

RECOGNIZING VALUE IN ONCOLOGY INNOVATION

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INTRODUCTION

In recent years, the United States has witnessed significant progress in the fight against cancer. In 2008, the American Cancer Society (ACS), the Centers for Disease Control and Prevention (CDC), the National Cancer Institute (NCI), and the North American Association of Central Cancer Registries (NAACCR) reported, for the first time, a decline in the incidence and number of deaths of all cancers combined in both men and women. In this report, the authors state that *“declines in cancer death rates indicate real progress in cancer control, reflecting a combination of primary prevention, early detection, and treatment.”*¹

Improved cancer therapies are a significant factor contributing to advances in cancer care, with recent research estimating that new medicines have accounted for 20-60 percent of the increase in cancer survival rates since 1975. Between 1990 and 2004, age-adjusted cancer mortality fell by 13 percent, due in part to advances in treatment, translating into an increase in life expectancy at birth of approximately half a year.^{2,3} Contrary to popular belief, this progress is not typically driven by dramatic, individual developments in cancer therapeutics, but more commonly is the result of recognizing incremental advances through clinical research over time.

At the same time considerable progress is being seen, biopharmaceutical companies engaged in oncology research and development are facing increasing pressure to demonstrate the value of new cancer medicines, some of which report seemingly modest survival benefits (in terms of weeks or months) at the time of initial Food and Drug Administration (FDA) approval. However, these seemingly modest benefits often demonstrate significant clinical advantages for patients as further research is conducted and, thus, it is important to note that the true clinical value of a therapy often cannot be fully captured in the clinical trial data submitted for initial FDA approval.

The development process for all therapies is rigorous, but, in order to comply with standards of medical ethics, oncology research is initially focused on sicker patients who have often tried and failed other available treatment options. This limits the

level of benefit that is likely to be observed in pre-approval testing. Additionally, initial approval is often centered on a single and specific disease indication due to regulatory requirements and practicalities of clinical trial design.

In some cases, where current treatment options may be lacking or ineffective, and patients are in need of new treatment options, the FDA may deem it appropriate to approve new cancer treatments based on compelling surrogate endpoints, such as tumor shrinkage or molecular markers. Following such an approval, companies are required to conduct further studies to validate the surrogate endpoints with long-term clinical outcomes data.

While the intrinsic “value” (or clinical properties) of a therapy does not change, our understanding of the benefits of the therapy evolves over time through the continual testing and validation that is common in oncology. Therefore, FDA approval often marks the “starting point” for a number of additional studies 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.

This white paper demonstrates why the full clinical value of a cancer therapy is often much greater than recognized at the time of initial FDA approval. First, we will discuss the clinical research paradigm and its impact on the data available at the time of initial approval. We will then identify the pathways by which additional clinical value is often recognized, including:

- Use in the initial FDA-approved indication
- Use earlier in treatment line and 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. Each of these pathways for demonstrating product benefit is qualitatively illustrated in **Figures 1-4** using several real-world examples, and will be discussed in this paper.

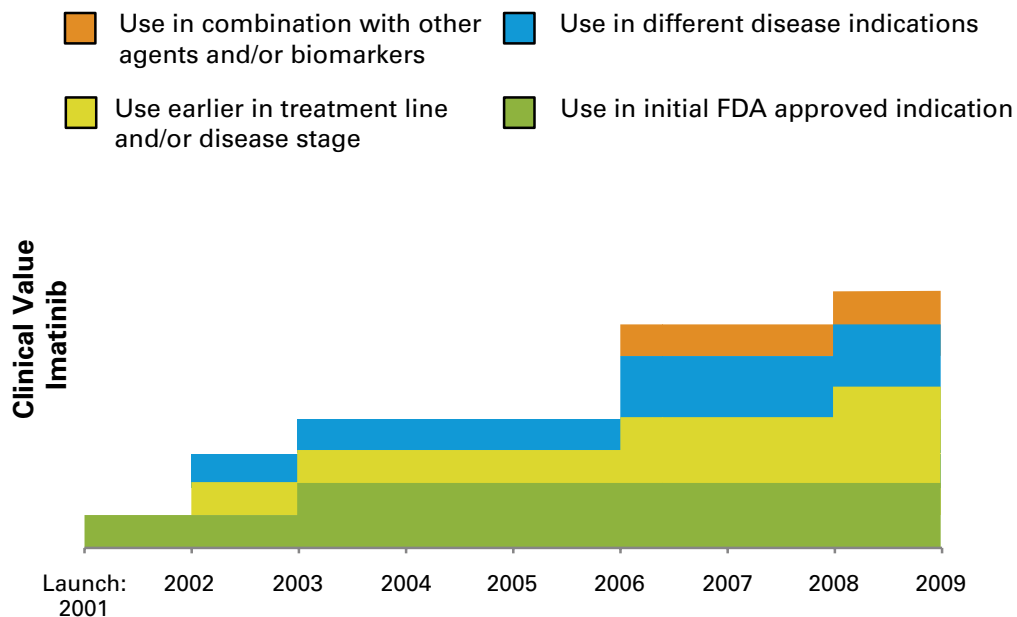
[†] This may include both new indications approved by the FDA and off-label uses supported by research and deemed clinically appropriate by physicians. The evidence in this paper focuses on new FDA-approved indications.

Imatinib (Gleevec®)

In 2001, the FDA approved imatinib for the treatment of advanced stages of chronic myeloid leukemia (CML) and second-line treatment for the earlier, chronic phase of the disease. Approval was based on surrogate endpoints showing that patients responded to the treatment at the cellular level, but long-term survival data were not yet available.

In 2007, the clinical benefit was confirmed with survival data, which showed 88 percent survival for patients after six years of treatment. This compared with an average five-year survival rate of 48 percent prior to imatinib.

FIGURE 1. Imatinib (Gleevec®): Clinical Value Over Time



Indications:⁴

- *Initial Indication - May 2001:* Patients with Ph+ CML in blast crisis, accelerated phase, or chronic phase after failure of interferon-alpha therapy (IFN)
- *Feb 2002:* Patients with Kit (CD117) positive unresectable (unable to be removed through surgery) and/or metastatic malignant gastrointestinal stromal tumors (GIST)
- *Dec 2002:* Newly diagnosed adult patients with Ph+ CML-chronic phase (CP)
- *May 2003:* Pediatric patients with Ph+ CML- CP recurrence after stem cell transplant or IFN resistance
- *Sep 2006:* Newly diagnosed pediatric patients with Ph+ CML-CP
- *Oct 2006:* Adult patients with relapsed or refractory Ph+ acute lymphoblastic leukemia (ALL); Adult patients with myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements; Adult aggressive systemic mastocytosis (ASM) patients without D816V c-Kit mutation or those with unknown c-Kit mutational status; Adult hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) patients with FIP1L1-PDGFR α fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and HES and/or CEL patients who are FIP1L1-PDGFR α fusion kinase negative or unknown; Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans
- *Dec 2008:* Adjuvant treatment of adult patients following resection of Kit (CD117) positive GIST

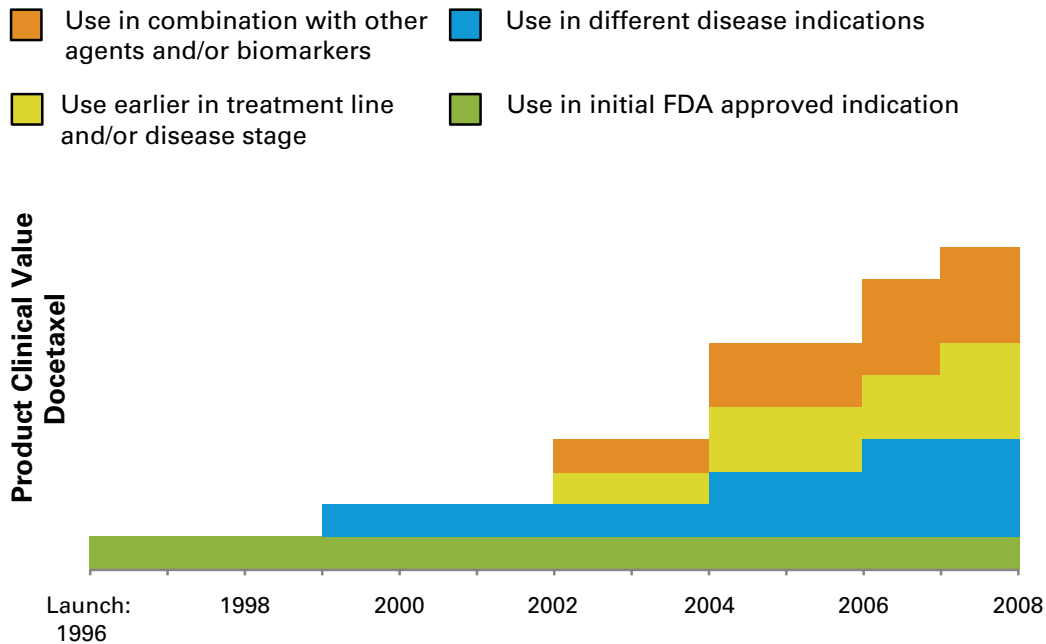
The above is a graphical representation of the change in demonstrated clinical value over time as additional data and evidence became available for the drug. Thus, increased clinical value is supported by the demonstration of an increase in clinical benefit, such as survival or other benefits, and/or by the demonstration of an increase in the range of possible uses, such as use in additional disease indications or use in combination with other agents.

Docetaxel (Taxotere®)

Docetaxel was initially approved in 1996 as a treatment for locally advanced or metastatic breast cancer. In 1999, it received approval as a second-line metastatic treatment for non-small cell lung cancer (NSCLC). Within three years, the FDA granted approval to move it to first-line treatment of NSCLC.

It was then approved for inoperable, locally-advanced squamous cell carcinoma of the head and neck (SCCHN) in 2006. In 2007, docetaxel was approved for use as adjuvant therapy in operable, locally advanced SCCHN after a trial established median survival of 70.6 months for patients on docetaxel compared to 30.1 months for the control group. Evaluation of docetaxel based on early trial results would have substantially underestimated its impact on survival by more than 4.5 years.

FIGURE 2. Docetaxel (Taxotere®): Clinical Value Over Time



Indications:⁴

- *Initial Indication - May 1996:* Treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy
- *Dec 1999:* Treatment of patients with locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy
- *Nov 2002:* In combination with cisplatin for first-line treatment of patients with unresectable, locally advanced or metastatic NSCLC
- *May 2004:* In combination with prednisone as a treatment for patients with androgen independent (hormone refractory) metastatic prostate cancer
- *Aug 2004:* In combination with doxorubicin and cyclophosphamide for the adjuvant treatment of patients with operable node positive breast cancer
- *Mar 2006:* In combination with cisplatin and fluorouracil for the treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have not received prior chemotherapy for advanced disease
- *Oct 2006:* In combination with cisplatin and fluorouracil for the induction treatment of patients with inoperable locally advanced SCCHN
- *Sep 2007:* In combination with cisplatin and fluorouracil for the induction treatment of patients with locally advanced SCCHN

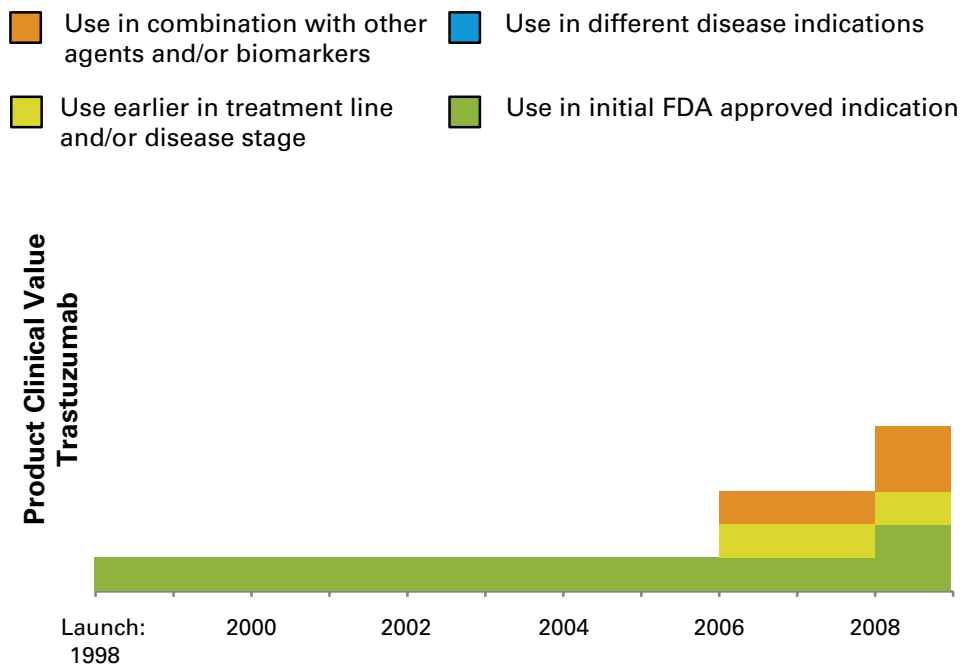
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Trastuzumab (Herceptin®)

In 1998, the FDA approved trastuzumab for limited use in metastatic breast cancer patients whose tumor expresses the protein HER2. At the time of approval, there was no data on overall survival, but the treatment in combination with chemotherapy slowed disease progression. In December 2001, clinical trial data showed that median overall survival increased 25 percent with the addition of trastuzumab.

Early in 2008, trastuzumab was approved for use in an earlier disease stage for women with HER2 positive disease, and has become a potentially curative first-line adjuvant therapy for patients with HER2 positive tumors.

FIGURE 3. Trastuzumab (Herceptin®): Clinical Value Over Time



Indications:⁴

- *Initial Indication - Sep 1998:* Second-line treatment of patients with HER2+ metastatic breast cancer; Trastuzumab + paclitaxel is indicated for first-line treatment of patients with HER2+ metastatic breast cancer
- *Nov 2006:* Trastuzumab + doxorubicin, cyclophosphamide, and paclitaxel, for the adjuvant treatment of patients with HER2-overexpressing, node-positive breast cancer
- *Jan 2008:* Use as a single agent for the second-line treatment of adjuvant treatment of HER2+ node-negative estrogen receptor/progesterone receptor (ER/PR) negative or with one high-risk feature) or node-positive breast cancer following multi-modality anthracycline based therapy
- *May 2008:* For adjuvant treatment of HER2+ node positive or node negative (ER/PR negative or with one high risk feature) breast cancer as (1) part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel, (2) with docetaxel and carboplatin, or (3) as a single agent following multi-modality anthracycline based therapy; In combination with paclitaxel for first-line treatment of HER2+ metastatic breast cancer; as a single agent for treatment of HER2+ breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease

The above is a graphical representation of the change in demonstrated clinical value over time as additional data and evidence became available for the drug. Thus, increased clinical value is supported by the demonstration of an increase in clinical benefit, such as survival or other benefits, and/or by the demonstration of an increase in the range of possible uses, such as use in additional disease indications or use in combination with other agents.

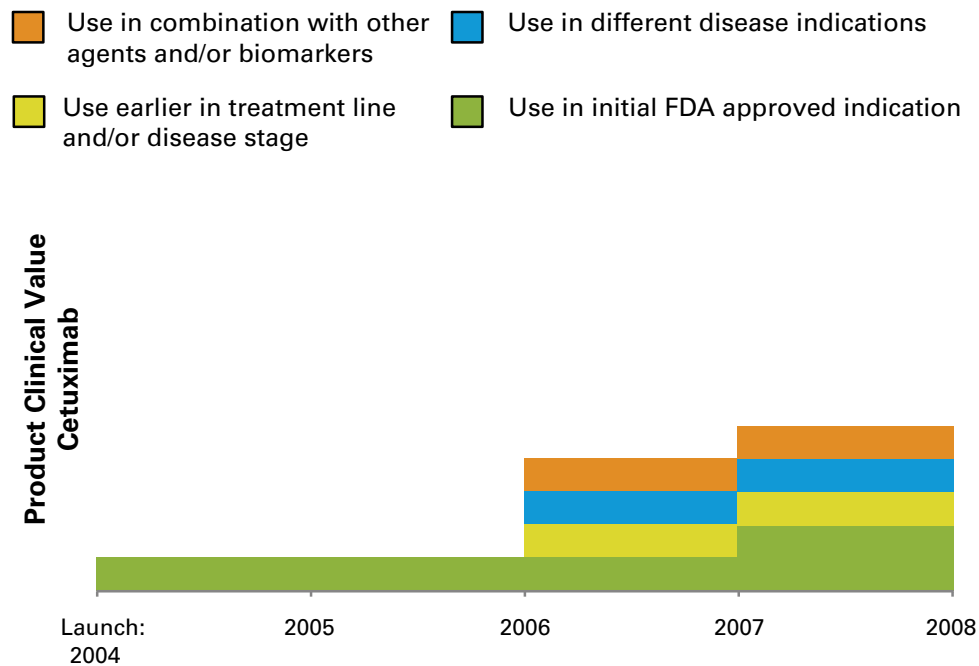
Cetuximab (Erbix®)

Cetuximab was first approved in 2004 for use in combination with irinotecan as a treatment for a type of metastatic colorectal cancer.

Subsequent studies revealed that the presence or absence of mutations in the KRAS gene could predict response to the treatment, allowing clinicians to confidently target treatment to a subgroup of patients likely to benefit. Analysis of pooled data reported an average overall survival of 5.6 months in patients with the KRAS mutation, compared to 15.6 months in patients with no mutation.

Other post-approval studies expanded the use of cetuximab. In 2006, it received a new approval in the treatment of squamous cell carcinoma of the head and neck (SCCHN). It is also used in combination with an existing treatment regimen (FOLFIRI), reducing the risk of colon cancer growth or spread by 15 percent.

FIGURE 4. Cetuximab (Erbix®): Clinical Value Over Time



Indications:⁴

- *Initial Indication - Feb 2004:* Use in combination with irinotecan, cetuximab is indicated for the treatment of epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal cancer in patients who are refractory to irinotecan-based chemotherapy; as a single agent, indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy
- *Mar 2006:* In combination with radiation therapy, for the treatment of locally or regionally advanced SCCHN, and for use as a single agent for the treatment of patients with recurrent or metastatic SCCHN for whom prior platinum-based therapy has failed
- *Oct 2007:* Single-agent for the treatment of EGFR-expressing, metastatic colorectal carcinoma after failure of both irinotecan- and oxaliplatin-based regimens

The above is a graphical representation of the change in demonstrated clinical value over time as additional data and evidence became available for the drug. Thus, increased clinical value is supported by the demonstration of an increase in clinical benefit, such as survival or other benefits, and/or by the demonstration of an increase in the range of possible uses, such as use in additional disease indications or use in combination with other agents.

IMPACT OF THE CLINICAL RESEARCH PARADIGM

Cancer is a complex, life-threatening cluster of diseases and the clinical development process for oncology therapeutics is equally and understandably complex. When any new drug or biologic reaches FDA review, it has already undergone years of research in the lab, in animal models, and in patients. Due to the complicated nature of cancer, clinical research for these medicines takes an average of 1.5 years longer than treatments for other disease areas.⁵

Even with this extensive testing, the clinical benefit demonstrated by the data at the time of initial FDA approval is often constrained because of the nature of oncology clinical research. Because of ethical concerns and regulatory requirements, pre-approval research is generally focused on proving the safety and basic efficacy for the proposed indication(s), rather than on demonstrating the full intrinsic therapeutic value of the treatment.

Due to the life-threatening nature of cancer, ethical standards are at the forefront of caring for patients and play a significant role in shaping cancer research and treatment. An oncologist must rely on proven therapies with known risks and benefits when treating newly-diagnosed cancer patients. Therefore, investigational therapies are necessarily tested first in patients with advanced stage cancer who have exhausted existing standard treatment options. These late-stage patients typically have been heavily pre-treated and have already failed most available treatments. While this does not impact the actual intrinsic properties of a therapy, it creates a theoretical “ceiling” on the amount of clinical benefit that can be observed during the initial phases of research. As a result, therapies that may significantly improve survival and/or convey other benefits in early-stage disease often fail to differentiate themselves in this late-stage, difficult-to-treat patient population. Only after the therapy has demonstrated efficacy in patients with late-stage disease or disease that is resistant to standard therapy can it be tested in earlier stage diseases or as a first-line therapy. It is typically in these earlier stages and treatment lines where it is possible to significantly improve patient survival by modifying the course of disease and slowing or halting the disease progression.

In addition to the ethical obligations associated with cancer research, regulatory requirements also influence clinical research in oncology. The FDA must consider both the amount of information it requires and the need to get promising treatments to seriously-ill cancer patients quickly. The agency appropriately requires clear demonstration of the safety and efficacy of a new treatment, and therefore pre-approval research activities are focused on these essential regulatory endpoints.

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 based on surrogate endpoints. Surrogate endpoints are markers such as tumor shrinkage, cellular response, or measurements of certain biomarkers that are often – but not always – correlated with clinical benefits such as overall survival or time to disease progression.

Medicines reviewed under the standard FDA pathway may be approved based on clinical benefits or *established* surrogate markers. The accelerated approval pathway for medicines that fill unmet medical needs for patients with serious diseases allows for approval based on less established markers that are “reasonably likely” to predict clinical benefit; however, the FDA requires further study and confirmation of clinical benefit after approval.^{6,7} As researchers continue to develop their knowledge of the molecular basis of cancer, surrogate markers have become a critical tool for more accurately evaluating medicines in a shorter period of time.

In addition to FDA-required post-approval studies, the innovator company may also initiate continued research to expand understanding of the full clinical value of the treatment. Post-marketing research may evaluate the therapy’s efficacy in less-advanced disease, in combination with other therapies, in patient sub-populations, and in different cancer types altogether. This research usually leads to a broader understanding of the product’s full clinical value and may prove a greater benefit to patients than demonstrated at the time of initial approval. It may also indicate patient sub-populations or treatment combinations in which

the therapy is either more or less beneficial than a proven alternative, leading to more targeted and effective prescribing by clinicians.

This accumulation of data and further recognition of benefit can also result in additional or expanded FDA-approved indications for an already-approved therapy. A recent study by Boston Consulting Group examined the post-marketing development of approved biological drugs. The study reported that in 2004, 47 percent of the Biologics Licensing Applications (BLAs) for recombinant DNA products and monoclonal antibodies regulated by the FDA Center for Drug Evaluation and Research (CDER) received at least one additional FDA-approved indication after initial approval.⁸ At least one-third of these agents are approved to treat oncology patients and, from 2005 to 2007, 25 oncology therapeutics received FDA approval for at least one expanded or additional indication.⁹

USE IN THE INITIAL FDA-APPROVED INDICATION

As discussed above, the FDA at times approves therapies based on promising molecular or cellular response and other surrogate endpoint data before the completion of the long-term studies. In these cases, the impact on overall survival or tumor progression may not be certain until long-term studies are completed – often years after the initial approval based on surrogate markers. 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.

The case of imatinib (Gleevec[®]) offers an example of the time lag between initial approval (based on surrogate endpoints) and demonstration of clinical benefit (based on conventional survival endpoints) (See Figure 5). In 2001, under the accelerated approval provisions of 21 CFR 314 Subpart H, the FDA approved imatinib for the treatment of advanced stages of chronic myeloid leukemia (CML) and second-line treatment for the earlier, chronic phase of the disease.¹⁰ In announcing the approval, the FDA noted that there was no evidence of clinical benefit, defined as a reduction in disease-

related symptoms or mortality.¹¹ The drug was approved because initial trial data demonstrated that patients were responding to the drug treatment on a molecular level, and the FDA noted that the benefit of an immediate approval for a treatment in a disease area with few effective treatment options outweighed the remaining uncertainty of the drug's overall clinical benefit.

It would take another six years for the clinical benefit of imatinib to be confirmed by survival data. In 2007, continued follow-up data from the International Randomized IFN vs. ST1571 (IRIS) study demonstrated that disease progression fell to zero percent in 553 CML patients treated with imatinib. Three hundred sixty-four of these patients were still taking the drug by the study's sixth year, with a reported overall survival of 88 percent.¹² This result stands in stark contrast to the average five-year survival rate of 48 percent for CML patients from 1990 to 2000, prior to the approval of imatinib.¹³

FIGURE 5.

Value Recognition: Use in Initial FDA-Approved Indication

Imatinib (Gleevec[®])

In 2001, imatinib was approved for second-line treatment in CML. Approval was based on hematologic and cytogenetic response rates in trial participants; there were no studies demonstrating clinical benefits such as improvement in disease-related symptoms or increased survival. In 2007, six years after initial approval of imatinib for use in CML, the IRIS study six year results reported that CML patients treated with imatinib had disease progression rates of zero percent, with an estimated overall survival rate of 88 percent.¹²

Similarly, while initial approval for use in gastrointestinal stromal tumors (GIST) patients was granted in 2002, clinical data demonstrating over four years of overall survival and 1.5-2 years of progression-free survival in GIST patients was not available until 2008.¹⁴

USE EARLIER IN TREATMENT LINE AND EARLIER DISEASE STAGE

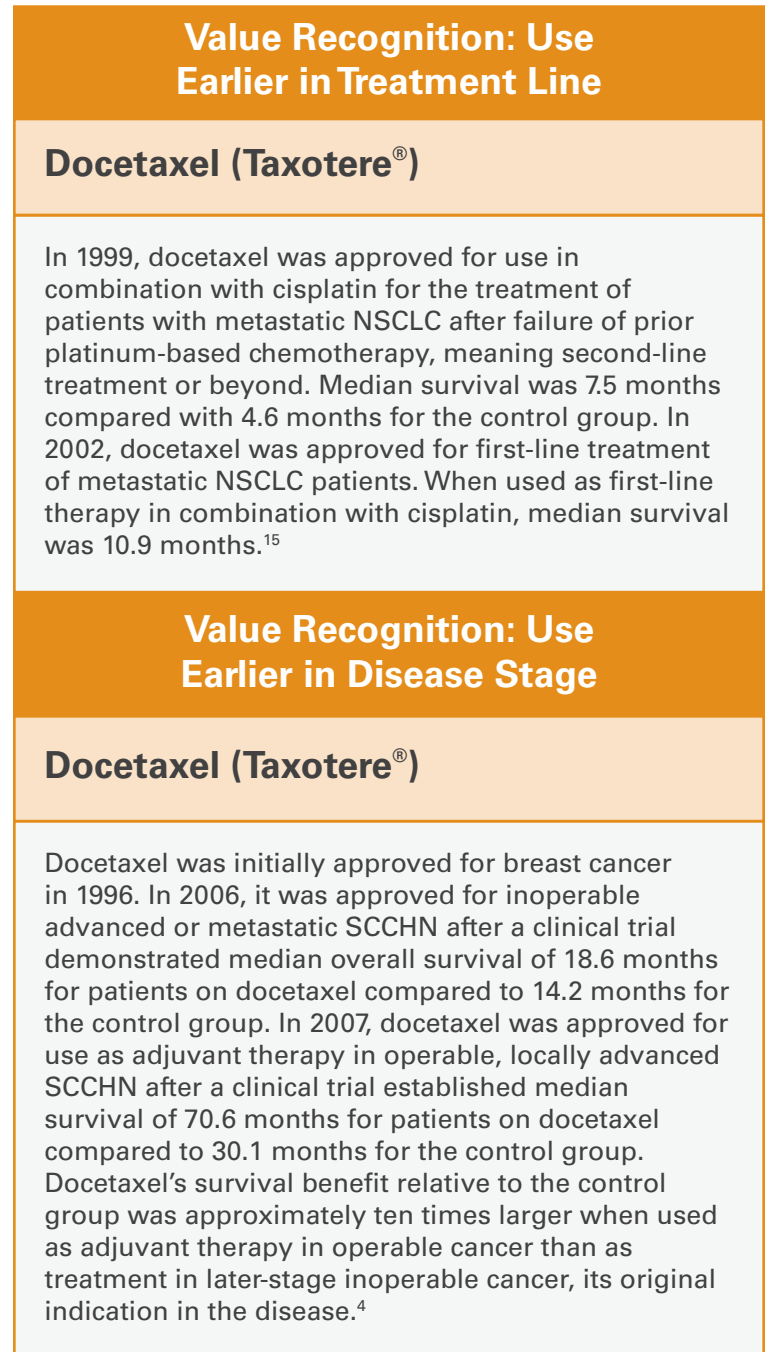
FDA-approved indications for oncology therapies are generally limited to a specific line of therapy and disease stage. Advancement in *treatment line* refers to the movement of an agent to be used as an earlier therapeutic option within a particular disease stage. Advancement in *disease stage* denotes 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). 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.

Docetaxel (Taxotere[®]) illustrates the progression of a drug's clinical use both earlier in treatment line and in disease stage (see Figure 6). Docetaxel received approval for use as a second-line metastatic treatment for non-small cell lung cancer (NSCLC) in 1999. And in 2002, the FDA granted approval for the use of docetaxel as a first-line treatment in metastatic disease in NSCLC, demonstrating movement earlier in the treatment line.⁴

In another disease area, docetaxel was approved for inoperable, locally-advanced squamous cell carcinoma of the head and neck (SCCHN) in 2006. In this advanced disease stage, patients treated with docetaxel had an overall survival of 1.5 years – four months longer than the control group.⁴ A year later, the FDA approved docetaxel as adjuvant treatment for patients with operable, locally-advanced SCCHN, where the therapy is associated with nearly six years of median overall survival, an improvement of more than three years over the control group.⁴ Evaluation of docetaxel based solely on its clinical data in the treatment of inoperable, locally-advanced SCCHN would have substantially underestimated the treatment's impact on overall survival in the disease by more than 4.5 years.

Earlier in docetaxel's history, a similar pattern was observed in breast cancer. The agent was initially approved for metastatic treatment, but was eventually moved earlier in disease stage for use in the adjuvant setting.

FIGURE 6.



[‡] 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

FIGURE 6. (cont.)

Value Recognition: Use Earlier in Disease Stage

Imatinib (Gleevec®)

In 2006, imatinib moved earlier in the CML treatment line when it was approved for first-line therapy in Ph+ CML- chronic phase patients. A similar pattern was seen in GIST, where approval for use in the adjuvant setting was granted in 2008 following termination of the pivotal trial after interim analysis demonstrated significant benefits with imatinib. Imatinib's clinical value continues to evolve and expand. Several trials are now underway to examine the efficacy of imatinib in neoadjuvant settings for treatment of GIST.¹⁶

Trastuzumab (Herceptin®)

In 2006, trastuzumab moved from treatment of metastatic breast cancer into adjuvant treatment for operable breast cancer, with a hazard ratio of 0.48 for disease-free survival events in patients treated with trastuzumab + paclitaxel versus paclitaxel alone after anthracycline. In other words, the rate of relapse or recurrence in patients treated with combinations including trastuzumab is approximately half of that in patients treated with paclitaxel alone. Trastuzumab use was also associated with a 33 percent reduction in risk of death.¹⁷ In 2008, a clinical trial found that when used as a single agent following chemotherapy, trastuzumab had a hazard ratio of 0.54 for disease-free survival events compared to observation, indicating that approximately twice as many patients on observation alone were relapsing as compared with those patients receiving trastuzumab maintenance therapy. When used both as a single agent and in combination, the rate of relapse or recurrence in patients on trastuzumab-based therapy was approximately half that when compared with observation of those on alternative therapeutic regimens.¹⁸

USE IN ADDITIONAL DISEASE INDICATIONS

Oncology therapies often 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 commonly explore additional indications and, in many instances, a therapy demonstrates significant clinical benefit in a different disease. The clinical development of imatinib, for example, did not end with the original CML indication. Imatinib's approved indications expanded to the treatment of unresectable** and/or metastatic gastrointestinal stromal cancer (GIST) in February 2002 based on surrogate endpoints, less than a year after initial approval for the CML indication.

In 2008, the earlier FDA decision was corroborated by clinical data demonstrating that GIST patients treated with imatinib experienced, on average, more than four years of overall survival, and between 1.5-2 years of progression-free survival.¹⁹ This represents a significant improvement in overall survival, as a study published in 2000 indicates overall survival for GIST patients prior to imatinib approval was approximately 14 months.²⁰ In addition, imatinib is now approved for an array of additional indications, ranging from second-line treatment for pediatric CML patients to adults with aggressive systemic mastocytosis (ASM) (see Figure 7). Research on imatinib continues today in other cancers, such as squamous cell carcinoma of the head and neck, mesothelioma, and glioblastoma.²¹

** An unresectable tumor is one that is unable to be removed through surgery.

FIGURE 7.

Value Recognition: Use in Additional Disease Indications

Imatinib (Gleevec®)

Less than a year after initial approval, imatinib was approved for use in GIST patients with Kit-positive tumors. Similar to its initial approval, the expanded GIST indication was based on a surrogate endpoint: objective response rate (percentage of cases in which tumor shrinkage occurred). A significant improvement in overall survival from approximately 14 months prior to imatinib use to over four years with imatinib was eventually realized and clinically validated. Ongoing trials are also investigating the use of imatinib in several additional disease areas, including squamous cell head and neck cancer, thyroid cancer, breast cancer, mesothelioma, and non-Hodgkin lymphoma.²¹

USE IN COMBINATION WITH OTHER AGENTS

Cancer's complexity requires continual research in order to learn how to utilize new therapies most effectively. Through experience and rigorous clinical testing, physicians develop an understanding of how best to use a therapy in combination with other chemotherapeutic agents and treatment modalities (e.g., surgical resection, radiation, and supportive care). As the available arsenal of oncologic agents continues to grow, effective use of these drugs in combination becomes paramount. However, the therapeutic value of a possible treatment combination is difficult to demonstrate through clinical testing, due to the great number of potential therapeutic combinations available, each potentially only applicable to small population subsets with specific characteristics. While combination therapies frequently result in improved clinical outcomes, they also can demonstrate instances where the hypothesized benefit of a specific combination is not supported by the empirical data. The development and dissemination of objective clinical data is a cornerstone of oncology research and serves to further the clinician's understanding of how to use available treatment options.

Despite the difficulty of demonstrating the effectiveness of drug pairs, combination therapy has become well-established in oncology for several reasons and a considerable amount of cancer research involves different combinations of new and existing therapies. Because many cancer therapies cause severe side effects, often a patient cannot tolerate a full dose of a highly toxic drug or biologic. Additionally, different therapies act through different mechanisms in the body to combat tumor growth. The combination approach has been demonstrated to enhance anti-tumor activity by allowing both the administration of full doses of agents while managing the dose-limiting adverse effects and utilizing multiple mechanisms of action to reduce tumor growth, often producing superior outcomes.²² For example, addition of cetuximab (Erbix®) to FOLFIRI [folinic acid (also known as leucovorin), fluorouracil, and irinotecan], demonstrates greater efficacy as first-line therapy for metastatic colorectal cancer than FOLFIRI alone (see Figure 8). One study found that the addition of cetuximab to FOLFIRI reduced the risk of cancer growth or spread by 15 percent.²³

Several other studies explored the clinical benefit of adding cetuximab to a regimen of capecitabine, oxaliplatin, and bevacizumab in the treatment of advanced metastatic colorectal cancer. The studies indicate that the addition of cetuximab to regimens containing the targeted therapy bevacizumab actually reduces median progression-free survival compared to the standard regimen without cetuximab.²⁴ These studies do not negate the benefits associated with cetuximab in combination with other cytotoxic chemotherapy regimens; however, they provide new insights into how cetuximab should and should not be used, ultimately maximizing the benefit it provides to cancer patients.

FIGURE 8.

Value Recognition: Use in Combination with Other Agents

Cetuximab (Erbix[®])

An analysis of first-line cetuximab alone or in combination with FOLFIRI (folinic acid, fluoracil, and irinotecan) in metastatic colorectal cancer found that at the end of the monotherapy phase, response rate was 27.6 percent. During the combination phase, however, this response rate increased to 55.2 percent. Progression-free survival for cetuximab + FOLFIRI was also significantly improved.²³ Additionally, initial results from the CRYSTAL trial have reported that the addition of cetuximab to FOLFIRI in first-line therapy reduces the risk for metastatic colorectal cancer growth or spread by 15 percent compared with FOLFIRI alone. Overall response rate to FOLFIRI + cetuximab was 46.9 percent compared with 38.7 percent with FOLFIRI alone, and median progression-free survival was 8.9 months and eight months, respectively.²⁵ Further follow-up results from the CRYSTAL trial noted that in patients with tumors without KRAS mutations, adding cetuximab to FOLFIRI statistically significantly increased the chance of a complete or partial tumor response ($p=0.0025$), reduced the risk of progression ($p=0.0167$), and increased median overall survival by 3.9 months ($p=0.22$).²⁶

Trastuzumab (Herceptin[®])

Following its 2006 approval for use in adjuvant breast cancer treatment, the FDA expanded trastuzumab's indications within adjuvant treatment, after a clinical study showed that trastuzumab + docetaxel and carboplatin, and trastuzumab + docetaxel following doxorubicin and cyclophosphamide had hazard ratios for disease-free survival events of 0.67 and 0.60, respectively.²⁷ In other words, the rate of relapse or recurrence in patients treated with combinations including trastuzumab is approximately two-thirds of that in patients treated with combination therapy without trastuzumab.

USE IN COMBINATION WITH SPECIFIC BIOMARKERS

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 targeted populations. Biomarkers are molecules or genetic markers that can be used to predict response to specific pharmacologic treatments, and they can often 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. Although much work needs to be done in this area, oncology researchers and those in other therapeutic areas are embracing the development of diagnostics that allow physicians to stratify patients and determine which subsets of patients may be most likely to benefit from therapy.

The approval of cetuximab in patients with metastatic colorectal cancer was based on clinical results that did not account for the impact of observable mutations in the KRAS gene, which have since been demonstrated to predict treatment response. Thus, the use of cetuximab now can be confidently targeted to a subgroup of patients with the greatest likelihood of response, while alternative regimens can be selected for the patient subgroup in which the KRAS biomarker suggests that cetuximab would not be effective.

Trastuzumab (Herceptin[®]) is another targeted therapy that has demonstrated additional clinical value in combination with a specific biomarker (see Figure 9). Initial investigation of trastuzumab in metastatic breast cancer established anti-tumor activity, but tumor response occurred only in patients with positive expression of human epidermal growth factor receptor-2 (HER2). Approval was then granted only for this specific subset of breast cancer patients, as they represent the subpopulation with the highest probability of receiving treatment benefit. Without knowledge of the HER2 biomarker's role in trastuzumab response, the efficacy of the drug may not have been realized; this may have stunted further recognition of its benefit. Early in 2008, trastuzumab was approved for use in an earlier disease stage for adjuvant therapy of women with HER2 positive disease, and has become a potentially curative first-line adjuvant therapy for patients with HER2 positive tumors.

FIGURE 9.

Value Recognition: Use in Combination with Specific Biomarkers

Cetuximab (Erbix[®])

In 2008, a clinical study found Kirsten ras oncogene homolog (KRAS) mutations present in 27 percent of 89 patients. The mutation was associated with resistance to cetuximab in all 24 of the patients whose tumor expressed the KRAS mutation. Among the 65 patients whose tumor did not express the KRAS mutation, a 40 percent response rate was observed. Overall survival was 10.1 months in patients expressing the mutation compared to 14.3 months in patients without the mutation. Further analysis of pooled data suggests average overall survival of 5.6 months in patients with the KRAS mutation, compared to 15.6 months in patients with no mutation.²⁸

In another study, also published in 2008, 113 patients with irinotecan-refractory metastatic colorectal cancer were treated with cetuximab. In patients without the KRAS mutation, median overall survival was 10.8 months compared to 6.8 months in patients expressing the KRAS mutation.²⁹ In a subset of these patients in whom an initial response was observed (decrease of tumor by >9.66 percent at week six assessment), the median overall survival was 18.7 months compared to 7.7 months. These studies indicate that KRAS status is predictive of response to epidermal growth factor receptor (EGFR) inhibitor therapy, allowing the use of better targeted therapy and resulting in improved survival.

Trastuzumab (Herceptin[®])

In 1998, the FDA approved trastuzumab for limited use in HER2+ metastatic breast cancer based on time to progression of 7.2 months for patients on trastuzumab + chemotherapy, compared to 4.5 months with chemotherapy alone. There was no overall survival data at the time, but there was evidence that trastuzumab elicited an objective response in HER2+ breast cancer. In December 2001, new data indicated median overall survival of 25.1 months for trastuzumab + chemotherapy as compared to 20.3 months for chemotherapy alone in patients with HER2+ metastatic breast cancer. The trial also demonstrated that patients with the greatest HER2 expression had median overall survival of 24.8 months on trastuzumab + paclitaxel compared to 17.9 months on paclitaxel alone, and 30.8 months overall survival on trastuzumab + anthracycline compared to 20.9 months on anthracycline alone.⁴

In 2002, the label would again be expanded to include the use of a fluorescence in situ hybridization (FISH) diagnostic test to quantify the HER2 status of patients, allowing the clinician to make more informed treatment decisions.⁴

CONCLUSIONS

As this paper demonstrates, the full clinical benefit of oncology medicines often is not known at the time of initial FDA approval. Oncology researchers continue to conduct additional research before and 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 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 drug or biologic is used and how it affects patients (see Figures 1-4). Therefore, the full impact of therapy is often recognized only after years of additional post-approval research. The potential for greater benefit still exists as long as the therapy is rigorously tested in innovative new ways.

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, and policymakers alike. Only by examining the entire set of evidence – sometimes accumulated over a period of time – are

we able to judge the clinical 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 anti-cancer therapy receives FDA approval is generally only a partial reflection of the ultimate benefit that will be understood for that therapy, as a direct result of the mechanisms outlined in this paper. Continued research investment into how biopharmaceuticals can be used to improve patient outcomes after approval remains a key priority and opportunity to achieve critical advances in oncology.

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