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Corresponding Author: Katarzyna J. Jerzak, MD, MSc, Division of Medical Oncology, Sunnybrook Odette Cancer Centre, University of Toronto, 2075 Bayview Ave, Rm T2 045, Toronto, ON M4N 3M5, Canada (katarzyna.jerzak@sunnybrook.ca).

Author Contributions: Dr Jerzak had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Sharma, Sahgal, Das, Lim-Fat, Jerzak.
Acquisition, analysis, or interpretation of data: Sharma, Corbett, Soliman, Sahgal, Jerzak.
Drafting of the manuscript: Sharma, Corbett, Sahgal, Jerzak.
Critical revision of the manuscript for important intellectual content: Sharma, Soliman, Sahgal, Das, Lim-Fat, Jerzak.
Statistical analysis: Sharma, Jerzak.
Administrative, technical, or material support: Sharma, Sahgal, Jerzak.
Supervision: Soliman, Sahgal, Jerzak.

Conflict of Interest Disclosures: Dr Sahgal's Disclosures: Consultant for Varian, Elekta (Gamma Knife Icon), BrainLAB, Merck, Abbvie, Roche; Vice President of the International Stereotactic Radiosurgery Society (ISRS); Co-Chair of the AO Spine Knowledge Forum Tumor; past educational seminars (honorarium) for AstraZeneca, Elekta AB, Varian, BrainLAB, Accuray, Seagen Inc; Research Grants: Elekta AB, Varian, Seagen Inc, BrainLAB; Travel accommodations/expenses: Elekta, Varian, BrainLAB; Dr Sahgal also belongs to the Elekta MR Linac Research Consortium and is a Clinical Steering Committee member, and chairs the Elekta Oligometastases Group and the Elekta Gamma Knife Icon Group. Dr Das reported personal fees from Ontario Health (Cancer Care Ontario), for which he serves as Provincial Lead for CNS Oncology, other from Subcortical Surgery Group, for which he sits on the advisory board and has received compensation for travel and accommodations, grants from Alkermes for basic laboratory collaborative work, and grants from Canadian Institutes of Health Research for basic laboratory work outside the submitted work. Dr Jerzak reported personal fees as a consultant and/or advisory board member from Amgen, AstraZeneca, Apobiologix, Eli Lilly, Eisai, Exact Sciences, Knight Therapeutics, Merck, Myriad Genetics Inc, Pfizer, F. Hoffmann-La Roche Ltd, from Novartis, and Seagen; as well as grants from AstraZeneca, Eli Lilly, and Seagen outside the submitted work. In addition, Dr Jerzak had a patent #WO/2017/106974 issued regarding the use of dronedarone and related derivatives as anticancer agents. No other disclosures were reported.

Data Sharing Statement: See Supplement 2.

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Exposure to US Cancer Drugs With Lack of Confirmed Benefit After US Food and Drug Administration Accelerated Approval

Between 2009 and 2022, the US Food and Drug Administration (FDA) approved 48 drugs for 66 oncology-related indications under the Accelerated Approval (AA) program.[1] Indications granted AA based on surrogate end points are subsequently required to confirm clinical benefit.[2] Since 2009, 15 indications (23%) have been withdrawn due to lack of benefit over standard of care.[3] We estimate the proportion of patients who received treatment for 5 oncology-related indications later withdrawn after failure to confirm efficacy under the AA program.

Supplemental content

Methods | This cross-sectional study included patients with advanced or recurrent breast, bladder, hepatocellular, gastric, or small cell lung cancer between May 18, 2016, and March 8, 2022, treated with at least 1 line of systemic therapy. We used deidentified, electronic health record (EHR)–derived, patient-level data curated via technology-enabled abstraction.[4] The Copernicus Group and University of Pennsylvania institutional review boards approved this study and granted waivers of informed consent owing to use of deidentified data. This study followed the STROBE reporting guideline.

We studied 5 disease-specific AA indications with subsequent published negative phase III confirmatory trials and indication withdrawal (**Table**). These drugs had additional biomarker-specific, cancer-agnostic indication approvals, such that they were available for use before AA and continued to be available after AA withdrawal. Outcomes were calculated for patients aged 18 years or older who initiated therapy and were eligible for the AA indication. Race and ethnicity were identified from the EHR and included as covariates because minority status is associated with decreased access to novel therapies. We excluded patients with 1 or more cancers or, for biomarker-specific indications, missing biomarker data. The primary outcome was initiation of AA therapies as a proportion of all indication-specific treatment initiations. We calculated the primary outcome at 3 intervals: AA to indication withdrawal, AA to negative confirmatory trial, and negative trial to indication withdrawal. Because 4 indications were reviewed at the April 2021 FDA Oncology Drug Advisory Committee meeting, we included this date as a discrete point. Logistic regression–estimated time trends with restricted cubic splines were used to estimate the daily percentage of treatment-eligible patients who initiated a withdrawn AA drug. Analyses were performed using SAS, version 9.4 (SAS Institute Inc).

Results | The cohort included 4342 patients who received 6560 eligible lines of therapy (median age, 70 [range, 24-85] years; female, 1639 [39%]; male, 2649 [61%]; Asian, 93 [2%]; Black, 348 [8%]; Hispanic, 248 [6%]; White, 2909 [67%]; Other, 637 [15%]), and 3709 (85%) received care at community practices. The median time from AA to indication withdrawal was 46 (range, 12-58) months. Between AA and subsequent withdrawal, 1361 oncology treatment initiations (26.1%) involved an AA therapy that was subsequently withdrawn (triple-negative breast, 23.1% [113 of 490]; bladder, 22.5% [695 of

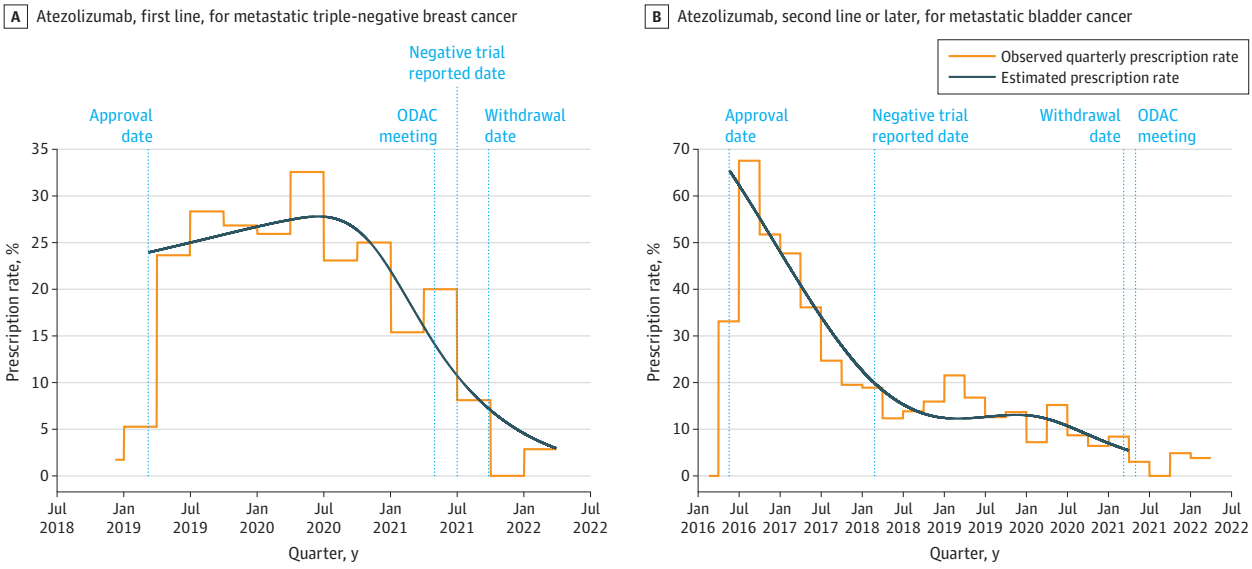
Table. Indications, Dates, and Observed Prevalence of Accelerated Approval (AA) Drug Usage

	Atezolizumab	Pembrolizumab	Atezolizumab	Nivolumab	Nivolumab
Indication[a]	Breast, triple-negative	Gastric, PD-L1 positive	Bladder	HCC	SCLC
Line of therapy	First	Third	Later	Later	Later
Date of AA	3/8/2019	9/22/2017	5/18/2016	9/22/2017	8/16/2018
Date of negative trial publication	7/1/2021	6/4/2018	2/24/2018	10/1/2019	5/1/2021
Date of withdrawal	9/25/2021	7/7/2021	3/8/2021	7/23/2021	12/29/2020
Prevalence per interval, %					
AA to withdrawal	23.1	41.4	22.5	38.8	23.6
AA to negative confirmatory trial	24.1	71.4	39.7	55.6	21.0
Negative confirmatory trial to withdrawal	8.6	38.6	12.8	20.3	2.5

Abbreviations: HCC, hepatocellular carcinoma; PD-L1, programmed cell death 1 ligand 1; SCLC, small cell lung cancer.

[a] All indications are for advanced cancer.

Figure. Representative Trends in Accelerated Approval (AA) Oncology Drug Use Over Time, 2016-2022



Shown are the trends in use of oncology drugs that received AA and were subsequently withdrawn between 2016 and 2022. Observed quarterly prescription rate of AA therapies is a proportion of all treatment initiations for an indication, and estimated prescription rate is the daily percentage of treatment-eligible patients who used an AA drug based on logistic regression with restricted cubic splines. ODAC indicates the US Food and Drug Administration Oncology Drug Advisory Committee.

3096]; hepatocellular, 38.8% [323 of 832]; gastric, 41.4% [101 of 244]; small cell lung, 23.6% [129 of 546]) (breast and bladder shown in the **Figure**). Prevalence of AA drug initiations was higher between AA and negative trial publication (overall, 35.5%; triple-negative breast, 24.1%; bladder, 39.7%; hepatocellular, 55.6%; gastric, 71.4%; small cell lung, 21.0%) than between negative trial publication and withdrawal (15.7%, 8.6%, 12.8%, 20.3%, 38.6%, 2.5%, respectively) (Table).

Discussion | Among 5 oncology indications, 26.1% of eligible treatment initiations involved an AA indication subsequently withdrawn due to lack of benefit. An expected trade-off exists between expediting access to promising cancer drugs and withdrawal of some indications.[5] Given the growth of withdrawals due to negative confirmatory trials and emerging evidence on the high spending associated with AA drugs, it is critical to balance early access against population-level exposure to cancer therapies with no benefit over standard of care.[6] Limitations included an inability to assess population-level exposure because only 5 withdrawn AA indications had sufficient sample and follow-up for analysis. Earlier access and more rapid FDA responses to negative confirmatory trial data, a key proposal of the Accelerated Approval Integrity Act proposed in March 2022, may minimize exposure to AA therapies with lack of benefit.

Ravi B. Parikh, MD, MPP
Rebecca A. Hubbard, PhD
Erkuan Wang, MA
Trevor J. Royce, MD, MPH
Aaron B. Cohen, MD, MSCE
Amy S. Clark, MD, MSCE
Ronac Mamtani, MD, MSCE

Author Affiliations: Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania (Parikh, Hubbard, Wang, Clark, Mamtani); Flatiron Health, New York, New York (Royce, Cohen).

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Corresponding Author: Ravi B. Parikh, MD, MPP, Perelman School of Medicine, University of Pennsylvania, 423 Guardian Dr, Blockley 1102, Philadelphia, PA 19104 (ravi.parikh@pennmedicine.upenn.edu).

Author Contributions: Dr Parikh and Mr Wang had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Parikh, Royce, Cohen, Mamtani.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Parikh, Wang, Royce, Clark.
Critical revision of the manuscript for important intellectual content: Parikh, Hubbard, Royce, Cohen, Clark, Mamtani.
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COMMENT & RESPONSE

Increased Tumor Mutation Burden Levels and Sensitivity of Non–Small Cell Lung Cancer to PD-L1 Blockade

To the Editor In their cohort study in *JAMA Oncology*, Ricciuti et al[1] found that increased tumor mutation burden levels were associated with immune cell infiltration and inflammatory T-cell-mediated response, resulting in increased sensitivity to programmed cell death-1 (PD-1) or PD-1 ligand (PD-L1) blockade in non-small cell lung cancer (NSCLC) across PD-L1 expression subgroups. These findings provide new insights into the use of PD-1/PD-L1 inhibitors in advanced NSCLC. However, we have several concerns.

First, according to the data of a phase 2 clinical trial,[2] PD-1 blockade monotherapy was used for first-line treatment of *EGFR*-mutant NSCLC, and the proportion of patients with PD-L1 expression 50% or greater accounted for 73%, while the objective response rate was only 9%. The clinical trial was terminated early due to lack of efficacy. In the retrospective study by Ricciuti et al,[1] 138 of 143 (96.5%) patients with NSCLC with *EGFR* mutation were defined as having low tumor mutation burden, and among them, patients with PD-L1 expression 50% or greater had an objective response rate as high as 38.1% (95% CI, 33.3%-43.0%). Therefore, we hope Ricciuti et al provide survival data of patients with common driver alterations independently to prove the authenticity of the data.

Second, more than 65% of the enrolled patients in the present study[1] had previously received 1 or more antitumor therapies, and it was inevitable that this would affect overall survival (OS). Multiple clinical trials have demonstrated that first-line treatment with tyrosine kinase inhibitors significantly prolonged OS in patients with positive driver alterations.[3,4] Therefore, we consider that the published results of this study[1] cannot exclude OS bias caused by inclusion screening. We recommend that Ricciuti et al provide survival data and duration of remission after initiation of immunotherapy for patients who did not receive immune checkpoint inhibitors in the first-line therapy, to provide meaningful guidance for clinical treatment selection.

In addition, we found a small mistake in panel C of Figure 1 of the original article.[1] The label of the vertical axis "Progression-free survival, %" should be corrected to "Overall survival, %."

Xinmu Zhang, MD, PhD
Li Zhang, MD

Author Affiliations: Department of Liver Surgery, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College (CAMS & PUMC), Beijing, China (X. Zhang); Division of Pulmonary and Critical Care Medicine, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College (CAMS & PUMC), Beijing, China (L. Zhang).

Corresponding Author: Li Zhang, MD, Division of Pulmonary and Critical Care Medicine, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College (CAMS & PUMC), 1# Shuai Fu Yuan, Dong Cheng District, Beijing, 100730, China (zhanglipumch1026@sina.com)

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