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Project Confirm: Accelerated Drug Approvals for Chronic Myeloid Leukemia

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Abstract

The Food and Drug Administration (FDA) has an accelerated approval program for drugs which have been identified as promising treatments for serious conditions when the available data suggests that the benefits outweigh the foreseeable risks. All of the currently available treatment options for chronic myeloid leukemia (CML) initially went through the accelerated approval program. Here a group of academic CML experts, patient panelists and members from the FDA convened to discuss the utility of the accelerated approval program as it pertains to CML, and the utility of this program in future drug development in this disease. The results of that discussion are summarized here.

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Introduction

The regulatory approval of imatinib mesylate revolutionized the treatment of chronic myeloid leukemia (CML) and malignant hematology. Imatinib, and later the second and third generation tyrosine kinase inhibitors (TKI), turned a disease that was once a leading indication for allogeneic hematopoietic stem cell transplant into a chronic disease, with a life expectancy similar to that of the general population.(1) Some patients have now successfully stopped therapy and remain in remission (2–4). The United States (US) Food and Drug Administration (FDA) initially approved these TKIs through the accelerated approval program to provide quicker access to effective drugs.

In February 2022, a virtual panel was convened with academic CML experts and two patient advocates. The meeting was conducted as part of the FDA Oncology Center of Excellence's (OCE) Project Confirm, an initiative to improve discussion around the accelerated approval program. The scope of the discussion included the history of the accelerated approval program, its merits, its future use in the context of the evolving treatment landscape and unmet medical need in patients with CML. This manuscript summarizes our discussions and highlights the benefits, uncertainties and challenges facing future opportunities for accelerated approvals for CML therapies.

Emergence of a Targeted Therapy for CML

Treatment for CML was permanently altered in the 1990's when the development of imatinib resulted in significant improvements in short- and long-term outcomes for patients with CML. Prior to this, hydroxyurea and busulfan provided hematologic and symptomatic control and with interferon-alfa (IFN) cytogenetic remissions occurred, but complete cytogenetic responses (CCyR) were uncommon.(5, 6) Rates of CCyR increased with a combination of IFN and low-dose cytarabine but were still achieved by a minority of patients. The importance being that CCyR (and to some extent, partial cytogenetic responses (PCyR), which together with CCyR constituted major cytogenetic response (MCyR)) correlated with improved long-term survival. This established MCyR as surrogate marker for long-term outcome (7) and patients who did not achieve MCyR often progressed to accelerated and blast phase. Patients eligible for allogeneic stem cell transplant (SCT) had the potential for cure. However, the upper age limit to be eligible for a SCT at that time was 55 years and donor could be identified in less than 50% of cases, with an overall survival of approximately 50%.(8)

From the phase 1 imatinib trials, it appeared clear that the treatment landscape was about to change. Dr. Charlie Schiffer, one of the original imatinib investigators, described that time as "fun and stressful, but it was very apparent from day one that you were doing something special." It became evident that imatinib was extremely effective at treating CML, and the safety profile was considered quite acceptable although the long-term toxicities had not been clearly identified.(9) It was perceived by investigators as approaching the optimal concept for a cancer therapy: a targeted agent with high efficacy and minimal toxicity. The goal then became to make this treatment available to as many patients as possible but there were far more patients in need than there were clinical trials' slots.

Mel Mann, a patient panelist, considers himself fortunate to have enrolled on the phase 2 clinical trial for patients who had experienced resistance or intolerance to IFN-based therapy. He was diagnosed with chronic phase (CP)-CML in 1995 at the age of 37. He was treated with hydroxyurea and IFN, however did not have a donor for transplant. Mr. Mann was told his estimated life expectancy was three years. In 1998, 2.5 years after being diagnosed with CML, he enrolled on the imatinib clinical trial and promptly responded to therapy. Today, he is 65 years old and remains on imatinib. Mel recollects that some of his friends were not as fortunate as he was to be able to enroll on the early imatinib trial.

FDA Accelerated Approval Program

The FDA's Accelerated Approval Program expedites the availability of promising therapies for serious conditions. Approvals are based on surrogate or intermediate clinical endpoints that are reasonably likely to predict clinical benefit(10). Of all drugs approved through this program, 85% have been oncologic drugs.(11) Table 1 illustrates the accelerated approvals for CML.

MCyR was chosen as an efficacy endpoint for the early imatinib trials because the IFN data suggested improved long-term survival for patients who achieved this response.(12) The accelerated approval for imatinib after failure of IFN-alfa occurred when it appeared clear that the benefits of imatinib outweighed the risks known at the time. FDA's clinical review of the application concluded that "For each indication, …the effect of imatinib treatment measured by [hematologic response, complete hematologic response, MCyR, and CCyR] is either better than available therapy or is similar to available therapy, and that toxicity is less. It is important that physicians and patients understand…the known risks of treatment with imatinib and understand that additional toxicities from chronic treatment may yet be discovered."(10) The new drug application (NDA) was submitted to the FDA on 2/27/2001 and was approved on 5/10/2001, less than three months later providing availability of imatinib to thousands of patients who needed this potentially life-saving therapy. On 12/8/2003, imatinib was granted full approval when a phase III study demonstrated significantly improved progression-free survival compared to the control arm in patients with newly diagnosed disease (13).

Critics of the accelerated approval program argue that it provides standard use of a drug in clinical practice before the long-term safety profile is known. In the case of imatinib, however, many patients in the US survived because of this accelerated approval program and many patients did not in countries where imatinib was not yet available. Balancing early access to promising drugs while awaiting long-term safety data can be challenging, yet imatinib is a prime example of why the accelerated approval pathway exists. This holds particularly true in cancers that significantly shorten patients' life expectancy knowing that the full safety profile of a drug may take years to completely uncover. Close follow-up and vigilant post-accelerated approval data collection may help provide that importance balance. For example, cardiac failure was not identified as an adverse event (AE) of imatinib on initial approval in 2001 (14), but was added to the prescribing information as an infrequent AE in 2003, and ultimately elevated to a Warning and Precaution in 2007, based on long-term follow-up data (15). It could be argued that withholding life-saving treatment from

patients with a potentially fatal condition when the short-term safety profile is acceptable, and the long-term toxicities not known is not an ethical approach.

Second Generation TKIs (2GTKI)

At least 30-40% of patients treated with imatinib as first line of therapy eventually become resistant or intolerant.(16, 17) For many of them, the accelerated approval of 2GTKI was life-saving. The phase 2 trial of dasatinib after imatinib failure enrolled 387 patients in just six months and the phase 2 trial of nilotinib after imatinib failure enrolled 318 patients in 18 months underscoring the need for alternative therapies in patients who had not benefited from imatinib. (18)

The accelerated approval of these 2GTKI also paved the way for their study in the frontline setting. As imatinib had already brought the overall survival of CML to approximate that of the general population, survival endpoints were not realized. However, 2GTKI in the frontline induce greater rates of cytogenetic and molecular responses and deeper molecular responses ultimately allow more patients to consider treatment discontinuation.(19–21)

Clinical Trial Endpoints in CML

Clinical trial endpoints in CML have evolved over the past two decades. Examples are the PACE trial, which returned to MCyR as a primary endpoint, and the more recent ASCEMBL trial which used major molecular response (MMR) in similar patient populations.(22, 23) Over time, investigators have gained a better understanding of the capability of TKIs to control CML, and of the benefits of earlier and deeper responses. Furthermore, different testing methods are now more reliable and standardized for monitoring patients, such as peripheral blood PCR rather than bone marrow aspirations, which has shifted the focus towards molecular endpoints over cytogenetics. The standard of care detection and monitoring of molecular “minimal residual disease” in patients with CML and the demonstrated relationship between achievement of MMR and long-term clinical outcomes have been critical in the acceptance of MMR as a measure of clinical benefit.(24)

Treatment goals for newly diagnosed patients have also evolved. During the development of imatinib, the goal was achievement of MCyR for second line therapy and beyond, and CCyR for frontline therapy. With the newer TKIs, the endpoints deepened to MMR. Some ongoing trials for frontline therapy are incorporating treatment free remission (TFR) as a major endpoint. TFR is a challenging endpoint for a frontline trial as only 20-30% of patients successfully achieve TFR (25), it takes years to be eligible for TKI cessation, and successful TFR can only be assessed with sufficient follow-up. There are no good biomarkers yet identified to predict for TFR, and therefore, a surrogate endpoint cannot be used. As an example, one might think a patient who has achieved MR4.5 and maintained that response for 10 years would have an extremely high likelihood of prolonged TFR after stopping treatment, however the data suggest it is still possible this person to have a molecular recurrence.(25) Developing treatments to produce higher rates of successful TFR with a goal of curing CML remains all-important and may require more potent single agents frontline or combination therapies. Identifying biomarkers, such as early molecular response, early

MR4.5 (1 or 2 years), T-cell subsets, NK-cell activity, or some combination of these, will allow earlier evaluation of novel treatments. In the absence of such biomarkers, however, it could be argued that frontline studies aiming for TFR as an endpoint are not suitable for accelerated approval.

The Future of Accelerated Approvals in CML

Refining Clinical Benefit for Patients with CML

Treatment goals differ for newly diagnosed patients versus resistant patients and clinical trial endpoints need to be adjusted to reflect these differences. For example, MCyR may still be an appropriate endpoint in a multiply refractory patient population and could offer survival benefits, while deeper molecular responses may not be a realistic expectation.(22) Better treatment options for multiply resistant patients are necessary, and this is where the accelerated approval program still plays an important role in CML. Even with the TKIs currently available, many patients experience resistance or intolerance to multiple agents. New drugs offering benefits in the most difficult circumstances (e.g., patients with compound mutations, or recurrent thrombocytopenia) are needed and these are the settings in which accelerated approval of a drug could be considered. The endpoints of such studies are early efficacy endpoints that are clinically meaningful, particularly in high-risk patients. This was illustrated by the approval of ponatinib, where there was an immediate clinical need to address patients with T315I mutations and others with refractory/serially resistant CML. For these patients, accelerated approval was appropriate before knowing the full safety data.(22) Only following its 2012 approval, however, did it become clear that arterial occlusive events (AOEs) were occurring at a much higher incidence than previously recognized, including in younger patients with no known risk factors. Ultimately, ponatinib was voluntarily withdrawn from the market in October 2013, and in December 2013, returned to the market with updated safety warnings in the prescribing information, a Risk Evaluation and Mitigation Strategy, a limited indication, and a post-marketing requirement to identify the optimal safe and effective dose for CP-CML.(26) Some may argue in retrospect that a more narrow clinical indication initially would have been preferential while learning additional toxicity information; however, the counter argument is that the vast majority of CP-CML patients enrolled on the PACE trial did not have remaining standard-of-care options available.

In addition, treatment goals often differ in intolerant patients. In clinical trials that have studied second or later lines of therapy, eligible patients have been either resistant or intolerant to prior treatment. Future trials will need to separate patients who are resistant from those who are intolerant. The accelerated approval program is likely not ideal for new drugs being looked at for intolerant patients as the full toxicity profile should be understood in this setting. In the frontline setting, new drugs may need to show similar efficacy with significantly better safety profiles than the currently approved drugs, unless they can markedly improve upon the rates of deep molecular responses, allowing more attempts at TKI cessation. The time it will take to collect this data, however, may not be suitable for the accelerated approval program.

Assessing the Importance of Chronic Low-Grade Toxicities

As the number of people living with CML rises, quality of life (QoL) has become increasingly more relevant. Still, until recently, little attention has been paid to these endpoints in clinical trials and the data remain challenging to capture and interpret.(27) Efforts are needed to develop comprehensive and established tools for evaluating QoL and should include developing treatment goals at specific time points such as those available for efficacy in national and international guidelines. Although certain toxicities are considered class-effects and are commonly seen across all TKIs, the side effect profiles of TKIs are quite idiosyncratic with profound effects in some patients and none in others. Historically, investigators and the FDA have emphasized grade 3-5 toxicities, yet when treatment is given indefinitely, even persistent grade 1-2 side effects can negatively impact QoL.

Many frontline CML trials stopped following patients after five years (e.g., DASISION, BFORE) yet patients receive treatment far longer than this. Consequently, clinical trials have not adequately captured the chronic, low-grade toxicities associated with each TKI. Furthermore, some AEs may only appear after years on a specific therapy or may continue to increase in incidence over time. Ideally, patients should be followed for safety and toxicity for the entire duration of time they are expected to remain on the drug to better understand the long-term toxicity profile. Post-marketing monitoring occurs, yet this is notoriously unreliable given the voluntary nature of reporting which likely leads to gross underrepresentation of adverse reactions. Future trials would benefit from requirements of a minimum long-term follow-up period that more closely mirrors the length of time most patients remain on therapy to get an accurate long-term toxicity profile. A plan for long-term toxicity monitoring would ideally be addressed in the study safety monitoring plan before initial accelerated approval such that the data may continue to be collected in the post-marketing setting and used to support eventual regular approval and labeling updates as appropriate.

Dose Optimization Early in Clinical Development

As a relic of chemotherapy clinical trial design, TKI dose-finding trials in CML have been designed to determine the maximal tolerated dose (MTD) of each drug. This approach is more appropriate for short-term cytotoxic treatments than for lifelong therapies, and it is unlikely that most CML patients require the MTD. The majority of CML experts agree that many patients could achieve the same clinical response on a lower dose of a TKI, particularly in the frontline setting. Initiating treatment at a higher dose and with a planned reduction after a response is achieved is another possible approach. This is frequently done successfully in clinical practice already to manage side effects. Formalized dose optimization studies would be valuable to address the long-term efficacy of low-dose TKIs, and the impact on chronic toxicities. The challenge in designing such trials comes from the immense volume of patients required, and the fact that many are not seen at academic medical centers where the trials are typically run. Furthermore, funding a trial such as this has not historically been of interest to the pharmaceutical industry. An alternative is to collect real-world data that informs on the effect of dose adjustments on efficacy and toxicity. Although heterogeneous, the data could provide valuable information on the correlation between dose adjustments and AE profile and response. There is precedent for

clinical trials evaluating low-dose TKIs in the frontline setting, as evidenced by studies using lower-dose dasatinib suggested they are equivalent to dasatinib 100 mg daily in newly diagnosed CP-CML patients.(28) Yet, several questions remain: should frontline patients be started at high doses and reduced based on response? Should they begin at a low dose and escalate based on response and tolerance? Should patients be maintained long-term on a lower dose? Perhaps the doses should be lower in the frontline setting than the salvage setting, when a higher dose may be required for efficacy and the willingness to accept toxicities may be different. In fact, two of the 2GTKI have different initial doses approved for frontline and salvage (nilotinib and bosutinib).

Finding the right balance between efficacy and safety of each TKI remains essential. This lesson was learned in the PACE trial when such intense focus was on lowering the PCR that the emergence of hypertension was often overlooked.(22) Additionally, that study highlighted the importance of focusing on all AEs regardless of perceived relatedness to the investigational agent. Many patients enrolled on the PACE trial had baseline cardiovascular risk factors, thus when they developed hypertension or other cardiovascular complications, these were considered expected events, not drug related. It was not until additional follow-up revealed a continued increase in the occurrence of these events that it became clear that ponatinib was itself a risk factor for their development. Further illustrating the importance of dose reductions, most patients who lowered their dose on PACE were able to maintain their response. Ultimately, results of the OPTIC trial, a post-marketing requirement issued at the time of ponatinib's return to the market in 2013, indicated that reducing the dose of ponatinib following achievement of MR2 led to efficacy outcomes comparable to PACE and with a lower incidence of AOEs. In the future, the ability of products to attain accelerated approval and confirm their clinical benefit will be better realized with dose optimization efforts centered early in clinical development, which is a key goal of FDA's Project Optimus.(29)

Conclusions

The revolutionary impact of the regulatory approval of imatinib in 2001 was unprecedented and few could question the necessity of this accelerated FDA approval. Prior to imatinib, patients with CP-CML had a median life expectancy of 3-5 years and a person diagnosed with CP-CML in 2022 has a life expectancy that mirrors the general population. Goals have shifted from prolonging life to pursuing treatment discontinuation. An emphasis is being placed on long-term toxicities of CML directed therapy, given that these are drugs patients take for many decades.

It is undeniable that the accelerated approval program has saved many lives for people with CML by providing earlier access to effective therapies for their leukemia. Accelerated approval for a serious condition is granted when a drug provides a meaningful advantage over available therapies based on initial evidence of safety and effectiveness, and the benefits outweigh the risks, albeit this approach considers only risks known at the time of the approval. It is imperative to continue following patients on CML clinical trials for many years to better understand the long-term impact of TKI therapy.

Moving forward, the goal remains a cure for CML. With that, the focus is shifting towards identifying ways to allow more patients to successfully achieve TFR. Furthermore, optimizing the dose of TKI therapy to treat patients with an effective and tolerable dose has become a priority, and clinical trials should aim to identify the minimal effective dose rather than the maximal tolerated dose. With each subsequent study, regulatory approval may be based on different endpoints than in the past. The currently approved drugs have met the mark regarding achievement of intermediate endpoints for clinical benefit, such as cytogenetic and molecular responses. Each future drug or drug combination will be expected to achieve these same endpoints at a minimum. The bar must be raised in order to improve upon long-term safety, health-related QoL and a marked increase in the rate of successful TFR. Designing these clinical trials will require a collaborative, innovative approach between diverse stakeholders including CML clinical investigators, basic scientists, behavioral health specialists, patient advocates, industry and FDA.

Research in CML is not complete. There is much more work to be done, and many patients still do not have adequate responses to available treatment options. However, the landscape is shifting. A cure is defined as a complete or permanent solution or remedy. Even with the extremely effective treatments available for CML, a cure has not yet been identified outside of allogeneic SCT. With motivated patients, dedicated investigators, and continued support of programs such as the FDA accelerated approval program, it is only a matter of time before a cure will become a reality.

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Table 1.

Accelerated Approvals in Chronic Myeloid Leukemia

Drug	Initial Indication (Excerpted)	Accelerated Approval Date	Regular Approval Date
Imatinib	CP, AP, BP-CML after failure of IFN	5/10/01	12/8/03
Imatinib	Newly diagnosed CP-CML	12/20/02	5/27/09
Imatinib	Pediatric CP-CML relapsed after stem cell transplant or resistant to IFN	5/20/03	9/27/06
Dasatinib	CP, AP, BP-CML resistant or intolerant to prior therapy including imatinib	6/28/06	5/21/09
Imatinib	Newly diagnosed CP-CML in pediatrics	9/27/06	4/1/11
Nilotinib	CP, AP CML resistant or intolerant to prior therapy including imatinib	10/29/07	1/14/11
Nilotinib	Newly diagnosed CP-CML	6/17/10	1/27/15
Dasatinib	Newly diagnosed CP-CML	10/28/10	8/12/15
Omacetaxine Mepesuccinate	CP, AP CML, resistant or intolerant to 2 or more TKIs	10/26/12	2/10/14
Ponatinib	CP, AP, BP CML, resistant or intolerant to TKI therapy or Ph+ ALL resistant or intolerant to prior TKI therapy	12/14/12	11/28/16
Bosutinib	Newly diagnosed CP-CML	12/19/17	5/14/21
Asciminib	CP-CML previously treated with 2 or more TKIs	10/29/21	Pending*

CP-Chronic Phase; AP-Accelerated Phase; BP-Blast Phase; IFN-Interferon Alpha; Ph+-Philadelphia Chromosome; TKI-Tyrosine Kinase Inhibitor; ALL-Acute Lymphoblastic Leukemia

*Post-marketing requirement stipulated at least 2 years follow-up on the ASCEMBL trial for all patients to confirm clinical benefit. (Data from U.S. Food and Drug Administration; ref. 30.)