

# Curtailing the High Rate of Late-Stage Attrition of Investigational Therapeutics Against Unprecedented Targets in Patients with Lung and Other Malignancies

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## ABSTRACT

A greater understanding of the pathogenesis and biology of cancer coupled with major advances in biotechnology has resulted in the identification of rationally designed, target-based (RDTB) anticancer therapeutics, ushering in new therapeutic opportunities and high expectations for the future as well as developmental challenges. Because these agents appear to principally target malignant cells, it is expected that they will produce less toxicity at clinically effective doses than nonspecific cytotoxic agents, but their target requirements are likely to be much more stringent. The innate complexity of the networks that contain elements targeted by these agents also decreases the probability that any single therapeutic manipulation will result in robust clinical activity and success when used alone, particularly in patients with solid malignancies that have multiple relevant signaling aberrations. In contrast, proof of principle and robust antitumor activity may be most efficiently demonstrated in nonrandomized evaluations involving tumors that are principally driven by aberrations of the specific target. The predominant therapeutic manifestation of RDTB agents in preclinical studies is due to decreased tumor growth rates and will likely be similar in the clinic; however, such manifestations are not readily detectable and quantifiable using nonrandomized clinical evaluations. To curtail the increasing rate of late-stage attrition of RDTB agents, which, if maintained, will stymie progress in cancer therapy, the design of initial nonrandomized evaluations, particularly the selection of tumors and patients, must be guided by the principal biological features of the agents. Next, evaluations, some of which must be randomized, can be performed in a wide range of tumor types, depending on the presence and relevance of the target. To validate the concept of RDTB therapeutics and to realize their full potential, radically different development, evaluation, and regulatory paradigms must be adopted.

## HIGH EXPECTATIONS WITH UNPRECEDENTED CANCER THERAPEUTICS

The oncologist's therapeutic armamentarium witnessed remarkable growth over the past several years and is poised for even more growth in the near future. An almost exponential increase in our understanding of the biology of cancer coupled with substantial advances in biotechnology has led to a vast increase in the approaches to treat cancer. It has been estimated that more than 40% of oncology agents in development and almost 70% of those currently in clinical trials are directed against novel targets (1). However, novel approaches have much higher intrinsic risks than "well-tested" approaches, and most of the high-profile recent setbacks in cancer therapeutic development have involved novel mechanisms, such as therapeutics targeting signal transduction and angiogenesis, despite a few high-profile successes (2, 3).

Based on revenue growth between 1998 and 2002, in which revenues generated in the oncology market increased from \$16.9 to \$23.4 billion, revenues in the total oncology market are projected to reach more than \$32 billion in 2005 (1). These projections do not only reflect the rate of growth over the last several years but are also based on many other driving forces on the demand side, particularly a general dissipation in nihilistic attitudes regarding cancer treatment, which has been brought about by a better understanding of cancer biology and the recent development of therapeutics that have modified the natural course of several malignancies (2). This positive trend has been fueled by an active patient population that demands access to the latest therapies, a trend toward aggressive use of therapeutics even in settings in which overall benefit is small, and extended premium pricing of anticancer agents due to high unmet needs in various disease settings. Furthermore, in contrast to the situation that existed only a decade ago, nearly all major pharmaceutical companies have active research and development programs in cancer therapeutics, and research and development efforts in oncology dwarf those of most other therapeutic areas in the biotechnology industry. Never have the prospects for sustained momentum in cancer therapeutic development appeared so great. However, a growing emphasis of investors, industry, and society on short-term expectations, which can lead to rushed and inherently flawed clinical developmental strategies, and in which good science does not always prevail, greatly threatens this momentum. The regulatory bodies must also share responsibility for the existing emphasis on late-stage end points such as survival in untreated patients. Given the logistical difficulties of performing clinical evaluation and the lack of robust surrogate end points, this end point may not be attainable for some therapeutics that will ultimately demonstrate clinical benefit in postapproval evaluations (4). Accelerated regulatory approval has certainly been granted on several occasions based on

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a wide variety of end points. However, the criteria for both accelerated approval and full regulatory approval based on more logistically feasible “middle ground” end points are somewhat unclear to those formulating regulatory strategies. Perhaps the lack of clarity is due in part to the failure of companies to develop long-term working relationships with the regulatory agencies and *vice versa*.

### THE THREAT OF LATE-STAGE ATTRITION OF CANCER THERAPEUTICS

Even with more than 500 oncology therapeutics in active development, only a small fraction are achieving regulatory approval each year, and there are only about 100 approved anticancer therapeutics in the United States today. Despite much positive momentum in research and development in cancer therapeutics, attrition of new cancer agents in late developmental stages is becoming a major threat to the potential for novel research ventures (1). The rate of late-stage attrition (*i.e.*, attrition in phase III) is especially high in oncology for several unique reasons. First and foremost, there is a relative lack of adequate preclinical models and translatable preclinical biomarkers in oncology, which, in other therapeutic areas, are relied on for early target validation. The inadequacies in the preclinical arena are further compounded by an almost complete lack of robust biomarkers that would otherwise be used to obtain proof of principle and gauge whether meaningful therapeutic targeting is occurring in early-stage clinical evaluations, particularly with therapeutics against unprecedented targets. Finally, there is a profound discordance between end points that can be feasibly used in early-stage evaluations and those required in late-stage trials. This point is illustrated by the suboptimal performance of tumor regression as an end point in Phase II studies of new agents in patients with recurrent non-small cell lung cancer in gauging the potential of new agents to increase the survival of untreated patients (2).

The late-stage attrition of new cancer therapeutics, as well as late-stage clinical and regulatory setbacks, is increasing at an alarming rate. Recent examples, which highlight the challenges that oncology drug candidates are facing, include Phase III studies of the erbB1 tyrosine kinase inhibitors gefitinib and erlotinib in untreated patients with advanced non-small cell lung cancer; the farnesyl transferase inhibitor tipifarnib in patients with refractory and recurrent pancreatic and colorectal cancers; the matrix metalloproteinase inhibitors marimastat, tanomastat, and prinomastat in patients with cancers of the pancreas, ovary, brain, stomach, breast, and lung; and the monoclonal antibody to vascular endothelial growth factor bevacizumab in patients with metastatic breast cancer (5). It would not be entirely outlandish to suggest that the recent success with bevacizumab demonstrated in patients with metastatic colorectal carcinoma in a Phase III study was, for the most part, unexpected, occurring in the absence of any concrete signs of success in early-stage clinical evaluations (3). The unpredictability of end points in single-arm, uncontrolled Phase II evaluations with regard to ultimately achieving success in Phase III helps illustrate why anticancer drug development is so challenging. Although oncology development programs typically have higher success rates in early-stage evaluations (Phase I and II) than programs in

other therapeutic areas, the success rates of late-stage oncology projects (Phase III) are lower than those in other therapeutic areas (1). This pattern of early success with late-stage failure likely reflects inaccuracy in interpreting early-stage trial results due to the lack of biomarkers and surrogates that reflect meaningful target effects and Phase III end points. For this reason, cancer therapeutic endeavors are riskier than those in other therapeutic areas, precisely at the stage of clinical development at which resource expenditure and costs are highest.

An increase in the number of failed drug candidates in late-stage development is taking place precisely at a time when advances in biotechnology are occurring at an exponential rate. A series of anticancer agents undergoing late-stage attrition will likely result in the dissipation of resources available for developing therapeutics against targets that have not yet been validated but represent the greatest hope for a positive cycle of progress in the field.

### ALIGNING REGULATORY STRATEGIES WITH THE SCIENCE

The high and often unpredictable risks incurred in late-stage development of anticancer agents indicate that additional efforts and resources must be directed toward improving preclinical models so that they more closely resemble the complexity of human malignancies. In doing so, predictive biomarkers must be developed, and the design and critical aspects of clinical evaluations (*e.g.*, patient population, tumor characteristics, and end points) must be aligned with the biological aspects of the target itself, similar to what has been accomplished in many other therapeutic areas. However, these are daunting tasks because understanding cancer has proven to be much more difficult than comprehending the pathogenesis of infections, cardiovascular disorders, and diseases in most other therapeutic areas. Moreover, the requirements for regulatory approval, particularly in untreated patients, may prove to be more stringent in terms of logistics, time, resources, and expense (6). These factors may preclude the development of many new clinical entities that might have demonstrated clinical benefit in postapproval evaluations if initial regulatory approval requirements were less rigid.

There are other critical factors driving the late-stage attrition of novel therapeutics. The most important factors relate to the unique challenges of developing rationally designed, target-based (RDTB) therapeutics compared with nonspecific cytotoxic agents and the difficulties inherent in aligning business and developmental models in the pharmaceutical industry with the biological principles responsible for the development of these agents in the first place. Business models that were derived for nonspecific cytotoxic therapeutics in an era of greater unmet need have not been modified to fit novel developmental and regulatory approval paradigms required for RDTB therapeutics with much more stringent target requirements. On the market side, the pharmaceutical industry has traditionally been under great pressure to undertake developmental studies that result in regulatory approval designed to capture the broadest possible market and label. As such, the most common early indications include one or more of the “big four” tumor types: breast cancer; colorectal cancer; lung cancer; and prostate cancer. This strategy

is also driven, in part, by the well-defined criteria for full regulatory approval specified by the regulatory agencies, which focus on demonstrating increased survival in untreated patients, whereas the regulatory ramifications of achieving “middle ground” surrogate end points are much less certain. Nevertheless, this traditional approach is becoming progressively more difficult and riskier because the standard clinical practice in the first-line and even second-line treatment of most of these tumor types often involves multiagent regimens. Risk is increasing because clinical studies need to show incremental improvement over multiagent regimens, which can be difficult to demonstrate, particularly in realistically sized trials. The logistics of performing such trials is becoming exceedingly difficult even for large oncology cooperative groups and multinational pharmaceutical companies, let alone much smaller biotechnology companies. For many of these tumor types, even second- and third-line indications are becoming saturated, and demonstrating clinical benefit in more heavily pretreated, advanced patients has become arduous in many settings and somewhat irrelevant in others because these patients may paradoxically constitute “survivors” with favorable disease characteristics and a natural propensity to response. Accelerated approval strategies in these populations, which involve achieving semivalidated surrogate end points in nonrandomized trials, are often labeled as inherently flawed, despite the fact that most therapeutics that have undergone accelerated approval by this route have ultimately demonstrated clinical benefit and unique roles in oncology practice in postapproval evaluations (7). To accelerate the development of RDTB therapeutics in an era of increasingly arduous clinical trial logistics, “middle ground” criteria for regulatory approval must be more clearly delineated.

### ALIGNING SCIENCE WITH DEVELOPMENTAL STRATEGIES

To some degree, the pharmaceutical industry has been undertaking more radical developmental paradigms with RDTB therapeutics, in which the developmental strategies are congruent with the biological aspects of the target. These paradigms involve seeking initial indications in smaller niche populations of patients whose tumors are driven by aberrations of the drug’s target, resulting in proof of principle and possibly accelerated approval [*e.g.*, imitinab in chronic myelogenous leukemia, bortezomib in multiple myeloma (7)]. Often, much information is acquired during these resource-intensive evaluations, which can then be constructively applied toward selecting disease settings for subsequent, broader evaluations. However, decreasing the intrinsic risk of such developmental paradigms mandates the concurrent development of a “fail-safe” scientific foundation, which entails a thorough understanding of the agent’s target, as well as the development of better predictive preclinical models and biomarkers. Although this notion is irrefutable in theory, one wonders if it can be realized for the majority of RDTB therapeutics at this stage in our understanding of cancer and our technological aptitude. Therefore, the degree to which the target is understood should dictate the degree to which alternate empirical strategies are incorporated into developmental strategies of RDTB therapeutics and the extent to which the regulatory agencies permit the use of middle ground criteria for approval.

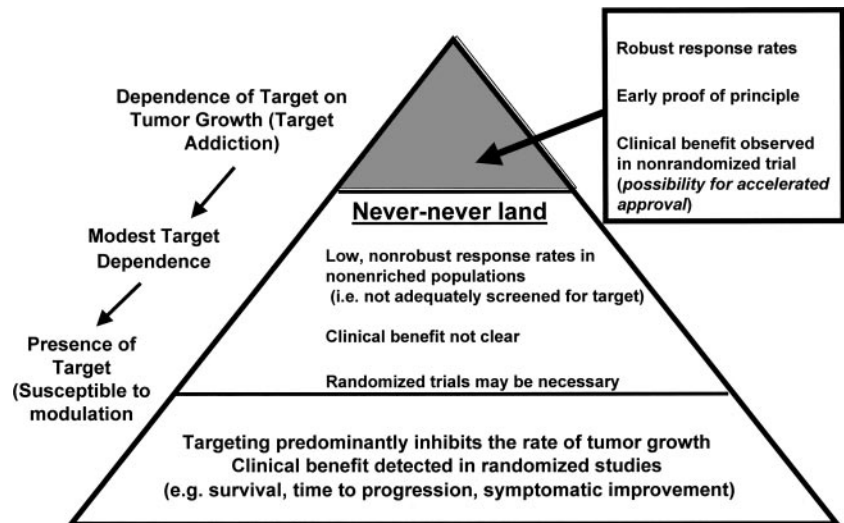
### THE CASE FOR EXPENDING MORE RESOURCES IN PRECLINICAL DEVELOPMENT

Nevertheless, it is essential that clinical development programs incorporate basic scientific methodologies into the early stages of clinical evaluations to curtail the mounting rate of late-stage attrition of anticancer agents. Although the scientific methods involved in characterizing targets and optimizing therapeutics at the molecular level have become dramatically more sophisticated, the development of preclinical models has been stagnant over the same period. The risks incurred in evaluating unprecedented approaches are amplified by our general inability to make accurate “go/no go” decisions in late preclinical evaluations and early clinical studies due to the unavailability of good preclinical models and of biomarkers that reflect target inhibition. Stagnation is an understatement with regard to advances in the development of model systems to optimize the development of combinations of novel therapeutics. Even the best therapeutics against specific targets may be totally ineffective as single agents but may confer considerable anticancer activity in combination regimens. At this juncture, the derivation of optimal combinations is largely guided by conjecture or hit-or-miss empiricism. Rigorous, systematic approaches to guide the development of combinations of targeting therapeutics, perhaps using genetic knockout techniques or short interfering RNAs, must be undertaken. Because of the vast division of knowledge about targets and therapeutics between companies, research collaborations in the form of consortia, allowing companies to share intellectual property as well as risk and cost, may be the only means to develop systems that will serve as broad foundations for further therapeutic development.

### RETHINKING REGULATORY END POINTS

A trend toward conservatism within the United States Food and Drug Administration over the last decade may be another factor responsible for the high late-stage attrition rates of cancer therapeutics. In the past, when there were fewer available therapies, the regulatory bodies were more apt to accept end points that were not rigorously validated as surrogates for true clinical benefit in untreated patients (*e.g.*, tumor regression, time to tumor progression). With the increased availability of new agents, however, the regulatory bodies have moved toward end points that irrefutably reflect clinical benefit (*e.g.*, increased survival) but are exceedingly difficult to demonstrate in patients with refractory and progressive malignancies. These higher regulatory hurdles, coupled with the lack of validated clinical surrogates that reflect therapeutic efficacy, increase the likelihood of late-stage attrition. Furthermore, regulatory posture may wax and wane with public sentiment and subjective advice from advisory committees whose members have relative short tenure. This has been recently demonstrated by the accelerated regulatory approval of gefitinib for non-small cell lung cancer after treatment with platinum- and taxane-based therapy on the basis of a modest rate of tumor regression, which is, at best, a loose indicator of clinical benefit in this disease, as well as symptomatic improvement in trials that lacked suitable control arms (8).

**Fig. 1** A pyramidal approach to the clinical development of rationally designed, target-based therapeutics. To obtain proof of principle, early clinical trials are performed in the tumor types most likely to possess functional aberrations (represented by the apex of the pyramid). After these studies, broader disease-directed evaluations, involving tumor types in which the target may contribute to a lesser extent in conferring a proliferative advantage, are then performed (represented by the base of the pyramid). Randomized clinical evaluations will likely be required nearer to the base of the pyramid because the benefits of therapeutics in tumors with multiple drivers of proliferation are likely to be manifestations of tumor growth delay, which are less apt to be quantifiable in nonrandomized trials.



## RETHINKING INITIAL CLINICAL INDICATIONS

Logical solutions must be wholeheartedly adopted by industry before mounting late-stage attritions decrease overall interest in oncology as a prime area for therapeutic development as well as investment. Investigators and academic institutions must also play a role in refraining from pursuing the same old late-stage, resource-intensive studies in the “big four” tumor types unless there is a solid scientific foundation or adequate proof of principle in early-stage disease. Both industry and academia must understand and admit that their relationships are problematic and undertake difficult measures toward forming durable alliances. Improved relationships between academic laboratories and industry in the preclinical stage will undoubtedly facilitate the development of accurate predictive preclinical models, biomarkers, and enrichment strategies for early clinical trials. With the assistance of investigators and academic institutions, pharmaceutical and biotechnology industries must pursue initial clinical evaluations and/or proof of principle studies in well-defined disease settings based on firm mechanistic and scientific rationale. Seeking initial regulatory approval in small “boutique” indications is often considered incongruent with traditional business models that seek to recoup research and development costs as early as possible in the relatively short life cycle of pharmaceuticals and to satisfy the short-term expectations of a rather near-sighted and impatient investment community. However, much momentum can be gained by an early demonstration of proof of principle despite the nature or small size of the first indication. Once an agent has received initial regulatory approval, new opportunities are then available to expand indications through additional postmarketing trials performed by academia, the community, and national cooperative oncology groups. For example, after the initial regulatory approval of paclitaxel in a relatively small indication (women with recurrent or refractory ovarian cancer based on early clinical observations), cooperative oncology groups such as the Gynecologic Oncology Group, National Cancer Institute of Canada Clinical Trials Group, and Eastern Cooperative Oncology Group

performed high-quality Phase III evaluations, resulting in the expansion of paclitaxel’s indications to previously untreated patients with ovarian cancer, non-small cell lung cancer, and advanced breast cancer (9).

## THE PYRAMIDAL APPROACH TO THE DEVELOPMENT OF RDTB THERAPEUTICS

To curtail the increasing attrition of cancer therapeutics, particularly those against unprecedented targets, pharmaceutical business and clinical development models that were once well suited for nonspecific cytotoxic agents in a vastly different era must be modified so that they are tailored to the specific characteristics of each novel therapeutic, enabling the incorporation of more logical scientifically and mechanistically based approaches into the earliest stages of therapeutic evaluations. One possible approach is illustrated in Fig. 1, which displays a pyramid whose volume represents the entire patient population that might benefit from a RDTB therapeutic. Early proof of principle and possibly accelerated approval will be most efficiently accomplished if initial clinical trials are performed in disease settings in which tumor growth is principally driven by aberrations of the target of the specific agent (*i.e.*, pathway addiction). Such settings are represented by the volume of the apex of the pyramid because it is likely that the growth of relatively uncommon tumor types will be most robustly inhibited, resulting in tumor regression (2). In such settings, in which tumor growth is highly dependent on the target, clinical benefit or surrogates thereof (*e.g.*, tumor regression) will be more readily appreciated in early-stage nonrandomized clinical trials (10). For example, several types of malignancies are associated with specific aberrations of the erbB1 receptor that confer constitutive activation and proliferative advantage. A common variant is the mutated erbB1 receptor EGFRvIII, which is found in carcinomas of the prostate, breast, ovary, non-small cell lung, and stomach in varying frequencies, suggesting broad clinical relevance (11–14). The EGFRvIII variant possesses a constitutively activated tyrosine kinase that results in ligand-independent transformation of cell lines, although the mutation results in

the deletion of a part of the extracellular domain that renders the receptor incapable of ligand binding and dimerization. Specific monoclonal antibodies have been isolated that can help to detect this variant on tumor cells by immunohistochemical means, permitting the identification of EGFRvIII in certain tumors that may not bind antibodies against wild-type erbB. Recent reports of impressive antitumor responses in patients with recurrent and refractory high-grade astrocytomas, some of which have been documented to possess EGFRvIII mutations, suggest that early proof of principle might have been most efficiently demonstrated in this tumor type (15, 16). Even more recently, investigators have demonstrated that the preponderance of robust regressive responses in patients with non-small cell lung cancer treated with gefitinib are due to heterozygous activating mutations that cluster in the ATP-binding domain in the *evBB1* tyrosine kinase (17, 18). Another example of optimal disease settings to demonstrate early proof of principle relates to rapamycin analogs (19). Although rapamycin and its analogs, which inhibit the mammalian target of rapamycin, are capable of prominently inhibiting the growth of a wide range of tumors with and without known aberrations in related signal transduction pathways, the most impressive antitumor effects have been noted after treatment of experimental tumors with *PTEN* mutations and constitutive aberrations of the phosphatidylinositol 3'-kinase pathway that, in turn, activate mammalian target of rapamycin (20–25). The most important of these aberrations involves deletions of *PTEN*, which occur in several types of solid malignancies, particularly endometrial and breast carcinomas and high-grade astrocytoma (19–25). These tumor types would constitute the ideal settings to provide proof of principle.

### SEEKING NICHE INDICATIONS DOES NOT RESTRICT THE RANGE OF EVENTUAL USAGE

This is not to say that the use of RDTB therapeutics will ultimately be restricted to such niche indications. It is possible that several targets will be highly restrictive and that the utility of many RDTB therapeutics may be limited to orphan indications. Nevertheless, because molecular aberrations and oncogenic events tend to be shared by many types of malignancies, many RDTB therapeutics validated in uncommon malignancies will ultimately be demonstrated to have broader therapeutic applications. After demonstration of proof of principle and/or initial regulatory approval of targeted agents in malignancies that are principally driven by aberrations of the target, there will be much greater enthusiasm on the parts of sponsors, academicians, and regulatory authorities to evaluate the potential merits of RDTB therapeutics in more common disease settings, represented by the volume at the base of the pyramid, in which the specific target contributes to but may not be the sole driver of tumor growth. In settings in which the target is not a principle driver of proliferation, relevant anticancer activity (*e.g.*, high tumor regression rates) will not likely be readily apparent in nonrandomized trials. Instead, the principal therapeutic effects of target inhibition in tumors in which there are multiple contributory target aberrations or no specific aberration, but yet susceptible to the drug for other reasons, may be optimally assessed in clinical trials with end points that reflect tumor growth inhibition. Randomized clinical trials that are suffi-

ciently powered to assess differences in survival, time to progression, and other end points that reflect tumor growth inhibition are suited to detect clinical benefit in settings where there are many relevant drivers of tumor growth. The results of nonrandomized, indiscriminate Phase II trials in tumors in which little is known about the principal drivers of growth, or when the agent is expected to decrease the rate of tumor growth as its predominant effect based on preclinical studies, will likely be uninterpretable. In contrast, demonstrating robust activity in proof of principle trials, which may involve screening for the target and niche tumor types with high incidences of relevant target aberrations, represented by the apex of the pyramid, may be well worth the investment of resources. Gains may be in the form of increased momentum and possibly accelerated approval, as well as enthusiasm to further evaluate the agent in settings represented by the base of the pyramid.

This pyramidal approach to the development of RDTB therapeutics, in which benefits are generalizable, is based on the assumption that relevant and aberrant targets are shared by many types of human malignancies. It also requires considerable knowledge about the target and its relevance as a “driver” in a wide array of complex human tumors. To increase the probability of success in the initial stages of disease-directed clinical evaluations, particularly when uncertainty persists about the functional aspects of the target, the concurrent development of biomarkers that not only reflect tumor burden but also reflect a relevant degree of target inhibition is essential. Given the advances in imaging over the decade, particularly functional imaging with positron emission tomography and other techniques, such studies can be a fruitful source of biomarkers. In addition, “omic” technologies, particularly proteomics, are potentially rich sources of biomarkers and should be incorporated into preclinical studies to identify those tumors represented by the apex of the pyramid, formulate patient enrichment strategies, and maximize target inhibition in both clinical evaluations and practice.

### THE IMPORTANCE OF AN ONCOLOGY CULTURE IN INDUSTRY

The pyramidal approach supported by biomarker development may be more readily adopted by pharmaceutical or biotechnology companies with an “oncology culture,” in which there is a realization that therapeutic development and use differ greatly from other therapeutic areas. The facts that most therapeutic development in oncology is performed postapproval and that the majority of use is off-label are best realized by pharmaceutical companies that specialize in cancer therapeutic development and/or those with autonomous oncology units whose models have not been tainted by those derived in vastly different therapeutic areas. Nevertheless, the initial “apex” stage of the pyramidal approach is resource-intensive, and the time until realization of the full clinical and commercial benefits of RDTB therapeutics may be much longer than for nonspecific cytotoxic agents. The time to full commercial realization may be incongruent with the life cycle of cancer therapeutics, given current regulations worldwide regarding exclusivity. To curtail the high rate of attrition of unprecedented cancer therapeutics, regulators and legislators must be made to understand the difficulties

inherent in the development of such agents and must consider extending patent protection and marketing privileges in situations that incur inordinate risk relative to life cycle duration.

Without substantial improvements in research, development, and evaluation paradigms, as well as the formulation of regulations to promote the development of RDTB therapeutics, the total risk-adjusted costs of research and development per chemical entity will greatly increase. Because of the fiduciary obligations of companies to their shareholders, industry will begin to pursue only targets in therapeutic areas that are perceived to affect populations large enough to make significant profits within the life cycle of a drug, should one be discovered. If late-stage attrition of cancer drugs is not curtailed by the adoption of developmental paradigms that, at first glance, may seem inefficient but are aligned with the scientific principles responsible for the development of the therapeutics in the first place, cancer as a therapeutic area will be threatened with the prospect of again becoming a step-child, as industry moves its focus to well-validated targets with perceived blockbuster potential in other therapeutic areas. However, this approach will continue to render the pharmaceutical industry highly vulnerable to blockbuster failure because a considerable proportion of their revenues will depend on fewer products.

## SUMMARY

Just a few years ago, it seemed that anticancer therapeutic development had come to a standstill, with a paucity of new agents with the potential for major impact. The exponential rate of acquisition of information about cancer biology during the last decade has led to the development of RDTB therapeutics directed against the inherent basis of cancer, such as aberrant growth signal transduction and the microenvironment. Although it is expected that RDTB therapeutics will result in greater specificity, less toxicity, and higher therapeutic indices, the requirements for robust antitumor activity will likely be more stringent than for nonselective cytotoxic agents, and the selection of tumor types for initial clinical evaluations to provide proof of principle must be guided by biological principles that enable identification of tumors driven by related target aberrations. Still, RDTB therapeutics may portend substantial clinical benefit in a wide range of tumor types, depending on the presence and relevance of the target. To perpetuate the notion of RDTB therapeutics and realize the full potential of this approach, the implementation of radically different development, evaluation, and regulatory paradigms must be considered.

## OPEN DISCUSSION

**Dr. Fadlo Khuri:** Sometimes there is a very sensitive signal interruption at one point in the pathway and that makes a difference for a time. The mammalian target of rapamycin signal may be interrupted, and then the system switches, so that it is reliant on mitogen-activated protein kinase. How do you think we are going to approach that problem?

**Dr. Eric Rowinsky:** Public enemy number one is molecular heterogeneity, but behind heterogeneity is genetic instability and 4 billion years of evolution. Cells can turn off pathways, so you target one particular pathway and you get effect, then you get resistance because of redundancy and instability. We are

going to have to develop preclinical models to discern what the evolution of this pathway is over time with regard to blockade. Why do tumors become resistant? We are going to have to understand that, or else we are going to fail big time, as we are failing right now.

**Dr. Khuri:** We don't have good *ex vivo* models. Are we going to develop specific imaging so we can tell, in real time, in a person's tumor?

**Dr. Rowinsky:** I think we have the capacity to have good models. Those models could be very artificial, yet they may somehow give us clues.

**Dr. Thomas Lynch:** One of our consensus statements is that we should be replacing xenografts with rational assessment of targets. But, when a company or an investigator asks us whether we want to participate in a study, they almost invariably show us tumor xenograft data. What do you think about that?

**Dr. Rowinsky:** There is nothing wrong with xenograft models for a cytotoxic drug, and if you see activity across the board in a xenograft model with a rational targeted therapy, you are going to get excited. But how many compounds are we going to throw out the window because we can't develop a model that lives up to our expectations in some of the xenografts? If we are developing a drug to hit a certain target and that target is not represented in the xenografts or is overrepresented, we are just going to do ourselves no good.

**Dr. Roman Perez-Soler:** It is in the quality of the preclinical efficacy studies where a big part of the problem resides. The Food and Drug Administration does not care about preclinical efficacy. The Food and Drug Administration basically says if you have money, you have a molecule and it's safe, go ahead. It must work somewhere or otherwise you would not want to do it. The models are suboptimal, and in addition they are not used properly. So I think there is a problem in the lack of regulation and the poor quality of the preclinical studies. If the preclinical work was looked at carefully by the regulatory authorities or had to be reproduced in different labs, I think we would select better drugs.

**Dr. Rowinsky:** We basically have to understand these agents a little bit more and develop our translational assays, as well as validate them, so that when they are ready to go into the clinic, we are collecting optimal data. We need to have assays that can be performed on archival tissue. We can do those serial biopsy studies in some institutions, but in large population studies, it is not going to happen.

**Dr. David Gandara:** You commented that the basic premise for targeted therapy is that you identify a population who might benefit and that it's not going to be tumor type specific, it's going to be target specific. If you take epidermal growth factor receptor as an example, regardless of how we measured the target as being present, the biologic effects in patients seem to be tumor type specific. Maybe there is a different aberrant driver in different tumor types, but certainly these agents seem to work in colon cancer and others don't, even though the target is highly expressed. I'm not so sure that we are going to completely divert our attention from tumor type, just because of the different biology, much less what happens in individual patients.

**Dr. Thomas Roberts:** I particularly appreciated your highlighting the approach of industry sponsors as being disease

specific and going for the largest market. In an analysis that Dr. Lynch and I recently did of about 400 Phase III trials, we found fewer than 10 sponsors actually had enriched the population or found subgroups or responders before going into Phase III. In a meta-analysis we are doing of Phase I trials, we are now finding that the prevalence of correlative science in Phase I trials has gone from something like 10% of trials in the early 1990s to almost 40% of Phase I trials now. Because much of the correlative science is National Cancer Institute or publicly funded, it is not integrated into the development process of the drug. In very few instances could we find that the correlative science actually helped to the sponsor make the development decision. It is not in the sponsor's interest to define responsive subgroups, even if it improves the efficiency of development and improves the success rate, because of the decimation of market size. Do you think there is a role for the Food and Drug Administration to mandate this kind of work, either before approval or post-approval?

**Dr. Rowinsky:** We blame big Pharma, but it's very possible that the markets are really going to be small niche markets, and there will be no extrapolatability, so that they will lose money, and we just are at a standstill. So not only the Food and Drug Administration but the National Cancer Institute could be utilized to do things that we can't do at institutions.

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