

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

2 (1:14 p.m.)

3 CHAIRMAN SANTANA: Okay, let's go ahead
4 and get started.

5 Just in case there is anybody new in the
6 audience or at the table, let's go ahead and
7 reintroduce ourselves. Dr. Rackoff, can you start
8 from the corner over there, please?

9 DR. RACKOFF: Wayne Rackoff. I'm a
10 pediatric oncologist in oncology drug development at
11 Janssen Research Foundation.

12 DR. BAYSSAS: Martine Bayssas. I work
13 with Debiopharm in Switzerland. I'm a medical
14 oncologist.

15 DR. COLTMAN: Chuck Coltman. I'm a
16 medical oncologist from San Antonio, Texas, and Chair
17 of the Southwest Oncology Group.

18 DR. BALIS: Frank Balis, Pediatric
19 Oncology Branch, National Cancer Institute.

20 DR. KODISH: Eric Kodish, Rainbow Center
21 for Pediatric Ethics in Cleveland, Ohio.

22 DR. SMITH: Malcom Smith, Cancer Therapy

1 Evaluation Program, NCI.

2 DR. BERNSTEIN: Mark Bernstein, Pediatric
3 Oncology at the University of Montreal and the
4 Children's Oncology Group.

5 DR. STEWART: Clinton Stewart, Department
6 of Pharmaceutical Sciences, St. Jude Children's
7 Research Hospital, Memphis, Tennessee.

8 DR. LEEDER: Steve Leeder, Clinical
9 Pharmacology at Children's Mercy Hospital in Kansas
10 City, Missouri.

11 DR. ROWINSKY: Eric Rowinsky, Medical
12 Oncology at the Clinical Research Institute for Drug
13 Development in San Antonio.

14 DR. GOODMAN: Steve Goodman, lapsed
15 pediatrician, now biostatistician -- (laughter) -- at
16 Hopkins Oncology Biostatistics.

17 DR. KORN: Ed Korn, Biometric Research
18 Branch, NCI.

19 DR. GOODMAN: Stephen George, Duke
20 University Medical Center and ODAC member.

21 DR. BOYETT: James Boyett, St. Jude
22 Children's Research Hospital, Chair of Biostatistics.

1 DR. PRZEPIORKA: Donna Przepiorka, Center
2 for Cell and Gene Therapy, Baylor College of Medicine,
3 Houston, and ODAC member.

4 CHAIRMAN SANTANA: Victor Santana,
5 Pediatric Oncologist from St. Jude's.

6 MS. ETTINGER: Alice Ettinger, pediatric
7 nurse practitioner from New Brunswick, New Jersey.

8 DR. WEINER: Susan Weiner. I'm a lapsed
9 developmental psychologist, was a parent, and am now
10 a patient advocate.

11 DR. PELUSI: Jody Pelusi, oncology nurse
12 practitioner, Phoenix Indian Medical Center, and I sit
13 as the consumer representative and also an ODAC
14 member.

15 DR. REYNOLDS: Pat Reynolds, Hematology
16 and Oncology, Children's Hospital, Los Angeles.

17 DR. COHN: Susan Cohn, Children's Hospital
18 in Chicago.

19 MS. KEENE: Nancy Keene, patient advocate.

20 DR. ADAMSON: Peter Adamson, Children's
21 Hospital, Philadelphia, and Children's Oncology Group.

22 DR. HIRSCHFELD: I want to yield my time

1 to my distinguished colleague from Los Angeles to
2 identify himself, and then we'll return.

3 DR. FINKLESTEIN: Thank you, sir. Jerry
4 Finklestein, Pediatric Oncologist, Long Beach,
5 California.

6 DR. HIRSCHFELD: Steven Hirschfeld, FDA.

7 DR. PAZDUR: Richard Pazdur, FDA.

8 CHAIRMAN SANTANA: Thank you.

9 This afternoon we are going to cover two
10 topics. One is issues of clinical trial design as it
11 relates to statistical design and validation of end-
12 points, and then I will briefly talk a little bit
13 about Phase II window studies, and then we will have
14 a discussion.

15 So, with that, I will introduce Dr.
16 Goodman. Who's going to go first? You are? Dr.
17 Goodman, please.

18 DR. HIRSCHFELD: While the screen is set
19 up, I believe Dr. David Poplack is on the telephone,
20 too, and should be identified.

21 CHAIRMAN SANTANA: Okay, David, can you
22 hear us, David? Well, he's on the telephone. He

1 can't hear us.

2 I also forgot to mention, we do have some
3 time for a public open hearing. If there is anybody
4 in the audience that wishes to address the Committee,
5 please come to the microphone and identify yourself.

6 (No response.)

7 CHAIRMAN SANTANA: If there is no one,
8 then we will proceed with Dr. Goodman's presentation.
9 Thank you.

10 DR. GOODMAN: I want to thank Dr.
11 Hirschfeld very much for inviting me. It would seem
12 that you heard from my intro that I had spent my whole
13 life preparing just for this meeting, even though I am
14 not a member of the panel, since I started off as a
15 pediatrician and then decided that I would serve the
16 health of the world's children by not touching them
17 anymore.

18 (Laughter.)

19 Went into biostatistics and clinical
20 trials and oncology and also ethics of clinical trial
21 design.

22 CHAIRMAN SANTANA: Dr. Goodman, let me

1 remind you that anything you say is public record, so
2 be careful what you say.

3 (Laughter.)

4 DR. GOODMAN: It's all in my C.V.

5 (Laughter.)

6 But one area where I never worked was at
7 the intersection of all these things, which this
8 Committee represents. So I have found this discussion
9 very, very interesting.

10 Now when Dr. Hirschfeld asked us to talk,
11 I think originally he did propose the topic there,
12 which just like the intersection was one area where I
13 didn't feel particularly expert. So we actually had
14 a back and forth about what we would talk about, and
15 this is actually literally from the email. So I just
16 wanted to show what the charge was for us to talk
17 about.

18 It will not be specifically on the title
19 that was given. This is what he wanted me to comment
20 on: Can one apply Bayesian analysis where the a
21 priori data comes from an adult population and the new
22 data come from pediatric population? So that's

1 actually what I will be spending a few minutes talking
2 about.

3 He sent this email on Halloween. Maybe
4 the other title was the trick or treat version. We'll
5 switch.

6 (Laughter.)

7 So the title is "What can Bayesian methods
8 do for us?" I will just be talking very, very
9 generally. I will warn you ahead of time, I'm just
10 going to show one equation; it's not to scare you.
11 It's not the Halloween component.

12 So, first of all, what are Bayesian
13 methods? Well, the simplest definition is they are
14 methods based on Bayes' theorem. So what is Bayes'
15 theorem. Here is the scary part.

16 (Laughter.)

17 You can just forget about this. I will
18 just translate this into words. It is some prior
19 knowledge plus data from the study that you're doing
20 which gives you your final summary knowledge. So that
21 is the simplest way to summarize it.

22 Now in English, we can talk about it in a

1 variety of ways. Bayesian methods are approaches that
2 combine information of different types in a
3 statistically-justifiable way. Another way to look at
4 it is it provides a formal way to make statistical
5 inferences from a clinical trial by incorporating
6 prior knowledge.

7 Different people have a different
8 perspective on what the calculations involve. You can
9 look at it as a calculus of uncertainty; that is, that
10 the most important thing it does is it properly
11 represents our uncertainty at the end of the day,
12 given how uncertain we were at the beginning.

13 You can look at it as a calculus of
14 belief, that it tells you what you should believe at
15 the end of the day, given what you believed before you
16 started looking at the data.

17 And, finally, you can also look at it as
18 a calculus of evidence; that is, a proper way to
19 measure the strength of the data and how strongly it
20 points to one hypothesis or not.

21 Different people fall into different
22 schools, but it has components of all of these things,

1 which is the important thing to recognize.

2 So in what settings have Bayesian designs
3 or analyses been used? Well, I will tell you, if you
4 will look at the statistical literature, you wouldn't
5 imagine that it is this somewhat poor cousin of
6 standard methods that it is in the clinical
7 literature, because these days Bayesian applications
8 and Bayesian methods occupy probably pretty close to
9 50 percent of what you find in a table of contents in
10 any modern statistical journal.

11 The actual applications in medicine have
12 been pretty much across the board. The heaviest
13 representation, you see if you do a search on Medline,
14 is in the area of pharmacokinetics. It has also been
15 applied in the Phase I arena; mainly, in the form of
16 the continual reassessment method, which I will just
17 talk about very briefly later in Phase II. These are
18 just representative authors who have written about
19 this. In Phase II studies it has been used combining
20 what is known historically about response or cure
21 rates to a particular trial. It has been used in
22 Phase III studies by a whole host of statisticians,

1 and it is also used extensively in med analysis.

2 This is just a representation of the
3 number of articles that use the "Bayes" that's
4 appeared in the medical journals over the past really
5 40 years, and you see that it is pretty much
6 exploding, and this doesn't necessarily capture all
7 the articles that do.

8 But, on the other hand, you also see that
9 the scale here, which represents 250 at the top, is
10 pretty tiny if you compare it to the number of
11 articles that are published in the medical literature.
12 So depending on what discipline you are in, it is
13 actually, except in the area of pharmacokinetics,
14 fairly unlikely that you will run across actually a
15 published application of Bayesian methods. So I
16 wouldn't be surprised if many of you might be
17 unfamiliar with them except through the CRM, the Phase
18 I design.

19 Now let's start off, before I start
20 telling you what they can do, let's start off by
21 saying what Bayesian methods cannot do with respect to
22 the charge. Thank you very much. What they cannot do

1 is tell us, in the absence of information, how alike
2 children and adults are and how relevant adult
3 information is for children. It cannot make this
4 extrapolation for us. It is sort of, sometimes
5 Bayesian methods are looked at as a way to produce
6 knowledge where other sources of knowledge are not
7 available. What it is useful for is encoding or
8 representing knowledge that we actually have. So it
9 is not going to help us make this extrapolation if we
10 can't do it biologically or we can't do it clinically
11 or we can't do it empirically.

12 So the charge again: Can we apply
13 Bayesian analysis where a priori data comes from the
14 adult population? Yes, but only if you make an a
15 priori judgment about how relevant the information is
16 for children from the adult population. We have heard
17 a lot this morning about the foundations for those
18 sorts of judgments, but we have to make those
19 judgments first before we can apply the calculus.

20 Now what sort of information do we look
21 for coming from adults? I was sort of alluding to
22 this in my comment before about the kinds of things

1 that we need to include in adult studies if we are
2 going to have an eye to extrapolate them to children.
3 Obviously, we have information on the
4 pharmacokinetics, although for every one of these we
5 could probably, and we have already had, a talk on why
6 these things are different.

7 But the issue is not that these parameters
8 are different, but how they are related. They can be
9 different, but we can know consistently for a certain
10 class of drugs that, because they are metabolized in
11 a certain way, the average dose in children should be
12 something greater than that in adults. That guess
13 plus its uncertainty can be reflected in a Bayesian
14 calculation.

15 We heard about pharmacogenomics. We can
16 learn about dose toxicity relationship from adults,
17 about the types of toxicity and frequency of toxicity.
18 Again, we don't know things perfectly, but even the
19 imperfection can be represented to some extent. We
20 learn something about efficacy. We learned about the
21 effects of patient characteristics, whether they are
22 genetic or clinical on all of the above. Finally, we

1 learn about the uncertainty in all of the above. We
2 rarely know any of these things, even in adults with
3 certainty.

4 So what allows extrapolation to children?
5 Well, I don't need to tell you this. Obviously,
6 empirical comparisons, and we heard some suggestion
7 about the kinds of studies, and we got articles on
8 comparison of MTDs in adult or pediatric populations;
9 basically, just outcomes comparisons, knowledge of
10 mechanisms in adults versus children, known
11 adult/child biologic and clinical properties of
12 analogous drugs, and known sensitivity of children to
13 specific toxicities, and we could probably make an
14 almost endless list if we went around the room.

15 Now how is prior information represented
16 in Bayesian analysis? They're represented as
17 probability distributions on key parameters that
18 express both our best guess and our degree of
19 uncertainty. These days there is a lot of emphasis
20 not just on a single representation, but on doing
21 sensitivity analysis; that is, representing
22 uncertainty by showing a whole range of possible

1 representations of uncertainty. Because for every
2 curve, while we might say it represents a certain
3 amount of uncertainty about a main effect, the flip
4 side of the coin is it will represent certainty as
5 well; that is, our certainty that an effect of a given
6 size is "X" probable.

7 You could look at that as certainty or
8 uncertainty. If you say that something has a 50
9 percent chance of happening, that actually can be
10 certainty. If I say that this coin has a 50 percent
11 chance of landing heads, that's actually a pretty
12 precise estimate. So there are two sides to that.

13 So what are these key parameters that we
14 might have guesses about? We might have guesses about
15 the MTD, about the response or survival rate, about a
16 toxicity rate, about the shape or slope of a dose
17 toxicity curve, which is particularly the case which
18 was used in the Continual Reassessment Method, or we
19 can have guesses about pharmacokinetic parameters.

20 Here's an example of the kinds of curves
21 that we might draw. Here we have on the "X" axis the
22 pediatric over the adult MTD. So one represents an

1 MTD that is exactly the same in the two populations
2 measured per kilo or per BMI, or whatever, or per-
3 meter-squared. This would represent a pediatric dose
4 that was twice as high; down here would represent a
5 pediatric dose that was half the adult dose, et
6 cetera.

7 So one possible representation might be
8 this: This is just a hypothetical curve which would
9 say that our prior guess is that the MTD is the same
10 as the adult MTD, but we think it could be -- and this
11 would actually represent what we would call a fairly
12 informative "prior" because it would restrict the
13 range of plausible values from about 2, or somewhat
14 less than 2, about 1.8, to about 1.5. So it would say
15 that a priori our guess is that the pediatric dose
16 does not vary by more than half the adult MTD and
17 doesn't go below one-half or above twice the adult
18 MTD.

19 This curve would be formally incorporated
20 into the calculations and combined with the
21 accumulating data from a study that you were doing.
22 Now if you didn't have that much confidence, you might

1 draw your prior probability curve like this, where you
2 say, well, my best guess is that they are equal, but
3 I will allow some probability that they are anywhere
4 up to three times, the MTD is three times as high in
5 the kids or three times lower, or you could draw
6 almost anything else that you wanted.

7 Similarly, you could reflect some of the
8 information that we saw this morning about drugs that
9 are metabolized in certain ways by saying our best
10 guess is that the pediatric MTD is twice as high as
11 the adults, going down as low as half as big and going
12 up to six times as high. Obviously, this would be
13 deemed to be somewhat improbable, but it allows that
14 if the information from your study accumulates
15 strongly enough, you will allow that possibility, and
16 a more informative guess would look like that.

17 So this is how prior information gets fed
18 into the Bayesian machine, by starting off with curves
19 like this. Now a lot of times what I hear, and the
20 main place where I interact with clinicians in doing
21 Bayesian analysis is with the Continual Reassessment
22 Method, where we talk about what the desired toxicity

1 is and what appropriate balance is, and what the
2 toxicity might be. A lot of times the investigator
3 will say, "Well, I really have no idea. I don't come
4 with that knowledge," and that, of course, is the
5 Achilles' heel or is thought to be the Achilles' heel,
6 of Bayesian analysis: that you have to have some sort
7 of prior idea of what you are going to see.

8 The fact is that most people do have some
9 pretty good guess about at least what are the
10 extremes; that is, what is implausible. I will give
11 you an example. Actually, well, this is just to say
12 that these prior probably distributions are pretty
13 much equivalent to information from prior individuals.
14 Some people describe it as made-up data.

15 But I want to make the point that actually
16 weak knowledge corresponds to a lot of individuals,
17 particularly when we are talking about pediatric
18 trials. For example, if we are talking about
19 inference about a response rate or a survival rate, if
20 you have pretty high confidence that the cure rate
21 lies within a 40 percent range -- that is, you say
22 it's unlikely to be less than 20 percent and it's

1 unlikely to be greater than 60 percent, and often
2 clinicians can, I would think people around this
3 table, make statements like that with a fair bit of
4 confidence.

5 This is roughly equivalent to 25 patients'
6 worth of experimental information. Now that is a lot
7 of information. That is not nothing.

8 This would be a typical situation where
9 the clinical investigator might come and say, "I
10 really don't know anything." But, in fact, they know
11 a tremendous amount compared to truly nothing.

12 The confidence of the cure rate lies
13 within a 20 percent range; that is, somewhere between
14 20 percent and 40 percent, corresponds somewhere in
15 the vicinity of about 100 patients' worth of
16 experimental information.

17 So if you come to a study with this
18 knowledge, based on either knowledge of other
19 treatments of this disease, the disease, the drug, or
20 whatever, it is actually equivalent to and potentially
21 saves a fair number of subjects from subsequent
22 experimentation.

1 So what do these methods do for us? I am
2 just going to sort of summarize this in a very broad-
3 brush way.

4 First of all, they properly account for
5 uncertainty and knowledge in both previous and current
6 experimental data.

7 They minimize the amount of information
8 necessary from the current experiment, but this, of
9 course, is only of value if your "priors" are
10 reasonably accurate. If your "priors" are total
11 guesses, then you will find that the amount of
12 diffuseness that you have to introduce to accurately
13 represent your prior uncertainty ends up producing
14 sample sizes of roughly the same order that you would
15 get now, because you're operating from nothing. So
16 you have to have a certain amount of humility
17 sometimes, all the time.

18 Another thing it does is it promotes -- I
19 shouldn't say research treatments -- research designs
20 and the choice of treatment for any particular subject
21 and choice of dose that reflects, hopefully, as
22 closely as possible, our best guess about what would

1 be the best for the child based on all prior
2 information. It allows a certain flexibility in
3 design because all Bayesian designs can be adaptive;
4 that is, responsive to data as it comes in.

5 Now I have found the most useful thing
6 that both Bayesian design and analysis does is that it
7 encourages extremely valuable discussions about prior
8 knowledge on uncertainty and about the goals of the
9 study. It is actually this discussion that is more
10 valuable than anything else that goes on, and it is
11 not necessarily discussion that is stimulated by
12 asking questions about, well, how much power would you
13 like for this effect size, which I find to be a fairly
14 empty exercise.

15 When I send people back to talk with their
16 colleagues about what sort of toxicity frequency would
17 be acceptable, they come back, or if I attend, I see
18 a really fascinating discussion around the table
19 talking about things that they have actually never
20 formally talked about with their colleagues before.
21 They find it very, very highly informative. Sometimes
22 they will tell me to start, well, we'll accept a

1 toxicity of up to 30 percent of the patients.
2 Sometimes they will come back, after discussion with
3 their colleagues, and say, well, no, it's really 5
4 percent, or vice versa.

5 So it is these sort of discussions about
6 what the real content of prior knowledge is and what
7 different people bring to the table. The most
8 valuable "priors" are, of course, those based on
9 collective expertise, not just one person's hunch or
10 interpretation. This is an extraordinarily useful
11 exercise. It brings out a lot of things that
12 sometimes are not brought out when sort of the cookie-
13 cutter, fill-in-the-blanks methods are used for
14 designing experiments.

15 Now I want to say, in a nod to all the
16 superb statisticians, many of whom I have learned
17 from, who are at my right here and my left, that most
18 standard approaches should flexibly and with common
19 sense, which is how anybody who has worked in clinical
20 trials more than five months is forced to operate, can
21 become operationally indistinguishable from Bayesian
22 ones. So it is very, very possible to get the same

1 sort of operational results by not hewing to any
2 extreme philosophies about how studies should be run.

3 But sometimes this requires a bit more "ad
4 hoc-ery." That is, the standard methods don't
5 necessarily have formal ways of representing prior
6 information. We sort of make up ways or we put
7 implicitly into the design our beliefs about what we
8 think are plausible effects, and we do it in the form
9 of also how many control patients we might choose, et
10 cetera, et cetera. Those methods don't always have a
11 coherent theoretic foundation.

12 So, to bring it full circle, can we apply
13 Bayesian analysis where the a prior data comes from
14 the adult patients? I would say, as I said before,
15 yes, but only if the adult data is deemed relevant or
16 informative, and more empirical studies of this
17 relevance need to be conducted, and they need to be
18 ongoing; that is, this needs to be a continuing area
19 for study.

20 As every new agent and every new mechanism
21 comes out, we are going to have a whole new set of
22 principles upon which we base our judgment about this

1 extrapolation, and it is those principles that will
2 guide the way we represent our knowledge in Bayesian
3 analysis that borrow strength from the adult studies
4 and are used in the pediatric studies.

5 So, with that, I will stop, and I guess I
6 will ask for any burning questions right now because
7 Ed will not be talking directly on this subject.

8 CHAIRMAN SANTANA: So any questions for
9 Dr. Goodman or comments? Jerry?

10 DR. FINKLESTEIN: From a clinical point of
11 view, if you use Bayesian analysis and if some of the
12 unpublished data gets verbalized, that perhaps the
13 Phase I data on adults is very close to the Phase I
14 data in children, as we now -- we have been using the
15 80 percent rule, but if it is pretty close to 100
16 percent, how would the Bayesian analysis help us to
17 fortify this impression?

18 DR. GOODMAN: Well, I'm going to think of
19 the Bayesian approach as, I think what that would do
20 -- I mean, much of what I'll say is just common sense;
21 you don't require Bayesian perspective to implement
22 it.

1 The first thing you do, if you actually
2 had pretty high confidence that the MTDs in the two
3 groups were the same, you would start at the same MTD
4 in children that you had in adults. It might allow
5 you to -- you would also represent that confidence in
6 the form, and I showed the "priors" before, in the
7 form of "priors" that were fairly tight around the
8 hypothesized MTD that was equal to the adults.

9 So you would have more confidence about
10 starting, which, again, you don't need Bayesian
11 analysis to tell you, but it might lead you to stop
12 the trial perhaps a bit earlier because you would
13 essentially have, in having a very tight high
14 confidence, that is, in a sense, equivalent to adding
15 subjects to Phase I study.

16 Now if you don't think that is legitimate
17 or you think that this particular agent doesn't
18 operate in the same way as the agents upon which that
19 original guess was based, that very high confidence
20 that you might have to start might not be justified.
21 So you have to look very, very carefully at the basis
22 for that confidence (a), and (b) at whether this new

1 agent that you are trying actually falls within the
2 class of agents or class of mechanisms that the
3 studies upon which that confidence is based. That is
4 the best way I would say it.

5 So if you think that this is the same kind
6 of agent that has shown equal MTDs in the past, you
7 will get a Phase I study that is smaller in general
8 than you would if you did it traditional method, which
9 is sort of stand alone and we'll use the same sample
10 size. But, of course, that is only of value if your
11 prior guess is right and reasonable.

12 CHAIRMAN SANTANA: Wayne?

13 DR. RACKOFF: Operationally, the real
14 question for this set of meetings has been how to get
15 drugs to kids sooner and then get them in and out of
16 trials faster. So, as I read your two papers and hear
17 you speak, the question that remains is: What would
18 you do operationally with Bayesian analysis that
19 would, access question aside, expedite the clinical
20 trials process? Because, as you said, if the
21 assumptions are made reasonably, standard methods and
22 Bayesian methods come together. So what advantage

1 would there be in terms of speeding trials along?

2 DR. GOODMAN: Well, the kinds of things
3 that you would have -- I mean, I will leave it to some
4 of my colleagues here to maybe suggest other things,
5 but the most direct way of adapting a standard method
6 to do in some sense operationally what a Bayesian
7 method would do would be to have a set of hypothetical
8 or real data which you incorporate into your current
9 analysis, just by averaging it in or pulling it in.
10 It is in a sense making believe that you have a larger
11 experiment than you actually have.

12 And the way this is typically done is just
13 taking prior clinical trial data or Phase I data, or
14 whatever, and giving it a certain weight relative to
15 the weight of your own trial. So, in that sense, you
16 can simulate it.

17 Bayesian, as I said here, in my mind,
18 Bayesian methods offer a better and more flexible way
19 to represent, first of all, multiple sources of
20 uncertainty and represent certainly in a variety of
21 different ways. But they will come close, but you
22 have to be able to hypothesize that the information

1 you have or the experiments you have are already
2 relevant to this question.

3 DR. RACKOFF: In this setting, if I can
4 follow up, Steve, in this setting that is almost a
5 given, because to invoke the Peds Rule, the assumption
6 is already in place that there is some linkage between
7 the adult disease and the disease in children.

8 DR. GOODMAN: When you say "linkage," you
9 have to be very, very precise. When you say
10 "linkage," I mean, the efficacy of the drug, the
11 mechanism of the drug, the toxicities of the drug,
12 survival, I mean --

13 DR. RACKOFF: To take an example, if AraC
14 were being developed today, in adult AML you would
15 have data and now you are moving it into pediatrics.
16 I mean, my sense is that if you use the prior
17 information, given the effect sizes, you would
18 probably have trials that would require fewer subjects
19 and, therefore, be finished sooner. Is that correct?

20 DR. GOODMAN: Yes. Yes, if you believe.

21 DR. RACKOFF: Right.

22 DR. GOODMAN: Absolutely. I mean, that is

1 essentially, if you add in statistically information
2 in the form of subject that you haven't experimented
3 on, you have effectively a larger sample size, even
4 though you haven't experimented on more subjects.
5 But, of course, it only buys you -- it is only
6 advantageous if that prior information is relevant,
7 and that is a judgment that has to be made by people
8 who aren't statisticians.

9 DR. HIRSCHFELD: This actually segues, I
10 think, with Dr. Rackoff's question, and I wanted to
11 ask Dr. Goodman to make a point that he stated earlier
12 and will rephrase it. In terms of practical
13 implications, if there were coordination among the
14 people designing the adult Phase I studies and the
15 pediatric Phase I studies, and the appropriate data
16 were being collected in the adult Phase I studies that
17 could be utilized in analysis for pediatric studies,
18 would that, then, facilitate this type of approach?

19 DR. GOODMAN: Yes.

20 (Laughter.)

21 DR. HIRSCHFELD: Thank you.

22 DR. ROWINSKY: I mean, the methodology for

1 the proposed pediatric trial, as far as dose
2 escalation, would be entirely unconventional in that
3 you would be selecting doses based upon a Bayesian
4 method. So I am just trying to understand
5 operationally.

6 DR. GOODMAN: Yes.

7 DR. ROWINSKY: And you are going to be
8 drawing, actually defining a precise dose toxicity
9 curve which will allow you to discern an MTD --

10 DR. GOODMAN: Right.

11 DR. ROWINSKY: -- with a certain order of
12 confidence with smaller numbers of patients?

13 DR. GOODMAN: Right. One other thing, I
14 mean to address the question before, this is maybe
15 getting beyond where we want to use them, but Bayesian
16 methods can be very, very effective in certain
17 settings at combining different sources and different
18 kinds of information that all have a bearing on the
19 inference you want to make.

20 For example, if the drug is similar, if
21 the basis for our extrapolation is similarities in
22 metabolisms, similarities in drug targets, or

1 variations thereof, you can construct Bayesian
2 hierarchical belief networks that sort of amalgamate
3 all this information in ways that are very, very
4 difficult to do using standard methods. I mean, when
5 I said make up patients with a certain outcome, that's
6 assuming that your uncertainty is focused on just one
7 particular outcome, like the MTD or the AUC, or
8 something like that.

9 But it sometimes the case that we learn
10 that a number of things are related, and that kind of
11 information, again, because the Bayesian methodology
12 is sort of a belief propagation or an uncertainty
13 propagation model, is easier to represent, much more
14 easy to represent, under a Bayesian model.

15 However, those models then become more and
16 more dependent on assumptions, and you may or may not
17 want to design a trial or save many patients based on
18 those assumptions. This is what I meant when I said,
19 depending on the kind of uncertainty and the levels of
20 uncertainty, it is much more awkward to start
21 constructing Bayesian equivalents using standard
22 methods because standard methods don't fundamentally

1 allow you to express uncertainty about these unknowns
2 in the same way that Bayesian methods do. It is an
3 issue of calculus.

4 CHAIRMAN SANTANA: Dr. Boyett?

5 DR. BOYETT: Actually, not being a
6 Bayesian and not wanting to endorse the methodology
7 broadly, I will say that in a Phase I setting I think
8 it is entirely appropriate. The traditional Phase I
9 design that we have used, three and six, et cetera,
10 and saying that we know what the maximum tolerated
11 dose is, that's not well-defined. It doesn't define
12 anything.

13 On the other hand, the CRM method, in
14 terms of actually realizing that what you are doing is
15 estimating a dose toxicity response curve, if you
16 will, and the method allows you to model that dose
17 response, and it is not picking an MTD -- it is saying
18 that I want to estimate the dose at which I have some
19 confidence that maybe 20 percent of the patients might
20 experience, unacceptable toxicity, or 30 percent of
21 the patients might experience unacceptable toxicity.
22 I think that is a far improvement over what we have

1 done in the past with our Phase I design.

2 Secondly, I can see how that, if you had
3 the actual data from a Phase I trial in adults, that
4 you use that to get a prior estimate of what this dose
5 response curve might be in children, though you might
6 weight it only 50 percent of what it would be if you
7 actually had children there, I can see how that can
8 definitely be an advantage.

9 CHAIRMAN SANTANA: Donna?

10 DR. PRZEPIORKA: I guess if we get down to
11 the nitty-gritty, if we usually 9 to 18 patients in a
12 standard 3-plus-3 design, what is the smallest number
13 of patients that you would expect in a CRM design, if,
14 as Dr. Finklestein says, the MTD in the kids is going
15 to be very close if not exactly the same as in the
16 adults?

17 DR. GOODMAN: Well, in the typical CRM
18 designs that I use, actually, I use very broad
19 "priors," very little prior belief. It can be shown
20 in lots of simulations and in reality that the CRM
21 designs tend to end at roughly the same time as
22 standard designs. They are most reliable when they go

1 up to about 24, between 20 and 24 patients. That is
2 with no prior belief.

3 I have actually never run one or simulated
4 one, sort of assuming that we had the equivalent of 10
5 patients of information already, but some of that time
6 is used in building up from lowest dose, and some of
7 that time is spent in making the estimate more
8 accurate when you start with no estimate, no
9 information about what the estimate should be.

10 So if you are starting very, very close to
11 the dose, that is, either at or very close to the
12 dose, within one dose level, and you are starting with
13 information that is equivalent to something on the
14 order of five to ten patients, then I would expect
15 that the study would end in more like 12 patients.
16 You know, this is really an off-the-cuff guess.

17 CHAIRMAN SANTANA: Dr. George I think had
18 a comment, too.

19 DR. GEORGE: I would just like to comment,
20 and maybe Steve would like to comment on this, too.
21 I think the Bayesian approach does have a lot of
22 attractions in pediatric oncology as well as oncology

1 in general, but the main advantages in terms of the
2 basic problem we are facing here with very small
3 numbers is that its main advantage would appear, as
4 you just mentioned in your example, when you have very
5 precise or more precise prior information, and that's
6 fine, although therein lies the risk.

7 Something else you said earlier was
8 mentioned briefly the sensitivity kind of analysis;
9 that is, that is where your real worry is. If you
10 think you have real precise information and, in fact,
11 you don't because you are making some faulty
12 assumptions, you can run into problems. That is
13 presumably why you use very diffuse priors in your CRM
14 approach.

15 I just wondered if you have any comments
16 on whether the Bayesian approach would, in fact, be
17 able to save time and patient resources, particularly
18 in the regulatory setting. In the scientific setting
19 I can see how it might, but if you are trying to, if
20 we are talking here from the FDA's perspective, I
21 think we may be talking philosophically, but not
22 practically.

1 DR. GOODMAN: Well, I would actually argue
2 the opposite. I would say that to conduct analyses
3 without formal incorporation of everything that we
4 know is to create, first of all, a lot of ethical
5 tension because there is this clinical sense, and
6 sometimes it is hard to articulate, and statisticians
7 can help make it more formal, that starting at a
8 particular dose or treating with a particular agent
9 does not represent what they know biologically or
10 clinically, is not what they would choose for their
11 own child if the child had the same illness.

12 If, to the extent we can, we incorporate
13 all that we can rationally incorporate into the
14 design, reflecting our prior knowledge, it is much
15 more likely that the child will be treated either at
16 doses or with agents that are most likely to be
17 effective. So I think it reduces the ethical tension.
18 It, in the end, also reflects our -- I mean, the
19 reason we are here today is because we believe that
20 there is relevance of the adult information to the
21 children. Otherwise, we wouldn't have to -- we would
22 always be starting anew. We wouldn't even be

1 necessarily starting with the same agents. We would
2 be testing, you know, have two completely different,
3 independent panels of testing. So we believe that
4 they are highly related.

5 I think that, because we are so sensitive
6 -- I mean, this beneficence argument really translates
7 into trying to do the best we can to, even sometimes
8 at the expense of, I would argue, being -- this is
9 going to sound wrong -- of being in the long term
10 correct, that is, this allows you to choose what you
11 think is best, given everything that you know now, for
12 the child with less emphasis on the value to society.
13 If that is the emphasis of the pediatric clinical
14 trials, then the emphasis switches from having the
15 maximum sample sizes to incorporating as much
16 information as possible in the treatment of each
17 individual patient, and then making as much use of the
18 collective of information as we can at the end, but
19 the priority is on beneficence for the individual.

20 I think that the Bayesian approach is the
21 most coherent way -- I'm not saying the only way, but
22 the most coherent way to represent all that we know

1 when we come to the next subject. So it really does
2 have to do, I think, with this balance between
3 societal interests and the interests of the
4 individual.

5 As I said, if you use smaller numbers of
6 patients, in the end you are going to be based with
7 empirical data that is based on smaller numbers than
8 we have for adults. Part of that is necessary because
9 there may be a fewer number of children subjects.

10 One might argue that that is less reliable
11 knowledge, but the choice for each child will be more
12 likely, given everything that we know now, given what
13 any rational parent or clinician would do, to reflect
14 what we think is best for that child. So I do think
15 it represents a different balance of interests than we
16 would have in adult populations, but the kind of
17 balance that, as was suggested this morning, we might
18 want to strike for children.

19 DR. HIRSCHFELD: I would like to add to
20 that that it is our goal, and I hope our practice,
21 that there is no distinction between the best science
22 and any regulatory policies or actions, but that they

1 are synonymous.

2 CHAIRMAN SANTANA: Malcom, do you want to
3 comment?

4 DR. SMITH: Yes. I would just say we
5 support Phase I trials, pediatric trials, both with
6 the CRM method that Jim has taken the lead in as well
7 as the standard 3-and-6 method.

8 I feel less of the ethical tension that
9 you describe. I think if we were starting at doses
10 that were very low, then I think it would be a much
11 stronger argument that we needed something like the
12 Continual Reassessment Method. Starting at 80 percent
13 of the adult MTD though, we are at a dose that, in
14 fact, is very close to the adult Phase II dose, and
15 there is enough experience on both sides, the Phase I
16 doses in children being both lower and higher than
17 that in adults, that I think, either way, either the
18 standard 3-and-6 method or the CRM method is an
19 acceptable, ethical way of conducting a Phase I trial
20 that really does provide as reasonable a chance of
21 benefit for each participating child as we can hope,
22 given the context of the Phase I trial.

1 DR. GOODMAN: This is getting away from
2 Bayesian issues and getting more into Phase I issues.
3 I would just say I disagree only to the extent that
4 the 3-and-6 method does not allow you to smoothly or
5 coherently calibrate the target toxicity that you want
6 to reach. That is, it doesn't allow you very easily
7 to say the optimal balance here is represented by a
8 toxicity rate of 5 percent or 50 percent. It is very,
9 very difficult to do that. In fact, it is essentially
10 impossible.

11 DR. ROWINSKY: But you can't do that in a
12 Phase I trial anyway, given --

13 DR. GOODMAN: You can with a CRM.

14 DR. ROWINSKY: Not in terms of efficacy
15 and activity. You can't --

16 DR. GOODMAN: No, no, no.

17 DR. ROWINSKY: Only with respect to
18 toxicity.

19 DR. GOODMAN: With respect to toxicity,
20 yes. So, in that sense, that is one of my stronger
21 arguments for the CRM, not necessarily the technology,
22 but the fact that it can be tuned properly to reflect

1 what the investigator thinks is the appropriate
2 balance of risk and benefits.

3 CHAIRMAN SANTANA: Okay, I would like to
4 go ahead and invite Dr. Korn to the podium for his
5 presentation.

6 DR. GOODMAN: Dr. Korn may not agree with
7 that.

8 (Laughter.)

9 I just have this sneaking suspicion that
10 I'm going to keep the microphone.

11 (Laughter.)

12 DR. KORN: Well, first, I would like to
13 thank Dr. Hirschfeld for inviting me to come talk, and
14 we are going to continue with the bait-and-switch --

15 CHAIRMAN SANTANA: We can't hear you very
16 well. Can you check your microphone or move a little
17 bit closer?

18 DR. KORN: Did you turn it off on me?

19 (Laughter.)

20 So we are going to continue with the bait-
21 and-switch approach, and I'm also not going to talk
22 about what was on the agenda.

1 (Laughter.)

2 But that's only because Dr. Hirschfeld
3 asked me to talk about Phase I trials, and I don't
4 completely disagree with Steve.

5 Let me start with cytotoxic agents, where
6 things are a little bit simpler. So we usually treat
7 cohorts of patients with escalating doses until
8 unacceptable toxicity is seen and then back off. The
9 rationale, of course, is that increased dosage of an
10 agent will offer more anti-tumor benefit, provided the
11 dose has acceptable toxicity.

12 Then we have heard talk about the standard
13 design where you use cohorts of three or six patients.
14 There are accelerated designs. I consider the CRM
15 perhaps an accelerated designs, where you treat less
16 than three patients in each dose level to begin with,
17 or possibly you have bigger jumps between the dose
18 levels, including some not dose-limiting toxicity, but
19 some Grade 2 toxicity, and then you treat more
20 patients at the dose levels or narrow the distance
21 between the dose levels.

22 As Malcom just said, and which I agree

1 with, I think these designs are most useful when you
2 have no good idea of a starting dose level, and you
3 don't escalate through ten dose levels before you
4 start seeing some biologic activity.

5 In the present situation, as I understood
6 it before the meeting started anyway, we are in a
7 setting where we are looking at a case where we think
8 we have efficacy data for adults. So I am sure we
9 have already at that point gone through the Phase I
10 trial for the adults, and so we probably have a fairly
11 good idea of the starting level. I don't think that
12 the accelerated designs have that much to offer.

13 Of course, you are going to still have to
14 do some Phase I design to make sure you have an
15 acceptable dose. In fact, I think you might even want
16 to do a larger Phase I trial than you might normally
17 do if you are planning perhaps on skipping directly to
18 a large, randomized Phase III trial.

19 So even though I am talking about Phase I
20 trial designs, let me just say that I think, to me,
21 that is perhaps where the big gains are here. If you
22 already have efficacy results in adults, since most

1 agents don't work and here you have one that does work
2 in adults, you might feel comfortable in jumping from
3 Phase I to Phase III in children and not doing Phase
4 II trials in children. It seems to me that would save
5 a lot of time and patience on trial. But if you were
6 going to do that, you would probably want to make your
7 Phase I experience a little bit larger to make sure
8 that you have the right dose.

9 So that's actually all I wanted to say
10 about cytotoxic agents because Dr. Hirschfeld asked me
11 to talk somewhat about the newer kinds of agents,
12 where you are not interested in getting to a maximum
13 tolerated dose. For these agents, you think that a
14 lower dose may be just as effective as going up to the
15 maximum tolerated dose and have less toxicity.

16 Well, if you are not going to use toxicity
17 in your Phase I trial, you have to use something.
18 Different things you might have -- if you had some
19 blood concentration of the agent or perhaps some PK
20 levels, you might use that. I am going to talk about
21 that. I am also going to talk about, when you don't
22 have that, then you might want to use some sort of

1 molecular targeted biologic response to try to decide
2 what the appropriate dose is.

3 So let's say you are in a situation where
4 you have a minimum effect of blood concentration of
5 the agent or its metabolite, and you know that, and
6 here's a situation where you might have some feeling
7 from the adult data what that is. Normally, when you
8 are doing the adult trials, it's based on pre-clinical
9 data which you may be a little less comfortable with.

10 So you could treat a cohort of patients at
11 a dose level and measure their concentrations.
12 Depending upon these concentrations, you would either
13 treat additional cohorts at higher or lower or the
14 same dose.

15 So, for example, if you treated five
16 patients and you saw concentrations like that, well,
17 if the minimum effective level is known from the adult
18 data, say, to be 80, then it looks like you might
19 treat the next cohort of patients with a lower dose.
20 But if it was 130, based on adult data, that you are
21 under it; you haven't reached it yet. So you would
22 want to go up.

1 Of course, if the minimum effective level
2 was 100, based on your adult data, well, then it is a
3 little unclear here. Your observed mean is 110. Your
4 lower 90 percent confidence level for the mean is 102,
5 which sounds good. Eighty percent of the observations
6 are bigger than 100, but the 90 percent confidence
7 interval for the true proportions that are above 100
8 is only 49 percent. So if you wanted to really be
9 sure, say, that 80 percent of the patients were going
10 to have levels above 100, you would have to treat more
11 patients at this dose level.

12 Sort of a bottom line here is you may into
13 somewhat larger trials, if you really want to be
14 confident that a good percentage of your patients are
15 achieving a certain concentration, a larger number of
16 patients than in the usual Phase I trial.

17 Now that's a situation where you have some
18 blood concentration. Now suppose you don't have that,
19 but you have some biologic response. I am not going
20 to even attempt to define that, but I am thinking of
21 some measured level of molecular target or change in
22 level of molecular target that you think is

1 associated, potentially associated with some clinical
2 benefit. Obviously, that is a difficult question what
3 that response should be.

4 But if you had it, you could design a
5 trial around it. So, for instance, if you treated 11
6 patients at a dose level and all 11 had this response,
7 biologic response, then the observed response rate is
8 100 percent, and you could be 90 percent confident
9 that the true response rate would be bigger than 81
10 percent, which you might feel is comfortable and that
11 is a good level to be at.

12 Of course, if you only observed 10 out of
13 the 11 responses, even though your observed response
14 is 91 percent, you could only be 90 percent confident
15 that your true response was bigger than 69 percent.
16 So, again, if you wanted to be really confident that
17 it was above 80 percent, then you would have to treat
18 more patients, and we are already up to 11. So,
19 again, if you are trying to achieve this kind of goal,
20 you are going to be into larger sample sizes than what
21 we usually see with Phase I trials.

22 Now partially because of that, we have, my

1 colleagues and I at NCI have been working on trying to
2 do some other things that would require less patients.
3 So one possible way is finding what we have been
4 calling a biologic efficacious dose. In the context
5 of dose escalation, rather than trying to ensure there
6 is a minimum biologic response rate, we are going to
7 only ensure that, if the true response rate is low,
8 then there is a high probability of escalating, and if
9 the true response rate is high, there is a low
10 probability of escalating it.

11 So I give you one possible trial design
12 here which is similar to a standard 3-6 phase
13 escalation. You could also do this in a Bayesian way.
14 You initially treat three patients at a dose level
15 with zero or one of these biologic responses. You
16 escalate the dose for the next cohort with two or
17 three responses. You expand the cohort to six
18 patients; with five or six responses, declare this
19 dose to be a biologically efficacious dose.

20 So the statistical characteristics of this
21 are that, if the true response rate was less or equal
22 to 40 percent, there would be a 96 percent probability

1 of escalating it to the next dose. If the true
2 response rate was bigger than 90 percent, there would
3 be only an 11 percent probability of escalating. If
4 you were willing to accept those characteristics, then
5 this would be a scheme that would only require three
6 or six patients per dose level. This is just one way
7 to do this. There's a lot of ways you could do this.

8 Now a question you can ask is: Is there
9 any dose response relationship between the agent and
10 the biologic response? This question is not really
11 trying to determine adults for further studies, but
12 occasionally people are interested in this, obviously,
13 for scientific reasons, proof-of-principle reasons.

14 So a typical trial design might be treat
15 20 patients at a low dose, treat 20 patients at a high
16 dose, and compare the response rates between the two
17 dose levels. With these sample sizes, you could
18 reliably detect a difference in true response rates of
19 50 percent versus 90 percent between those two doses.

20 So, again, I should probably cross out
21 "power" here, so Steve doesn't get offended.

22 (Laughter.)

1 DR. GOODMAN: I like the "alpha equals
2 one."

3 (Laughter.)

4 DR. KORN: You like the alpha equals one?
5 Okay. We'll just cross out that one.

6 (Laughter.)

7 However you look at it, this is the kind
8 of sample size you would be required to detect this
9 kind of difference reliably, which is actually a
10 fairly large difference, 50 percent versus 90 percent.
11 So sometimes one sees studies with these very small
12 sample sizes that are looking for dose response
13 curves; well, they are kind of fooling themselves.

14 If they are fooling themselves, the people
15 who say they are going to find the optimal biologic
16 dose are even fooling themselves more. You
17 occasionally see studies like this, too. Well, first
18 of all, it is not clear what the optimal biologic dose
19 is defined as, but let's just say we want to really
20 assess the shape of the dose response curve. Well,
21 you are into even larger sample sizes here.

22 What I did was I simulated some data, and

1 I'm not even a Bayesian and I make up data --
2 (laughter) -- where I know what the true response
3 rates are, and the true response rates go from 50, 60,
4 70, 80, and 90 percent, corresponding to the five dose
5 levels here. I generated simulated data; 10 patients
6 reached dose level. So this is a 50-patient study,
7 which is, we'll agree, is not small.

8 So the true response rate is a straight
9 line. So this is the first time I did it, and that
10 looked pretty good. But then I did it again and said,
11 well, now, if you just saw this, you might say, gee,
12 things are kind of leveling off at the third dose
13 level. Maybe that is my optimal biologic dose. And
14 I did it one more time. Well, here it looks like
15 things are actually going down, so maybe we should
16 stop it. Biologists have a word for this which I have
17 forgotten.

18 When you look at this kind of data, you
19 can easily get fooled, even with 50 patients. So if
20 you really want to find the shape of the curve, you
21 are talking about hundreds of patients.

22 DR. HIRSCHFELD: Is that close enough for

1 government work?

2 (Laughter.)

3 DR. KORN: So one way to not fool
4 yourself, of course, is to put confidence intervals on
5 the proportions, and that gives you a better feel
6 that, gee, I don't really know what is going on here
7 with the shape of this curve.

8 (Laughter.)

9 So let me summarize here in two slides.
10 For cytotoxic agents, I think standard designs should
11 work well, since you typically know about where to
12 start from the adult data. I have no objection to
13 Bayesian designs. I mean, I think you are going to
14 get, if you start about the right place, you are going
15 to get to about, you are going to use about the same
16 sample size and end up about the same place.

17 For non-cytotoxic agents, things can be
18 hard or easy, depending. If you actually have an
19 effective blood concentration to target or something
20 similar to that, that's good and you can go after that
21 dose. If you have a targeted biologic response
22 available, you can try to use that to determine the

1 dose in the different ways I described.

2 Now I should say that usually using these
3 targeted biologic responses is problematic at least in
4 the adult -- in the first studies of agents. The
5 reason tends to be that the assays and the techniques
6 for measuring the response are being worked out
7 simultaneously with the clinical testing of the agent.
8 So no one feels comfortable in using those assays and
9 techniques to decide what dose to use.

10 So we have these discussions all the time:
11 "Gee, wouldn't it be nice, since this is a targeted
12 agent, if we used a target to determine the dose?"

13 Then somebody says, "Well, how are you
14 going to measure the target? Do you really believe
15 it's that? Do you think it's this or the other
16 thing?"

17 But it seems like in this present
18 pediatrial setting we have a big advantage. If a
19 bunch of the adult studies have already been done, you
20 actually may have worked out some of these techniques,
21 and you may really be able to put your hands on the
22 target. Surely that would be a more optimal approach

1 than basing it on -- excessive toxicity would be to
2 use the targeted response so that you could actually
3 measure it.

4 Thank you. I think I will stop there.

5 CHAIRMAN SANTANA: Thank you, Dr. Korn.

6 Any comments or questions for Dr. Korn?
7 Malcom?

8 DR. SMITH: Ed, in your 50-patient trial
9 to determine the optimal biologic dose, the variation
10 that you were describing was just statistical
11 variation?

12 DR. KORN: That's correct. I didn't add
13 any biases or anything. That's random variation of
14 what it looks like with ten patients per dosage.

15 DR. SMITH: Okay. Now the other kind of
16 variation that you can get is in the assay itself.
17 Any assay looking for a biologic target is going to
18 have a certain variability and a certain imprecision.
19 When you factor that in, how does that affect your
20 enthusiasm for the optimal --

21 DR. KORN: Okay. Well, actually, that is
22 a good point. I mean, I was pretending that the

1 response was a yes/no binary decision. If you do
2 that, then the assay variability is sort of already
3 factored in, in that I was saying that the true
4 response is going from 50 percent to 90 percent.

5 Another way to do this, of course, is to
6 actually measure something on a continuous scale and
7 try to use that to determine the optimal biologic
8 dose. That, from a statistical point of view, is
9 attractive because you are kind of using more
10 information rather than dichotomizing things into
11 yes/no, but then you do get into these whole issues
12 about, well, how reliable is the assay? In that
13 situation, the more unreliable the assay, the more
14 spread you see about these points, and the larger the
15 sample size which results.

16 CHAIRMAN SANTANA: Eric?

17 DR. ROWINSKY: Just a comment on that: I
18 think we should only be so lucky to have assays that
19 are validated at the end of Phase I to give you hand-
20 off -- even binary assays.

21 DR. KORN: But my understanding is you are
22 not only done with Phase I, you are going into the FDA

1 asking for an indication; you are probably done with
2 Phase II. You still don't have the assays?

3 DR. ROWINSKY: We still don't have the
4 assays, and there are rare drugs that we have
5 developed -- I am trying to think of them here -- in
6 which we would be able to hand off information to you.

7 CHAIRMAN SANTANA: Martine?

8 DR. BAYSSAS: One of your comments, you
9 said you would like to go from Phase I to Phase III.
10 Looking at what you have done, I don't know where is
11 the Phase II here, because, okay, it's a Phase I. To
12 some extent, you have a certain end-point which you
13 hope will relate to efficacy, but you still don't have
14 an efficacy end-point. So I don't see how you go from
15 Phase I to Phase III. You need to have a Phase II
16 built into Phase III or some element of Phase II into
17 Phase I, but I don't see how you --

18 DR. KORN: Yes. Well, first, my easy
19 answer is Dr. Hirschfeld only asked me to talk about
20 Phase I.

21 (Laughter.)

22 But the more serious answer is that, I

1 mean, Phase II is a lot of times just used to screen
2 agents to find the most promising ones to go to Phase
3 III. If you already have -- I mean, here we can think
4 of using the adult trials to be the screening trials.
5 The adult trials can do all these tests to these
6 agents, and most of them are negative, and they find
7 a good one. Well, I would have no trouble taking that
8 good one directly to Phase III for children, provided
9 that evidence was there from adults.

10 The only reason to go to Phase II, I
11 think, is if you had so many adult agents that were
12 promising from Phase III trials that you didn't have
13 enough patients to test them all, then you would have
14 to say, okay, well, maybe I need to do Phase II trials
15 in children to pick which ones to go to Phase III.
16 But I don't know that there's that many promising
17 agents that have shown efficacy in Phase III that are
18 ready to go for children that we couldn't perhaps skip
19 Phase II.

20 DR. SMITH: Ed, could I just clarify? You
21 are assuming that the Pediatric Rule has been invoked
22 and, hence, there is an adult tumor that is similar to

1 the pediatric tumor?

2 DR. KORN: Yes.

3 DR. SMITH: Okay.

4 CHAIRMAN SANTANA: Yes, I think we are
5 talking in that context, not beyond that.

6 Frank?

7 DR. BALIS: For I think a lot of practical
8 reasons, in looking at other trial designs, the most
9 likely one that we would be pursuing in pediatrics,
10 for a couple of reasons, would be the one where we
11 were trying to achieve a minimally-effective of
12 effective concentration, only because, first of all,
13 it is much more difficult to do biologic end-points in
14 pediatric patients unless you are willing to accept a
15 surrogate tissue instead of a tumor as the site that
16 you look.

17 Secondly, because it is very possible that
18 by the time we do the trials that relationship would
19 be defined at least in different types of cancers in
20 adults. If that is the case, then I think that the
21 way that you would approach that would be different
22 than doing a dose escalation with the intent of

1 defining what dose it took to achieve that
2 concentration.

3 Firstly, if you knew the concentration was
4 effective, that would be the way you would dose all
5 patients. You would individualize them to achieve
6 that, as Clinton was saying.

7 Secondly, unless the kinetics are
8 nonlinear, which would be an unusual situation, you
9 would be able to get information from every patient
10 you treated. So, for example, if you gave a patient
11 a dose and they were half the target level, then you
12 could assume, knowing what the kinetics were in
13 adults, that if you doubled the dose in that patient,
14 it would give you an effective concentration.

15 I don't know that you would need to go in
16 and take another patient and prove that necessarily.

17 DR. KORN: Right, but don't you have to
18 start, wouldn't you want to even start the first
19 patient at a targeted lower concentration than the
20 adult? I mean rather than put 10 patients on at once?

21 DR. BALIS: Yes, what you would really be
22 doing I think in a trial like that is defining, is

1 determining whether the concentration you defined as
2 your active concentration was tolerable.

3 DR. KORN: Right.

4 DR. BALIS: You wouldn't want to be
5 defining what dose it took to achieve that in some
6 percentage of the patients.

7 CHAIRMAN SANTANA: Steve?

8 DR. HIRSCHFELD: Again, I think there is
9 a segue between Frank Balis' comment and a question I
10 wanted to ask, which is a followup on a comment that
11 Dr. Coltman made this morning.

12 If you have a drug that has as its target
13 in the modeling that you were discussing, let's say,
14 BCR-able in one disease, CKIT in another disease,
15 PDGF, binding site in another disease, and perhaps
16 even a fourth target, how do you go about thinking
17 about your dose-finding studies? Would you do four
18 different dose-finding studies for each target or
19 would you look at a panel of different assays for each
20 one, or should you think of a totally different
21 paradigm than trying to look at the targeted dose?

22 I don't expect you to have an answer for

1 that --

2 DR. KORN: Thank you.

3 DR. HIRSCHFELD: -- but I wanted to raise
4 the question and think about it in terms of both
5 modeling and the types of advice that is given.
6 Anyone is welcome to respond.

7 DR. PAZDUR: Could you perhaps have a
8 different dose for different tumors, you know, aimed
9 at the molecular target that you have? Generally, we
10 have not done that, but if you are evolving to that
11 situation where you have multiple targets here,
12 perhaps one has a target-specific dose that they are
13 going to be looking at. I don't know. Here again,
14 that is quite hypothetical, but I think this whole
15 discussion has some hypothetical connotations to it at
16 this time.

17 DR. HIRSCHFELD: Well, I think it is quite
18 real, and that would be the sequential model then.
19 For each tumor, you would have a dose-finding study,
20 depending on each target. I just wanted to raise the
21 issue, if there were other ways to approach it. Maybe
22 Dr. Rowinsky has some thoughts.

1 DR. ROWINSKY: I can give you a
2 hypothetical answer, which would be measuring,
3 assessing the tumor and titrating your drug to some
4 level of inhibition that you can measure, but in the
5 real world you are most likely going to escalate to a
6 dose that you are pretty confident that is going to
7 suppress all those targets, and then figure it out
8 later. I mean, I'm sorry to have to say that, but
9 that's usually what happens.

10 CHAIRMAN SANTANA: Dr. Boyett?

11 DR. BOYETT: Yes. I was going to comment
12 that a similar issue is that traditionally in Phase I
13 studies we put heterogeneous types of patients on
14 these trials and look to toxicity. When you start
15 talking about optimal biologic response modifying
16 dose, it may be worse than the 50 that you saw up here
17 because then they have to be all alike. They may have
18 to have some particular polymorphism and you are
19 looking for the optimal dose in that particular set.

20 So, similar to what you are saying, I
21 think in some settings you are going to have to study
22 different types of diseases separately to find the

1 optimal dose that you want to use in those diseases.

2 CHAIRMAN SANTANA: Dr. Bernstein?

3 DR. BERNSTEIN: Well, just to comment on
4 the last point, that assumes that our drugs have
5 gotten so good that we are not limited by toxicity,
6 but rather we have the luxury of actually targeting
7 the dose to the tumor target as opposed to being
8 limited by the toxicity incurred. That would be nice.

9 CHAIRMAN SANTANA: Dr. Reynolds?

10 DR. REYNOLDS: I think one of the issues
11 in this that we haven't discussed is that, if you are
12 talking about this theoretical magic bullet that Mark
13 just alluded to, and the discussion earlier of going
14 for a maximal practical dose or biologically-effective
15 dose rather than an MTD is that, when you go from one
16 disease to another, you are going from very different
17 tissue distributions that you need to effect the
18 tumor.

19 So, for example, the penetration of drugs
20 into bone marrow to effect leukemia and the lymph
21 nodes and blood is going to be very different than the
22 penetration in the solid tumors. So I think you have

1 to be very cautious about thinking about those issues,
2 and that what works in one setting may not be what you
3 need to get into the next setting and get the job
4 done.

5 CHAIRMAN SANTANA: Dr. Boyett?

6 DR. BOYETT: Yes, one comment about
7 physician belief, and this is a recent experience I
8 had with soliciting belief to use CRM or a traditional
9 model. I had this one particular study where we chose
10 to continue to use the 3-and-6 rule because the belief
11 was we were almost there -- six dose levels later.

12 We have another drug that was assured to
13 be nontoxic. We got about six or seven dose levels
14 we're going to go up to. We had DOT at the first dose
15 level.

16 So, Steve, maybe the people you work with
17 have better belief patterns than the ones --

18 (Laughter.)

19 CHAIRMAN SANTANA: Any further comments or
20 questions?

21 (No response.)

22 CHAIRMAN SANTANA: Okay, thank you, Dr.

1 Korn.

2 Dr. Hirschfeld asked me to address this
3 variation in Phase II design that's called window
4 studies. I am not going to summarize the experience.
5 That would be three hours' worth of talk. But what I
6 am going to do is to try to summarize some of the
7 rationale behind this variation in the Phase II design
8 and the pros and cons, and then briefly touch on some
9 of the ethical issues of this kind of design.

10 Okay, so I am going to be talking for the
11 next 15 minutes or so about this variation in study
12 design for Phase II studies that are called Phase II
13 upfront windows.

14 In my recollection, and there are
15 certainly others at the table who know this better or
16 just as well as I do, probably the first indication of
17 this design was about 10 years ago. There have been
18 now a number of studies, primarily done in the
19 pediatric arena, using this type of design.

20 For the uninitiated, in essence, what this
21 design calls for is an end-point of response, like any
22 other Phase II study; also, trying to assess toxicity

1 as is relevant to any Phase II study, but the
2 difference is that the population of patients that are
3 being studied is different. These are populations
4 that are receiving these -- these are patients that
5 are receiving this agent or this combination of agents
6 early on in their therapy, prior to them receiving
7 standard treatment. So, in essence, it is a window
8 because it is an opportunity, prior to receiving
9 standard therapy, and it is upfront because it is
10 occurring temporarily prior to these patients getting
11 their extended therapy.

12 Then, for the purpose of discussion, I
13 wanted to contrast a little bit some of the issues of
14 the classical Phase II design versus the window Phase
15 II design. The patients may be different. In the
16 classical Phase II design, usually these are patients
17 that have a failed, a prior therapy, so they're very
18 highly selected, and they are also highly selected in
19 the sense that, because they have had prior therapy,
20 their end organ, their toxicity issues are unique, and
21 some of those patients obviously would not be eligible
22 for the classic Phase II design based on some

1 eligibility criteria. So they are usually a very
2 small number of patients.

3 In the contrast, for the window trials,
4 these are patients that have not received prior
5 therapy and are going to get this experimental drug or
6 these experimental drugs prior to the standard
7 therapy. It can be a very well-defined population.
8 For example, the high grade brainstem gliomas, and
9 that entire population can then be the subject of this
10 type of design. So it could capture a much larger
11 population of patients with a particular disease,
12 because they don't have some of the other limitations
13 that this group of patients would have.

14 In terms of response, like any Phase II
15 study, we are interested in assessing the response of
16 the particular agent or the combination of agents, and
17 the argument has been made that in the Phase II window
18 upfront the response is most representative because
19 these are patients who have not received prior
20 chemotherapy, who do not have issues of tumor
21 resistance and/or toxicity.

22 So these patients probably will give us a

1 better representation of the true activity of this
2 agent or this combination of agents, whereas patients
3 in the classical Phase II design, these patients may
4 have lower responses because their tumors may have
5 acquired resistance or they may have had issues of
6 toxicity because of prior therapy, whereas in the
7 window setting these patients are truly virginal to
8 prior therapy. So the toxicity represents a unique
9 observation of the true toxicity of that agent or that
10 group of agents.

11 So this is just to contrast a little bit
12 of the differences between these two designs. Having
13 said that, I think we need to remember that the intent
14 of the Phase II window design is to provide some
15 effective therapy; that is, to produce some tumor
16 response.

17 But I think the ethical tension in these
18 kind of designs is that then we very carefully have to
19 assess the risk and benefits of these designs in the
20 context of two major issues. One is that window
21 therapy is occurring in the context of a larger trial.
22 So the patients are not only getting the window

1 upfront therapy, but that's followed by some
2 additional standard therapy.

3 That's relevant, as you will see later on
4 in my presentation, because that raises the issue of
5 the potential negative impact of the window therapy on
6 the ability of the patients to get the standard
7 therapy, but I think it has to be considered as a
8 whole, not separate, in terms of the therapeutic
9 intent.

10 I think the other thing that was briefly
11 mentioned this morning is that in pediatric oncology
12 this concept of standard of therapy usually is in the
13 context that patients are participating in an
14 investigational trial. So Phase II window trials are
15 not occurring alone; they are occurring in the context
16 of a larger trial that has another component that
17 follows the window. Okay?

18 Now let's talk a little bit about the
19 scientific validity of these kind of designs in
20 contrasting them to the classical Phase II design.
21 While in the classical Phase II design one of the
22 rationales for doing upfront windows is that, by doing

1 an upfront window, you really get a better estimate of
2 the true activity of a new agent, for the reasons that
3 I have exposed before.

4 In contrast, in Phase II classical designs
5 one may overestimate the toxicity because one has a
6 population of patients that have been exposed to many
7 other agents, and therefore, the agent may be declared
8 as highly toxic just because of the population we have
9 chosen in the classical design.

10 So an argument has been made that the
11 window design allows us then to more accurately get a
12 better estimate of the true activity of the agent in
13 a patient population.

14 Now one of the criticisms for the upfront
15 Phase II window trials has been that so far there has
16 been no conclusive evidence that these studies improve
17 or impact on survival. I think that is a valid
18 criticism.

19 The counterpoint to that is that a similar
20 situation occurs in the classical design, that there
21 have been many agents used in Phase II classic studies
22 that ultimately were incorporated into therapy, and

1 there was no demonstration of the impact on survival
2 of incorporating those agents. So I think that
3 criticism is valid for both types of designs.

4 The relevant issue in the upfront window
5 is, how do we balance that against issues of tumor
6 progression and other risks that the patient may be
7 exposed to? We will come back and visit those later.

8 The other issue is that, although some of
9 these trials have now, the initial trials were
10 initiated about 10 years ago, and there have been
11 quite a number of them, many of these trials require
12 a lot of time. I have given you some examples here of
13 some studies that we did at St. Jude with the window
14 of ifasfamide in osteosarcoma, something similar that
15 was done in POG, some of the issues of ifosolin
16 osteosarcoma in a randomized trial in a cooperative
17 group and how long it took to complete that trial, and
18 then some of the trials that are currently ongoing
19 with Irinotecan in pediatric randomized sarcoma.

20 So it is really very hard for me to stand
21 here today and truly give this group a final
22 conclusion about the impact of using this trial design

1 in terms of the impact that it has had on the survival
2 of pediatric oncology patients because of the long
3 time that it takes to complete these studies.

4 Let me focus a little bit on this issue of
5 risk and benefit, because I think a lot of the
6 discussion that has occurred around this design has
7 been relevant to that ethical tension of whether these
8 trials pose some unique ethical questions.

9 So let's talk about benefits because,
10 whenever we offer a new therapeutic drug to a patient,
11 I think our intent is to, hopefully, offer some
12 benefit. Well, potentially if the agent is proven to
13 be active, you could get a very prompt tumor response.
14 Most of these agents that are being tested potentially
15 have non-cross resistance to some of the other classic
16 agents the patients are potentially going to receive.

17 I think the example of that is some of the
18 issues of camptothecins that Clinton talked about
19 earlier this morning, which these compounds clearly
20 have some activity in a wide variety of pediatric
21 tumors. I think there is some literature in pediatric
22 oncology to support that the promptness of a tumor

1 response ultimately gives us some idea of the
2 potential for that particular therapy to improve the
3 survival of patients. So if the agents are proven to
4 be effective, prompt tumor response is a potential
5 benefit.

6 There's no clear indication in many
7 studies that there is a benefit in terms of improved
8 outcome, but there are some data that at least in some
9 combinations there may be an improved outcome.

10 Then the other issue is the issue of
11 decreased toxicity, that clearly because these
12 patients are now virginal to prior therapy, they have
13 not been heavily pre-treated, potentially their
14 toxicity spectrum is much different, and there could
15 be decreased toxicity in these patients also.

16 The other issue is that, as far as I know,
17 of all the Phase II studies that have been conducted
18 so far, there clearly has not been a major issue with
19 tumor progression in these patients that have
20 participated in the Phase II window trials. However,
21 I say that with a grain of salt because, clearly, that
22 data is evolving.

1 One of the problems that we need to
2 address in this design, though, is which agents we
3 bring up to this type of design, because clearly this
4 type of design has to be very selective in terms of
5 the agents that we are going to test and the patient
6 population that we are going to test. I think as we
7 talked earlier this morning, I think we do need some
8 pre-clinical data to help us sort out which of these
9 agents we should be using in these kind of designs.

10 As was mentioned briefly this morning, I
11 think to the present, we are very dependent on some of
12 the pre-clinical xenograft data that represents
13 particular pediatric tumors, testing those agents in
14 that setting, and then from that, selecting those
15 agents that potentially could be used in these Phase
16 II window trial designs.

17 The other issue is, in terms of selecting
18 what agents we are going to incorporate into this
19 design, like we mentioned earlier, there is a limited
20 number of patients. There may be more drugs than
21 patients or ideas that we have. So we have to be very
22 selective in terms of how we prioritize which agents

1 we adapt to this design.

2 I have outlined here at least two concepts
3 that at least we use at St. Jude when we consider
4 whether an agent should be incorporated into an
5 upfront window. One is that it either has a novel
6 mechanism of action or it is an analog of an agent
7 that we know that is effective, but potentially has an
8 improved toxicity profile. So by incorporating that
9 earlier in the therapy, we may negate some of the
10 issues of toxicity while still, hopefully, providing
11 an effective therapy.

12 The other point is which patients we
13 should select for these kind of unique trials. I
14 think this is one of the questions that Dr. Hirschfeld
15 wanted us to address at the end of this afternoon.
16 This is one that I don't have a quick answer or a
17 threshold answer; it is truly open for a lot of
18 discussion.

19 One of the concepts that we have used at
20 St. Jude, when we accept these designs in in our
21 trials, is that we try to define which patients
22 ultimately would be at the greatest risk of treatment

1 failure with the conventional standard therapy that we
2 have. Those are the patients that I think ethically
3 and scientifically then one could justify
4 incorporating into these kind of designs.

5 I give you a brief example: Patients with
6 malignant brainstem gliomas have a survival of less
7 than 10 percent. So I think in these group of
8 patients there's an imperative to assess new therapies
9 that potentially could impact that disease.

10 And then the counterpoint to that in terms
11 of patient selection is that we have to carefully
12 assess the risk and benefit for the individual
13 patient. We have to have some prior experience with
14 the agent, whether it comes from adult data or whether
15 it comes from pre-clinical data, and that we also have
16 some idea about the potential toxicity profile of that
17 agent.

18 Having said that, I think we need to
19 recognize that many of our pre-clinical models do not
20 really help us in defining toxicity for patients. So
21 a classic example of a Phase II window trial that,
22 unfortunately, was not very successful was the use of

1 melflan in rhabdomyosarcoma in which the animal model
2 did not predict that myelosuppression was going to be
3 so excessive. Unfortunately, these patients that got
4 melfalan prior to conventional therapy had excessive
5 toxicity.

6 So I think we need to look at toxicity, if
7 it exists in humans in other settings, and not in
8 animal models, because it will not help us in
9 selecting the best approach for these patients.

10 Let me briefly finish by talking a little
11 bit about some of the issues that Eric kind of
12 challenged me this morning to discuss. He and I did
13 not talk before this. So I wasn't aware he was going
14 to bring this up.

15 It is the whole issue of, how do we
16 approach the consent for these patients? I want to
17 outline three basic principles, and then I am going to
18 come back to a little bit more discussion about this,
19 based on a consensus meeting.

20 First of all, like any study, I think we
21 need to recognize that enrollment is voluntary and
22 that this has to be carefully explained to the parents

1 and to those patients that are ultimately going to
2 participate, and that I think we need to carefully
3 educate our parents and our local IRBs in the concept
4 and the scientific and ethical rationale between
5 these kind of trials, so that they can understand
6 what the ultimate reason for performing these trials
7 is.

8 Having said that, about four, four-and-a-
9 half years ago, CTAP, Malcom Smith and other
10 investigators at the NCI formed a consensus meeting
11 that actually was held here in Washington, if I
12 remember correctly, in July of 1997, and this
13 Committee produced a paper on this issue of trying to
14 assess the ethical validity of these Phase II upfront
15 windows. I think this is available on a website, and
16 it certainly is available through CTAP.

17 I want to focus on two issues that they
18 specifically discussed that I think help us in terms
19 of minimizing the risk that these patients potentially
20 could be exposed to when we apply this kind of design.

21 One of the risks is obviously the risk of
22 tumor progression. So we need to be very careful when

1 we do these upfront window designs that we have very
2 strict rules about stopping the study based on tumor
3 progression. That has occurred in some of these
4 trials, but in other trials we have been fortunate
5 that tumor progression has not been an issue. So
6 tumor progression does need to be addressed in the
7 statistical design of this kind of study in terms of
8 the stopping rules.

9 We need to recognize that there may be
10 unique toxicities. Since these are patients that have
11 not been previously treated with any chemotherapy,
12 their toxicity profile may be very different than
13 patients who otherwise have been treated, and the
14 impact of the window therapy prior to the standard
15 conventional therapy in terms of the future therapy
16 that the patients may receive, I gave you kind of a
17 negative example in terms of melfalin producing
18 myelosuppression and then not allowing those patients
19 to get effective standard therapy. So we do need to
20 pay some attention to the impact of the window in the
21 context of the standard therapy or the other
22 investigational therapy that the patients may get

1 subsequently.

2 I mentioned to you briefly in terms of the
3 benefits, the early response, and also that if
4 patients respond to this agent during the window phase
5 or the upfront window, that I think serious
6 consideration should be given to incorporating this
7 agent into the subsequent therapy that these patients
8 receive. I would be happy to hear other opinions
9 about this issue, but I truly do believe that, if an
10 agent is proven to benefit the patient early on in a
11 window trial, that that agent should be seriously
12 considered in the subsequent therapy that the patient
13 will receive.

14 Then the duration of the participation in
15 the upfront window should be kept as short as
16 possible. If the other mechanisms in which we can
17 identify responses by maybe potentially looking at
18 other surrogates, we should also attempt to do that,
19 so that we can limit the exposure of patients to the
20 minimum while giving them the maximum benefit of
21 participating in that trial.

22 Then in terms of the informed consent,

1 that consensus meeting touched on some very important
2 points. I think the issue of the upfront window
3 therapy should be clearly identified in the consent
4 separate from the other elements of the consent that
5 relate to the standard therapy or to the other
6 investigational therapy, not necessarily that there be
7 a separate consent for the window, but within the
8 informed consent document and within the informed
9 consent discussion, that this be identified as a
10 separate, unique component of the trial; that patients
11 and parents be given the opportunity not to
12 participate in the window component, if they so choose
13 and so desire.

14 It has been very interesting because I
15 think at St. Jude, as we have done a number of these
16 trials, we have come to appreciate that now a greater
17 number of parents and patients opt not to participate
18 in some of the window trials that we have designed.
19 So I think people are becoming -- I think we are doing
20 a better job in terms of the informed consent and
21 providing alternatives to patients.

22 I think, very importantly, the consent

1 document in the process should clearly identify how
2 this window differs from the subsequent therapy. That
3 should be clearly identified. Then I think a
4 potential risk is that of delaying the standard
5 therapy or making the patients ineligible for other
6 future therapies. I think all this needs to be
7 included, in addition to all the other requirements
8 and the elements of the informed consent.

9 Another issue that needs to be addressed
10 in the informed consent for these window trials is the
11 issue of the impact on quality of life. If there is
12 any additional procedures that the patients may
13 require, if we are using some surrogate end-points
14 during the exposure to that agent, and then the
15 potential impact on quality of life of extending the
16 duration of therapy, because if we are now giving a
17 window trial that lasts six weeks, that may be six
18 more weeks of total therapy that the patient would
19 receive. So I think that needs to be considered, too,
20 in the discussions of the consent.

21 We need to clearly indicate in the consent
22 document any pre-clinical or clinical data that would

1 support the use of that particular agent or agents,
2 and, as we all know, treatment alternatives should
3 clearly be identified and, as necessary, provisions
4 for assent or refusals should also be part of the
5 elements of informed consent in these window trials.

6 So I am going to finish that by saying, up
7 to the present, I think there is some scientific
8 evidence to suggest that these trials are
9 scientifically-justified. I think given the
10 constraints of some of the discussion and points that
11 I made, they are acceptable under certain conditions.
12 I think, more importantly, scientifically, they also
13 provide us an effective mechanism to identify active
14 agents within this issue of the developmental program
15 of drugs for children, but, unfortunately, we are
16 still too very early in this process, and the number
17 of trials is still very limited, that we can have a
18 final conclusion on the ultimate impact of this design
19 on treatment outcome of patients that participate in
20 these trials.

21 So, with that, I will finish, and I will
22 entertain some comments or questions. So I guess, as

1 the Chair, I get to choose, right? Eric?

2 For the purpose of discussion, I am going
3 to sit down, okay?

4 DR. ROWINSKY: I think you have presented
5 very cogent argument, pros and cons of these trials.
6 You alluded to something. Phase II trials are really
7 screening trials, and I don't think that they're just
8 screening trials to screen for drugs that are active.
9 You suggested that perhaps active drugs in a Phase II
10 window should be considered for incorporation into
11 frontline therapy, but I think what we are trying to
12 do now, especially now with so many agents, is not
13 only to find active agents, but agents that agents
14 that are really going to incrementally impact.

15 I think that one disadvantage of the
16 windows screening trials is that when you find a drug
17 that is active at the back end in patients who are
18 refractory, I think you are more inclined -- that drug
19 is much more likely to demonstrate an impact, an
20 incremental impact on disease.

21 I think that you are selecting the best
22 situation, of course, patients that are most apt

1 toxicity-wise and host-wise, but I am not so certain
2 that we are really -- in the upfront window situation
3 we may be screening for "me-too" drugs, many drugs
4 with very similar mechanisms of actions as opposed to
5 the back end. At least from the adult experience,
6 drugs that have been shown to be active in patients
7 who are totally refractory are drugs that have made an
8 incremental impact. So it's one of the arguments that
9 is a con argument for that design.

10 CHAIRMAN SANTANA: It's a valid argument.
11 I am not going to take a position.

12 DR. ROWINSKY: No.

13 CHAIRMAN SANTANA: Mark?

14 DR. BERNSTEIN: I think that I agree as
15 well. I think, however, there are some times when
16 there are biological differences in tumors at
17 diagnosis and then recurrence where it is still
18 possible that, for instance, methotrexate versus
19 trimetrexate in osteosarcoma is something we are
20 hoping to look into. There may be reasons that tumors
21 are resistant at the time of recurrence where they may
22 not be at the time of initial diagnosis, and still

1 adding an agent at the time of initial diagnosis may
2 have an incremental impact. It needs to be tested,
3 but I think that it may be possible.

4 CHAIRMAN SANTANA: Peter?

5 DR. ADAMSON: To throw perhaps some
6 controversy into this, Victor, you concluded with four
7 points: that Phase II windows are scientifically-
8 justified, ethically acceptable; they can identify
9 active agents, and it is too early to judge whether
10 that works. So I will go out on a limb and say, to
11 varying degrees, I disagree with all of those
12 conclusions. Let me tell you why.

13 CHAIRMAN SANTANA: It's the first time
14 we've disagreed today, right?

15 DR. ADAMSON: It had to happen sooner or
16 later.

17 (Laughter.)

18 I think it is important to look
19 historically as to how Phase II windows first evolved
20 and where they ended up, and why we are sort at the
21 crossroads we are today. You spoke about Mark
22 Horowitz' trial with melfalin. I believe the main

1 thrust then was we would do a Phase II window so we
2 wouldn't dismiss a potentially active agent. For
3 others, melfalin in the relapse setting had
4 uninteresting activity, and in a Phase II window
5 setting had interesting activity, and it set the
6 paradigm that we will do Phase II windows so we don't
7 wrongly dismiss active agents.

8 What then evolved is that we did a host of
9 Phase II window studies of drugs that we knew had
10 activity. So I would challenge you that you say it
11 gives us a better response estimate, and I would say,
12 what do we do with that information? So if we have
13 set a threshold for relapse patient of 20 percent and
14 for newly-diagnosed patients a threshold of 40
15 percent, we are still left with we have an active
16 agent. Does it improve curability? I would argue
17 that there has not been a Phase II window trial that
18 has ultimately impacted on the need to do a Phase III
19 study, nor has it impacted on identifying an agent
20 that's active.

21 I don't think anyone can come up past
22 melfalin with an example where we have identified an

1 active agent that we didn't already know was active.
2 So the whole problem that we find ourselves in with
3 ethics, and that is probably where I agree with you
4 most, is that in certain situations these are ethical,
5 but I think scientifically and how we move forward, my
6 concept of when is a Phase II window going to be
7 scientifically-justified and productive has gotten,
8 that window has gotten a lot smaller. Knowing that VP
9 ifos is active, ifos carbo is active, still hasn't
10 answered the question, are these agents going to
11 improve curability?

12 CHAIRMAN SANTANA: I have to agree with
13 you that I think one of the problems with this
14 approach is that, to date, I don't think there has
15 been any conclusive data that it impacts survival.
16 But I would say that that is true of the Phase II
17 design in general, that I think we've got to be
18 careful that we define the end-point. The end-point
19 of a Phase II trial is not to impact survival of the
20 patient. The end-point of a Phase II trial is to give
21 us some idea about the efficacy of this drug or this
22 combination of drugs in a particular tumor system, in

1 a particular patient group. It is only until you take
2 it to the next level that you clearly can demonstrate
3 whether there has been an impact of that drug in the
4 disease or in the process.

5 So I think we've got to be careful because
6 I think we have been maybe a little bit too critical
7 of the Phase II window design in terms of, well, we
8 shouldn't be doing it because to date it hasn't
9 impacted on survival of patients. I would argue that
10 the same argument could be made for the classical
11 Phase II design, that the number of drugs in
12 pediatrics that we have potentially brought to Phase
13 III that have had impact on survival is still very
14 limited. So I think the argument is for both.

15 I agree with your points. I am taking
16 both positions here because I also wrestle with some
17 of these Phase II window design studies, but I think
18 in certain patient populations, in special conditions,
19 I think this is a unique way that maybe would allow us
20 to benefit the patients to a certain degree that
21 otherwise they would not, because of prior history of
22 treatment, and so on and so forth.

1 DR. ADAMSON: But I don't think that the
2 Phase II window study is a prerequisite for Phase III,
3 for doing a Phase III study, and that, in essence, is
4 what it has not evolved into, in that we're saying,
5 well, before we move to Phase III, we need to a Phase
6 II window study. My argument is we are not going to
7 learn enough from the Phase II window study to help us
8 decide whether to do the Phase III or not.

9 If we have an active agent in a relapse
10 setting in a classic Phase II, we can sit down and
11 decide, is this a high enough priority that we should
12 do in Phase III? We don't need to repeat the
13 experiment and learn that it is more active in newly-
14 diagnosed than in relapsed patients.

15 DR. COLTMAN: The sole example you gave
16 was brainstem glioma with a 10 percent survival rate
17 at best. Now what is the boundary of responsiveness
18 to therapy that you use? Is that the bottom or the
19 top of the criteria?

20 Furthermore, if there is a treatment that
21 is available, even if it has a 10 percent survival,
22 and since you have been at this for 10 years, one

1 should be in a position to look at what the impact on
2 standard therapy is that is bound to follow this, and
3 has this Phase II window upfront in previously-
4 unresistant patients generated resistance which might
5 negatively impact on the standard treatment, even
6 though it is only a 10 percent five-year survival?

7 CHAIRMAN SANTANA: The data that I know
8 that potentially could indirectly answer your question
9 is derived from a POG study in neuroblastoma in which
10 there were sequences of windows, and maybe Dr. Korn or
11 Dr. Reynolds can comment, or maybe Dr. Cohn, since
12 she, I think, participated in this trial.

13 My interpretation of the end result of
14 that trial was that none of the windows negatively
15 impacted on the ultimate survival of the patients
16 after they received the standard therapy. That is
17 kind of an indirect way of looking and trying to
18 answer your question.

19 DR. COLTMAN: Well, I think that is very
20 important, because if this upfront window has a
21 negative impact, unless they are dated to show that it
22 doesn't, then I think it is not ethical to do it.

1 CHAIRMAN SANTANA: No, and I think you are
2 correct, but that is the only, I think, big body of
3 data that at least compared different windows. So
4 there was some variability in the windows, and then
5 the impact of those windows on the subsequent
6 treatment that all the patients received, whereas all
7 the other trials -- and Malcom and Mark or Peter can
8 correct me -- all the other Phase II window trials
9 that I have been familiar with have been single
10 windows followed by some standard therapy. That trial
11 I think was very informative because there were
12 different windows for different patients, and then
13 they all got the same therapy subsequently. So I
14 think that trial gave us some idea that at least there
15 was no negative impact on the ultimate survival of the
16 patients.

17 The issue of thresholds is very important.
18 I think that needs to be clearly defined when one
19 undertakes a Phase II window trial in terms of the
20 population of patients, and what you would find
21 acceptable in terms of the ultimate survival of those
22 patients in the absence of the window, to define that

1 population very carefully.

2 So this is a very small group of patients.
3 This is not promulgated for the larger number of
4 patients, but for a very unique patient population.

5 Sue, do you want to comment on that?

6 DR. COHN: Sure. I don't know the data
7 intimately, but I do know that there were four Phase
8 II upfront windows. There was no negative impact in
9 terms of ultimate survival, depending on which window
10 somebody was initially randomized to.

11 Of the four upfront windows, there were
12 definitely differences in terms of response. So
13 because of that, some agents have been subsequently
14 further studied; others have been dropped in
15 neuroblastoma.

16 It also, however, depending on which of
17 the four arms, not only was there no negative impact,
18 but there was also no difference in positive outcome.
19 So Peter is right in that regard as well. So there
20 was no advantage to have gotten even one of the more
21 activations, like Topotecan. Had you gotten the two
22 cycles of Topotecan prior to your standard therapy,

1 there was a very beautiful response with Topotecan
2 upfront, but the ultimate survival of the group who
3 got the Topotecan versus the group who got nothing
4 versus the group that got a different Phase II was not
5 different.

6 DR. COLTMAN: Of course, if you intercede
7 with a Phase II window, then you had substantial lead
8 time bias, so that you would have to be in a position
9 to know that at the time of the initiation of the
10 standard treatment going forward, was there an impact
11 on that? And these studies didn't address that. They
12 looked at overall survival.

13 One can imagine that the Phase II window
14 may have had an impact, but it inhibited the way they
15 responded to the standard treatment, and therefore,
16 the overall survival was not different, but the impact
17 following the initiation of standard therapy may have
18 been worse. That is the question that needs to be
19 addressed.

20 I can tell you in adults we have lots of
21 tumors that don't respond to therapy. There are no
22 standard therapies for many of those tumors. We have

1 been doing Phase II windows in that population upfront
2 because we don't have good therapies.

3 So, early on, therapy in a Phase II agent
4 in patients with incredibly refractive disease,
5 refractory disease, is something that has been done
6 for years. As a matter of fact, when I heard Archie
7 Blair first present this at the Vail Course, I pointed
8 out to him that my first Phase II window I
9 participated in in the Southwest Oncology Group in
10 1964, and that was the use of hydroxyurea upfront in
11 the treatment of malignant melanoma for which there
12 was no treatment.

13 CHAIRMAN SANTANA: Dr. Finklestein?

14 DR. FINKLESTEIN: I would like to submit
15 the data is not in yet for pediatrics. As Dr. Cohn
16 knows, many of us believe we have not really impacted
17 on the overall survival of -- Malcom is going to smile
18 because I have been saying it for decades -- the
19 overall survival of neuroblastoma since day one. So
20 I am not sure, no matter what you do to neuroblastoma,
21 you are going to change the survival.

22 So I think, however, many of us would like

1 to see the four windows, if that is the analogy, with
2 some other tumor before we would be able to say that
3 it is in for, at least the data is available for
4 pediatrics. I think neuroblastoma is the wrong tumor
5 in that regard.

6 CHAIRMAN SANTANA: Malcom, do you want to
7 make any comment? You don't have to if you don't want
8 to.

9 (Laughter.)

10 DR. SMITH: I will let Eric go first.

11 CHAIRMAN SANTANA: Okay, Eric?

12 DR. KODISH: Thank you, Victor, for your
13 comments on Phase II windows. It is an
14 extraordinarily complex, ethical issue. I think to do
15 a good, moral analysis of the area, one needs to do a
16 thought experiment essentially and unbundle, if you
17 can, the scientific appeal of this study design from
18 the clinical care of the child.

19 The thing that struck me in your comments
20 as most exciting was the possibility of incorporating
21 the Phase II window agent later on in the design for
22 that particular child. So morally that resonated as

1 something that might tip the scale to balance and
2 justify it. But, short of that, I am not sure that we
3 are going to find a lot of examples where a Phase II
4 window study can be morally justified.

5 I also have to make the Tolstoy point that
6 all happy families are alike, but unhappy families are
7 unlike in different ways. The difference between a
8 child with a brainstem glioma, though it might high-
9 grade, versus a rhabdo or a neuroblastoma or Ewing's,
10 these seem to be very important points here. I think
11 it would be dangerous to try to put all Phase II
12 windows into one group because of that.

13 CHAIRMAN SANTANA: Wayne?

14 DR. RACKOFF: One comment, Victor, and one
15 question. It was a very nice summary of a very
16 complicated area.

17 I think that one comment is that, with
18 some of the newer agents, because of one of your
19 specifications, that the window be of short duration,
20 I think we have to be careful. Some of the agents
21 are, by their very design, expected to work only with
22 prolonged duration therapy. Actually, a couple of

1 them have been subjected to windows already, and I am
2 skeptical of that. So that is just a comment.

3 The question is: Putting the ethical
4 issues aside and assuming some scientific validity,
5 because I think there is some to the approach -- it is
6 at least intellectually attractive, if not empirically
7 validated yet -- how does it accelerate drug
8 development in pediatric patients?

9 CHAIRMAN SANTANA: If I could share my
10 thoughts on it, I think potentially an agent in which
11 there is some pre-clinical data of efficacy and some
12 limited adult data could quickly be moved to
13 previously untreated patients before it gets tested in
14 previously treated patients, to identify its response
15 characteristics and its toxicity profile earlier on.

16 I think, to me, that would be one
17 potential advantage of doing these kind of designs, to
18 more quickly identify the true spectrum of activity
19 and toxicity of an agent.

20 Let me go down the list. Donna? Go
21 ahead.

22 DR. RACKOFF: And your sense is, because

1 these studies actually take longer in some cases, that
2 that's why I ask. I am trying to see how it really
3 accelerates the overall timeline of a drug coming to
4 an indication in pediatrics, as opposed to a classical
5 Phase II, which may be done along the same timeline,
6 I guess.

7 CHAIRMAN SANTANA: That has been the issue
8 I think that Peter was addressing earlier. I think
9 both things are happening, and they're happening at
10 least in selected tumors concomitantly. The issue is,
11 is there an advantage of one versus the other, and are
12 we really gaining any more time by doing the window in
13 terms of ultimately identifying a drug that we may use
14 in a Phase III setting?

15 I don't know, because I think the ones
16 that I have the most experience with are the Topo I
17 inhibitors. Clearly, Irinotecan was introduced
18 probably a little bit earlier into the rhabdo trials
19 than it would have, I think, if an historical approach
20 to a Phase II setting would have been done. But I
21 didn't participate. I mean, I am not a member of that
22 Committee; I don't know how that came about. Maybe

1 Mark or Malcom can comment.

2 Certainly in Topotecan there was already
3 data in the relapse setting concomitantly to the study
4 that Sue referred to. So those studies kind of were
5 occurring concurrently.

6 So you're right, I think the proof is
7 still not there that it in any way has accelerated our
8 ability to move an agent or a group of agents any
9 quicker.

10 DR. BAYSSAS: Is it possible to reserve
11 the support, for example, to some eliminate the
12 cytostatics of this approach? Would that be a
13 possibility, and to select for which agents you would
14 apply?

15 Also, you know, if you take patients with
16 potential cure versus patients that first relapse, and
17 another question I have is that, if you had in the
18 CTAP thing, I have heard about Phase II, that it was
19 sort of abducing maybe: first, taken only one cycle,
20 very short, to have some characteristics about the
21 drug, and it could maybe kind of screen for further
22 combination therapy? So I wonder if this could also

1 be an approach in this type of design?

2 CHAIRMAN SANTANA: Yes, I do think that
3 the upfront window doesn't have to be restricted to a
4 single agent. It can be a combination of agent. So
5 it doesn't have to be a single drug. I think it could
6 be two drugs that potentially one wants to investigate
7 in combination.

8 The second point, or your first point was,
9 how this design potentially could be applied to some
10 of the newer biologics. I think that is a challenge.
11 This design is going to be a challenge because,
12 clearly, many of these biologics are cytostatic or
13 they require a long period of observation before one
14 sees a clinical response. I think the potential way
15 to get around that is that one would then have to look
16 at some other marker of potential efficacy and
17 activity, so that one would not have to wait for six
18 months of therapy in order to define the role that
19 this agent may play.

20 So that is going to be a challenge, too,
21 if one were to use biologics, use this design to test
22 some biologics, and one would have to think of what