HEALTH CARE POLICY AND LAW

Quality of Life, Overall Survival, and Costs of Cancer Drugs Approved Based on Surrogate Endpoints

The lack of evidence of a clinically meaningful benefit for many cancer drugs approved by the US Food and Drug Administration (FDA) through expedited pathways raises questions about whether physicians and patients can make informed treatment decisions. Kim and Prasad reported that for 18 of the 36 cancer drugs that were approved by the FDA from 2008 to 2012 on the basis of a surrogate endpoint—typically, tumor shrinkage or progression-free survival—postmarket studies did not indicate any overall survival (OS) benefit. To determine other potential benefits of these 18 drugs, we analyzed all peer-reviewed findings and FDA review summaries for quality of life (QoL) and calculated the drugs’ annual cost to assess their value.

<table>
<thead>
<tr>
<th>Effect of Life</th>
<th>Drug Name</th>
<th>Cancer Type</th>
<th>Quality of Life Measures</th>
<th>Quality of Life Comparison Groups</th>
<th>Annual Cost, $</th>
<th>Average Annual Cost, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better</td>
<td>Crizotinib</td>
<td>Non–small-cell lung cancer</td>
<td>EQ-5D, QLQ-C30, QLQ-LC13</td>
<td>Pemetrexed plus either cisplatin or carboplatin; pemetrexed or docetaxel</td>
<td>169,680</td>
<td>169,680</td>
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<tr>
<td>No statistical difference</td>
<td>Pazopanib hydrochloride</td>
<td>Soft-tissue sarcoma</td>
<td>QLQ-C30, EQ-5D</td>
<td>Placebo</td>
<td>112,572</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bevacizumab*</td>
<td>Breast cancer^</td>
<td>FACT-B, TOI-B</td>
<td>Placebo</td>
<td>134,125</td>
<td></td>
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<tr>
<td></td>
<td>Bendamustine hydrochloride</td>
<td>Chronic lymphocytic leukemia</td>
<td>QLQ-C30, QLQ-CLL25</td>
<td>Chlorambucil</td>
<td>53,315</td>
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<td></td>
<td>Axitinib^</td>
<td>Renal cell carcinoma</td>
<td>EQ-5D, FKSI-15, FKSI-DRS</td>
<td>Sorafenib</td>
<td>143,184</td>
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<tr>
<td></td>
<td>Rituximab</td>
<td>Follicular lymphoma</td>
<td>EQ-5D, FACT-G, QLQ-C30</td>
<td>Observation</td>
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<tr>
<td></td>
<td>Ofatumumab</td>
<td>Chronic lymphocytic leukemia</td>
<td>QLQ-C30, QLQ-CLL16</td>
<td>Observation</td>
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<td>Worse</td>
<td>Peginterferon alpha-2b</td>
<td>Melanoma</td>
<td>QLQ-C30</td>
<td>Observation</td>
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<td>Cabozantinib-S-malate</td>
<td>Medullary thyroid cancer</td>
<td>MDASI-THY</td>
<td>Placebo</td>
<td>169,836</td>
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<tr>
<td>Mixed^</td>
<td>Everolimus</td>
<td>Renal cell carcinoma</td>
<td>QLQ-C30, FKSI-DRS</td>
<td>Placebo, Nivolumab, Sunitinib</td>
<td>144,640</td>
<td></td>
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<tr>
<td></td>
<td>Pazopanib</td>
<td>Renal cell carcinoma</td>
<td>CTSQ, EQ-5D, FACT-F, FKSI-DRS, QLQ-C30, SQOL</td>
<td>Placebo</td>
<td>112,572</td>
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<tr>
<td></td>
<td>Everolimus</td>
<td>Breast cancer</td>
<td>QLQ-BR23, QLQ-C30</td>
<td>Placebo</td>
<td>144,640</td>
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<td></td>
<td>Bevacizumab</td>
<td>Glioblastoma</td>
<td>QLQ-BN20, QLQ-C30</td>
<td>Placebo, Lomustine alone or lomustine combined with bevacizumab</td>
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<tr>
<td>No evidence</td>
<td>Nilotinib</td>
<td>Ph-positive chronic myeloid leukemia</td>
<td>N/A</td>
<td>N/A</td>
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<td>Bevacizumab</td>
<td>Renal cell carcinoma</td>
<td>N/A</td>
<td>N/A</td>
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<td>Everolimus</td>
<td>Pancreatic neuroendocrine tumor</td>
<td>N/A</td>
<td>N/A</td>
<td>144,640</td>
<td>125,528</td>
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<td>Bendamustine</td>
<td>Indolent non–Hodgkin lymphoma</td>
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<td></td>
<td>Dasatinib</td>
<td>Ph-positive chronic myeloid leukemia</td>
<td>N/A</td>
<td>N/A</td>
<td>130,392</td>
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</table>

Abbreviations: CTSQ, Cancer Therapy Satisfaction Questionnaire; EQ-5D, EuroQol Group 5-Dimensions Self-Report Questionnaire; FACT-B, Functional Assessment of Cancer Therapy-Breast; FACT-F, Functional Assessment of Cancer Therapy-Fatigue; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-I, Functional Assessment of Chronic Illness Therapy-Fatigue; FKSI-15, Functional Assessment of Cancer Therapy Kidney Symptom Index; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Symptom Index Disease-Related Symptoms subscale; MDASI-THY, MD Anderson Symptom Inventory Thyroid module; N/A, not applicable; Ph, Philadelphia chromosome; QLQ-BN20, Quality of Life Questionnaire-brain cancer module; QLQ-BR23, Quality of Life Questionnaire-breast cancer module; QLQ-C30, quality of life core questionnaire; QLQ-CLL16, Quality of Life Questionnaire-chronic lymphocytic leukemia 16; QLQ-CLL25, Quality of Life Questionnaire-chronic lymphocytic leukemia 25; QLQ-LC13, Quality of Life Questionnaire-lung cancer module; SQOL, Supplementary Quality of Life Questionnaire; TOI-B, Trial Outcome Index-Breast.

* US Food and Drug Administration (FDA) review noted that the sponsor stated one study found a difference in quality-of-life deterioration that was statistically significant in favor of bevacizumab.

^ On November 18, 2011, the FDA revoked the accelerated approval of the breast cancer indication for bevacizumab.

One subgroup analysis of Japanese patients found a quality-of-life benefit.

Includes any combination of the other effects on quality of life (better, no statistical difference, worse).
Methods | We obtained a list of the 18 cancer drugs approved by the FDA between 2008 and 2012 (V. Prasad, MD, MPH, and C. Kim, MD, MPH, email communication, December 2015). These drugs were not shown in postmarket studies to significantly prolong OS. Between January 11, 2016, and February 4, 2016, we searched PubMed for clinical trials using the drug’s name, cancer type, and MeSH (Medical Subject Heading) terms quality of life and treatment outcome. We also examined the FDA review summaries on fda.gov.

Because many patients with cancer are 65 years or older, we estimated annual Medicare costs for each drug using a method similar to that described by Bach. Calculation of the cost of drugs reimbursed under Medicare Part B (eg, intravenous drugs) was based on the October 2015 ASP Pricing Files, while calculation of the cost of drugs reimbursed under Medicare Part D (eg, oral drugs) was based on the Full Cost of Drug reported in the Medicare Plan Finder by the Humana Enhanced Prescription Drug Plan for zip code 98155. The health care costs in this zip code are representative of the average health care costs in the United States. This investigation of published reports was exempt from institutional review board approval.

Results | Our search on PubMed identified 466 articles, 31 of which met our inclusion criteria of a clinical trial with a comparison group using a validated QoL survey instrument. We accessed FDA review summaries, which were publicly available for 15 of the 18 drugs. The QoL studies compared 7 drugs with placebo or observation groups and found that 2 drugs demonstrated worse effects on QoL, 4 drugs showed no statistical difference, and 1 drug had mixed results. Compared with another drug, 1 drug (ofatumumab) reduced OS, while 6 drugs had no OS benefit in comparison with placebo or observation groups.

The average cost of the 6 drugs with no different or worse QoL was $87,922 per year (ranging from $20,237 to $169,836). Despite having no OS or QoL benefit compared with placebo or observation, while presenting significant risks for serious adverse effects, all but 1 of the drugs retains FDA approval. (FDA rescinded bevacizumab for breast cancer in 2011.) Of the 6 drugs with QoL data comparing them to another drug, 1 drug demonstrated better QoL, 2 drugs did not differ significantly from the comparator, and 3 had mixed results. There was no apparent trend in loss to follow-up that could have confounded the results.

The estimated annual costs of the 18 drugs ranged from $20,237 for rituximab to $169,836 for cabozantinib-S-malate, and 13 drugs had annual costs that exceeded $100,000 (Table). The most expensive drug, cabozantinib, did not improve OS and worsened QoL, compared with placebo. The average annual drug costs were similar, regardless of QoL.

Discussion | Requirements for the FDA’s various expedited pathways are less stringent than for other drug reviews, often including only 1 pivotal trial, fewer patients, shorter follow-up, and surrogate endpoints rather than clinically meaningful outcomes such as OS or QoL. As a condition of these cancer drug approvals, postmarket studies that evaluate OS are usually required.

Unfortunately, the randomized control design of postmarket studies can be lost due to the crossover from the control to treatment group or vice versa, raising questions about the true effect of treatment. For example, most patients in the control group of the crizotinib study subsequently received crizotinib outside the study. In several studies, when there was no statistically significant increase in OS, post hoc statistical analyses were conducted as an attempt to control for such changes in treatments. Post hoc analysis is inherently subject to confounding, however, especially when treatments are no longer random.

If a new cancer drug does not have a statistically significant OS or QoL benefit, compared with the benefit of other drugs, physicians and patients must weigh the known risks and the costs of treatment choices. However, our analysis indicates that, even when postmarket studies show the new drugs to have no clinically meaningful benefit compared with placebo or observation, most drugs retain FDA approval and remain on the market at prices comparable to those of the most expensive cancer drugs. This situation adds to the skyrocketing costs of cancer care, Medicare, and other health care programs.

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Author Contributions: Drs Zuckerman and Rupp had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Zuckerman.

Acquisition, analysis, or interpretation of data: Both authors.

Drafting of the manuscript: Both authors.

Critical revision of the manuscript for important intellectual content: Both authors.

Statistical analysis: Rupp.

Administrative, technical, or material support: Both authors.

Conflict of Interest Disclosures: Dr Zuckerman reported owning stock in Johnson & Johnson. No other disclosures were reported.


Editor's Note
Improving the Accelerated Pathway to Cancer Drug Approvals

The US Food and Drug Administration (FDA) must balance the need to bring potentially lifesaving drugs to market with the need to ensure the safety and effectiveness of these drugs. To balance these competing goals, the FDA has increasingly used the accelerated pathway, which is meant for drugs that treat serious conditions and fill an unmet medical need. Approval is based on a surrogate or an early clinical endpoint and is conditional on the completion of confirmatory trials, which are planned prior to the approval process.

Once granted, accelerated drug approvals are subject to withdrawal if “a postmarketing clinical study fails to verify clinical benefit.”1 The FDA defines clinical benefit as prolonging life or improving the quality of life (QoL). Withdrawal of approval is rare. The only drug for which the FDA withdrew approval—a as a result of failure of confirmatory data—was bevacizumab for metastatic breast cancer in 2011. However, Medicare and other major insurers still cover bevacizumab for this indication, despite the FDA ruling or the drug’s lack of clinical benefit.

In this issue of JAMA Internal Medicine, Rupp and Zuckerman2 examine 18 cancer drugs that received accelerated FDA approval but were found in postmarketing confirmatory trials to have no overall survival (OS) benefit.3 Less than half of these drugs had been studied using QoL outcomes. Although 6 drugs lack OS or QoL benefit, all but 1 (bevacizumab) have retained their approval and are still on the market.

We suggest 3 improvements to the accelerated pathway for cancer drug approvals. First, confirmatory postmarketing studies for accelerated drug approvals should include both OS and QoL outcomes because these are the 2 facets of clinical benefit currently being used by the FDA. Second, preapproved QoL measures should be published for specific drug classes. Third, anticipated or clinically significant changes in OS and in QoL measures should be defined a priori to facilitate the identification of drugs whose “postmarketing clinical study fails to verify clinical benefit.”

In following the principle of “first, do no harm,” the FDA should promptly withdraw approval for cancer drugs that are proven to have no clinical benefit. Removing these drugs, each of which costs between $20 000 and $170 000 per year, from the market will improve the quality and value of cancer care.

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Letters

Sleep Loss in the Homeless—An Additional Factor of Precariousness: Survey in a Group of Homeless People

Sleep is a key component of good health.1 Sleeping less than 6 hours per night is associated with increased risk of obesity, type 2 diabetes, cardiovascular disease, depression, anxiety, pain, and accidents.2 Being homeless makes sleep particularly difficult. Homeless facilities are often closed at night, and homeless people face inclement weather, darkness, and fear for their personal security. Owing to limited resources, many facilities limit the number of nights per individual. Thus, many homeless persons have no regular access to a safe and warm bed at night.

Methods | This survey was approved by both the CNIS (Conseil national de l’information statistique) and the French National Institute for Demographic Studies (INED) ethics committee. Participants who agreed to participate were informed by interviewers at the moment of the survey, but written informed consent was not required by the committees for this epidemiological survey. To better characterize this problem, we collected information on sleep from a health survey conducted by the French National Institute on Statistics and Economic Studies and the INED.3 We surveyed 3741 persons who met the definition of homeless (attending sites that offer free meals, associated with social and medical assistance services, and in French cities with more than 20 000 inhabitants). After excluding 288 incomplete questionnaires, we analyzed responses from 3453 individuals: 2068 men and 1385 women, with a mean age of 39.8 years. At the time of the survey, 197 respondents were living on the street, 447 were in collective short-term shelters (housing for <1 week), 1320 in collective long-term shelters (housing for >1 month), 240 in small social services paid hotels, and 1249 in individual facilities (1 or 2 bedrooms for homeless persons with children).

The questionnaire asked about total sleep time at night and over the 24 hours prior to the interview; insomnia defined by the International Classification of Sleep Disorders, Third Edition; whether drugs or alcohol were used to promote sleep, and whether the participant experienced frequent daytime fatigue. We compared homeless persons to age-, sex-, and location-matched controls enrolled in the 2010 National Health Barometer, a large representative survey of the French adult population that asked similar questions on sleep.3

Results | Homeless persons reported significantly shorter total sleep time than the general population (6 hours 31 minutes vs 7 hours 9 minutes) (Table). Among the homeless, 8% reported less than 4 hours of total sleep time over the past 24 hours compared with 3% of the general population; homeless women were twice as likely as men to report that they slept less than 4 hours. Insomnia was reported by 41% of homeless individuals compared with 19% of controls. Daytime sleep...