

Emerging Value in Oncology

HOW ONGOING RESEARCH EXPANDS THE
BENEFITS OF ONCOLOGY MEDICINES

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Introduction

Emerging science continues to drive progress in the fight against cancer

The advances in research and development (R&D) of new treatment options seen in recent decades have yielded great progress in the fight against many cancers. This new era of cancer treatment is driven by a greater understanding of the molecular and genetic underpinnings of cancer and breakthrough discoveries that have fueled novel treatment approaches. The resulting paradigm shift in cancer treatment has in turn led to improved survival across a wide range of cancers.¹

Central to this transformation is an increasing focus on personalized or precision medicine, including the development of medicines which directly target mechanisms that drive cancer cell growth.² Medicines today are increasingly capable of targeting the specific genetic features of an individual patient's tumor or enlisting the immune system to fight cancer, improving treatment outcomes and revolutionizing the way the disease is treated. As a result, due in large part to many remarkable treatment advances and improved detection, cancer death rates have declined by 33% since peaking in the early 1990s, with some of the biggest annual declines seen in more recent years.³


A growing body of evidence underscores the role of new medicines in the recent declines in mortality and improved survival across a range of cancers. For example, dramatic declines in lung cancer and melanoma mortality are widely attributed to advances in targeted therapies and medicines targeting the immune system.^{4,5} One study, looking across the 15 most common tumor types, found that new cancer medicines approved between 2000 and 2016 alone were associated with nearly 1.3 million prevented cancer deaths. In particular, this finding translated to nearly 130,000 prevented breast cancer deaths, nearly 400,000 prevented lung cancer deaths, and nearly 500,000 prevented prostate cancer deaths over this period alone.⁶

Today, there are now more than 18 million cancer survivors in the United States, and 69% of cancer survivors have lived more than five years since their diagnosis.⁷ While significant unmet medical need remains, in this new era of cancer treatment, the application of groundbreaking treatment approaches and the development of new medicines to address unmet needs offer enormous potential to continue to improve survival for patients with a wide range of cancers in the years ahead.

Ongoing research reveals additional benefits to patients over time

While each medicine approved by the U.S. Food and Drug Administration (FDA) adds another tool in the fight against cancer, many advancements for patients are realized through continued investment in R&D after initial approval, known as post-approval R&D. Initial FDA approval is a significant milestone based on a medicine's safety and efficacy demonstrated through robust clinical studies, but it may not reflect a new medicine's full therapeutic potential. Afterwards, additional scientific knowledge is gained through post-approval R&D, which involves evaluating the safety and efficacy of an approved medicine for new uses. This critical R&D often requires lengthy and complex clinical trials exploring the potential benefit of a medicine for different cancer types, settings and patient populations. It also includes the continued conduct of clinical trials to determine the benefits of medicines to patients over the long-term for already approved uses.

Post-approval R&D is particularly important in cancer and much of the unprecedented progress seen in the fight against cancer over the past decade has been the result of this form of research and driven by growing bodies of evidence and R&D to advance subsequent approved uses in different forms of cancer or treatment populations.⁸ In fact, the majority of cancer medicines receive approval for more than one indication, with many received years after the medicine's initial approval.^{9,10}



The critical role of post-approval R&D in advancing new cancer treatments is in part due to the nature of cancer itself, the practical manner in which research on the value and benefits of a medicine is conducted, and how scientific evidence accumulates over time. This process often reveals a better understanding of the disease pathways shared by different cancer types to inform potential new uses of medicines in different forms of cancer. As a result of these shared pathways, oncology medicines are increasingly developed to treat multiple cancer types.¹¹ Likewise, researchers typically begin cancer R&D in narrowly defined patient populations with advanced stages of cancer or that have exhausted other treatment options.^{8,11} But once a medicine has been shown to be safe and effective in these populations, researchers may seek to introduce the medicine in earlier stages of the disease where a new treatment is more likely to significantly modify the disease course by slowing or halting progression.¹² Additionally, as cancer is often best attacked on multiple fronts to prevent treatment resistance, patients with cancer frequently benefit from combination treatment approaches which may also be explored after initial approval. As a result, post-approval R&D can lead to a greater understanding of the use of combinations of multiple medicines that may have greater efficacy than a single therapy.¹³

In addition to post-approval R&D driving new uses, it also brings greater knowledge on the benefits of medicines. Due to the life-threatening and progressive nature of cancer, long-term follow-up of patients in clinical studies is often needed to evaluate overall survival, which is the length of time that patients with the disease are still alive since beginning treatment. These additional studies conducted after approval are an important way to see how well a cancer treatment works and though they can take significant time are critical to realizing the full therapeutic value of cancer treatments.¹⁴

New law threatens innovation

The recently enacted Inflation Reduction Act (IRA) fails to acknowledge the importance of post-approval R&D in oncology, jeopardizing future treatment discovery and innovation. That is because specific provisions of the law allow the government to set prices for eligible medications well before the treatments would otherwise typically face generic or biosimilar

competition (see *Government Price-Setting Impact on Treatment Innovation*). This shortened timeframe means biopharmaceutical companies must make difficult decisions about whether it is feasible to invest in post-approval R&D that could lead to important new uses for already approved medicines. In addition, the law in particular jeopardizes the development of small molecule medicines—those which typically come in pill or capsule form—by affording them a shorter timeframe on the market before government price setting than other medicines. This “pill penalty” means, the law risks leaving patients without desperately needed treatment options.

Specifically, the IRA price-setting provisions compress the timeline manufacturers have to earn revenues on their products, particularly for small molecule medicines and post-approval research, which may prevent manufacturers of cancer medicines from pursuing critical research for patients. Because post-approval research is particularly critical to the advancement of new treatments for cancer patients and small molecule treatments are so central to the treatment of cancer, the IRA has a disproportionate impact on oncology R&D. Moreover, as post-approval R&D often leads to treatments for additional forms of cancer, including rare cancers (see *Rare Cancers*) and for other patient populations where existing treatment options may be lacking, such as children or the elderly, the impact of the IRA on advancing new treatments for these patients can be expected to be more severe.

As a result of the disincentives created by the law, companies may now have to make the difficult decision to choose early indications with the greatest economic value rather than the greatest unmet need. As a result, in many cases, patients with rare types of cancers may have to wait until later in the development program or worse, those indications may not be pursued at all.

Understanding the full clinical value of a cancer treatment

This publication provides a framework for understanding the typical course by which value evolves for cancer medicines. Case studies of cancer treatments approved in the last decade show some of the primary mechanisms through which the full clinical value of a cancer therapy typically emerges over time following

initial FDA approvals. This additional value is often revealed through the following categories:

- *Additional Benefits Revealed within an Approved Indication:* After initial approval, years of continued research and accumulation of data may demonstrate even greater benefits to patients within an FDA-approved indication.
- *Use in Earlier Treatment Line or in Earlier Disease Stage:* Cancer medicines are often initially approved in patients with more advanced stages of disease and in those who have exhausted other treatment options. Additional research may reveal over time that the medicine is beneficial before trying other treatments or in earlier disease stages.
- *Use in Additional Types of Cancer:* Additional R&D may

reveal a medicine is beneficial in other types of cancer.

- *Use in Combination with Other Agents:* Oftentimes, research reveals a medicine is more effective when used in combination with another therapy than when used alone.
- *Use as Tumor-Agnostic Treatments based on Biomarkers:* After initial approval, additional studies may reveal a cancer medicine is beneficial to patients with a specific biomarker—regardless of where the cancer originated in the body.

Exploring these examples of clinical value through the case studies detailed in this report underscores the importance of ongoing research that has driven the unprecedented advancements in cancer treatment, specifically those occurring over the last decade.

Importance of Distinct Treatment Approaches

All types of cancer begin with certain changes to genes that control cell function, especially how they grow and divide. These genetic changes, or mutations, can originate in almost any part of the body and can cause cancerous cells to grow unchecked and subsequently spread.¹⁵ Historically, cancer has often been treated with chemotherapy that broadly attacks actively dividing cells, including healthy cells. Though these medicines are often effective and broadly used today, due to their less targeted approach they can also cause significant side effects.¹⁶

As more has been discovered about the genetic changes that lead to the development of various types of cancer, researchers have been able to design therapies capable of targeting specific mechanisms of cancer, such as genes or proteins that are present or active in cancer cells or on the surface of cancer cells. At the same time, an increasing understanding of the complex ways in which a patient's immune system can interact with cancer cells has led to the development of groundbreaking new treatments that enlist the immune system to fight cancer. Collectively, the emergence of these novel treatment approaches has produced a paradigm shift in treatment, enabling a move away from chemotherapy towards more targeted approaches focused on the drivers of cancer.¹⁷

Cancer cell growth is driven by a diverse set of molecular changes and underlying mechanisms that affect a patient's disease, including how their cancer will respond to a particular treatment.^{18,19} Cancer biomarkers are genes, proteins, or other substances that can be tested to reveal important details about a patient's cancer. These biomarkers are critical for the advancement of precision medicine as they can help identify patients most likely to benefit from certain therapy options.²⁰ The variability in cancer, in both the disease and response to treatment, highlights the importance of targeting cancer through different mechanisms with a range of therapeutic options to improve patient outcomes.¹⁹

Cancer therapies may come in two different forms which each bring unique benefits based on the way they interact with cancer cells within the body. As a result, each of these forms of medicines are essential components of the cancer treatment arsenal as they provide the tools necessary to target the distinct mechanisms involved in the many different diseases collectively known as cancer.²¹

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Small molecule medicines Due to their size, small molecule medicines can cross cell membranes to affect processes within the cell. For example, targeted small molecule cancer therapies can act upon specific proteins or genetic material inside cancer cells, causing cancer cells to die.²² As cancer begins with genetic changes occurring inside cells, targeted small molecule medicines provide an essential tool in combating the cause of cancer. Moreover, as they are often taken orally, they offer convenience to patients.^{16,23}

Biologic medicines Also referred to as large molecule medicines, biologics are a type of treatment that is made from or in living organisms and structurally more complex than small molecule medicines.²⁴ Due to their larger size, biologics are generally unable to enter cells, but rather are designed to reach therapeutic targets on the surface of cells. For example, monoclonal antibodies, a common form of biologic targeted therapy, are immune system proteins created in the lab to interact with specific targets found on cells, such as cancer cells.²⁵ Usually, biologics are administered to the patient via an injection or infusion.²⁶

Researchers have developed a range of small molecule and biologic treatment approaches in recent years, which collectively address the variability in cancer and have revolutionized the field of oncology. Examples of key breakthrough drug classes that are featured throughout the report include:

- **Antibody-drug conjugates (ADCs)** are *small molecule/biologic hybrid medicines* that bind to specific proteins on target cells and attack those cells directly.^{27,28}
- **Chimeric antigen receptor (CAR) T-cell therapies** are *biologic medicines* which involve isolating a patient's own immune cells and genetically modifying them in a lab to fight cancer. The modified cells are then returned to the body to attack cancer cells (see *Groundbreaking Cell and Gene Therapies*).²⁹
- **Immune checkpoint inhibitors** are *biologic medicines* that block certain proteins that regulate immune cells, which helps activate a patient's own immune system to fight cancer cells (see *Immune Checkpoint Inhibitors: Revolutionizing Cancer Care*).³⁰
- **Poly ADP-ribose polymerase (PARP) inhibitors** are *targeted small molecule medicines* that are known to target pathways that preferentially kill cancer by preventing cancer cells from repairing their damaged DNA.³¹
- **Tyrosine kinase inhibitors (TKIs)** are *targeted small molecule medicines* that block enzymes called tyrosine kinases that may be too active or occur at high levels in certain cancers. TKIs may target a single or multiple tyrosine kinases and blocking them may help to keep cancer cells from growing.^{32,33}

While new therapies have made critical contributions to the treatment arsenal in cancer, a wide range of different types of these therapies are very much needed to attack cancer on multiple fronts as cancer cells can find ways to become resistant to treatment. Resistance can happen for a number of reasons. The target itself can change, and therefore a therapy may no longer be able to interact with the target, or sometimes cancers can adapt and find ways to rely on other pathways to grow that do not depend on the original target. For these reasons, continued R&D to find effective combination treatment approaches provides the best opportunity to fight cancer and combat resistance.¹⁷

Government Price-Setting Impact on Treatment Innovation

The IRA, signed into law in August 2022, includes several provisions that will allow the government to set the prices of eligible prescription medicines in Medicare. Small molecule medicines can be selected just seven years after U.S. FDA approval and biologics, or large molecule medicines, can be selected at year eleven—with the government-set price taking effect two years later. Additionally, the number of drugs the law requires to be selected for government-set prices will increase over time.³⁴

The IRA's timeline for price setting will have substantial unintended consequences on drug development, especially as biopharmaceutical manufacturers will be forced to rethink how they invest in medical innovation and make difficult decisions on researching and developing new uses for a treatment after initial approval. This shortened timeline for earning potential revenues will impact the future development of treatments and post-approval R&D with a particularly acute impact on cancer where this type of research is so important. In fact, among small molecule cancer medicines that received initial FDA approval between 2006-2012, 61% received approval for at least one additional indication, and 22% received three or more. Of these post-approval indications, 41% of them occurred seven or more years after the medicine's initial FDA approval.⁹ Unfortunately, the shorter timeline afforded small molecule medicines especially disadvantages these medicines which are so critical to the treatment of cancer. Currently, small molecule medicines typically have 13 to 14 years on the market before they face generic competition.³⁵ Because small molecule medicines can be selected after only seven years on the market and the necessary clinical trials to support post-approval R&D can take up to four or longer years to complete, companies may find it infeasible to continue additional R&D even 3-4 years after initial approval—well before current timeframes for ongoing investment in critical post-approval R&D.³⁶ This shift will significantly curtail expected returns which often support future R&D, forcing companies to make tough decisions about how and where to invest.

IRA Price Setting Impact

Small Molecule Medicines



Biologic Medicines



**Given the uncertainty imposed by the potential for government price-setting, manufacturers must consider the feasibility of initiating and completing clinical trials as well as having sufficient time to earn revenues well in advance of selection. Given the complexities and variability of these considerations from molecule to molecule—including those unique to biologic medicines relative to small molecule medicines—the timeframe noted for "R&D decisions accounting for price setting" is intended to be viewed as illustrative only.*

A range of factors are considered by biopharmaceutical companies when weighing which therapeutic areas to invest in and whether to move forwards with R&D programs specific to a particular molecule. Historically these decisions have been driven by promising science. However, the IRA's price setting provisions compress the time period during which companies may conduct R&D, receive FDA approval and potentially earn revenues on those investments. As a result, companies are now being forced to reconsider R&D decisions and reassess future investments.³⁷ Unfortunately, with disincentives placed on post-approval R&D, the full value of medicines may never be realized, and patients may be left without desperately needed treatment options. Underscoring this impact, a recent survey of biopharmaceutical companies found when facing hard investment choices, 95% said they expect to develop fewer new uses for already approved medicines, with 82% expecting "substantial" impacts on cancer R&D.³⁸

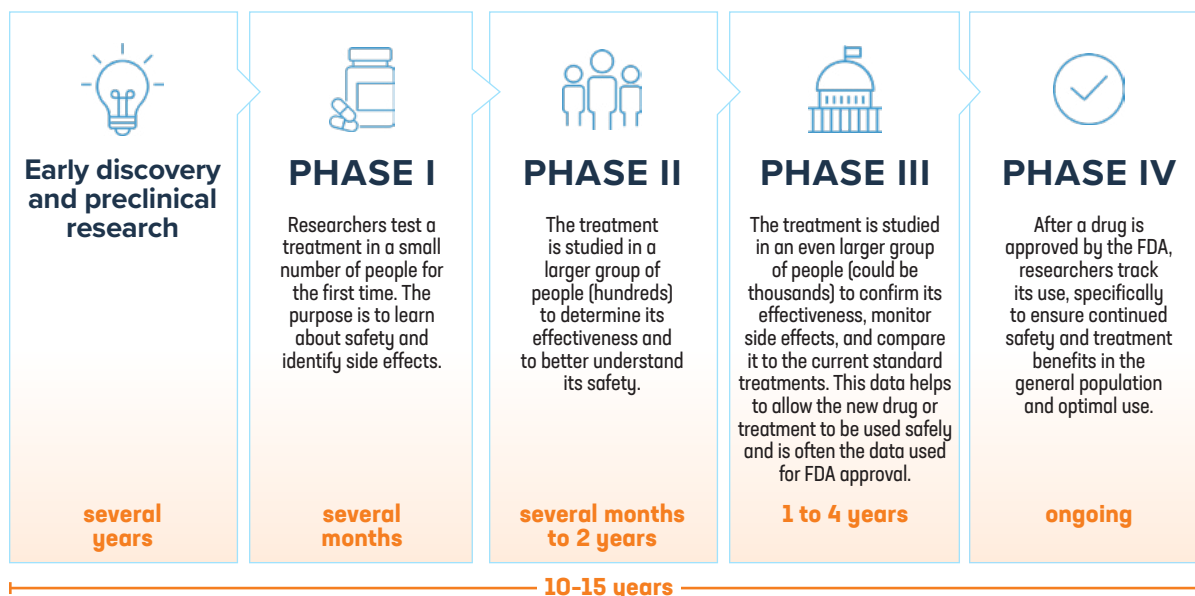
Research and Development Process

The path from understanding a disease to treating it with a safe and effective medicine is long, complex and costly. Before a drug is tested in patients in clinical trials, basic research aims to discover clues about how to treat a disease and its symptoms, with the goal of identifying targets for new potential medicines.³⁹ At this stage, thousands of compounds may be potential candidates for development as a medicine.⁴⁰ Only after this initial research is a lead compound identified: a promising molecule that could influence the target, via laboratory experiments, and, potentially, become a medicine. Then researchers must investigate whether the candidate medicine has the potential to cause serious harm, also called toxicity, while also verifying its effect on the disease, typically employing various testing methods.³⁹

Following this research and pre-clinical testing, an investigational new drug application is submitted to the FDA, at which point the medicine enters clinical trials and is tested in actual patients—a lengthy, multi-phase, rigorous process—to generate the scientific evidence required for FDA approval.³⁶ From drug discovery to approval, it takes an average \$2.6 billion and 10-15 years to demonstrate that a drug is effective and safe.^{39,41} Yet, even with significant investment and effort to bring forth a new medicine, the odds of success are quite low, with just about 12% of investigational medicines entering clinical trials estimated to obtain FDA approval.³⁷

Three types of clinical trials are often conducted prior to approval (Phase I, II and III), and one type is completed after FDA approval (Phase IV)⁴²:

Clinical Trial Phases



After initial FDA approval, additional clinical studies—often involving Phase II or Phase III trials—are conducted to understand the benefits of a medicine in other types of cancer, treatment populations or in combination with other therapies. Additionally, many of these clinical trials may be ongoing and continue after FDA approval to determine the long-term outcomes of treatment that could not be known at the time of approval.

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Clinical Trials in Oncology

Significant investments over the last decade have catapulted oncology to the forefront of medicine, where not only are the most innovative technologies advancing the development of new therapies, but the newest techniques and approaches are driving innovative conduct of clinical trials. As a result of these advances, oncology trials utilize novel trial designs more often than other disease areas, with 13% of oncology trials in 2021 utilizing novel mechanisms.⁸

Oncology trials can be more complex than other therapeutic areas due to the greater number of trial endpoints required for these trials as well as the time needed for long-term endpoints like survival. At the same time, the greater eligibility criteria required for oncology trials and difficulties faced by patients with life-threatening diseases such as cancer contribute to the growing challenge of recruiting and retaining patients to successfully advance through the trial process. Though increased complexity can contribute to extended trial timelines, advances in novel trial designs can also drive efficiencies in the process, by enabling the consolidation of phases, facilitating program efficiencies, and identifying patients responding to treatment more effectively across a range of options, potentially bringing treatments to patients in a shorter timeline.^{8,43,44}

Due to the growing complexities and challenges associated with oncology clinical trials, failures are an inevitable consequence of conducting research in this area, particularly as researchers explore new frontiers to address high unmet medical needs. For example, one analysis of nine different cancers found between 1998 and 2020, there have been 1,366 unsuccessful investigational medicines that failed to achieve FDA approval, with just 115 actually gaining FDA approval.⁴⁵ While disappointing, researchers leverage the information gained from these setbacks to inform R&D projects and the collective evidence to advance new treatments for patients. This knowledge and continued advances in research have contributed greatly to the improved treatment outcomes many cancer patients are experiencing today.

Additional Benefits Revealed within an Approved Indication

When studying a new potential treatment, it may take an extended period of time—sometimes many years—to measure and confirm a drug’s long-term clinical benefit through endpoints such as overall survival. For new drugs that fill a significant unmet medical need for a serious condition, the FDA may grant approval based on surrogate or intermediate clinical endpoints to get needed medications to patients more quickly. Surrogate and intermediate endpoints—such as measures of tumor shrinkage—are not direct measurements of clinical benefit themselves but are used to predict clinical benefit.⁴⁶

The FDA has a number of expedited approval programs aimed to speed the development and review of drugs that are intended for serious conditions with unmet medical need with the goal of making those drugs available to patients sooner. These include fast track review, breakthrough therapy and priority review designation and accelerated approval.⁴⁷ The accelerated approval pathway enables earlier access to medicines that address an unmet medical need for serious or life threatening diseases and conditions, while preserving FDA’s high standards for safety and effectiveness. Accelerated approval has been very successful in providing earlier access to treatment for patients with cancer. Treatments approved under accelerated approval are often approved utilizing a surrogate endpoint that are reasonably likely to predict clinical benefit and require additional research to confirm the clinical benefit.⁴⁶

This approach to expedite drug development and regulatory review can save valuable time in the process, allowing patients earlier access to potentially life-saving treatments. In many cases, in addition to confirming the predicted clinical benefit, years of continued research and accumulation of data may demonstrate even greater benefits to patients—such as reduced risk of death and improved survival—than could be known at the time of initial approval.

Fam-trastuzumab deruxtecan-nxki (ENHERTU®)

Trastuzumab deruxtecan*—a treatment that targets the human epidermal growth factor receptor 2 (HER2) protein—is part of a class of targeted cancer medicines called ADCs, which bind to specific proteins found on target cells and attack those cells directly.^{27,55} It was initially granted accelerated approval in 2019 for patients with hard-to-treat HER2-positive metastatic breast cancer after two prior lines of anti-HER2-based treatment. Trastuzumab deruxtecan was given an FDA priority review designation, which expedites the review

“The main goals of therapy for advanced breast cancer are to control the disease and improve survival, and it is therefore critical to continue to improve upon existing treatment options, particularly in the metastatic setting. For patients with HER2-positive breast cancer who experience disease progression following initial treatment in the metastatic setting, ENHERTU has shown significant improvement in survival compared to [standard of care], further confirming this medicine as the new standard of care.

—Sara Hurvitz, MD, Medical Oncologist, Professor of Medicine, and Director of the Breast Cancer Clinical Trials Program in the Division of Hematology-Oncology at the David Geffen School of Medicine at UCLA, and Medical Director for the Clinical Research Unit at the UCLA Jonsson Comprehensive Cancer Center in Santa Monica, CA⁵⁸

*Full US generic name: fam-trastuzumab deruxtecan-nxki

Clinical Trial Endpoints

A clinical endpoint is an outcome that can be measured objectively to determine the benefit of investigational medicines.⁴⁸ The FDA uses study endpoints to evaluate whether an investigational medicine is beneficial to inform drug approval decisions. While prolonging overall survival is the primary goal of cancer treatments, survival data can take years to mature, so medicines are sometimes approved using surrogate endpoints—such as measures of tumor shrinkage—that are not direct measurements of clinical benefit themselves, but are used to predict clinical benefit.⁴⁹ Some of the most common clinical measures in cancer research include^{43,50,51}:

- **Overall survival (OS):** Measures how long patients live compared to a control group. OS is considered the most reliable endpoint, and if a clinical study demonstrates improved OS, it provides evidence of the drug's value in prolonging a cancer patient's life.
- **Progression-free survival (PFS):** Measures how long patients live without the disease worsening.⁵² PFS results are often available earlier than OS data, which can take years to mature.
- **Objective response rate (ORR):** Indicates the proportion of patients in a clinical study whose cancer shrinks or disappears after treatment, which offers tangible proof that a treatment is working.⁵³
- **Duration of response (DOR):** Measures the length of time that a tumor continues to respond to treatment without growing or spreading. Cancer medicine with improved DOR can produce a meaningful delay in disease progression, as opposed to treatments that provide a temporary response without a lasting benefit.

There are a variety of other endpoints that can be used in oncology clinical trials. Measuring efficacy in ways that are appropriate to the specific type of disease or disease stage sometimes requires nuanced endpoints (such as disease-free survival or event-free survival) that add valuable information about quality of life and treatment failure.⁴³ Measuring clinical benefit of cancer treatments is complex, particularly given the life-threatening and progressive nature of the illness. These issues can be compounded as advances in the understanding of biomarkers and the underlying genetic drivers of cancer lead to more personalized and targeted treatment approaches that are evaluated in cancer trials involving smaller patient populations selected based on a tumor's molecular profile.⁵⁴ As a result of these growing complexities, clinical endpoints will continue to expand and evolve as cancer therapies with novel mechanisms of action are developed.

of drugs to treat serious conditions and fill an unmet medical need.⁵⁶ The treatment was approved with a clinical study showing that 60% of patients responded to the treatment. Approximately one in five breast cancers have a mutation that makes excess HER2 protein, which promotes the growth of cancer cells.⁵⁵ HER2-positive cancers are known to be aggressive, and historically, patients with HER2-positive breast cancer often experience disease progression, underscoring the importance of treatment options that improve certain outcomes.⁵⁷

The accelerated approval for patients with HER2-positive metastatic breast cancer was converted to a

traditional approval in 2022, at which time the use of trastuzumab deruxtecan was simultaneously broadened to an earlier treatment line. In the clinical study supporting this indication expansion, patients treated with trastuzumab deruxtecan were 72% more likely to be alive without their cancer worsening than patients on another anti-HER2 treatment.⁵⁷ Through additional follow-up, the clinical study data published later in 2022 revealed a survival improvement in patients with HER2-positive metastatic breast cancer.^{58,59} These study results illustrate the constantly evolving clinical value that cannot be fully realized until often many years after a drug's initial approval.

Pembrolizumab (KEYTRUDA®)

Pembrolizumab is a remarkable example of a breakthrough treatment for which extensive research years after initial approval has revealed significant clinical value for cancer patients. Pembrolizumab is a PD-1 inhibitor, part of a treatment class called immune checkpoint inhibitors that work by increasing the ability of the body's immune system to help detect and fight tumor cells. This class of medicines has dramatically changed the way certain tumor types are treated.⁶⁰ Initially approved in 2014 to treat patients with advanced metastatic melanoma, long-term clinical studies have demonstrated that pembrolizumab can extend life for patients with non-small cell lung cancer (NSCLC), the leading cause of cancer death in the US.^{61,62}

In 2017, pembrolizumab was granted accelerated approval, in combination with chemotherapy, for

the treatment of patients with untreated metastatic non-squamous NSCLC.⁶³ NSCLC accounts for about 85% of all lung cancers, and 70% of these diagnoses are classified as non-squamous.⁶⁴ Over half of lung cancer patients are diagnosed with metastatic disease, and the 5-year survival for patients diagnosed at this advanced stage is only 8%.⁶⁵ In a clinical study, 55% of patients on pembrolizumab and chemotherapy experienced significant tumor shrinkage compared to only 29% on chemotherapy alone.⁶⁶ In 2018, this approval was converted to a traditional approval for metastatic non-squamous NSCLC based on impressive longer-term data demonstrating that pembrolizumab could change survival expectations for these patients. In a clinical study, patients treated with pembrolizumab and chemotherapy were over 50% more likely to be alive versus chemotherapy alone.⁶⁷

Immune Checkpoint Inhibitors: Revolutionizing Cancer Care

The emergence of immune checkpoint inhibitors, a type of immunotherapy, represents one of the most significant advances in recent years. This breakthrough treatment class activates a patient's own immune system to fight cancer cells and has dramatically improved outcomes—including prolonged survival—for some patients with advanced cancer that previously had poor prognosis.⁶⁰

Groundbreaking research over the past few decades has revealed that T-cells, a type of immune cell, are naturally capable of destroying cancer cells. However, cancer cells can develop in a way that avoids destruction by T-cells, specifically by increasing the levels of certain proteins (immune checkpoint proteins) that stop T-cells from attacking the cancer. Immune checkpoint inhibitors block these proteins, triggering the T-cells to destroy cancer cells. With this unique mechanism of action, immune checkpoint inhibitors work by activating the patient's own immune system.⁷²

A wide range of immune checkpoint inhibitors are now available to patients which target various proteins involved in regulating the immune system—such as CTLA-4, PD-1, PD-L1, and LAG-3*—and can activate the immune cells to fight tumors across many cancer types. Continued R&D on treatments in this class is paramount to realizing the full clinical value these treatments may provide to patients in other forms of cancer.⁷² Scientists continue to explore biomarkers that may predict which patients are most likely to benefit from immune checkpoint inhibitors and investigate treatments in combination to uncover synergistic effects that attack cancer through multiple mechanisms and extend life. For example, there are more than 5,500 active clinical trials investigating PD-1/L1 inhibitors across a range of cancer types—80% of which are in combination with other therapies—including small molecule medicines and other immune checkpoint inhibitors, underscoring the potential clinical value still to come with this practice-changing treatment class.⁸

*CTLA-4: cytotoxic T-lymphocyte associated protein 4, LAG-3: lymphocyte-activation gene 3, PD-1: programmed cell death protein 1, PD-L1: programmed cell death-ligand 1

In addition to this practice-changing approval, pembrolizumab has earned many other approvals across lung cancer. It has been approved for certain metastatic NSCLC patients in the first- and second-line setting as both a single agent and in combination with chemotherapy.^{68,69,70} In 2023, nearly a decade after initial approval, pembrolizumab was also approved following surgery and chemotherapy for earlier stages of NSCLC, offering the opportunity for patients to benefit from the therapy before their disease advances to the metastatic stage. Beyond its current five indications in lung cancer and 35 indications overall, pembrolizumab has a promising clinical program—with more than 1,600 clinical trials across a wide variety of cancers and treatment settings—that continues to build evidence with the potential to reveal the full clinical value of this transformative treatment.⁷¹

Axicabtagene ciloleucel (YESCARTA®)

Axicabtagene ciloleucel, a CAR T-cell therapy, earned initial FDA approval in 2017 for the treatment of patients with certain types of large B-cell lymphoma (LBCL) who have not responded to or who have relapsed after at least two other kinds of treatment. In addition to priority review and breakthrough therapy designation, the FDA granted axicabtagene ciloleucel orphan drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.⁷³

As one of the first CAR T-cell therapies approved, every dose of axicabtagene ciloleucel is manufactured specifically for individual patients. Most commonly, a patient's T-cells—a type of immune system cell—are collected from the bloodstream and genetically modified to express an artificial receptor that allows T-cells to recognize cancer cells. Once returned to the body, the modified cells work by attacking cancer cells.⁷⁴

Initial approval for axicabtagene ciloleucel was based on a groundbreaking response rate to a single dose of treatment, with 72% of patients responding to the therapy and more than half no longer showing signs of cancer.⁷⁵ In 2021, after five years of follow-up of these patients, clinical data showed a 5-year survival rate of 43%. Among those patients, 92% had received no additional treatment since their one-time infusion of axicabtagene ciloleucel. These long-term outcomes showed a sustained survival benefit in this patient population, who previously had a life expectancy of just six months, signaling a transformative shift in the standard of care.⁷⁶

In addition to positive efficacy results, extensive clinical research of axicabtagene ciloleucel in late stage LBCL resulted in a label update supporting the use of prophylactic corticosteroids to help physicians manage—and potentially prevent—side effects. Only through continued research to optimize CAR T-cell therapy, years after initial approval, were these improvements in survival and patient management strategy realized.⁷⁷

“Today marks another milestone in the development of a whole new scientific paradigm for the treatment of serious diseases. In just several decades, gene therapy has gone from being a promising concept to a practical solution to deadly and largely untreatable forms of cancer.

—Scott Gottlieb, MD, FDA Commissioner⁷³



Use in Earlier Treatment Line or in Earlier Disease Stage

Due to the life-threatening and progressive nature of cancer, for ethical and practical reasons, novel oncology agents are often tested in patients with the highest unmet medical need, such as those with more advanced disease whose cancer has progressed or relapsed after trying existing treatments.⁸ While this approach provides significant benefits to patients with few alternative options and the greatest need for new treatments, it can create a narrow understanding of the full clinical benefit of such treatments at the time of initial FDA approval. That is because the clinical data available at approval often does not include the effect of treatment on newly diagnosed patients or in patients with an earlier disease stage. Treating cancer earlier can significantly impact the course of a patient's disease, potentially changing treatment goals from slowing disease progression to eliminating the cancer altogether.¹²

FDA-approved indications typically specify the cancer population in which an oncology treatment should be used. For example, first-line treatment is approved for newly diagnosed patients, while second-line treatment is given when the initial treatment does not work or stops working.⁷⁸ An approval also indicates the disease stage during which patients will be treated, such as advanced or metastatic cancer (when the cancer has spread to different or secondary parts of the body beyond the initial cancer site), or for earlier stage, operable disease.⁷⁹ An approval may also indicate the treatment is appropriate in the adjuvant setting, meaning given after a primary treatment, such as surgery, radiation, chemotherapy or other targeted therapy, to prevent the cancer from coming back.⁸⁰ Generally, cancer medicines advance first in treatment line, then in disease stage. For example, many immune checkpoint inhibitors have advanced in treatment line as well as in treatment setting as continued R&D after

initial approval has led to an expansion of evidence on the benefits of these medicines.^{72,81,82,83}

Venetoclax (VENCLEXTA®)

Venetoclax is a targeted oral B-cell lymphoma 2 (BCL-2) inhibitor and an example of how a robust development program with significant post-approval evidence can reveal a medicine's additional value. It is designed to selectively block the BCL-2 protein, which is overexpressed in many cancers and helps restore the process in which cancer cells self-destruct.⁸⁴ In 2016, the FDA granted venetoclax accelerated approval to treat patients with chronic lymphocytic leukemia (CLL), the most common leukemia in adults, who have a specific chromosomal abnormality and have been treated with at least one prior therapy.^{84,85} Venclexta was granted orphan drug designation for the treatment of CLL, recognizing the importance of encouraging the development of drugs for rare diseases.⁸⁵ Additional clinical research resulted in expansion of the label through an approval in combination with rituximab for second-line treatment of all patients with CLL—regardless of chromosomal abnormality—as well as patients with small lymphocytic lymphoma (SLL), a cancer which, similar to CLL, affects the lymph nodes.⁸⁶

In 2019, venetoclax was approved in combination with obinutuzumab for previously untreated patients with CLL or SLL.⁸⁷ Not only did this allow patients with CLL and SLL access to the medicine earlier in their disease treatment, but it was approved as the first chemotherapy-free, fixed-duration treatment for CLL and SLL, giving newly diagnosed patients the opportunity for a chemotherapy-free therapy and to cease treatment after just one year. Some other treatments require patients to continue therapy until the disease progresses.⁸⁸ In 2022, post-approval

clinical trial results with long-term follow-up showing a majority of patients treated with one year of venetoclax in combination with obinutuzumab remain without relapse after four years off treatment.⁸⁹ A fixed duration of treatment for newly diagnosed patients has helped transform the treatment landscape for CLL and SLL, and the long-term clinical benefit could only be recognized through data accumulated years after initial FDA approval.⁹⁰

Axicabtagene ciloleucel (YESCARTA®)

Axicabtagene ciloleucel, a CAR T-cell therapy, illustrates how ongoing research after initial approval can reveal additional value in an earlier treatment line. Axicabtagene ciloleucel was initially approved in 2017 to treat adult patients with certain types of LBCL who have not responded to or who have relapsed after at least two other kinds of treatment.⁷³ In the study supporting initial approval, 72% of patients treated with a single dose of axicabtagene ciloleucel responded to therapy, and over half no longer showed signs of cancer.⁷⁵ In 2022, the label was expanded to include treatment of adult patients with LBCL after first-line treatment, making axicabtagene ciloleucel available to patients in an earlier line of therapy. In this global clinical study, 2.5 times more patients who received a single dose of axicabtagene ciloleucel were alive at two years versus the standard of care. Throughout the previous three decades, the standard of care was a difficult, multi-step process for patients, expected to end with an intensive stem cell transplant.⁹¹ This second-line approval means more patients with LBCL can receive the benefits of this

“To be able to see this innovative advance become available as an earlier line of treatment is truly remarkable. Current standard of care is a difficult process for patients... [now] patients will have earlier access to this potentially curative treatment.

—Lee Greenberger, PhD, Chief Scientific Officer of The Leukemia & Lymphoma Society⁹¹

Groundbreaking Cell and Gene Therapies

The emergence of cell and gene therapies represents the next generation of advanced medicines. These groundbreaking therapies offer tremendous potential across a wide range of diseases and have already made enormous contributions to advancements in oncology care. Both cell and gene therapies modify a patient's genetic material to fight cancer at its source and alleviate the underlying cause of the disease.^{93,94} In cell therapy, new or modified cells are transferred into a patient's body to treat disease. In gene therapy, a patient's disease-causing genes are replaced, repaired, or inactivated.⁹³ Recently, some of these treatments have shown long-term or potentially curative benefits, with the ability to eradicate certain cancers and keep them at bay for many years.⁷⁴

One of the most promising areas in this field and in cancer treatment are CAR T-cell therapies, a transformative treatment approach that activates both cell and gene therapy mechanisms. CAR T-cell treatments target cancer by isolating the patient's own immune cells and genetically modifying them in a lab to be more powerful and efficient at fighting the tumor. The modified cells are then returned to the body to attack cancer cells. Currently, there are six approved CAR T-cell therapies, all for the treatment of blood cancers. Some of these therapies have shown success in pediatric cancers or aggressive lymphomas for which there were previously no treatment options, and in certain patients, a single administration of CAR T-cell therapy could now replace years of chemotherapy.^{74,95}

With the first CAR T-cell therapy approved in 2017, many more years of research are needed to uncover the full potential of these medicines. Globally, there are nearly 900 clinical trials investigating CAR T-cell therapies across a range of blood cancers and solid tumors. These trials are also exploring these therapies in combination with other therapies and across various therapeutic targets.⁹⁶ This impressive pipeline will require difficult, complex, and lengthy R&D to create important advancements that will continue to revolutionize patient care.

transformational medicine earlier in the progression of their disease, without having to endure several other lines of treatment. In 2023, long-term clinical data showed that axicabtagene ciloleucel significantly improved survival for patients, demonstrating the importance of ongoing research to reveal the full clinical value of cancer treatments.⁹²

Olaparib (LYNPARZA®)

Olaparib, a targeted cancer therapy, became the first PARP inhibitor approved by the FDA in 2014 to treat patients with advanced ovarian cancer who had already exhausted three or more treatment options and whose cancer tested positive for a BRCA mutation.* PARP inhibitors are known to exploit pathways that preferentially kill cancer cells, including those involving BRCA mutations.⁹⁷ Additional research revealed significant clinical benefits when patients with certain types of advanced ovarian cancer are treated with olaparib earlier in the course of their disease as maintenance therapy.⁹⁸ Maintenance therapy is given to patients to help keep cancer from coming back after initial therapy.⁹⁹ As a high proportion of those diagnosed with ovarian cancer already have late-stage disease and recurrence rates in ovarian cancer patients are high, maintenance therapies are critical to extending survival.^{100,101}

In 2017, olaparib was approved as maintenance treatment for patients with recurrent advanced ovarian cancer who are responding to chemotherapy, with

clinical data showing that olaparib substantially delayed the cancer from returning.⁹⁸ In 2018, the FDA approved olaparib as a first-line maintenance treatment for BRCA-mutated advanced ovarian cancer, making the targeted therapy available to patients earlier in their disease. Clinical data at the time of approval showed that patients treated with olaparib were 70% more likely to live without their cancer getting worse compared with patients taking no maintenance therapy.¹⁰² Several years later, in 2022, long-term follow up from this clinical study showed that a majority of patients taking olaparib were alive after seven years, which marked the longest follow-up for any PARP inhibitor in this setting.¹⁰³ Only through research many years after initial approval could these clinical benefits be realized and made available to patients earlier in their cancer treatment.

BRCA = BRCA1 and BRCA2 genes

**The approval in fourth-line advanced ovarian cancer was voluntarily withdrawn as longer-term overall survival data indicates that chemotherapy treatment may be more beneficial than PARP inhibitors for this indication.¹⁰⁴ This underscores the importance of ongoing research to continue to inform the best uses of medicines for patients in their cancer journey.*

Abemaciclib (VERZENIO®)

Abemaciclib, a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, is approved to treat certain types of breast cancer that are hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-), both as a single-agent and in combination with hormone therapy.^{105,106} Hormone therapy is often helpful for patients with HR+ breast cancer, and certain targeted drugs—like CDK4/6 inhibitors—can make hormone therapy even more effective.¹⁰⁷ In breast cancer, CDK4/6 proteins can cause cells to grow and divide uncontrollably. Abemaciclib targets the CDK4/6 proteins, interrupting this process to slow or even stop rapid cell growth in breast cancer.¹⁰⁸ Abemaciclib was initially approved in 2017 to treat HR+, HER2- advanced breast cancer that has progressed following hormone therapy.¹⁰⁵ Ongoing clinical research has demonstrated that abemaciclib, in combination with hormone therapy, is also effective in HR+, HER2- early breast cancer.¹⁰⁹

In 2021, abemaciclib was approved, in combination with hormone therapy, for patients with HR+, HER2- early breast cancer that is present in the lymph nodes (or node-positive). After breast cancer is removed through surgery, cancer cells in the lymph nodes can indicate a higher chance of the cancer returning and

“This approval will likely change the way we treat women with BRCA-mutated advanced ovarian cancer. The ability to offer this important first-line maintenance treatment option to eligible patients may slow down or even stop the natural course of disease progression.

—Kathleen Moore, co-principal investigator of the SOLO-1 trial and Associate Director for Clinical Research, Stephenson Cancer Center at The University of Oklahoma, Oklahoma City, Oklahoma¹⁰²

spreading. Abemaciclib was specifically approved as an adjuvant treatment (after surgery) for patients whose tumors express a biomarker (Ki-67) that indicates rapid cancer growth with a high risk of tumors returning.¹⁰⁹ The goal of adjuvant therapy is to prevent the cancer from coming back.⁸⁰ Clinical data showed that patients treated with this combination after surgery were 37% more likely to be alive and free of any signs of breast cancer compared to hormone therapy alone. With this approval, abemaciclib became the first addition to adjuvant hormone therapy in nearly two decades for this indication.^{109,110} Approximately 20% of patients with this type of early breast cancer will experience recurrence potentially to incurable metastatic disease, so therapies that prevent cancer from returning are critical for this patient population.¹¹¹

In 2022, long-term follow-up data at four years was favorable for these early breast cancer patients who took this combination therapy when compared to patients taking only hormone therapy. The clinical data showed that more patients treated with the combination were alive and free of any signs of breast cancer than those treated with only hormone therapy.¹¹¹ This long-term data resulted in the FDA granting abemaciclib a label expansion in 2023 to remove the need for Ki-67 biomarker testing when treating patients with HR+, HER2-, node-positive early breast cancer at a high risk of returning.¹¹² Since the goal of adjuvant treatment after surgery is to prevent cancer from coming back, adjuvant therapy with abemaciclib has the potential to be curative for some patients with this type of early breast cancer.^{80,112} The full clinical value of abemaciclib for patients with early breast cancer was only revealed years after initial approval by the accumulation of evidence over time.

“ The design and results of [this] study are practice-changing and represent the first advancement in adjuvant treatment of HR+ HER2- breast cancer in a very long time. This FDA approval for Verzenio in combination with [hormone] therapy in the early breast cancer setting has the potential to become a new standard of care for this population.

—Sara M. Tolaney, MD, MPH, Harvard Medical School, Dana-Farber Cancer Institute, and investigator on the monarchE study¹⁰⁹



Use in Additional Types of Cancer

Decades of research unlocking the secrets of the human genome and the role of genetic changes in the development of cancer at the molecular and cellular level has led to a greater understanding of the more than 200 diseases that we collectively call cancer.^{21,113} Cancer is caused by certain changes to genes that control how cells grow and divide, which can lead to the unchecked spread of cancer cells.¹⁵ Understanding the role genetic changes play in the development of various cancers has not only fueled the development of treatments that can target these mechanisms, but it has also helped to establish similarities among different cancer types, including how they may respond to treatment.^{15,18}

Biomarkers serve a critical purpose in this process as they help to identify and characterize alterations in cancer cells, including some that may be present across multiple tumor types independent of where they originate, and indicate whether a certain treatment is likely to be effective.^{20,114} With the growing knowledge of genetic changes, including biomarkers, and an expanded treatment arsenal, clinical studies increasingly allow researchers to discover how to use existing therapies for the treatment of very different, though often genetically-related forms of cancer.¹¹⁵ Importantly, these advances in cancer biology research first create tremendous clinical value for the original cancer type for which a new medicine is approved, and then for many other cancer types for which a medicine is found to provide benefit due to continued research after initial FDA approval.

Crizotinib (XALKORI®)

Crizotinib exemplifies how research to understand biomarkers can identify other types of cancer in which a treatment may be effective. In 2011, crizotinib was first granted accelerated approval to treat certain patients with NSCLC whose tumors have a particular abnormality caused by a rearrangement in the anaplastic lymphoma kinase (ALK) gene. Alterations in the ALK gene lead to cancer growth, and crizotinib

was the first FDA-approved therapy to target this specific biomarker.¹¹⁶ In 2013, additional clinical trial data confirmed the benefit of this medicine in patients with ALK-positive NSCLC, converting the accelerated approval to a traditional approval.¹¹⁷

A decade after initial approval, crizotinib earned approval to treat another cancer type in which the ALK gene plays an important role. In 2021, crizotinib was approved for the treatment of pediatric and young adult patients with ALK-positive anaplastic large cell lymphoma (ALCL) that has returned or not responded to prior treatment.¹¹⁸ ALCL is a rare form of non-Hodgkin lymphoma with approximately 100 new cases in the US every year.^{118,119,120,121,122,123} In addition to priority review and breakthrough designation, the FDA granted crizotinib orphan drug designation for this indication, which is granted to medicines that prevent, diagnose, or treat rare conditions.¹²⁴ This marks the first FDA-approved, biomarker-driven therapy available to children and young adults with this specific type of ALCL. In the clinical trial supporting approval, 88% of patients responded to treatment with crizotinib.¹¹⁸

The following year, in 2022, crizotinib was approved for the treatment of adult and pediatric patients with ALK-positive inflammatory myofibroblastic tumors (IMT) that have returned, not responded to prior treatment or cannot be removed by surgery.¹²⁵ IMT is very rare with only 150–200 people diagnosed in the US annually—most commonly children and young adults.¹²⁶ Up to 50% of cases have this particular ALK gene abnormality.¹²⁷ Crizotinib was also granted orphan drug designation for the treatment of IMT.¹²⁵

Conducting clinical trials in rare diseases is challenging and developing targeted therapies to improve outcomes for children with conditions such as ALCL and IMT is essential.¹²⁸ Only through ongoing research of crizotinib to identify other diseases impacted by the ALK gene were these approvals made possible, marking particularly valuable treatment advances for these patients.

Rare Cancers

Nearly one-third of patients diagnosed with cancer have a rare tumor type.¹²⁹ Many of these patients tend to have fewer treatment options and poorer outcomes than patients with more common cancers.¹³⁰ Researching and developing effective treatments for rare cancers is inherently difficult due to small population sizes and limited tumor tissues to help researchers study and learn about the specific disease.¹³¹ These same difficulties contribute to the high risks associated with investing in this type of research, particularly given the limited ability to recoup investment costs.

Due to these challenges, as well as those associated with research and developing medicines to treat rare diseases more broadly, the United States passed the Orphan Drug Act (ODA) in 1983 to incentivize companies to invest in R&D that addresses critical unmet medical need for patients with these illnesses.¹³² The ODA allows the FDA to grant orphan drug designation to new medicines that prevent, diagnose or treat rare conditions to help encourage investments in drug development that benefit smaller patient populations.¹³³ Since it was established, the ODA—combined with the FDA’s expedited review programs—have played a central role in bringing forward timely patient access to needed medicines which have completely changed the face of therapeutics for many rare diseases, including rare cancers.^{132,134} In fact, more than 40% of drugs approved to treat rare diseases in recent years have been for rare cancers.¹³⁵

Unfortunately, the IRA’s price setting provisions threaten to undermine the success of the ODA by discouraging investment in post-approval R&D on medicines—a critical source of new treatments for rare cancers. One study found, while multiple orphan indications for the same medicine are increasingly common, multiple orphan indications for the same medicines are seen most often in rare cancers. This is because post-approval R&D often reveals a medicine targeting a single pathway can have an impact across several different types of cancer.¹³⁵

Under the price-setting provisions of the IRA, orphan drugs are exempted from government-set prices. However, this exemption only applies if the medicine has a single orphan designation and is approved only for indication(s) within that designation, thereby ignoring the critical R&D that often brings forward new treatments after initial FDA approval—particularly for rare diseases and rare cancers.¹³⁶

As a result, the IRA will force manufacturers to make difficult R&D decisions about pursuing additional uses for medicines treating rare diseases as they must consider the potential for price-setting.¹³⁶ This shift in incentives could mean many new uses of existing medicines to treat rare forms of cancer—including those featured throughout this report—may have been at risk if the IRA had been in place at the time of initial approval (see additional discussion in the following sections: *Additional Benefits Revealed Within an Approved Indication; Use in Earlier Treatment Line or Disease Stage; Use in Additional Types of Cancer; and Use in Combination with Other Agents*).

Fam-trastuzumab deruxtecan-nxki (ENHERTU®)

Trastuzumab deruxtecan* is a treatment that targets HER2, a protein which can promote cancer growth. In some cancers with higher levels of HER2 protein than normal, the cancer cells grow more quickly and may spread to other parts of the body.^{137,138} This overexpression of HER2 has been

seen in different cancers, such as breast, ovarian, bladder, pancreatic, stomach, and esophageal.¹³⁷

Trastuzumab deruxtecan was initially approved in 2019 for patients with HER2-positive metastatic breast cancer previously treated with two or more anti-HER2 based regimens, and further research has demonstrated clinical benefit in other HER2-positive cancers.^{138,139,140}

*Full US generic name: fam-trastuzumab deruxtecan-nxki

“ This approval represents the first time a HER2-directed medicine has demonstrated a significant improvement in survival compared to chemotherapy following initial treatment in the metastatic setting, and it has the potential to become the new standard of care for this patient population.

—Ronan Kelly, MD, MBA, Director of the Charles A. Sammons Cancer Center and the W.W. Caruth, Jr. Chair of Immunology at Baylor University Medical Center, Dallas, Texas¹⁴¹

In 2021, trastuzumab deruxtecan was approved to treat patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma previously treated with a prior trastuzumab-based regimen. This approved use was granted orphan drug designation. Approximately one in five gastric cancers are HER2-positive, and prior to this approval, no other approved HER2-targeted medicines were available to patients who progressed after first-line therapy. Gastric cancer is frequently diagnosed in the advanced stage and patients often have poor outcomes, with only 5% of patients surviving beyond five years. In a clinical study supporting this approval, trastuzumab deruxtecan demonstrated a 41% reduction in the risk of death and a response rate more than three times higher than chemotherapy. This marked the first new HER2-directed medicine approved to treat gastric cancer in a decade, representing a critical advance for this patient population.¹⁴¹

Olaparib (LYNPARZA®)

Olaparib, a targeted oral therapy called a PARP inhibitor, was initially approved in 2014 and has since shown significant promise as maintenance therapy in some cancers.¹⁴² Maintenance therapy is given to patients to help keep cancer from returning after initial therapy.⁹⁹ PARP inhibitors are known to exploit pathways that preferentially kill cancer cells, including those involving BRCA* mutations—and olaparib has shown substantial benefits in cancers that are BRCA-mutated, including advanced ovarian and pancreatic cancers.¹⁰²

In 2019, olaparib was approved as first-line maintenance therapy for patients with metastatic pancreatic cancer whose cancer tested positive for a BRCA mutation and whose disease has not progressed on chemotherapy.¹⁴³ The FDA granted orphan drug designation for this indication, which supports the development of medicines that treat a rare disease or condition.^{133,144} Olaparib was the first therapy approved in these biomarker-selected patients with advanced pancreatic cancer, which historically has had few effective treatment options. Pancreatic cancer is a deadly disease with a high unmet medical need. Around 80% of patients are diagnosed at an advanced stage, and it has the lowest survival outcomes of the most common cancers with an average survival rate of less than a year. In a clinical study, olaparib nearly doubled the time patients with BRCA-mutated pancreatic cancer lived without their cancer getting worse compared to placebo.¹⁴³ Long-term follow up data at 3 years showed that treatment with olaparib improved survival for some patients.¹⁴⁵ The clinical value of olaparib for patients with this aggressive disease was only revealed through continued post-approval research and the accumulation of clinical evidence over time with research completed seven years after initial FDA approval.

BRCA = BRCA1 and BRCA2 genes

“ Metastatic pancreatic cancer patients have been waiting a long time for new therapy options for their devastating disease. [This approval] of LYNPARZA provides an exciting new treatment option for patients with germline BRCA-mutated metastatic pancreatic cancer.

—Julie Fleshman, President and CEO, Pancreatic Cancer Action Network¹⁴³

Use in Combination with Other Agents

Research continues to reveal new therapies that may be beneficial for patients with cancer and, increasingly, that the use of two or more therapies taken in combination can be more effective than the use of a singular therapy alone.^{8,13} Consequently, combination therapies have become a cornerstone of treatment for many cancers. The advantage of combination therapy in many cancers is due in part to the complexity of cancer itself. The highly interconnected pathways involved in cancer cell growth and spread allow cancers to adapt and use alternate pathways to overcome treatment. Therefore, while targeting one pathway with one therapy may prove beneficial for some time, eventually cancer is known to adapt and become resistant to individual treatments. But by targeting multiple pathways at once, combination therapy offers opportunities to attack cancer through different mechanisms, producing a synergistic or additive effect thereby helping to address the issue of treatment resistance and potentially improving survival.^{146,147}

It is challenging to determine which treatments may bring clinical benefit when taken in combination. For example, certain combinations may only be effective in specific patient populations, such as those with a certain biomarker or with specific characteristics of disease. Continued research is therefore critical to understand the value of possible different combinations of new and existing therapies.

Ipilimumab (YERVOY®)

Ipilimumab is an immune checkpoint inhibitor, a treatment class that helps activate a patient's own immune system to fight cancer cells and has fundamentally changed outcomes for certain groups of patients with cancer (see *Immune Checkpoint Inhibitors: Revolutionizing Cancer Care*).^{81,148} In recent years, a range of immune checkpoint inhibitors have become available to patients targeting various

immune checkpoints which are involved in a range of different types of cancers. Ipilimumab, a CTLA-4 immune checkpoint inhibitor, was the first checkpoint inhibitor to be approved.⁸¹ It initially earned FDA approval in 2011 as a single agent for unresectable or metastatic melanoma, a deadly skin cancer that is difficult to treat.¹⁴⁹ This initial approval was a significant advancement for patients as it was the first approved drug ever shown to help patients with late-stage melanoma live longer.¹⁵⁰

Since the initial approval, clinical studies have shown that ipilimumab has improved survival in melanoma as well as several other cancers, specifically when taken in combination with nivolumab, a PD-1 immune checkpoint inhibitor.^{82,151} The combination of anti-CTLA-4 and anti-PD-1 therapies, which each target different checkpoints of the immune system, potentially works synergistically to increase the body's ability to fight cancer.¹⁵²

In 2015, ipilimumab was granted accelerated approval in combination with nivolumab, for the treatment of patients with unresectable or metastatic melanoma who did not express the BRAF V600 mutation. This marked the first FDA approval for two immune checkpoint inhibitors in combination for the treatment of cancer. In the study supporting this approval, patients who received the combination of ipilimumab and nivolumab had a higher response rate than patients who received ipilimumab alone, demonstrating the potential of targeting distinct and complementary immune system pathways.¹⁵³ This accelerated approval was expanded in January 2016 to include all patients with unresectable or metastatic melanoma, regardless of BRAF mutation.¹⁵⁴

In 2019, long-term clinical data for the combination showed a significant improvement in survival over ipilimumab alone—the first drug to show survival in this deadly skin cancer—and supported converting the accelerated approval to a traditional approval.^{83,155} With 7.5 years of follow up in this clinical study, the combination of ipilimumab and nivolumab showed

durable survival with a survival rate of 48%.¹⁵⁶ Prior to novel therapies such as ipilimumab, the five year overall survival rate was only about 5%.¹⁵⁷

In 2023, the approval of ipilimumab and nivolumab was expanded to include the treatment of metastatic melanoma in pediatric patients 12 years and older.¹⁵⁸ Pediatric melanoma is rare, accounting for less than 1% of all new cases of melanoma, which makes it particularly difficult to investigate in clinical trials.¹⁵⁹ The combination was granted orphan drug designation for the treatment of melanoma and this approval marked a critical new treatment option for this patient population.¹⁵⁸

The benefits of the combination extend beyond metastatic melanoma, gaining FDA approvals in six additional cancer types, including advanced renal cell carcinoma, metastatic colorectal cancer, hepatocellular carcinoma, metastatic non-small cell lung cancer,

malignant pleural mesothelioma, and metastatic esophageal squamous cell carcinoma.⁸² These approvals highlight not only the tremendous progress that has been made with this class of treatments but underscore how critically important combination treatment approaches are to advancing the treatment paradigm for many forms of cancer.

Venetoclax (VENCLEXTA®)

Venetoclax is a powerful example of a medicine for which additional clinical value was revealed when investigated in combination with other treatments. Venetoclax is a BCL-2 inhibitor designed to selectively block a protein overexpressed in many cancers and restore the process in which cancer cells self-destruct. In clinical studies, the therapy has been shown to have a synergistic effect with other medicines that cause

Combination Therapy in Rare Cancer

Malignant pleural mesothelioma (MPM) is a rare cancer type most often caused by exposure to asbestos fibers. Approximately 2,600 people are diagnosed each year, most often men who worked in industries with high rates of asbestos exposure, like building and manufacturing.¹⁶⁰ MPM is often particularly aggressive and associated with poor outcomes for patients, with 5-year relative survival rates ranging between just 7-24%.^{161,162} Though MPM is not curable, treatments aim to extend survival.¹⁶⁰ When approved in 2020, the ipilimumab and nivolumab combination became the first new treatment in more than 15 years for patients with MPM, demonstrating superior overall survival versus standard-of-care chemotherapy.¹⁶³ The combination was granted orphan drug designation for this indication, which provides incentives to assist and encourage the development of drugs for rare diseases.¹⁶⁴ In 2021, follow-up clinical data showed patients taking the combination had a 27% reduction in risk of death.¹⁶⁵ Only through continued research were survival benefits realized for this rare and difficult-to-treat cancer through an FDA approval earned nearly 10 years after ipilimumab's initial approval.

“ In this aggressive cancer that historically has had limited treatment options, we've now not only seen the potential for patients to live longer with nivolumab plus ipilimumab, but that this benefit is sustained at three years compared to treatment with chemotherapy. These results give us further proof of the durability of the outcomes achieved with this combination

—Solange Peters, M.D., Ph.D., Medical Oncology Service, Chair, Thoracic Oncology, Lausanne University Hospital, Lausanne, Switzerland¹⁶⁵

cancer cell death.¹⁶⁶ Initially approved in 2016 for patients with a subset of hard-to-treat CLL, venetoclax was granted two additional approvals in this disease area: one in combination with rituximab for all patients with CLL/SLL who had at least one prior line of therapy, and one in combination with obinutuzumab in previously untreated CLL/SLL patients (as discussed in the *Use in Earlier Treatment Line* section).^{86,88}

In 2018, venetoclax earned accelerated approval in combination with low-intensity therapy to treat newly-diagnosed acute myeloid leukemia (AML), specifically patients 75 years of age and older or who cannot be treated with intensive chemotherapy.¹⁶⁷ AML is one of the most aggressive blood cancers, with a very low survival rate and few options for patients who are unable to be treated with intensive chemotherapy.^{167,168} The FDA granted orphan drug designation for this indication, which is given to medicines that treat a rare disease or condition.^{133,169} In 2020, the accelerated approval was converted to traditional approval based on additional clinical data, including demonstrated superior survival versus chemotherapy.¹⁷⁰ At the time of initial approval for this indication, clinical data on survival outcomes was not available; only through the ongoing research and collection of evidence was this benefit demonstrated.

Venetoclax is also being explored in combination with other treatments across numerous cancer types, including mantle cell lymphoma, myelodysplastic syndrome, multiple myeloma, and pediatric acute leukemia.¹⁷¹

Dabrafenib (TAFINLAR®)

A deeper understanding of the genetic underpinnings of cancer has prompted the use of two therapies in combination that target drivers of cancer cell growth. Dabrafenib is a targeted oral cancer medicine called a BRAF inhibitor, which is specifically designed to block activity of the BRAF gene.¹⁷² The BRAF* gene and MEK* gene work together in the same pathway leading to cancer cell growth. Research has shown that combining a BRAF inhibitor like dabrafenib with a MEK inhibitor and blocking both points along the pathway concurrently can reduce the development of drug resistance that is commonly associated with treatment with a single therapy, providing improved clinical benefit.¹⁷³ Initially approved in 2013 as a single agent to treat patients with metastatic melanoma whose tumors express the BRAF mutation, extensive research has shown that dabrafenib is more effective against BRAF-mutated cancers when taken in combination with trametinib, a MEK inhibitor.^{173,174}

Dabrafenib has earned approvals in combination with trametinib across numerous BRAF-mutated cancer types, including anaplastic thyroid cancer (ATC).¹⁷⁵ The combination of dabrafenib and trametinib was the first treatment approved specifically for ATC, a rare and aggressive type of thyroid cancer accounting for approximately one to two percent of all thyroid cancers. The FDA granted dabrafenib orphan drug designation for this indication, recognizing the importance of encouraging the development of drugs for rare diseases.¹⁷⁶

“Having a new medicine to treat AML is encouraging for my patients and their families. VENCLEXTA's approval is a true breakthrough for AML patients ineligible for intensive chemotherapy.

—Dr. Daniel Pollyea, clinical director of leukemia services at University of Colorado Hospital¹⁶⁷



This approval was based on results from a specific type of clinical trial called a basket trial, in which drugs are tested based on specific molecular pathways, rather than where the cancer originated in the body, an important advancement in clinical trial methodology that supports the development of precision medicine. For uncommon tumors like ATC, it is challenging to accrue enough patients for a large, randomized trial, so basket trials can help identify therapies for patients who suffer from rare diseases.¹⁷⁷ In 2022, long-term follow-up data from this study showed a median overall survival of 15 months and a 12-month survival rate of 52%. These findings are notable, given a historical median survival of less than 6 months.¹⁷⁸ Only through pursuing research with a novel trial design over many years was it possible to identify and validate this critical treatment option for patients with this rare cancer type.

**BRAF = v-raf murine sarcoma viral oncogene homolog B1; MEK = mitogen-activated extracellular signal-regulated kinase*

“This is the first FDA-approved treatment for patients with this aggressive form of thyroid cancer... This approval demonstrates that targeting the same molecular pathway in diverse diseases is an effective way to expedite the development of treatments that may help more patients.

—Richard Pazdur, M.D., director of the FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research¹⁷⁶

Use as Tumor-Agnostic Treatments Based on Biomarkers

Historically, cancer treatments were approved based on where the cancer started in the body. With new understanding of the role of specific genes and proteins in cancer, some recent approvals have been based on specific biomarkers rather than cancer type. These are called tumor-agnostic treatments or tissue-agnostic treatments. To date, the FDA has approved six tumor-agnostic treatment regimens—including a range of targeted oral cancer therapies and immunotherapies—each of which were approved with biomarkers indicating the likelihood of patients responding to treatment.¹⁷⁹

Executing clinical trials based on genetic subtypes of a disease can be challenging, particularly due to the relatively small number of patients that may fall into these treatment populations. One of the novel approaches to clinical trials that has emerged and helped to facilitate the move toward precision medicine is called a basket trial, in which drugs are tested based on specific molecular pathways that drive cancer, regardless of cancer type or location. Basket trials benefit patients with genetic subtypes as they enable testing specific biomarkers across various cancer types. In particular, basket trials can be beneficial for those in whom conducting clinical trials is uniquely challenging due to small population sizes—including pediatric patients, patients with rare cancers and cancer subtypes, and those with advanced cancer who do not have standard treatment options.^{180,181,182}

Pembrolizumab (KEYTRUDA®)

In 2017, pembrolizumab became the first FDA-approved tumor-agnostic therapy, representing a major breakthrough in precision medicine and a revolutionary approach to cancer treatment. Pembrolizumab was granted accelerated approval for the treatment of adult

and pediatric patients with metastatic microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) solid tumors that have progressed following prior treatment and have no remaining treatment options.¹⁸³ The FDA granted this approval based on an understanding of the biology of MSI-H/dMMR across different tumors and clinical data observed in patients across five clinical studies.¹⁸⁴

Scientists have found that immunotherapy drugs like pembrolizumab are more effective for cancers with many mutations than for cancers with low numbers of mutations.¹⁸⁵ MSI-H/dMMR can occur when a cell is unable to repair mistakes when copying DNA during the cell division process, which can result in a high number of mutations.^{186,187} As a result, pembrolizumab was investigated in several clinical trials with patients that had a range of cancer types possessing MSI-H/dMMR biomarkers. Across the studies, approximately four out of ten patients responded to pembrolizumab, with 78% percent of those patients responding for six months or longer.¹⁸³

In 2023, the FDA converted pembrolizumab's MSI-H/dMMR tumor-agnostic indication, meaning any tumor with MSI-H/dMMR regardless of where the cancer originated in the body, to a traditional approval based on additional clinical data from three studies, including basket trials, with over 500 adult and pediatric patients across more than 30 types of cancer. The data demonstrated meaningful tumor response rates and durable responses, with one in three patients responding to treatment and 77% of those patients responding for a year or longer.¹⁸⁸ This unique clinical trial approach—based upon research guided by genetic characteristics rather than where cancer originates in the body—offers a new paradigm in treating patients with limited options.¹⁸⁵

“This is the first time in the history of oncology that a cancer medicine has been approved by the FDA using a pan-tumor predictive biomarker rather than a tumor-specific approach. This approval for KEYTRUDA is a transformational milestone in our progress toward personalized immunotherapy, offering certain patients with difficult-to-treat cancers a medicine based on the genetic makeup of the tumor—regardless of tumor type.

—Dr. Luis A. Diaz, Jr., head of the Division of Solid Tumor Oncology, Memorial Sloan Kettering Cancer Center¹⁸⁹



Dabrafenib (TAFINLAR®)

Dabrafenib with trametinib was the first BRAF/MEK* inhibitor combination to earn a tumor-agnostic FDA approval. Following approvals in specific types of cancer—including metastatic melanoma, lung, and anaplastic thyroid cancer—the combination was granted accelerated approval in 2022 for the treatment of certain children and adults with solid tumors, specifically whose cancer cannot be removed by surgery or has spread throughout the body and express a common BRAF mutation, after progressing on a prior treatment and have no alternative treatment options. BRAF mutations drive tumor growth across more than 20 tumor types, including rare cancers that often have limited treatment options and can be challenging to study in large, randomized clinical trials.¹⁸⁹

The approval of the dabrafenib and trametinib combination was supported by results of three clinical studies, including basket trials that enrolled patients based on the molecular features of their tumors. In two of these trials, up to 80% of patients experienced a clinically meaningful benefit from the combination, many of whom had previously received multiple therapies and had few remaining treatment options.^{189,190} This tumor-agnostic approval marked a critical advancement for patients with BRAF-mutated solid tumors and demonstrates the importance of continued and novel approaches to clinical research that can reveal benefits for patients with limited options.

*BRAF = v-raf murine sarcoma viral oncogene homolog B1; MEK = mitogen-activated extracellular signal-regulated kinase

Closing



Research continues to highlight the substantial role of new medicines in driving down cancer mortality in recent decades.^{3,5,6,191,192} Despite this progress, cancer remains the second leading cause of death in the US with nearly 1,700 Americans dying of cancer every day, underscoring the continued need for effective oncology treatments.¹⁹¹ As demonstrated by the case studies highlighted throughout this paper, while initial FDA approval of a medicine is critical, the full clinical value and most beneficial use of an oncology treatment may not be realized until well beyond this milestone. Only through additional research—often many years after initial FDA approval—can new clinical data reveal the full value a therapy can bring to oncology patients.

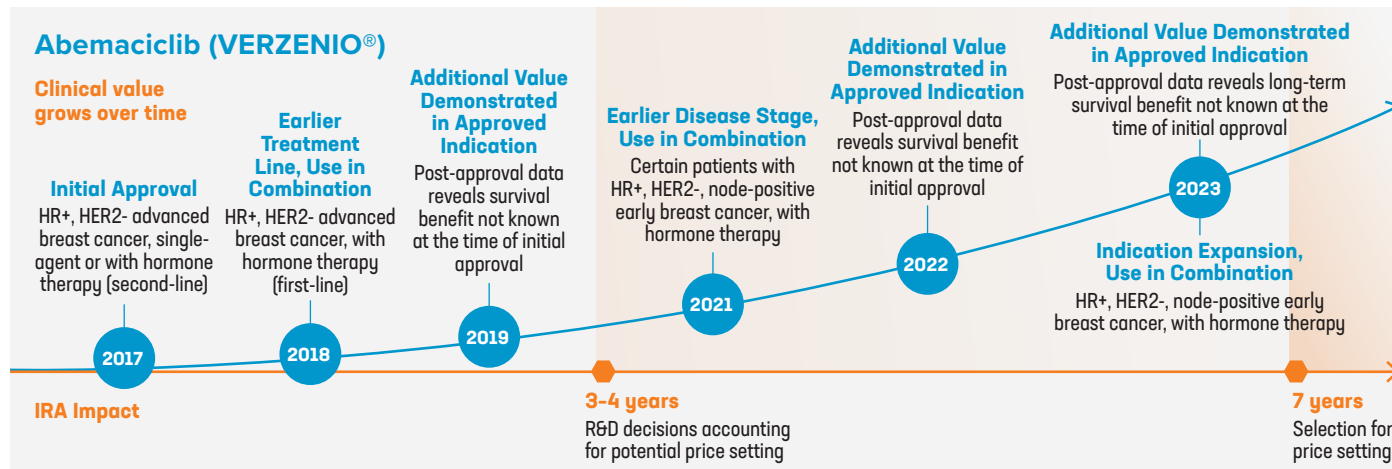
Due to the life threatening and progressive nature of cancer and the R&D process, the accumulation of data for oncology treatments can only happen over time and under a policy environment that incentivizes the pursuit of promising scientific leads. The examples highlighted here demonstrate how ongoing research often reveals additional benefits over time, including through demonstration of improved survival. They also highlight how cancer medicines can establish value in an earlier treatment or disease stage, in a different type of cancer, or in combination with another therapy after initial approval. These mechanisms by which the clinical benefit of a treatment typically emerges following initial FDA approval underscore the value provided by ongoing R&D after initial FDA approval to uncover additional information about the way medicines can benefit patients (see *Product Overviews*).

Post-approval research extends well beyond the 10-15 years on average it takes to bring a new medicine to patients as it involves a process of rigorously testing current therapies to discover their full therapeutic value. As demonstrated in this report, much of this research has contributed greatly to the unprecedented advancements in cancer treatment witnessed over the past decade. Unfortunately, the IRA threatens the future of post-approval R&D by shortening the timeframe under which it is feasible to invest in this critical research. As a result, the long-term clinical value provided by a therapy may never be fully realized, leaving cancer patients without desperately needed innovative treatment options (see *Government Price-Setting Impact on Treatment Innovation*).

To continue to advance the next generation of treatments, it is vitally important that the constantly evolving nature of scientific progress and oncology R&D be recognized by researchers, clinicians, patients, payers, and policymakers alike. Treatment innovations that will continue to decrease cancer mortality rates rely upon a policy environment that rewards the accumulation of evidence over time. Now more than ever, researchers must be able to build upon existing scientific knowledge and follow the science to advancing promising new breakthroughs. It is only through these discoveries, revealed over time, that researchers can understand the full therapeutic value of a medicine and achieve critical advances for patients.

Abemaciclib | VERZENIO®

In 2017, the FDA granted approval to abemaciclib, in combination with the hormone therapy fulvestrant, to treat women with hormone receptor positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer whose disease has progressed following hormone therapy.¹⁰⁵ HR+ means that tumor cells have receptors for hormones that can promote the growth of tumors.¹⁹³ Abemaciclib was simultaneously approved as a single agent to treat adult patients with this subtype of breast cancer whose cancer spread after treatment with prior hormone therapy and chemotherapy.¹⁰⁶ Abemaciclib is a CDK4/6 inhibitor, a type of oral therapy that inhibits proteins (cyclin-dependent kinase 4 and 6) involved in cell replication and interrupts the process through which breast cancer cells multiply.¹⁰⁸ This treatment class has rapidly transformed the landscape for HR+/HER2- advanced breast cancer, which makes up more than two out of three breast cancer cases and is rarely curable.^{108,194} Since the initial approval, clinical studies have shown that abemaciclib can be used as adjuvant treatment after surgery to treat earlier stages of breast cancer, specifically when taken in combination with certain hormone therapies. The goal of adjuvant treatment after surgery is to prevent cancer from coming back and adjuvant therapy with abemaciclib has the potential to be curative for some patients with early breast cancer.^{80,109}



Earlier Treatment Line (February 2018): Approved, for the treatment of postmenopausal women with HR+, HER2- advanced or metastatic breast cancer, in combination with a type of hormone therapy called an aromatase inhibitor. Clinical data showed that patients treated with this combination were 46% more likely to live without their cancer getting worse than patients treated with only hormone therapy.¹⁹⁵

Additional Value Demonstrated in Approved Indication (September 2019): Follow-up data shows abemaciclib, in combination with the hormone therapy fulvestrant, significantly extends life by a median of 9.4 months compared to the hormone therapy alone.¹⁹⁶ New treatment options are important given the challenge of survival among women with more advanced breast cancer, with 5-year survival dropping from 99 percent for localized disease to 30 percent for cancer that has spread.¹⁹⁷

New Indication, Earlier Disease Stage (October 2021): Approved, in combination with hormone therapy, for patients with HR+, HER2- early breast cancer that is present in the lymph nodes (node-positive). After breast cancer is removed through surgery, the presence of cancer cells in the lymph nodes indicates a higher chance of the cancer returning and spreading. Specifically, abemaciclib was approved as an adjuvant treatment (after surgery) for patients whose tumors express a biomarker (Ki-67), indicating rapid cancer growth with a high risk of tumors returning.¹⁰⁹ The goal of adjuvant therapy is to prevent the cancer from coming back.⁸⁰ Clinical data showed that patients treated with this combination

were 37% more likely to be alive and free of any signs of breast cancer compared to hormone therapy alone. With this approval, abemaciclib became the first addition to adjuvant hormone therapy in nearly two decades for this indication.^{109,110}

Additional Value Demonstrated in Approved Indication (December 2022): Follow-up data at four years was favorable for HR+, HER2-, node-positive, high-risk early breast cancer patients who took adjuvant abemaciclib, in combination with hormone therapy, compared to patients taking only hormone therapy. The clinical data showed that more patients treated with the combination were alive and free of any signs of breast cancer than those treated with only hormone therapy.¹¹¹

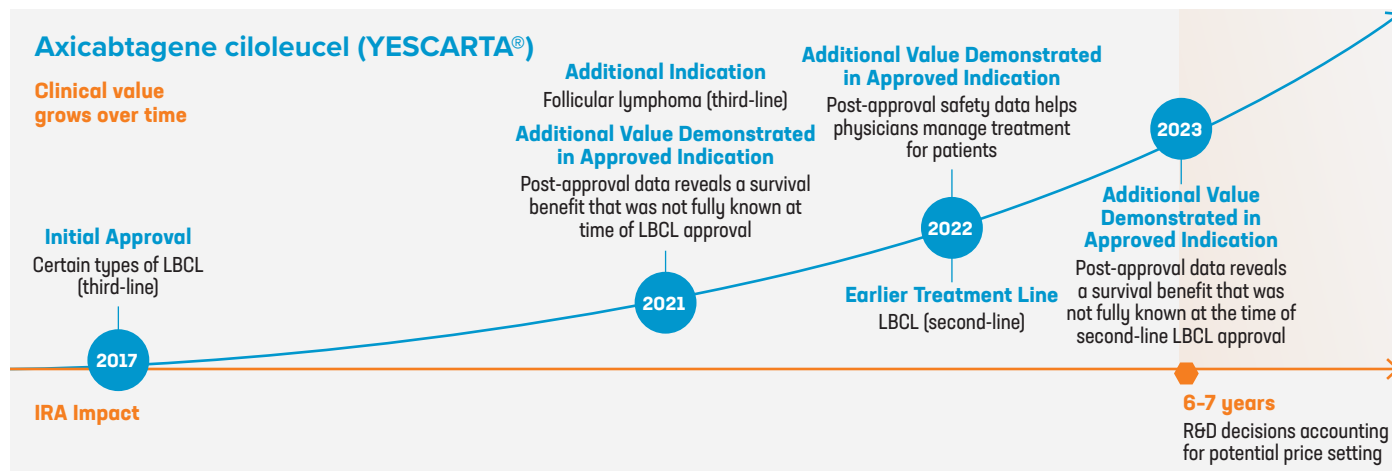
Additional Value Demonstrated in Approved Indication (March 2023): Long-term follow-up data confirms a significant survival benefit for patients with HR+, HER2- advanced breast cancer who were treated with abemaciclib in combination with the hormone therapy fulvestrant after their disease progressed on hormone therapy, with 41% of patients alive after five years compared to only 29% of patients who received hormone therapy alone.¹⁹⁸

Expansion of Label, Use in Combination (March 2023): Granted label expansion to remove the need for a Ki-67 biomarker test to treat patients with HR+, HER2-, node-positive early breast cancer at a high risk of returning. The label expansion is supported by four-year data showing that the combination reduces the risk of the cancer returning by 35% compared to hormone therapy alone.¹¹²

Axicabtagene ciloleucel | YESCARTA®

Axicabtagene ciloleucel stems from a promising class of immunotherapy known as chimeric antigen receptor (CAR) T-cell therapy, in which every dose is manufactured specifically for the patient. In the manufacturing process, a patient's T-cells are collected from the bloodstream and genetically modified to express an artificial receptor that allows T-cells to recognize cancer cells. Once returned to the body, the modified cells work by attacking cancer cells. CAR T-cell therapies are among the most promising areas in cancer treatment, often allowing patients to achieve long-term, cancer-free effects with a single administration.⁷⁴

In 2017, the FDA approved axicabtagene ciloleucel for patients with certain types of large B-cell lymphoma (LBCL) who have not responded to or have relapsed after at least two other lines of treatment.⁷³ In the study supporting initial approval, 72% of patients treated with a single dose of axicabtagene ciloleucel responded to therapy, and over half no longer showed signs of cancer.⁷⁵ Ongoing research and clinical trials have revealed additional benefits and offered insights to optimize CAR T-cell therapy that were not recognized at the time of initial approval. Axicabtagene ciloleucel continues to be studied across a variety of other types of hematologic cancers.¹⁹⁹



Additional Indication (March 2021): Granted accelerated approval for treatment of adults with relapsed or refractory follicular lymphoma after two or more lines of therapy. The FDA granted priority review, orphan drug designation, and breakthrough therapy designation for this indication, and the approval was based on an overall response of 91%.²⁰⁰

Additional Value Demonstrated in Approved Indication (December 2021): Clinical evidence demonstrates long-term survival in certain patients with LBCL who had not responded to or relapsed after prior treatment. After five years of follow-up of these patients, clinical data showed a 5-year survival rate of 43%. Among those patients, 92% had received no additional treatment since their 1-time infusion of axicabtagene ciloleucel. These long-term outcomes showed a sustained survival benefit in this patient population, who previously had a life expectancy of just six months.⁷⁶

Additional Value Demonstrated in Approved Indication (January 2022): Clinical trial data on axicabtagene ciloleucel in late stage LBCL helped support a safety management update of prophylactic corticosteroids. This addition to the label helps physicians manage and potentially prevent side effects. Without continued research efforts to optimize CAR T-cell therapy, this improvement in patient management may not have been realized.⁷⁷

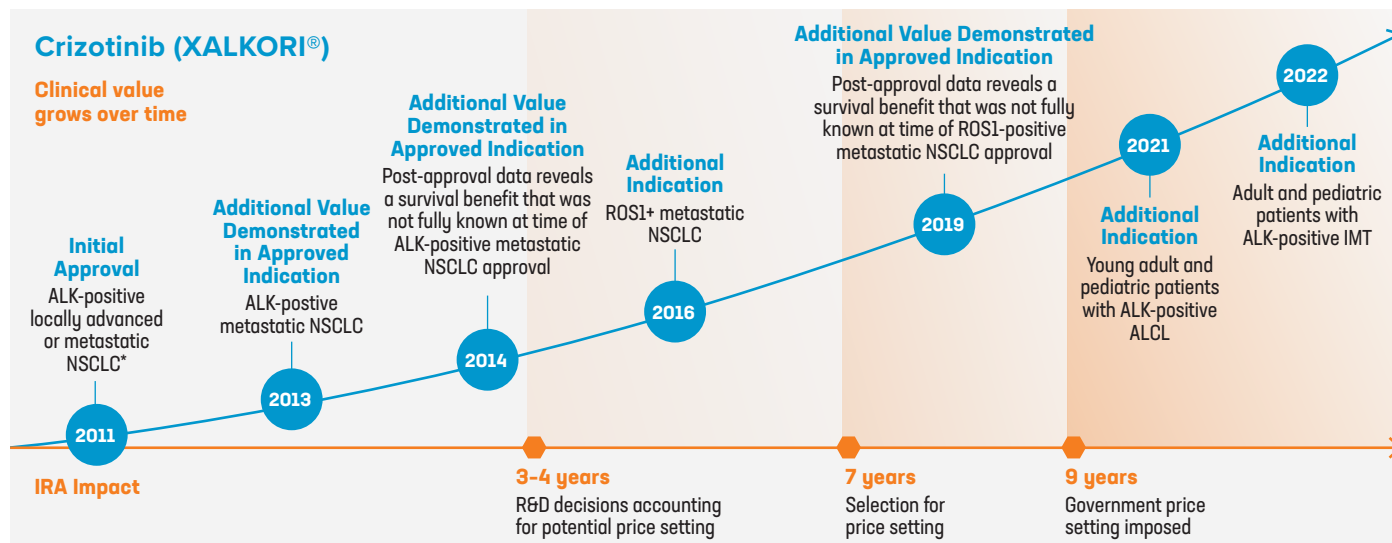
Expanded Use for Earlier Treatment Line (April 2022): Approved to treat adult patients with LBCL after first-line treatment. As the most common type of non-Hodgkin lymphoma, more than 18,000 people are diagnosed with LBCL in the US each year. In a Phase III global clinical trial considered the first and largest trial of its kind, 2.5 times more patients receiving axicabtagene ciloleucel were alive at two years versus standard-of-care. Only with continued clinical research were the survival benefits of axicabtagene ciloleucel fully realized, leading to the approval of the first LBCL treatment to improve upon the standard of care in this patient population in nearly 30 years.⁹¹ Most importantly, this expanded use earlier in the treatment line also allowed these patients to achieve these benefits without having to endure several prior lines of treatment.

Additional Value Demonstrated in Approved Indication (March 2023): Long-term clinical data showed that axicabtagene ciloleucel significantly improved survival for patients with LBCL after first-line treatment, demonstrating the importance of ongoing research to reveal the full clinical value of cancer treatments.⁹²

Crizotinib | XALKORI®

In 2011, FDA granted accelerated approval to crizotinib, a targeted oral cancer therapy known as a tyrosine kinase inhibitor. The medicine was approved to treat patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)* whose tumors have a particular abnormality caused by a rearrangement in the anaplastic lymphoma kinase (ALK) gene, which leads to cancer cell growth.¹¹⁶ Ongoing research and clinical studies in certain types of lung cancer have revealed survival benefits that were not known at the time of initial approval of crizotinib based on available data.²⁰¹

As changes in the ALK gene have been found in tumors across several cancer types, crizotinib has since been studied and approved across several indications, including FDA approvals granted a decade after initial approval.^{118,125} These approvals provide important new treatment options for both adult and pediatric patients in certain rare cancer types.



*Indication was later modified to metastatic ALK-positive NSCLC²⁰²

Additional Value Demonstrated in Approved Indication (November 2013): Granted traditional approval for the treatment of metastatic ALK-positive metastatic NSCLC, based on clinical data in previously treated patients demonstrating over 50% improvement in progression-free survival compared to standard-of-care chemotherapy at the time.^{117,203} Patients with ALK-positive cancer tend to be younger than the average lung cancer patient and have little to no smoking history.²⁰⁴

Additional Value Demonstrated in Approved Indication (December 2014): New clinical data showed that crizotinib, for the treatment of patients with previously untreated ALK-positive metastatic NSCLC, significantly improved progression-free survival vs. chemotherapy. This data underscores the importance of biomarker-driven treatment in patients newly diagnosed with lung cancer, the leading cause of cancer death worldwide.²⁰⁵

Additional Indication (March 2016): Approved for the treatment of patients with metastatic NSCLC whose tumors are ROS1-positive. Occurring in approximately 1-2% of NSCLC cases, rearrangements in the ROS1 gene can contribute to cancer cell growth.^{206,207} Patients with ROS1-positive cancer tend to be younger than the average lung cancer patient and have little to no smoking history.²⁰⁷ As the first treatment to specifically target the ROS1 biomarker, FDA granted breakthrough therapy designation to crizotinib.^{206,208}

Additional Value Demonstrated in Approved Indication (July 2019): Updated clinical study data for crizotinib

in ROS1-positive NSCLC showed mature median overall survival data of 51.4 months, continuing to demonstrate the clinically meaningful benefit of this targeted therapy. This data served as a new benchmark for overall survival in patients with ROS1-positive NSCLC.²⁰¹

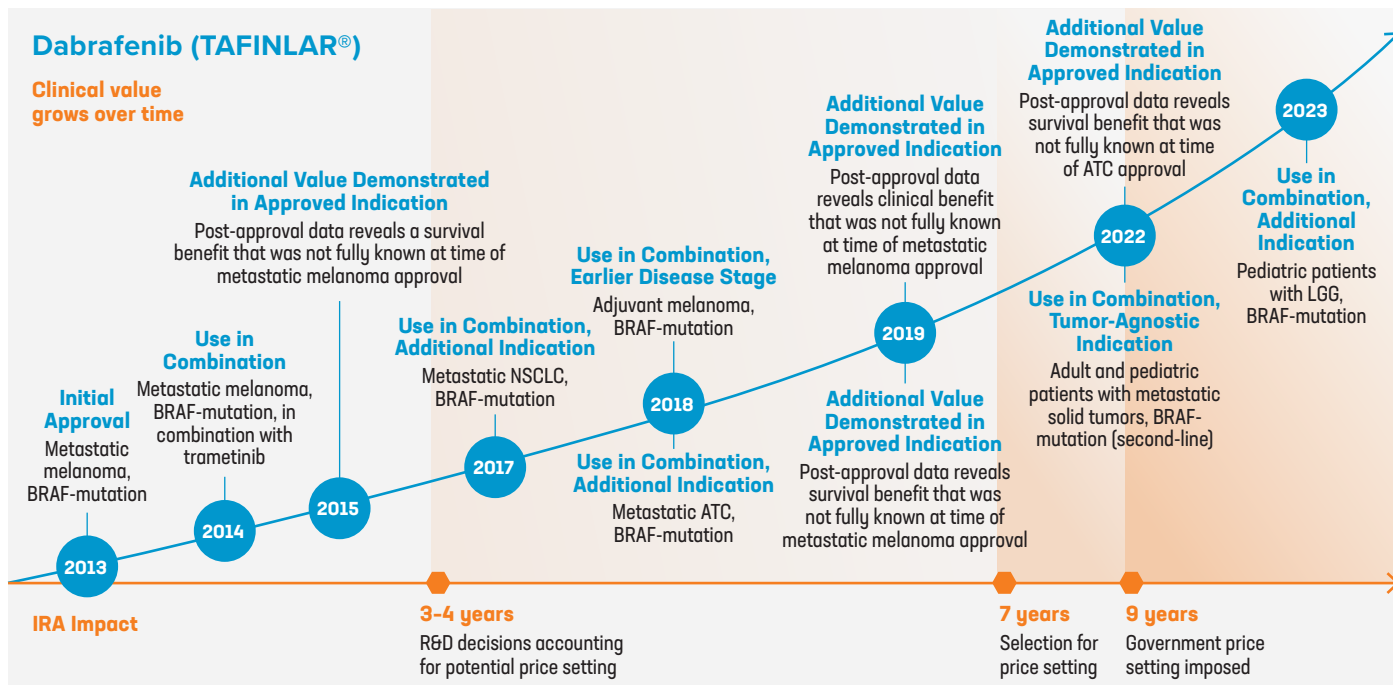
Additional Indication (January 2021): Approved for the treatment of pediatric and young adult patients with ALK+ anaplastic large cell lymphoma (ALCL) that has returned or not responded to prior treatment. The FDA granted priority review, orphan drug designation, and breakthrough designation for this indication.¹²⁴ ALCL is a rare form of non-Hodgkin lymphoma with approximately 100 new cases in the US every year.^{118,119,120,121,122,123} This marks the first FDA-approved, biomarker-driven therapy available to children and young adults with this specific type of ALCL and was based on an 88% response rate. Approximately 90% of ALCL cases in children and young adults are ALK-positive and this approval marked a particularly valuable treatment advance for these patients.¹¹⁸

Additional Indication (July 2022): Approved for the treatment of adult and pediatric patients with ALK-positive inflammatory myofibroblastic tumors (IMT) that have returned, not responded to prior treatment, or cannot be removed by surgery.¹²⁵ IMT is very rare with only 150-200 people diagnosed in the US annually—most commonly children and young adults.¹²⁶ Up to 50% of cases have this particular ALK gene abnormality.¹²⁷

Dabrafenib | TAFINLAR®

In 2013, FDA granted approval of dabrafenib, a targeted oral cancer medicine, for the treatment of patients with metastatic melanoma whose tumors express the BRAF mutation, a genetic change that can cause some melanoma tumors to grow and spread.¹⁷⁴ About half of all metastatic melanoma cases involve changes in the BRAF gene, which has been identified as a driver of cancer growth across a wide range of other solid tumors.^{173,189} Dabrafenib was approved as a single agent. It is a BRAF inhibitor designed to block activity of the BRAF protein directly.¹⁷²

Since its initial approval, dabrafenib has demonstrated clinical benefit in numerous cancers that have the BRAF mutation, specifically when taken in combination with trametinib, another targeted oral cancer medicine known as a MEK inhibitor. The MEK gene and BRAF gene work together in the same pathway leading to cancer cell growth.¹⁷² The combination of these therapies, targeting cancer cell growth at multiple points along the pathway, has been studied extensively across many indications, including pediatric patients and rare cancer types that often have limited treatment options, revealing a wide range of benefits that were not known at the time of initial approval.¹⁸⁹



Use in Combination (January 2014): Granted accelerated approval in combination with trametinib for patients whose melanomas have spread or cannot be removed completely by surgery (metastatic or unresectable melanoma) and express the BRAF mutation. In initial clinical trials, 76% of patients treated with dabrafenib and trametinib responded to the combination, compared to 54% for those on dabrafenib alone.²⁰⁹ This indication was later converted to traditional approval because of a superior survival benefit of the combination.²¹⁰

Additional Value Demonstrated in Approved Indication (November 2015): Granted traditional approval in combination with trametinib to treat patients with unresectable or metastatic melanoma whose tumors express the BRAF mutation. Two Phase III clinical trials demonstrated a survival benefit confirming the superiority of the dabrafenib and trametinib combination vs one BRAF-targeted treatment alone.²¹⁰

Use in Combination, Additional Indication (June 2017): Approved in combination with trametinib for the treatment of patients with metastatic NSCLC whose tumors express the BRAF mutation, the first approved treatment to

specifically target this type of lung cancer. In the clinical trial supporting this approval, the response rate to the combination was over 60%.²¹¹

Use in Combination, Earlier Disease Stage (April 2018): Approved in combination with trametinib for the adjuvant treatment of patients with melanoma whose tumors express the BRAF mutation and have lymph node involvement. Adjuvant therapy is an additional treatment after surgical resection to help reduce the risk of melanoma returning.⁸⁰ In the Phase III study supporting this approval, the risk of disease recurrence or death for patients treated with the combination of dabrafenib and trametinib was reduced by over 50% compared to patients who were not prescribed treatment after surgery.²¹²

Use in Combination, Additional Indication (May 2018): Approved in combination with trametinib for the treatment of patients with metastatic anaplastic thyroid cancer (ATC) whose tumors express the BRAF mutation. This is the first treatment approved specifically for ATC, a rare and aggressive type of thyroid cancer accounting for approximately one to two percent of all thyroid cancers.^{176,213}

Additional Value Demonstrated in Approved Indication

(October 2019): Clinical trial results in patients with metastatic melanoma whose tumors express the BRAF mutation and whose tumors have metastasized to the brain, demonstrated an intracranial response for 50% of patients treated with the dabrafenib and trametinib combination.^{175,214} Brain metastases are one of the most common and difficult-to-treat complications in melanoma. Given more than 60% of patients with metastatic melanoma will develop brain metastases, research on this specific type of metastases remains critical to advance improved treatment outcomes for patients.²¹⁵

Additional Value Demonstrated in Approved Indication

(June 2019): Long-term clinical data demonstrated that the dabrafenib and trametinib combination led to a 5-year survival rate of one-third among patients with BRAF-mutated metastatic melanoma, an aggressive skin cancer with a historically poor prognosis. These results represented the largest collection of data and the longest follow-up among patients with this type of melanoma who were treated with these targeted therapies.²¹⁶

Additional Value Demonstrated in Approved Indication

(January 2022): Clinical data with four years of additional follow-up confirmed the substantial clinical benefit of the dabrafenib and trametinib combination in BRAF-mutated ATC. Study results showed a median survival of 15 months and a 12-month survival rate of 52%. These findings are notable given a historic median survival of less than six months.¹⁷⁸

Use in Combination, Tumor-Agnostic Indication (June 2022):

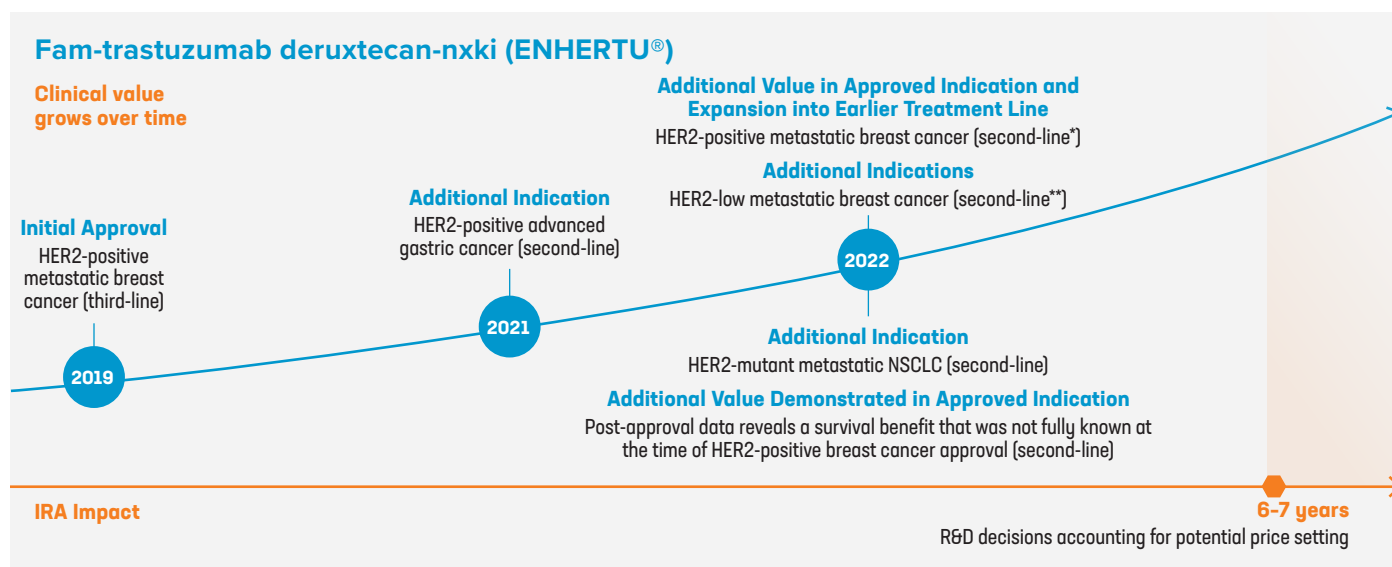
Granted accelerated approval in combination with trametinib for the treatment of adult and pediatric patients with metastatic solid tumors that express the BRAF mutation who have progressed on previous treatment and have no alternative treatment options. As the first approved tumor-agnostic treatment targeting the BRAF mutation, which drives cancer growth in more than 20 different tumor types, this new indication marked a significant advance for patients. It also marked the first combination approved to target the BRAF mutation in pediatric patients.¹⁸⁹

Use in Combination, Additional Indication (March 2023):

Approved, in combination with trametinib, for the treatment of pediatric patients with BRAF-mutated low-grade glioma (LGG). LGG is the most common pediatric brain cancer. BRAF-mutated tumors account for 15-20% of LGGs and are associated with poor patient outcomes and limited response to available treatments. In a clinical study, 47% of patients responded to the combination, compared to only 11% of patients taking chemotherapy. The FDA also approved a liquid formulation suitable for children who cannot swallow pills, demonstrating how additional research can advance treatment options that can improve administration for specific patient groups, including pediatric populations.²¹⁷

Fam-trastuzumab deruxtecan-nxki | ENHERTU®

In 2019, the FDA granted trastuzumab deruxtecan[†] accelerated approval for patients with hard-to-treat metastatic breast cancer who test positive for the human epidermal growth factor receptor 2 (HER2) and have received two or more prior lines of anti-HER2-based treatment. Approximately one in five breast cancers have a mutation that makes excess HER2 protein, which promotes the growth of cancer cells. HER2-positive breast cancers are an aggressive form of breast cancer.⁵⁵ Trastuzumab deruxtecan is a HER2-directed antibody-drug conjugate, a class of targeted cancer medicine that binds to specific proteins on target cells and attacks those cells directly.²⁷ The therapy has shown clinical benefit in other types of cancer that express certain levels of the HER2 protein, in addition to breast cancer. Ongoing research continues to study trastuzumab deruxtecan in other HER2-positive cancers.¹³⁹



Additional Indication (January 2021): Approved to treat patients with advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma previously treated with a trastuzumab-based regimen. Gastric cancer is frequently diagnosed in the advanced stage and patients often have poor outcomes, with only 5% surviving beyond five years. In a clinical study supporting this approval, trastuzumab deruxtecan demonstrated a 41% reduction in the risk of death versus chemotherapy.¹⁴¹

Additional Value in Initial Indication and Expansion into Earlier Treatment Line (May 2022): Converted the initial approval in metastatic HER2-positive breast cancer from accelerated to traditional approval and broadened its use to an earlier treatment line (from third-line to second-line*). In a clinical study supporting this expanded indication, trastuzumab deruxtecan showed a 72% reduction in the risk of disease progression or death versus another anti-HER2 treatment.⁵⁷

Additional Indication (August 2022): Approved to treat patients with HER2-low metastatic breast cancer after prior treatment with chemotherapy.** Study data revealed patients treated with trastuzumab deruxtecan lived a median of 10.1 months without their cancer growing, nearly twice as long as those treated with standard chemotherapy; and lived a median of 23.9 months, about six months longer overall.^{218,219} This was the first approved therapy targeted to patients with HER2-low breast cancer, a newly defined subset of previously HER2-negative breast cancer.²²⁰ Prior to this approval, only people with breast cancer whose tumor cells produce high levels of HER2 (also called HER2-positive) had been shown

to benefit from drugs that target HER2. This critical post-approval research revealed that patients with this historically difficult form of the disease could be treated with HER2-targeted therapy, fundamentally changing the way these cancers are classified and treated.²²¹

Additional Indication (August 2022): Granted accelerated approval to treat patients with unresectable or metastatic HER2-mutant non-small cell lung cancer (NSCLC) cancer who have received prior therapy. This aggressive form of NSCLC more commonly impacts younger patients who have previously had limited treatment options and poor prognosis. This marks the first HER2-directed treatment option for patients with this specific type of lung cancer.²²²

Additional Value Demonstrated in Approved Indication (December 2022): Post-approval clinical study data revealed a survival improvement in patients with HER2-positive breast cancer. These patients lived a median of 28.8 months, nearly two years longer without their disease progressing compared to those on another anti-HER2 treatment.⁵⁹ Historically, patients with HER2-positive breast cancer often experience disease progression, underscoring the importance of the availability of treatment options that improve survival and delay disease progression.⁵⁸

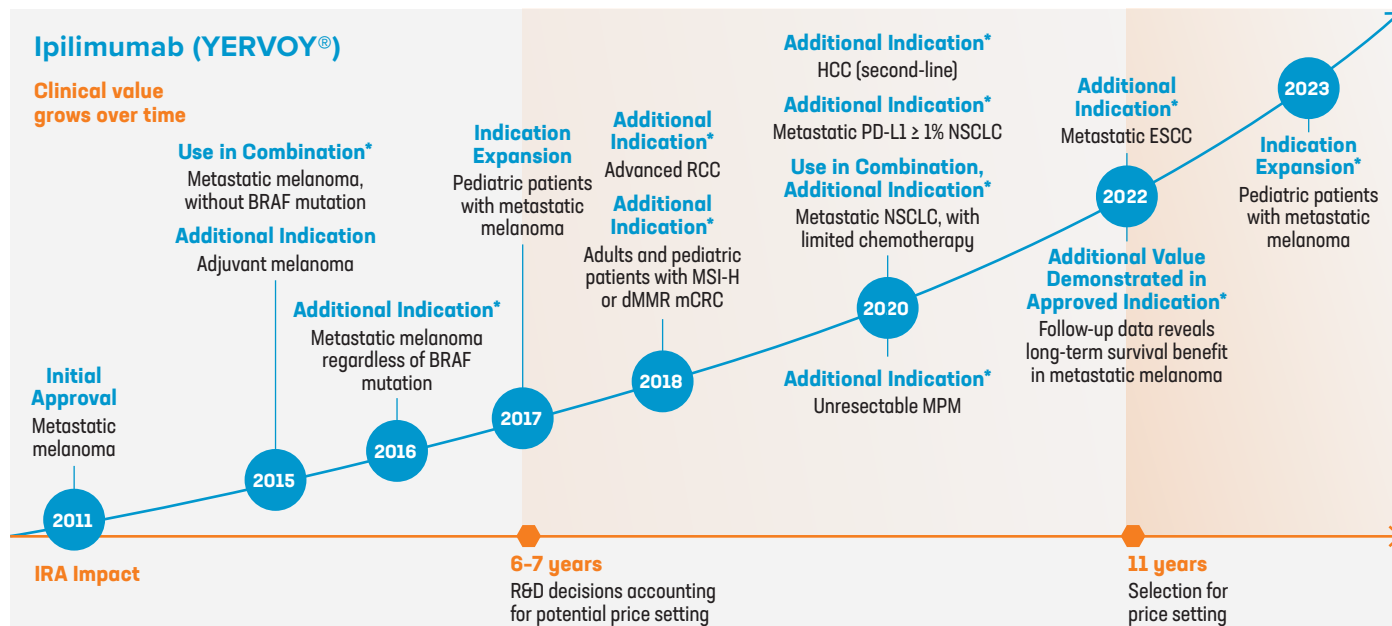
[†]Full US generic name: fam-trastuzumab deruxtecan-nxki

*The broadening of this indication included use after one prior anti-HER2-based regimen in the metastatic, or in the neoadjuvant or adjuvant settings and experienced a disease recurrence within six months of completing treatment

**Indication included use after prior chemotherapy in the metastatic setting or after disease recurrence during or within six months of completing adjuvant treatment

Ipilimumab | YERVOY®

In 2011, the FDA approved ipilimumab for the treatment of unresectable or metastatic melanoma, a late-stage skin cancer and one of the deadliest cancers at the time, with a historic average survival of just six months.¹⁴⁹ Ipilimumab stems from a class of immunotherapies known as immune checkpoint inhibitors, a treatment class that helps activate a patient's own immune system to fight cancer cells and has fundamentally changed outcomes for certain groups of patients with cancer.^{81,148} Ipilimumab was the first checkpoint inhibitor to be approved and targets a specific protein involved in regulating the immune system, called CTLA-4.⁸¹ Since the initial approval, clinical studies have shown that ipilimumab has improved survival in melanoma and several other cancers, specifically when taken in combination with nivolumab, a checkpoint inhibitor that targets a different protein on immune cells, called PD-1.⁸² The combination, which targets two different checkpoints of the immune system, potentially works synergistically to increase the body's ability to fight cancer and has been studied extensively for over a decade, revealing clinical benefits that were not known at the time of initial approval. These benefits highlight not only the tremendous progress that has been made with this class of treatments but underscore how critically important combination treatment approaches are to advancing the treatment paradigm for many forms of cancer.



* Ipilimumab approved in combination with nivolumab

BRAF: v-raf murine sarcoma viral oncogene homolog B1, dMMR: deficient mismatch repair, ESCC: esophageal squamous cell carcinoma, HCC: hepatocellular carcinoma, mCRC: metastatic colorectal cancer, MPM: malignant pleural mesothelioma, MSI-H: high microsatellite instability, NSCLC: non-small cell lung cancer, PD-L1: programmed cell death-ligand 1, RCC: renal cell carcinoma

Use in Combination (October 2015): Approved, in combination with nivolumab, for the treatment of patients with unresectable or metastatic melanoma whose tumors did not express the BRAF V600 mutation. In a clinical trial, 60% of patients treated with ipilimumab and nivolumab responded to the combination. This was the first FDA-approved combination of two immune checkpoint inhibitors in oncology, demonstrating the potential of targeting distinct and complementary immune system pathways involved in this type of cancer.¹⁵³

Additional Indication (October 2015): Approved for the adjuvant treatment of certain patients with stage III melanoma who are at high risk of the cancer returning following surgery. Among these patients, the cancer returns in almost six out of every 10 patients, and patients have a historically low survival rate once the disease returns. Clinical data shows that patients treated with ipilimumab had a 25% reduction in the risk of recurrence or death than patients who received no treatment.^{223,224}

Use in Combination, Indication Expansion (January 2016): Granted label expansion, based on accelerated approval, in combination with nivolumab for the treatment of patients

with unresectable or metastatic melanoma, regardless of BRAF mutation. Clinical data showed that patients on the combination were significantly less likely to have their disease progress than ipilimumab alone.¹⁵⁴

Indication Expansion (July 2017): Approved for the treatment of pediatric patients 12 years and older with unresectable or metastatic melanoma.²²⁵ Pediatric melanoma is rare, accounting for less than 1% of all new cases of melanoma, which makes it particularly difficult to investigate in clinical trials.¹⁵⁹ This approval marked a critical new treatment option for this patient population.²²⁶

Use in Combination, Additional Indication (April 2018): Approved, in combination with nivolumab, as the first immune checkpoint combination therapy for patients with intermediate- and poor-risk advanced renal cell carcinoma (RCC) which affects 75%–80% of those with advanced RCC. These patients historically have had particularly poor prognosis and limited options to improve survival. Clinical data showed that patients treated with the combination had a 37% reduced risk of death versus a standard of care treatment.²²⁷

Use in Combination, Additional Indication (July 2018):

Granted accelerated approval, in combination with nivolumab, for the treatment of patients 12 years of age and older with microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) metastatic colorectal cancer (mCRC) whose disease has progressed following treatment with chemotherapy. MSI-H and dMMR are biomarkers that may indicate likelihood of clinical benefit. Clinical data showed 46% of patients treated with this combination saw their tumor size or amount of cancer in their body decrease.²²⁸

Use in Combination, Additional Indication (March 2020):

Granted accelerated approval, in combination with nivolumab, for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. Clinical data showed that one out of every three patients with this aggressive disease saw their tumor size or amount of cancer in their body decrease when treated with the combination therapy.²²⁹

Use in Combination, Additional Indication (May 2020):

Approved, in combination with nivolumab, for patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1. Clinical data showed that patients had a 21% reduction in the risk of death with the combination versus chemotherapy alone.²³⁰

Use in Combination, Additional Indication (May 2020):

Approved, in combination with nivolumab and two cycles of limited chemotherapy, in patients with metastatic or recurrent NSCLC, regardless of PD-L1 expression. At one year, more patients treated with the combination and limited chemotherapy were still alive versus those treated with chemotherapy alone.²³¹

Use in Combination, Additional Indication (October 2020):

Approved, in combination with nivolumab, for the treatment of adults with unresectable malignant pleural mesothelioma (MPM). MPM is a rare cancer type, that is often aggressive and associated with poor patient outcomes. The combination, demonstrating superior survival to standard of care chemotherapy, was the first new systemic therapy in over 15 years to be approved by the FDA for MPM.¹⁶³

Additional Indication (May 2022): Approved, in combination with nivolumab, for the treatment of patients with advanced or metastatic esophageal squamous cell carcinoma (ESCC). Clinical data showed patients treated with the combination had a 26% reduction in the risk of death compared to patients on chemotherapy.²³²

Additional Value Demonstrated in Approved Indication

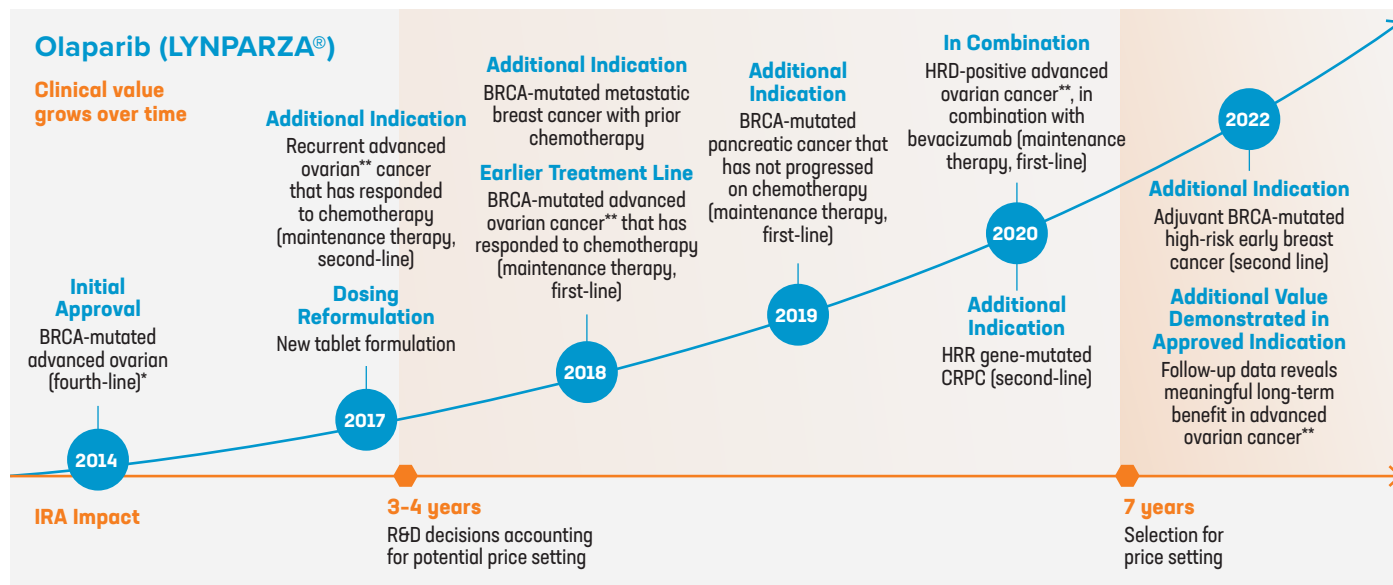
(July 2022): Follow-up data at 7.5 years showed a durable response for patients with metastatic melanoma treated with ipilimumab in combination with nivolumab, demonstrating a long-term survival rate of 48%, which was higher than either therapy taken alone. Prior to more recent novel therapies in melanoma, only about 5% of patients with metastatic melanoma survived for greater than five years.^{156,157,233}

Use in Combination, Indication Expansion (February 2023):

Approved, in combination with nivolumab, for the treatment of pediatric patients 12 years and older with unresectable or metastatic melanoma.¹⁵⁸ This approval occurred over a decade after initial approval, highlighting the critical importance of ongoing research for rare childhood cancers like melanoma.²²⁶

Olaparib | LYNPARZA®

In 2014, olaparib became the first PARP inhibitor approved by the FDA.⁹⁷ PARP inhibitors are a type of targeted oral cancer treatment that help keep cancer cells from repairing damaged DNA, causing them to die.³¹ Olaparib was initially granted accelerated approval for patients with advanced ovarian cancer who had already exhausted many treatment options and whose cancer tested positive for a BRCA mutation.⁹⁷ Continued development of this targeted cancer medicine has led to various additional indications in breast, ovarian, pancreatic, and prostate cancers and a dosing reformulation to improve patient convenience.^{98,234} Olaparib has earned approval as maintenance therapy for some cancers, which is given to patients to help keep cancer from coming back after initial therapy.⁹⁹ Research has also revealed significant survival benefits that could not have been known until years after initial approval.



Additional Indication (August 2017): Approved as maintenance therapy for patients with recurrent advanced ovarian cancer**, who have a response to chemotherapy, regardless of BRCA mutation status.⁹⁸ As recurrence rates in ovarian cancer patients are high, maintenance therapies are used to help prevent and extend the time until recurrence following surgery or positive response to chemotherapy.^{99,100} In a clinical study, patients treated with olaparib were 27% more likely to be alive compared to patients taking no maintenance therapy.⁹⁸ A high proportion of patients diagnosed with ovarian cancer already have later stage disease.¹⁰¹ As this type of cancer is a leading cause of cancer death in women, the availability of treatment options that can help extend survival in these patients is critically important.⁹⁸

Dosing Reformulation (August 2017): Approved dosing reformulation switched the daily dosing regimen from many capsules twice per day to two tablets twice per day, improving patient convenience.⁹⁸

Additional Indication (January 2018): Approved for patients with BRCA-mutated, HER2-negative metastatic breast cancer previously treated with chemotherapy. Olaparib was the first PARP inhibitor approved to treat this aggressive, difficult-to-treat cancer. In a clinical study, the therapy was shown to reduce risk of disease progression or death by 42% compared to standard of care chemotherapy.²³⁶

Earlier Treatment Line (December 2018): Approved as a first-line maintenance therapy for patients with BRCA-mutated advanced ovarian cancer** who responded to chemotherapy.¹⁰² The BRCA gene mutation is present in up to 15% of all ovarian cancer cases.²³⁷ In a clinical trial, patients treated with olaparib were 70% more likely to live without their cancer getting worse compared to patients taking no maintenance therapy.¹⁰²

Additional Indication (December 2019): Approved as a first-line maintenance therapy for patients with metastatic pancreatic cancer whose cancer tested positive for a BRCA mutation and whose disease has not progressed on chemotherapy. In a clinical study, olaparib nearly doubled the time patients lived without their cancer getting worse. Pancreatic cancer has the lowest survival rate among the most common cancers, making treatments that can extend survival critical for patients with this disease.¹⁴³

Use In Combination (May 2020): Approved in combination with bevacizumab as a first-line maintenance treatment for patients with HRD-positive advanced ovarian cancer** who have responded to chemotherapy. Approximately half of all patients with advanced ovarian cancer have a tumor that is HRD-positive. Clinical study results showed that treating patients with olaparib in combination with bevacizumab resulted in a median progression-free survival of 37.2 months compared to 17.7 months with bevacizumab alone.²³⁸

Additional Indication (May 2020): Approved to treat patients with a specific type of metastatic prostate cancer whose disease progressed after treatment with another medication. In a clinical study, patients treated with olaparib were 31% more likely to be alive compared to patients treated with another medication.²³⁹

Earlier Disease Stage (March 2022): Approved for the adjuvant treatment of patients with a specific high-risk early breast cancer (BRCA-mutated HER2-negative) after treatment with chemotherapy. In a clinical study, olaparib demonstrated a meaningful survival benefit, reducing the risk of death by 32% compared to placebo.²⁴⁰

Additional Value Demonstrated in Approved Indication (September 2022): Long-term follow up data showed improvement in survival for patients with BRCA-mutated advanced ovarian cancer who were treated with olaparib

as first-line maintenance therapy. A clinical study showed that a majority of patients taking olaparib were alive after seven years, which marked the longest follow-up for any PARP inhibitor in this setting. Given the high mortality rate associated with ovarian cancer this demonstration of long-term survival benefit marked a critically important advance for these patients.¹⁰³

**Indication voluntarily withdrawn: Although the early results from clinical studies supported the use of PARP inhibitors, including olaparib, as a treatment option for BRCA-mutated recurrent advanced ovarian cancer, longer-term overall survival data indicates that chemotherapy treatment may be more beneficial than PARP inhibitors for this indication. No other olaparib indications were affected, including indications for maintenance therapy in advanced ovarian cancer.^{104,235}*

***Indication specifically includes epithelial ovarian, fallopian tube, or primary peritoneal cancer*

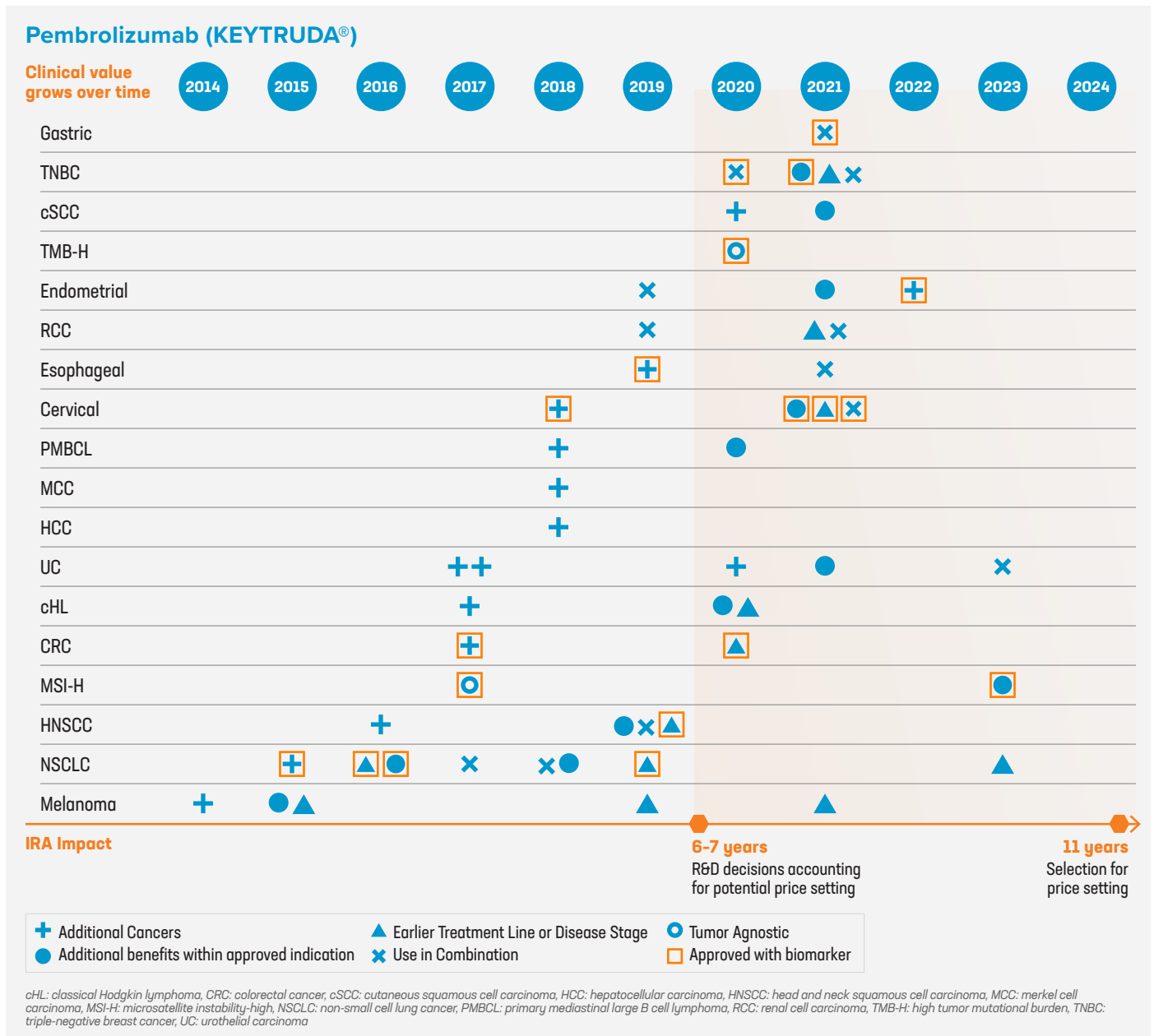
BRCA: breast cancer gene, CRPC: castration resistant prostate cancer, HER2: human epidermal growth factor 2, HRD: homologous recombination deficiency, HRR: homologous recombination repair, PARP: poly ADP-ribose polymerase

Pembrolizumab | KEYTRUDA®

In 2014, pembrolizumab became the first FDA-approved anti-PD-1 therapy, a type of immunotherapy called an immune checkpoint inhibitor.²⁴¹ This treatment class blocks certain checkpoints of the immune system, such as PD-1, to help activate a patient's own immune system to detect and fight cancer cells.¹⁴⁸ Immune checkpoint inhibitors like pembrolizumab have revolutionized oncology care and fundamentally changed outcomes for certain groups of patients with cancer.⁸¹

Since the initial approval to treat advanced metastatic melanoma, pembrolizumab has been studied extensively in common and rare cancers and has transformed the way many cancers are treated. Multiple clinical studies have demonstrated that pembrolizumab improves survival in advanced diseases as a single agent or in combination with other therapies.²⁴² Continuing research has also revealed the importance of factors, such as biomarkers, that identify patients most likely to benefit from treatment with pembrolizumab.

As of early 2023, pembrolizumab had earned approvals in 35 indications across many tumor types and as a tumor-agnostic therapy, with more than 1,600 clinical trials across a wide variety of cancers and treatment settings.⁷¹ The breadth and depth of approvals and the size of this clinical program underscore the importance of ongoing research and the potential clinical value still to come for this practice-changing cancer treatment.



Select Approvals

Additional Indication (October 2015): Granted accelerated approval for the treatment of patients with metastatic NSCLC (mNSCLC) whose tumors express a high level of PD-L1, a protein involved in the body's immune response, and whose cancer has progressed on or after chemotherapy treatment.^{69,243}

For patients with certain other tumor mutations, disease progression after certain targeted therapies must happen prior to receiving pembrolizumab. Clinical data showed four out of 10 patients had significant tumor shrinkage in response to treatment.⁶⁹

Earlier Treatment Line (October 2016): Approved for the treatment of patients newly diagnosed with certain mNSCLC whose tumors express high levels of PD-L1. A clinical study showed that patients on pembrolizumab were 40% more likely to be alive than those on chemotherapy. This data demonstrated pembrolizumab's superiority in newly diagnosed patients, and the trial was stopped early to give patients still on chemotherapy the opportunity to receive pembrolizumab.⁷⁰ Lung cancer is the leading cause of cancer death in the US, and treatments that extend life, like pembrolizumab, are critically important.⁶²

Tumor Agnostic (May 2017): Granted accelerated approval for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) solid tumors—biomarkers indicating potential response to treatment across numerous cancer types—that have progressed following prior treatment and have no remaining treatment options. Pembrolizumab became the first-ever FDA-approved tumor-agnostic therapy, representing a major breakthrough in precision medicine and a revolutionary approach to cancer treatment. Clinical data showed approximately four out of 10 patients responded to pembrolizumab, with 78% percent of those patients responding for six months or longer.¹⁸³

Label Update, Dosing Schedule (April 2020): Granted accelerated approval to a new six-week dosing regimen across all currently approved adult indications as an alternative to the previous three-week dosing regimen. This approval offers doctors the option to reduce how often a patient must visit the clinic to receive their infusions, which was valuable to address the unique challenges of cancer patients during social distancing measures recommended during the COVID-19 pandemic. The new dosing regimen created flexibility to help adhere to planned treatment schedules.²⁴⁴

Additional Value Demonstrated in Approved Indication and Expansion into Earlier Treatment Line (October 2020): Converted accelerated approval in late-line classical Hodgkin lymphoma (cHL) to traditional approval and broadened its use to earlier treatment lines, which includes the treatment of adult patients with cHL who have progressed after first-line treatment, as well as pediatric patients with cHL that has stopped responding to treatment or cHL that has returned after two or more therapies.^{245,246} Clinical trial data showed patients were 35% more likely to live without their cancer getting worse than those on another treatment, a particularly meaningful improvement compared to a historically poor prognosis.²⁴⁶

Singular FDA Indication, Earlier Disease Stage (July 2021):

Approved as the first immunotherapy for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC), first in combination with chemotherapy prior to surgery, and then continued as a single agent after surgery. This new indication built upon a prior FDA approval in metastatic TNBC in combination with chemotherapy for patients expressing a certain biomarker.^{247,248} TNBC is an aggressive cancer and makes up approximately 10-15% of breast cancer diagnoses. It has a high rate of recurrence and is more common among younger women and black women. Clinical data showed patients on this treatment regimen saw a 37% decrease in the risk of certain kinds of disease progression—specifically events indicating the cancer has returned or worsened—or death when compared to only chemotherapy prior to surgery.^{248,249}

Additional Indication, Use in Combination (August 2021):

Approved, in combination with lenvatinib, for the treatment of patients with advanced renal cell carcinoma (RCC). Clinical data showed that patients taking this combination were 34% more likely to be alive versus a standard of care treatment at the time. Almost one in three patients with renal cancer are diagnosed with metastatic disease with a 5-year survival rate of only 13%, so this approval marked an important new treatment option that may extend life for RCC patients.²⁵⁰

Additional Value Demonstrated in Approved Indication, Earlier Treatment Line, Use in Combination (October 2021):

Approved, in combination with chemotherapy, with or without bevacizumab, for the treatment of PD-L1+ cervical cancer patients with persistent, recurrent, or metastatic disease. In the US, less than one in five patients diagnosed with advanced cervical cancer live more than five years. Clinical data showed patients were 36% more likely to live on the chemotherapy-based treatment regimen when combined with pembrolizumab than without it. Additionally, the FDA converted to traditional approval the 2018 accelerated approval of pembrolizumab as a single agent for the treatment of patients with PD-L1+ recurrent or metastatic cervical cancer whose cancer progressed on or after chemotherapy.²⁵¹

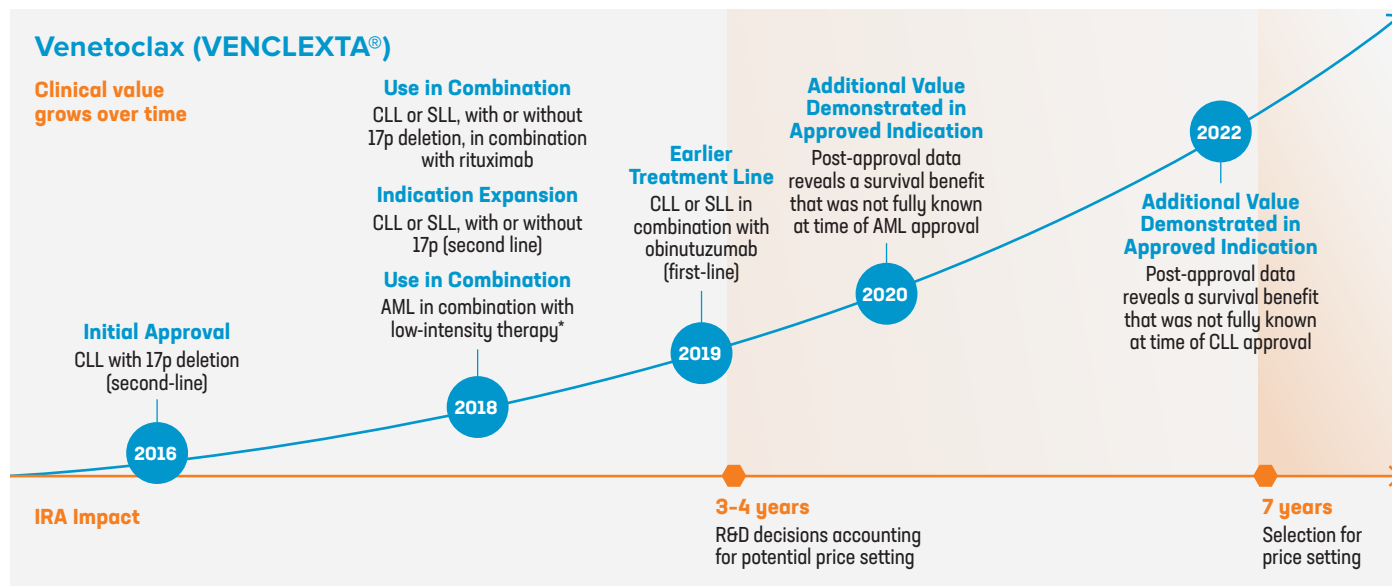
Indication Expansion, Earlier Disease Stage (December 2021):

Approved for the adjuvant treatment of patients 12 years and older with certain stages of melanoma following surgery. This approval expanded the label to include pediatric patients and patients with an earlier stage of melanoma, allowing more patients the opportunity to help prevent melanoma recurrence. In a clinical study, patients treated with pembrolizumab after surgery were 35% more likely to be alive without signs of cancer than patients who received no treatment.²⁵²

Earlier Disease Stage (January 2023): Approved for the adjuvant treatment of patients with certain types of NSCLC following surgery and chemotherapy. Patients who received pembrolizumab in addition to chemotherapy following surgery were 27% more likely to be alive without signs of cancer than patients who did not receive pembrolizumab. Additionally, the median survival for patients taking pembrolizumab was nearly two years longer without disease progression than those patients who did not take pembrolizumab.⁷¹

Venetoclax | VENCLEXTA®

In 2016, FDA granted venetoclax, a targeted oral therapy, accelerated approval to treat patients with hard-to-treat chronic lymphocytic leukemia (CLL) with 17p deletion who have received at least one prior therapy.⁸⁴ CLL is the most common leukemia in adults, and the 17p deletion is a genetic abnormality associated with poor prognosis.^{84,253} Venetoclax is a B-cell lymphoma 2 (BCL-2) inhibitor, designed to selectively block a protein that is overexpressed in many cancers and helps restore the process in which cancer cells self-destruct.^{84,85} After initial approval for CLL 17p deletion, venetoclax was researched further, including in combination with other treatments and across numerous cancers, revealing additional benefits that were not recognized at the time of initial approval.



Use in Combination, Indication Expansion (June 2018):

Approved in combination with rituximab to treat CLL or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least one prior therapy. In a clinical trial, the combination was shown to reduce the risk of disease progression or death by 81% compared to the prior standard of care in CLL. The FDA also granted venetoclax traditional approval for the initial indication as a single agent for hard-to-treat CLL and SLL, and expanded the indication to include patients with or without 17p deletion.⁸⁶

Use in Combination, Additional Indication (November 2018):

Granted accelerated approval in combination with low-intensity therapy* to treat newly-diagnosed acute myeloid leukemia (AML) in adults at least 75 years of age or who cannot be treated with intensive chemotherapy. Many of these patients cannot tolerate the standard chemotherapy required to achieve optimal results in this aggressive form of leukemia.¹⁶⁷

Use in Combination, Earlier Treatment Line (May 2019):

Approved in combination with obinutuzumab for the treatment of people with newly diagnosed CLL or SLL. This was the first chemotherapy-free fixed-duration treatment for patients with CLL allowing newly diagnosed patients to go off therapy after just one year. The 12-month treatment reduced the risk of disease progression or death by 67% compared to a prior standard of care.⁸⁸

Additional Value Demonstrated in Approved Indication

(October 2020): Granted traditional approval in combination with low-intensity therapy* to treat newly diagnosed AML in adults at least 75 years of age or who cannot be treated with intensive chemotherapy. This approval was based on additional data, including demonstrated superior overall survival versus chemotherapy.¹⁷⁰ At the time of initial approval for this indication, clinical data on survival outcomes was not available; only through the ongoing collection of evidence was this benefit demonstrated.

Additional Value Demonstrated in Approved Indication

(June 2022): New CLL clinical trial results with long-term follow-up show a majority of patients treated with one year of venetoclax in combination with obinutuzumab remain without relapse after four years off treatment. This ongoing research reinforced the clinical benefit of the venetoclax-based combination treatment that has helped transform the therapeutic landscape for patients with this disease.⁹⁰

*Approved in combination with azacitidine, decitabine, or low-dose cytarabine

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