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Editorial comment

A new anti-cancer drug in the market: Good news for investors or for patients?

Giovanni Apolone[a,*], *Giovanni Tafuri*[b,c], *Francesco Trotta*[b], *Silvio Garattini*[a]

[a]*Mario Negri Institute for Pharmacological Research, via La Masa 19, 20156 Milan, Italy*
[b]*Italian Medicines Agency (AIFA), via della Sierra Nevada 60, 00144 Rome, Italy*
[c]*Utrecht University, Utrecht Institute for Pharmaceutical Sciences, PO Box 80 082, 3508 TB Utrecht, The Netherlands*

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It is not infrequent to hear ethical appeals in order to shorten the validation process of a new health technology, but ethical considerations are difficult to reconcile with studies that have essentially a commercial aim. Pharmaceutical companies seek to maximise the profit of their product while users/buyers look for drugs that maximise health at an 'affordable' cost. It is hoped that drugs are rapidly released for patients who need them but the willingness to help patients should not be at the expense of adequate knowledge about the benefit of drugs.

Opinions on an earlier-than-ideal endpoint in the drug approval path vary from those who view it as an important step in improving public health by ensuring that beneficial drugs are made available as quickly as possible to those who see it as a dangerous shortcut that might jeopardise consumer health due to unsafe and ineffective drugs being marketed and prescribed. Research and development for a new drug is a long and complex process that has at least three critical steps: the passage from pre-clinical to clinical phases when first-time-to-men studies are to be done, the evaluation of its clinical risk-benefit ratio at the end of the clinical phase before granting market approval, and the evaluation of its cost-effectiveness before deciding its market access and price. Decision-makers such as governmental regulatory agencies, purchasers of pharmaceuticals, physicians and patients need to have risk-benefit and cost-effectiveness indicators to judge its therapeutic value in the real world.

In an effort to obtain quick regulatory approval, pharmaceutical companies, under the pressure of the market, test their new anti-cancer drugs on human beings at the earliest possible point without fully knowing the true mechanism by which new drugs exert their clinical benefit. The testing process involves very specific sub-samples of progressing or refractory patients in an effort to obtain the status of 'accelerated approval' or 'under exceptional circumstances', using the simplest possible study design. Doubts about the incremental/added value of the new generation of drugs have indeed been raised in the framework of drug approvals either in the USA or Europe. In the past, the challenge was the use of non-comparative studies and/or surrogate endpoints to document the efficacy of new products.[1–5] Other critics have suggested that the introduction of economic incentives to accelerate the drug review process, such as the Prescription Drug User Fee Act (PDUFA) in the USA, have actually reduced the time required for granting market approvals but have also increased the probability of discovering safety issues after the medications are in clinical use, either in terms of safety-based withdrawals or black-box warnings.[6]

New issues arise with the (inappropriate) utilisation of interim analyses to prematurely stop a clinical trial for benefit. Usually, interim analyses are planned to prematurely

* *Corresponding author:* Tel.: +39 02 39014515; fax: +39 02 33200231.
E-mail address: apolone@marionegri.it (G. Apolone).
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terminate a randomised clinical trial (RCT) for three reasons. First, for reasons of harm due to unacceptable toxicity; secondly, for "futility" as the efficacy of the new treatment is so trivial that is unlikely that the continuation would detect a relevant difference; and finally, for apparent benefit. Previous research has documented that the number of RCTs stopped early for benefit has more than doubled since 1990.[7] Results of these trials should be interpreted with caution because statistical stopping rules are prone to stop a trial when a disproportionate number of events have occurred by chance thus exaggerating the estimated treatment effect.[8] In at least one third of trials stopped early for apparent benefit, it was not possible to confirm the statistical significance of preliminary results.[9,10] Recently, two independent teams of researchers carried out a secondary analysis of published papers to evaluate the use of interim analyses focussing on oncological clinical trials stopped early for benefit.[10,11] Wilcox et al.[10] reviewed the study characteristics, features related to the decision to monitor and stop the study early, the number of events, and the estimated treatment effects reported in 29 RCTs evaluating the efficacy of health interventions in oncology. They estimated the correlation between the absolute number of events in each trial and the apparent treatment effect using the relative risk (RR), either reported or calculated. They found a median RR of 0.54, an effect that may be considered higher than expected in this setting, and an inverse association between RR and number of events (r 0.75; p-value= 0.0001): the majority of RCTs (73%) that had an RR less than the median also evaluated fewer than the median number of events. This suggests that RCTs stopped after only a few events tend to report large treatment effects, while the risk of significantly overestimating the treatment effect diminishes when the number of events accrued is large. Trotta et al. identified 25 RCTs stopped early for benefit out of a total of 93 studies evaluating anti-cancer drugs. They found that evaluation of efficacy was protocol planned through time-related primary end points; >40% of them used overall survival as primary endpoint. In 95% of studies, at the interim analysis, efficacy was evaluated using the same end point as planned for the final analysis. As a consequence of early stopping after the interim analysis, 3300 patients/events across all studies were spared. Out of the 14 trials stopped and published between 2005–2007, 11 (79%) were used to support an application for marketing authorisation at the European Medicines Agency (EMEA) or at the Unites States Food and Drug Administration (FDA); before 2005, only 9% of the RCTs were used for registrative purposes. The most frequent consequences of the interim analysis were: stopping enrolment (48%), cross-over to the experimental group (24%) and disclosure of results (20%). The median time lag between the end of the enrolment and the study publication was indeed quite long: 22 months (range: 3 months–15 years), possibly because of confidentiality concerns.

According to this evidence, there is a high risk that drugs approved on the basis of preliminary and not fully validated evidence are utilised in a number of patients before other confirmative trials are carried out leading to an over-estimation of the impact of drugs in the cure/control of the cancer disease. This, in turn, leads to over-treatment, high costs, safety problems and poor outcomes. In addition, when interim analysis makes the provision of commercial drugs to patients possible, this can interfere with patient accrual in confirmatory studies.[3] Finally, the publication delay may suggest a market-driven intent.

In most European countries, final users are neither the decision makers nor the direct payers (physicians choose a drug they will not eventually use, patients take a drug that they will not pay for and payers pay/reimburse for a drug they have not chosen at all). Supply and demand have little to no role to play in the pharmaceutical market. The price and the level of reimbursement are actually the result of a negotiation between producers (on behalf of share holders) and governments (on behalf of citizens and patients). Final decisions about market access, final price and reimbursement depend on the amount and completeness of data available on the proven efficacy (without information about its actual effectiveness) and future (predicted) cost of the system. In other words, the value of a drug reflects the quality of data and information available that predicts the impact on individuals and population health rather than the potential, but not fully demonstrated, attributes. In this context, the increasing use of interim analysis to prematurely stop clinical trials for benefit is a shortcut that puts decision-makers in a difficult situation with implications for consumers' health and for the economic balance of health systems. But, unfortunately, soft news about marketing approval and inclusion of drugs in lists of reimbursed health technologies have a much greater financial impact than validated clinical and economic yields. The pace of finance is more all-encompassing and dominant than the pace of clinical research, practice and even the 'real' economy.[12,13] Therefore, the arrival of a new anti-cancer drug, given a lack of complete and sound evidence, the controversies in the interpretation of results and ethical problems, may be considered better news for investors rather than for physicians and patients.

Conflict of interest statement

None declared.

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