MEDICINES IN DEVELOPMENT / 2015 REPORT

FROM HOPE TO *cures*

BLOCK CANCERS

IN PARTNERSHIP WITH

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

MEDICINES IN DEVELOPMENT FOR LEUKEMIA & LYMPHOMA

A REPORT ON CANCERS OF THE BLOOD

JUST THE FACTS[1]

162,020

Estimated number of Americans to be diagnosed with a blood cancer in 2015

54,270

Expected new cases of leukemia in 2015

80,900

Expected new cases of lymphoma in 2015

26,850

Expected new cases of myeloma in 2015

PhRMA
RESEARCH PROGRESS HOPE

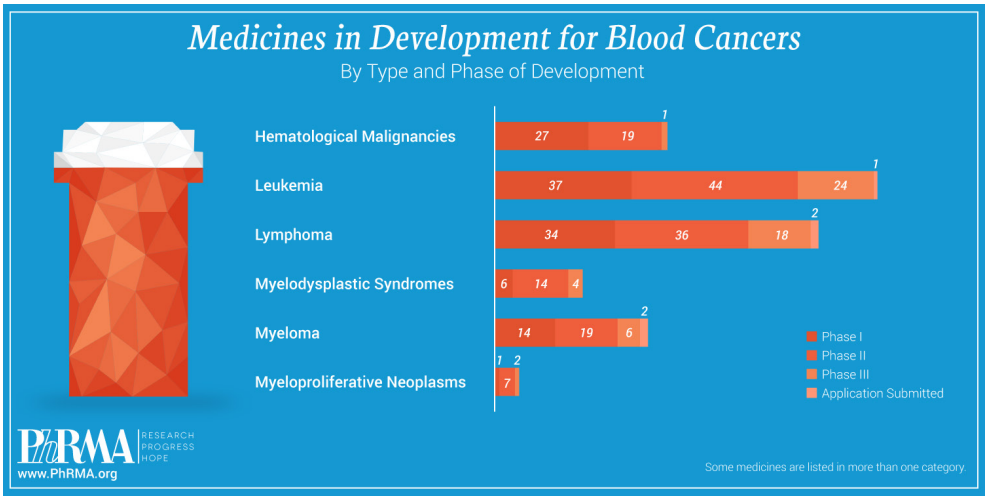
More Than 240 Medicines in Development for Leukemia, Lymphoma and Other Blood Cancers

Each year, more than 162,000 Americans are diagnosed with a blood cancer[1]—accounting for more than 9 percent of all new cancer diagnoses.[1] Major types of blood cancers include leukemia, lymphoma and myeloma.

In recent years, science has advanced quickly and opened doors for more precise treatment, as we have seen exciting progress in our understanding of and ability to treat blood cancers. For example, we now know that "diseases of the blood" – as they were known a few decades ago – include at least 35 types of leukemia and 50 different lymphomas, based on genetic differences. Many new medicines are able to target cancers at the molecular level and the treatment outlook has never been better for patients.

Survival rates reflect the remarkable progress in diagnosis and treatment. Highlights include:

- Five-year relative survival rates for acute lymphoblastic leukemia (ALL) in children under age 15 jumped from 3 percent in 1964 to 92 percent in 2010.[2]
- The overall five-year relative survival rate for leukemia patients has more than quadrupled since 1960 from 14 percent to 60.3 percent.[2]
- For Hodgkin lymphoma, five-year relative survival rates have more than doubled since 1960, reaching 87.7 percent in 2010 and nearly 94 percent in patients diagnosed at age 45 or younger.[2]
- Five-year relative survival rates for patients with myeloma, a cancer of plasma cells, have increased from 12 percent in the 1960s to 46.7 percent in 2010.[2]



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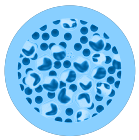
Despite the progress researchers and clinicians have made in the treatment of blood cancers, the need is great for continued innovation and access to new medicines. Biopharmaceutical research companies are currently developing 247 medicines[3] targeting leukemia, lymphoma, myeloma and other blood cancers. These medicines are either in human clinical trials or under review by the U.S. Food and Drug Administration (FDA). The medicines in development include:



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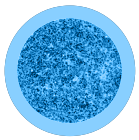
for several types of leukemia, which affect more than **54,000** people in the United States each year.[1]

90

for lymphoma, including Hodgkin and non-Hodgkin lymphoma, which affects more than **80,000** Americans each year.[1]



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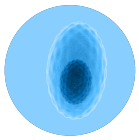
target hematological malignancies, which affect bone marrow, blood and lymph nodes.[1]



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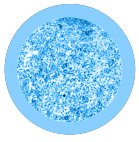
for myeloma, which impacts nearly **27,000** people each year in the United States.



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for myeloproliferative neoplasms, such as myelofibrosis, polycythemia vera and essential thrombocythemia; and for myelodysplastic syndromes, which are diseases affecting the blood and bone marrow.[1]

Some medicines are listed in more than one category. For a complete list of the 247 medicines in development, please visit http://www.phrma.org/sites/default/files/pdf/blood-cancers-list.pdf

A Decade of Innovation in Leukemia

During the last decade, researchers have pushed the scientific envelope, working at cellular and molecular levels to dramatically advance the treatment of blood cancers. They have had particular success in the fight against chronic lymphocytic leukemia and chronic myeloid leukemia. A look at treatment advances over the last 10 years demonstrates the rapid pace of progress.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

CLL is a rare form of blood cancer in which patients have an over-proliferation of abnormal lymphocytes. Lymphocytes are blood cells that normally play an important role in helping the immune system fight infection. As their immune system weakens, CLL patients may experience swelling of the lymph nodes, debilitating fatigue, and an increase in fever and infections. More than 14,000 cases of CLL are diagnosed each year in the United States.

TREATMENT THEN: 2005

For a patient diagnosed with CLL in 2005, chemotherapy was the predominant first-line treatment. But CLL weakens a patient's immune system, making it sometimes difficult to tolerate chemotherapeutic regimens that can further weaken the immune system. Additional treatment options for CLL patients with immune systems unable to tolerate chemotherapy-based treatment were very much needed.

TREATMENT NOW: 2015

A patient diagnosed today with CLL has a range of approved targeted therapies, including monoclonal antibodies and B-cell receptor pathway inhibitors, that treat the root cause of the disease with fewer risks to the immune system and often result in remission. In addition, combinations of these targeted therapies are being explored providing potential new treatment options for CLL patients with fewer side effects.

CHRONIC MYELOID LEUKEMIA (CML)

CML is a rare form of blood cancer in which abnormal blood cells (leukemia cells) crowd out normal white blood cells, red blood cells, and platelets so that the body is prevented from carrying out normal cellular and immune functions. More than 6,600 cases of CML are diagnosed each year in the United States.

TREATMENT THEN: 2005

Over a decade ago, a new treatment option revolutionized the outlook for patients diagnosed with CML. The first tyrosine kinase inhibitor (TKI) for CML, imatinib, was approved in 2001. TKIs transformed the treatment paradigm for patients, nearly tripling a patient's odds of survival by targeting cancer at the cellular level. However, some patients did not respond or could not tolerate treatment with imatinib. For these patients, as well as those who developed resistance despite having responded to the drug initially, there was a substantial need for other treatment options.

TREATMENT NOW: 2015

Today, there are additional targeted therapies that are able to effectively treat many of the identified mutated forms of CML by disrupting signals that lead to cancer cell growth. A wider range of therapeutic options allows for more tailored treatment plans that are adapted to a patient's particular genetic profile. Survival rates have improved dramatically, and CML patients are living close to normal life spans.

For more on advances in treatments for patients with CML and CLL, please see A Decade of Innovation in Rare Diseases.

Medicines in Development for Blood Cancers

"OVER THE PAST 65 YEARS, SURVIVAL RATES FOR MANY BLOOD CANCER PATIENTS HAVE DOUBLED, TRIPLED AND EVEN QUADRUPLED. ALMOST 40 PERCENT OF THE NEW ANTI-CANCER DRUGS DEVELOPED SINCE 2000 WERE FIRST APPROVED FOR BLOOD CANCER PATIENTS, AND ARE NOW HELPING PATIENTS WITH OTHER CANCERS AND CHRONIC DISEASES."

LOUIS DeGENNARO, PhD
PRESIDENT AND CEO,
LEUKEMIA & LYMPHOMA SOCIETY

Many of the 247 medicines in the pipeline are building on novel scientific approaches and looking at new ways to treat blood cancers. Examples of innovative treatments in development include:

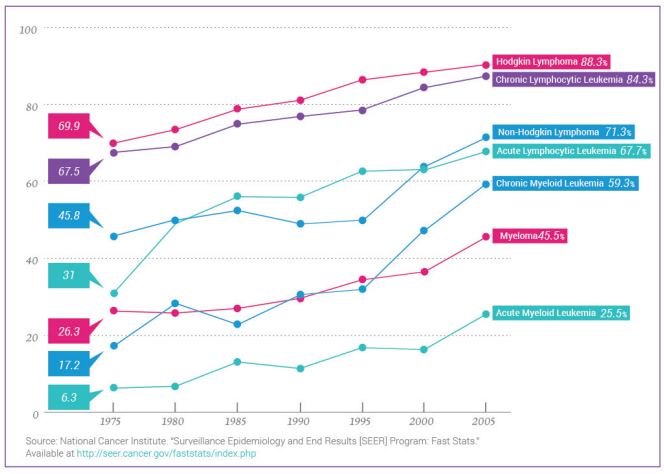
- A second-generation tyrosine kinase inhibitor in development for leukemia may block activation of the FLT-3 cell receptor, which is mutated in about one-third of all patients with **acute myeloid leukemia** (AML). Activation of this receptor by different types of mutations appears to play an important role in tumor cell proliferation, resistance to programmed cell death, and prevention of normal cell development. Research into new treatments for AML is important, as no new therapies have been approved for 90 percent of AML cases in the last 40 years.

- Several therapeutic antibodies in development for **multiple myeloma** target CD38, a protein that is found on the surface of myeloma cells. The therapeutics work by binding to the CD38 protein on the surface of the myeloma cell and then signaling the immune system to attack the cancerous cells.

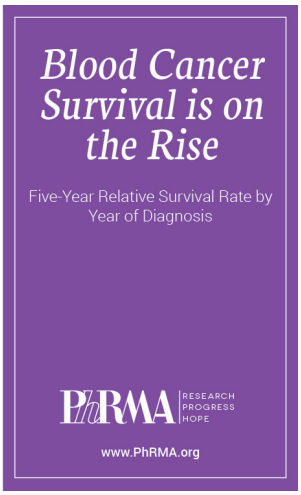
- Cutting-edge next generation sequencing has identified a number of genetic mutations that may lead to new treatment options for patients. For example, a medicine in development for advanced **hematological malignancies** inhibits a mutated form of the IDH2 gene, which encodes a metabolic enzyme. The genetic mutation can lead to increased production of an oncometabolite that prevents immature white cells from developing into healthy infection-fighting cells. The immature white blood cells accumulate and squeeze out normal blood cells and platelets, leading to hematological malignancies, such as leukemia.

- Through genomic screening, it was found that more than 90 percent of patients with **hairy cell leukemia** have a mutation in the gene that encodes BRAF kinase. Researchers are now studying an inhibitor of BRAF kinase that is currently approved for the treatment of melanoma. High rates of response, which were achieved early after the onset of therapy, have been observed.

- A fully human monoclonal antibody in development for **Hodgkin lymphoma** targets the PD-1 (programmed death-1) checkpoint receptor. This receptor is expressed on T-cells and is part of a normal pathway that inhibits the immune system when needed. Cancer cells may



Source: National Cancer Institute. "Surveillance Epidemiology and End Results [SEER] Program: Fast Stats."
Available at http://seer.cancer.gov/faststats/index.php



exploit this pathway to protect the tumor from attack by the immune system. Blocking activation of this pathway may allow for immune responses that recognize and destroy cancer cells. Medicines that block the PD-1 receptor have been approved by FDA for the treatment of malignant melanoma and advanced non-small cell lung cancer.

LEUKEMIA & LYMPHOMA SOCIETY SUPPORTS RESEARCH INTO NEW TREATMENTS

Partnerships among patient advocates, industry, academia and others are important to moving biopharmaceutical research forward. The Leukemia & Lymphoma Society (LLS) is a leader in driving and supporting research into new medicines and supporting diagnostics through the Therapy Acceleration Program (TAP). TAP helps fund research projects that have the potential to change the standard of care for patients with blood cancers, especially in areas of high unmet medical need. Examples of research projects funded by TAP include:

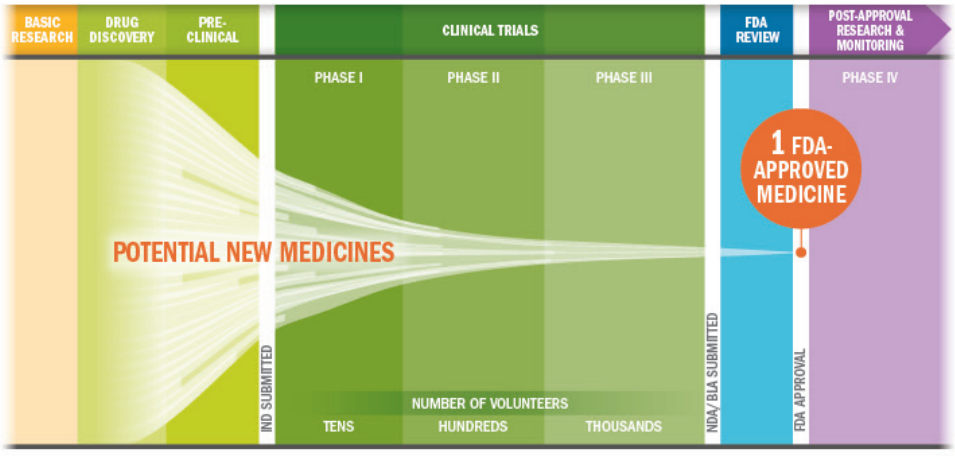
- A potential first-in-class DOT1L-targeted histone methyltransferase inhibitor is in development for **mixed lineage leukemia (MLL)**, a devastating genetically-defined type of acute leukemia that affects both pediatric and adult patients. DOT1L is a novel and important epigenetic target. Proteins called histone methyltransferases attach methyl groups to histones, proteins that help package DNA. This histone modification affects gene expression and is a type of change called an epigenetic change. The DOT1L protein is a histone methyltransferase that has been implicated in MLL.

- A novel targeted therapy in development is an engineered fusion of recombinant interleukin-3 (IL-3) with truncated diphtheria toxin, and is directed to cancer stem cells and tumor bulk. The therapy is in development for **acute myeloid leukemia (AML)** and **blastic plasmacytoid dendritic cell neoplasm (BPDCN)**, a rare hematological disorder with high unmet medical need and no standard treatment.

The impressive progress made against blood cancers has resulted in more effective treatments that have extended and improved patients' lives. The 247 medicines in the pipeline today are our best hope for continuing this progress and reducing the burden of blood cancers for generations to come.

THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS

From drug discovery through FDA approval, developing a new medicine takes at least 10 years on average and costs an average of $2.6 billion.* Less than 12% of the candidate medicines that make it into Phase I clinical trials will be approved by the FDA.



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be $2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

Source: PhRMA adaptation based on Tufts Center for the Study of Drug Development (CSDD) Briefing: "Cost of Developing a New Drug," Nov. 2014. Tufts CSDD & School of Medicine., and US FDA Infographic, "Drug Approval Process," http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf (accessed Jan. 20, 2015).

Footnotes:
1. American Cancer Society.

2. Leukemia & Lymphoma Society.

3. Number of medicines obtained through public, government and industry sources, and the Adis "R&D Insight"; current as of February 24, 2015.

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