

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Wall Street's Perspective on Oncology Drug Development

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H&O How does Wall Street view oncology drug development?

RG “Wall Street” is a term used to describe a complex set of views and opinions that center around financial stakeholders. As such, I do not represent a consensus opinion of Wall Street nor Merrill Lynch & Co. for that matter. That said, I do regularly speak with many stakeholders, so I have some sense of their viewpoints. Oncology is considered one of the most important areas for research because it represents a great unmet need due to the high death rates from cancer. Furthermore, oncology is attractive in terms of the fact that the basic science and pharmacology research is translatable to patients. Finally, from a sales perspective, it is possible to reach 12,000 oncologists with a relatively small sales force. Therefore, unsurprisingly, approximately half the biotechnology industry is devoted to oncology drug development. On the other hand, oncology drug development is highly expensive and financially risky. Approximately 3–5% of drugs that enter clinical development are eventually approved. Approximately 600–700 drugs are currently in clinical development, with another 1,300–1,400 in preclinical development, yet only a handful of drugs receive regulatory approval for use in patients each year. The attrition rate between investigational new drug (IND) status and approval is quite

high. I believe that if Wall Street were to view these data on the success rates for drug development in a rational, risk-adjusted way, oncology drug development would be considered somewhat frightening. Despite the large need for new therapies and supportive care entities, it is difficult to find a drug that meets the statistical criteria for approval. As a result of the long, risky, and expensive process of drug development, the financial world does not ascribe a lot of value to early-stage products.

H&O What positive effects on oncology drug development are attributable to Wall Street?

RG The capital markets have been able to provide resources to companies efficiently in order to develop drugs that might otherwise not be developed. Many small biotechnology companies are not profitable and thus require capital from investors, public or private, to push their drugs toward approval. Aside from these small firms, investors may look to large pharmaceutical companies, but oftentimes the major companies do not embark upon drug development plans that meet the criteria investors seek. Investors look for data that suggest eventual regulatory approval and commercial use. They may be more demanding than academic institutions or large companies in terms of ensuring that trials are efficiently designed in a way that will demonstrate whether an agent under investigation will have regulatory and/or commercial viability. Many investors are quite knowledgeable with regard to cancer drug development or else seek out consultants externally who have relevant experience.

For private, early-stage companies, the required money tends to come from either “angel investors” or venture capitalists, who often are very sophisticated and knowledgeable in evaluating drugs prior to a definitive proof of concept in the clinic. Their goal is not necessarily pushing a drug through the regulatory approval process. Rather, it is to garner an exit on their investment. They need to show some sort of proof of concept that will attract either the public markets or potential strategic buyers. However, sometimes the same venture capitalists engage in later-stage investments or carry their products for longer periods of time and create durable companies around them.

H&O How do investors learn about oncology drug development?

RG Institutional investors today are quite savvy. There are many former doctors and scientists managing funds or serving as investment analysts today. Firms also consult with practicing doctors, scientists, and investigators who reflect on a product's scientific underpinnings and existing data in order to assess its probability of commercial and regulatory success. Additionally, investors, bankers, consultants, and other industry personnel attend conferences, just as clinicians do, in order to learn about new developments in the oncology community. It could be argued that sophisticated institutional investors evaluate data more deeply than many academics because of the high financial stakes involved.

H&O What factors contribute to the attrition rates in oncology drug development, which can make the field unattractive to investors?

RG I spoke at the AACR-NCI-EORTC conference in 2005 on phase II trial design as part of a session including three other physicians, Dr. Mark Ratain of the University of Chicago, Dr. Susan Desmond-Hellman of Genentech, and Dr. Bob Temple of the US Food and Drug Administration. I identified four factors contributing to the rates of attrition. The first is that the “low-hanging fruit” have already been picked, meaning that it is statistically far easier to prove the effectiveness of an agent when no other agent is currently available for that indication than it is to prove effectiveness over the combinational agents that have led to improved responses or survival. For example, it required fewer patients and less chance of failure to demonstrate the efficacy of the mechlorethamine, vincristine, procarbazine, prednisone (MOPP) regimen versus placebo in Hodgkin lymphoma than it would to power a trial showing that an additive to that regimen further enhances survival. Superiority implies improvement over the standard of care, and when no standard exists, benefit as compared to no therapy at all is relatively straightforward to demonstrate statistically. As another example, the survival and response rates have doubled in colorectal cancer from the days when oncologists used 5-fluorouracil (5-FU) and leucovorin to today when these agents are combined with bevacizumab (Avastin, Genentech) and either irinotecan (Camptosar, Pfizer) or oxaliplatin (Eloxatin, Sanofi-Aventis). To further illustrate this general difficulty, the mean clinical development times for antineoplastic agents have increased from 40 months in 1991 to 100–120 months in 2005.

The second factor relates to poor early-stage science. If one reviews the list of drugs in development, he or she will

find that approximately 70% of drugs are unprecedented, meaning there is no proof in randomized trials that the drug class is effective. The joint McKinsey & Company and Lehman Brothers “Fruit of Genomics” study, done in 2000, illustrated that target validation is poorer today than it was years ago, as shown by the reduction in the number of literature references per target entering drug discovery. Today, researchers are taking compounds out of databases quickly and conducting a small amount of research in comparison to years ago, when a long period of scientific research was used to validate a target.

The third factor relates to the poor predictive capabilities of today's preclinical cancer models. Obviously, cell lines and rats are inadequate comparators to humans, but the problem goes beyond that. Pharmacologists could do a better job of testing their drug candidates in ways that mirror the potential clinical programs and could use more rigorous endpoints, eg, tumor regression or animal survival rather than lack of progression.

The fourth factor, for which I believe a solution exists, relates to poor clinical trial design. There is a lack of predictability in the way phase II trials are conducted in cancer because few are done in a comparative fashion. As a result, problems arise in late-stage trials, which lead to high attrition rates. Noncomparative or uncontrolled trials have limited generalizability due to inherent biases based on trial effects. These trial effects include (1) selection biases based on differential patient selection, (2) investigator- and institution-based biases and over-enthusiasm for new agents (investigators have reasons to want to show that the new agent or combination under their study is superior to standard of care), and (3) random and chance improvements from small numbers of patients in trials. Zia and colleagues in the *Journal of Clinical Oncology* in 2005 eloquently compared phase II and III trials using identical chemotherapeutic regimens and showed that in similar patient populations with the same regimens, far greater responses and survival were observed in the phase II trials as compared to the phase III trials. Noncomparative, uncontrolled phase II trials often will show a result better than historical controls due to these trial biases. One should never get excited when a drug performs better than historical controls unless the effects are dramatic.

It is necessary for the oncology community to shift to a paradigm in which comparative trials are done earlier. If these problems in trial design are not addressed, the larger problems of attrition will continue to grow because of the competitive and difficult subject recruitment environment. Inclusion criteria are generally narrowing while demand for patients grows. For example, the trial of irinotecan plus 5-FU/leucovorin required 457 patients, whereas the trial of bevacizumab plus 5-FU, leucovorin,

and oxaliplatin (FOLFOX) plus or minus panitumumab required approximately 1,200 patients. Yet less than 5% of adult patients participate in clinical trials and that percentage is not growing much. To compound this problem, many patients are enrolled in single-arm trials, which do not yield adequate information. Because of patient recruitment problems, it may be quite difficult for effective drugs to obtain regulatory approval. In summary, by basing drug discovery efforts on strong science, using relevant in vivo preclinical models, and designing phase II trials that better predict phase III success, the entire oncology community will benefit.

Complicating this discussion, however, as has been recognized, is that in oncology, as compared to other disease states, many factors contribute to determining an agent's phase III program. Choosing the appropriate tumor type, disease stage, patient characteristics, molecular subtype, dose, schedule, combination of drugs, and biomarkers is quite complex. As a result, oftentimes, much of what oncologists determine about the best way to use a drug occurs after its approval.

H&O Does a financial incentive exist for pharmaceutical corporations to show success in phase II trials?

RG This question is important, but ultimately the issue is one of short- versus long-term corporate success. It is possible that a porous filter exists in companies with drugs in phase II trials, which means that the need to show success in phase II in order to create a milestone and attract investment capital can lead to the kinds of uncontrolled phase II trials I discussed. However, a randomized phase II trial that trends strongly toward the positive will give investors much more confidence that an agent will eventually make its way toward regulatory approval. Also, encouraging data from a randomized phase II trial can lead to potentially positive regulatory guidance, such as a special protocol assessment. It is true that there will be short-term damage to a company if a randomized phase II trial fails, but for the industry at large, the use of such trials will allow capital to be allocated to the programs with the best chances of overall success.

H&O What is your view of drug development efforts that include cooperation between government, academia, and industry?

RG If such a partnership can be done efficiently, cost-effectively, and in a manner that leads to useful answers, I would encourage it. However, when I was a full-time practicing oncologist at Cornell University, I observed that although our institution enrolled patients into

important cooperative group studies, these studies were done very slowly. Furthermore, many cooperative group studies seek answers to questions involving drugs already on the market. The average single-institution, noncomparative drug development trial is, in my opinion, not designed to answer important questions. Cooperative groups do a better job of addressing such questions in randomized trials, though not necessarily for drugs in development.

H&O How does regulation by the US Food and Drug Administration or the Securities and Exchange Commission affect Wall Street's relationship with companies developing drugs for cancer?

RG If an agency makes the approval process more stringent, investment will be negatively affected. However, this concern must be balanced with the long-term interests of patients. For example, if it were relatively easier to approve a cancer therapy and test it in terminally ill patients who have no other therapeutic options, science would not benefit because researchers would not be able to show where exactly the new therapies are most effective. If, hypothetically speaking, bevacizumab had been approved in the setting of colorectal cancer based on results from a single-arm trial but there were already five agents available based on results from other, non-randomized trials, the drug would be relatively underutilized today as doctors would not know how it exactly fits into the clinical algorithm. It is necessary for there to be a strong regulatory filter that still allows the oncology community to understand in what settings novel agents should be used and clarifies cooperative group research after the regulatory approval of agents to maximize their potential. Much of the best research has been done after drugs are approved. If taxanes had not been approved until they met the highest criteria, many patients who benefited from them would not have received the drugs. The Society for Clinical Trials put together a white paper in 2006 on this subject, opposing legislation to permit marketing of unproven medical therapies for seriously ill patients.

H&O What is your view of uncommon cancers, which may attract fewer resources?

RG I do not believe that it is a good idea to ignore uncommon cancers because they often allow much quicker paths to regulatory approval and can eventually reach a broader patient base. For example, vorinostat (Zolinza, Merck) was recently approved in cutaneous T-cell lymphoma
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(CTCL), which is a relatively uncommon cancer, but that agent may be shown in the future to have broader applicability. Secondly, some cancers, eg, gastric, are relatively uncommon in the US but have market-favorable demographics in Asia. Finally, these cancers often have not seen many of the newer agents and thus offer the opportunity for development of novel indications, providing so-called low-hanging fruit.

On the other hand, the only way to generate a return on investment in uncommon cancers is to charge high prices for the drugs and/or hope for eventual broader applicability. There are many disease states, some outside oncology, where drugs can be successful from a financial perspective by meeting a high unmet need in a small population, eg, enzyme replacement therapy in patients with lysosomal storage diseases. The difficulty in developing drugs in uncommon cancers is accruing a sufficiently large patient population to conduct a randomized, controlled trial. However, even with common cancers (eg, lung, breast, colon), so many trials are underway that there is competition to recruit patients in those settings as

well. We are today seeing drugs developed in uncommon cancers, such as peripheral T-cell lymphoma, CTCL, sarcomas, and acute lymphoblastic leukemia. I would hope to see more uncommon cancers investigated, but I do not think that research in these settings has been discouraged for financial reasons.

Suggested Readings

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