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Authors

Prasad, Vinay
McCabe, Christopher
Mailankody, Sham

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Low-value approvals and high prices might incentivize ineffective drug development

*Vinay Prasad[1,2,3], Christopher McCabe[4] and Sham Mailankody[5]**

Drug regulators' acceptance of any statistically significant improvement shown in a single randomized trial and lofty drug prices has created a situation where it is now, hypothetically, profitable for a company to run a clinical trials portfolio of chemically inert compounds. While the current cancer drug pipeline is certainly superior to inert drugs, we must rethink market incentives to encourage transformational drug development.

[1]*Division of Hematology Oncology, Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA.*

[2]*Department of Public Health and Preventive Medicine, Oregon Health & Science University, Portland, OR, USA.*

[3]*Center for Health Care Ethics, Oregon Health & Science University, Portland, OR, USA.*

[4]*Executive Director and CEO of the Institute of Health Economics, Edmonton, Canada.*

[5]*Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA.*

**e-mail: mailanks@mskcc.org*

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In recent years, several observations regarding clinical trials in oncology have generated debate, but a unifying theme has not been elucidated. First, the clinical trial portfolios of several pharmaceutical companies seem to have grown and include studies pursued with a limited potential to improve the standard of care, which might duplicate the trials of similar drugs pursued by rival companies[1]. Second, the FDA has shown a willingness to approve anticancer drugs based on the findings of a single randomized trial that achieves statistical significance, even if the magnitude of benefit is marginal or only quantified using a surrogate outcome. Third, the price of anticancer drugs has escalated steadily, and even drugs with indications restricted to small populations of patients often achieve a billion US$ in annual sales and billions in profit over their patent cycle.

The current regulatory system in the USA has seen the approval of several effective drugs, but the low level of efficacy required for approval has also led to a 'me too' mentality and the pursuit of drugs and indications that provide only modest levels of clinical benefit[2]. Embarking on unpromising trials agendas that involve testing marginally effective or even ineffective drugs, is now potentially profitable for pharmaceutical companies because the reward for even one rare successful trial generates enough revenue to support the costs of all the failures. Using a mathematical model, we show that the current regulatory and reimbursement system applied to cancer drugs in the USA and to varying degrees in many other health systems has reached the point at which companies can logically run a low-value and possibly even no-value clinical trials portfolio. We certainly do not believe that pharmaceutical companies are actively pursuing ineffective drugs, although the current oncology drug development and regulatory environment does little to discourage such an agenda.

First, emerging evidence suggests that anticancer drugs are tested in broad portfolios of trials, which are often redundant and duplicative. Consider the example of the >1,000 clinical trials involving immune-checkpoint inhibitors[1]. In many cases, the biological rationale for these studies is either limited or absent. In some scenarios, immune-checkpoint inhibitors are being tested in combination with other agents in the absence of single-agent activity, even though such activity is generally considered a promising prerequisite for the inclusion of anticancer drugs in combination therapies[3]. Multi-targeted kinase inhibitors have been repeatedly tested in patients with solid tumours, often revealing little to no single-agent activity[4]. For example, sunitinib, which is currently approved by the FDA for the treatment of renal cell carcinoma (RCC) and neuroendocrine cancers, has been tested as a monotherapy in 80 phase II trials and 7 phase III trials, including a total of 18 randomized studies, according to the published literature alone[4]. A clear example of a pharmaceutical company funding a risky phase III trial in the absence of a strong rationale occurred with everolimus as a second-line treatment of hepatocellular carcinoma. Specifically, the EVOLVE-1 study was a phase III trial with over 500 accrued patients that revealed no significant difference in the efficacy of everolimus versus best supportive care in this setting[5]. In the trial report[5], the authors disclosed that the rationale supporting the phase III trial was limited to phase I data, and biological plausibility derived through laboratory studies, but that no dedicated phase II trial had been conducted.

Second, the FDA has shown willingness to approve drugs based on small statistically significant improvements observed in a single randomized trial. For example, neratinib was approved for patients with HER2-positive breast cancer based on a 2.3% improvement in invasive disease-free survival (DFS), a surrogate end point, in a single randomized trial[6]. Similarly, sunitinib was approved for adjuvant treatment of RCC based on

the results of one positive randomized trial showing an improvement in DFS, despite a second cooperative group trial failing to show a DFS benefit — neither trial showed an improvement in overall survival[7]. Of note, the median improvements in progression-free survival and overall survival with 71 consecutive therapies approved by the FDA for metastatic cancer between 2002 and 2014 were 2.5 months and 2.1 months, respectively[2].

Third, modern anticancer drugs are highly profitable. In an analysis of ten anticancer drugs that came to the market between 2006 and 2015, we calculated median post-approval revenues of $1.67 billion at a median of only 4 years after approval[8]. On average, approved anticancer drugs carry 14 years of exclusivity, suggesting that the total revenue generated per approval could be greater in the years to come[8].

On the basis of these observations, we performed a thought experiment (FIG. 1). How much revenue is needed per approved drug to permit a company to test a portfolio of ineffective chemical compounds and turn a profit? Of course, we do not believe that approved anticancer drugs are inert — however, we chose this as a worst-case scenario for illustrative purposes. To make this calculation, first we note that accepting a single trial with a P-value < 0.05 as the threshold of significance means that, if one ran 100 trials for which the null hypothesis were true (that the drug is ineffective), on average, 5 trials would produce false-positive 'statistically significant' results. Second, we note that a recent report by the Department of Health and Human Services[9] provides an estimated cost of conducting a single phase III trial in oncology of approximately $22.1 million. Thus, if one ran 100 phase III trials involving ineffective compounds, the cost would be $2.21 billion and could be expected to result in 5 approvals by chance. Therefore, we found that if a single approved drug generates $440 million in profit, it would justify a no-value trials portfolio if one trial were needed for drug approval. If two trials are needed for approval, then the break-even point rises to $8.8 billion dollars. This difference occurs owing to the much smaller chance that two trials of an ineffective agent independently yield statistically significant false-positive results (P (N positive trials of ineffective drug) = $0.05^{N\ trials}$). Finally, our model does not imply that costs accrued before the pivotal study are irrelevant; however, these costs are sunk and, therefore, are not part of the investment assessment behind launching the registration study.

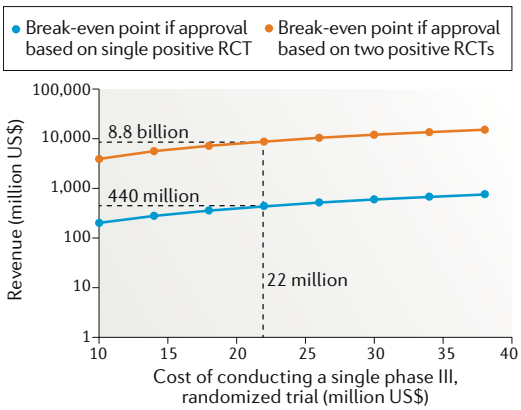

Fig. 1 | **Break- even point at which a null trials agenda would turn a profit based on one or two nominally significant randomized trials.** Revenue needed per approved agent for such a strategy to be profitable. Since this example illustrates a worst- case scenario, the break-even point for a portfolio of more promising compounds would be lower. RCT, randomized controlled trial.

Anticancer drugs probably earn companies several billion dollars over their patent cycle, and the outcomes of our thought experiment suggest that investing in trials with limited biological rationale could be a rational approach for companies that can maintain a substantial trial portfolio. However, launching many trials with little chance of achieving meaningful or transformative success could have undesirable consequences. Many patients are recruited to such trials, raising the important ethical question of the balance between risks and benefits. Only a finite number of patients are available for participation in trials, and thus low-value trials might compromise the recruitment of patients to more-promising studies.

The current situation could be remedied either by demanding a minimum of two independent randomized trials to support approval decisions, as is the norm in areas of medicine outside of oncology and/or changing the financial incentives relating to the use of anticancer drugs, such that prices or reimbursement of drugs are based on their clinical benefit, according to robust value frameworks[10], and not mere statistical significance.

In short, in the current system, pharmaceutical companies could, hypothetically, turn a profit by testing inert chemical compounds in phase III trials — this effect is the culmination of a series of limitations in the regulatory system and their integration with drug-funding systems, both of which are in need of correction in order to protect patients and society from the adverse effects of misallocating limited research and health-care resources.

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Competing interests
The authors declare no competing interests.