

EDITORIALS



Why do cancer drugs get such an easy ride?

Rushed approvals result in a poor deal for both patients and cancer research

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Unlike most other diseases, cancer instils a special fear and “is treated as an evil, invincible predator, not just a disease.”¹ The ability of drug companies to charge very high prices, even when most approved cancer drugs provide little gain for patients, drives much of the research, as desperate patients lead some governments and private insurers to pay whatever companies charge. Officials within the US Food and Drug Administration are enthusiastic about new cancer drugs. Richard Pazdur, who oversees oncology activities for the FDA says that new cancer drugs are so effective that “We don’t have a lot of questions on [these] drugs because they’re slam dunks. It’s not if we’re going to approve them. It’s how fast we’re going to approve them.”²

The methodological weaknesses in oncology trials do not support such enthusiasm. Researchers compared 8942 oncology clinical trials conducted between 2007 and 2010 with trials for other diseases.³ Trials for cancer drugs were 2.8 times more likely not to be randomised, 2.6 times more likely not to use a comparator (single arm), and 1.8 times more likely not to be blinded. Each undermines the validity of outcomes but reflects what regulators will allow.

Less valid trials reflect an easy ride from regulators for drugs that usually offer few significant benefits for patients. A review of drugs for solid cancers approved by the European Medicines Agency (EMA) in its first 10 years found that, overall, new oncology drugs improved survival by a mean and median of 1.5 and 1.2 months, respectively.⁴ The 71 drugs approved by the FDA from 2002 to 2014 for solid tumours have resulted in median gains in progression-free and overall survival of only 2.5 and 2.1 months, respectively.⁵ Further, only 42% met criteria set by the American Society of Clinical Oncology Cancer Research Committee for meaningful results for patients.⁶

Accelerated approval and surrogate outcomes

A second easy ride comes from regulators creating more ways to shorten review times.⁷ In Europe between 1999 and 2009, oncology drugs were the class that was most likely to be approved through an accelerated pathway.⁸ Priority approval shortens the FDA review time from the standard 300 days to 180 days, but the two processes are supposed to be equivalent.

In practice, postmarketing label changes are substantially more common for oncology drugs approved by priority review than for those subject to standard reviews, suggesting possible deficiencies in the priority review evaluation.⁹ Cancer drugs approved using early stage evidence had “a 72% greater odds of serious adverse events occurring in their pivotal trials than did cancer drugs that were approved with more rigorous studies.”⁷ Once drugs are available, even if they subsequently prove to be ineffective, withdrawing them can be a lengthy process and generates substantial opposition, as the case of bevacizumab for metastatic breast cancer demonstrates.⁷

A third easy ride comes from European and US regulators allowing companies to test cancer drugs using surrogate measures instead of survival and other patient centred measures. The three most commonly used surrogate endpoints all use radiological measurement of tumour size as evidence of benefit, even though the exact date of tumour progression can never be precisely known from these measurements.¹⁰

Surrogate endpoints are highly variable in their ability to predict overall survival.¹¹⁻¹³ A review by the German Institute for Quality and Efficiency in Health Care concluded that the validity of tumour response measures as surrogates for patient relevant endpoints in colon and breast cancer remains unclear.¹⁴ Despite these limitations drug companies are eager to use surrogate endpoints because the trials require fewer patients and can be completed faster and more cheaply than trials that test for survival. The FDA and EMA find them acceptable and base most of their approvals on them. The FDA used surrogate endpoints to approve 68% (39/57) of oncology drugs processed through the standard approval pathway and for all 14 applications granted accelerated approval from January 1990 to November 2002.¹⁵ In Europe, from January 1995 to December 2004, most cancer medicines were approved on the basis of surrogate endpoints such as “tumour shrinkage [that] did not translate most of the time into significant survival benefit.”¹⁴

In 2013, over 100 oncologists protested against the high prices charged for cancer drugs, when 11 out of 12 approved in 2012 provided only small benefits to patients.^{16 17} The easy ride syndrome and lowering the efficacy bar encourage “the pursuit of marginal outcomes and a me-too mentality evidenced by the

duplication of effort and redundant pharmaceutical pipelines.”^{15 18} Beyond cancer drugs, low bars for approval are why 90% of new drugs that companies develop are judged to add few or no clinical advantages over existing ones and yet have substantial risks of serious adverse events.^{19 20} Easy ride regulators serve both patients and research badly.

A few changes could greatly improve the quality of cancer drugs and research. Leaders of Italy's Mario Negri Institute have long advocated a coherent model for the development, regulation, and use of better medicines.²¹ They see no reason why regulators cannot insist on randomisation, improved overall survival, and phase III trials since good results in phase II are often not persuasive.⁴ Patients and their doctors need to insist that regulators, established to protect the public, should require clear evidence that new drugs are clinically effective, based whenever possible on trials that compare them to current effective therapy using designs that are methodologically rigorous.

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