A Decade of Innovation in Cancer 2006-2016
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4 Introduction

6 Metastatic Melanoma: Deeper Understanding of Disease Leads to Discoveries

10 Breast Cancer: Targeted Therapeutic Advances Drive Survival Gains for Patients

16 Cervical Cancer: Saving Women’s Lives through Prevention

19 Lung Cancer: Personalized Medicines Improving Outlook for Patients

25 Kidney Cancer: New Options for Advanced Disease

29 Blood Cancers: Scientific Advances Help Unravel Disease Complexities

35 Pediatric Cancers: Scientific Advances Spur New Options for Patients

39 Accelerating Progress for Patients with Cancer

41 References
Introduction

Cancer, in its many forms, has long been one of the most devastating and confounding health concerns worldwide.¹

Characterized by the uncontrolled growth and spread of abnormal cells, cancers wreak havoc on the body and, if left unchecked, can lead to malfunction of various health systems and, eventually, death. Cancer can originate anywhere in the body and, depending on the type of cancer and the extent to which the cancer has spread throughout other areas of the body, patients may experience a variety of symptoms. For patients and their loved ones, a cancer diagnosis has a life-changing impact, creating significant physical and emotional burdens arising from both the disease, as well as treatments that limit activity and disrupt their daily lives.

Cancer accounts for one of every four deaths in the United States, making it the second most common cause of death, surpassed only by heart disease. In 2016 alone, more than 1.6 million new cases of cancer are expected to be diagnosed and nearly 600,000 Americans are expected to die of cancer. In addition to the substantial clinical burden of cancer on patients, cancer also imposes a significant economic burden, with annual direct medical costs associated with cancer care in the United States recently estimated to be nearly $75 billion.

Rapid technological advances and an emerging understanding of the underlying drivers of disease are changing the face of cancer. We now know that cancer is not a singular condition but, rather, a collection of diseases, each with unique characteristics and features.² Researchers are learning more about what may cause various forms of cancer. Some cancers are known to be caused by environmental factors, including sun exposure and tobacco use, and some cancers are known to be related to infectious diseases. In many cases, steps can be taken to prevent these forms of cancer. However, many cancers seem to occur at random, without a specific environmental cause.

Researchers have made great strides in recent years in identifying the genetic mutations and related factors that can drive the seemingly random formation and proliferation of abnormal cells in cancer, as well as genetic markers that may identify patients at a greater risk of developing cancer. These learnings not only enable better screening and diagnoses but also drive the development of a new era of cancer treatments.

“We are in the midst of a sea change in how we are treating cancer. We’re really seeing the fruits of many years of research into what drives cancer and how it interacts with the immune system to defeat it and survive.”

—Louis Weiner, M.D., Director of the Georgetown Lombardi Comprehensive Cancer Center
Scientific Advances Drive Progress

Since its peak in 1991, the cancer death rate has dropped 23%. Researchers attribute these gains not just to decreases in smoking and improvements in detection, but also to advances in treatment. New cancer medicines are delivering important gains for patients, improving survival outcomes while providing patients with options that, in many cases, are easier to tolerate with potentially fewer long term side effects, improving their quality of life. Additionally, many emerging therapeutic options can be taken orally, which can help reduce patients’ time in clinics or hospitals. The emergence of personalized medicine, sometimes referred to as precision medicine, is driving many of these changes and transforming how many cancers are treated.

This report examines several types of cancer where significant advances over the last decade have improved outcomes for patients and are opening doors to new avenues of research. Although in many ways the cancers examined here—including melanoma, breast cancer, cervical cancer, lung cancer, kidney cancer, blood cancers, and pediatric cancers—are very unique, ongoing research has revealed important commonalities as well, which are driving a new era of cancer treatment.

Personalized medicines that are meant to target specific mutations in one cancer are often shown through ongoing research to be effective among a variety of cancers, giving patients important new treatment options. Uncontrolled growth and proliferation of cancer is spurred by changes in the way certain signals are transmitted on the surface of cancer cells. These changes are driven by genetic mutations and in many cases the microenvironment around the cancer cells themselves. Researchers have identified common molecular pathways that drive a variety of forms of cancer, and in turn have developed medicines that target these specific pathways.

Many cancer cells have found ways to evade detection by the immune system. Several new types of treatment are able to activate the immune system either by disabling the mechanism by which cancer cells stay undetected, or by helping to alert the immune system to the presence of cancer cells. Researchers are discovering that these mechanisms are present across a number of forms of cancer, opening new avenues for treatment.

Propelled by the rapid pace of science and technology, advances in cancer treatment over the last decade are shifting the treatment paradigm and offering many patients a brighter outlook for the future. However, for many forms of cancer there is still a tremendous need for better understanding and new medicines. Innovation over the last decade has given researchers important insight into the underlying biology of cancer, providing an important foundation for the next wave of cancer treatments.

A note on methodology: advances covered over the past decade occurred between January 1, 2006 and June 1, 2016.
Skin cancers, including basal cell carcinomas, squamous cell carcinomas, and melanoma, are among the most common forms of cancer in the United States. Melanoma originates in clusters of cells called melanocytes found on the skin’s surface, eyes, or mucous membranes and is most commonly caused by direct skin exposure to ultraviolet (UV) rays, along with various genetic and environmental factors. Melanoma has a five-year survival rate of about 97% if caught and treated in early stages. However, once cancer cells have metastasized, or spread to other organ tissues of the body, as is the case with metastatic melanoma, the cancer becomes significantly more deadly. Metastatic melanoma, or stage IV cancer, is fast-moving, with a five-year survival rate of just 15% to 20%. Fortunately, after decades of research, our
understanding of the underlying biology of melanoma and the body’s immune response to the cancer has increased dramatically, providing new options and new hope for patients fighting this devastating disease.

A Decade Ago: Few Options for Patients

Historically, advanced-stage, metastatic melanoma has been a very difficult cancer to treat. A patient diagnosed with this advanced form of the disease a decade ago had limited therapeutic options. Chemotherapy, radiation, and early immunotherapies—including interferon alpha and interleukin-2—were standard treatments. Unfortunately, many of these treatments came with significant side effects, including flu-like symptoms, weakness, fatigue, low blood pressure, and loss of appetite. Even with treatment, there was little evidence of prolonged survival and many died within a year of diagnosis.

Today: Innovative Therapies Born from Greater Understanding of Disease

Recent research advances have shed new light on the underlying biology of the disease and the role the immune system plays in advanced-stage melanoma, giving scientists insights into potential new pathways for treatment. In the past four years alone, seven new molecularly-targeted medicines and immunotherapies have been approved, providing a wider range of options to patients—options which are achieving remarkable benefits never seen before. These breakthroughs reflect many years of research seeking a greater understanding of the disease and the development of effective treatments to improve and extend the lives of patients.

Advances in Immunotherapy: Immune Checkpoint Inhibitors

The body’s immune system must include many checks and balances to protect the body from invading pathogens and also to prevent itself from inadvertently attacking normal cells in the body. The immune system uses “checkpoint” proteins in order to either activate or prevent an immune response. Years of research have revealed that some tumors have high levels of proteins that put the brakes on the immune system, preventing it from attacking cancer cells. Following this discovery, researchers have worked to understand the role of these checkpoint proteins and to target them in order to “release the brakes” on the immune system.

These immune therapies offer tremendous promise to patients, with the American Society of Clinical Oncology (ASCO) naming them the Cancer Advance of 2015. These medicines are showing promise across a number of cancer types, including bladder, kidney, liver, blood, and head and neck cancers. (See more in chapter on Non-Small Cell Lung Cancer).

Research on the function of the checkpoint protein CTLA-4 began decades ago. Although the protein was first discovered in 1987, it took another eight years to clarify the protein’s role in inhibiting the immune system from fighting cancer, and it took another 16 years before researchers were able to translate this knowledge into an actual therapy for patients with metastatic melanoma.

The U.S. Food and Drug Administration (FDA) approved ipilimumab, the first “checkpoint inhibitor,” targeting the CTLA-4 protein, in 2011. Ipilimumab is a monoclonal antibody which works by enabling the immune system to recognize, target and attack melanoma cells. The approval
was not only a major scientific advance, but it also marked the first new treatment for stage IV melanoma in more than a decade.\textsuperscript{25} The drug is used in metastatic melanoma patients whose cancer cannot be removed by surgery, and has been shown to help patients live longer.\textsuperscript{26} Ipilimumab has also been approved for use as an adjuvant treatment to reduce the risk of recurrence of disease following surgery in patients with stage III melanoma.\textsuperscript{27}

In parallel to the work on CTLA-4, researchers have worked to unleash the power of the immune system through other mechanisms. The discovery of another checkpoint pathway called PD-1/PD-L1 (PD-1 “programmed cell death” receptor and its ligand called PD-L1) was made in 1992.\textsuperscript{28, 29} Like CTLA-4, research showed PD-1 played a central role in helping tumors evade attacks from the immune system.

The first immunotherapy targeting this process, pembrolizumab, was approved by the FDA in 2014 for the treatment of metastatic melanoma in patients whose cancer cannot be removed by surgery and who have failed existing therapies.\textsuperscript{30, 31} In 2015 the FDA expanded the indication of pembrolizumab, designating it as a first-line treatment for patients with metastatic melanoma.\textsuperscript{32} Long term data has revealed tremendous survival outcomes in advanced melanoma, with 40% of patients receiving pembrolizumab were alive three years after starting treatment.\textsuperscript{33} Before the arrival of the first immunotherapy in 2011, survival for these patients was measured in months. These long term data mark the first time three-year survival has been able to be measured.

In 2014, the FDA approved another PD-1 targeted immunotherapy: nivolumab.\textsuperscript{34} Clinical trials also have demonstrated promise for nivolumab, with 40% of patients still benefiting from the drug after three years.\textsuperscript{35}

Building on the success of first-generation immunotherapies, researchers have discovered the important impact some of these medicines can have when used in combination. In 2015, the FDA approved the first-ever combination immunotherapy, nivolumab plus ipilimumab, for patients with a particular BRAF mutated form of metastatic melanoma.\textsuperscript{36} Just a few months later, the indication for these combination therapies was expanded to a broader scope of metastatic melanoma patients, beyond those with the specific mutation, illustrating the rapid pace of innovation in the immuno-oncology space.\textsuperscript{37}

With promising results such as these, immune checkpoint inhibitors are just beginning to transform the landscape of treatment for patients with metastatic melanoma. Many checkpoint inhibitors are showing promise in clinical trials targeting different types of cancer.\textsuperscript{38}

“The new therapies that block the PD-1 are extending survival for many patients, and for some may offer the prospect of living longer than ever after a diagnosis with advanced melanoma. In a matter of a few years, these therapies have truly transformed the outlook for patients with melanoma and many other hard-to-treat cancers.”

—Don Dizon, M.D., F.A.C.P., Clinical Co-Director of Gynecologic Oncology at the Massachusetts General Hospital\textsuperscript{39}

Advances in Targeted Therapy
Within the past decade, scientists have discovered and linked specific gene mutations to the development of melanoma. In 2002, researchers discovered that the BRAF gene mutation—which is found in approximately half of all melanomas—was linked to the overproduction and spread of cancer cells.\textsuperscript{40} This finding led researchers to pursue and develop new drugs targeting the abnormal BRAF proteins in order to stop or slow tumor growth.\textsuperscript{41}

Success came nearly a decade later with vemurafenib, the first BRAF inhibitor approved for patients whose tumors expressed the BRAF gene mutation. Another BRAF inhibitor, dabrafenib, followed soon thereafter, gaining approval in 2013. The same year the FDA also approved trametinib, which, unlike vemurafenib and dabrafenib, inhibits another gene called MEK. Because the MEK gene shares the same signaling pathway as the BRAF gene, MEK inhibitors also help treat melanomas with a BRAF gene mutation.\textsuperscript{42} Alongside these medicines came the approval of companion diagnostic tests which help identify patients whose tumors express the BRAF mutation, allowing for more effective targeting of treatment.\textsuperscript{43}

In the past several years, medicines targeting the signaling pathway impacted by the BRAF gene mutation, as well as combinations of these therapies, have expanded treatment options and improved outcomes for patients, including lengthened survival. In 2014, for the first time ever, the FDA approved the combination use of two molecularly-targeted therapies: trametinib and dabrafenib. In clinical trials these medicines, each blocking different components of the same signaling pathway, were found to have a sustained impact on the cancer when used in combination, shrinking tumors for nearly double the length of time than when dabrafenib was used alone.\textsuperscript{44, 45} Similarly, a second MEK inhibitor,
cobimetinib, was approved in 2015 for use in combination with vemurafenib to treat patients with BRAF-positive metastatic melanoma. The scientific community anticipates that combinations such as these will become a critical component of cancer treatment as researchers continue to gain a greater understanding of cancer biology.

New Frontiers: Oncolytic Virus Therapy
In 2015 the FDA approved the first in an entirely new class of medicines called oncolytic virus therapies for the treatment of melanoma lesions that cannot be removed by surgery or recurred after surgery. This first-of-its-kind treatment is a genetically modified virus that, when injected directly into a cancerous lesion, replicates inside cancer cells and causes them to rupture.

Looking to an Even Brighter Future for Metastatic Melanoma Patients
Decades of research have culminated in the development and approval of an arsenal of novel therapies for metastatic melanoma, which are demonstrating reduced side effects, substantial tumor shrinkage, prolonged remissions, and improved survival for patients. These advances represent remarkable progress, especially when compared to the prognosis faced by patients just a decade ago. But there is still a long path ahead, and this is just the beginning.

Today there are more than 100 melanoma drugs in clinical development across disease stages in the United States. Researchers are also continuing to explore innovative combinations of checkpoint inhibitors and molecularly targeted medicines, as well as standard chemotherapies and other novel treatments, in order to utilize a variety of different mechanisms to battle cancer on multiple fronts. The future has never been brighter for patients as researchers learn more about the underlying biology of melanoma, the body’s immune response to the disease, and how various targeted combinations can maximize impact of treatment.

“These combinations are driven by science...from a treatment point of view, this is a very exciting time, and we’re seeing durable responses that can sometimes last for years and are still ongoing.”

–Siwen Hu-Lieskovan, M.D., Ph.D., Oncologist and Clinical Instructor, UCLA, Jonsson Comprehensive Cancer Center

METASTATIC MELANOMA

Then
- Chemotherapy, radiation, and high-dose immunotherapy using interleukin-2 were standards of treatment.
- Patients typically died within a year of diagnosis of metastatic melanoma.
- Side effects of available treatments were sometimes severe, with patients experiencing flu-like symptoms, weakness, fatigue, low blood pressure, and loss of appetite.

Now
- Discovery of the immune checkpoint pathways CTLA-4 and PD-1 has led to the development of a whole new class of medicines called immunotherapies or immune checkpoint inhibitors.
- Discovery of BRAF gene mutation has led to new targeted medicines and companion diagnostic approvals.
- Side effects from treatment have been substantially reduced and survival rates are on the rise with the availability of an arsenal of new immunotherapies, molecularly-targeted medicines, and innovative treatment combinations targeting the disease from all angles.
Breast Cancer: Targeted Therapeutic Advances Drive Survival Gains for Patients

Greater understanding of cancer pathways yields new wave of personalized medicines.

QUICK FACTS

• Breast cancer is one of the most common cancers in the United States, with an estimated 246,000 new cases expected to be diagnosed in 2016. One in eight American women will be diagnosed in their lifetime.

• Breast cancer is the second highest cause of cancer death in women, with more than 40,000 deaths related to breast cancer expected in 2016.

• Due to advances in screening and treatment, there are more than 2.8 million breast cancer survivors living in the United States.

• There are many different forms of breast cancer, and even a single tumor may actually be characterized by several different types.

• Breast cancer most commonly occurs in middle-aged and older women.

One in eight American women will be diagnosed with breast cancer in their lifetime, making it one of the most common cancers for women in the United States. Although the disease continues to be among the deadliest forms of cancer for women, advances in detection and treatment have dramatically improved the outlook for breast cancer patients in recent decades. Today, if detected early, most patients with breast cancer have a favorable prognosis, with a relative five-year survival rate of 89%. Further, since peaking in the late 1980s, death rates have declined by 36%.

In the past decade alone, increased understanding of breast cancer risk factors and molecular pathways has supported important advances in screening, diagnosis, and treatment.
Continued identification of risk factors provides new ways to advance public health and inform discussions between doctors and patients. Several environmental factors may increase the risk of developing breast cancer, including smoking, drinking alcohol, and diet, but in recent years, scientific research has also helped identify genetic risk factors for the disease.\textsuperscript{61,62} For example, alterations to the BRCA1 and BRCA2 genes have been associated with breast cancer. These two genes produce proteins that help repair damaged DNA.\textsuperscript{63} Mutations or other alterations of these genes affect the cell’s ability to repair DNA damage and can lead to cancer. The risk of developing breast cancer by the age of 70 is greater for women who inherit certain mutations in the BRCA1 or BRCA2 gene—with an estimated average risk of 57-65% and 45-55%, respectively—than for women in the general population, who have a 7% risk.\textsuperscript{64} Women who inherit a mutated form of either gene have a greater lifetime risk of both breast and ovarian cancer. By understanding cancer risk, doctors can work with their patients to determine who may benefit from cancer screening and at what age. Risk factor information may also be used to determine whether certain interventions should be considered to lower cancer risk, such as surgery or medication.

There are many forms of breast cancer. Among breast cancer patients, differences in clinical outcomes, response to treatment, and cancer’s molecular and cellular characteristics can be considerable. Given the diversity in breast cancer types, doctors and researchers use a variety of factors to classify breast cancers in a science-based and clinically meaningful manner. Such factors include determining where the cancer originated; the cancer’s size and how far it has spread (termed stage); and the cancer’s grade, which is an assessment of how quickly the cancer cells are growing and how abnormal they look relative to healthy cells. In addition, biological factors can be used to help classify breast cancer, including gene expression and protein levels in cancer tissue. For example, sensitivity of the cancer to the hormones estrogen or progesterone can be a factor, as well as the genetic expression or protein levels of a receptor involved in cell growth, called human epidermal growth factor receptor 2 (HER2). Information about breast cancer’s cellular and molecular characteristics can be used to describe its subtype. The table \textit{Common Molecular Subtypes of Breast Cancer} provides additional information on four of the currently identified most common molecular subtypes of breast cancer.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Prevalence</th>
<th>Disease Characteristics</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A (HR+/HER2-)</td>
<td>Majority of breast cancers (30-70%)</td>
<td>Slow growing, less aggressive</td>
<td>Most favorable prognosis, likely to respond to hormonal therapy</td>
</tr>
<tr>
<td>Hormone receptor-positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(either estrogen or progesterone)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HER2-negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple-negative (HR-/HER2-)</td>
<td>15-20% of breast cancers (Nearly 2X more common in African American women than Caucasian women; more common in women with a BRCA1 gene mutation)</td>
<td>Fast growing and aggressive</td>
<td>Currently a poor prognosis due to lack of response to hormonal or HER2 targeted therapies</td>
</tr>
<tr>
<td>Hormone receptor-negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(neither estrogen nor progesterone)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2-negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal B (HR+/HER2+)</td>
<td>10-20% of breast cancers</td>
<td>Tend to be more aggressive than luminal A breast cancers due to high levels of Ki67 protein, which triggers excess cell growth</td>
<td>Fairly high survival rates due to high treatment response</td>
</tr>
<tr>
<td>Hormone receptor-positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(either estrogen or progesterone)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2-positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2-enriched (HR-/HER2+)</td>
<td>5-15% of breast cancers</td>
<td>Fast growing and spreads aggressively</td>
<td>Recent advances in HER2-targeted therapies improve prognosis</td>
</tr>
<tr>
<td>Hormone receptor-negative</td>
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<tr>
<td>(neither estrogen nor progesterone)</td>
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<td></td>
</tr>
<tr>
<td>HER2-positive</td>
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Abbreviations: HR (hormone receptor; either estrogen or progesterone); HER (human epidermal growth factor receptor). A positive (+) sign denotes the presence of a receptor, while a negative sign (-) denotes the absence.
Doctors use a range of screening and diagnostic tools to determine whether an individual has breast cancer and, if so, to classify the cancer. Information about the cancer is used to inform treatment decisions, including whether to use treatments that are localized, systemic, or both. Many patients have surgery to remove the cancer, which is then often followed by another form of treatment, such as radiation, chemotherapy, hormone therapy, or a form of targeted therapy. The goal of treatment after surgery is to increase the probability that the cancer is fully eliminated, will not spread to other parts of the body, and will not return. Patients may also receive treatment before surgery to help shrink the size of a tumor and allow for less invasive surgery. See Overview: Breast Cancer Treatment for the range of therapeutic options used to treat breast cancer.

A Decade Ago: Most Available Treatment Options Impacted Cancerous and Noncancerous Cells, Resulting in Wide Range of Negative Side Effects

A decade ago, most women with breast cancer underwent some type of surgery, often in combination with radiation therapy or systemic therapies, such as chemotherapy or hormone therapy. It was an important time in the evolution of breast cancer treatment, given that a targeted biologic therapy, trastuzumab, was also available to some women. The U.S. Food and Drug Administration (FDA) approved trastuzumab in 1998 for treating breast cancer as, what many recognize as, the first personalized medicine. As part of a
natural immune response, the body makes antibodies, which recognize and bind to specific proteins. Researchers can design antibodies that target proteins found on cancer cells and then make copies of the antibody in the lab to develop a monoclonal antibody (mAb) medicine, like trastuzumab.

Trastuzumab was approved originally for use in women with advanced, metastatic HER2-positive recurring breast cancer. About 20% of breast cancer patients have HER2 positive cancer, which is driven by an excess of HER2 receptor proteins and represents a particularly aggressive form of the disease. Additional clinical research was conducted to determine the effects of trastuzumab in the adjuvant (post-surgical) setting on women with early-stage HER2-positive breast cancer. Clinical studies showed tremendous survival benefits in this setting: use of trastuzumab reduced the risk of recurrence by 52% and risk of death by 33% in women with early-stage HER2-positive breast cancer. Research findings demonstrated that women treated after surgery with trastuzumab in combination with standard chemotherapy had fewer relapses for up to three years after surgery than women who received chemotherapy alone. The FDA expanded the approved use of trastuzumab in 2006 to include treatment of HER2-positive breast cancer in combination with chemotherapy following primary treatment for early stage breast cancer.

Although the improvement in treatment realized through targeted therapy brought new hope to patients, additional treatment options were needed. Most women do not have HER2-positive breast cancer and, thus, could not benefit from this targeted treatment. In addition, some HER2-positive breast cancers are either resistant to trastuzumab or become resistant over time. Chemotherapy provided a way in which to kill cancer cells broadly across different patients, which is why it was considered a mainstay of breast cancer treatment. However, chemotherapy is also toxic to some healthy cells, resulting in unwanted side effects including fatigue, hair loss, nausea, and increased risk of infections. Given the unwanted side effects, better targeting of the chemotherapy was needed.

There was also a need to further our scientific understanding of breast cancers and leverage those advances to develop new medicines, increase treatment precision, and offer patients treatment options that had fewer associated side effects.

**Today: Targeted Therapies Improve Survival and Decrease Side Effects**

In recent years, a new arsenal of therapeutic options has been made possible by leveraging new knowledge about the molecular causes of breast cancers. These new medicines can reduce the need for invasive surgical procedures or allow for less invasive procedures and treatments. Although treatment options available a decade ago continue to be important mainstays of breast cancer treatment for many patients, researchers have made substantial progress in treating various subtypes of the disease in a more targeted manner. By focusing on cellular pathways specific to different forms of breast cancer, patients have access to more personalized medicine options. Such targeted therapies can also have fewer or less severe side effects than traditional chemotherapy, and treatment regimens may be shorter and less frequent. In some cases, newer therapies can be administered in the neoadjuvant (pre-surgical) setting to change the timing of treatments and procedures for patients or to shrink the tumor enough that the scope of surgery can be reduced.

**Growing Advances in HER2 Therapy**

In recent years, several medicines have been approved that build on the success of the first HER2-targeted therapy, trastuzumab. These provide new approaches to disrupt the activity of the HER2 protein. Trastuzumab is a large mAb protein that works by attaching to HER2 receptor proteins on the portion of the receptor located outside of the cell. In 2007, a new medicine, lapatinib, was approved for use in combination with another cancer drug for patients with advanced, metastatic breast cancer that is HER2 positive. Lapatinib is a small molecule that enters cancer cells and blocks the function of the HER2 and other proteins from within the cell. Because it acts through a different mechanism of action than that of trastuzumab, lapatinib provides a new treatment option for some HER2-positive breast cancers that are no longer responding to treatment with trastuzumab and other cancer medicines.

“The successful target of HER2 with therapies such as trastuzumab has dramatically improved the survival for women with HER2-positive cancer and has been one of the major success stories of targeted cancer therapy.”

–Wendy Chen, M.D., M.P.H., Medical Oncologist, Dana-Farber Cancer Institute
In 2012, a second mAb therapy was approved to target the HER2 protein. Like trastuzumab, pertuzumab also binds to the HER2 receptor protein on the outside of the cell, but the location of its binding on the protein differs from that of trastuzumab. When used in combination with both trastuzumab and a standard docetaxel chemotherapy regimen, pertuzumab results in even greater slowing of cancer growth and longer patient survival. Pertuzumab is indicated for use both as a precursor to surgery (neoadjuvant treatment) in patients with early-stage disease and also for patients with advanced metastatic forms of breast cancer.

“Smart Bombs” Enhance Precision of HER2 Treatment
The ability to more precisely target breast cancer cells and leave healthy cells unharmed has resulted in fewer or less severe side effects for patients. HER2-targeted therapies, for example, are useful for zeroing in on cancerous cells and slowing their growth. However, traditional chemotherapy medicines are often considered more effective at actually killing cancer cells. In 2013, the FDA approved a new treatment for breast cancer called ado-trastuzumab emtansine for patients with HER2-positive, metastatic breast cancer who had previously received trastuzumab and a taxane (a chemotherapy medicine), separately or in combination. The new medicine, called an antibody-drug conjugate, consists of the mAb therapy trastuzumab linked to the emtansine chemotherapy.

This type of medicine is sometimes referred to as a “smart bomb” because it enables the delivery of the highly potent chemotherapy directly to the tumor cells. Clinical research demonstrated that ado-trastuzumab emtansine resulted in tumor shrinkage, slowed disease progression, and prolonged survival.

New Era of Targeted Therapies
In addition to the important influx of HER2-targeted treatments, significant progress has been made in the development of medications that use novel approaches to kill cancer cells and inhibit cancer cell growth through other targeted mechanisms. In patients with hormone receptor-positive breast cancer that is not HER2-positive, the approval of everolimus in 2012 offered an important treatment advance. A member of a class of medicines known as mTOR inhibitors, everolimus is a targeted therapy that blocks the mTOR protein on cancer cells. This protein normally promotes cell growth and proliferation. When used in combination with standard hormonal therapy, everolimus has been shown to slow cancer cell growth and halt the formation of new blood vessels, which can fuel tumor growth. The medicine has demonstrated fewer side effects than traditional forms of chemotherapy and, as an oral medication, offers a reduced treatment burden.

Another new targeted therapy, palbociclib, uses an entirely new approach to halt cell growth in breast cancer. The first in a class of medicines called cyclin-dependent kinase (CDK) inhibitors (specifically, types CDK4 and CDK6), palbociclib blocks the function of the cell growth modulating proteins CDK4 and CDK6 proteins, thereby inhibiting cell multiplication. The medicine is indicated for use in combination with hormonal therapy in patients with advanced hormone receptor-positive, HER2-negative breast cancer that are post-menopausal and have either not previously received hormonal therapy or have not responded to previous hormonal therapy.

“The availability of a first-of-its-kind treatment option like [palbociclib] for women dealing with HR+/HER2-metastatic disease represents a very important advance.”

–Dr. Marisa Weiss, M.D., Chief Medical Officer and Founder of Breastcancer.org
Building Understanding of Molecular Pathways Holds Promise for Treatment Innovation

Researchers are leveraging a growing understanding of the many factors that contribute to a defining a particular breast cancer diagnosis into new avenues for treatment, and in many cases identifying genetic similarities among different forms of cancer. By identifying cancer types based on the genetic or molecular mutations that may be causing disease, there are opportunities for treatments to have significant impact on a variety of cancers.

Researchers continue to explore ways to inhibit breast cancer growth by interrupting the HER2 pathway but are also exploring several other mechanisms. For patients with triple-negative breast cancer, a particularly aggressive form of the disease, advances in the pipeline that do not rely on interruption of the HER2 pathway or hormone receptor inhibition hold particular promise as their cancers do not respond to existing hormonal or HER2-targeted therapies.

In clinical studies, immunotherapies, already having great success in treating patients with forms of advanced melanoma, lung cancer, bladder cancer, and kidney cancer, are demonstrating benefits for patients with metastatic forms of breast cancer. Acting on the surface of cells, these monoclonal antibody medicines block programmed-cell-death-1 (PD-1) receptors from interacting with corresponding ligands, triggering the so-called PD-1 pathway in the cell which unleashes the immune system to attack cancer cells.

Research is also revealing the potential of vaccines as another means of triggering the immune system to mount an attack against cancer cells. A recent study of an experimental DNA vaccine, for example, demonstrated that the medicine elicited an immune response and that preliminary results showed improved progression-free survival.

Researchers are also exploring how other medicines within the broader class known as signal transduction inhibitors may be able to halt the progression of breast cancer. One type of these medicines, called poly ADP-ribose polymerase (PARP) inhibitors, slows cancer cell growth and is showing particular promise for patients who express the BRCA1 or BRCA2 mutations, as the first approved PARP inhibitor was indicated for ovarian cancer patients with these same gene defects. PARP enzymes are involved in many aspects of the cellular response to various forms of damage. PARP inhibitors work by blocking the function of the enzyme in cancer cells; by halting repairs, the cancer cells eventually die. These medicines have the potential to be used in a broad spectrum of breast cancer patients.

The rapid pace of scientific innovation gives patients with breast cancer great hope for the future, as researchers explore novel treatment pathways, as well as ways to optimize the use of existing medicines in combination or in sequence with each other. Currently, there are more than 150 medicines in development in the United States for the treatment of breast cancer, offering promise for continued treatment advances.

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**BREAST CANCER**

**Then**

- Standard systemic therapies, including chemotherapeutic and hormonal medicines, resulted in devastating short and long term side effects for many patients.
- Existing therapeutic options often required lengthy treatment regimens delivered in a physician’s office/medical facility as the medicines were primarily infused.
- A singular targeted therapy provided an important first step for patients with HER2+ breast cancer, but additional options were needed to address other breast cancer subtypes and for patients whose cancer no longer responded to initial therapy.

**Now**

- A new era of targeted therapies offers patients improved survival and reduced side effects.
- Treatment regimens are more varied and provide easier routes of administration and in many cases less frequent dosing, reducing patient burden.
- New neoadjuvant (pre-surgery) treatment options that shrink tumors may reduce the scope of surgical procedures required to remove breast cancer and reduce recovery times for patients.
- Advances in immunotherapy, cancer vaccine technology, and a growing understanding of signal transduction pathways show promise for future therapeutic advances.
Cervical Cancer: Saving Women’s Lives through Prevention

A new generation of preventative vaccines has led to dramatic reductions in the prevalence of viral infections that cause this deadly disease, providing hope for a future without cervical cancer.

QUICK FACTS

- Human papillomavirus (HPV) is the cause of nearly all cervical cancers.\(^\text{106}\)
- If caught and treated early, survival rates are relatively high for women. However, in later stages, survival rates range from 15-35%.\(^\text{107}\)
- In the United States this year, an estimated 12,900 new cases of cervical cancer will be diagnosed and 4,100 women are expected to die of cervical cancer.\(^\text{108}\)
- Over the past 30 years, the death rate has declined by 50% thanks in large part to screening and early intervention.\(^\text{109}\)

Cervical cancer used to be the leading cause of cancer death for women in the United States. However, in the 1950s, the Papanicolaou test (abbreviated as Pap test or Pap smear) was introduced as a screen approach to detect precancerous and cancerous cervical lesions. Since that time, the incidence of invasive cervical cancer and related mortality has decreased markedly. Now, in the United States, most women diagnosed with cervical cancer have either never been screened or not been screened in the last five years.\(^\text{110}\)

Although remarkable progress was made in preventing cervical cancer through regular screening, the threat to women’s health was not eliminated, and additional tools to prevent or treat the disease were needed. A key historical challenge in developing effective medicines for cervical cancer was the lack of understanding of the disease’s cause. In the 1980s, researchers discovered a link between infection with a sexually transmitted virus, called human papillomavirus (HPV), and cervical cancer. This important scientific finding opened the door to more progress in understanding how to prevent cervical cancer. Researchers were able to begin identifying which HPV types among the more than 100 strains lead to risk of developing cervical cancer as well as uncover evidence that HPV infection is associated with other forms of cancer in both men and women.\(^\text{111}\)

Thanks to these and related scientific advances, we now know that certain HPV strains can lead to cervical and other types of
Cervical cancer is the most common HPV-associated cancer and virtually all cervical cancer is caused by HPV. More than 79 million people are currently infected with HPV worldwide, making it the most prevalent sexually transmitted infection. In the United States, 14 million new cases of HPV infection are diagnosed each year. The vast majority of people who are sexually active will acquire HPV in their lifetime. In many cases, HPV goes away on its own and does not cause serious health problems. But given that individuals infected with certain HPV strains are at risk for developing cervical or other cancers, HPV infection is an important target for new medicines.

A Decade Ago: Screening and Early Intervention Aims to Prevent Cervical Cancer

Ten years ago, women were relatively limited in their protection against cervical cancer, relying on tools such as regular screening. Women with abnormal screening results then had to undergo further invasive procedures, such as scraping or removal of cervical tissue, to conduct biopsies and remove precancerous cells before they developed into cancer. Although regular screening has proven important in improving patient outcomes, it was not possible a decade ago to eliminate the virus that causes the life-threatening disease. Moreover, among women with limited awareness or inadequate access to regular preventive care, obtaining screenings remained a hurdle, and developing cervical cancer remained a significant risk.

Today: Vaccines Offer to Prevent the Root Cause of Cervical Cancer

Fortunately, women today have powerful new tools to prevent cervical cancer. These tools were built on the research linking almost all cervical cancers to prior HPV infection as well as a growing understanding of how chronic infection over time can transform normal cells into abnormal and cancerous cells. They also leverage our understanding of the association between specific strains of HPV and risk for developing cervical and other cancers. Among the tools that have become available during the last decade are three new vaccines that protect against infection by cervical cancer-causing strains of HPV.

In 2006, the FDA approved the first vaccine for the prevention of cervical cancer and precancerous lesions for use in women and girls 9-26 years of age. As an HPV quadrivalent recombinant vaccine, it does not contain live virus and is effective against four strains of the virus: two that cause cervical cancer—HPV strains 16 and 18—and two that do not cause cervical cancer but are instead responsible for approximately 90% of genital wart cases. Since its original approval, this vaccine has also been approved for prevention of vulvar and vaginal cancer, and approved for use in men and women ages 9 through 26 years for prevention of anal cancer and associated precancerous lesions. Recent studies show that the vaccine has resulted in a 64% decrease in HPV infections among girls ages 14-19.

In 2009, an HPV bivalent recombinant vaccine was approved by the FDA, which protects against HPV types 16 and 18. The vaccine is approved for use in women and girls aged 9-25 years of age. With HPV types 16 and 18 responsible for approximately 70% of cervical cancer cases, these two vaccines represent significant advances in protecting women’s health.

In 2014, the FDA approved a vaccine that protects against nine different strains of HPV. In addition to the strains protected against by previous vaccines, this approval marked the first-ever vaccine to protect against five additional types of HPV.

PREVALENCE OF HPV INFECTIONS TARGETED BY THE QUADRIVALENT HPV VACCINE

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<td>PRE-VACCINE ERA (2003-2006)</td>
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of cervical-cancer causing strains: HPV 31, 33, 45, 52, and 58.\textsuperscript{122} The vaccine also provides protection against other cancers caused by HPV beyond cervical, including anal and vaginal cancers, and was approved for use in both males and females.\textsuperscript{123} With the addition of these strains of HPV, this most recently approved vaccine provides protection against 90% of cervical cancers.\textsuperscript{124} The vaccine also protects against 80-95% of vulvar, vaginal, and anal cancers.\textsuperscript{125}

**A Future Offering Broad Protection against Cervical Cancer**

The introduction of HPV vaccines has been accompanied by increased efforts to educate the public about the link between HPV and cervical cancer and the importance of cervical cancer screening. Young women through the age of 26 and young men through the age of 21 can get the vaccine, and the CDC currently recommends the vaccination for preteen boys and girls beginning at around 11 and 12 years of age, before they might be exposed to the virus.\textsuperscript{126} Given that current vaccines do not prevent against all types of cervical cancer, regular Pap screenings will continue to be a crucial prevention measure.\textsuperscript{127, 128}

The introduction of vaccines has resulted in substantial reductions in HPV infections among many groups of patients.\textsuperscript{130} However, HPV vaccination coverage (the number of people who have received a particular vaccine) lags significantly behind other routine vaccinations for adolescents.\textsuperscript{131, 132} Recent trends are encouraging, though, with CDC data suggesting that vaccination rates are increasing. Vaccination coverage among adolescents increased 3.3% in 2014 relative to 2013.\textsuperscript{133}

“We’re seeing the impact of the vaccine as it marches down the line for age groups, and that’s incredibly exciting. A minority of females in this country have been immunized, but we’re seeing a public health impact that is quite expansive.”

--Amy B. Middleman, M.D., M.P.H., M.S.Ed., Chief of Adolescent Medicine at the University of Oklahoma Health Sciences Center\textsuperscript{130}

Cervical cancer was once a leading cause of cancer death for women in the United States; today, cervical cancer has fallen to the 14\textsuperscript{th} most common cancer among women.\textsuperscript{134} Although much of this progress is due to improvements in screening and prevention over the past 50 years, today women have the unique and unprecedented opportunity to prevent cervical cancer at its root cause and to further drive down death rates. There are currently 20 medicines in development in the United States for the prevention of HPV infection.\textsuperscript{135} With continued efforts to educate the public about the link between HPV and cervical cancer and improve vaccination rates among adolescents, women can look to a future in which virtually all forms of cervical cancer can be eliminated.

In addition to pursuing new mechanisms for preventing HPV infections, which could lead to cervical cancer, researchers are also working to develop treatments to help those who have developed cervical cancer. Currently there are 20 treatments for cervical cancer in development in the United States. As with many other forms of cancer, an increasing understanding of the molecular and genetic underpinnings of the disease is offering the hope of a new generation of targeted therapy for patients with cervical cancer.\textsuperscript{136}
Lung Cancer: Personalized Medicines Improving Outlook for Patients

A deeper understanding of the genetic mutations that cause cancer unleashes a wave of innovative targeted treatment options.

QUICK FACTS

• In the United States, 14% of all new cancer diagnoses are lung cancer, making it the second most common cancer among both men and women.\(^\text{137}\)

• In 2016 alone, it is estimated over 224,000 Americans will be diagnosed with a form of lung cancer.\(^\text{138}\)

• Non-small cell lung cancer is the most common form of lung cancer, encompassing 85-90% of lung cancer diagnoses.\(^\text{139}\)

• Lung cancer is the leading cause of cancer death in the United States, accounting for about 25% of all cancer deaths.\(^\text{140}\)

• The most important risk factor for lung cancer is smoking, which causes 80% of lung cancer deaths. Environmental exposure to cancer-causing agents like radon and asbestos are also known causes of lung cancer.\(^\text{141}\) Recent research has also revealed the prominent role of genetic mutations in driving many forms of lung cancer.
Lung cancer is not only one of the most frequently occurring forms of cancer, but it is also one of the deadliest. There are two main forms of lung cancer, differentiated based on the type of cell where the cancer originates:

- **Non-small cell lung cancer (NSCLC)**: NSCLC, the most common form of lung cancer, accounts for 85-90% of all lung cancer diagnoses, originates in the epithelial cells of the lungs, normally either in small air sacs (called alveoli) or the bronchial tubes in the center of the lungs.
  - **Adenocarcinoma**: A subtype of NSCLC, adenocarcinoma accounts for 40% of lung cancers. Although commonly occurring in current and former smokers, adenocarcinomas are the most common type of lung cancer among non-smokers. These cancers tend to originate in the outer cells of the lungs and grow more slowly than other forms of lung cancer.
  - **Squamous cell carcinoma**: Between 25% and 30% of lung cancers are squamous cell carcinomas, which originate in the flat (squamous) cells that line the airways in the central part of the lungs. Squamous cell carcinoma is the form of NSCLC most strongly associated with smoking.

- **Small cell lung cancer**: Sometimes referred to as oat-cell cancer, small cell lung cancer accounts for 10-15% of lung cancers and is a very aggressive form of cancer. Small cell lung cancer is almost always associated with cigarette smoking.

Like many forms of cancer, patients with lung cancer face a variety of treatment and intervention options depending on the type, location, spread, and stage of their disease.

Patients with early-stage NSCLC often first undergo a surgical procedure to remove their tumor, which may entail removing all or part of an affected lung. To ensure that all cancer cells have been removed and to prevent the potential recurrence or spread of the cancer to other parts of the body, patients often receive some form of radiation following their surgery. Additionally, the use of adjuvant therapy (provided after surgery) may help prevent the return of the cancer. Patients with more advanced forms of NSCLC may also receive chemotherapy before surgery (neoadjuvant chemotherapy) to make the cancer easier to remove surgically and to increase the effectiveness of radiation.

Small cell lung cancer is difficult to treat; the disease grows quickly and often metastasizes to other sites around the body, making localized procedures like surgery and radiation less effective treatment options. Small cell lung cancer is generally characterized as either limited, meaning it exists in one lung or one part of a lung, or extensive, meaning it has spread to other areas. Because this form of cancer has often spread by the time it has been diagnosed, chemotherapy is usually used to treat small cell lung cancer. Combination chemotherapy regimens are standard treatment options for these patients.

Reducions in tobacco use in recent decades have had a tremendous impact on lung cancer mortality. Death rates declined 38% among males and 12% among females between 2002 and 2012, largely as a result of smoking cessation. In addition to advances in prevention, researchers are also making great strides in identifying hereditary or genetic causes of lung cancer; this increased understanding is driving major therapeutic gains for patients.
patient’s treatment plan, can also result in similar side effects to chemotherapy, impacting health outcomes and quality of life.

Building on a growing understanding of the molecular mechanisms driving lung cancers, researchers have developed medicines to target specific lung cancer cells, rather than wreaking havoc on the whole body. These early advances in personalized medicine were important steps forward, but much remained unknown or not fully understood. A decade ago, patients were just beginning to benefit from increased understanding of the molecular and genetic underpinnings of lung cancer. Two medicines, part of a class called tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, had just become available to treat patients with locally advanced or metastatic NSCLC whose disease had progressed despite other treatments. These medicines work by blocking cell growth signals that are in part mediated by enzymes called tyrosine kinases. Both erlotinib and gefitinib appeared to be more effective in a subpopulation of patients with a mutation in the epidermal growth factor receptor (EGFR) gene, which is associated with the tyrosine kinase enzyme, but further research was needed to fully understand the genetic drivers of disease. While these early treatments were effective in adenocarcinoma forms of NSCLC, additional options were needed for patients with other forms of lung cancer.

Today: New Era of Personalized Medicine is Opening Novel Treatment Pathways for Patients

In the last decade, researchers have continued to expand their knowledge and understanding of the molecular drivers of cancer to develop a new era of treatment for patients with lung cancer. For patients with NSCLC, several new targeted therapies have changed the way their disease is treated. Many of these targeted therapies are administered orally, reducing the burden on patients who previously underwent extensive intravenously-administered chemotherapeutic regimens. The use of these medicines as first-line treatment or in the neoadjuvant (pre-surgery) setting, may have enough of an effect that additional localized procedures (surgery or radiation), and even chemotherapy, can be minimized or in some cases avoided altogether. Additionally, a new era of immunotherapy is enabling the body to redirect and re-energize the immune system, so it can recognize and attack lung cancer cells. Together with the use of novel molecular diagnostics, doctors are able to help direct patients to the medicine most likely to work for them, opening new treatment pathways and giving hope for the future.

Targeted Therapies for Non-Small Cell Lung Cancer
EGFR Inhibitors

A decade ago, early targeted therapeutic options were believed to be more impactful for patients who expressed mutations in the EGFR gene. But much remained unknown about the specific mechanisms by which this mutation affected tumor growth. Researchers have learned more about the specific mutations that can impact the EGFR gene, and, subsequently, how cellular growth with the tyrosine kinase enzyme can be affected. Over the last decade, several new medicines have been approved that target very specific types of EGFR mutations, allowing researchers to direct patients to the therapies most likely to affect their particular form of NSCLC. Erlotinib, gefitinib, and afatinib are treatment options for patients with very specific EGFR mutations (exon 19 deletion or exon 21 [L858R] substitution).
Because cancer cells are able to evade and adapt to various treatments, and may develop other mutations, it is important to have several options within a particular class. This allows patients to switch to another medicine when their current treatment no longer works. A new medicine, osimertinib, is effective for patients with another EGFR mutation (T790M) and is indicated for patients expressing this mutation whose disease has progressed after receiving other EGFR-blocking therapy (indicating that their cancer may have mutated).

Patients with an advanced rare form of NSCLC, called squamous NSCLC, who express the EGFR mutation, now also have a targeted treatment option with the approval of necitumumab. Up to this point, targeted therapies for patients with EGFR-mutated NSCLC were primarily for patients with adenocarcinomas (non-squamous forms of cancer) as opposed to squamous forms of cancer. There was a tremendous need for new medicines as advanced squamous forms of NSCLC have a five-year survival rate of just 5%.

The new medicine, indicated as a first-line treatment, is the first biologic therapy available for patients with this difficult to treat form of lung cancer. Afatinib, already available to NSCLC patients with the EGFR mutation, has also recently been approved to treat advanced squamous NSCLC, providing an important oral therapeutic option for patients.

**ALK Inhibitors**

In recent years, researchers have uncovered other genetic mutations that can cause lung cancer cells to grow and proliferate. About 5% of patients with NSCLC have a rearrangement in the gene for the anaplastic lymphoma kinase (ALK), a specific type of tyrosine kinase; these patients are described as being ALK-positive. Like other members of the tyrosine kinase family, an abnormal ALK leads to rapid cancer growth and spread. By blocking the abnormal ALK receptor, ALK inhibitors can be effective at stopping tumor growth, and even shrinking tumors, in ALK-positive patients.

Crizotinib received accelerated approval from the FDA in 2011 as the first medicine approved to treat patients with locally-advanced or metastatic ALK-positive NSCLC. Researchers recently discovered that crizotinib is also effective in patients whose tumors have an even more rare genetic mutation called ROS-1. Crizotinib is the first and only treatment for patients with this rare form of cancer, which is only found in about 1% of NSCLC. However, this mutation has been found in other forms of cancer, giving researchers hope that this medicine will be found to be effective for additional patient populations.

Because cancers are often able to adapt to and evade treatment, continuing to expand therapeutic options within a particular class is very important for patients. Two new medicines, ceritinib and alectinib, were recently approved for ALK-positive patients who were previously treated with crizotinib, the only other approved ALK-inhibitor. These medicines offer patients important therapeutic options when their cancer no longer responds to existing therapy or if they cannot tolerate other forms of treatment.

**Angiogenesis Inhibitors**

Cancer tumors rely on nourishment from blood vessels to grow. An innovative class of intravenously-administered targeted therapies called angiogenesis inhibitors block the formation of the blood vessels that stimulate tumor growth. One recently approved medicine, ramucirumab, is indicated for use in combination with the chemotherapy docetaxel to treat patients with advanced NSCLC. Another angiogenesis inhibitor, bevacizumab, is also indicated for use in treating patients with NSCLC. Angiogenesis inhibitors have been shown to be effective treatments for a number of other forms of cancer as well, including advanced brain, colorectal and renal cell cancers.
**Immunotherapies**

Immunotherapies have emerged as a powerful new tool for combatting a number of other difficult-to-treat forms of cancer, including various types of lung cancer. Some tumors produce molecules that block the normal processes of the immune system, allowing cancer cells to grow unchecked. Emerging forms of immunotherapy release the breaks on the immune system, allowing immune cells to target and attack cancer cells. Targeting the programmed-cell-death protein or its receptor (PD-1/PD-L1) is one pathway that has been shown to elicit a significant tumor immune response in several forms of cancer, including NSCLC. (See more in chapter on Melanoma.) A PD-1 inhibitor, nivolumab, was recently approved by the FDA to treat both squamous and non-squamous forms of NSCLC. Similarly, another PD-1 inhibitor, pembrolizumab, was also recently granted approval for use in treating patients with advanced NSCLC. A new type of companion diagnostic test, the first designed to detect PD-L1 expression, emerged with the approval. This test enables doctors to assess whether a tumor expresses the protein that is indicative of the faulty immune pathway, providing an opportunity to target the patients who may be most likely to benefit from the medicine.

**Looking Ahead: Targeted Therapies and Immune Treatments Open New Doors for Patients**

Advances in tumor genetics are propelling a much deeper understanding of the molecular drivers of many forms of cancer, especially NSCLC. A recent study indicated that two-thirds of lung adenocarcinomas have at least one cancer-causing genetic mutation. This research gives hope to patients that they may benefit from medicines that can target the cancers caused by these genetic drivers. Treatments currently exist for a small percentage of the mutations identified (ALK, EGFR, and ROS-1); there is no treatment available for patients with the most common genetic abnormality, in the KRAS gene. Several studies underway are showing promise in a variety of targeted therapies aimed at a number of genetic mutations, including KRAS.

Additionally, many personalized medicines that are undergoing clinical studies are either already approved for use in other forms of cancer or for targeting other genetic mutations. For example, researchers have identified that the targeted therapies used to treat patients with chronic myeloid leukemia

"No recent cancer advance has been more transformative than immunotherapy. These new therapies are not only transforming patient lives, they are also opening intriguing avenues for further research."

—Julie Vose, M.D., M.B.A., F.A.S.C.O., President of the American Society of Clinical Oncology
“When I was diagnosed with lung cancer 10 years ago, I was overwhelmed less by my diagnosis than by the dismal state of lung cancer research... I wondered if I would live to see any significant improvement in the state of lung cancer. Frankly, now I cannot keep up with the changes. Every day brings a very real possibility of another breakthrough therapy or discovery. I am so encouraged by what researchers are doing in the realm of lung cancer.”

–Dusty Donaldson, 10-year lung cancer survivor, founder of the Dusty Joy Foundation, and co-chair of the Lung Cancer Action Network (LungCAN)

may have a benefit for up to 10% of NSCLC patients whose cancers have similar mutations. Another class of medicines, known as PARP inhibitors, show great promise in small cell cancers, where genetic mutations may cause a high level of an enzyme used to repair damaged DNA in tumor cells. By inhibiting this enzyme in cancer cells, PARP inhibitors can cause the cells to die. These medicines are also demonstrating early success in ovarian and breast cancers. (See chapter on Breast Cancer.)

Recent advances in immuno-oncology are opening new avenues for lung cancer patients. Continuing research in immunotherapy checkpoint inhibitors is showing great promise for lung cancer patients, as well as cancer vaccine treatments, which also work by boosting the immune response to cancer cells. By using different mechanisms to trigger an enhanced immune reaction, these medicines have the potential to enable a patient’s immune system to fight the cancer.

Building treatment advances in lung cancer offer great hope for the future, especially for patients with small cell forms of the disease, where treatment advances are desperately needed. With more than 200 medicines currently in development across the United States, including more than 40 for small cell forms of lung cancer, the future has never looked more promising for lung cancer patients.

LUNG CANCER

Then
- Patients relied primarily on surgery and radiation as first-line treatment options.
- Existing chemotherapeutic treatments had devastating side effects.
- Early small-molecule therapies showed promise for a small number of patients, but much remained unclear about why some patients responded and others did not.

Now
- Targeted therapeutic advances are transforming the treatment paradigm for patients with certain forms of NSCLC.
- Immunotherapies and vaccines are opening new avenues for treatment, enabling the patient’s immune system to mount an attack against cancer cells.
- A growing understanding of tumor genetics is propelling treatment advances, with more than 200 medicines in development for various forms of lung cancer.
Kidney Cancer: New Options for Advanced Disease

Targeted medicines and immunotherapies are transforming the treatment paradigm for many patients.

QUICK FACTS

- In 2016, an estimated 62,700 new cases of kidney cancer are expected to be diagnosed in the United States.\(^{200}\)
- Men are twice as likely to be diagnosed with kidney cancer as women.\(^{201}\)
- The most common form of kidney cancer is renal cell carcinoma, accounting for 90% of kidney cancer diagnoses.\(^{202}\)
- Two-thirds of kidney cancers are diagnosed at the local stage, which has a five-year survival rate of 92%.\(^{203}\) However, the five-year survival rate for advanced metastatic forms of kidney cancer remains low at 12%.

The kidneys play a critical role in maintaining healthy body functioning, working to filter waste, including excess water and salt, from our blood.\(^{204}\) The most common form of kidney cancer, renal cell carcinoma (RCC), usually occurs in the cells lining ducts in kidneys called tubules, which perform an important part of this cleaning and filtering function in the blood.\(^{205}\) More than 65% of kidney cancers are diagnosed in the localized stage, where they are still confined to the kidney; these tumors can often be removed surgically, which may entail removing the cancer or even removing a whole kidney.\(^{206, 207}\) Although the kidneys serve an essential role in the body, many people can still function normally with less than one complete kidney. For this reason, surgery is often used as a first course of treatment, regardless of how far the cancer has progressed. Patients with advanced metastatic forms of kidney cancer, where the cancer has spread to distant places in the body, will also often receive some form of additional treatment to attack cancer cells not removed by the surgery.
A Decade Ago: Additional Options Needed for Advanced Kidney Cancer

Ten years ago, significant progress had been made in understanding the underlying causes of kidney cancer, but much remained unknown about the molecular drivers of disease. Patients a decade ago faced a difficult road in terms of treatment options. For many patients, an invasive surgical procedure called a radical nephrectomy was the standard first-line-treatment. This procedure entailed complete removal of the entire affected kidney as well as surrounding fat and gland tissues.

For patients with metastatic forms of disease whose cancer was not removed completely with surgery, the main therapeutic treatment options at the time were cytokine-based immunotherapies. Cytokines are proteins that play a role in the body’s immune system and inflammatory responses. Manufactured versions of these natural proteins can be used as immunotherapies with the goal of harnessing the body’s immune system to help fight off or destroy cancer cells. The medicines most often used to treat kidney cancers were interferon alpha and interleukin-2 (IL-2). Although important therapeutic options, these medicines were administered intravenously and sometimes were associated with toxic side effects. Additionally, these medicines produced only modest treatment effects and were often only impactful for small subsets of patients. When administered at high doses, IL-2 had the best chance of shrinking RCC tumors and was for a time considered one of the standard first-line therapeutic options for advanced stages of disease. However, the serious side effects often associated with the treatment, including extreme fatigue, fever, organ malfunction, and even heart attack, created substantial concern. As a result, IL-2 could only be used in patients at a certain level of baseline health and administered in specific treatment centers.

Additional therapeutic options were needed to effectively treat the cancer, while producing fewer side effects. New options were particularly important for patients with advanced forms of disease, where surgery was often not enough to eliminate their cancer.

Today: Wave of New Treatments Transforms Treatment Paradigm

The rapid pace of science has given patients with kidney cancer a new range of treatment options over the last decade. Many of these options have lessened the need for invasive surgical procedures or reduced the need for surgical procedures altogether. Laparoscopic surgical procedures are executed through several small incisions rather than one large one and are now commonplace. In addition to less invasive surgical procedures, patients with advanced forms of kidney cancer that cannot be removed completely by surgery have a variety of new medicines available to them; in many cases, they may receive therapeutic options ahead of, or instead of, surgery. Many of the new medicines have been shown not only to be impactful when taken on their own, but to produce even greater results when used in combination with other treatments.
Targeted Therapies

A growing understanding of the molecular and genetic changes that cause cancer has enabled researchers to develop medicines that target these changes. Because these targeted therapies hone in on specific biological pathways, they often produce less severe side effects than traditional chemotherapy or early forms of immunotherapy (like cytokines). New targeted therapies often work by blocking the genesis of new blood vessels, which can nourish cancer cells, or by inhibiting the biological pathways that trigger cell growth and proliferation. A group of medicines called tyrosine kinase inhibitors (TKIs) have emerged as a potent targeted approach for treating a number of cancers, including advanced RCC. By 2006, two medicines in this group had been approved by the U.S. Food and Drug Administration (FDA) to treat lung cancer. Sorafenib and sunitinib were the first new medicines for kidney cancer available to patients in more than a decade. These medicines work by both interrupting cancer cell growth and halting the formation of blood vessel growth. Administered orally, these medicines give patients important new options that are better tolerated than traditional immune treatments (like interferon) and improve patient quality of life.

In 2009, a new TKI, pazopanib, was approved to treat advanced RCC. This medicine affects cell growth by inhibiting specific cell signaling pathways and works through a slightly different mechanism of action than earlier TKIs (sorafenib and sunitinib). This represents an important advance for patients who do not respond or may have stopped responding to those medicines. Similarly, in 2012, another oral TKI, axitinib, joined the wave of medicines that help inhibit the growth of kidney cancer cells, marking the seventh new kidney cancer therapy to emerge over the past decade. Axitinib is designated for use following first-line treatment with other medicines, giving patients a key therapeutic option when they may not have responded to earlier treatments.

In addition to TKIs, several other new targeted therapies have been approved by the FDA, giving patients important options to inhibit the growth and spread of kidney cancer. These include monoclonal antibody (mAb) medicines, a relatively new innovation in cancer therapy. Two of the mAbs approved for kidney cancer inhibit the mTOR protein, which is an essential component of a cell signaling pathway that controls cell growth and division and is also involved in blood vessel formation. Termed mTOR inhibitors, everolimus and temsirolimus stop the growth of cancer cells and reduce the cancer’s ability to receive nourishment from the blood. These medicines are also effective in treating other forms of cancer, including breast cancer (see chapter on Breast Cancer).

Bevacizumab, another mAb cancer treatment that has been shown to be an effective therapeutic option in breast cancer and other forms of cancer, also emerged in the last decade as an effective therapy for advanced RCC. In combination with interferon alpha, patients treated with bevacizumab lived nearly twice as long as patients who received interferon alpha alone, giving patients an important additional treatment option.

“This unprecedented level of drug development within this time period [since 2005] has significantly altered the treatment paradigm of metastatic kidney cancer, and offers patients multiple treatment options.”

—Richard Pazdur, M.D., Director of the Office of Hematology and Oncology Products, U.S. FDA Center for Drug Evaluation and Research

New Types of Immunotherapies

Capping a wave of treatment innovation over the last decade, a new class of immunotherapies has emerged as a potent therapeutic option for advanced kidney cancer. One of these, nivolumab, helps unleash the body’s own immune system to detect and attack kidney cancer cells. Building on a growing understanding of immune cell action, scientists now understand that immune cells have checkpoints that can be turned on or off to elicit a response to an invader. Cancer cells may be able to avoid being attacked by altering these checkpoints. Nivolumab works by inhibiting specific checkpoints, enabling the immune system to kill the cancer cells. In clinical studies, patients that received nivolumab experienced significantly increased survival. The medicine, called a checkpoint inhibitor, is also approved to treat advanced melanoma, non-small cell lung cancer, and Hodgkin Lymphoma (see sections on Melanoma, Non-Small Cell Lung Cancer, and Blood Cancers), and researchers are energized by the new avenues these advances may be creating in a variety of forms of cancer.
Looking Ahead: Promising Science Drives Continued Innovation

Scientific advances are spurring a new era of targeted medicines and immunotherapies for patients with kidney cancer. Building on the advances of the last decade, researchers are not only uncovering new therapeutic options, but also determining the optimal sequencing and combination regimens for existing medicines, which promise to deliver even greater benefits for patients.226 Researchers are leveraging a growing understanding of the genetic mutations that may be driving cancer to uncover new targeted therapeutic options. Additionally, researchers are exploring new ways to enhance or unleash the immune system in attacking cancer cells. Building on the success of nivolumab, studies are focused on how other checkpoint inhibitors may work in treating advanced kidney cancer and how combinations of these therapies may be particularly impactful.227 Research is also exploring how therapeutic vaccines could be used to treat forms of kidney cancer.228 Designed to help the body mount a response to cancer cells, much like the body would react to an infection, therapeutic vaccines in trials are showing promise in stimulating the immune system to attack cancer cells. One other novel approach under study involves extracting tumor cells from the body and altering them in a lab to make a vaccine that, when returned to the patient, will help identify the tumor cells and elicit an immune response.229

Biopharmaceutical researchers are working to leverage scientific advances into new treatment options for patients. The horizon is full of promise, with 50 medicines currently in development in the United States for kidney cancer.230

KIDNEY CANCER

Then
• Much remained unknown about the biological drivers of advanced kidney cancer.
• Surgical procedures to remove kidney cancers were often very extensive and invasive.
• Existing immune medicines for advanced kidney cancer often resulted in debilitating side effects.

Now
• Greater understanding of the genetic mutations that can cause kidney cancer has given patients with advanced disease a range of new targeted therapies.
• Advances in immunotherapy are giving patients with advanced kidney cancer important options with greater survival benefits.
• Rapid scientific advances are opening new doors for kidney patients, with several innovative therapeutic options in the pipeline, including cancer vaccines.
Blood Cancers: Scientific Advances Help Unravel Disease Complexities

Growing understanding of immune cell functioning drives treatment advances.

QUICK FACTS

- In the United States, a person is diagnosed with a blood cancer about every three minutes.\(^2^3^1\)
- Blood cancers are expected to account for about 10% of all new cancer diagnoses in 2016 as well as 10% of cancer-related deaths.\(^2^3^2\)
- Survival rates for blood cancers vary widely depending on the type of cancer but have increased in recent years across all forms due to advances in detection and treatment.\(^2^3^3\)

Blood cancers, also known as hematologic malignancies, affect the production and function of various blood cells.\(^2^3^4\)

Similar to other forms of cancer, blood cancers occur when normal cell growth and development is interrupted by uncontrolled growth of abnormal cells. In patients with blood cancers, these abnormal cells tend to originate in the bone marrow where blood cells are produced. Specific forms of blood cancers are classified based on the type of blood cell they impact (red blood cells, white blood cells, or platelets).

A growing understanding of the molecular basis of disease has transformed what was once known collectively as “disease of the blood” into multiple subtypes of blood cancer, including about 40 types of leukemia and 50 types of lymphoma (see sidebar on Common Blood Cancers).\(^2^3^5\)
### Common Blood Cancers

#### Leukemias:
- Most often affect white blood cells but can affect other blood cells.
- Second most common form of blood cancer in the United States.
- Overproduction of abnormal white blood cells disrupts immune system’s ability to fight infection and interferes with normal production of red blood cells.
- Four main forms of leukemia, classified according to:
  - Rate of growth (acute, or aggressive and fast growing, versus chronic, or slow growing)
  - Type of white blood cells they impact:
    - Lymphocytic cells, which include T-cells (immune cells that attack the body’s own tissues that have turned abnormal) and B-cells (which produce antibody immune cells)
    - Myeloid cells, which are precursors to red blood cells, platelets, and certain white blood cells besides lymphocytes
- Types of leukemia include:
  - Acute lymphocytic leukemia (ALL)
  - Acute myeloid leukemia (AML)
  - Chronic lymphocytic leukemia (CLL)
  - Chronic myeloid leukemia (CML)

#### Lymphomas:
- Affect various white blood cells (lymph/immune cells).
- Most common blood cancer in the United States; about half of blood cancers diagnosed each year are lymphomas.
- Overproduction of abnormal white blood cells crowds lymph system and interferes with immune system functioning.
- Two main forms of lymphoma:
  - Non-Hodgkin: most common lymphoma; affects various white blood cells, usually B cells
  - Hodgkin: affects specific white blood cells in the lymph nodes

#### Myelomas:
- Affects plasma blood cells, a type of white blood cell that produce antibodies.
- Third most common form of blood cancer in the United States.
- Overproduction of abnormal plasma cells interferes with immune system functioning, and crowding of these cells at sites throughout the body, especially in bone marrow, can result in organ damage.

Blood cancers most often affect adult patients, with 91% of leukemia diagnoses in adults 20 years of age or older. However, one form of acute leukemia, acute lymphocytic leukemia (ALL), is among the most common forms of childhood cancer, accounting for 75% of leukemia in children (see chapter on Pediatric Cancers). Because most blood cancers impact white blood cells, which are integral in immune system functioning, patients with these conditions suffer from fatigue, weight loss, fever, joint pain, and repeated infection. However, patients with multiple myeloma often face a slightly different set of symptoms because their cancer is characterized by the overproduction of plasma blood cells. Plasma blood cells overproliferate and crowd at sites throughout the body, often leading to anemia, bone deterioration, kidney malfunction, and organ damage.

Many factors contribute to increased risk of blood cancers. Environmental exposure to chemicals or previous treatment with chemotherapy or radiation can contribute to a higher risk of leukemia and myelomas. Patients with a weakened immune system, especially those with previous or existing severe viral infections, have an increased risk for certain forms of lymphoma. In recent years, researchers have also begun to identify the molecular underpinnings of blood cancers and discovered that some forms of disease can be passed down within the family. The outlook for patients diagnosed with a form of blood cancer varies depending on the specific subtype of blood cancer and how advanced the disease is when diagnosed, but science is driving earlier diagnoses and treatment advances that are resulting in survival gains for many patients with blood cancer.
Patients with most types of blood cancers are traditionally treated using chemotherapy or radiation, either in sequence or in various combinations. Patients may also receive medicines or procedures to help address systemic problems caused by either their cancer or side effects of treatment. Although effective for many patients in killing their cancer cells, chemotherapies also kill some types of healthy cells in the body, which can result in side effects, including fatigue, nausea, vomiting, hair loss, increased infections, and in some cases, permanent organ damage. In a patient population already weakened by cancer, these side effects can be particularly challenging. Additionally, most chemotherapies are administered intravenously, requiring periodic dosing in a clinic or physician’s office for several months on end, creating a significant treatment burden for patients. Some patients who receive high doses of chemotherapy or radiotherapy subsequently require a stem cell transplant, sometimes referred to as bone marrow transplant, to replace normal blood-forming cells affected by the chemotherapy. However, not all patients are eligible for or able to undergo stem cell transplants. Given the potential side effects and treatment burden of chemotherapy and radiation treatment, additional therapeutic options are needed to meet patient needs.

A Decade Ago: Early Targeted Therapies Begin to Transform Outlook for Patients

A decade ago, patients were just beginning to benefit from non-chemotherapy therapeutic options, opening doors for innovation in treatment.

Monoclonal Antibody Therapies
Antibodies play a particularly important role in driving immune system function by identifying foreign entities in the body and targeting them for the immune system. Rituximab was the first monoclonal antibody (mAb) approved for the treatment of cancer, in 1997, as a new therapeutic option for patients with non-Hodgkin lymphoma. By binding to a particular antigen protein, CD20, found on the surface of certain mature immune cells, including abnormal cancerous cells, this mAb therapy activates the immune system to attack the cancer cells. The underlying science behind the approval of rituximab led to the approval of several more mAb therapies over the next few years, including alemtuzumab for chronic lymphocytic leukemia (CLL), which targets the CD52 antigen on cancer cells, and a novel mAb-chemotherapy combination medicine called brentuximab vedotin for both non-Hodgkin and Hodgkin lymphomas, which targets the CD30 antigen on cancer cells.

Proteasome Inhibitors
In normal cells, enzymes called proteasomes help degrade proteins in the cell, particularly those responsible for regular cell processes like cell cycle control, signaling, and death. Cancer patients sometimes have higher than normal levels of these proteasomes, resulting in greater cancer cell proliferation, as the cells that normally control cell death are degraded. Proteasome inhibitors block these over-active proteasomes, allowing cancer cells to undergo normal cell death. The first proteasome inhibitor, bortezomib, was approved to treat patients with multiple myeloma in 2003.

Tyrosine Kinase Inhibitors
By the early 2000s, a growing understanding of the genetic mutations driving many forms of blood cancer, especially leukemias, was beginning to deliver important targeted advances for patients. Beginning with the approval of imatinib in 2001, a class of medicines known as tyrosine kinase inhibitors (TKIs) would emerge as an integral therapeutic option for leukemia patients (and eventually, for patients with other forms of cancer). Researchers had identified a particular genetic abnormality that caused chronic myeloid leukemia (CML) patients’ cancers to grow rapidly. The TKI imatinib, one of the first targeted therapies, inhibits that biological pathway, halting the proliferation of cancer cell growth. Since the introduction of imatinib, the five-year survival rate for CML has nearly tripled. Ultimately, this meant that medicines could be targeted to treat cancer without harming healthy cells, thereby minimizing side effects. In cancer, where chemotherapy had been the primary mode of treatment, this was truly game-changing for patients.
Although the introduction of the first TKI revolutionized the treatment of this particular form of leukemia, additional options were needed as imatinib did not work for every patient, and in some cases, patients who responded to the drug initially developed resistance later on. Additionally, although the introduction of mAb and proteasome therapies were important first steps, additional medicines were needed as many forms of blood cancer still lacked treatment options. Finally, while the TKIs were able to be taken orally, chemotherapies, mAbs, and proteasome therapies had to be administered intravenously, creating a treatment burden for patients. The rapid pace of the science had begun to build toward a new wave of therapeutic options for blood cancers.

**Today: Scientific Advances Propel New Treatment Era**

Over the last decade, a wide variety of therapeutic options have become available to patients with blood cancers. Building on the rapidly-evolving understanding of the underlying biology of each disease, targeted treatment options have emerged for many forms of blood cancer. While we now understand that blood cancers are not one monolithic disease, research has also uncovered many similarities among different forms of blood cancer in terms of how cancer cells send signals and how they grow. As a result, scientific advances over the past decade have not only yielded new medicines for specific blood cancers but have also revealed the effectiveness of many treatment modalities across multiple forms of blood cancer.

**Subsequent Generation TKIs**

Today, an arsenal of subsequent generation TKI medicines, which inhibit the cellular pathways that trigger uncontrolled cancer cell growth, is available for patients with CML. These medicines, dasatinib, nilotinib, bosutinib, and ponatinib, are particularly important in instances where mutations may have rendered imatinib ineffective or nonresponsive. These medicines have also emerged as important treatment options for patients with ALL, representing a significant advance over existing chemotherapeutic options, which came with sometimes serious side effects.

**B-Cell Receptor Pathway Inhibitors**

New insight into the biological pathways of blood cancer cell growth has also led to therapies that target the mechanisms by which CLL cells proliferate. Scientists discovered that a pathway called the B-cell receptor (BCR) pathway is abnormal in CLL, allowing for the survival and proliferation of cancerous cells. Two new oral medicines, ibrutinib and idelalisib, inhibit two different proteins involved in the BCR pathway, Bruton’s tyrosine kinase and the P13K protein, respectively, and halt the progression and development of CLL. These BCR inhibitors have demonstrated long-lasting remission for CLL patients with minimal side effects. Furthermore, these medicines are now effective treatment options for many other forms of blood cancer, including rare forms of lymphoma.

**New Wave of Monoclonal Antibodies**

Building on the success of early mAb therapies, a new wave of treatments has emerged for blood cancers in recent years. Researchers have identified additional antigen proteins on the surface of cancer cells that mAb treatments can bind to and mark for the immune system to attack. One major advance was the approval of blinatumomab for a rare form of ALL.
This new medicine, the first in a new class of medicines called bispecific T-cell engagers, has a totally unique mechanism of action where it binds to both the CD19 antigen on abnormal cancer cells and also binds to a receptor on a type of immune cell called a T-cell. These T-cells, a type of lymphocyte, then attack and destroy the cancer cells. Two major mAb treatment advances have also emerged for CLL in recent years, with the introduction of obinutuzumab and ofatumumab. Obinutuzumab was the first medicine with the U.S. Food and Drug Administration’s (FDA) breakthrough designation to receive FDA approval. Another important treatment advance, daratumumab, was approved in 2015 as the first mAb therapy for multiple myeloma. This medicine binds to the CD38 antigen on cancer cells and represented a significant advance for multiple myeloma patients, who often develop resistance to existing treatments.

**Histone Deacetylase Inhibitors**
A class of medicines called histone deacetylase (HDAC) inhibitors, which have been used as mood stabilizers and anti-epileptic medicines, also emerged in the last decade as an important treatment option for patients with forms of myeloma and non-Hodgkin lymphoma. HDAC inhibitors can affect what genes are active inside cells by interacting with large proteins called histones. By interfering with histones, gene expression is interrupted and the cancer cells die. Two of these medicines, belinostat and romidepsin, are offering patients with a particular form of lymphoma called T-cell lymphoma an important therapeutic advance over longstanding chemotherapy options. Building on those advances, the first HDAC inhibitor for patients with multiple myeloma, panobinostat, was approved in 2015.

**Oral Proteasome Inhibitors**
Capping off an important year for patients with multiple myeloma in which the first mAb therapy and the first HDAC therapies for myeloma were approved, a third important treatment option emerged for patients with multiple myeloma in 2015. The first oral proteasome inhibitor, ixazomib, was approved for use as part of what researchers call triplet therapy, where three medicines are used together as part of a monitored regimen. The new medicine demonstrated improved progression-free survival and clinical benefit. Researchers noted that the new medicine provides patients with a more convenient, once-weekly treatment option, and opens doors to fully oral combination regimens for patients.

**Looking Ahead: Harnessing the Immune System to Drive Treatment Advances**

The science has never been more promising for patients with blood cancers, as researchers build on the tremendous advances of the past decade and explore new avenues for treatment. The success of targeted TKI therapy continues to grow, as researchers are uncovering similarities among the molecular drivers of various blood cancers, revealing the efficacy of many treatments in forms of cancer beyond those in which they were originally approved, as well as new pathways to target. Researchers are also exploring use of TKIs in combination with other cancer-fighting agents, including vaccines and immunotherapies. By using two different modalities together researchers are hopeful that patients may experience complete elimination of cancer from their bone marrow. In parallel, researchers are exploring new ways to use vaccines to help the immune system recognize and target cancer cells. These experimental therapies are showing promise across a number of types of cancer, including many blood cancers.

The success of mAb therapy has also opened important new channels for research as scientists explore new surface antigens on the surface of cells that may be likely targets, and then develop the medicines to treat them. One type of medicine called an antibody-drug conjugate links a mAb directly to chemotherapy, allowing for the targeted delivery of the toxic chemotherapeutic directly to the cancer cells. One of these medicines has already shown tremendous success in treating breast cancer. New antibody-drug conjugates in development target a protein called the surface antigen in leukemia (SAIL) and are showing great promise across a number of leukemias.

A new era of immunotherapy is also beginning to transform the treatment of blood cancers. Medicines called immune checkpoint inhibitors help unleash an anti-cancer immune response by targeting the molecules that serve as the brakes on the immune system. Several studies are under way to assess the efficacy of these medicines in treating various forms of blood cancer. The field of cancer treatment, and multiple myeloma in particular, has never seen a watershed moment like this. With two breakthrough designation drug approvals in the treatment of multiple myeloma in the last week... the transformation in the treatment of myeloma is clearly underway.”

—Walter M. Capone, President and CEO of the Multiple Myeloma Research Foundation
Many have already been approved for the treatment of advanced melanoma, non-small cell lung cancer, and renal cell carcinoma, and very recently the first immunotherapy was approved for the treatment of Hodgkin Lymphoma. In clinical studies, two-thirds of patients responded to treatment with nivolumab, with a benefit that appears to be sustained over time. This medicine provides an important treatment option for patients whose disease relapses or progresses after initial treatment and stem cell transplant.

Significant research is focused on another class of immunotherapy called adoptive cell therapy, in which immune cells are removed from a patient, adapted to target cancer cells, then returned to the patient to identify and kill cancer cells. Emerging trial results on a type of adoptive cell therapy called chimeric antigen receptor (CAR) T cell therapy are demonstrating efficacy in a range of blood cancers, eliciting more potent and longer-lasting immune responses against cancer cells.

The rapid pace of scientific learning is leading to tremendous advances in the treatment of blood cancers, with new medicines emerging quickly. Growing insight into the best use of existing therapeutic options is also giving patients hope for the future. Currently there are more than 400 medicines in development for blood cancers in the United States.

—Irene Ghobrial, M.D., Dana-Farber Hematologic Oncology Treatment Center

“...We’re starting to see a lot of hematologic malignancies benefit from immunotherapy. The excitement is there for so many trials and several new drug combinations that are being tested right now.”

BLOOD CANCER

Then

• Early targeted therapies offered important treatment avenues but additional options were needed for patients who did not respond or developed resistance to treatment.
• Existing chemotherapeutic and radiation treatment options left patients with sometimes debilitating side effects.
• Advances in monoclonal antibody therapies were just beginning to open doors to immune therapy.
• Most therapies available were administered intravenously, creating a significant treatment burden for patients.

Now

• Multiple targeted treatment options are available for patients, enabling the attack of cancer cells specifically while leaving healthy cells intact.
• The array of targeted therapies available provides patients with expanded options if they do not respond to a specific therapy or if their cancer develops resistance to a particular treatment.
• Oral treatment options are offering both improved outcomes and reduced burden of treatment for many patients by reducing, or in some cases eliminating, the need for intravenously administered medicines.
• A constantly growing variety of monoclonal antibody therapies is available, helping to identify cancer cells so that the immune system can attack them.
• New avenues of treatment, including cancer vaccines, immunotherapies and adoptive cell therapies, are showing great promise in treating a variety of blood cancers.
Pediatric Cancers: Scientific Advances Spur New Options for Patients

*Increased pediatric research activity is unraveling the causes of many diseases.*

**QUICK FACTS**

- Cancer is the second leading cause of death in children, exceeded only by accidents.
- The most commonly occurring forms of cancer in children are acute lymphocytic leukemia (ALL), brain and other central nervous system (CNS) tumors, and neuroblastoma, a rare nerve-cell cancer.
- The five-year survival rate for all childhood cancers combined has increased 43% percent over the last four decades, which experts attribute to treatment advances and to the high proportion of pediatric patients participating in clinical trials.

Although childhood cancers are fairly rare, making up less than 1% of cancer diagnoses each year, they remain the leading cause of death by disease past infancy among children in the United States. Over the last few decades, however, the outlook for pediatric cancer patients has improved significantly. In 1975, just 50% of children with cancer survived five years or more and today that number is more than 80%. Advances in treatment are thought to be a major driver of these survival gains, as well as high participation of pediatric cancer patients in clinical trials. Although innovative therapies are producing dramatic improvements in survival for many childhood cancers (e.g., in leukemia and lymphoma), brain and central nervous system tumors remain the leading cause of cancer-related death in children, where ongoing research has a potential to develop advances for children who need them most. Conducting clinical research in pediatric oncology can be very challenging, with
a number of unique hurdles for researchers to navigate (see sidebar on Challenges in Pediatric Cancer Research).

Depending on the form of cancer, pediatric cancer patients may undergo surgery or receive chemotherapy and radiation treatment for their disease. In many cases, patients undergo multiple treatment regimens to address their cancer. Because most childhood cancers are very fast growing, intensive use of chemotherapy is often effective in treating the cancers. However, these treatments often result in increased short- and long-term side effects that impact patients’ ability to tolerate the treatments. Additionally, the use of radiation in children can cause more serious side effects in children than in adults as their bodies are still in the process of growing and developing. These effects, often referred to as late effects, can lead to heart or lung problems, delayed growth or development, and increased risk of secondary cancer occurrence later in life.

Biopharmaceutical companies are committed to advancing treatments for this particularly vulnerable population and are working alongside members of the pediatric cancer community to leverage emerging science and translate insights into effective treatments for young patients. Important regulations such as the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) have been critical to accelerating research in children (see sidebar on BPCA and PREA: Spurring Pediatric Drug Development).

### A Decade Ago: Need for Greater Understanding of Pediatric Cancers

Although researchers had made great strides in treating pediatric patients with cancer, additional options were needed that could effectively treat cancers while reducing the occurrence of both short- and long-term side effects, as well as the need for subsequent treatment later in life. There still also remained a dearth of pediatric-specific information available for patients, caregivers, physicians and other prescribers to inform treatment decisions. Finally, there was also a tremendous need for new medicines to treat pediatric forms of cancer. Although the passage of BPCA and PREA had instilled important infrastructure for pediatric research, a decade ago these laws were in their infancy. A new wave of research was under way as a result of BPCA and PREA legislation, but given the long timelines for drug development, their impact continues to emerge. By necessity, due to the lack of clinical studies involving pediatric patients at the time, many were treated with medicines “off-label,” meaning that the medicine was approved for use in other patient populations (often for adult forms of cancer) but had not yet been approved for specific use in children.

### Today: New Options Open Doors for Pediatric Cancer Patients

There has been an increase in R&D investment in pediatric cancer research in recent years, giving patients new therapeutic options and providing essential insight regarding the important differences adults and children with cancer may experience with various therapies.

Cumulative research has given clinicians a greater understanding of how to use existing cancer treatments in children. Many pediatric cancer treatment advances are the result of a recent increase in the number of studies that examine the use of existing cancer medicines, which are often already approved for use in treating cancer in adults, in the pediatric population. Because demonstration of clinical efficacy in an adult population does not necessarily indicate that a medicine will perform similarly in a pediatric population, these studies are very important in informing treatment plans. For example, imatinib, a breakthrough therapy for the treatment of chronic myeloid leukemia, was recently approved to treat children with acute lymphoblastic leukemia (ALL), a blood cancer that is the most common form of pediatric cancer. This approval was based on results from continuing pediatric clinical studies.

Although much remains unknown about risk factors for pediatric cancers, a growing understanding of the role of genetic mutations in driving cancer cell growth has opened...
new avenues for treating these diseases. Researchers recognize important differences in childhood and adult forms of cancer; pediatric cancers are often the result of genetic changes that take place spontaneously very early (even before birth) and are not strongly linked to environmental or lifestyle risk factors.

Building on these advances in cancer genetics, researchers have uncovered several new therapeutic options for some of the most devastating forms of childhood cancer. These new targeted therapies, though often still used alongside other forms of treatment, including chemotherapy, often have less severe short-term side effects than other forms of treatment that then go away at the end of treatment, providing children with cancer treatment options that are easier to tolerate. Additionally, while intensive chemotherapy and radiation used to leave pediatric cancer survivors with late effects, including secondary cancers and heart disease, research has shown that, today, many fewer survivors are experiencing late effects and, as a result, more patients are living longer compared to just a few decades ago. Due in part to advances in understanding of how best to use chemotherapy and radiation in children compared to adults, these gains for patients also reflect the impact of using these treatments in a more targeted way, leading to improved patient outcomes.

One new medicine, dinutuximab, was recently approved for first-line use in pediatric patients with high risk neuroblastoma. Neuroblastoma is a rare type of cancer that usually forms in nerve cells and most often occurs in young children. Children with neuroblastoma may experience a variety of symptoms depending on where the neuroblastoma originates. These symptoms often include fatigue, decreased appetite, fever, and pain around the site of the tumor. This new medicine, the first approved to treat this rare cancer, introduces a new mechanism for inducing cell lysis, or destruction, and has been shown to drastically improve survival outcomes. Dinutuximab works by attaching to a specific receptor on the surface of neuroblastoma cells, which causes the cells to self-destruct. This mechanism is much more targeted than traditional forms of treatment, opening doors to therapeutic options that are less indiscriminate and, in turn, may cause fewer side effects.

“The FDA approval of dinutuximab represents the culmination of a remarkably productive collaboration... Children with neuroblastoma will benefit from this collaboration, and the drug development pathway blazed by dinutuximab will likely be followed in the future to develop other novel agents directed against pediatric cancer therapeutic targets.”

–Malcolm Smith, M.D., Ph.D., Associate Branch Chief, Pediatrics in the Cancer Therapy Evaluation Program at the National Cancer Institute
Looking Ahead: Rapid Scientific Advances Spur Pediatric Research

Continued research in novel targeted therapeutic areas is giving patients hope that they will not have to undergo chemotherapy and radiation treatments and that they will be able to prevent some of the possible late effects of these treatments (including secondary cancer occurrence). Advances in immunotherapy, for example, are opening new doors for patients with ALL. Recent research shows that one emerging form of immunotherapy called adoptive cell therapy is showing great promise. In adoptive cell therapy, immune cells are collected from a patient, genetically modified, then infused back into the patient, where they enable the modified immune cells to recognize and attack cancer cells. One specific form of this new treatment, chimeric antigen receptor (CAR) T-cell therapy, is emerging as a leading type of adoptive cell therapy for the treatment of many forms of blood cancers, with early results especially promising in pediatric ALL.

Several studies are also under way examining cancer vaccines for treatment of various forms of brain cancer, which are some of the most commonly occurring cancers in children. These therapeutic vaccines would help enable the immune system to attack cancer cells by delivering substances that induce a specific immune response. Additionally, the growing recognition of the role of certain receptors on the surface of cancer cells in controlling cell growth is spurring new research into the use of medicines to interrupt these pathways. Recent studies of certain tyrosine kinase inhibitors (already being used across a variety of cancers, including imatinib for ALL, for example) are showing exceptional promise for many pediatric cancer patients.

Researchers are also examining the biological basis for differences in treatment response in children compared to adolescent patients. A recent uptick in the number of adolescents enrolling in clinical trials is giving hope for more options and better outcomes for these patients, where additional clinical insights and advances are needed for these patients specifically.

In order to advance the science and accelerate the development of new therapeutic options for children, including children with cancer, members of the pediatric research and drug development community have come together to form a new consortium that will support the development of a first-of-its-kind global pediatric clinical trials network. The network will create a sustainable infrastructure for pediatric clinical trials to speed up recruitment and completion of trials, including trials in pediatric oncology.

The rapid pace of science coupled with the determination of the pediatric cancer community is opening new avenues for treatment, giving patients hope for the future. Currently, there are more than 500 studies underway for treating children with cancer. These novel therapeutic approaches have the potential to change the treatment paradigm for this vulnerable group of patients.

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PEDiATRIC CANCER

Then

- Standard chemotherapy and radiation options often resulted in debilitating long-term and late side effects.
- Lack of understanding of how cancer in children differs from cancer in adults made treatment difficult.
- Additional research needed to illuminate how to appropriately use existing treatments in pediatric patients.

Now

- A greater understanding of molecular drivers of disease is spurring new era of targeted therapies.
- There is a growing understanding of important differences between cancers occurring in adults versus children.
- New medicines are beginning to offer pediatric cancer patients effective treatment options with fewer late side effects.
- Research into cancers that occur in adolescents and young adults, where there has traditionally been a dearth of research, is growing.
Accelerating Progress for Patients with Cancer

The rapid pace of scientific advances has resulted in tremendous progress for cancer patients over the last decade. Researchers’ understanding of the underlying biological mechanisms that initiate and control cancer cell growth have created new avenues for treatment advances. A growing recognition of the role genetic mutations play in driving these biological mechanisms has led to remarkable advances in personalized, or precision, medicine. Furthermore, the emergence of a new wave of immunotherapies, which can help unleash a patient’s own immune system against a cancer, are creating entirely new therapeutic options.

New medicines are not only improving survival outcomes for many patients, but are also, in many cases, reducing side effects and improving quality of life over the previous standard therapeutic options. Many traditional forms of cancer treatment, including chemotherapy, were active not only against abnormal cancer cells, but also against normal cells within the body, and in many cases resulted in debilitating toxicities. Many of the treatment options that have emerged over the last decade are able to specifically target cancer cells, thus reducing the impact on surrounding cells and avoiding some of the short- and long-term side effects of traditional treatments.

While new drug approvals over the past decade represent significant advances for many patients across many forms of cancer, there is still a great need for new cancer treatments and potential cures. Cancers continue to present some of the greatest complexities for scientists.

Advances in cell biology and genetics have led to expanded treatment options for many forms of cancer, but there are many identified mutations for which there are no treatment options available yet, as well as an unknown number of genetic drivers of disease that have yet to be identified.

Researchers are also learning about the significant impact the microenvironment surrounding the cancer cells may have on cancer cell growth and cancer cell response to treatment. The microbiome, our bodies’ own flora and fauna, may impact drug metabolism, and the epigenome, factors that control DNA packaging and organization, may also impact cell genetics and tumor growth. On top of all of this, as a result of these and many other emerging factors, cancers change and mutate over time, and progress in unpredictable ways, making it very difficult for scientists and researchers to determine the best treatment plan for each patient.

Biopharmaceutical researchers are committed to working with others across the oncology community to address these challenges and deliver new treatment options to patients. There is tremendous promise for targeted therapies; biopharmaceutical companies report that 73% of medicines in their oncology pipeline have the potential to be personalized medicines.

The remarkable progress we are seeing today represents decades of research seeking to unlock the underlying mechanisms of many forms of cancer, and to develop medicines that target those mechanisms. But this path is long, costly, and fraught with many setbacks. Between 1998 and 2014, for example, 96 melanoma medicines did not make it through advanced clinical development and there were just seven new medicines approved. Similarly, during this same time period, 167 lung cancer medicines did not make it through later stage clinical development and there were just ten new medicines approved. These so called “failures,” while frustrating, are not wasted efforts. These learnings help direct future research efforts and, as illustrated by recent advances in both melanoma and lung cancer, can result in great advances for patients.

We are at a time of remarkable change in cancer care. Increased screening, early detection, and therapeutic advances are transforming the treatment paradigm for many, and the science has never presented greater opportunity for new therapeutic advances for patients. In order to realize the promise of future innovation, it will be increasingly important to foster an environment that recognizes the role of new medicines in improving patient outcomes and in delivering high value cancer care.

“There has been a sea change in our basic understanding of what cancer is... and in the way that we treat patients with cancer. This has led to significant decreases in cancer mortality rates on an annual basis. The majority of cancer researchers agree that these are exciting times and that the pace of discovery and application of new knowledge to patient care is rapidly accelerating.”

–Jose Baselga, M.D., Ph.D., Physician-in-Chief, Memorial Sloan Kettering Cancer Center, New York, NY, President of the American Association for Cancer Research
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