THE CANCER LETTER

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SPECIAL ISSUE

A Year at NCI: Harold Varmus Reflects On Provocative Questions, Duke Scandal, Financial Disaster and Grant Review

A year after he became the NCI director, Harold Varmus sat down for a conversation with The Cancer Letter.

The interview, which will continue in next week's issue, focuses on the following subjects:

• The intellectual underpinnings of the "provocative questions" initiative, Varmus's signature program.

• The fortuitous aspect of the Duke Scandal: it focuses attention on the challenges of bringing genomic technologies into the practice of oncology.

• The difficulties—and opportunities—the NCI's current financial difficulties present.

• The new process for deciding on funding grants that fall into what Varmus calls "a zone of uncertainty."

The interview was conducted by Paul Goldberg, editor and publisher of The Cancer Letter.

Paul Goldberg: ***I have seen NCI directors propose provocative answers. You came to Bethesda with provocative*** **questions.** ***This has to be significant. Why questions?***

Harold Varmus: That's *one* of the things I came to Bethesda with.

There were a couple of reasons for that.

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The Avastin Question:

NCCN Committee Reaffirms Clinical Guideline Covering Avastin For Breast Cancer Indication

A panel of breast cancer experts who update the guidelines of the National Comprehensive Cancer Network voted to maintain the breast cancer indication for the Genentech drug Avastin (bevacizumab).

At its regularly scheduled meeting July 10-12, the NCCN panel voted to reaffirm its previously stated position on the drug—just as FDA is seeking to remove its accelerated approval for the breast cancer indication.

On June 28-29, FDA held its first-ever hearing to withdraw an accelerated approval. At the hearing, the agency's Oncologic Drugs Advisory Committee voted unanimously, 6-0, to uphold the agency's position (The Cancer Letter, July 1).

The agency has never forcibly removed a drug's accelerated approval. The final decision will be made by the FDA Commissioner Margaret

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"Almost All Good Science Begins With a Good Question"

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First, it's very useful for people in charge of funding programs to start with some notion of ways to challenge the scientific community to do novel things. I saw that experience worked quite well when I was chairing the Gates Grand Challenges in Global Health.

We got a lot of people excited about global health just by getting some smart people together, thinking as a group, and asking the scientific community to give us ideas for things they thought would be worth spending extra time on.

People are nervous. People want to be in the mainstream. But I think there is a reason to urge them into the eddies and currents of uncertainty.

At the current moment in cancer research, there are a lot of very obvious things to do. They are very important, but they are very obvious:

Find out the genes that are mutated in cancers, and other things that are wrong with cancer cells; then figure out some way to use those observations to diagnose and treat cancer more effectively.

But, it does seem to me that if you look at the history of clinical cancer and the history of cancer research, there are a lot of things that we've allowed ourselves to take for granted and not really probe deeply. Those things are worth going back to, especially with new technologies.

The second issue is to get people off the safe and narrow path and get into some more turbulent waters at a time of fiscal restraint.

People are nervous. People want to be in the mainstream.

But I think there is a reason to urge them into the eddies and currents of uncertainty. Underlying the way in which I framed this, I do believe that almost all good science begins with a good question.

PG: Most things do.

HV: Some people can go out in the field, and just by wandering around the field, and they'll see something that's interesting, and then they'll ask the question.

But most of us operate by finding someone else's observation, and suddenly saying to themselves, "Gee, I wonder how that works."

There is always this problem of granularity in respect to questions.

A good provocative question is not "How do I cure cancer?" Nor is it "What buffer do I use to inject this plasmid?"

Those are the significant questions in certain contexts, but getting the right level of question, I thought, would be a useful way to bring people together—and part of this was community-building, quite frankly.

One of the things that has been a lot of fun for me is spending a day with a bunch of interesting colleagues, many of whom I don't know, or haven't known well, and talking about what they think are the big unsolved problems in cancer that we ought to be thinking more about.

We have had four workshops here, and I've had a whole lot more discussions and unofficial events, and all these things have been really stimulating. Talking about provocative questions has been one of the most interesting things I've been doing.

PG: It's about storytelling, I guess, in some ways.

HV: Some of it is, and some of it is saying**:** "Look, Lance Armstrong; that guy was cured of his cancer with a drug that we don't like very much in most settings."

PG: What the hell?

HV: Yeah. What's that about? And, you know, we hold it up as a notch in our bow, but we don't think too much about how it works.

PG: We could probably do the entire interview on this. I guess it's like storytelling with someone else telling the story.

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HV: It's about conversation. It's about trying to get beyond the usual sphere of activity.

PG: I guess we should probably move off of this one, although it's fascinating. What's your favorite part of the job? I hope it's not the commute. [Varmus commutes by bicycle from his apartment in Northwest Washington to the NIH campus.]

HV: Well, we don't want to disregard the commute. The commute puts me in a good mood and keeps me in good shape, and it is a pleasure—but, obviously, that's not the job. Getting to the job is not the same thing as doing the job, and what's fun for me is thinking about new programs.

I knew it would be when I was sitting in the NIH Director's Office, and I was looking on enviously at the institute directors who were having fun shaping the programs. Now, I'm not someone who thinks that people who sit in these jobs at Bethesda should be shaping the agenda.

The issue is getting people stimulated by broad ideas and opportunities to do things in their own way that brings the novelty of the entire scientific community to bear on the problems. But, there is a reshaping that goes on.

I'd rather have life be fiscally easier, but, frankly, when budgets are rising, it's very hard to shut anything down.

The NCI has a lot of things going on. Some of them are terrific. Some of them not so terrific. Some of them are probably mis-sized. And we are dealing with difficult times. Difficult times are interesting in ways that I think can be useful.

I'd rather have life be fiscally easier, but, frankly, when budgets are rising, it's very hard to shut anything down.

So that's an issue. People understand, when things are tight, that you are going to take money out of some programs and put them into other things, because you can justifiably say, "We've got to always do new things. Otherwise, we are not going to make optimal progress."

PG: Something fascinating just blinked by. Did you scope out this job when you were over there, in Building One [the NIH Director's Office]?

HV: Well, I didn't scope out this job specifically.

I obviously couldn't help but be aware of what's going on in the Cancer Institute. But, what I was conscious of was the fact that people who were running the institutes—especially the big, interesting ones: Cancer, NIAID, Heart and Lung, Mental Health, Genome—were really engaged in the day-to-day execution of science.

I think things have improved for the NIH director.

I'm happy to think that I had something to do with making it better, because I complained a lot as I was leaving, and I know that the Reauthorization Act for NIH did take some of my commentary into consideration. For instance, having the Common Fund among ways for the NIH director to reshape general priorities is refreshing.

When I was here, I used to have to go around and beg the institute directors to put some money into a common pot so we could try to do some things. The Mouse Genome Project is one example. The Zebrafish Initiative. There were a number of things that I tried to do, but after a while, the institute directors began to say, "Give us a break. We can do these things on our own. We don't need to have you taking our money away or begging from us."

That was a bit frustrating, because I had a trivial discretionary budget of about $10 million, and it's very hard to do anything with that. I realized that people were being nice to me in the first year when I requested funds to pool to do things that were consensual—I wasn't going to be able to do that forever.

PG: But you did something. You launched systematic assessment of NIH programs, of intramural—

HV: Bringing in advisory groups. I did a lot of that, but that doesn't require serious money.

PG: You did that with your meager NIH budget.

HV: Right. From the beginning, we had a group come in to re-evaluate the intramural program—the [1994] Marks-Cassell report—and I had another come in and evaluate the Clinical Center—the Smits report. I instituted five-year evaluations for every institute director. One of the most important reports that was done here when I was NIH director was the Levine report on the AIDS program.

So, yes. I think that this kind of review is one way to maintain some discipline, especially when you are dealing with big programs and prestigious people.

We all knew that there were some successes and some non-successes, and getting at the core issues there was actually pretty important.

PG: One of the first things that happened when you took this job was I threw the Duke scandal at you. You took it extremely seriously and did a lot with it. Why did you think it was important?

HV: Look, there are two concerns here. One is the misconduct itself. That's something for Duke to handle with the Office of Research Integrity. That's not what interested me.

When I came here, I knew that one of the big problems we were going to have—irrespective of anything that happened at Duke—was the difficulty of bringing genomic technologies into the practice of oncology.

I had seen that at Sloan-Kettering. I could see that we had regulatory issues there, and we had uncertainty about which possible biomarkers were going to useful in making decisions about drugs.

I could see from personal experiences, with friends who were being treated for cancer, that there was very uneven uptake of new information by community physicians, who, after all, treat 85 percent of cancer patients in the country.

Long before I knew that there was this problem at Duke, I had made plans to take on this problem.

One of the reasons why I am bringing all of the genomics stuff we are doing at NCI into one new center, which I call the Center for Cancer Genomics, is not just because there are different people doing genomic activities.

I want to have a center, where we are not just doing a lot of sequencing and copy number determination, but actually thinking about how we are working with other agencies, how we work with ASCO and with community physicians to bring about a modern era in cancer diagnosis, treatment, and prevention—based on information that comes from the examination of genomes and gene expression and proteomics and other technologies.

The Duke episode, from my perspective, was simply another way of illustrating the dangers of not doing it right, not having the right kinds of safeguards. And with my various colleagues, including colleagues at Duke, I asked the Institute of Medicine to do a study.

The intention there was not to investigate wrongdoing, because that was going to be taken care of in other ways, but to think about what needs to be in place to ensure that correct evaluation of new approaches to cancer care had been undertaken, that we met competing standards, and that the evidence base for changing diagnosis itself or evaluation of responses or, more importantly, choice of therapies—was based on good evidence.

I asked the IOM and the Cancer Policy Board to think carefully about what kinds of hoops people need to jump through before new information about cancer is actually used in a clinical setting. The risks are high here.

PG: As a former police beat reporter, I'm wondering to what extent it's futile to try to derive a high-level lesson from something that's pretty low-level.

HV: I think you are seeing it the wrong way. There is a falsified CV. That's of no interest to me. That's someone else's problem.

PG: But it was crucial to the case.

HV: It was crucial to the case only because it helped people pay more attention to the underlying issue, and brought the statisticians out of the woodwork and had them write to me.

Having the statisticians write to me was more important than any revelations about a CV.

The CV had to be revealed to trigger their response, and make them confident enough in their views to write to me.

The Duke episode, from my perspective, was simply another way of illustrating the dangers of not doing it right, not having the right kinds of safeguards.

PG: That was kind of unusual in the American context.

HV: It was a very unusual story, and you do get people's attention with the kind of stuff that you've dug up, but the issue for me is higher-level.

I don't want to interfere with what's going on at the IOM study. I think most people participating in that study understand that their charge is to operate on a pretty high level, and that has to begin by assuming that there is going to be integrity in the process of making clinical decisions.

The real challenge here is to figure out how to evaluate data and set up standards that will guide therapy by a lot of people who may not even have a deep understanding of the research, but have to have an understanding of what goes into a determination of when something can be used.

For example, people have a fair amount of confidence that if the FDA approves something, it is based on evidence that says that it is beneficial.

I think now we are in a slightly more difficult situation, because we are not simply treating something that's called "lung cancer." We are treating something that's got genetic characteristics, characteristics with respect to regulation of gene expression, or phosphorylation of target proteins.

There are new sets of standards that are going to guide diagnostics, and therefore guide therapeutics.

PG: Did you anticipate the financial crisis going in? And you mention that this is an opportunity to make the Institute more rigorous.

HV: Look, I knew the country had a financial crisis, so that was a not a surprise. I knew that the NIH budget had been losing buying power over the last decade.

The one-percent decrease was fairly important symbolically. It's not unreasonable to expect that this year we will have another reduction.

It wasn't a surprise to me to come here and find this crisis, despite the good intentions of President Obama. I worked in his campaign and I'm convinced from talking to him that he thinks medical research is one of the most important things the country does.

If he were presiding in an earlier era, he would have supported with the budget increase that the NIH saw in the late '90s and early 2000s.

But under these circumstances, he doesn't have too many options. So it's not a surprise to me.

PG: So you knew going in that this was going to be tough financially?

HV: I knew that it would be a tough time. I didn't think that we would be on the chopping block. I was surprised to see the budget dip below previous years' levels.

I thought we would continue to see an erosion of our buying power by sub-inflationary increases or totally flat budgets.

The one-percent decrease, to me, was fairly important symbolically. And I think it's not unreasonable to expect that this year we will have another reduction.

PG: You mentioned the campaign. The campaign document you co-authored was suggesting a doubling.

HV: The doubling doesn't mean anything unless you say over how many years. The NIH budget was to double over ten years.

We now are making decisions that are very difficult, and sometimes approach the arbitrary.

The NIH budget, in general—over its long history—has doubled every ten years.

You have to do the adjustment to constant dollars. That's very tricky. And one of the reasons it's tricky: there are three levels of inflation. There is general inflation, which right now is about two percent or so.

There is the Biomedical Research and Development Price Index—BRDPI—which is generally twice general inflation, but it's pegged to certain commodities that are used in research. It's based on test tubes.

But that is an unrealistic estimate of what the true inflationary cost is—at least the kind of research that I and many of my colleagues in the cancer research community do, because our dependence on animal models, on kits, on genomics, on informatics has driven up the cost of research as we tend to measure it, which is: How much does the average post-doc spend in a year doing research in our labs?

There is no doubt that that escalator, which I cannot accurately quantify, has gone up a lot. At the same time, we've trained a large cohort of individuals, we've been building buildings, we've expanded our faculties—so the cost of doing cancer research for the country could be a lot greater than it is with our current budget. But our budget's going down.

This makes life pretty tough, and we are struggling with success rates that are unlikely to get to 15 percent.

Those of us who have been in this environment for a long time know that the system seems to work pretty well when we fund one application out of three—as a rough measure.

But now we are down to one in six or one in seven. We now are making decisions that are very difficult, and sometimes approach the arbitrary.

PG: What's your hope, or what's your goal, for next year, for payline, or...

HV: I don't use the term "payline."

PG: Which term would you like to use?

HV: I think it's important to know how many new awards we are making.

And the success rate is a useful thing to look at.

But I don't use payline, because I don't think—based on my experience so far—that we should be slaves to percentiles, to the computed priority scores.

I think the grants that do extremely well—this year "extremely well" means seventh percentile or better—we will almost always fund, but then I think we have to look more carefully within what I've been calling "a zone of uncertainty"—and there are a few people who have not been happy with this.

Within this zone, there is no doubt that the score is very influential. The better your score, the more likely

you are to succeed.

But at this point, I think, the experts that are sitting around the table at our meetings—those are the heads of all the NCI centers, the divisions, importantly, and many of the offices here—need to hear about and discuss the individual grants.

The program officers in those divisions—almost all the grants come through the divisions—spend a lot of time looking at their portfolios, evaluating how people have done in the past, and how important the grant might be to their overall objectives.

We have clearly singled out grants that would not otherwise have been paid and paid them. We have taken grants that might have otherwise gotten paid and not paid them.

PG: How do you make sure that this doesn't amount to a re-peer-review?

HV: We are not trying to redo peer review in our programmatic evaluation.

We depend very heavily on the peer review report that comes out of the study section. But we apply other kinds of criteria.

It's not perfect, but I have seen many, many examples in which we have clearly singled out grants that would not otherwise have been paid and paid them.

We have taken grants that might have otherwise gotten paid and not paid them. One of the by-products of this has been a much clearer sense among the scientific program leaders [the group that does these determinations is called the Scientific Program Leaders or the SPL group]. These folks know a lot more about the whole portfolio and try to make use of their expertise in making a second-level determinations.

But, I am going to stick to my guns here, and we are going to do this so we can try to get as close as we can to getting it right.

The idea that the NCAB or the other advisory groups can do second-level reviews is just not feasible. The portfolio is much too big.

Two groups have been given an awfully amount of time to do this, but with benefit.

First are the program officers, who have looked with much more scrutiny at the grants and at the reviews than they have usually done. It's a big workload, but I think it's worth it.

Second, the program leaders themselves are looking not just at how many grants they are going to fund or where they should put the payline, but instead have been looking more broadly at hundreds of grants. I think it's allowed very informed discussions.

I think we've improved the way we've given out grants over what would happened if we had just determined what the payline was going to be and made discrimination based totally on the scores.

Remember, we still have a scoring system that leaves much to be desired. Grants go to study sections that may have members who may be variable in their wisdom. The grants at different study sections may be of a different quality, but they get percentiles within each study section.

As a result, I think there are grants that have numbers that are less good than other grants, but actually are more important for us to fund.

We are making a real effort to try to find those grants.

PG: I guess there's a point where it comes down to a judgment anyway.

HV: We respect the judgment that's made by the peer reviewers. That's the first cut. We pay attention to numbers. We try to understand the rationale.

It should be also clear that not every application gets deeply scrutinized. For some things, we just say: "Yes, it got a very good score; it's high on the list that the division brings to us; and we like what we hear." We fund it.

Not everything generates debate, but a lot of grants do generate debate, and I think it's been a useful debate, and I try to make it clear to everybody what we are trying to do.

I've heard complaints from three or four people in the last few months—I suspect these are probably people who didn't get their awards. But I can understand why someone who didn't get their award, but thinks they have a score that should have been funded, wouldn't like the process.

PG: So it is a process?

HV: It is definitely a process.

And the process has gotten better and better with time, because program staff have gotten used to what the group wants to hear: what the objectives are, what the problem is that the applicant is trying to solve, why this is important to the division or center that's funding

it, how it fits into the portfolio, and how it fits into the ambitions of the NCI to control cancer more effectively.

Next week:

• The significance of the National Lung Screening Trial. Can there be another trial like it in the future?

• Looking at detection trials differently, perhaps launching phase I, II, and III detection trials.

• Re-examining the configuration of NCI: How money is distributed among divisions.

• Reassessment of SAIC-Frederick.

• Redesign of the NCI clinical trials cooperative groups. The most interesting phase is yet to come, Varmus says.

• What the NIH National Center for Advancing Translational Sciences can accomplish.

• The artificial nature of boundaries between "basic," "clinical," and "translational" research.

• The role NCI can—and cannot—play in the Obama health care reform.

• Why so many scientists don't want to run NCI and how to fix the problem.

The Avastin Question:

NCCN Keeps Avastin Guideline As FDA Considers Withdrawal

(Continued from page 1)

Hamburg. There is no deadline for Hamburg to act.

The NCCN panel voted 24-0, with one abstention, in favor of maintaining the recommendation, which states: "Bevacizumab in combination with paclitaxel is an appropriate therapeutic option for metastatic breast cancer with the evidence designation 2A."

The following footnote accompanies the recommendation:

"Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first or second line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time to progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel."

FDA News:

ODAC Votes For Accelerated Approval For Adcetris For Two Lymphomas

An argument can be made that Seattle Genetics Inc. was in an enviable position when the FDA Oncologic Drugs Advisory Committee considered its two applications for the drug Adcetris (brentuximab vedotin) July 14.

The Bothell, Wash., company was essentially guaranteed an accelerated approval for two indications: Hodgkin's lymphoma in patients who relapse after autologous stem cell transplant, and the treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma.

However, Seattle Genetics argued that its data warranted full approvals for both indications. The agency disagreed, and ODAC upheld the agency's position in two separate 10-0 votes.

FDA is expected to act on the two Biologics License Applications by Aug. 30.

Adcetris is an antibody-drug conjugate comprising an anti-CD30 monoclonal antibody attached by a protease-cleavable linker to a potent, synthetic drug, monomethyl auristatin E (MMAE), utilizing Seattle Genetics' proprietary technology.

The ADC employs a linker system that is designed to be stable in the bloodstream but to release MMAE upon internalization into CD30-expressing tumor cells. This approach is intended to spare non-targeted cells and thus may help minimize the potential toxic effects of traditional chemotherapy while allowing for the selective targeting of CD30-expressing cancer cells, thus potentially enhancing the antitumor activity.

Seattle Genetics is developing Adcetris in collaboration with Millennium: The Takeda Oncology Company.

The applications prompted FDA officials to spell out their current thinking on the distinction between regular and accelerated approval. These distinctions were spelled out by Richard Pazdur, director of the agency's Office of Oncology Drug Products.

The text of Pazdur's opening statement to the committee follows:

I'd like to summarize the issues to be discussed during today's meeting for brentuximab for two indications proposed by the sponsor: relapsed or refractory Hodgkin's lymphoma and relapsed or refractory systemic anaplastic large cell lymphoma.

The Hodgkin's lymphoma application will be

discussed this morning and the afternoon session will focus on the systemic anaplastic large cell lymphoma application.

Both submissions provide separate single-arm trials as the primary trial to support the applications.

These submissions represent the first applications for brentuximab and, hence, we do not have any prior regulatory history or experience with brentuximab.

As discussed in the Feb. 8, 2011, ODAC on accelerated approvals, single-arm trials have limitations both in terms of providing data on clinical benefit and safety.

In general, response rate and duration are the only efficacy endpoints that are considered from a regulatory perspective from single arm trials.

Time-to-event endpoints, such as progression-free survival and overall survival, cannot be adequately interpreted from single arm trials.

Similarly, the safety evaluation of a drug in a single arm trial is also difficult since a comparison cannot be made to a control and, hence, attribution is not possible.

Single arm trials generally also have limited numbers of patients. The Hodgkin's Lymphoma application has 102 patients enrolled in the trial and 58 patients were enrolled in the anaplastic large cell lymphoma trial.

Because of these issues a clear understanding of a risk to benefit evaluation may not be optimal from single arm trials. Hence, the Agency has recommended that the accelerated approval pathway be used for these two applications with subsequent trials being mandated to more clearly provide an understanding of a risk benefit evaluation.

Complete response rate of a sufficient duration has been acknowledged by the Agency as a possible endpoint for the demonstration of clinical benefit; however, this activity must be placed in the context of a risk to benefit analysis.

There are two accelerated approval pathways.

ODAC discussions have generally focused on accelerated approval with the reliance on a surrogate endpoint "reasonably likely to predict clinical benefit."

Alternatively, accelerated approval may also be granted on a clinical endpoint other than survival or irreversible morbidity, such as the complete response rates observed in the trials under consideration.

Accelerated approval is given with the "requirement that the applicant study the product further to verify and describe the clinical benefit."

In this case, the Agency is asking for randomized trials to be conducted post-approval to further elucidate the risk to benefit evaluation of the drug due to the limitations of the single arm trials submitted to support both applications.

The agency has clearly conveyed to the Sponsor this concern and the belief that accelerated approval would be the preferred approval pathway on several occasions since July 2008.

However, the sponsor has asked for regular approval of these applications.

Both this morning's presentation by Dr. De Claro and this afternoon's presentation by Ms. Karen McGinn will highlight the difficulties in assessing a risk to benefit evaluation posed by the single arm trial design.

We will be asking you to vote whether these applications should be approved and, if approved, the type of approval you would recommend. Also, we will be asking you to comment on future trial designs.

Please remember that confirmatory trials may be performed in related, but not identical, indications that were granted accelerated approval.

Usually sponsors have conducted trials in an earlier setting of the diseases (for example, less heavily pre-treated patients) and may use the drug in combination with other agents.

Turning to the trial for the relapsed or refractory Hodgkin lymphoma indication, the sponsor submitted a single-arm phase II trial as the primary trial to support this application.

The study population consisted of patients with Hodgkin lymphoma who relapsed after autologous stem cell transplant.

The primary endpoint was Objective Response Rate, and the key secondary endpoints were Duration of Response and Complete Remission Rate. Responses were determined by an Independent Review Facility.

Overall response rate was 73% with a median duration of 6.7 months.

Complete remission rate was 32% with a median duration of 20.5 months.

Partial remission rate was 40% with a median duration of only 3.5 months. Hence, clinical relevance of these partial remissions with relatively short durations with relatively short durations should be discussed in your deliberations.

Peripheral neuropathy was the main adverse event noted by the sponsor.

Also for the Hodgkin's Lymphoma indication, the Sponsor is conducting a phase III, double-blind, placebo controlled, randomized trial of post-transplant therapy in Hodgkin lymphoma.

Patients may not be in remission at the time of

randomization, which raises concerns regarding the heterogeneity of the study population.

We will be asking you to comment on this trial in terms of trial design, primary endpoint, and patient population to be enrolled.

For the relapsed or refractory systemic anaplastic large cell lymphoma indication to be discussed this afternoon, the sponsor again submitted a single-arm phase II clinical trial as the primary trial to support this application.

The study population consisted of patients with relapsed or refractory anaplastic large cell lymphoma.

The primary endpoint was Objective Response Rate, and the key secondary endpoints were Duration of Response and Complete Remission Rate. Responses were determined by an Independent Review Facility.

A total of 58 patients were enrolled. Patients had either relapsed or recurrent disease and the median number of prior systemic therapies was two.

Overall response rate was 86% with a median duration of 12.6 months.

Complete remission rate was 57% with a median duration of 13.2 months.

Partial remission rate was 29% with a median duration of only 2.1 months.

Similar to my comment regarding the Hodgkin lymphoma trial, we will also be asking you to discuss the clinical relevance of the partial remission rate with the relatively short response duration in your deliberations.

Similar to the Hodgkin's lymphoma application, peripheral neuropathy was the main adverse event noted by the sponsor.

There are currently no randomized trials of brentuximab in anaplastic large cell lymphoma being conducted that could serve as a confirmatory trial if the accelerated approval pathway is used.

For these applications, consideration for accelerated approval would be consistent with regulatory actions taken in the past decade for applications of hematologic malignancies based on single arm clinical trials.

Of the 12 applications for hematologic malignancies approved over the past decade (2001-2011) on the basis of single arm trials, all-- but two-- received accelerated approval.

The two applications that received regular approval based on single arm trials were for vorinostat (2006) and romidepsin (2009) for cutaneous T-cell lymphoma.

However, at the meeting regarding romidepsin in 2009, ODAC recommended that subsequent approvals for CTCL require randomized trials.

In Brief:

Ohio State Opens New Center; Pakfar Joins City of Hope as VP

THE OHIO STATE UNIVERSITY Comprehensive Cancer Center–Arthur G. James Cancer Hospital recently opened the JamesCare Comprehensive Breast Center.

The new radiation oncology wing offers radiation treatments in the same location as digital mammography, diagnostic imaging, and other breast health services.

The 114,400 square-foot breast center also offers access to nuclear imaging, clinical trials, chemotherapy, laboratory services, nutrition services, financial services, chemotherapeutic agents, reconstructive surgery, along with social and psychological counseling.

HEIDI MARCHAND was appointed assistant commissioner of the **FDA**'s Office of Special Health Issues, within the Office of External Affairs, in the Office of the Commissioner.

Since 2010, Marchand was director of the agency's Healthcare Professional Liaison Program.

She began her career as a clinical pharmacy practictioner at Suburban Hospital, in Bethesda, Md., eventually becoming director of hospital pharmacy and materials services.

Marchand has been director of international planning and administration at Novartis Pharmaceuticals; director of regulatory affairs at Pfizer Inc.; and executive director of global regulatory intelligence and policy at Amgen Inc.

TINA PAKFAR was appointed vice president of development at **City of Hope**.

Pakfar will be responsible for capital projects and will oversee the cancer center's "Grateful Patient" fundraising program.

"Her expertise, particularly in the area of major gifts, will be a tremendous asset to City of Hope as we continue our ambitious fundraising efforts to advance research and treatment for cancer, diabetes and other life-threatening diseases," said Paul Blodgett, senior vice president of development.

Before City of Hope, Pakfar was senior executive director of development at University of Southern California Norris Comprehensive Cancer Center.

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PHILIP HOWE was appointed associate director of basic science at the **Hollings Cancer Center at the Medical University of South Carolina**. Howe was also named the Hans and Helen Koebig Chair in Clinical Oncology at MUSC.

"Dr. Howe brings scientific expertise and leadership in critical areas of research - cancer molecular biology, genetics, and signaling," said Yusuf Hannun, chairman of MUSC's Department of Biochemistry and Molecular Biology.

Before MUSC, Howe was a faculty member at the Cleveland Clinic for 20 years. His recent research focuses on cellular pathways in tumor development.

TIMOTHY COTE has joined the **National Organization for Rare Disorders** as chief medical officer. He was formerly the director of the Office of Orphan Products Development at FDA.

NORD provides advocacy, education and services for rare disease patients and their families.

Before joining FDA, Cote was affiliated with CDC, serving as country director for Rwanda. He was responsible for scientific and administrative leadership in patient care and research initiatives, and directed programs in HIV/AIDS, malaria and avian influenza.

Cote has also served as senior federal advisor to the director at the District of Columbia Department of Health; as branch chief of Therapeutics and Blood Safety, at the FDA Center for Biologics Evaluation and Research; and as medical director of the Cancer Statistics Branch at NCI.

In addition to his role at NORD, he will serve on the faculty of the Keck Graduate Institute, a specialized graduate school in Claremont, California.

FREDERICK ALT and **ANTHONY GREEN** have each been awarded grants from **The Leukemia and Lymphoma Society** to research new approaches in the treatment and diagnosis of leukemia, lymphoma and myeloma.

The society's Marshall A. Lichtman Specialized Center of Research grants awards $1.25 million a year, for five years. The program is the society's largest academic research grant, awarding more than $235 million since it began in 2000.

The Leukemia & Lymphoma Society awarded two Marshall A. Lichtman Specialized Center of Research grants to Frederick Alt, of Harvard Medical School, and Anthony Green, of the University of Cambridge. Each grant is valued at $1.25 million a year for five years, for a total of $6.25 million.

Alt, of Harvard Medical School, is working on the project "Pathogenetic Mechanisms and Therapeutic Targets in B-Cell Lymphoma," with the goal of learning more about the specific ways B cell lymphomas develop, and to create new targeted therapies to eliminate these malignant cells. The team is investigating both mouse lymphoma models and clinical samples from lymphoma patients in order to learn more about the genetic abnormalities that cause these tumors to develop.

Green, of the University of Cambridge, is studying "Genome-Wide Analysis of Drug Response in the Myeloproliferative Neoplasms," aimed at understanding at the genomic scale how these patients respond to therapy. This grant connects three United Kingdom institutions--Cambridge, Sanger Genome Institute and Addenbrookes Hospital--with a national clinical trial network.

Funding Opportunity:

Defense Department Awarding Postdoctoral Grants of $240,000

THE DEPARTMENT OF DEFENSE Peer Reviewed Cancer Research Program is offering Visionary Postdoctoral Fellowship awards of $240,000 each for direct costs of research in several cancer specialties.

The funds will support postdoctoral fellows training in the laboratory of early career investigators with expertise in one or more of the following cancer areas: blood, colorectal, kidney, pancreatic, pediatric, mesothelioma, melanoma and other skin cancers, genetic cancer research, listeria vaccines, and radiation protection utilizing nanotechnology.

The awards are part of $16 million in funding from the Fiscal Year 2011 Defense Appropriation Act. The awards will not fund breast, prostate, lung (excluding mesothelioma) and ovarian cancer research programs. Preliminary data is not required, and clinical trials will not be supported. The awards support postdoctoral training to include a budget option for research supplies.

A pre-application is required and must be submitted through the CDMRP eReceipt website (https://cdmrp.org) prior to August 10, 2011.

Applications must be submitted through the federal government's single-entry portal, www.grants.gov.

A listing of all USAMRMC funding opportunities can be obtained on the Grants.gov website by performing a basic search using CFDA Number 12.420.