The Value of Innovation in Oncology: Recognizing Emerging Benefits Over Time

In recent years, the United States has witnessed significant progress in the fight against cancer, with survival rates increasing from 49 percent in the mid-1970s to 68 percent today. 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. The progress driving 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.

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. 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.

This additional value is recognized through a number of pathways, including those described below:

**Use Within a Singular FDA-Approved Indication**

In some cases, where patients are in need of new treatment options, the FDA may deem it appropriate to approve new cancer treatments based on compelling surrogate endpoints (e.g., tumor shrinkage) before the completion of the long-term studies. As clinical investigation of safety and efficacy continue, the impact on overall survival and tumor progression can be fully realized using the long-term clinical outcomes data.

**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 tests positive for the protein anaplastic lymphoma kinase (ALK). Approval was based on two studies that 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 updated labeling to reflect the clinical benefit of crizotinib that had been revealed through ongoing studies. 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.

**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. This creates a theoretical “ceiling” on the amount of clinical benefit that can usually be observed during initial clinical research. As additional testing is conducted following FDA approval, a therapy may demonstrate efficacy earlier in treatment line (when used prior to other available therapies) and/or disease stage (when used earlier in disease progression).

**Bortezomib (VELCADE®).** Bortezomib was initially approved in 2003 to treat multiple myeloma patients who had received two prior therapies and were not responding (third-line therapy). In 2005 the label was expanded to include use earlier in the treatment regimen as a second-line therapy. Study data revealed that the time for the disease to progress was significantly longer in patients that received bortezomib (6.2 months) compared to those receiving standard treatment (2.5 months). In 2008 the FDA granted approval for the use of bortezomib as a first-line multiple myeloma treatment after study results showed that patients treated with bortezomib experienced significantly longer time to progression (20.7 months) compared to standard treatment (15 months). Ongoing research revealed the value of using bortezomib as a first-line treatment, earlier in the progression of the disease, than initial results suggested.
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.

Lenalidomide (Revlimid®). Lenalidomide was originally approved in 2005 to treat patients with myelodysplastic syndrome (MDS) who had a specific genetic mutation.10 MDS is collection of disorders where the bone marrow fails to produce enough healthy blood cells. In clinical studies, patients treated with lenalidomide no longer needed blood transfusions. In 2006, lenalidomide received approval for use in combination with dexamethasone to treat patients with multiple myeloma who had failed other treatments11 (and in 2015 lenalidomide was approved as a first-line treatment). In 2013, lenalidomide was approved for use against mantle cell lymphoma, as the first oral therapy available for patients with this rare blood cancer.12

Use In Combination With Other Agents

A considerable amount of cancer research involves investigating different combinations of new and existing therapies that can improve outcomes. The combination approach has often proven to produce superior outcomes by enhancing anti-tumor activity by both allowing patients to receive a full-dose of drugs while managing adverse effects, and by attacking the tumor through multiple mechanisms of action, helping to combat resistance to treatment.

Everolimus (Afinitor®). Everolimus, a rapamycin (mTOR) inhibitor, was originally approved by the FDA in 2009 for the treatment of advanced renal cell carcinoma (RCC).13 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.14 In this form of 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, over time, many tumors developed resistance to these treatments. Everolimus helped prolong the effectiveness of these treatments by combatting that resistance.

Use In Combination With Specific Biomarkers

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 (biomarker). Biomarkers 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.

Ibrutinib (Imbruvica®). In February 2014, ibrutinib received approval for the treatment of patients with chronic lymphocytic leukemia (CLL) who have tried at least one prior therapy.15 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.16 The clinical study resulting in this expanded indication 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.17