Clinical Approval Success Rates for Investigational Cancer Drugs

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We examined development risks for new cancer drugs. For the full study period, the estimated clinical approval success rate for cancer compounds was 13.4% (9.9% for the first half of the study period, 19.8% for the second half). Small molecules had a somewhat higher clinical approval success rate than did large molecules (14.3 vs. 11.5%). Compounds studied solely in hematologic indications had markedly higher estimated clinical approval success rates than did compounds studied only in solid tumor indications (36.0 vs. 9.8%). The first, second, and third cancer indications pursued had estimated clinical approval success rates of 9.0, 8.2, and 6.9%, respectively. Success rates of second and third indications were found to be highly dependent on the success or failure of the first indication pursued (54.9 and 42.4%, respectively, for second and third indications if the first indication is a success, but 2.5 and 1.8%, respectively, if the first indication is a failure).

The biopharmaceutical industry is increasingly focusing on the development of new targeted therapies for cancer, a number of which have been approved in the past few decades.[1] Drugs of particular note in this category are small-molecule protein kinase inhibitors (e.g., pazopanib, crizotinib, ruxolitinib, vemurafenib, and axitinib) and monoclonal antibodies (e.g., cetuximab, bevacizumab, panitumumab, ofatumumab, ipilimumab, and brentuximab vedotin). Development of these products depended on understanding the molecular characteristics of the various types of cancer and the modes of action of the drugs. Despite progress in this area, there remains substantial unmet medical need for new cancer drugs with superior efficacy and better safety profiles that can be administered using methods that provide greater patient convenience.

A variety of innovative approaches to cancer drug development are being simultaneously explored by companies, including focusing on new targets within validated pathways and new pathways, design of novel drug formats, and improved clinical study design and protocols that may expedite the process. Development of new drugs, however, is lengthy, is very expensive, and has substantial technical risks.[2–17] To foster a better understanding of the technical risks specifically associated with development of new cancer drugs, we examined the biopharmaceutical industry pipeline of cancer drugs that entered clinical study from 1993 to 2004 and estimated clinical phase transition rates and overall clinical approval rates. We analyzed these data to determine success rates for cancer drugs in general, and examined factors such as the composition of matter, the type of cancer investigated, and successive indications pursued clinically overall and conditional on the success or failure of the lead indication.

We collected data relevant to the clinical development and approval of cancer drugs that first entered studies during 1993 to 2004 from the public domain and the archives of the Tufts Center for the Study of Drug Development. Public sources accessed included company websites such as ClinicalTrials.gov and Drugs@FDA, the commercial pipeline databases such as IMS Health R&D Focus and Thomson Reuters Partnering, and the medical literature. Pipeline data were obtained for companies located worldwide and of all sizes.

INCLUSION/EXCLUSION CRITERIA

Clinical study was sponsored, at least in part, by a commercial firm. Candidates either originated at a company or were licensed from a commercial, government, or academic source. Candidates sponsored in clinical study exclusively by academic, government, or nonprofit organizations were excluded. Cooperative group or other noncommercial sponsorship of trials postapproval or after the commercial sponsor abandoned the compound were excluded.

Clinical study was first initiated during the interval between 1 January 1993 and 31 December 2004. This criterion allowed us to follow the development of a given group of investigational drugs over time, with a sufficient amount of time to have elapsed

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for a substantial number of the compounds to have reached a final fate.

The candidate's activity was primarily directed against cancerous cells or it functioned secondarily to affect cancerous cells. Candidates studied for supportive care use (e.g., nausea and pain drugs) or as adjunct treatments (e.g., erythropoietin) were excluded, as were candidates that improved the efficacy of cancer therapeutics but had no inherent anticancer activity (e.g., radio and chemosensitizers, detoxifying agents, multidrug resistance gene/protein inhibitors).

Candidates included an active ingredient that had not been previously approved for any indication. Covalently modified therapeutics (e.g., pegylated molecules) were considered new relative to the parent molecule. New formulations (e.g., liposome encapsulation) of candidates or previously approved products were excluded.

The majority of studies carried out during clinical development were for cancer indications. Candidates in clinical study primarily for noncancer indications were excluded even if some cancer studies were performed. Products first marketed for noncancer indications but later studied for cancer (e.g., thalidomide) were excluded. Indications were defined at the level of the organ system affected. Changes in the line of therapy for the same organ system (e.g., first-line therapy for breast cancer after prior approval as second-line therapy for breast cancer) or combination therapy after approval as monotherapy in the same organ system were not considered to be separate indications for purposes of this analysis.

Candidates studied for precancerous conditions (e.g., myelodysplastic syndrome) were included, but candidates for conditions involving noncancerous cellular proliferation (e.g., actinic keratosis and benign prostatic hyperplasia) were excluded.

Composition of matter was assigned on the basis of the drug's molecular structure. The cancer drugs were classified as small molecule, natural product, peptide, oligonucleotide, monoclonal antibody, recombinant protein, or biologic (i.e., matter derived from a natural source). For analysis, the small-molecule drug (SMD) category was composed of synthesized chemicals, peptides, and oligonucleotides, as well as natural products. The biologics drug category was composed of monoclonal antibodies, recombinant proteins, and biologics.

Data available for the complete clinical development programs, including study start dates and specific indications studied, were collected for all candidates. Indication data for candidates that were first evaluated in exploratory studies of patients with a variety of solid tumors were collected, but these exploratory studies were not included during assignment of lead, secondary, or follow-on indications. The lead, secondary, and follow-on indication categories were assigned on the basis of the start dates for defined tumor types, that is, the lead indication was the first specific indication studied, the secondary indication was the second specific indication studied, and follow-on indications comprised all other indications studied. The specific tumor types defined for this study were biliary tract, bladder, brain, breast, cervical, central nervous system, colorectal, esophageal, gastrointestinal, head and neck, kidney, leukemia, liver, lung, non–small cell lung, small-cell lung, lymphoma, melanoma, mesothelioma, myeloma, neuroendocrine, ovarian, pancreatic, peritoneal, prostate, sarcoma, stomach, thyroid, and urinary tract cancers. The more general categories of hematological malignancies, cancers of the female reproductive organs, and solid tumors were assigned in cases when patients with multiple relevant tumor types were included in the studies. For example, studies defined as for female reproductive organ cancers included patients with ovarian, fallopian tube, or peritoneal cancer.

CALCULATION OF SUCCESS-RATE ESTIMATES

Candidates were considered terminated if no clinical studies were active or recently concluded. The clinical development status of the candidates was assigned on the basis of data available through mid-2012. Candidates were categorized as in phase I, phase II, phase III, US regulatory review, approved in the United States, approved outside the United States, or discontinued. Clinical approval success-rate calculations were determined as the product of estimated clinical phase transition probabilities. Percent completion was defined as the percentage of products with a known fate (US approval or worldwide discontinuation). Clinical phase transition rates were calculated as follows: the number of candidates that completed a given phase and entered the next was divided by the difference between the number of candidates that entered the phase and those that were still in the phase at the time of the calculation. Transitions occurring between phases of clinical studies conducted worldwide were included. Phase transition and clinical approval success rates were calculated at both the molecule level and the indication level. Estimates at the molecule level were determined regardless of indication pursued. That is, a molecule was taken as having progressed from one clinical phase to the next if testing was initiated in at least one indication, even if other indications were abandoned at the earlier phase. A success at the molecule level is defined as US regulatory approval for marketing in at least one indication. Analyses performed at the indication level were calculated in the same way as at the molecule level, except that phase progression and success are defined for particular indications. The indication level analyses reported here are for the lead, second, and third indications.

BASE DATA SET CHARACTERISTICS

The data set of investigational cancer drugs that fulfilled the inclusion/exclusion criteria was composed of 625 candidates. Of these, 449 (72%) were SMDs and 176 (28%) were biologics. The annual shares of investigational cancer compounds varied from 64 to 80% for SMDs. Overall, the number of investigational cancer drugs entering clinical study per year increased 50% between the first half of the study period and the second half (from 250 to 375). Increases were observed for both the SMD and biologics categories, with a somewhat greater increase observed for biologics (59%) than for SMDs (47%). A final outcome (success or failure) across all indications studied was known for 72% of the compounds. Final outcomes were known for 84% of the compounds in the first half of the study period (first clinical

testing during 1993 to 1998) and 65% of the compounds in the second half of the study period (first clinical testing during 1999 to 2004).

ONCOLOGY SUCCESS-RATE TRENDS

For the entire study period, we estimated that 13% of the investigational cancer molecules would be approved for marketing in the United States (Figure 1). This compares to an estimated overall approval success rate of 16% for all compounds originated by top 50 firms found in a prior study.[1] Although three-quarters of the oncology compounds that entered clinical testing progressed from phase I to phase II, less than half of the compounds that entered phase II moved on to phase III, and of those compounds that underwent phase III testing, less than half of those made it to submission of an application for marketing approval to the US Food and Drug Administration. The pattern was, in part, different for compounds originated by top 50 firms and studied clinically during the same period. For the top 50 firms, the estimated transition rate was somewhat lower (approximately two-thirds) than that for the oncology compounds analyzed here, whereas the phase II to phase III transition rates were similar at ~40%. However, we found a dramatic difference in phase III success rates (transitions from phase III to New Drug Application/Biologic License Application submission). Although ~65% of the compounds originated by the top 50 firms across all therapeutic areas that entered phase III were estimated to progress to regulatory review, we estimated that only 47% of oncology compounds will do so.

Figure 1 also shows estimated phase transition and overall clinical approval success rates for oncology compounds when the study sample is divided into two equal periods. The results indicate a nearly doubling of the clinical approval success rate from ~10% for cancer compounds that first entered clinical testing during 1993 to 1998, to ~20% for those that first entered clinical testing during 1999 to 2004. Across the two periods, the transition rates for early-stage clinical testing were similar and actually slightly lower for the later period. However, the transition rates for late-stage clinical testing and regulatory review were notably higher for the later period. Whereas only slightly more than one in three of the compounds from the earlier period that entered phase III testing progressed to regulatory review, two in three of the compounds from the later period did so. The success rate for regulatory submissions was also higher for compounds tested in the later period. The results from our previous study on compounds originated by top 50 firms across all therapeutic categories show no appreciable change in the overall clinical approval success rate for these two study subperiods. The results were qualitatively similar to those for all oncology compounds in that phase transition rates were lower for the later period for early-stage clinical testing but higher for late-stage clinical testing and regulatory review. However, unlike the case for all oncology compounds, for the top 50 companies and all therapeutic categories combined these changes in phase transition rates approximately offset each other so that the overall clinical approval success rate was stable.

ONCOLOGY SUCCESS RATES BY MOLECULE AND CANCER TYPE

We examined phase transition rates and overall clinical approval success rates by molecule type. Specifically, we estimated success rates separately for SMDs and biologics (Figure 2). The results for the overall clinical approval success rate were similar (11.5% for biologics vs. 14.3% for SMDs), but the patterns of phase transitions were different. SMDs had higher transition rates in early to mid-stage clinical testing, particularly for phase II to phase III transitions (12% higher). However, biologics were more successful in transitioning from phase III to regulatory review and from regulatory review to approval. The higher later-stage transition rates were not large enough to completely offset the lower early-stage transition results.

The biologics category was dominated by monoclonal antibodies. Of the 176 biologics, 121 (69%) were monoclonal

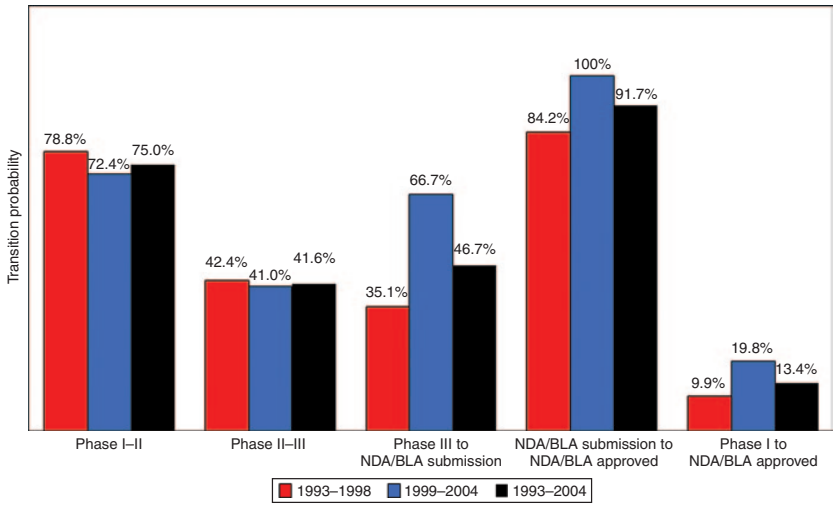

Figure 1 Phase transition probabilities for cancer compounds by period of first clinical testing. NDA/BLA, New Drug Application/Biologic License Application.

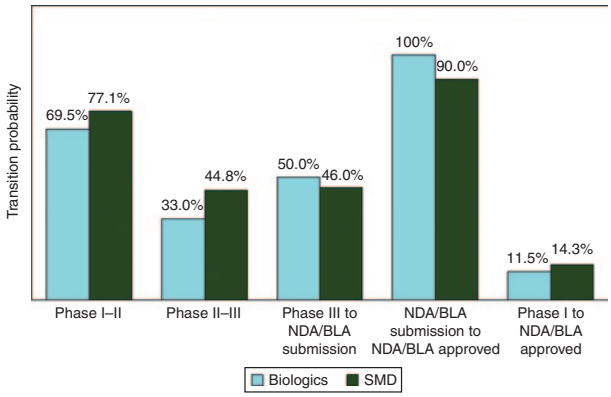

Figure 2 Phase transition probabilities for cancer compounds by molecule type (first clinical testing, 1993–2004). NDA/BLA, New Drug Application/Biologic License Application; SMD, small-molecule drug.

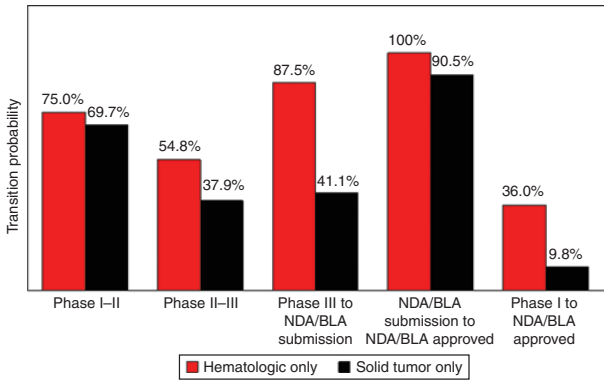

Figure 3 Phase transition probabilities for cancer compounds by cancer type (first clinical testing, 1993–2004). NDA/BLA, New Drug Application/Biologic License Application.

antibodies. This was the only biologics subcategory with a sufficient number of observations to conduct a separate success-rate analysis. The overall clinical approval success rate for monoclonal antibodies was similar to that for biologics as a whole (12.6 vs. 11.5%, respectively). However, the early-phase transition rates were somewhat lower for monoclonal antibodies (65.6% for phase I to phase II and 30.2% for phase II to phase III), whereas the phase III to regulatory submission transition rate was somewhat higher (63.6 vs. 50.0%).

The results for SMDs and biologics contrast sharply with those of our previous study for all compounds originated by the top 50 firms studied clinically during the same period. The early-stage transition rates for the full set of oncology SMDs were higher than those for compounds originated by the top 50 firms across all therapeutic areas (77 vs. 63% for phase I to phase II, and 45 vs. 38% for phase II to phase III). However, a much higher percentage of the oncology compounds that reached phase III failed in that phase than was the case for all compounds originated by the top 50 firms. The phase III to regulatory submission transition rate was 61% for the SMDs of the top 50 firms as compared with 46% for the oncology compounds. The regulatory submission to approval transition rate was similar (91% for top 50 firm SMDs vs. 90% for all oncology compounds). However, on net the overall clinical approval success rate for oncology SMDs was slightly higher than that for top 50 firm SMDs (14.3 vs. 13.0%).

The results for biologics were notably different for all oncology biologics as compared with biologics originated by top 50 firms in general. We found that the estimated clinical phase transition rates for all oncology biologics were consistently and substantially lower than those for the top 50 firm biologics. Phase I to phase II transition rates were 84% for top 50 firm biologics as compared with 70% for all oncology biologics. The difference in the phase II to phase III transition rate was much more pronounced, with 53% of the top 50 firm biologics progressing from phase II to phase III whereas only 33% of the oncology compounds did so. The difference in successful phase III transitions was greater still; 74% of the top 50 firm biologics transitioned from phase III to a regulatory submission, as compared with only 50% for all oncology biologics. Overall, the clinical approval success rate was more than twice as high for the top 50 firm biologics than that for the set of all oncology biologics (32 vs. 12%).

The data set for this study was large enough to distinguish between compounds that were developed solely to treat solid tumors and those developed only for hematologic indications. Of the 625 compounds in the data set, 72% were developed only for solid tumor indications, 8% were developed only for hematologic cancers, and 20% were developed for both solid tumor and hematology indications. There were some differences in the distribution of compounds by cancer type across molecule type. SMDs were more likely to be studied in both solid tumor and hematologic indications than were biologics. Whereas 10% of the biologics were studied in both cancer types, 25% of the SMDs were tested in both. For biologics, 76% of the compounds were studied in solid tumors only, and 14% were studied in hematologic indications only. In the case of SMDs, 70% were tested only in solid tumors, and just 5% were tested only in hematologic cancers.

The success-rate results for hematologic-only and solid tumor-only compounds were pronounced (**Figure 3**). All of the transition rates were higher for hematologic-only compounds than for solid tumor–only compounds. However, the distinctions were greatest for mid-to-late-stage clinical transitions. Whereas only 38% of the solid tumor–only molecules progressed from phase II to phase III, 55% of the hematologic molecules did so. The differences in outcomes were especially pronounced for phase III transitions. The estimated successful transition rate from phase III to a regulatory submission was 41% for solid tumor–only compounds but a remarkable 88% for hematologic-only compounds. As a result, the estimated overall clinical approval success rate for hematologic-only compounds was more than three times higher than that for solid tumor–only compounds (36 vs. 10%).

DEVELOPMENTAL SETTING

The safety and efficacy of candidate cancer drugs in humans is not known before study. Therefore, because of ethical concerns,

these drugs are commonly evaluated in late-stage cancer patients who may have been heavily pretreated with approved products. Our data indicate that most phase III studies of cancer drugs are performed in patients with metastatic disease or who have inoperable, locally advanced tumors. We examined the details of phase III clinical studies for cancer drugs in the data set that were either currently in phase III studies or had been terminated at phase III to determine what percentage were studied in an adjuvant setting, i.e., administered to patients after surgery to remove solid tumors. We found few instances of studies performed in an adjuvant setting. Of the 77 cancer drugs evaluated in phase III studies of any solid tumor type, we identified 12 (16%) drugs that had been studied specifically in an adjuvant setting. In these cases, the most frequent indications studied were brain, ovarian, and breast cancers. The number of drugs studied in an adjuvant setting that transitioned to regulatory review or from review to approval was insufficient for analysis.

Of the cancer drugs studied at phase III as treatments for metastatic cancer, the clinical phase transitions were similar regardless of whether the drug was studied exclusively in a metastatic setting or in a combination of metastatic, locally advanced/inoperable, or adjuvant settings (50.0% for all metastatic vs. 51.6% for metastatic only for phase III to regulatory submission; 47.2% for all metastatic vs. 51.5% for metastatic only for phase III to regulatory approval).

ONCOLOGY SUCCESS RATES FOR LEAD AND SECONDARY INDICATIONS

We obtained information on cancer indications studied in the clinic and their development status for the 625 compounds included in the study data set. We ordered the indications according to when they were first studied. Each compound has a first, or what we refer to as a lead, indication, and many had additional indications studied clinically. In total, the data set contains information on 2,055 cancer indications for the 625 compounds, or an average of 3.3 indications per compound. The number of indications for individual compounds ranged from 1 to 23. Sixty percent of the molecules were studied clinically in more than one indication.

The average number of indications per molecule was 3.5 for SMDs and 2.7 for biologics. Examining molecules by cancer type, we found that the average number of indications per molecule was 2.8 for molecules studied only in solid tumors, 3.9 for molecules studied only in hematologic indications, and 4.8 for molecules studied in both solid tumor and hematologic indications. A final outcome was available for 78% of the first indications, 65% of the second indications for those compounds that had a second indication pursued, and 55% of the third indications for those compounds that had a third indication pursued.

The transition and success-rate estimates shown above are all for analyses performed at a molecule level. That is, they are estimates of the likelihood that a molecule will proceed from one phase to the next or be approved if the molecule enters clinical testing for some indication. A molecule that obtains regulatory marketing approval for any indication is taken above to be a success, even if the compound fails in a number of other indications. The molecule is counted as a failure only if it has failed in all indications pursued. With the exception of first indications, success rates at an indication level, in theory, can be lower, higher, or the same as success rates at the molecule level. The qualitative relationship cannot be determined *a priori*. The relationship, therefore, is an empirical, not theoretical, issue. Because all compounds in the data set have a first cancer indication, for first indications, the indication success rate can be no higher than the molecule success rate.

Figure 4 shows estimated phase transition rates and overall clinical approval success rates for first, second, and third indications pursued, for those compounds that had such indications. Note that the success rate for the lead, or first, indication need not be the same as the molecule success rate. This is because although every compound in the data set had a first indication, the first cancer indication pursued could fail, whereas a later indication could succeed. The results show this to be the case because the estimated clinical approval success rate for the lead,

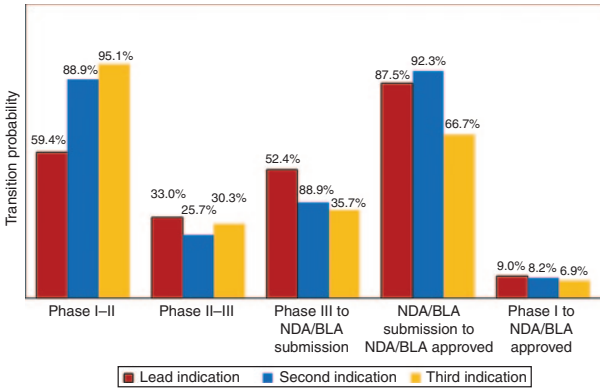

Figure 4 Phase transition probabilities by cancer indication number for cancer compounds first entering clinical testing (1993–2004). NDA/BLA, New Drug Application/Biologic License Application.

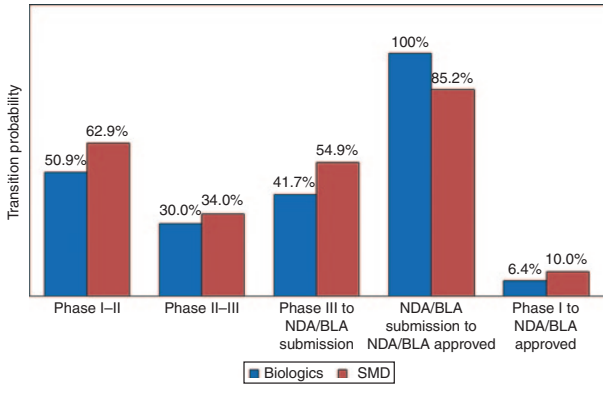

Figure 5 Phase transition probabilities for lead indications of cancer compounds first entering clinical testing during 1993–2004 by molecule type. NDA/BLA, New Drug Application/Biologic License Application; SMD, small-molecule drug.

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