ings could be due to a chance or unmeasured confounding and need confirmation in other studies, they do represent the first analytical data of this potential association. If true, the observed association could either be attributed to the unmasking of a latent demyelinating disease[6] or to the emergence of a de novo demyelinating disease.[1]

The rarity of demyelinating diseases limited the statistical power and capacity to adjust for or match on potential confounder variables. Thus, the estimates should be interpreted with caution because confounding cannot be excluded.

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HEALTH CARE REFORM

Cancer Drugs Approved on the Basis of a Surrogate End Point and Subsequent Overall Survival: An Analysis of 5 Years of US Food and Drug Administration Approvals

Most contemporary approvals of new cancer drugs are made on the basis of a surrogate end point, such as response rate or progression-free survival (PFS).[1] When the approval is based on a surrogate end point, subsequent studies are advised and often obligated to clarify the drug's effect on overall survival. One such drug is bevacizumab, which received accelerated approval on the basis of PFS for patients with metastatic breast cancer. Later findings revealed no improvement in overall survival and significant toxicity, which required a removal of marketing authorization.[2]

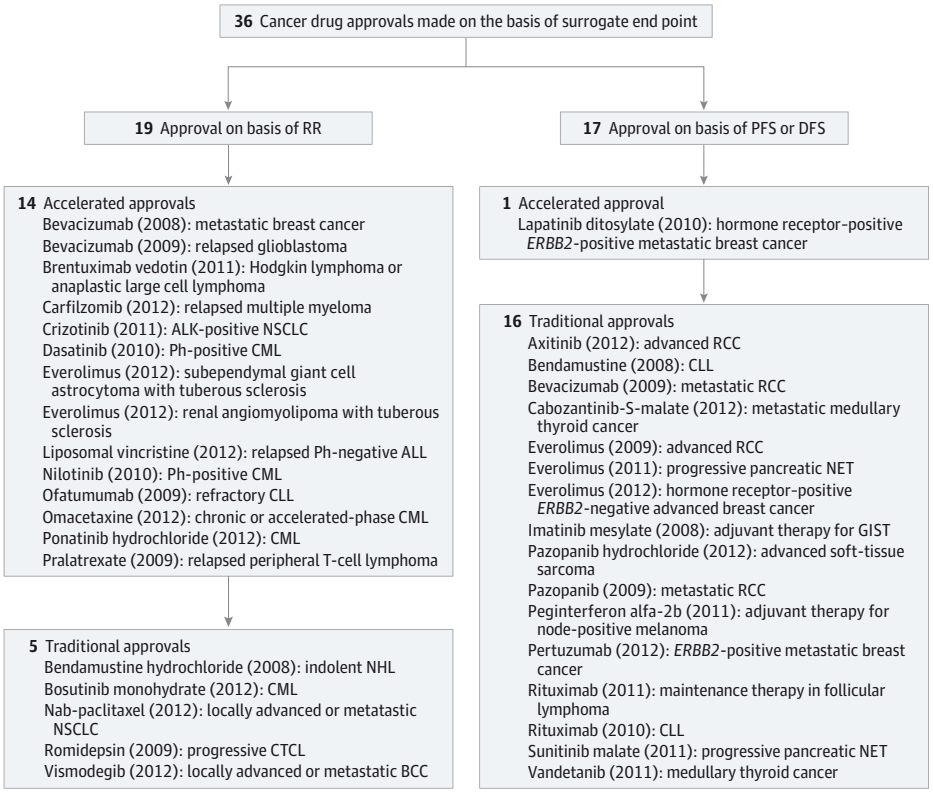
A 2009 Government Accountability Office report criticized the US Food and Drug Administration (FDA) for failing to enforce postmarketing study commitments for surrogate approvals. Among the more than 400 postmarketing studies requested, approximately 30% were pending, ongoing, delayed, or terminated years later, yet the FDA never exercised its authority to remove a product from the market.[3] For these reasons, we sought to investigate how often cancer drugs are approved based on a surrogate end point, whether subsequent studies for these drugs are reported, and whether the drugs improve overall survival.

Methods | We examined all marketing approvals by the FDA from January 1, 2008, through December 31, 2012. We identified the pathway for approval (accelerated vs traditional) and the surrogate end point used, such as tumor response rate or PFS. This investigation of published reports was exempt from institutional review board approval.

For all drugs approved on the basis of a surrogate end point, we performed a systematic search of the published literature using Google Scholar as of August 22, 2015, and identified any subsequent reports of the drug's effect on overall survival. We credited a drug for improving overall survival if that drug improved survival as the sole investigational agent in any combination or in any line of treatment (eg, if approved for second-line treatment of metastatic disease, but the drug improved survival in first-line treatment, we would credit the drug as improving survival). We identified whether crossover (from the control arm to the investigational agent) was used in the randomized clinical trial or via a postprotocol expansion study. We analyzed the study data from August 22 to September 1, 2015.

Results | We identified 54 approvals made during our search period, with 36 drugs (67%) approved on the basis of a surrogate end point. **Figure 1** shows all surrogate approvals, the efficacy end point at the time of approval, and the regula-

Figure 1. Oncology Drug Approvals Made on the Basis of a Surrogate End Point During the Study Period

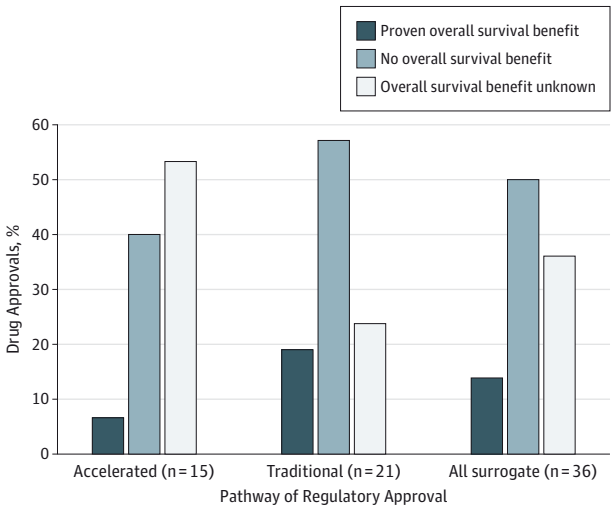


The study period extends from January 1, 2008, through December 31, 2012. ALK indicates anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; BCC, basal cell carcinoma; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CTCL, cutaneous T-cell lymphoma; DFS, disease-free survival; *ERBB2* (formerly *HER2* or *HER2/neu*), erb-b2 receptor tyrosine kinase 2; GIST, gastrointestinal stromal tumor; NET, neuroendocrine tumor; NHL, non-Hodgkin lymphoma; NSCLC, non–small cell lung cancer; PFS, progression-free survival; Ph, Philadelphia chromosome; RCC, renal cell carcinoma; and RR, response rate.

tory pathway. Approval was granted on the basis of a surrogate for all 15 accelerated approvals (100%) and 21 of 39 traditional approvals (54%). Rate of response, measured by a reduction in tumor size or volume, was the primary measure of efficacy for 19 of 36 surrogate-based approvals (53%), whereas PFS or disease-free survival was cited as the basis of 17 of 36 approvals (47%).

With a median follow-up of 4.4 years, 5 drugs were subsequently shown to improve overall survival in randomized studies (in 1 of 15 accelerated approvals and in 4 of 21 traditional approvals), 18 drugs failed to improve overall survival (in 6 of 15 accelerated approvals and in 12 of 21 traditional approvals) as primary or secondary outcomes, and 13 drugs continue to have unknown survival effects, meaning they remain untested or they have no reported survival results as primary or secondary outcome (in 8 of 15 accelerated approvals and in 5 of 21 traditional approvals). **Figure 2** compares the percentage of approved drugs with known and unknown effects on overall survival based on our systematic review of subsequent literature. The use of crossover occurred in 11 of 36 trials (31%) and did not differ among trials that found a survival advantage vs those that did not (1 of 5 [20%] vs 10 of 18 [55%]; $P = .16$).

Figure 2. Overall Survival Results for Cancer Drug Approvals Granted on the Basis of a Surrogate End Point



Exact numbers of approvals depicted in this graph are given in the Results section.

Discussion | During our study period, 36 of 54 contemporary cancer drug approvals (67%) were made on the basis of a surrogate end point. With several years of follow-up, 31 (86%) of these approvals (57% of the 54 drugs approved) have unknown effects on overall survival or fail to show gains in survival. Our results show that most cancer drug approvals have not been shown to, or do not, improve clinically relevant end points.

Since 2008, the FDA has approved a higher percentage of drugs than previously,[4] and cancer drugs are approved on the basis of surrogates that have poor correlations with overall survival.[2] Our results suggest that the FDA may be approving many costly, toxic drugs that do not improve overall survival. Enforcement of postmarketing studies is therefore of critical importance.

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Study concept and design: Both authors.
Acquisition, analysis, or interpretation of data: Both authors.
Drafting of the manuscript: Prasad.
Critical revision of the manuscript for important intellectual content: Kim.
Statistical analysis: Kim.
Study supervision: Prasad.

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LESS IS MORE

Appropriate Prescribing for Patients With Diabetes at High Risk for Hypoglycemia: National Survey of Veterans Affairs Health Care Professionals

Evidence is accumulating that older individuals with diabetes mellitus have little to gain from the treatment burdens of stringent blood glucose control.[1,2] In addition to concerns about increased mortality with tight control,[1] some older patients with diabetes may also be at risk for hypoglycemia-related harms from medications prescribed to meet standard hemoglobin A_{1c} (HbA_{1c}) targets.[3] This problem has motivated patient safety campaigns that cue health care professionals to limit medications for certain older patients (eg, those with an HbA_{1c} level <7.5%, renal disease, or dementia) (to convert HbA_{1c} to a proportion of total hemoglobin, multiply by 0.01).[4] In this study, we examined beliefs of primary care health-care professionals (PCPs) to anticipate how PCPs might receive such recommendations.

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Methods | We surveyed a national random sample of practicing nontrainee Department of Veterans Affairs (VA) PCPs, including physicians, nurse practitioners, and physician assistants. The study, including a waiver of signed informed consent, was approved by the institutional review board of the Ann Arbor VA Healthcare System and was conducted from October, 6, 2014, to December, 8, 2014. Participants answered questions about practice characteristics, performance incentives, beliefs about decreasing use of inappropriate services, and demographics. They also received a scenario about a 77-year-old man with long-standing type 2 diabetes mellitus at high risk for hypoglycemia (HbA_{1c} level, 6.5%; severe kidney disease; and receiving glipizide, 10 mg, twice daily). Barriers to and facilitators of medication deintensification were identified using statements answered on a 4-point scale (strongly disagree to strongly agree) (**Table 1**). In addition, participants were asked to rate the level of difficulty they anticipated in following the Choosing Wisely recommendation to "avoid using medications other than metformin to achieve HbA_{1c} less than 7.5% in most older adults."[5(p1)] Data were analyzed from March 18, 2014, to April 2, 2014. We used logistic regression to identify PCP and practice setting characteristics associated with anticipated difficulty following the Choosing Wisely HbA_{1c} recommendation.

Results | Of 1222 eligible PCPs, 594 returned usable surveys (48.6% response rate; numbers vary due to item nonresponse). Of these, 311 (53.0%) were women, 138 (23.4%) were nurse practitioners, 46 (7.8%) were physician assistants, and 405 (68.8%) were physicians.

A total of 217 PCPs (38.6%) thought that the 77-year-old patient at high risk for hypoglycemia would benefit if his HbA_{1c} level was maintained below 7.0%, and 252 participants (44.9%) reported that they would not worry about potential harm from tight control. In addition, 236 PCPs (42.1%) would worry that deintensification in this context (HbA_{1c} level, 6.5%) would lead to an HbA_{1c} level that is outside of current performance measures; 132 of the participants (23.5%) worried that deintensification could leave them vulnerable to future malpractice claims. Table 1 presents participant responses to all scenario questions.

A total of 161 of 562 PCPs (28.7%) agreed it would be somewhat or very difficult to follow the Choosing Wisely HbA_{1c} recommendation for older adults. The PCPs who agreed that maintaining the HbA_{1c} level below 7.0% would benefit the patient and who reported worrying about malpractice claims were more likely to report difficulty following the HbA_{1c} recommendation in the final adjusted regression model (P = .02). Conversely, PCPs who reported worrying that the patient would be harmed with tight blood glucose control were less likely to report difficulty following the HbA_{1c} recommendation (P = .04) (**Table 2**).