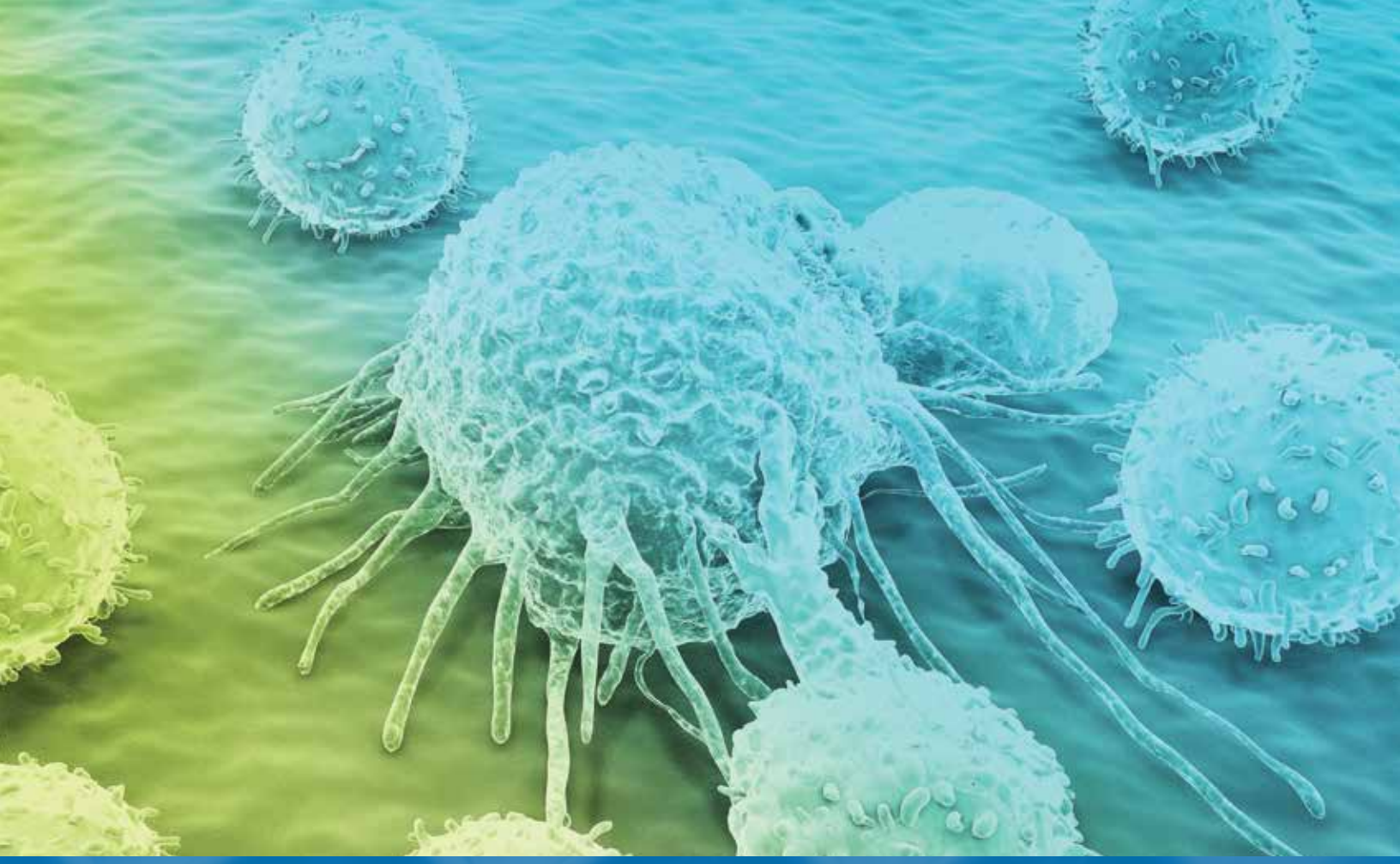
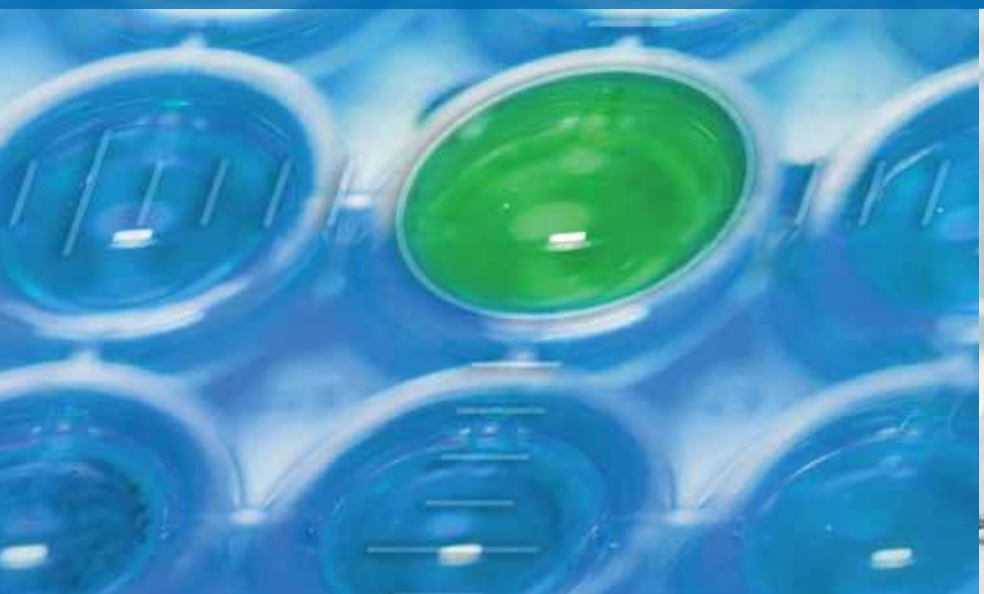


PhRMA
RESEARCH • PROGRESS • HOPE

Researching Cancer Medicines:
Setbacks and Stepping Stones



Researching Cancer Medicines:
Setbacks and Stepping Stones

Cover image: T-lymphocytes (immune system cells) attack a migrating cell. (Getty Images)

Executive Summary

A cancer diagnosis can be devastating to individuals faced with the disease, along with their families and caregivers supporting them in their fight. While recent scientific advances have led to improved prevention, earlier diagnoses, and innovative treatments for many cancers, there is still tremendous unmet medical need. The more we learn about the hundreds of diseases that we now know make up cancer, the more complexity we uncover.

Novel medicines that target the underlying causes of the disease are improving the outlook for many patients. But behind every medicine that makes it to patients there are many that do not. The biopharmaceutical pipeline is littered with so-called "failures." These setbacks are an inevitable part of the process, but researchers use the knowledge gained from them to better understand cancer and inform research on other medicines in development.

A new analysis of three difficult-to-treat cancers – **melanoma, lung cancer, and brain cancer** – shows just how difficult the process can be. Since 1998, there have been 96 unsuccessful attempts to develop drugs to treat melanoma, 167 for lung cancer, and 75 for brain cancer. In the same period we also saw medicines that beat the odds and advanced care: 7 new drugs to treat melanoma, 10 for lung cancer, and 3 for brain cancer were approved by the Food and Drug Administration.

These numbers underline the challenges of the process but also the unprecedented new treatments that emerge from years of research and setbacks. Many of these medicines target the root cause of cancers at the molecular level and some harness the body's immune system to attack cancer cells.

Although cancer continues to be a major challenge, biopharmaceutical companies are dedicated to transforming the outlook for cancer patients from a devastating diagnosis to a chronic, manageable condition. This goal drives researchers past the setbacks to discover innovative medicines that bring hope to patients and their families, and an end to cancer as we know it today.

Introduction

When a person receives a cancer diagnosis he or she begins a fight and, often, medicines are among the most valuable tools in the arsenal. For some cancers we have a number of effective treatments, but for many others, we are still in need of new and better treatment approaches. America's biopharmaceutical researchers are working diligently every day to develop new options to provide hope to patients and allow them to beat cancer and live longer, healthier lives.

The mapping of the human genome in 2003 ushered in a new era of research and discovery aimed at identifying the causes and progression of cancer at the molecular level. With this progress, we have gained many potential new approaches to stop or slow tumor progression. With these unprecedented advances, researchers are uncovering many layers of complexity. In fact, we now know that cancer is not one single disease but rather a collection of hundreds of unique diseases.

In recent years, we have begun to see the fruits of this growing knowledge and innovative new medicines are revolutionizing treatment for some cancer patients. These medicines are recognized for the many benefits they bring to patients, but behind these successes there are also many so-called "failures." Not only are research setbacks inevitable, but they are integral to the process of learning about disease. Researchers apply the findings from every unsuccessful candidate medicine to inform future projects.

1 out of 2:
U.S. males will be diagnosed with cancer.

1 out of 3:
U.S. women will be diagnosed with cancer.

1 of every 4:
Deaths in the United States is due to cancer.

— American Cancer Society[1]

This report highlights the human and economic burdens of cancer, where the current science is leading researchers, and the challenges they face as they continue to advance cancer research. We focus on three particularly difficult-to-treat cancers – ***melanoma, lung cancer,*** and ***brain cancer*** – and examine recent progress and drug failures in these areas. We discuss how setbacks have informed new treatment advances and contributed to improving outcomes for patients.

The Human Burden

The pain and suffering caused by cancer can be devastating to patients, their families, and caregivers.

This year alone, more than 1.6 million people in the United States will be told, "You have cancer," and more than 585,000 are expected to die from cancer.[2] It is the second leading cause of death in the United States but as the U.S. population continues to age, combined with the higher incidence of obesity, continued tobacco use, and other factors, cancer is on a trajectory to surpass cardiovascular disease as the leading cause of death for Americans in the next 16 years.[3,4] According to the American Cancer Society, the number of Americans diagnosed with cancer annually will dramatically rise to 2.4 million over the next two decades as our population ages.[5]

There has been remarkable progress against many cancers, and the death rate for cancer overall has dropped 20% since 1990.[6] However, the number of treatment advances varies widely across cancer types and there remain substantial unmet medical needs.

"Cancer patients are parents and grandparents, children and cherished friends; the disease touches almost all of us and casts a shadow over families and communities across our Nation."

— President Barack Obama[7]

The Economic Burden

In addition to the effect cancer has on a person's health and quality of life, it also places an enormous economic burden on cancer patients, their caregivers, and society.

With the more than 45% increase in new cancer cases by 2030[8] and the continued growth in cancer survivorship each year, the demand for cancer prevention, screening, and treatment services will dramatically increase as well as the overall costs to care for the growing number of patients.

The latest estimates from the National Institutes of Health put the overall direct treatment costs associated with cancer at $86.6 billion annually. The indirect costs – costs associated with lost productivity due to premature death – are even higher, at an estimated $130 billion annually.[9]

Understanding Cancer

From decades of scientific research, we now know that cancer is not just one disease but instead a collection of hundreds of diseases characterized by the growth and spread of abnormal cells.[10]

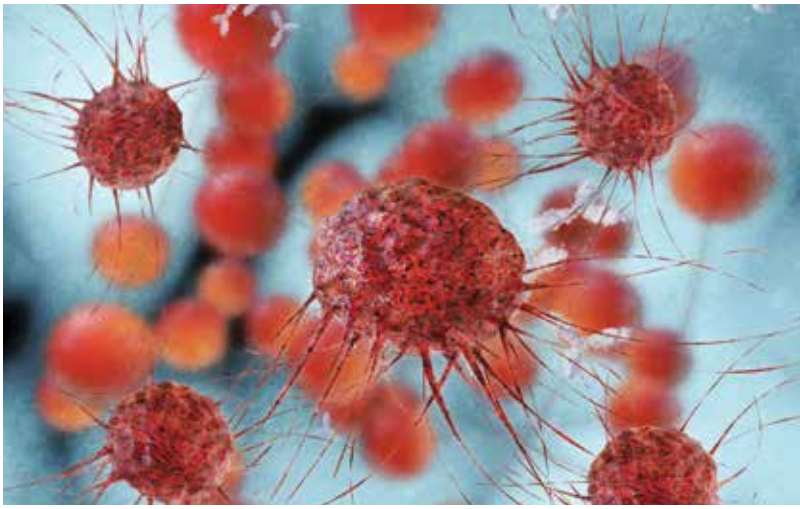
While a particular type of cancer has historically been classified based on the tissue in which the cancer cells first began to develop, researchers are working to more precisely and accurately define cancer based on its cellular and molecular characteristics. The ability to identify particular cancers in scientifically and clinically meaningful ways is a tremendous challenge in and of itself – even before considering the incredible hurdles of exploring potential drug compounds and ultimately developing a drug that will be safe and effective.

For some cancers, the scientific understanding of their root causes provides researchers with better targets for discovering and developing medicines, particularly in some cases when the disease is associated with a single gene mutation or known set of mutations. For many other cancers, however, advances in scientific knowledge have revealed the redundancy and complexity of the pathways involved. In these cases, a combination of medicines that hit the cancer from different angles will likely be needed as targeting just one molecule could allow the cancer to develop resistance. This is just one example of why the development of effective medicines is extremely challenging.

So while we have made enormous progress in understanding many cancers, we have also learned how much more there is to learn about this remarkably complex set of diseases. The potential for progress has never been greater but realizing that promise is a challenge that requires talented, dedicated researchers.

"Scientifically, we have never been in a better position to advance cancer treatment… We now understand many of the cellular pathways that can lead to cancer. We have learned how to develop drugs that block these pathways."

— Richard L. Schilsky, M.D., FACP, FASCO
Chief Medical Officer, American Society of Clinical Oncology; Professor Emeritus, University of Chicago[11]



Challenges in Developing Cancer Medicines

The complexity of cancer is reflected in the drug development process. Cancer medicines can take an average of 1.5 years longer to develop than medicines for other diseases.[12]

Drug developers continue to be challenged in their pursuit of successful new cancer medicines for many reasons. For example:

- To have a comprehensive view of how a particular cancer develops and progresses, researchers must also examine the complex biological environment within which the tumor lives. Gene mutations, immune system response, and external environment factors all contribute to the complexity of the disease.[13,14]

- Cancers are very adaptive. A drug may target a key protein involved in the disease, but the cancer may in turn respond by finding a new pathway to continue its spread.[15]

- Even within a given tumor the biologic drivers (e.g., genetic mutations, gene expression) of the cancer can vary from cell to cell. This tumor heterogeneity adds to the complexities of cancer detailed above.[16] More sophisticated tools are needed to characterize the diversity of the cancer cells found within a single tumor to inform development of new medicines, enable physicians to more accurately diagnose patients, combat cancer drug resistance, and ensure that patients receive the medicine most likely to work for them.

Additional challenges exist that are specific to clinical development. Because cancers are such complex and life-threatening diseases, in early phases of development (e.g., phase 1 clinical trials), investigational therapies are administered only to those patients where standard therapy has failed or other treatment options have been exhausted. Only after approval and real-world use will most medicines have the opportunity to be tested in earlier stages of disease progression. Similarly, cancer medicines often work best in combination with other drugs, but testing all possible drug combinations is impossible to do in clinical studies.[17]

Because of these challenges, research must continue over the life of each medicine to fully understand the medicine's effects. The nature of oncology clinical research often leads to cumulative progress over time. The approval by the Food and Drug Administration (FDA) of a new therapy is a significant milestone for patients, but it is often only the beginning. Our knowledge of the full benefits of a therapy emerges over time, through continued research and real-world clinical practice.[18,19]

"We've learned that there is unlikely to be a single breakthrough that defeats all cancers. No scientist or drug developer I've ever met is working on "the cure for cancer." Instead, they are trying to understand one or more of the myriad ways in which cancer arises, nurtures itself, and spreads. Or they are shepherding through clinical testing one of the nearly 1,000 molecules targeting cancer that are in the pipelines of the pharmaceutical industry. Tying such learning together allows progress against cancer to move forward in small steps. These steps add up to significant progress against cancer over time, but there is no denying that they are stubbornly and painfully slow."

— John C. Lechleiter, Ph.D.
Chairman, President, and CEO, Eli Lilly and Company[20]

Today's Treatments for Cancer

Treatment options and outlooks vary widely from one cancer type to another. Over the past several decades, we have seen remarkable progress in the treatment of specific forms of cancers, whereas for others there remain few or no treatment options or more treatments are needed.

While early detection and innovative medicines have helped increase cancer survival rates to levels that were almost unthinkable a generation ago, leading to the nearly 14.5 million cancer survivors in the United States,[21] there remain substantial unmet medical needs. Together with their patients, clinicians determine the most appropriate treatment plan for the individual patient. The treatment regimen may include chemotherapy, radiation therapy, surgery, or other novel approaches. Many of the exciting, novel cancer treatments are therapies which target specific proteins or cells that cause cancer while leaving healthy cells unaffected. By not killing healthy cells (e.g., blood cells, hair follicles) as standard chemotherapies do, many negative side effects can be avoided.

New approaches that are adding to the cancer treatment toolbox include (but are not limited to):

- ***Angiogenesis Inhibitors.*** Tumors need blood vessels to grow and spread. Angiogenesis is the process by which new blood vessels are formed. Angiogenesis inhibitors work by preventing the formation of new blood vessels to stop or slow the growth or spread of tumors.[22]

- ***Epigenetics.*** Researchers have discovered that cancer can be influenced by changes in gene expression caused not only by genetic mutations (changes in the DNA sequence) but also by chemical modifications of DNA (epigenetic changes). By targeting these "epigenetic" marks, genes associated with a cancer may be able to be turned "on" and "off".[23]

"Cancer relapses and treatment resistance have always been among the most daunting challenges in cancer care…The good news is that genomic medicine is helping to overcome these challenges by revealing new ways to target a cancer cell's inner workings."

— Gregory A. Masters, M.D., FACP
Director, Medical Oncology Fellowship,
Helen F. Graham Cancer Center[24]

Immunotherapies. The body's immune system may provide a platform for fighting cancer. Researchers are studying therapies, such as cancer vaccines and non-specific immunotherapies that enhance the immune system to help it prevent cancer or attack cancer cells. Scientific advances have also made it possible to make immune system components, such as antibodies that are designed to attack specific parts of a cancer cell, halt the cell's growth or kill it.[25]

- ***Preventive Vaccines.*** Preventive vaccines leverage the body's immune system to protect against infectious agents that may cause cancer. There are currently several FDA-approved vaccines to prevent liver cancer and cervical cancer.[26]

- ***Therapeutic Vaccines.*** Unlike preventive vaccines, therapeutic vaccines are intended to treat an existing cancer by strengthening the body's immune system to fight the cancer. In addition to a therapeutic cancer vaccine treating metastatic prostate cancer which was approved in 2010, there are many more cancer vaccines in active clinical trials targeting 14 different types of cancer.[27]

- ***Antibody-Drug Conjugates.*** Sometimes called immunoconjugates or immunotoxins, these cancer therapies consist of an antibody (an immune system protein that recognizes specific targets for the immune system) and a chemotherapy drug, or a radioactive molecule. The antibody can deliver toxic molecules directly into the cancer cell without harming other cells in the body.[28] The FDA has already approved 3 drugs using this innovative approach.[29]

These and other new treatment approaches are already improving the outlook for many patients, but they are also offering proof of concept that similar medicines and vaccines could work for patients with other cancers.

"Early evaluation of immunotherapeutic combinations is important toward potentially accelerating the development of new options for patients with cancer."

— Eric Rubin, M.D.
Vice President, Oncology Clinical Development, Merck Research Laboratories[30]

Personalized Medicine Is Here and Growing

Personalized medicine is becoming central to cancer care and many of the innovative types of medicines above are personalized. This approach to treatment uses diagnostic tools to identify specific biological markers, often genetic, and help assess which medical treatments and procedures will be best for each patient. It holds potential to prevent disease, find the correct treatment more quickly, prevent or reduce negative side effects, improve patients' quality of life, and treat disease more effectively. As the overall cost of healthcare continues to rise, personalized medicine could help to control costs by reducing unnecessary treatments and side effects.[31]

The role of personalized medicine is growing. According to the Personalized Medicine Coalition, there were 13 prominent examples of personalized medicines, treatments, and diagnostics available in 2006; by 2014, there were 113 examples.[32] Likewise, a 2010 survey by the Tufts Center for the Study of Drug Development found that 94% of biopharmaceutical companies surveyed are investing in personalized medicine research, and 12% to 50% of the products in their pipelines are personalized medicines.[33]

"Every cell has the ability to differentiate, divide and make a tumour; the cells are almost virus-like in their ability to change."

— Professor Inder M. Verma, M.Sc., Ph.D.
Salk Institute for Biological Studies[34]

Research Setbacks and Stepping Stones in Cancer

The remarkable new generation of cancer treatments that have come out in recent years was not produced overnight and the process was anything but simple.

Behind each and every approved medicine are numerous others that did not make it. So-called "failures" are an inherent part of the process because treating human disease is one of the most complex undertakings on the planet. But these projects are not wasted efforts; researchers learn from all of them. Their findings inform future study and direct research efforts toward new approaches to addressing the causes, growth, and progression of cancer.

Melanoma, lung cancer, and ***brain cancer*** provide just three examples of cancers where there still exist tremendous unmet medical needs, but researchers have made progress with some very promising advances. Let's take a look at what it took to translate the substantial research efforts across the life sciences ecosystem into the new medicines we have in each of these therapeutic areas and the tremendous value to patients they provide.

"The scientific process is thoughtful, deliberate, and sometimes slow, but each advance, while helping patients, now also points toward new research questions and unexplored opportunities."

— Clifford A. Hudis, M.D., FACP
President, American Society of Clinical Oncology (2013-2014); Chief, Breast Medical Service, Memorial Sloan-Kettering Cancer Center; Professor, Weill Cornell Medical College[35]

Melanoma – Progress Emerging from Years of Setbacks

According to the Centers for Disease Control and Prevention (CDC), skin cancer is the most commonly diagnosed cancer in the United States. Each year in the United States, nearly 5 million people are treated for all skin cancers combined, with an annual cost estimated at $8.1 billion.[36]

Melanoma is a type of cancer generally found in the skin that forms in cells called melanocytes, which make the pigment melanin.[37] Melanoma is responsible for the large majority of deaths of all skin cancers.[38] The National Cancer Institute estimates that more than 76,000 new cases of melanoma will be diagnosed in 2014 and more than 10,000 people will die from this form of cancer. The disease is among the most common types of cancer for adolescents and young adults in the United States. Annually, about $3.3 billion in treatment costs are attributable to melanoma.[39]

Recent Progress in Treating Melanoma – Focus on Metastatic Melanoma

If detected early, melanoma has a 5-year survival rate of 97 percent. However, it is an aggressive cancer that once it has spread to other organs, or metastasized (stage 4), the 5-year survival rate decreases dramatically to 15-20 percent.[40] Metastatic melanoma has historically been a very difficult cancer to treat. In the past few years, however, we have seen huge leaps in our ability to fight this form of the disease.

Historically, the primary treatment option for patients with metastatic melanoma has been surgery accompanied by adjuvant therapy (additional therapies) including chemotherapy, radiation, and early immunotherapies (interferon alpha 2b and interleukin-2). Unfortunately, the side effects of these treatments are often significant, and while some patients experience a lasting benefit, many patients still die within a year of diagnosis.[41,42]

In recent years, new targeted therapies and immunotherapy approaches – medicines that harness the body's own immune system to attack cancer cells – have yielded breakthroughs for patients with advanced melanoma. Between 1998, when interleukin-2 was approved by the FDA, and 2011, no new medicines were approved. In the last three years, however, 6 new medicines became available. Five of these were specifically indicated for late-stage or metastatic melanoma.[43]

"There has been notable progress in the cancer immunotherapy field over the last year, with new clinical data showing promising efficacy and tolerability for emerging therapies – particularly those that target the PD-1 pathway."

— Mace L. Rothenberg, M.D.,
Senior Vice President, Clinical Development and Medical Affairs and Chief Medical Officer, Pfizer Oncology[45]

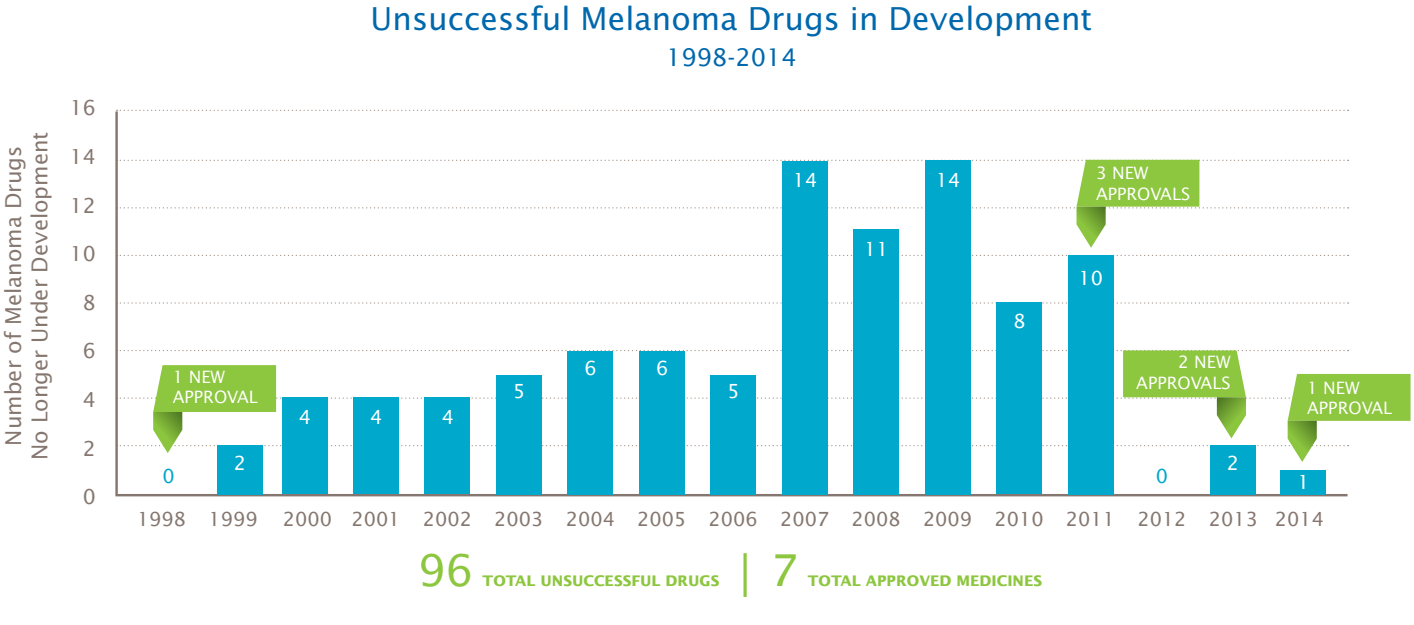
In 2002, researchers identified the BRAF gene mutation, which is found in approximately half of all melanomas and leads to the overproduction and spread of cancer cells. Further research led to the development and FDA approval of 3 new drugs — vemurafenib, dabrafenib, and trametinib — that target specific gene mutations to disrupt cell-signaling pathways and stop or slow tumor growth.[44]

Researchers are also developing a new generation of immunotherapies. After nearly 25 years of research and development, scientists identified a treatment that activates the immune system by blocking a molecule known as CTLA-4, which is thought to be involved in preventing the immune system from attacking cancer cells. In approving this drug, ipilimumab, in 2011, the FDA described it as "the first therapy ... to clearly demonstrate that patients with metastatic melanoma live longer when taking this treatment."[46,47]

Another immunotherapy was approved in 2014. Pembrolizumab is the first in a new class of medicines approved by the FDA that blocks the PD-1 cellular pathway. The protein "programmed death receptor," PD-1, normally prevents the immune system from attacking healthy cells, but cancer cells attach to PD-1 to escape destruction. By inhibiting the connection between the tumor and PD-1, pembrolizumab allows the immune system to attack the melanoma cells.[48,49] Many experts are calling this treatment a "game-changer" and are awaiting results of PD-1 inhibitors in other forms of cancer. In fact, researchers reported at the 2014 meeting of the American Society of Clinical Oncology that of 411 patients with advanced metastatic melanoma who were taking pembrolizumab, 1-year overall survival was 69 percent.[50]

Building on Failures

The recent advances in melanoma resulted from many clinical trials and other research efforts that either never made it to or failed in clinical trials. Since 1998, a total of **96 investigational medicines** in development for melanoma were "discontinued," "suspended," or had "no development reported." These unsuccessful research efforts paved the way for the **7 medicines** approved by the FDA over the same period, a nearly **14:1 ratio** of "failures" to "successes." (See "Unsuccessful Melanoma Drugs in Development – 1998-2014.)



Source: PhRMA analysis of Adis R&D Insight Database, 15 September 2014.

Looking Ahead

These new melanoma treatments have improved survival and reduced side effects for melanoma patients. While these new medicines represent critical milestones in terms of increasing treatment options for patients, there remains a great need for more tools to treat the disease and prolong and improve quality of life for patients.

In addition to developing new medicines, continued research is also showing that when used in combination, some of these existing therapies may be more effective in treating the disease than when used alone.[51] In fact, the combination of two targeted therapies that work on the BRAF pathway nearly doubles the length of time before metastatic melanoma develops resistance and progresses.[52]

Researchers are actively pursuing many new approaches to addressing melanoma, and today, more than **50 new melanoma medicines** are in clinical development in the United States.[53] A 2013 study by Analysis Group found that 91% of medicines in development for melanoma globally have the potential to be first-in-class medicines, which means that they use a different mechanism of action than any other existing drugs.[54]

"We are currently in a time of unprecedented progress in the development of effective treatments for melanoma. As has been shown for many medical challenges (HIV and TB), it is clear that only through combinations of different therapies will the most significant and durable results be achieved."

— Jedd D. Wolchok, M.D., Ph.D.
Memorial Sloan Kettering Cancer Center[55]

"Multiple attempts to improve upon existing therapies for metastatic melanoma may not have been successful in phase III trials, but have added significantly to our understanding of the disease. The molecular alterations important to the pathogenesis of melanoma continue to be elucidated, and there has been a steady progress in our knowledge of the biology of this disease."

— S. Bhatia, S.S. Tykodi, J.A. Thompson.
"Treatment of Metastatic Melanoma: An Overview",
Oncology, 2009; 23(6), 488-496.[56]

Lung Cancer – A New Era Just Beginning

Lung cancer is the second most common form of cancer in men and women and the leading cause of cancer deaths in the United States.[57] According to estimates from the National Cancer Institute, in 2014 alone, more than 224,000 people will be diagnosed with lung cancer, and nearly 160,000 individuals will die from the disease.[58]

The overall 5-year survival rate for lung cancer patients is 16 percent. For those patients diagnosed in early, localized stages of the disease, the 5-year survival rate is 54 percent, whereas those diagnosed in advanced stages, where the cancer has spread, have a 5-year survival rate of only 4 percent.[59]

Although lung cancer incidence remains high, it has decreased considerably since the 1990's thanks to increased emphasis on screening, prevention, and the identification of specific environmental threats to lung health.[60]

Lung cancer is classified into two main types, each with unique characteristics:

- ***Non-small cell*** lung cancer accounts for between 85-90% of all lung cancers and includes squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.[61] Non-small cell lung cancer can grow and spread slowly or quickly.

- ***Small cell*** lung cancer accounts for 10-15% of lung cancers and is an aggressive cancer that spreads quickly within lung tissues and throughout the body.[62]

The type of lung cancer and stage of the disease determine the treatments needed. Treatments for lung cancer include various surgical options, chemotherapy, radiation, targeted therapies, or a combination of therapies.[63]

Recent Progress

Recent research on the differences between subtypes of lung cancers has given rise to new genetic tests to identify particular gene mutations and inform the development and use of targeted treatment strategies. The progress has been particularly notable in non-small cell lung cancer (NSCLC).

Mutations in the epidermal growth factor receptor (EGFR) gene, which are present in approximately 10% of all non-small cell lung cancers, cause cancer cell growth. Knowing this, researchers have developed a new class of EGFR-inhibitors, including erlotinib and afatinib, to stop or slow the growth of lung cancer. Erlotinib was first approved by the FDA in 2004, and a diagnostic to identify patients with the EGFR mutation followed in 2013, which improved clinicians' ability to target the medicine to those patients most likely to benefit from the treatment.[64,65,66,67]

"The last decade of progress in lung cancers has been extraordinary. Expansion of our understanding of the biology of these illnesses, coupled with advances in agent development and a revolution in the molecular characterization of tumors, have ushered in an era of targeted therapies and precision medicine."

— American Society of Clinical Oncology[68]

Researchers have also identified changes in the anaplastic lymphoma kinase (ALK) gene that drives cancer progression in approximately 5% of non-small cell lung cancer patients.[69] In 2011, the FDA approved a targeted medicine called crizotinib, which acts by blocking the mutated form of the ALK gene, thereby disrupting cell signaling and preventing cancer cells from growing and dividing. In 2014, a new ALK inhibitor, ceritinib, was approved by the FDA for patients who have previously taken crizotinib, but whose tumors developed resistance and progressed. Clinical trial findings indicated that patients with ALK-positive metastatic NSCLC whose tumors had grown while on crizotinib or who became intolerant to crizotinib responded to ceritinib.[70,71,72,73]

Further advances in lung cancer treatments have also been realized through use of angiogenesis inhibitors. Medicines in this class cut off the blood vessel growth that tumors need to grow and survive. In 2006, the FDA approved bevacizumab to be used in combination with chemotherapy for patients with non-small cell lung cancer. Clinical trial results indicated that overall survival was significantly longer in patients that received bevacizumab in combination with chemotherapy than in patients that received chemotherapy alone.[74]

A relatively recent innovative approach is the use of nanotechnology to produce nanodrugs. Nanotechnology is the study and application of very small things – on the order of one millionth the size of a millimeter.[75] A nanodrug is made up of a cancer fighting molecule and a nanosized carrier that is designed to deliver the drug through the body to the site of the cancer. This approach can make it possible to get more of the drug directly to the tumor with fewer systemic side effects. In 2012, the FDA approved nanoparticle paclitaxel based on studies that showed the nanoparticle form benefited more patients than the traditional paclitaxel chemotherapy on its own.[76]

Building on Failures

The medicines that have been approved by the FDA in the last several years were built upon a substantial number of failed clinical research efforts. Since 1998, only **10 drugs** have been approved to treat lung cancer, whereas **167 other drugs** failed in clinical trials.[77]

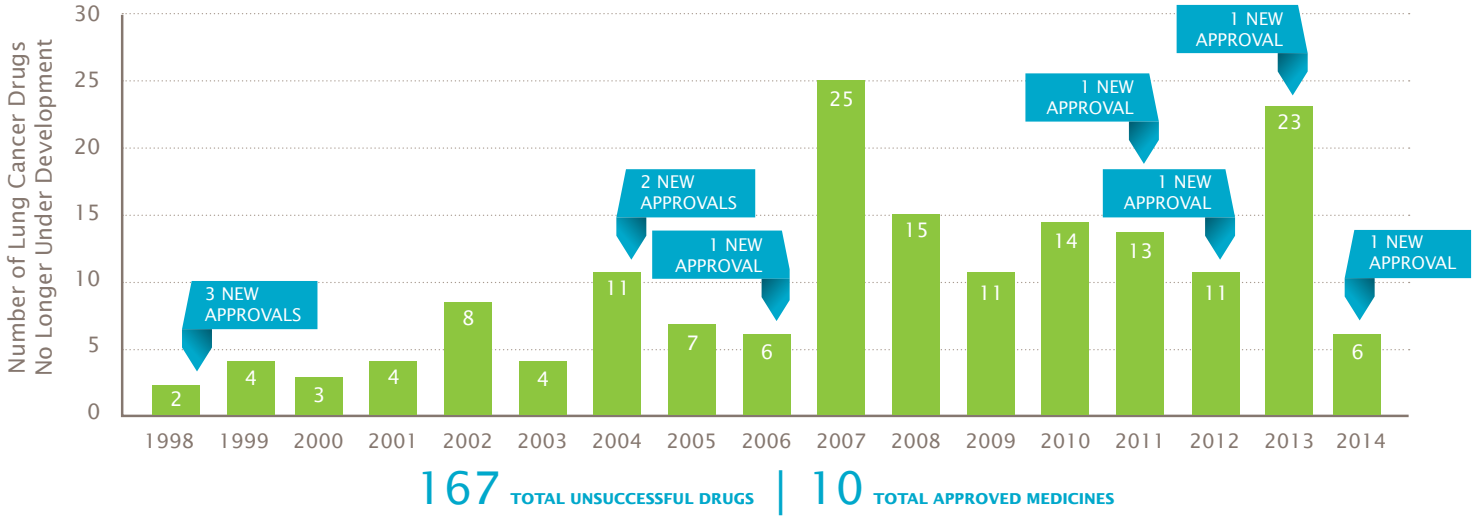
Many factors contribute to the number of unsuccessful drug candidates for lung cancer. One example is the difficulty of determining which genes and proteins are driving the cancer and which are bystanders. Hundreds of genes can be expressed differently in cancer cells than in healthy cells, making it difficult to know which hold the most promise for targeting drug development.[78] The identification of molecular markers to identify the patients most likely to respond to specific targeted therapies is particularly important in lung cancer given that the number of genetic alterations associated with lung cancer cells is particularly high relative to other cancers.[79]

Looking Ahead

Although we have seen remarkable progress in recent years, these treatments are effective for only a subset of lung cancer patients. There remains substantial unmet medical need and researchers are working to build on recent successes and are studying **98 new lung cancer medicines** in the United States. One particularly exciting area they are exploring is immunotherapy, which could help to spur the immune system to fight lung cancer as we have seen in melanoma and prostate cancer.[80]

Unsuccessful Lung Cancer Drugs in Development

1998-2014



Source: PhRMA analysis of Adis R&D Insight Database, 15 September 2014.

"At the time of diagnosis with lung cancer, more than half of all patients have progressed to advanced stages of the disease, with a poor prognosis for long-term survival. There is a high unmet need for additional effective treatment options for patients and their families."

— Glenn J. Gormley, M.D., Ph.D.
Senior Executive Officer and Global Head of Research & Development[81], Daiichi Sankyo Ltd.
Chairman and President, Daiichi Sankyo, Inc.

Brain Cancer – Research Brings Hope to a Difficult Disease

The American Cancer Society estimates that more than 14,000 people (adults and children) will die this year from brain and spinal cord tumors, and 24,000 new cases will be diagnosed.[82] Cancer can occur in the brain as either a primary brain tumor (originating in brain tissue) or when cancer cells from other parts of the body spread (metastasize) to the central nervous system. Primary tumors can be either benign (non-cancerous) or malignant (cancerous). Both forms can be serious and life-threatening.

Benign brain tumors are usually not aggressive and do not generally invade surrounding tissue, but they can grow and damage normal brain tissue. Malignant primary brain tumors tend to grow faster and be more invasive than benign tumors. Among the many types of malignant primary brain tumors, glioblastoma multiforme (GBM) is the most common and aggressive form in adults. Patients with GBM have an average life-span of 14.6 months after diagnosis and a 5-year survival rate of less than 10 percent.[83,84,85,86]

Metastatic (secondary) brain tumors, which have spread from other parts of the body to the brain, are more common than primary brain tumors and may require different treatments. This report focuses on primary brain tumors.

The brain is among the most complex organs in the human body, and brain tumors can be extremely difficult to treat. We still know very little about what causes most brain tumors, which makes identifying therapeutic targets challenging. We are also limited in our ability to treat brain tumors with anti-cancer drugs because the body has a protective 'blood-brain barrier' designed to keep chemicals in the blood from getting into the brain. Many medicines, including some chemotherapy drugs, are not able to pass through the blood-brain barrier.[87]

Recent Progress

The treatment options for brain tumors often vary based on the specific location of the tumor, its size and type, patient age, and other factors. Surgery is often the first step in the treatment of brain tumors, followed by radiation and chemotherapy. For patients with certain types of tumors, including GBM, these treatments are limited in their effectiveness, often only relieving symptoms and slowing tumor progression.[88]

In recent years, researchers have begun developing novel strategies through advances in targeted therapies.[89] Tumors need increasing amounts of blood to continue to grow and spread. Angiogenesis inhibitors use a targeted approach to slow brain tumor growth by preventing new blood vessels from forming. One such treatment, bevacizumab, was approved by the FDA in 2009 for the treatment of GBM. This treatment, in combination with chemotherapy, helps to stop tumor growth after surgery.[90,91] Angiogenesis inhibitors are also being further explored for their potential to treat multiple tumors post-surgery as an adjuvant therapy.

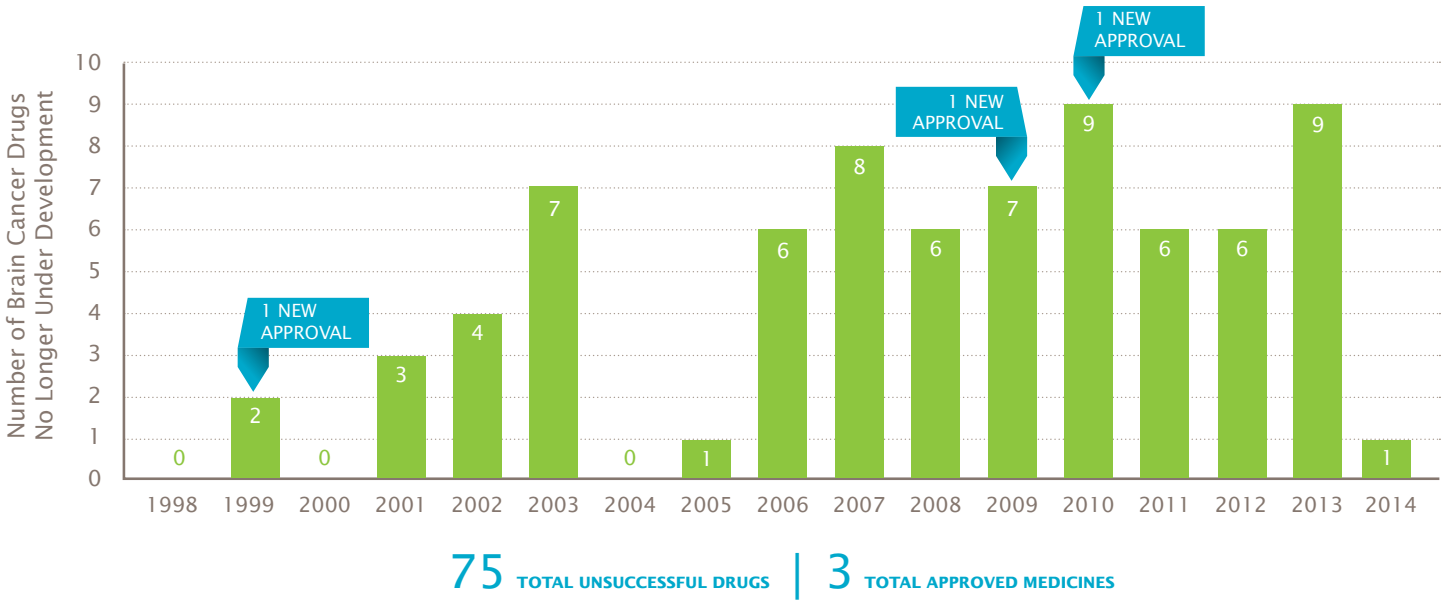
A second targeted therapy, everolimus, was approved by the FDA in 2010 to treat subependymal giant cell astrocytoma, a slow growing brain tumor. The drug targets a protein called mTOR that helps cells grow and divide. Like bevacizumab, this medicine may shrink or slow the growth of the tumor, but whether it extends survival is not yet clear.[92]

Building on Failures

Researchers continue on their search for effective new treatments for the more than 120 forms of brain cancer, but they face great challenges.[93] Since 1998, there have only been **3 new drug approvals** for brain cancer, while another **75 medicines** have failed in the development process having been discontinued, suspended, or had no development reported.[94] That is a **25:1 ratio** of unsuccessful attempts to FDA-approved medicines. Decades of research have provided limited treatment options for patients facing aggressive, late-stage forms of brain cancer. Although challenges persist, researchers continue to use past setbacks to inform future discoveries in brain cancer therapies.

Unsuccessful Brain Cancer Drugs in Development

1998-2014



75 TOTAL UNSUCCESSFUL DRUGS | **3** TOTAL APPROVED MEDICINES

Source: PhRMA analysis of Adis R&D Insight Database, 15 September 2014.

Looking Ahead

As we learn more about the brain and its functions, this knowledge can inform the development of targeted therapies to eliminate the disease. Scientists began mapping the genome of GBM in 2005, and successfully identified three key mutations associated with the growth and spread of GBM cancer cells in 2008.[95] In addition, nine genes have been identified that may predict the therapeutic response in GBM cells.[96]

"Brain cancer presents unique challenges for clinical trials. The incidence is fairly low (less than 2% of cancer cases worldwide), making patient enrollment a challenge."

— The Global Brain Cancer Alliance[97]

Further research into vaccines targeted to kill brain cancer cells as well as into growth-factor inhibitors (drugs targeted to stop the growth of cancer cells) offer promising innovations to more precisely treat brain tumors.[98] Nanotechnologies appear to be a potentially promising platform for helping anti-cancer agents pass through the blood-brain barrier and reach the tumor.[99]

Scientists continue to face challenges in developing medicines that treat and cure brain malignancies and prolong patient lifespans. Today, **47 medicines** are in development in the United States to fight brain cancer.[100] Given the complex nature of the brain, it is likely that setbacks in treatment advances will still occur but biomedical researchers will continue to apply what they learn to inform new methods of delivering treatments and the development of new targeted therapies.

"Glioblastoma multiforme is the most common and most aggressive type of malignant primary brain tumor, and patients have few treatment options and a five-year survival rate of less than 3 percent."

— Gary B. Gordon, M.D., Ph.D.
Vice President, Global Oncology Development, AbbVie Inc.[101]

Transforming Research Setbacks into New Hope for Patients

Today, we know more than ever before about the underlying causes of the many diseases that make up cancer. We have a better understanding of how cancer cells originate, grow, and spread on the molecular and cellular level. Biopharmaceutical research companies are using this knowledge to develop innovative therapies that improve the quality of life for patients, turn many cancers into manageable conditions, prevent cancers from occurring or recurring, and, in an increasing number of cases, cure patients of the disease.

As we have seen with some difficult-to-treat cancers, such as melanoma and lung cancer, only in recent years have we been able to translate scientific discoveries into promising new treatment options. In other areas, such as brain cancer, we still have much to learn in order to effectively treat patients and help them live longer and healthier lives.

Progress in our fight against cancer comes along with many disappointing roadblocks along the way, as researchers explore all potential avenues to medical progress. While many are aware of the successes that come out of research and development, less attention is paid to the so-called failures. However, researchers learn from each setback and use those findings to refine other lines of research, making them more likely to succeed. The nature and complexity of cancer and the development of new cancer drugs make finding treatments and cures difficult.

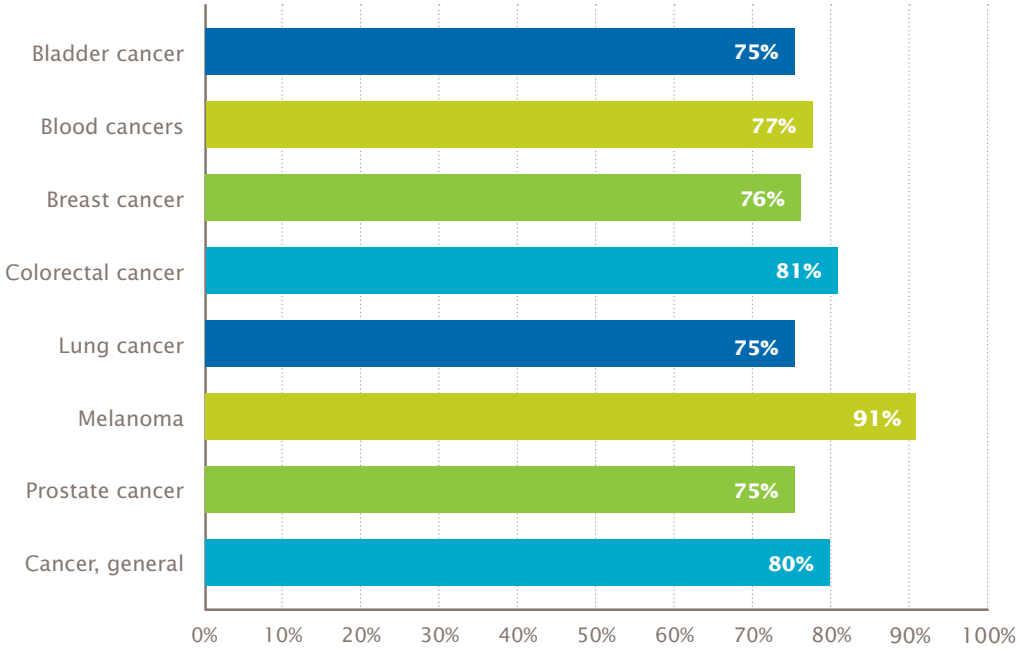
It is important to recognize that without continued research and the setbacks that accompany the successes, we would not realize the advances that we are seeing today against some of our most challenging cancers.

Today, we have **771 new medicines** in development to fight cancer.[102] These investigational drugs are as diverse as the types of cancer they are targeted to treat. Up to 80% have the potential to be first-in-class medicines, meaning they would represent novel approaches to combating cancer.[103] (See figure on page 22.)

The findings of this report illustrate the need for a robust research and development ecosystem to continue to explore the frontiers of scientific innovation and to find new ways to transform that knowledge into tomorrow's new treatments and cures. Public policies must foster an environment that supports continued innovation in cancer research and care. Accelerating the long and costly discovery and development process to deliver new medicines and potential cures to patients in need must be one of the nation's highest health priorities.

The Majority of Cancer Medicines in the Pipeline Have the Potential to Be First-in-Class

Percentage of Projects in Development that Are Potentially Novel Approaches in Selected Cancer Areas, 2011



Researchers are using novel approaches to attack cancer at the molecular level. An average of 80% of drugs in the oncology pipeline may be first-in-class medicines.

G. Long and J. Works. "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Boston, MA: Analysis Group, January 2013. Available at: http://www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf

"The history of scientific research assures that there will always be setbacks. At Astellas, we try to benefit from such setbacks to strengthen our resolve to provide patients, physicians, and caregivers around the world with better medicines. We strive to learn as much as we can from every experiment and apply those learnings to our future research. Over time this has yielded, and will continue to yield, substantial progress against cancer and the other challenging medical conditions we tackle."

— Stephen Eck, M.D., Ph.D.
Vice President, Oncology Medical Sciences, Astellas Pharma Global Development[104]

A note on methodology:

Data are drawn from the Adis R&D Insight database which compiles publicly available information on medicines in development. Projects were counted as "failures" and included in the analysis if they were categorized in the database as "suspended," "discontinued," or "no development reported" for the indication "melanoma," "brain cancer," or "lung cancer". Only projects in clinical development or Food and Drug Administration review were included. In cases where more than one delivery mechanism was tested or where the history included more than one category from our list (e.g., "no development reported" in 2006 and "suspended" in 2007) the latest date included was counted. Diagnostic imaging agents were excluded.

Adis' Definitions:

- ***Suspended:*** "This term is used when a company has suspended development of a drug, often in order to focus on the development of some other drug. Development has not been discontinued."
- ***Discontinued:*** "The company has chosen to stop development."
- ***No development reported:*** "If there has been no activity associated with a drug (no commercial information released, no recently published studies) for 18 months to 2 years, the term 'no development reported' is assigned. The time frame depends on the last phase of the drug. This is the term used until a drug is confirmed as discontinued, withdrawn or suspended, or activity is resumed."

According to correspondence with Adis R&D Insight database editors regarding "inactive" projects, they report that although exact percentages are not available, only a very small proportion of projects categorized as "no development reported" are reactivated and the majority go on to be "discontinued" after more time has elapsed. "No development reported" status is used when development goes silent and the editors see that no activity appears to be happening. They use the term "suspended" when a company states that it is suspending development for any reason. It is quite difficult to determine what percentage of these programs are reactivated because it depends whether another company picks up a license to develop it or whether the company itself will reactivate development at another stage. Generally when a company suspends development a very small percentage of drug programs are reactivated by the same company. A small percentage of suspended projects are out-licensed at which point the chances of reactivation become much higher. There is a very small percentage of discontinued programs that are reactivated.

The analysis goes back to 1998 as the Adis data is less comprehensive before this time. Data are current as of September 15, 2014.

References

1. American Cancer Society. "Cancer Facts and Figures 2014." Atlanta, GA: American Cancer Society; 2014. http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf
2. American Association for Cancer Research. AACR Cancer Progress Report 2013. Clini Cancer Res 2013; 19(Supplement1):S1-S88. http://cancerprogressreport.org/2013/Documents/2013_AACR_CPR_FINAL.pdf
3. American Association for Cancer Research. AACR Cancer Progress Report 2014. Clin Cancer Res 2014;20(Supplement 1):SI-S112 (Page 2). http://cancerprogressreport.org/2014/Documents/AACR_CPR_2014.pdf
4. American Society of Clinical Oncology. "The State of Cancer Care in America, 2014: A Report by the American Society of Clinical Oncology." Journal of Oncology Practice, 2014. http://jop.ascopubs.org/content/early/2014/03/10/JOP.2014.001386
5. American Cancer Society. "Cancer Treatment and Survivorship Facts & Figures 2014-2015." Atlanta: American Cancer Society; 2014. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-042801.pdf
6. American Cancer Society. "Cancer Treatment and Survivorship Facts & Figures 2012–2013." Atlanta, GA: American Cancer Society, 2013. http://www.cancer.org/Research/CancerFactsStatistics/cancer-treatment-survivorship-facts-figures.pdf
7. The White House. "Presidential Proclamation -- National Cancer Control Month." http://www.whitehouse.gov/the-press-office/2012/04/02/presidential-proclamation-national-cancer-control-month-2012
8. Smith B, et al. "Future of cancer incidence in the United States: burdens upon an aging, changing nation." J Clin Oncol 27:2758- 2765, 2009.
9. American Cancer Society. "Cancer Facts and Figures 2014." Atlanta, GA: American Cancer Society; 2014. http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf
10. National Cancer Institute. "NCI Dictionary of Cancer Terms." http://www.cancer.gov/dictionary?expand=C
11. Goss, T, et al. "Recognizing Value in Oncology Innovation." Boston Healthcare Associates, June 2012. http://www.phrma.org/sites/default/files/flash/phrma_innovation_oncology.pdf
12. DiMasi JA and Grabowaki HG. Economics of New Oncology Drug Development. Journal of Clinical Oncology. 2007, 25(2): 209-216.
13. Kean M, Lessor T (Eds). "Sustaining Progress Against Cancer in an Era of Cost Containment Discussion Paper." Cambridge, MA: Feinstein Kean Healthcare; June 2012. http://turningthetideagainstcancer.org/sustaining-progress-discussion-paper.pdf
14. American Association for Cancer Research. AACR Cancer Progress Report 2013. Clini Cancer Res 2013; 19(Supplement1):S1-S88. http://cancerprogressreport.org/2013/Documents/2013_AACR_CPR_FINAL.pdf
15. Mark R Lackner, Timothy R Wilson, Jeff Settleman. "Mechanisms of Acquired Resistance to Targeted Cancer Therapies." Future Oncol. 2012;8(8):999-1014. httpwww.medscape.com/viewarticle/769431

16. Burrell, R, et al. "The causes and consequences of genetic heterogeneity in cancer evolution." Nature 501, 338–345 (19 September 2013)
http://www.nature.com/nature/journal/v501/

17. Goss, T, et al. "Recognizing Value in Oncology Innovation." Boston Healthcare Associates, June 2012.
http://www.phrma.org/sites/default/files/flash/phrma_innovation_oncology.pdf

18. Goss, T, et al. "Recognizing Value in Oncology Innovation." Boston Healthcare Associates, June 2012.
http://www.phrma.org/sites/default/files/flash/phrma_innovation_oncology.pdf

19. PhRMA. "Cancer Medicines: Value in Context Cancer Chart Pack." Spring 2014.
http://www.phrma.org/sites/default/files/pdf/cancer-chart-pack-5-22-14.pdf

20. Forbes. "How We Can Pick Up The Pace In The Race To Cure Cancer."
http://www.forbes.com/sites/johnlechleiter/2012/09/19/how-we-can-pick-up-the-pace-in-the-race-to-cure-cancer/

21. American Cancer Society. "Cancer Treatment and Survivorship Facts & Figures 2014-2015." Atlanta: American Cancer Society; 2014.
http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-042801.pdf

22. National Cancer Institute. "Angiogenesis Inhibitors Fact Sheet."
http://www.cancer.gov/cancertopics/factsheet/Therapy/angiogenesis-inhibitors

23. American Association for Cancer Research. AACR Cancer Progress Report 2013. Clini Cancer Res 2013; 19(Supplement1):S1-S88.
http://cancerprogressreport.org/2013/Documents/2013_AACR_CPR_FINAL.pdf

24. American Society of Clinical Oncology. "Studies Reveal Potential New Targeted Therapies for Common, Hard-to-Treat Cancers."
http://www.asco.org/press-center/studies-reveal-potential-new-targeted-therapies-common-hard-treat-cancers

25. American Cancer Society. "Cancer Immunotherapy."
http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/immunotherapy/immunotherapy-types

26. National Cancer Institute. "Cancer Vaccines Fact Sheet."
http://www.cancer.gov/cancertopics/factsheet/Therapy/cancer-vaccines

27. National Cancer Institute. "Cancer Vaccines Fact Sheet."
http://www.cancer.gov/cancertopics/factsheet/Therapy/cancer-vaccines

28. National Cancer Institute. "Targeted Cancer Therapies Fact Sheet."
http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted

29. National Cancer Institute. "Biological Therapies for Cancer Fact Sheet."
http://www.cancer.gov/cancertopics/factsheet/Therapy/biological

30. Pfizer. "Pfizer And Merck To Collaborate On Innovative Anti-Cancer Combination Studies." Press Release: February 5, 2014.
http://www.pfizer.com/sites/default/files/partnering/recent_partnership/Pfe%20Merck%20Collaboration%20Release%202-5-2014.pdf

31. Personalized Medicine Coalition. "The Case for Personalized Medicine: 4th Edition." Washington, DC: PMC.
http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/pmc_case_for_personalized_medicine.pdf

32. Personalized Medicine Coalition. "Personalized Medicine by the Numbers." Washington, DC: PMC: 2014. http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/pmc_personalized_medicine_by_the_numbers.pdf

33. Tufts Center for the Study of Drug Development. "Personalized Medicine Is Playing a Growing Role in Development Pipelines." Impact Report. 2010; 12(6). http://csdd.tufts.edu/files/uploads/nov-dec_ir_report_summary.pdf

34. National Foundation for Cancer Research. "Cure Brain Cancer International Scientific Meeting 2014." http://www.nfcr.org/cure-brain-cancer-international-scientific-meeting-2014

35. Journal of Clinical Oncology. "Clinical Cancer Advances 2013: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology." http://jco.ascopubs.org/content/early/2013/

36. Skin Cancer: Quick Facts. Surgeon General. http://www.surgeongeneral.gov/library/calls/prevent-skin-cancer/fact-sheet.html

37. National Cancer Institute. "Melanoma Treatment PDQ®." http://www.cancer.gov/cancertopics/pdq/treatment/melanoma

38. Centers for Disease Control and Prevention. "The Surgeon General's Call to Action to Prevent Skin Cancer." http://www.surgeongeneral.gov/library/calls/prevent-skin-cancer/index.html.

39. Centers for Disease Control and Prevention. "The Surgeon General's Call to Action to Prevent Skin Cancer, Executive Summary." http://www.surgeongeneral.gov/library/calls/prevent-skin-cancer/exec-summary.html#ref11

40. American Cancer Society. "Melanoma Skin Cancer." http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-survival-rates

41. S. Bhatia, S.S. Tykodi, J.A. Thompson, "Treatment of Metastatic Melanoma: An Overview", Oncology, 2009; 23(6), 488-496. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2737459/pdf/nihms129601.pdf

42. Korn, E. L., Saxman, S., Chapman, J. W., Lee, S. J., Liu, P., Kirkwood, J. M., et al. (2008). Meta-Analysis of Phase II Cooperative Group Trials in Metastatic Stage IV Melanoma to Determine Progression-Free and Overall Survival Benchmarks for Future Phase II Trials. Journal of Clinical Oncology, 26(4), 527-534.

43. Adis R&D Insight Database, 15 September 2014

44. American Cancer Society. "Melanoma Skin Cancer." http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-survival-rates

45. Pfizer. "Pfizer And Merck To Collaborate On Innovative Anti-Cancer Combination Studies." Press Release. February 5, 2014. http://www.pfizer.com/sites/default/files/partnering/recent_partnership/Pfe%20Merck%20Collaboration%20Release%202-5-2014.pdf

46. American Association for Cancer Research, AACR Cancer Progress Report 2013. Clini Cancer Res 2013; 19(Supplement1):S1-S88. http://cancerprogressreport.org/2013/Documents/2013_AACR_CPR_FINAL.pdf

47. Food and Drug Administration, "FDA Approves New Treatment for a Type of Late-Stage Skin Cancer," 25 March 2011. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm1193237.htm

48. Food and Drug Administration, "FDA Approves Keytruda for Advanced Melanoma," 4 September 2014. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm412802.htm

49. P. Loftus, "FDA Approves Merck's New-Wave Cancer Drug," Wall Street Journal, 4 September 2014. http://online.wsj.com/articles/fda-approves-mercks-cancer-drug-1409856320

50. N. Osterweil. "Internal Medicine News Digital Network High rate of durable responses to pembrolizumab in metastatic melanoma." http://www.internalmedicinenews.com/home/article/high-rate-of-durable-responses-to-pembrolizumab-in-metastatic-melanoma/2ee0a6381e4207d641c36befc87299e0.html

51. American Association for Cancer Research. AACR Cancer Progress Report 2013. Clini Cancer Res 2013; 19(Supplement1):S1-S88. http://cancerprogressreport.org/2013/Documents/2013_AACR_CPR_FINAL.pdf

52. American Association for Cancer Research. AACR Cancer Progress Report 2014. Clin Cancer Res 2014;20(Supplement 1):SI-S112 http://cancerprogressreport.org/2014/Documents/AACR_CPR_2014.pdf

53. Adis Insight database, 22 September 2014.

54. G. Long and J. Works. "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Boston, MA: Analysis Group, January 2013. http://www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf

55. Melanoma Research Foundation. "Mission of the MRFBC." http://www.melanoma.org/research-center/research-initiatives/mrfbc/mission-of-the-mrfbc

56. National Institutes of Health. "Treatment of Metastatic Melanoma: An Overview." Oncology, 2009; 23(6), 488-496. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2737459/pdf/nihms129601.pdf

57. American Cancer Society. "What are the key statistics about lung cancer?" http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-key-statistics

58. National Cancer Institute. "Surveillance, Epidemiology, and End Results Program. Turning Cancer Data Into Discovery. Cancer of the Lung and Bronchus." http://seer.cancer.gov/statfacts/html/lungb.html

59. American Cancer Society. Cancer Facts and Figures 2013. Atlanta, GA: American Cancer Society; 2013. Atlanta, GA: American Cancer Society; 2013. http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/2013-cancer-facts-and-figures.pdf

60. American Society of Clinical Oncology. Progress & Timeline. "Timeline: Lung Cancer." http://cancerprogress.net/timeline/lung-cancer

61. American Cancer Society. "What is non-small cell lung cancer?" http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-what-is-non-small-cell-lung-cancer

62. American Cancer Society. "What is small cell lung cancer?" http://www.cancer.org/cancer/lungcancer-smallcell/detailedguide/small-cell-lung-cancer-what-is-small-cell-lung-cancer

63. Cancer.Net. "Lung Cancer: Treatment Options." http://www.cancer.net/cancer-types/lung-cancer/treatment-options?sectionTitle=Treatment

64. American Association for Cancer Research. AACR Cancer Progress Report 2013. Clini Cancer Res 2013; 19(Supplement1):S1-S88.
http://cancerprogressreport.org/2013/Documents/2013_AACR_CPR_FINAL.pdf

65. American Cancer Society. "Lung Cancer (Non-Small Cell)."
http://www.cancer.org/acs/groups/cid/documents/webcontent/003115-pdf.pdf

66. U.S. Food and Drug Administration. News & Events. "FDA Approves New Combination Therapy for Lung Cancer."
http://www.fda.gov/newsevents/newsroom/pressannouncements/2006/ucm108766.htm

67. U.S. Food and Drug Administration. News & Events. "FDA approves first companion diagnostic to detect gene mutation associated with a type of lung cancer."
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm352230.htm

68. American Society of Clinical Oncology. "Chemotherapy for Lung Cancers: Here to Stay."
http://meetinglibrary.asco.org/content/11400375-144

69. American Association for Cancer Research. AACR Cancer Progress Report 2014. Clin Cancer Res 2014;20(Supplement 1):S1-S124.

70. Massachusetts General Hospital. "New drug successfully treats crizotinib-resistant, ALK-positive lung cancer." Massachusetts General Hospital, Boston, MA.
http://www.massgeneral.org/about/pressrelease.aspx?id=1689

71. American Society of Clinical Oncology. Progress & Timeline. "Timeline: Lung Cancer."
http://cancerprogress.net/timeline/lung-cancer

72. American Cancer Society. "Lung Cancer (Non-Small Cell)."
http://www.cancer.org/acs/groups/cid/documents/webcontent/003115-pdf.pdf

73. American Association for Cancer Research, AACR Cancer Progress Report 2013. Clini Cancer Res 2013; 19(Supplement1):S1-S88.
http://cancerprogressreport.org/2013/Documents/2013_AACR_CPR_FINAL.pdf

74. American Cancer Society. "Lung Cancer (Non-Small Cell)."
http://www.cancer.org/acs/groups/cid/documents/webcontent/003115-pdf.pdf

75. Nano. "What is Nanotechnology?"
http://www.nano.gov/nanotech-101/what/definition

76. American Association for Cancer Research. AACR Cancer Progress Report 2013. Clini Cancer Res 2013; 19(Supplement1):S1-S88.
http://cancerprogressreport.org/2013/Documents/2013_AACR_CPR_FINAL.pdf

77. PhRMA Analysis of Adis R&D Insight Database, 27 September 2014.

78. I.Petak, et al., "Integrating Molecular Diagnostics into Anticancer Drug Discovery," Nature Reviews Drug Discovery,July 2010: 9, 523-535.
http://www.nature.com/nrd/journal/v9/n7/full/nrd3135.html

79. B.Vogelstein, "Cancer Genome Landscapes," Science, March 2013: 339 (6127), 1546-1558.
http://www.ncbi.nlm.nih.gov/pubmed/23539594

80. American Association for Cancer Research. AACR Cancer Progress Report 2013. Clini Cancer Res 2013; 19(Supplement1):S1-S88.
http://cancerprogressreport.org/2013/Documents/2013_AACR_CPR_FINAL.pdf

81. ArQule, Inc. "ArQule and Daichi Sankyo Announce Completion of Patient Recruitment in Phase 3 Clinical Trial of Tivantinib in Non-Small Cell Lung Cancer." http://dsi.com/documents/10710/10995/ArQule+and+Daiichi+Sankyo+Announce+Completion+of+Patient+Recruitment+in+Phase+3+Clinical+Trial+of+Tivantinib+in+Non-Small+Cell+Lung+Cancer/24b8d148-e1ee-47f8-bb71-954495a4588e?version=1.0&WT.z_oss_s=1

82. American Cancer Society. "ACS Fact Sheet, Brain and Spinal Cord Tumors in Adults." http://www.cancer.org/acs/groups/cid/documents/webcontent/003088-pdf.pdf

83. Wainwright, D. A., Nigam, P., Thaci, B., Dey, M., & Lesniak, M. S. (2012). Recent developments on immunotherapy for brain cancer. Expert Opinion on Emerging Drugs, 17(2), 181-202. http://www.ncbi.nlm.nih.gov/pubmed/22533851

84. American Cancer Society. "What are adult brain and spinal cord tumors?" http://www.cancer.org/cancer/braincnstumorsinadults/detailedguide/brain-and-spinal-cord-tumors-in-adults-what-are-brain-spinal-tumors

85. The Cancer Genome Atlas. "Glioblastoma Multiforme." http://cancergenome.nih.gov/cancersselected/glioblastomamultiforme

86. American Brain Tumor Association. "Malignant and Benign Brain Tumors." http://www.abta.org/brain-tumor-information/diagnosis/malignant-benign-brain-tumors.html

87. American Cancer Society. "How are brain and spinal cord tumors in adults treated?" http://www.cancer.org/cancer/braincnstumorsinadults/detailedguide/brain-and-spinal-cord-tumors-in-adults-treating-general-info

88. American Cancer Society. "ACS Fact Sheet, Brain and Spinal Cord Tumors in Adults." http://www.cancer.org/acs/groups/cid/documents/webcontent/003088-pdf.pdf

89. MD Anderson Cancer Center. "Q&A: Understanding glioblastoma – Cancerwise." http://www2.mdanderson.org/cancerwise/2013/04/qa-understanding-glioblastoma.html

90. American Cancer Society. "Surgery for adult brain and spinal cord tumors." http://www.cancer.org/cancer/braincnstumorsinadults/detailedguide/brain-and-spinal-cord-tumors-in-adults-treating-surgery

91. American Cancer Society. "ACS Fact Sheet, Brain and Spinal Cord Tumors in Adults." http://www.cancer.org/acs/groups/cid/documents/webcontent/003088-pdf.pdf

92. American Society of Clinical Oncology. Progress & Timeline. "Timeline: Brain Cancer." http://www.cancerprogress.net/timeline/brain-cancer

93. American Cancer Society. "Targeted therapy for adult brain and spinal cord tumors." http://www.cancer.org/cancer/braincnstumorsinadults/detailedguide/brain-and-spinal-cord-tumors-in-adults-treating-targeted-therapy

94. PhRMA Analysis of Adis R&D Insight Database, 15 September 2014.

95. American Society of Clinical Oncology. Progress & Timeline. "Timeline: Brain Cancer." http://www.cancerprogress.net/timeline/brain-cancer

96. American Society of Clinical Oncology. Progress & Timeline. "Timeline: Brain Cancer." http://www.cancerprogress.net/timeline/brain-cancer

97. National Foundation for Cancer Research. "The Global Brain Cancer Alliance (TGBCA)." http://www.nfcr.org/tgbca

98. American Cancer Society. "ACS Fact Sheet, Brain and Spinal Cord Tumors in Adults." http://www.cancer.org/acs/groups/cid/documents/webcontent/003088-pdf.pdf

99. Kewal K Jain. "Nanobiotechnology-Based Strategies for Crossing the Blood–Brain Barrier Nanomedicine." 2012;7(8):1225-1233. http://www.medscape.com/viewarticle/770396_5

100. Adis R&D Insight Database, 27 September 2014.

101. AbbVie. "AbbVie Presents Results from Study of Investigational Compound in Patients with Glioblastoma at the American Society of Clinical Oncology's 50th Annual Meeting." http://abbvie.mediaroom.com/2014-05-30-AbbVie-Presents-Results-from-Study-of-Investigational-Compound-in-Patients-with-Glioblastoma-at-the-American-Society-of-Clinical-Oncologys-50th-Annual-Meeting

102. PhRMA. "Medicines in Development for Cancer." 2012. http://www.phrma.org/sites/default/files/pdf/phrmamedicinesindevelopmentcancer2012.pdf

103. G. Long and J. Works. "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Boston, MA: Analysis Group, January 2013. http://www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf

104. Interview with Stephen Eck, M.D., Ph.D. September 2014.

105. National Cancer Institute. "NCI Director John E. Niederhuber's Address to the American Association for Cancer Research on Plan to Accelerate Cancer Research" http://www.cancer.gov/newscenter/qa/2009/aacrspeech2009qa

"Cancer is, after all, an old problem, and it is the nature of science to move judiciously and incrementally. Yet, today's pace of discovery — of the genetic basis of disease — is unfolding at a rate never before envisioned. Even so, we must be mindful that our task is far from complete. Patients still need answers. Patients still need better treatments, better prevention, and better early detection. We must recommit ourselves to answering that call."

— John E. Niederhuber, M.D.
Director, National Cancer Institute (2006-2010)[105]

PhRMA

RESEARCH • PROGRESS • HOPE

www.PhRMA.org

950 F Street, NW, Washington, DC 20004