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The Value of Innovation in Oncology:

Recognizing Emerging Benefits Over Time

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INTRODUCTION

In recent years, the United States has witnessed significant progress in the fight against cancer, attributed to both earlier diagnosis and improved treatments.[1] In 2014 alone, the U.S. Food and Drug Administration (FDA) approved 19 cancer medicines, including seven that were approved under an accelerated pathway.[2] Improved therapeutic options are a significant factor contributing to advances in cancer care, with research estimating that new medicines have accounted for 50-60 percent of the increase in cancer survival rates since 1975.[3] The five-year relative survival rate for all cancers diagnosed in 2004-2010 increased to more than 68 percent from 49 percent during the late 1970s.[4] Cancer death rates began to fall for the first time in the 1990s and are continuing to decline. In fact, according to the National Cancer Institute's (NCI) Surveillance, Epidemiology and End Results (SEER) database, since its peak in 1991, the cancer death rate has fallen by 20 percent.[5] According to the American Cancer Society, these developments translate into approximately 1.18 million fewer deaths from cancer since 1991, with 152,900 of these deaths averted in 2009 alone.[6] As a result, there are now more than 13.7 million cancer survivors in the United States, almost two million more than in 2008.[7]

We have seen the emergence of many new cancer therapies in recent years, each representing an important step towards the advancement of treatment options for patients, while contributing to notable survival gains. The progress driving each of these advances is not typically driven by dramatic, individual approvals, but more commonly is the result of an accumulation of knowledge over time, as a greater understanding of the science underlying the more than 200 diseases we collectively call cancer grows. Scientists are constantly building on the growing body of knowledge to develop new therapies, with each new medicine providing important information informing future advances.

Although initial approval by the FDA is a significant milestone based on the rigorous demonstration of safety and efficacy through carefully designed and controlled clinical trials, the research does not stop when a medicine is approved by the FDA. Once a medicine is available to patients, additional knowledge is gained through ongoing research and the accumulation of data from the real-world use of these medicines in patients. Over time, a medicine may show even greater efficacy when administered earlier in the progression of the disease than was tested in the clinical trials. A therapy may prove to be even more effective than initially demonstrated when used in combination with another therapy. The emergence of molecular diagnostics may enable even greater precision in the selection of a treatment for a particular disease. And in some cases, a therapy may be found to be effective in other types of cancer or for different patient populations (e.g., pediatric patients).

While the intrinsic "value" (or clinical properties) of a therapy does not change, our understanding of the benefits and risks of the therapy evolves over time as knowledge accumulates. In this sense, FDA approval marks the "starting point" for additional study of the therapy, followed by the development of a larger body of evidence to help us understand the full value of the treatment and, more importantly, to help clinicians understand how best to use available therapies when treating their patients.

> "When we measure what we knew about cancer 40 years ago against what we know now, the transformation is simply revolutionary."
>
> Dr. Harold Varmus
> Former Director, National Cancer Institute[8]

Published literature reflects a growing recognition of this dynamic. An article published last year, for example, noted that in oncology, "a more complete picture of clinical effectiveness and patient value does not emerge until the treatment enters real-world clinical use. Not surprisingly, improvement in patient outcomes is generally observed only over time, through an incremental process, as experience is gained with new treatments and interventions."[9]

This white paper, an update from 2012, demonstrates some of the primary mechanisms through which the full clinical value of a cancer therapy typically emerges following initial FDA approval. For many medicines, additional benefits are revealed beyond what was demonstrated prior to launch to obtain approval, through ongoing research and the use of the therapy in real-world treatment settings. This additional value is recognized through a number of pathways, including:

- Use within a singular FDA-approved indication
- Use earlier in treatment line and in earlier disease stage
- Use in different disease indications*
- Use in combination with other agents
- Use in combination with specific biomarkers

These pathways may provide a framework for a better understanding of the true clinical value of a therapy over time.

*This may include both new indications approved by the FDA and off-label uses supported by research and deemed clinically appropriate by physicians. The evidence in this paper focuses on new FDA-approved indications.

CLINICAL TRIAL ENDPOINTS: SELECT COMMON MEASURES FOR ASSESSING THE CLINICAL BENEFIT OF CANCER THERAPEUTICS[10]

There are a variety of clinical trial endpoints that are used to determine the efficacy and clinical benefit of investigational medicines. Many early-phase trials assess the safety of the drug and also identify biological activity of a drug through the use of surrogate endpoints. Surrogate endpoints are used to assess whether the medicine is reasonably likely to predict clinical benefit, and the FDA may consider these when giving a medicine an accelerated approval. Ongoing studies evaluate the clinical benefit of a medicine through the evaluation of various disease progression and survival measures.

Listed here are those endpoints that are mentioned in the examples discussed in this paper. There are many other additional measures that can be used in cancer studies.

OBJECTIVE RESPONSE RATE (ORR)

The objective response rate evaluates the proportion of patients that attain a specified reduction in either tumor size or the number of cancer cells within a minimum amount of time (set in the trial protocol). ORR is often considered a direct measure of drug antitumor activity and is often recognized by the FDA as a surrogate endpoint to evaluate for accelerated approval.

OVERALL SURVIVAL (OS)

Overall survival is defined as the time from beginning of the trial (randomization to a treatment) until the time of death from any cause. Survival is considered the most reliable clinical trial endpoint.

PROGRESSION-FREE SURVIVAL (PFS)

Progression-free survival measures the length of time between treatment and measurable worsening of the disease. Though similar to time to progression, PFS includes deaths and is often considered to be a better correlate to overall survival.

TIME TO PROGRESSION (TTP)

Time to progression assesses the time from the beginning of the trial until the tumor or cancer gets worse or spreads to another part of the body.

USE WITHIN A SINGULAR FDA-APPROVED INDICATION

Long-term outcomes data can take many years to develop, and studies evaluating survival and other long-term endpoints are often still ongoing when a therapy is first approved. In situations where there is a significant unmet need for a serious condition, the FDA may use an accelerated approval pathway in order to get new medicines to patients ahead of these longer confirmatory studies.[11] In these cases, the FDA will approve therapies based on promising surrogate or intermediate clinical endpoints, before the completion of long-term survival or outcome studies. Surrogate endpoints may include measures of tumor shrinkage or cellular response, or measurements of certain biomarkers that are often – but not always – predictive of clinical benefits.[12] Biomarkers are molecules or genetic markers that can be used to predict therapeutic response and/or sensitivity to adverse events, allowing clinicians to better select patients who are most likely to benefit from targeted therapies.

The FDA carefully balances the need to get new medicines to patients with few treatment options with the need for conclusive scientific evidence supporting surrogate markers. Biopharmaceuticals approved under these circumstances are granted approval contingent upon continued research and clinical investigation of safety and efficacy. In many cases, this continued research and accumulation of evidence may demonstrate even greater benefits than initially established with the surrogate or intermediate endpoints.

Ibrutinib (Imbruvica®)

In February 2014, the FDA granted accelerated approval to ibrutinib for the treatment of chronic lymphocytic leukemia (CLL) in patients who have received at least one prior therapy. This approval was based on data indicating that 58 percent of patients had their cancers shrink.[13] This measurement, described as the objective response rate (ORR), is a surrogate endpoint that indicates that the medicine is reasonably likely to predict clinical benefit. In July 2014, the FDA approved new labeling to reflect that ongoing clinical studies had demonstrated an actual improvement in progression-free survival (PFS) and overall survival (OS). Analysis of PFS indicated that, compared to another CLL treatment (ofatumumab), there was a 78 percent reduction in the risk of the disease progressing, and analysis of OS revealed a 57 percent reduction in the risk of death.[14]

Assessment of clinical value at time of FDA approval would have failed to capture the survival gains that were demonstrated in later trials.

Crizotinib (Xalkori®)

Crizotinib was initially granted accelerated approval by the FDA in 2011 for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK) positive as detected by an FDA-approved diagnostic test.[15] This accelerated approval was based on the results of two single-arm studies that enrolled patients whose tumors tested positive for the ALK biomarker. The studies examined the percent of patients who experienced partial or complete shrinkage of their tumors (the ORR). The two studies demonstrated that 50 percent and 61 percent of patients, respectively, experienced shrinkage of their tumors, indicating that the medicine was reasonably likely to predict a clinical benefit in patients.

In 2013, the FDA revised the labeling to reflect the clinical benefit of crizotinib that had been revealed through ongoing studies. Notably, patients receiving crizotinib experienced prolonged progression-free survival of 7.7 months, which was more than double the three months of the chemotherapy arm of the trial. Additionally, the objective response rate, reflecting tumor shrinkage, was significantly higher for the patients who received crizotinib (65 percent) compared to those who received chemotherapy (20 percent).[16] Although earlier data indicated that crizotinib was effective against this form of NSCLC, the accumulation of data following initial approval revealed even greater efficacy than anticipated. This value would not have been recognized based on data available at the time of initial approval but revealed itself through the additional accumulation of clinical evidence.

USE EARLIER IN TREATMENT LINE AND IN EARLIER DISEASE STAGE

Because of the life-threatening, progressive nature of cancer, investigational therapies in clinical trials are necessarily tested first in patients with advanced stages of cancer who have exhausted existing standard treatment options. While this does not impact the innate properties of a therapy, it creates a theoretical "ceiling" on the amount of clinical benefit that can usually be observed during initial clinical research.

FDA-approved indications for oncology therapies are generally limited to a specific line of therapy and disease stage. Advancement in treatment line refers to the movement of an agent to be used as an earlier therapeutic option within a particular disease stage (e.g., from second-line use, where the medicine is taken following the use of other therapies, to first-line use, where is it indicated for use in newly diagnosed patients).[17] Advancement in disease stage denotes the movement of an agent for use in an earlier stage of disease progression (e.g., movement from end-stage therapy in advanced or metastatic cancer† to adjuvant therapy‡ in early-stage, operable disease).[18] Though a medicine may initially be approved by the FDA after demonstrating safety and efficacy in patients with advanced cancer, it is typically at earlier stages of disease that a new treatment is more likely to significantly modify the course of the disease by slowing or halting its progression. For example, a medicine may shift from third- to second- to first-line treatment. These shifts may signal a change in therapeutic intent from palliative to potentially curative use. Generally, oncology drugs advance first in treatment line, then advance in disease stage.

Bortezomib (VELCADE®)

Bortezomib is a powerful example of how accumulated evidence post-approval can reveal additional value for a medicine, particular in its earlier use. Bortezomib was initially approved in 2003 to treat multiple myeloma patients who were not responding to available treatment options.[19] Representing the first in a new class of cancer medicines known as proteasome inhibitors, bortezomib offered an important new treatment option for patients after demonstrating that it had activity against multiple myeloma cells as well as bone marrow stromal cells, which can sometimes promote tumor cell survival.[20] In 2005, the label was expanded to include use earlier in the treatment regimen, in patients who had received at least one prior therapy.[21] Study data revealed that the time for the disease to progress was significantly longer in patients that received the bortezomib regimen (6.2 months) compared to those receiving dexamethasone (2.5 months).[22] Additionally, bortezomib demonstrated superior overall survival.

The benefits of bortezomib also extend beyond multiple myeloma. In 2006, bortezomib was approved by the FDA for the treatment of an extremely rare form of B-cell Hodgkin's lymphoma called mantle cell lymphoma (MCL) for patients who have received at least one prior therapy. These early indications from the FDA meant that patients were meant to receive bortezomib much later in the progression of their disease, either after trying other approved options, or progressing to the point that their disease was no longer responding to available options. In 2008, the FDA granted approval for the use of bortezomib in patients with previously untreated multiple myeloma after study results (from the VISTA trial) showed that patients treated with the bortezomib regimen experienced significantly longer time to progression (20.7 months) compared to standard treatment (15 months).[23] In 2014, the FDA expanded the labeling to include patients with previously untreated MCL. These approvals mean that patients can now receive the medicine as a first-line treatment, earlier in the progression of the disease.

> "This comes as wonderful news for patients. The VISTA trial showed 30% complete remission rate with bortezomib compared to 4% for the control arm. Importantly, patients treated with bortezomib also experienced a survival benefit."
>
> Dr. Paul Richardson
> Clinical Director, Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute and a senior investigator of the bortezomib clinical study[24]

†Metastatic cancer occurs when cancer cells travel from the primary tumor site to other parts of the body and continue to grow in the new location(s); it is indicative of more advanced, or progressing, disease.

‡Adjuvant therapy is administered postoperatively, where there is no visible cancer but there is still risk of cancer cells in the body.

Lenalidomide (Revlimid®)

In 2006, lenalidomide was approved in combination with dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.[25] In February 2015, the FDA expanded the indication for this combination to be used earlier in the treatment regimen, for newly diagnosed patients with multiple myeloma.[26] The clinical study for this new use evaluated the effect of a lenalidomide-dexamethasone combination in comparison with melphalan-prednisone-thalidomide (MPT), which has long been considered standard therapy for patients with multiple myeloma.[27] The results indicated that the continuous use of lenalidomide-dexamethasone given until disease progression was associated with a significant improvement in progression-free survival (25.5 months) compared to MPT (21.2 months), as well as overall survival (58.9 months compared to 48.5 months). This demonstrated the clinical benefit of using lenalidomide as a first-line treatment option. This recent development in the drug's approval history illustrates the constantly evolving value story that cannot be fully realized until months or years after approval of a drug's initial indication.

> "The approval of lenalidomide as an option for use in all patients with multiple myeloma represents a new paradigm in the management of this disease. We now have clinical evidence demonstrating that starting and keeping newly diagnosed multiple myeloma patients on Revlimid® significantly improves progression-free survival."
>
> Dr. Kenneth Anderson
> Director, Jerome Lipper Multiple Myeloma Center
> Dana-Farber/Brigham and Women's Cancer Center[28]

USE IN ADDITIONAL DISEASE INDICATIONS

The underlying mechanisms that trigger initiation, growth and invasion of cancer cells are governed by the same set of cell signaling pathways that are activated and involved in normal cell functioning across the human body. In cancers, however, small changes in elements of these pathways trigger the uncontrolled growth and spread that is characteristic of cancer cells.[29] Understanding the pathways that drive disease progression can uncover genotypic similarities between various cancers and other diseases that may appear phenotypically distinct (the way the symptoms are physically visible). Advances in cancer biology research have allowed identification of oncology therapies that have clinical value in types of cancers distinct from the original indication(s) for which they are approved. Studies conducted and reported after the initial approval of a medicine commonly explore additional indications and, in many instances, a therapy demonstrates significant clinical benefit in a different disease.

Everolimus (Afinitor®, Zortress®, Afinitor Disperz®)

Everolimus provides a clear example of the broad value a medicine can bring to various forms of cancer, as well as other diseases, with underlying biological similarities. Following initial approval in 2009 for the treatment of renal cell carcinoma (RCC), everolimus has been approved for several additional indications, including some outside cancer.

Following initial approval, everolimus was found to have an immunosuppressive effect that aided in prevention of organ rejection following transplant procedures. In 2010, everolimus (under the trade name Zortress®) was approved to prevent organ rejection in patients who receive kidney transplants[30] and in 2013 it became the first immunosuppressant approved for the prevention of liver transplant rejection.[31] For many organ transplant recipients, this new treatment option reduced the need to take other traditional forms of immunosuppressant medicines, which sometimes had harmful side effects.

Everolimus also went on to gain approval for the treatment of a variety of non-cancerous tumors that result from a very rare genetic disorder called tuberous sclerosis (TSC). In 2010 it was approved to treat adults with abnormal growths, referred to as subependymal giant cell astrocytoma (SEGA), associated with TSC, which was previously treated primarily with surgery.[32] In 2012, the FDA expanded the approval of everolimus

> "Today's approval [of everolimus] demonstrates the value of further studying a drug to better characterize its benefits and how it should be used in pediatric patients."
>
> Dr. Richard Pazdur
> Director of the Office of Hematology and Oncology Products, Center for Drug Evaluation and Research (CDER), FDA[33]

for the treatment of patients who have non-cancerous kidney tumors called renal angiomyolipomas which can lead to kidney failure.[34]

Also in 2012, a new dosage form of everolimus (Afinitor Disperz®) was approved as the first drug formulated for children with rare brain tumors (SEGA) associated with TSC.[35] Building on the original adult indication for the treatment of SEGA abnormal growths, further research led to this new dosage form, which dissolves more quickly and provides for smaller dosing increments, offering an important treatment option for children with TSC, who tend to have these growths as a primary symptom.

Finally, continued research and accumulation of evidence has led to additional approvals in other cancer indications for everolimus. In May 2011, everolimus was approved to treat patients with a rare form of pancreatic cancer referred to as progressive neuroendocrine tumors of pancreatic origin (pNET). Everolimus' approval was a very significant advance for patients with this deadly form of cancer, as treatment options were previously limited to the surgical removal of cancer tissues. The clinical study demonstrated a 65 percent lower risk of the disease progressing in patients treated with everolimus compared to the placebo-controlled group.[36] Another approval followed in 2012 for treatment in combination with exemestane for women with advanced, hormone-receptor positive, HER2-negative breast cancer. See *Use in Combinations* section.

Lenalidomide (Revlimid®)

Lenalidomide was originally approved in 2005 to treat a form of myelodysplastic syndrome (MDS).[37] MDS is collection of disorders where the bone marrow fails to produce enough healthy blood cells. Patients with MDS may rely on blood transfusions to supplement low levels of healthy blood cells, as well as antibiotics to combat infections that may result from a weakened immune system. Lenalidomide was approved for patients who had a specific genetic mutation — a 5q deletion chromosomal abnormality. The approval of lenalidomide gave patients an important new treatment option, with clinical trials demonstrating that patients treated with the medicine no longer needing blood transfusions. Following the initial approval by the FDA in 2005, lenalidomide went on to show efficacy in several other indications.

In 2006, lenalidomide received approval for use in combination with dexamethasone to treat patients with multiple myeloma who had failed other treatments.[38] In 2015, lenalidomide received expanded approval as a first-line treatment for multiple myeloma. (See *Use Earlier in Disease State* section).

In 2013, lenalidomide was approved for use against mantle cell lymphoma (MCL).[39] This new treatment option, for patients whose disease has relapsed or progressed after two prior therapies, represented a tremendous advance in treatment, as it was the first oral therapy available for patients.

> "There remains a tremendous unmet need for patients with previously-treated mantle cell lymphoma. The approval of lenalidomide delivers a new option, and the first oral therapy in this area of lymphoma."
>
> Dr. Andre Goy
> Chairman and Director and Chief of Lymphoma, Clinical and Translational Cancer Research, John Theurer Cancer Center at Hackensack University Medical Center[40]

Ibrutinib (Imbruvica®)

Ibrutinib was originally approved in 2013 for the treatment of patients with MCL who have received at least one prior therapy.[41] Since that initial approval ibrutinib has demonstrated significant value in several additional forms of cancer. In addition to being approved for use in treating CLL (as previously discussed in the section on *Use in Initial Indication*), ibrutinib was approved in January 2015 for the treatment of patients with Waldenstrom's macroglobulinemia (WM), another very rare form of non-Hodgkin's lymphoma. This marked the very first approval of a medicine indicated specifically for patients with this very rare form of cancer.[42]

USE IN COMBINATION WITH OTHER AGENTS

As the available arsenal of oncologic agents continues to grow, effective use of these drugs in combination becomes paramount. Because of cancer's complexity and adaptability it can often become resistant to a given therapy. By using multiple medicines which attack the cancer through different mechanisms, there is a reduced chance of the cancer developing resistance to treatment.[43] The use of multiple therapies, given at more moderate dosing levels, can help diminish the severe side effects that patients often experience.

However, it can be difficult to demonstrate the therapeutic value of a possible treatment combination through clinical testing. There are many potential therapeutic combinations available and each may only be effective in small subsets of patients with the disease, based on specific characteristics or biomarkers. Despite the difficulty of researching countless therapy combinations, the approach has become well-established in oncology, and a considerable amount of cancer research involves different combinations of new and existing therapies.

Ramucirumab (Cyramza®)

Ramucirumab was originally approved as a single agent for second-line treatment of patients with advanced stomach cancer or gastroesophageal junction (GEJ) adenocarcinoma, which is a difficult to treat cancer that occurs where the esophagus joins the stomach. This approval represented an important advance for patients, offering the first FDA-approved treatment for these advanced forms of stomach cancer.[44]

Since that time, accumulating post-approval data has strongly supported expanded indications of ramucirumab in combination with other therapies. In November 2014, ramucirumab was approved for use in combination with paclitaxel for the treatment of patients with advanced gastric cancer or GEJ adenocarcinoma. In the study supporting this approval, patients who received the combination of ramucirumab and paclitaxel had an overall survival rate that was 2.3 months longer than patients who received paclitaxel alone, a result described as "astonishingly good" for this type of cancer.[45]

Everolimus (Afinitor®)

Everolimus, a rapamycin (mTOR) inhibitor was originally approved by the FDA in 2009 for the treatment of advanced renal cell carcinoma (RCC).[47] Following initial approval, everolimus was evaluated in several additional treatment settings, including one cancer area where its use in combination with existing therapies was found to be an important treatment advance. In July 2012, everolimus was approved for use in combination with exemestane to treat post-menopausal women with advanced hormone-receptor positive, HER2-negative breast cancer.[48] In this advanced form of hormone-receptor positive cancer, a class of medicines called aromatase inhibitors had proven very effective at controlling tumors by depriving them of the estrogen hormone, which had been found to spur their growth. However,

> "There is a high unmet medical need in patients with this disease. This approval represents a meaningful advance for patients and gives those of us who treat them an important new second-line treatment option."
>
> Dr. Charles Fuchs
> Director of the Gastrointestinal Malignancy Program, Dana-Farber Cancer Institute
> and principal investigator of the pivotal clinical study of ramucirumab[46]

over time, many tumors developed resistance to these treatments. Everolimus helps prolong the effectiveness of these treatments by combatting that resistance.

Without continuing research and collection of clinical evidence following the original approval of everolimus in 2009, these important additional benefits would not have been realized. Dr. Pazdur of the FDA noted, "This is the first approval from the class of drugs known as mTOR inhibitors for the treatment of postmenopausal women with advanced hormone-receptor positive breast cancer. Afinitor® is another example of the value of continuing to study drugs in additional types of cancer after their initial approval."[49]

> "Afinitor is the first and only treatment that boosts the effectiveness of endocrine therapy, significantly extending the time women with advanced breast cancer live without tumor progression. This approval redefines the treatment and management of advanced hormone receptor-positive breast cancer, offering a critical new option for physicians and patients."
>
> Dr. Gabrial Hortobagyi
> Former Chair, Breast Medical Oncology,
> University of Texas MD Anderson Cancer Center[50]

USE IN COMBINATION WITH SPECIFIC BIOMARKERS

In recent years, advances in personalized or precision medicine and targeted therapy have had a significant impact on cancer treatment advances. A growing understanding of cancer at the molecular level has translated to new diagnostic tools that allow physicians to identify patients as candidates for a therapy based on the presence or absence of a particular gene or mutation, resulting in patient access to treatments that are more effective earlier in the care paradigm.

In certain patient subsets, specific genetic profiles are associated with improved activation and/or metabolism of a drug or improved activity, thereby demonstrating the potential for marked increases in clinical benefit in particular patient groups.

Biomarkers are molecules or genetic markers that can be used to predict therapeutic response and/or sensitivity to adverse events, allowing clinicians to better select the patients who are most likely to benefit from particular targeted therapies. According to the FDA, there are currently 55 oncology therapies with a pharmacogenomic biomarker in the drug labeling.[51]

Ibrutinib (Imbruvica®)

In February 2014, ibrutinib received approval for the treatment of patients with CLL who have received at least one prior therapy.[52] In July of that year, FDA expanded the use of ibrutinib to treat patients with CLL who carry a deletion in chromosome 17 (17p deletion), regardless of whether or not they have received prior therapy.[53] Patients with this genetic mutation traditionally show a poor response to standard CLL treatments. The clinical study resulting in this expanded indication (the RESONATE study) demonstrated that patients with the 17p deletion who were treated with ibrutinib experienced a 75 percent reduction in the risk of disease progression and death.[54]

Being able to target use of a therapy for CLL patients who have this chromosome deletion is an important advance in the treatment paradigm and reflects the impact of accumulated knowledge and data on a medicine even after FDA approval.

> "The RESONATE data expands our understanding of the efficacy and safety of Imbruvica® to an even greater degree. This approval is particularly exciting for people with del 17p CLL, considering Imbruvica is the first treatment to be approved specifically for this difficult-to-treat patient population."
>
> Dr. John Byrd
> Director of the Division of Hematology, Ohio State University Comprehensive Cancer Center, and lead investigator of the clinical study (called the RESONATE study) for ibrutinib[55]

Crizotinib (Xalkori®)

As previously discussed in the section on *Use in Initial Indication*, crizotinib was granted accelerated approval in 2011 for the treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive as detected by an FDA-approved test. This particular diagnostic test received FDA approval at the same time to enable the detection of ALK gene rearrangement and identify patients who may benefit from treatment with crizotinib. This targeted therapy provided significant benefit to patients with this specific mutation, but researchers speculated that the medicine might have an effect in other forms of lung cancer. In November 2014, clinical results were published from a phase I study that examined crizotinib in patients with advanced ROS1-rearranged NSCLC, as a second potential molecular subgroup of NSCLC, in addition to ALK, for which crizotinib is highly active. In the phase I trial, the drug induced clinical responses for a stastically significant majority of patients in the study.[56] In April 2015, the FDA awarded breakthrough therapy status to crizotinib for ROS1-positive metastatic NSCLC, meaning that FDA will expedite the development and review of crizotinib for ROS1-positive patients, potentially increasing the overall value of the therapy for an entirely new group of patients.[57]

> "One of the most recent advances has been an explosion in the use of predictive genomics for the interrogation of genetic alterations in tumors and, from that, making predictions about the biology of these cancers and how to treat them… As we discover to what degree an increasing number of individual cancer-driving genes are altered in a tumor, the number of potential drug targets and drugs to block those targets should also increase."
>
> Dr. Carlos L. Arteaga
> AACR President, 2014-2015, Professor of Medicine and Cancer Biology at Vanderbilt-Ingram Cancer Center[58]

CONCLUSION

Although the initial approval of a medicine by the FDA is a critical milestone, achieved only after careful demonstration of safety and efficacy, there is clearly much more to be learned about the full benefit and best use of oncology medicines beyond that timepoint. The full clinical benefit of oncology medicines is often not entirely known at the time of initial FDA approval. Oncology researchers continue to conduct additional research after initial approval, and oncologists in the clinic explore the best ways to use a new medicine when it becomes available. It is through this accumulation of data that a therapy's clinical value can be more fully evaluated and understood over time. Because of the nature of the research process, initial trial data alone cannot reflect the clinical value of a therapy earlier in treatment or disease stage, across different diseases, in combination with the complete array of other therapies, or within target populations identified through specific biomarkers. In some cases, it may not even fully reflect the therapy's clinical value within the initial FDA indication if the medicine is approved based on surrogate markers rather than long-term outcomes.

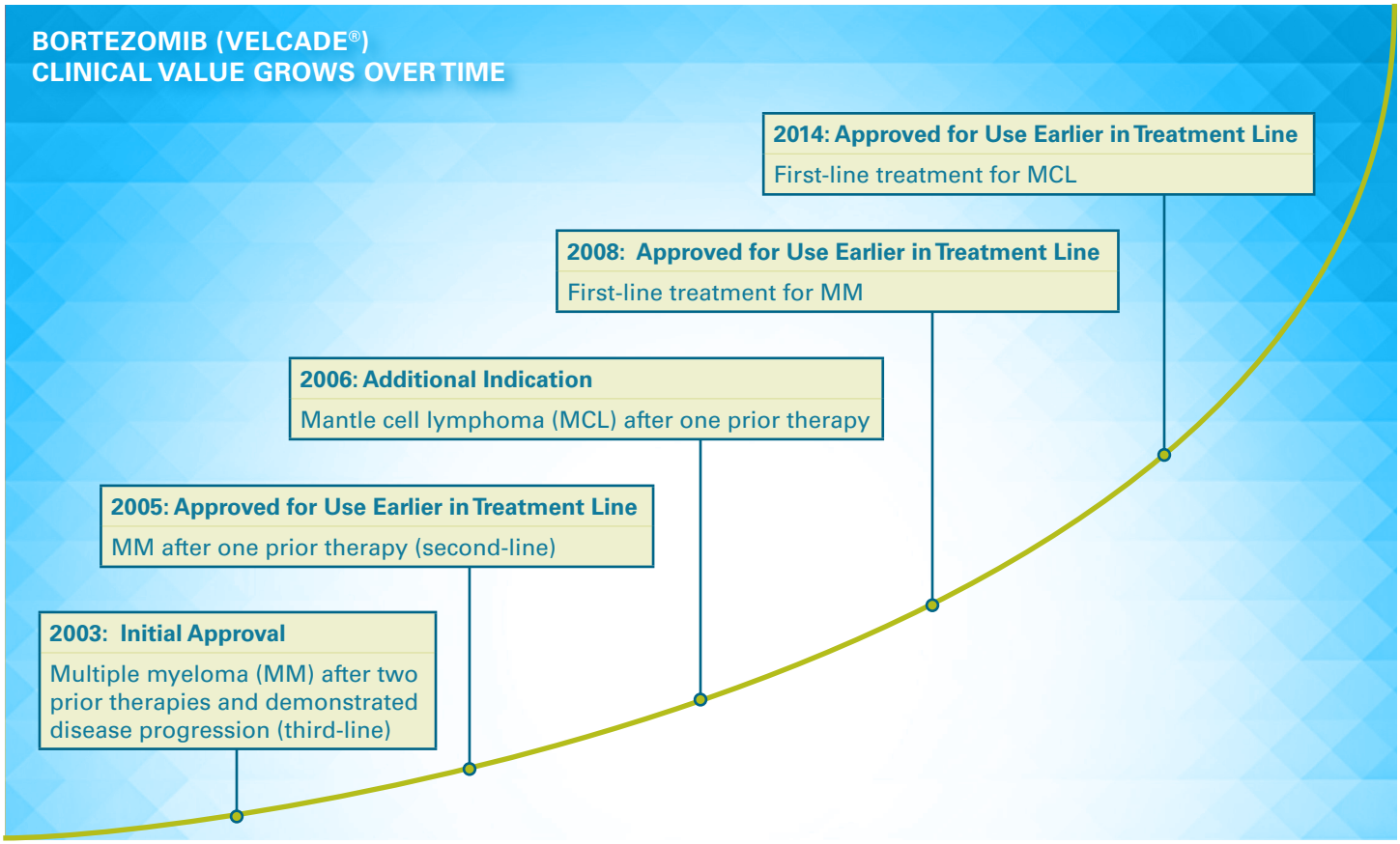
Demonstrating the clinical benefit of a treatment is an ongoing process in which researchers and clinicians evaluate all aspects of how the medicine is used and how it affects patients (see Appendix). Therefore, the full impact of cancer therapy is often recognized only after years of additional post-approval research. The potential for greater benefit continues to exist as current therapies are studied and rigorously tested in new areas.

As a result of many interrelated factors, dramatic advances in overall cancer survival have been realized by the cancer community in recent years. Because innovative cancer therapies play a significant role in these advances, it is vitally important that the ongoing and incremental nature of oncology research be recognized by researchers, clinicians, patients, payers, and policymakers alike. Assessments of clinical value must reflect ongoing accumulation of evidence over time in order to reflect the value that individual therapies can bring to treating patients, often across several different cancers. Thus, the clinical benefit we observe at the time that a new anticancer therapy receives FDA approval is generally only a partial reflection of the ultimate benefit that will be understood for that therapy. Patient access to new therapies is essential in order to both ensure that the emerging benefits of treatments are available to those in need, but also to contribute to ongoing research and evidence collection. Building on the accumulation of knowledge over time, researchers can achieve critical advances in oncology.

APPENDIX

BORTEZOMIB (VELCADE®)

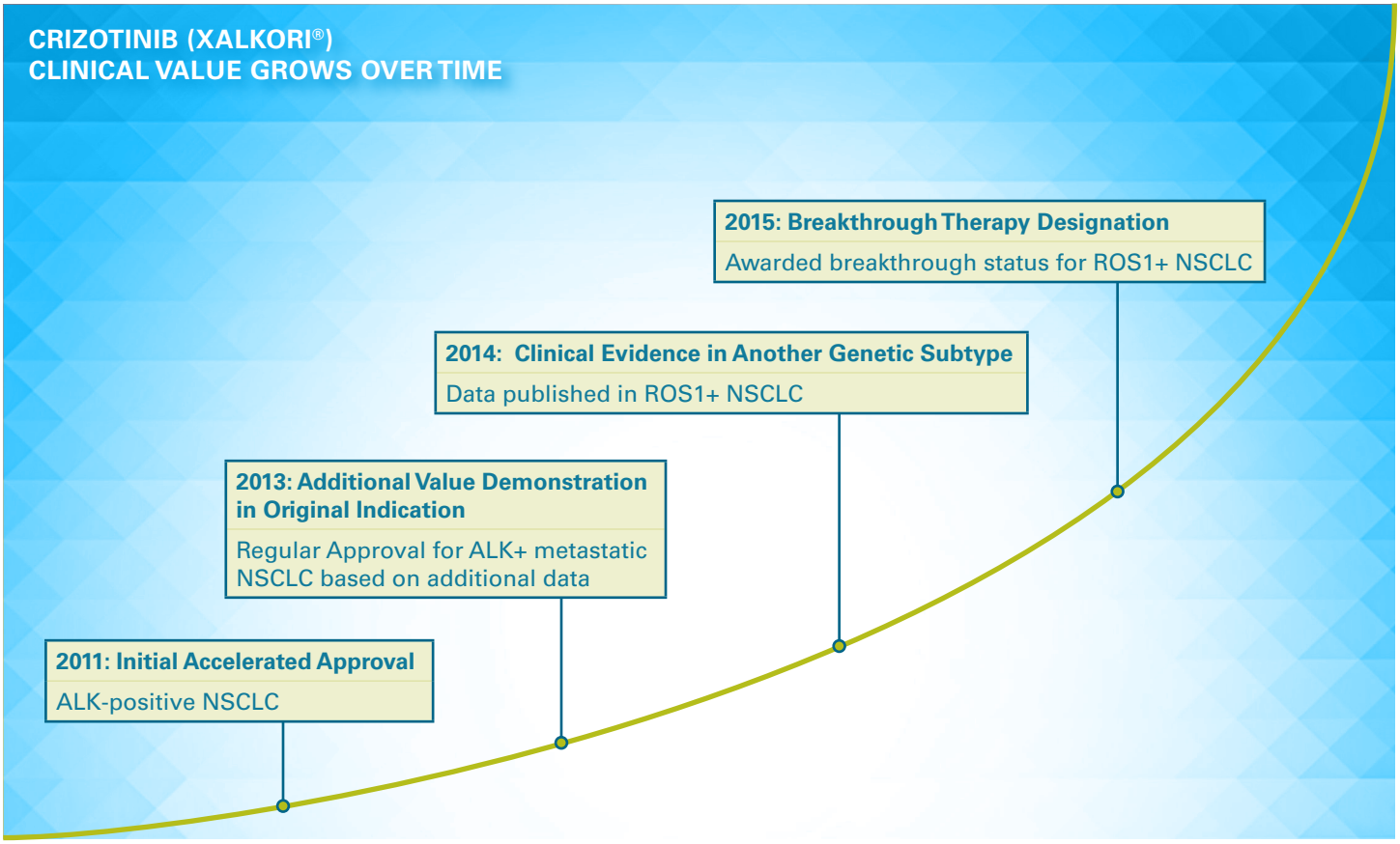
In 2003, bortezomib was awarded accelerated approval for use in treating **multiple myeloma** (MM) patients who have received at least two prior therapies and have demonstrated disease progression on their last therapy. Bortezomib was the first in a new class of medicines known as proteasome inhibitors, and represented an important treatment advance for patients. In the studies FDA evaluated for approval, bortezomib demonstrated that it had activity against MM cells as well as bone marrow stromal cells, which can sometimes promote tumor cell survival. Since that initial approval, ongoing research and evidence collection has demonstrated survival benefits that could not have been assessed at the time of original approval, and has also revealed the benefits of using the medicine to treat another form of cancer.



- **Approved for Use Earlier in Treatment Line:** March 2005: Bortezomib approved for the treatment of MM after patients have tried at least one prior therapy (**second-line use**). Study data revealed that time for the disease to progress was significantly longer in patients that received the bortezomib regimen (6.2 months) compared to those receiving dexamethasone (2.5 months).
- **Additional Indication:** December 2006: Approved for the treatment of patients with relapsed or refractory **mantle cell lymphoma** (MCL) who have received at least one prior therapy (**second-line use**).
- **Approved for Use Earlier in Treatment Line:** June 2008: Approved for use as **first-line treatment of MM** following data from ongoing clinical trials that demonstrated a 30 percent complete remission rate with bortezomib compared to 4 percent in the control arm.
- **Approved for Use Earlier in Treatment Line:** October 2014: Approved for use as **first-line treatment of MCL**, making bortezomib the first treatment in the United States to be approved for use in previously untreated patients with MCL. Clinical trial data demonstrated a 59 percent relative improvement in progression-free survival for patients who received the bortezomib regimen compared to the standard of care treatment arm.

CRIZOTINIB (XALKORI®)

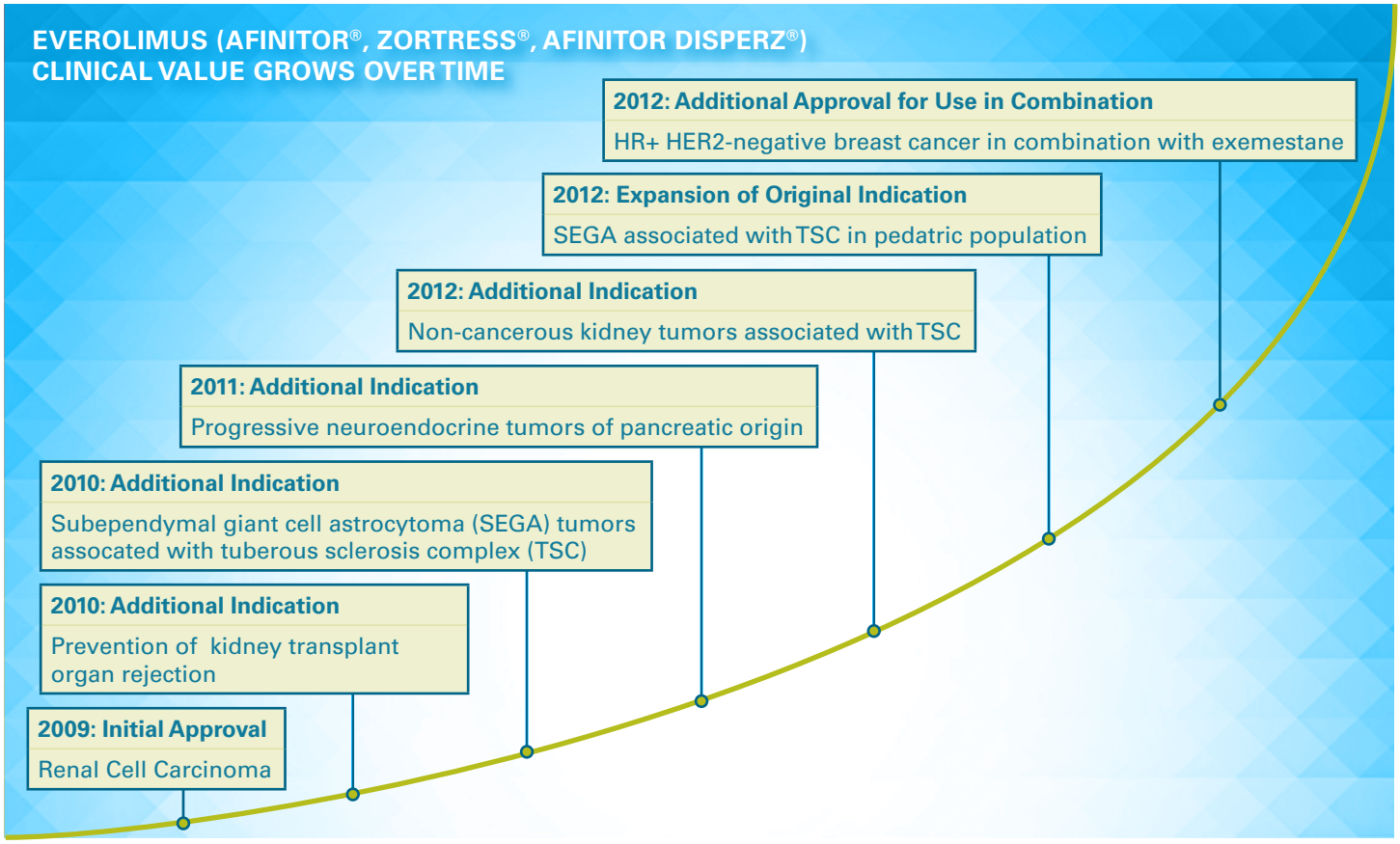
In August 2011, FDA granted accelerated approval to crizotinib for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors have a particular abnormality described as being anaplastic lymphoma kinase (ALK)-positive. The clinical studies for this approval were based on a surrogate endpoint that the FDA determined was reasonably likely to indicate clinical benefit. In this case, the study examined the objective response rate (ORR) of patients' tumors, which measures tumor shrinkage. In the two clinical studies, 50 percent and 61 percent of patients, respectively, experienced an objective response, where their tumors shrank. The labeling for crizotinib requires testing the patient's mutation status with an FDA-approved diagnostic, which was approved concurrently with crizotinib to detect rearrangements of the ALK gene. Since initial approval, ongoing clinical studies have revealed survival benefits that could not have been known at the time of initial approval based on available data. Crizotinib also is being studied in other molecularly targeted patient groups in NSCLC.



- **Additional Value Demonstration in Original Indication**: November 2013: Crizotinib receives confirmatory approval from the FDA based on **demonstration of superior progression-free survival and objective** response rate compared to chemotherapy. At the time of initial approval of crizotinib, clinical data on survival outcomes was not available; only through the ongoing collection of evidence was this benefit demonstrated.
- **Clinical Evidence in Another Genetic Subtype**: November 2014: Clinical evidence published demonstrating the efficacy of crizotinib in patients with advanced **ROS1-rearranged NSCLC**, identifying ROS1 rearrangement as a second molecular subgroup of NSCLC, in addition to ALK, for which crizotinib is potentially highly active.
- **Breakthrough Therapy Designation**: April 2015: Crizotinib awarded breakthrough therapy status by the FDA for **ROS1-positive metastatic NSCLC**, meaning that they will expedite the development and review of crizotinib for patients with this genetic subtype of the disease.

EVEROLIMUS (AFINITOR®, ZORTRESS®, AFINITOR DISPERZ®)

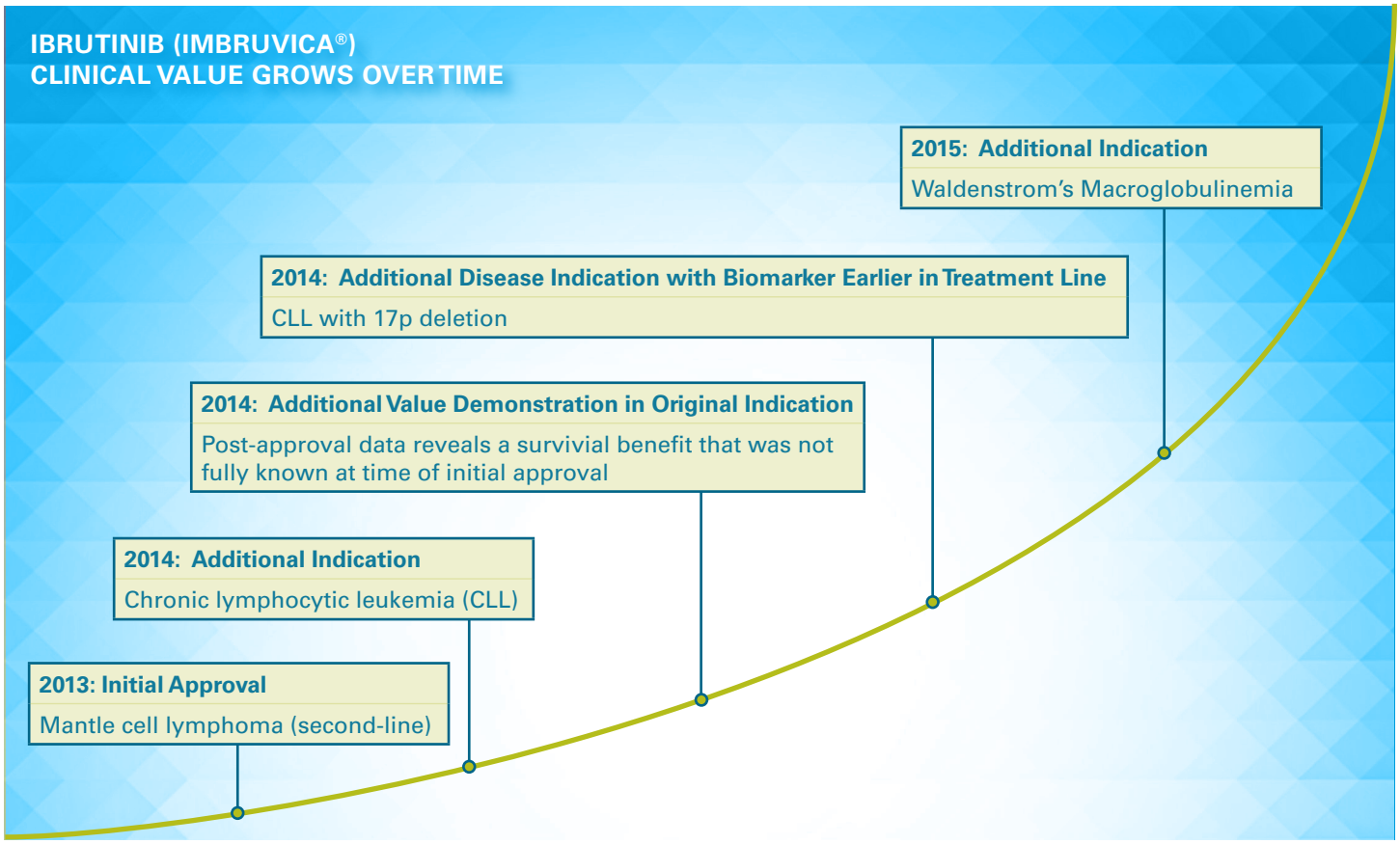
In 2009, everolimus was initially approved by the FDA for the treatment of advanced **renal cell carcinoma** (RCC) in adults who failed previous treatments. Since initial approval in 2009, ongoing research and accumulation of clinical evidence has revealed additional benefits of everolimus beyond those initially realized for RCC. These additional benefits have been found in some additional forms of cancer but also in areas outside oncology altogether, demonstrating value that was not recognized at the time of initial approval.



- **Additional Indication:** April 2010: Approved for the prevention of organ rejection in patients with **kidney transplants**. For these patients, everolimus provided an important opportunity to lower doses of other immunosuppressants that sometimes had severe side effects.
- **Additional Indication:** November 2010: Approved for the treatment of non-cancerous tumors, **subependymal giant cell astrocytoma** (SEGA), that are associated with a very rare genetic disorder called **tuberous sclerosis complex** (TSC).
- **Additional Indication:** May 2011: Approved to treat a rare form of pancreatic cancer called **progressive neuroendocrine tumors of pancreatic origin** (pNET). Results of clinical studies were so promising that everolimus has become standard of care for this devastating disease.
- **Additional Indication:** April 2012: Approved **additional indication** for the treatment of patients with non-cancerous **kidney tumors** associated with TSC.
- **Approved for Use in Combination:** July 2012: Approved in combination with exemestane to treat **breast cancer** in postmenopausal women whose cancer is hormone-receptor positive, HER2-negative. A class of medicines called aromatase inhibitors had proven very effective at controlling tumors by depriving them of the estrogen hormone, which had been found to spur their growth. However, over time, many tumors developed resistance to these treatments. Everolimus was the first medicine found to boost the effectiveness of hormone therapy by combatting that resistance.
- **Expansion of Original Indication:** August 2012: New formulation approved to treat **SEGA** associated with **TSC** in children. This was the **first drug formulated for children with a rare brain tumor**.
- **Additional Indication:** February 2013: Approved for use in preventing organ rejection in patients with **liver transplants**. First immunosuppressant approved for liver transplantation in over a decade.

IBRUTINIB (IMBRUVICA®)

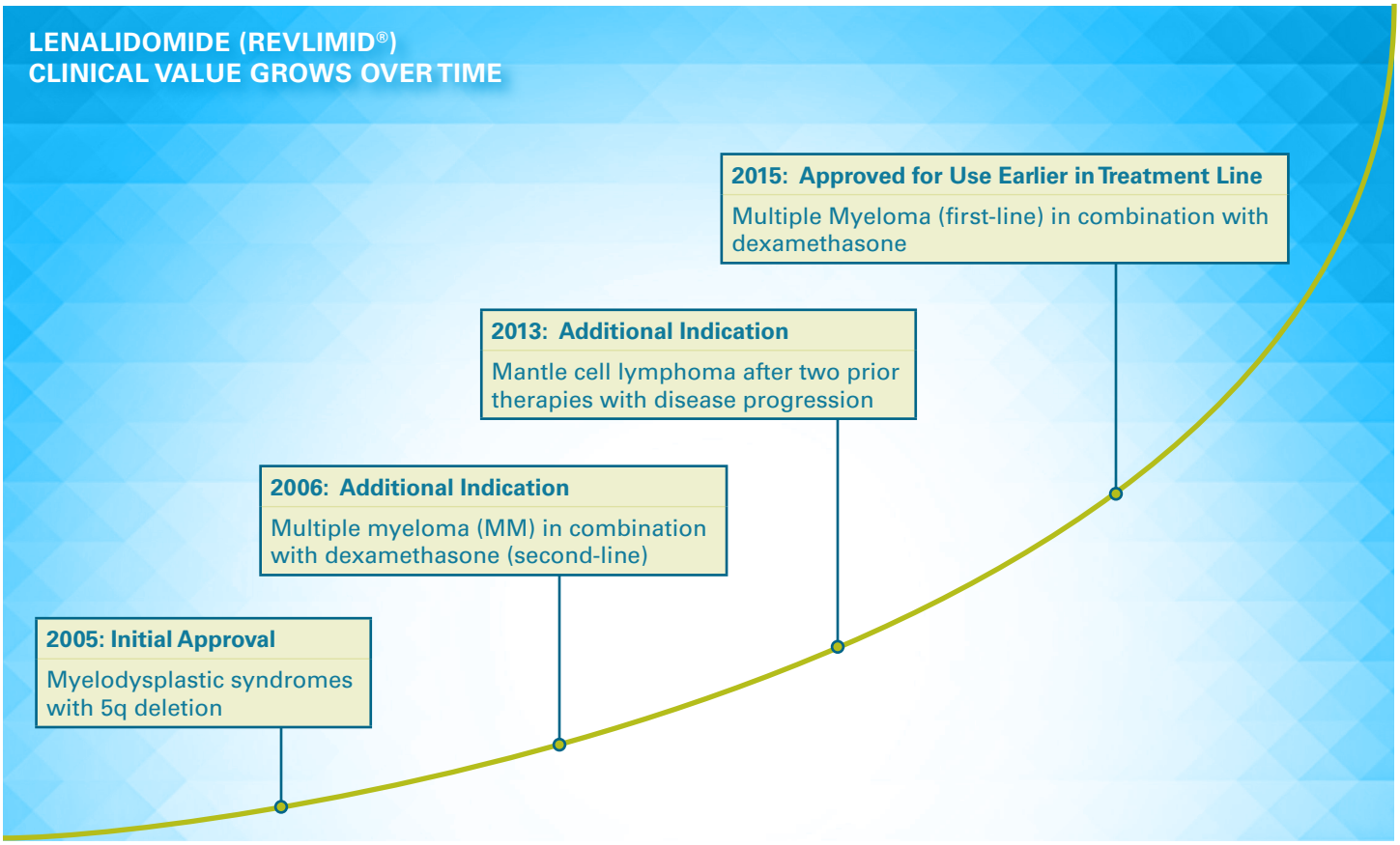
In November 2013, the FDA granted accelerated approval to ibrutinib for the treatment of patients with **mantle cell lymphoma** (MCL) who have received at least one prior therapy. MCL is a very rare form of B-cell non-Hodgkin's lymphoma. The approval of ibrutinib was an important milestone for patients with this sometimes deadly blood cancer. Since that time, continuing research has revealed additional benefits of using ibrutinib that were not recognized at the time of initial approval.



- **Additional Indication:** February 2014: Ibrutinib is granted accelerated approval for treatment of patients with **chronic lymphocytic leukemia** (CLL) who have received at least one prior therapy.
- **Additional Value Demonstrated in Original Indication:** July 2014: New **CLL** clinical trial results (post-approval) reveal 78 percent progression-free survival. At the time of initial approval for CLL, the available data demonstrated that 58 percent of patients had their tumors shrink, but no survival data was yet available.
- **Approval for use with Biomarker:** July 2014: Approved as a **first-line therapy** to treat patients with **CLL** who carry a **deletion in chromosome 17** (17p deletion) because the 17p deletion is associated with poor responses to standard treatments for CLL.
- **Additional Indication:** January 2015: Approved to treat patients with **Waldenstrom's macroglobulinemia**. This is the **first treatment** approved for this rare form of blood cancer.

LENALIDOMIDE (REVLIMID®)

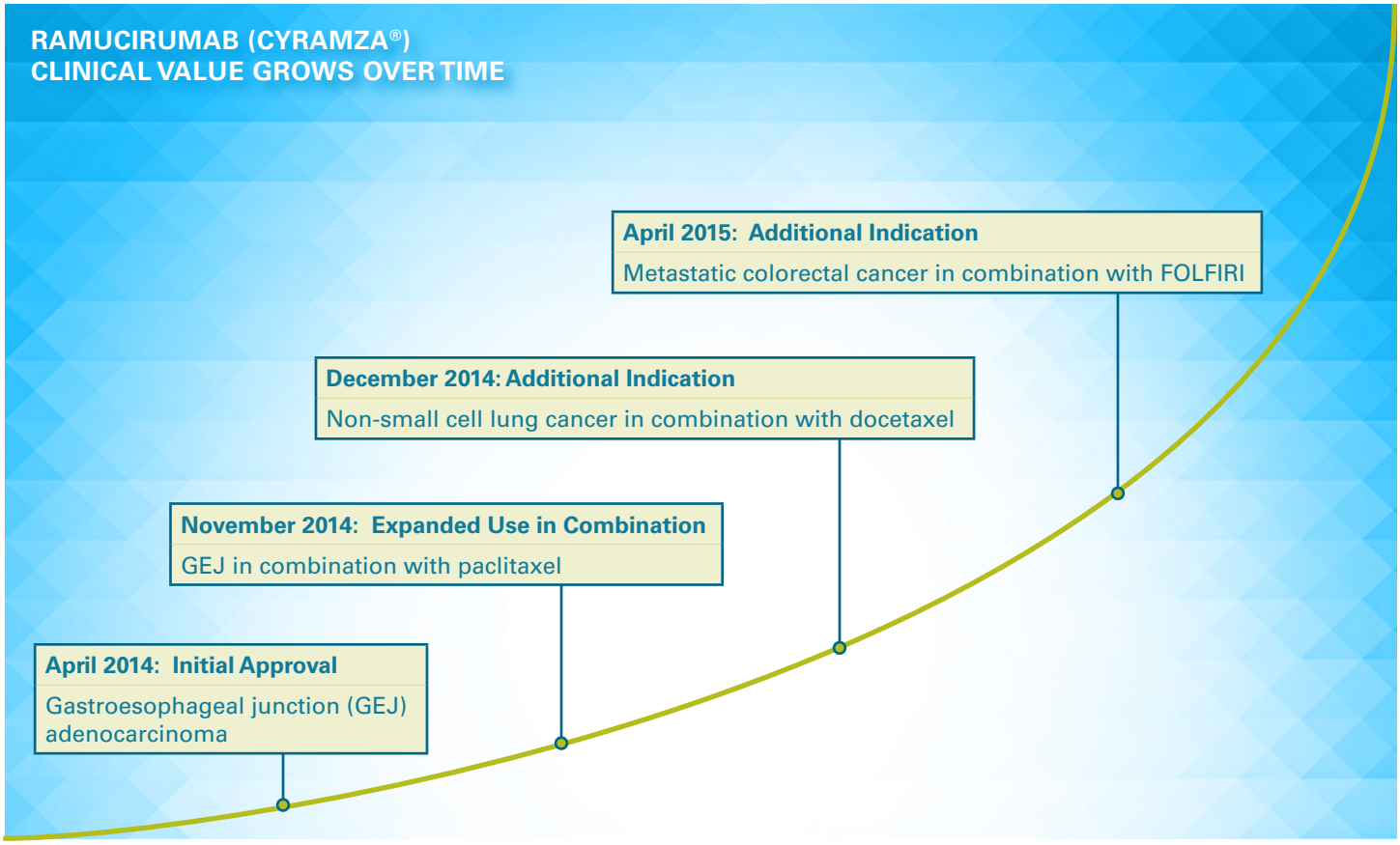
In 2005, the FDA approved lenalidomide for the treatment of patients with a subtype of **myelodysplastic syndrome** (MDS). MDS is collection of disorders where the bone marrow fails to produce enough healthy blood cells. Patients with MDS may rely on blood transfusions to supplement low levels of blood, as well as antibiotics to combat infections that may result from a weakened immune system. The approval of lenalidomide gave patients an important new treatment option, with clinical trials demonstrating that patients treated with the medicine no longer needed transfusions. Since initial approval in 2005, additional benefits of lenalidomide have been revealed over time, many of which would not have been evident at the time of the medicine's initial approval.



- **Additional Indication:** June 2006: Lenalidomide approved for use in combination with dexamethasone to treat patients with **multiple myeloma** (MM) who have received at least one prior therapy.
- **Additional Indication:** June 2013: Approved to treat patients with **mantle cell lymphoma** whose disease has relapsed or progressed after two prior therapies. Lenalidomide represents the **first oral therapy** available for patients with this rare form of **B-cell non-Hodgkin's lymphoma**.
- **Approved for Use Earlier in Treatment Line:** February 2015: Approved for use as a first-line treatment in **combination** with dexamethasone to treat patients with **newly diagnosed MM**. Clinical data from post-approval studies revealed a significant improvement in progression-free survival (25.5 months) when compared to melphalan-predinisone-thalidomide (21.2 months), which had long been considered standard of care in treating MM patients.

RAMUCIRUMAB (CYRAMZA®)

Ramucirumab was originally approved in April 2014 for the treatment of patients with a rare form of stomach cancer called **gastroesophageal junction (GEJ) adenocarcinoma**. In just the last year, accumulating data and ongoing research have revealed additional benefits of ramucirumab when used against other forms of cancer. Furthermore, the impact of ramucirumab has been shown to be even greater in many of these diseases when used in combination with other anticancer agents. Initial assessments of the value of ramucirumab at the time of approval would not have recognized these accumulating benefits.



- **Expanded Use in Combination**: November 2014: Approved for use in combination with paclitaxel to treat patients with **advanced GEJ** adenocarcinoma on or after prior fluoropyrimidine- or platinum-containing chemotherapy. Mean overall survival for patients that took ramucirumab plus paclitaxel was 9.6 months compared to 7.4 months for paclitaxel alone.
- **Additional Indication**: December 2014: Approved for use in combination with docetaxel for the treatment of **metastatic non-small cell lung cancer** with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab.
- **Additional Indication**: April 2015: Approved for use in combination with FOLFIRI for the treatment of patients with **metastatic colorectal cancer** whose disease has progressed on a first-line bevacizumab-, oxaliplatin- and fluoropyrimidine-containing regimen.

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