FRIENDS of CANCER RESEARCH

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Modernizing Expedited Development Programs

FRIENDS OF CANCER RESEARCH ANNUAL MEETING 2020

Introduction: Expedited development programs and pathways

Advances in our understanding of disease processes, genetics, manufacturing technologies, and innovative trial designs have enabled the development of novel, effective, and greatly improved therapeutic agents. Particularly in oncology, the ability to target a novel agent against a driver oncogene or protective immune checkpoint has led to several therapeutic breakthroughs in diseases with limited or no systemic treatment options. These breakthroughs have established new classes of therapeutics leading to, in some instances, unprecedented efficacy results for serious, life-threatening diseases. In situations where substantial benefit over existing therapies is observed in early clinical studies addressing unmet need, expedited drug development pathways help balance the need to provide individuals with serious diseases or conditions with expedited access to breakthroughs while also maintaining the rigorous standards established for approving drugs.[1,2]

The US Food and Drug Administration (FDA) currently uses several tools to expedite the development of promising new medicines aimed at treating serious disease with unmet needs. These include the following tools: 1) Fast Track; 2) Breakthrough Therapy; 3) Regenerative Medicine Advanced Therapy (RMAT); 4) Priority Review; and 5) Accelerated Approval.[3,4]

Objectives

- **Evaluate current use and application of expedited drug development pathways**
- **Recommend proposals to clarify and simplify expedited programs that facilitate the development of promising therapies and address emerging drug development challenges**
- **Delineate optimal processes and actions that occur following the initial designation of an expedited development program(s)**

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1. **Fast Track** is a process designed to facilitate the development and expedite the review of drugs that treat serious diseases and address unmet medical needs. It entails early and frequent communication between the FDA and sponsor throughout the development and review process. Under this program, a sponsor may submit complete sections of a New Drug Application (NDA) or Biologics License Application (BLA) as they are ready ("rolling review"), rather than the standard requirement to submit the complete NDA or BLA application in one submission.

2. **Breakthrough Therapy** designation expedites the development and review of drugs that are intended to treat a serious condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy. A drug with Breakthrough Therapy designation is also eligible for all considerations of the Fast Track designation. In addition, Breakthrough Therapy affords intensive FDA drug development guidance with an FDA organizational commitment with early involvement of senior managers and early manufacturing consultation. An NDA/BLA submission will be provided rolling review with potential for priority review.

3. **RMAT** designation includes all the benefits of the Fast Track and Breakthrough Therapy designation programs, including early interactions with FDA. RMAT designation is granted for advanced therapies (which is defined as a cell and gene therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products) intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such a disease or condition. RMAT does not require evidence to indicate that the drug may offer a substantial improvement over existing therapies. Due to the definition of regenerative medicine, these products will be reviewed by the Center for Biologics Evaluation and Research (CBER).

4. **Priority Review** is available to drugs that provide a significant improvement in the treatment, prevention, or diagnosis of a disease when compared to standard NDAs or BLAs. It shortens the goal review time from 10 months to 6 months from the 60-day filing date (or from 12 months to 8 months respectively from date of submission of the application). A Priority Review designation directs attention and resources to evaluate drugs that would significantly improve the treatment, diagnosis, or prevention of serious conditions.

5. **Accelerated Approval** allows a drug to receive FDA approval based on an early efficacy endpoint (such as objective response rate) considered reasonably likely to predict a clinical benefit (such as prolonged survival). Accelerated Approval is a critical pathway for expediting access to new therapies in disease settings in which the effect on an intermediate clinical endpoint that predicts the drug's clinical benefit can be shown much sooner than the effect on an endpoint that directly demonstrates clinical benefit. This pathway is reserved for drugs/biologics that seek to treat a serious or life-threatening disease and that provide meaningful therapeutic benefit to patients over existing treatments. Drugs approved via the Accelerated Approval pathway should undergo further clinical testing to confirm the predicted clinical benefit ("confirmatory trial/clinical evidence"). If the confirmatory trial/

evidence does not show that the drug provides clinical benefit for patients, FDA may seek to remove the drug from the market, or remove the indication from the drug's labeling in cases where the drug is approved for other uses.

Some of these pathways are used throughout the development lifecycle of the drug before the NDA/BLA is submitted (Fast Track, Breakthrough Therapy, and RMAT) while other tools are applied once the license application is submitted (Priority Review and Accelerated Approval). **Table 1** provides a comparison of features associated with these pathways. This white paper prioritizes discussions on the programs intended to be utilized prior to NDA/BLA submission; opportunities to optimize accelerated approval are discussed in the companion white paper "Optimizing the Use of Accelerated Approval."

It is also worth noting that some of the elements associated with these FDA expedited pathways are mirrored by health authorities outside of the United States.[5] For example, this is seen with the European Medicines Agency's (EMA) Priority Medicines (PRIME) program and the Pharmaceuticals and Medical Devices Agency's (PMDA) SAKIGAKE designation, which share characteristics of FDA's Breakthrough Therapy designation.[6–8] In addition, the EMA has several approval frameworks (approval under exceptional circumstances and conditional approval), which allow approval using an intermediate endpoint and are similar, in this respect, to FDA's Accelerated Approval. It is important to note that regional differences can add complexity to global clinical drug development for therapies aimed at treating serious or life-threatening conditions.

With the creation of the FDA's Oncology Center of Excellence (OCE), several pilot projects have successfully launched to test novel approaches to regulatory review for oncology drugs, such as Real-Time Oncology Review (RTOR) and the Assessment Aid.[9,10] The RTOR Pilot Program aims to improve the efficiency of the review process for clinical applications through data and analysis standardization and early iterative engagement between the FDA and applicant by allowing for the submission of key efficacy and safety tables/figures and datasets prior to the complete dossier submission. Eligible applications include oncology NDAs and BLAs for drugs or biologics likely to demonstrate substantial improvements over available therapies (e.g., Breakthrough Therapy, Accelerated Approval, and Priority Review eligible indications) and based on clinical trials with straightforward study designs and easily interpretable endpoints. The Assessment Aid is a unified FDA review document that contains an applicant assessment (submitted at the time of (s)NDA/BLA submission) and an FDA assessment and improves the efficiency of the FDA review. The regulatory review process for pharmaceutical drugs is a resource intensive undertaking for both the drug sponsor and the FDA. Therefore, continued evaluation of current pathways is necessary to ensure pathways facilitate the science and make sense for patients.

Landscape Analysis of Expedited Pathways

Expedited programs at the FDA have been highly utilized by sponsors and with increasing frequency for oncology drugs in the US (**Table 2**). Between 2012-2019, 90% of initial oncology drug approvals utilized an expedited program versus only 55% of new non-oncology drug approvals. Accelerated Approval, Breakthrough Therapy designation, and Priority Review are overwhelm-

ingly used more for oncology products than non-oncology products. While this can be partly attributed to the fact that many non-oncology diseases may not meet criteria for expedited programs if they are not deemed serious or life-threatening, it may also highlight differing approaches across review divisions within FDA.

Priority Review and Fast Track appear to have been the most popular tools, followed by Breakthrough Therapy (**Table 2**), which was available after the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law in July 2012, with the first products receiving Breakthrough Therapy designation in January 2013. It is interesting to note that approximately half of the programs with Breakthrough Therapy designation followed the Accelerated Approval pathway.

Value of Expedited Programs Across Disease Areas and at Key Points in Development

As depicted in **Table 3**, these programs are not mutually exclusive and can be used in combination with the other expedited programs. Expedited programs can have different utility within different disease settings. The exact pathway a promising therapy might take will depend on several factors including the disease setting and indication sought, endpoint(s) used, as well as the magnitude and durability of the signal relative to the existing standard of care. The ultimate decision-maker for assigning an expedited pathway to a drug development program is the review division. Therefore, consulting the review division before applying for a respective expedited program is highly recommended. Coordinating the added benefits of these programs should be considered to minimize unnecessary administrative work for the Agency and sponsor. For example, it may not be necessary to apply for both Breakthrough Therapy designation and RMAT since they provide similar opportunities to facilitate development of a promising agent. The highest value for sponsors noted to date in using RMAT or Breakthrough Therapy designation has been the ability to meet with the Agency often.

In a cohort of drugs that utilized Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval (n=9), **Figure 1** helps depict the utilization of these programs across the development lifecycle of a drug. The use of Fast Track and Breakthrough Therapy designation often occurs later in the life cycle of a drug development program (several years after IND submission) and close to the time of submitting an NDA/BLA, likely indicative of having greater confidence in the clinical data. However, the benefit of these expedited development programs may be most realized earlier in development and could enable more meaningful interactions on other key aspects of a development program (e.g., chemistry, manufacturing, and controls [CMC], co-development of a diagnostic assay).

Learnings from Current Experience with Expedited Pathways

Expedited development programs at the FDA have had a positive impact on ushering new drugs through clinical development to reach patients more quickly. Drugs that qualified for an expedited program are approved on average two years earlier than drugs not under an expedited program (*Friends* Drug Development Dashboard).[11] This is, in part, due to development and

appropriate identification of promising drugs, increased dialogue with the FDA, and the positive momentum and collaborative mindset created within companies and at the FDA when a drug development program qualifies for an expedited pathway. While these pathways have been quite successful, cataloguing the learnings from these past experiences can help optimize their use moving forward.

Addressing current unmet need is becoming increasingly challenging. At the time many of these expedited development pathways were designed, treatment options in oncology, for example, consisted primarily of surgery, radiotherapy, and cytotoxic chemotherapy. As the treatment paradigm in oncology has shifted to therapies targeted against specific oncogenic proteins or pathways and immunotherapies, patients' lives have been improved and extended. Nonetheless, most of these newer treatments still are not curative; therefore, despite the availability of new anti-cancer therapies, significant unmet need remains, especially in the setting of metastatic disease. Furthermore, while significant advancements have been made in serious and life-threatening non-oncology conditions, most remain without a treatment to significantly alter the course of the disease. Hence, there is still a need for expedited pathways to facilitate development of promising therapies.

It can be difficult, though, to decipher which program/tool has been or will be the most beneficial in accelerating development to bring the right product to the right patient at the right time. ***Is there redundancy in terms of benefits from these expedited programs and how could we either simplify or improve them so that their intrinsic value increases?***

To help start answering these questions, the working group extracted several learnings based on the landscape analysis, sponsor/FDA interactions, and the wealth of experience gained over the past decade through drug approvals.

It is important to coordinate the use and timing of expedited pathways with clinical need and appropriate drug development stage. When creating each expedited development program, significant attention was paid to the eligibility criteria necessary for a new treatment to qualify for each program or designation. This has resulted in numerous potential duplicative application and review processes that the same drug may go through when qualifying for each program. Less attention has been devoted to assessing what occurs following a successful designation or delineating the steps applied to optimally expedite development post-designation for all disciplines (CMC, nonclinical and clinical areas of development). As experience is gained with each expedited development program, it is important to identify the subsequent actions that helped foster successful development so that those approaches can be anticipated and replicated as appropriate in a consistent manner.

Streamlining expedited programs where less redundancy exists can lead to more optimal and successful use within the lifecycle of a drug to avoid confusion as to when they can be used during a development program. Informal assessments revealed that recurring reasons for Breakthrough Therapy designation or RMAT denials included that the application was simply submitted too early or included data from an insufficient number of patients, there were issues with durability of response, or manufacturing concerns existed (for example, when early clini-

cal data were generated with a previous manufacturing process that subsequently changed significantly). Critical elements that can impact a program regardless of how good the clinical data or product are, include: non-oncology safety database issues, clinical site/Good Clinical Practice (GCP) concerns, lack of product stability data, and manufacturing site/Good Manufacturing Practice (GMP) concerns. Codifying processes and best practices for expedited programs could result in more impactful use of the expedited pathways to guide drug development programs through these critical stages of drug development (e.g., manufacturing, clinical pharmacology/toxicology, and clinical development). Later stage components such as manufacturing site inspections, diagnostic test development, or design of potential post-market commitments that may occur later in development could be sufficiently planned for through earlier interactions with the FDA.

Delineating the optimal early stage versus late stage development milestones important for expediting development is critical to help coordinate efforts within the sponsor and across the different teams at the FDA. Breakthrough Therapy designation and RMAT are both helpful to accelerate clinical development but challenges remain in accelerating CMC development particularly for novel therapies using emerging manufacturing technologies. There is an opportunity to utilize a more holistic approach where the FDA provides advice that will help synchronize clinical development and CMC development.

Expedited pathways and associated tools may be most needed for emerging therapies or for complex development programs to increase frequency and depth of interactions with the FDA. This can create a paradoxical scenario where comparatively less-novel products in better understood disease areas receive greater research and development (R&D) investment as there is an increased likelihood of qualifying for an expedited pathway. Consequently, greater investments lead to a better understanding of the disease and established class of products.

An important first step to qualifying for expedited pathways is to establish whether there is an unmet need or urgent public health concern. This helps determine the degree of regulatory flexibility to which novel or atypical regulatory pathways may be leveraged. The level of regulatory flexibility can be impacted by the confidence or how much trust is in the package being brought forward for review. This is driven by the development stage where the drug currently is, and what the biological and clinical evidence is to inform safety and efficacy. However, in a novel space it can be hard to be truly confident. For example, in the 1990s when monoclonal antibodies were entirely novel, the regulatory confidence was very low. However, with increasing numbers of monoclonal antibody therapies being developed, approved, and on the market, sponsors had more mature expertise on how to manage the complexity of manufacturing and development of monoclonal antibodies, while Health Authorities had a better understanding of where more stringency or flexibility could be applied in the regulatory process. The same can be said about increased regulatory confidence as there was increasing evidence supporting use of intermediate clinical endpoint (e.g., progression free survival in specific cancer types) that predicts the drug's clinical benefit rather than directly measuring clinical benefit using overall survival.

It will be important to develop mechanisms to ensure expedited development programs can be

used in diseases and classes of products with less certainty and understanding to identify the most important steps to take to enable the use of these expedited pathways. Understanding what constitutes meaningful improvement over standard of care and determining standard of care in a crowded class of drugs or rapidly evolving disease area can become very challenging. Enabling innovative trial designs or approaches incorporating novel elements (e.g., real-world evidence, ctDNA, digital tools, in vitro diagnostics, impact of COVID-19, decentralized trials) to participate in programs designed to accelerate clinical development could help more rapidly advance learnings and harmonize approaches.

Proposals for Modernizing Expedited Pathways at the FDA

Based on the above learnings, the working group recommends several proposals that can translate to actionable opportunities to facilitate drug development.

1. Maximize Intent of and Modernize Expedited Programs in the Pre-NDA/BLA Stage

Reconfiguring expedited development programs at the FDA to utilize a more simplified approach with a common entry point for drugs intended to treat a serious or life-threatening condition and the potential to address an unmet need may make the goal of these programs more apparent and streamline their use. This can also help reduce administrative burden for the agency and sponsor. The redundancy of the various qualification criteria for these pathways can often result in duplicative efforts as sponsors assemble applications and set up meetings while the FDA formally reviews each application.

One approach could be to reimagine expedited development programs utilized in the pre-NDA/BLA space by condensing them into a single pathway where the application requirements associated with Fast Track and RMAT are bundled into a pre-Breakthrough Therapy designation pathway. Any drug that would previously qualify for Fast Track or RMAT would qualify for pre-Breakthrough Therapy designation. This may help efficiently usher drugs through key development stages as clinical evidence is generated to support qualifying for Breakthrough Therapy designation. This can help maximize earlier interaction and iterative rapid feedback between sponsors and FDA.

This simplistic approach should be centered around the conversations or interactions that ought to occur when a development program sees early, promising data and when it sees clear, confirmatory data to transition from pre-Breakthrough Therapy designation to qualifying for Breakthrough Therapy designation and eventually approval.

2. Codify a Process for Utilizing Expedited Programs

Much attention is given to whether a product is a breakthrough therapy or not, but little focus is given to the processes that follow a Breakthrough Therapy designation. Identifying scenarios where earlier and more frequent interaction would have benefited a program, especially where it was less successful at expediting development, could help elucidate best practices. A comprehensive effort to assess what happens "Beyond Breakthrough," following a designation, is

needed to delineate the obligations and deliverables for sponsors and the FDA once a program qualifies for an expedited program. This should inform the development of updated FDA guidance documents.

A. Early Stage Development: Pre-Breakthrough Therapy Designation

This is a key place for intervention—when a company is setting up its manufacturing, characterizing its product, conducting a nonclinical program, and starting to generate data to support a Breakthrough Therapy designation or even planning a pivotal trial. Iterative interactions during this key phase of development when clear trends from clinical data are starting to emerge and when important decisions are being made can be extremely valuable. A structured process should be defined that enables early and frequent feedback/dialogue in a more standardized way with shorter timelines than currently available with formal interactions to address early stage questions in a development program, such as optimal analytical tools, discussion on planned manufacturing changes (improved processes, scale up), design of any additional nonclinical studies, dose finding, proof of concept, design of pivotal studies, and approval pathway.

B. Seeking Breakthrough Therapy Designation

Table 4 provides an outline of actions within the Agency and best practices for sponsors leading up to and following a Breakthrough Therapy designation.

C. Late Stage Development: After receiving Breakthrough Therapy designation

Actions associated with manufacturing site inspections, strategies for associated diagnostic test development, or design of potential post-market commitments may need to occur following the development of initial clinical evidence. A cross-disciplinary project lead for Breakthrough Therapy designated/RMAT products should use a holistic multidisciplinary approach to begin to map out various processes and the necessary interactions that should occur with different groups within FDA.

D. Post Approval

Continued interaction and flexibility may also be necessary post-approval for clinical supplements, long-term follow-up studies including the use of real-world data to provide confirmatory clinical evidence, and prior-approval CMC supplements to sustainably provide Breakthrough Therapy designated products to patients.

3. Facilitate Development of Emerging Therapies and Complex Development Programs

Synchronizing Key Components of Drug Development for Emerging Therapies

Dedicated and more frequent meetings for emerging therapies, such as cell and gene therapies and next generation immunotherapies, in a pre-Breakthrough Therapy designation setting may

be necessary to keep key development components in sync to get these potentially transformative therapies to patients quickly and safely. For example, sponsors and FDA could initiate manufacturing meetings in a pre-Breakthrough Therapy designation space in instances where clinical data is indicative of a "breakthrough product" but duration of follow-up is not at the point to support a designation, but likely will in 6 months or so, if data holds.

As considered in the Expedited Programs for Serious Conditions guidance, "*The sponsor of a product that receives an expedited drug development designation may need to pursue a more rapid manufacturing development program to accommodate the accelerated pace of the clinical program,"* and *"Although sponsors must ensure the availability of quality product at the time of approval, FDA may exercise some flexibility on the type and extent of manufacturing information that is expected at the time of submission and approval for certain component."*[3]

The FDA Expedited Programs for Serious Conditions guidance and the FDA Expedited Programs for Regenerative Medicine Therapies for Serious Diseases guidance should be amended to provide additional recommendations on how a sponsor should consider acceleration and flexibility for CMC development and formalizing extended CMC discussions at critical milestones in development. However, it is acknowledged that granting this flexibility may be challenging for very novel therapeutics with limited precedents, such as gene editing products, and will be determined on a case by case basis, requiring additional CMC-specific dialogue with sponsors as well as robust quality risk assessments.

Development of a pilot program to accelerate CMC for products with complex innovative manufacturing processes should be explored. For example, extending the concept of real-time review to manufacturing for these products could further support improvement of the expedited pathways and support innovation. While "rolling review" allows for submission of individual completed modules one at a time rather than at once all together, "real time review" takes this concept a step further and allows the Agency to start the review of a module before the application is complete and may allow submission of pre-agreed CMC data during the NDA/BLA review.

Complex Development Programs

Current, expedited pathways are for drugs that treat serious illnesses and show promise in early trials. However, to demonstrate initial promise, a clinical program may try to utilize a complex innovative design or require advice earlier on for complex manufacturing to generate the early clinical evidence. Products that are completely novel may require considerably more coordination across disciplines within FDA (Clinical, CMC, in vitro diagnostics). A structured process for iterative, holistic cross-discipline interactions (as early as pre-IND) regarding the development program with promise to qualify for expedited pathway(s) should be defined.

Establishing a dialogue very early in the process (phase 1 or earlier) between the sponsor and the FDA would help sponsors devise an efficient development plan and may incentivize sponsors to establish harmonized strategies more likely to generate meaningful clinical data that would be of potential use for multiple therapeutic products. These early dialogues should also acknowledge the complexity of global development as sponsors will be trying to have early

parallel dialogue outside the US. This is an important aspect for global sponsors as feedback is integrated from multiple health authorities while also reconciling the different development speed/pace of each region due to the constraints or limitations of the respective regions. This is especially important when there may be novel aspects to the development program as well (e.g., rapidly changing science, digital tools/endpoints, CMC complexity, decentralized trial design).

Conclusion

Expedited development programs are highly utilized at the FDA, especially for oncology drugs, and sponsors and the FDA have gained substantial experience in identifying and qualifying drugs for these pathways. However, the processes that occur downstream and the interactions between the sponsor and agency that help expedite drug development should be surveyed and more clearly delineated and codified in FDA guidance documents. Over the past several decades, expedited programs have continued to grow to address current needs and facilitate drug development; however, redundancy in the qualification criteria and benefits across the current programs can make it difficult to understand when to apply for one or all in a particular development program. This white paper outlines proposals to streamline expedited development programs, codify a process for expedited programs that outlines pre and post designation processes, and ensure emerging therapies and complex development programs using innovative trial designs can benefit from expedited development pathways.

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Table 1: Expedited development and review pathways

	Fast-track Designation	Regenerative Medicine Advanced Therapy	Breakthrough Therapy Designation	Priority Review	Accelerated Approval
Eligibility	1. Treat serious condition 2. Potential to fill an unmet medical need (clinical or nonclinical data)	1. The drug is a regenerative medicine therapy, which is defined as a cell and gene therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products 2. Intent to treat, modify, reverse, or cure a serious condition 3. Preliminary clinical evidence indicates potential to address unmet medical need	1. Treat serious condition 2. Preliminary clinical evidence drug may demonstrate substantial improvement over existing therapies	1. An application for a drug that treats a serious condition 2. If approved would provide a significant improvement in safety or effectiveness	1. Treat serious condition 2. Provide meaningful therapeutic benefit over existing therapies 3. Surrogate endpoint reasonably likely to predict clinical benefit
Designation	With IND or after; FDA has 60 days to respond	With IND or after, ideally no later than end-of-phase 2 meeting; FDA has 60 days to respond	With IND or after, ideally no later than end-of-phase 2 meeting; FDA has 60 days to respond	Within 60 days of receipt of original BLA, NDA, or efficacy supplement	Not applicable. Agreed upon during formal meetings (typically Type B meeting)
Features	Earlier and more frequent communication	All Breakthrough Therapy designation features, including early interactions to discuss any potential surrogate or intermediate endpoints	Intensive guidance on efficient drug development; earlier and more frequent communication; delegation of senior reviewers and cross-disciplinary review team	Not applicable	Accelerated Approval granted based on early endpoints
Review Process	Option for rolling NDA/BLA submission; official review clock begins when last module is submitted	Option for rolling BLA submission; potential for shorter review time	Option for rolling NDA/BLA submission; potential for shorter review time	NDA/BLA data submitted in one package; review time shortened to 6 months after filling	Confirmatory post approval clinical evidence part of post-marketing requirement

Table 2: Utilization of current expedited programs from 2012-2019

Expedited Program	Total (n=327)	Oncology (n=88)	Non-Oncology (n=239)
Fast Track	123 (38%)	49 (56%)	84 (35%)
Breakthrough Therapy designation	72 (22%)	36 (41%)	36 (15%)
Priority Review	195 (60%)	71 (80%)	124 (52%)
Accelerated Approval	45 (14%)	35 (40%)	10 (4%)
None	116 (35%)	9 (10%)	107 (45%)

Note: Percentages calculated using totals within each clinical group. Percentages total greater than 100% because multiple programs can be used for a single drug. Data from "Compilation of CDER New Molecular Entity (NME) Drug and New Biologic Approvals."[12]

Table 3: Frequency of use for different combinations of expedited programs from 2012-2019

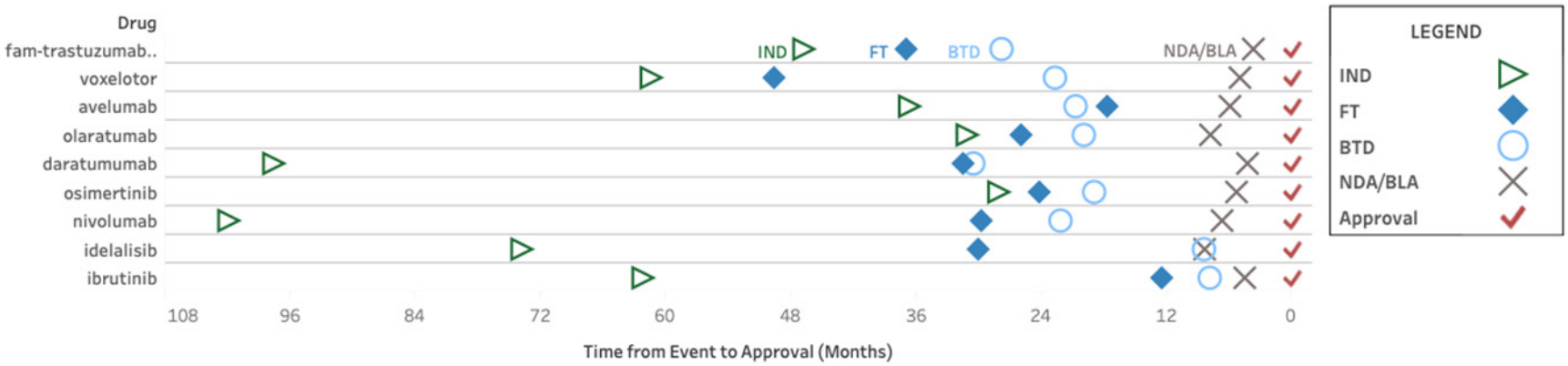
Expedited Program	Total (n=327)	Oncology (n=88)	Non-Oncology (n=239)
PR only	46 (14%)	14 (16%)	32 (13%)
FT only	13 (4%)	5 (6%)	8 (3%)
PR + AA	3 (1%)	1 (1%)	2 (1%)
BTD + PR	20 (6%)	7 (8%)	13 (5%)
FT + PR	63 (19%)	15 (17%)	48 (20%)
AA + FT	1 (0%)	1 (1%)	0 (0%)
PR + BTD + AA	19 (6%)	18 (20%)	1 (0%)
FT + PR + AA	13 (4%)	7 (8%)	6 (3%)
FT + BTD + PR	24 (7%)	3 (3%)	21 (9%)
FT + BTD + PR + AA	9 (3%)	8 (9%)	1 (0%)

Note: Fast Track, FT; Breakthrough Therapy designation, BTD; Priority Review, PR; Accelerated Approval, AA. Data from "Compilation of CDER New Molecular Entity (NME) Drug and New Biologic Approvals."[12]

Table 4: Key steps and processes within the FDA and drug Sponsor

Steps	FDA Procedures	Sponsor Actions & Best Practices
Preliminary Breakthrough Therapy Designation Request • Summary briefing document • Preliminary Breakthrough Therapy teleconference	Review preliminary Breakthrough Therapy briefing document and discuss internally Share thoughts regarding appropriateness of Breakthrough Therapy submission in teleconference	Sponsor initiates dialogue with review division by preparing and submitting a concise (2-pager) document that summarizes the eligibility of the drug/therapy, the preliminary data supports the promising therapy. Recommend that the pivotal study dose is selected and that there is sufficient data to support the safety profile and preliminary activity (e.g., 30+ patients with at least 6 months follow-up with an established endpoint). The preliminary request is reviewed, and a full Breakthrough Therapy designation application should only be submitted after receiving support from the respective review division.
Breakthrough Therapy Review • 60-day review	Review by Division/Office and review by CDER Medical Policy Counsel (via email or presentation depending on complexity)	A full Breakthrough Therapy designation request will be granted or denied following a 60-day review period.
Post-Breakthrough Therapy Designation Review (when granted) • Multidisciplinary Breakthrough Therapy meeting • Subsequent Type B Meetings • Critical IND milestone meetings • Other communications	All disciplines invited to attend and participate in the multidisciplinary meeting The frequency of subsequent meetings determined by the communication plan established at the initial comprehensive multidisciplinary meeting	Once Breakthrough Therapy has been granted, the Sponsor can request formal multidisciplinary and milestone meetings with the Agency with increased frequency and to ensure real-time collaborative dialogue. Initially, it may be beneficial to have a broad meeting with several FDA disciplines to ensure alignment for the overall program (e.g., clinical, pharmacology, CMC, CDRH). Subsequent meetings may require more detailed and focused discussion with the primary review discipline. However, Sponsors are encouraged to leverage the clinical FDA project manager to ensure consistent communication and dialogue with all FDA review disciplines.
Application Review (NDA/ BLA)	Early internal discussions about the appropriateness of an expedited review Consideration of real-time oncology review/ ORBIS/Priority Review/Assessment Aid	Sponsors are encouraged to communicate key milestones to FDA in advance, which allows an ongoing dialogue and advice on whether additional tools, pathways, or pilots can be leveraged for the license application review. One such milestone is communicating to the Agency potential pivotal data availability/unblinding approximately 4 months in advance, which would enable both FDA and the Sponsor to prepare for expedited submission and review, if applicable.

Figure 1. Time of key regulatory actions in relation to drug approval



Investigational New Drug, IND; Fast Track, FT; Breakthrough Therapy Designation, BTD; New Drug Application, NDA; Biologics License Application, BLA

Note: These drugs were selected because they utilized Fast Track, Breakthrough Therapy, Priority Review, and Accelerated Approval expedited programs.