



Pursuing Accelerated Approval in Oncology Indications: Regulatory, Medical and Logistical Considerations

May 2016

Cheryl Askew, PhD

Senior Director, Global Project Management, Hematology/Oncology

Philippe Chahinian, MD

Executive Medical Director, Hematology/Oncology

Carolyn Finkle

Senior Vice President, Regulatory Affairs

Eric Hailman, MD, PhD

Senior Medical Director, Medical & Scientific Affairs, Hematology/Oncology

Donna Levy

Principal Statistician

Thomas Moehler, MD, PhD

Vice President, Medical & Scientific Affairs, Hematology/Oncology

Robert Millham

Senior Vice President & General Manager, Hematology/Oncology

Joseph O'Connell, MD

Vice President & Global Therapeutic Head, Hematology/Oncology

Dannelle Palmer, MBA, PMP

Vice President, Global Project Management, Hematology/Oncology

Shannon Williams

Senior Director, Regulatory Affairs

Pursuing Accelerated Approval in Oncology Indications: Regulatory, Medical and Logistical Considerations



Table of Contents

| | |
|--|----|
| Expedited Development/Review Options in the US | 4 |
| Is Accelerated Approval a Misnomer? | 5 |
| The Risks of Conditional Approval | 6 |
| Planning for Accelerated Approval | 6 |
| Executing Trials for Accelerated Approval | 10 |
| Critical Success Factors | 11 |
| Conclusion..... | 12 |
| References | 12 |
| About inVentiv Health | 12 |

Pursuing Accelerated Approval in Oncology Indications: Regulatory, Medical and Logistical Considerations

For many years, sponsors in the US have been able to apply for Accelerated Approval from regulators based on a surrogate endpoint. This approach is intended to speed products to market that treat serious or life-threatening conditions and that offer a benefit over current treatments. Similarly, in the EU, a conditional marketing authorization can be granted to drugs that fill an unmet need and treat rare or life-threatening diseases using less clinical data than would typically be required. Both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) require that the sponsor complete certain post-authorization study obligations. The pathway for Accelerated Approval is well established in these markets, and industry experts have gained considerable experience in guiding products through the process.

In the US, from the inception of the Accelerated Approval program in 1992 through 2015, 97 drugs have been granted approval via this pathway, and another 52 supplemental Accelerated Approvals have been granted. Nearly half have been in oncology (46 percent in the initial applications and 62 percent in the supplemental applications). The proportion of Accelerated Approvals related to oncology rose to 78 percent (22 of 28) between 2011 and 2015.

Overall, since 2006, close to 10 percent of the new drug approvals granted by the FDA have been via the Accelerated Approval pathway. In 2015, the FDA granted a record 45 drug approvals, with 6 approved under the Accelerated Approval program. In 2015, EMA granted 39 authorizations, with 5, or 13 percent, under conditional authorization.

As a result, patients have benefited from earlier access to critical medications, and sponsors have enjoyed the accompanying market advantage. The benefits of Accelerated Approval are not inexhaustible, however, and the decision to seek this program should be made carefully with an understanding of regulatory, medical, and logistical implications. Here we review a number of those considerations, offer advice on how to follow the regulatory pathway most expeditiously, and highlight examples that illustrate both the advantages and challenges of pursuing Accelerated Approval.

US Regulatory Definitions

Priority Review Designation: Directs attention and resources within the FDA to evaluation applications for drugs that could offer significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions. The FDA's goal is to take action on an application within six months (compared to 10 months under standard review).

Accelerated Approval: A pathway that allows drugs targeting serious or life-threatening disease and that fulfill an unmet medical need to be approved based on a surrogate endpoint, provided that the company conducts a confirmatory trial to verify the anticipated clinical benefit.

Fast Track Designation: An approval pathway for drugs intended to treat serious conditions that have the potential (based on nonclinical and clinical data) to address an unmet need, or for drugs that treat infectious disease; affords Rolling Review (in which sections of the application are submitted as ready); may be eligible for Accelerated Approval or Priority Review. Provides for more frequent communications with the FDA.

Breakthrough Therapy Designation: An approval pathway for treatments that demonstrate the potential to address unmet medical needs related to life-threatening diseases or conditions; provides eligibility for Priority Review or Rolling Review. Provides the benefits of Fast Track designation along with intensive guidance from the FDA.

Meaningful Advantage over other Therapies: With respect to a serious condition, this involves providing improved diagnosis or detection, mitigating or preventing a treatment-related side effect or serious adverse event, or preventing the condition or reducing the likelihood that it will progress to a more serious condition.

Serious Condition: A disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent and recurrent. (Guidance, for Industry, Expedited Programs for Serious Conditions—Drugs & Biologics, FDA, May 2014)

Pursuing Accelerated Approval in Oncology Indications: Regulatory, Medical and Logistical Considerations

Expedited Development/Review Options in the US

The US Food & Drug Administration (FDA) has provided four different processes by which drug sponsors can speed the delivery of drugs for unmet medical needs or serious conditions to market:

- Priority Review Designation
- Accelerated Approval
- Fast Track Designation
- Breakthrough Therapy Designation

Note, the Orphan Drug program provides for orphan status to products intended for safe and effective treatment of rare diseases and disorders that affect fewer than 200,000 people in the US. These products are afforded an expedited development program as well.

These options are not mutually exclusive; it is possible, for example, that a drug receiving Fast Track designation can also be eligible for Accelerated Approval or Priority Review. Fast Track designation may be afforded to a drug intended to treat a serious disease for which nonclinical or clinical data is available demonstrating the potential to address the unmet need. In addition, the Breakthrough Therapy Designation program may apply to the drugs intended to treat life-threatening disease if there is preliminary clinical evidence available indicating the drug may demonstrate substantial improvement over available therapies on a clinically significant endpoint and thus, meet unmet medical needs. This program provides sponsors with intensive FDA guidance by senior FDA managers on the drug development program. Each approach, however, has defining characteristics, as outlined in the FDA's document, *Guidance for Industry, Expedited Programs for Serious Conditions—Drugs & Biologics*, published in May 2014.

EMA Regulatory Definitions

PRIME Designation: A regulatory scheme (**PR**ioity **ME**dicines) by which products that have the potential to address an unmet medical need can receive accelerated assessment and early engagement with health authorities. Preliminary (proof of concept) clinical data must show the potential to address this need and bring a major therapeutic advantage to patients and there must be evidence of clinical response in patients (i.e., generated in exploratory clinical studies).

Pursuing Accelerated Approval in Oncology Indications: Regulatory, Medical and Logistical Considerations



Multiple, Expedited Designations

Daratumumab (Darzalex™, marketed by Janssen Biotech), the first monoclonal antibody approved for the treatment of multiple myeloma, was granted Accelerated Approval in November 2015 in the US for patients who have received at least three prior treatments. Approval was based on two open-label studies evaluating response rates in patients with relapsed or refractory multiple myeloma treated with daratumumab monotherapy. The two studies enrolled 106 and 42 patients, yielding response rates of 29%¹ and 36%, respectively.² The product also received Breakthrough Designation, Priority Review, and Orphan Drug Designation. A condition of the Accelerated Approval was the requirement to conduct a multicenter, randomized trial establishing the superiority of daratumumab over standard therapy to verify and describe the clinical benefit.

¹Daratumumab achieves 29.2% overall response rate in heavily pre-treated patients with multiple myeloma," News-Medical.net, May 30, 2015.

²Lokhorst, H. M., Plesner, T., Laubach, J. P., Nahi, H., Gimsing, P., Hansson, M., ... & van de Donk, N. W. (2015). Targeting CD38 with daratumumab monotherapy in multiple myeloma. *New England Journal of Medicine*, 373(13), 1207-1219.

The Accelerated Approval program was started in response to the AIDS epidemic, when research in the field was progressing rapidly but new, life-saving drugs were not being made available to patients quickly enough. The shift toward oncology drugs reflects a similar environment, when scientific advances are producing new anticancer drugs that represent significant advances for patients who have exhausted other treatment options and/or who have molecularly defined cancers amenable to targeted therapy.

The distinguishing features of Accelerated Approval, as laid out in the FDA guidance document, are that:

- The drug must treat a serious condition and provide a meaningful advantage over available therapies. (Note: A marketed product that has gone through Accelerated Approval but that has not yet verified clinical benefit with its post-marketing trials is not considered "existing therapy" in this context. Thus, a sponsor can seek Accelerated Approval even if

another drug in the class is on the market—if that product has not yet attained full approval.)

- Approval is based on demonstration of an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit as measured by more usual endpoints.
- Confirmatory trials are required to verify and describe the anticipated effect on Irreversible Morbidity or Mortality (IMM). If the anticipated effect is not proven, the product's label may be changed or the project may be subject to expedited withdrawal from the market for that indication.
- The timeline for FDA review is not specified (as it is for Fast Track, Breakthrough Therapy, and Priority Review designations).

The first oncology treatment approved via the Accelerated Approval process in the US was bicalutamide (Casodex®), approved in 1994 in combination with a luteinizing hormone releasing hormone (LHRH) analogue for prostate cancer, based on a randomized trial with time to progression as the approval endpoint. Since then, the Accelerated Approval program has been instrumental in the timely approval of a large number of cancer therapies, moving from more established types of therapy such as hormonal and chemotherapy agents to novel classes of cancer therapy such as monoclonal antibodies, tyrosine kinase inhibitors, and immune checkpoint inhibitors.

Is Accelerated Approval a Misnomer?

The principal advantage for sponsors to seeking Accelerated Approval is that the drug may be approved for marketing prior to the completion of the Phase III trial. Data from Phase II trials (or preliminary data from Phase III) must indicate an expected clinical benefit based on a surrogate endpoint of efficacy. This provision, of course, allows companies to launch products into the market sooner than they would otherwise be able and, usually, to enjoy "first mover advantage."

The ability to proceed on the basis of data from a surrogate endpoint is particularly valuable in oncology where demonstrating the drug's effect on Overall Survival (OS) can require lengthy—and generally large—trials. Today, in the era of targeted agents that provide a greater margin of benefit than was achievable in the past, it can take quite a long time to demonstrate incremental

Pursuing Accelerated Approval in Oncology Indications: Regulatory, Medical and Logistical Considerations

gains in Progression Free Survival (PFS) and OS. For example, the median PFS benefit reported in the control arm of a Non-Small Cell Lung Cancer (NSCLC) trial today may be 10 months, compared to 10 weeks for a chemotherapy product of a decade ago.

Whether Accelerated Approval actually speeds regulatory approval time is a question worthy of current analysis. A study performed on drugs approved between 1995 and 2008 found that the median approval for nine biologic New Molecular Entities (NMEs) took longer via Accelerated Approval than via Regular Approval (9.2 months vs. 6.7 months).¹ The study included very few targeted biologics or monoclonal antibodies, and so begs the question as to what a similar analysis that covers today's product mix, would show. The same study did reveal, however, that the median development time for nonbiologic NMEs was markedly shorter via Accelerated Approval than Regular Approval: 5.5 years vs. 7.3 years. To the extent that this holds today, the shortened development time via Accelerated Approval offers a tremendous advantage for sponsors. Hence, while the official name may be a misnomer, it may be appropriate to think of this as an Accelerated Path to Approval.

Another benefit to Accelerated Approval for sponsors is that they are able to consult with the FDA more often and at higher levels within the agency throughout the development process. (The same is true for applications submitted to the EMA with the PRIME Designation.) Also, the FDA is often willing to make some concessions in what is required in the Chemistry, Manufacturing & Controls (CMC) package for the New Drug Application (NDA) or the Biologics License Application (BLA), the production requirements, and the post-approval requirements. The Office of Pharmaceutical Quality works in concert with the agency's review division in making these decisions, and they can often be swayed by the Lead Medical Reviewer or Division Director. For example, a sponsor may be allowed to provide stability data in real time, as it becomes available, and the range of specifications deemed acceptable might be slightly wider than what would otherwise be required.

The Risks of Conditional Approval

The greatest risk for sponsors in seeking Accelerated Approval is that the confirmatory trial might fail to confirm the intended clinical benefit or reveals a new safety issue not detected in the earlier, smaller, trial population.

When that is the case, approval is withdrawn and the sponsor will be required to either (1) withdraw the drug from the market completely or (2) revise the product's label to reflect new efficacy and/or safety data. The less precedent there is surrounding the biomarker or method of action, the greater the risk that this will be the case. Regulators and even physicians may be "forgiving" when this happens, but the general public will probably not be clued in to the fact that the approval was conditional. Therefore, there could be some fallout that affects the sponsor's public image.

Also, because pre-launch and launch activities will have been conducted based upon the initial Accelerated Approval label, potential label changes may have significant impact on the strategies being implemented across the commercial and medical affairs organizations. The investment in this work is made at considerable risk to the sponsor; if significant label changes are required or approval is not granted, it will have been for naught. (See "Launch Preparation.")

The Risk Has a Downside

In 2008, bevacizumab (Avastin® from Genentech) received accelerated approval for use in metastatic breast cancer in combination with paclitaxel chemotherapy for patients who had not previously received chemotherapy for metastatic HER2-negative breast cancer. Approval was based on progression free survival as the surrogate endpoint. However, the Phase III trial failed to demonstrate an improvement in overall survival, so in 2011, the FDA withdrew approval for Avastin for breast cancer.

Planning for Accelerated Approval

The Decision Process

The decision to apply for Accelerated Approval is not always clear-cut. Rather, it requires careful analysis of the product's market potential, the chances of meeting the qualifying criteria, the strength of the data in hand, and the logistical challenges of going to market early.

In some cases, when a drug addresses a well-known target in a setting of unmet need and early clinical data are cause for great confidence in the compound,

Pursuing Accelerated Approval in Oncology Indications: Regulatory, Medical and Logistical Considerations

sponsors can foresee the possibility that a drug might qualify for Accelerated Approval. In others, the possibility may only become clear upon discovery of compelling new data down the road. In either case, we recommend that sponsors proceed as follows, calling upon expert advisors as needed:

- On the basis of a market evaluation, perform a cost/benefit analysis of the possible routes to market. Weigh the risks involved against the market potential in the indication.
- Tap the commercial team for insights into stakeholder needs, the patient profile, and the competitive landscape.
- Assess whether the therapy will qualify with regulators. Does it meet the requirements of treating a serious condition or providing a meaningful advantage over existing treatment?
- Evaluate the acceptability of the surrogate endpoint as the basis for accelerated approval. This evaluation should involve studying the regulatory guidance closely and analyzing the precedents that have been set in the same therapeutic area.
- Keep a watchful eye on the market in the process. If other therapies in the class are apt to come to market first, a sponsor can lose its “window of opportunity” to meet the regulators’ criteria. Citing precedents that are even a few years old may invalidate an argument for Accelerated Approval in the eyes of regulators.
- Request a meeting with regulators, submit a package to them demonstrating how the Accelerated Approval requirements will be met, and prepare a briefing document for use in the meeting.

Selecting a Surrogate Endpoint

Selecting the most appropriate surrogate endpoint is a critical step in gaining Accelerated Approval, and trials have been known to fail due to the use of the wrong endpoint. To be viable, the endpoint chosen must be reflective of the true clinical benefit—and that relationship must be validated. In specific indications, such as in early-stage breast cancer, the FDA has made clear, specific recommendations on surrogate endpoints that can be used for Accelerated Approval.² Regardless of the specificity of industry guidance documents, the best approach is to work closely with the FDA, starting with a pre-meeting in which the agency can provide direction.

Also, of course, the surrogate endpoint and the actual endpoint must be appropriate for the indication and the intended population; they cannot always be extrapolated from one indication or population to another. For example, PFS is accepted as a surrogate endpoint for Overall Survival (OS) in some oncology indications and not others. Therefore, each surrogate endpoint must be validated specifically for each intervention.

Planning for Accelerated Approval Early vs. Later

The experiences of two sponsors preparing for Accelerated Approval for drugs to treat NSCLC have been very different because of when they were able to make the decision to apply.

Genentech knew early on what mutation was the driver for overall survival in the disease, so they planned to apply for Accelerated Approval with Alectinib (Alecensa™) from the outset. The company was able to design its Phase I trial such that it could move quickly into pivotal studies.

In contrast, Pfizer did not discover the mechanism of action in Crizotinib (Xalkori®), until the drug was in a safety trial. Consequently, the study morphed into a pivotal, single-arm registration trial that has had numerous amendments over several years.

There is always a chance that the selected surrogate endpoint will fail its validation test and, when that is the case, the sponsor must determine whether the fault lies with the selection of surrogate endpoint or with the efficacy of the drug itself. If the surrogate endpoint was a solid index of therapeutic benefit, then the value of the drug would be called into question. If, however, there is some question as to the appropriateness of the surrogate endpoint, a sponsor may elect to continue the development program, studying the drug’s effect on the final endpoint.

Surrogates that are not within the causal pathway of the disease process or those having mechanisms of action that are independent of the disease process are often unreliable.

Pursuing Accelerated Approval in Oncology Indications: Regulatory, Medical and Logistical Considerations

Within oncology, many researchers consider OS to be the gold standard endpoint due to the fact that it is reliable and the endpoint (death) is an unequivocal measure. It is not, however, the most practical endpoint to study, especially in oncology, because of long follow-up periods and because other treatments (taken after the patient leaves the study or in crossover studies) can confound the analysis.³ For these reasons, surrogate endpoints are used as primary endpoints for Accelerated Approval.

Currently, tumor response, as measured by Objective Response Rate (ORR), is a commonly used surrogate endpoint for overall survival in oncology as it *usually* predicts clinical benefit with malignancies, as demonstrated via a meta-analysis of colorectal cancer trials. This is not always the case, however, as with extensive NSCLC⁴ or gastrointestinal stromal tumors (GIST). Nor does the ORR (as measured by RECIST⁵) in GIST correlate well with Time to Progression (TTP) or Disease Specific Survival (DSS).⁶ When ORR is used as a surrogate, the response should be confirmed independently by an expert review panel.

The Need for Independent Confirmation with ORR

Osimertinib (Tagrisso™ from AstraZeneca) is a third-generation oral EGFR tyrosine kinase inhibitor approved in November 2015 for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy. The Accelerated Approval was based on two multicenter, single-arm, open-label clinical trials in patients with metastatic EGFR T790M mutation-positive NSCLC who had progressed on prior systemic therapy, including EGFR TKI. The major efficacy outcome measure was objective response rate (ORR) according to RECIST v1.1 as evaluated by a Blinded Independent Central Review (BICR). Duration of response (DOR) was an additional outcome measure.

Disease Evaluation Definitions

Disease-Free Survival (DFS): Time from initial treatment to relapse, progression or death. Can also be called relapse-free survival.

Duration of Response (DOR): Time from initial response (complete (CR) or partial (PR)) until progression or death.

Objective Response Rate (ORR): Sum of partial response plus complete response with respect to the specific population.

Overall Survival (OS): Time from randomization/enrollment to death. If no event is reported, patients are censored at their last date of contact.

Progression-Free Survival (PFS): Time from randomization/enrollment to progression or death. If no event is reported, patients are censored at their last evaluable tumor assessment.

Time to Progression (TTP): Time from randomization/enrollment to progression. If no event is reported, patients, in general, are censored at their last evaluable tumor assessment.

Pursuing Accelerated Approval in Oncology Indications: Regulatory, Medical and Logistical Considerations

Other surrogate endpoints used in oncology trials are: Progression-Free Survival (PFS), Disease-Free Survival (DFS), and Time-to-Progression (TTP). PFS is growing in popularity⁷, and TTP can be useful, but only when evaluated in a randomized trial to evaluate the rate of disease progression in the absence of a treatment effect on overall survival.

With the advent of non-cytotoxic drugs, where the outcome is often to stabilize the disease rather than to shrink the size of tumors, there is a need to validate new surrogate endpoints that can assess the drug's effect on the target population.

Patient Selection

The goal in defining the target population should be to identify the patients for whom the drug will produce a good response rate. The higher the response rate, the greater the likelihood that regulators will grant Accelerated Approval. Biomarkers are a characteristic that is objectively measured as an indicator of normal biological, pathogenic, or pharmacologic responses to a therapeutic intervention. Biomarkers can be used to identify the patient population that will benefit from the potential therapy. Planned biomarker evaluations in Phase II studies may allow for the design of a more efficient Phase III trial. The population may be defined sufficiently using clinical parameters, such as specifying failure on prior therapy. Otherwise, the trial can be enriched by using inclusion criteria to specify the patients who express a specific target (via a biomarker) that will predict a good response. One option is to explore several biomarkers in expansion cohorts within a Phase I study and then narrow the patient profile to be enrolled in the registrational trial.

If a target population is defined by a biomarker which is not detected with a standard clinical assay, it will be necessary to plan for parallel development of the biomarker and submission for approval as a companion diagnostic test. This route to accelerated approval requires significant investment of resources and careful planning, but has gained momentum. Recent examples (since 2014) of accelerated approvals in oncology that were linked to approvals of companion diagnostic tests include Lynparza (olaparib), with the BRCAAnalysis CDx assay for germline BRCA mutations; Keytruda (pembrolizumab), with the PD-L1 IHC 22C3 pharmDx test for PD-L1 expression; and Tagrisso (osimertinib) with the Roche cobas EGFR v2 test for the EGFR T790M mutation.

Either way, it is important to have a clear target population and to ensure that sites and investigators understand the importance of the population definition. More than one trial has failed because too many patients were included who did not meet the inclusion criteria.

The Need to Define the Patient Population Narrowly

Gefitinib (Iressa[®] from AstraZeneca) was granted Accelerated Approval for marketing in the US for NSCLC in 2003. The surrogate endpoint was tumor response rate. However, the product was withdrawn after two studies failed to show an improvement in overall survival. Subsequently, in 2015, the product was approved for NSCLC for tumors that contain specific types of epidermal growth factor receptor (EGFR) gene mutations with sensitizing EGFR mutations. This example demonstrates the need to specifically identify the mechanism of action so that the target patient population can be narrowed appropriately to ensure that follow-up studies will demonstrate the desired results achieved during the initial studies.

Study Design

A common route to Accelerated Approval in oncology is a single-arm trial using response rate as an endpoint, generally in a patient population defined by resistance to approved therapy, i.e., with a clear, unmet, medical need. Many of these have been Phase II trials, although recently large Phase I trials have led to Accelerated Approval based on response rate (e.g., Keytruda[®], pembrolizumab). This allows rapid clinical development toward an initial approval in a small patient population, with subsequent trials leading to full approval in a larger population in earlier lines of therapy.

We recommend that sponsors:

- Evaluate each situation uniquely; it is unwise—and potentially disastrous—to “cut and paste” the trial design of the current standard of care.
- Consult with regulators early on in the trial design to make sure that it will meet their requirements; they will not look favorably on submissions that have undergone multiple revisions to get it right.

Pursuing Accelerated Approval in Oncology Indications: Regulatory, Medical and Logistical Considerations



- Ensure that the health outcomes of the trial will meet the needs of payers who are increasingly looking for demonstration of benefits to the patient's well-being and function.
- As protocol changes are quite common in these studies, adding complexity to patient enrollment, sponsors should consider adaptive trial designs, such as providing for expansion cohorts to verify signals of activity in initially enrolled patients.

Safety/Adverse Events

The review of safety data and adverse events reports is an important part of the FDA's process for all marketing approvals, and Accelerated Approval is no exception. Researchers have found (based on the aforementioned FDA study conducted on Accelerated Approvals completed between 1995 and 2008) that the process resulted in the market entry of drugs that were generally safe and effective.⁸

However, the agency's review is often based on small Phase II studies, and sufficient data may not be available at the time to fully assess toxicity.⁹ And, there is always the risk that uncommon or previously unrecognized adverse events, as well as, rare drug interactions, may be missed until the drug becomes more widely used.¹⁰ One example is the previously unrecognized thromboembolic toxicity of irinotecan.¹¹

Geographic Considerations

One of the first orders of business in developing the overall development strategy is to determine which countries offer an accelerated route to approval. At this writing, the list includes: the US, all EU member states, and Japan. Usually, sponsors plan to run Phase II studies in those regions, and then they run the confirmatory trial in an expanded list of secondary countries. Part of this decision will depend upon whether the selected surrogate endpoint is harmonized across countries. When that is not the case, the sponsor must narrow the geographic scope of the Phase II trial and wait for the confirmatory trial to launch in those countries that did not accept the surrogate endpoint.

Executing Trials for Accelerated Approval

Pursuing Accelerated Approval naturally compresses the time frame for preclinical, clinical and pre-commercial activities, requiring careful planning and coordination so that there are no unnecessary, self-imposed, hold ups along the way.

Pre-Clinical

Preparation of the CMC package, which will usually be on the product's critical path, must necessarily begin earlier when Accelerated Approval is sought than when regular approval is the goal. Sponsors will likely have to be performing CMC work in parallel with early clinical work in order to have a final formulation ready in time for submission. Since there is always a chance that some aspect of the CMC work fails, it is prudent to have a risk mitigation plan in place for developing the necessary CMC. Having a backup plan running in parallel is highly recommended.

Also, regulators require stability data on what will be the commercial product, so the active pharmaceutical ingredients and manufacturing process must be set earlier than with trials for regular approval.

Early Stage Trials

Before defining the endpoint for Phase II, sponsors must determine if it will be accepted as surrogate for durable benefits such as PFS and OS.

While the novel therapies that qualify for Accelerated Approval are generally of interest to investigators, trial participation can be challenging for them. Investigators must be prepared to deal with complex protocols, many unknowns, more administrative work, and more demanding patient relations. And because patient enrollment may be very strong for such trials, sponsors should ensure that sites have sufficient data entry and screening support.

Because the timeframe is condensed, interim data and final analyses should be generated in submission-ready format, thus avoiding the time-consuming step of reformatting them.

Pursuing Accelerated Approval in Oncology Indications: Regulatory, Medical and Logistical Considerations

The Confirmatory Study

The Phase III confirmatory study, which must be started by the time of marketing approval, must be a gold-standard trial conducted in accordance with the Clinical Trial Authorizations and Investigational New Drug Provisions. The product's efficacy must be measured in terms of an actual endpoint (as opposed to a surrogate endpoint) such as disease-free survival or overall survival.

Early planning is critical to success. The design for the confirmatory trial should be created well in advance, and any third-party vendors (such as Contract Research Organizations (CROs)) should also be prepared early.

Very likely, the most scientifically-minded investigators will be less interested in participating in the confirmatory trial than in the earlier phase study since the product is already approved, so it may be necessary to turn to community care providers as sites. These sites typically have less experience with trials and less administrative support, so they may require extra time and additional training.

Launch Preparation

Ordinarily, companies begin their pre-launch activities one to two years in advance of the expected marketing approval date. However, when they seek Accelerated Approval, companies are working within a condensed time frame between filing and approval, so they will begin many of their commercial preparations prior to even filing the application. Thus, these activities are done “at risk,” implying work proceeds without evidence supporting a positive approval, and work is performed even though significant changes may be required when the data – and approved label – become available. Further, the label approval may also come with unexpected restrictions to use or distribution.

Given the undefined review timeline for Accelerated Approval, it is possible that approval can happen sooner than expected, and so it is advisable to prepare for a scenario where approval may occur three to four months post submission.

The list of necessary pre-launch activities is long, and requires the effort of the broad organization – including manufacturing, distribution, marketing, sales, medical affairs, and so on. Approximately 20 percent of the launch activities will be significantly impacted by Accelerated

Approval, which will need to be done earlier in a condensed manner or with additional risk. Examples include:

- Development of core promotional materials is accelerated and at risk. The FDA requires all promotional material and messages planned for the first 120 days post-launch of products granted Accelerated Approval to be submitted to OPDP prior to use.
- Key Opinion Leader (KOL) community engagement through Medical Science Liaisons (MSLs) needs to be accelerated.
- Patient advocacy engagement and associated initiatives needs to be accelerated.
- Packaging needs to be accelerated, and is done at risk.
- Pricing and access strategy needs to be accelerated.
- Training of field teams needs to be accelerated.

To limit their exposure, companies can engage outsourcing partners – to not only support organizational planning and product-specific deliverables or materials, but to also support tactical execution in the field prior to launch (i.e., contract MSLs and disease state education). A flexible outsourcing strategy can alleviate the risk of investing in permanent resources, and all vendor contracts should be structured with appropriate clauses to minimize financial exposure should approval be delayed or denied.

Critical Success Factors

To ensure that they are able to take full advantage of the Accelerated Approval process and optimize the potential for reducing time to market, sponsors should:

- Use the opportunity afforded by the pathway to be in regular conversations with higher levels of staff within the regulatory agencies. The EMA has recently launched PRIME, a program to accelerate medicines of major public health interest. A key feature is enhanced scientific and regulatory support for sponsors.
- Have the prospect of Accelerated Approval in mind from the outset of a development program and prepare contingency plans to be used in the event that it becomes a possibility.
- Similarly, from the first day of the clinical work, ensure that all data are formatted to be “submission ready” to save a step prior to submission.

Pursuing Accelerated Approval in Oncology Indications: Regulatory, Medical and Logistical Considerations



- Define the patient population to achieve a high response rate. This definition may be possible using clinical parameters or inclusion criteria specifying patients who express a specific target, identified via a biomarker.
- Give careful consideration to identifying the surrogate endpoint that will provide an index of the clinical benefit.
- Consult the commercial team in Phase I to ensure that the product will offer a clinical benefit beyond what is—or will be—on the market. The development must proceed on the basis of what will be most important to patients, physicians, and payers.
- Do not simply “copy” the study methodology or endpoint used by competitors. The study design and the endpoint selected must be validated as appropriate for the drug, the indication, and the intended population.
- Perform scenario planning based on what could come out of the confirmatory trial and be prepared to address any contingency.
- Begin pre-commercial preparations early—mitigating the risk through contract provisions with vendors.

CONCLUSION

Whether or not Accelerated Approval actually delivers remarkably faster review by the FDA, it does provide for improved communications with the agency that can be invaluable in ensuring that sponsors embark on the right development path. It also has been shown to shorten the development timeline dramatically as well as to give most successful applicants “first mover advantage” in the market. At the same time, it requires more careful planning and coordination across the development and pre-commercial activities within the sponsor organization. The earlier in the development process that sponsors are aware that seeking Accelerated Approval might be a viable possibility, the better.

REFERENCES

1. Lanthier, ML, et al., *JCO*, 2010; 28: e226-e227.
2. “Guidance for Industry: Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval,” FDA, October, 2014.
3. “Guidance for Industry: Clinical Endpoints for the Approval of Cancer Drugs and Biologics,” FDA, May, 2007.
4. Schilsky, R L, *JCO* 2003; 21:3718-3720.
5. Response Evaluation Criteria in Solid Tumors. To use RECIST, there must be at least one tumor that can be measured on X-rays, CT scans, or MRI scans. The types of response a patient can have are a complete response (CR), a partial response (PR), progressive disease (PD), and stable disease (SD).
6. Benjamin, R.S., et al. (2007). We should desist using RECIST, at least in GIST. *Journal of Clinical Oncology*, 25(13), 1760-1764.
7. Lebwohl, D. et. al, (2009). Progression-Free Survival: Gaining on Overall Survival as a Gold Standard and Accelerating Drug Development. *The Cancer Journal*, 15(5), 386-394.
8. Richey A E, et al., *JCO* 2009; 27: 4398-4405.
9. Richey A E, et al., *JCO* 2009; 27: 4398-4405.
10. Schilsky, R L, *JCO* 2003; 21:3718-3720.
11. Shah, et. al, *JCO* April 10, 2005 vol. 23 no. 11 2574-2576.

About inVentiv Health

inVentiv Health is a global professional services organization designed to help the biopharmaceutical industry deliver new drugs and therapies to market. Our combined Clinical Research Organization (CRO) and Contract Commercial Organization (CCO) is made up of more than 14,000 employees who have the ability to service clients in more than 90 countries. We offer a differentiated set of solutions designed to improve client performance and accelerate the process of bringing products to market. For more information, visit inVentivHealth.com.