Division of
Pharmacoepidemiology & Pharmacoeconomics
Department of Medicine, Brigham & Women's Hospital, Harvard Medical School

Accelerated Approval and Aducanumab

Aaron S. Kesselheim, M.D., J.D., M.P.H.
Professor of Medicine, Harvard Medical School
Director, Program On Regulation, Therapeutics, And Law (PORTAL)
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Disclosures

- No one in our Division has personal financial relationships with any pharmaceutical company

- Current research funding from Arnold Ventures, Anthem Public Policy Institute, West Health, Kaiser Permanente Institute of Health Policy, FDA, Greenwall Foundation, Commonwealth Fund

- (Former) Member of the FDA Peripheral and Central Nervous System Advisory Committee that reviewed aducanumab

Accelerated Approval

- Approval based on surrogate measure "reasonably likely to predict clinical benefit"
  - Serious/life-threatening illnesses providing meaningful therapeutic benefit over existing treatments
- FDA-initiated in 1992 in wake of HIV crisis as a way of expediting certain drugs
  - 1987-2014: 9% of new drug approvals via accelerated approval; now closer to 15%
- Surrogate measures are laboratory tests, radiologic tests or other biomarkers; to be contrasted with clinical endpoints (how a patient feels, functions or survives)
  - AA requires that the surrogate measures used as endpoints only be "reasonably likely"
- Required to conduct post-approval "confirmatory" study
  - May also be required contain line in labeling "This indication approved under accelerated approval based on XXXXX. Continued approval for this indication may be contingent on verification and description of clinical benefit in a confirmatory trial." *or* "An improvement in survival or disease-related symptoms have not been established."

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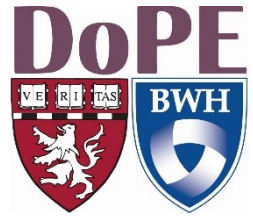
Darrow, Avorn, Kesselheim, NEJM, 2014



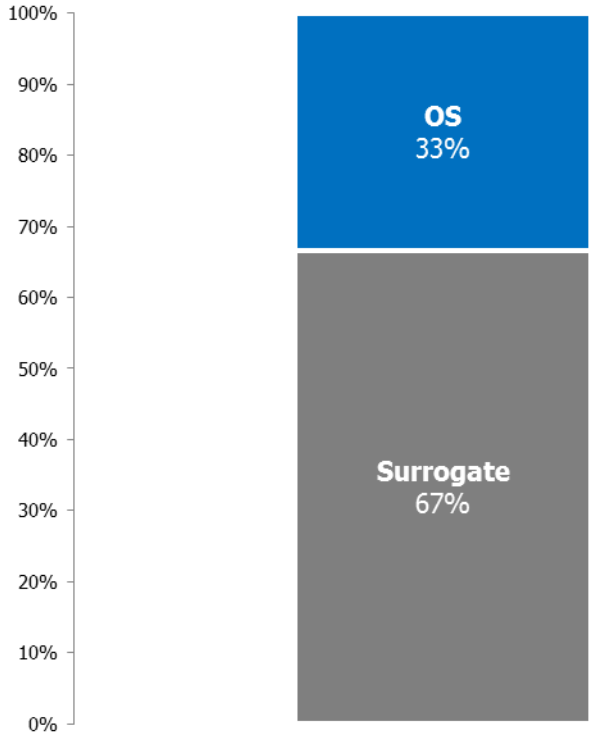
Advantages of surrogate measures

- Predicting efficacy
- Identifying drug safety problems earlier
- Reduce cost, size, and duration of clinical trials
- Validation: (1) The biological marker must be correlated with the clinical endpoint; and (2) the marker must fully capture the net effect of the intervention on the clinical efficacy endpoint
  - Typically requires a meta-analysis of numerous trials
- Examples: blood pressure and heart disease; viral load and HIV; disease-free survival and overall survival in HER2+ breast cancer or stage 3 colon cancer

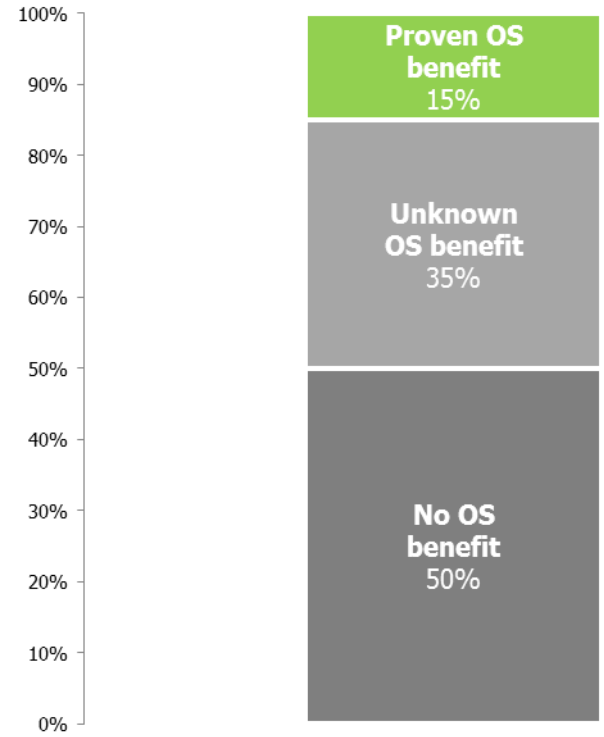
Fleming, Health Affairs, 2005; Gyawali et al, eClinicalMedicine, 2020

Problems with surrogate measures: Efficacy

% of approvals based on surrogate



% with OS benefit (with follow-up)



Kim, Prasad, JAMA Intern Med, 2015. Includes all cancer drugs approved by FDA between 2008-2012.

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Surrogate measures may fail because they are not on the causal pathway of the disease process or because the intervention being tested may affect only one of several causal pathways

DoPE

Problems with surrogate measures: Safety

Drug	Use	Surrogate	Actual Outcome
Aprotinin	High-risk cardiac surgery	Decreased need for transfusion	Mortality
Clofibrate	Increased cholesterol in healthy men	Decreased cholesterol	Mortality
Doxazosin	Hypertension and other CV risk factors	Decreased blood pressure	Congestive heart failure
Encainide	Ventricular premature beats post-MI	Decreased ventricular ectopic beats	Mortality
Erythropoietin	Anemia due to chronic renal failure	Increased hemoglobin to >12.0	Mortality
Estrogen/ progestin	Cardiovascular disease prevention in postmenopausal women	Decreased LDL cholesterol and increased HDL cholesterol	CV disease and breast cancer
Flecainide	Post -MI patients with ventricular premature beats	Decreased ventricular ectopic beats	Mortality
Flosequinan	Chronic congestive heart failure	Improved ventricular function	Mortality
Fluoride	Fracture prevention in postmenopausal women with osteoporosis	Increased bone mineral density	Nonvertebral fractures
Ibopamine	Severe congestive heart failure	Increased exercise tolerance and decreased vascular resistance	Mortality
Metoprolol	Patients with CV risk factors undergoing non-cardiac surgery	Decreased postoperative myocardial ischemia	Increased mortality
Milrinone	Severe congestive heart failure	Increased cardiac contractility	Mortality
Moxonidine	Congestive heart failure	Decreased plasma norepinephrine	Mortality

Svensson et al. JAMA IM, 2013

Problems with surrogate measures: Cost

- US drug prices set by manufacturer at whatever level they want

Selected Drugs That Have Received Accelerated Approval since 2011 and Their Listed Cost.*

Approval Year	Drug (Brand Name)	Initial Indication	Surrogate Measure Used for Approval	Current Cost ($/mo)
2011	Crizotinib (Xalkori)	Anaplastic lymphoma kinase (ALK)–positive locally advanced or metastatic non–small-cell lung cancer	Overall response rate based on Response Evaluation Criteria in Solid Tumors	14,353
2012	Bedaquiline (Sirturo)	In combination therapy for pulmonary multidrug-resistant tuberculosis	Time to sputum culture conversion	6,000
2013	Pomalidomide (Pomalyst)	Multiple myeloma that has progressed despite receipt of two prior therapies	Overall response rate, based on European Group for Blood and Marrow Transplant criteria	14,165
2014	Blinatumomab (Blincyto)	Philadelphia chromosome–negative relapsed or refractory B-cell acute lymphoblastic leukemia	Complete remission or complete remission with partial hematologic recovery rate	56,262
2014	Pembrolizumab (Keytruda)	Unresectable or metastatic melanoma with disease progression	Overall response rate based on Response Evaluation Criteria in Solid Tumors	9,252
2014	Ceritinib (Zykadia)	ALK-positive locally advanced or metastatic non–small-cell lung cancer with disease progression or intolerance to crizotinib	Overall response rate based on Response Evaluation Criteria in Solid Tumors	14,628
2015	Panobinostat (Farydak)	Multiple myeloma that has progressed despite receipt of two prior therapies	Progression-free survival based on European Group for Blood and Marrow Transplant criteria	10,625
2015	Palbociclib (Ibrance)	Postmenopausal women with metastatic estrogen receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer	Progression-free survival based on Response Evaluation Criteria in Solid Tumors	11,224
2016	Eteplirsen (Exondys 51)	Duchenne's muscular dystrophy in patients with confirmed mutation amenable to exon 51 skipping	Increase in dystrophin in skeletal muscle	57,600

Gellad & Kesselheim, NEJM, 2017

FDA's summary of Accelerated Approval outcomes

- 1992-2017: 64 cancer drugs for 93 new indications

- Of the 93 AAs, 51 (55%) have fulfilled their postmarketing requirement and verified benefit in a median of 3.4 years after their initial AA
  - *For 14 (58%) of 24 indications granted AA from 2009 to 2013, results from required confirmatory studies were not available after a median of 5 years of follow-up*

- 5 indications receiving AA (5%) have been withdrawn from the market
  - Only 1 (bevacizumab for metastatic breast cancer) done over objection of manufacturer

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Beaver et al., JAMA Oncology, 2018; Carpenter, Kesselheim, Joffe, NEJM, 2011; Naci, Smalley, Kesselheim, JAMA, 2017

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BWH

Deeper look at the data

Table 1. Updated Properties of Confirmatory Trials for Cancer Drugs Granted Accelerated Approval[a]

Variable	No. of Trials (%)
Original FDA Report	93
Confirmed benefit	51 (55)
+Clinical outcome[b]	15 (16)
+Surrogate outcome, same as preapproval trial[b]	19 (20)
+Surrogate outcome, different from preapproval trial[b]	17 (18)
Randomized clinical trials	45 (48)
Nonrandomized trials	6 (6)
Did not confirm benefit	5 (5)
Unknown	37 (40)

Zombie Accelerated Approvals

Table 2. Recent Cancer Drug Indications That Received Accelerated Approval From US Food and Drug Administration Without Overall Survival Changes in the Postapproval Trial

Drug	Indication	Basis for Accelerated Approval	Primary End Point for Confirmatory RCTs	Results of Confirmatory RCTs	Current FDA Status
Bevacizumab	Glioblastoma	RR in phase 2	OS	OS HR, 0.95 (95% CI, 0.74-1.21); $P = .65$ PFS improved[25]	Converted to regular approval
Nivolumab	Melanoma after ipilimumab/ BRAF-inhibitor	RR in phase 3	OS	OS HR, 0.95 (95.54% CI, 0.73-1.24) PFS not improved[26]	Submitted/undecided (April 2019 status: delayed)
Atezolizumab	Urothelial	RR in phase 2	OS	OS HR, 0.87 (95% CI, 0.63-1.21); $P = .41$ PFS not improved[27]	Submitted/undecided (April 2019 status: submitted)
Pembrolizumab	Head and neck cancer	RR in phase 2	OS	OS HR, 0.82 (95% CI, 0.67-1.01) in 2018 OS HR, 0.80 (95% CI, 0.65-0.98) PFS not improved[24]	Submitted/undecided[a] (April 2019 status: delayed)

Abbreviations: FDA, US Food and Drug Administration; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized clinical trial; RR, response rate.

[a] This trial was considered as "confirmation of benefit" for our analysis.

- We identified 18 accelerated approval indications for 10 cancer drugs that failed to improve the primary endpoint in post-approval trials
  - 11 voluntarily withdrawn (6 in 2021 alone), 1 revoked, and 6 remain on the labeling
  - NCCN provides high level of endorsement for all 6
- "If there are clear reasons why a trial may not have achieved its primary end point and an unmet medical need still exists, the FDA works with sponsors to identify subsequent clinical trials that could satisfy the accelerated approval requirement."

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Gyawali, Hey, Kesselheim, JAMA IM, 2019; Beaver and Pazdur, NEJM, 2021; Gyawali, Rome, Kesselheim, BMJ, 2021

DoPE BWH

How AA is supposed to work: Imatinib for CML

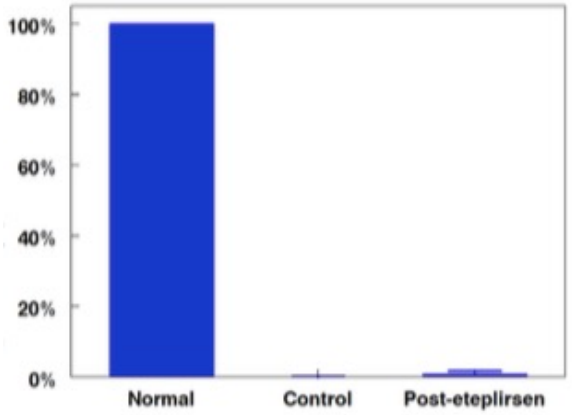
- 2001: Three Phase 2 studies in CML-CP, CML-AP, and CML-BC, enrolled total of 1027 patients resistant to interferon therapy
  - Show improvement in cytogenetic **Response Rate** (CML-CP, 49%) and hematological **Response Rate** (CML-AP [63%] and CML-BC [26%])
  - Median duration of response (~90%) of 6 months
  - 2.5 months of regulatory review
- Confirmatory study: show improvement in **PFS**
  - Example (CML-CP): estimated 87.8% of patients who achieved major response maintained response 2 yrs
  - After 2 yrs, 85.4% of patients were free of progression to accelerated phase or blast crisis, comparing favorably to IFN therapy
- Result: 2003 (2.6 years later) converted to regular approval

Cohen et al; Clinical Cancer Research, 2005

How AA is supposed to work: Bevacizumab for MBC

- 2/08: E2100, a cooperative-group randomized trial that showed a 5.5-month increase in median progression-free survival associated with the addition of bevacizumab to paclitaxel therapy (non-placebo-controlled)
- 2010: Completion of confirmatory placebo-controlled RCT in 736 pts
  - 0.8 month increase in median PFS
  - No increase in OS
  - ODAC: 12-1 to remove AA indication
- Genentech argue against the move has no precedent; second, the possibility of benefit in subgroups of patients justifies continued approval; third, individual patients' choice ought to be paramount; and fourth, the FDA's move will obfuscate the drug-development picture and discourage innovation
- 11/2011: indication removed from labeling

How AA is NOT supposed to work: Eteplirsen for DMD



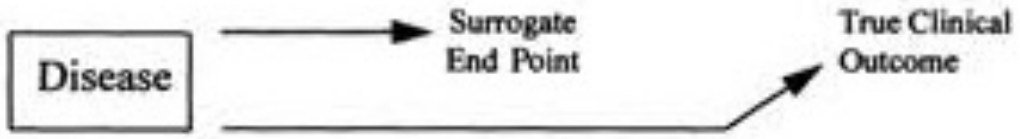
- "Exon skipping" drug to allow recovery of Becker-like functional dystrophin protein in muscle
- 4th muscle biopsy at 3-3.5 years: **0.93 ± 0.84%**
  - Compare to **0.08% ± 0.13%** dystrophin level in controls
- AdComm, FDA reviewers find that does not meet substantial evidence standard
- 9/2016 approval; overruled by OND Director Janet Woodcock
  - FDA report: *Dr. Woodcock cautioned that, if Sarepta did not receive accelerated approval for eteplirsen, it would have insufficient funding to continue to study eteplirsen and the other similar drugs in its pipeline. She stated that, without an approval in cases such as eteplirsen, patients would abandon all hope of approval for these types of products and would 'lapse into a position of' self-treatment*
- FDA require conduct of follow-up trial by May 2021; price set at $300K/yr
- 1/22/20: FDA notice of concern "have not initiated your required confirmatory study"

"The Worst Drug Approval Decision in Recent FDA History": Aducanumab for AD

- Phase 1b study: substantial reduction in amyloid, but amyloid is not a known treatment surrogate measure for clinical improvement in Alzheimer's disease
- Pivotal trials: 2 nearly identically designed placebo-controlled RCTs (EMERGE and ENGAGE) testing low- and high-doses in MCI/mild AD stopped for futility about halfway through
- As last data roll in, show statistically significant treatment effect in clinical outcome for high-dose arm in 1 of the 2 trials (high-dose arm in other trial non-sig effect that favored placebo)
  - Absolute difference in CDR-SB of 0.39 after 18 months
  - 35% of patients in high-dose groups experienced vasogenic brain edema
- Nov 2020 AdComm: "We're not using the amyloid as a surrogate for efficacy"
- June 7 2021: Accelerated Approval granted "for treatment of AD," then later revised
  - Mfr granted 9 years to complete post-approval confirmatory trial

Amyloid plaque changes as a surrogate measure?

- Amyloid cascade hypothesis: two dozen therapies in late-stage clinical trials, including at least two γ-secretase inhibitors and five β-secretase inhibitors
  - Reduce production; inhibit aggregation; promote disaggregation; increase brain clearance of beta-amyloid
  - None have produced meaningful clinical benefit, some worsen cognition
- Why?
  - One possibility: Plaques not directly cause AD: accumulation of beta-amyloid plaques in Alzheimer's disease could represent a brain response to some primary, upstream physiological event



Alexander et al, NEJM, 2021

Alternative explanation

- Failed past clinical studies may have included participants without brain amyloid, used doses too low to affect pathophysiology or clinical progression, or recruited patients with later-stage disease in whom irreversible neurologic damage had already occurred
- Donanemab (different epitope) Phase 2 RCT of 257 patients published in NEJM
  - Using composite cognitive-function end point (integrated AD rating scale, 0-144), after 18 months of treatment, −6.86 with donanemab and −10.06 with placebo (p=0.04)
  - No significant difference in CDR-SB (secondary outcome)

Is AA appropriate for aducanumab?

- Is it "reasonably likely" that a change in observable amyloid plaques caused by high-dose aducanumab will improve the course of patients with Alzheimer's disease?
- A recent meta-analysis of amyloid-lowering drugs concluded that "amyloid reduction is unlikely to substantially alter disease course within a reasonable time frame"
- Before aducanumab's approval, the FDA itself in its own guidance suggested that it did not consider beta-amyloid a valid pharmacodynamic biomarker, much less an acceptable surrogate end point for clinical trials
- An effective surrogate should correlate with a clinical end point in clinical studies, but an FDA statistical review of EMERGE and ENGAGE found no evidence that amyloid changes correlated with cognitive or functional changes, concluding that "it is not clear that there is any linkage between reduction in plaque and long term clinical change"

Glymour et al, BMJ, 2021

AA-related concerns for aducanumab approval

- Hard to reconcile the lack of convincing clinical benefit across two prospective randomized trials with the FDA's conclusion that accelerated approval was appropriate because it expects some clinical benefit of unknown magnitude over an unknown time frame
- Why 9 year follow up? What happens then?
- Poor communication of basis of approval ("*Aduhelm (aducanumab), developed by Biogen and Eisai, was approved by the U.S. Food and Drug Administration in June 2021, making it the first disease-modifying therapy for the treatment of Alzheimer's disease*.")
- Cost/coverage

CTSL Project Idea: Improving Accelerated Approval

- Confirmatory trials should use clinical endpoints
- Protocol for the confirmatory trials should be finalized, and agreed upon, as a condition of accelerated approval, so that trial enrollment can begin concurrent with approval (ideally before)
- Withdrawal of accelerated approval should be automatically triggered when the confirmatory trial is negative
- Price of accelerated approval drugs should be curtailed
  - Capping the price of drugs prescribed for their accelerated approval indications at cost of production plus an additional small percentage
  - Excluding them from standard drug coverage mandates affecting Medicare and Medicaid
  - MACPAC proposed adding an inflationary rebate penalty if the confirmatory trials are not completed within a specified time period

Thank you!

Medicare spending on accelerated approval drugs from 2015-2019

- 67 drugs had at least one accelerated approval indication (50 were for cancer)
- Result: Increase $3 billion to $9 billion, most concentrated in Part B
- 2.5% of $127 billion in estimated total net Part D spending and 16% of $57 billion in total Part B drug spending in 2019
- 11% of Medicare spending on drugs with accelerated approval was for drugs ***exclusively*** marketed under the accelerated approval pathway

Economic analysis

- Medicaid spending on 88 accelerated approval drugs from January 2015 to September 2020
- $5.9 billion on these drugs
  - $2.1 billion (37%) occurred in quarters when the drug was exclusively marketed for AA indications
  - 33% was on drugs with an AA more than 5 years old
  - As a percent of overall Medicaid spending, increased from 2.3% to 3.5% of spending from 2015-2017
- Assuming higher rebates (30-80%), Medicaid could have saved $0.6 to $4.6 billion over this six-year period
  - But indication-specific pricing is hard to implement