Exploratory Analysis of the Factors Associated With Success Rates of Confirmatory Randomized Controlled Trials in Cancer Drug Development

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This study examined the outcomes of recent confirmatory randomized controlled trials (RCTs) in phase III that were initiated between 2005 and 2017 for oncologic drugs in the United States and identified several factors that were associated with the success of RCTs. Our regression analysis showed that studies with progression-free survival or response rate as primary end point were more likely to succeed than studies with overall survival (odds ratio (OR) = 2.94 and 6.23, respectively). The status of development was also linked with success rates. Studies for non-lead indication tended to have lower success rates than studies for lead indication (OR = 0.68). Studies for first-line therapy were observed to have low success rates compared with studies for post second-line therapies (OR = 0.37). Studies for which strong prior evidence was not listed in their publication tended to be more successful than studies that followed rigorous RCTs or single arm studies for the indication. These results suggest that historical success rates may reflect not only the important features of trials, which can be observed directly from study design and results, but also the background status of trials in clinical development pathways.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✔ Historical success rates of confirmatory randomized controlled trials (RCTs) for oncologic indications were much lower than ones for nononcologic indications on average.

WHAT QUESTION DID THIS STUDY ADDRESS?

✔ We focused on outcomes of oncologic confirmatory RCTs in the United States and explored associations between success rates and study features, some of which reflect the status of clinical development and characteristics of drug companies.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✔ Observed success rates were lower for studies primary end point of which was overall survival. Lower success rates were also observed in studies for first-line therapies and for non-lead indication. These results suggest that historical success rates may reflect not only the important features of trials, which can be observed directly from study design and results, but also the background status of trials in clinical development pathways.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✔ This study can directly help predict the probability of success of current oncologic phase III studies. In addition, observed associations between success rates and development pathways provide clues to adjusting the real-world data on success rates.

Growing costs and stagnant numbers of successful products in the past decade indicates the increasing difficulties in pharmaceutical research and development (R&D) activities. Costs for conducting phase III studies have been reported to occupy 28% of the whole R&D cost, and more detailed research showed that the mean period of phase III studies is as long as 45.1 months and the mean cost is 5 times higher than that of phase II studies in the industrial R&D process. To improve the success rates of phase III studies has a substantial impact on a company's management over time.

Cancer drug development is one of the most competitive areas of the pharmaceutical industry. Drugs targeting cancer as a disease category exceed those targeting other areas and represent 26.2% of the total pipeline. The requirements for marketing approval have changed to reflect recent modes and methodologies of clinical development, and some products have been granted marketing approval without conducting large phase III studies. However, phase III studies are still considered necessary for the registration of most products. The average success rate for transition from phase III to new drug application (NDA)/biologics license application (BLA) for all indications was reportedly 60.1% for over 7,300 drug development paths from 2003 to 2011, whereas the average success rate for oncologic

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indications remains as low as 45%. In another large survey targeting 7,455 programs, the success rates were reportedly 58.1% and 40% for all diseases and oncologic indications, respectively. Previous studies have demonstrated that the transition rates from NDA/BLA to approval were as high as 85%. This knowledge underscores the importance of the improvement of methodology in clinical development stages.

There have been many studies that explored historical success rates in drug development, focusing on drug features, market access order, indication feature, and experience on development. Lead indication was shown to be positively associated with success rates. Partnered projects seemed to have higher success rates than self-originated compounds. A study demonstrated that the outcome of the primary endpoint depended heavily upon the nature of that end point. Another study demonstrated that phase II study duration before phase III and the prevalence-like measure (i.e., number of patients with the condition treated worldwide) were inversely related to the success of drug development.

Drug companies use success rates for two different purposes. The success rate ex-post indicates a measure of how “effective (and probably efficient)” observed drug development programs are. Every company is eager to improve the success rate in this sense within the restrictions of the real world. Drug companies having several possible options of development programs, such as candidate compounds, indications, dosage, places of trials, and timing of entry, consider success rates that have been historically observed as success rates ex-ante (i.e., expected success rates). Expected success rates play a critical role in business decisions of drug companies because they are the key parameters in a drug company’s decision to promote drug development. For example, a very low success rate historically observed and expected for a specific indication does not necessarily prevent a company’s motivation to implement development projects; this is often the case for orphan drugs and indications.

In most previous studies on the success rates of clinical trials, analysis and discussion has not explicitly evaluated the associations with development status. The results of analysis without appropriately adjusting background factors, including expected success rates, could lead to biased interpretations for impact on observed ex-post success rates. In pharmaceutical R&D, the dilemma remains as to whether company experience and evidence prior to a trial would affect the possibility of success, and, if so, to what extent.

The purpose of our study was to explore how success rates relate to study design and target diseases, and the background status of clinical development, which has not been fully examined in previous studies. We aimed to provide our results mainly for predictive purposes, and causalities behind the observations were discussed to the extent that it was reasonable for the purposes.

METHODS

We collected interventional, randomized, and commercially funded phase III studies conducted in the United States between January 1, 2005, and December 31, 2017, with the purpose of testing superiority of the study drug. Data collection flow is shown in Figure 1. A total of 206 randomized controlled trials (RCTs) satisfied our criteria. For 10 trials, details of study results were not posted in ClinicalTrials.gov or other public domain, and finally 196 trials were included in our analysis. This might lead to a bias in the results of this study.

We analyzed the success of phase III trials using mixed-effect logistic regression analysis in which drugs were treated as a random effect variable. We also confirmed that fixed-effect models with a different set of variables yielded
similar results. We considered a phase III study is successful if the prespecified statistical goal was achieved, or in cases where prespecified goals were unavailable in either ClinicalTrials.gov or publications, statistical significance \((P < 0.05)\) for two-tailed test on the primary analysis was confirmed. There were two studies for which prespecified threshold was lenient (i.e., \( \alpha > 0.05 \)), one study showed superiority even at the level of \( P < 0.05 \) and the other one failed. We also checked whether the targeted indication was approved by the US Food and Drug Administration (FDA) with the latest package insert.

The control in our sample included active drugs, placebo, active drugs combined with drug placebo, best practice care, and best supportive care. We defined the success rate as the proportion of successful phase III studies. Our definition, which is based on the success of each trial, requires attention because in some previous studies successful phase transition was used as the definition of success.\(^{8,9,14,15}\)

We used explanatory variables, reflecting features of sponsors, drugs, subjects, study design, lead/non-lead indication, therapeutic line, and prior evidence to implement the phase III study. The choice of explanatory variables was based on similar previous studies.\(^{8,9,14,15}\) Cancer type was used to control background of indication. We applied the following categorical variables: the rank of sponsor’s R&D expenses (top 10, 11th–25th, or others); sponsor’s development experience on the product (license-in product, in-house developed product, or the sponsor acquired the product through mergers and acquisitions); therapeutic line (first-line, post-second-line, or adjuvant therapy); combination and control (test drug vs. active control, test drug vs. placebo control, combination of test drug and active drug vs. active control, or combination of test drug and active drug vs. combination of placebo and active drug); primary end point (overall survival (OS), disease-free survival, progression-free survival (PFS), or response rate/other primary end point; development indication (lead indication, or non-lead indication); main prior clinical evidence presented in the publication (single arm trial for the same cancer type, study for other cancer type, or drug, or RCTs for the same cancer).

With respect to study design, best practice care was considered active drug and supportive care was considered placebo. The studies with a coprimary end point including OS was categorized into “OS,” and the other studies with a coprimary end point including PFS was categorized into “PFS” for the purpose of regression analysis. Cancer stage could be an important indicator that characterizes an oncologic study. However, classification of severity and implications for treatment at each stage vary by cancer type, and we were not able to categorize them in a simple way for our analysis. We did not apply such variables directly, but the variables indicating therapeutic line of the usage and functional conditions of the sample might reflect cancer stage to some extent. Lead indication was defined as the indication for which the product’s first approval was given. If there was no regulatory approval at the timing of the phase III study completion, we regarded the target indication of the study as lead indication.

Median age of subjects was collected for 172 studies and the functioning level of subjects and main basis for the study were collected for 117 studies from publications. We used these variables in several different models after confirming that the background of samples did not differ significantly in terms of cancer type.

Prior clinical evidence that was explicitly presented in the published papers of the observed phase III trial was categorized and used as an explanatory variable. We scrutinized the introduction section and extracted sentences that explained the background and justification for conducting the study. In cases where there were several prior studies mentioned to justify the implementation of the study, we chose a randomized study for the same cancer type with the largest sample size.

The variables were collected from the Japan Pharmaceutical Manufacturers Association homepage, ClinicalTrials.gov, publications, US package inserts, and a commercial database (Bio Today).\(^{16}\) The results of phase III studies were collected from ClinicalTrials.gov and publications. The latest approved US package inserts were collected from the FDA website. All the variables, data collection methods, and the regression command are shown in Table S1. The significance level was set at \( P < 0.1 \) similar to previous exploratory studies.\(^{17,18}\)

The logistic regression analysis was performed using Stata Statistical Software version 14.

RESULTS

Success rates of phase III trials varied significantly between different cancer types (Table 1). The overall success rate was 40.3% (79/196). The success rates for hematological cancers and solid tumors were 57.5% (23/40) and 35.9% (14/39), respectively, which were similar to those observed in a previous large survey.\(^{8,9}\) Success rates were relatively high in studies on lymphatic leukemia, multiple myeloma, ovarian cancer, melanoma, gastric cancer, and colorectal cancer. Our sample provided success rates similar to those in a previous study on myelocytic leukemia, lymphatic leukemia, multiple myeloma, non-small cell lung cancer success rates, and slightly higher success rates for studies on melanoma, ovarian cancer, gastric cancer, and colorectal cancer.\(^{9}\) The transition rates from phase III to NDA/BLA approval for lead indications and all indications were 29.2% and 28.6%, respectively, which were close to that observed in a previous study (33.0%).\(^{9}\)

Descriptive statistics of explanatory variables and the associations between the variables and success rates are shown in Table 2. About half of the studies were conducted by sponsors with large R&D expenses (i.e., top 10 companies). Test drugs were developed in-house for most of the studies in our sample. Studies for post second-line therapy accounted for 54.6%.

Studies for first-line and adjuvant therapies showed lower success rates of 32.1% and 9.1%, respectively, than those for post second-line therapies (49.5%). Studies comparing test drug (monotherapy) and active control showed higher success rates than studies with other design (51.9%). With respect to primary end point, studies on OS and disease-free survival showed much lower success rates (28.6% and 10.0%, respectively) than studies on PFS or response rate (53.1% and 64.3%, respectively).
Table 1 Summary of success rates for phase III clinical trials in different cancer types

| Cancer type              | N   | Success rates |
|-------------------------|-----|---------------|
| Myelocytic leukemia     | 10  | 3/10 (30.0%)  |
| Lymphatic leukemia      | 20  | 13/20 (65.0%) |
| Multiple myeloma        | 10  | 7/10 (70.0%)  |
| Hematological cancers   | 40  | 23/40 (57.5%) |
| Non-small cell lung cancer | 27  | 8/27 (29.6%)  |
| Small cell lung cancer  | 3   | 0             |
| Ovarian cancer          | 8   | 5/8 (62.5%)   |
| Brain tumor             | 5   | 0             |
| Prostate cancer         | 20  | 3/10 (30.0%)  |
| Breast cancer           | 29  | 10/29 (34.5%) |
| Hepatocellular carcinoma| 10  | 1/10 (10.0%)  |
| Bladder cancer          | 1   | 0             |
| Melanoma                | 8   | 3/4 (75.0%)   |
| Adrenocortical cancer   | 1   | 0             |
| Gastric cancer          | 6   | 1/2 (50.0%)   |
| Renal cell cancer       | 7   | 3/7 (42.9%)   |
| Sarcoma                 | 7   | 3/7 (42.9%)   |
| Pancreatic cancer       | 7   | 3/7 (42.9%)   |
| Endometrial cancer      | 1   | 0             |
| Endocrine tumor         | 2   | 1/2 (50.0%)   |
| Head and neck cancer    | 3   | 1/3 (33.3%)   |
| Colorectal cancer       | 8   | 5/8 (62.5%)   |
| Thyroid cancer          | 1   | 1 (100.0%)    |
| Mesothelioma            | 2   | 0             |
| Solid tumors            | 156 | 14/39 (35.9%) |
| Overall                 | 196 | 79/196 (40.3%)|

Studies in which subjects had a high-performance status tended to show low success rates, although no statistical significance was observed ($\chi^2$ test). Regarding the evidence prior to the study, studies for which RCTs for the same type of cancer had been conducted showed lower success rates (35.2%) than studies for which single arm trial (50.8%) and/or trial for other types of cancer or drug (80.0%) had been done. In general, the success rates for studies for which the part of the study information (e.g., subjects' median age and prior studies) was unavailable in publication tended to be lower than those for studies that provided full information.

The results of logistic regression analysis are shown in Table 3. Studies for which the primary end point was PFS or response rate were more likely to succeed compared with those with OS as primary end point (PFS: coefficients = 1.08, 1.50, and 2.12 in models 1, 2, and 3, respectively; response rate: coefficients = 1.83, 2.16, and 2.51 in models 1, 2, and 3, respectively). These results were consistently observed in all regression models.

The status and objective of a trial in clinical development was associated with the likelihood of success. The success rates of trials for non-lead indication purposes seemed to be lower than those for lead indication (coefficient = -0.83 in model 2). Studies on drugs for first-line therapy tended to have low success rates compared with studies for post-second-line therapies (coefficients = -0.99, -1.48, and -0.93 in models 1, 2, and 3, respectively). In model 2, trials for molecular target drugs showed higher success rates than trials for nonmolecular target drugs (coefficient = 0.90).

Regarding the characteristics of the study subjects, a higher median age of > 65 years was associated with a higher success rate in model 2 (coefficient = 1.62). Patients' average performance status was not related to likelihood of success in the regression analysis results.

Studies sponsored by companies with large R&D expenses tended to have lower success rates, other conditions being the same (coefficient = -1.89 in model 3). Studies comparing combination therapies and active control showed lower success rates than studies comparing monotherapies (test drug) and active control (coefficient = -1.82 in model 3).

The type of clinical evidence prior to the phase III study was associated with success rates. Studies that did not necessarily have solid evidence for the same cancer type tended to be more successful than studies with rigorous RCT and/or single arm studies (model 3).

Clinical studies for melanoma, pancreatic cancer, and colorectal cancer tended to have higher success rates than the studies for other cancer types (coefficients = 2.34, 2.97, and 2.80, respectively, in model 2).

DISCUSSION

We examined the outcomes of recent phase III trials for oncologic drugs in the United States and identified several factors that were associated with the likelihood of success. Our analysis showed that important features of study design (e.g., OS as primary end point) and also the background status of drug development (e.g., therapeutic line and lead indication) are significantly associated with success rates. These results indicate that the historically observed success rates reflect not only the superficially observable characteristics of a trial, but also the stage of development of the drug at the time the trial was conducted.

The descriptive results in Table 2 indicate that success rates and key design components show interesting associations, and some associations may be influenced by several confounding factors. Some confounding factors are measurable and applicable in quantitative analysis (e.g., subjects' age and severity), and others are unmeasurable. For example, the development of first-in-class drugs or drugs for rare cancer always face a higher level of "challenge," which may be difficult to ascribe to some specific measures.

Our regression analysis indicated that studies with OS as the primary end point had lower success rates than studies that consider PFS or a response rate as the primary end point. OS is considered to be the most common hard end point, and acceptability of other surrogate end points for standard or accelerated approval depends on the cancer type.\textsuperscript{5,6,19} OS is also more commonly used in advanced or metastatic settings, where prognosis is poor. In our dataset, many studies for lymphoid myeloma, multiple myeloma, ovarian cancer, and melanoma set PFS or response rate as the primary end point, and the success rates were generally high for these cancer types. Our regression analysis showed that even after adjusting the impact of cancer type, studies with the primary end point
### Table 2 Success rates of phase III clinical trials categorized by the characteristics of sponsor, drug, study subject, and study design

| Categorical variable | Number of studies (% out of 196 studies) | Number of successful studies (success rate, %) | P value |
|----------------------|------------------------------------------|-----------------------------------------------|---------|
| **R&D expenses of the sponsor** | | | |
| Ranked 1–10 | 98 (50.0) | 41 (41.8) | 0.89 |
| Ranked 11–25 | 40 (20.4) | 16 (40.0) | |
| Ranked after 26 | 58 (29.6) | 22 (37.9) | |
| **Development experiences on the product** | | | |
| In-house development | 104 (53.1) | 42 (40.4) | 0.98 |
| Product license in | 66 (33.7) | 27 (40.9) | |
| Company M&A | 26 (13.3) | 10 (38.5) | |
| **Development indication** | | | |
| Lead indication | 106 (54.1) | 44 (41.5) | 0.71 |
| Non-lead indication | 90 (45.9) | 35 (38.9) | |
| **Therapeutic line** | | | |
| Post-second-line | 107 (54.6) | 53 (49.5) | < 0.01 |
| First-line | 78 (39.8) | 25 (32.1) | |
| Adjuvant therapy | 11 (5.6) | 1 (9.1) | |
| **Drug feature** | | | |
| Molecular target drug | 87 (44.4) | 39 (44.8) | 0.25 |
| Others | 109 (55.6) | 40 (36.7) | |
| **Study design (masking)** | | | |
| Masking | 98 (50.0) | 34 (34.7) | 0.11 |
| No masking | 98 (50.0) | 45 (45.9) | |
| **Study design (combination and control)** | | | |
| Test drug vs. active control | 54 (27.6) | 28 (51.9) | 0.20 |
| Test drug vs. placebo control | 38 (19.4) | 15 (39.5) | |
| Combination of test drug and active drug vs. active control | 48 (28.5) | 18 (37.5) | |
| Combination of test drug and active drug vs. combination of placebo and active drug | 56 (28.6) | 18 (32.1) | |
| **Study design (primary end point)** | | | |
| OS | 91 (46.4) | 26 (28.6) | < 0.01 |
| OS only | 79 (40.3) | 21 (26.6) | |
| OS + DFS | 1 (0.5) | 0 (0) | |
| OS + PFS | 7 (3.6) | 3 (42.9) | |
| OS + response rates | 4 (2.0) | 3 (75.0) | |
| DFS | 10 (5.1) | 1 (10.0) | |
| PFS | 81 (41.3) | 43 (53.1) | |
| PFS only | 80 (40.8) | 42 (52.5) | |
| PFS + response rates | 1 (0.5) | 1 (100.0) | |
| Response rate or other end point | 14 (7.1) | 9 (64.3) | |
| **Subjects’ median age enrolled in the study** | | | |
| < 65 | 141 (71.9) | 61 (43.3) | 0.04 |
| > 65 | 31 (15.8) | 14 (45.2) | |
| Data not available | 24 (12.2) | 4 (16.7) | |
| **Subjects’ level of functioning enrolled in the study** | | | |
| ≥ 10% of subjects with PS > 2 | 27 (13.8) | 8 (29.6) | 0.18 |
| < 10% of subjects with PS > 2 | 99 (50.5) | 47 (47.5) | |
| Data not available | 70 (35.7) | 24 (34.3) | |
| **Main basis to conduct the study** | | | |
| Randomized controlled trial for the same cancer | 54 (27.6) | 19 (35.2) | < 0.01 |
| Single arm trial for the same cancer | 63 (32.1) | 32 (50.8) | |
| Trial for other cancer or drug | 10 (5.1) | 8 (80.0) | |
| Data not available | 69 (35.2) | 20 (29.0) | |

Significance test was performed by χ² test.

DFS, disease-free survival; M&A, mergers and acquisitions; OS, overall survival; PFS, progression-free survival; PS, performance status; R&D, research and development.
of OS show low success rates compared with studies using other end points. We conducted supplemental analysis adding the interaction term for OS and post-second-line and found a positive association. This result suggests that primary end point and therapeutic line are associated with success rates in a complicated way, which warrants further analysis.

Lower success rates of studies for first-line therapy compared with studies for second-line therapy are an interesting result, but it is not evident as to which aspects of first-line therapy actually lead to the results observed. The lower success rates of first-line therapies might be addressed from several aspects. First, there could be some unobserved differences in the features between first-line and second-line trials, which could substantially affect the likelihood of success. Although our study included cancer type and several basic features of trials as explanatory variables, it is possible that some other features, including inclusion/exclusion criteria, were substantially different between the two types of trials and lead to disparities in success rates. Second, the result may depend on some unobserved confounders that affect both the status of

| Table 3 Logistic regression analysis results for success rates of phase III clinical trials |
|------------------------------------------|----------------|----------------|----------------|
| Variable                                | Coef. SE  | P value | Coef. SE  | P value | Coef. SE  | P value |
| Company attributes                       |            |        |            |        |            |        |
| R&D expenses (base: R&D expenses ranked below 16th) |            |        |            |        |            |        |
| R&D expenses ranked 1–10th               | 0.13 0.48 0.790 | 0.42 0.56 0.456 | -1.89 0.96 0.048** |
| R&D expenses ranked 11–15th             | 0.41 0.55 0.449 | 0.02 0.60 0.978 | -0.94 0.92 0.311 |
| Development experiences on the product (base: in-house development) |            |        |            |        |            |        |
| Product license                         | 0.08 0.43 0.860 | 0.04 0.48 0.927 | 0.35 0.69 0.612 |
| Company M&A                             | -0.38 0.59 0.519 | -0.07 0.63 0.905 | -0.59 1.06 0.577 |
| Therapeutic characteristic              |            |        |            |        |            |        |
| Development indication (base: lead indication) |            |        |            |        |            |        |
| Non-lead indication                     | -0.39 0.43 0.371 | -0.83 0.48 0.086* | -0.66 0.71 0.353 |
| Therapeutic line (base: post-second-line) |            |        |            |        |            |        |
| First-line                               | -0.99 0.43 0.023** | -1.48 0.51 0.004*** | -0.93 0.76 0.222 |
| Adjuvant therapy                         | -1.03 1.70 0.544 | -2.05 1.77 0.247 | 0.38 2.30 0.868 |
| Drug feature                             |            |        |            |        |            |        |
| Molecular target drug                    | 0.49 0.44 0.270 | 0.90 0.50 0.072* | 1.22 0.75 0.105 |
| Study design (sample size, masking)      |            |        |            |        |            |        |
| Sample size (100 subjects)              | -0.04 0.05 0.421 | -0.08 0.06 0.180 | -0.03 0.08 0.726 |
| Masking (base: no masking)              | -0.49 0.74 0.508 | -0.65 0.83 0.430 | 0.47 1.24 0.705 |
| Study design (combination and control) (base: test drug vs. active control) |            |        |            |        |            |        |
| Test drug vs. placebo control            | 0.25 0.79 0.751 | -0.09 0.86 0.918 | -1.65 1.46 0.257 |
| Combination of test drug and active drug vs. active control | -0.81 0.58 0.158 | -0.77 0.64 0.230 | -1.82 0.96 0.059* |
| Combination of test drug and active drug vs. combination of placebo and active drug | -0.18 0.76 0.810 | -0.16 0.84 0.849 | -2.12 1.34 0.114 |
| Year of clinical trial                   | >-0.01 0.12 0.969 | 0.10 0.15 0.481 | -0.01 0.20 0.945 |
| Primary end point (base: OS)            |            |        |            |        |            |        |
| DFS                                      | -0.14 1.82 0.938 | 1.22 1.81 0.499 | 0.51 2.42 0.832 |
| PFS                                      | 1.08 0.52 0.038** | 1.50 0.90 0.011** | 2.12 0.87 0.015** |
| Response rates or other end points       | 1.83 0.81 0.023** | 2.16 0.87 0.013** | 2.51 1.21 0.038** |
| Subjects enrolled                        |            |        |            |        |            |        |
| Subjects' median age in the study (base: < 65) |            |        |            |        |            |        |
| > 65                                     | 1.62 0.82 0.049** | 0.60 1.26 0.635 | 1.06 1.01 0.294 |
| < 10% of subjects with PS > 2 (base: > 10%) |            |        |            |        |            |        |
| Main basis to conduct the study (base: RCT of the drug for the same cancer) |            |        |            |        |            |        |
| Single arm study of the drug for the same cancer | 0.92 0.66 0.165 | 3.73 1.43 0.009*** |
| Trial for other cancer or drug           |            |        |            |        |            |        |
| Cancer type (adjusted)                   |            |        |            |        |            |        |

Log likelihood = −102.8 Log likelihood = −87.9 Log likelihood = −51.0

P, 0.05 P, 0.01. * P, 0.1. ** P, 0.05. *** P, 0.001.
trials and the likelihood of success. In general, trials for first-line treatment follow trials for second-line treatment in commercial drug development, which reflects the intrinsic difficulties of clinical development in oncology and the regulatory guidelines for clinical development. These backgrounds may generate spurious association between treatment line and success rates, because they were not explicitly included in the regression models. “Regression to the mean” is another possible explanation from the statistical perspective.

The present results further indicated that studies for lead indication (i.e., first-approved indication) have higher success rates, as has been reported previously. As mentioned before, the issue of unobserved confounding factors made it impossible to verify the real picture of causality. However, higher likelihood of success for second-line therapies and lead indication may suggest that the status and objective of commercial clinical development, including the sequential order of development, is an important predictive factor of success rates of oncologic trials.

With respect to evidence prior to each study, our analysis showed that phase III trials that were based on studies of other cancer types or other drugs showed higher success rates than trials for which rigorous RCTs were done before the trial. Many trials with relatively poor justification were those for molecular target drugs with clear pharmacological mechanisms. Previous research on drug features showed that success rates vary by molecular features and that biologics/large molecules tend to have higher success rates than small molecules. However, higher success rates for trials with relatively poor justification did not disappear even in a regression model adjusting the possible impact of molecular target drugs (model 3). These results may also suggest possible (unobserved) confounding factors that reflect complicated industrial decisions on implementing phase III programs. For example, if a company believes the data from a phase I study is convincing enough, it may skip phase II and implement phase III study to obtain regulatory approval as early as possible, which is likely to affect both prior evidence and success rates. It should be noted, however, the interpretation of this analysis, which depends on publications, has its limitations. Proper medical plausibility for a phase II study may not be adequately captured by labeling RCTs as “strong” and some other types of evidence as “poor.” An article publishing the result of a trial dose may not necessarily list all the evidence available prior to the trial. As with other analysis, this one is not free from publication biases caused by business intentions.

We observed higher success rates for monotherapies than the same kind of study design for combination therapies. Combination therapy is an important modality in cancer disease. Combination therapies are likelier to be studied as later line treatment or in cancers with poorer prognosis, so higher success rates for monotherapies might not be surprising. Targeted monotherapy has raised the efficacy bar for developers, but combined drug therapy with synergistic activity promises to substantially improve efficacy and maximize the chances of clinical and commercial success.

Median age of subjects at enrollment was positively associated with success rates. However, it is necessary to pay attention to possible discrepancies between the characteristics of subjects of the protocol and those of subjects actually enrolled. Median age and subject’s level functioning at enrollment were obtained after the trial, whereas inclusion/exclusion criteria (e.g., the range of subjects’ age) in the protocol were prepared before the trial.

This study can help drug development in several ways. The methodologies and results can be used directly to predict the probability of success of phase III trials. The results enable to estimate the probabilities of success for different modes of drugs, disease areas (cancer types), and study design. Compared with the models of previous research, our model includes a broad set of variables, some of which might reflect development status and characteristics of drug companies. Observed prediction between success rates and development pathways may provide some clues to adjusting the real-world data on success rates.

Finally, this research has several limitations. First, the analysis model used in our study is difficult to pursue the causalities behind the success of trials. Our analysis is for exploratory purposes and provides predictions rather than causalities in a strict sense. As is mentioned in the Discussion section, it is highly likely that there are several unobserved confounders. Second, this research is likely to be affected by publication bias. It is unclear to what extent background information of trials, including evidence prior to trials, has been published for drugs with commercial sponsorship. The findings of this study would be applicable and valid depending on the level of homogeneities in trial markets, especially in terms of mode of drugs, target cancer types, and important components of study design, such as the primary end point.

**Supporting Information.** Supplementary information accompanies this paper on the Clinical and Translational Science website (www.cts-journal.com).

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**Author Contributions.** S.O. and C.W. wrote the manuscript, designed and performed the research, analyzed the data, and contributed new reagents/analytical tools.

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