Fall 2016

HIGHLIGHTS

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Progress happens when smart money and smart research meet. The Leukemia & Lymphoma Society (LLS) values the generosity of donors who make life-saving advances possible.

Changing the Treatment Paradigm for AML Patients

The standard of care for patients with acute myeloid leukemia (AML) hasn't changed in four decades and only one in four people with the disease survive beyond five years. In 2013, LLS took a stand to change this with a large-scale collaboration known as ***Harry T. Mangurian, Jr. Foundation – Beat AML.***

Beat AML uses advanced genomics to understand the mutations that drive AML, determine how genetic mutations interact and how the interactions affect response to therapy. Its goal is to identify patient-specific AML drivers and target them with appropriate therapies that can be validated in larger scale trials.

Initial academic partners were Oregon Health & Science University (OHSU), Stanford University, University of Texas Southwestern Medical Center, University of Utah and University of Colorado – Denver. Five more came on board this year: The Ohio State University, University of Miami, University of Florida, Fox Chase Cancer Center and National Heart, Lung, and Blood Institute.

To date, the centers collected 600 patient samples to analyze and build a biological map of AML. The collection goal is 900 samples. The OHSU bioinformatics team recently completed genomic sequencing on 300 samples (Wave 1) and shared it with Beat AML collaborators. The data will be mined for genetic or clinical factors to predict drug sensitivity. Subsequent testing of Waves 2 and 3 data will validate the first data set. All information, once published in a peer-reviewed journal, will be shared publicly to build a large resource of AML knowledge.

Nine commercial partners contributed 27 proprietary compounds. Because AML almost always becomes resistant to monotherapies, pairs of drugs are also being tested, revealing specific combinations that kill AML cells more effectively than either drug used alone.

The drug sensitivity screen is being used in a Phase 2 clinical trial to select optimal FDA-approved therapies for relapsed/refractory patients. Similarly, a Phase 1 trial uses the screen to select therapies for newly diagnosed patients following chemotherapy. As Beat AML continues, more drugs will be added, including not-yet-approved agents from the commercial partners.

What's Next?

This important step toward precision medicine sparked the interest of researchers, regulators, policy experts, patients, clinicians and pharmaceutical companies. To bring the stakeholders together to explore next steps, LLS used its unique position to convene a gathering in 2014. The group's conclusion was unanimous: LLS was the clear choice to lead a large-scale master trial.

The multi-arm, multi-site Phase 2 Beat AML Master Trial will facilitate FDA approval of new drugs and change the treatment paradigm by developing individualized, effective treatment approaches. The FDA approved the protocol in July 2016.

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Changing the Treatment Paradigm for AML Patients *continued from cover*

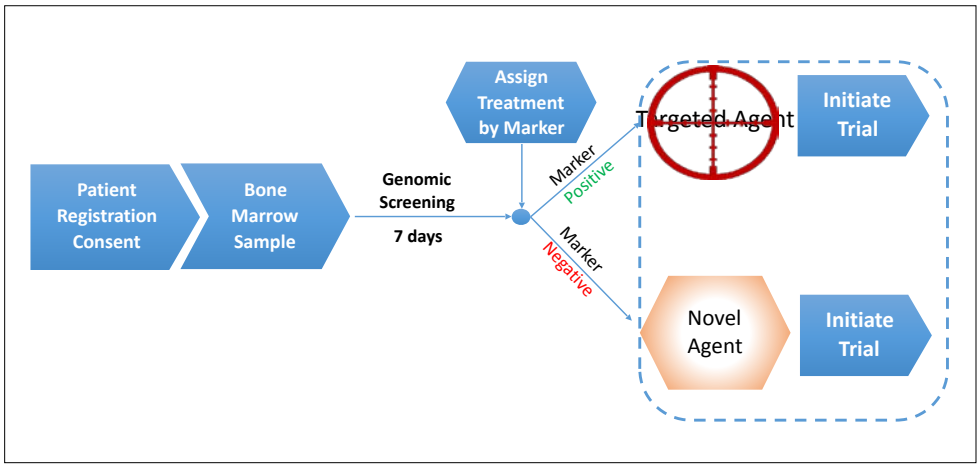
Newly diagnosed AML patients, age 60 years and older, can participate in the study. This distinguishes the trial from most others that enroll previously treated patients for whom other treatments have failed. AML is a heterogeneous disease and when treatments are tested in relapsed or refractory patients, the disease has already mutated after initial therapy.

In the Beat AML Master Trial, patients' bone marrow samples will be screened by a genomic provider **within seven days of diagnosis**. Genetic sequencing will identify specific biomarkers so each patient can receive a personalized therapy in one of the sub-studies (research "arms") in the trial.

…the Beat AML Master Trial exemplifies collaboration across medical, research, pharmaceutical and government sectors.

Targeted treatments will be available for the most prominent AML subsets. Initially, there will be five study arms that will include driver mutations identified in Beat AML. By next year, a total of ten therapies or novel combinations are anticipated. This continues the unique feature of the initial Beat AML effort. Most new drug development is pursued one drug at a time. Testing two agents in combination is relatively new ground.

When multiple markers are present, an algorithm will determine the most appropriate arm. "Marker-negative" patients with mutations that do not correlate to a specific treatment will receive a novel AML agent with broad activity against the microenvironment or immune system. Essentially, every patient will have an option for treatment.



The trial will open by December 2016. Total enrollment is anticipated at 500 patients.

Who Are The Collaborators?

LLS is the lead sponsor of the Beat AML Master Trial with expert guidance from Dr. John Byrd at The Ohio State University (OSU), Dr. Ross Levine at Memorial Sloan Kettering Cancer Center (MSK) and Dr. Brian Druker at Oregon Health & Science University (OHSU). It is the first time that LLS has functioned as a clinical trial sponsor.

Initially, five institutions will each offer all arms of the trial: OSU, MSK, OHSU, Dana-Farber Cancer Institute and Massachusetts General Hospital. Clinical trial sites in eight more states have been approved for activation starting in the spring of 2017.

How Will Patients Gain Access?

A concerted education and awareness effort is underway to encourage trial participation. Outreach focuses on patients, clinicians, oncology nurses and Emergency Room physicians. It is important, for example, that healthcare providers are aware that immediate treatment would make a patient ineligible for the Master Trial that requires a one week waiting period so that genomic analysis can inform treatment decisions. Studies show that waiting seven days has no adverse impact. LLS offers focused education to healthcare providers at www.LLS.org/beat-aml.

The American Society of Hematology will promote the Beat AML Master Trial in printed publications, digital channels and at its annual conference this December in San Diego.

A Model for the Future

The Beat AML Master Trial is a collaborative, fast-acting clinical trial consortium that represents an attractive venue for testing new agents. Further, it exemplifies the Cancer Moonshot's goals for collaboration across medical, research, pharmaceutical and government sectors; data sharing; and increasing patient access to clinical trials to speed progress towards finding cancer cures.

Targeting a Myeloma Trigger

Nearly all cases of myeloma originate in a precursor state known as a monoclonal gammopathy of undetermined significance (MGUS). This occurs when plasma cells produce abnormal proteins in the blood. It's not harmful for most people but if too many proteins accumulate, they crowd out healthy cells in the bone marrow.

The risk of MGUS progressing to myeloma is particularly increased in patients with Gaucher Disease, an inherited disorder that leads to the accumulation of fat molecules. Incidence is low, but Gaucher Disease is more frequently found in people of eastern and central European Jewish heritage.

Madhav Dhodapkar, MD, at Yale University is exploring how the abnormal immune system triggers the transition to myeloma. Using Gaucher Disease mouse models, Dr. Dhodapkar discovered that the accumulation of certain fat molecules triggers cells that eventually cause myeloma. He also found that a new class of drugs that inhibit fat molecule formation prevents gammopathy from developing in mice. The treatment will now be used in patients with Gaucher Disease who also have a monoclonal gammopathy to determine whether it reduces gammopathy. This will provide insights into the origins of myeloma and provide proof of principle whether targeting the underlying trigger can help prevent this blood cancer.

Preventing Myeloma Relapse

Multiple myeloma is the second most common hematological malignancy in the United States and Europe. Multiple therapies, including four new agents approved by the FDA in 2015, are improving outcomes so that half of myeloma patients can expect to survive 5-10 years after diagnosis. Nevertheless, the disease is considered incurable and most patients eventually relapse.

William Matsui, MD, at Johns Hopkins University School of Medicine, is developing new strategies to prevent relapse by targeting cancer stem cells (CSCs). They differ from most myeloma tumor cells in that CSCs are resistant to many drugs, capable of extensive growth and can produce more tumor cells. Eliminating CSCs will prevent tumor regrowth and relapse.

Dr. Matsui recently found that a signaling molecule called Growth Differentiation Factor 15 (GDF15) dramatically increases both the number of myeloma CSCs and their ability to produce more tumor cells by turning on SOX2. This protein controls the expression of specific genes in normal cells and is essential for self-renewal. Dr. Matsui is examining how GDF15 and SOX2 regulate myeloma stem cells to decrease relapse rates and eventually how to develop agents to eliminate cancer stem cells.

Collaborative Grant Encourages Immunotherapy Research

LLS and the Switzerland-based Rising Tide Foundation for Clinical Cancer Research joined forces with a global request for proposals for immunotherapy research. The invitation produced a flood of responses. Four projects were selected for funding.

Margaret Shipp, MD, at Dana-Farber Cancer Institute, is studying two subsets of aggressive B-cell lymphomas: primary central nervous system lymphoma and primary testicular lymphoma. Both have poor therapeutic responses. Dr. Shipp identified frequent alterations in PD-1 inhibitory molecules that cancer cells use as a brake on the immune system to evade attack. This team is studying how PD-1 can be blocked to release the brake so the immune system can fight the cancer.

Ann Leen, PhD, at Baylor College of Medicine, is using immune T cells against acute myeloid leukemia. T cells can distinguish healthy and cancer cells by the tumor-associated antigens (TAAs) expressed only on malignant cells. But cancer cells might express more than one TAA so Dr. Leen is generating T cells that recognize multiple TAAs to kill a wide array of malignant cells.

At the University of Sydney, David Gottlieb, MD, uses cell therapy to reduce post-transplant infections. In a recent trial of patients who responded poorly to antibiotics, Dr. Gottlieb used T cells capable of responding to common pathogens. The cells were not provided by the patient or their transplant donor but rather by third-party individuals. Although not fully tissue matched with the patient, when infused, they effectively controlled viral infections for long periods. He will now test whether third party cells will be equally effective or better if given when patients first develop infections.

A Stanford University team led by Ron Levy, MD, triggered the immune system to fight lymphoma in animals by killing tumor cells in one place and simultaneously activating the immune system to destroy the tumor throughout the body. This will be tested in patients with follicular lymphoma. Dr. Levy will combine low dose radiotherapy with an immune activator in the same place and the oral drug, Ibrutinib, which both kills the tumor and enhances the immune system.

New Clinical Trial Model Succeeds

Community oncologists who see 70 percent of cancer patients are not always aware of available trials in specific blood cancers. Further, patients who might live far from a comprehensive cancer center often prefer to avoid the time and expense of travel. As a result, researchers struggle to enroll enough participants to evaluate new therapies and too many patients miss out on new treatment options.

In 2013, LLS and the Dana-Farber Cancer Institute launched a collaboration to bring clinical trials to where patients are found – in the community. LLS committed $1 million over three years to create the Blood Cancer Research Partnership (BCRP) to bring Phase 1 and 2 trials to community treatment centers. Results so far have met all expectations.

- Patients gained access to innovative trials in 12 states—California, Colorado, Connecticut, Georgia, Kansas, Maine, Michigan, Minnesota, New Jersey, New York, Tennessee and Washington State.
- Eight new clinical trials opened. Two were completed and six remain active.
- Patient enrollment rates were significantly accelerated. One trial decreased overall accrual time by six months and contributed 30 percent of the patients accrued.
- Staff at community sites received up-to-date clinical research training.

As an example of how trials help to advance treatments, response rates and patient survival, a 23 year-old man had undergone 16 different therapies for his refractory Hodgkin lymphoma. All prior treatments failed him. When he enrolled in a clinical trial at a BCRP site in Georgia, he achieved a stable disease response after two cycles of treatment.

Another trial, which offered a new agent for multiple myeloma, opened in five sites and accrued 14 patients in six months. Findings showed a 30 percent response rate and the data was presented at professional national conferences in 2015.

The high quality data produced over a relatively short period of time confirms the benefit of this new trial model. To ensure its continued success, LLS committed to extend financial support for two more years.

I support LLS *because...*

"... it's a meaningful memorial to my husband. Like so many blood cancer stories, ours begins with a routine doctor visit. The morning before Thanksgiving in 2006, Joe's cardiologist found abnormalities in his blood. As a result, our holiday menu included a large dish of worry. When we learned that Joe's diagnosis was chronic myeloid leukemia, our oncologist provided comfort – CML can be treated with a drug called Gleevec. By late December, Joe's white blood cell count returned to normal.

With his disease in check, I returned to my passion of running half marathons. In one race, I saw Team in Training at the Health Expo and learned that LLS supported the development of Gleevec. I promptly signed on to fundraise for LLS through the Nike Half Marathon in San Francisco and Joe accompanied me to the pre-race pasta dinner. Wow! The energy, the passion, the excitement hooked us.

When Joe passed away in 2014 from another cause, I wanted to honor his memory in a way that would be special to both of us. We've made a charitable investment to LLS for life-saving research."

— Drenda Vijuk, Florida

To help advance research in the area of greatest concern to you, contact us at **1-888-773-9958**.