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Letter to the Editor

How the US Food and Drug Administration's approval of aducanumab for Alzheimer's disease has implication for oncology and beyond



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On 7th June 2021, the US Food and Drug Administration (FDA) approved aducanumab for the treatment of Alzheimer's disease [1]. This is the first approved therapy for Alzheimer's since 2003 and is the first drug to lower levels of amyloid plaque within the brain of affected patients. Two years ago, Biogen halted all clinical development of aducanumab, after an interim analysis of two phase III trials (ENGAGE and EMERGE trials), suggested both were unlikely to show cognitive benefit [2]. However, subsequent re-analysis of one trial (EMERGE) in a subgroup of patients prompted Biogen to seek FDA approval [3]. The FDA's Peripheral and Central Nervous System Drugs (PCNS) Advisory Committee meeting met on 6th November 2020 to evaluate the Biologic License Application for aducanumab. After reviewing the application, the committee was critical of the study results and the statistical methodology [3]. Overall, of the 11 panelists, 10 voted against the drug's efficacy, with 1 abstention (10-0-1). Six months later, the FDA approved this antibody, via its accelerated pathway, deeming amyloid plaque a

surrogate end-point 'reasonably likely to predict clinical benefit'. Notably, this conclusion contradicts a 2018 advisory document by the agency that found, 'there is unfortunately at present no sufficiently reliable evidence that any observed treatment effect on such biomarker measures would be reasonably likely to predict clinical benefit'. [4]. The FDA decision to approve aducanumab has far reaching implications in the Alzheimer's drug space, but simultaneous implications for new cancer drug approvals. Here, we consider six consequences.

First, accelerated approval for cancer drugs is now poised for a dramatic expansion. Most cancer drugs that receive accelerated approval do so on the basis of response rate, a measure of tumour shrinkage, often derived from a single-arm study. Novel measures of disease reduction, such as pathologic complete response rates, or reduction in minimal residual disease have also served as the basis for accelerated approval. The FDA's decision around aducanumab suggests that any intra-cellular or molecular marker may now be submitted for accelerated approval. Amyloid reduction has no surrogate validation study supporting its use, and the FDA's own statistical analysis has rejected it as a surrogate end-point, yet the agency nevertheless used this end-point for approval. As such, a regulatory basis now exists to approve drugs on the basis of single-arm studies that

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have no single agent activity—0% response rates—if these drugs alter intracellular signalling cascades. Given the sheer number of putative molecules in development, such a shift could result in an order of magnitude more approvals annually.

Second, approximately 1 in 3 cancer drugs currently come to the market based on improvements in overall survival in adequately powered randomised controlled trials [5]. The FDA's treatment of aducanumab has direct implication for these studies. If these trials are positive, the manufacturer has a case to seek traditional or regular approval. If these trials are negative, but there is a numerical difference in response rate or any other biomarker, the company has a case for accelerated approval. In other words, all positive trials are positive, but so too are some negative trials. This shift has profound implications for the incentives around large randomised clinical trials. As success rates rise, the threshold to fund a study falls. Drugs with real toxicity, minimal activity or threadbare preclinical rationale may on balance be more likely to be taken to pivotal study.

Third, new oncology therapies approved by accelerated approvals that have negative confirmatory trials (as highlighted by the Oncology Drug Advisory Committee (ODAC) meetings of April 2021) often continue to maintain approval status. Once new therapies are approved, it is unlikely that mandated withdrawal by the FDA will occur. Finally, the FDA has required a confirmatory trial to validate the anticipated benefit of aducanumab; however, it has granted an unprecedented period of 9 years for completion of this. Typically, in oncology, when a drug is granted accelerated approval, the FDA mandates confirmatory trials should be underway by the time of approval. This decision sets another undesirable practice for delaying necessary confirmatory trials for drugs approved by accelerated approval.

Fourth, aducanumab gives cancer drug regulators ability to grant broad sweeping approvals. For aducanumab, the clinical trials were conducted on specific populations (patients with mild cognitive impairment or early-stage Alzheimer's, whose brains contain higher than normal amyloid levels); the FDA label initially went beyond this indication stating, 'for the treatment of Alzheimer's disease', implying more ubiquitous use. However, after widespread reproval from both supporters and critics of the drug, one month after approval, the FDA announced revisions restricting the indication to 'mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trial'. [1] In cancer medicine, many drugs are initially approved with restrictions on therapy line. For example, sotorasib was approved after platinum and/or immunotherapy, based on a 36% response rate [1]. Now, the FDA can grant targeted drugs an accelerated approval irrespective of

the line, even if registration trials use this as a key inclusion criterion.

Fifth, a negative advisory vote is not binding, but now even a unanimous negative vote is not binding. The FDA's Oncology Centre of Excellence has approved new oncology therapies despite negative votes from the ODAC [6,7]. However, the approval of aducanumab pushes this to the extreme where a 10-0-1 vote leads to approval. As such, the ability of a negative advisory panel has limited significance.

Sixth, the approval of aducanumab also reminds us there is a difference between cost and budgetary impact. Biogen will charge an estimated \$56,000 annually for treatment, with over 6 million patients eligible in the United States of America alone; this immediately guarantees blockbuster status [3]. The cost of cancer therapies approved based on surrogate biomarkers of efficacy is significant (\$150,000 annually) [8]. However, the actual observed growth in cancer drug expenditure is not as large as predicted, suggesting a sizable fraction of eligible patients are not receiving it or receiving a significant discount. If aducanumab is reimbursed by Medicare, then cancer drug makers will be incentivised to push their market share in unprecedented ways.

Aducanumab is the first approval of any new drug in a therapy area which has not seen any clinical development for 20 years. At the same time, the decision by the FDA to ignore the PCNS Advisory Committees' clear recommendation has been received with criticism from the experts, patient groups and investigators on the original trials [3]. Most concerning, the approval of aducanumab in Alzheimer's disease will have unintended consequences well beyond the scope of this disease, affecting drug development in other therapeutic areas and undermining essential regulatory standards. We have highlighted 6 implications between the approval of aducanumab and oncology regulatory approvals. We hope this will have the potential to change the regulatory process at the FDA and beyond, prioritising patients' rights to receive safe and efficacious therapies.

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Conflict of interest statement

Dr Vinay Prasad disclosures and conflicts of interests include Arnold Ventures (Research Funding & Royalties), Johns Hopkins Press (Royalties), Medscape (Honoraria), Evicore (Speaking fees) and Plenary Sessions (funding from Patreon backers). Dr

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