

1 Now for the last part of the talk I would
2 like to address the issue of increased clearance
3 during maturation and the requirement for larger doses
4 in children on a milligram-per-kilogram basis relative
5 to what adults require.

6 This particular issue has arisen from a
7 number of therapeutic drug-monitoring studies in which
8 people compared the doses of drugs such as
9 theophylline or, the next slide I'm going to show you,
10 cyclosporine, where doses have been titrated to
11 achieve a particular target concentration. In this
12 slide you see that the most common dose of
13 theophylline to achieve a target concentration was
14 between 10 and 14 milligrams per kilogram per day. In
15 pediatric populations -- and these are children aged
16 one to nine years of age -- the bulk of the
17 individuals were between 18 to 26 milligrams per
18 kilogram per day to achieve the same target
19 concentrations.

20 Now one could see that if we just went
21 directly from adult data and, say, selected a dose of
22 12 milligrams per kilogram per day, we would be down

1 in this area of the dosage distribution and are at
2 high risk of underdosing children based on adult
3 dosing recommendations.

4 This is a more dramatic example of
5 differences between children and adults. Cyclosporine
6 is somewhat dependent upon P450 3A4 for its
7 metabolism, and these are the doses at different weeks
8 post-liver transplant required to achieve a target
9 concentration.

10 The blue bars are the doses on a
11 milligram-per-kilogram-per-day basis for children who
12 had a mean age of 2.2 years compared to, in yellow,
13 adults with a mean age of 42.3 years.

14 Now the easiest interpretation is that the
15 clearance of cyclosporine is greater in children than
16 it is in adults. It turns out that you can't just
17 interpret these data directly because the transplanted
18 liver in children does not have the gall bladder, and
19 bile is required for cyclosporine absorption.

20 However, I also have a slide that shows
21 FK506 dosing differences between children and adults.
22 FK506 is not as dependent upon bile, and the same

1 relationship holds, although it is not quite as
2 dramatic.

3 But it is examples like this that have led
4 us to believe that on a milligram-per-kilogram-per-day
5 basis, children require higher doses of medications
6 than do adults. Certainly there are data in other
7 forms that suggest that perhaps something like P450
8 3A4 activity is, indeed, higher in children than it is
9 in adults.

10 This is a study that was conducted in
11 Denmark looking at the cytochrome P450 3A metabolite
12 carbamazepine 10-11-apoxite and expressing the
13 metabolite as a ratio of the parent compound, with the
14 higher ratios implying higher 3A4 activity. We can
15 see on the abscissas is post-natal age in weeks, and
16 there is a tendency for the ratio implied here that
17 the conversion of carbamazepine to the 10-11-apoxite,
18 which is almost primarily a 3A4-dependent activity,
19 shows higher values, certainly wider ranges, early on
20 in life, but tends to decline as the child gets older,
21 as the children get older.

22 On the other hand, there recently have

1 been some data using warfarin, S-warfarin, that has
2 been published. S-warfarin is dependent upon
3 cytochrome P450 2C9 for its metabolism and the S-
4 enantiomerase the one that's thought to have the anti-
5 coagulant activity.

6 These investigators in Japan demonstrated
7 that, yes, indeed, when the clearance of unbound
8 warfarin was corrected for body weight, that the
9 clearance was statistically significantly greater, and
10 in this case around 40 percent greater, in prepubertal
11 children compared to either pubertal children, and
12 these were children age 12 to 18 years, or adults with
13 a mean age of 60 years.

14 When you corrected the clearance values
15 for body surface area, there was still a tendency for
16 the -- and this is statistically significant -- for
17 clearance to be higher in the prepubertal children
18 mean age of 6 years compared to the adults. But when
19 the data were corrected for liver weight, and this was
20 estimated from pathological data, the statistical-
21 significant relationship ceased to exist.

22 The implication here was that these

1 developmental differences in drug clearance that
2 necessitate the higher doses is simply a function of
3 the change in the ratio of liver mass to total body
4 mass. Indeed, this is a slide that I put together
5 from using similar pathologic data. These are data
6 that are found in pediatric pathology textbooks, and
7 I have corrected them using the 50th percentile from
8 the growth charts, but you can see that there is a
9 spike or a peak in the ratio of liver mass to total
10 body weight around the age of three to four years of
11 age, and somewhere around puberty here things flatten
12 out.

13 On the other hand -- and I have to be
14 careful what I say here because these data came from
15 St. Jude's, and right now I'm the meat in a St. Jude's
16 sandwich over here on this side of the room (laughter)
17 -- but these are data that were published by D. J.
18 Murray and his colleagues at St. Jude's. Here, using
19 antipyrine as a sort of measure of global P450
20 activity, yes, indeed, there was a statistically-
21 significant difference in antipyrine clearance between
22 children less than six years of age and post-pubertal

1 kids. This relationship held even when the data were
2 corrected for liver volume, and in this case by MRI.

3 So, to wrap up the talk, these raise a
4 number of points that need to be considered not only
5 by those of you who are involved in pediatric cancer
6 chemotherapy, but those of us who are involved in
7 pediatric pharmacotherapy, period. That is that the
8 increased clearance or dose requirements of some
9 compounds in children may be a function of this growth
10 phenomenon. This particular issue may be most
11 relevant if the liver is the predominant organ
12 involved in the elimination of that compound and is
13 likely to be enhanced if there is a single enzyme that
14 is quantitative important in the elimination of the
15 particular compound.

16 I say this because, in the case of P450
17 3A4/3A5, where it's often difficult to distinguish
18 between the relative contribution of these two similar
19 P450 isoforms, the fact that there is a high 3A
20 content in intestine and also a high content in liver,
21 or in kidney, it is not reasonable to expect that
22 there would be a good correlation with liver mass,

1 especially if a compound is orally-administered and
2 must first get past P450 3A in the intestinal mucosa
3 before it gets into the systemic circulation.

4 So, just to summarize then, drug
5 metabolism pathways, and I've only dealt with the
6 cytochromes P450 -- if we had an infinite amount of
7 time, we could talk about glucotransformases and many
8 other different drug-metabolizing enzyme families --
9 they appear to be acquired in isoform-specific
10 patterns. It is no longer sufficient to say that
11 cytochrome P450 is absent in the fetus and increases
12 in expression over the first year of life. We really
13 need to look at individual isoforms because now we
14 have a better understanding of which specific isoforms
15 are involved in the biotransformation of specific
16 compounds.

17 I have not addressed the issue of tissue
18 specificity, but it is likely that there are
19 developmental changes in expression in the intestine.
20 One would argue that we really don't need P450 3A4 in
21 our gut until such time as we try to poison ourselves
22 by eating our external environment. The same thing

1 may be true for P-glycoprotein, that when we introduce
2 solid oral foods, that's the time at which we need to
3 protect ourselves from our environment.

4 Activities do appear to peak in young
5 children. After all, we are starting from zero as a
6 fetus and ramping up to 60 miles an hour probably in
7 the first year of life. It is uncertain to what
8 extent an increased liver-mass-to-total-body-mass
9 ratio or increased functional expression per unit area
10 of endoplasmic reticulum or volume of cytoplasm is
11 involved in the variability that we see, but it is
12 likely to be drug-specific.

13 Finally, this issue of shunting is a
14 theoretical consequence of developmental changes in
15 drug biotransformation, but probably is an issue that
16 we ought to be mindful of as we look at the
17 development of new compounds for new indications.
18 Thank you.

19 (Applause.)

20 CHAIRMAN SANTANA: Thank you, Steven.

21 We have two other presentations that
22 relate to issues of pharmacokinetics,

1 pharmacodynamics, and pharmacogenomics, and then we
2 are going to have a period of discussion. But if
3 anybody has any burning comments or questions, I think
4 we will have a minute or two to take that now.

5 Anybody at the table? Eric?

6 DR. ROWINSKY: Maybe this is just, I
7 guess, to possibly feed the fuel for further
8 discussions later. That was an excellent
9 presentation --

10 DR. LEEDER: Thank you.

11 DR. ROWINSKY: -- and it just illustrates
12 how simple we have it in adult pharmacology and in
13 adult medicine, just illustrating the dynamics of
14 childhood metabolizing systems and the differences in
15 really pharmacokinetics of drugs which portends
16 dosing.

17 But I think that I would just like to --
18 and this is a premise for future studies, when we
19 think about bridging between adults and children,
20 potentially shooting for pharmacologic concentrations
21 that might be effective or AUCs between adults and
22 children to accelerate Phase I trials. But can we

1 assume that pharmacodynamics between adults and
2 children are less disparate, meaning the Cmaxs and the
3 AUCs that we're going to potentially target in
4 childhood studies, can we assume that at the maximum
5 tolerated dose of a drug in children as compared to
6 adults we have similar pertinent pharmacokinetic
7 variables; that is, steady-state concentrations, Cmaxs
8 or AUCs? Are the pharmacodynamics or the effect on
9 relationships similar, which would make bridging
10 studies a lot easier at least?

11 DR. LEEDER: My own personal bias is that,
12 when trying to address the issues of effect, we are
13 probably going to look at, need to look at, the
14 developmental changes in the drug target, whatever
15 that is. We may not need to achieve the same Cmax if
16 there are differences in receptor density, for
17 example, that are a function of development.

18 We do a lot of this dosing without knowing
19 what's going on at the effect end of the spectrum.
20 Part of it is because it is easier for us to measure
21 a target drug concentration than it is to come up with
22 some quantitative measure, validated quantitative

1 measure of drug effect.

2 I am treading a little bit on thin ice now
3 by trying to use a cancer illustration, but the issue
4 that was raised earlier is that decrease in tumor size
5 is probably one step removed from whatever it is that
6 the drug is supposed to be targeting. I don't know
7 just how things like receptors or intracellular
8 signaling pathways differ with development.

9 DR. ROWINSKY: Well, I know that that's a
10 very difficult question. I am not even asking you to
11 think about the tumor, but just think about toxicity.
12 Are the pharmacokinetic variables in children and
13 adults similar at comparable toxicological severities,
14 meaning at the MTD? Can we assume that?

15 DR. LEEDER: Well, that I don't know. For
16 some medications we use similar -- again, I can only
17 talk about things like phenytoin or carbamazepine.
18 The targeted serum concentrations are the same, and we
19 assume that those apply, but many of the ranges were
20 actually derived from adult studies. So it is
21 difficult to know.

22 Perhaps the other --

1 MS. RELING: Both Clinton and I can jump
2 in here. I mean, there's many examples in oncology
3 where the indices might be the same. You might still
4 want to look at AUC or steady-state concentration or
5 time-above-some-minimum-threshold concentration, but
6 kids tolerate higher drug exposures than adults do.
7 They've got better protoplasm, and that means we may
8 be able to push the concentrations higher and get a
9 better effect. Taxol is a beautiful example.

10 DR. ROWINSKY: Well, that is a very
11 important issue because at least we can have a goal.
12 If we can assume that goal is stable, then it serves
13 as a starting point.

14 CHAIRMAN SANTANA: I think this
15 presentation reminded me that during a period of
16 discussion one of the things, one of the goals that we
17 have is to advise the Agency, when they are trying to
18 implement this rule, what kind of studies and the
19 level of rigor in the studies that they are going to
20 require.

21 In your presentation I was reminded,
22 having seen some recent protocols, particularly Phase

1 I studies in which this concept of looking at PK in
2 different age groups was introduced into the study.
3 I would caution that we need to balance that against
4 this issue that was discussed earlier this morning
5 about minimizing risk, and maybe those kinds of
6 studies should not be part of the Phase I design in
7 the early dose groups, but should include patients
8 maybe once the MTD has been defined or closer to the
9 MTD, or maybe those different age groups should have
10 PKs when the Phase II studies are designed.

11 I think that's a point that I would like
12 for us to discuss later on. We will put it on the
13 notepad here and come and revisit it later.

14 Donna, one last question and then we will
15 take a break.

16 DR. PRZEPIORKA: Just one quick question,
17 if you can give us two sentences on changes in renal
18 function with age?

19 DR. LEEDER: Renal function appears to be
20 mature by a year of age, and the kidney receives 20,
21 25 percent of cardiac output by that stage. Looking
22 at it from the field perspective, immature newborns

1 will acquire renal function at a similar rate as term
2 newborns, but they start at a lower level. The two
3 issues involved are nephrogenesis, which is not
4 necessarily complete in the immature newborn, and
5 recruitment of functional nephrons, which is acquired
6 after birth. So probably by a year of age.

7 CHAIRMAN SANTANA: Let's go ahead and take
8 a 15-minute break, and we will reconvene at half past
9 the hour. Thank you.

10 (Whereupon, the foregoing matter went off
11 the record at 10:12 a.m. and went back on the record
12 at 10:35 a.m.)

13 CHAIRMAN SANTANA: If I can ask everyone
14 to take their seats, please.

15 Kimberly has two brief administrative
16 announcements. So, Kimberly?

17 MS. TOPPER: When we break for lunch,
18 there is a table in the restaurant that is right
19 behind us that has been reserved for the Committee, so
20 that you can get in and get out, and we will get
21 started back quicker.

22 Then somewhere over along here there is a

1 transportation form. If you need us to arrange for
2 the taxi to get you back to whichever airport, please
3 indicate your airport, your flight time, and that
4 information, and we will make sure the taxis are
5 waiting when the meeting is over. Thank you.

6 CHAIRMAN SANTANA: Thank you, Kimberly.

7 We will resume, and I will invite Dr.
8 Stewart to do his presentation; then after that, Dr.
9 Relling, and then we will have a period of discussion.

10 Dr. Stewart?

11 DR. STEWART: Thank you very much, Dr.
12 Santana.

13 I would like to thank Dr. Hirschfeld for
14 his kind invitation to present today. My presentation
15 is entitled, "Challenges of pharmacokinetic and
16 pharmacodynamic assessments in pediatric oncology.
17 Due to the time limitations, I don't really want to
18 review all the pediatric oncology. I know pediatric
19 oncology pharmacokinetic and pharmacodynamic studies;
20 I know those of you in the audience who are very glad
21 that I'm not going to do that.

22 What I would rather do, however, is to

1 focus on the area of pediatric oncology, the PK/PD
2 studies that we have spent the last eight to ten years
3 studying. That is in the area of the topoisomerase I
4 inhibitors, and in doing that what I would like to do
5 is to just sort of generalize, where appropriate, on
6 sort of the adult pediatric comparisons, generalize on
7 issues dealing with model systems, and also talk about
8 approaches perhaps that we might use for future
9 pediatric studies.

10 Now in terms of the presentation, my
11 outline is broken up into four parts that consist of
12 -- the first part will be a summary of results of
13 early clinical pharmacokinetic studies that we
14 performed with topoisomerase I inhibitors at St. Jude.
15 I guess what I should say before I move into that is
16 that there have been a lot of studies performed by a
17 number of investigators within this room as well as
18 internationally with these particular compounds, but
19 what I have chosen, again, with the time limitations,
20 given the time limitations, I have chosen to do is to
21 focus on the work that we have done.

22 Then what I would like to do is talk a

1 little bit about some of the results from some of the
2 non-clinical studies that we have done and how those
3 were used to help in the design of some of our
4 clinical trials of these agents, specifically some of
5 the Phase I(b)(2)(a) studies, then summarize some of
6 the results of these latter clinical trials, again the
7 Phase I(b)(2)(a), and then spend one slide talking
8 about some of my thoughts regarding design of the
9 clinical PK studies of these targeted drug therapy
10 approaches, and then have a final slide.

11 So, in terms of the application of non-
12 clinical PK/PD studies to enhance anti-cancer drug
13 development, I realize perhaps a lot of you in the
14 room understand the different phases of drug
15 development, but what I would like to do is to spend
16 just a minute to perhaps get everyone up-to-speed on
17 this; for those of you who may not think about this on
18 an everyday basis, talk about the different phases of
19 drug development, and in doing that, talk about how we
20 use non-clinical PK/PD studies in a very general sense
21 in terms of drug development.

22 So, obviously, drugs come from a variety

1 of sources. At our institution they come from drug
2 companies, from the NCI, from a variety of sources.
3 But the studies that we conduct then lead to -- the
4 results from the PK/PD studies lead to the design of
5 the Phase I clinical trials. Then, not unlike a lot
6 of other institutions, the data from those studies
7 feed back into perhaps design of additional non-
8 clinical PK/PD studies with the goal there to evaluate
9 perhaps additional schedules, dosing, look at
10 additional efficacy studies, so that that will feed
11 into additional Phase I clinical trials with the goal
12 to then move into Phase II clinical trials, looking
13 more at the efficacy of the compound.

14 Now the results of these Phase II clinical
15 trials often feed back into the Phase I clinical
16 trials, where we are evaluating the clinical safety of
17 new schedules, dosages, and combinations, based upon
18 some of the results from the Phase II clinical trials,
19 and oftentimes the results of the Phase II clinical
20 trials will carry us back into the non-clinical models
21 to evaluate additional aspects of the compound. Then,
22 as you well know, the Phase III clinical trials and

1 then the Phase IV post-marketing studies are
2 conducted.

3 So, again, what I will want to talk about
4 today are studies with the topoisomerase inhibitors,
5 and for those of you who don't think about those on a
6 daily basis, there are basically two of these
7 compounds that are available for use in pediatric
8 oncology, Topotecan and Irinotecan. What I have
9 depicted on the slide is the camptoesin backbone
10 molecules, the penylcyclic structure.

11 One of the things that we've had to face
12 when we do these PK studies that is a little bit of a
13 challenge, however, it is not something that we
14 haven't been able to overcome, is the fact that this
15 compound, the E-ring system, the lactone ring, which
16 has been thought to be the active moiety, and to
17 measure this we've had to stabilize this by doing a
18 methanolic precipitation within a relatively short
19 period of time. If this is not done, the compound,
20 the camptoesin molecule undergoes a reversible PH-
21 dependent hydrolysis to an open hydroxy acid form,
22 which is thought, conventional wisdom is right now,

1 that that's an inactive form, does not have anti-tumor
2 activity. So that is one of the challenges that we
3 faced with these particular molecules.

4 Now the two molecules, like I have said,
5 Irinotecan is basically a pro-drug for the active
6 moiety SN-38. It basically has a moiety that's
7 cleaved off here, and then Topotecan is the dimethyl
8 aminomethyl moiety up here at the R3 position. We
9 will talk more about that later.

10 Most of the studies that I will talk about
11 today will deal primarily with Topotecan, not because
12 I have -- as Kimberly read, I don't have stock in
13 Topotecan, but we've done most of our studies with
14 Topotecan. I will mention a little bit of the work
15 that we have done with Irinotecan. It is just a
16 matter of the sequencing of the way that the studies
17 have been done.

18 Most of the work that we have done with
19 Topotecan we are planning now to sort of move into
20 Irinotecan and do a lot of the same kinds of studies.
21 So it is basically a paradigm that can be used in
22 both, although I will tell you that Irinotecan is a

1 little more complex to deal with. I will talk about
2 that in a little bit.

3 So let me just move into some of the
4 initial clinical trials that we deal with
5 topoisomerase I inhibitors. The first study we did
6 way back when, in collaboration with Dr. Charles
7 Pratt, was a 72-hour continuous infusion. We saw
8 Topotecan -- this was in children with recurrent solid
9 tumors -- we saw anti-tumor activity, although, as I
10 have asterisked here, this was not what we thought,
11 based on our non-clinical studies, to be the optimal
12 method of administering this particular compound.

13 The dose-limiting toxicity was
14 myelosuppression. What was interesting for the PK
15 part of this was that this provided the preliminary
16 data for the derivation of a limited sampling model
17 which we used for future studies. I will get into
18 that a little bit later in my talk.

19 The other aspect of this particular study
20 was that we did pharmacodynamics, and the
21 pharmacodynamic relationship that we saw from this
22 study was very similar to what had been published

1 earlier by other investigators, Dr. Lewinsky and
2 colleagues and others also.

3 The second study we performed was in
4 collaboration with Dr. Wayne Furman. It was a 120-
5 hour continuous infusion of Topotecan in children with
6 recurrent leukemia. This is a little bit different
7 from this Phase I study in that we used what was
8 called, what Dr. Bill Evans has coined the term,
9 "maximally-tolerated systemic exposure."

10 Perhaps the figure here will help me
11 describe that, in that as opposed to escalating to
12 dose to toxicity, what we did here was we escalated
13 the exposure, the Topotecan plasma concentrations, to
14 toxicity. So patients were enrolled in different
15 concentration cohorts, and those cohorts were
16 increased until they observed toxicity. So the dose
17 was individualized for those patients based on what
18 systemic exposure cohort they were enrolled in.

19 In this study we also observed an anti-
20 leukemic effect; again, the asterisk meaning we didn't
21 really think this was the right regimen to use. We
22 could talk about that later on.

1 But this limiting toxicity here was
2 mucositis, which was interesting because this 120-hour
3 continuous infusion is really the only time the
4 mucositis has been seen as the DLT.

5 The PK/PD observations were also
6 interesting, and that is what I have presented in the
7 slide here, because what I am plotting on the vertical
8 axis is proportion of patients or proportion of
9 courses versus the plasma systemic exposure, and the
10 green line represents the oncolytic response, and the
11 red or fuchsia or pink or peach-colored line
12 represents the dose-limiting toxicity or mucositis.

13 What we observed from this study was that,
14 once you got above a systemic exposure of
15 approximately two, you really didn't get any more in
16 the way of anti-leukemic effect or oncolytic response,
17 but what you did do was you got more in the way of
18 mucositis. So that was the results from that
19 particular study.

20 Then we moved into a series of oral
21 Topotecan studies where we evaluated 15- and 21-day
22 dosing of oral Topotecan, showed that it was well-

1 absorbed, saw wide interpatient variability, but also
2 observed that it was less than the inpatient
3 variability.

4 In all of these studies we were fortunate
5 that, for various reasons, patients had -- we were
6 able to get access, or we had access, to Topotecan or
7 to CSF samples. We measured Topotecan and found that
8 there was extensive penetration similar to what Dr.
9 Frank Balis had published in the primate model, Frank
10 Balis and Susan Blaney had published, in the primate
11 model, as depicted on this overhead or this figure,
12 where we are plotting Topotecan CSF penetration on the
13 vertical axis. There was really no difference in the
14 extent of penetration for the 30-minute infusion, 24-
15 hour infusion, or the 72-hour infusion.

16 What you will note is that this is a
17 really very high penetration for an anti-cancer drug,
18 and we will take advantage of this particular
19 characteristic of this drug in subsequent clinical
20 trials.

21 Now the adults had moved forward with a
22 short infusion given daily for five days, and this was

1 the first study in which we, the pediatric community,
2 did this. It was a Pediatric Oncology Group Study
3 92-75. Dr. David Tubergen was the principal
4 investigator, and we did the pharmacokinetic studies
5 at St. Jude. This was in children with recurrent
6 solid tumors. It then moved to children with
7 recurrent leukemia, and then there was a study in
8 which we did it just in recurrent leukemia. We noted
9 anti-tumor activity in this particular trial, DLT with
10 myelosuppression, again, similar to what adults had
11 seen.

12 Here was where we applied our limited
13 sampling model, because this was a study that was
14 conducted in a cooperative group and required, if we
15 were going to do this, we had to simplify this. We
16 had to make it where it was exportable, something that
17 could be done and accomplished on a reasonable basis.

18 So we were able to export this, using a
19 limited sampling model, and then in a subset of
20 patients we were able to validate this particular
21 limited sampling model. We observed a very wide
22 interpatient variability in Topotecan systemic -- I'm

1 sorry, Topotecan clearance, which led to overlap in
2 systemic exposure because the differences in dose
3 levels were so narrow.

4 So you have 20 percent differences in dose
5 levels, and yet the difference in the interpatient
6 variability and clearance was around 500 percent,
7 let's say, at the 2.4 milligram-per-meter-squared
8 level.

9 So it is interesting to me, when we talk
10 about the fact that we want to have these differences
11 in dose levels between patients, and yet no one, or it
12 is very rare that you really hear people talk about
13 the fact that there is pharmacokinetic variability
14 which is going to lead to a difference in systemic
15 exposure.

16 So you can change your dose from 1.4 to
17 1.7 to 2.0 to 2.4, but it is very likely that the
18 systemic exposure that a patient will achieve is not
19 going to be different between the different patients.
20 So I think this is -- I have this opportunity to have
21 a soapbox, so I got on my soapbox; now I'll get off of
22 it.

1 So those are the studies that I wanted to
2 talk about in terms of our early clinical trials for
3 Topotecan. What I would like to do now is talk about
4 a clinical trial that we did at St. Jude with
5 Irinotecan.

6 This is Irinotecan. The Irinotecan
7 molecule is in the middle of the slide. It is a
8 compound that undergoes conversion by
9 carboxylesterases to form SN-38, which is the active
10 moiety that undergoes metabolism by the CYP 3A4 to
11 form two inactive metabolites, the APC and NPC, and
12 then SN-38 is converted by glucuronidation to SN-38G.

13 So this study was a 60-minute infusion in
14 children with recurrent solid tumors. We used a
15 schedule of daily times five times two, and I will
16 talk about that in a few minutes, when I talk about
17 some of our non-clinical studies where that particular
18 schedule came from.

19 But what we did was we noted very
20 significant anti-tumor activity for the compound on
21 this schedule. As noted by adults that have reported
22 data from this compound, the DLT was diarrhea. As you

1 can imagine, the pharmacokinetics of this compound are
2 very complex, and the metabolism, as I have depicted
3 over here, is a very complex issue, although not
4 something that can't be handled.

5 SN-38, also something else that has to be
6 considered is that it is a very highly protein-bound
7 compound.

8 Then, finally, this is a compound that is
9 a pharmacogeneticist's dream with all the different
10 metabolites and metabolic pathways.

11 So let me just spend a summary slide
12 comparing the results of the adult and pediatric Phase
13 I studies for the topoisomerase I inhibitors. So
14 let's talk about the pharmacokinetics.

15 Topotecan lactone systemic clearance, and
16 I think it is fair to say the Irinotecan lactone
17 systemic clearance, have been similar between the
18 adults and children. I qualify that by saying in
19 early studies, and I asterisk that. I will clarify
20 that in a subsequent slide. So let's not get too
21 carried away with that. That is not completely true.
22 So if you happen to doze off and don't hear the rest

1 of my talk, it is not completely true that Topotecan
2 lactone clearance is similar between the two groups.
3 It was in the early studies, but it is not overall.
4 Okay?

5 The problem with that is that in the early
6 studies we were studying limited patient populations.
7 We had small numbers of patients. I will tip my hand
8 by saying the age ranges were fairly narrow in the
9 early populations, and we didn't have the drug-drug
10 interaction studies that we have had in subsequent
11 studies.

12 What about PD? This is something maybe
13 that Eric was alluding to. It looks like the
14 relations, the PD relationships, between the two
15 groups are similar for the most part. There is an
16 interesting slide that I prepared that, if I had time,
17 I would like to show you, but in the interest of time
18 I wasn't able to.

19 The MTD, as Mary said, is higher typically
20 for comparable schedules, but part of the problem we
21 have is that our schedule, this daily times five times
22 two, is different from what has been used in adults.

1 So it makes for a problematic comparison. The dose-
2 limiting toxicity between the two groups for the most
3 part is very comparable.

4 Now let's talk about the application, the
5 results, results from non-clinical studies of Topo I
6 inhibitors to the design of clinical trials. Again, I
7 will just refresh your memory about the first slide
8 that I showed with this sort of paradigm of using non-
9 clinical studies as sort of a bedrock for the design
10 of the Phase I/Phase II studies.

11 So at St. Jude's, for those of you who
12 have heard Dr. Peter Houghton talk, one of the models
13 that we use quite extensively is the xenograft model.
14 That is where one takes a tumor from a child and
15 implants it into a immunocompromised mouse, currently
16 a skid mouse, and evaluates both schedules and doses
17 of different drugs.

18 The other aspect that we have done, or we
19 have done quite a bit of, with the Topo I inhibitors
20 is then to evaluate the pharmacokinetics in the murine
21 model, the murine xenograft model, and compare that
22 with humans.

1 Now there has been a lot of criticism
2 about this particular approach. It is very
3 justifiable if the pharmacokinetics for that
4 particular compound of interest are different between
5 humans and mice. We have been very fortunate for
6 Topotecan that the PK between mice and man are very
7 similar. The half-life, shape of the curve, the
8 systemic exposure are all very similar.

9 Irinotecan is a little bit different in
10 the sense that mice have quite a bit of esterase in
11 their plasma. So they have a very different profile
12 in terms of the production of the SN-38. However, we
13 are studying now a different transgenic mouse, ES1-
14 minus mouse, which is deficient in esterase, so it has
15 no esterase in the plasma. It is a little bit
16 different in terms of its production of SN-38. It may
17 be a little more like the human in terms of the
18 production of SN-38. So what we are trying to do is
19 find the most appropriate model to be able to evaluate
20 Irinotecan in this particular setting. The take-home
21 message from this slide is this is a good model to use
22 as long as you are cognizant of the differences in

1 your species.

2 So what are the lessons that we have
3 learned? Well, Pete's done a lot of studies with
4 these drugs and these animals, and I am summarizing
5 probably 12 years of his life in one slide. So bear
6 with me.

7 What he has found is that these agents are
8 very schedule-dependent. The duration of therapy is
9 critical. The administration interval is very
10 important, and that is what has led us to be a very
11 large proponent of the protracted dosing schedule and
12 saying that that is associated with very significant
13 anti-tumor activity.

14 The fact that these compounds are very
15 dose-dependent, such that at very high doses you don't
16 get any more anti-tumor activity; you can't kill the
17 tumor cell any more at higher doses. However, there
18 is a critical threshold drug exposure that is
19 necessary for anti-tumor activity, and that's depicted
20 on this figure on the righthand side, where we are
21 plotting AUC versus different neuroblastomas'
22 intergraft lines, showing that once you exceed a

1 certain AUC, you have a very good response rate.

2 So what this has led us to do is to
3 develop in our clinical dosing schedule this low-dose
4 protracted schedule, this Dx5x2 that I have alluded to
5 a little bit earlier in a previous slide.

6 Now the other model that we use quite a
7 bit, the other animal model we use quite a bit, is the
8 non-human primate. Now Dr. Balis and Dr. Poplack both
9 have used this quite extensively. We have used this
10 to study Topotecan in CNS malignancies.

11 We have used it, in addition to studying
12 the penetration, what we have looked at this model for
13 is to evaluate the effect of Topotecan infusion rate
14 on the CSF concentrations throughout the neuraxis,
15 looking both at ventricular and lumbar concentrations,
16 and using it as a prelude to the design of a clinical
17 trial. Also, to try to help us generate a PK model
18 that would describe the plasma and CSF disposition, so
19 that we could then take the data from this particular
20 model and use it to design a clinical trial to treat
21 children with CNS tumors.

22 Now what I would like to do is to move

1 into a summary of the results of some of our later
2 clinical trials of Topo I inhibitors, talking about
3 some of the 1B, 1B2A studies. I am really sort of
4 pressed for time, so I really can't spend a lot of
5 time talking about this whole concept of PK-guided
6 dosing. A lot of you have heard me talk a lot about
7 this.

8 Suffice it to say that dose intensity in
9 clinical response for a lot of -- there's a lot of
10 good rationale for it, for the appropriate kinds of
11 tumors, but dose intensity doesn't equal systemic
12 intensity, for a number of reasons. One of the most
13 important reasons -- and Steve just alluded to this
14 earlier before the break in his very good talk -- is
15 that there is pharmacokinetic variability. A lot of
16 it is maturation-related.

17 We have observed with Topotecan a lot of
18 interpatient variability and systemic clearance. I
19 have already mentioned the maturational changes, renal
20 and hepatic impairment due to other concomitant drug
21 therapy. Mary will talk a lot about the obvious
22 problems with -- or not problems, but the

1 considerations of pharmacogenetics, and then drug-drug
2 interactions.

3 So there are a number of considerations we
4 have for selecting drugs for pharmacokinetically-
5 guided dosing, and let me just go ahead and get them
6 all out there. There are general considerations, and
7 they are listed here on the slide, logistical
8 considerations.

9 Our dosage schedule really lends itself
10 well, the Dx5x2 lends itself well to that. We have an
11 assay method available.

12 The fact that we have done these earlier
13 studies, we well-characterized our PK model. We have
14 population priors available for a Bayesian analysis,
15 and the fact that we have the limiting sampling model
16 available makes it very easy for us to be able to do
17 these particular studies.

18 So the selection of our initial dose, we
19 used our non-clinical studies to be able to assist in
20 doing that. The second thing that you have to deal
21 with, and we would spend a lot of time talking about
22 how one selects the pharmacokinetic metric to express

1 your exposure. We have used for our studies the area
2 under the concentration and time curve, but there are
3 a lot of ways you could do it: Cmax, Cmin, time above
4 a threshold. There's just a lot of ways to do it.

5 This particular slide just shows the setup
6 of one of our pharmacokinetically-guided studies,
7 where the drug is administered daily for five days.
8 We do PK studies on day one, three, eight, ten, and
9 twelve. This was our first study, which was kind of
10 a feasibility study.

11 Then based upon whether the patient was
12 in-target or out, we would adjust the dose to get the
13 patient in-target, and this is basically sort of the
14 general schema of how we have done most all of our
15 studies.

16 So the first study we did basically was
17 the feasibility study. We noted anti-tumor activity.
18 We were able to achieve our target exposure, and we
19 reduced interpatient variability. Then we have done
20 subsequent studies, a couple of studies where we have
21 done pharmacokinetically-guided Topotecan in
22 combination with Vincristine. We have noted anti-

1 tumor activity, myelosuppression. We had to use a
2 little bit lower Topotecan target.

3 Let me just move on. Okay, so in a Phase
4 II study -- this is the study that Dr. Santana is the
5 principal investigator on -- we've done PK-guided
6 dosing in this particular study in children with high-
7 risk neuroblastoma. You will have to ask Dr. Santana
8 about the clinical results, although I am sure that
9 they are very good. The last data I had, the partial
10 response rate was greater than 50 percent. We were
11 able to achieve our target exposure and decrease the
12 interpatient variability by doing this
13 pharmacokinetically-guided dosing.

14 Now this is one of the things I really
15 wanted to get into, and I brought this up a little bit
16 earlier. We have studied on this protocol, and those
17 of you who treat children with neuroblastoma, you are
18 aware of this. This is a disease of children of a
19 younger age.

20 We studied ten infants that were less than
21 two years of age, and in this population of patients
22 we noted that Topotecan lactone systemic clearance was

1 significantly less than in other patients. The
2 clearance was 12 versus 21 in other patients.

3 So what we have learned from this is a way
4 to dose Topotecan in children that were less than 12
5 years of age. So it is, I think, a very important
6 contribution.

7 We have done a study in children with
8 high-risk medulloblastoma, where we used PK-guided
9 dosing to attain drug exposure and a minor exposure
10 compartment.

11 Manageable toxicities, what I would like
12 to get to here is we have noted a couple of drug-drug
13 interactions which I don't think have really been
14 alluded to in adults. The enzyme-inducing
15 anticonvulsant has for 9-AC and enzyme-inducing
16 anticonvulsants and for Irinotecan, but the Topotecan
17 enzyme-inducing anticonvulsants really hasn't been
18 reported in adults. We also reported that
19 dexamethasone increases Topotecan clearance. Both of
20 these were observations that came out of this
21 particular study.

22 So those were the results of some of our

1 latter clinical drug development studies. The next-
2 to-the-last slide are some issues that I would like to
3 bring up as it relates to the design of molecular
4 target-based anti-cancer drugs in children. I am
5 afraid that what I have got here is I've got more
6 questions than I have answers.

7 We are in the process of designing a lot
8 of these studies ourselves at St. Jude, and so we have
9 a lot of these sort of questions. Maybe I look
10 forward to the discussion period so we can profit from
11 the corporate wisdom in the room.

12 So, you know, probably the first question
13 that would come to mind is, when you start talking
14 about molecular target-based anti-cancer drugs, what
15 is the target? I think that is an important question.
16 So is the target just the expression of the protein in
17 vivo or do you have to have an expression of the
18 protein in vivo and data from an in vitro study that
19 says that protein is actually sort of important? Or
20 do you actually have to have some studies that say
21 there's some prognostic significance to the protein
22 that is your target?

1 So I think there's a lot of questions that
2 remain to be determined about what a target is. Then
3 I think if we could ever come on an agreement of what
4 a target is, then I think there is a need for the
5 development of a relevant model in which we could
6 evaluate that target. The in vitro model is
7 important, the xenograft model, the transgenic model,
8 but I think, regardless of which model we pick, it is
9 going to require that we have a complete understanding
10 of the pathway or pathways that are involved.

11 Then, as we have these questions answered,
12 which I don't necessarily think there are answers for
13 them, but if we do come to some kind of consensus, it
14 is going to be important to come up with some sort of
15 pharmacokinetic metric, just as we face that same
16 question with PK-guided dosing: Is it IC-50 in the
17 plasma tissue, is it an AUC, is it some other measure
18 of drug exposure? What do we use as a metric perhaps
19 to convert between adults and pediatrics or between
20 the lab and the clinic?

21 Then I think it is important to consider
22 that pediatric tumors -- and I say "likely" -- what I

1 should say here is "may have" different biological
2 pathways from adults and that, therefore, they may
3 have different targets. So that is just something,
4 perhaps a provocative thought.

5 So I haven't really talked a lot about
6 challenges per se because I am very fortunate that the
7 resources and infrastructure at St. Jude are in place
8 to be able to make these studies possible. However,
9 because of a lot of the work of Mark Bernstein and
10 Peter Adamson, the infrastructure I think is in place,
11 or is coming in place, in the developmental
12 therapeutics community and the COG to be able to make
13 these studies possible. I shouldn't just stop with
14 Mark. I mean, there are a lot of people that have
15 worked in COG and CCG to make these kinds of studies
16 possible.

17 But I think the challenge for the future
18 is to apply what we have learned in these studies of
19 Topotecan to combination studies for the future. I
20 just bring forth one example. This is a study that
21 Victor and I and Julie Park have talked about a little
22 bit, about a combination of Topotecan with

1 cyclophosphamide in one aspect of therapy for
2 neuroblastoma, and the question becomes how to dose
3 Topotecan.

4 We are in the midst of doing a population
5 pharmacokinetic study. Everything that I have told
6 you so far is all single pharmacokinetics, single
7 patients. We have done non-mini-mAnalysis of
8 Topotecan, and what we have found from our non-mini-
9 mAnalysis is that Topotecan clearance is related to
10 BSA, concomitant phenytoin therapy, serum creatinine
11 in age, and perhaps a model that includes these
12 patient co-variants is something we could use to
13 prospectively dose Topotecan, much like we dose
14 carboplatin based on creatinine clearance.

15 The other aspect is PK studies will
16 provide insight into differences in drug disposition,
17 which can then be explained in many cases by genetic
18 variations and drug metabolism or transport or the
19 genotype approach.

20 So, with that, I will close, and I thank
21 you very much for your kind attention.

22 (Applause.)

1 CHAIRMAN SANTANA: Thank you, Clinton, for
2 a rather extensive overview of this issue using the
3 camptothecins as a model. I think we have a brief
4 time for some questions while we change computers.
5 Maybe I will ask the first question, which is kind of
6 a little bit of followup of what Rowinsky was alluding
7 to earlier.

8 Using the camptothecins as a model, because
9 we're not really talking here about the drug
10 specifically but as a model, and I want to make that
11 clear for the audience and for the discussion. But
12 using it as a model, do we have enough data in this
13 class of compounds that we can address the question
14 that Eric asked earlier, whether for this class of
15 compounds systemic exposures that are seen in adults
16 to some percentage should be what we use in children
17 when we design our trials, or vice versa? How do we
18 use the pediatric data in relation to what we know
19 about similar exposures in adults?

20 DR. STEWART: Yes. See, the problem is,
21 and I was actually giving that a lot of thought while
22 I was putting the talk together, I think the problem

1 becomes one of comparable schedules. So you can't
2 look at exposures independent of schedule. So the
3 schedule that most adult studies are on are daily
4 times five. I think the study that Wayne did, Wayne
5 Furman did, in the Pediatric Oncology Group, fairly
6 convincingly showed that, and other studies that we
7 have done fairly convincingly have shown that schedule
8 is very important to the anti-tumor effect of the
9 camptothecins.

10 So I don't think it is fair to compare a
11 five-day schedule at some exposure to a ten-day
12 schedule at some other exposure. So I don't think you
13 can just -- it would be very easy to say, oh, okay, so
14 the cumulative exposure is this and the cumulative
15 exposure is this, so let's just start making
16 comparisons.

17 You can't remove schedule from that
18 comparison. Do you see what I'm saying?

19 CHAIRMAN SANTANA: Yes.

20 DR. STEWART: So I think that complicates
21 it a little bit.

22 CHAIRMAN SANTANA: Donna, you had a

1 comment or question?

2 DR. PRZEPIORKA: Just a quick question for
3 either you or Dr. Leeder: Another class of drugs
4 coming out now are the biologics and the monoclonals.
5 Could either of you have any information on the
6 pharmacology of monoclonal antibody in pediatric
7 patients?

8 DR. STEWART: Steve?

9 DR. LEEDER: I don't.

10 CHAIRMAN SANTANA: Do you have any more
11 detail?

12 DR. LEEDER: Do you want to comment?
13 Malcom, do you want to comment?

14 DR. SMITH: I think it probably depends to
15 some extent on the monoclonal. For example, for
16 Atoxomab, there's an extensive body of experience in
17 adults and some limited experience in children, but we
18 are heavily building upon the adult experience to base
19 our dosing and schedule and combinations that we use
20 in children.

21 DR. ROWINSKY: There is probably less
22 concern with antibodies, as antibodies generally

1 behave in a very similar way, and the target may not
2 be as important. So just knowing the differences in
3 antibody clearance between children and adults, one
4 can extrapolate. I think it becomes much simpler than
5 the issue with drugs that behave in so many different
6 ways and are cleared with so many different variables
7 impacting. I think it is much simpler with
8 antibodies.

9 DR. GOOTENBERG: I represent biologics,
10 and with all due deference to Dr. Pazdur and Dr.
11 Hirschfeld here, we think that biologics, monoclonal
12 antibodies, and cytokines, and cellular therapies are
13 a big wave of the future. So I think that your
14 question is right, Donna, it is right on target, and
15 it is not just monoclonal antibodies. That forms a
16 very small part of the spectrum of biologics that will
17 be coming down the pathway soon.

18 I think it is going to be a crucial
19 question. Since the rule applies to these also, the
20 differences in the pharmacokinetics and the
21 pharmacodynamics, and wait until you try to work this
22 out with cellular therapies and gene therapies and the

1 different vectors that are being developed now. It's
2 just somewhere where I think a lot of attention is
3 going to need to be paid.

4 CHAIRMAN SANTANA: Malcom?

5 DR. SMITH: Just one comment. It was an
6 excellent presentation.

7 You talked about targets and defining a
8 target and whether a target needed to be a prognostic
9 factor. I would point out something like BCR-able,
10 for example, is an outstanding target, but with MPH-
11 positive leukemias, it is not prognostic because every
12 case has it. So it is not so key that it be a
13 prognostic factor, but just that I would say it needs
14 to be central to growth, survival of the cells; it
15 needs to be intrinsic to some signaling pathways that
16 are required for cell growth, like BCR-able, like
17 mutated CKID and CKIT.

18 CHAIRMAN SANTANA: Other comments or
19 questions?

20 (No response.)

21 CHAIRMAN SANTANA: Then, Dr. Relling,
22 please.

1 MS. RELING: Thank you, and I also
2 appreciate the opportunity to be here. Obviously, I
3 think this is an important topic.

4 So how do we relate pharmacogenetics to
5 translating oncology studies to pediatrics? First of
6 all, I guess the current interest in pharmacogenetics
7 has been partly precipitated by the realization from
8 the fruits of the human genome project, that every
9 human gene is polymorphic. So, as we look around the
10 room and we see how we all differ from each other, it
11 is obvious that there are lots of genes that must
12 contribute to all the different phenotypes that we are
13 seeing around us.

14 It has now been proven that one single
15 nucleotide polymorphism or genetic variation occurs
16 about every 400 to every 1500 base pairs. That means
17 that there's certainly at least one variation per
18 gene. In fact, there are enough that there's almost
19 certain a functional variation in every gene. Since
20 the actions of drugs in children or anyone are going
21 to be due to their interaction with the host genome
22 and the tumor genome, pharmacogenetics is going to

1 affect the action of drugs.

2 In oncology we have the added complication
3 that cancer has acquired mutations. Of course, some
4 of these tumor mutations are common to children and
5 adults, although many, many, many are not. As Dr.
6 Smith just alluded to, the 9;22 translocation that's
7 proven to be such an interesting target for new agents
8 in adults, CML is certainly present in the very rare
9 disease of childhood CML, but also present in children
10 and adults with acute lymphoblastic leukemia, and the
11 function of that translocation seems to be affected
12 quite differently in those diseases.

13 So even if we do identify common targets
14 in adults and in children, we can't assume that they
15 can be expected to respond to drugs in the same way.
16 But the germline host polymorphisms are the germline
17 host polymorphisms that are going to be present no
18 matter what the age of the person is. Of course, they
19 may express themselves a little bit differently in
20 children than adults, but the principles are going to
21 be the same.

22 So this just illustrates the fact that in

1 cancer we have two genomes to worry about: the host
2 genome with this at least one variation per gene
3 characteristic and the tumor genome that by definition
4 has acquired at least one, and probably many,
5 variations that differ from the host tissue from which
6 it arose.

7 Genetic variation in both the host -- and
8 that's what we really mean by talking about genetic
9 polymorphisms and pharmacogenetics -- as well as
10 genetic variation in the tumor will contribute to the
11 bioavailability of drugs; that is, their availability
12 to the tumor that will affect the intrinsic
13 sensitivity of the tumor to anti-cancer drugs and that
14 will affect the host risk of toxicity.

15 By the relative size of the host versus
16 the tumor genomes depicted here, as well as the degree
17 of interaction, we get an idea, of course, that host
18 polymorphisms and tumor polymorphisms are going to
19 affect how much drug gets to the tumor. So a
20 p-glycoprotein polymorphism is not going to only
21 affect how much drug is absorbed and how much is
22 excreted in the bile and how much is excreted in the

1 kidney, but it is also going to have some baseline
2 effect on the tumor. If the tumor has acquired
3 mutations in p-glycoprotein, then that will also
4 affect drug bioavailability to the tumor.

5 Of course, the risk of toxicity from anti-
6 cancer drugs is largely determined by the host
7 polymorphisms. So many of the clues that we get about
8 host polymorphisms from adult oncology, we can
9 certainly extrapolate or at least test in pediatric
10 oncology.

11 So, given a similar schedule of drugs and
12 similar regimens, pharmacogenetics should have similar
13 implications for children and adults. In terms of
14 host polymorphisms, the developmental changes that are
15 expressed in semantic tissues certainly contribute to
16 the child versus adult differences in pharmacokinetics
17 that we just heard about from Dr. Leeder and from Dr.
18 Stewart, but those germline polymorphisms should
19 affect the hosts similarly in children and in adults.

20 For the tumor, we know that there are
21 certainly many tumors that are quite different in
22 children versus adults, but for purposes of today's

1 discussion we are assuming that we need to test drugs
2 in both patient groups, and the germline polymorphisms
3 that are present could affect the tumor responsiveness
4 or invasiveness similarly in children and in adults.
5 So that if the polymorphism affects the degree of
6 metastasis, the effect of the anti-angiogenesis, we
7 assume that those things are going to be acting in
8 both patient groups.

9 I am going to give a few examples of how
10 pharmacogenetics has already been shown to have
11 implications for anti-cancer therapy. To back up a
12 second, I guess we all acknowledge that anti-cancer
13 drugs are the one therapeutic area that is clearly
14 going to benefit by optimizing the dosage of the
15 drugs. That is certainly going to be true in
16 children, where we want to give enough drug to have
17 anti-tumor effect, but not so much drug to result in
18 unacceptable host toxicity. So anything that we can
19 use to more intelligently determine the way to give
20 these drugs is worthwhile, and pharmacogenetics is
21 going to play a part in that.

22 Polymorphisms in gene products involved in

1 metabolism distribution and transport, receptors and
2 targets of the host, which all affect toxicity and
3 pharmacokinetics, as well as tumor receptors and
4 targets, as well as polymorphisms in the pathogens,
5 which still result in an incredible amount of
6 morbidity and mortality in children with cancer, all
7 have an effect on the risk of cancer development
8 itself, on the risk of host toxicity, the probability
9 of tumor response, and on the probability of severe
10 infectious complications.

11 So I will just give you a few examples.
12 The glutathione-S transferases, or GSTs, have been
13 shown to affect the risk of toxicity from anti-cancer
14 drugs as well as the chance for cure. Anti-cancer
15 drugs often have metabolites that are free-radicals or
16 electrophiles, and they can be conjugated with a
17 tripeptide glutathione, and that conjugation is
18 facilitated by glutathione transferases.

19 So that if patients have wild-type or
20 normal glutathione transferases levels, they are
21 likely to more efficiently inactivate the drugs, and
22 therefore, probably have less toxicity, but, of

1 course, that may also mean that they have less anti-
2 cancer effect. Conversely, patients with mutant
3 glutathione transferases or low glutathione
4 transferases activity will have less inactivation of
5 the drugs, potentially more toxicity, but also
6 potentially more anti-tumor effect.

7 There have actually been nice studies to
8 demonstrate both of these principles published in the
9 last couple of years. Stella Davies, as part of the
10 CCG, published a nice study where they did a
11 randomized trial in children with acute myeloid
12 leukemia, where the question was very simple. They
13 were testing a five-drug regimen of dexamethasone,
14 Atoposite, AraC, thioguanine, and daunomycin, given on
15 a standard timing schedule where the patient was
16 allowed a bit of time to recover in between courses or
17 an intensive timing schedule where one pushed on,
18 despite the presence of toxicity, which, of course, we
19 all recognize is often done in patients with AML. The
20 question was: Which schedule is better? The overall
21 results in these over 300 children was that there was
22 a slight advantage for the intensive timing schedule,

1 but whether you benefited from pushing the dosages of
2 the drug depended very much on a single genetic
3 polymorphism and glutathione transferase.

4 So they divided patients into those who
5 received the standard timing that were wild-type or
6 had the GSTT1 gene product present, standard timing
7 that were null, so no GSTT1 enzyme present, and then
8 the same genotypic groups in intensive timing.

9 You can see that in the intensive timing
10 group there was a statistically-significantly inferior
11 survivor, 43 percent versus 59 percent, in the
12 patients who received intensive timing who were
13 lacking in this single enzyme. This is a common
14 polymorphism. So 15 to 30 percent of the American
15 population is completely lacking; it's a total gene
16 deletion in the germline of this GSTT1.

17 That translated into a threefold, almost
18 a threefold, higher risk of death in remission from
19 this intensive timing regimen. That risk was not
20 present in the patients who were GSTT1 wild-type. So
21 by looking at a single gene product, we may be able to
22 start to get at individualizing therapy, and just the

1 way that we give the exact same drug combination.

2 But this contrasts with studies published
3 from Sweeney, et al., from the SWOG, who looked at
4 patients with breast cancer. So these were adult
5 women with breast cancer who received cyclophosphamide
6 and anthrocycline-containing regimens, and they looked
7 at a different form of the GST, the P1 enzyme.

8 Here the mutant form, this is looking at
9 the proportion of women surviving of their breast
10 cancer. They were more likely to survive if they did
11 have a mutant form of the GST enzyme versus the
12 patients who had at least one wild-type copy of the
13 gene for that enzyme. So there the hypothesis was
14 toxicity wasn't the main problem in overall survival.
15 Having enough drug onboard to cure the breast cancer
16 was.

17 So we can contrast these results, and I
18 apologize that these colors are the same. It's not as
19 effective as if we showed -- this is the result in the
20 adult women with breast cancer where mutant GST was
21 associated with a great anti-cancer drug effect in
22 these women with breast cancer, never given the kind

1 of intensive chemotherapy regimens we give to children
2 with AML, but the opposite was true in children with
3 AML, and that is, the mutant form of the enzyme was
4 associated with the worst overall event for survival
5 on the basis of unacceptable life-threatening toxicity
6 in those who had the null enzyme.

7 So this illustrates that the effect of
8 every polymorphism has to be evaluated in the context
9 of the disease and the intensity of the therapy. So
10 intensifying therapy in GST wild-type patients may be
11 correct in children with AML, but not necessarily in
12 adults with breast cancer.

13 Another example of polymorphisms affecting
14 anti-cancer drugs is one that was discovered many
15 years ago by D'Ozio, and others have established the
16 molecular basis of this polymorphism:
17 dihydrophyrimidine dehydrogenase is a gene product
18 that metabolites 5-fluorouracil, and it inactivates 5-
19 fluorouracil, and therefore, the lower the DPD
20 activity, the more parent drug is available to be
21 activated.

22 This is on the basis of a single single-

1 nucleotide polymorphism, a SNP, that's actually at an
2 exon-enteron border, and the presence of that SNP
3 affects whether the exon 14 is present in the gene
4 product or not. So that single mutation results in
5 the complete lack of exon 14 in the transcript, and
6 therefore, a nonfunctional protein.

7 About 3 percent of patients are
8 heterozygous for this mutation and are at very high
9 risk for severe and life-threatening toxicity from
10 5-fluorouracil when they're given doses of this drug.
11 Well, 5-fluorouracil has as its target, so it's
12 metabolized by DPD, but its target in the tumor tissue
13 is thymidylate synthase. Thymidylate synthase
14 undergoes a common genetic polymorphism, which, of
15 course, is also present -- it is present in the
16 germline tissues, and so, therefore, affects host
17 toxicity. It is also, of course, present in the tumor
18 tissues, and therefore, can affect tumor
19 responsiveness.

20 So, again, this is a case of two repeats
21 of a 28-base pair section of the promoter versus three
22 of these tandem repeats, and the individuals who have

1 two tandem repeats have lower expression of the enzyme
2 and lower TS activity. Therefore, there's less of the
3 target that has to be inhibited by the 5-fluorouracil,
4 and they have a better anti-tumor response to 5-FU.
5 Those who have three repeats have increased target
6 present, and therefore, they have a slightly worse
7 anti-tumor response to 5-FU.

8 So this slide just puts it together,
9 showing that the enzyme polymorphisms and the enzymes
10 that metabolize the drug and polymorphisms in the
11 target for the drug both will have an effect on an
12 individual patient's probability of toxicity and their
13 probability of efficacy from that drug. So that
14 germline polymorphisms can affect tumor responsiveness
15 as well as toxicity, and it illustrates that more than
16 one gene product polymorphism is likely to affect drug
17 efficacy.

18 Speaking of multiple gene products, I want
19 to illustrate some polymorphisms affecting
20 methotrexate, another commonly-used anti-cancer drug,
21 widely used in many pediatric tumors. This is an
22 extremely simplified diagram of the cellular targets

1 and enzymes involved in metabolism of methotrexate,
2 which is activated intracellularly and interacts with
3 many different targets, all of which are probably
4 involved in its anti-tumor effect as well as in its
5 toxicity.

6 I am just going to focus on one
7 polymorphism in the methylene tetrahydrofolate
8 reductase gene product. This is, again, a very common
9 polymorphism. Ten percent of us are homozygous mutant
10 for this mutation that results in lower MTHFR
11 activity. I'm one of that 10 percent. I'm at higher
12 risk for cardiovascular disease and various
13 neurological complications, so I'm taking my folic
14 acid supplementation every day. Forty percent are
15 heterozygous and 50 percent are homozygous wild-type.

16 You can tell folate metabolism, which is
17 the target of methotrexate, is complex, so it is a
18 little difficult to predict what the affected MTHFR
19 might be on methotrexate effects, but the general idea
20 was that MTHFR mutants tend to be lower folate
21 patients, and therefore, they might be more
22 susceptible to the adverse effects, and maybe also

1 higher probability of response to methotrexate.

2 Published from Seattle this year in
3 "Blood" is an analysis of the risk of oral mucositis,
4 OMI, Oral Mucositis Index, in transplant patients who
5 were given low-dose methotrexate as a preparative
6 regimen. They showed that this one single nucleotide
7 polymorphism that affects whether one is homozygous
8 mutant, heterozygote, or a wild type has an effect on
9 the risk of oral mucositis from this methotrexate. So
10 that 10 percent of the population who are homozygous
11 mutant were at a significantly higher risk from
12 mucositis from low-dose methotrexate.

13 Of course, we give a lot of methotrexate
14 at St. Jude's. So we have been curious as to what it
15 would mean for us, but we have not found that MTHFR
16 genotype status affects toxicity after high-dose
17 methotrexate. That is higher doses that are given
18 with a rescue agent called leucovorin, and this is
19 looking at toxicity assessed as the delay in therapy
20 after a dose of high-dose methotrexate. This is in
21 several hundred patients, 50 percent wild type, 40
22 percent heterozygote, 10 percent homozygous mutant.

1 You can see absolutely no difference in the number of
2 days required to recover from that high dose, possibly
3 because we're abrogating the effect of this
4 polymorphism because we supersupplement with folate
5 supplementation after high-dose methotrexate.

6 So another principle is that the effect of
7 each polymorphism may be dependent upon the dose and
8 the schedule of the anti-cancer agent. As Dr. Stewart
9 just alluded to, there's lots of cases where we dose
10 anti-cancer drugs differently in children than has
11 been done in adults, not necessarily because we all
12 couldn't benefit from learning from each other, but
13 that is just the way it happens.

14 Another polymorphism in UGT1A1 that Dr.
15 Stewart was alluding to has been shown to affect the
16 risk of Irinotecan toxicity in adults with cancer.
17 This UGT is a glucuronacyl transferase. It is
18 involved in inactivating the active metabolite of
19 Irinotecan that's then excreted in the bile. So
20 individuals who have low UGT1 activity, and that's on
21 the basis, again, of a promoter polymorphism, so about
22 15 percent of the population has low activity, low

1 expression, and low glucuronidation, and therefore, at
2 higher risk for dose-limiting diarrhea and leukopenia
3 from Irinotecan than the majority of the population
4 who have higher or normal UGT1 activity.

5 We are starting to evaluate the importance
6 of this in pediatric studies. Our colleague at St.
7 Jude, Dr. Chris Cruz, has shown that in a pediatric
8 schedule of Irinotecan, which is this very prolonged
9 oral exposure, which again has been more tested in
10 children than in adults, it doesn't seem that the
11 UGT1A1 polymorphism will have the same important
12 effect.

13 So when drugs are dosed to be below those
14 KMs or those thresholds for saturation, polymorphisms
15 and enzyme metabolism that may be present with higher-
16 dose bolus doses may not be manifest themselves with
17 low exposure to chronic doses.

18 Finally, I want to give you just a hint of
19 our own experience with the thiopurine methyl
20 transferase polymorphism. It illustrates, I think,
21 several nice principles that have come up this
22 morning.

1 6-mercaptopurine is one of the two
2 backbones of ALL therapy. It was discovered and
3 approved by the FDA at less than two years from its
4 discovery in 1953. It has been used for treating
5 childhood ALL for almost that entire 50-year time
6 period, and I will submit to you that we are just
7 starting to learn how to dose this agent. So while I
8 am enthusiastic that we are talking about better ways
9 to dose anti-cancer drugs, I am a little worried that
10 some of these things may take a long time.

11 Mercaptopurine is a substrate for a
12 polymorphic enzyme called thiopurine methyl
13 transferase or TPMT, which inactivates the parent
14 drug, shunting it away from its activation pathway by
15 HPRT, where it is metabolized into TGNs or thioguanine
16 nucleotides. These acts as false guanines, are
17 incorporated into DNA and RNA, and that is part and
18 parcel of the way that 6-MP kills leukemia cells. It
19 is also part of the way that it causes toxicity.

20 One in 300 individuals is homozygous
21 mutant, so both maternal and paternal alleles have at
22 least one point mutation that inactivates the enzyme.

1 Ten percent are heterozygote, and 90 percent are wild
2 type or have normal high TPMP activity. That
3 translates into an inverse relationship in terms of
4 the systemic exposure to the active thioguanine
5 nucleotide concentrations. The rare patients that are
6 homozygous mutant have sky-high levels of TGNs. The
7 majority who are wild type have relatively low level
8 of TGNs. The heterozygote patients have intermediate
9 exposure to these TGNs.

10 Those who are homozygous mutant are at
11 increased risk of myelosuppression and I shall show
12 you at increased risk of an unacceptable late effect
13 of secondary cancers, whereas the wild-type patients
14 are at lower risk for toxicity, but there is some
15 evidence that they may be at increased risk of
16 relapse, illustrating the tightrope we all know
17 between efficacy and toxicity.

18 So we showed in a protocol at St. Jude
19 called Total XII that accrued about 190 patients in
20 the late eighties/early nineties, that the cumulative
21 incidence or probability of requiring a dosage
22 decrease was 100 percent in the rare mutant patients,

1 and it was very rare in the majority of patients who
2 are wild type. So when we give 75 milligrams-per-
3 meter-squared 6-MP per day to kids with ALL, that
4 comes from this majority of the population, but a
5 significant proportion, 10 percent of patients, are
6 heterozygote and will require dose decreases in their
7 6-mercaptopurine to be able to acutely tolerate 6-MP.

8 But, as was brought up earlier, we don't
9 think about acute toxicities; we're also interested in
10 long-term outcomes. We are really interested in
11 event-free survival.

12 So when we divided patients into those who
13 had at least one mutant allele for TPMT versus those
14 that were wild type for TPMT, we did see a trend for
15 improved event-free survival in the patients who had
16 one mutant copy. That makes sense. They have higher
17 exposure to TGNs; they have more active drug around,
18 so they should be at lower risk of relapse.

19 But what we found was that several years
20 out that we were seeing failures, and the failures
21 were not due to relapse of the primary disease, but
22 they were due to a development of a secondary brain

1 tumor, a malignant brain tumor, in almost all cases a
2 glioblastoma.

3 We looked very hard to find why we saw a
4 high frequency of brain tumors on this protocol and
5 what was it among the patients who did develop
6 secondary brain tumors that was different than the
7 patients who did not. All of the patients who have
8 developed secondary brain tumors received cranial
9 irradiation. So that was a necessary, but not a
10 sufficient hit for the development of this devastating
11 complication.

12 But the one factor that was statistically
13 predictive of the risk of secondary brain tumor was
14 this single mutation in this single gene. Having one
15 defective allele for TPMT put patients at almost a 50
16 percent cumulative incidence risk of secondary
17 glioblastoma compared to a still unacceptably high,
18 but a lower risk of the occurrence of this devastating
19 complication in patients who were wild type for TPMT.

20 So we have been giving irradiation to
21 children with ALL for many, many years, and presumably
22 10 percent of the patient have always been TPMT

1 heterozygote. So we had to look at why we were seeing
2 this high frequency of this complication of patients
3 with this secondary brain tumor on this protocol. Of
4 course, the fact that TPMP was related made us look at
5 the chemotherapy that was given along with the
6 irradiation. Since thiopurine methyl transferase
7 affects an anti-metabolite, we concentrated on
8 methotrexate and 6-mercaptopurine intensity just
9 during the two-and-a-half-week time period that
10 patients received their cranial irradiation.

11 These are four successive protocols at St.
12 Jude. On total, 11 where over 200 children received
13 the same dose of irradiation, there's still not been
14 a single secondary brain tumor, but every single dose
15 of anti-metabolite therapy on that protocol was
16 rescued with leucovorin, and there was no systemic
17 anti-metabolite during the period of cranial
18 irradiation, whereas on total 12 patients didn't
19 receive a single dose of leucovorin with any of their
20 intrathecal therapy during the irradiation and they
21 received full-dose systemic methotrexate and
22 6-mercaptopurine.

1 Now four years ago you could have asked
2 anyone and they would have thought that the safest
3 drugs to give during the additional carcinogenic hit
4 of cranial irradiation would be anti-metabolite
5 therapy, but we and others have gone on to show that
6 thioguanine nucleotides, especially in these patients,
7 this 10 percent of patients, who have a defect in this
8 single enzyme, are actually acting pretty much like
9 alkalating agents and can be quite carcinogenic.

10 So an example of how a genetic
11 polymorphism interacts with treatment, interacts with
12 drug therapy, the polymorphisms can be in drug-
13 metabolizing enzymes or obviously many other targets,
14 and there may be non-drug influences, in this case
15 cranial irradiation, but diet, many other things, that
16 may all have to be present to result in an unfortunate
17 intersection in this Venn diagram of risk factors that
18 result in an unacceptable adverse effect.

19 Of course, what we really want to do is
20 find those factors that will identify patients who
21 will have an improved anti-cancer outcome. This just
22 takes this a step further to show that this is true in

1 many, many cases where drugs are interacting with
2 germline polymorphisms and drug-metabolizing enzymes
3 in targets and transporters and non-drug influences to
4 result in patients at increased risk for thrombosis
5 from asparaginase or increased risk of a fatal
6 arrhythmia from a simple drug like erythromycin, and
7 that we really have to do a better job of identifying
8 these germline polymorphisms and how they interact
9 with drug and non-drug influences to more
10 intelligently dose drugs in the future.

11 So another lesson that this teaches us is
12 that elucidating the clinical implications of each of
13 these polymorphisms can take a long time. We have
14 known since 1980 that 6-MP was a substrate for these
15 enzyme, and we're just starting to learn now how to
16 utilize these drugs. I think, as Ms. Keene alluded to
17 earlier, we don't know the unintended consequences and
18 the long-term effects of many of the therapies that we
19 are using, and that protocol-specific, long-term
20 followup rather than specific protocols aimed at long-
21 term followup are really required in order to
22 understand the long-term effects of the therapies that

1 we are giving to these patients.

2 So I guess I am a strong believer, and I'm
3 risking what Boyett accuses me of, of being a true
4 believer when I say this, I really think that
5 pharmacogenetics should be incorporated into all
6 clinical trials, not just cancer trials. Clinical
7 trials are expensive. The hard part about doing a
8 clinical trial is doing the clinical trial, enrolling
9 the patients, administering the drugs, keeping track
10 of the therapy, keeping track of the outcome, data
11 managers, research nurses. That is what takes the
12 money.

13 Getting a tube of blood from every patient
14 is real cheap. They make plastic purple type tubes.
15 You need one tube of blood, and we can genotype
16 everything we need from that for the next few hundred
17 years. I really think that we, as the public, should
18 insist that NIH-funded trials incorporate
19 pharmacogenetics.

20 Genotyping is expensive now, but it is
21 going to get cheaper and cheaper and cheaper
22 exponentially. It is important to get proper consent

1 for future pharmacogenetic studies, so that we have
2 the option to capitalize on the genetic revolution
3 that's taking place, so we can do better and more
4 detailed pharmacogenetic studies as we learn more in
5 the future. Let's not pretend now that we have any
6 idea what we should be looking at ten years from now
7 or even two years from now.

8 Just to also say that these polymorphisms
9 affect all elements of supportive care, which are
10 still important for treating kids with cancer. We
11 still lose a huge percentage of patients to infectious
12 complications or nasty side effects of therapy. So
13 this doesn't just affect oncology drugs; it affects
14 everything we do.

15 I really like this quote from Gery Levy,
16 who is the father of pharmacokinetics. It
17 specifically addresses what we are talking about:
18 that "emphasis should not be focused on population
19 averages, but rather on providing prescribers with the
20 tools to determine the most effective and the safest
21 drug dosage for individual patients with a minimum of
22 trial and error," and pharmacogenetics is part of what

1 can do that. I hope that it will be incorporated into
2 studies with children with cancer.

3 Thank you for your attention.

4 (Applause.)

5 CHAIRMAN SANTANA: Thank you, Mary, for a
6 very nice review of this issue of pharmacogenomics and
7 how it impacts some of the issues in pediatric
8 oncology.

9 What I would like to do is start the
10 discussion. I know we are running a little bit behind
11 time, but I think we do need to have a discussion on
12 these three presentations.

13 Then I do want to bring the Committee to
14 help answer one of the questions that the FDA has
15 posed to us to answer as it relates to the topics we
16 have discussed this morning: How do we take the
17 information, how do we use this information in
18 clinical trial design for pediatric studies that the
19 Agency may be asked to evaluate in support of
20 indications as the Pediatric Rule is implemented?

21 I want to finish the discussion on that
22 subject, but I will allow some questions and comments

1 on the presentations earlier. Donna?

2 DR. PRZEPIORKA: A question for Dr.
3 Kodish, just to bring the early morning into the late
4 morning: When Dr. Hirschfeld gave his presentation,
5 he presented the current paradigm for drug
6 development, which is to at least get some information
7 in the adults on safety and efficacy before offering
8 it to kids. That seemed a reasonable thing from an
9 ethical point of view.

10 In the late morning we learned all about
11 the tremendous differences between adults and kids,
12 and how the information in adults may not be of that
13 much value in kids, and we really do have to study it.
14 If we delay things, we may delay the benefit to the
15 children.

16 Dr. Hirschfeld also presented a second
17 paradigm which is to go straight from pre-clinical
18 studies into pediatric studies without the benefit of
19 any information about safety and efficacy in adults.
20 From an ethical point of view, how would you feel
21 about that paradigm?

22 DR. KODISH: My overall feeling about it,

1 it is, again, hard to generalize because I think there
2 are going to be differences with different drugs and
3 different diseases, but, as a general matter, I think
4 that the prior approach is outdated. I think that we
5 are in a time that it would be more appropriate to
6 look at a paradigm shift that allows us to go directly
7 to Phase I studies in children, especially older
8 children who are able to be part of the assent
9 process. The younger a child is, the more reluctant
10 I would be to proceed along that line of thinking.

11 But, allowing for all the things that I
12 mentioned this morning, and the special emphasis on
13 the best interest issue for the child, I think it
14 would be reasonable to abandon the old paradigm.

15 CHAIRMAN SANTANA: Eric, I would agree
16 with that, with the caveat that the first paradigm,
17 which there is some adult data, and we use some of
18 that adult data interpretative in terms of the Phase
19 I design in children. In the absence of that, and
20 doing it in parallel, that you do Phase I trials in
21 parallel or at the same time as you do in adults and
22 children, is that you do have some substantive

1 data, pre-clinical data, that will give you some idea
2 of where to start and where you are going. Because,
3 if not, then I think we are ignoring the issue of
4 safety, because the whole premise of the Phase I is to
5 define a safe dose and some level of safety built into
6 the clinical investigation that allows you to proceed
7 in a manner that is ethically and scientifically
8 valid.

9 So I would agree with you that I think we
10 do need to shift and we need to think that maybe it is
11 time to start doing these studies earlier in children
12 or in parallel as they are happening in adults, but
13 with the caveat that I think there has to be a
14 scientific rationale and there has to be some pre-
15 clinical data that would support where we start.
16 Because traditionally what we have done is started
17 based on the adult data, but now, if we don't have
18 that, we are going to have to have some data, probably
19 from pre-clinical models, to support that.

20 Other than that, I do agree with you. I
21 think we need to start shifting in our thought.

22 DR. LEEDER: On the other side, I would

1 argue that the older the children, the closer they are
2 -- in terms of strictly from a drug metabolism or a
3 drug clearance and dose requirement issue, the closer
4 that the children are to being adults, the smaller the
5 difference one would expect, and where the largest
6 difference is and the biggest problems are going to
7 be, in the youngest children.

8 CHAIRMAN SANTANA: Eric?

9 DR. ROWINSKY: Just being rhetorical, is
10 there any reason -- and maybe we should think about
11 encompassing some of the older children, the
12 teenagers, in adult studies and shifting our
13 infrastructure to incorporate them, perhaps working
14 together, adult and pediatric oncologists, in the same
15 studies.

16 We are often faced with referrals without
17 any scientific or pharmacological reasons to preclude
18 those teenagers from entering the studies. It seems
19 like that would be one starting point.

20 CHAIRMAN SANTANA: Malcom or somebody in
21 that corner want to comment on that? Or maybe Peter
22 over here? Mark?

1 DR. BERNSTEIN: I think that it is an
2 interesting idea that in practice I think it turns out
3 to be very difficult. I think the other thing that
4 has occurred practically, and an issue that I faced
5 and that Peter faces, is that it is going to take us
6 years to catch up with the drugs we haven't had access
7 to, for which there already are adult Phase I data.
8 So that it would be an interesting idea to consider
9 doing Phase I studies in children much earlier than we
10 have done them in the past, but our major problem has
11 been not having access to drugs, for a variety of
12 reasons, which hopefully we can address here, where
13 there are adult data and we just haven't been able to
14 get a hold of the agent for study.

15 CHAIRMAN SANTANA: Peter?

16 DR. ADAMSON: I think that we can do a
17 better job of coordinating with adult trials and
18 utilizing adult data to bring Phase I studies into
19 pediatric patients at an earlier time.

20 I know Frank has proposed doing a combined
21 adult/pediatric Phase I study in certain circumstances
22 where adults will lead the way, but one doesn't need

1 to wait until completion of a trial before one even
2 begins considering a pediatric study.

3 I think once you have some exposure
4 information in adults, and you have some biologic
5 effect observed in adults that are telling you that
6 you are entering an arena where you may observe
7 biologic effects in children, one can safely begin
8 pediatric studies. I think we may have to move away
9 from some of the traditional dose escalation schemes
10 in children where we can better utilize pharmacologic
11 data as well as adult data to say, "All right, here's
12 our exposure in children. Do we need to take 30
13 percent increments or should we, in fact, catch up to
14 where the adults are?"

15 Right now, as Mark has pointed out, the
16 greatest challenge is the tremendous lag in our
17 initiating studies relative to adults, where we seem
18 to be waiting an endless period of time before we even
19 have access.

20 I think we are going to have to move more
21 rapidly in starting pediatric trials, and therefore,
22 getting some adult data, but, in fact, not necessarily

1 waiting until drugs are on market before we approve
2 performing a pediatric Phase I trial.

3 CHAIRMAN SANTANA: Malcom?

4 DR. SMITH: There really is a balance
5 here, though. We want to get good drugs to children
6 as quickly as we can. The balance comes in, when do
7 we have enough information to know that this is really
8 something that is going to be a good anti-cancer drug?

9 The risk of starting early is that we pick
10 the wrong horse; we pick drugs that are, in fact,
11 going to turn out to be too toxic. There are examples
12 of that where both drugs that have entered adult
13 trials have been determined too toxic, never studied
14 in children, or cases where pediatric trials were
15 started early and where they had to be stopped
16 because, in fact, the drug turned out to be too toxic
17 in adults. So it was dropped for further development.

18 So I think the key is having enough data
19 from the adult experience and more pre-clinical data
20 relevant to pediatric tumors to pick the good drugs
21 that we really want to study in children. Our only
22 problem in terms of studying drugs in children isn't

1 that we have had delayed access.

2 Another challenge to us, and one that we
3 don't bemoan but are thankful for, is that there are
4 a much smaller number of children available to
5 participate in Phase I trials and Phase II trials than
6 there are for adults. The article that Steve
7 distributed by Dr. Bruce from Germany made this point
8 very well.

9 So we can't study every drug that adults
10 are choosing. We have to use information from their
11 studies to pick the ones that, in fact, are going to
12 be best and to use that information to make our
13 pediatric Phase I trials and Phase II trials as
14 efficient and as quick as possible.

15 DR. GOODMAN: I certainly agree that we
16 need to speed up the -- well, in any case, speed up
17 the process, but it seems to me that what's critical
18 is that we also modify the design or include end-
19 points in the adult Phase I studies to gather
20 information that's relevant to the extrapolation.

21 I think what happens now is that a lot of
22 pharmacokinetic and pharmacodynamic data is gathered

1 in a pre-clinical setting. Then the Phase I trial
2 does not include continued measurement of these
3 parameters to see the relationship of, say, Cmax or
4 AUCs, or whatever, to toxicities. This can be
5 absolutely critical to the extrapolation and the rapid
6 evolution of the adult knowledge into the pediatric
7 population. We can't just use the MTDs. We need to
8 know what is behind the MTDs.

9 So it seems that, if we are going to move
10 quicker, we need to be designing both the pre-clinical
11 and the Phase I and the Phase II studies with an eye
12 towards the critical information that's going to be
13 necessary to rationally design the pediatric trials.

14 CHAIRMAN SANTANA: Eric?

15 DR. ROWINSKY: It seems to me there has to
16 be a synthesis of two major issues. One, which Malcom
17 brought up, is the selectivity of drugs. I am not so
18 certain that we are at the point that pre-clinical
19 models will ever sort of supply us enough data, at
20 least within the next several years, to really justify
21 a rationale for studies in children, but if there is
22 a drug that we definitely have a good gestalt that it

1 might benefit children, one potential compromise with
2 regard to where we start would be to at least obtain
3 a point in adult studies in which we are seeing some
4 biological activity. That could be the toxic dose
5 low, the point at which we stop our accelerated
6 accrual in accelerated accrual schemes, when we start
7 to see consistent Grade 2 drug-related toxicity;
8 define some element, some target element, be it one of
9 the PK maxims, an AUC, a Cmax, whatever might be
10 valuable for that particular drug, and then hand it
11 off to the pediatric studies with regard to a target.

12 DR. BALIS: I think the point of what we
13 are here for today is to talk about diseases that are
14 comparable in adults and children, meaning that we
15 would be developing the drug for both populations.
16 Hopefully, we will know better pre-clinically where we
17 are going to target those agents before we start
18 trial, so we have a strong scientific rationale to
19 take it to that disease before there may be a lot of
20 clinical data in adults.

21 If that is the case, then probably the
22 most important thing that we glean from doing separate

1 trials in children and adults is: What are the
2 differences between them? I think, as Peter brought
3 up, we had proposed doing simultaneous trials to try
4 to overcome some of the barriers to doing that with
5 the current setup. That is, separate trials are done
6 in kids and adults at separate institutions at a
7 separate period of time -- oftentimes, previously,
8 with maybe different definitions of dose-limiting
9 toxicity or MTD, using different labs to assay drugs,
10 different scheduling times to do that, maybe even on
11 different dosing schedules. Certainly the dose levels
12 are always different because pediatric trials are
13 started at 80 percent of the adult MTD, which is
14 usually not a dose level that was studied in adults,
15 and then escalated on a different schedule.

16 So we ended up defining a dose, not
17 looking at the same dose levels, maybe using different
18 definitions as to how we define an MTD, and not in the
19 end being able to compare either the pharmacokinetics
20 or the clinical data that we derive from those trials.

21 So I think if we're thinking about
22 developing drugs for a disease that occurs in both

1 populations, we need to have the forethought at least
2 to make the trials, if they're separate, designed in
3 the same ways in terms of all those definitions, and
4 maybe even coordinate them so that the
5 pharmacokinetics can be done at the same places with
6 the same sampling times.

7 DR. PRZEPIORKA: Just to get back, if we
8 do choose to go directly to the pediatric population,
9 obviously, there is going to be a problem with the
10 first dose of the drug for the first patient in the
11 first study. In the adults there are guidelines for
12 how to extrapolate from the animal models up to the
13 first dose for adults.

14 Has anyone looked at whether or not that
15 guideline is appropriate for pediatric patients, if
16 you've gone backward from later Phase I studies in
17 kids to what the adult MTD or what the adult first
18 dose was? Is there enough information that we have
19 now that we could actually make similar guidelines for
20 pediatrics?

21 DR. STEWART: I'm not sure if that data
22 has been published, but I am sure the data -- I am not

1 sure if the data for that analysis has been published,
2 but the data is available to do that kind of analysis.
3 So, typically, for adults, Eric, what is it, 10, 20
4 percent MELD?

5 DR. ROWINSKY: Jerry Collins published
6 sort of the landmark paper --

7 DR. STEWART: Right.

8 DR. ROWINSKY: -- for adults.

9 DR. STEWART: At NCI, 1990?

10 DR. ROWINSKY: Well, I think it's even
11 cancer treatment reports back years ago, where they --

12 DR. STEWART: I'm not that old. I don't
13 remember that far back.

14 (Laughter.)

15 DR. ROWINSKY: -- where he looked at the
16 ratio of starting doses and doses in which we finished
17 and determined that one-tenth of the LDT was grossly
18 safely for most agents.

19 I think that definitely can be done with
20 children's studies very easily.

21 CHAIRMAN SANTANA: But the answer is we
22 don't know. Malcom, do you have a comment?

1 DR. SMITH: Just a comment on Eric's
2 proposal. It is an interesting idea and it does
3 protect against some things. You are now starting at
4 a dose that is probably sure to be inactive.

5 When we have done this, the concern or the
6 problem has been that, again, because there's so many
7 more adults with cancer and so many more adults
8 entering Phase I trials, that a center like Eric's is
9 going to have patients lined up and ready to go. So
10 that Phase I study is completed relatively quickly.

11 So when we start the Phase I study in
12 pediatrics, we start and the adult study has gone
13 three or four dose levels ahead, and you are
14 constantly saying, okay, we need to amend this study
15 to jump up, to skip two or three dose levels, because
16 the adults got ahead. So when you get to the end of
17 the game, in fact, you've basically waited for the
18 adults to determine the MTD; you've adjusted your dose
19 schedule to the adult MTD, and you haven't gained a
20 lot of time, because the adult Phase I studies are
21 inherently conducted quicker in almost all cases than
22 a pediatric study could be. So that is the downside.

1 The other thing it doesn't protect against
2 is the possibility that the toxicities that you hadn't
3 anticipated in the adult study crop up and the drug
4 that looked promising, in fact, had some anticipated
5 toxicity, and whatever time and effort and pediatric
6 patients that had been entered is all for loss.

7 DR. ADAMSON: I think there is,
8 unfortunately, a window of opportunity that we can
9 perform Phase I trials in an efficient manner. One of
10 the byproducts of an increasing number of agents on
11 market now is that there are an increasing number of
12 children being treated off-label. Although that is
13 probably a topic of discussion for a different time,
14 what that results is every time a child is treated
15 off-label is potentially one less patient who could
16 have been treated on a Phase I or Phase II study,
17 where we could have learned something.

18 If we only embark on Phase I trials after
19 a drug is on market, and I am not saying that people
20 are advocating that, but the longer we delay in
21 starting our trials, the greater the risk is that
22 there is going to be an increasing population of

1 children who are exposed to drugs without any
2 information, where we learn nothing from.

3 So I agree with Malcom it is a fine -- we
4 have to strike a balance between when is it safe to
5 start versus waiting until all the data is in, and
6 then ultimately what we have is a shrinking population
7 of patients who haven't already been exposed in an
8 uncontrolled setting to the drug.

9 DR. BOYETT: To go back to the question
10 about the existing data that is out there that might
11 relate the pre-clinical model that was used to choose
12 the starting dose in adults that you might be able to
13 relate to pediatric, I think I am less enthusiastic
14 that you may be able to do that. The reason is I
15 think what you have is biased data.

16 The adult studies that started and got
17 some horrendous toxicity, et cetera, those drugs are
18 out. The only ones that you have data on are the ones
19 that went on and had some success in adults, and then
20 you did them in pediatrics. So I am not as
21 enthusiastic that you are going to have unbiased data
22 to assess that model.

1 DR. ROWINSKY: What you can do is you can
2 basically look at some of the drugs that have been
3 valid drugs of impact in both diseases and look at the
4 toxic dose low in adults and relate that to the dose
5 where we ended up in children -- here may not be too
6 many of those agents -- to give us an idea of how
7 many, I hate to use the term "wasted resources."

8 I mean, I think that these trials, Phase
9 I trials, in general, we may be talking a lot about
10 very small numbers of patients who really get
11 ineffective dosages if we utilize that proposal. We
12 are not talking about scores and scores of patients.
13 I mean, entire adult trials reaching the MTD, even in
14 modified Fibronacci conservative dose escalation
15 schemes, generally, about 20 to 30 adult patients, and
16 that is probably a high guesstimate.

17 I would imagine that we proposed a way in
18 which children could get onto trials, at least an
19 adult toxic dose low with subsequent escalation, it is
20 really not going to subject too many children to
21 ineffective doses that might be unethical or construed
22 as being unethical.

1 DR. BOYETT: We also could consider some
2 other models like the CRM for studying those.

3 CHAIRMAN SANTANA: David? Dr. Poplack
4 should be on teleconference. Are you there, David?

5 DR. POPLACK: Yes.

6 CHAIRMAN SANTANA: Okay, that's fine. I
7 just want to make sure for the public record that he
8 is listening in.

9 Donna, did you have another comment?

10 DR. PRZEPIORKA: Yes. Our good friends at
11 the FDA have recognized that we sometimes cannot
12 interpret the CFR and provide us with guidance
13 documents instead. If one had the opportunity to
14 contribute to a guidance document when it comes to
15 dosing in pediatric studies and PK studies and
16 designing these, I have heard a lot this morning about
17 the difference in surface-to-volume ratio as kids grow
18 up, and the difference in pharmacokinetics.

19 My question would be: Would you prefer to
20 have all drugs dosed per kilo versus per meter squared
21 in these studies? How many patients would you have to
22 study PKN in order to say these are valid PK?

1 CHAIRMAN SANTANA: Dr. Coltman, do you
2 want to address that?

3 DR. COLTMAN: I just wanted to make
4 another point, that with targeted therapies, we have
5 targets in adult diseases that are present in such
6 diverse clinical situations as chronic myeloid
7 leukemia, gastrointestinal stromal tumors, myeloid
8 dysphasia, ovarian cancer, prostate cancer, all
9 targeted by a single molecule that has potential
10 extraordinary effect. So our concept about the
11 differences between adult and pediatric tumors, while
12 they morphologically look different and may behave
13 differently, we should be addressing the target
14 question.

15 With this targeted therapy, while there is
16 some degree of toxicity, they are in no way comparable
17 to the level of toxicity you see in the standard
18 cytotoxic therapy. I think that is the direction we
19 are going to be going in, although I certainly
20 wouldn't want to muck around with the successful
21 management of pediatric lymphatic leukemia, but there
22 are other issues that need to be addressed, looking

1 toward the future with more targeted therapy.

2 CHAIRMAN SANTANA: Let me see if I can
3 summarize what I have heard to satisfy the requirement
4 that the FDA has of us.

5 I'm sorry?

6 DR. BAYSSAS: I just wanted to say that
7 for targeted therapies, in adults at the moment, even
8 at Phase II, the dose is not established. So I don't
9 know, the definition of the OBD itself has not
10 currently even in adults been well-established. So I
11 don't see how you can extrapolate from adults to
12 children. You have to wait until the end of Phase II
13 in adults to know which is the OBD in adults that you
14 can extrapolate.

15 CHAIRMAN SANTANA: Susan?

16 DR. COHN: Yes, I just wanted to say
17 again, to follow up in terms of all these ideas of
18 trying to speed up getting these drugs into pediatric
19 trials, to go back to what Malcom had mentioned, which
20 is, you know, you don't want to -- fortunately, we
21 have relatively few patients. So you want to make
22 sure that whatever drug you use, you make sure that it

1 is being used in a patient with a disease that will
2 potentially respond, the disease will potentially
3 respond to the therapy.

4 So the other plea that I think that we
5 ought to consider is in the pre-clinical trials that
6 you don't just use, as pre-clinical trial models,
7 breast cancer, colon cancer, and lung cancer, but that
8 we include some pediatric cancers in these pre-
9 clinical trials. I think that is where we really can
10 get together in terms of making sure the models are
11 representative of pediatric diseases, when you are
12 testing initially these new agents. Then when you do
13 get a little bit of information from the adult
14 studies, we will know that that agent is something
15 that potentially will be effective in some of these
16 pediatric cancers.

17 DR. ROWINSKY: I hope that no one will be
18 offended by these remarks, and I am glad that Dr.
19 Houghton is not here, but the question is: When is a
20 breast cancer pre-clinically a breast cancer
21 clinically, when is a neuroblastoma -- and I don't
22 think we are at that point yet where we could really

1 -- I think when we see activity pre-clinically that
2 might portend for something of impact in the clinic,
3 but where that tumor, what tumor is going to impact,
4 I --

5 DR. COHN: Right, no, and I absolutely
6 agree with you, but the reality is that a lot of these
7 drugs are initially tested in these pre-clinical ones.
8 The ones that potentially look -- it may or may not be
9 at all effective in the patient or you may have a
10 totally separate -- but that's, indeed, where we
11 start. I am just saying that if, indeed, we really do
12 want to try to move these drugs faster into clinical
13 trials for children, I think that, whatever basis is
14 being used to define a drug that potentially should be
15 moved into an adult Phase I trial, whatever that
16 laboratory data is, that we ought to try to
17 incorporate those same experiments with pediatric
18 cancer cells.

19 CHAIRMAN SANTANA: Pat, Dr. Reynolds?

20 DR. REYNOLDS: I think one of the things
21 that you are missing when you think that there is no
22 value to pre-clinical data is that --

1 DR. ROWINSKY: I didn't say that.

2 DR. REYNOLDS: -- whereas you may not be
3 predictive of a response in patients, if you under
4 ideal conditions in a pre-clinical model have a drug
5 that may work in breast cancer, but doesn't do
6 anything at all in neuroblastoma, you can probably
7 think that maybe you don't want to do any trials in
8 neuroblastoma. If it doesn't do anything in a panel
9 of pediatric tumors, then you could think, that's
10 really an adult drug, not a pediatric drug. So it is
11 going to provide us some guidance that we really
12 should seek.

13 DR. ROWINSKY: I am not certain that we
14 have the knowledge to even imply that those models
15 will even -- that they will be even slightly selective
16 for pediatric tumors. I would be afraid not to try a
17 drug that was inactive in certain pediatric
18 xenografts, or vice versa. I just don't think we are
19 there yet whatsoever. I think pediatric tumors may be
20 oversensitive or may be undersensitive with regard to
21 selectivity.

22 DR. COHN: Yes, but I was going to say the

1 reality is, though, as we were saying, because we have
2 so few patients and there are so many drugs, we have
3 to prioritize.

4 DR. REYNOLDS: That's the point exactly.
5 Pediatrics is not the adult community where you have
6 the ability to say, well, let's make sure this is not
7 an active drug and do a study. We have to be able to
8 select before we get to the patient. The only way to
9 do that is intelligent pre-clinical data.

10 DR. ROWINSKY: Well, you're preaching to
11 the converted, but I'm not so certain that the models,
12 the xenograft models, are really the key.

13 DR. REYNOLDS: I agree with you, but I
14 think that that's why we need to study pre-clinical
15 models and find out what is going to work. Unless we
16 do that in the context of or together with clinical
17 trials, we will never learn anything.

18 CHAIRMAN SANTANA: Let me see if I can
19 summarize because the hour is running late, and
20 certainly I hope I express the view of the Committee
21 when I make the summary.

22 First of all, I think we recognize that

1 the world is imperfect. All these models and all
2 these trials are not perfect. It limits our ability,
3 when we are making decisions of how well we ultimately
4 end up at the end of the day.

5 But recognizing the limitations, I think
6 I get a strong sense from the community here that, as
7 the FDA decides, and other groups decide, what studies
8 should be done in pediatrics, that pre-clinical data
9 that is relevant to the diseases under consideration
10 in children are paramount. I think that is one very
11 important point.

12 That doesn't mean that we have to go out
13 there and do every single drug on neuroblastoma
14 xenografts, but there should be some scientific
15 validity in the pre-clinical models as it relates to
16 the clinical condition in children. I think that is
17 one concept that I think was fairly well expressed by
18 the Committee.

19 The second, I think we have limitation of
20 resources, and by "resources," we not only mean
21 economic, we also mean in terms of patients. It is a
22 very limited population. We cannot do everything that

1 we think we need to do. Given that, I think we have
2 to allow the clinical investigators who are experts in
3 this field, to allow us to make those decisions in
4 terms of what drugs based on the relevant information
5 are the drugs that they want to prioritize and they
6 want to test.

7 That obviously means that there will be
8 some drugs that will not be tested, but I think we do
9 have to have some confidence in the clinical
10 investigators and scientific community in pediatric
11 oncology of what drugs they want to prioritize, given
12 the limited resources.

13 Having said that, then I think there is
14 potentially no fast rule. There may be different
15 models that the Agency could use in terms of applying
16 the rules in terms of some of the studies that they
17 will request. I heard Frank say that, if the disease
18 is similar in adults and children, then I think under
19 that model scientifically it may be appropriate to
20 allow Phase I studies to occur concurrently, because
21 there may be some differences in toxicity. So just
22 waiting until the adult trial is done is probably,

1 given the same disease, it is not something that
2 probably should do.

3 But in those scenarios, probably parallel
4 studies or concurrent studies for the same disease,
5 the same biology, those studies should occur
6 concurrently. In all the others, I think history has
7 served us well. I mean, I think some adult data and
8 some pre-clinical data has allowed us to define some
9 dose levels which are reasonable for us to start.
10 That will be completely different with biologics. I
11 don't think those rules automatically apply to
12 biologics. I think in biologics we may have to think
13 of a completely different paradigm, maybe doing
14 studies concurrently or some other way. I am not an
15 expert in that area of biologics, but I think in
16 biologics, which is a topic that I think we do need to
17 discuss maybe further this afternoon, the paradigm may
18 have to be a little different.

19 That is what I think I heard the Committee
20 say this morning.

21 DR. HIRSCHFELD: Thank you, Dr. Santana.

22 I would want to, just for the purposes of

1 focusing the discussion, clarify again the conditions
2 where the rule is triggered. That is, the diseases
3 would be considered the same or essentially the same,
4 sufficiently similar, plus the prospective therapy
5 should be considered a therapeutic advance. That is,
6 the rule is not meant to be triggered for -- and I
7 don't want to malign any particular class of drugs, so
8 I will try to avoid that, but it should not be
9 triggered for any "me-too" drugs.

10 That is, if they are already -- and the
11 way the Agency as a whole has interpreted -- if there
12 is already a drug of the same class that is labeled
13 for children, then the bar becomes much higher for
14 subsequent drugs of that class in order to have this
15 triggered.

16 So, within those constraints then, I think
17 we can then focus our discussion, and the broader
18 discussion of Phase I studies and how one relates
19 diseases is in the background, and this is a special
20 case.

21 CHAIRMAN SANTANA: If there are no further
22 comments, we will adjourn for lunch, and we will try

1 to reconvene at one o'clock, so we can keep ourselves
2 on time. Thank you.

3 (Whereupon, the foregoing matter went off
4 the record for lunch at 12:17 p.m. and went back on
5 the record at 1:14 p.m.)

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