1 risk factors, and first of all, to remind us that	11 predictor, we just have to think about them	
1	2 those risk factors will vary based on whether we're	12 carefully and not exclude patients because they	
1	.3 talking about neuropathy or pain.	13 have diabetes if it's not really relevant.	
1	4 In our duloxetine study because we were	14 DR. HERTZ: Bob?	
1	.5 using a drug to target central nervous systems	15 DR. DWORKIN: Sharon, yes.	
1	6 mechanisms in a population with chronic pain, we	16 This is Dr. Sharon Hertz, who joined us	
1	7 did stratify by diabetes and did not exclude that	17 late. Dr. Hertz is the director of the Division of	
1	8 population, and found no differences in the end	18 Anesthesia, Analgesia, and Addiction Products at	
1	9 result.	19 FDA. Sharon?	
2	So is that because the pathophysiologic	20 DR. HERTZ: Thank you. Sorry for the late	
2	1 mechanisms of diabetes I don't know enough about	21 arrival.	
2	2 this. But is there a central effect of diabetes,	22 Just getting back to the diabetes thing, I	
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	1 or is it more peripheral? So if it's more	1 guess I have a few more questions, though, because	164
	<ol> <li>or is it more peripheral? So if it's more</li> <li>peripheral, then the fact that somebody has</li> </ol>	<ol> <li>guess I have a few more questions, though, because</li> <li>what I can imagine with a drug like duloxetine and</li> </ol>	164
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	<ol> <li>or is it more peripheral? So if it's more</li> <li>peripheral, then the fact that somebody has</li> <li>diabetes shouldn't influence whether or not we get</li> <li>a central nervous system mechanism related effect.</li> </ol>	<ol> <li>guess I have a few more questions, though, because</li> <li>what I can imagine with a drug like duloxetine and</li> <li>a situation with diabetes is it depends on the</li> <li>extent of the diabetes, the duration, any evidence</li> </ol>	164
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1	participate if they had asymptomatic, so they	1	goes to the community.
2	didn't have they may have had diabetes, but they	2	DR. DWORKIN: To some extent, Dr. Cleary,
3	didn't have symptoms at baseline. It might have	3	the way I think about this is I use clinical trials
	been, again, a question of degree, right? If we		in relapsing and remitting multiple sclerosis as an
	had included people that had symptomatic diabetic		example, where the phase 2 trials are smaller and
	neuropathy, then maybe our outcomes would have been		use MOI [ph] endpoints, and the phase 3 trials are
	diluted.		substantially larger, longer in duration and have
8	DR. HERTZ: Did they have any baseline		clinical endpoints.
9	electrophysiology, F waves, anything like that?	9	
10	DR. LAVOIE SMITH: No.		there a possible role in phase 2 for the biomarkers
11	DR. HERTZ: No?		in developing treatments for CIPN, but then later
12	DR. LAVOIE SMITH: No.		on, the larger trials would look at the clinical
13	DR. DWORKIN: Dr. Cleary?		endpoints.
14	DR. CLEARY: Getting to trial design, the	14	
	one trial that I'm aware of that's looked at FOLFOX		doing the same thing in oncology where we're doing
	is infusing was a phase 3 placebo-controlled		tumor biopsies to see if the drug's hitting the
	trial looking at calcium infusions before and after		cancer target in small phase 1 and phase 2 studies,
	FOLFOX, trying to see if it lessened the		but in a large phase 3 study, we're not doing
	neuropathy.		biopsies just to help accrual.
	Similar to a point made before, it was a	20	
20	large study. It was 353 patients. Unfortunately,		
	it was negative, but it just shows that these	21	same point, so I won't make it again. But I do
22	it was negative, but it just shows that these	22	same point, so I won't make it again. Dut I do
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	trials to get statistical power are going to have		want to make a somewhat different point that
	trials to get statistical power are going to have to be large.	2	
2 3	trials to get statistical power are going to have to be large. However, getting to your point, I do think	2	want to make a somewhat different point that touches really on the intersection between biomarkers and PROs.
2 3 4	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	2 3 4	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
2 3 4 5	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	2 3 4 5	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
2 3 4 5 6	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	2 3 4 5 6	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
2 3 4 5 6 7	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	2 3 4 5 6 7	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
2 3 4 5 6 7 8	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	2 3 4 5 6 7 8	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
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1	influence may add noise to the study design.	1	too, in terms of I think you said you would clearly
2	Would you feel that excluding other	2	exclude people who have neuropathy from something
3	neuropathies, not only diabetic but of other	3	else, but not people who are at risk for such as
4	causes, will be sufficient to reduce that noise,	4	age, and not exercising, and drinking a bit of
5	let's say, in the mid stages of development or	5	alcohol, and diabetes. But if they have diabetic
6	later on?	6	neuropathy and most of us in practice have done
7	DR. FIELDS: I think in general in these	7	it by history and examination. We don't biopsy
8	trials to avoid the noise or confusion, we do	8	every patient that comes in to prove that they
9	exclude patients with other neuropathies.	9	don't have these sorts of things.
10	DR. DASTROS-PITEI: That's what I'm	10	I think that's what's going to be in
11	thinking, that by using neuropathy at baseline,	11	practice at the end of the day when you have a drug
12	presence of neuropathy at baseline of any other	12	that you're going to use for prevention of, or
13	cause before the CIPN has occurred	13	treatment of, eventually you're not going to go and
14	DR. FIELDS: That would be excluded	14	say we got to biopsy to make sure you don't have
15	DR. DASTROS-PITEI: they would come out	15	anything before I give this to try and prevent it.
16	of the trial from the beginning?	16	It's just not feasible.
17	DR. FIELDS: Yes.	17	DR. CAVALETTI: No, Charles. I understand
18	DR. HERTZ: It depends. It depends what	18	your point. My question was a little bit
19	you're looking and where you think the target of	19	provocative because of course, I can't screen a
20	the drug is. So if you have something that	20	patient, I understand, if he has a neuropathy or
21	wouldn't impact other neuropathies and you're going	21	not.
22	to be looking at symptoms that are responsive or	22	My question was, which is the level? Is it
	Page 170		Page 172
1	other outcomes that are responsive to that	1	only because he is at risk? No, this is the
2	intervention, then you can decide whether or not	2	answer. It's not just because he's at risk. But
3	you need to cut down on that, if it would be	3	how many patients aged 70 or 65 with some
4	relevant to actually create noise or not. If it's	4	impairment in the reflexes, has a neuropathy? Is
5	something more nonspecific, then that depends on	5	it just aging?
6	how much you think you have a noise issue and a	6	So again, I'm not really convinced that
7	sick detection issue.	7	being too strict in the enrollment of this
8	Clearly, it can be done with patients who	8	population would really improve the quality of the
9	have diabetes under some constraints, and we don't	9	data. I think if someone is clear in neuropathy
10	know how far one can push that in terms of the	10	because he has let's say in retinal neuropathy
11	extent of potential overlapping diseases. I don't	11	that is well known, of course, I wouldn't include
12	think that there's a clear answer yet.	12	it. But I think the priority, we need to stay a
13	DR DWORKIN: Guido?	12	little bit closer to real life

- 13 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
- 20 that they consume alcohol? It's not so easy21 probably.
- 22 DR. LOPRINZI: I think there's a difference,

- little bit closer to real life.
   We have a lot of patients 70 years old, no
- 15 reflexes, it is not a disease. It is not a
- 16 neuropathy. It's just age. So I think we should
- 17 have a very clear idea of what we consider a
- 18 patient with a neuropathy before stating that we
- 19 don't want to enroll patients with neuropathy in a
- 20 clinical trial on CIPN.
- 21 DR. HOWIE: I'll defer this to further
- 22 discussion from the COA group, but it may be, too,

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1	that having baseline assessment and having that	1 other.
2	patient be their own control can help better	2 I'm convinced as a non-physician that
3	understand the actual effect of the drug.	3 Guido's assessment of the 70-year-old patient he
4	One of the things about PROs in the cancer	4 just described would end up in a different place
5	space is that cancer patients have a lot of symptom	5 than a non-neurologist doing an assessment of that
6	burden regardless of what the treatment is, and so	6 patient than a 23-year-old study coordinator hired
7	to figure out what the change, if any, in symptom	7 out of college to work on clinical trials.
8	burden is due to the anti-cancer therapy, you have	8 I think we could talk for hours about study
9	to know what the symptom burden was to begin with.	9 execution issues just with respect to your question
10	That's been one of the big issues about PROs	10 of how do you evaluate whether there's a peripheral
11	in the oncology space is trying to figure out	11 neuropathy in a patient who's being recruited for
12	what's the baseline symptomatology, what's the	12 one of these studies. We don't have the time for
13	effect of the drug, and then what's the unfortunate	13 that before lunch.
14	effect of the progressive disease.	Jen, you get the last word, last question.
15	That is still a work in progress, but I	15 DR. GEWANDTER: My comment is related. I
16	think that if you're thinking about potential	16 was just going to say that I think that's a very
17	heterogeneity among the patients as far as their	17 hard question, but obviously, excluding people who
18	baseline risk, knowing what the intrapatient change	18 have the symptoms that are included in your outcome
19	is might be helpful.	19 I think we probably can all agree is a good idea.
20	DR. DASTROS-PITEI: Even before the injury	20 Like if the patient presents with numbness and
21	occurs, so at least you know what these patients	21 tingling already, then we would want to exclude
22	have come in into the study before, let's say, the	22 them.
	Page 174	Page 176
1	Page 174 chemotherapy induces the chemotherapy-induced	Page 176 1 DR. HOWIE: Even endpoint is going to change
	-	
	chemotherapy induces the chemotherapy-induced	1 DR. HOWIE: Even endpoint is going to change
2 3	chemotherapy induces the chemotherapy-induced neuropathy, right.	<ol> <li>DR. HOWIE: Even endpoint is going to change</li> <li>2 based</li> </ol>
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**ACTTION - Chemotherapy-Induced Peripheral Neuropathy (CIPN) Trial Design Considerations** 

March 23, 2017		March	23,	2017
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	ropatily (CIPN) Trial Design Considerations		Warch 25, 2017
	Page 177		Page 179
1	they have a different risk of developing the CIPN,	1	AFTERNOON SESSION
2	the more serious CIPN.	2	(1:16 p.m.)
3	My question was based on that. If we use	3	DR. FREEMAN: Let's begin the afternoon.
4	very, very strict criteria to include patients	4	It's a pleasure to introduce my co-chair, Jennifer
5	within these trials, we accept the risk of probably	5	Gewandter, a pleasure not just because you're going
6	leaving out of the trial those patients with a	6	to hear a great talk, but also as you all know,
7	higher risk of developing CIPN.	7	she's done all of the backbreaking work putting
8	Again, my suggestion is to be not too strict	8	this meeting together, and we all owe her an
9	in enrollment criteria for these kind of things.	9	enormous amount of thanks just for that.
10	If a patient has no story and no symptoms, who	10	Jennifer is an assistant professor at the
11	cares about the fact we would randomize those	11	University of Rochester School of Medicine and
12	patients, and of course this is another point	12	Dentistry, and why don't you come up, Jennifer?
13	raised by Charles we need to run fairly big	13	Presentation – Jennifer Gewandter
14	sizes, unfortunately. This is not good news	14	DR. GEWANDTER: Thank you. Thanks, Roy, for
15	because it costs.	15	that introduction.
16	But again, if we have 55 years that's	16	Today I'm going to cover the methodological
17	right, Joanna. If we are 55 years later here	17	challenges of studying CIPN during chemotherapy.
18	talking about which is the best way to screen	18	So I'm not going to discuss the trials that
19	patients, which is the best way to assess, which is	19	Dr. Horn mentioned that would occur after the end
20	the drug, probably we have not a simple problem to	20	of chemotherapy.
21	be addressed. That's probably the point.	21	Today for my talk, I have three main goals.
22	DR. DWORKIN: Thank you very much. It's an	22	First, I'm going to outline the design challenges
	Page 178		Page 180
1	excellent challenge for us to think about over	1	and issues to consider when designing a CIPN study
2	lunch. We have a one-hour lunch break. I don't	2	during chemotherapy. Next, I'm going to summarize
3	know where it is.	3	how published RCTs have addressed these design
4	Valerie could you mezzanine where we had	4	challenges in the past, and finally, propose topics
5	dinner last night. We'll see you all promptly at	5	for our design discussion.
6	1:00.	6	These are the main challenges as I see them.
7	(Whereupon, at 12:04 p.m., a lunch recess	7	First, you have to pick from one of multiple trial
8	was taken.)	8	objectives. Second, as we've had some discussion
9		<b>^</b>	
		9	already, you have to choose your eligibility
10			already, you have to choose your eligibility criteria. Then you have to decide how to measure
10 11		10	
		10 11 12	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
11		10 11 12 13	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
11 12		10 11 12 13 14	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
11 12 13 14 15		10 11 12 13 14 15	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
11 12 13 14		10 11 12 13 14 15 16	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
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INE	ropathy (CIPN) Trial Design Considerations		March 23, 2017
	Page 181		Page 183
1	prevention study where you initiate the treatment	1	Then there were two symptomatic treatment trials.
	after the start of chemotherapy but before any CIPN	2	The next challenge is eligibility. I think
	symptoms are detectable. You can do a tertiary		we covered this quite a bit today, but the way I
	prevention study where you initiate the preventive		think about this is that we're trying to balance
	treatment after detection of early neuropathy signs		the feasibility of recruitment and the
	or symptoms in order to prevent them from	6	
	worsening, or you can do a symptomatic treatment		internal validity of the study, so the ability of
	trial where you're treating established CIPN		the study to give an accurate effect estimate of
	symptoms.		the treatment for the population that was included
10	Now, in regards to the prevention studies, I		in the study.
11	think we've covered this a little bit already	11	For all trials of CIPN during chemotherapy,
	today. It might be a little bit logistically	12	this can be particularly challenging because, as
	easier to do a secondary prevention study than a		we've spoken about today, there are multiple cancer
	primary prevention study, and a tertiary prevention		types. There are multiple chemotherapy types, and
	study could have higher power with fewer patients.		within those types, there are multiple agents. And
	But both secondary prevention and tertiary		within those agents, there are multiple dosing
	prevention studies could potentially miss the		regimens, and all of these things can create
	therapeutic window that a primary prevention study		variability in our outcome measures.
	would hit. So these are the things we need to	19	You also have the question of early stage
	consider when deciding between these objectives.	20	versus metastatic, which we've also addressed. On
21	What have the currently published RCTs done?	21	the one hand including only patients with
22	We did a systematic review of randomized controlled	22	metastatic chemotherapy could be good for earlier
	Page 182		Page 184
	trials of pharmacologic treatments for CIPN that		studies where we have a safety concern, but on the
	were used concurrently with chemotherapy, and they		other hand, if you include patients with metastatic
	also had to be focused mainly on CIPN to be		cancer, they're more likely to discontinue the
	included in our review and published before		study or their chemotherapy treatment for reasons
5	November of 2015.	5	other than neuropathy, which can hurt the study.
6	We identified 38 RCTs. Thirty-six of them	6	Then something we've talked about a lot,
	had some kind of prevention design. Twenty-three		should we include patients who have other
	had a primary prevention design so the treatment	8	conditions that are associated with neuropathy like
	was initiated before or on the same day as the	9	
10	chemotherapy. In 10 of them, the exact timing was	10	patients who had prior exposure to neurotoxic
	not clear, but there was no indication that CIPN	11	treatments whether it be cancers or chemotherapies
12	not clear, but there was no indication that CIPN symptoms had appeared prior to treatment.	11 12	or HIV treatments but don't have any symptoms
12 13	not clear, but there was no indication that CIPN symptoms had appeared prior to treatment. In one of them, the timing was described as	11 12 13	or HIV treatments but don't have any symptoms associated with neuropathy yet?
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12 13 14 15 16 17 18 19 20 21	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	11 12 13 14 15 16 17 18 19 20 21	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?

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1	remainder of the studies included either two cancer	1	it? Do you need a neurologist? Can it be another
2	types or multiple cancer types.		clinician? Could it be a research assistant?
3	Interestingly, 40 percent included both	3	Also, when are you going to assess CIPN in
4	early and advanced stage cancers, and 21 percent	4	relation to chemotherapy treatment? Are you
5	included only advanced cancers. The remainder of	5	interested in the acute-type symptoms that we heard
6	the articles did not say what stage cancers were	6	talked about this morning, or are you interested
7	included in the studies.	7	maybe in the cumulative symptoms that increase over
8	For treatments, 60 percent of the studies	8	time with cumulative dosage of chemotherapy? Those
9	used platinums only, and this is not a big surprise	9	would be measured most likely before a dose of
10	given the majority of the cancers that were studied	10	chemotherapy.
11	were GI cancers. Then I'm not going to read the	11	Then how in relation to the enrollment in
12	remainder there, but you can see that there were	12	the study, when are you going to measure them? If
13	some studies that used multiple different types of	13	you detect neuropathy if you're interested in acute
14	chemotherapy in the same study.	14	symptoms, do you treat people right away, or would
15	One thing that I found interesting was that	15	you wait till the next cycle?
16	40 percent of the studies specifically stated that	16	Also, do you have a minimum severity
17	they included only 1 regimen, and what I mean by	17	requirement for CIPN or just the presence of CIPN?
18	regimen is 1 dosing paradigm. Those were the	18	If there is a minimum severity requirement, which
19	results for the chemotherapy and cancer-related	19	symptoms are you interested in? This will very
20	exclusion criteria.	20	likely be determined by what the primary outcome or
21	For the neuropathy-related exclusion	21	primary endpoint is of your trial.
22	criteria, just like I think we all agreed on in the	22	There were only two symptomatic treatment
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1	discussion, over 80 percent of the studies excluded	1	trials, so we don't have a lot of examples to go by
	patients with preexisting neuropathy. Then the	2	
	studies were half and half split whether they		conducted during chemotherapy. But in one study,
	allowed patients to have diabetes or not.		they included patients who were reporting a
5	Approximately 40 percent excluded neuropathy		distressing acute neurotoxicity after
	treatments, and that ranged in the studies anywhere		administration of their oxaliplatin-based
	from a list of drugs like anti-epileptics,	7	
	antidepressants, and vitamins to a statement saying	8	
	something like patients who are on drugs thought to	9	
	alter neuropathy were excluded.		scores.
11	The other exclusion criteria that occurred	11	Measurement is my next challenge. For all
12	commonly in the studies were previous neurotoxic	12	trials of CIPN, I think we all know this, that
13	chemotherapies, previous chemotherapies of any	13	there is a lot of variability in between patient
14	kind, alcoholism, and a minimum life expectancy as	14	symptom and sign presentation, and this occurs even
15	well as previous radiation therapy.	15	within one type of chemotherapy.
10	That applies to all studies for CIPN, and	16	I've listed a few of the symptoms here, but
16	That applies to all studies for on 14, and		
	then for studies in which the goal is symptomatic	17	as you all know, there are more. The challenge
17		17	as you all know, there are more. The challenge really is taking this amalgam of symptoms and
17 18	then for studies in which the goal is symptomatic	17 18	
17 18 19	then for studies in which the goal is symptomatic treatment, you have to define what you mean by	17 18	really is taking this amalgam of symptoms and turning it into one primary outcome measure that is
17 18 19 20 21	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	17 18 19 20 21	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
17 18 19 20 21	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	17 18 19 20 21	really is taking this amalgam of symptoms and turning it into one primary outcome measure that is clinically meaningful and sensitive to change.

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1	to outcome measures, but one thing that I will	1	dependent on the number of different chemotherapy	
2	bring up to think about is just this idea of should	2	regimens that you include in the study. If you	
3	we be including composite measures that include	3	only include one chemotherapy regimen, you might be	
4	symptoms and signs, or both, and should we	4	able to decrease a lot of these issues that would	
5	potentially be trying to think about targeting to	5	complicate measurement of CIPN.	
6	only a few symptoms if we think our drug could work	6	The one thing that we can control in our	
7	for those symptoms.	7	studies fairly easily is the scheduling of the	
8	For example, an easy and obvious one is if	8	assessments. What has been done in the past, 9 of	
9	we have an analgesic that we know works for pain,	9	the prevention trials reported the timing of the	
10	in other conditions, we would probably think about	10	assessments in relation to chemotherapy; 7 of them	
11	maybe making pain our primary endpoint for that	11	made the assessments prior to the chemotherapy	
12	trial. But in the future, potentially we'll have	12	doses; and 2 of them made the assessments on very	
13	things that maybe would target numbness, and if	13	specific days after the chemotherapy doses. That	
14	that's an important symptom, it could potentially	14	was also done in the one symptomatic treatment	
15	ease our measurement if we could focus on that.	15	trial that reported the timing. The rest of the	
16	I'm just listing here, these are the primary	16	studies did not specify when their assessment were	
17	outcome measures 22 of the studies identified one	17	made.	
18	that were used in the trials that we reviewed.	18	I'd like to emphasize that this doesn't mean	
19	Really, the take home message here is that it's all	19	that they weren't specific about it when they did	
20	over the place. There really isn't a consensus on	20	their study. It could just be not super great	
21	what we should be using for CIPN in measurement.	21	reporting. But it does highlight that it's really	
22	We have at the top clinician- or	22	important to be specific and consistent so that	
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1	patient-reported symptom or function interference	1	you're measuring the same thing all the time and we	
2	measures, and then clinician-reported symptom and	2	don't introduce too much variability in the	
3	sign measures. There were a few studies that based	3	outcomes.	
4	their primary outcome measure on sign measures	4	After measurement, we have to decide how are	
5	only, and then there was one study that looked at	5	we going to use those measurements and how are we	
6	the receipt of 6 cycles of chemotherapy without	6	going to turn them into trial endpoints. This is a	
7	significant peripheral neuropathy as their primary	7	challenge in prevention studies because there are a	
8	outcome measure.	8	lot of options. We can use a neuropathy occurrence	
9	One other thing I wanted to mention, other	9	measure, we can use a neuropathy severity measure,	
10	than outcome measures, it's important to think	10	or we can use how much chemotherapy is received as	
11	about the variability that can be introduced into	11	a measure.	
12	the severity of CIPN measurements because the	12	Then, for example, just within the	
13	severity depends on the type of chemotherapy, the	13	neuropathy severity category, you could measure it	
1		1		

- 13 severity depends on the type of chemotherapy, the
   14 cumulative dosage of chemotherapy, the timing of
   14 at a specified cycle number, at a specified time
- 15 the dosing regimen, as well as the time since the
- 16 last dose of chemotherapy.17 The times since the last dose of
- 18 chemotherapy can be affected by dose delays and
- **19** discontinuations, as well as the scheduling of
- 20 assessments, so how precise you are when scheduling
- 21 your assessments.
- 22 Obviously, a lot of these things are
- 20 When trying to decide between these

15 point after the initiation of chemotherapy, at a

16 specific time point after the completion of

19 different options to choose from.

21 different endpoints, we should consider things that

17 chemotherapy, and over a summary of multiple time

points during chemotherapy. So there are a lot of

22 might introduce variability or affect the power of

18

1	our analyses.	1	used some type of severity either at completion of
2	Just to give a couple of examples and	2	chemotherapy, or a specific cycle, or a summary of
3	this may be a little less relevant if we're only	3	multiple time points. Then one study each looked
4	going to be including one regimen in our studies,	4	at severity after a specific time point after
5	but in studies that don't include only one regimen,	5	initiation of chemotherapy and after completion of
6	there's variability in timing of the chemotherapy	6	chemotherapy. Then again, there was that one study
7	dosing. This will likely have more of an effect on	7	that looked at the number of patients who received
8	outcomes that measure severity of neuropathy than	8	6 cycles as their primary endpoint.
9	those just look at occurrence of neuropathy by the	9	For symptomatic treatment trials, it's a
10	end of chemotherapy. But then if you want to	10	little bit less complicated. I can think of fewer
11	occurrence of neuropathy by the end of	11	options for the endpoints. So obviously, you can
12	chemotherapy, you have to consider that that's a	12	look at severity at one or multiple specified time
13	dichotomous endpoint and could potentially have	13	points after chemotherapy infusions or before
14	lower power.	14	chemotherapy infusions. You could look at the
15	In another example, regardless of the	15	percentage improvement in symptoms, and this could
16	endpoint you'd choose, if a lot of patients	16	either be from the time you initiate the
17	discontinue their chemotherapy due to causes other	17	experimental treatment or potentially relative to a
18	than neuropathy before they get neuropathy, your	18	previous chemotherapy dose where no experimental
19	trial's likely going to have trouble detecting a	19	treatment was given.
20	difference between the groups.	20	For both of these options, you could look at
21	If a lot of people discontinue due to	21	these endpoints after either a single dose of
22	neuropathy, then a neuropathy occurrence endpoint	22	chemotherapy or over multiple doses of
22	neuropathy, then a neuropathy occurrence endpoint	22	chemotherapy or over multiple doses of
22	neuropathy, then a neuropathy occurrence endpoint Page 194	22	chemotherapy or over multiple doses of Page 196
1	Page 194	1	Page 196
1	Page 194 or an endpoint that looks at the amount of	1	Page 196 chemotherapy. If you look at these endpoints after
1 2 3	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,	1 2 3	Page 196 chemotherapy. If you look at these endpoints after only a single dose of chemotherapy, you eliminate a
1 2 3 4	Page 194 or an endpoint that looks at the amount of chemotherapy received won't be affected by these	1 2 3 4	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
1 2 3 4 5	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	1 2 3 4 5	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
1 2 3 4 5 6	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	1 2 3 4 5 6	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
1 2 3 4 5 6 7	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	1 2 3 4 5 6 7	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
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- **19** Occurrence of neuropathy by the end of chemotherapy
- ${\bf 20}\;$  was the most commonly used endpoint, and then one
- 21 study used a time-to-occurrence endpoint.
- 22 Then most of the remainder of the studies

19

Unfortunately, our neuropathy incidence

20 rates by cancer and chemotherapy type are not that

22 probably because the studies often use inconsistent

21 reliable. There's a lot of variability. This is

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1	CIPN measurement tools, and the question is whether	1	get in the beginning.	
	these estimates will be useful when we're using	2	How have people handled this so far in the	
	different assessment tools potentially in our	3	published literature? There were 9 prevention	
	study. So better understanding of the natural		studies that indicated how they handled this. So	
	history would really help us in planning our	5		
	studies.	6	number or cumulative dosing of chemotherapy were	
7	The other thing is I know a lot of	7	eliminated from the analyses. In 2, patients were	
8	oncologists will say that patients will discontinue	8		
	chemotherapy due to their neuropathy, but I have	9	chemotherapy all the way up to the time point of	
	not been to find any actual data that give those		the assessments, and then 1 study used a summary	
	rates. If you want to make the endpoint of your		statistic that was prorated for the number of	
	study whether or not someone finishes chemotherapy		chemotherapy cycles received.	
	or dose reduces, it's really important to know how	13	In the symptomatic trial that indicated how	
	many people are going to actually discontinue	14	they handled these participants, the participants	
15	chemotherapy. Obviously, this is going to be	15	who discontinued chemotherapy before they achieved	
	different depending on which population of patients		what they called a responder status, which was the	
17	you're including, which type of cancer and what	17	endpoint, were called non-responders.	
18	stage of cancer. A better understanding of these	18	I've covered all of the challenges that I	
19	things would really help us.	19	see or that I think of when I think about designing	
20	Finally, for all trials, not just prevention	20	these studies, and now I would like to outline the	
21	trials, I think we all know that CIPN affects the	21	things that I'm hoping we can talk about in our	
22	quality of life of patients, but there actually is	22	discussion.	
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1	little data out there in the published data that	1	Our first goal is to establish	
	little data out there in the published data that	1	Our first goal is to establish	
2	helps us understand which symptoms are the most	2	recommendations for the eligibility criteria	
2 3	helps us understand which symptoms are the most important to patients. If we had some more data on	2 3	recommendations for the eligibility criteria related to the following things on the slide as	
2 3 4	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	2 3 4	recommendations for the eligibility criteria related to the following things on the slide as well as other things that you guys might think of	
2 3 4 5	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	2 3 4 5	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	
2 3 4 5 6	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.	2 3 4 5 6	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.	
2 3 4 5 6 7	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	2 3 4 5 6 7	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	
2 3 4 5 6 7 8	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	2 3 4 5 6	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	
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22 chemotherapy that you thought they were going to

22 chemotherapy they received, that's a traditional

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1	ITT analysis, and that obviously will prevent us	1 (Laughter.)		
	from getting a biased estimate, but if a lot of	2 Presentation – Michael McDermott		
	participants discontinue before getting a	3 DR. McDERMOTT: Roy has just set you up for		
	reasonable amount of chemotherapy to get a	4 disappointment, that's for sure.		
	neuropathy, this could make it difficult for us to	5 (Laughter.)		
	detect a true treatment effect.	6 DR. McDERMOTT: These are some of the things		
7	So is it reasonable to remove participants	7 that Jen mentioned that I'm going to focus on for		
8	who don't receive a minimum cumulative dosage of	8 just a few minutes. Outcome measurement is going		
	chemotherapy? And if that's reasonable, how do we	9 to predominate what I talk about because that's		
	define what that minimum dosage is?	10 really, I think, the hardest thing to think about		
11	Would it be reasonable to adjust for the	11 in these studies. I'll say a little bit about some		
12	amount of chemotherapy that has been received or	12 strategies for analysis and maybe just a little bit		
	not? Which of these are reasonable as primary	13 about defining the population, but we've talked		
	analyses or potentially only as sensitivity	14 about some of those issues already.		
	analyses? And if they're identified only as	15 When thinking about how to define outcome		
	sensitivity analyses, what would that mean to the	16 for people, I think that it's important to try to		
	FDA in terms of an indication? Would that be	17 think about what really constitutes success for		
	meaningful to them?	18 treatment for an individual patient, and there are		
19	With that, I'll end here, and I'd just like	19 many different things to think about. Certainly,		
	to thank the people who helped me put the talk	20 absence of neuropathy would be fantastic, having		
	together, especially Roy and Bob really had a lot	21 less severe neuropathy, less time with neuropathy,		
	of input on how to get everything in my brain in a	22 less time with important neuropathy, the ability to		
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1	hopefully potentially clear manner. And the rest	1 complete your chemotherapy regimen without		
2	of the people listed here are co-authors on the	2 interruption and with minimal discomfort, or even		
3	systematic review that we've submitted for	3 going a bit further than this, having a good		
4	publication.	4 response considering both the neuropathy outcome		
5	(Applause.)	5 and the cancer-related outcome. Those are some of		
6	DR. FREEMAN: Wasn't that a wonderful talk?	6 the things to consider.		
7	What we will do is now have two of the three	7 When I first spoke with Jen about this, I		
8	discussants, third discussant Yan Zhou is here as	8 haven't worked in this area at all before, she was		
9	an observer, not as a discussant for reasons beyond	9 explaining some of the complications that she just		
10	my capability of understanding.	10 discussed. One of the things that occurred to me		
11	You will explain that to me one day, won't	11 at first was, well, it seems that you are concerned		
12	you?	12 about not only the neuropathy but how is the		
13	The first is going to be Scott Evans, who is	13 patient going to be doing overall clinically. And		
14	a senior research scientist at Harvard University.	14 part of that, of course, is how they not only		
15	I'm getting the other way around.	15 complete the chemotherapy but respond to it		
16	The first is going to be Mike McDermott, who	16 perhaps, too. So is there some way of integrating		
17	is a professor of biostatistics and neurology at	17 all of that information into some sort of composite		
18	the University of Rochester Medical Center,	18 outcome?		
19	Rochester, New York. He's spoken at these meetings	19 Now, I suspect that people don't consider		
20	many times, and he and Scott are probably the only	20 the cancer outcome so much because it's sort of an		
21	two statisticians in the world who give	21 off-target effect, one could argue, and one might		
22	entertaining talks, so we look forward to this.	22 expect if you have a neuropathy treatment to have		

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1	minimal effect on that dimension of the outcome.	1	prevention trial or a trial of treatment.	
	But on the other hand, chemotherapy success is	2	So the outcome of something like area under	
	arguably more important to the patient so that it	3	the severity time curve in that sense appeals to	
	could be that a composite that incorporates both of		me, that even if the neuropathy is transient, you	
	those dimensions is useful.		still, as long as you get neuropathy, would	
6	I'm going to talk mainly about some ideas		seemingly care about how severe it is and how long	
7	about incorporating the interruption or		it lasts.	
	discontinuation of chemotherapy with other measures	8	So I tried to come up with some integration	
	of severity, and Scott Evans, who is going to	9	of the severity over time. It seems like a	
	follow me, will talk also about some ideas for		reasonable way to try to think about approaching	
11	combining information from different aspects of	11	the problem of measurement in this condition.	
12	this.	12	Now, if you have different chemotherapy	
13	One of the things that I have been thinking	13	regimens and different timing of when you have	
14	about is this notion in a prevention trial	14	cycles and so forth, that can complicate things a	
15	of and this is very common time to an	15	bit, particularly if you have different durations	
16	important event occurs. And time to neuropathy has	16	of chemotherapy. But one can always normalize area	
17	been used in some of these trials and arguably is	17	under the curve, for example, to account for how	
18	an important outcome to consider.	18	long you've had the chemotherapy, for example, in	
19	How meaningful that is depends, of course,	19	order to deal with that.	
20	on how severe I think the neuropathy is that you're	20	One issue, I should go back, at the very	
21	preventing. So if somebody is going to develop	21	bottom here, is how frequently can symptoms be	
22	neuropathy but it is relatively mild and transient,	22	measured. If it's something you have to come into	
	Page 206		Page 208	
1	Page 206 preventing it isn't the end all and be all,	1	Page 208 the clinic for, that's going to be not so	
	-		-	
2	preventing it isn't the end all and be all,	2	the clinic for, that's going to be not so	
2 3	preventing it isn't the end all and be all, perhaps. On the other hand, if it's going to be	2 3	the clinic for, that's going to be not so frequently, but if it's going to be a	
2 3	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	2 3 4	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	
2 3 4 5	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.	2 3 4 5	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	
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1	and that's going to be their outcome regardless.	1	that people discontinue for reasons unrelated to	
2	So that's one strategy.	2	neuropathy, but we're going to stop following them	
3	Another strategy is to think about it as,	3	at that anyway and just sort of impute what would	
4	well, what I really want to know is what would the	4	have happened to them if they had stayed on the	
5	area under the curve have been if they had stayed	5	chemotherapy and base that imputation on people who	
6	on chemotherapy. Now, we're not going to observe	6	actually completed chemotherapy. And you have an	
7	that, but maybe that's the thing that we're	7	idea of how they did up to the point where that	
8	actually trying to estimate.	8	person discontinued. So you can use that	
9	If that's the case, those are two different	9	information to try to impute what would have	
10	kinds of measurements, right, two different kinds	10	happened to that person had they continued on	
11	of outcomes. We have to think about how we deal	11	chemotherapy anyway.	
12	with the missing data problem, depending upon which	12		
13	of those we think is more relevant to try to	13	try to deal with that issue. I think the more	
	quantify.	14	complicated issue is how you deal with people who	
15	What some people I think have done in some		discontinue chemotherapy due to neuropathy because	
16	of these trials is used what they call a prorated	16	those are the people who are coming off of	
	area under the curve. They measure the area under	17	chemotherapy, and if they had stayed on, perhaps	
	the curve up until a certain point, and then they	18		
	discontinue chemotherapy. And after that, they	19		
	just say, well, half the time they had this area	20	That's a more difficult imputation problem	
	under the curve so let's just double it and make it	21	because you're flying blind in a way. You're	
	that the rest of the time.		trying to impute something that you really have no	
	Page 210		Page 212	
1	Page 210 If they discontinue chemotherapy, their area	1	Page 212 really good information on how to impute it.	
	-	1	really good information on how to impute it.	-
2	If they discontinue chemotherapy, their area	2	really good information on how to impute it.	
2 3	If they discontinue chemotherapy, their area under the curve probably in that second half would	2 3	really good information on how to impute it. One way to deal with it is something like	
2 3 4	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	2 3 4	really good information on how to impute it. One way to deal with it is something like worst case imputation. Give them the worst	-
2 3 4 5	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	2 3 4 5	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	
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1	and direction depending upon who you exclude from	1	could consider perhaps the more important endpoint.	
	the analysis. So I think that's one principle	2	The way this works is that overall you would	
	that, if at all possible, we should try to follow.	3	just rank everybody from worst to best outcome, and	
4	The other is that I would advise trying to		the first thing you would do is consider the people	
5	avoid adjusting for things that happened after	5		
	randomization such as adjusting for cumulative	6	earliest discontinuation to latest discontinuation.	
7		7	So you rank them from, again, worst to best. And	
8			then the people who've completed chemotherapy, you	
	to do is incorporate things like interruption or		rank those people according to area under the curve	
10	discontinuation of chemotherapy somehow into the	10	from worst to best.	
11	measurement of outcome.	11	You get an overall ranking of worst to best	
12	I've already said a few words about that.	12	outcome, but essentially what you're doing is that	
13	I'll say another couple of words.	13	the people who are discontinuing chemotherapy,	
14	I want to borrow an idea from another area	14	again because of neuropathy, was severe enough to	
15	of neurology. This happens in trials of ALS, and	15	discontinue chemotherapy, you would argue they	
16	there are some similarities I think with CIPN in	16	should be assigned the worst outcomes, and then the	
17	the sense that in traditional ALS trials, one tries	17	people that continued chemotherapy but had worst to	
18	to see if treatment has an effect on function by	18	best outcomes in terms of AUC, you have this	
19	following people over time in terms of, in this	19	complete ranking of people.	
20	case, the ALS Functional Rating Scale.	20	Now, the assumption here, of course, is that	
21	So one tries to see what the trajectory of	21	people who have discontinued chemotherapy have had	
22	decline is over time in the treated group versus	22	worse outcomes than people who've completed	
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	the placebo group, and the complication in ALS is		chemotherapy but maybe have some severe area or	
2	the placebo group, and the complication in ALS is that 40 to 50 percent of the people are going to be	2	chemotherapy but maybe have some severe area or some high area under the curve. That's something	
2 3	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	2 3	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	
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2 3 4 5	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	2 3 4	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.	
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I	Neuropathy (CIPN) Trial Design Considerations			March 23, 2017		
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	1	types, chemotherapy types, dosages and so forth,	1	15 years about the wisdom of sample size		
		obviously, it's going to be cleaner to have within		re-estimation that happens within the context of		
	3	study homogeneity. Then of course, you have to		the study. You accumulate information on part of		
	4	balance that with the difficulties of recruiting	4	the clinical trial cohort, and then in some way,		
	5	patients, obviously.	5	you can use that data to re-estimate what the		
	6	So it may be unavoidable to allow some of	6	sample size should be; in other words, to reinform		
	7	these factors to vary in a study, but one would	7	the assumptions that you make about the sample size		
	8	have to strongly consider stratifying by these	8	calculation to perhaps adapt that midstream so that		
	9	factors, especially in the analysis if one were to	9	you make sure that at the end of the study, you end		
	10	allow them to vary in this study.	10	up with at least approximately adequate power. So		
	11	Obviously, allowing these things to vary is	11	that's a strategy that can be helpful perhaps in		
	12	going to lead to more variability in the outcomes,	12	this context.		
	13	but if you can stratify by some of these factors,	13	Finally, I'm not sure even why I put this		
	14	that will in the analysis reduce that variability	14	slide together because what effect size would be		
	15	and still preserve, I think, a good deal of power.	15	important to detect? Obviously, that's going to		
	16	The final couple points I want to make are	16	depend on the outcome of interest, but in the		
	17	about study planning, and I think that extensive	17	absence of good data on some of these outcomes,		
	18	natural history data, as somebody has already	18	even if you had good data, sometimes it's very		
	19	mentioned I think Joanna mentioned earlier that	19	difficult to come up with the effect size that's of		
	20	having an effort like that go on is going to be	20	minimal importance to try to detect in a trial. So		
	21	enormously helpful in coming up with sensible plans	21	I think that some work needs to be done in this		
	22	for these studies.	22	area in order to think about how large these trials		
-		Page 218		Page 220		
	1	I think that even more ideal would be if we	1	need to be.		
		had data from many placebo groups of clinical	2	If you're thinking about something, for		
		trials. One of the things I've learned over the	3			
		years in conducting clinical trials is that natural	4			
		history groups don't necessarily behave the same as		about power in that context? Well, if it's a rank		
		placebo groups in clinical trials, particularly if		analysis like that, then what the power depends on		
		the outcomes are somewhat subjective. I think that		is something that's a little bit nonstandard. It's		
		that's something to be aware of.	8			
	9	Sometimes what happens in studies that are	9	What does that mean? It means that if you		
	10	not in the context of treatments being given, the	10	took a randomly selected person from a treatment		
	11	behavior of people can be somewhat different than		group and a randomly selected person from the		
	12	in the context of a clinical trial. That's a	12	placebo group, it's the probability that the person		
	13	caution in terms of the use of natural history	13	on treatment would do better than the person on		
	14	data.	14	placebo. If the treatment doesn't work, that		
	15	The other thing one can do in terms of	15	probability is a half.		
	16	sample size planning, especially at the stage that	16	So how far away from a half would that have		
	17	I perceive that the field is at, at the moment, if	17	to be in order to make it important to try to		
	18	one is going to conduct a trial, there are a lot of	18	detect is the way to think about it, and that's		
	19	uncertainties regarding what the sample size inputs	19	what drives the sample size in that kind of study.		
	20	are, the variability, or the rates of some event	20	Those are the things that I think that		
	21	occurring and so forth.	21	I'm done with that; some things to think about in		
		There have been a lot of papers in the past	22	terms of outcome and analysis, and I'm sure we'll		
	22	There have been a lot of papere in the paet	22			

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1	talk about that a lot more later.	1	neuropathy outcomes. So you've got a really
2	(Applause.)	2	difficult problem here.
3	DR. FREEMAN: As you see, we're considering	3	Now, I want to motivate thinking about
4	these three talks all as one package, and we'll	4	should we try to disentangle all of the different
5	have a break and then the discussion.	5	types of outcomes, different parts of patient
6	The third talk is by Scott Evans, who is a	6	outcomes, that can happen during the course of
7	senior research scientist at Harvard University.	7	treatment of any disease, so let me try to motivate
8	He has contributed substantially to the HIV	8	this.
9	research study group, and people may know him from	9	Here's a bit of a test. Suppose you measure
.0	these conferences previously.	10	a duration of peripheral neuropathy, or maybe you
1	Come up, Scott.	11	measure an AUC as Mike described either
.2	Presentation – Scott Evans	12	using maybe you figure out how to set this up
.3	DR. EVANS: Thank you very much.	13	using the TNS, something representing a total
4	Statistics, we have a saying that there are	14	disease burden based on the duration and severity
5	lies, damn lies, and alternative facts.	15	of peripheral neuropathy.
6	(Laughter.)	16	Shorter duration is better, or is it? The
7	DR. EVANS: Maybe applies to Mike and I	17	faster that a patient withdraws from chemo, the
8	being good speakers.	18	shorter the duration, potentially failing the chemo
9	I did want to thank Jen and Bob and Roy for	19	because of the withdrawal, or the faster the
0	the opportunity to be part of this interesting and	20	patient dies, the shorter the duration. Not
1	informative meeting over today and tomorrow. I	21	necessarily shorter is always better.
2	want to thank Jen for an excellent presentation.	22	Interpretation of any AUC or duration or any
	Page 222		Page 22
1	Mike and I actually had a chance to chat	1	of that measure needs context of what else is
	about Jen's slide, and I agree with what Mike has		
			happening to the patient. This happens a lot.
	said. He's done such a thorough job at explaining		Obviously, if the patient is not surviving, that
	many of the issues that it frees me up to discuss		plays into how you might interpret certain things.
	what Bob referred to this morning, potentially some	5	Here's another question. Suppose the person
	novel or innovative out-of-the-box thinking.		you care about the most has just been diagnosed
7	,		with a cancer requiring chemotherapy? You've got
8			three treatment options for preventing or treating
	Please excuse me if I don't know as much about CIPN		chemotherapy-induced peripheral neuropathy, A, B,
	as everyone else in the room, but what I'm going to		and C, three treatments.
	show you are some ideas that are being developed in	11	Let's suppose there are two outcomes you're
			most worried about. There's the peripheral
2	other areas of medicine, and I'm going to try to		
2 3	motivate why they're being developed and how they	13	neuropathy outcome, and there's a chemotherapy
2 3 4	motivate why they're being developed and how they may or may not apply in CIPN.	13 14	neuropathy outcome, and there's a chemotherapy outcome. And let's suppose they're both binary,
2 3 4 5	motivate why they're being developed and how they may or may not apply in CIPN. We have this somewhat hard problem here	13 14 15	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.
2 3 4 5 6	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,	13 14 15 16	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
2 3 4 5 6	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	13 14 15 16 17	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
2 3 4 5 6 7 8	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	13 14 15 16 17 18	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
2 3 4 5 6 7 8 9	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	13 14 15 16 17 18 19	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
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2 .3 .4 .5 .6 .7 .8 .9 .0 .1	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	13 14 15 16 17 18 19 20 21	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

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1	Which treatment do you choose? Well, they all have	1	all the other endpoints, and then at the end,	
2	the same peripheral neuropathy rate. A has the		trying to put it together and make sense of it,	
	lowest chemo failure, so probably you're leaning		it's not quite the right order.	
	towards A. It seems reasonable. We're all	4	What we need to be doing is thinking about	
5	reasonable people here. B and C are somewhat	5	how patients are doing, taking our endpoints within	
	indistinguishable.		patient, then aggregating over treatment A and	
7			aggregating over treatment B and making	
8	endpoints, and this is what we typically do in		comparisons. That's what representing how well two	
9	trials. We say here's endpoint number 1. I'm		treatments compare to another in a pragmatic way.	
10	going to aggregate what happens over treatment A.	10	This is what we're going to show you, and	
11		11	I'll show you some examples about how this is	
12	I'll make a contrast between the two, and I'm going	12	progressing in other areas.	
13	to repeat that for the other outcomes.	13	Here's another question about benefit-risk.	
14	I'm going to switch that around. Instead of	14	We've got toxicities. We've got benefits and so	
15	analyzing the endpoints, I'm going to analyze what	15	forth. During the analysis of a trial, you define	
16	happened to the patients. Now, there are four	16	analysis populations. You do an efficacy analysis,	
17	possible outcomes if you've got a binary peripheral	17	you do ITT. You do a safety analysis, you do a	
18	neuropathy outcome and a binary chemotherapy	18	safety population. Those populations are not the	
19	outcome. Let's look at what happens to the	19	same.	
20	patients.	20	Then at the end, you combine the efficacy	
21	Now, in A what happened is that the	21	analyses and the safety analysis to do a	
22	association between peripheral neuropathy and	22	benefit-risk analysis. To whom does this	
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1	whether you failed chemotherapy or not, there was	1	benefit-risk analysis apply? I ask you this	
2	no association, no correlation. But peripheral	2	because I've been teaching clinical trials for	
3	neuropathy was positively correlated with good	3	15 years, and I don't know the answer. But that's	
4	chemo failure outcomes in B and negatively	4	what we do.	
5	correlated with C such that your rate of	5	We published a paper recently that described	
6	chemotherapy success without peripheral neuropathy	6	this particular vision in clinical trials, and if	
7	is 30 percent in A, 0 percent in B, and 50 percent	7	you look at what we do today in terms of treatment	
8	in C.	8	effects, on the left side you see well, we	
9	What's happening? Well, our culture in	9	usually estimate few treatment effects, and by	
10	trials is that we take the patients in the trials,	10	"few," I mean usually in a clinical trial, we	
11	we analyze each of the endpoints, and there are	11	estimate a global treatment effect for the patient	
12	thoughts these days about how to turn this around.	12	population.	
13	Isn't the point of a trial in collecting	13	But tomorrow and we already see the	
14	information on outcomes to evaluate how the	14	movement is what we're going to do is we're	

- 14 information on outcomes to evaluate how the
- 15 patients are doing? Instead of using the patients
- 16 to analyze the endpoints, use the endpoints to
- 17 analyze what happens to the patient.
- 18 My father told me many years ago, the order 19 of operations is important. What he meant by that
- 20 is again, instead of aggregating over treatment A,
- 21 aggregating over treatment B, making a comparison
- 22 for endpoint number 1, and then repeating that for

22

15 going to be taking a look at individual patient

17 personalized effects for individual patients.

18 That's the personalized medicine movement. But the

20 right now we have many. We measure efficacy. We

Now, tomorrow doesn't necessarily mean that

19 flip side of that is looking at the endpoints where

21 measure toxicity. We measure quality of life.

16 characteristics and be able to estimate

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1	we're going to measure any fewer, but somehow we're	1	minimal. Everybody is happy.
	going to have to compose that information in a more	2	
	reasonable way to try to make sense of it. It may		second category might be you have a positive chemo
	become a patient outcome rather than analyzing each		response but you've got some issues with peripheral
	of the endpoints in its own separate analyses.		neuropathy. Maybe below that there are negative
6	These were a few of the papers that came out		chemo responses with either small or large
	recently. The top one, again, you'll recognize,	7	
	Using Outcomes to Analyze Patients Rather Than	8	
	Patients to Analyze the Outcomes: A Step Towards	_	doesn't have to be defined this way. This is just
	Pragmatism in Benefit-Risk Evaluation.		somewhat of a generic example, but I'm going to
11			show you an example of something like this that was
12			applied elsewhere.
13		13	
	statistician in Europe, and is very related to		this is here are the five categories, and you have
	another statistic that I proposed called DOOR,		a control group. For the control group, the
	which is Desirability of Outcome Ranking.		patients fall wherever they fall in these five
17	You think about what those words mean.		categories. What are you looking for with the new
18			treatment?
	a patient level, the desirability of their outcome.	19	Well, I'm looking for some sort of northward
	And what I'm going to show you is a potential		migration of the patients relative to control, and
	adoption or adaptation of that to perhaps this		if I can get some northward migration in a
	area.		benefit-risk, a global sense, we're doing better.
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1	Now, I know some people from Washington	1	So the idea is can we get some sort of a shift
2	University, a colleague of mine, a friend of mine,	2	northward with treatment, and that's in a global
3	David Clifford, I heard him once say to a	3	sense, a benefit-risk totality sense.
4	colleague, he said, "Treat the patient, not the	4	There are a couple of different ways you can
5	disease."	5	analyze this. One is what we term the DOOR
6	So we're going to take this as somewhat of a	6	probability, which is essentially what Mike
7	perspective. And what if we evaluate the	7	described. This is the probability that if you
8	intervention by how well they treat the patient	8	randomly take a patient in the new experimental
9	rather than trying to divide and conquer on every	9	arm, you'll have a more desirable outcome than the
10	outcome? A systematic evaluation of the benefits	10	patient in the control arm.
11	and harms and a bit more pragmatism in the	11	This is a probability that is although
12	research question we're after.	12	it's perhaps new and you're not used to it, but
1 2			
13	Here's an example, and again, the naivete of	13	some of you treat patients. You have to make a
	-		some of you treat patients. You have to make a choice. Do I treat them with A, or do I treat them
14	Here's an example, and again, the naivete of	14	
14 15	Here's an example, and again, the naivete of it, but you might think of it this way. This is a	14 15	choice. Do I treat them with A, or do I treat them
14 15 16	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	14 15	choice. Do I treat them with A, or do I treat them with B? Are You asking me about what the hazard
14 15 16 17	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	14 15 16 17	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?
14 15 16 17 18	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	14 15 16 17	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
14 15 16 17 18	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.	14 15 16 17 18	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
14 15 16 17 18 19 20	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.	14 15 16 17 18 19 20	<ul> <li>choice. Do I treat them with A, or do I treat them</li> <li>with B? Are You asking me about what the hazard</li> <li>ratio is or what the p-value on the T test is?</li> <li>It would seem to me that one of the most</li> <li>intuitive things for you to ask is what's the</li> <li>probability the patient is going to be better off</li> </ul>
14 15 16 17 18 19 20 21	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	14 15 16 17 18 19 20 21	<ul> <li>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?</li> <li>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.</li> </ul>

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1	is what Pocock had proposed, the win ratio.	1	What I'm going to do is show you an analysis
2		2	that shows you how two treatments compare no matter
3	called partial credit, and I'll end with this		what you choose, and if you want to make a
	partial credit idea, but it takes a little while to		different choice than you, that's fine. I'll show
	sink in and a minute to explain.		you what your answer is.
6		6	
7	minute. Suppose you get your peripheral	7	side, you see the scores, 100 on the top, 0 on the
	neuropathy/chemotherapy outcome in four categories.		bottom. What I'm going to do is show you a plot
9	The top category, again, everything goes right.		where the partial credit for category 2 is on the
	Patient survives. They have good cancer and		vertical axis, the partial credit for category 3 is
	peripheral neuropathy outcomes. Bottom category is		on the horizontal axis.
	death, but a couple of layers in between, mild	12	If you decide you're an easy grader, all you
	problems in category 2, more severe problems in	13	got to do is survive and you win, this is
	category 3, but they all survive.		equivalent to mortality. I give 100 as long as you
15			survive. 100 is the score, then you're in the
16	scoring these categories. We're going to score it		upper right-hand corner.
	like an academic test. If you're in the top	17	
	category, you get 100. Everything went right,	18	of similar treatment effects when I compare the
	perfect score. You die, you get a zero. If you're		academic scores of treatment with control. So in
	in the middle two categories, you're going to get	20	D, what I see is a 5-point advantage for
21	partial credit.	21	category D. If you follow the line down, you'll
22	Now, I'm going to show you how you might	22	see the number that the red line in the middle
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1	think about the partial credit problem. Of course,	1	represents where two treatments would be equivalent
2	if you're doing a trial, you want to prespecify and	2	in this particular case. I didn't show you the
3	be transparent and all of that, and you can survey	3	exact this was an actual dataset in which we ran
4	expert clinicians in the room. It'd be interesting	4	this.
5	to see what you say, but I'm going to show you	5	The red line represents a line where if you
6	another idea, too.	6	had those combinations of partial credit, two
7	There's also ways you can get this from the	7	treatments would be completely equivalent.
8	patient. If you're giving quality of life	8	If you decide you want to score 100 to 100,
9	instruments from the patient, you could say well,	9	all you got to do is survive, you're in the upper
10	look, let me take the patients in the top category.	10	right-hand corner, and you get 5-point advantage
11	They have sort of an average quality of life score	11	for the new treatment. If you're in the lower
12	through what you've given them. Now let me look at	12	left-hand corner, you say, listen, he's a tough
13	the patients in the second category. They're	13	grader. Unless you survive with a good cancer
14	telling me what their quality of life is.		outcome and no peripheral neuropathy, you're
15	So maybe the ratio of the second category to		getting a zero. In that particular case, there's a
	the first category tells me about how to score that	16	6-point advantage for the control.
17	second category, straight from the patients.	17	,
18			well, listen, I'll score 100 for category 2 but a
19	The family of all the manual the many statement of the second statement and the statement of the second statement of the secon	1	zoro, in which case it's about 11 point advantage
			zero, in which case it's about 11-point advantage
	this. I'm going to say, well, fine, smart people	20	for new treatment, or you can compromise and say,
21	this. I'm going to say, well, fine, smart people can disagree, and who am I to say what your partial	20 21	for new treatment, or you can compromise and say, well, if I do 80/60, maybe it's about a 4-point
21	this. I'm going to say, well, fine, smart people	20 21	for new treatment, or you can compromise and say,

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1	This particular plot is constructed based on	1	that came up in Jen's talk and then in the talk by
2	the data that's collected from the trial, but it	2	the two statisticians.
3	allows you some personalized decision where you	3	Yes?
4	might face the case where you've got a 20-year-old	4	DR. DOUGHERTY: One of the assumptions that
5	woman who wants to make a different choice than a	5	I seem to hear and I am happy to be
6	75-year-old man. This may allow you for some	6	corrected was that the organizing principle to
7	personalized choices, if you'd like to do that.	7	the data structure would be time, the length of
8	I guess maybe I'll end there. Thanks.	8	time on therapy, et cetera, but not cumulative
9	(Applause.)	9	dose. There's been repeated studies, amongst those
10	DR. FREEMAN: It is about 2:10, I think. We	10	mine, that have clearly shown that the level of
11	had asked Dan for a break at 2:00 to 2:30, which		neurotoxicity is clearly dependent on the
	seemed a little premature to me, but even so, let's		cumulative dose of the agent and not necessarily
	go ahead with that. Maybe come back at 2:35, and		the number of cycles. Now, number of cycles does
	we'll dissect these three interesting and		impact the effect on the tumor, but here we're
	provocative talks.		talking about a toxicity and not an anti-tumor
16	(Whereupon, at 2:20 p.m., a recess was		effect.
	taken.)	17	The reason, just to clarify why I think
18	Q&A and Panel Discussion		cumulative dose is important, most chemotherapeutic
19	DR. FREEMAN: Okay, folks. Let's begin the		agents are quite polar, so they don't distribute
	final session of the day. If speakers and panel		into the adipose tissue. You're going to have a
	members can come up, we'll try and finish on time.		very high initial plasma level, and that's going to
	There's a lot of stuff going on which you can join		hit the ganglion, which again, I'm assuming that
	····· , · · · · · · · · · · · · · · · ·		
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1	in on. There's the Affordable Care Act hearings.	1	the ganglion in the peripheral endings are the
2	(Laughter.)	2	substrate of importance, with a much higher dose.
3	DR. FREEMAN: There's the Gorsuch	3	I was just looking for clarification in that
4	nomination. There's the Trump company in collusion	4	assumption.
5	with the Russians. The choice is all yours. Lots	5	DR. FREEMAN: I'm going to say let's go in
6	of fun in Washington this week.	6	the order of speakers, Jen to Mike to Scott, and
7	I do want to introduce two speakers or two	7	then the other two panel members if they wish to
8	participants on the panel who I have not yet	8	contribute.
9	introduced. That's Matt Jarpe, who's the associate	9	DR. GEWANDTER: I think that in what's been
10	vice president of biology of Regenacy	10	done in the literature, there was really only that
11	Pharmaceuticals in Boston and Ellen Smith, who is	11	the cumulative dose to chemotherapy hasn't been
12	an associate professor at the University of	12	used so far, but I do think that's a reasonable
13	Michigan School of Nursing from Ann Arbor,	13	endpoint to use. I agree with you that the
14	Michigan.	14	cumulative dose is more important than the time.
15	I think the way to do this this afternoon	15	Maybe we could think about doing some kind
16	because there is a lot to discuss is to begin by	16	of area under the curve that is in relation to dose
17	asking with respect to the previous three talks	17	instead of time. But I think when Mike was I
18	that you heard whether there are any questions	18	won't speak for Mike.
19	which fall under the heading of clarification	19	I'll let you answer what you were talking
20	questions. And then I'm going to go through	20	about with area under the curve.
21	somewhat systematically because there was an	21	DR. McDERMOTT: Feel free.
22	enormous amount of information, all of the issues	22	DR. GEWANDTER: Okay.
22	· · · · · · · · · · · · · · · · · · ·		,

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1	(Laughtor)	1 about paripharal pouropathy outcomes. But of
1	(Laughter.) DR. GEWANDTER: When Mike was using time	<ol> <li>about peripheral neuropathy outcomes. But of</li> <li>course, in the context of a randomized trial,</li> </ol>
2	-	
3	DR. McDERMOTT: Interpretation of the	3 you're going to be comparing your treatment
	question.	4 strategies, and the doses are going to be what the
5	DR. GEWANDTER: I think what he was	5 doses are.
	saying was that instead of just using a time to	6 You can build that into you can figure
	event or a cumulative dose to event, that	7 out if I can use lower reduce the doses somehow,
	especially depending on the grade or the severity	8 then I can study strategies that would reduce doses
	of neuropathy that you're looking for to be that	9 and may have better peripheral neuropathy outcomes
	event, potentially what's more meaningful is the	10 and maybe even with circularity have better
	continual trajectory upward and how long that	11 chemotherapy outcomes.
12	lasts.	12 I'm not sure I fully grasp I guess I'm
13	When I'm thinking about it, how long that	13 thinking in terms of randomized trials, trying to
14	lasts wouldn't just necessarily be until the end of	<b>14</b> figure out whether particular interventions work.
	chemotherapy but potentially long after	15 I'm not going to be adjusting for how things were
	chemotherapy is over. I think that from that	16 dosed. You get a randomized trial. You're going
17	perspective, that's why talking about time in terms	17 to compare randomized strategies.
18	of trying to instead of just having it be a one	18 DR. FREEMAN: Matt, any thoughts?
19	event of time to event, try to look at it over	19 DR. JARPE: I feel like I do understand the
20	time. And I'm not sure if there would be a way to	20 question, and the fact that the statisticians don't
21	somehow normalize to the cumulative dose instead of	21 makes me think I may not understand it.
22	time.	22 (Laughter.)
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1	DR. McDERMOTT: I couldn't imagine saying	1 DR. JARPE: I tried to think of visualizing
	DR. McDERMOTT: I couldn't imagine saying that better.	<ol> <li>DR. JARPE: I tried to think of visualizing</li> <li>this. If you were to plot cumulative dose versus</li> </ol>
	DR. McDERMOTT: I couldn't imagine saying that better. DR. GEWANDTER: Thank you.	<ol> <li>DR. JARPE: I tried to think of visualizing</li> <li>this. If you were to plot cumulative dose versus</li> <li>neuropathy severity on a graph, what's that going</li> </ol>
2	DR. McDERMOTT: I couldn't imagine saying that better.	<ol> <li>DR. JARPE: I tried to think of visualizing</li> <li>this. If you were to plot cumulative dose versus</li> <li>neuropathy severity on a graph, what's that going</li> <li>to look like? Say it's correlated, so you would</li> </ol>
2 3 4	DR. McDERMOTT: I couldn't imagine saying that better. DR. GEWANDTER: Thank you.	<ol> <li>DR. JARPE: I tried to think of visualizing</li> <li>this. If you were to plot cumulative dose versus</li> <li>neuropathy severity on a graph, what's that going</li> </ol>
2 3 4 5	DR. McDERMOTT: I couldn't imagine saying that better. DR. GEWANDTER: Thank you. DR. McDERMOTT: I think the other thing is	<ol> <li>DR. JARPE: I tried to think of visualizing</li> <li>this. If you were to plot cumulative dose versus</li> <li>neuropathy severity on a graph, what's that going</li> <li>to look like? Say it's correlated, so you would</li> </ol>
2 3 4 5 6	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	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 sexpect that to be a line more or less; is that fair
2 3 4 5 6 7	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	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 sexpect that to be a line more or less; is that fair to
2 3 4 5 6 7	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	<ol> <li>DR. JARPE: I tried to think of visualizing</li> <li>this. If you were to plot cumulative dose versus</li> <li>neuropathy severity on a graph, what's that going</li> <li>to look like? Say it's correlated, so you would</li> <li>expect that to be a line more or less; is that fair</li> <li>to</li> <li>DR. DOUGHERTY: Yes. I showed a number of</li> </ol>
2 3 4 5 6 7 8 9	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	<ol> <li>DR. JARPE: I tried to think of visualizing</li> <li>this. If you were to plot cumulative dose versus</li> <li>neuropathy severity on a graph, what's that going</li> <li>to look like? Say it's correlated, so you would</li> <li>expect that to be a line more or less; is that fair</li> <li>to</li> <li>DR. DOUGHERTY: Yes. I showed a number of</li> <li>slides earlier that showed the toxicity getting</li> </ol>
2 3 4 5 6 7 8 9	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	<ol> <li>DR. JARPE: I tried to think of visualizing</li> <li>this. If you were to plot cumulative dose versus</li> <li>neuropathy severity on a graph, what's that going</li> <li>to look like? Say it's correlated, so you would</li> <li>expect that to be a line more or less; is that fair</li> <li>to</li> <li>DR. DOUGHERTY: Yes. I showed a number of</li> <li>slides earlier that showed the toxicity getting</li> <li>greater and greater.</li> </ol>
2 3 4 5 6 7 8 9 10 11	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.	<ol> <li>DR. JARPE: I tried to think of visualizing</li> <li>this. If you were to plot cumulative dose versus</li> <li>neuropathy severity on a graph, what's that going</li> <li>to look like? Say it's correlated, so you would</li> <li>expect that to be a line more or less; is that fair</li> <li>to</li> <li>DR. DOUGHERTY: Yes. I showed a number of</li> <li>slides earlier that showed the toxicity getting</li> <li>greater and greater.</li> <li>DR. JARPE: Right.</li> </ol>
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1100	iropatity (CIIII) Inal Design Considerations	101a1 chi 25, 201
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1	toxicity start to emerge. And so	1 outcome, and if dose predicts outcome as you say,
2	DR. JARPE: Does the severity	2 then like you said, it would be sensible to make
3	DR. DOUGHERTY: a really small skinny	3 sure that you have that predictor be evenly
	person will be what that means is going to be on	4 distributed between treatment groups at the outset
5	therapy longer.	5 ideally. Whether that be on the basis of
6	Again, if you power it adequately so that	6 somebody's body weight or you know what their
7	you have equal numbers of small and heavier people	7 regimen is going to be, whatever it is, but you
8	in your study, you'll be fine. But if you haven't	8 stratify by that in the beginning and in the
9	got that partitioned out carefully, then you're	9 analysis so that you can reduce the variability
10	going to miss things.	10 that's associated with that. But I think that that
11	To me, the thing that is most predictive of	11 would be the way that you would deal with it in the
12	toxicity is the cumulative dose that the nervous	12 trial.
	system sees.	13 So it isn't that we would want to ignore
	-	C C
14	DR. JARPE: If you had a group that had just	14 that, but personally, I was talking mainly about
	chemotherapy and a group that had chemotherapy plus	15 measurement of trying to quantify somebody's
16	your preventative agent and you plotted that	16 outcome.
17	cumulative dose versus neuropathy severity, you	17 DR. FREEMAN: Gordon?
18	would expect them to cluster	18 DR. G. SMITH: Yes. You've really helped me
19	DR. DOUGHERTY: I think that's where you're	19 think about this, but now I'm more confused. I've
20	going to get your best possibility of seeing an	20 been kind of puzzling in my mind this dosing issue,
21	effect. It's not going to be the number of cycles	21 and it seems to me that an oncologist will have
	that each group took. It's going to be if you look	22 to help me that even within the confines of a
	Page 246	Page 248
1	-	
	at the cumulative dose for each group, one group is	1 clinical trial, if there's an effective agent at
2	at the cumulative dose for each group, one group is showing toxicity at one rate, and the other group	<ol> <li>clinical trial, if there's an effective agent at</li> <li>preventing chemotherapy, presumably there will be</li> </ol>
2 3	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.	<ol> <li>clinical trial, if there's an effective agent at</li> <li>preventing chemotherapy, presumably there will be</li> <li>fewer dose reductions because of adverse events in</li> </ol>
2 3 4	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	<ol> <li>clinical trial, if there's an effective agent at</li> <li>preventing chemotherapy, presumably there will be</li> <li>fewer dose reductions because of adverse events in</li> <li>the treated group.</li> </ol>
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2 3 4 5 6	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	<ol> <li>clinical trial, if there's an effective agent at</li> <li>preventing chemotherapy, presumably there will be</li> <li>fewer dose reductions because of adverse events in</li> <li>the treated group.</li> <li>What I've been puzzling in my mind is if</li> <li>that's the case, the cumulative dose in the</li> </ol>
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	ropainy (CIPN) I rial Design Considerations	March 25, 2017
	Page 249	Page 251
1	DR. GEWANDTER: You wouldn't prevent that	1 I feel like there's probably something there
2	from happening. That could be your outcome. So	2 that could be developed analogous to dose of the
3	you could make some kind of composite that would	3 treatment and the actual outcome with some type of
4	include the percentage of planned chemotherapy the	4 definition based on what might be capable of
	person received and something somehow estimating	5 demonstrating either separation for the treatments
	their toxicity or their neuropathy.	6 groups that's somehow clinically relevant.
7	DR. FREEMAN: I'm interested on the	7 It would have to be explored. To the extent
8	regulatory side because this is obviously a	8 that there are databases to start looking at that
	challenge. One can create a caricature where	9 once trials move forward, I think it would be
	there's a wonder drug. Patients fly through the	10 interesting to explore different things there.
	trial. They get their full complement of	11 So it sounds like that would be something
	chemotherapy, but they have a neuropathy because	12 akin to looking at a responder definition.
	they do do that, whereas patients who are on	13 Otherwise, when you have opposite movement that
	placebo drop out. They develop neuropathic	14 both mean the same thing in terms of good and/or
	features during the trial. And then six months	
	C C	15 bad depending on the direction, it can be very
	later when we've satisfied Lynn Howie's safety	16 challenging.
	concerns, patients are assessed at that time point,	17 DR. FREEMAN: James?
	and those that got active drug plus chemo have a	18 DR. CLEARY: I was going to say I'm not as
	worse neuropathy than those who were in the trial.	19 worried about the dose reductions of chemotherapy
20	I'm creating a caricature, and I know that.	20 and the cumulative dose. I agree. I think
	But I'm interested from the regulatory standpoint,	21 cumulative dose of chemotherapy does predict how
22	is there any way that one can create some kind of	22 bad the neuropathy will be, but if it's a
	Page 250	Dama 050
		Page 252
1	an endpoint which factors in both the amount of	1 randomized trial, I think we'll get the same on
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2	an endpoint which factors in both the amount of	1 randomized trial, I think we'll get the same on
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1	if you have an effective agent, you're able to then	1	afternoon.
	give more of the oxaliplatin. Whether you actually	2	Good. Okay. So
	have to, we'll find out in a while from the IDEA	3	DR. McDERMOTT: Can I make one quick comment
	trial that's going to be presented at ASCO this	4	on the last points that were being made about I
	year, I understand, with 3 months versus 6 months.		guess the one of the points is that the active
	Then you may have that problem.		treatment group, if I'm understanding correctly,
7	The other way of looking at it is a slope in		might get more of the chemotherapy that's
8	the curve over dose or time, and that way, you		prescribed because the anti-neuropathy agent is
9	could see if they are different there by dose. If,	9	working. Okay. So I finally got that straight.
10	in fact, you've given more dose to one arm, you can	10	I think that the analysis I was proposing,
11	check the slope per dose, and then see your	11	the joint rank, what would happen there is that
12	differences there.	12	people in the placebo group would then have more
13	When we actually set up the initial trial,	13	interruptions or discontinuations of chemotherapy,
14	we did think about all those different things, and	14	and so that would then perhaps properly reflect
15	since it was a negative study, everything just	15	what the benefit was of the anti-neuropathy agent.
16	lined up as it should. Now, if we saw that	16	They might have more neuropathy at the end,
17	neuropathy is the same but they got a whole big	17	but they would still in a sense have a better
18	dose, then we would have changed our opinion on	18	outcome. Now, the question is whether that's a
19	things, that it made a difference in that.	19	sensible thing or not, I suppose.
20	DR. FREEMAN: Okay. Any other Sharon,	20	DR. EVANS: Maybe I can comment on that,
21	yes?	21	too, because we've had this issue in other studies.
22	DR. HERTZ: I think given how early we are	22	If it turns out that that strategy, if you have not
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1	in thinking about these designs, when studies are	1	only a peripheral neuropathy advantage but then
	being conducted, even if they're commercial or		because they're able to tolerate therapy better,
	otherwise, it would be nice to take a look at some		that you may also have a better chemotherapy
	of these different approaches, either as secondary		advantage.
	or post hoc style analyses, and start to get a feel	5	When you start to think about these
6	for what's reflecting the outcomes that are	6	compositions that I talked about or Mike was
7	considered valuable and start to build that data to	7	discussing, sometimes you can even gain sample size
8	support what might be useful for a commercial	8	efficiency because the effects are happening in
9	development plan.	9	both dimensions. You get to add them up, and you
10	DR. LOPRINZI: That's actually a wonderful	10	see a totality of evidence. I not only have to win
11	idea, and there are a number of trials where	11	here, but I'm building in a composite information
12	there's a protocol and there's a manuscript at the	12	where I have advantages elsewhere.
13	end. Looking at that would be probably darn	13	So the advantages start to add up in
14	helpful, if I were the FDA and look and say, hey,	14	totality, so sometimes you can get smaller sample
15	what happened to these past trials and what made	15	sizes in those kinds of trials.
16	sense and what didn't, and throw out all the things	16	Now, if it turns out it's going the other
17	Loprinzi did, and then you got the answer.	17	way, you get a different problem because you're
18	(Laughter.)	18	weighing benefits and harms, and you really got to
19	DR. LOPRINZI: But that is a great idea.	19	figure out is the benefit I'm getting worth what
20	DR. FREEMAN: Any other clarifying	20	I'm giving up, and you have to think that through.
21	questions? Then what we will do is go through	21	DR. FREEMAN: I've got one clarification
	somewhat systematically what has been covered this	22	question mainly for the statisticians, and that is
22	Somewhat Systematically what has been covered this	22	

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1	the challenge of differentiate. To take a step	1	DR. FREEMAN: Scott, any additional
2	back, we've spoken about symptomatic treatment on	2	comments?
3	the one hand and disease-modifying treatment on the	3	(Dr. Evans gestures no.)
4	other hand. Clearly, at the extremes, these are	4	DR. FREEMAN: Anybody else, any other
5	two very discrete kinds of trials and perhaps even	5	comments on that? It is an issue and will be an
6	with discrete endpoints, but there is a gray zone	6	issue.
7	in between.	7	(No response.)
8	This is a challenge or has been a challenge	8	DR. FREEMAN: Okay. can you put the slides
9	in a number of diseases in which disease-modifying	9	up? These are the terminal 3 slides of Jennifer's
10	therapy has been attempted. Parkinson's disease is	10	talk, which really sum up, I think, the issues that
11	one of the best examples of this where at the end	11	are on the table, essentially going through a
12	of the study, it has often been very difficult to	12	clinical trial from start to finish.
13	know whether a treatment was disease-modifying or	13	The first question is who should enter the
14	whether it was symptomatic.	14	clinical trial. And there was some discussion this
15	This could well be the case over here, and	15	morning about end stage, metastatic, treatment
16	it obviously is a major issue as far as labeling,	16	
17	what is a drug going to be called. And that never	17	little bit as we move forward in terms of
	really came up in any of the two of your	18	developing a final work product.
	discussions, and it is a concern. Just knowing	19	Any comments on the first, maybe two,
	about the couple of drugs that are circulating at	20	
	the moment, they may be symptomatic treatments, and	21	multiple cancer types?
22	how do we address that issue?	22	DR. RICHARDSON: Well, I think you have to
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1	The obvious thing is to say, well, what	1	be very disease specific. Essentially, just
2	happens when you stop the drug, but it's more	2	speaking in the myeloma space, newly diagnosed
3	complicated than that, I think.	3	patients have a very different profile than those
4	DR. McDERMOTT: I have a little bit of	4	who are multiply relapsed. And as Jim and I were
5	experience with this in the Parkinson's world, and	5	talking about with Joanna earlier, now in myeloma,
6	if you're familiar with some of those delayed	6	our patients are living 10, 15, 20 years where
7	starts sorts of studies, it's just inherently very	7	before they lived 2 or 3 if they were lucky. We're
8	difficult to try to get at mechanism in a clinical	8	moving into a very different era of designing new
9	trial. That's just number one.	9	trials.
10	So you try these manipulations of stopping	10	This is one of the reasons, for example, we
11	drug to see what happens to people after you	11	did our initial assessment in bortezomib newly
12	withdraw. Do they maintain a benefit over time,	12	diagnosed, untreated naive patients because you
13	for example, and there are just so many	13	essentially couldn't that was the cleanest
14	difficulties with doing that.	14	signal you could get to best understand what was
15	Probably what I would anticipate regulators	15	going on.
16	would tell you is that you need to have some	16	The other thing is that, obviously, you've
17	evidence not only clinically but on a biomarker	17	got combination therapies and how they impact. And
18	level that tells you something about mechanism in	18	again, speaking to the myeloma space, we have to be
19	order to try to get at that issue. I don't know	19	very treatment specific because the interaction
20	that it's going to be easy to get at clinically,	20	between, say, an antibody and our IMiDs and our
21	especially in a condition like this with so many	21	proteasome inhibitors is quite different to that,
		1	

22 for example, of just the IMiDs and proteasome

22 different treatments going on at the same time.

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1	inhibitors alone.	1	Now, if you have a drug that you don't know
2	So again, there are a lot of variables, but	2	if it's safe to give, et cetera, et cetera, how
3	I think in our disease, we will be thinking	3	safe it is you think it is, but then I think a
4	primarily of newly diagnosed, relapsed, and then	4	pilot evaluation for safety in the metastatic
5	relapsed refractory.	5	disease setting looking for neuropathy makes some
6	I thought the FDA's position that you come	6	sense to me. But trying to get the end
7	into the end stage situation, for us in myeloma any	7	neuropathy that's for the safety aspect of it,
8	way, is probably not ideal. I think you've got	8	for the end neuropathy endpoint, I think you really
9	surround sound with so many things going on, and as	9	need a more adjuvant setting. It's much, much
0	you look to risk factors for CIPN, renal	10	cleaner a process of things.
1	dysfunction being one of them, as our patients get	11	The other part of the thing on cancer type,
2	sicker, their renal dysfunction tends to worsen.	12	on our other study whether a person had pancreas
3	Frankly, we'd want to be in the upfront space.	13	cancer or colon cancer, if they're both NED and
4	The good news in the FDA is we have a	14	likely to go through it, I don't know that the
5	fabulous relationship with our division. There's	15	cancer type I probably wouldn't mix that with
6	Anne Farrell and colleagues. I'm not sure if it	16	myeloma because those are too disparate, but
7	would come under her or go somewhere else, but the	17	otherwise, it's really the effect on the drug that
8	fact is they understand the disease extremely well	18	you're looking at.
9	so we're well placed, the best place where we	19	Just like our nausea and vomiting studies,
0	should be, speaking specifically for us.	20	if they're getting FOLFOX, we don't care what it's
1	DR. FREEMAN: What about the solid tumor	21	for. We just want to see the effect of the drug
2	people? Yes, Charles?	22	and if we can counteract that effect of the drug.
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1	DR. LOPRINZI: If you have safe stuff,	1	DR. DOUGHERTY: I totally agree with Charles
	calcium magnesium, which we've given and that sort		and Paul. You want a group that is otherwise
	of thing, then and we actually didn't use either		treatment naive.
	localized or metastatic. We used NED. A person	4	
	had to have NED is no evidence of disease.		such a crazy, chaotic clinical course, don't know
6	So they had primary colon cancer or rectal		if I would start with Velcade. That's a tough
	cancer, didn't really matter which there you can		agent to deal with. But the adjuvant setting,
	say they're different, but it's basically the		platinum, taxane-type therapy, those folks are
	same or they could have had metastatic disease,		going to go through a pretty steady clean
	which was completely resected.		chemotherapy regimen, and it would probably be the
.1			easiest group to target.
	treated, not likely to recur during the six months	12	DR. RICHARDSON: If I may, Pat, just comment
	of chemotherapy, less than 5 percent chance of		on that, though. I think we're seeing greater
	recurrence during that period of time, and so you		stability now with three-drug, four-drug regimens,
	have a relatively healthy group of people, and that		and we're seeing extraordinarily long survivals. I
	way, you get your best endpoint for there.		think we're a more stable population than perhaps
.7	If you use metastatic disease, then they've		we were.
	had chemotherapy before, although some are newly	18	
		1-0	

- But you're right, if you're going in with 18
- 19 your real toxicity driver, which in our case would
- 20 be the bortezomib, basically the good news there is
- 21 you know what you had before, it's been highly well
- 22 studied, and it's well validated. So your

19 diagnosed metastatic, but you don't know if their

21 months of therapy, and you're not going to be able

20 cancers will respond. They might fail over two

22 to get your endpoint very well.

1100	iropatity (CIPN) I riai Design Considerations		March 25, 2017
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1	comparisons can be helpful.	1	cancer, we'll use 12 in a curative setting. So
2	I think also frankly, that as we were	2	just being aware that even though it's the same
3	discussing earlier, some of our alternative	3	chemo, there might be a different number of cycles.
4	treatments unfortunately have different toxicities	4	In a trial design, I would say this is a
	that made them just as challenging. We probably	5	patient who is getting, say, FOLFOX, never been
	will remain bortezomib focused in our work in		treated before, and is going to get a planned
7	myeloma for neuropathy, but with the understanding,		12 cycles or however many cycles.
	to your point, that we want a relatively stable	8	
	population.	_	question since you mentioned that. There's been
10	DR. DOUGHERTY: Is that time to initial		some discussion initiated by Patrick about cycle
	transplant now fairly constant, or is that still		versus a cumulative dose.
	Very	12	, , , , , , , , , , , , , , , , , , ,
13	DR. RICHARDSON: It's a great question. You		accumulated dose? Are there cutoffs? Is there a
	see, the confounder we have in myeloma is that		point and perhaps Guido can comment on this
	alkylators following neurotoxic therapies now have		better than anybody.
	their own intrinsic neurotoxicity that we see,	16	
	which points to this cumulative effect that's so		cumulative dose being so critical, is this a linear
	interesting, probably free-radical-mediated. Who	18	effect?
19	knows?	19	DR. CLEARY: It's definitely a linear effect
20	In fact, transplants being pushed back.	20	in that the more cycles of chemotherapy he has, the
21	We're becoming more and more like diffuse large B	21	higher the amount of toxicity. I think it makes
22	cell where with the advent of antibodies,	22	sense that the higher the cumulative dose, the
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	Page 266		Page 268
	particularly daratumumab, we've basically got		higher the rate of toxicity, but I haven't really
2	particularly daratumumab, we've basically got R-CHOP rituxan. So basically RVd dara, for		higher the rate of toxicity, but I haven't really seen that studied in that way.
2 3	particularly daratumumab, we've basically got R-CHOP rituxan. So basically RVd dara, for example, is probably going to be R-CHOP rituxan or	2 3	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
2 3	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.	2 3 4	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
2 3 4 5	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,	2 3 4 5	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
2 3 4 5	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.	2 3 4 5	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
2 3 4 5 6 7	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	2 3 4 5 6	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.
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1	on that issue, which now would be a good time to	1	proteasome inhibition and IMiD, you can also see it
2	flesh that out.	2	flare. So it's not that one excludes the other, if
3	Joanna and	3	you see what I mean.
4	DR. BRELL: I'll just make one comment that	4	My other comment would be to your point
5	hasn't been made yet, is it depends on what our	5	about cumulative dose. In myeloma, we see with
6	secondary outpoints are as to whether or not we use	6	thalidomide that there's a cumulative effect.
7	patients who are having adjuvant therapy with all	7	Interestingly with bortezomib, it doesn't appear to
	their tumor resected or with metastatic disease.	8	
9	Because if we need that tumor safety issue, testing	و	if you haven't had neurotoxicity that's of note by
	a group of adjuvant patients, we won't get to		then, generally speaking, you don't see it.
	measure any disease outcomes.	11	
12	If we don't want to wait for disease-free		see, for example, in light chain disease highly
	survival or overall survival, at least tumor		responsive patients who are a little bit more prone
	recurrence, time to progression, we won't get any		to neurotoxicity versus classic isotypes like IgG
	of that with an adjuvant therapy. But if we use an		or IgA. And these are real interesting nuances
	early metastatic cohort such as the colorectal		that are actually quite tricky to tease out, but
	cancer patients getting their first metastatic or		they appear to be quite real.
	second metastatic regimen, we could get those other	18	DR. FREEMAN: Does that in any way relate to
	tumor outcomes without having a 20-year trial.		the likelihood of an underlying perhaps subclinical
	DR. CLEARY: Just following that, I agree		neuropathy?
20			
	with that. And maybe using the metastatic patients	21	-
22	for those early outcome measures and also for the	22	really have the numbers to comment on that for
	Page 270		Page 272
1	biomarker data we were talking about this morning.	1	those patients who've been properly studied, but
	So maybe on the metastatic patients, you could do	2	
	the biopsy, just very small trials, and then when		other words, there must be an inflammatory profile
	you want to do a large phase 3, you can move into		perhaps with a light chain patient.
	the adjuvant setting.	5	There's definitely biological difference.
6	DR. RICHARDSON: I think you still have to		There's definitely biological difference.
			Light chain natients for example, are more prone
	he very careful though because you could lose		Light chain patients, for example, are more prone
	be very careful, though, because you could lose	7	to have kidney injury, obviously, which may change
8	your signal in that end-stage population for all	7 8	to have kidney injury, obviously, which may change that as well. But moreover, they tend to be more
8 9	your signal in that end-stage population for all the biological reasons that we've heard about	7 8 9	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
8 9 10	your signal in that end-stage population for all the biological reasons that we've heard about because your interventions to your point,	7 8 9 10	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
8 9 10 11	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	7 8 9 10 11	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
8 9 10 11 12	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	7 8 9 10 11 12	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.
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110	aropathy (Chris) That Design Considerations		11ui cii 20, 201
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1	can I be pragmatic in answering a real-world	1	broad and narrow later, now with great caution,
2	question.	2	that there are consequences to selection along the
3	Typically in trials, we're a bit more	3	way. But those types of things are becoming
4	focused on biology and mechanisms of action and can	4	possible, and they're sort of thought leaders about
5	I show an effect in earlier phase trials. We're	5	how to deal with that.
6	supposed to get a bit more generalizable and	6	DR. FREEMAN: Go ahead.
7	pragmatic as we move to late phase trials, but	7	DR. HAROUTOUNIAN: I just wanted to raise
8	there's also been a question about even whether our	8	one point that I think we didn't consider when
9	late phase trials are pragmatic enough.	9	thinking about adjuvant setting or maybe metastatic
10	Califf was trying to move us in that	10	setting for, for example, oxaliplatin used in
11	direction. I'm not sure we're going to continue to	11	peripheral neuropathy, is that in the adjuvant
12	move in that direction with him gone.	12	setting, patients would typically get their
13	The idea behind the pragmatism is you get	13	12 cycles of FOLFOX, which is very standardized.
14	closer to addressing the question, and if you throw	14	But in the adjuvant setting, patients may continue
15	this into clinical practice, what's going to	15	the 12, and then as palliative treatment, some
16	happen? And if you start excluding people, whether	16	patients get additional rounds of chemo.
17	it's for diabetes or whatever, and they're a big	17	I think this is something that may introduce
18	part of the population, then you're not addressing	18	some noise if we're to focus our initial efficacy
19	the question of what happens if you throw it into	19	study in the metastatic patient setting.
20	clinical practice.	20	DR. BRELL: Like we said, depending on what
21	That's a little bit different than if you're	21	the other outcomes are, and so somewhere, we have
22	the drug company. You're just trying to somehow	22	to make sure there's no effect on the cancer. I
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1	get on the market, but then if it gets on the	1	don't think we're trying to build one phase 3,
2	market and gets thrown out there and you've got no	2	tell-all trial right now. I think we're
3	data on anybody who's in these subgroups of	3	speculating what it could be, but we're probably
4	patients, that's not a great thing either.	4	going to have to start thinking about some smaller
5	There's one other idea that can be thought	5	trials to get to where we can design the phase 3
6	about for some of these cases, and I just got an	6	study.
7	email at the break from a colleague of mine. I'm	7	DR. FREEMAN: That's a good working
8	sitting on a DSMB for a trial that was an adaptive	8	approach.
9	enrichment trial. They start out with two cohorts	9	DR. GEWANDTER: I guess this question is
10	of patients and play the trial forward.	10	really for Sharon, or maybe Lynn really needed to
11	There's some advance methodologies in place	11	be here, too, for this.
1		1	

12 such that you evaluate how that's going, and if it

13 turns out both cohorts are looking promising, you

14 continue with both cohorts, but if it's only 15 looking promising for one cohort, then you drop one 16 off.

17 Now, there's a selection process there,

- 18 which increases -- has a multiplicity consequence
- 19 to it and you have to do some fancy adjustment for
- 20 it. And there's a lot of adaptive design integrity
- 21 things to make sure you've got it under control.
- 22 But there may be opportunities where if you start

12

15

18

If we did the first study in the metastatic

16 considered -- would a phase 2 study be good enough 17 for that endpoint, and then it wouldn't matter what

the result was on the neurotoxicity, and then move

13 setting and there was no demonstration of efficacy

14 on the neurotoxicity, but it showed that there was

no effect on the cancer, I don't know if that's

19 to efficacy in the adjuvant setting where it's

22 you move for efficacy?

20 cleaner? Would that be reasonable, like if your

21 goal in the first study is really safety, and then

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1	DR. HERTZ: That's a very good question.	1	that would be phase-1-type studies where you don't
2	The input we get from oncology about the concern of	2	look at efficacy. Efficacy is not the point in
3	reducing long-term survival through the use of	3	phase 1 treatment trials. So this would be modeled
4	interventions for CIPN, we don't know yet exactly	4	after a phase 1 study.
5	what would allay those concerns.	5	AARC, there's a publication, I don't know
6	I think it's possible the scenario that you	6	how many years back now, but it talked about really
7	just described could be one way to do that. It's	7	the basics of how you would design each of these
8	hard to say. I guess we would have to look at what	8	studies. They have that for therapeutic drugs for
9	the agent was, what the risk was of it interfering,	9	cancer, and then they also have where symptom
10	and what the data were based on that, how long	10	management drugs could fall in as well. It might
11	patients were followed, and whether that plus other	11	be wise for us to look at some of that and think
12	evidence was enough to allay that concern. But	12	about this as a phase 1.
13	that's one of the biggest areas of the consults	13	DR. FREEMAN: Let's move on to the
14	that we get from the oncologists, is the initial	14	one and we're moving thoroughly one or more
15	population and the risk for changing long-term	15	multiple chemotherapy types, agents, arrangements.
16	survivability, so we would have to look at all	16	Now, the take-home message that at least I
17	that.	17	got is you want to be homogenous over here. You
18	Most of my answers today are going to be we	18	want to use one agent, and even within class, there
19	don't know because we don't know. We don't have a	19	are sufficient variations in the toxicity, the time
	ton of experience. Pam described to you what we've		course of the chemotherapy-induced peripheral
	been seeing and where we're trying to use related		neuropathy that one shouldn't even do a study of
22	experience to help guide programs, and obviously,	22	drugs within the same class.
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1	-	1	-
	we're working closely with the oncology divisions,	1	Is there any nuance to that at all? Is
2	we're working closely with the oncology divisions, but the answers are not yet in. But it sounds like	2	Is there any nuance to that at all? Is there any way the statement that I made should be
2 3	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.	2 3	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
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2 3 4 5	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	2 3 4 5	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.
2 3 4 5 6	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	2 3 4 5 6	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.
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1	doing that.	1	together because I think they're fairly
2		2	similar patients who either have a subclinical
3	[indiscernible] ketamine, and didn't say it had to	3	neuropathy because they are predisposed to,
4	be any particular one drug.	4	prediabetic patients, diabetic patients, patients
5	Ellen, you did a taxane or oxaliplatin, so	5	who have received HIV neurotoxic therapy,
6	you had the two there. That makes a bunch of sense	6	chemotherapy, patients who may have drunk excessive
7	for me, and you looked at a subset analyses and	7	amounts of alcohol, patients who have a preexisting
8	that sort of stuff, but you used the whole thing	8	neuropathy, whether it's diagnosed using standard
9	from there.	9	clinical neurophysiology or it's Patrick's pegboard
0	DR. FREEMAN: I'm sorry to interrupt, but I	10	test.
.1	want to be sure. Are you talking about acute	11	There really were two themes over here. The
2	treatment in disease modifying, or are you talking	12	one that I think both Guido and I espoused, that is
3	about chronic treatment?	13	to say that not just that we don't want them in the
4	DR. LOPRINZI: The first part, we talked	14	trial, but that we actually do want them in the
5	about the adjuvant prevention	15	trial because these are the patients that are going
6	DR. FREEMAN: Yes, yes.	16	to actually show the chemotherapy-induced
7	DR. LOPRINZI: and the second one is	17	peripheral neuropathy, and it's going to make our
.8	treatment of established.	18	study have a much smaller SOP size, perhaps even
.9	DR. FREEMAN: So are we talking about	19	have a greater effect size if the drug works,
20	symptomatic treatment of an established neuropathy?	20	whereas the view of Charles and others was that we
21	DR. LOPRINZI: Yes. People are done with	21	exclude those patients.
22	chemo	22	It would be nice to flesh this out a little
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1	DR. FREEMAN: Ellen Smith's study?	1	bit, have this controversy at least have a little
2	DR. LOPRZINI: Yes.	2	bit more flesh to it.
3	DR. FREEMAN: Okay.	3	DR. LOPRINZI: Let me clarify. I don't
4	DR. LOPRINZI: And others along that way.	4	think I said that you necessarily have to exclude
5	So done with their neuropathy done with their	5	those patients. We didn't exclude them. They
6	neurotoxic chemotherapy, ideally out for three or	6	could have had diabetes, but they couldn't have
7	four months or longer, and then they go ahead, and	7	neuropathy associated with that. But we didn't
	you're treating that established neuropathy only		
8	you're treating that established neuropathy only	8	exclude those, and we didn't exclude people who
	because the patient's having problems, which could		exclude those, and we didn't exclude people who were overweight or who didn't exercise.
9			
9	because the patient's having problems, which could	9 10	were overweight or who didn't exercise.
9 10	because the patient's having problems, which could be numbness, tingling, pain.	9 10 11	were overweight or who didn't exercise. DR. FREEMAN: Okay. Then I suppose the
9 .0 .1 .2	because the patient's having problems, which could be numbness, tingling, pain. DR. FREEMAN: We're not so much, in fact,	9 10 11 12	were overweight or who didn't exercise. DR. FREEMAN: Okay. Then I suppose the question is, if we say they have neuropathy and
9 10 12 13	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	9 10 11 12 13	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?
9 10 11 12 13 14	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	9 10 11 12 13	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
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AC Nei	1 11ON - Chemotherapy-Induced Peripheral iropathy (CIPN) Trial Design Considerations		March 23, 2017
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	Page 285		Page 287
1	oncologist, if they have neuropathy it's because	1	group. You may even want to enrich for that group
2	they say I've got numbness, tingling, shooting,	2	because they're more predisposed. You're likely to
3	burning pain. If I miss a reflex on somebody, that	3	get the occurrence of neuropathy with your
4	doesn't mean they have neuropathy.	4	treatment so you actually have a robust group to
5	DR. FREEMAN: I understand. There are	5	test. Otherwise, just stratify for it and let it
6	fairly simple tests from Patrick's test to testing	6	sort itself out.
7	reflexes	7	The overt neuropathies, diabetic, alcoholic,
8	DR. LOPRINZI: Yes, but	8	HIV I think we had this discussion earlier if
9	DR. FREEMAN: tuning fork, something	9	they're already symptomatic and they have symptoms
10	that's not too elaborate. But the average	10	that are going to interfere with your expected
11	clinician would say, yes, there's vibration loss.	11	measurement outcome, you're creating a real
12	There's no pain. There's not even any numbness,	12	complication.
13	but there's I'm trying to make this discrete for	13	So if they have those as risk factors,
14	everybody, and in doing so, I'm creating a	14	diabetes, alcoholism, and HIV, I wouldn't
15	caricature. Vibration sense is decreased.	15	necessarily kick them out, but if they are overtly
16	Patrick's pegboard test or feeling the bumps is	16	symptomatic, then you're probably just creating a
17	decreased.	17	large problem.
18	So these patients we would say have a	18	DR. FREEMAN: That's I think the point made
19	clinical neuropathy, not even a subclinical	19	very nicely by Jen and Sharon.
20	neuropathy but a clinical neuropathy, why not have	20	DR. HERTZ: As a neurologist, I'm a little
21	them in the trial?	21	distressed by some of what we're saying because
22	DR. DOUGHERTY: Let me clarify. The	22	what could end up happening is a very different use
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1	patients that we've tested and detected what I'm	1	of terminology here. Using no evidence of
2	calling subclinical neuropathy, if you handed them	2	neuropathy in one setting may have just not looked
3	a neuropathy questionnaire, you would come up with	3	for and detected evidence of neuropathy in another.
4	zero. You would basically conclude based on	4	I think that as we think about this, and
5	talking to them and in cursory examination,	5	particularly as we think about it, whether we
6	pinprick is not decreased. They usually don't have	6	decide to include people with concurrent neuropathy
7	any change in grip strength or gait.	7	or not, it might be helpful to define what is that
8	It's only when you have them do something	8	going to be. Is it going to be there's nothing on
9	really fine, really standardized that you can now	9	somewhat coarse level testing, or is it really
10	pick up. But if they just walked into your clinic,	10	nothing in terms of what we define as the baseline?
11	you would say this patient does not have	11	I would argue that your asymptomatic
12	neuropathy. And that's for what is disease tumor	12	diabetics probably all had neuropathy if they had
13	related, and we've detected this, as I said, both	13	long-standing type 2, and I could probably find it
14	in patients where you would expect it, non-small	14	with the right set of tools. But that's okay
	cell lung, myeloma, but as well in colorectal where		because they met a certain criteria, and up to that
16	you wouldn't expect this to occur; even head and	16	criteria, you did not find an effect.

- 17 I don't know that there needs to be one
  - 18 specific answer about that. My request is that we
  - 19 think about how to define, in terms that we can all
  - 20 agree on, the presence or absence of neuropathy in
  - 21 people who either have clear risk factors, like
  - 22 diabetics or other exposures, and people who are

18

17 neck cancer patients have subclinical neuropathies.

20 give you a pegboard test. If you show two standard

21 deviations out of the expected norm for your age,

22 you're excluded. That's probably an important

19 your cohort if you're going to say we're going to

So you may be wiping out a whole bunch of

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1	simply at risk for conditions that could. But I	1	let's hope randomization takes care of it.
2	think that understanding whether those conditions	2	I think there are ways of dealing with it,
	have an effect or not could be very difficult to	3	but the advantage of that is that if our
4	discern if we're not defining the baseline the	4	chemotherapy is neurotoxic and if a predisposing
	same.		neuropathy really makes the neurotoxicity manifest
6	DR. FREEMAN: Yes, Bob?	6	and our drug works, we will see. We will be able
7	DR. DWORKIN: So, Roy, I want to see if I	7	to test our drug.
8	understand what I think you're proposing. It	8	DR. DWORKIN: I came prepared with a backup
9	sounds like you're saying if a patient with	9	question because I thought you'd have an answer.
10	diabetes has subtle signs of peripheral neuropathy	10	It seems if we accept that, then there's another
11	but no symptoms, you would include that patient.	11	problem, which is it means your endpoint for the
12	Presumably, you mean in a trial where the	12	CIPN trial has to be limited to symptoms, and we
13	endpoint is a symptom measure like a patient-	13	heard this morning that there is great interest at
14	reported outcome of symptoms but not signs as an	14	the agency in function.
15	endpoint because they've already got subtle signs	15	I just wonder do we want to do large
16	from their diabetes.	16	challenging trials where our endpoint is limited to
17	As I was struggling to understand this, I	17	patient-reported outcomes, and we can't look at
18	guess that sort of makes sense. They've got subtle	18	signs and we don't look at function because the
19	signs of DPN, no symptoms of DPN, and you're going	19	diabetics in the trial already have subtle signs.
20	to do a trial to look at symptoms of CIPN. On the	20	DR. FREEMAN: I would say I wouldn't
21	face of it, that sounds reasonable. However, I'm	21	necessarily accept that premise because I would say
22	not a neurologist.	22	that if we stratify by the presence of diabetes and
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	-		
1	If we're going to do some kind of prevention		we have cutoffs, and we say that we're going to
	trial that could last 3 to 6 months, isn't it		randomize them, then we can look at anything. I
	possible that the diabetic with subtle signs at		don't think you are precluded from looking at signs
	baseline develops symptoms of diabetic peripheral		or symptoms or function because of randomization and stratification.
	neuropathy over the next six months, that then	5	and stratification.
	totally confounds your ability to assess symptoms	-	Quide you had come viewe. What do you
1		6	Guido, you had some views. What do you
	of CIPN?	7	think?
8	of CIPN? I would still vote for excluding even the	7 8	think? DR. CAVALETTI: I think the major issue,
8 9	of CIPN? I would still vote for excluding even the subtle signs DPN patient because ultimately in a 3-	7 8 9	think? DR. CAVALETTI: I think the major issue, again, is what we decide to use as a threshold to
8 9 10	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	7 8 9 10	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
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8 9 10 11 12 13 14 15 16 17 18 19 20	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	7 8 9 10 11 12 13 14 15 16 17 18 19 20	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

22 change significantly in six months, and if it does,

22 factor, we need to start discussing which of those

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1	neuropathies we don't want to have into the study.	1	cancer has peripheral neuropathy, clinical
	For diabetic patients, I'm sure that we can		examination, 2 out of, I don't know, 100 patients,
	randomize because it's a bit difficult for me to		or neurophysiology, 50 out of 100 patients. That's
4	talk about diabetic neuropathy because it's very		a critical issue, what we want to use to say this
	hard right now to find patients with diabetic		patient has neuropathy.
	neuropathy in Italy, for instance, because our	6	DR. FREEMAN: Before we move on, maybe one
	diabetologists are so aggressive that they just	7	other detail, which I think is worth resolving, and
	have 111 glucose blood level, they would be killed		that is and again, let me make the extreme case
	by the diabetologist. So it's difficult find to		just for discussion patient who has received
	patients with a real diabetic neuropathy right now,		neurotoxic therapy previously, a taxane, a platin,
	but they are frequent, so you can randomize.		but even with Guido's most exquisite testing, does
12	HIV patients, probably they are not so		not have evidence of a neuropathy, do we exclude
13	frequent in this population, so maybe we could stay		those patients from these kinds of trials, and if
	on the safe side and exclude those patients. There		so, why?
	would be probably one or two per trial. But then	15	DR. LOPRINZI: That's for me?
	we have a lot of other tricky conditions, alcoholic	16	
	patients, which is the definition.		aiming it directly at you.
18	So we need to set up a clinical or an	18	
	instrumental or a patient-reported outcome again to	19	
	say those patients have a neuropathy that	20	
	necessarily excludes those patients from the trial.		may be that they got some neurotoxic chemotherapy
22	In my mind, it probably should be discussed		and it's going to be predisposed, and therefore,
	Page 294		Page 296
1	case by case. I understand that is not the best	1	they only need a little bit more, but that could be
	case by case. I understand that is not the best way to approach a clinical trial protocol, of		they only need a little bit more, but that could be the same argument as the diabetic, et cetera,
2	-	2	
2 3	way to approach a clinical trial protocol, of	2	the same argument as the diabetic, et cetera, et cetera.
2 3 4	way to approach a clinical trial protocol, of course, but I would accept the cost to admit all	2 3 4	the same argument as the diabetic, et cetera, et cetera.
2 3 4 5	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	2 3 4 5	the same argument as the diabetic, et cetera, et cetera. On the other hand, there are some people who
2 3 4 5 6	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	2 3 4 5 6	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-
2 3 4 5 6	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	2 3 4 5 6	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
2 3 4 5 6 7 8	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.	2 3 4 5 6 7 8	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
2 3 4 5 6 7 8 9	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	2 3 4 5 6 7 8 9	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
2 3 4 5 6 7 8 9	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	2 3 4 5 6 7 8 9	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
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1	would exclude those patients because probably they	1	add to that, if I may, is just the whole construct
	are resistant. They are probably lucky enough to		that in our myeloma experience, we actually looked
	be protected by chemotherapy-induced neurotoxicity.		at disease characteristics. In other words, we did
	We don't know why. But they would exclude for that		a sort of biomarker analysis of the tumor in terms
	reason.		of certain gene expression profiles, and certain
6	DR. DOUGHERTY: That's the answer I thought		
7	Charles was going to give.		responses were associated with higher risk of
8	DR. CAVALETTI: Exactly, but we agree.		neuropathy.
9	DR. LOPRINZI: That's what I tried to say.	9	So looking not just at the genotype of the
10	(Laughter.)	10	patient but also the genotype of the tumor is
11	DR. FREEMAN: While we're talking about	11	recommended because essentially, we've already
12	this, perhaps this might be the time, although it	12	hinted at that, that there's a relationship between
13	wasn't discussed earlier, biomarkers, genetic	13	disease biology and neurotoxicity, and that we find
14	predisposition, is there anything new that you can	14	quite informative actually with the work we did
15	add to this discussion, and should this be a factor	15	with the bortezomib study.
16	in any chemotherapy-induced peripheral neuropathy	16	DR. FREEMAN: Any additional comments so
17	discussion?	17	far?
18	DR. HAROUTOUNIAN: There have been a few	18	(No response.)
19	papers on risk factors, sodium channel	19	DR. FREEMAN: We've got roughly another 10,
20	abnormalities, TNS transfers, et cetera. It	20	15 minutes left. We are not going to cover
21	probably makes sense to have those as additional	21	everything, but this is what the final summing up
22	risk factors as we would collect some demographic	22	session is. I think a lot of these details, I'm
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	-		
	factors. I don't see reason as an explorative type		not sure they'll need to be covered in much detail
2	factors. I don't see reason as an explorative type of outcomes, why not collect them if there is some	2	not sure they'll need to be covered in much detail again.
2 3	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	2 3	not sure they'll need to be covered in much detail again. Concomitant treatments for neuropathy, I
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1	stopped it because there are stories both ways.	1	anxiety because there's not really any good
2	Where we've kind of been before, if there's		evidence that they have analgesic effects. There's
	no proof that it's beneficial, then we haven't		some, but weak. That way the patients who are
	tried to exclude it. If they're taking something		depressed or have generalized anxiety disorder are
	for established neuropathy but then I don't		allowed treatment, but you exclude the dual
	allow them on with neuropathy like gabapentin. If		reuptake inhibitors.
	they're taking an antidepressant because of	7	DR. LOPRINZI: If they were taking regular
	depression but not for neuropathy, then we've not		Tylenol because they had arthritis, then you could
	excluded them before.		say, well, they're taking something for pain. I
10	So I wouldn't be taking people who have		don't feel terribly strongly on it one way or the
	neuropathy, so it wouldn't be neuropathy, but if		other.
	you're taking drugs that might affect neuropathy, I	12	DR. FREEMAN: Others, any other comments on
	don't feel quite as strongly about that aspect.		this? And here, I think, Daniela, you were one of
			-
	It's not like those drugs work that well that we		the people in the audience who's thought more about
	know about.		this than most of us. Any thoughts on these
16	DR. LAVOIE SMITH: Well, with maybe the		eligibility criteria, what have you done in your clinical trial?
	exception antidepressants given that we know that		
	one might have an effect. And it depends upon the	18	DR. DASTROS-PITEI: I was wondering about
	drug that we're testing, so the other thing to		the comments because some of these patients, we
	consider is drugs that would have a combined		know that many of the other drugs have not shown to
	synergistic side effect profile that might be contraindicated.		have effect apart from duloxetine in a relatively
22		22	small study, which may be more of an argument that
	Page 302		Page 304
1	I'd be a little bit concerned about	1	they may work. But if it was on a stable dose,
2	duloxetine, but of course we have no evidence that	2	would you still allow them with the condition that
3	anything else works. But is that because the trial	3	they stay on a stable dose? They're on a stable
4	designs were not sufficient, so do we really know	4	dose, and they stay on.
5	that they don't work?	5	DR. GEWANDTER: I think we think that it
6	DR. LOPRINZI: I agree with you, probably	6	might be a good idea when it's a treatment trial
7	not duloxetine because it's been shown clearly to	7	because they still have pain or whatever symptoms
8	be beneficial, not as beneficial as we want, but	8	of a minimum level. But for prevention, I think
9	the only one that really has been. But if	9	it's a little bit more worrisome because if one of
10	venlafaxine, which are mixed data, much negative as	10	those drugs would hide pain that comes up and if
11	positive, I wouldn't feel as strongly on that. But	11	pain is part of your outcome, then that could be a
12	if it interacted with the drug that you're planning	12	problem because you don't know if it would work for
13	to give, then yes, I agree.	13	them.
14	DR. FREEMAN: I can say I personally would	14	So I think that, personally, if I were going
15	be concerned about doing any kind of trial in which	15	to do a prevention study and pain was going to be
16	pain was part of the endpoint using any alpha 2	16	part of my composite or one of my main things, then
17	delta ligand like pregabalin, or an SNRI, or a	17	I would also want to exclude those drugs. But if
18	tricylic. I would just feel to me, that's	18	numbness was my main outcome, then I wouldn't be as
19	troublesome. I don't know if I see Bob nodding.	19	concerned. I think it depends on what your outcome
20	DR. DWORKIN: Yes. What's often done with	20	is.
21	clinical trials in painful diabetic peripheral	21	DR. DASTRO-PITEI: Which in a way takes us
22	neuropathy is to allow SSRIs for depression or	22	back to the PROs and to the measures and what are
22			

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	-		
	we looking for because we all agreed that this		correlation is not that good with anything else. I
	indication, the CIPN, is not so dominated by pain.		understand historically that it would be good to
	It's more the numbness and the tingling, the		look at that. I see your point, but I just don't
4	dysesthesia, the paresthesia.	4	think it's gotten us anywhere to date.
5	I'm still thinking about this discussion	5	,
	about perhaps co-primaries or co maybe		comments? Simon.
	co-primaries is too far to go, but how do we look	7	<b>3</b>
	at the PROs and the discontinuation rates, or the		discussed, I think, especially in the context of
	cumulative dose? Are we going to look at this	9	treatment trials is differences in patient sensory
10	together	10	
11	DR. GEWANDTER: Composite, you mean.		peripheral neuropathy.
12	DR. DASTROS-PITEI: Composite, yes.	12	
13	DR. GEWANDTER: That's maybe tomorrow.		and sometimes they have profound differences in the
14	That's tomorrow's discussion.		way that the neuropathy presents itself in terms of
15	(Laughter.)		if we're thinking about C fiber damage or A delta
16	DR. FREEMAN: I'm hoping a good night's		fiber damage, cold hypersensitivity versus numbness
	sleep will clarify that for all of us, but I'm not	17	versus hyposensitivity, et cetera.
18	optimistic.	18	
19	(Laughter.)		prevention trials is less relevant, but in the
20	DR. DASTRO-PITEI: Also, can I just say we		treatment trials, should we at least try to
	have gone away from NCI CTCAE, which has been the		get I'm not talking about very extensive QST
22	staple of CIPN measures in the past. Is this	22	battery, but at least some sense either stratifying
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	Page 306		Page 308
	something which the room feels that is probably not		or just getting some baseline data because
	something which the room feels that is probably not that relevant anymore?	2	or just getting some baseline data because potentially, they might have different mechanisms
2 3	something which the room feels that is probably not that relevant anymore? DR. GEWANDTER: I don't think it's a great	2 3	or just getting some baseline data because potentially, they might have different mechanisms in terms of their neuropathy, and then potentially
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