In acute myeloid leukemia (AML), a disease that hasn’t had a new therapy for 40 years, recently released data showed significant improvement in survival when an investigational therapy CPX-351 (VYXEOS™) was compared to the standard treatment known as 7+3. The promising data from a Phase 3 clinical trial was the result of a partnership that began in 2009 when the Leukemia & Lymphoma Society (LLS) Therapy Acceleration Program committed $4 million to a small company with a big idea to test a new method of delivering standard therapies.

The CPX-351 therapy from Celator Pharmaceuticals encapsulates cytarabine + daunorubicin in fat-containing “liposomes” that are administered by injection. Encased together, the drugs maintain the desired ratio for maximum effectiveness, enhance uptake in fat-loving cancer cells, and reduce toxicity.

LLS funded a Phase 2 trial and was so encouraged by the results that it committed an additional $5 million for a Phase 3 trial that opened in December 2012. It enrolled newly diagnosed patients aged 60-75 years old who developed AML after a prior myeloid disease such as myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN) or as a result of harsh therapies from other cancers. These patients are considered high risk with an exceptionally poor prognosis.

Data on the multi-site trial showed an improvement in overall survival of 60.7 percent. Survival at 12 and 24 months is illustrated below.

Thirty-four percent of patients treated with CPX-351 went on to receive a stem cell transplant compared to 25 percent of patients treated with the standard of care.

Based on these results, Celator expects to file a new Drug Application with the FDA by autumn. If approval is received, it would provide the first approved therapy in decades to extend survival for patients with high-risk AML.

Moving a new therapy from clinical development into the healthcare market is the goal of the LLS Therapy Acceleration Program. This is but one of nearly two-dozen such projects currently in the Therapy Acceleration Pipeline.

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In April, the U.S. Food and Drug Administration approved venetoclax (Venclexta) to treat certain patients with chronic lymphocytic leukemia (CLL). The new treatment is for CLL patients who are missing a piece of chromosome 17p and for whom at least one prior therapy failed. These patients generally have a poor prognosis and about 30 percent of CLL patients who don’t respond to therapy or who have relapsed have this mutation.

Venetoclax (formerly known as ABT-199) is an oral medication and the first approved treatment that targets BCL-2, a protein that can act to keep cancer cells alive. When tested in a trial of 106 CLL patients with the 17p deletion who had been previously treated, 80 percent experienced a remission.

Since 2002, LLS has invested more than $16 million in research that led to the drug’s development. Funding to Jerry Adams, PhD, and Andrew Roberts, MD, PhD, at the Walter and Eliza Hall Institute on Medical Research in Melbourne, Australia supported studies to develop small molecule inhibitors of BCL-2. About the same time, Anthony Letai, MD, PhD, at Dana-Farber Cancer Institute in Boston used LLS grants to determine what kind of cancers would be sensitive to BCL-2 inhibitors. He showed that the secret of cancer cell dependency lay in proteins binding to each other on their mitochondria (little organelles inside our cells). Mitochondria are the “power plants” that are key decision-makers in whether a cell lives or dies. Dr. Letai’s team confirmed that CLL would be a sound target for a BCL-2 inhibitor.

Conventional therapies trigger cancer cell death indirectly and cause damage to DNA and proteins in normal cells. Venetoclax directly causes cancer cell death without damaging DNA and proteins in normal cells. That makes it potent and tolerable and relatively easy to combine with other agents. Further, it is plausible that drugs like venetoclax, which prime the cell death pathway of tumor cells, might make tumor cells more sensitive to immunotherapies.

The Human Side of Clinical Trials

It took 14+ years of trial and error to develop venetoclax. But for a family practice physician in Sacramento, the drug became available just when needed.

Dr. Larry Saltzman is the developer of the recently-launched LLS Patient-Caregiver Online Community. Diagnosed in 2010 with CLL, he endured “watch and wait” protocol until becoming symptomatic three years later. Bendamustine + rituximab put the disease into remission but eleven months later he relapsed. A highly regarded CLL specialist offered two options: a new FDA-approved therapy or a trial of an investigational drug that required a relocation to New York. He chose the approved therapy but a few months down the road, side effects became intolerable. Larry needed surgery to remove a colon obstruction and had to discontinue the therapy. He relapsed a second time.

The Phase 2 trial of venetoclax seemed an ideal option except for one problem. The trial that opened two years earlier for CLL patients with 17p deletion was now maxed out and closed. With persistence, he found that the trial was extended for 60 patients without the 17p mutation. But each new patient had to be tested by the sponsor and treatment had to begin within 28 days. Larry promptly started testing last December but hadn’t anticipated the university’s two week holiday break. He was becoming sicker and the trial window was closing.

Larry enrolled in the trial January 12, exactly 28 days after testing. When the dose-escalation reached the therapeutic level of 400 mg., lymph nodes started to shrink. Larry is becoming stronger, regained an appetite, and completed a run/walk Half Marathon with his wife, Sharon.

What’s Larry’s advice? Get a second opinion at an academic medical center. Experience with new diagnoses and knowledge about current options are important. Larry also advises, “Never overlook the difficulty of the experience for the caregiver.”

Sharon and Larry Saltzman after recently completing a half marathon.
The newest investment in our Therapy Acceleration Pipeline is with the Dutch biopharmaceutical company Kiadis Pharma. LLS is providing financing for a Phase 2 trial of a therapy that can reduce the risk of transplants. Although the most effective curative treatment for blood cancer patients, stem cell transplants have a high risk of life-threatening infection and graft versus host disease (GVHD), where donor immune cells mistakenly attack the patient’s normal cells. Incidence of severe-grade GVHD can reach 30 percent and with potentially lethal effects.

When considering transplant as an option, patients seek matched donors, often a sibling, who are most likely to have similar human leukocyte antigens (HLAs) that give everyone their unique tissue type. But only one in four patients have a matched family member donor and about a third of patients eligible for transplant won’t find a matched donor in time. When needed, clinicians have used partially compatible sibling donors to haploidentical recipients (both carry the same chromosome from one parent). In a transplant, the bone marrow with the diseased cancer cells is completely destroyed and replaced in the graft by stem cells from a healthy donor. During the six to twelve month recovery period, the patient is highly vulnerable to infections and disease relapse.

...this treatment used along with the primary therapy can significantly expand the number of patients who can benefit from stem cell transplantation.

A new therapy developed by Kiadis Pharma, ATIR101™, is used as an add-on to partially matched related donors. T cells in ATIR101 fight infections and remaining tumor cells and bridge the time until the immune system recovers. And because T cells that would cause GVHD are eliminated from the donor lymphocytes, risk is minimized.

In data released this April from a Phase 2 trial of patients in the United States, Canada, Belgium and the United Kingdom, ATIR101, given as a single dose, was compared to a historical control group of similar, partially matched patients. The control group had a 40 percent incidence of high grade GVHD. The trial group had none. Forty percent of the control group died within six months after transplant; in the trial group it was 13 percent. And one-year survival in the control group was 20 percent; in the trial group it is close to 80 percent.

A new Phase 2 trial supported by LLS is testing whether a second dose of this new therapy, which does not require immunosuppression drugs, can further improve outcomes for transplanted patients.

Because almost all patients can find a partially matched family member as a prospective donor in a short time frame, this treatment used along with the primary therapy can significantly expand the number of patients who can benefit from stem cell transplantation.
What is the Cost of Innovation?

As treatment for many cancers is undergoing a renaissance, the “financial toxicity” of new therapies is a growing concern. The value of treatments is part of a national debate among patients, providers, payers and policy experts. The American Society of Clinical Oncology has gone so far as to suggest that physicians should discuss financial burdens with patients when presenting options about treatment benefits and risks.

Little is known about whether and how physicians, medical groups, health systems and pharmacies counsel patients regarding costs. And there is little information about how patients and physicians define “valuable” cancer treatment innovation when costs are considered alongside clinical benefits.

Central to the LLS mission is ensuring access to quality, affordable and coordinated care. To determine the extent to which out-of-pocket costs are a barrier to treatment and the factors that define value, LLS is funding and partnering on a research study to collect contemporaneous, nationally representative data. It will test the following hypotheses:

- Most physicians are not aware of the out-of-pocket costs of cancer treatments for patients.
- Most physicians do not believe it is their job to communicate the cost of cancer treatment to their patients undergoing care.
- It is rare for physicians/provider groups to create formal mechanisms to counsel patients regarding costs and availability of assistance.
- Patients commonly change their spending and saving to finance treatment.

Patients seek multiple assistance programs.
- Patients equally weigh clinical benefits, side effects, convenience and cost when considering options.

The LLS study will focus on patients with chronic lymphocytic leukemia and multiple myeloma, who are currently in active treatment along with the physicians who treat them. These were chosen because a number of new and costly therapies for these two blood cancers have been introduced in recent years.

Central to the LLS mission is ensuring access to quality, affordable and coordinated care.

The study will be led by Rena Conti, PhD, a health economist at the University of Chicago. The research team includes a pharmaco-epidemiologist, a physician, an expert in survey design, and a community psychologist skilled in improving access to quality of life and care in medically underserved communities.

Using at least half of the 46 sites in the existing NCI Community Oncology Research Program, the study is expected to include 1,000 patients and 200 physicians. From the start in early 2016, it will take approximately 30 months for development, recruitment, data collection and analysis. Findings have the potential to directly inform the decision-making of policy makers, payers, providers, manufacturers and advocates focused on delivering the best treatment to patients and maximizing access to this care.

A Tax-Smart Choice Can Save Lives...

For many people, an IRA, 401k or other retirement account can represent a significant portion of assets. Smart planning can maximize the productivity of those assets for you, your heirs and causes that matter to you. How? Name your favorite charities as full or partial beneficiaries of retirement accounts and leave non-retirement assets such as stock, business interests or real estate to heirs.

Tax-deferred accounts left to individuals are subject to substantial tax burdens that minimize your bequest. But when left to a tax-exempt organization like LLS, those assets are fully used for purposes you designate, like life-saving research. For heirs, leave non-retirement assets that can be eligible for special treatment to avoid capital gains taxes.

Naming a charitable beneficiary is simple and cost free. Contact your retirement plan administrator or access your account online to include The Leukemia & Lymphoma Society as a beneficiary. If you choose to let us know of your thoughtfulness, we’d be glad to express our sincere thanks. Your tax advisor can help. And we’re ready to answer questions at 888-773-9958 or at legacy@LLS.org.