Commentary

Cancer Research in the United States: A Critical Review of Current Status and Proposal for Alternative Models

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INTRODUCTION

Cancer research in the United States has undergone seismic changes in the past 6 decades. In the early phases, before the second half of the 20th century, cancer laboratory research focused on tissue histology and animal xenograft models, with surgery and radiotherapy being the mainstays of treatment. The 1950s brought both an increased use of patient-derived, transformed cell lines (eg, HeLa cells, first cultured in 1951) and the dawn of the first active anticancer drug therapies (eg, antifolates in 1948 and thiopurines in 1951). Their success prompted the establishment of the Cancer Chemotherapy National Service Center, the predecessor of the National Cancer Institute (NCI) Developmental Therapeutics Program.[1] This public focus, and the resources that followed, led to major breakthroughs in cancer therapy, including curative approaches in some subtypes, such as Hodgkin and non-Hodgkin lymphoma, some acute leukemias, and choriocarcinoma.[2-7] In 1956, choriocarcinoma became the first solid tumor to be cured with chemotherapy.[7]

Over the next 40 years, there were multiple important advances in chemotherapy, including the development of novel antimetabolites, alkylating agents, nucleoside analogs, platinum analogs, anthracyclines, taxanes, interferons, interleukins, and hormone antagonists. Combinations of these drugs (chemotherapy alone or as an adjunct to surgery, radiotherapy, or hematopoietic stem cell transplantation) improved the outcomes of patients with select solid and hematologic malignancies, with curative therapies established for testicular cancer,[8] subtypes of breast cancer,[9-13] and acute myeloid leukemia.[14,15]

In the late 20th century, researchers began to unravel the molecular pathophysiology of cancer, leading to the identification of hundreds of tumor-associated genetic alterations, oncoproteins, and other biomarkers. These advances facilitated the development of more precise targeted therapies, primarily in the form of monoclonal antibodies and small molecule inhibitors. Some of the resulting therapeutic breakthroughs included imatinib (a BCR-ABL tyrosine kinase inhibitor to treat chronic myeloid leukemia),[16,17] rituximab (a CD20 monoclonal antibody to treat lymphoma and acute and chronic lymphocytic leukemias),[18-21] bortezomib and lenalidomide (a proteasome inhibitor and thalidomide derivative with immunomodulatory properties, respectively, to treat multiple myeloma and myelodysplastic syndromes),[22,23] and trastuzumab (monoclonal antibody to treat human epidermal growth factor receptor 2 [HER2]/*neu*-positive breast cancer),[24,25] to name a few.

More recently, the discovery that the host immune defenses can be modulated to eliminate cancer cells has led to a wave of immune-oncology modalities, including checkpoint inhibitors and cytotoxic cellular therapies. Consequently, tumors traditionally resistant to cytotoxic drugs, such as advanced melanoma or non-small cell lung cancer, now can be controlled or even cured, albeit at modest rates (3-year estimated disease-free survival rates of 20%-50%).[26,27] Similarly, bioengineered chimeric antigen receptor T-cell (CAR-T) therapy produced complete response rates of $\geq$80% in patients with refractory acute lymphocytic leukemia.[28-31]

The US Food and Drug Administration (FDA) responded to the need for more rapid reviews and approvals of cancer drugs, as demonstrated by the increasing inventory of life-improving and potentially life-saving therapies. In the past

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30 years, the FDA has approved at least 37 monoclonal antibodies (33 therapeutic and 4 diagnostic agents) and 37 protein kinase inhibitors for cancer-related indications (see Supporting Tables 1 and 2).[32-35] Since 2011, 6 checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab) have been approved by the FDA for >25 indications in 11 cancers (see Supporting Table 3). In late 2017. the FDA greenlighted the first CAR-T cell therapies, tisagenlecleucel (to treat recurrent/refractory acute lymphocytic leukemia in patients aged ≤25 years) and axicabtagene ciloleucel (to treat recurrent/refractory lymphomas).[28,29]

The drug discovery, development, regulatory, and commercial successes led to substantial investments in cancer therapeutics by the public through the National Institutes of Health (NIH) and the NCI, as well as by the biopharmaceutical industry. Nearly 800 new molecules are under investigation for various cancer indications, including rare tumors.[35,36] This bodes well for improving survival for many cancer subtypes in the near future.

Despite the excitement over new therapies, the number of drugs being explored, and the vast array of laboratory techniques available to define the unique molecular signatures of patients' neoplasms, a malaise plagues cancer research. Although there have been improvements in the process of getting a drug to the market, it still takes an average of 10 to 12 years from development to approval. This has occurred despite the availability of more research funds, strategies, novel concepts, molecules, and targets than ever before. Investigators and sponsors are frustrated by the slow pace of clinical drug development and the prolonged time to market approval and penetration of many novel treatments. Cancer trials commonly are delayed by complicated regulatory requirements and unrealistic eligibility criteria. Many drug industry sponsors are developing "me-too" molecules such as antibodies against programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), or cytotoxic T-lymphocyte-associated protein 4 (CTLA4), rather than focusing on novel approaches. The devolution of research responsibilities to contract research organizations (CROs) has increased bureaucracy without clearly improving patient safety or the quality of trial conduct and clinical research. There also is growing concern regarding the exorbitant prices of new cancer drugs, as well as the unrelenting annual price increases of 10% to 20% among older agents, even in cases in which the drug is off-patent.[37-53] This results in a diminishing percentage of patients able to access affordable therapies.

How did we reach this current state of cancer research, and can we do better?

History of the Cancer Research Structure in the United States

In the early 1950s to 1960s, cancer research for the most part was entrepreneurial, with a limited number of investigators or cancer centers studying the individual drugs, such as nitrogen mustard and alkylating agents, made available to them by academic laboratories or chemical companies. The hope was that drugs would "target" the cancer cells. For example, L-phenylalanine mustard was named "mel-phalan" because of the recognition of phenylalanine in the biochemistry of melanin synthesis, and the hypothesis that the drug would be useful for the treatment of melanoma. During this phase, cancer research was funded by academic or private institutions, philanthropy, and foundations such as the American Cancer Society (founded in 1913), the Lasker Foundation (founded in 1942), and the Robert Roesler de Villiers Foundation (founded in 1949). The latter became the Leukemia Society of America, and then the Leukemia & Lymphoma Society.

The scale of cancer research began to change when President Richard Nixon famously "declared war" on cancer in 1971 and allocated substantial resources to research.[54] The NCI was created in 1937, but its budget increased significantly in the 1970s. Under this federal cancer research model, through funding of the NIH and the NCI, thousands of drugs were screened against cell lines and animal models for potential anticancer efficacy, and then allocated to experts and cancer centers for investigation via collaborative research, including through cooperative groups. Promising drugs were transferred to pharmaceutical companies to fund further studies and safety investigations. This first model of cancer therapeutic research relied partly on the pharmaceutical industry pipeline, but was driven mainly by the NIH-NCI funding axis and by independent investigators and experts collaborating with the NCI.

The 1980s and 1990s witnessed the emergence of the pharmaceutical industry as the dominant force in cancer research. This started with a few startling discoveries, such as the development of interferons as cancer therapies.[55,56] The original natural human leukocyte interferon research was funded by private philanthropy. Once interferon demonstrated activity in different tumors, the pharmaceutical industry developed synthetic versions, which

later were approved by the FDA for the treatment of hairy cell leukemia and chronic myeloid leukemia.[55-57] Synthetic interferons signaled the beginning of the era of high-priced cancer drugs. Recombinant hematopoietic growth factors, which were developed in the 1980s, also cost thousands of dollars per treatment cycle.

The development of rituximab[18-21] and of the rationally targeted small molecule inhibitor imatinib in the 1990s[16] exemplified the potential for successful pharmaceutical and academic partnerships. Rituximab was approved by the FDA in 1997, and imatinib was approved in 2001. These were followed by numerous approvals of other monoclonal antibodies and targeted therapies in cancer (see Supporting Tables 1 and 2).[33-35]

The Shift to a Drug Industry-Driven Cancer Research Model

The gradual shift from the NCI-based and independent academic collaboration to a pharmaceutical industry-based cancer research model was a positive and necessary step to fund and accelerate the pace of discoveries. This allowed drug development on commercial timelines and avoided some academic and government inefficiencies. Several important events prompted this transition.

The first was the unraveling of the molecular underpinnings and pathophysiology of many cancers. For example, before imatinib could be developed, investigators had to understand the Philadelphia chromosome *BCR-ABL*-associated molecular events at the DNA, RNA, and oncoprotein levels, and then mimic the human chronic myeloid leukemia disease in animal models. The same was true for the development of the *HER2/neu* monoclonal antibodies in breast cancer, and of the epidermal growth factor receptor (*EGFR*) inhibitors for multiple other cancers. Each time a targetable cancer pathophysiology was identified, there were opportunities to create selective therapies in the form of monoclonal antibodies and small molecule inhibitors.

The second development was the passage by the US Senate of the Bayh-Dole Act, enacted in December 1980, which concerned the ownership of inventions discovered with federal funding.[58-61] Before the act, any inventions resulting from contracts and grants supported by federal funding were assigned to the federal government. By 1980, the US government had accumulated 28,000 patents, but <5% of them were licensed commercially. The Bayh-Dole Act allowed inventions made through federally funded research (at universities, small businesses, academic research centers, and nonprofit institutions) to be pursued for patent ownership, and created unique opportunities and incentives for financial gains from the inventions. The result was a proliferation of biotechnology companies founded by academic researchers and institutions. The structures built at each academic institution to bring the inventions to market were leveraged for nonfederal/private financial support, thereby creating a virtuous cycle and fueling the proliferation of commercialization opportunities for the pharmaceutical industry.

The third important development in the shift toward the industry development of cancer therapies was the realization that, gradually, the prices of drugs were escalating at increments that made cancer medicine lucrative. The launch prices of synthetic interferon, rituximab, and other monoclonal antibodies, as well as imatinib and later small molecule inhibitors, led drug companies and investors to believe that, when it comes to cancer drug prices, "the sky is the limit." Imatinib was launched in 2001 at a price of approximately $26,000 for a year of therapy, based on the cost of a similar course of interferon-α, the standard of care at the time. Defying more common laws of economics, the price increased to $146,000 by 2016,[52,53,62] despite the advent of competing drugs, and helped to justify even higher launch prices of new-generation BCR-ABL tyrosine kinase inhibitors (dasatinib, nilotinib, bosutinib, and ponatinib). Similarly, lenalidomide, which was approved for the treatment of patients with multiple myeloma and myelodysplastic syndrome in 2006, was launched at a price of $89,000 for a year of therapy but escalated to $184,000 in 2017. In 2015, the average launch price of new cancer drugs approved by the FDA was $145,000 per year or treatment course. The 2 recently approved CAR-T products for lymphoma and for acute lymphocytic leukemia of childhood or young adulthood were priced at $375,000 to $475,000 for a single dose of the modified expanded lymphocyte products (exclusive of the preinfusion and postinfusion medical care, which could amount to >$1 million).[30,31]

With the plethora of cancer targets, the explosion of the biotechnology industry ripe for timely buyouts by larger companies, and the unlimited potential for financial profits, the pharmaceutical industry implemented gradual steps to tighten its control of the research process, as well as the communication of research results through publications, advertisements, presence at cancer meetings, and other forums.[63-68] Additional steps implemented by the drug industry that increased the cost of research included: 1) outsourcing the monitoring of research to contract (or clinical) research organizations (CROs) [69-72];

2) shifting the drug cancer discovery process from internal research and development (R&D) to building >75% of their pipelines by buying out smaller biotechnology companies[73,74]; and 3) a significant buildup of administrative personnel at most large pharmaceutical companies, leading to increasing R&D costs.[75-77]

At this point, a brief history of CROs is in order. The birth of CROs can be traced to the initial need of the NCI and other organizations to monitor cancer research. To the best of our knowledge, Theradex Oncology (Princeton, New Jersey) and Quintiles IMS Holdings Inc (now IQVIA; Durham, North Carolina) were 2 of the first companies to offer these services. The original intent of outsourcing these duties was to develop a cost-efficient way to monitor research at a time when pharmaceutical companies were expanding cancer clinical trials and had determined that in-house monitoring infrastructures were inefficient and expensive. The scope of CRO activities expanded rapidly in the 1990s to include developing advisory boards, interfacing with and selecting investigators and institutions to conduct the research, collecting data regarding procedures and tests, conducting laboratory and translational studies, conducting appropriate analyses, managing protocol-related queries, and preparing regulatory submissions, among others. These endeavors proved lucrative, and created a "CRO industry" that gradually deviated from its original intent. Although analyses estimate the CROs' figures quite differently, as of 2017, there were > 1100 CROs worldwide collecting estimated revenues of >$33 billion annually (which are projected to increase to $65 billion by 2021). This may account for >33% of the total cost of R&D by the drug industry. In 2017, revenues of the top 10 CROs were estimated to be $20 billion.[69-72]

After taking into consideration this evolution and assessing the productivity and quality of delivered results, many experts perceive CROs to be a cancer within the cancer research and clinical trials process. The overinterpretation of regulatory requirements, reliance on poorly trained monitors, misunderstanding of the intents of trials, and insistence on investigator oversight of the operational minutiae of CROs have inflated the cost of conducting clinical research while impeding efficiency. In short, CROs are widely viewed as being so mired in process that they have lost sight of the ultimate purpose of cancer clinical trials: to discover new therapies for a desperate patient population.

In fairness, the inefficiency of conducting cancer research today does not fall entirely on the shoulders of CROs. They are, after all, frequently responding to Byzantine regulatory requirements, as well as to well-intentioned, but poorly executed incentives to maximize trial efficiency. They continue to perpetuate the notion that they are necessary firewalls between investigators and the FDA. In fact, the only time such firewalls are necessary, if at all, is during the conduct of advanced-phase pivotal trials, to ensure that high-quality objective data will lead to cancer drug approvals. All preclinical and early-phase or nonregistration trials can be conducted and monitored within academic centers or the pharmaceutical industry, because these stages of investigation are intended to be hypothesis-driven, and because the appropriate patient protection safeguards required by the regulatory authorities are well understood by all stakeholders. It is time to take a critical look at the benefits and procedures of CROs. To achieve this, a form of a "quality assessment index" of CROs by cancer experts could help to generate a quantifiable measure of a CRO's value, against which others could be compared, leading to higher quality services driven by market forces and competition. And "quality" would not be defined by the numbers of queries issued or forms signed.

The 2018 Cancer Research Model: A Slow, Expensive Process With a Low Success Rate and Increasingly Shorter Patent Times

As a new cancer drug progresses through the drug industry pipeline from preclinical status to clinical research, the process is owned, controlled, and directed by the upper management of the industry. This group consists mostly of business-savvy experts, as well as investors, but rarely does it involve cancer research experts (despite a veneer of active participation and contribution through advisory boards and consultancies). The research path is narrowly focused: 1 drug for 1 cancer. Research and protocols tend to be developed with only distant support from and advice of cancer experts, and with the more intimate support of CROs. This research model suffers from multiple problems (Table 1).

First, the narrow focus on 1 cancer in a "do-or-die strategy" reduces the potential for advancement. The rate of FDA approval, reported to be as low as 1% to 5% when debate occurs surrounding high cancer drug prices, actually is as high as 15% to 20% for drugs that have entered the clinical research arena since 2000.[78,79] This includes the approximately 50% of cancer drug discoveries that are made serendipitously, or in areas peripheral to the original focus. Recent examples include the bispecific CD3-CD19 antibody conjugate blinatumomab and the CD22 toxin-conjugated monoclonal antibody inotuzumab, both of

TABLE 1. Comparison of Current and Proposed Cancer Research Models

Parameter	Current Model	Proposed Model
Entity driving the research	Drug company	Shared between tumor experts and the drug company
Focus of investigation	1 drug, 1 tumor	Multiple agents investigated in parallel across multiple tumors in pilot/phase 1 to 2 trials
Potential success rate (FDA approval)	5%	Anticipated to exceed 20%
Timeline of research	Longer; long decision loops	Shorter (based on go-no-go analyses); shorter decision loops
CROs involved	Yes	No
Cost of research	High ($50-$100,000/patient)	Lower (estimated at <30% of current research models)
Patent time duration	Shorter	Longer

Abbreviations: CRO, contract research organization; FDA, Food and Drug Administration.

which originally were developed as therapies for lymphoma, but were found to be highly active against acute lymphocytic leukemia. Another example is crizotinib, which first was developed as a MET inhibitor. In the phase 1 trial, 2 patients with non-small cell lung cancer achieved dramatic responses. On further assessment, both were found to have tumors that expressed anaplastic lymphoma kinase (*ALK*) fusion genes, resulting in the later development of the drug as an ALK inhibitor.

Second, the majority of drug companies now elect to develop and monitor protocols through CROs rather than through their own internal research groups. Although CROs may be useful for FDA pivotal trials, their value as protocol developers and monitors in the early phase 1 and 2 and extended pre-phase 3 studies is questionable, expensive, and potentially harmful. Nevertheless, pharmaceutical companies argue that CROs are cost-effective, obviating the need for a continuously maintained research organization inside the company that may not be used at times of low research activities. Consequently, the per-patient cost for cancer clinical trials has escalated from a low of <$3000 in the 1990s to $70,000 to $100,000 or more per patient in 2015. Such costs will almost certainly be passed on (should the drug be approved) to payor organizations and financially burdened patients, and are a detriment to our health care system.

Third are the numerous redundant and costly research steps and procedures that slow the process and increase its cost.[80-84] Indeed, it is essential to replace today's compliance-centered regulation (appropriate for non-life-threatening conditions) with "progress-centered regulation" in lethal cancers, for which the pre-eminent goal should be the efficient development of active new treatments. To accomplish this, we need to overhaul the clinical trial process to make it quick and efficient, including creating just-in-time approvals that permit multisite activations around the country when a patient is identified. Just-in-time approvals would allow patients access to investigational drugs without having to mortgage their lives to travel around the country. Establishing partnerships among clinical trial centers would allow a budget, contract, and scientific/institutional review board approval at 1 center to be immediately accepted at partner sites. Part and parcel with this is the need to drastically reduce the requirements for low-value documentation and procedures, and replace them with sensible postmarketing surveillance. As an example, in reviewing early-phase protocols, we found that, in <10 years, the mean number of study-related mandated procedures grew from 45 to 104 over the first 4 weeks on the protocol, and some studies had >40 procedures within a single day. Nevertheless, tighter regulation, requirements for increased documentation, and additional procedures have had a negligible impact on the toxicity-related mortality, perhaps because it already is so low (approximately 0.5%).[80] It also is crucial to reduce the number and restrictiveness of eligibility criteria, which have expanded dramatically over the past 2 decades. These render the majority of real-world patients ineligible for most clinical trials, and introduce a culture of fear of protocol deviations that unfairly excludes patients for whom the clinical trial would be in their best interests were it not for clinically insignificant eligibility shortcomings.[81] They also make many FDA-approved drugs less useful to the average patient with cancer.

The above issues in cancer research and proposals for modifications in the process have been detailed in numerous publications. Sadly, to the best of our knowledge, none of the proposed remedies have been implemented.[76,77,82-85] The increasing bureaucracies are promulgated and justified as necessary to improve the quality of research and to protect patients. The reality is that they do neither. Federal rules and regulations that govern human subject research have not changed in >60 years, since they were created after the Tuskegee

experiment and other incidents of egregiously irresponsible research. What has changed is their interpretation by a growing layer of conservative regulatory oversight. This has slowed cancer research, reduced the rate of discoveries, prevented hundreds of thousands of patients from benefiting from potentially effective therapies, and increased the cost multifold. Today, the exponential increase of bureaucracy is paralyzing cancer research in the United States. We often forget that the worst risk to a patient with cancer is the unchecked cancer itself, rather than the treatment risks, and many already have exhausted existing standards of care.

Proposal for a New Cancer Research Model

Today's hybrid cancer research model evolved from a publicly financed and philanthropically supported orientation in the 1970s to one that, by the late 1990s, was heavily influenced by the commercial interests of the biopharmaceutical industry. As a result, drug industry cancer research imperatives and priorities are favored and, when implemented by CRO surrogates, in the majority of cases exclude cancer experts from the drug discovery, development, and commercialization decision making processes. What results is a commercially driven rather than a science-based orientation, in which the needs of substantial patient populations are potentially unmet.

To review, the current model suffers from several flaws. First, it empowers the pharmaceutical company and CRO-affiliated individuals to develop the research path of a new cancer drug, often with limited and more distant input from cancer experts. Second, it focuses on a "1-drug, 1-tumor" approach, which reduces opportunities to make discoveries across tissue, genomic, or organ boundaries. This industry-driven, reductionist approach, in which complex phenomena are reduced to simple constituents, leads to the exploration of drugs and combinations driven less by science and more by the potential of commercial returns. Third, the current research model interposes CROs into research, thus increasing costs, extending research timelines, and delaying access to much-needed cancer treatment discoveries by desperate patients. The last point is important because it is estimated that delays in research ultimately cost patients their health, and cost pharmaceutical companies up to $1 million of downstream revenues after approval for every day of delay.

Considering these issues and limitations, cancer experts and pharmaceutical industry partners are exploring alternate research paradigms. In one, a steering committee composed of tumor-specific experts reviews and provides input regarding the pipeline of the partner drug company. After these collaborative discussions, the steering committee creates a developmental therapeutics proposal encompassing the company pipeline and focusing on a range of malignancies. These proposals produce a more inclusive approach to drug development and research based on the biological integration and dynamic interactions of cancer networks or systems. They also can focus on underserved patients, including populations with poor prognoses, who typically are excluded from the industry-sponsored studies.

Specifically, the steering committee proposes, and the drug industry partners approve, a series of parallel investigator-initiated pilot trials of single new investigational drugs, combinations of investigational drugs with existing therapeutic standards, or combinations of $\geq$2 investigational drugs within the drug company pipeline or within the pipelines of 2 different companies participating in such research alliances with the tumor experts. These pilot trials aim to discover major antitumor activity of specific agents or combinations that, if significant, would translate into advanced-phase pivotal trials aimed at an FDA approval. If the pilot trial results are minimal or modest, then the steering committee proposes a second series of pilot trials, building on the initial discoveries until a path to FDA approval is developed or the concept is judged not worthy of further exploration.

The proposed research model has several advantages (Table 1). First, it would resurrect some of the entrepreneurial principles of the 1970s, whereby the steering committee of tumor experts and affiliated institutions assumes financial risk-sharing in the transaction ("skin in the game"). This in turn would encourage expert focus on innovation and on the elimination of redundancies or unnecessary diversions. Second, the partnering drug company would rely on the advice of and opinions from the best tumor-specific experts, marrying business and science. Third, individual and combinations of drugs would be evaluated across a range of tumors, thus increasing the chances of success when compared with the "1-drug, 1-tumor" approach. Fourth, specific proposals would be originated, conceptualized, and designed to rapidly address the real (rather than perceived) potential risks and benefits to patients, and to preserve the quality of the research in an economically efficient way. Fifth, the process would remove the intermediary CROs, which presumably would accelerate the research process, incorporate the minimum translational research elements required to achieve high-quality discoveries, and reduce costs. Sixth, the decision loops would be abbreviated, and

decisions regarding modifications, protocol amendments, and changes in plans based on emerging findings could be addressed without unnecessary bureaucracy and delays. Seventh, the proof-of-concept and "fast-to-failure" (also known as "go vs no-go") decisions would end costly delays that impact both the access of patients to needed therapies and drug commercialization priorities. This in turn would increase potential drug patent durations. Ultimately, the costs in such a research model would be significantly lower, estimated at <20% to 30% of the price tag of existing paradigms. Moreover, administrative costs and the time required to set up and maintain these broad forms of collaborative research are a fraction of those in conventional "1-off" industry-driven trials.

This new research model is not theoretical, but in fact has been piloted between the leukemia research program at The University of Texas MD Anderson Cancer Center (MDACC) in Houston and Bristol-Myers Squibb (BMS), under the designation of the "rare populations malignancy" program. The rare populations malignancy program at MDACC is the first of its kind and was founded by 3 of us (H.M.K., F.P. and J.L.) to explore the BMS immune-oncology pipeline across multiple hematologic malignancies. It was pursued under several guiding principles. First, the collaboration provides the MDACC leukemia research program with substantial latitude to explore the BMS pipeline as its experts judge best according to their leukemia expertise. Second, select high-risk populations typically excluded from BMS-sponsored studies are eligible for the program at the discretion of the leukemia experts. Third, BMS provides the MDACC research program with a set level of funding and access to its pipeline drugs, as well as scientific expertise around these therapeutics. These funding and periodic disbursements are subject to accomplishment milestones. Progress is reviewed every 3 to 6 months by a joint committee composed of leukemia experts from MDACC and BMS partners. All protocol decisions and research steps are subject to final approval by the BMS partners in the joint committee.

The success of this initiative has resulted in the expansion of the program in several directions. First, BMS extended the program and its principles to other clinical and research departments at MDACC. Second, BMS is partnering with other institutions, including the University of California at Los Angeles, Northwestern University in Chicago, and Johns Hopkins in Baltimore. Third, the MDACC leukemia research program and other departments have established similar alliances with other drug industry partners such as Pfizer, Cellectis, ADC Therapeutics, Daiichi Sankyo, Amgen, and AbbVie. This new cancer research model is flexible and modifiable according to existing needs, and does not pretend to create a "one-size-fits-all" approach. Indeed, many of these alliances have significant variations that accommodate the partnering drug company, its pipeline, and its research needs, as well as financial and other considerations.

The rapid uptake of these research alliances confirms the need for innovative cancer research models, and will lead to discoveries that hopefully are significantly more cost-efficient. If successful, they will translate into higher success rates of cancer drug discoveries that will become available to patients earlier, more widely, and at more affordable prices. In addition, they will stimulate increased longer term profits for the pharmaceutical industry by producing more new drugs with longer patent durations and lower costs of research. In turn, these improvements in capital efficiency will generate further investment in cancer research to the benefit of patients worldwide.

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CONFLICT OF INTEREST DISCLOSURES

David P. Steensma has received personal fees from Otsuka, Takeda, and Tesaro and has acted as a paid member of the Data and Safety Monitoring Committees for Onconova and Janssen for work performed outside of the current study. Razelle Kurzrock has received research funding from Incyte, Genentech, Merck Serono, Pfizer, Sequenom, Foundation Medicine, and Guardant Health; has acted as a paid consultant for Sequenom, LOXO, Actuate Therapeutics, and Genentech; receives speaker fees from Roche; and has an ownership interest in Curematch Inc for work performed outside of the current study.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the concept, commentary design, writing, analyses, review of the article, and final approval of the article.

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