FDA Trends for Accelerated Drug Approvals in Oncology Indications

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The FDA has modified and increased expectations around data needed to support accelerated approvals in oncology. Unlike prior trends, randomized controlled trials will be the preferred approach to support an application for accelerated approval moving forward; the acceptability of single arm trials for accelerated approval will receive significant scrutiny. Prolonged duration on the market for drugs with accelerated approval without confirmatory studies will no longer be acceptable.

Background & Objectives

The regulatory landscape for accelerated approvals for oncology drugs is changing with the announcement of **Project Confirm** and as documented in the March 2023 FDA **draft guidance "Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics**."

The purpose of this poster is to **characterize recent trends in accelerated approvals (AA) in oncology** with respect to study design, highlight considerations that might be sensitive to changing regulations, and **discuss future considerations** for drug developers planning to use this pathway.

Methods

A retrospective analysis of FDA databases (please see References), was conducted to analyze utilization of the AA pathway, sample sizes, and study designs used in pivotal clinical trials, use of companion diagnostics to select patient populations, time to convert an AA to a regular approval by completing post marketing requirements, and number of market withdrawals after an AA. The time period of collection/reporting is listed along with the source.

Results

Use of the accelerated approval pathway

As shown in Table 1, the use of accelerated approval showed a trend towards a decrease in 2022 compared to 2021 and 2020.

Table 1: Oncology AA vs regular approvals from 2018-Jun 2023

Type of Approval	2018	2019	2020	2021	2022	2023*	Total
Accelerated	9	8	22	17	10	6	72
Regular	36	27	35	34	31	11	174
Converted	1	1	3	6	3	1	15
Total	45	35	57	51	41	17	246
% of AA	20.0%	22.9%	38.6%	33.3%	24.4%	35.3%	29.3%

*Data from January 1, 2023- June 30, 2023

AA vs regular approval study designs

Study designs differ significantly for accelerated versus regular approval in number of treatment arms, sample sizes, endpoints and use of companion diagnostics to select patient population.

- **Treatment arms:** 63 of the 72 (87.5%) AAs were supported by single-arm trials. Single arm trials are much less frequent in regular (and converted) approvals, with only 35/174 (20.1%) trials using a single arm design whereas 130/174 (74.7%) trials were controlled, either using placebo or an active control.
- **Sample size:** AA trials ranged from 27 (selpercatinib trial in *RET* fusion-positive thryoid cancer) to generally < 300 patients, with the outlier of 902 (Atezolizumab in mTNBC), as shown in Figure 1 (A). Regular approval trials ranged from 13 patients (Tagraxofusp in dendritic cell neoplasm) to 2003 patients (Abemaciclib in breast cancer). Smaller sample size in regular approval trials were often due to rare indication.
- **Endpoint:** As shown in Figure 1 (B) 65/72 (90.3%) drugs approved under AA used ORR as a primary endpoint, 2/72 (2.8%) used PFS. PFS was used by 50/174 (28.7%) of trials for regular approval, 28/174 (16.2%) used OS, 14/174 (8.0%) used PFS and OS, and 29/174 (16.7%) used ORR as primary and/or coprimary endpoints
- **Use of companion diagnostics:** Overall, a greater proportion of AA (23.6%) compared to regular and converted approvals (17.2%) used companion diagnostics. Among drugs utilizing AA, use of companion diagnostic has tended to increase while the use for regular approval has decreased (Table 2).

Figure 1: Sample Size and Endpoint by Approval Pathway

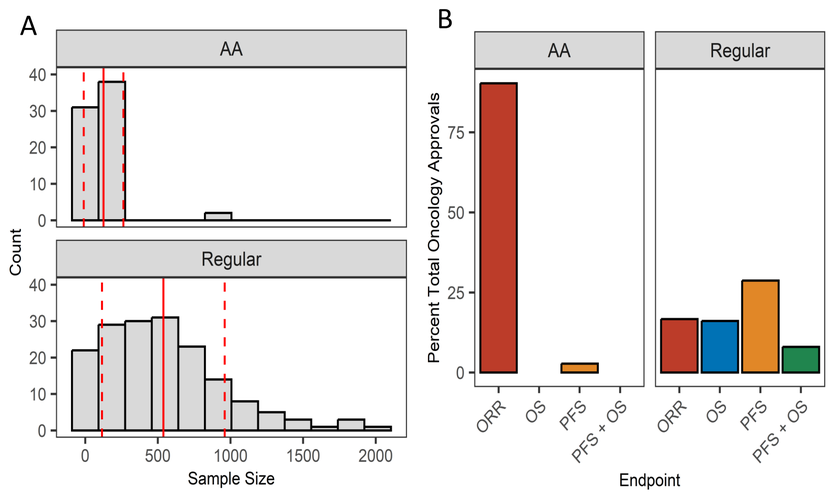


Table 2: Percent (%) of Approvals with Companion Diagnostics

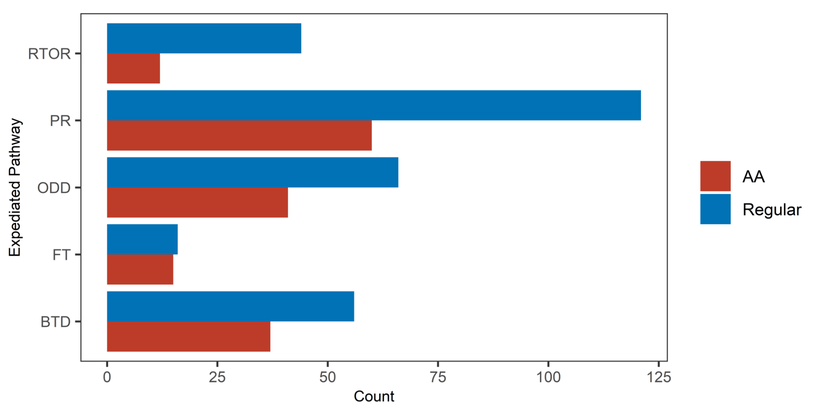
Type of Approval	2018	2019	2020	2021	2022	2023*	Overall
Accelerated	0%	25.0%	27.3%	35.3%	30.0%	0%	23.6%
Regular	27.8%	25.9%	14.3%	8.8%	12.9%	9.1%	17.2%

Use of other expedited pathways

Among all approvals, 215/246 (87.4%) drugs used at least one expedited pathway (breakthrough designation [BD], fast track designation [FTD], orphan drug designation [ODD], real time oncology review [RTOR], or priority review [PR]). Among the 72 AAs, 68 (94.4%) used at least one other expedited regulatory designation. In most cases, multiple expedited pathways were combined.

Figure 3 shows the frequency of use of expediated pathway in accelerated vs regular approvals.

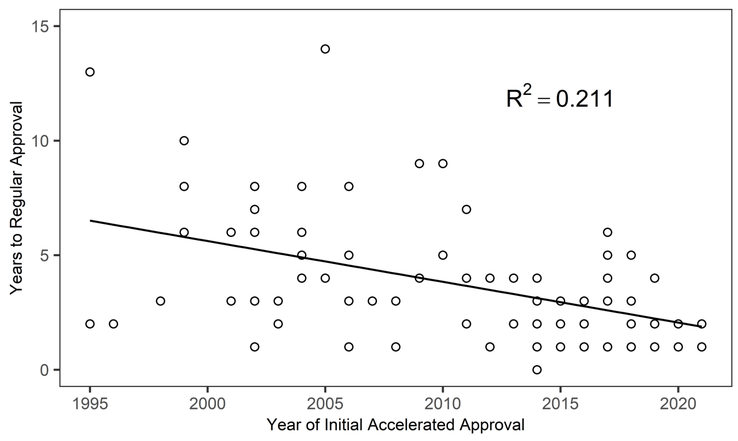
Figure 3: Expediated Pathway Use



Conversion times from AA to a regular approval

We probed whether there was a correlation between "year of AA" and "time to conversion of accelerated to regular approval", the latter signifying time required to complete confirmatory trials and submitting evidence to the FDA. As shown in Figure 2, conversion times between accelerated and regular approval has decreased in recent years.

Figure 2: Conversion Time From AA to Regular Approval



FDA withdrawal of accelerated approvals

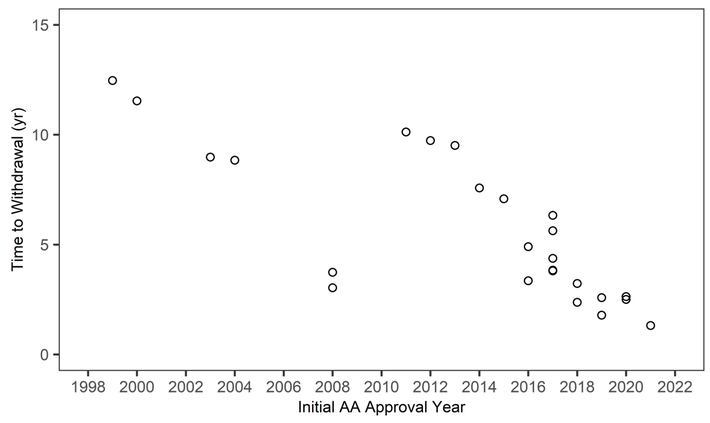
A total of 26 drugs have been withdrawn after AA since 1999. The launch of the public FDA webpage summarizing oncology drugs which have had AA indications withdrawn, combined the uptick in withdrawals in 2020-2022 suggest that the FDA is increasingly willing to exercise its powers to take such drugs off the market (Table 3). Drugs with incomplete PMRs or that fail to demonstrate clinical benefit in controlled studies have also been taken off the market much faster in recent years (Figure 4)

Table 3: Drugs withdrawn after AA

Year of withdrawal	2011	2012	2013	2014-2019	2020	2021	2022	2023*
Number of withdrawals$	3	2	1	-	2	7	7	3

* Data from January 1, 2023- June 30, 2023
$ withdrawal for each indication of a drug was counted separately

Figure 4: Time to Withdrawal



Discussion and Conclusion

Our findings are consistent with the FDA's recent messaging that a **prolonged duration on the market for drugs with accelerated approval without confirmatory studies will no longer be acceptable**. The March 2023 draft guidance indicates that there will be **increasing scrutiny on the acceptability of single arm trial designs intended to support AA**. The guidance also states that **confirmatory trials should be underway at the time of initial NDA/BLA submission for AA** and **well underway, if not fully enrolled, by the time of the AA action**. A single trial with earlier or interim endpoints can support AA and confirm benefit or sponsors may choose to conduct two 2 separate studies. Either way, it is imperative to plan for the confirmatory trials while developing an AA strategy.

The AA pathway is caveated by the indication having an unmet need. There is significant risk to development plans if this unmet need is met by competitors. **Sponsors should consider the state of development of their competitors and develop alternate plans for clinical development, potentially planning for pivots to regular approval**. Similarly, the competitive landscape and standard of care can change rapidly. **An outdated comparator arm might significantly hamper enrollment or deem trial conclusions irrelevant**. To adapt to these evolving commercial realities, **we may see increasingly specific populations based on molecular biomarkers apply for AA.** These commercial decisions should ideally be realized early in clinical development. **Robust dose finding studies could provide for substantial evidence to support AA**.

In summary, important changes in regulatory expectations are occurring in oncology drug development. Drug developers should consider the factors discussed herein in planning their development strategies for oncology indications.

References:
1. Oncology/Cancer Hematologic Malignancies Approval Notifications (from Oct 1, 2018 to Jun 30, 2023)
2. Verified Benefit of Cancer Accelerate Approvals (Oct 1995 to Oct 2021[a])
3. Withdrawn Cancer Accelerated Approvals (Dec 1999 to Feb 2021[a])
4. Ongoing Cancer Accelerated Approvals (Sep 2009 to Jun 2023[a])
[a] Date of initial drug approval

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