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 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-
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.

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, and cancer drugs are approved on the basis of surrogates that have poor correlations with overall survival. 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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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. In addition to concerns about increased mortality with tight control, some older patients with diabetes may also be at risk for hypoglycemia-related harms from medications prescribed to meet standard hemoglobin A1c (HbA1c) targets. This problem has motivated patient safety campaigns that cue health care professionals to limit medications for certain older patients (eg, those with an HbA1c level <7.5%, renal disease, or dementia) to convert HbA1c to a proportion of total hemoglobin, multiply by 0.01). In this study, we examined beliefs of primary care health-care professionals (PCPs) to anticipate how PCPs might receive such recommendations.