Throwing the Brake on the Drug Approval Train

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Author's disclosures of potential conflict of interest are found at the end of this article.

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One of the most meaningful developments in oncology, and health care in general, has been the move to evidence-based practice. Most would likely indicate that if they or their loved ones were ill, they would want to have the treatment that has been proven to be the most effective in achieving a positive outcome. At the same time, we live in an "I want it now!" society. We want the latest software version, 4G cell phones, and the vehicle that parallel parks itself. Unfortunately, evidence-based practice requires time in order to collect and evaluate the evidence.

In February 2008, the US Food and Drug Adminstration (FDA) granted accelerated approval for the use of bevacizumab (Avastin) in metastatic breast cancer in combination with paclitaxel chemotherapy (FDA, 2008). The decision was met with some debate, but was based on results from the phase III E2100 trial (Miller et al., 2007).

Most recently, on December 16, 2010, the FDA announced that it was now recommending the "removal" of the breast cancer indication for bevacizumab. The recommendation was based on results of confirmatory trials that were required at the time of the initial accelerated approval (FDA, 2010). So was the initial evidence wrong?

SEE PAGE 268

Use your smartphone to view the original ASCO abstracts on the pivotal AVADO and RIBBON-1 bevacizumab trials.

Expediting the FDA Approval Process—Riding the Express Train

The FDA requires an extremely rigorous review of critical evidence prior to granting drug approval and marketing rights to a new agent (McKee et al., 2010) (Figure 1). However, a variety of methods are currently in place to expedite the availability of new drugs to individuals with serious disease. The process helps address the fact that someone with a serious disease does not always have the luxury of time when it comes to the maturation of data. Three major approaches have been established to accomplish safe but faster access to promising therapies: Fast Track, Accelerated Approval, and Priority Review (FDA, 2011).

Fast Track designation is given to drugs (at the pharmaceutical company's request) that are deemed to fill an unmet need in a serious disease. The designation may be given when no other drug exists to treat an illness or when the agent in question may avoid serious side effects of a current treatment. The status may also be given when a drug may treat a serious toxicity of a current therapy. A Fast Track designation typically allows for closer and more frequent FDA involvement with the pharmaceutical company in the drug and clinical trial development plans, and establishes eligibility for Accelerated Approval and possible Priority Review. Requests submitted for Fast Track designations are evaluated by the FDA, and decisions are made within 60 days (FDA, 2011).

Accelerated Approval is a regulation adopted by the FDA in 1992 to provide for earlier approval of agents that meet an unmet need in serious illness based on a surrogate endpoint. The surrogate endpoint proposed by the drug company must be accepted by the FDA as representing a clinically meaningful outcome. For

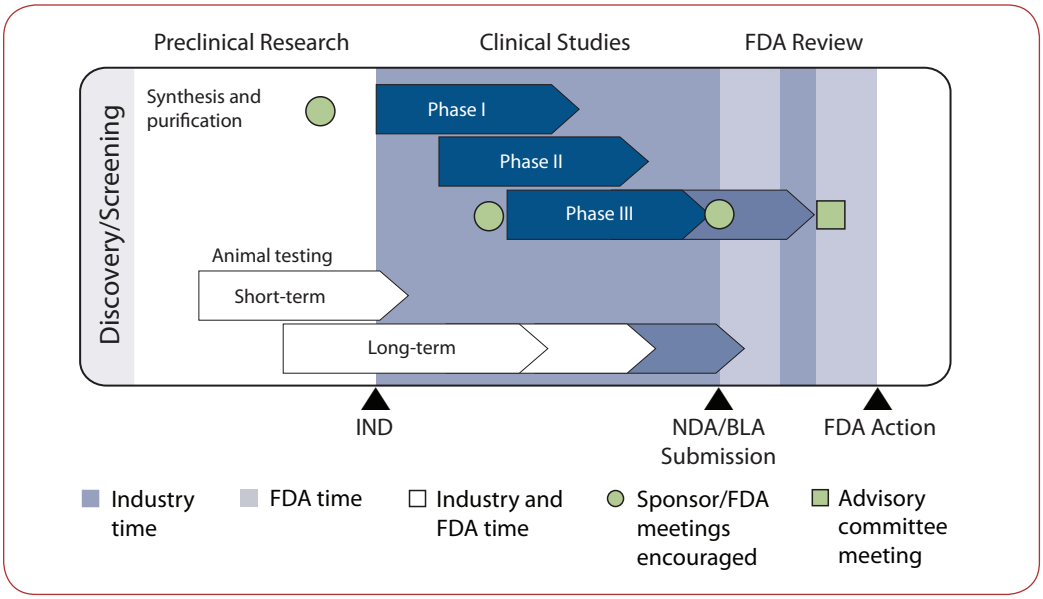

Figure 1. FDA New Drug Development & Review process (www.fda.gov).
BLA = Biologics License Application; FDA = US Food and Drug Administration; IND = Investigational New Drug; NDA = New Drug Application.

Table 1. Clinical Trial Endpoints and Regulatory Approval

Endpoint	Definition	Use in regulatory approval	Comments
Overall survival	The time from random assignment until the patient's death occurs (regardless of cause)	Endpoint identified as "gold standard" for seeking regular drug approval	Requires larger patient numbers Longer follow-up intervals Subsequent cancer treatment can confound results
Disease-free survival	The time from random assignment to recurrence or death from any disease	May be a primary endpoint for approval in adjuvant studies Used as surrogate endpoint for accelerated approval if survival benefits of other therapies have been established	Beneficial when overall survival anticipated to be long and impractical to measure Timing of tumor assessments can result in bias
Objective response rate	Typically uses radiographic or other measurement to determine percent change in tumor size during a specified time period	May be used as surrogate endpoint for accelerated approval in refractory disease states	Allows shorter time interval for evaluation Single-arm studies possible Incomplete measure of drug activity
Progression-free survival	Measures from time of randomization to documented tumor progression or death	May be used as surrogate endpoint for accelerated approval as well as for regular approval in specific disease settings	Allows for smaller patient sample and shorter follow-up Results not impacted by crossover or subsequent treatment Risk inability to statistically validate in future studies

Note. Information from McKee et al. (2010); Sridhara et al. (2010).

example, a drug that was shown to consistently result in a significant decrease in tumor size could be considered a reasonable predictor of long-term clinical benefit in some illnesses, instead of waiting for the data to confirm that the decrease actually results in patients living longer. Confirmatory trials are required with Accelerated Approval in order to demonstrate that the predicted benefit was actually seen. If data from the confirmatory trials are insufficient or absent, the FDA has the authority to withdraw approval (FDA, 2011).

Priority Review designation is given by the FDA to new agents that are believed to offer major advancement in treatment, as in cases where no treatment currently exists. As opposed to the 10-month time frame established for the Standard Review of a new drug application, a Priority Review designation means that the FDA will complete its review in 6 months. Table 1 reviews the various endpoints utilized in clinical trials and how they may be suited for the different types of FDA approval.

Evaluating the Evidence—Waiting for the Next Train

The confirmatory trials required by the FDA following the accelerated approval of bevacizumab as a first-line treatment for metastatic breast cancer in combination with paclitaxel were the AVADO and RIBBON-1 trials. The results of these phase III studies have been detailed by Georgia Litsas in the review on page 270.

The median progression-free survival (PFS) difference of 5.5 months seen in the E2100 trial had been the surrogate endpoint accepted by the FDA for accelerated approval (FDA, 2008). The confirmatory trials, as reported, did not demonstrate a statistically significant difference in overall survival and "failed to confirm the magnitude of the PFS treatment effect observed in the E2100 trial" (FDA, 2010). It was the review of the confirmatory trial data to establish the direct clinical benefit, as opposed to the surrogate endpoint of PFS used for accelerated approval, that led to the current FDA recommendation.

Is There Another Train?

The purpose of this paper is to neither oppose nor support the recommendation of the FDA. Instead, the intent is to provide a brief overview of how evidence-based practice principles are applied in the approval of new agents by the FDA. When as clinicians, we face emotionally charged issues such as the decision to revoke the approval of a drug that is used to treat a serious illness, it is important that we remember to step back and clearly evaluate the evidence before us. We must ask the following questions:

- What is the evidence?
- Do we have *all* the evidence?
- Are there additional questions that should be asked?
- What will provide the best possible outcome for the patients we treat?

As we strive to provide excellence in clinical care for our patients by utilizing evidence-based practice, we need to understand how clinical trials are designed and how endpoints are used in determining a "positive" clinical trial. This is often quite challenging, and the developments with bevacizumab are illustrative of this. Interpretation of data is difficult as patients with metastatic breast cancer average between three and six lines of treatment. Trials with crossover arms can confound survival analyses. Endpoints most critical to patients include survival, but they also include tolerability, symptom relief, convenience, and time until initiation of next treatment. These latter endpoints are not routinely quantified in clinical trials, which makes it challenging to ascertain the real worthiness of new agents and regimens (Burstein, 2011).

It has been suggested that perhaps the approval process has become too lenient, and that more stringent or indication-specific guidelines need to be in place for new drug approval (McKee, Farrell, Pazdur, & Woodcock, 2010; Melton, 2011; Sridhara et al., 2010). The validity of using a statistically significant *p* value as the sole indicator of a positive clinical trial is in question (Ocana & Tannock, 2011). Hopefully, as research advances in the field of patient-directed therapy based on pretreatment identified tumor targets, there will be fewer concerns regarding the potential for "runaway trains."

DISCLOSURE

Peg Esper has served on an advisory board for Genentech.

REFERENCES

Burstein, H. J. (2011). Bevacizumab for advanced breast cancer: All tied up with a RIBBON? *Journal of Clinical Oncology*, *29*, 1232–1235. doi:10.1200/JCO.2010.33.2684

McKee, A. E., Farrell, A. T., Pazdur, R., & Woodcock, J. (2010). The role of the U.S. Food and Drug Administration review process: Clinical trial endpoints in oncology. *Oncologist, 15*(suppl 1), 13–18. doi:10.1634/theoncologist.2010-S1-13

Melton, C. (2011). FDA panel recommends stricter process for accelerated approval of cancer drugs. *The Oncology Nurse, 4*(2), 54. Retrieved from http://www.theoncologynurse.com/article/fda-panel-recommends-stricter-process-accelerated-approval-cancer-drugs

Miller, K., Wang, M., Gralow, J., Dickler, M., Cobleigh, M., Perez, E. A., . . . Davidson, N. E. (2007). Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *The New England Journal of Medicine, 357*(26), 2666–2676.

Ocana, A., & Tannock, I. (2011). When are "positive" clinical trials in oncology truly positive? *Journal of the National Cancer Institute, 103*(1), 16–20. doi:10.1093/jnci/djq463

Sridhara, R., Johnson, J. R., Justice, R., Keegan, P., Chakravarty, A., & Pazdur, R. (2010). Review of oncology and hematology drug product approvals at the US Food and Drug Administration between July 2005 and December 2007. *Journal of the National Cancer Institute, 102*(4), 230–243. doi:10.1093/jnci/djp515

U.S. Department of Heajlth and Human Services, Food and Drug Administration. (2008). Label and approval history. Retrieved from http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2008/125085s091ltr.pdf

U.S. Department of Health and Human Services, FDA Center for Drug Evaluation and Research. (2010). Memorandum to the file BLA 125085 Avastin (bevacizumab), December 15, 2010. Retrieved from http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM237171.pdf

U.S. Department of Health and Human Services, Food and Drug Administration. (2011). Fast Track, accelerated approval and priority review. Accelerating availability of new drugs for patients with serious disease. Retrieved from http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm