THE CANCER LETTER

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FDA Asks Advisory Group To Define Role Of Single-Arm Studies In Four Applications

By Paul Goldberg

Four applications FDA presented to its clinical advisors at a meeting earlier this week had a striking common thread:

All were based on single-arm studies, and the agency's goal was to get feedback on settings where such studies can be accepted and where randomization should be required.

This "theme" meeting of the Oncologic Drugs Advisory Committee was reminiscent of the group's previous gathering, where advisors were asked to consider two applications and deliberate on a different theme: the threshold of clinical benefit that has to be demonstrated for drugs that delay disease progression (The Cancer Letter, July 19).

At the Sept. 2-3 meeting, ODAC formulated a nuanced message on

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In the Cancer Centers:

CTRC Wins Renewal Of Cancer Center Grant; New Mexico To Lead Systems Biology Center

CANCER THERAPY & RESEARCH CENTER at University of Texas Health Science Center at San Antonio has won renewal of its NCI Cancer Center Support Grant for three years. The grant provides $5.4 million through 2012 to sustain the center's research programs.

"Keeping the words 'NCI-designated Cancer Center' next to our name is the Good Housekeeping seal of approval from the NCI," said Tyler Curiel, executive director of CTRC. "We are enormously proud that the quality of our programs has merited this highly competitive designation without interruption since 1991."

Texas has three NCI-designated Cancer Centers. The CTRC is the only one in South Texas and serves 4.4 million people in the high-growth corridor of Central and South Texas that includes Austin, San Antonio, Laredo and the Rio Grande Valley. The other two are in Houston: the U.T. M.D. Anderson Cancer Center and the Dan L. Duncan Cancer Center at Baylor.

UNIVERSITY OF NEW MEXICO CANCER CENTER has been selected by NIH to lead the 10th National Center for Systems Biology with a five-year, $14.5 million grant. "This grant will bring together people from many different disciplines and backgrounds, including biologists, engineers, mathematicians and physicists at UNM, Los Alamos National Laboratory and Sandia National Laboratories," said **Janet Oliver**, principal investigator of

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ODAC Recommends Approval Of Two Drugs, Nixes Two

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single-arm studies, recommending against approval of two therapies, but giving a nod to two others:

• The committee voted 9-3 against approval of the supplemental New Drug Application of Clolar (clofarabine) for previously untreated adults aged 60 and older with acute myeloid leukemia with at least one unfavorable baseline prognostic factor.

The application, by Genzyme Corp., didn't go through Special Protocol Assessment and was backed by three single-arm studies. FDA officials said Genzyme had been told that "it would be difficult to interpret the results without a control."

• Separately, ODAC voted unanimously 13-0 against Onrigin (laromustine) for remission induction therapy for patients 60 years or older with de novo poor-risk acute myeloid leukemia.

The application was based on two single-arm studies and didn't go through the SPA process. In meetings with the company, FDA raised questions about the adequacy of remission rate and its duration, balanced against the drug's pulmonary toxicity.

However, ODAC recommended approval of two other drugs, despite the fact that they were based on single-arm studies:

• The committee voted 10-0 with one abstention for approval of Istodax (romidepsin) for cutaneous T-cell lymphoma, including relief of pruritus in patients who have received at least one prior systemic therapy.

The application, sponsored by Gloucester Pharmaceuticals Inc., was based on two single-arm studies and had gone through the SPA process. In the past, FDA accepted the results of single-arm trials as a basis for approval of therapies for cutaneous lesions.

Unlike FDA, the European Medicines Agency has not approved this agent, and generally the agency prefers even underpowered randomized trials to single-arm studies.

While voting for approval, ODAC appeared to have closed the door to subsequent applications based on phase II studies for this indication. Though it upheld the conditions of the SPA for Istodax, the committee voted 7-3 with one abstention that randomized trials should be required for future approvals in this disease.

• The committee voted 10-4 for accelerated approval of Folotyn (pralatrexate) for relapsed or refractory peripheral T-cell lymphoma. The committee noted that the agent, sponsored by Allos Therapeutics Inc., appeared to demonstrate activity in some patients with this treatment-resistant disease. The agent went through the SPA process.

ODAC meetings that focus on a specific theme appear to be particularly important, because they are intended to define approval standards at a time when the agency is trying to be explicit about prospectively distinguishing applications that are viable from those that are not.

At these events, the opening comments by Richard Pazdur, director of the Office of Oncology Drug Products, spell out the agency's thinking and likely play the role of an informal guidance to everyone involved in development of cancer drugs.

The text of Pazdur's remarks on the four applications follows:

Clolar: Randomization Preferred

In [this] ODAC meeting, we will be discussing four applications. All of these applications are submitted with single arm trials, and our discussions will focus on the regulatory challenges involved with the analysis of safety and efficacy from single arm trials.

The application in this morning's session is clofarabine for the treatment of previously untreated adults aged 60 or older with acute myeloid leukemia with at least one unfavorable baseline factor, including age greater than or equal to 70 years, antecedent hematologic disorder, ECOG performance status of 2, or intermediate or adverse karotype.

The main study is a phase II single arm study

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(CLO243) of 116 patients. Two other supportive phase II single arm studies were submitted--Study BIOV-121 and UWCM-0001.

Study BIOV-121 was conducted by a predecessor company in Europe. Genzyme conducted retrospective monitoring of case report form data for all patients where possible. Sixty-six patients age 65 years or older with newly diagnosed AML considered not suitable for intensive chemotherapy were studied.

The critical inclusion criteria in the pivotal study (CLO243) were not part of this study protocol. Investigators decided which patients were not suitable for intensive chemotherapy. Most patients in this study had intermediate karyotype.

Other differences from the pivotal study were a different Clolar treatment regimen and lack of an independent review board to confirm the diagnosis of AML, the response rates and the response duration.

The other supplemental study, UWCM-0001, was conducted at ten sites in the UK. Forty patients age 60 years or older with untreated AML considered not suitable for intensive chemotherapy were studied. Individual patient data were not submitted for this study without which the required FDA independent and in depth review cannot be performed.

In the pivotal study (CLO243) 112 patients ≥ 60 years old were included in the analysis. The CR + CRp rate was 45.5%, median duration of response for CR + CRp was 51.6 weeks.

It's important to understand that this was not a study of elderly AML patients who were not fit for standard induction chemotherapy because of poor general health. Patients were eligible for the study because they had one or more of four adverse AML prognostic factors specified in the protocol eligibility criteria. On this basis, they were deemed unsuitable (unlikely to benefit from) standard induction or other intensive chemotherapy.

Focusing on the pivtol study (CLO243), the first issue is that a substantial number of study patients (25% and possibly as many as 41%) may have been suitable candidates for standard induction chemotherapy or other intensive chemotherapy, based on the four protocol-specified adverse AML prognostic factors.

This is supported by the fact that post Clolar, 23 (21%) study patients did receive such therapy with a 48% CR or Cri/CRp rate. Twelve (11%) study patients had hematopoietic stem cell transplantation post Clolar. Post-Clolar, 7 patients received both standard induction or other intensive chemotherapy and hematopoietic stem cell transplantation, so that the total number of patients receiving one or both is 28 (25%).

The second issue is that the lack of a randomized study combined with the heterogeneous patient population regarding AML prognostic factors makes interpretation of the study results difficult.

The FDA has repeatedly emphasized the need for a randomized trial in this disease setting to the applicant. The FDA agreed that the unfavorable prognostic factors should be used, but *only* in the context of a randomized trial. There was no Special Protocol Assessment for any of the Clolar studies.

Minutes of an FDA meeting with the sponsor on 12/4/07 state the following regarding whether the results of study CLO243 would be sufficient to achieve approval of the proposed new indication:

"Determination of a clinically meaningful complete response rate and response duration along with an acceptable safety profile will be a review issue. Generally, approval of new drugs for initial treatment of AML is based on results of randomized controlled trials. It will be difficult to interpret the results of this trial without a control; we recommend that you conduct a randomized controlled study."

The FDA believes that cross study comparison is generally not an appropriate scientific basis for drug marketing approval and is especially not appropriate for single arm studies.

A similar Clofarabine Marketing Application was submitted to the European Medicines Agency, and they provided similar advice. The application was withdrawn by the applicant on March 18, 2008.

The requested indication was for "treatment of acute myeloid leukemia in elderly patients who have one or more of the following: adverse cytogenetics, secondary AML, ≥ 70 years old or significant co-morbidities and are therefore not considered suitable for intensive chemotherapy. Safety and efficacy have been assessed in studies of patients ≥ 65 years old".

The EMEA Application was supported by two supplemental studies BIOV-121 and UWCM-0001 to the US application. The pivotal study for this US submission, CLO243, was not completed and was not submitted to the EMEA.

However, the comments from the EMEA are pertinent to today's discussion.

The EMEA comments included the following:

"The population included seems too heterogeneous regarding unsuitability for intensive chemotherapy. These criteria (according to the Draft guidelines from the British Committee on Standards in Haematology) were not well defined and some patients, for instance without

adverse cytogenetics, were included. The apparently promising results may be due to a bias of selection of some patients suitable for intensive chemotherapy or of patients with a relatively good prognosis…. In the absence of randomisation, no conclusion can be made regarding a potential benefit related to treatment with clofarabine."

The only previous application submitted to the FDA for initial treatment of elderly patients with AML was Zarnestra (tipifarnib), presented to the ODAC in May 2005. That application had similarities to this Clolar application in that there was no randomized controlled study and many of the patients could have been treated with standard induction chemotherapy. The ODAC cited lack of a randomized study and the fact that many of the patients were suitable candidates for standard induction chemotherapy in voting against approval

In conclusion, please consider the following in your deliberations:

First, the pivotal study included a heterogeneous population. The FDA believes that a substantial number of patients in the study population could likely have received intensive treatment with available agents, such as 7 + 3.

Second, it cannot be excluded that the observed response rate and duration noted in this clofarabine application is a result, at least in part, of recruitment of relatively good prognosis patients. The submitted data is derived from a phase 2 single arm study. The absence of a control group makes it impossible to compare results of clofarabine treatment to other possible AML therapies to treat the elderly.

Third, in addition, other prognostic markers have been identified in AML patients of all ages, including multidrug resistance protein and molecular markers such as nucleophosmin 1 and FLT3 internal tandem duplications. These markers were evaluated sparsely or not at all in the submitted study.

Fourth, 59 of 112 patients received post-clofarabine therapies. The premise that older patients would not benefit from conventional drug regimens is refuted by a CR plus CRi/CRp rate of 50% or greater from post-clofarabine treatment with standard cytarabine/ anthracycline or other intensive chemotherapy..

The ODAC has discussed the value of randomized trials on numerous occasions. Randomized trials allow the evaluation of additional endpoints rather than solely relying on response rates. An important caveat regarding randomization is that the randomization process allows us to address prognostic factors that we know about—and more importantly—prognostic factors we do not know about.

We will be asking a single voting question at the conclusion of your deliberations. This question will focus on whether a randomized study should be completed and reviewed to establish safety and efficacy in the proposed indication.

Presently, here are three Clofarabine randomized controlled trials in elderly AML patients: two in progress and one planned. A UK trial (NCRI AML16) is an ongoing phase II/III multi-center program in older patients with AML without prior treatment or high-risk MDS patients.

ECOG is planning a phase III multi-center study that will compare induction with single-agent clofarabine to daunorubicin plus cytarabine in patients ≥60 years of age with newly diagnosed AML, considered fit for an intensive approach. Those patients who achieve CR will receive intermediate-dose cytarabine or clofarabine consolidation.

In addition, Genzyme (CLO342) is conducting a randomized, double-blind, placebo-controlled study comparing Clofarabine + Intermediate dose cytarabine with Intermediate dose cytarabine alone in adult patients ≥55 years old with AML who have relapsed or are refractory after receiving up to 2 prior induction regimens.

Remarks On Laromustine

This afternoon's presentation will review the NDA for laromustine in the proposed indication for remission induction in patients 60 years or older with de novo poor risk AML.

Patients for the indication would be those who have any one of the following poor risk features: age ≥70, ECOG PS equal to 2, unfavorable cytogenetics and cardiac, pulmonary or hepatic dysfunction.

As noted in the morning comments, ODAC has discussed the value of randomized trials on numerous occasions. Randomized trials allow the use of additional endpoints rather than solely relying on response rates.

In addition to complete response rates, a randomized trial would allow an evaluation of important time-to-event endpoints, including progression-free survival and overall survival. Remember, the endpoint of overall survival is not only an efficacy endpoint, but is a critical endpoint in evaluating safety—a point that I will come back later to.

An important caveat regarding randomization is that the randomization process allows us to address prognostic factors that we know about—and more

importantly—prognostic factors we do not know about.

Several meetings have been held over the past eight years between the FDA and Vion about the development of laromustine.

At the "End of Phase I Meeting" in June 2004, the FDA expressed concern about Vion's proposal to combine hydroxyurea with laromustine as remission induction therapy in the proposed CLI-033 phase II single arm trial:

"Administration of both hydroxyurea and cloretazine or laromustine to all patients enrolled to this non-comparative study will make it difficult to evaluate the contribution of each drug to the treatment effect, especially given Vion's proposal that hydroxyurea could enhance treatment effect by inhibiting DNA repair."

At the Jan. 7, 2006, "End of Phase II Meeting," the FDA requested a randomized comparison of Laromustine against standard therapy:

"We strongly encourage you to conduct a randomized study which can identify and isolate the safety and efficacy of cloretazine or laromustine. If you choose to conduct and submit an NDA based on two single arm studies, the adequacy of the CR rate and duration will be a review issue and will likely require discussion with ODAC."

Data from two phase II single arm studies were submitted in support of the proposed indication:

1. CLI-043 was designed to test the efficacy and safety of laromustine in patients ≥ 60 with AML who were prospectively enrolled to be "poor risk". This trial involved laromustine induction and cytarabine consolidation.

2. CLI-033 was originally designed as a broad phase II trial, which studied hydoxyurea given with laromustine as induction therapy for both AML and MDS (previously untreated and relapsed). Fifty-five patients ≥ 60 with de novo AML were then retrospectively selected from the original CLI-033 trial,who were deemed to be similar in their pre-treatment poor risk characteristics to patients on CLI-043 for the NDA efficacy analysis.

The FDA review of this trials note that the remission rate observed in the two single arm trials is 28% in CLI-043 and 29% in CLI-033. Of importance, is that the duration of response is less than 90 days in 38% of responders in the 043 trial and 31% of responders in the 033 trial.

The median leukemia-free survival was 174 days in CLI-043 and 111 days in CLI-033. Overall survival was a median of 98 days in CLI-043 and 103 days in CLI-033.

An important toxicity that will need to be addressed in your deliberations is that of pulmonary toxicity. Pulmonary toxicity was in the top three causes of all toxicity listings in the single arm trials and caused 21% of treatment deaths in a phase III trial that will be discussed subsequently.

Both acute and delayed pulmonary toxicities were documented in both CLI-043 and CLI-037 trials.

As mentioned previously, an additional trial, a randomized trial designated as CLI-037, deserves attention in your discussions. The trial's objective was to study the effect of adding laromustine to cytarabine on the response rate, overall survival and toxicity in patients with relapsed AML who were 18 years or older. The therapy was a 2:1 randomization between the combination of laromustine with cytarabine vs. placebo with cytarabine.

Nineteen per cent of the 86 patients (16/86) who received placebo and cytarabine achieved a complete remission or a CRp, whereas 35% (62/177) of the patients who received cytarabine with laromustine achieved a complete remission or a CRp.

However, the mid-point review led Vion and the FDA to place the trial on hold due to excess mortality in the laromustine arm despite the improvement in complete remission rate associated with the addition of laromustine to cytarabine.

There was a greater than a three-fold increase in adverse events leading to deaths on the laromustine-containing arm compared to the placebo-containing arm—12.8% versus 40.1%. The causes of death on the laromustine-containing arm were primarily infections and pulmonary.

Pulmonary deaths comprised 21% of the deaths on the laromustine arm whereas, no pulmonary deaths were observed on the placebo arm. The list of pulmonary toxicities from this randomized trial is similar to the listing in the two single arm trials.

The same dose of laromustine is used in all trials, including the randomized trial. The detrimental effect on survival observed in this randomized trial enrolling a younger population of patients with AML, albeit in a refractory setting and in combination with cytarabine, raises concerns about the use of this drug in an older population of patents proposed in this indication.

I would like to remind the committee as I pointed out in my opening remarks is that overall survival is not only an efficacy endpoint, but is an important safety endpoint and can only be evaluated adequately in a randomized trial.

The single arm trials submitted with this application

cannot address this issue. Hence, we would like the committee to discuss the single arm trial findings in the context of this randomized trial demonstrating a detrimental survival effect despite an improvement in complete response rate.

Additional concerns we would like the ODAC advice and discussion include the following.

The results of the CLI-033 single arm trial have not isolated the effects of laromustine from hydroxyurea on remission rate in CLI-033. This raises the question whether CLI-033 can be considered a controlled trial.

The results of the CLI-043 single arm trial have not isolated the effects of laromustine from cytarabine on leukemia- free survival and overall survival in CLI-043

The data from the single arm trials do not define the treatment effect of laromustine in the patient population proposed for the indication.

The population of poor-risk patients age ≥60 with AML who may benefit from laromustine is not well-define. Of the responders, 29% of patients in 043 trial and 38% of patients in the 033 trial had age greater than 70 years and/or PS =2 as the only risk factors. These patients may have qualified for available standard induction therapy.

SPA Leads To Recommendation For Vorinostat

As pointed out in the FDA review, three systemic medications have been approved for use in cutaneous T cell lymphoma.

The most recent approval is Vorinostat. Vorinostat, like romidepsin, is a histone deactylase inhibitor. It was approved in 2006 on the basis of two single-arm studies which showed 29.7% and 24.2% response rates along with median response durations of 148 and 106 days, respectively.

Denileukin diftitox or Ontak was given accelerated approval in 1999 based on a dose dependent response rate. Recently, its regular approval was based on a dose dependent improvement in PFS

Finally, Targretin (bexarotene) received regular approval in 1999 based on response rates of 54% and 45% from single arm trials with response durations of 107 and 159 days, respectively. Topical Targretin was also approved on the basis of response rates in a single-arm trial

In general, the FDA has looked at well-documented responses of adequate duration in clinical trials of CTCL trials to be of direct clinical benefit.

This is due to the fact that this disease is primarily cutaneous and an improvement in skin lesions would be of face value correlating with improvement in cosmesis and potentially improving symptoms and reduction of supportive care medications, such as antibiotics and anti-pruritic medications.

This viewpoint has led to the approval of drugs by the FDA on single arm trials with a primary endpoint of response rate in CTCL.

As noted several times during our discussions during this session of ODAC, single arm trials are problematic. They do not allow time to event endpoints, such as time-to-progression or overall survival, from being evaluated.

Also, toxicities of a therapy may be difficult to evaluate from baseline characteristics of the disease, particularly if a drug in this disease would cause cutaneous toxicites. The evaluation of response rate attributed to test drug may be confounded by coadministration of antibiotics, either systemic or topical, that could reduce cutaneous manifestations of the disease process, such as redness and swelling.

In addition, single arm trials do not allow us to compare therapies and prioritize treatments. From a medical practice viewpoint, with the advent of larger number of therapeutic options, health care providers and patients desire this information.

Alternatively, randomized trials require larger patient numbers and longer follow-up than single arm trials. This may be problematic in diseases where patient numbers are limited.

In visiting the EMEA earlier this year and on-going discussions, I noted that the EMEA Scientific Advice Working Group Party has offered different advice from that given by the FDA.

In contrast to our acceptance of a single arm trial for registration with response rate as the endpoint, the EMEA has requested randomized trials….

After the discussion of the today's application on romidepsin prior to the second question, we would like your advice and discussion regarding requiring randomized trials in this disease and this will be a second voting question.

The application of Romidepsin has been through a Special Protocol Assessment with the agreement of the agency on the single arm registration trial. Hence, the question of risk benefit that we will ask you to vote on should be in the context of previously approved drugs by the FDA and our previous commitment to the Sponsor.

Again, the discussion regarding requiring randomized trials in CTCL should be confined to future prospective advice given to applicants rather than the

application under review.

Accelerated Approval for Pralatrexate

Similar to the three previous sessions of ODAC, we will be discussing a single arm trial for the registration.

The proposed indication is pralatrexate as a single agent for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma, or PTCL. The basis for the application is an overall response rate from one single-arm trial. This protocol was subject to a special protocol assessment in 2006 with the caution that "the magnitude and duration of response would be a review issue."

Patients entered on this trial were required to have histologic confirmation of PTCL by a central pathology review and there needed to be documented progressive disease after *at least* one prior therapy. Of the 109 evaluable patients, 27% of patients (29 total patients) had responses. The majority of these responses were partial responses. Of the evaluable patients, 18% had partial responses, 6% had CRs, 2% had Cru.

FDA agrees that 29/109 evaluable patients had responses seen on their initial scan; however, we were concerned with duration of response—less than half of the responders (13/29 responders) had response durations greater than 14 weeks—the time between scans.

In addition, responses in 15 of the 29 responders or 52% were adjudicated due to the disagreement between central reader one and two of the independent review committee. Although there are no approved drugs specifically for PTCL, 70% of patients received subsequent therapies after pralatrexate.

FDA is reviewing this application under the provisions of accelerated approval. Accelerated approval of drugs is for serious and life-threatening disease and must demonstrate an improvement over available therapy. The benefit of the drug is determined by the drug's effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. Confirmatory studies to demonstrate clinical benefit should be performed with "due diligence."

As I have stated on several occasions to ODAC, the drug approval process is not merely a screening process for drug activity. The magnitude of effect and the duration of the effect in this single arm trial must be able to allow you to state that it is reasonably likely for these results to predict a clinical benefit.

In lymphomas, we have generally accepted an improvement in overall survival as clinical benefit. A robust effect in progression-free survival that would be expected to translate into an improved survival has also been accepted as a surrogate for clinical benefit in disease settings with prolonged natural histories, such as indolent lymphomas and CLL.

In your deliberations, we ask you to keep in mind several issues.

First, the majority of responses were partial responses—of the 29 patients having responses, 20 were partial responses, 7 were CRs, and 2 were Cru's. Hence, the response rate is driven by partial responses. We ask you to comment on the clinical meaningfulness of partial responses in lymphomas in your deliberations.

In all registration trials with primary endpoints of response rate, FDA has repeatedly and consistently emphasized that the duration of response is of importance in evaluating efficacy. Responses were evaluated per the IWC criteria first published in 1999.

These IWC criteria do not require confirmatory scans for response evaluation as other response criteria require. In this trial, the first scan was obtained at week 7 to determine initial tumor size reduction, then subsequent scans were obtained every 14 weeks.

After reviewing the data, FDA agrees that 29 of the 109 evaluable patients had responses observed on their initial scan, however, only 13 of 29 responders (12% of the evaluable patients) had durations of response greater than or equal to 14 weeks—the time between scans.

Revised IWC response criteria for malignant lymphomas published in 2007 cautioned that "response rates do not necessarily influence other measures of overall clinical benefit or outcome in patients with lymphoma. Durable complete responses, if associated with measures of clinical benefit, may be relevant."

We ask you to consider if these findings—a large number of PRs comprising the overall response rate and the fact that only 13 of the 29 responders had response duration greater than or equal to 14 weeks—are "reasonably likely" to predict clinical benefit—an improvement in overall survival. Unfortunately, a single arm study does not reliably allow the assessment of patient reported outcomes, such as symptom improvement or aspects of quality of life.

Over the past years, we have frequently discussed with ODAC problems encountered with the evaluation of response and time to progression where there is adjudication of results. Discrepancies in interpreting radiographs between readers point to potential problems of reliability and reproducibility of results.

In this single arm trial, 52% (15 of the 29 responders) were adjudicated due to the disagreement

between central reader 1 and 2 of the independent imaging review committee. Radiographic evaluation of tumor measurements has an inherent subjectivity as evidenced by this adjudication rate with a potential for the introduction of bias. We would like you to discuss this issue with regard to the interpretability, reliability and reproducibility of this endpoint, especially since we are dealing with a single, non-randomized, non-blinded trial.

In giving advice to applicants regarding single arm trials, the FDA has consistently emphasized the need to define a homogeneous group of patients in single arm trials. If a heterogeneous population is enrolled, adequate responses must be observed in all subgroups to be included in the indicated population in subsequent labeling. We ask you to discuss the issue of patient heterogeneity in this trial.

In summary, we would like to point out that the FDA believes that pralatrexate does have biologic activity in PTCL demonstrated by response rates. We all want more therapeutic options for treatment of patients. However, the mere demonstration of biological activity is not sufficient for either regular or accelerated approval.

We have identified in our review areas we would like to comments and discussion. These include the clinical meaningfulness of partial responses in this disease, the finding that only 12% of evaluable patients had responses greater than 14 weeks, the adjudication rate of 52% for the 29 responders between readers, and patient heterogeneity of the studied population.

Lymphoma Experts Support Pralatrexate

The committee disregarded the objections by Thomas Fleming, professor of biostatistics at the University of Washington and a temporary voting member of the committee.

"Is this a reasonably likely to predict clinical benefit?" Fleming said. "I don't see the basis for justifying that. When in doubt, don't approve. I have really serious concerns about the idea that you are going to advance the field by giving more options. Overuse of accelerated approval not only provides a risk to these patients who are now going to be treated under a marketing setting, and it's going to be years before we have a validation trial. And that validation trial now is going to take a lot longer, and it does slow the development of other interventions that are desperately needed."

ODAC member Wyndham Wilson decided to vote for the application because the agent appeared to be benefiting some patients in a "very unique setting."

"This is a disease group that is extremely rare, extremely heterogeneous," said Wilson, chief of the NCI Lymphoma Therapeutics Section. "I think the lack of big studies, the lack of approved drugs tells you how difficult this is to study. And I was impressed with the long, durable responses in a subgroup here. So, I think that there is reasonable evidence that this drug will provide activity."

In the Cancer Centers:

Deininger Named Director Of Tulane Cancer Center

(Continued from page 1)

the new center, called the New Mexico Spatiotemporal Modeling Center. "Together, we expect to develop the new tools needed to understand the dynamic biochemical and spatial events that control the behavior of immune and cancer cells."

Center co-leaders include **Bridget Wilson** and **Jeremy Edwards** from the UNM Cancer Center; **Stanly Steinberg** from the UNM Department of Mathematics and Statistics; **William Hlavacek** from Los Alamos National Laboratory; and **Anup Singh** from Sandia National Laboratories. Oliver's combined team will include more than 50 biologists, biophysicists, physicists, mathematicians, engineers and material scientists, and will grow to include more faculty, postdoctoral researchers and students.

PRESCOTT DEININGER was named director of the Tulane Cancer Center and the Joe W. and Dorothy Dorsett Brown Foundation Regents Distinguished Chair in Molecular Cancer Pharmacology. Deininger, a professor of epidemiology in the Tulane University School of Public Health & Tropical Medicine, was serving as interim director of the cancer center and co-director of the Louisiana Cancer Research Consortium, Tulane's cancer research partnership with LSU and Xavier universities, since July 2007. He is principal investigator on two NIH R01 grants and a $10.7 million COBRE grant that supports development of young faculty. . . . **PETER SHIELDS**, deputy director of the Lombardi Comprehensive Cancer Center at Georgetown was elected president-elect of the American Society of Preventive Oncology. Shields will serve as president-elect for two years before becoming president of the society in 2011. Shields, an expert in biomarkers of cancer risk and tobacco harm reduction strategies, has served as molecular epidemiology interest group chair and conference chair for the society. . . . **WILMOT**

CANCER CENTER at University of Rochester Medical Center has recruited **Aram Hezel** as assistant professor of medicine on the Gastrointestinal Oncology Team, where he will focus on the research and treatment of pancreatic and liver cancers. He relocated from Massachusetts General Hospital Cancer Center and Harvard Medical School. Hezel will also develop a multidisciplinary clinic with the liver transplant team. He received a career development award from NCI and a Howard Hughes investigator award. . . . **ROSWELL PARK CANCER INSTITUTE** appointed two physicians to the Department of Diagnostic Radiology. **James Gannon** will serve in the Division of Nuclear Medicine and **Thomas Laudico** will join the faculty in the Division of Body Imaging. Gannon completed a fellowship at University of Pittsburgh Medical Center. Laudico served as a resident in diagnostic radiology at Fletcher Allen Health Care, University of Vermont Medical Center. . . . NICHOLAS VOGELZANG has joined the US Oncology Research Network and will treat patients at Comprehensive Cancer Centers of Nevada, an affiliate of US Oncology Inc. Vogelzang will serve as chair and medical director of the Developmental Therapeutics Committee for US Oncology Research and co-chair of the Genitourinary Committee. Vogelzang served as a faculty member at the University of Chicago and later as the director of the University of Chicago Cancer Research Center. In 2004, he joined the Nevada Cancer Institute as its director. . . . **M. D. ANDERSON CANCER CENTER** and EMD Serono Inc. announced a strategic alliance designed to provide M. D. Anderson with early insight into potential cancer treatments and to accelerate EMD Serono's preclinical and early clinical research to ultimately bring new drugs to patients faster. The agreement is for three years with the potential to renew the alliance. Both parties decided not to disclose financial details. This non-exclusive strategic alliance will collaboratively draw on the expertise and resources of M. D. Anderson and EMD Serono to design and conduct clinical trials for EMD Serono's oncology product candidates. "The strategic alliance with EMD Serono allows us to collaborate with a leading biopharmaceutical organization to gain important, earlier insights into preclinical and clinical investigational compounds," said **Robert Bast**, vice president for translational research at M. D. Anderson. "We believe there are many opportunities within this alliance to further expand both organizations' research initiatives and programs within oncology to bring more effective treatments to our patients." . . . **FOX CHASE CANCER CENTER** made two appointments: **Yun Shin Chun** was named an attending surgeon in the department of surgical oncology. She comes to Fox Chase from M.D. Anderson Cancer Center, where she was a clinical specialist in the department of surgical oncology and the department of critical care and where she completed her surgical oncology fellowship. **Jeffrey Farma** joined Fox Chase Cancer Center as an attending surgeon in the department of surgical oncology. Farma completed his clinical surgical oncology fellowship at Moffitt Cancer Center. . . . **Jason Brickner**, assistant professor of biochemistry, molecular biology and cell biology in the Weinberg College of Arts and Sciences, and member, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, has been named one of the five Distinguished Young Scholars in Medical Research for 2009 by the W. M. Keck Foundation, a leading supporter of high-impact medical research, science and engineering. Northwestern, Brickner's sponsoring institution, will receive $1 million over five years in support of Brickner's research. . . . **CITY OF HOPE** will use a $3.5 million bequest from Liliane Elkins to establish a

a professorship and endow supportive care programs in the Sheri & Les Biller Patient and Family Resource Center. **Matthew Loscalzo**, administrative director of the Biller Patient and Family Resource Center and executive director in the Department of Supportive Care Medicine, will be the first holder of the Liliane Elkins Professorship in Supportive Care Programs. Elkins died in September 2008. Her bequest not only creates a $2 million endowed professorship, but also adds $1.5 million to the Biller Patient and Family Resource Center's endowment. Interest from the endowment provides dependable funds for patient care, research and education. . . . **SUSAN BROWN** is the new chief nursing officer for The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute. Brown comes from the Virginia G. Piper Cancer Center in Scottsdale, Ariz., where she served as associate vice president for oncology services and director of the center for the past 12 years. Prior to this, Brown served as administrative director of oncology services for Anne Arundel Medical Center in Annapolis, Md. . . . **VANDERBILT-INGRAM CANCER CENTER** epidemiologist **Wei Zheng** received a MERIT Award from NIH for his research on women and cancer. The MERIT (Method to Extend Research in Time) awards provide long-term support to investigators with impressive records of scientific achievement in research areas of special importance or promise. Fewer than five percent of NIH-funded

investigators are selected to receive MERIT awards, which provide financial support for up to 10 years without competitive review. The award will support continuation of the Shanghai Women's Health Study, a population-based study of 75,000 women who were recruited between 1997 and 2000 with a major focus to identify associations between diet and lifestyle and diseases such as cancer. Zheng and his team are studying the impact of soy foods, tea, ginseng and cruciferous vegetables on cancer risk and health. In addition to answering detailed surveys, the women provide blood and urine samples for identification of exposure to dietary influences as well as potential disease biomarkers.

NIH News:

Francis Collins Sworn In As 16th Director Of NIH

FRANCIS COLLINS became the 16th director of the National Institutes of Health on Aug. 17. He was nominated to lead the NIH by President Barack Obama on July 8, and was unanimously confirmed by the U.S. Senate on Aug. 7.

In his nomination announcement, President Obama stated: "The National Institutes of Health stands as a model when it comes to science and research. My administration is committed to promoting scientific integrity and pioneering scientific research and I am confident that Dr. Francis Collins will lead the NIH to achieve these goals. Dr. Collins is one of the top scientists in the world, and his groundbreaking work has changed the very ways we consider our health and examine disease."

"As a scientist, physician, and passionate visionary, Dr. Collins will further NIH's ultimate mission to improve human health," said Health and Human Services Secretary Kathleen Sebelius. "He is an ideal choice to lead the NIH and I look forward to working closely with him."

"I am truly honored and humbled to take the helm today of the world's leading organization supporting biomedical research," Collins said. "The scientific opportunities in both the basic and clinical realms are unprecedented, and the talent and dedication of the grantees and the staff guarantee that this will be a truly exciting era."

Collins, 59, a physician-geneticist noted for his discoveries of disease genes and his leadership of the Human Genome Project, served as director of NIH's National Human Genome Research Institute from 1993-2008.

Raynard Kington, who has served as acting NIH director since mid-October, will return to his role as NIH principal deputy director.

More information about Collins is available at http://www.nih.gov/about/director/.

NCI News:

$36 Million In Stimulus Funds Put Toward Clinical Trials

NCI plans to distribute a portion of its economic stimulus funds to a program to support early-phase clinical trials.

The institute will commit $36 million to a program called Accelerating Clinical Trials of Novel Oncologic Pathways (ACTNOW). The program will use $31 million to fund 37 phase I and II trials, plus $5 million for support contracts, including those to assist the investigators with data monitoring and statistical analysis.

Members of NCI's funded clinical trial networks nominated the studies, chosen by a peer-review panel composed of NCI and non-NCI clinicians, the institute said. The review criteria stressed the scientific evidence for the clinical research and selected strong early phase trials that were stalled by lack of available funding.

"This is money that will pay compound dividends in health care and jobs for physician scientists, oncology nurses, clinical research coordinators, statisticians, medical assistants, and other staff members who will help administer ACTNOW trials at institutions all over the country," NCI Director John Niederhuber wrote on the institute's website.

One of the trials will test a compound called ABT-888, which inhibits the function of certain nuclear proteins that sense and repair DNA damage. A phase I trial funded through ACTNOW will test the safety of ABT-888 as a potentiator of carboplatin and paclitaxel for patients with *BRCA* gene mutations who have inoperable breast cancer, as well as other solid tumors.

Another trial will explore the use of two experimental agents, an oral gamma-secretase inhibitor (which alters the function of certain protein machinery in cells) and GDC-0499 (an inhibitor of the hedgehog signaling pathway that has been implicated in numerous cancers), to treat women with invasive breast cancer.

A third trial will test the use of temsirolimus,

recently approved for renal cell carcinoma, along with an antibody that targets the IGF-1 receptor for people who have metastatic soft tissue and bone cancers.

The ACTNOW studies are designed to integrate the latest imaging technologies and correlative laboratory research studies to understand the underlying biological mechanisms of action. Examples include comparing a positron emission tomography probe that tracks DNA replication and cell proliferation with standard computed tomography in assessing treatment response in early stage, resectable, non-small cell lung cancer. Another trial involving patients with late-stage Hodgkin lymphoma will use response-adapted therapy using early interim PET with a probe that measures glucose metabolism. To ensure reproducibility and reliability of the data, the assays will be CLIA (Clinical Laboratory Improvement Amendments) certified.

ACTNOW awards are also contingent on a very strict, accelerated timeline. Study investigators will be required to finalize institutional review board approval and begin enrolling patients within 90 days, and enrollment must be completed within two years. Investigators will submit metrics related to the economic impact of their project quarterly throughout the funding period.

Most of the ACTNOW studies are being funded as grants, but NCI will use contracting agreements to fund a portion of the clinical trials. The contracts will have targeted deliverables and built-in reporting requirements necessary for stimulus funds.

In Brief:

ASCO Honors Bloomberg, Rings NYSE Closing Bell

On Aug. 19, the American Society of Clinical Oncology presented New York City Mayor Michael Bloomberg with the Society's 2009 Public Service Award for his support of tobacco control and dietary health programs.

The award was presented to Bloomberg following the ringing of the New York Stock Exchange (NYSE) Closing Bell by The ASCO Cancer Foundation (TACF) and U.S. Olympic swimmer and cancer survivor, Eric Shanteau.

"Through his Bloomberg Initiative to Reduce Tobacco Use partnerships, grants are being awarded in low- and middle-income countries to deliver high-impact tobacco control interventions," said ASCO President Douglas Blayney. "Mayor Bloomberg has contributed enormously to the health and welfare of not only the people in the City of New York, but of countless people around the world, and we are pleased to present him with the 2009 ASCO Public Service Award."

The ASCO Cancer Foundation is the philanthropic arm of ASCO. The NYSE event was in honor of the TACF's 10th anniversary and to raise awareness of the need for continued funding for cancer research, improving cancer prevention and patient care through education, and giving patients the best, most reliable cancer information.

Standing side by side, Shanteau and his physician, TACF board member Larry Einhorn, rang the NYSE Closing Bell, signifying the important bond they share as doctor and patient. Diagnosed shortly before the U.S. Olympic trials, Shanteau risked allowing the cancer to spread to fulfill his dream of competing in Beijing. Despite weakness, he made the team in the 200 meter breaststroke, though he was eliminated in the semifinals. After successful removal of the cancerous testicle, he was back in full form, competing at the FINA World Championships in Rome in July, where he won a gold medal in the 400m medley relay, silver medal in the 200m breaststroke and a bronze medal in the 200m individual medley.

Einhorn, who also led the team that treated Lance Armstrong in 1996, was instrumental in guiding Shanteau's cancer treatment.

Accompanying Shanteau and Dr. Einhorn were TACF Chairman, Joseph Bailes, Blayney, ASCO President-Elect George Sledge, ASCO Immediate Past-President, Richard Schilsky, ASCO CEO Allen Lichter, and TACF Executive Director Nancy Daly.

The Radiation Oncology Institute named its first Board of Trustees. The ROI Board is made up of 11 members, including the Immediate Past Chair and President-elect of the Board of Directors for the American Society for Radiation Oncology (ASTRO), six radiation oncologists at large and three public trustee seats. The ASTRO CEO will serve as an ex-officio nonvoting member.

Leading the Board as President is Theodore Lawrence, from the University of Michigan, Ann Arbor, and Vice-president, Colleen Lawton, from the Medical College of Wisconsin.

Named for the Trustee at Large seats: Theodore Lawrence, Colleen Lawton, Deborah Kuban of M.D. Anderson Cancer Center, Christopher Rose of Valley Radiotherapy Associates Medical Group in Los Angeles, Carl Bogardus Jr, of University of Oklahoma Health

Sciences Center, Louis Harrison, from Beth Israel Medical Center-Continuum Cancer Centers.

The following were approved for the Public Trustee seats: Timothy Guertin, Joe Jachinowski, J. Frank Wilson. ASTRO representatives are: Louis Harrison, Anthony Zietman, and Laura Thevenot, ASTRO CEO.

ROI was established in 2006 to promote the critical role of the radiation oncologist in the world cancer community by supporting research and education on radiation therapy.

American Society for Radiation Oncology has announced the results of its Board of Directors and Nominating Committee elections. Those elected will begin their terms at ASTRO's 51st Annual Meeting in Chicago, which will be held Nov. 1-5.

- Leonard Gunderson, Mayo Clinic, Scottsdale, Ariz. President-elect.
- Najeeb Mohideen, Northwest Community Hospital, Arlington Heights, Ill., Health Policy Council Vice-chair.
- Jacqueline Patricia Williams, University of Rochester Medical Center, Rochester, N.Y., Research Council Vice-chair.
- Carol Hahn, Duke University Medical Center, Nominating Committee, Academic Physician.
- Jeff Michalski, Washington University Medical Center, St. Louis, Nominating Committee, Academic Physician.
- Thomas Eichler, Thomas Johns Cancer Center, Richmond, Va., Nominating Committee, Community Practice Physician.
- Patrick Kupelian, M.D. Anderson Cancer Center, Orlando, Nominating Committee, Community Practice Physician.
- William McBride, David Geffen School of Medicine at UCLA, Nominating Committee, Radiobiologist.
- Randall Ten Haken, University of Michigan, Ann Arbor, Nominating Committee, Physicist.

US Oncology Holdings Inc. and its wholly owned subsidiary, US Oncology, Inc. announced that effective Sept. 1, R. Dale Ross retired as Executive Chairman and from the Board of Directors. Bruce Broussard, the company's CEO and president, will also become Chairman of the Board.

Ross founded US Oncology 17 years ago. "Now is the appropriate time for me to retire and to turn over full leadership of the company to Bruce Broussard. Bruce has done an outstanding job since becoming the CEO in February 2008, and I have tremendous confidence in his ability, dedication and integrity," Ross said.

Broussard joined US Oncology in 2000 as Chief Financial Officer, assumed responsibility of the Pharmacy division in 2003, was appointed president in November 2005 and became CEO in February 2008.

Vice Chairman Lloyd Everson will continue in his role of fostering and expanding engagement of US Oncology's network physicians, growing the Company's research and related operations and expanding Innovent Oncology.

Funding Opportunities:

Pancreatic Cancer Research Grant Applications Sought

The 2010 Pancreatic Cancer Action Network Grants Program offers new and expanded funding opportunities for pancreatic cancer research. Nine grants totaling nearly $2.3 million will be awarded. This represents the largest annual dollar amount disbursed since the Pancreatic Cancer Action Network introduced the program in 2003, and reflects an almost 90% increase in funding since last year.

The goals of the Research Grants Program emphasize the urgent need to expedite scientific and medical break-throughs that benefit patients, build a cadre of researchers dedicated to the field, and encourage collaborations, information-sharing and innovation. Importantly, the Pancreatic Cancer Action Network not only provides financial support for research but has created a mentor program to maintain ongoing involvements with grantees to help leverage their funding and enhance their career development. The grants program will once again be administered through the American Association for Cancer Research (AACR) to ensure a rigorous peer-review system.

Qualified candidates are invited to apply. Four grant mechanisms are available: ***Pathway to Leadership Grant*** (new); ***Fellowship Award***; ***Career Development Award*** (funding level doubled); and ***Innovative Grant*** (formerly Pilot Grant, and changed to involve a streamlined application process). See below for a description of each grant.

Applications must be submitted online through proposalCENTRAL (https://proposalcentral.altum.com) beginning Sept. 9. For additional information, visit http://www.pancan.org/Research/grants2010.html. Funding decisions will be available mid-February 2010. The grant term begins July 1, 2010.

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