PRESCRIBING CHANGES IN RESPONSE TO US FOOD AND DRUG ADMINISTRATION ACCELERATED VS. REGULAR APPROVAL OF ONCOLOGY THERAPIES

RAVI B. PARIKH MD, MPP; ERNESTO ULLOA PEREZ PHD; MARTIN KURIAN, REBECCA HUBBARD PHD; STEVEN JOFFE MD, MPH; HOLLY FERNANDEZ LYNCH JD, MBE; RONAC MAMTANI, MD

Penn
University of Pennsylvania

Center for Health Incentives & Behavioral Economics

HACLAB

EXECUTIVE SUMMARY

Background: The FDA Accelerated Approval (AA) Program facilitates early access to drugs based on unvalidated surrogate endpoints deemed reasonably likely to predict clinical benefit. Oncology drugs constitute over 85% of all AAs, with 172 approvals in the past decade. While AA expedites patient access to treatments by over three years on average, challenges persist, including delays in initiating confirmatory trials (averaging 18.5 months post-approval) and substantial withdrawal rates (23% since 2009). Recent reform efforts, such as the Food and Drug Omnibus Reform Act (FDORA) and FDA's Project FrontRunner, seek to strengthen post-marketing commitments and ensure earlier confirmatory testing, yet key questions remain regarding real-world drug utilization of AA drugs and clinical outcomes.

Problem Statement: The AA program is hampered by delays in confirmatory trials, high withdrawal rates due to lack of benefit, and overreliance on surrogate endpoints. Measuring the real-time impact of AA and confirmatory approvals is difficult due to limitations in traditional data sources. This study leverages Flatiron's longitudinal disease cohorts to track prescribing patterns and patient exposure to AA oncology drugs.
Study Design A cohort study analyzed 63,434 patients with advanced solid malignancies receiving systemic therapy between 2011 and 2024. Utilizing the Flatiron Health Database and FDA data, we identified 161 AA indications and focused on 29 with sufficient information on patient eligibility. Drug utilization was assessed based on prescription trends before and after AA or regular approval (RA), including off-label use in first-line settings and among biomarker-negative patients.

Research Findings: Among 16 AA indications converting to RA, prescribing increased significantly after AA (6.2% to 29.6%) but showed minimal change post-RA (32.8% to 33.9%). Indications eventually receiving RA saw greater initial uptake post-AA, suggesting that these indications may have had stronger preliminary evidence or clinical need at the time of approval. Off-label prescribing remained low (2.7 percentage points for line-discordant use and 1.0 percentage points for biomarker-discordant use). These findings suggest that oncologists prioritize access to AA drugs despite provisional evidence, while modest changes post-RA indicate limited distinction between AA and RA in clinical practice.

Implications: Rapid uptake of AA drugs underscores the program's role in addressing unmet medical needs. However, the minimal prescribing increase post-RA, coupled with stagnant drug prices post-confirmatory trials, suggests weak incentives for manufacturers to expedite post-marketing requirements. Recent reforms emphasizing timely confirmatory trials, single continuous studies for AA and RA, and streamlined withdrawal procedures may enhance the program's effectiveness and ensure faster generation of robust clinical evidence.

BACKGROUND

The FDA Accelerated Approval Program provides access to drugs on the basis of improvement in surrogate endpoints that are "reasonably likely" to predict clinical benefit. Oncology drugs make up over 85% of all AAs.[1] The pace of AAs in oncology is staggering: in just the past decade, there have been 172 AA indications granted for anticancer therapies, and the pace of approvals has increased in the past 5 years.[2] While the AA program speeds access to novel therapies by over 3 years[3], there are several challenges with the AA program. First, drugs granted AA must undergo confirmatory studies to verify clinical benefit, but these studies begin on average 18.5 months after initial approval.[4] Second, since 2009, 15 oncology AA indications (23%) have been withdrawn due to lack of superiority over standard of care.[5] We estimated that 26% of eligible individuals are exposed to oncology AA indications that are subsequently withdrawn.[6] Furthermore, the median time from AA to withdrawal of an indication is nearly 4 years and has ranged to over 12 years in some cases.[1] This is important because the FDA has had difficulty withdrawing AA drugs or removing AA indications – even when confirmatory studies fail to demonstrate clinical benefit.

Recent reforms have sought to address these gaps in the accelerated approval program. The Food and Drug Omnibus Reform Act (FDORA) gives the FDA additional authority to enforce standards for post-marketing requirement studies and to require such confirmatory studies to be underway at the time of AA, in order to minimize exposure time to drugs without benefit. FDORA also gives FDA the option to use expedited procedures to withdraw approval if the confirmatory trial fails to verify the product's clinical benefit. Additionally, in 2022, the FDA Oncology Center of Excellence unveiled Project FrontRunner, which encourages drug sponsors seek approval of new cancer drugs in earlier clinical settings, rather than late-stage settings when most AAs are sought.[7] While these changes represent positive steps forward, several important questions remain.

First, it is unknown, across accelerated approval indications, how often AA drugs are utilized between the dates of AA and full approval and/or withdrawal

Second, it is unknown how recent FDA reforms will change the pace of utilization of AA drugs related to drugs receiving full approval.

Problem Statement: Currently, the FDA AA program suffers from lengthy delays between initial AA and subsequent confirmatory trials, substantial rates of withdrawal of indications after initial AA, and heavy reliance on tumor-centric surrogate endpoints (e.g., response rate) rather than patient-centric clinical endpoints (e.g., overall survival) for AA studies. There have been several major proposed reforms to the AA program. However, quantifying real-time patient impact of AAs and federal reforms is challenging given the limitations of traditional claims-based data sources, including data lag and missing data on performance status, biomarker status, and line of therapy. We use longitudinal disease cohorts from a nation-wide real-world data repository to track prescribing patterns of FDA AA oncology indications.

STUDY DESIGN

This cohort study included patients diagnosed with advanced solid malignancies from January 1, 2011, to October 31, 2024, who received at least one systemic therapy. To obtain drug utilization information, we used patient-level electronic health record (EHR) data from the Flatiron Health Database, curated through technology-enabled abstraction from ~280 US cancer clinics.[8]

Information on 161 AA indications granted between January 1, 2011, and July 1, 2023, was obtained from publicly available FDA databses.[9,10] We identified 29 AA indications in our dataset with at least 30 eligible patients in both the pre- and post-approval periods. Patients were deemed eligible for an AA indication if they were aged ≥18 years and met cancer-, line of therapy-, and biomarker-specific criteria for an indication.

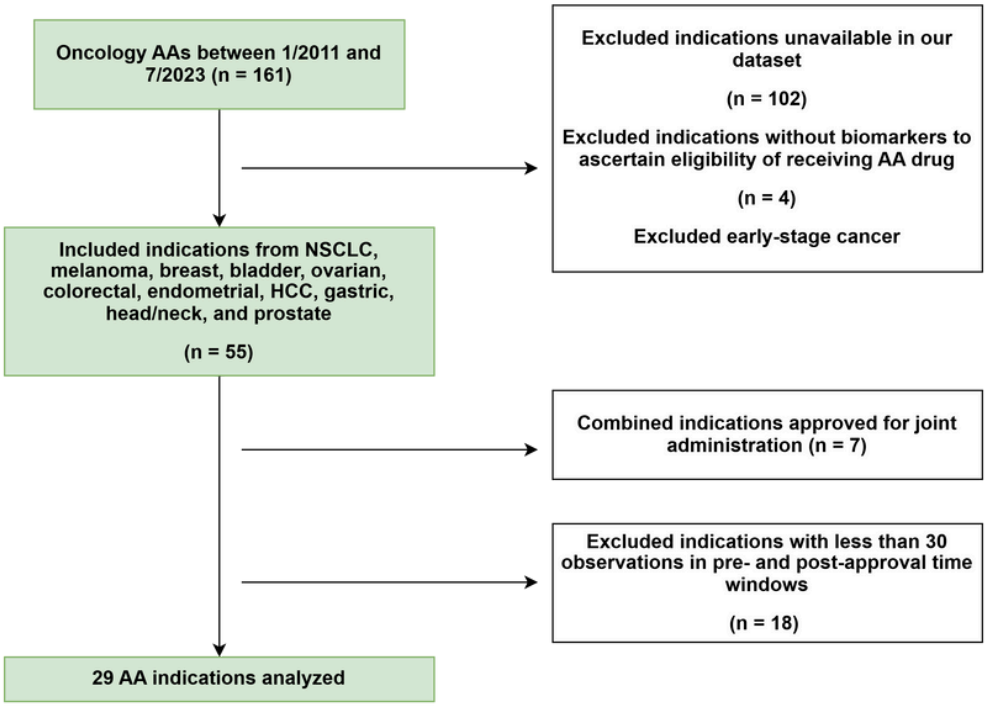

FIGURE 1: INCLUSION CRITERIA FOR AA INDICATIONS

For each indication, the primary outcome was the average absolute difference in the proportion of eligible patients who received the drug in the 6 months before and after AA or RA. For example, if 10% and 25% of eligible patients received the drug pre- and post-AA, respectively, the absolute difference was 15%. For off-label use, we examined 2 scenarios: 1) use of AA drugs in the first-line setting that were approved for a later-line indication (line-discordant); and 2) use of biomarker-specific AA drugs among biomarker-negative patients (biomarker-discordant). Analyses were conducted using R, v4.

RESEARCH FINDINGS

The cohort included 63,434 patients (median age, 67 years; 32,749 [51.6%] female; 47,412[74.7%] receiving care at community practices) who received 128,917 eligible lines of therapy. Among 16 (55%) eligible AA indications converting to RA, prescribing increased 23.4 percentage-points after AA (6.2% pre-AA; 29.6%post-AA) and 1.1 percentage-points after RA (32.8% pre-RA; 33.9% post-RA).

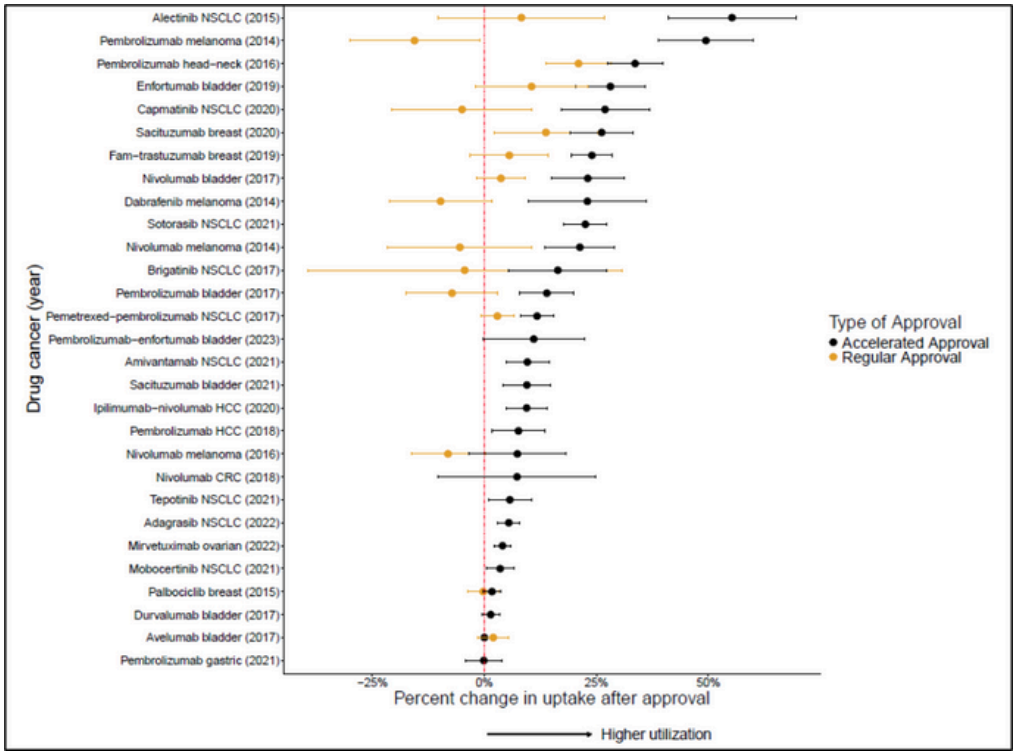

FIGURE 2: CHANGES IN UPTAKE OF CANCER DRUGS BY TYPE OF FDA APPROVAL

AA prescribing response varied by indication; alectinib in non-small cell lung cancer had the largest increase after AA (55.2 percentage-points). AA prescribing responses were larger for indications eventually granted vs. not granted RA (23 [95% CI 13-34] vs. 7 [95% CI 3-12] percentage-points). Off-label prescribing increases after AA were small (2.7 percentage-points for line-discordant use; 1.0 percentage-points for biomarker-discordant use) (**Figure 2**).

RESEARCH FINDINGS

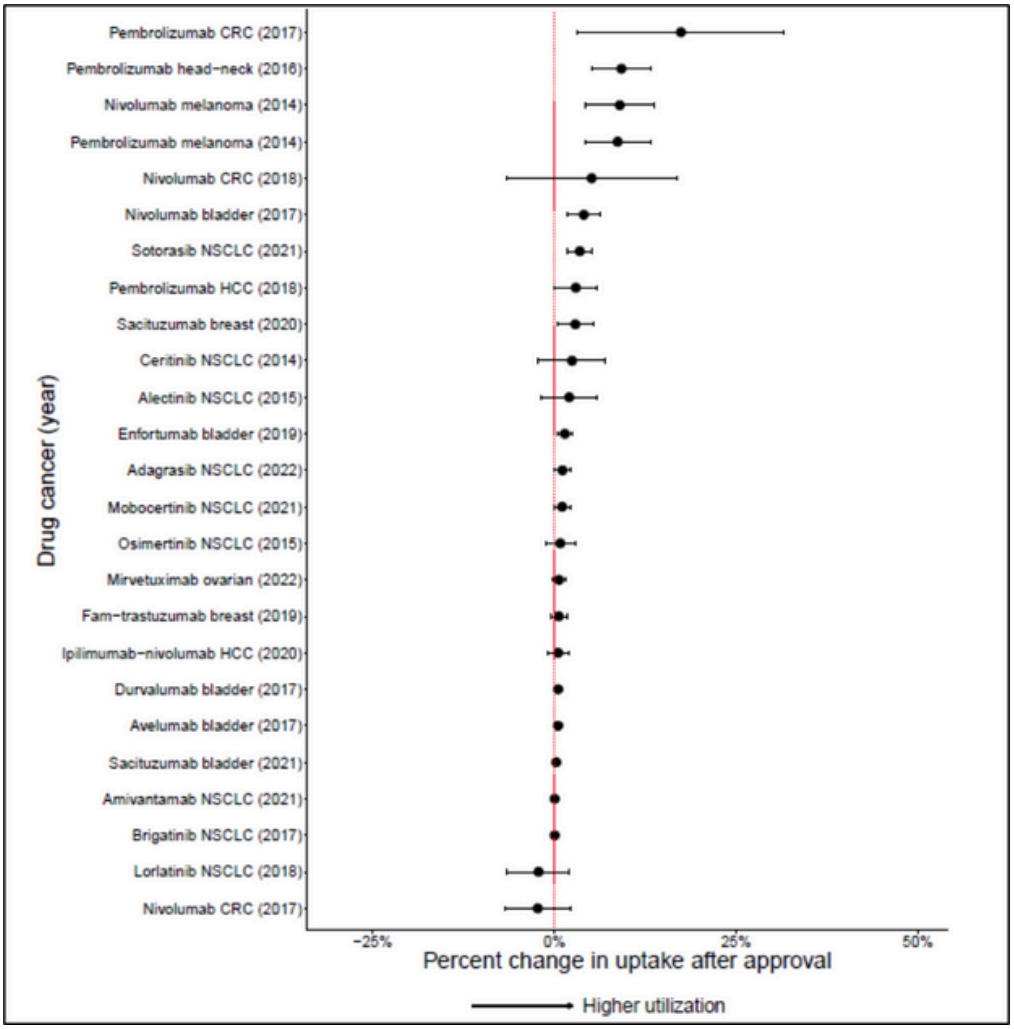

FIGURE 3 OFF LABEL (FIRST LINE THERAPY) CHANGES IN UPTAKE OF CANCER DRUGS IN ACCELERATED APPROVALS FOR SECOND OR SUBSEQUENT LINES OF THERAPY

RESEARCH FINDINGS

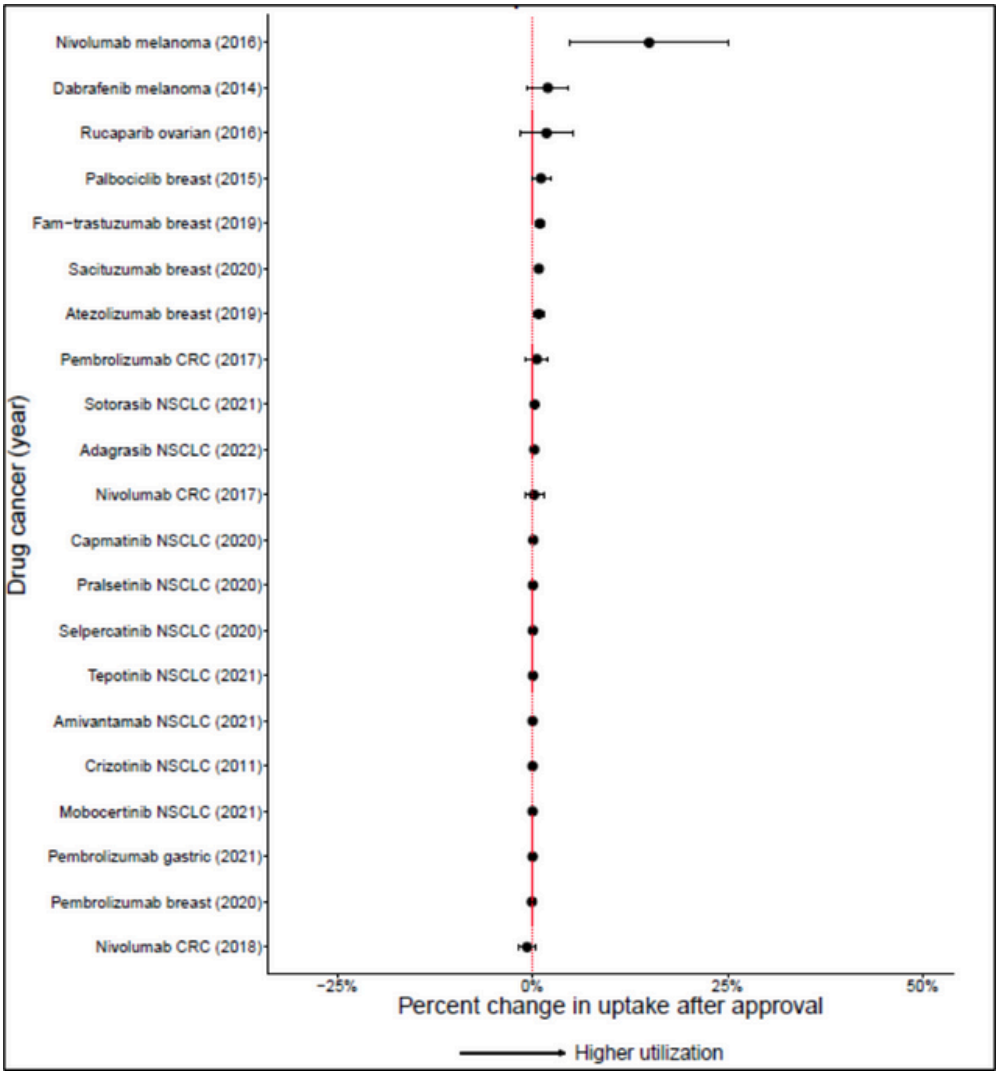

FIGURE 4 OFF LABEL (DISCORDANT BIOMARKER) CHANGES IN UPTAKE OF CANCER DRUGS IN ACCELERATED APPROVALS WITH BIOMARKER REQUIREMENT

IMPLICATIONS

In this study of cancer drug indications granted AA, increases in prescribing were greater after AA than after RA. Indications eventually converted to RA had larger initial uptake after AA, suggesting that these indications may have had stronger evidence or therapeutic need at the time of AA. Additionally, off-label prescribing after AA was rare, suggesting that oncologists are not extending the uncertainties associated with AA to other indications. Limitations of this study included the inability to examine all AAs, given unavailability or limited sample size in our dataset.

Substantial prescribing increases after AA likely reflect that this pathway is intended to address unmet medical need. These robust responses may indicate that many oncologists are unaware of or unconcerned about the provisional evidence underlying AA. In contrast, the modest average prescribing increases after conversion to RA suggest that oncologists do not distinguish between AA vs. RA, do not recognize the different evidentiary standards supporting them, or attach low incremental value to RA compared to AA.

Our findings, along with evidence that prices do not increase after positive confirmatory trials,5 suggests that drug manufacturers have little incentive to complete AA post-marketing requirements quickly. Recent reforms,6(p),7 including expectations for confirmatory studies to be underway at the time of AA, use of single continuous studies to support both AA and RA, and streamlined withdrawal procedures, may facilitate the timely confirmatory evidence for AA drugs, an important goal given the observed rapidity of AA uptake.

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