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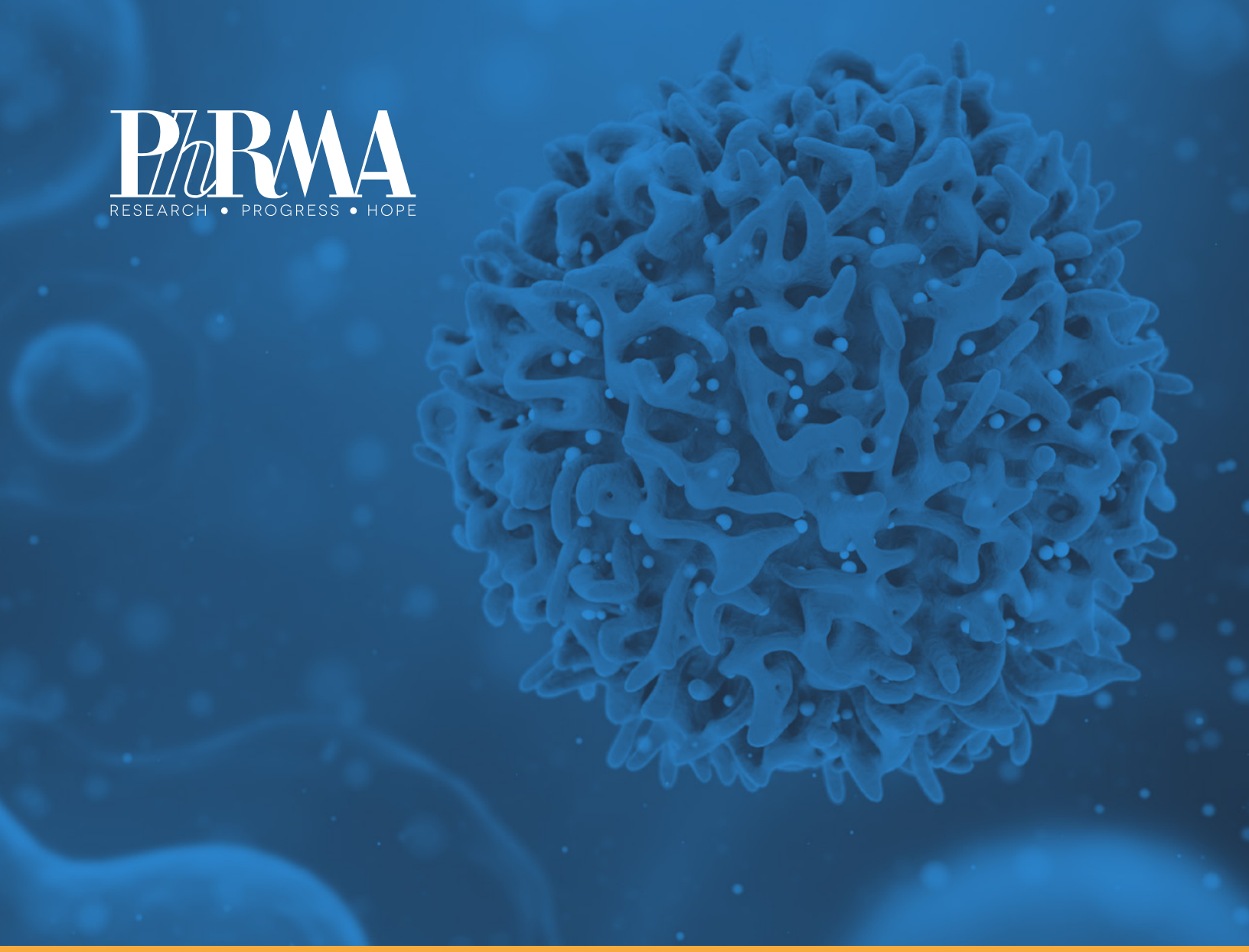

Researching Cancer Medicines

Setbacks and Stepping Stones

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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. The advances in research and treatment options seen in recent years have made great progress toward improved prevention, earlier diagnoses, and better outcomes for many cancers. However, there is still tremendous unmet medical need. The more we discover about the hundreds of diseases that we now know make up cancer, the more complexity and challenges 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 investigational medicines that fail. The biopharmaceutical pipeline includes many of these so-called "failures" which should more appropriately be considered setbacks. The nature of conducting research in areas of high scientific complexity and regulatory uncertainty is that failure is inevitable. The knowledge gained help inform future research and development projects, including new therapeutic strategies and potential treatment combinations.

Analysis of nine different cancers – ***malignant melanoma, brain cancer, acute myeloid leukemia, kidney cancer, liver cancer, lung cancer, pancreatic cancer, ovarian cancer*** **and** ***prostate cancer*** – shows just how challenging the process can be. Since 1998, there have been many unsuccessful attempts and also some triumphs with medicines beating the odds and garnering approval by the Food and Drug Administration:

- 158 drug failures, 12 approvals to treat malignant melanoma
- 122 drug failures, 3 approvals to treat brain cancer
- 91 drug failures, 7 approvals to treat acute myeloid leukemia
- 96 drug failures, 11 approvals to treat kidney cancer
- 73 drug failures, 5 approvals to treat liver cancer
- 268 drug failures, 32 approvals to treat lung cancer (51 failures, 4 approvals for small-cell lung cancer)
- 131 drug failures, 7 approval to treat pancreatic cancer
- 139 drug failures, 13 approvals to treat ovarian cancer
- 237 drug failures, 21 approvals to treat prostate cancer

While these numbers cannot be extrapolated into success rates that predict future odds, they do give a sense of the magnitude of the complexities. These numbers underscore the hurdles inherent in the process, as well as the progress represented by new treatments that emerge from years of research and setbacks. Many of these medicines target the root cause of cancers at the molecular level, some harness the body's immune system to attack cancer cells, while some work in conjunction with other medicines to unlock new progress.

Although cancer continues to be a major challenge, biopharmaceutical companies have over 1,100 potential cancer medicines in development and are dedicated to transforming cancer from a devastating diagnosis to a chronic, manageable condition. This goal drives researchers past the setbacks to discover how to apply the knowledge gained to inform the development of innovative medicines that bring hope to patients and their families and ultimately win the battle against cancer.

Introduction

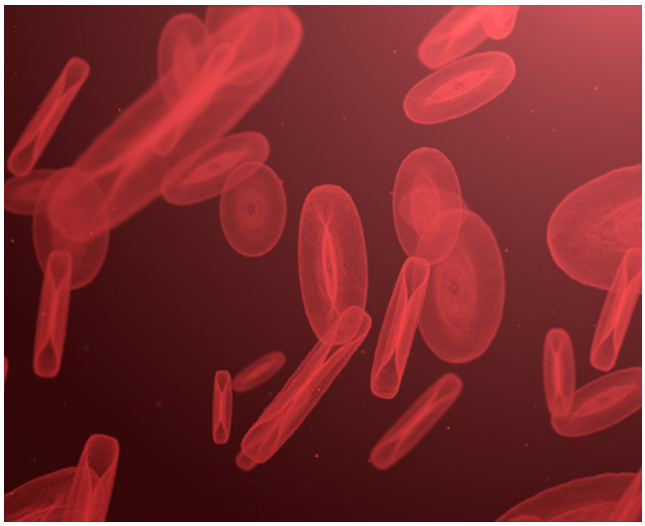
Remarkable advances in cancer medicines are ushering in a new era for patients. Today, thanks to America's biopharmaceutical researchers' relentless work developing new treatment options, the outlook for cancer patients is brighter than it has ever been. While we have come far in the fight against cancer, for many of the difficult-to-treat and very rare forms we are still in need of new and better options to deliver hope to patients and allow them to live longer, healthier lives.

From unlocking the secrets of the human genome to understanding the causes and progression of cancer at the molecular and cellular level, advances in medical research have led to a more fulsome understanding of cancer and enabled innovative new treatments. But the countless benefits to cancer patients provided by these breakthroughs in treatment would not be possible without the advances in understanding provided for by the many, inevitable so-called "failures" or setbacks along the way. Research setbacks are a critical part of the cancer research and development process allowing researchers to gain much-needed knowledge about the disease and informing future areas of research. The learnings from unsuccessful research efforts are integral to informing the next breakthrough treatment.

40% **of U.S. males will be diagnosed with cancer in their lifetime.[1]**

39% **of U.S. women will be diagnosed with cancer in their lifetime.[2]**

20% **of deaths in the United States are due to cancer.[3]**



This report highlights the human and societal 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 a range of cancers — ***malignant melanoma, brain cancer, acute myeloid leukemia, kidney cancer, liver cancer, lung cancer, pancreatic cancer, ovarian cancer and prostate cancer*** — and we discuss how setbacks have informed new treatment advances and contributed to improving outcomes for patients.

The Human and Societal Burden

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

This year alone, more than 1.8 million people in the United States will be told, "You have cancer," and more than 600,000 are expected to die from the disease.[4] It is the second leading cause of death in the United States and as the population continues to age the annual number of cancer diagnoses and deaths will rise.[5]

Due to earlier detection and new treatments, along with successful efforts to reduce smoking, meaningful progress has been made in the fight against cancer. Since peaking in 1991, cancer death rates in the U.S. have declined by 29%, which translates into more than 2.9 million avoided cancer deaths.[6] According to the most recent data, between 2016 and 2017 alone, death rates declined by 2.2%, the largest single-year drop ever recorded.[7] Notably, the steepest declines in cancer deaths in recent years have occurred in areas where there have been significant treatment advances—including in melanoma and lung cancer.

"The accelerated drops in lung cancer mortality as well as in melanoma that we're seeing are likely due at least in part to advances in cancer treatment over the past decade, such as immunotherapy. They are a profound reminder of how rapidly this area of research is expanding, and now leading to real hope for cancer patients."

William G. Cance, MD, Chief Medical and Scientific Officer, American Cancer Society[8]

The number of cancer survivors has increased by an estimated 1.4 million over the last three years, with more than 16.9 million U.S. adults and children currently living with a history of cancer.[9] However, the number of treatment advances varies widely across cancer types and there remain substantial unmet medical needs. With an expected increase in new cancer cases of 45% by 2040, the demand for cancer prevention, screening, and treatment services as well as the overall costs to care for the growing number of patients are projected to dramatically increase.[10]

Today the direct medical costs of cancer care are estimated at $80.2 billion in the U.S. annually. And the indirect costs of lost productivity each year due to cancer-related mortality include $94.4 billion in lost earnings.[11] With cancer incidence expected to increase, these costs underscore not only the need for new treatments but for earlier diagnosis and treatment to head off these costs in the years ahead.

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.

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 cancers based on cellular and molecular characteristics. The ability to identify particular cancers in scientifically and clinically meaningful ways lays the groundwork for the hurdle ahead: researching and developing new medicines that will be safe and effective in treating those cancers.

For some cancers, the basic scientific understanding of their root causes provides researchers with better targets for discovering and developing medicines, particularly in 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 molecular driver could allow the cancer to develop resistance. This is just one example of why the development of effective medicines is extremely challenging.

While there has been enormous progress in understanding many cancers and the underlying biology which drive them, 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.

Challenges in Developing Cancer Medicines

The complexity of cancer is reflected in the drug development process. Researchers face many unique and daunting challenges in developing medicines to treat the myriad forms of cancer, as they often find ways to evade the immune system and mutate to resist treatments.

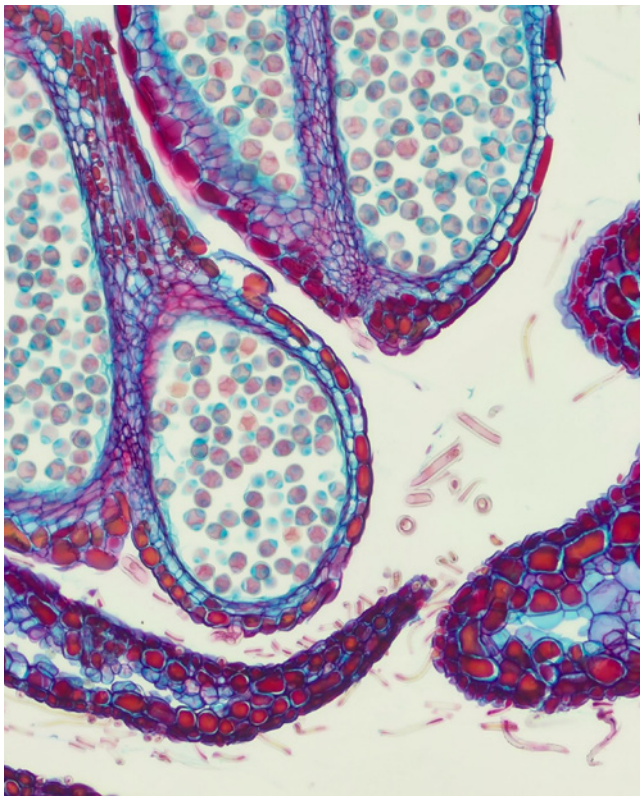
Researchers continue to face substantial scientific challenges in the pursuit of new cancer medicines for many reasons. For example:

- To have a comprehensive view of how a particular cancer develops and progresses researchers must 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.[12] [13]
- 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.[14]
- 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.[15]

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 more accurate diagnosis, 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 complex and life-threatening diseases, investigational therapies are usually 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 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.[16]

Even after approval, research continues throughout the lifecycle 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.[17] For example, the American Association of Cancer Research found that while the FDA approved 17 new cancer treatments between August 1, 2018 and July 31, 2019, they also expanded approvals for 10 previously approved cancer treatments in additional types of cancer.[18] These subsequent approvals are often first-time treatments or even breakthrough options for many cancer patients, highlighting the tremendous value resulting from ongoing research post-FDA approval.

Today's Treatments for Cancer

The arsenal of treatment options for cancers has expanded in recent years, however the availability of new treatments varies greatly depending on the type of cancer. While treatments for some cancers are considered curative, treatment approaches for other cancers do little to extend life.

A remarkable increase in our understanding of the biology of cancer as well as expanded research on the application of existing medicines in a broad range of cancers has enabled a shift away from a one-size-fits all approach to treatment. Today patients have a range of options available to tackle the individual drivers of his or her form of cancer, which increasingly include the genetic characteristics. While chemotherapy, radiation, and surgery are still the hallmarks of first-line treatment across many cancers, recently, new approaches are becoming more common and offering exciting and innovative ways to fight the disease. For example:

Targeted Therapies

The goal of targeted therapies, which specifically target the molecules that influence cancer cell proliferation, is to more effectively fight tumors with fewer side effects. Relative to chemotherapies – which indiscriminately target all rapidly dividing cells in the body – targeted therapies are often more precise in approach. As one example, antibody drug conjugates are a form of targeted therapy which can deliver a previously broadly delivered chemotherapeutic agent directly to the tumor site via a tumor-specific antibody. This approach can provide patients with more effective treatment and fewer side effects.

Targeted therapy is a broad category that includes a range of medicines that address the molecular underpinnings of the cancer and its immediate environment. These approaches have reached an exciting new era with the application of testing for tumor mutations and biomarkers. Understanding the mechanisms driving cancers associated with genetic mutations have resulted in a wide range of new therapies that are producing meaningful results for patients. For example, as we explore later in the report, new treatments have helped improve the outlook for patients by targeting the BRAF gene in some metastatic melanoma patients and the ALK and EGFR gene mutations in some lung cancer patients.[19] These are just a few examples of tremendous progress that has been made against several forms of cancer.

Targeted therapies can work in several ways including:[20]

- Blocking or turning off signals that tell cancer cells to grow and replicate,
- Preventing cancer cells from living longer than usual,
- Destroying cancer cells.

In recent years, the FDA has approved three therapies that are targeted towards a specific genetic change across any cancer, rather than in a specific type of cancer. These approvals, known as tissue-agnostic therapies, serve as evidence of the tremendous progress made in understanding the underlying biology of cancer as well as the genetic drivers of cancer cell growth. Because these therapies are approved in adults and children with a specific genetic biomarker (a measurable substance in the body that indicates the presence of disease), rather than the tissue in which the cancer originated, they provide hope to patients with a wide range of cancers.*

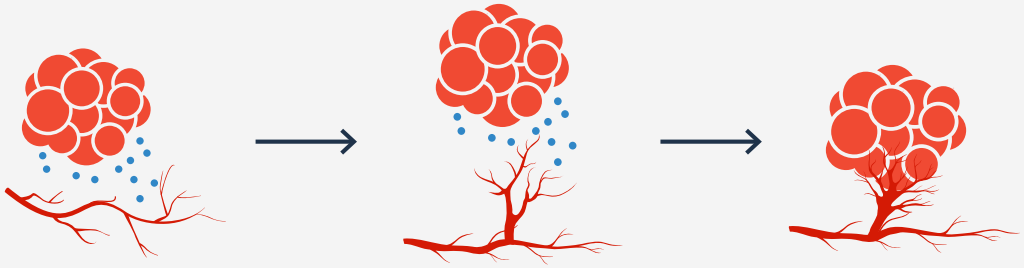
* Note that tissue-agnostic treatments are not included in the data on recent approvals and unsuccessful investigational therapies presented in this report as the search criteria were based on individual cancers, and tissue-agnostic threatments, by definition, cut across various types of cancer when defined by tissue of origin.

Angiogenesis Inhibitors

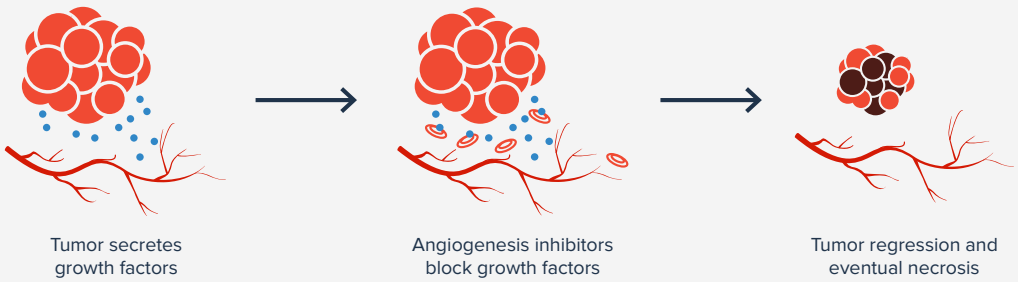
The development of angiogenesis inhibitors has advanced significantly since their introduction in 2004. These medicines are a type of targeted therapy that block the development of new blood vessels. Unlike most cancer medicines, angiogenesis inhibitors do not stop or slow the growth of cancer cells directly. Instead they work on the tumor's microenvironment – the area surrounding the tumor including blood vessels and immune cells with which the tumor interacts extensively. Angiogenesis inhibitors impede the formation of new blood vessels preventing tumors from growing beyond a few millimeters and spreading throughout the body. Angiogenesis inhibitors have therefore been found to be effective across a wide range of cancers.

How Angiogenesis Inhibitors Work

Tumors promote blood vessel formation, or angiogenesis...



Angiogenesis inhibitors block this process



Adapted from LUNGevity Lung Cancer 101: https://lungevity.org/for-patients-caregivers/lung-cancer-101/treatment-options/angiogenesis-inhibitors

In 2019 scientists received the Nobel Prize in Physiology or Medicine for research on how cells sense and adapt to oxygen needs. One of the recipients, William G. Kaelin, Jr, cited the potential development of angiogenesis inhibitors as a motivation for his research which began in the early 1990s. According to Dr. Kaelin, at the time there was a lot of speculation that, "angiogenesis inhibitors might be the cure to cancer." He added, "I always liked the idea, but I thought we first had to understand the molecular circuits that controlled angiogenesis so that we could create drugs with defined mechanisms of action."[21]

While this class of cancer treatment has been available for more than a decade, researchers are continuing to research the benefit of these drugs in additional types of cancer and in combination with other treatments. For example, research is under way with medicines previously approved by the FDA to determine if and how angiogenesis inhibitors can improve outcomes in combination with other cancer therapies, including immunotherapies like immune checkpoint inhibitors.[22] [23]

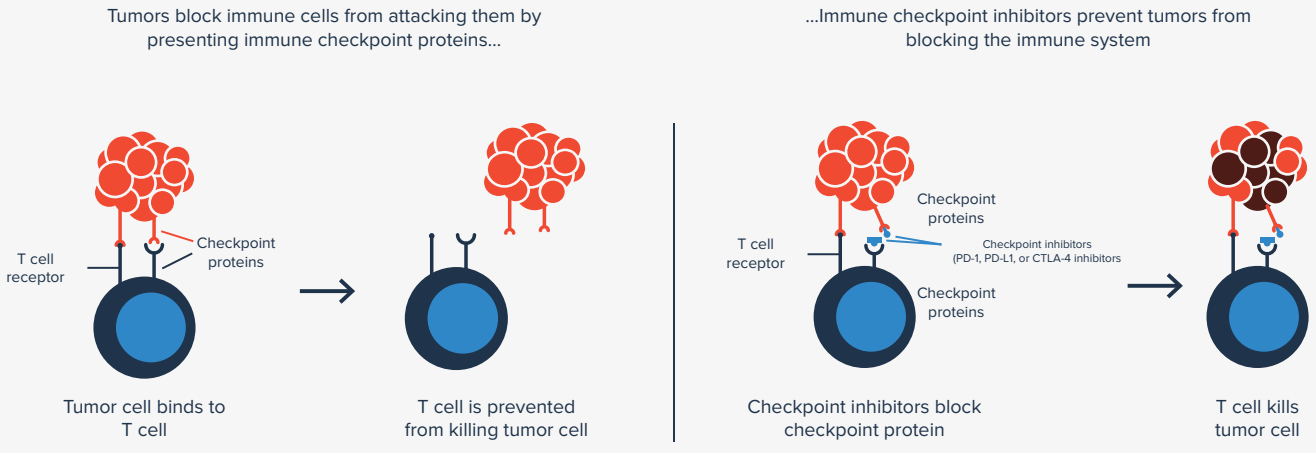
Immunotherapy

Immunotherapy represents another entirely new approach to treating cancer that has been transforming treatment for many cancer patients in recent years. This approach harnesses or unleashes the body's own powerful immune system to target and kill cancer cells. For some patients, immunotherapies have resulted in remarkable improvements that last over time, generating considerable excitement around the promise of these therapies.[24]

Cancer cells can produce proteins called immune checkpoints, which help the cancer evade the immune system. Immune checkpoint inhibitors are immunotherapies that these block these proteins to trigger the development and activation of immune cells that have the capability to attack cancer cells. In recent years, immune checkpoint inhibitors became available to patients, targeting various checkpoints such as PD-1, PD-L1 and CTLA-4. The first checkpoint inhibitor was approved to treat melanoma in 2011 and subsequently this class of medicines has proven effective in a range of cancers, many of which are featured throughout this report.[25]

How Checkpoint Inhibitors Work

Main subtypes include PD-1, PD-L1, or CTLA-4 inhibitors



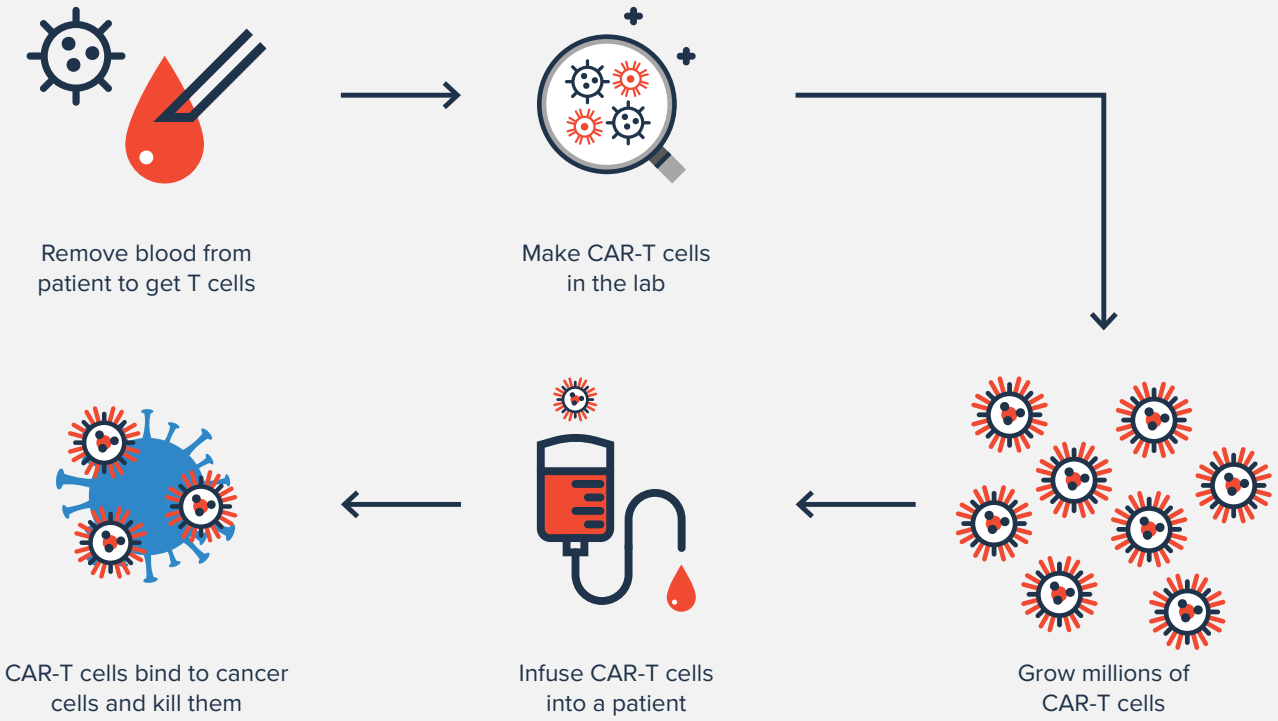
Adapted from FDA "Impact Story: Determining the Clinical Benefit of Treatment Beyond Progression with Immune Checkpoint Inhibitors": https://www.fda.gov/drugs/regulatory-science-action/impact-story-determining-clinical-benefit-treatment-beyond-progression-immune-checkpoint-inhibitors

Another promising area of immunotherapy is CAR-T cell therapy, using a patient's own modified immune cells to treat cancer. T-cells are separated from patient blood samples and genetically engineered to produce specialized receptors on their cell surface. These receptors, called chimeric antigen receptors (CAR), provide T-cells with the capability to recognize and attack tumor cells with specific proteins called antigens on their surfaces. These potent CAR-T cells are modified and duplicated outside the body and infused into the patient, where they recognize and kill cancer cells.

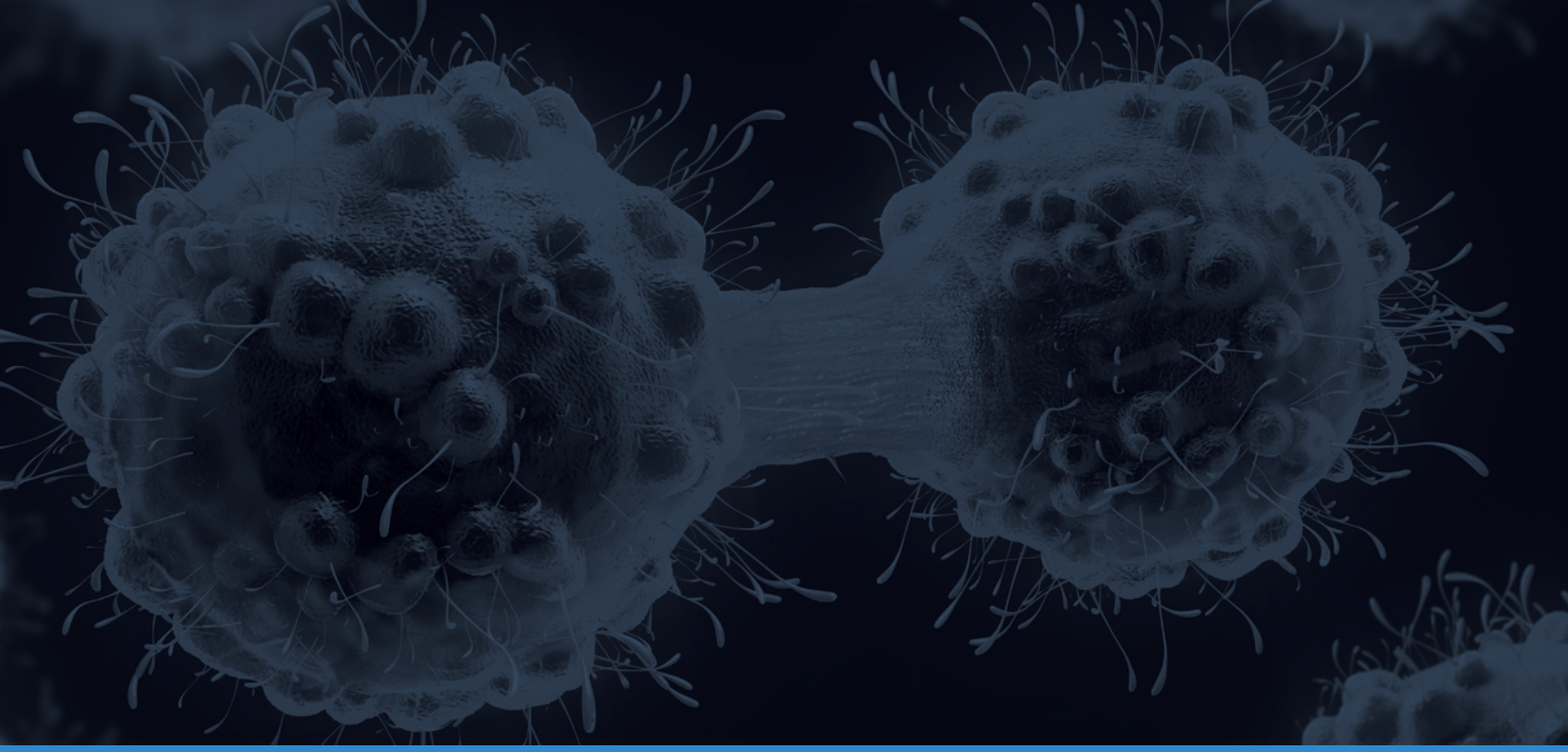
As CAR-T cell therapy involves genetic alterations and the infusion or transplantation of whole cells into the body in order to treat disease, it is also part of a broader cutting-edge field known as cell and gene therapy. Though these therapies are currently being explored for a broad range of diseases—often genetic or inherited conditions—CAR-T cell therapy was the first to be approved by the FDA as a cancer treatment.

The first two CAR-T cell therapies were approved in 2017 for children with acute lymphoblastic leukemia and adults with advanced lymphomas. Extensive research is underway to expand use into more patients and other types of cancer. The development of CAR-T cell therapy has been groundbreaking for many areas of treatment, and research is ongoing to make the therapy more readily available. In addition to investigating new areas of treatment, biopharmaceutical researchers are developing innovative manufacturing processes to cut down the time it takes to produce CAR-T cells from several weeks to now less than 7 days.[26]

How CAR-T Therapy Works



Adapted from NIH, National Cancer Institute, "T-Cell Transfer Therapy":
https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/t-cell-transfer-therapy



Personalized Medicine: A New Mainstay for Treating Many Cancers

Personalized medicine has become an important tool in cancer care, and many innovative types of medicines for treating cancers are personalized, including several targeted therapies and immunotherapies. This approach to treatment – also known as precision medicine – uses diagnostic tools to identify genetic mutations, the presence of proteins, or other molecules that relate to the disease, called biomarkers. Using these tests, clinicians can assess which medical treatments and procedures will be best for each patient. Personalized medicine helps to 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 health care continues to rise, personalized medicine helps to make the health care system more efficient, getting the right treatment to the right patient at the right time, reducing unnecessary treatments and improving outcomes.[27]

The role of personalized medicine is growing, with more than one in every four medicines granted FDA approval in the last six years classified as a personalized medicine, according to the Personalized Medicine Coalition. This is a significant increase compared with 2005 when just 5% of newly approved drugs were personalized medicines.[28] A survey by the Tufts Center for the Study of Drug Development found 73% of cancer drugs in the pipeline are possible personalized medicines and that researchers predict a 69% increase in the number of personalized medicines in the next five years.[29]

Increasingly, personalized medicine is the common thread across many of the most exciting recent advances in cancer treatment, including angiogenesis inhibitors, immunotherapies and targeted therapies – all of which use the molecular characteristics of the cancer to guide treatment. Personalized medicines seek to address the underlying drivers of the cancer with fewer impacts on healthy cells and accompanying side effects.[30]

Because of the great promise personalized medicine holds for treating cancer and many other diseases, stakeholders across the U.S. health care system – clinicians, providers, insurers, industry, the patient advocacy community, and academia – must continue to work collaboratively to ensure the infrastructure and policies needed to support this growing field are in place. Research investments today hold the potential to unlock treatment and prevention methods tailored to individual patients for years to come.[31]

Research Setbacks and Stepping Stones in Cancer

The latest groundbreaking treatments for cancer traveled a winding road with countless hurdles and setbacks over many years of dedicated time and scientific rigor before reaching patients.

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 as researchers learn from all of them. Their findings inform future study and direct research efforts toward new approaches to addressing the cancer causes, growth, and progression.

The cancers explored in this report – ***malignant melanoma, brain cancer, acute myeloid leukemia, kidney cancer, liver cancer, lung cancer, pancreatic cancer, ovarian cancer*** **and** ***prostate cancer*** – are examples where there are still unmet medical needs, but researchers have made progress with some very important advances. This report examines what it took to translate the substantial research efforts across the life sciences ecosystem into the new medicines we have and the tremendous progress researchers are making in the fight against these cancers.[†]

[†] Note: Although the data throughout this report can be expressed as a ratio it should not be interpreted as a success rate because we do not take into account all of the failures that came before the early approvals. For example, if an approval occurred in 1998, the earliest year in our data set, there would have been many setbacks in the 10-15 years that are typically required for drug development.

Setbacks in Immunotherapy

Biopharmaceutical companies have successfully brought a range of immunotherapies – medicines that harness the patient's own immune system to fight the cancer – to market in recent years. These range from immune checkpoint inhibitors that help take the brakes off the immune system to CAR-T therapies that reprogram the patient's own immune cells.

But researchers have also met significant challenges advancing this field. Immunotherapy is a fairly new technology and an entirely novel approach to treating cancer. As such, each new immunotherapy faces long odds of success and it can be difficult to determine which patients will benefit from the treatment. In recent years we have seen a number of examples of setbacks in the development of immunotherapies, including the following:

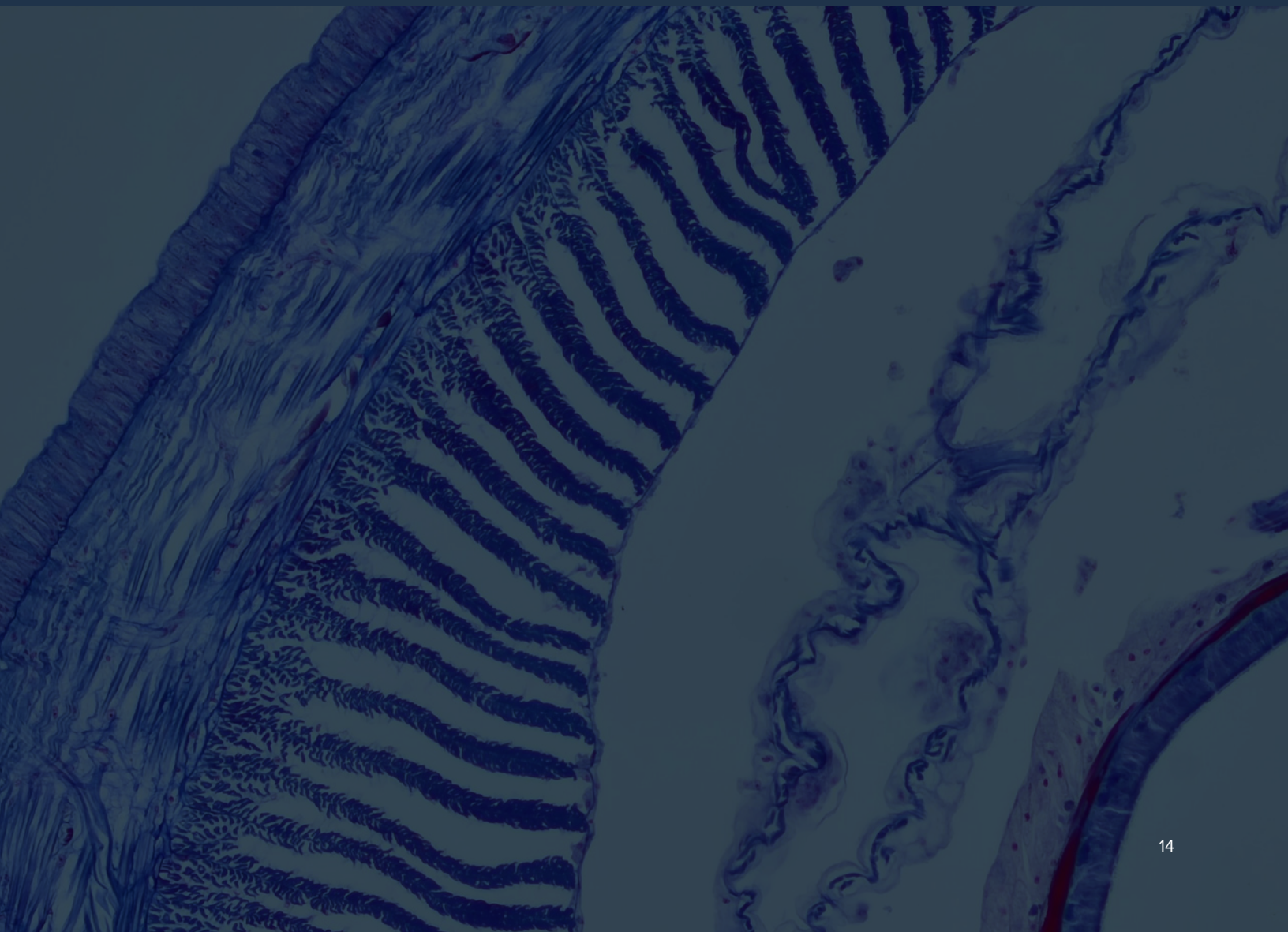
- Glioblastoma is an aggressive form of brain cancer that is notably difficult to treat. While nivolumab, an immune checkpoint inhibitor of PD-1, did not meet the primary endpoints in phase III clinical trials in 2019 for the treatment of newly diagnosed glioblastoma in combination with radiation, the results "contributed to gaining a deeper understanding of the potential role of biomarkers in patient care."[32] The checkpoint inhibitor was one of the first approved immunotherapies, and to date is approved for the treatment of a range of cancers including: metastatic melanoma, kidney cancer, liver cancer and lung cancer which are detailed in this report. Today, ongoing trials continue to investigate nivolumab as a potential treatment for glioblastoma.
- An investigational medicine, epacadostat, was being tested in 2018 in combination with an approved immunotherapy, pembrolizumab, to treat malignant melanoma. The experimental immunotherapy targets IDO1, a protein which impedes immune cells and is considered a promising approach to unleashing the immune

system to fight cancers. Despite this promise, researchers were disappointed that the large Phase III trial did not meet its primary endpoint and halted the study in April 2018.[33] Though the trials results represented a setback, the researchers stated that the trial data "will contribute to our understanding of the role of IDO1 inhibition in combination with PD-1 antagonists."[34] Research on epacadostat is currently ongoing.[35]

- In October 2019, a Phase III trial testing pegilodecakin, an immunotherapy targeting IL-10 receptors, for the treatment of metastatic pancreatic cancer was terminated because the trial did not reach its primary endpoint of overall survival. According to researchers, "[p]ancreatic cancer has proven to be one of the most difficult tumor types to treat and there have been very few recent treatment advances in the later-line metastatic setting." Subsequently, researchers had hoped to continue to learn more about the drug's novel mechanism and tested its efficacy in the treatment of other types of cancer, such as lung cancer and kidney cancer. But as data accumulated in non-small cell lung cancer trials, the company announced they would not pursue further studies of the drug.[36] [37]

"While the promise of immunotherapy is real and success seems inevitable, it is still important to consider factors that currently limit the approach's effectiveness. Failure is a natural part of the scientific process and should not come as surprise in such a fast-evolving field."

Luis Felipe Campesato, PhD, Memorial Sloan Kettering Cancer Center[38]



Malignant Melanoma – Advances are a Bright Spot in Cancer Treatment

Malignant melanoma accounts for about 1% of all skin cancers, but because it is more likely to grow and spread, it is responsible for the vast majority of deaths from skin cancer. Rates of melanoma have been rising over the past few decades. The American Cancer Society estimates about 6,850 people will die from the disease and about 100,350 new melanomas will be diagnosed in 2020. The overall 5-year survival rate for melanomas is 92%.[39] For stage IV malignant melanoma, the 5-year survival rate drops to 15-20%.[40]

While surgery is the primary option for melanoma diagnosed in early stages, metastatic, or advanced, melanoma is generally not conducive to surgery. Researchers have been taking advantage of the incredible advances in immunotherapy and targeted therapy to apply to aggressive late-stage melanoma.[41]

Recent Progress

In recent years, treatment of metastatic melanoma has been transformed with the introduction of a range of immunotherapies and targeted treatments. A recent study found that annual deaths from melanoma among whites (who account for the vast majority of cases) in the U.S. increased by 7.5% between 1986 and 2013 and then fell by 17.9% between 2013 and 2016 – a drop that study authors attributed to the introduction of new medicines.[42] One of the study authors noted, “This roughly 5% drop per year over 4 years is the largest drop ever seen over such a short period, for any cancer.”[43]

The wave of new treatments which ultimately changed the treatment landscape for metastatic melanoma patients, and subsequently many other forms of cancer detailed in this report, began with the approval of the first immune checkpoint inhibitor, ipilimumab, in 2011. This immunotherapy was approved for metastatic melanoma and works by inhibiting the immune checkpoint protein CTLA4.[44] Ipilimumab was the first drug to improve how long people with metastatic melanoma live, representing a breakthrough for melanoma patients and underscoring the potential promise of this class of immunotherapies.[45] Two additional checkpoint inhibitors were later approved, nivolumab and pembrolizumab, both of which target the PD-1 protein and are typically the first drugs tried for patients with metastatic melanoma.[46] [47] Although checkpoint inhibitors do not work for all patients, those who do respond can have long-term – or even permanent – results.

These immunotherapies have since proven to be effective in different stages of treatment and in combinations. For example, in 2015 the FDA approved ipilimumab and nivolumab as a first-line treatment for some patients with advanced melanoma after a clinical trial showed that 60% of patients responded to the combination compared with 11% who responded to ipilimumab alone. The combination nearly doubled progression-free survival.[48]

Another innovative immunotherapy approach is genetically-modified oncolytic virus therapy, which is classified as a type gene therapy. Talimogene laherparepvec, a first-of-its kind treatment, was approved in 2015 to treat melanoma that cannot be removed entirely by surgery. This medicine helps the patient’s own body fight the root cause of melanoma at the cellular and genetic level. The treatment uses a genetically modified herpes virus which is believed to work by multiplying inside the cancer cells, both killing some cancer cells and flagging the tumor for the immune system to attack.[49]

Targeted therapies have also been an important source of progress against metastatic melanoma.

About half of all melanomas are driven by changes in the BRAF gene which is involved in cell growth, and medicines in two classes of personalized medicines have been approved that help patients with this mutation: BRAF inhibitors and MEK inhibitors.[50] The MEK and BRAF genes work together in cells. The FDA has approved three BRAF inhibitors designed to attack the BRAF protein directly: vemurafenib, dabrafenib, and encorafenib.[51] [52] [53] [54] FDA approved MEK inhibitors, which impact the BRAF gene indirectly, include trametinib, cobimetinib, and binimetinib. Each are approved for melanoma that has spread or cannot be removed completely by surgery.

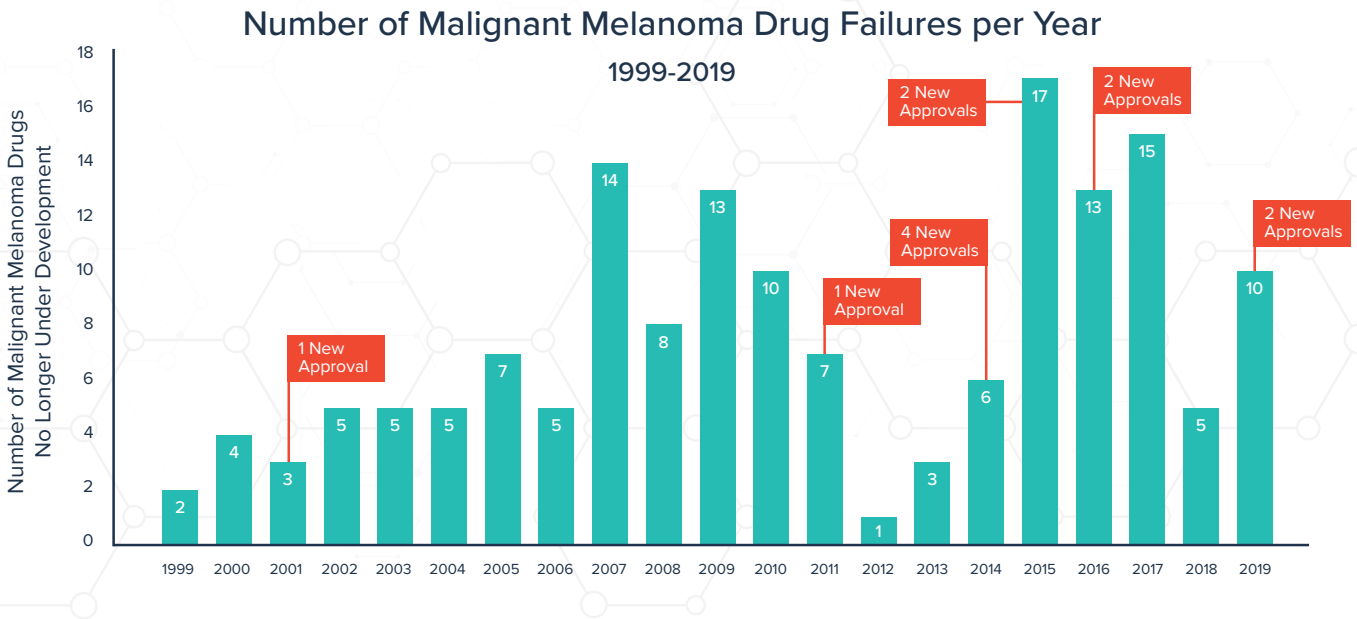
Clinical trials have shown that BRAF inhibitors can quickly shrink metastatic melanoma in many patients with a BRAF mutation but have also found that the response lacked durability and the cancer would come back within about 9 months. Combining BRAF and MEK inhibitors was found to double the time to progression.[55] [56] FDA approved two different combinations of BRAF and MEK inhibitors for patients with melanoma in 2018, each with a diagnostic test to determine which patients would benefit from treatment.[57] [58]

Building on Failures

The progress made in treatments for metastatic melanoma is a particular bright spot in the cancer treatment landscape. In recent years, immunotherapy and targeted therapy drugs have delivered positive treatment options for patients.[59]

But those advances would not be possible without the learnings from many clinical trials and other scientific research that did not yield positive results. For instance, IDO was identified as a protein involved in helping cancer cells evade the immune system. As previously noted, an IDO inhibitor, in combination with an immune checkpoint inhibitor progressed to Phase III of the clinical trial process in 2018 only to fail to meet key endpoints. Many researchers had hoped IDO inhibitors would expand the immunotherapy treatment arsenal, but following these disappointing results, other companies pursuing IDO inhibitors were forced to reevaluate their research plans.[60] (See page 13 for more.)

Since 1998, there have been 12 new drug approvals for the treatment of malignant melanoma while another 158 medicines have failed in the development process having been discontinued, suspended, or had no development reported.[61] That is a 13:1 ratio of unsuccessful attempts to FDA-approved medicines.



158 Total Unsuccessful Drugs | **12** Total Approved Medicines

Looking Ahead

Researchers are working to build on the remarkable progress in treating metastatic melanoma of the past decade. Immunotherapies have been a huge advance but only a subset of patients have a complete response. Studies are under way that aim to increase understanding of why some patients respond and some do not. Thus far, researchers have found that tumors with a greater number of mutations may be more likely to respond to immunotherapies.[62] Studies are even looking at the impact of the gut biome, or "good" bacteria in the digestive tract on immunotherapy response.[63] To that end, clinical trials with advanced melanoma patients are exploring potential treatments that modulate the microbiome in combination with immunotherapies.[64]

There are many facets of immunotherapy to explore including the best way to combine and sequence medicines for the maximum immune response. On top of that, researchers are grappling with how to combine immunotherapies with targeted therapies. Results are eagerly expected in 2020 for two Phase III studies of so-called "triplet therapies" which combine a checkpoint inhibitor with BRAF and MEK inhibitors.[65]

Researchers are working to improve outcomes with targeted therapies in melanoma as well. To help slow or stop the tumor's resistance to therapy, the timing of administering treatments is another variable being examined for targeted therapies. Researchers are studying intermittent dosing, in which patients take the targeted therapies for a certain period and then take a break before resuming.[66]

Research has shown that BRAF and MEK inhibitors slow or halt growth but are less effective in killing the melanoma cells. As such, researchers are working to identify new potential biomarkers for metastatic melanoma. For example, they are looking at medicines to reach new targets such as mutations in the KIT and NRAS genes which drive some melanomas.[67] Additionally, a protein has been identified that is involved in preventing melanoma cells from dying called MCL-1. Drugs that block MCL-1 are in development for blood cancers and may soon be studied for melanoma.[68]

"Metastatic melanoma was previously a field without any effective treatment option. Through a concerted effort to understand the biology of cancer and the immune system, we now have numerous effective treatments. Continued partnerships between scientists and clinicians are necessary to move the bar higher and cure more patients."

Dr. Douglas Johnson, Assistant Professor of Medicine and Melanoma Clinical Director, Vanderbilt-Ingram Cancer Center[69]

"We are very excited about what has been accomplished in treating patients with melanoma. The field continues to move forward at a rapid pace in terms of research discoveries and advances in therapy."

Ahmad Tarhini, MD, PhD, Director of the Melanoma and Skin Cancer Program and Director of the Center for Clinical and Translationa Immuno-Oncology Research at Cleveland Clinic Cancer Center[70]

Brain Cancer – Pipeline Brings Promise to a Difficult Disease

The American Cancer Society estimates about 17,760 adults and children in the U.S. will die this year from brain and spinal cord tumors, and about 23,820 new cases will be diagnosed.[71] 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.

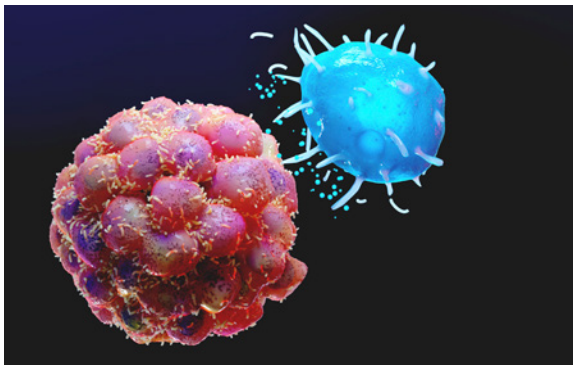
There are more than 130 different types of brain tumors.[72] Benign brain tumors are usually not aggressive and do not generally invade surrounding tissue, but they can grow and damage normal brain tissue. Malignant primary brain tumors, the main focus of this report, tend to grow faster and be more 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 lifespan of 11-15 months after diagnosis and a 5-year survival rate of 5-19% depending on age.[73] [74]

The treatment options for brain tumors vary based on the specific location of the tumor, its size and type, the patient's age, and other factors. Surgery is often the first step in the treatment of brain tumors, followed by radiation and chemotherapy. Successfully treating brain tumors can be a challenge but research in the past 20 years has helped to lengthen the lives of people with brain tumors—including through a better understanding of the types of tumors that respond to chemotherapy and more targeted delivery of radiation.[75]

Recent Progress

Progress in the form of innovative medicines has been slow for brain cancer leaving a critical need for continued research and new approaches. But despite the many challenges in developing medicines against this aggressive disease, one targeted therapy approval succeeded in making its way to patients with recurrent GBM. Bevacizumab, an angiogenesis inhibitor, received accelerated approval to treat recurrent GBM in adults in 2009.[76] [77] This treatment can help to delay disease progression and reduce the need for corticosteroids over the course of the disease, which is an important treatment goal in this difficult-to-treat cancer.[78] [79]

Building on Failures

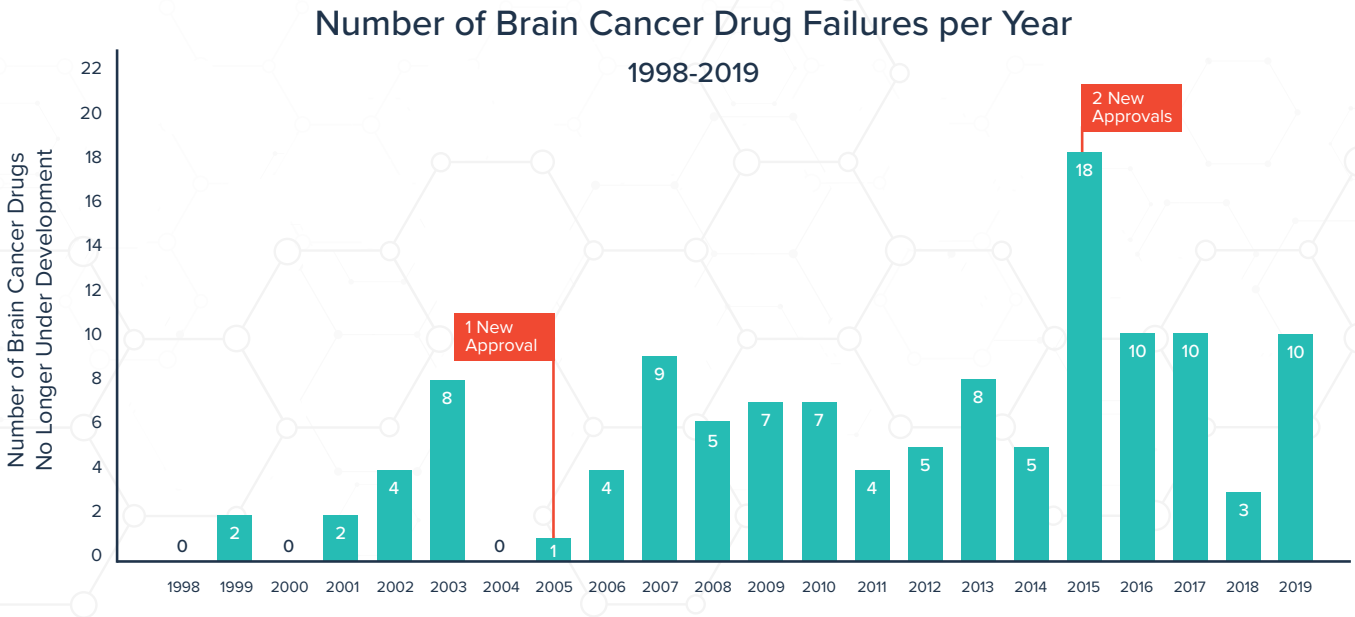


Committed to meeting the significant unmet need for patients with this aggressive form of cancer, researchers continue in their efforts to research and develop new treatments, but they have faced significant hurdles. Since 1998, there have only been 3 new drug approvals for brain cancer, while another 122 medicines have failed in the development process having been discontinued, suspended, or had no development reported.[80] That is a 41:1 ratio of unsuccessful attempts to FDA-approved medicines.

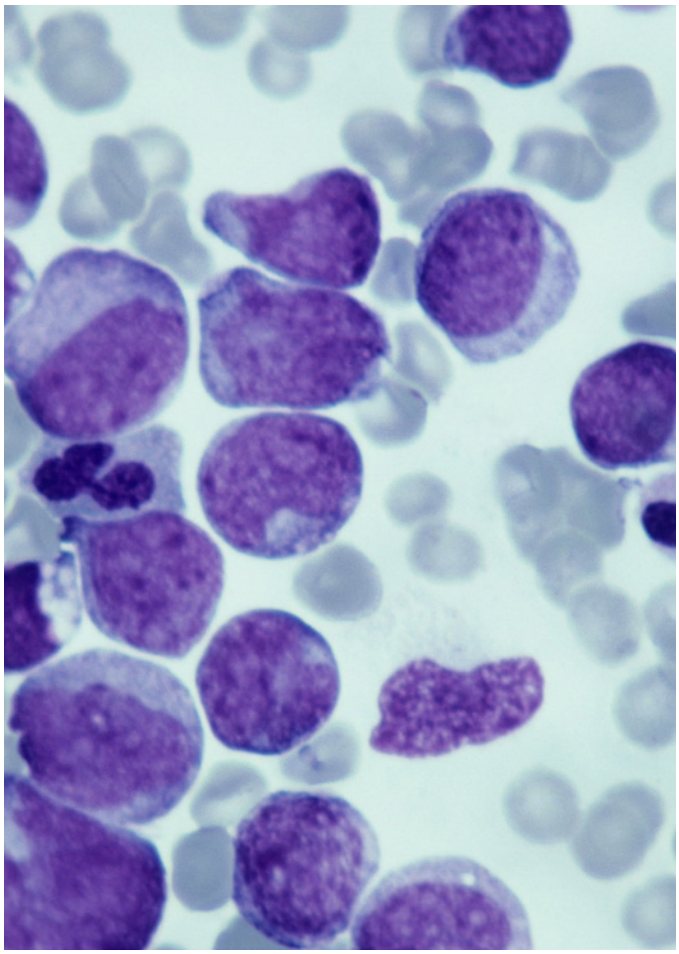
A central complicating factor in treating brain cancer is the blood-brain barrier, which is designed to keep chemicals in the blood from getting into the brain. It serves as a limiting factor to treatment as it can block anti-cancer drugs from entering the brain to target the tumor.[81] Treatment for brain tumors is also complicated by the varied mutations and pathways stimulating the tumor growth. Drugs are less able to kill varied cancer cells that are driven by different mechanisms. In addition, therapy-resistant tumor cells can emerge from these diverse cells found within the tumor.[82]

Many proteins have been identified as potential targets for attacking GBM but these have led almost entirely to disappointing results. A large part of the challenge is that drug candidates struggle to reach a therapeutic concentration at the site of the tumor. Even those that cross the blood-brain barrier may be quickly pushed back out. For example, researchers reviewed two failed clinical trials of EGFR inhibitors for GBM. These drugs had been found to be effective in preclinical testing but had no effect in clinical trials, likely due to the complexity of crossing the blood-brain barrier.[83]

Although challenges persist, researchers continue to use past setbacks to inform future discoveries in brain cancer therapies.



122 Total Unsuccessful Drugs | **3** Total Approved Medicines



Looking Ahead

Like most cancers, researchers are working to better understand brain tumors at the molecular level, the mutations driving them, the biomarkers that reflect their state, how they interact with the immune system, and how best to treat each patient individually.

Immunotherapies that harness the body's own powerful ability to kill cancer cells are considered particularly promising. A recent trial for GBM patients tested pembrolizumab, an immune checkpoint inhibitor and found that when pembrolizumab was given to GBM patients before surgery it nearly doubles median survival time (417 days compared with 228 days).[84]

Researchers are also exploring the development of vaccines in the fight against glioblastoma. One study that released promising results in 2019 looked at a therapeutic vaccine made from the patient's own tumor cells designed to help the immune system recognize and attack the tumor. The study showed that the vaccine suspended cancer growth, slowed recurrence, and extended survival.[85] In addition, preclinical research has suggested that combining three immunotherapies which work by three different mechanisms may have potential in leading to long-term remission.[86]

"The brain tumor community is very united in our quest for finding better treatments for our patients, and I think the progress will come through clearly planned and orchestrated clinical trials, looking at both approaches, immunotherapies ... and appropriate uses of targeted therapies, which will go and attack the genes that drive a particular tumor."

Dr. Manmeet Ahluwalia, Professor and Director of Brain Metastasis Program, Cleveland Clinic[87]

"Given the extent of the challenges involved, the slow pace of progress on brain cancer treatment should not be a reason to be discouraged. Thanks to the generosity of people who enroll in trials, and the determination of researchers and clinicians who continue to collaborate and foster treatment initiatives, we can still gain important insights."

Nature Editorial[88]

Acute Myeloid Leukemia (AML) – Research Tenacity Brings Treatment Advances

Acute myeloid leukemia (AML) is a rare and aggressive cancer of the blood and bone marrow which affects the development and maturation of several types of blood cells, including white blood cells.[89] As a result, the disease renders the body less able to fight off infections. Because leukemia cells reproduce quickly and don't die when they should, these cells build up in the bone marrow and can spill into the bloodstream, where they can spread to other organs. In addition to impacting the immune system, AML is also associated with symptoms such as excessive fatigue, joint pain, and fevers.

AML accounts for approximately 25% of all adult leukemias worldwide. While the disease predominantly affects older adults (average age of diagnosis is 68 years old), about 500 children in the U.S. are diagnosed with AML each year, making it the second most common leukemia in children. If not treated, AML can progress quickly and be fatal in a few months. In fact, it has the lowest survival rate of all adult leukemias, with a 5-year survival rate ranging from 24% to adults (age 20 and older) to 67% in children (age 0-19).[90] [91]

AML is characterized by genetic heterogeneity (variations in genetic mutations across the cells of the tumor and across patients with the disease) and cytogenetic abnormalities (how cells replicate in relation to chromosomes), complicating treatment. Researchers have identified several genes that are often mutated in AML, opening the door to the development of more individualized treatment options.[92]

Recent Progress

Scientists have worked hard to uncover the underlying drivers of this devastating disease in order to develop new therapeutic options. Until recently patients only had traditional chemotherapies available to them but new approvals have ushered in a new set of targeted personalized medicines to treat AML for the first time.[93]

In 2017, there were three personalized medicine drug approvals to treat AML in the U.S. representing the first major steps forward in this disease area in almost 20 years.[94] The first of these personalized therapies was midostaurin, which FDA approved for use, in combination with chemotherapy, for the treatment of adults with newly dianosed AML who have a FLT3 mutation.[95] This mutation occurs in approximately one-third of AML patients, causing the FLT3 protein to be overactive, thus driving the proliferation and survival of leukemia cells.[96] FDA also used its expedited approval programs to grant approval of the personalized therapy enasidenib for patients with AML that has relapsed or is not responding to treatment and has an IDH2 mutation.[97] This enzyme is part of a key pathway underpinning the disease in 20% of AML patients.[98]

Additionally, Gemtuzumab ozogamicin was approved in 2017 for patients not responding to treatment who have experienced a relapse and whose tumors express the CD33 antigen (CD33-positive AML). Gemtuzumab ozogamicin is an antibody-drug conjugate, meaning that it combines a therapeutic molecule with a monoclonal antibody, which specifically targets the CD33 antigen and delivers the toxic agent directly to the cancer cells.[99] [100]

The following year saw additional personalized medicine approvals, each expanding care and treatment options for patients with AML. The FDA granted expedited approved to gilteritinib for relapsed or refractory AML in patients with an FLT3 mutation.[101] Gilteritinib is an FLT3 inhibitor, which blocks cancerous cells from dividing and kills a subset of leukemia cells that have the FLT3 mutation.[102] The trial found that the treatment increased overall survival significantly compared with standard chemotherapy and achieved higher rates of complete remission and fewer serious side effects.[103]

The FDA also approved another personalized therapy in 2018, ivosidenib, on an expedited pathway for the treatment of relapsed or refractory AML with a rarer mutation associated with AML: the IDH1 mutation.[104] This was the first drug to treat this particular mutation and Richard Pazdur, MD, the director of FDA's Oncology Center of Excellence, commented that the medicine "fills an unmet need for patients with relapsed or refractory AML who have an IDH1 mutation" and is "associated with a complete remission in some patients and a reduction in the need for both red cell and platelet transfusions."[105] The following year the FDA expanded the approval of ivosidenib as a first-line treatment for AML with IDH1 mutation for patients over 75 that do not tolerate chemotherapy.[106]

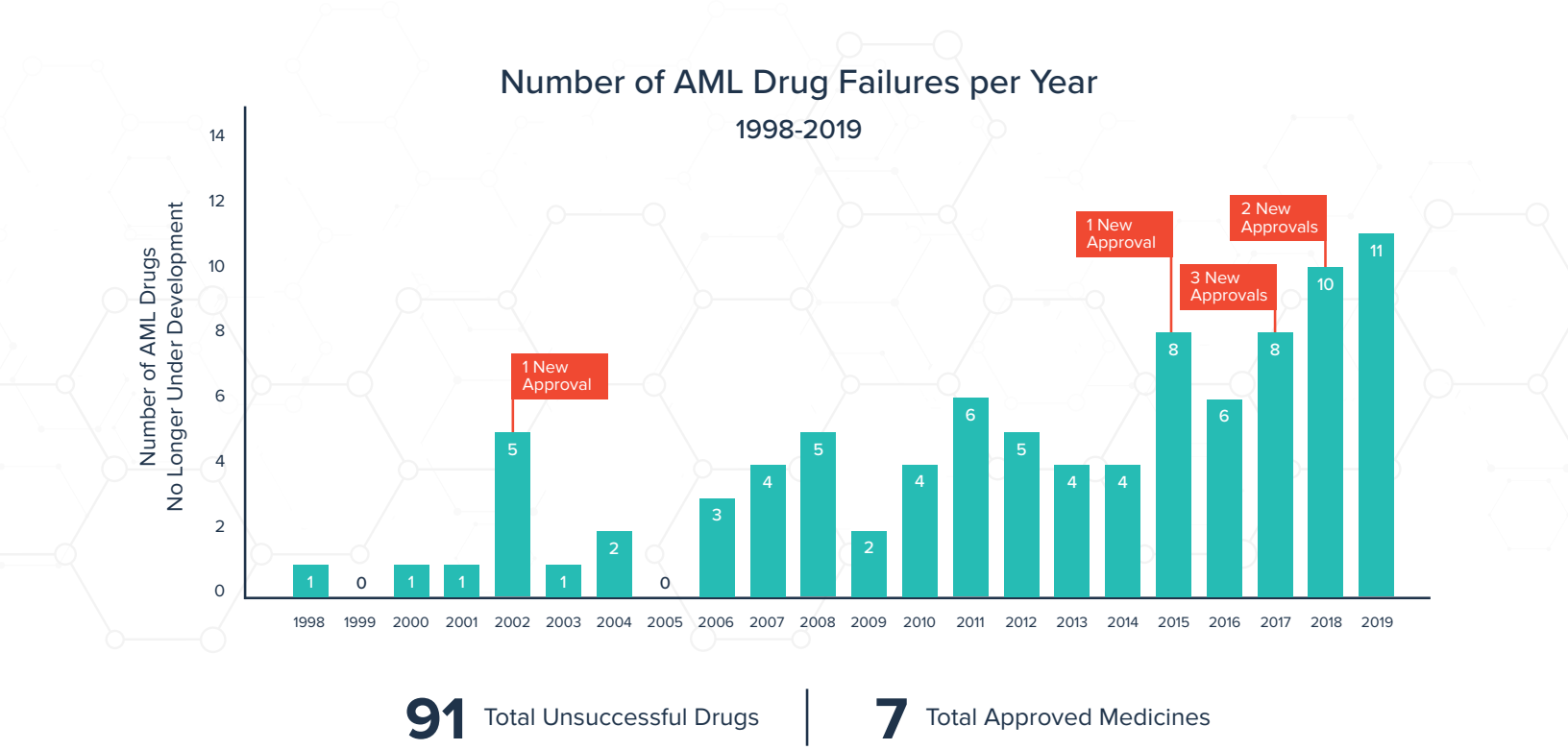
"Since 2017, there has been an explosion of newly approved treatment options both nationally and internationally, with the majority of new drugs targeting specific gene mutations and/or pivotal cell survival pathways."

C Lai, et al., Journal of Hematology & Oncology[107]

Building on Failures

The recent flurry of approvals for AML followed nearly two decades without major new treatment options for the disease. But, during that time, researchers were tirelessly working to better understand the genetic drivers of AML and testing potential treatments.

AML is an extremely heterogeneous disease. A wide range of mutations are involved and different drivers are responsible for the development of AML from patient to patient, and even cell to cell.[108] Preclinical models struggle to capture the heterogeneity of the disease making success in clinical trials less likely.[109] In the years since 1998, 91 medicines intended for AML failed in the development process having been discontinued, suspended, or had no development reported.[110] Meanwhile, 7 medicines received approval. That is a 13:1 ratio of unsuccessful attempts to FDA-approved medicines. The setbacks laid the groundwork for the recent approvals as well as future progress.



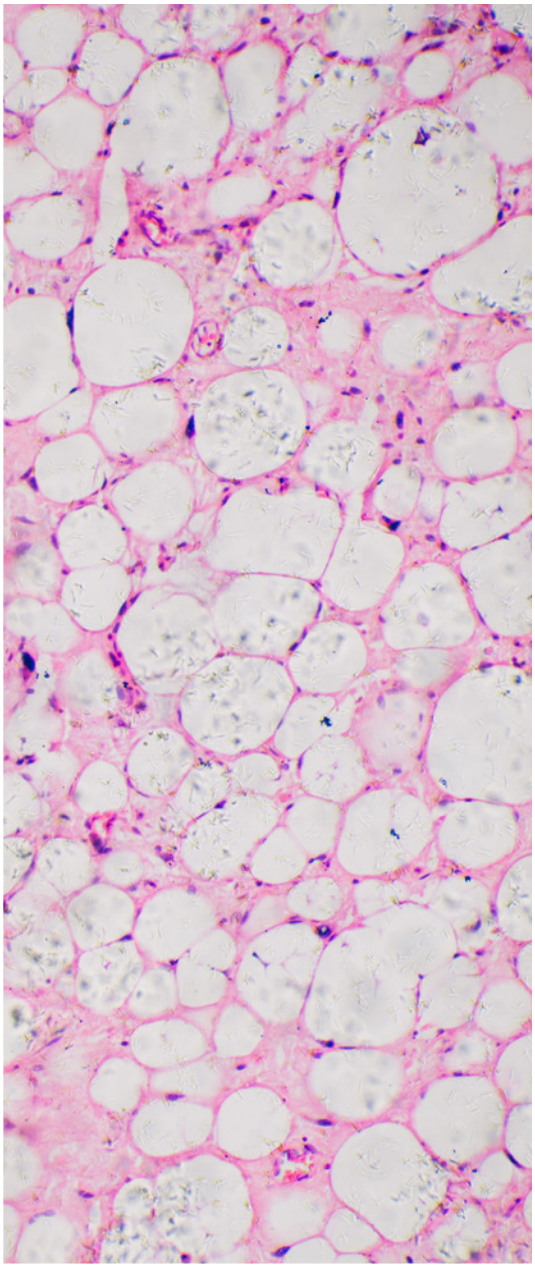
91 Total Unsuccessful Drugs | **7** Total Approved Medicines

Looking Ahead

The last few years have been very active for advancements in AML treatments but much more remains to be done and research is ongoing. As in many other cancer areas, researchers are working to better understand how best to use these new treatments in combination or in a particular sequence.[111]

Understanding which patients will benefit most from which approach is also an important area to expand our knowledge. In 2018, an extensive dataset for AML covering genomic, clinical, and drug data was published by a partnership called Beat AML. The partnership brought together 11 pharmaceutical and biotechnology companies as well as 11 academic medical centers. Over 30,000 data points were collected spanning across treatments and outcomes, pathology and genetic reports, demographics of patients, and diagnostic information. One way this data set is expected to be helpful is the potential to provide predictions for markers of drug sensitivity and resistance, in turn supporting the development of more effective drugs.[112]

Finally, immunotherapy is a promising approach that has actually been used for AML for many years. Stem cell transplants are a form of immunotherapy and have been used for nearly four decades to treat AML. Researchers are currently working to better understand how AML interacts with the immune system and have identified multiple immune checkpoints that are involved including PD-1 and OX40. Clinical trials are currently underway targeting these pathways with checkpoint inhibitors. While PD-1 Inhibitors have been successful in several other forms of cancer, inhibitors of OX40 represent a novel approach.[113]



"In the past two years, at least four new personalized medicines targeting key genes have given patients much better outcomes and have changed the landscape of how we manage acute leukemia…it's a paradigm shift."

Dr. Mrinal Patnaik, Mayo Clinic, 2019[114]

"After many years, we are finally seeing progress in the treatment of AML, which has renewed my hope in improving outcomes for my patients."

Dr. Jorge Cortes, MD, Deputy Chair and Professor of Medicine, Department of Leukemia, University of Texas MD Anderson Cancer Center[115]

Kidney Cancer – Increased Treatment Options Bring New Hope

Approximately 73,750 new cases of kidney cancer are expected to be diagnosed in the U.S. this year and about 14,830 people will die from this disease according to the American Cancer Society. Kidney cancer is among the ten most common cancers in both men and women. The average age of diagnosis is 64 and the 5-year survival rate is 75%. Renal cell carcinoma (RCC), which starts in the lining of small tubes in the kidney, is the most common form of kidney cancer, accounting for approximately 85% of cases.[116]

The most common treatment options for kidney cancer include surgery, radiation, targeted therapies, and immunotherapy. Surgery, involving partial or complete removal of the kidney, is the first-line treatment for patients with early stage kidney cancer, but can cause serious side effects for kidney function, or can even lead to related kidney disease. Furthermore, not all patients are candidates for surgical or radiation interventions and most cases of kidney cancer are resistant to chemotherapy, making other therapies a critical option.[117] [118]

Recent Progress

Advanced RCC has recently seen a considerable shift in treatment approach with the advent of immunotherapy and targeted therapies. While surgery and radiation may be used for some patients, for patients ineligible for these approaches recent treatment advances are offering critical new options.[119]

Within the last couple of years, immunotherapy combinations have become first line treatment for many patients with metastatic RCC.[120] [121] The move to combination approaches is similar to that seen with other cancers, as these regimens may lead to more benefits by preventing the development of drug-resistant cancer cells.

In April 2018, the FDA approved the first combined immunotherapy regimen for patients with advanced RCC comprised of the immune checkpoint inhibitors nivolumab and ipilimumab.[122] These therapies are inhibitors of the immune chekpoint proteins PD-1 and the CTLA-4, and target RCC by allowing T cells to attack cancer cells.[123] This advancement is significant as the combined therapy approach produces positive results in over 50% of patients diagnosed with metastatic RCC, a marked improvement from the 27% response rate that one study found with single-immunotherapy treatment.[124]

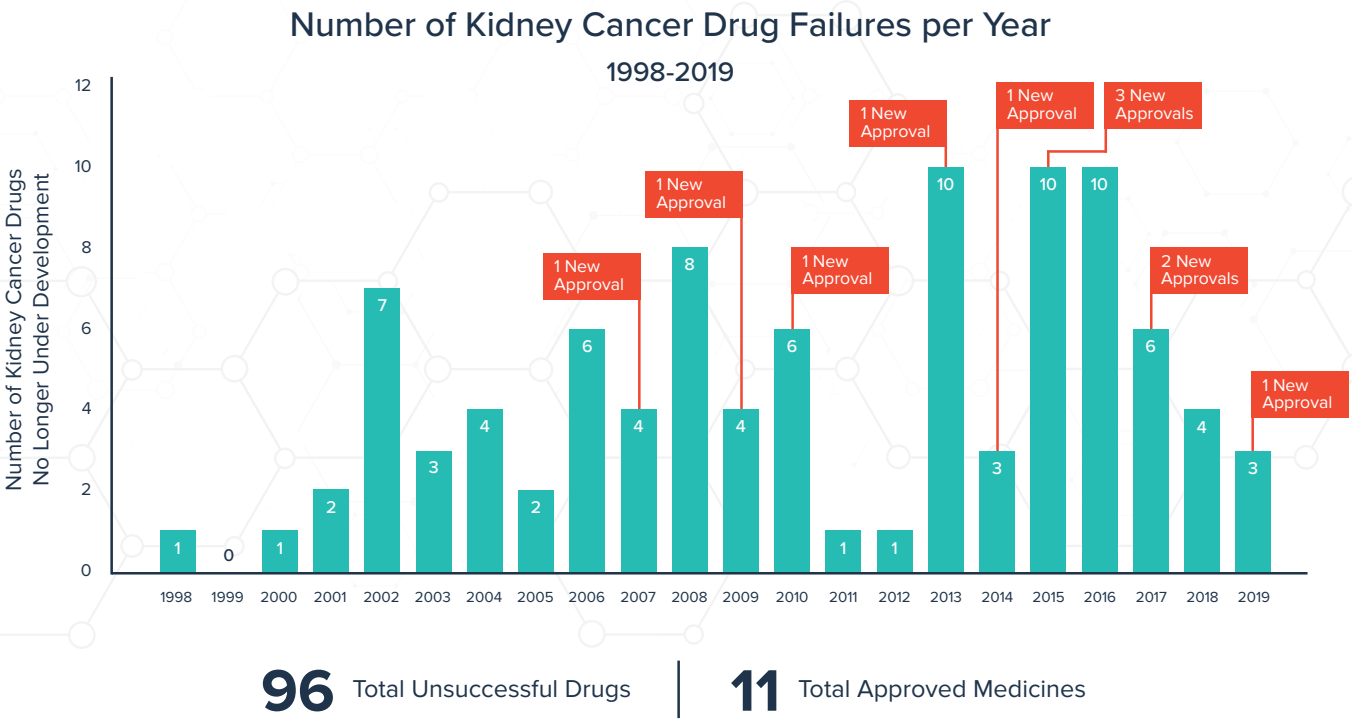
Two immune checkpoint inhibitors were granted approval in 2019 for advanced RCC when used in combination with the angiogenesis inhibitor axitinib. Axitinib inhibits the tyrosine kinase receptor, which interferes with the development of blood vessels needed for the tumor to grow. The PD-1 checkpoint inhibitor pembrolizumab was approved for use in combination with axitinib in 2019, demonstrating an impressive overall survival rate of 90% in clinical trials after one year.[125] [126] The second combination approved for use pairs axitinib with the PD-1 checkpoint inhibitor avelumab. Clinical trials showed the combination led to statistically significant progression-free survival in advanced RCC patients.[127]

Building on Failures

Since 1998, there have been **11 new drug approvals** for kidney cancer, while another 96 investigational medicines have failed in the development process having been discontinued, suspended, or had no development reported.[128] That is a **9:1 ratio** of unsuccessful attempts to FDA-approved medicines.

Kidney cancer is a relative bright spot in the larger cancer fight. Recent drug approvals, continued progress in addressing the disease at the genomic level, new immunotherapies and targeted treatments are providing hope to advanced RCC patients.[129] At the same time, research in this area presents specific challenges. The metabolic pathways – or how cells use energy – involved in kidney cancer are unique, as kidney cells generally are

exposed to high blood volumes but low oxygen levels compared with other cells.[130] The tumor microenvironment, including surrounding cells, blood vessels, and matrix, is also unique. T-cell concentrations in the kidney tumor microenvironment are low, yet, counter-intuitively, the disease responds relatively well to immunotherapy. In most cancers low T-cell concentration is associated with a worse prognosis, but in kidney cancer it is the reverse. The mechanisms behind this paradox are not understood.[131] More research is needed to understand the unique tumor environment and, beyond that, to take advantage of these unique attributes with new treatment approaches.



96 Total Unsuccessful Drugs | **11** Total Approved Medicines

Looking Ahead

With a range of recent approvals, research is currently underway to understand how best to continue enhancing the use of existing tools, including how to determine which treatment is best for an individual patient and how best to combine and sequence treatments.[132] Many clinical trials are underway to test various medicines either before surgery (neoadjuvant therapy) or after surgery (adjuvant therapy.) Providing the right medicine at the right time can help to make surgery for kidney cancer safer and more effective by minimizing tumors with immunotherapy and chemotherapy and potentially improving response rates and outcomes for patients.[133]

There are still many patients with RCC or other forms of kidney cancer that do not respond to medicines. Research is underway to better understand these patients' cancers at the molecular and genomic level in order to find better treatment options.[134] [135] One approach researchers are exploring is new therapeutic cancer vaccines which are designed to treat the cancer by stimulating the body's immune system. The vaccines can be made from the patient's own tumor cells after surgery, or they can be made from proteins most commonly found on the surface of kidney cancer cells.[136] [137]

"Today, there are so many options that are available. Patients are doing well. They're living longer, and with the advent of newer targeted agents, combined agents and immunotherapy, it's really gratifying for me to treat kidney cancer patients, because they are living longer than the projected survival that's set out for kidney cancer. I'm very excited to treat these patients, because we have a lot of options."

Dr. Sandy Liu, MD, UCLA Medical Center[138]

Liver Cancer – Years of Setbacks Pave the Way for Progress

The American Cancer Society estimates about 30,160 people will die from liver cancer in the U.S. this year, and approximately 42,810 new cases will be diagnosed.[139] The incidence of liver cancer has more than tripled since 1980 and it is the most rapidly rising cause of cancer-related death in the US.[140] The 5-year survival rate for liver cancer is 19%, partly because only 30-40% of patients are diagnosed before the cancer has spread and is more treatable.[141]

Hepatocellular carcinoma (HCC) is the most common type of liver cancer. In the United States, the most frequent cause of HCC is hepatitis C.[142] This viral infection causes cirrhosis of the liver, or an increase in scar tissue, which causes an elevated cancer risk. In recent years antiviral therapies have become available that can cure hepatitis C, cutting down the prevalence of the disease and reducing dangerous liver scarring, and, in doing so, offering tremendous promise in reducing incidence of HCC in the years ahead.

Treatments for HCC fall into two categories. The first is “curative-intent” options with the goal of ridding eligible patients of their cancer. The second category includes treatments with the goal of extending life.[143] Surgery is a curative-intent option and often a first-line tool for liver cancer, followed by radiation and radiofrequency ablation (using heat to destroy cancer cells). Life-extending treatments include chemoembolization (chemotherapy in which the drug is injected into the hepatic artery), targeted therapies and immunotherapies.[144]

Recent Progress

After years of minimal progress, recent advances are beginning to offer new, much needed options for HCC patients, but more research is still needed.[145] Standard chemotherapy is generally not effective in treating HCC, and so researchers have been particularly interested in targeted therapies and immunotherapies. In recent years, we have seen the advent of these approaches with new life-extending therapies available for advanced HCC patients in whom surgery is not an option.[146]

The primary type of targeted therapy for advanced HCC are angiogenesis inhibitors.[147] The angiogenesis inhibitor sorafenib has been a mainstay of first-line treatment for advanced HCC since 2007.[148] In 2017, the FDA then approved regorafenib, the first drug approved in almost a decade for HCC, which works by a similar mechanism but seeks to bring better tolerability and effectiveness. Regorafenib has earned expanded approval for patients whose tumors are no longer responsive to sorafenib.[149]

More angiogenesis inhibitors were approved in the two years that followed, providing additional options for advanced stage patients. Lenvatinib was approved in 2018 as another first-line treatment option for advanced HCC patients.[150] The following year saw additional approvals for patients for whom first-line sorafenib stopped working: cabozantinib and ramucirumab.[151] [152] Ramucirumab is also a personalized medicine as it was approved

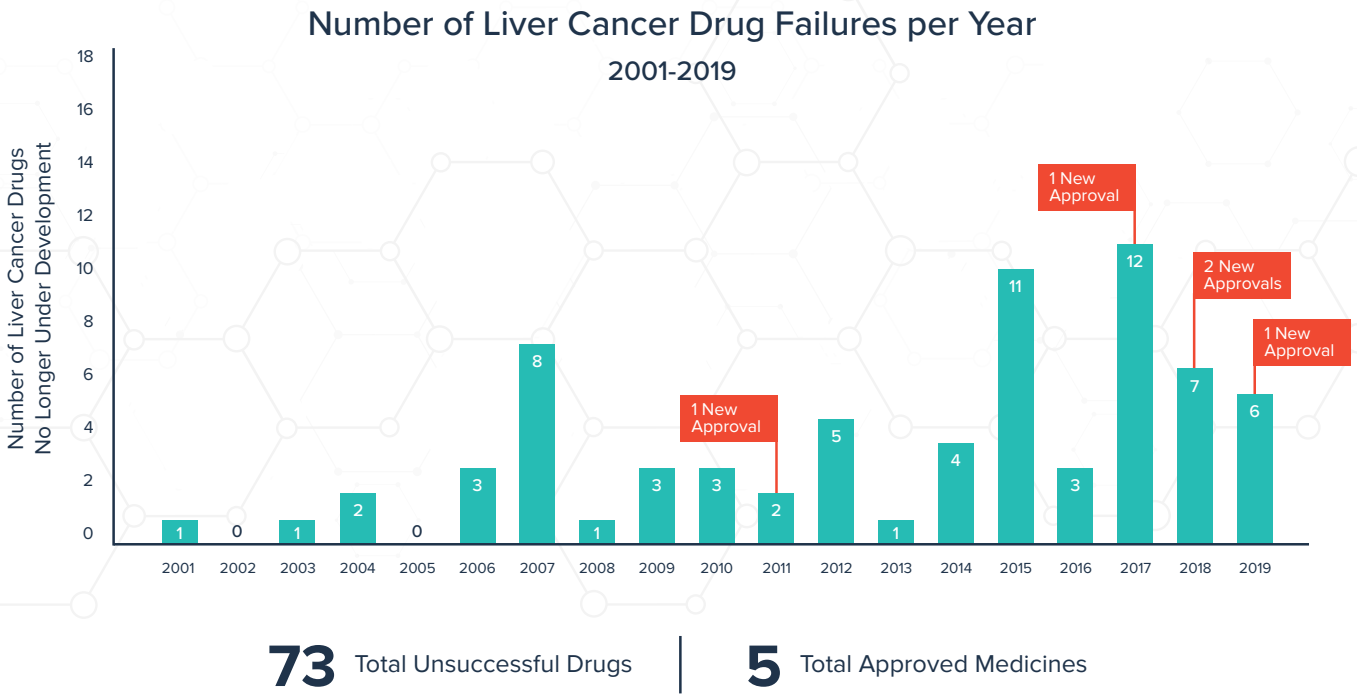
for patients testing high for alpha-fetoprotein (AFP), a serum protein which is elevated in more aggressive tumors. Ramucirumab is the first treatment specifically for patients with this type of HCC, which often has a worse prognosis due to increased angiogenesis feeding cancer growth.[153]

In addition, three immunotherapies—specifically immune checkpoint inhibitors—have recently been approved to treat patients with advanced HCC whose cancer has progressed following treatment with sorafenib.[154] [155] In 2017 and 2018, the FDA granted accelerated approval to nivolumab and pembrolizumab, which are PD-1 checkpoint inhibitors. In 2020, nivolumab was also approved for use with ipilimumab, another CTL-4 checkpoint inhibitor.[156] One reason immune checkpoint inhibitors are particularly promising in HCC patients is due to the immune dysfunction that can lead to the development of liver cancer itself. Hepatitis causes inflammation in the liver and can prevent the immune system from targeting cancer cells. Immunotherapies work by reversing this dysfunction, enabling the immune system to attack the HCC cells.[157]

Building on Failures

Liver cancer has been difficult to treat, delivering many setbacks along the way for researchers. Like all cancers, liver cancer is heterogeneous – with variations in mutations between tumor cells and between patients – and resistant to treatment. The risk factors for liver cancer exacerbate these issues. Chronic hepatitis infection, alcohol abuse, and obesity can all contribute to the heterogeneity. In addition, the tumor microenvironment, or immediate surroundings of the tumor, can impact the disease. Varying degrees of inflammation or liver fibrosis and cirrhosis change the microenvironment. Researchers have also struggled to identify subgroups of patients to inform the development of more targeted or personalized medicines.[158]

Since 1998, there have been just 5 new drug approvals to treat liver cancer, while another 73 medicines have failed in the development process. Trials for these investigational medicines have either been discontinued, suspended, or had no development reported.[159] That is a 15:1 ratio of unsuccessful attempts to FDA-approved medicines. It is hoped that the persistence of researchers, along with the number of promising clinical trials under way, will yield new treatment options for liver cancer patients in the future.



Looking Ahead

Despite recent progress, HCC remains challenging to treat and survival benefits have been modest for patients with advanced disease. However, this has begun to change with the introduction of immunotherapies and additional angiogenesis inhibitors. To improve how treatments are deployed and developed, researchers are working to better understand the underlying biological and molecular mechanisms behind the disease, as well as the varied conditions that lead to liver cancer, including chronic hepatitis and cirrhosis.[160]

One potential approach is expanding the use of immunotherapies to treat liver cancer. To date immune checkpoint inhibitors have been important in treating many cancers, and researchers believe that HCC may offer a particularly notable opportunity to treat liver cancer. According to Ghassan Abou-Alfa, MD, of Memorial Sloan Kettering Cancer Center, "Liver cancer, because of its inflamed nature to begin with, appears to drive a very receptive environment for treatment with checkpoint inhibitors.... there is no doubt that this is really where the future will be coming."[161]

Despite this promise, about 30-40% of liver cancer patients are resistant to individual immunotherapy options.[162] One of the greatest concerns with respect to liver cancer treatment is how to combine these immunotherapy options to decrease the risk of resistance.[163] Researchers are exploring many combination approaches in clinical trials that pair two immune checkpoint inhibitors that have different mechanisms of action, including those that target PD-1, PD-L1, and CTLA-4 proteins. They are also combining checkpoint inhibitors with angiogenesis inhibitors.

Some experts predict that combination regimens will quickly become the default. According to Dr. Josep Llovet of Mount Sinai Hospital in New York City, "We are moving to the next period, which [involves] combinations. Forget about single agents.... The bar has been set higher. You have to hit very good outcomes to beat the drugs that are currently approved. So I think that we are moving, in the next five years, to where we will see combinations of agents in the front and second line."[164]

Other potential new types of treatment lie further on the horizon. For example, researchers announced the first study of CAR-T cell therapy in liver cancer in 2019.[165] CAR-T cell is a type of immunotherapy in which the patient's T cells are removed, reprogrammed to target a small protein that is highly expressed in HCC, and then returnedto the body to attack the tumor. As noted previously in this report, the approach has shown to be effective in certain blood cancers, and researchers are excited about the potential to transform liver cancer if the approach proves successful.

"This has been an incredible year and positive time regarding our therapies for [patients with] liver cancer. We have been trying for the past 10 years to see how we can improve on the outcome of sorafenib by trying different things — going into combination therapies or even looking at second-line therapy. Many great efforts have been done, and, unfortunately, all of them have been negative. However, this year [2018] has been quite impressive."

Ghassan K. Abou-Alfa, M.D., Memorial Sloan Kettering Cancer Center[166]

Lung Cancer – Progress on the Horizon for a Challenging Cancer

Lung cancer is the leading cause of cancer death among men and women in the U.S., taking more lives than colon, breast, and prostate cancer combined annually. For 2020, the American Cancer Society estimates about 136,00 people will die from lung cancer in the U.S. while about 229,000 new cases will be diagnosed.[167] By far the leading cause of lung cancer is smoking, which is associated with about 80% of cases.[168] Incidence of lung cancer has fallen by half since the 1990s largely due to decreases in smoking rates.[169]

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

- ***Non-small cell lung cancer (NSCLC)*** accounts for 84% of all lung cancers and includes squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.[170] Non-small cell lung cancer can grow and spread slowly or quickly. The five-year survival rate is 24%.[171] [172]
- ***Small cell lung cancer (SCLC)*** accounts for 10-15% of lung cancers and is an aggressive cancer that spreads quickly within lung tissues and throughout the body.[173] The five-year survival rate is 6%.[174] About 70% of people with SCLC will have cancer that has already spread to other parts of the body at the time they are diagnosed, which is characterized as extensive stage SCLC.[175]

The type of lung cancer and stage of the disease determine the potential treatment options. Treatments for lung cancer generally include various surgical options, chemotherapy, radiation, targeted therapies, or a combination of therapies.[176]

Recent Progress

Progress in NSCLC treatments have outpaced progress in SCLC treatments over the years. Though new approaches are emerging in both types of cancer, new SCLC treatments are particularly needed for this aggressive form of cancer, as the standard of care has not changed in more than 30 years.[177]

NSCLC

Treatment of NSCLC has been recognized as a success story in what can be achieved with personalized medicine. Over the past two decades, researchers have identified a range of mutations which facilitate NSCLC growth. In particular, advances in understanding the role of the EGFR gene mutation and the ALK gene mutation played in NSCLC have proven instrumental in improving treatment for these patients. Subsequently, a wide range of other important genetic drivers have been identified and led to important treatment advances.[178] [179] Today, collectively it is estimated that up to 69% of NSCLC tumors have an actionable genetic driver.[180] This dramatic expansion in the understanding of the genetic basis of this disease has revolutionized the standard of care for this cancer and lead to a wide range of targeted treatments that have improved patient outcomes.[181]

In the last five years, a range of immunotherapies have been approved by the FDA, further transforming the treatment landscape for advanced stage NSCLC patients. This treatment approach has been particularly important for patients with advanced NSCLC whose tumor does not have a mutation that can be treated with a targeted therapy. For these patients, immune checkpoint inhibitors targeting the PD-1 and PD-L1 proteins (sometimes combined with chemotherapy) are often the first line of treatment.[182] The first immunotherapy for NSCLC, nivolumab, was approved in 2015 and recent long-term clinical trial results showed that five-year survival for previously-treated advanced NSCLC patients taking nivolumab was five times higher than the survival rates for those treated with chemotherapy alone (13.4% vs 2.6%).[183]

SCLC

As SCLC involves very aggressive tumor growth, approximately two-thirds of patients diagnosed already have extensive-stage cancer that has already

spread to other areas of the body. Unfortunately, surgery is not an option for these patients. Most of these patients receive chemotherapy for first- and second-line therapy, and the tumors often respond quite well initially but within a few months become resistant and continue to grow. Unfortunately, there are very few second-line options. On average, patients with extensive-stage SCLC live no more than 10 months after diagnosis.[184] [185]

Until recently, the standard of care for SCLC patients had not changed in over 30 years. Recent FDA approvals of immune checkpoint inhibitors for the treatment of extensive-stage SCLC are opening up new possibilities for these patients:[186]

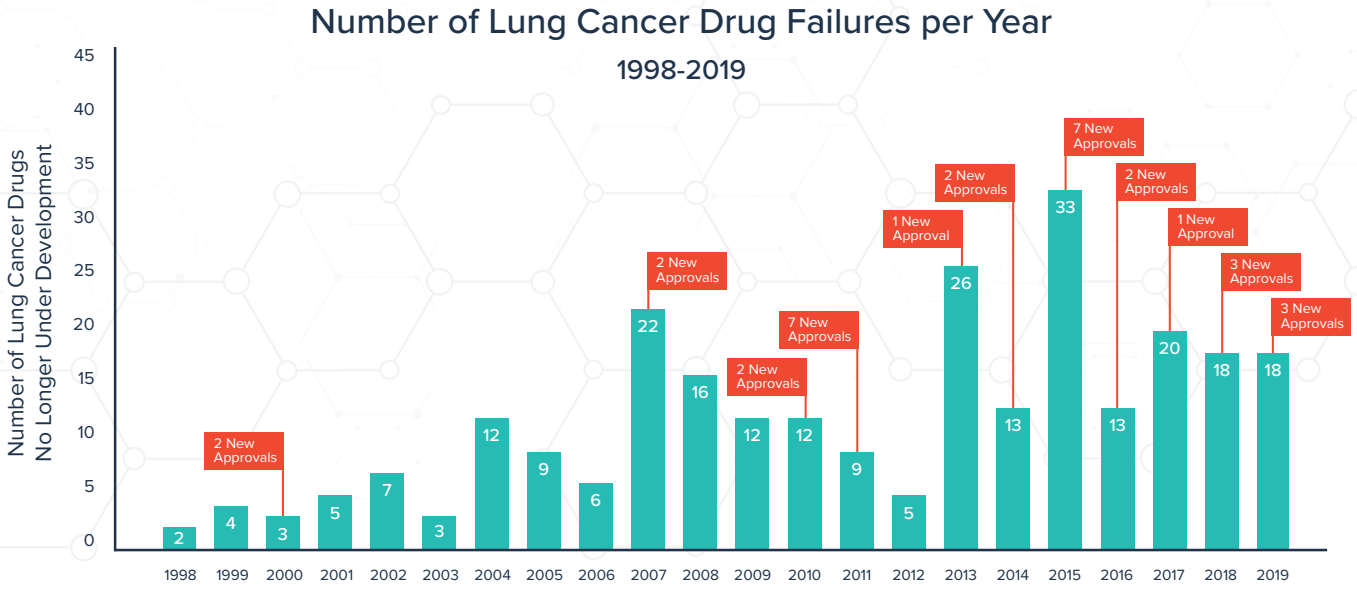
- In August 2018, nivolumab was granted accelerated FDA approval for SCLC that has spread to other parts of the body, specifically in cases where disease progression persisted even after two lines of therapies.[187]
- In March 2019, the FDA approved atezolizumab, which is used in combination with chemotherapy, as a first-line treatment for patients with extensive-stage SCLC.[188] In clinical trials, this combination was the first to achieve an increase in overall survival for extensive-phase SCLC patients in over 30 years.[189]
- Expedited approvals of pembrolizumab in 2019 and durvalumab in combination with chemotherapy in 2020 followed, both for extensive-stage SCLC.[190] [191] [192]

Building on Failures

Since 1998, there have been 32 new drug approvals for lung cancer overall while research related to 268 potential medicines were discontinued at the clinical trial stage. Meanwhile, only 4 new drugs were approved for SCLC in that time, while 51 failed in the development process.[193] That is a 8:1 ratio of unsuccessful attempts to FDA-approved lung cancer medicines in general. For SCLC, the ratio is 13:1.

Unlike NSCLC, the underpinnings of SCLC are not understood.[194] The driver mutations of SCLC have not been identified, so options for targeting on the molecular level are limited. In addition, SCLC tumors appear to carry multiple co-existing mutations suggesting that a single medicine is unlikely to be effective alone.[195]

Many researchers have been focused on finding novel biomarkers to better target SCLC on the molecular level. Using a unique research platform, researchers discovered that 80% of patients with SCLC carried a protein called delta-like protein 3 (DLL3) and that cells with this protein continued to divide generation after generation like stem cells. Researchers theorized that DLL3 was a key driver of SCLC. An antibody-drug conjugate that targets cells expressing DLL3 and carrying a cytotoxic agent was tested in clinical trials, but despite promising early results it demonstrated no survival benefit.[196] [197]



268 Total Unsuccessful Drugs | **32** Total Approved Medicines

Looking Ahead

Though progress in the fight against SCLC has not been at the same pace as NSCLC, new treatments are expanding the options for these patients. Research efforts under way provide prospects for improving the standard of care and increase options for patients who experience recurrence of their cancer. With the onslaught of new data emerging from clinical trials (currently 79 clinical trials are underway in the United States),[198] there is reason for optimism.

"Immunotherapy is the most promising SCLC treatment in recent years, "according to a recent comprehensive review of potential new treatments.[199] Experts believe that the "high mutation burden" of SCLC could be an asset; because SCLC tumors tend to have many genetic mutations – due to tobacco or other exposures – the cells look very different from regular cells, making it easier for the immune system to recognize and attack when prompted with immunotherapy. Despite this potential recognition, significant challenges remain with immunotherapies, since efficacy is modest and only about 20% of SCLC patients respond. Experts hope that predictive biomarkers could help select the patients who could benefit most from immunotherapies and combination treatments could increase the number of patients who respond.[200]

Researchers have several trials under way to assess the safety and efficacy of immunotherapies in several ways, including in combination with first-line chemotherapies; as second-line (or later) therapies alone or in combination; and as maintenance therapy. In addition, immunotherapy combined with radiotherapy is being explored in clinical trials.[201] SCLC remains a challenging disease to research as actionable targets have continued to elude researchers. Whereas in NSCLC researchers have

found a range of mutated proteins that drive the disease, in SCLC two of the main cancer-driver mutations are “loss of function mutations” which result in an inactive or less active protein. Drugs cannot target inactive or less active proteins the way they can target “gain-of-function mutations”.[202] Nevertheless, clinical trials have explored the use of several targeted therapies, including poly ADP ribose polymerase (PARP) inhibitors, drugs targeting DNA repair systems in cancer cells that leads to their death. This approach, paired with chemotherapy, has shown some efficacy in early phase studies.[203] [204] [205]

Studies are also underway to maximize use of chemotherapy for SCLC, with a range of chemotherapies tested as second-line options with only modest results. One of these opportunities is iurbinectedin, a cytotoxic drug is believed to inhibit hyperactive pathways in tumor cells that typically increase the number of cancer cells. The objective response rate (proportion of patients with tumor size reduction) was remarkable in clinical trials at 39.3% for patients with recurrent SCLC.[206] Iurbinectedin is currently undergoing FDA review.

“Immunotherapy has helped us break the code a little bit but not enough. So, clearly, combinations of immunotherapies with radiation or with chemotherapies are going to be important. Therapeutic targeting will also be important. I see, in the next five years, a revolution for SCLC that will help us break open the code even more.”

Ravi Salgia, M.D., PH.D., Arthur & Rosalie Kaplan Chair, City of Hope’s Cancer Center[207]

“Overall, there seems to be hope on the horizon for patients with SCLC after many decades of negative trials and promising but failed strategies that did not improve patient outcomes.”

Sen Yang, et al, Journal of Hematology & Oncology[208]

“Despite the history of clinical research in this disease, I am very optimistic about the likelihood of substantial change in the next decade [in SCLC].... This is a disease with a terrible prognosis and in tremendous need of clinical progress, but there is real hope that meaningful change will be accomplished with emerging targets and therapies.”

Charles Rubin, MD, PhD, Chief of Thoracic Oncology Service, Memorial Sloan Kettering Cancer Center[209]

Pancreatic Cancer – Looking for Greater Understanding After Setbacks

The American Cancer Society estimates about 57,600 new cases of pancreatic cancer will be diagnosed in the U.S. in 2020, and about 47,050 people will die from the disease. Pancreatic cancer accounts for about 3% of all cancers in the U.S. and about 7% of all cancer deaths, with a 5-year survival rate of just 9%. It is slightly more common in men than in women. The disease is often diagnosed at an advanced stage (53%) but even for those diagnosed when the disease is still localized, meaning it has not spread beyond the pancreas, 5-year survival is just 37%, compared with 3% for those with advanced-stage disease.[210] Studies project that pancreatic cancer will be the second leading cause of cancer-related death by 2030.[211]

Pancreatic cancer is a difficult disease to both diagnose and treat. It grows in an unusual pattern with long tentacles that spread into nerves and blood vessels making it hard to remove surgically. It also spreads to other parts of the body very quickly. The location of the pancreas and lack of early symptoms limit early diagnosis. By the time patients are diagnosed, the disease is often in late stages and treatment options are limited. The best outcomes are possible only at early stages when surgery is an option. Clinicians also currently rely on radiation and chemotherapy but are beginning to have new targeted therapies and immunotherapies available to help improve outcomes.[212]

Recent Progress

Although the 5-year survival rate for pancreatic cancer stands at just 9%, this actually reflects recent progress. If fact, there has been a 50% increase since 2010 when the survival rate was 6%, much of which is attributed to both improved treatments and an increase in the number of cases identified at an early stage.[213] [214] As with many cancers, surgery, radiation and chemotherapy remain the predominant treatment options to treat pancreatic cancer.

Many experts believe that the future of pancreatic cancer treatment lies in targeted therapies and immunotherapies – and recent advances have started to add these approaches to the treatment mix.[215] Despite these advances, finding success with these approaches has proven to be a particularly challenging road for this difficult to treat form of cancer.

For the most part, immunotherapies have not proven to be effective in improving outcomes for patients with pancreatic cancer, so research is underway to determine the reasons for this resistance (see “Looking Ahead” section below). However, there is one exception. In 2017, pembrolizumab, an immune checkpoint inhibitor, was granted accelerated approval by the FDA for an unprecedented tissue-agnostic indication. The immunotherapy was approved for use in patients with any solid tumor – regardless of place of origin in the body – that carries a specific mutation known as “microsatellite instability high” (MSI-high) or “mismatch repair deficient” (dMMR). The new indication not only marked the first tissue-agnostic oncology medicine to be approved by the FDA but also the first “personalized immunotherapy” for all cancer patients.[216] [217] However, it is estimated that 1 in 50 pancreatic cancer patients have such a characteristic, many of whom may have run out of other treatment options for this aggressive form of cancer. Scientists have shown that pembrolizumab can jumpstart the immune response in these patients, resulting in significant tumor shrinkages.[218]

This immunotherapy was followed by two similar tissue-agnostic targeted therapies with particular implications for patients with pancreatic cancer. Larotrectibim was approved in 2018 and entrectinib in 2019 for tumors with a neurotrophic receptor tyrosine kinase (NTRK) mutation, which is found in about 6% of pancreatic cancer patients.[219] [220] They can be used for any solid tumor with the mutation that is either metastatic, cannot be removed by surgery, has advanced after treatment, or has no good standard therapy available. Though these approvals mark another

important advance in providing treatments for all cancer patients, regardless of the tissue in which the cancer originated, these approvals are particularly important for those with pancreatic cancer who have limited treatment options.

Additionally, large-scale efforts have uncovered that some genetic mutations carried by pancreatic cancer patients can inform treatment in some cases. In 2019 the FDA approved the targeted therapy olaparib, a PARP inhibitor previously used for ovarian and breast cancer, as a maintenance therapy for patients with BRCA-mutated metastatic pancreatic cancer. This personalized medicine was shown to prevent progression of the disease for twice as long as placebo.[221]

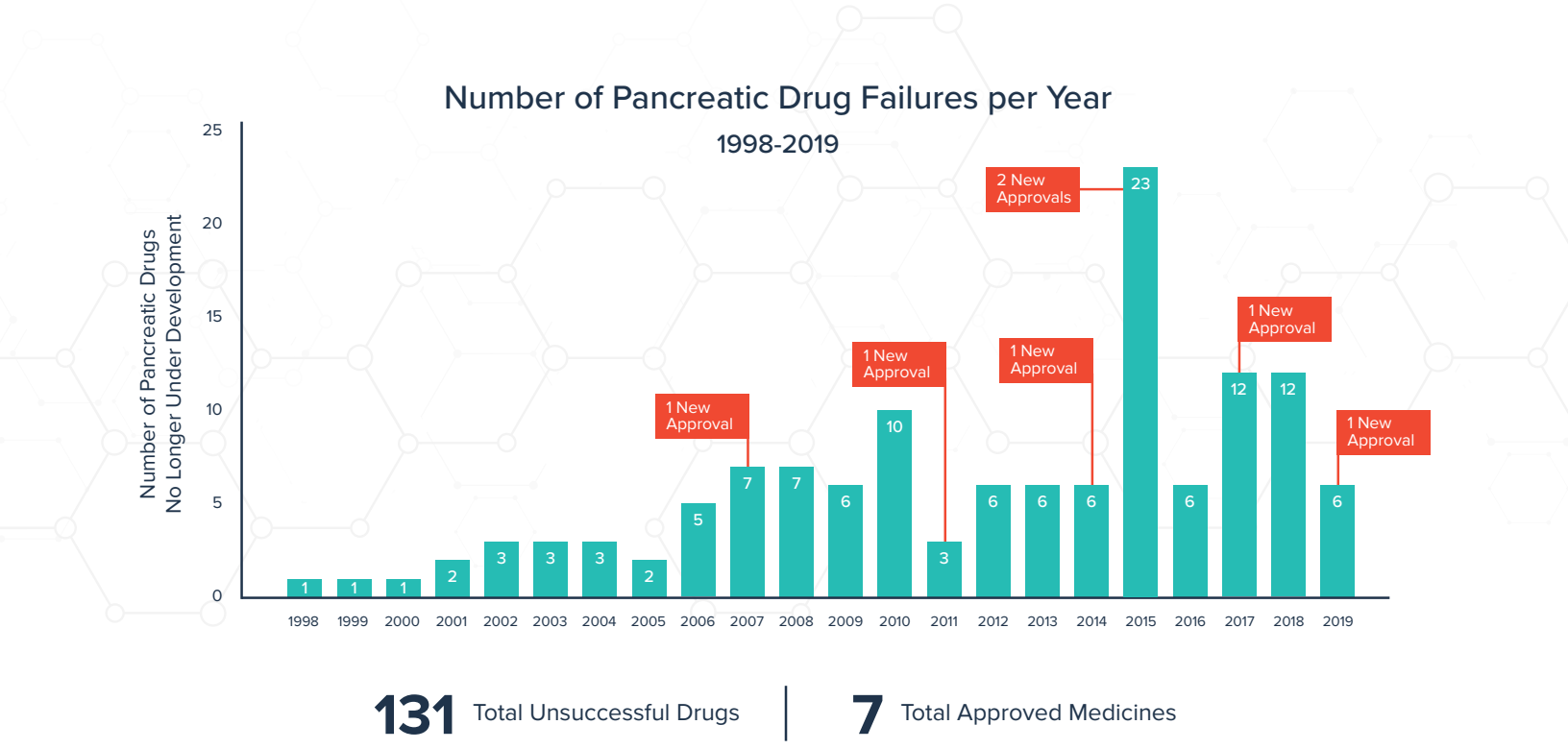
Collectively, these advances are offering hope to patients with pancreatic cancer and options where previously there had not been many for this particularly challenging cancer.

Building on Failures

Pancreatic cancer continues to be a difficult cancer to treat, as there have been many setbacks in drug research. Since 1998, there have only been 7 new drug approvals for pancreatic cancer while another 131 medicines have failed in the development process having been discontinued, suspended, or had no development reported.[222] That is a 19:1 ratio of unsuccessful attempts to FDA-approved medicines.

Pancreatic cancer has presented unique challenges to researchers. It has been less responsive to immunotherapies than other types of cancer for a range of reasons that researchers are working to understand. The driver mutations that have been found have not yielded successful drugs. For example, around 90% of patients with pancreatic cancer carry the KRAS mutation but researchers have struggled to find a drug that works against this mutation. As a result of these factors, combined with its tendency to progress quickly and to be diagnosed at an advanced stage, progress has lagged behind most other cancer areas.[223] [224]

Despite the challenges, immunotherapy and combined targeted therapies in conjunction with chemotherapy are believed to be the leading candidates paving the way for future treatment advancements.



131 Total Unsuccessful Drugs | **7** Total Approved Medicines

Looking Ahead

Researchers are determined to change the outlook for pancreatic cancer. Many approaches are being explored in the lab and there are currently more than 700 active or recruiting clinical trials for pancreatic cancer.[225]

Targeted therapies approved for other cancers, such as angiogenesis inhibitors, are being studied specifically for pancreatic cancer in clinical trials.[226] Another targeted therapy being explored involves using drugs that can target the stroma, the fibrous connective tissue around cancer cells that helps to support the cancer. Drugs that can disrupt the area around the cancer could make it easier for chemotherapies and other treatments to reach to tumor.[227]

Many experts believe that immunotherapy is the path to future progress against pancreatic cancer. So far though, pancreatic tumors have proven resistant to immunotherapies tested in clinical trials and no immunotherapies are approved specifically for pancreatic cancer. So researchers are working to better understand why this type of cancer is able to hide so effectively from the immune system – and how to overcome those barriers.[228] [229] Studies are examining why there are few immune cells in the vicinity of the tumor, how the dense surroundings impact the delivery of drugs and immune cells, and what signals the tumor produces to fool the immune system. In addition, pancreatic cancer cells carry an average of 45 mutations compared with 135 for melanoma, potentially explaining why melanoma is more readily susceptible to immunotherapies, as the cells appear more different from typical cells and the immune system more readily recognizes them.[230]

Additionally, researchers are studying treatments that can change how pancreatic cancer cells present themselves to the immune system in order to increase their visibility to the immune system and increase responsiveness. They are also exploring approaches to make the tumor microenvironment more conducive to immune activity, potentially combining drugs that impact the environment with immune checkpoint inhibitors.[231]

"Clearly, given the otherwise poor survival statistics for pancreatic cancer using our classical therapy options, the future of pancreatic cancer treatment lies in the development of novel agents to supplant or be added to current chemotherapy regimens."

Nathan Bahary, MD, PhD, UPMC Hillman Cancer Center[232]

"Immune therapy is the future. For the past 20 years, we've been using chemotherapy regimens with minor benefits. We need more tolerable medicines that allow for a good quality of life. Pancreatic cancer has been one of the most difficult cancers, no question."

Howard Crawford, PhD, Director of the Pancreas Disease Initiative, University of Michigan[233]

Ovarian Cancer – Working towards Transforming a Deadly Disease to a Chronic Illness

The American Cancer Society estimates about 21,750 women will receive a diagnosis of ovarian cancer this year and about 13,940 women will die from the disease in the U.S. A screening test for ovarian cancer is not available for widespread use and, as a result, a high proportion (59%) of those diagnosed already have distant-stage disease. The 5-year survival rate is 48% overall. For those with distant-stage ovarian cancer the rate drops to 29%, compared with 92% for localized disease.[234]

There are more than 30 different types of ovarian cancer, each classified based on the type of cell from which it originated. The most common type is epithelial ovarian tumors which start in the cells covering the outer lining of the ovaries and account for 85-90% of all ovarian cancers.[235]

The treatment for ovarian cancer includes surgery, chemotherapy, and targeted therapies. Surgery remains central to treatment of ovarian cancer and is also important to determining the extent of the disease. Chemotherapy is used in conjunction with surgery either before (neoadjuvant) to reduce the size of the tumor or after (adjuvant) to destroy any remaining cancer.[236]

Recent Progress

Advances in surgery and chemotherapy have resulted in high rates of remission of ovarian cancer, however the rate of recurrence is high as well.[237] For patients diagnosed at stage III or IV the chances of recurrence are between 70 and 95%.[238] Despite this, women are living longer; between 2007 and 2016 the death rate from ovarian cancer fell 1.6% per year.[239]

While surgery and chemotherapy remain the typical frontline therapy for newly diagnosed patients, new treatments have been added to the arsenal in recent years including several types of targeted therapies, many of which are given based on genetic testing. Due to these advances in treatment, many patients are able to have periods of no symptoms. As a result, a new goal has emerged of continuing to extend time to recurrence and managing the disease on a long-term basis, with the goal of transforming recurrent ovarian cancer into a chronic and more manageable illness.[240]

To achieve this goal, researchers have turned to maintenance therapies to help prevent and extend the time until cancer recurrence in ovarian cancer patients following surgery and/or positive response to chemotherapy. Significant improvements have

been made in this area in recent years using PARP inhibitors, which block one of the pathways cells use to repair DNA. In tumor cells, PARP inhibitors work alongside mutations in the BRCA genes (BRCA1 and BRCA2) to prevent DNA repair, leading the cancer cells to die.[241] Fifteen percent of women with ovarian cancer have tumors that possess a BRCA mutation and are unable to repair this DNA damage.[242]

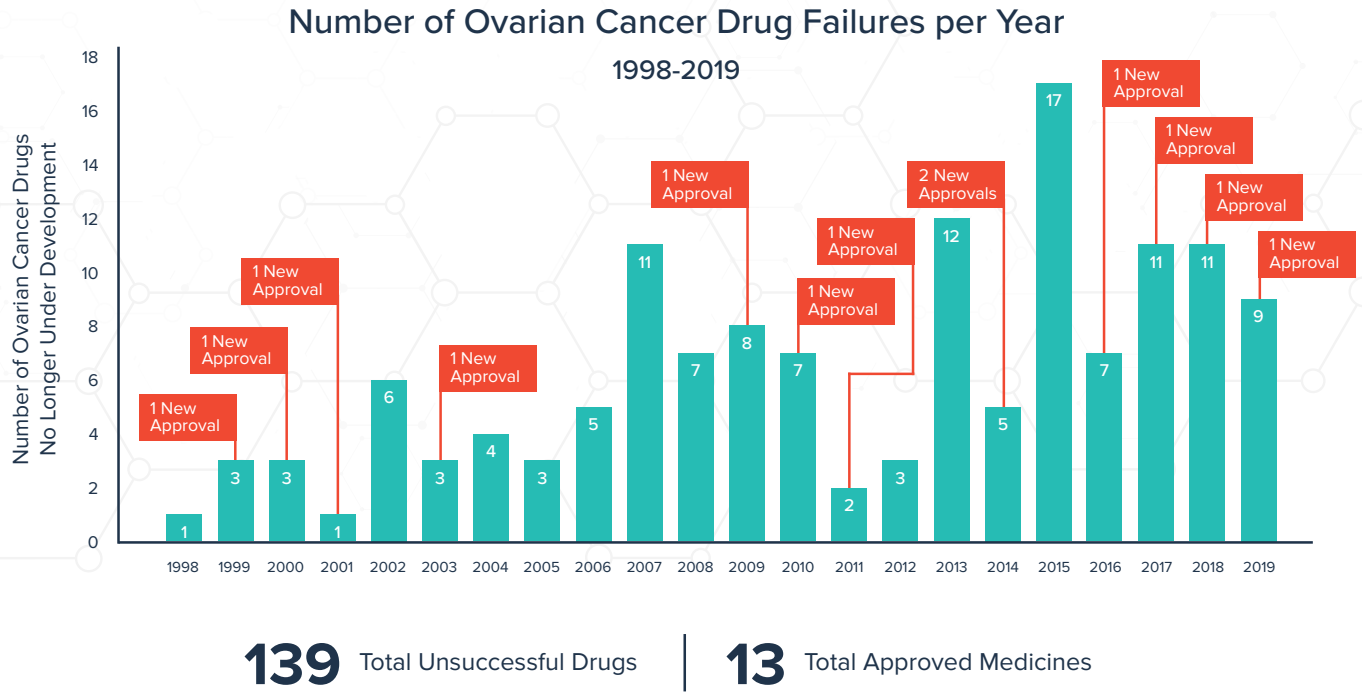
Three PARP inhibitors have been approved in the past several years as maintenance therapy for recurrent ovarian cancer patients: olaparib, rucaparib, and niraparib.[243] [244] [245] Each of these have been approved with a diagnostic test to determine who may best respond to treatment—including for those with a BRCA mutation and other biomarkers.

Angiogenesis inhibitors have also been shown to be effective in increasing response to treatment and extending the time to recurrence. Bevacizumab was approved in 2018 in stage III or IV disease combination with chemotherapy, followed by use alone to prevent the return of the cancer.[246] In trials leading to this recent approval, bevacizumab combined with chemotherapy treatment demonstrated a progression-free survival rate of 18.2 months compared to 12.8 months for patients receiving chemotherapy without bevacizumab, bringing patients one step closer to making recurrent ovarian cancer a chronic disease.[247]

Building on Failures

Since 1998, there have been 13 new drug approvals for ovarian cancer while another 139 medicines have failed in the development process having been discontinued, suspended, or had no development reported.[248] That is a 11:1 ratio of unsuccessful attempts to FDA-approved medicines.

Ovarian cancer presents a range of challenges to researchers. Because tools to diagnose the disease early are lacking, patients are largely diagnosed at late stages at which point it is more difficult to treat.[249] In addition, there is great variation across patients and a lack of understanding of how to group tumors into meaningful sub-groups.[250] While ovarian cancer remains challenging to treat, advances in new chemotherapy drugs, targeted therapies, and other approaches are helping transition this type of cancer to a chronic condition.



Looking Ahead

The momentum in recent drug approvals and critical data from clinical trials in ovarian cancer therapies has provided the framework for continued progress. In pursuit of making ovarian cancer a chronic disease, researchers are particularly focused on using new approaches to achieve longer lasting results and improve options for patients whose cancer recurs.

In addition to treating advanced ovarian cancer patients, research exploring PARP inhibitors in clinical trials are finding that the drugs might also benefit women who are newly diagnosed. Unfortunately, ovarian cancers can become resistant to PARP inhibitors. Scientists are seeking to better understand the causes of resistance, what biomarkers predict response, and ways to counteract it.[251] [252] They are also working to understand which patients are most likely to respond and why.[253]

Another targeted therapy, nintedanib, an angiogenesis inhibitor, is showing promise in preventing the growthof cancer cells in several tumor types, including ovarian cancer, in clinical trials. As a post-surgery therapy added to chemotherapy, nintedanib showed notable improvement in progression-free survival rates.[254] The availability of multiple angiogenesis inhibitors for ovarian cancer could allow for more personalized approaches to selecting treatments.[255]

Immunotherapies are also being actively explored for ovarian cancer with more than 220 active clinical trials under way. Immune checkpoint inhibitors have not been found to be particularly effective individually, but trials are testing whether they can improve outcomes when combined with chemotherapy or as part of a trio with chemotherapy and an angiogenesis inhibitor or PARP inhibitor.[256]

Another interesting immunotherapy under investigation is genetically-modified oncolytic virus therapy which uses a virus to infect and kill cancer cells and also promote a vaccine-like immune response. One study combines an oncolytic virus with a checkpoint inhibitor to stimulate the immune system in more than one way.[257]

"The standard of care seems like it's going to be changing very rapidly with the numerous trials that are on the horizon. So, it's a very exciting time to be taking care of women with ovarian cancer."

Dr. Thomas Krivak, MD, Director of Gynecologic Oncology, AHN Cancer Institute[258]

"Ovarian cancer is a disease where we really need new therapeutic interventions... there is going to be a lot that will begin to be put out there in the next 24 to 36 months, which will look pretty exciting."

Dennis J. Slamon, MD, PhD, Director Revlon/UCLA Women's Cancer Research Program, Comprehensive Cancer Center[259]

Prostate Cancer – New Options Target Remaining Needs

The American Cancer Society estimates about 191,930 new cases of prostate cancer will be diagnosed in the U.S. and about 33,330 people will die from the disease in 2020. Other than skin cancer, prostate cancer is the most common cancer in American men. Most prostate cancer cases (90%) are discovered at the early stage and 5-year survival approaches 100%. For those discovered at distant stage survival drops to 31%. The 5-year survival rate overall is 99%.[260]

Treatment options for prostate cancer are relatively broad depending on stage of diagnosis and characteristics of the patient. When diagnosed early, the most appropriate treatment for many patients is active surveillance rather than treatment because the cancer is often slow to progress. Early stage treatment options include surgery or radiation, which are often delayed until the cancer progresses. For patients with advanced cancer, the primary treatment options include hormonal therapy, chemotherapy, and radiation. Targeted therapies and immunotherapies are also beginning to be used.[261]

Recent Progress

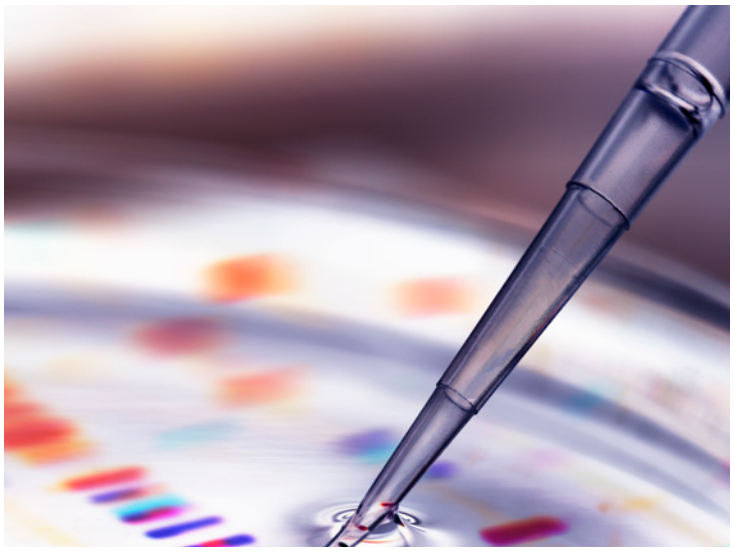
Mortality rates for prostate cancer have declined by more than 50% since their peak in 1993.[262] Much of this improvement has been due to increases in early detection, but we have also seen some encouraging advances in new treatment approaches. New therapies are needed for advanced and recurrent cancers because, although they often respond to treatments like chemotherapy and hormone therapy, they eventually become resistant in most cases.[263]

There has been a need for treatment options for patients who stop responding to hormonal therapy, also called androgen deprivation therapy (ADT), which lowers the levels of androgens (male hormones) in the body, slowing prostate cancer growth.[264] Hormonal therapy can sometimes control late-stage prostate cancer for long periods, but nearly all patients eventually develop “castration-resistant prostate cancer” (CRPC) where the cancer stops responding to ADT and continues to grow.[265] Chemotherapy may be an option in these cases, but researchers have made strides in recent years to develop novel strategies to address this unmet need in patients with CRPC.[266]

The FDA recently approved the first two PARP inhibitors to treat patients with metastatic CRPC and mutations in genes involved in DNA repair who have progressed following other treatments.[267] [268] PARP inhibitors target the DNA repair protein PARP, which causes the cancer cells to die.[269] One of the newly approved drugs, olaparib, indicated for the 20-30% of metastatic CRPC patients with a homologous recombination gene mutation, was shown to more than double progression-free survival compared to an existing treatment.[270]

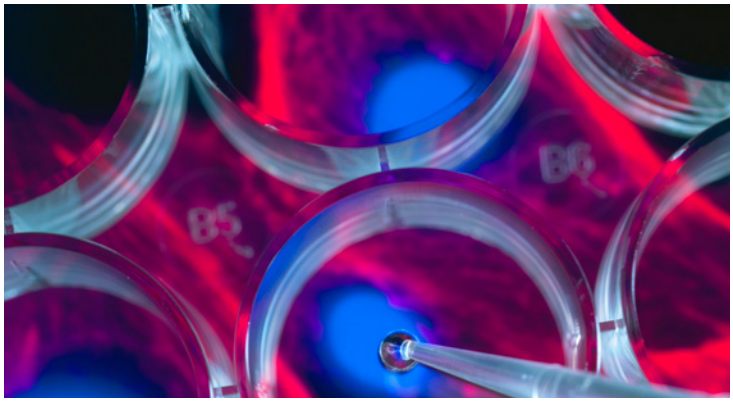
In addition, a new generation of treatments target androgen receptors (AR) on the tumor, blocking testosterone from binding and therefore improving outcomes in patients with CRPC by slowing proliferation of prostate cells.[271] In the last several years, there have been three new approvals for these targeted therapies for patients diagnosed with advanced prostate cancer. The latest AR inhibitor, darolutamide, received expedited approval in 2019 for non-metastatic CRPC. Darolutamide more than

doubled metastasis free survival (meaning the length of time that a patient survives and the cancer has not spread to other parts of the body) compared with placebo (40.4 months vs. 18.4 months).[272]



We have also seen some early progress with immunotherapy treatment of prostate cancer. In 2010 FDA approved sipuleucel-T, the first therapeutic vaccine to treat any cancer, for metastatic castration-resistant prostate cancer. The vaccine helps men with advanced prostate cancer live longer and is developed for the individual patient using their own white blood cells, and works by stimulating the immune system to attack the tumor.[273] As an early immunotherapy, an understanding of the benefits of the treatment were not fully realized until years later with real world use. A 2020 study found sipuleucel-T reduced the risk of death by 45% at three years when added to existing treatment regimens for CPRC patients.[274] With a lack of significant side effects, therapeutic vaccines can induce an immune response that can continue to adapt and expand following the initiation of the vaccine, warranting future exploration from researchers.[275]

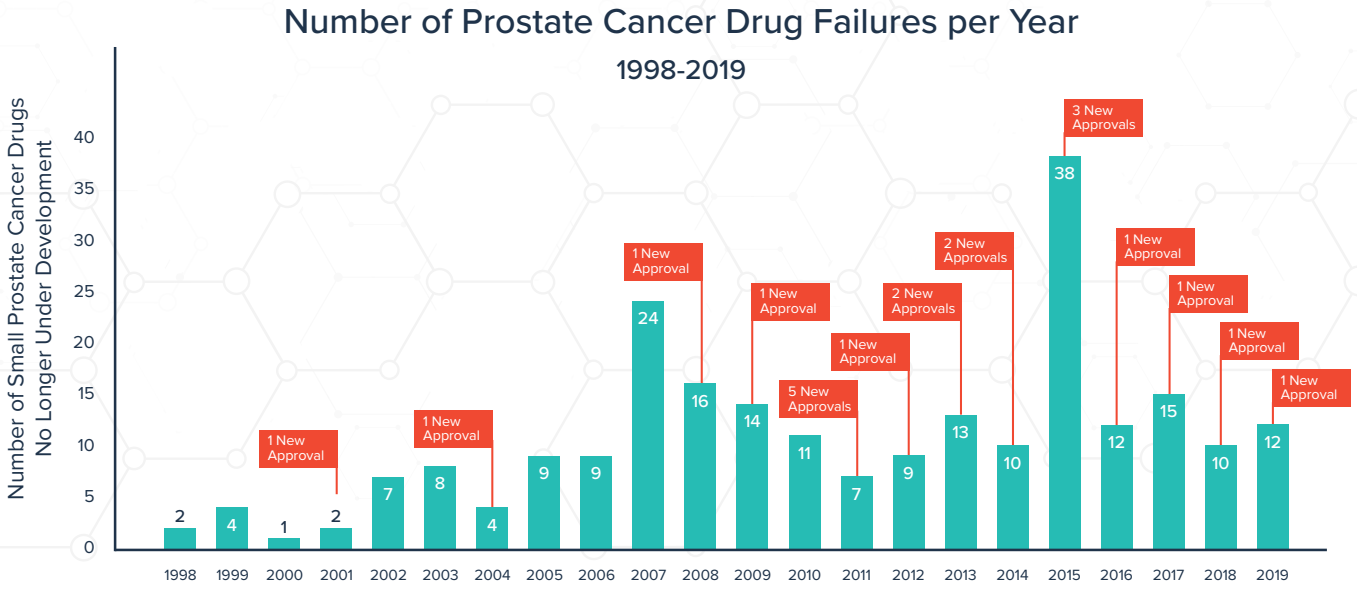
Although immunotherapy was available early for prostate cancer patients, very few immunotherapy treatments have followed. The only other immunotherapy approval that is available for prostate cancer patients is the checkpoint inhibitor pembrolizumab, which is a tissue agnostic therapy approved for any cancer patient with certain mutations , regardless of where the cancer originated. The treatment is approved only for patients with MSI-H or MMR who have progressed after other treatments and who have no satisfactory treatment options remaining.[276] [277] Only about 3% of prostate cancers are believed to carry these mutations.[278]



Building on Failures

Although a wide range of treatments are available to treat prostate cancer and survival rates are high, effective drugs are still needed – particularly for advanced, resistant or recurrent disease. Since 1998 there have been 21 new drug approvals for prostate cancer while another 237 medicines have failed in the development process having been discontinued, suspended, or had no development reported.[279] That is a 11:1 ratio of unsuccessful attempts to FDA-approved medicines.

Researchers have faced many challenges in making progress against more advanced forms of the disease. In the immunotherapy space, immune checkpoint inhibitors have generally not proven effective in treating prostate cancer, in part because few T cells are found in the tumor microenvironment of prostate cancer, but also because the relative number of mutations “in prostate cancer cells is relatively low compared to cancers where checkpoint inhibitors have been more successful. When the number of mutations is high, a cancer cell will look distinct from healthy cells, sometimes making it easier to induce an immune response. Only in the case of MSI-H/MMR mutations have checkpoint inhibitors been more effective, possibly because those mutations impact the tumor’s ability to repair DNA, increasing the number of mutations within the tumor.[280]



237 Total Unsuccessful Drugs | **21** Total Approved Medicines

Looking Ahead

New approaches to the treatment of prostate cancer are increasing optimism regarding the pipeline. Gene therapies are also being pursued for prostate cancer, but their use is limited because of a lack of delivery mechanisms that can deliver the therapy to the cancer cells. A "seek-and-destroy" nanomedicine is currently being tested in preclinical studies that is able to deliver gene therapy by targeting a receptor – lactoferrin – found on the surface of cancers. Early lab results show this potential treatment kills 50-70% of cells in the forms of prostate cancer studied.[281]

Given the recent advances in immunotherapy across many cancers, researchers are also testing the efficacy of this class of medicines in prostate cancer. Currently, clinical trials are assessing immune checkpoint inhibitors and T cell-stimulating immunotherapies. The goal is to use immunotherapy as a combination strategy, and to ultimately transition advanced prostate cancer to a chroni and manageable illness rather than a life-threatening disease.[282]

Although immunotherapies currently work for a subset of prostate cancer patients, researchers are working to help many more patients benefit. Earlier studies found that treating prostate cancer with a CTLA-4 checkpoint inhibitor brought more T cells to the area of the prostate tumor but did not kill the cancer cells. Instead, the cancer cells increasingly blocked the immune system with other molecular pathways such as PD-1 or PD-L1. Subsequent studies added a PD-1 inhibitor to the treatment regimen which improved the response rate with some patients having a durable response. A key question of the research is why some patients benefit and others do not.[283]

"Since 2010, there have been several new drugs that have been FDA approved for prostate cancer, but none of them are curative. And so the point of clinical trials is we hope that we are finding rational combinations that will improve the patient's outcome and especially with immunotherapies, we're hoping to lead to a cure."

Sumit K. Subudhi, MD, PhD, Assistant Professor, Department of Genitourinary Medical Oncology, University of Texas MD Anderson Cancer Care Center[284]

Transforming Research Setbacks into New Hope for Patients

We know more than ever before about the underlying causes of many cancers. With a better understanding of how cancer cells originate, grow, and spread on the molecular and cellular level, biopharmaceutical research companies continue to make strides in developing innovative therapies that improve the outlook for patients. The more that is gleaned from research, the greater opportunity for turning many cancers into manageable conditions, preventing cancers from occurring or recurring, and even curing patients of the disease.

In recent years we have seen tremendous progress in treating some difficult-to-treat cancers, such as melanoma and non-small cell lung cancer. In other areas, such as pancreatic, brain, and small-cell lung cancer, we still have much to learn in order to more effectively treat patients and help them live longer and healthier lives.

As researchers explore all potential avenues to stem the tide against cancer, the road to progress is paved with many disappointing setbacks along the way.

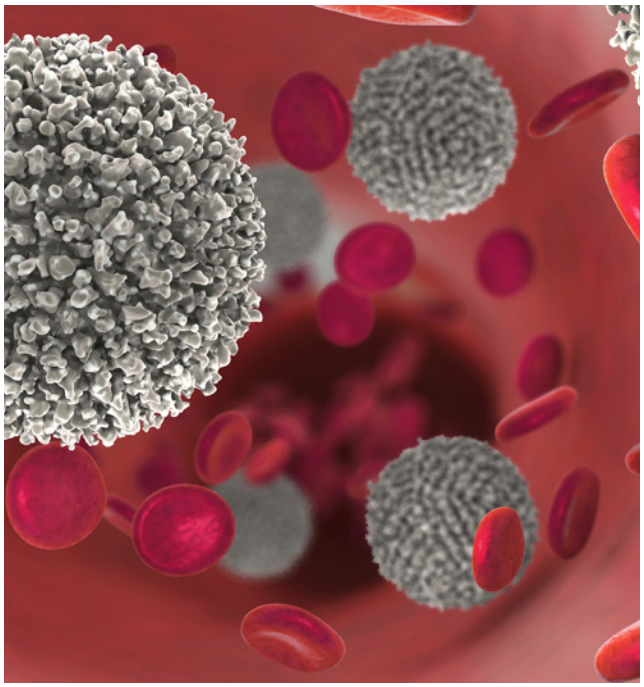
While many are aware of the successes reported from clinical trials, less attention is paid to the so-called failures. However, learnings from each setback is applied to inform other lines of research, making them more likely to succeed. The nature and complexity of cancer and the development of new cancer drugs make finding treatments and cures extremely 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 1,100 new medicines in clinical development to fight cancer.[285] These investigational drugs are as diverse as the types of cancer they are targeted to treat. An average of 74% have the potential to be first-in-class medicines, meaning they would represent novel approaches to combating cancer.[286]

The findings of this report reinforce the value and importance of a robust research and development ecosystem to continue to explore the frontiers of scientific innovation and to find new ways to transform today's 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 should be one of the nation's highest health priorities.

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 "acute myeloid leukemia," "brain cancer," "kidney cancer," liver cancer," "lung cancer," "small cell lung cancer," "malignant melanoma," "ovarian cancer," "pancreatic cancer," or "prostate." 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. The year that each event occurred was determined by the date associated with the entry in the Adis database.



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 November 5, 2019.

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