



Changing Oncology REGULATIONS

Uncertainty surrounds oncology drug development as the FDA considers tightening the standards for accelerated approval of new cancer products.

Developing oncology therapies can be complex. These products often have a tough time making it to the market. In fact, a study released in February by the Biotechnology Industry Organization and BioMedTracker shows that oncology products had the lowest Phase III success rate among seven therapeutic areas, with only 34% of candidates succeeding at this stage over a seven-year period.

At the same time, officials at the Food and Drug Administration are considering tightening the accelerated approval standards. In February, the agency's Oncologic Drugs Advisory Committee recommended that sponsors should generally conduct randomized trials rather than single-arm studies — trials without a control — and that there should be more extensive postmarketing studies to confirm clinical benefit. The advisory committee members agreed that single-arm trials should be used for rare diseases and when there is a pronounced treatment effect.

Accelerated approval for serious and life-threatening illnesses was first allowed in 1992. Approval can be based on a surrogate that is reasonably likely to predict a clinical benefit, and approval requires well-controlled trials that are conducted with due diligence, i.e., postmarketing studies. The agency now has

the authority under FDAAA to impose financial penalties for not conducting postmarketing studies.

Jeffrey Weisberg, senior medical director of i3 Research, says the accelerated approval section of Title 21 was added in part because of political pressure for the rapid approval of drugs for breast and other cancers, as well as for AIDS treatments, in response to the perceived slowness of the agency to approve new drugs for serious and life-threatening illnesses.

"Since then, there has been some pushback that these drugs may have been approved too easily, since some have had to be withdrawn from the market for safety reasons or less than stellar efficacy on further examination of the longer-term endpoints," he says.

According to FDA officials, the accelerated approval pathway continues to be widely used for new oncology drug indications. They have formed the basis for more than half of the accelerated approvals for oncology drugs to date.

The average number of approved oncology drug indications per year has increased from about 2.9 to 3.3 when comparing the period before 2005 with the period after 2005. But some drugs have failed to confirm clinical benefit in postmarketing trials. FDA officials say about 10% of accelerated oncology approvals have failed to verify a clinical benefit.

One recent example is Genentech's Avastin for breast cancer. In December 2010, the FDA announced that the agency was beginning the process of removing the breast cancer indication from the product's label. The product is

FAST FACT

ABOUT 1.5 MILLION NEW CANCER CASES ARE EXPECTED TO BE DIAGNOSED IN 2010.

Source: American Cancer Society

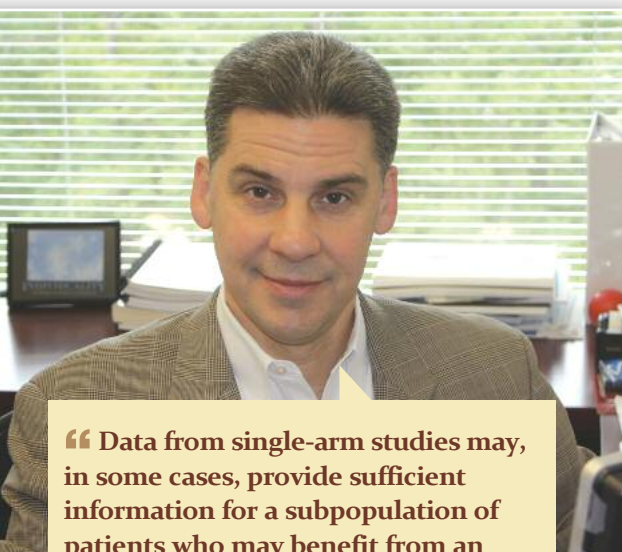
also approved to treat colorectal, lung, and kidney cancers, as well as glioblastoma.

The agency reviewed the results of four clinical studies of Avastin and determined that the data show that the drug does not prolong overall survival in breast cancer patients or provide a sufficient benefit in slowing disease progression to outweigh the risk to patients. These risks include severe high blood pressure; bleeding and hemorrhage; the development of perforations in the nose, stomach, and intestines; and heart attack or heart failure.

In July 2010, an independent advisory committee voted 12-1 to remove the breast cancer indication from Avastin's label.

Another high-profile example is Mylotarg for patients with acute myeloid leukemia (AML). In June 2010, Pfizer withdrew the product from the U.S. market after results from a postmarketing study raised concerns about the product's safety.

At its initial approval in 2000, Mylotarg was associated with a serious liver condition called veno-occlusive disease, which can be fatal. This rate increased in the postmarketing study.



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SCOTT BAZEMORE / US Oncology Research



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DR. JENS OLIVER FUNK / EMD Serono

Impact on Development

With cancer, patients differ greatly from one to the next, making clinical trials much less straight-forward than other areas of medicine, says Garo Armen, Ph.D., chairman and CEO of Agenus.

“Randomized trials are built on the assumption that we can identify uniform patient populations to determine the effect of a drug,” he says. “But often these definitions or understandings as to what constitutes uniformity of populations change over time based on increasing knowledge of disease factors. My concern is that if the requirements for randomized trials in cancer become more stringent, we could witness more studies failing, despite the fact that they might work for many, but not an ‘entire patient population’ as defined by a given protocol.

“As the field of oncology development moves toward the use of targeted molecular agents and immunotherapies used in combination regimens, I think both developers/manufacturers and regulatory agencies will need to consider carefully any changes to underlying study design requirements, so that we don’t throw the proverbial baby out with the bathwater,” Dr. Armen continues. “Even a ‘failed’ randomized trial might show strong treatment effects in a subset of the population that may be biologically, scientifically and/or methodologically plausible and sensible.”

Scott Bazemore, director of clinical development at US Oncology Research, says while the recent ODAC proposals are certainly understandable given the high-profile cases of Mylotarg and Avastin, these recommendations will likely slow the progress of approvals for targeted therapies.

“No one would argue against placing patient safety first and foremost, and as we take that into consideration, we should also consider approvals based on single arm studies, particularly in situations where no other therapeutic option is available,” Mr. Bazemore says. “There is no black-and-white answer to the issue. Specifically, over the last five years, there have been notable instances where a drug clearly demonstrated a statistically significant biologic effect in early studies, which appeared to be an overwhelming case for approval. Many experts worried that a denial could stall the industry’s drug discovery efforts. In many of these cases, the industry breathed a collective sigh of relief as the FDA trended toward granting accelerated approvals on the condition that the sponsor conduct postmarketing studies to further establish the efficacy. In a few cases, these subsequent studies provided somewhat contradictory results to earlier studies and the path to full approval was less clear.”

Mr. Bazemore adds that data from single-arm studies may, in some cases, provide sufficient information for a subpopulation of patients who may benefit from an accelerated approval.

“Given the latest data on the genomic profiles of various cancers, it is becoming evident that each person’s cancer is as individual as he or she is,” he says. “As this complexity continues to be researched, the idea of a one-size-fits-all treatment is quickly fading away. Targeted therapies are not the future, they are here now. Patients with the same tumor type are likely to respond differently based on their genetic makeup, environment, and many other factors. A single-arm study should be an option as long as the trial is designed with these key endpoints

in mind. Without this refinement to the process, oncology drugs will be more difficult, as well as more expensive, to develop.”

Kirsten Hanton, senior VP and managing partner at Harrison and Star, says the ODAC rulings could actually shift pressure in the opposite direction: away from personalized medicine and toward the old blockbuster model.

“The more subtypes of a tumor that are identified, the smaller each patient population becomes,” she says “The twin issues of accrual and timeliness will become more difficult.”

Jens Oliver Funk, M.D., senior VP and global head of TA oncology at EMD Serono, says another concern is that randomized trials take longer than single-arm trials.

“In principle, it is a valid proposal to primarily aim for randomized trials with new anti-cancer drugs in development,” he says. “It is also key to strive for meaningful clinical comparison of a new drug and put data and its clinical relevance in perspective early on. Such a consideration should override thoughts on, for example, performing the leanest possible study with the minimum response rate increase needed purely based on time considerations. Importantly, there should still be a case-by-case analysis of studies, as some indications or settings make randomized designs hard or close to impossible. Therefore, experienced judgment is needed in this dialogue. If randomized Phase II trials help to bring data-driven development stops to an earlier decision point, over time we should see a higher success rate of Phase III trials leading to value for cancer patients.”

Mr. Weisberg points out that while using randomized controlled trials (RCTs) over single-arm trials, which use historical controls, is more scientific, RCTs require a greater invest-

ment in time and money and expose more subjects to the standard of care treatment or placebo vs. experimental treatment.

"RCTs are more scientific because they help eliminate bias by using contemporaneous cohorts, which are treated identically except for the experimental treatment," he says. "The ultimate outcome of using RCTs over single-arm results is greater development expense and longer time to get a drug to market, but the studies will be more scientific and thus lead to fewer drugs either being recalled or found to have clinical benefit discordant with the surrogate marker that led to their early approval."

Ms. Hanton says patients will be delayed access to important therapies.

"We can also expect to see the strong incentive currently in place to develop new drugs for large markets like colorectal, lung, and breast cancers become even more powerful if proposed limits to the accelerated approval process are enacted," she says. "Conversely, this will make it tougher to ensure drugs are designed to treat less common tumors and get the necessary regulatory approvals."

Impact on Patient Recruitment

Ms. Hanton says it will be harder to accrue the requisite number of patients to fill the ranks of trials now that larger randomized trials are required to get an agent through the approval process.

"This reinforces the existing incentive to aim at the largest markets," she says. "To recruit efficiently, there has to be a large enough patient pool to draw from for trial accrual. Additionally, companies need a large enough patient pool that can benefit from the drug to offset the increased costs of bringing the drug to market. For less common tumors, this may effectively preclude the development of any new drugs at all — from a rational business perspective — unless exceptions are made."

Mr. Bazemore says it is well-known that the percentage of patients enrolled in oncology clinical trials is far below desired levels.

"There are many contributing factors and much depends on the institution enrolling patients and the tumor type in question," he says. "From a general perspective, enrolling to confirmatory or postmarketing trials can be even more difficult because of their size and need for long-term follow-up while the product's patent life is ticking away. This is compounded by the public perception of the drug being investigated once it has experienced an approval reversal. This may cast a shadow of suspicion on all investigational agents with similar mechanisms of action."

Dr. Armen adds that patient recruitment impacts future patient outcomes.

"If we are to learn about these diseases and

FAST FACT

**BIOPHARMACEUTICAL
RESEARCHERS ARE NOW WORKING
ON 887 MEDICINES FOR CANCER.**

Source: PhRMA

improve treatments, we must explore the effectiveness of new innovations," he says. "My concern is that if greater emphasis is placed on randomized trials, patients will be less willing to be involved because randomized trials have both 'experimental' and 'control' arms, and often patients are desperate for new options and are reluctant to be potentially part of the control group. I also believe that for the patients themselves, increased access to a potentially promising new treatment is incredibly important. Single-arm trials make this possible for greater numbers of patients."

But Dr. Funk points out that the dynamic of patient recruitment will likely vary a great deal and not, per se, be impacted by a stronger orientation toward randomized clinical trials.

"Attractiveness for patients will depend, for example, on their expectation of the new investigational drug, activity and safety aspects of the standard-of-care in comparison, choice of therapeutic options in general, and other factors," he says. "Obviously, trial feasibility is a question from the start, as some indications or settings make randomized designs hard and thus may slow down patient recruitment rates. It, therefore, remains key to have an informed dialogue with patients before they enter these clinical trials to set expectations and clarify the benefit for them, versus establishing the activity of new drugs."

Impact on Marketing

Ms. Hanton says marketing oncology therapies will become increasingly difficult, as drug manufacturers will be required to promote the therapies in line with their labeled indications, but these may no longer be in line with the clinical utility of the therapy.

"Historically, postmarketing studies have been used to validate the findings of the single-arm study for initial accelerated approval," Ms. Hanton says. "Now the question is, what will these studies focus on? A worthy goal would be to find answers to some of the questions raised about how to use these therapies in the clinic, helping to close the relevancy gap."

"Ultimately, the FDA needs to work to find a way to bring these life-saving therapies to the community quickly and safely," Ms. Hanton continues. "Oncology is volatile and complex, so we need to find a way to create policy solutions that are reasonably agile and responsive

to nuance. I envision a transparent, collaborative dialogue between the FDA and the oncology research community at large, not as a one-off, but on an ongoing basis. This dialogue should not be focused on short-term political ends but on the long-term objective of optimizing the pace and quality of improvement in the care that cancer patients receive."

Dr. Armen says once a product has reached the point of commercialization, his concern would turn to understanding the resource and financial impact of postmarket restrictions and reporting requirements through REMS and requirements for further trials.

"Safety and efficacy are our ultimate priorities, yet supporting these postmarketing requirements takes resources, and if those needs outpace revenue, ultimately, patients could lose access to needed treatments," he says. **PV**

PODCAST



**ONCOLOGY TRIALS:
A NOVEL APPROACH
TO PATIENT ACCRUAL**

Ed Watson, Director of Oncology,
Acurian, Inc.

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EXPERTS

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