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SPRING/SUMMER 2016

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## Combining Drugs Improves Survival for Patients with Advanced Sarcoma

Adding a novel monoclonal antibody therapy to traditional chemotherapy has increased median survival by nearly a year in patients with advanced sarcoma. Findings from a multicenter clinical trial of the combination therapy, led by the senior investigator **Gary K. Schwartz, MD**, Chief of the Division of Hematology and Oncology at NewYork-Presbyterian/Columbia University Medical Center, and Associate Director of the Herbert Irving Comprehensive Cancer Center, represent the first appreciable improvement in sarcoma survival in decades. The study was published online in *The Lancet* on July 30.

"We estimated from preclinical data that the new drug – olaratumab – might improve survival in these patients by a few months, but the extent of the improvement exceeded everybody's expectations," says Dr. Schwartz, who began his research leading to the current study while at Memorial Sloan Kettering Cancer Center. "While sarcoma remains a fatal disease, we are encouraged that we're on the right track and hope to build on this progress."

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Gary K. Schwartz, MD

## Treating Acute Leukemias: Addressing the Cancer Cells Left Behind

Despite tremendous technologic advances that have richly rewarded, for example, the lymphomas and other types of cancer with therapeutic advances, the world of acute leukemias has not yet reaped the same benefit. Acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL) remain devastating and largely incurable diseases in adults.

"A major part of our current research efforts is going after minimal residual disease, which is what we believe to be the Holy Grail in acute leukemias," says **Gail J. Roboz, MD**, Professor of Medicine and Director of the Clinical and Translational Leukemia Program at Weill Cornell Medicine. Minimal residual disease

**"I would like to encourage leukemia doctors and patients to make sure to consider additional therapies while in remission and not to trust the state of remission as a durable one."**

— Dr. Gail J. Roboz

– the term given to leukemic stem cells (LSCs) that survive standard chemotherapies – is a critical area of focus for Dr. Roboz and **Duane C. Hassane, PhD**, Assistant Professor of Computational Biomedicine

in Medicine at Weill Cornell Medicine. "It is well known that standard chemotherapeutics fail to eradicate a resistant population of leukemic cells, sometimes referred to as leukemic stem cells, in acute leukemias, and it is well-described

that residual cells after chemotherapy are probably what ultimately cause relapse."

By surviving chemotherapy, the LSCs can regrow the acute leukemia, resulting in a relapse, typically within eight months of remission. This hypothesis

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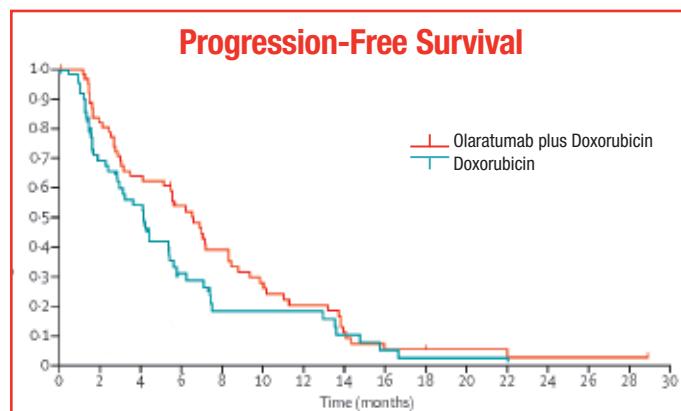
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## Combining Drugs Improves Survival for Patients with Advanced Sarcoma (continued from page 1)



Source: Tap, et al. 2016. *The Lancet*.

There are more than 50 types of soft tissue sarcomas, which if caught early, can be treated effectively with surgery. However, if the disease metastasizes, treatment with chemotherapy does relatively little to slow disease progression or improve survival. The median survival time after diagnosis of advanced disease is 12 to 16 months. In 2015, 12,000 people were diagnosed with soft tissue sarcomas and 5,000 died of the disease, according to the American Cancer Society.

Several years ago, Dr. Schwartz reported that platelet-derived growth factor receptor alpha (PDGFR-alpha) – a cell-surface receptor found in many people with soft tissue sarcoma – appeared to play a key role in tumor growth in specific subtypes of soft tissue sarcoma. By inhibiting this receptor, he was able to get the sarcoma cells to stop growing in his laboratory.

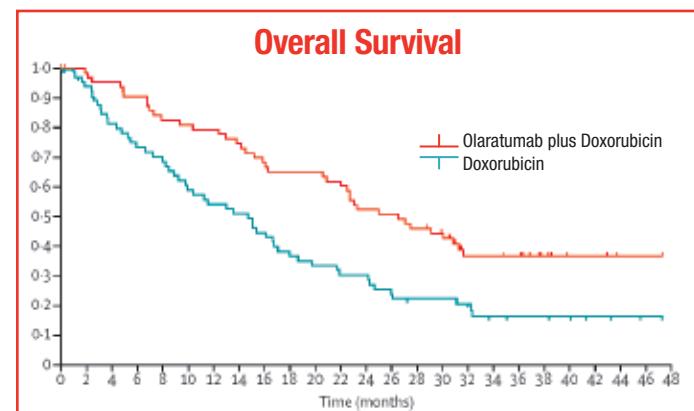
**"We estimated from preclinical data that the new drug – olaratumab – might improve survival in these patients by a few months, but the extent of the improvement exceeded everybody's expectations. While sarcoma remains a fatal disease, we're encouraged that we're on the right track and hope to build on this progress."**

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Working in close association with scientists at ImClone, since acquired by Eli Lilly and Company, Dr. Schwartz developed the clinical trial with the agent olaratumab, a human monoclonal antibody that blocks PDGFR-alpha and disrupts this signaling pathway, which is critical for sarcoma growth. The drug was also shown to enhance the effects of a standard chemotherapy – doxorubicin – which is routinely used in the treatment of sarcoma.

In a Phase II clinical trial, 133 patients with metastatic soft tissue sarcoma were given either doxorubicin or doxorubicin plus olaratumab. The median overall survival of patients in the doxorubicin group was 14.7 months, compared with 26.5 months in the doxorubicin-olaratumab group. Adding olaratumab to standard chemotherapy did not significantly increase treatment side effects.

"As an oncologist, I am ecstatic that the drug worked as well as it did," says Dr. Schwartz. "As a physician-scientist, however, I

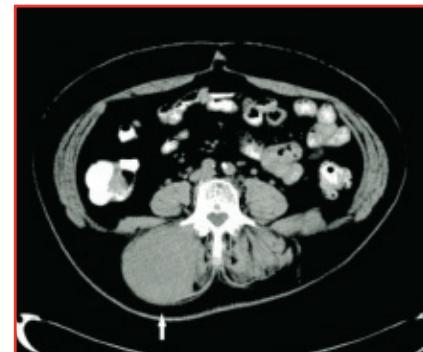


remain frustrated because we still don't know exactly why it worked as well as it did. It might be directly affecting the tumor cells, the tumor microenvironment, or even the immune cells. The future development of this drug will be helped by figuring this out."

Dr. Schwartz and his colleagues are currently studying other potential drug targets for arresting the progression of soft tissue sarcomas.

"Sarcomas are complex. There are, in fact, multiple receptors on the cell surface. PDGFR-alpha is just one of the receptors that are overexpressed on sarcoma cells. We now have some ideas about how to combine drugs that block multiple types of these receptors, which will probably be more effective than targeting a single type of receptor," says Dr. Schwartz.

Lilly has submitted the results of this study to the U.S. Food and Drug Administration and European Medicines Agency (EMA) for regulatory review. The FDA recently granted Lilly Priority Review status for olaratumab. Lilly also has received additional designations for olaratumab from the FDA, including Breakthrough Therapy, Fast Track and Orphan Drug, for this indication. Additionally, the EMA is currently reviewing olaratumab under an accelerated assessment schedule.



CT image of soft tissue sarcoma

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### For More Information

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## Treating Acute Leukemias: Addressing the Cancer Cells Left Behind *(continued from page 1)*



Gail J. Roboz, MD, and Duane C. Hassane, PhD

is supported by clinical evidence showing that patients who have a higher percentage of LSCs demonstrate poorer outcomes. Despite this evidence, characterizing, measuring, and treating these residual cells have proven elusive.

"If you can imagine that chemotherapy might get rid of a large volume of the bulk disease of leukemia, you might also imagine that the cells that remain are the strongest and most powerful, persevering no matter what therapy is given to the patient," says Dr. Roboz. "There are a variety of theories as to the characteristics of the cells in acute leukemias that remain after chemotherapy. One theory suggests that if they are biologically fundamentally different from the bulk leukemic cells, then the residual cells may work in a way that is simply not sensitive to the effects of chemotherapy."

Additionally, Dr. Roboz notes that these residual cells may be able to hide or position themselves within the bone marrow microenvironment where chemotherapy is unable to penetrate. The literature also points to niche type theories in which the leukemic cells, in an almost parasitic manner, harness the resources of the bone marrow microenvironment to establish a shield to protect themselves from the effects of whatever therapy is being deployed.

"It's a several-fold problem," Dr. Roboz acknowledges. "First of all, these cells may have properties that are different from the rest of the bulk leukemia. Secondly, they might actually be able to hide to escape the effects of treatment. Probably both are true, which makes it very difficult to find and eliminate these cells."

According to Dr. Roboz, in leukemia treatment, while you may be successful in eradicating one clone, others quickly arise. "Acute myeloid leukemia, for example, is molecularly very heterogeneous in its initial presentation, and the disease that relapses may be molecularly different from the original," she explains. "Many in the field say that AML is polyclonal at presentation and then monoclonal at relapse. What's not fully understood is whether or not the therapy that the patient is getting manipulates, in a reliable or reproducible way, what we might see molecularly when the patient relapses. From what we have been able to figure out, hitting an individual target in a leukemia patient may not be enough. What we probably need is a combination of either a targeted medication plus

chemotherapy, or several targeted therapies together. Regardless, the leukemia is often several hundred steps ahead of us and constantly evolving, leaving us to continually debate whatever our most current therapy is."

### Improving Survival with Sustained Remission

Dr. Roboz states that it is critical to develop treatment strategies to maintain remission for those patients who achieve it, in addition to developing novel approaches for patients who do not achieve remission. "If we could better identify, characterize, and ultimately treat the left-over leukemia cells that remain once the patient is in remission, it would be an enormous advance," she says. "Finding the residual cells that are either well-hidden, or that are different from the cells that you started out with, is proving to be a very difficult task."

The answers may reside in the laboratory of Dr. Hassane, with whom Dr. Roboz closely collaborates. Dr. Hassane's laboratory performs translational research that uses genomics, including novel liquid biopsy and genome sequencing platforms, to develop new ways of improving cancer treatment. In collaborations with Weill Cornell physicians and researchers, he is producing genome-scale portraits of how various types of cancer therapeutics affect the behavior, survival, and gene regulatory networks in cancer stem cells with a major focus on acute leukemias.

"The ultimate goal of our research is to understand the molecular evolution of acute leukemias from diagnosis, minimal residual disease, and relapse to develop a high resolution map for identifying therapeutic opportunities with greater precision," says Dr. Hassane.

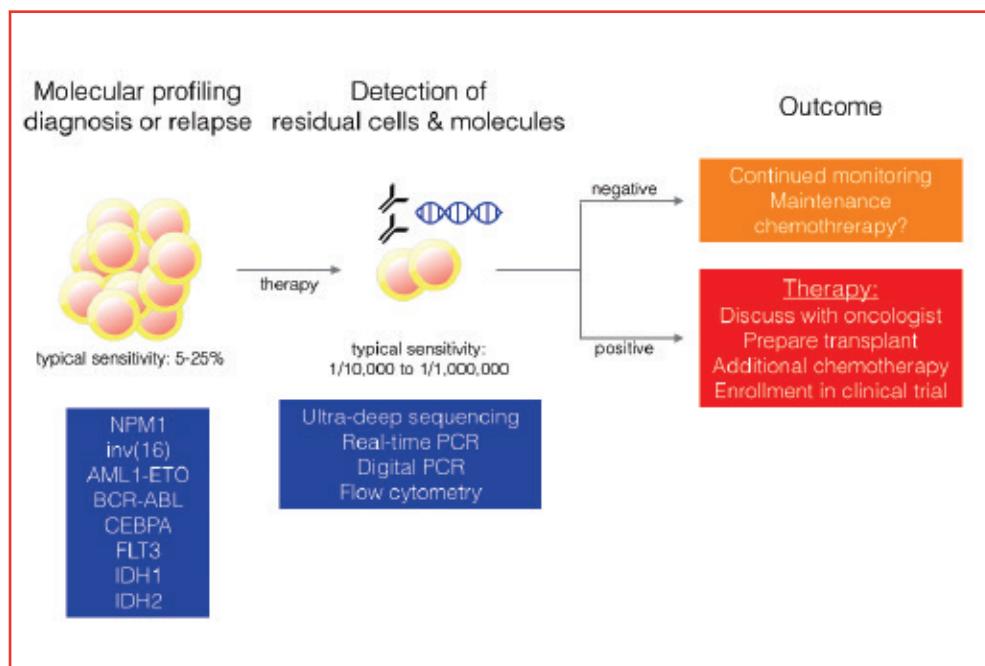
**"The ultimate goal of our research is to understand the molecular evolution of acute leukemias from diagnosis, minimal residual disease, and relapse to develop a high resolution map for identifying therapeutic opportunities with greater precision."**

— Dr. Duane C. Hassane

In particular, he and his colleagues want to push the envelope in minimal residual disease assessment using next generation genome sequencing and novel ultra-sensitive molecular assays to understand how leukemias and their stem cells respond when challenged with various drugs. Developing blueprints for defining the genes and pathways to destroy LSCs can lead to the identification of drugs and drug combinations tailored to each patient as well as inform the timing of therapeutic intervention.

Dr. Hassane is employing a plurality of cutting-edge technologies to piece together an individual patient's entire genomic portrait. "This is where the concept of personalized medicine comes in," says Dr. Roboz. "The question here is how to put together several different technologies to get a complete picture of what's going on with the patient. This is being pursued in a very selective and individual manner, looking very carefully at that particular patient's molecular phenotype. It is an approach unique to Dr. Hassane's research."

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The laboratory of Dr. Duane Hassane uses state-of-the-art genome analytics and other advanced technologies to detect and ablate leukemic stem cells.

Adds Dr. Hassane, "Next-generation sequencing and other advanced technologies are taking us from where we were a few years ago from the equivalent of a 'black and white television' view of tumor heterogeneity, to something closer to 'Ultra HD.'"

While the research is promising, it is still in the experimental stage, according to Dr. Hassane. "Sometimes the most valuable testing and the most relevant results are emerging from a research laboratory and not a commercial laboratory," says Dr. Hassane. "Through truly translational scientific collaborations we are aiming to try to figure out the best way to implement them clinically."

"Finally technology is at a point that enables us to characterize residual cell populations and to start to learn how to quantify and make sense of them," says Dr. Roboz. "I can tell you that I can find one in a million cells of leukemia, but what am I going to do with it? Is it important? What if there are two in the million or three in the million? How do these numbers become prognostically relevant, first of all, and how do you know if you're getting anywhere if you're treating three cells and one of them goes awry? There are no statistics available on any of this. So we are working extensively on turning the technology into quantitatively assessing in addition to qualitatively understanding the cells. The quantitative understanding is what a clinician could use to measure how much leukemia remains and whether or not a relapse is expected and when. This would be a tool of enormous value."

In the meantime, Dr. Roboz notes that obtaining morphologic complete remission in acute leukemias is, in many ways, only a cosmetic result. "Our goal is to make sure that neither treating physicians nor patients are fully satisfied with the achievement of a morphologic remission," she says. "There is still relapse occurring in the vast majority of AML patients. What I would like to encourage in the world of leukemia doctors and patients is to make sure to study, follow up, and consider additional therapies while in

remission and not to trust the state of remission as a durable one."

More recently, there is renewed interest in employing post-remission treatment other than stem cell transplant for patients with acute leukemia. "Historically, patients were either given chemotherapy and then declared done with treatment, or, for a select minority of patients who were able to undergo stem cell transplantation, they were offered transplant in remission," says Dr. Roboz. "However, there might be ways to use chemotherapeutic-targeted, immunomodulatory, or other agents in the post-remission setting in an effort to reach these leftover cell populations."

To this end, Dr. Roboz is directly involved in developing and implementing clinical trials of novel regimens for patients with AML and ALL who have already achieved

complete remission, with the goal of prolonging the duration of remission. "If you're in remission you have normal blood counts, less need for doctor visits, and less need for antibiotics, transfusions, and other medical interventions. The purpose of these trials is to try to prolong the duration of remission because remission correlates not only with length of life, but also quality of life."

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#### For More Information

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## Dr. Lewis Cantley Awarded Prestigious 2016 Wolf Prize in Medicine

**Lewis C. Cantley, PhD**, Meyer Director, the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine/ Ronald P. Stanton Clinical Cancer Program at NewYork-Presbyterian, has been awarded the 2016 Wolf Prize in Medicine from the Wolf Foundation for his groundbreaking discovery of a family of enzymes that are fundamental to understanding diabetes and cancer. Considered “Israel’s Nobel Prize,” the Wolf Prizes are given annually to scientists and researchers who have made seminal achievements in their fields.

Dr. Cantley was recognized for his groundbreaking discovery of the enzyme phosphoinositide 3-kinase (PI3K) and the signaling pathway that it controls. He found that human cancers frequently occur due to activation of PI3K, a breakthrough that has led to the development of drugs that target that signaling pathway. Many PI3-kinase inhibitors are now in clinical trials and, in 2014, the first such drug was approved for treating chronic lymphocytic leukemia based on clinical trials conducted at the Meyer Cancer Center. In addition, Dr. Cantley demonstrated that insulin activates PI3-kinase and this discovery revealed a link between obesity, diabetes, and cancer.

Dr. Cantley shares his award with C. Ronald Kahn, MD, from Harvard Medical School, whose work has provided critical insights into the biochemical mechanism by which insulin controls metabolism. Dr. Cantley and Dr. Kahn



*Lewis C. Cantley, PhD*

collaborated in a series of papers that elucidated links between insulin, PI3-kinase and diabetes.

“It is a tremendous honor to receive this award on behalf of myself and the incredible group of brilliant students, postdoctoral fellows, and collaborators with whom I have worked throughout my career to help elucidate the PI3-kinase pathway and its role in cancer,” says Dr. Cantley. “It is also a privilege to share the prize with Dr. Kahn, whose pioneering work in insulin signaling has facilitated our studies on the role of PI3-kinase in mediating insulin responses.”

## NewYork-Presbyterian Researchers Honored with NCI Outstanding Investigator Awards

Three NewYork-Presbyterian scientists are among the first class of 60 National Cancer Institute Outstanding Investigator Award recipients: **Andrea Califano, PhD**, **Jean Gautier, PhD**, and **Holly G. Prigerson, PhD**. The NCI Outstanding Investigator Award supports accomplished leaders in cancer research who are providing significant contributions toward understanding cancer and developing applications that may lead to a breakthrough in biomedical, behavioral, or clinical cancer research.

Dr. Andrea Califano is the Clyde and Helen Wu Professor of Chemical Biology in Biomedical Informatics and the Institute for Cancer Genetics and Professor of Biochemistry and Molecular Biophysics and Chair, Department of Systems Biology at Columbia University Medical Center. Dr. Califano's research

focuses on developing a novel methodological framework integrating both experimental and computational approaches to systematically identify key mechanisms driving tumor initiation and progression, including understanding how tumor heterogeneity drives the emergence of drug resistance.

Dr. Jean Gautier is Professor of Genetics and Development at Columbia University and leads the Genetics and Epigenetics Program in the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian/Columbia. Dr. Gautier is building a map of protein-protein interactions for repair factors common to multiple repair pathways and identifying protein-protein interactions that are specifically enhanced or reduced following treatment. These differentially regulated modules will identify potential vulnerabilities in the DNA repair networks of cancer cells, opening the possibility for precise, targeted therapies.

Dr. Holly Prigerson is the Irving Sherwood Wright Professor of Geriatrics, Professor of Sociology in Medicine, and Director, Center for Research on End-of-Life Care at Weill Cornell Medicine. Dr. Prigerson conducts primary research in the field of end-of-life medical communication, decision-making, comparative effectiveness, and care, and is developing research tools to develop psychosocial interventions to improve end-of-life cancer care.



*Andrea Califano, PhD*



*Holly G. Prigerson, PhD*



*Jean Gautier, PhD*

## Advances in Oncology

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## NIH T32 Institutional Research Training Grant Awarded in Molecular Oncology

The Division of Hematology/Oncology at NewYork-Presbyterian/Columbia has received a National Institutes of Health T32 Institutional Research Training Grant to support its postdoctoral program in molecular oncology for clinically trained medical oncologists. The Molecular Oncology Training Program is a five-year award of more than \$1 million that will fund four hematology/medical oncology fellows to pursue advanced training in clinical or laboratory-focused research in preparation for careers as translational investigators.

"The T32 grant is a highly competitive teaching award given out to only the most distinguished cancer centers in the United States," says **Gary K. Schwartz, MD**, Chief of Hematology and Oncology and Associate Director of the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian/Columbia. "This is a great achievement for our program and it speaks to our emerging success

in clinical medicine, translational clinical research, and now in medical education, placing us in an elite group of cancer centers based on our excellence in teaching and mentoring."

Under the direction of **Mark L. Heaney, MD, PhD**, Director of the Medical Oncology and Hematology Fellowship Program at Columbia, the research fellowship will train physicians in research techniques that will form the basis of careers in



*Mark L. Heaney, MD, PhD*

translational investigation of cancer biology, diagnosis, and treatment. The comprehensive two-year program centers around three major overlapping research themes: growth dysregulation and genetic abnormalities, intracellular signaling and metabolism, and cancer immunology and tumor microenvironment and includes individualized training within the research programs of Columbia University faculty.

"The rapid technological advances in oncology that have encompassed treatments that precisely target signal transduction pathways, cell division, metabolism, genetics, immunology, and the tumor microenvironment necessitate training of clinically qualified physicians to translate scientific discoveries to the bedside and to optimize the applicability of cancer research to important unmet clinical needs," says Dr. Schwartz.

The Molecular Oncology Training Program faculty comprises 26 independent investigators who are uniformly funded by the National Cancer Institute, other branches of the NIH, and cancer-focused research organizations. They have established themselves as thought-leaders in a broad range of cancer-related disciplines and have been identified on the basis of their research productivity and quality, demonstrated collaboration with other investigators – often across research disciplines – and a history of supporting and developing research careers that transition beyond the postdoctoral level. The trainees will be chosen from a highly select group of physician researchers on the basis of past accomplishments and their potential to develop careers as productive, independent translational investigators.