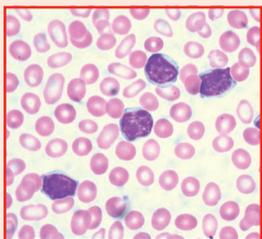


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## Chronic Lymphocytic Leukemia: Bringing New Drugs to Market...Now

*"I have a patient with chronic lymphocytic leukemia who should have died about four years ago," says Richard R. Furman, MD. "He was one of the first people treated with ibrutinib. After not responding to almost all of the chemotherapy agents used in CLL, his lymph nodes started to regress within days after starting ibrutinib and he felt well for the first time in years. Ironically, he qualified as having progressive disease, as his WBC rose to over 700,000. Eighteen months after starting ibrutinib, his WBC reached the normal range and he qualified as having achieved a partial response. Four years later, he demonstrates disease only at the molecular level. He's had an amazing response and is in complete remission."*

Perhaps nothing provides a physician-scientist with greater satisfaction than to see the fruits of his or her labor in the laboratory realized in the development of therapies that improve outcomes for patients. For Dr. Furman, a member of the Lymphoma/Myeloma Service in the Division of Hematology/Oncology at New York-Presbyterian/Weill Cornell Medical Center and Director of the CLL Research Center at Weill Cornell Medical College, this has happened not once but twice in the past year – bringing to fruition eight years of studying targeted molecules as potential therapeutic agents for CLL – the most common leukemia in adults.

"Therapies for symptomatic CLL consist predominantly of chemotherapeutic and immuno-

therapeutic agents, which combined provide treatments that are effective, but also highly toxic," says Dr. Furman. "Additionally, these regimens, available for only younger, fit patients, are not curative, as everyone will eventually relapse. Chemotherapy also leads to DNA damage and creates genomic instability that can lead to transformation of the CLL to an aggressive lymphoma or damage the bone marrow resulting in myelodysplastic syndrome."

During the past four years, Dr. Furman and his colleagues have been working on two drugs – now known as idelalisib and ibrutinib – which inhibit enzymes important in the survival of CLL cells. "In essence, these inhibitors target enzymes that are critical to, and specific for, the survival of CLL cells

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## N=1: A New Take on Glioblastoma Treatment

Glioblastoma (GBM) represents about 54 percent of all gliomas. Not only is it the most common type of primary brain tumor, it is also the most aggressive with an average survival of one to two years. Despite a century of research dedicated to the understanding of the biology of glioblastoma and related tumors, and new advances in treatment of other cancers, therapies for brain tumors remain unacceptably limited.

"On top of the fact that the treatments are not particularly effective for glioblastoma, they can also be toxic," says Andrew B. Lassman, MD, Director of Neuro-Oncology at New York-Presbyterian/Columbia University Medical Center. "Because it affects the brain, even a small tumor in the wrong place can have devastating neurological consequences. Patients can have trouble walking, weakness, and memory loss.

It also creates problems for the family in terms of physical, emotional, and financial burdens."

The challenges of treating GBM are being addressed on many fronts and, says Dr. Lassman, there is some good news on the horizon. "We know, for example, from a study in 2005 that introduced temozolomide chemotherapy as part of the standard treatment, that while it only extended survival by about two and a half months for the majority of patients, the five-year survival for a select group of patients was nearly 30 percent," says Dr. Lassman. "That group of patients consisted of those who were under the age of 50 at diagnosis and who had few to no symptoms. We'd like that to be 100 percent, but nearly 30 percent is better than nearly zero. This was, at least, an encouraging first step toward improving outcome."

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## Copper Depletion: A New Way of Treating Triple-Negative Breast Cancer

Oncologist Linda T. Vahdat, MD, has helped bring to market the last four major breast cancer drugs, playing a leading role in developing two of them. Director of the Breast Cancer Research Program and Chief of the Solid Tumor Service at Weill Cornell Medical College, Dr. Vahdat has devoted her career to treating patients with advanced stages of disease, earning recognition for her translational research. But when Dr. Vahdat started sharing an idea for a new therapy – one that involves depleting patients' copper levels – she was met with deep skepticism.

"I'm an established investigator, and then all of a sudden, I'm talking about copper depletion," recalls Dr. Vahdat. "People thought it was a little bit of a crazy notion, but many were willing to quietly follow along to see how it developed. I'm sure more than one colleague thought I had shifted my focus to a more alternative and complementary medicine approach compared to my hardcore approach – which I have not."

Dr. Vahdat enrolled her first patients in a clinical trial for a copper depletion drug called tetrathiomolybdate (TM) in 2007. Originally slated to run for two years, the clinical trial continues today; earlier this year she published the first phase II results in the *Annals of Oncology*. "The bottom line is, we are very encouraged by our trial results. We have many people in our clinical trial who, statistically speaking, shouldn't even be alive," Dr. Vahdat says. "We have kept extending the duration that patients are kept on the trial because we have scientific evidence that we are interfering with processes that we believe are critical to tumor progression. The net result is that we may be preventing tumors from recurring. If this is so, we feel we have a moral obligation to keep providing them with TM and continuing to study its effect."

**"We are very encouraged by our trial results. We have many people in our clinical trial who, statistically speaking, shouldn't even be alive."**

— Dr. Linda T. Vahdat

Copper depletion has shown particular efficacy in patients with triple-negative cancer, so-called because the tumors test negative for estrogen, progesterone, and HER2 receptors and therefore do not respond to hormonal therapies or to Herceptin®. Between 15 and 25 percent of breast cancer diagnoses fit this profile and as a result have a poor prognosis; once such a tumor metastasizes, patients have a median survival rate of just nine months.

The second woman Dr. Vahdat enrolled in the study had triple-negative breast cancer that had spread to her liver. Luckily, she was able to undergo therapy to remove all traces of it prior to starting on the TM trial. At the end of two years in the trial, she was well and disease free – an observation that was not what one would expect. This inspired Dr. Vahdat to look closely at how copper depletion affects that population. "You have to be open-minded," she says. "This is part of being a scientist. You have to be able to process observations and try to make sense of them."

After seeing positive results, Dr. Vahdat was eager to understand the mechanism by which copper depletion might work, above and



Dr. Linda T. Vahdat

beyond what could be learned from the clinical trial. She proposed a study with longtime collaborator Vivek Mittal, PhD, Director of the Neuberger Berman Foundation Lung Cancer Laboratory and an Associate Professor of Cell and Developmental Biology in the Department of Cardiothoracic Surgery at Weill Cornell Medical College. They had begun working together several years earlier, when Dr. Mittal's lab was looking for microRNA – the noncoding RNA molecules that regulate gene expression – involved in breast cancer metastasis. Earlier this year, Drs. Vahdat and Mittal coauthored a paper in which they identified a microRNA that is highly suppressed in metastatic triple-negative breast cancer. When its function is restored in mouse models, tumors do not spread. Drs. Vahdat and Mittal are now in talks with pharmaceutical companies to further pursue that angle of research.

They have also done extensive work investigating how new sites are prepared for metastasis, a process in which primary tumors recruit bone marrow-derived progenitor cells to establish niches where new tumors can grow. "What we thought could be happening is that depletion of copper might be destroying this pre-metastatic niche," explains Dr. Mittal. "If you destroy those niches, the primary tumor will not be able to metastasize."

As a first step, Dr. Mittal's lab depleted copper in mice whose breast cancer had spread to the lungs, reaching levels as low as Dr. Vahdat had in human patients. They observed that depletion did not stop the primary tumor from growing – but did affect its ability to metastasize. The lab is now conducting experiments on a copper-dependent enzyme essential to the establishment of pre-metastatic niches, and Dr. Mittal is confident they will soon detail the full mechanism by which copper depletion prevents metastasis.

Dr. Mittal admits he wouldn't normally have been interested in testing such a strategy in the lab. But when Dr. Vahdat showed him her early clinical data, he got excited. "She is treating triple-negative breast cancer patients. There is no therapy for these people – yet this copper depletion is clearly benefiting them," he says. "You can discover a lot of interesting things in humans, then study

(continued on page 3)

## Dr. Gary K. Schwartz Appointed Chief of Hematology and Oncology at NewYork-Presbyterian/Columbia University Medical Center

In January 2014 NewYork-Presbyterian/Columbia University Medical Center welcomed Gary K. Schwartz, MD, as Chief of the Division of Hematology and Oncology and Associate Director of the NCI-designated Herbert Irving Comprehensive Cancer Center.

A board-certified medical oncologist and internist, Dr. Schwartz joins NewYork-Presbyterian/Columbia from Memorial Sloan-Kettering Cancer Center, where he served as Chief of the Melanoma and Sarcoma Service. He continues to care for patients with these respective diagnoses.

“Dr. Schwartz has made multiple contributions to the development of new, decisive anti-cancer therapies and has based his career on the ability to move discoveries from the benchtop to the bedside,” notes Stephen G. Emerson, MD, PhD, Medicine Director, Herbert Irving Comprehensive Cancer Center.

For nearly 25 years, Dr. Schwartz has been involved in drug development on a clinical level across oncology disciplines, applying his understanding for the need for better, less toxic, and more personalized therapies gained in his large clinical practice to his own laboratory and translational research pursuits. While at Memorial Sloan-Kettering, Dr. Schwartz directed the Laboratory of New Drug Development. His studies focused on understanding the mechanisms underlying

cell cycle and cell death in order to improve the effectiveness of currently available treatments and to identify novel targeted agents for cancer therapy. Many of the drugs that originated in his laboratory have been evaluated in clinical trials. Dr. Schwartz will continue this research at Columbia, where his laboratory will concentrate on the development of new therapeutic approaches in sarcoma and melanoma with an emphasis on translational research and clinical trials of new drug therapies. In addition, Dr. Schwartz will work collaboratively with his colleagues in the cancer programs at Weill Cornell Medical College.

**“Dr. Schwartz has made multiple contributions to the development of new, decisive anti-cancer therapies.”**

— Dr. Stephen G. Emerson

Dr. Schwartz has served on a number of review committees for the National Institutes of Health and is Co-Chairman of the Experimental Therapeutics Committee of the Alliance for Clinical Trials in Oncology and Associate Editor of the *Journal of Clinical Oncology and Clinical Cancer Research*.



Dr. Gary K. Schwartz

“NewYork-Presbyterian/Columbia has an incredible cancer program with amazing science, excellent clinicians, and a record of success in translating cancer discoveries to cancer medicine,” says Dr. Schwartz. “We now stand on the precipice of amazing opportunities at Columbia. Together we have the ability to transform the field of medical oncology. I look forward to leading this effort by drawing upon the great resources available at Columbia for the benefit and betterment of patients.”

## Copper Depletion: A New Way of Treating Triple-Negative Breast Cancer *(continued from page 2)*

the nuts and bolts in mouse models and figure out better ways of treatment to go back to the patient.”

Drs. Vahdat and Mittal agree that the need to develop therapies to fight metastasis is dire, since all currently available drugs target only primary tumors. “The focus has to move to metastasis, because the primary tumor is not what kills people,” says Dr. Mittal. And time, Dr. Vahdat says, is of the essence. “These patients are desperate for something. The longer we take, the more people will die. And I really feel like we could be on to something important.”

While cautioning that they are still gathering data, Dr. Vahdat notes that copper depletion has the potential to become standard therapy for triple-negative breast cancer in the way that tamoxifen is for hormone-receptor positive disease. The foundation for the next set of clinical trials is being laid to assess, once and for all, if this is an effective strategy. Still, Dr. Vahdat admits, “Every time I say ‘copper,’ I think it’s a little bit crazy. But it is what it is, and there’s the science to back it up.”

[This article is adapted from “Heavy Metal: Is copper the key to treating triple-negative breast cancer?” by Andrea Crawford, *Weill Cornell Medicine*, Summer 2013.]

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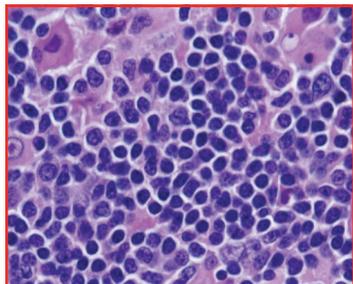
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## Life After Therapy for Hodgkin Lymphoma: Minimizing Long-Term Toxicities

Hodgkin lymphoma is the most common type of cancer in the adolescent and young adult age groups. While this cancer is curable, survivors of the disease are at very high risk for late complications, including premature death and chronic health conditions, as a result of the treatments. “This is a disease where one of the major approaches has been to try to identify



*Hodgkin lymphoma*

treatments that reduce these complications,” says Kara M. Kelly, MD, Associate Director of the Division of Pediatric Hematology/Oncology/Stem Cell Transplantation at NewYork-Presbyterian/Morgan Stanley Children’s Hospital.

Beginning in the 1970s, the first cures for pediatric cancers were realized, notes Dr. Kelly, but in the 1980s there was the recognition that the cure came with a price, primarily for leukemia and Hodgkin’s survivors – the two groups that were most curable. “Since that time, our challenge has been not just to try to cure more patients, but also to identify treatments that are not going to leave them disabled in the future,” says Dr. Kelly. “The problem is that these patients die prematurely of secondary cancers, cardiovascular disease, or restrictive lung disease. Those that don’t succumb to these complications are at higher risk for infertility, chronic cardiopulmonary disease, thyroid problems, and other non-life-threatening cancers. In fact, it has been found that Hodgkin’s survivors have about an eight-fold risk of having more than two chronic health conditions. This is a young population – the median age is 27 years – being left with chronic disabilities in their 30s, 40s, and 50s.”

According to Dr. Kelly, one of the issues with Hodgkin lymphoma compared to other cancers in the pediatric population is that the distinction between pediatrics and adults is artificial. “A 17-year-old with Hodgkin’s is essentially the same as a 22- or 23-year-old, but the approaches that have been developed are quite different, driven by a number of factors,” says Dr. Kelly. “For example, the female breast during the period of adolescent development is more sensitive to radiation and could lead to a 40-fold increased risk for developing breast cancer down the line. Therefore, in pediatrics, the dose of radiation therapy is 60 to 70 percent of those most often used in adults, and the fields in which radiation is given have been more restricted.”

### Influencing Treatment on a National Scope

In 2011, with a record of impressive leadership in the field, Dr. Kelly was named the Chair of the Hodgkin Lymphoma Committee of the Children’s Oncology Group (COG), charged with developing and directing nationwide clinical trials, as well as correlative studies. These studies focus on improving event-free survival, reducing relapses, and minimizing short- and long-term side effects of treatment. Additional research seeks to further the understanding of the pathogenesis of Hodgkin lymphoma to help identify who is at risk and develop strategies to reduce that risk. Dr. Kelly is also overseeing an effort to incorporate measures of quality of life into treatment trials across risk groups.

“We are currently developing two very large phase III trials for treating Hodgkin lymphoma,” says Dr. Kelly. “One trial is focused on the high risk pediatric population under 18 years old, comparing our basic backbone chemotherapy, which uses the drug bleomycin, to a modified chemotherapy and radiotherapy protocol that replaces bleomycin with a new targeted drug, brentuximab vedotin – an antibody-drug conjugate directed to the protein CD30, which is expressed in classical Hodgkin lymphoma. This drug is currently approved for relapse after autotransplant, and we’re now beginning to look at it for newly diagnosed Hodgkin lymphoma. The trial, which was recently approved by the NCI, will involve 600 patients across North America. We hope to open the study for enrollment by early summer.”

The four-year study has improvement in event free survival as its primary goal, but will also incorporate many correlative studies, including the evaluation of translational biology to identify molecular targets.

**“The advantage of coming to a place like Columbia for care in Hodgkin lymphoma is that we are not only offering these clinical trials, we’re also developing and leading them.”**

**— Dr. Kara M. Kelly**

The second trial targets low risk patients and is a collaborative trial with the NCI-sponsored Alliance Lymphoma Committee, chaired by John P. Leonard, MD, Clinical Director of the Center for Lymphoma and Myeloma at NewYork-Presbyterian/Weill Cornell Medical Center. The 1,000-patient study, which has no age restrictions, will also evaluate brentuximab vedotin integrated with the standard ABVD therapy. “Current data show that if you look at survival curves for Hodgkin’s patients, once you go out 10 to 20 years, the curves plateau for relapses,” says Dr. Kelly. “But if you look at overall survival, the curves continue to go down and never plateau primarily due to deaths from late complications of treatments. I’m hopeful that these trials serve as a first step toward being able to replace some of the conventional cytotoxic drugs that leave our survivors with long-term disabilities.”

### Surviving Cancer Treatment with Fertility Intact

Jennifer M. Levine, MD, MSW, MS, began her career at Morgan Stanley Children’s Hospital as the Medical Director of the Center for Survivor Wellness in 2006 after completing her fellowship in pediatric oncology here. Having previously received a master’s degree in social work, Dr. Levine was perfectly suited to lead the Center, which provides ongoing follow-up for survivors of childhood cancer, with a focus on the medical and psychosocial long-term consequences of treatment. She has a particular interest in fertility preservation.

“We are looking at the longer-term toxicities that might result from chemotherapy, radiation, surgery, or any of the other curative attempts,” says Dr. Levine. “One of the issues that’s very concerning to families is whether the patients remain fertile after their therapies. A number of the treatments, including surgery that removes reproductive organs, radiation to the testes, ovaries or uterus, or chemotherapy agents, such as alkylating agents, can



Dr. Kara M. Kelly and Dr. Jennifer M. Levine

cause infertility or diminished fertility. This is a survivorship issue because our patients could have received therapy at two, 10, or 15 years old, therefore infertility may not manifest itself until long after therapy is completed.”

Dr. Levine, who serves as leader of the Female Reproductive Task Force for Survivorship and Outcomes of COG, notes that it is difficult to determine who is potentially at risk for infertility. “We know that there are treatments that put patients at risk, and there’s some evidence that age may be a factor, but nobody really knows for sure and whether there are individual variations,” says Dr. Levine. “What complicates this further is if you could know that somebody had the potential to be infertile, what would you do about it?”

In post-pubertal males, sperm banking is an established methodology and, for females it is no longer considered experimental to preserve eggs, but this is a complicated and invasive procedure. “So in girls, in particular, it is compelling to try to identify who’s potentially at risk before making a recommendation that they preserve their fertility,” continues Dr. Levine. “Freezing gonadal tissue, either testes or ovaries, is also a possibility, although there are limitations in both the techniques and the utility, along with concerns about reintroducing malignant cells.”

With a grant from the Leukemia and Lymphoma Society, Dr. Levine hopes to shed light on two basic questions: Are there patients who lose their chance for biologic children if we don’t preserve their fertility right up front? And is there a group who retains some fertility potential post-therapy, but who might lose it before they’re ready economically and emotionally to have children? The research focuses on the acute effects of lymphoma therapies on reproductive endocrine function and ovarian reserve in adolescents and metabolizing alkylator chemotherapy as a risk factor for the development of acute ovarian failure or premature menopause. “Specifically, we will be looking at changes in markers

of ovarian function and reserve compared to a cross-sectional cohort of healthy controls,” says Dr. Levine. “Alkylating agents used in most lymphoma treatment regimens are particularly toxic to ovarian follicles. The damage can be immediate with acute ovarian failure or delayed, resulting in premature menopause. Improving assessment of risk for acute ovarian failure or premature menopause is critical to enable us to counsel patients about their options for fertility preservation and for developing interventions to minimize toxicity to the follicles.”

The research, which is taking place at sites around the country in 200 lymphoma patients, will identify how many eggs are present before, during, and in the short term after chemotherapy. “The study will enable us to estimate the egg pool at a point in time,” says Dr. Levine. “This exploratory study represents the first phase of a longer journey. Future studies will seek to identify variations in this patient population. If somebody shows a very abnormal pattern, it will be interesting to see what makes that person so different from the others. There also may be individuals who are affected differently by the same drug dose because of the way their body metabolizes that drug. Ultimately we want to stratify our patients for risk of infertility so we can advise them accordingly.”

### Giving New Meaning to Personalized Medicine

Focusing on long-term outcomes of child, adolescent, and young adults with cancer drives the pediatric oncology care model at Morgan Stanley Children’s Hospital. “From the very beginning of disease onset, we want to be thinking about what the lives of our patients are going to be like post-treatment and how we can help them achieve optimum quality of life long-term,” says Dr. Levine.

To accomplish this, Andrew L. Kung, MD, PhD, Chief of the Division of Pediatric Hematology/Oncology/Stem Cell Transplantation at Morgan Stanley Children Hospital, along with the Division’s faculty members, made a decision that they would remain the “oncology home” throughout their patients’ lives, guiding them through any future subspecialty care they may need as adults.

“I think our philosophy is, in some ways, the other side of thinking about personalized medicine – taking care of the whole person,” says Dr. Kung. “We are trying on all levels – medical, psychosocial, personal – to learn and understand the individual needs of our patients and have strategies in place to meet those needs. Our obligation of stewardship in pediatric oncology extends far beyond treatment of disease to the child as a whole and the adult they will grow up to be.”

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## N=1: A New Take on Glioblastoma Treatment *(continued from page 1)*

“We are also finally beginning to understand – if not the cause of these brain tumors in terms of why they happen – at least the cause in terms of their underlying biology,” continues Dr. Lassman. “This



*Dr. Andrew B. Lassman*

is changing our thinking on treatment approaches, and we are adapting lessons from other tumor types. For example, lung cancer is no longer just divided into two categories: small cell and non-small cell lung cancer. Non-small cell lung cancer has been further differentiated into at least 12 molecular subtypes. There are now molecularly oriented therapies that have been designed and are effective for some of those subtypes.”

By applying this information to research on glioblastoma, Dr. Lassman and his colleagues are uncovering molecular subtypes that are potentially treatable by different strategies. “Rather than a ‘one size fits all’ or a ‘one size doesn’t fit anyone’ approach, I think the future lies in a ‘one size fits one’ strategy, identifying the molecular drivers of an individual patient’s tumor in order to personalize treatment,” says Dr. Lassman. “To do this, every patient, if possible, would undergo detailed molecular analysis of resected tumor tissue for the molecular and genetic underpinnings.”

### The Emergence of N=1 Clinical Trials

The development of more precise treatments for the various subtypes of GBM by Dr. Lassman and his colleagues will be largely informed by the work of Andrea Califano, PhD, Chair of the new Department of Systems Biology at Columbia University Medical Center. Dr. Califano and his researchers are pursuing a novel approach to

cancer clinical trials in which therapies are designed and tested one patient at a time.

“Our work is based on the concept of tumor heterogeneity, which essentially means that not only are there different tumors in different people, there are also different cells within the same tumor,” says Dr. Califano. “A drug may kill 90 to 99 percent of the tumor cells, but the remaining one percent may eventually kill the patient because they were not sensitive to the drug – whatever the reason. To address this problem, we are trying to understand how each patient’s tumor is regulated. Eventually, we hope to be able to treat patients not one by one, but based on common vulnerabilities of the cancer cellular machinery, of which genetic mutations are only indirect evidence. Genetic alterations are clearly responsible for tumorigenesis, but control points in molecular networks may be better therapeutic targets.”

So rather than focusing on the usual mutated genes, only a very small number of which can be used to guide successful therapeutic strategies, Dr. Califano and his group developed a novel method based in systems biology that analyzes the regulatory logic of the cell to identify genes and gene pairs that are critical for the survival of the tumor, but are not critical for normal cells. “We reverse engineer the patient’s tumor, much as you would an unknown piece of machinery that no longer works properly,” says Dr. Califano. “We analyze DNA and RNA sequences from a single tumor using systems biology tools, including computational models that require supercomputers, to understand how tumor cells are regulated and to identify the key genes whose activity is necessary to maintain the tumor.”

Once the mechanism of the patient’s individual tumor has been identified, the next step is to test a small number of the appropriate FDA-approved drugs, first in laboratory cultures and then in an existing mouse model that closely matches the patient’s tumor or one created by implanting the patient’s tumor tissue into a mouse. Drugs that are effective in the mouse model, individually or in combination, would then be considered as a therapeutic option for the patient. “There are probably drugs already in the repertoire

of FDA-approved compounds that can be combined to treat virtually every single tumor,” says Dr. Califano.

This protocol is in the final phase of testing in a handful of patients, and the Columbia researchers are currently awaiting IRB approval to evaluate the approach on a larger scale. When a drug is effective, the researchers expect that other patients whose tumors have the same master regulators could be treated with the same drug, extending the benefits from one patient to many.



*Dr. Andrea Califano*

### Applications to Glioblastoma

The N=1 approach of Dr. Califano is closely aligned with the research of Dr. Lassman, and the two will be collaborating to develop better therapies for glioblastoma based on the biological mechanism of a patient’s tumor. Clinical trials are already underway by Dr. Lassman’s group in GBM that incorporate molecular eligibility criteria. “We have multiple clinical trials in our portfolio for brain tumors based on a new paradigm that restricts eligibility to those patients most likely to benefit,” says Dr. Lassman. “For example, two of these studies are designed for patients with EGFR abnormalities in their tumor where we’ll apply an EGFR inhibitor. This trial differs from prior clinical trials of EGFR inhibitors in which patients were enrolled regardless of whether their tumor had an EGFR abnormality. To no surprise, those less selective trials were unsuccessful.

“It’s very exciting to be involved in this research at NewYork-Presbyterian,” says Dr. Lassman. “The Hospital has made a major commitment to advancing care in both neurology and cancer. I happen to fall into both camps.”

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## Chronic Lymphocytic Leukemia (continued from page 1)

so inhibiting them doesn't have systemic effects," says Dr. Furman. "That's been the wonderful aspect of all of this. They really have been home runs.

"CLL is a cancer of mature B lymphocytes and therefore categorized as a subtype of non-Hodgkin lymphoma," explains Dr. Furman. "Idelalisib inhibits signaling through the phosphatidylinositol 3-kinase (PI3K) delta enzyme." PI3K was discovered in the laboratory of Lewis C. Cantley, PhD, Director of the Meyer Cancer Center of Weill Cornell Medical College and NewYork-Presbyterian Hospital.

"Ibrutinib targets B-cell malignancies by inhibiting Bruton's tyrosine kinase (BTK)," continues Dr. Furman. "Both enzymes play critical roles in B-cell receptor signaling. Inhibition of these enzymes promotes apoptosis by blocking proliferation, migration, and adhesion of CLL cells. Given the importance of B-cell receptor signaling and the central role of BTK and PI3K in this pathway, we believed targeting these kinases would be an attractive treatment strategy."



Dr. Richard R. Furman

In 2008, Dr. Furman and the lymphoma group at Weill Cornell began the phase I studies with idelalisib (named CAL-101 at the time). Shortly thereafter, the phase I studies with ibrutinib (named PCI-32765) started. Both phase I studies demonstrated marked clinical activity with minimal toxicities in patients with relapsed or refractory B-cell lymphomas.

### Ibrutinib: The Rapid Road to Market

Preliminary results from the phase I study prompted the initiation of a phase Ib/II study of ibrutinib in CLL. "Once we completed phase I, we wrote the phase II study to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of ibrutinib in patients with relapsed or refractory CLL or small lymphocytic lymphoma," notes Dr. Furman. The study, conducted in collaboration with other medical centers with large CLL populations, involved treatment with two different doses: 420 mg or 840 mg orally, given once daily.

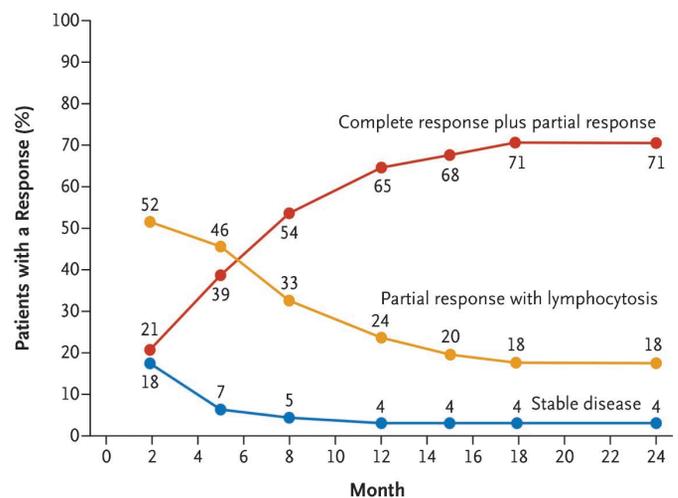
In total, 85 patients were enrolled at eight sites to study this first-in-class drug. The patients – both those with CLL and those with small lymphocytic lymphoma (SLL) – were generally considered to have high-risk disease and had received a median of four previous therapies. "The responses to ibrutinib were more durable than expected on the basis of previous experience with other single-agent therapies," says Dr. Furman. "The ibrutinib monotherapy was capable of inducing a high response rate of 71 percent among these patients, with limited toxic effects. The responses proved durable with prolonged therapy – median follow-up was 22.1 months – suggesting that many patients may now be

treated successfully with monotherapy. And because the drug is in pill form, it's very well-tolerated." The results were published in the July 4, 2013 issue of *The New England Journal of Medicine*.

Subsequently, Dr. Furman presented data of the phase Ib/II study at the 2013 Biennial International Workshop on CLL (iwCLL) held in Cologne, Germany, in September 2013. In addition to the 85 patients with relapsed or refractory CLL or SLL, the ibrutinib trial studied a second patient population of 31 treatment naïve CLL patients greater than 65 years of age treated with ibrutinib monotherapy. In this group of previously untreated patients, all patients continue to respond beyond 26 months, supporting that ibrutinib is highly active, well tolerated, and induces durable responses.

"Although the trial is now closed, patients who continue on ibrutinib treatment have been rolled over to a long-term extension study where they can continue with the study drug," notes Dr. Furman. "Randomized phase III trials are now underway comparing the safety profile of ibrutinib with those of other therapeutic agents for CLL. It is important to note that the drug does not work for large cell lymphomas, so patients with CLL who have developed transformations will not respond to this therapy. The hope is that when we move these therapies up to the front of the treatment algorithm to newly diagnosed patients, patients will be able to avoid the complications of chemotherapy, including transformation to large cell lymphoma, myelosuppression, immunosuppression, bone marrow failure, and other toxicities commonly associated with chemotherapy."

### Response to Ibrutinib Over Time



On November 13, 2013, the U.S. Food and Drug Administration granted accelerated approval to ibrutinib for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy. It is anticipated that approval for its use in CLL won't be far behind. Within the year, idelalisib is expected to follow suit. The phase III trial evaluating idelalisib in combination with rituximab in previously treated CLL patients who could not tolerate chemotherapy was, in fact, stopped in October 2013 for positive efficacy, having demonstrated that it significantly reduces rate of disease progression or death.

*(continued on page 8)*

## Advances in Adult and Pediatric Oncology

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### Chronic Lymphocytic Leukemia (continued from page 7)

“Both of these drugs have a patient experience that goes beyond 2,000 patients with a near 100 percent response rate,” says Dr. Furman. “However, because agents that inhibit the B-cell receptor cause a rise in the white blood cell count, these patients are often classified initially as progressive disease. So early clinical trials often report on response rates of approximately 80 to 90 percent that take into account this progressive disease concept.”

#### Inspiring a New Generation of Medications

Dr. Furman and his colleagues at Weill Cornell have been involved with the clinical development of these newer agents to treat CLL from the beginning. Having identified the enzymes that are high value targets, and with both ibrutinib and idelalisib well on their way to becoming available to patients with CLL, the researchers continue their breakthrough work.

“From my perspective, CLL patients die because their disease stops responding to treatment or because their bone marrow was destroyed by the chemotherapy,” says Dr. Furman. “Having CLL patients who achieve remissions with chemotherapy and then develop myelodysplasia or acute myeloid leukemia at year 10 is a tremendous loss for me. These tyrosine kinase inhibitors change the treatment paradigm for patients with CLL and will hopefully

make CLL a truly chronic disease. We now have three other BTK inhibitors and two additional PI3K inhibitors in clinical development. Even if these new agents only work for five years, having multiple agents that I can cycle patients through would certainly allow me to avoid chemotherapy and enable us to keep patients alive for much longer periods of time than we could have ever considered before. This is an exciting, new time in oncology and such a great step forward for patients.”

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