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Commentary

Consideration of the Root Causes in Candidate Attrition During Oncology Drug Development

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Keywords

attrition reasons, cancer types, clinical phases, drug attrition, medication class, oncology drugs

Cancer remained the second-leading cause of death in the United States in 2020, based on the data from the US Centers for Disease Control and Prevention. While there have been lots of money and time devoted to this therapeutic area, the needs from these patients with cancer were still substantial. The fundamental issue is high attrition rate for oncology drugs, which contributes to the higher cost for oncology drug developers. The study for the success rate from first-in-human trials to registration for 10 big pharmaceutical companies in the United States and Europe indicated that the average success rate in all therapeutic fields was about 11% from 1991 to 2000.[1] The success rates varied between different therapeutic areas, whereas oncology drugs had a relatively low success rate, approximately 5%. In other words, only 1 in 20 new chemical entities passed through clinical trials and received an approval from the European and/or the US regulatory authorities. Kola and Landis also studied the reasons for drug attrition during drug development from 1991 to 2000. They discovered that the primary reason for drug attrition changed from inappropriate pharmacokinetics (PK) and low bioavailability (approximately 40%) in 1991 to a lack of efficacy and safety (approximately 60%) in 2000.[1] Kola and Landis concluded 2 strategies that may reduce the rate of attrition. First, in some therapeutic areas with lower success rates (eg, oncology and central nervous system), appropriate animal models and biomarkers have to be carefully chosen during early drug discovery and development stages.[1] For example, a transgenic animal model is more suitable than a xenograft animal model for preclinical studies of oncology drugs. Second, Kola and Landis observed that biologics had a higher success rate to launch from the first-in-human studies, especially in the areas of immunology and cancer, implying that biologics are safer than conventional chemical drugs.[1]

Antibody drugs, 1 group of biologics, generally have fewer safety concerns and fewer PK issues.[2,3] In general, antibodies possess a few pharmacological characteristics, including high potency, limited off-target toxicity, and a low risk of biotransformation to toxic metabolites.[4] Thus, the possibility of drug-drug interactions or renal and hepatic impairment on drug excretion is relatively low, which could significantly eliminate a few matters that could potentially result in drug attrition.

On the other hand, Walker and Newell analyzed the data for small molecular cancer drugs on the attrition from 1995 to 2007, indicating that the attrition rate within the oncology field was 82%; however, the attrition rate of kinase inhibitors was 53%.[5] It is worth noticing that kinase inhibitors were more successful in the high-risk transition from Phase 2 to Phase 3.[5] In addition, Hutchinson and Kirk concluded that the estimated glomerular filtration rate and vascular endothelial growth factor targeted agents and/or other kinase inhibitors had relative high success rates, especially adjunctly treating with antiangiogenic drugs.[6] Overall, for small molecular cancer drugs, molecularly targeted

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drugs demonstrated the potential to reduce attrition rates.

Moreover, Waring et al found that safety and toxicology were the largest sources of drug failure from 4 major pharmaceutical companies from 2000 to 2010, suggesting a lack of safety was the main factor to contribute drug attrition.[7] The links between physicochemical properties and frequent causes of attrition (eg, preclinical toxicology, clinical safety, and human PK) were also assessed. Waring et al concluded that none of the physicochemical properties correlated with the attrition of the drugs. The work was the first study to investigate the relationship between hydrophobicity and clinical failure, implying the stringent control of physicochemical attributes may not be a key to mitigating attrition in small molecular drug development.[7]

In this study, to understand the root causes of discontinued oncology drugs from 2005 to 2013, the correlated factors were analyzed. Further, a questionnaire was created and disseminated to group leaders in the pharmaceutical industry, the Food and Drug Administration (FDA), and oncology clinicians for first-hand feedback. A few strategies, such as investment on the paradigm-shifting drugs and investigation of biomarkers, were concluded to mitigate attrition. Furthermore, using biomarkers could guide adaptive clinical trials to improve the efficiency of drug discovery and development.

Methods

Literature Review for Discontinued Oncology Drugs (2005-2013)

Kelland summarized discontinued oncology drugs in 2005,[8] and Williams published an annual summary for discontinued oncology drugs from 2006 to 2008 and 2010 to 2013.[9–15] All 8 published manuscripts listed the discontinued oncology drugs, the medication classes, targeted indication(s), reasons for discontinuation, and the reached phase of clinical trials. In this study, 4 individual factors (ie, latest clinical phase studied, treatment modalities, attrition reasons, and target indication[s], respectively) were categorized for the discontinued drugs in each year. For example, in individual years, discontinued drugs terminated in each clinical phase were grouped, and sequentially the total number of discontinued drugs in each phase was recorded. Similarly, discontinued drugs were grouped in each year by different drug classes, attrition reasons, and indications, respectively, in individual years. The drug classes were classified into "small molecules," "antibodies" (including monoclonal antibodies, antibody drug conjugates, and vaccines), and "others" (including peptides, proteins, oligonucleotides, gene therapy, and other modalities). The attrition reasons for oncology drugs were categorized in 5 groups: "efficacy," "toxicity," "strategic," "unspecified," and "PK/formulation." Finally, the indication for individual discontinued drugs could be designated for 1 or multiple cancer types. If a failed drug with multiple indications were reported, all indications were considered for the specific year for statistical analysis. Thus, for the cancer type analysis, there were more indications than the total number of the discontinued drugs in each year.

An analysis of variance (ANOVA) was performed using Microsoft Excel to determine differences among different parameters in each factor. For example, within the factor of the attrition reasons, "efficacy," "toxicity," "strategic," and "unspecified" were the individual parameters. When these parameters were determined to be significantly different from each other, these parameters could be used for further statistical analysis (eg, correlation analysis). Significant differences were declared for $P < .05$. Sequentially, the parameters as variables were used to understand the correlations within each aforementioned factors (ie, attrition reasons, clinical trial phases, drug classes, and cancer types). When there was no drug categorized for the parameters, 0.2 was used to replace 0 to accomplish the requirement of statistical analysis.[16] The principal component analysis and correlation analysis were performed in SAS OnDemand for Academics (SAS Institute). Due to scarcity of some of the parameters, they were either combined into the "others" category in medication classes or included only in the top-ranking parameters as variables in the cancer types.

Survey

To obtain the up-to-date, insightful information with respect to attrition of oncology drugs, 8 questions were created to retrieve the first-hand responses from experts and clinical professionals. The questions included whether kinase inhibitors and/or biologics could be promising for development of oncology treatment. In addition, whether there are any measures during early drug development stages could effectively prevent attrition of oncology drugs. To secure the information, the questionnaire was disseminated to 11 experts across different sectors of oncology research on July 29, 2022, and there were 5 full responses received from July 29, 2022, to January 4, 2023 (Table 1). Because the survey neither constituted any human subject research, nor demonstrated any risk to compromise the participants' rights and welfare, after consulting with the Institutional Review Board at the University of Pennsylvania, it was determined that an ethical statement was not required. The responses from individuals were summarized and discussed in the section Summary of Feedback From Survey.

Table 1. Experts and Group Leaders Participated in This Study

Name	Date of receipt	Affiliation
Jeff Skolnik, MD	7/29/2022	INOVIO Pharmaceuticals
Peter Adamson, MD	10/30/2022	Sanofi
Hong Zhao, PhD[a]	11/1/2022	FDA
Hilario Yankey, MD	12/14/2022	Fox Chase Cancer Center
Charles Lee, MD, PharmD	1/4/2023	Fox Chase Cancer Center

[a] The response was reviewed and approved by Dr Atiqur Rahman.

The details of the questionnaire are listed below:

1. It has been reported in previous therapeutic area performance reviews that molecularly targeted drugs (eg, kinase inhibitors) had a higher success rate among oncology drugs[5,6]; however, the discontinued kinase inhibitors were approximately one fourth of the discontinued oncology drugs between 2011 and 2013.[13–15] Are kinase inhibitors still considered promising in oncology? If so, is it as part of a combination therapeutic regimen or as a single agent?
2. Could biologics (monoclonal antibodies) and/or cell or gene therapy become dominant agents in the future for cancer treatment? If so, are they likely to be part of a combination therapeutic regimen or used as single agents?
3. As cancer vaccines offer the promise of both preventive and/or treatment modalities, they have great potential in oncology. However, except for the HPV vaccine, are there any cancer vaccines moving to later stages of drug development? If so, what is the target indication (eg, specific cancer type and rationale)?
4. One of the recently published review studies did not conclude any relationship between failed drugs and the corresponding physicochemical properties,[7] while most people believe the drug structure affects the toxicity and bioavailability.[17] In your opinion, can identifying a drug candidate with a favorable structure or physicochemical property facilitate reducing the attrition in oncology drugs? Additionally, are studies of drug structure more likely to be successful when applied to specific cancer types?
5. There are several strategies for lowering oncology drug attrition[1,9–15,18,19]:
   a. moving proof-of-concept studies to Phase 1
   b. appropriate biomarker selection
   c. appropriate animal model selection
   d. appropriate druggable target selection
   e. stratifying patient populations
   f. fully utilizing in vitro model and tissue banks
   g. using molecular pathology tools for the characterization of efficacy models
   h. optimizing patient selection criteria

   Please rank it from the most important to the least and elaborate why.
6. The term *undruggable* was used to describe proteins that may not be targeted pharmacologically. Conversely, a few oncology drugs have been developed to target RAS and MYC proteins. Is there a rationale for considering undruggable targets? Could you also share your opinion regarding the most critical challenge in this field?
7. Could we do more in the preclinical phase (animal, in vitro studies, etc.) prior to the clinical trials for oncology drug development?
8. Please rank the top 3 cancer types for which the drug development has a relatively high attrition rate.

Results and Discussion

Clinical Phase as a Factor

Information of discontinued oncology drugs from 2005 to 2013[8–15] was retrieved and sorted by 4 different factors, whereas the failed supportive drugs were excluded from all analyses. First, discontinued oncology drugs in each year were sorted by clinical phases through which the drugs advanced during drug development (Table 2). There was a trend that the total number of failed drugs increased with time. It was approximately a 2-fold increase in 8 years. When a linear model was used to describe this increasing trend and to project the total number of discontinued oncology drugs to 2023, there were 66 failed oncology drugs, representing a 3-fold increase from 2005. Although this extrapolation had no scientific rationale and likely does not reflect the complicated facets of oncology drug development, an increasing trend could prompt us to understand the cause(s) for drug attrition, which reduces profitability for pharmaceutical sponsors.

About half of the discontinued drugs occurred in the clinical Phase 1 trials, and the other half of the discontinued drugs had been approximately split in Phase 2 and Phase 3 studies (Table 2). This indicated that half of the discontinued drugs can be terminated at the early stage of development. This could minimize the financial loss of attrition, compared to attrition at the later stage.[19,20] In addition, the groups between different clinical phases were not the same from 2005 to 2013, based on the results ($P = 1.8 \times 10^{-3}$) of ANOVA.

While the principal component analysis and correlation analysis were conducted, there was no high correlation observed, due to small numbers of samples.[21] Similarly, no high correlation can be concluded for attrition reasons, medication classes, and cancer types.

Table 2. The Number of Discontinued Oncology Drugs From 2005 to 2013, Indexed by Clinical Phases, Attrition Reasons, and Medication Classes, Respectively.

	2005	2006	2007	2008	2010	2011	2012	2013
Total	20	12	23	23	28	37	30	40
Clinical phases								
Phase 1	10	5	9	12	11	23	14	20
Phase 2	6	5	10	5	12	9	9	8
Phase 3	4	2	4	6	5	5	7	12
Attrition reasons								
Unspecified	7	3	12	8	13	8	11	6
Strategic	5	2	5	6	3	17	7	14
Efficacy	7	5	5	3	7	9	11	15
Toxicity	1	2	1	6	4	4	0	4
PK/formulation	0	0	0	0	1	2	1	1
Medication classes								
Small molecules	10	9	15	17	22	20	20	26
Antibodies	6	1	5	4	4	13	8	9
Others (peptides, proteins, etc)	4	2	3	2	2	4	2	5

PK, pharmacokinetics.

Attrition Reason as a Factor

Table 2 also depicts the number of failed drugs, categorized by individual attrition reasons, including a lack of efficacy, unmanageable safety and toxic issues, strategic considerations, unspecified concerns, and PK or formulation issues. Herein, the strategic considerations included financial concerns, project priorities, and company mergers and acquisitions; and the unspecified concern incorporated the undisclosed reasons. The undisclosed reasons could also be, in part, related to financial considerations. Some pharmaceutical companies decided not to disclose the attrition reasons. Usually, 1 drug was subject to discontinuation with only a single reason. However, there were 3 drugs discontinued with 2 reasons (a lack of efficacy and safety issues). These were AZD-7762 and AZD-2461, terminated in phase 1, and AZD-8055, terminated in phase 2 in 2011.[13] All the reasons were included and analyzed by ANOVA, except PK/formulation, due to scarcity. The P value, 1.7×10^{-2}, was less than .05, which suggested the attrition reasons were not identical in individual years. Prior to 2009, unspecified concerns were the predominant attrition reasons; however, after 2009, strategic considerations and a lack of efficacy became the major reasons for drug attrition. Excluding unspecified concerns, the majority of the reasons for drug failure was "efficacy" and "strategic," and the proportion of the corresponding attrition reasons was 29% and 27%, respectively. A lack of efficacy has been concluded in many studies[20,22,23] to be the primary reason for drug attrition. Interestingly, the annual discontinued drugs from both "strategic" and "unspecified" reasons were more than the failed drugs caused from "efficacy" and "toxicity" reasons between 2005 and 2013, except 2006. This observation could imply that financial elements play a critical role during drug development, and mostly financial elements could drive the drug development plan over sciences and/or technology. For example, when the competitors are aware that they are behind in the drug development pipeline, they will "strategically" discontinue the drug, since profitability of a new drug is the primary concern in the business. While the financial concerns were recognized as a primary factor for drug attrition, this study focused on the discussion of drug design/development, modality selection, preclinical studies, and adaptive clinical trials.

Medication Class as a Factor

Compared to small-molecule drug candidates,[24] it has been shown that biologics have lower attrition rates, which may be related partly to the fact that fully human or humanized monoclonal antibodies have reduced toxicity concerns.[19] Thus, the relationships between drug classes of the discontinued drugs were studied from 2005 to 2013 (Table 2). During this time period, there were only a few failed drugs that were categorized in the classes other than small molecules and antibodies. These included peptides, proteins, DNA, oligonucleotides, and gene therapy, which were combined into 1 category, "others," in this study. It was observed that the failed small-molecule drugs significantly increased with time, whereas antibodies had only a modest increasing trend. In addition, antibodies and the "others" class did not have this significant increasing linear trend (P value of slope = .08 and .56, respectively). This indicated that antibodies and "others" exhibited less attrition risk during drug development from 2005 to 2013. While the success rate for biologics was higher than for

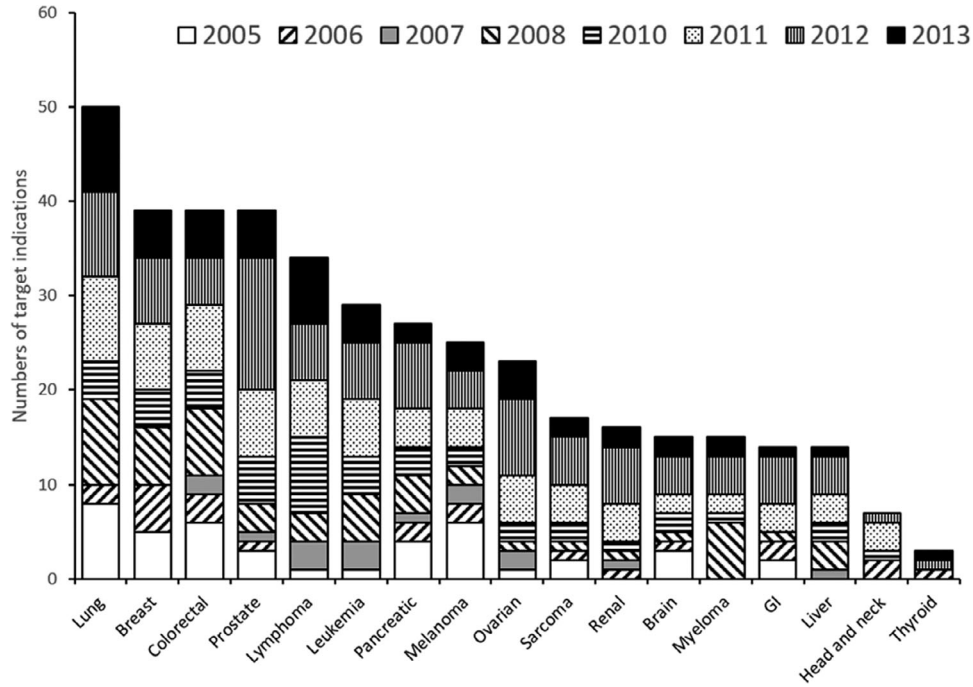

Figure 1. The number of targeted indications, excluding others and unspecified/general/solid tumors, of the discontinued oncology drugs from 2005 to 2013. The tabular details are listed in Table S1.

small molecules during 2012-2014,[25] the success rate of new biologics appears to have leveled out from 2011 to 2013, which may reflect capacity levels within the regulatory agency.[26] Additionally, the P value, 1.2×10^{-6}, from ANOVA also indicated these 3 classes were different.

Cancer Type as a Factor

Some failed oncology drugs had only 1 indication, while most of them had multiple indications. In this study, all the indications for these failed drugs were included and studied. Because of the limited number of certain cancer types from 2005 to 2013, 16 different cancer types (eg, mesothelioma, esophageal, neuroendocrine, etc.) were combined to "others." In addition, unspecified, general, or solid tumors were grouped into 1 category: "unspecified/general/solid." However, due to a lack of specificity, "others" and "unspecified/general/solid" were excluded from statistical analysis, while these 2 groups had relatively more failed drugs incorporated. Figure 1 illustrates the total number for the targeted indications of the discontinued drugs from 2005 to 2013, and lung cancer was the top indication. Because there were 19 groups (Table S1), which may complicate statistical analysis, only the top 9 cancer types were selected for analysis: lung cancer, breast cancer, colorectal cancer, prostate cancer, lymphoma, leukemia, pancreatic cancer, melanoma, and ovarian cancer. Using ANOVA, the selected 9 individual cancer types were significantly different from each other ($P = 1.9 \times 10^{-2}$).

Summary of Feedback From Survey

Because cancer is an extremely complex group of diseases, treatment and prognosis for cancer has encountered more challenges than other diseases. For example, when cancer progresses, tumors can evolve to comprise various cell types with distinct genome and cell morphology, let alone the heterogeneity of cancer.[27] The heterogeneity of cancer includes interpatient heterogeneity, intrapatient intertumor heterogeneity, intratumor heterogeneity, and multifocal diseases.[24,27–29] After acknowledging these complexities of cancer, the intrinsic causation of tumor formation and development is not just 1 or a few mechanisms, and it may not be the same across the entire population of patients with cancer. Thus, a one-size-fits-all oncology drug may not be realistic for drug developers with regard to the complicated nature of cancer. Recently, kinase inhibitors and immune checkpoint inhibitors have been developed in combination with conventional chemotherapy and radiotherapy to treat cancer. Both of these therapies have had promising treatment outcomes. While attrition of kinase inhibitors possessed an increasing trend from 2005 to 2013 (Figure 2), kinase inhibitors could also be effective for subpopulations of patients with cancer as a monotherapy or in combination with other drugs. Over the past decade, oncology

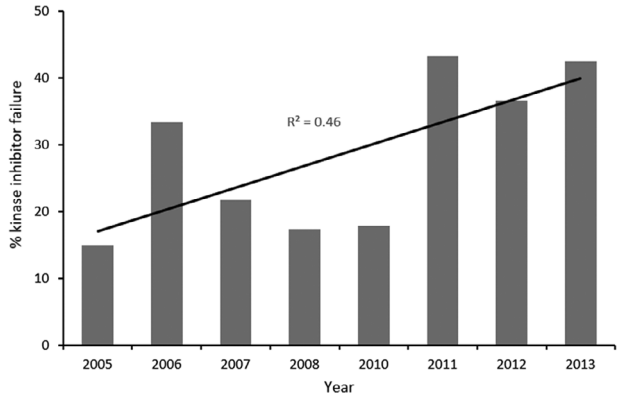

Figure 2. An increase of discontinued kinase inhibitors during oncology drug development from 2005 to 2013.

drug developers have been focused on developing immune checkpoint inhibitors, such as PD-1 and PD-L1 antibodies, especially chimeric antigen receptor T-cell therapies have become standards of care for various hematological cancers. Therefore, biologics have been used for many anticancer treatments and may become a mainstay of treatments due to the growing approval and applications.[26]

Therapeutic vaccines are another treatment modality to combat cancer. However, among all the studied vaccines over the past a couple of decades, only 3 therapeutic vaccines have been approved by the FDA. Currently, there are a few vaccine candidates reaching Phase 3 studies, and those are for human papillomavirus-induced cervical cancer (INOVIO pharmaceuticals and ISA Pharmaceuticals). In addition, due to the success of mRNA vaccines for COVID-19, this emerging technology applied to therapeutic vaccines in oncology has also involved in the early stage of drug development. In my opinion, similar to the drugs, a combination of a few treatment modalities may greatly benefit all patients with cancer.

Another important aspect for a promising drug candidate is to determine if there are favorable physicochemical properties for drug developers to guide the design of next-generation drugs. Although all experts agreed that the physicochemical properties are critical for designing a drug for drug discovery and development, the main reason driving drug attrition was still a lack of efficacy, which may not be associated with the physicochemical properties. There were 2 points concluded:

(1) Whereas the physicochemical properties were highly related to toxicity and bioavailability for small-molecule drugs, the control on physicochemical properties had no direct impact on modulating the other essential requirement of drugs (ie, efficacy). In addition, altering the physicochemical properties could affect PK/pharmacodynamics of a drug, which could result in either more or less efficacy of the drug, due to the heterogeneity of tumors. The efficacy of a drug can only be determined by proper designs of clinical studies.
(2) Biologics could be prominent in the near future, and the physicochemical properties could only stand for the attributes of purity and/or identity but cannot represent the potency of biologics. Meanwhile, the dose-to-response relationship is not as clear as small molecular drugs have. Thus, attempting to search perfect physicochemical properties may not directly facilitate the development for successful biologics.

In addition to selecting physicochemical properties of drugs, during drug discovery, target validation is crucial to ensure that the drug candidate has the correct engagement with the right target.[30] The list of druggable targets is evolving, especially for the diversity of cancer. To seek a breakthrough for oncology drug development, finding a novel target could be a "high-risk, high-reward" project. Securing a new validated target is key to moving forward a new drug candidate from clinical trials to launch.[19] As a result, developing other paradigm-shifting drugs might enhance the success of the drug candidates for next-generation treatment.

The experts also raised the concerns that there have been a limited number of model systems in the immuno-oncology area, although choosing appropriate animal models may be able to approximately demonstrate clinical efficacy. Nonetheless, one important concern was raised that any effort in the preclinical study may or may not impact ultimate clinical success. That is, failure to demonstrate positivity in preclinical studies could eliminate the candidacy of the drugs, but promising results in preclinical models may not directly link to success of clinical trials. The efficacy still needs to be examined in the clinical trials, similar to the aforementioned points. An identified, validated biomarker can be used to validate target engagement as well as to evaluate early "go/no go" decisions in the development of many drugs and biologics, especially in oncology. The consensus has been reached that a proper biomarker offers a basis for rational drug development, including efficiency improvement. Currently, the "Omics" technologies can be used to facilitate the process to search the biomarkers, which could be highly associated with tumor formation.

Instead of the conventional phased design for drug development, adaptive clinical trials have been used to expedite the processes of phased clinical studies.[31] Overlapping the phases and/or conducting seamless trials could accelerate the clinical trials to deliver a new drug to more patients, for example, the alternative "quick win, fast fail" drug development design.[19]

It is worth noting that while the compressed or seamless clinical trials could efficiently expedite the clinical studies and may minimize time and financial loss, the concerns for these less well-understood adaptive designs need to be carefully addressed prior to implementation. For example, the sponsors should discuss with regulatory authorities for the adaptions during milestone meetings. Furthermore, the adaptions need a good study design (eg, sample size and initial dose) and a solid statistical model to support the data analysis.[31]

To optimize patient selection criteria is also key to exactly targeting the right patients for the drug candidates, especially for patients with cancer. Using biomarkers can facilitate correct patient selection. For instance, in the proof-of-concept study, this biomarker-driven clinical design can exactly pinpoint the efficacy of drug candidates from subgroup of patients and secure useful clinical results to explain and understand the mechanism of action of drugs. One of the useful tools is next-generation sequencing, which can help stratify patient populations for whom is most likely to be beneficial.[32] When executing the next-generation sequencing companion diagnostics, a few accompanying strategies have to be well defined; for example, the designation of gene expression cutoff level and the model/algorithm applied to patient profiling. Most importantly, the hypothesis of a clinical study has to be defined clearly and unbiasedly, prior to the initiation of studies. Especially due to heterogeneity of tumors in the area of oncology, a drug developed for biomarker-positive patients may not be suitable for the whole population. Enriched trials could be considered to maximize the knowledge gained from clinical studies and reduce the redundancy caused by the faulty clinical design.

Based on the coincidence between the top 4 new cancer cases (breast, prostate, lung, and colorectal cancer) diagnosed in the United States in 2019 (Centers for Disease Control and Prevention results) and the top 4 indications (lung, breast, colorectal, and prostate cancer) that the discontinued oncology drugs targeted in 2005-2013, the incentive of drug development was highly correlated with prevalence of the specific cancer types. Intriguingly, the responses from experts regarding the top 3 cancer types with relative high attrition rate was diverse and only prostate cancer (from the top 4 indications of the discontinued drugs) was mentioned once by 1 expert. This discrepancy may imply that there could be some cancer types, for example, pancreatic cancer and glioblastoma, which may still be short of effective treatment options. A lack of commonality of tumor formation and the difficulties to deliver drugs to the target site could be the main reasons to explain why the current anticancer drugs are not efficacious to these cancer types. In addition, due to the specialty and complexity of cancer, the dilution of talent to support oncology drug development would be another factor of attrition. For these unmet medical needs, we have to identify novel ways to move a drug candidate from drug discovery and development stages more effectively and efficiently and, most importantly, with higher successful rate to launch to the public.

Conclusions

The study sought to assess factors associated with a relatively high attrition rate for oncology drug candidates, which is centric to the problem of how drugs could be adequately designed and how the clinical studies could be employed effectively and efficiently. Recent paradigm shifts in early-stage development and clinical development plans suggest that candidate selection is less influenced by toxicity reduction with more emphasis placed on biologic activity aligned with efficacy expectations. It may suggest that even when the oncology drug candidates had low safety concerns, a lack of efficacy may still be present and impactful. Further, both the attrition cases of antibodies and small molecules increased from 2005 to 2013, which is similar to the fact that the success rate of biologics had leveled out from 2011 to 2013.[26] Since efficacy can only be studied by clinical trials, the clinical trials should be unbiasedly designed, and it could be designed in the adaptive ways. For example, with fewer toxicity concerns, the efficacy of biologics could be examined at the early stage of clinical trial to make the process of drug development more efficient and more cost effective. A few options may be considered, such as having Phase 0 to study PK/pharmacodynamics[33] and/or moving the proof-of-concept study to Phase 1.[19] Regardless of what adaptions are chosen, prior to implementing the adaptions, effective communications with regulatory agencies are needed to ensure that the regulatory infrastructure is flexible enough and ready to review these adaptions. Otherwise, these adjustments may incur even more issues during panel review.

In addition, there are unmet needs for a few cancer types in the cancer community. The current advancing technologies can help us identify genomics and/or biomarker alterations, and yet could guide us to design effective clinical trials and further facilitate targeting the right patients. A recent study revealed that the tests from whole genome sequencing for a patient with metastatic colorectal cancer identified more than 2000 genomic alterations.[34] Along with the results from transcriptome sequencing, the most differentially expressed genes were the members of 2 proto-oncogene families, FOS and JUN. These results strongly suggested that blocking the reninangiotensin system could render therapeutic benefit.[34] Thus, the antihypertensive

angiotensin II receptor antagonist irbesartan was considered for drug repurposing to an oncology treatment, resulting in the patient experiencing a dramatic and persistent response. Although this was the successful application of precision medication, it did demonstrate that these molecular-level technologies can accurately aim at the right patients/targets. Similarly, the application of these tools could lead a correct design in the clinical trials, especially for targeting correct subgroup patients.

Considering cancer as a group of complicated and highly heterogeneous diseases, the majority of tumors should provide multiple targets. Therefore, the combination of drugs for oncology treatment is likely required. Given the successful aforementioned example of precision medicine, the genomic-based or biomarker-driven stratification for targeting correct subpopulation of patients can significantly facilitate the outcomes of treatment and prognosis. Additionally, the other key to this successful example was drug repurposing. Based on the fact that to date drugs are skyrocketed in nature, not to mention the failed drugs, the possibility of drug repurposing for oncology treatment should be scrutinized. Drug repurposing can save lots of money and time on drug discovery and development and maximize the capability of a drug. To cope with high demands of combination treatments for the "targeted cancer therapies," new drug discovery including drug repurposing, companion diagnostics, and adaptive clinical designs with flexible regulatory review should all be comprehensively considered.

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Conflicts of Interest

The authors declared no competing interests for this work.

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Supplemental Information

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