Trading based on material nonpublic information is a criminal violation of the Federal Securities Exchange Act of 1934 and is punishable by a maximum sentence of 20 years and a fine of $5 million. Thus, the suggestion by Rothenstein et al. (1) in this issue of the Journal that insider trading is the cause of observed differences in company stock prices before and after public announcements related to oncology drugs is of grave concern.

Specifically, Rothenstein et al. (1) analyzed the stock prices in the 120 days leading up to public announcements regarding phase III trials, and they appear to reject the null hypothesis that the outcome of the trial is unrelated to the stock price behavior before the announcement. Indeed, companies that reported a positive trial demonstrated better price performance (an increase of approximately 14%) during that period compared with companies.
that reported a negative trial (a decrease of approximately 1%); however, the difference was not statistically significant ($P = .09$). Even if this finding was statistically significant, one must carefully scrutinize the authors’ explanation for these results because of their implication that some investigators involved in phase III trials are illegally tipping the results, which would be a criminal violation of the Securities Exchange Act.

Although the authors should be congratulated for undertaking this novel analysis at the intersection of medicine and Wall Street, it is important to keep in mind that the positive and negative trials may not be comparable. In this context, we calculated the market capitalization (ie, the total shares outstanding times the price per share) for each company at 120 days before each of the public announcements using data derived from Supplementary Tables 1 and 2 in Rothenstein et al. (1) and publically available information. This analysis demonstrated a remarkable difference between companies that had positive and negative announcements. Specifically, the median market capitalization was approximately 80-fold greater for the companies with positive trials vs companies with negative trials ($17.8 billion vs $220 million, $P < .001$, two-sided Mann–Whitney test). Furthermore, there were no positive trials among the 21 micro-cap companies (ie, companies with less than $300 million market capitalization [http://www.investopedia.com]), whereas 21 of 27 studies reported by the larger companies analyzed (greater than $1 billion capitalization) were positive.

The difference in the market capitalization at day −120 most likely reflects publically available information regarding the phase I and II clinical trials (as well as other factors, including competition and management), which has been incorporated into the market value of a stock. The stock market is known to anticipate future events, as opposed to reacting to the past. Thus, it is not surprising that sophisticated investors are able to judge the probability of success, which is reflected in the share price.

Drugs that succeed in phase III clinical trials tend to be owned and developed (or acquired) by larger companies that have strong records of accomplishment in drug development. Investors have greater confidence in these companies and therefore reward them with larger market valuations and increasing stock prices ahead of the public announcement of trial results. The opposite tends to be true for drugs that fail phase III trials: Such drugs tend to be owned by smaller companies that lack the confidence of investors and may be saddled with low market valuations and falling stock prices before announcements of trial results. Furthermore, the latter companies may have been of little or no interest to potential acquirers due to their perceived low probability of success.

Some of the negative trials included in the study by Rothenstein et al. (1) have been discussed in the financial media. Consider, for example, Point Therapeutics, the maker of talabostat. Results from a phase II study of talabostat in pancreatic cancer, announced in January 2007, raised important questions about the drug’s activity (2). Investors surely had those data in mind when handicapping the outcome of the phase III study of talabostat in non–small cell lung cancer. The failure of that study, announced in May 2007, should not have been a surprise. More likely, the negative result was widely expected, which is why the company’s market capitalization was just $15 million. Isis Pharmaceuticals ran an open-label phase III study of ISIS 3521 in non–small cell lung cancer, which potentially gave doctors and patients insight into the drug’s efficacy and safety before final negative results were announced in March 2003 (3). Cell Genesys was forced to restrict patient enrollment in a lung cancer phase II study of its GVAX immunotherapy because of patient deaths (4). These problems with GVAX, disclosed in 2004, raised the risk profile for the entire phase III program, including the prostate cancer studies that were stopped for futility in 2008 (5).

The findings of Rothenstein et al. (1) are also of interest because they further illustrate the low success rate for phase III oncology trials (39% for the studies analyzed), which has been attributed to poor phase II design (6–8), specifically the infrequent use of randomization. However, as noted above, the phase III success rate for the studies conducted by larger companies was excellent (78%) and is consistent with success rates outside of oncology (9). Thus, the perceived high risk of failure of phase III oncology trials is primarily limited to smaller oncology companies. Furthermore, when considering very small oncology companies (ie, those with a market capitalization under $300 million) with a drug in phase III trials, the best investment strategy appears to be to short the stock (ie, borrow shares and sell them) (10) before the announcement of the pending negative results.

References


Notes

The authors report no conflict of interest.

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