Organizational Scope and Investment:

Evidence from the Drug Development Strategies of Biopharmaceutical Firms*

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ABSTRACT

This paper compares the clinical trial strategies and performance of large, established ("mature") biopharmaceutical firms to those of smaller ("early stage") firms that have not yet successfully developed a drug. We study a sample of 235 cancer drug candidates that entered clinical trials during the period 1990-2002 and were sponsored by public firms. We find that early stage firms are more likely than mature firms to advance from Phase I clinical trials to Phase II, but that the clinical results of their Phase II trials are less promising. Early stage firms are also less likely to advance to Phase III. This pattern is more pronounced for early stage firms with large cash reserves. The evidence points to an agency problem between shareholders and managers of single-product early stage firms who, we argue, are reluctant to abandon development of their only viable drug candidates. By contrast, the managers of mature firms are more willing to drop unpromising drug candidates because they have other ones they can easily bring to clinical trials. The findings appear to be consistent with the benefits of internal capital markets identified by Stein (1997).

1. INTRODUCTION

How does organizational scope affect investment and performance? We study this question by examining the project-level R&D decisions and performance of biopharmaceutical firms. We believe that this is an ideal setting to address this question for two reasons. First, there is considerable heterogeneity in how biopharmaceutical firms are organized. Many are well-established firms with a number of drugs on the market and large portfolios of drug candidates at various stages of development. Others are early stage firms with no products on the market and just a single drug in development. Second, there is a wealth of detailed, publicly available information on the project-level investments that these firms undertake --- namely the clinical trials required by the U.S. Food and Drug Administration (FDA) to determine the safety and efficacy of drug candidates. Moreover, the outcomes of these investments are measurable. Thus, one can compare, at a very fine-grained level, the investment behavior and performance of firms with different organizational structures.

Why might we expect the scope of an organization to affect investment behavior and performance in biopharmaceuticals? Our hypothesis is a variant of Stein (1997) who identifies the conditions under which an internal capital market that allocates funds across n competing projects is preferable to an external capital market that funds n single-project firms. In his framework, the problem with single-project firms is that if they have poor investment opportunities they may still invest because their managers will be reluctant to return funds to shareholders and lose the private benefits that come from running firms and projects. This conflict is mitigated in an internal capital market to the extent that higher-level managers can retain funds for investment, but have a broader range of

projects in which to invest, some of which may have positive net present value.   Our

point is similar although we adapt the basic story to fit the biopharmaceutical industry.

The biggest investments in this industry are the clinical trials that are required for a drug

to receive marketing approval from the FDA.[1] A particular drug candidate must go

through three phases of clinical trials on human subjects: small Phase I trials designed in

most cases to determine the safety of the drug candidate; larger Phase II trials to test both

safety and efficacy; and finally very large Phase III trials with as many as a several

thousand subjects. At each point along the way, the company must decide based on

scientific, clinical, and financial information whether to continue to the next, more

expensive phase of clinical trials.

We argue that the managers of early-stage biopharmaceutical firms --- those with

only a single drug in development --- will be excessively reluctant to end clinical trials

after Phase I. Pulling the plug at this point would mean either that the firm would have to

be liquidated or that research on a new drug would have to be started. If the firm is

liquidated, the manager would likely suffer a reduction in his human capital to the extent

that it is firm-specific. If a new research program is begun to replace the failed one, the

manager's human capital might not fit well with the new project. Therefore, we argue

that managers of early-stage firms would be willing to take marginally uneconomic

projects forward from Phase I to Phase II.

We think that this is likely to be less of a problem in more mature

biopharmaceutical firms with numerous drug candidates in pre-clinical and clinical

testing. In these sorts of firms, managers know that there is a pipeline of drug candidates

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[1]The most recent estimate of the cost of getting a single drug approved is $802 million (deflated to 2000).
This estimate factors in the expected costs associated with failed attempts to develop a drug.

that they can roll out for Phase I testing should a Phase I trial yield unpromising results.

Managers of one clinical trial can be easily redeployed into another project with little

effect on their human capital. We predict that these firms will be more selective in taking

a drug candidate forward from Phase I to Phase II.

This perspective suggests both that early-stage firms will be more aggressive in

taking trials from Phase I to Phase II, and that these firms will be more likely to have

unpromising clinical results at Phase II and also less likely to take a trial forward from

Phase II to Phase III.[2]

Financial constraints could mitigate the tendency of early stage firms to be overly

aggressive in moving forward to Phase II. To the extent that firms lack the cash reserves

to fund Phase II trials, we would expect them to be less prone to move forward and,

conditional on moving forward, to have better clinical results. These financially

constrained early-stage firms would therefore also be *more* likely to move forward from

Phase II trials to Phase III.

Our results are very much consistent with these predictions. Early-stage firms are

more prone than mature firms to move into Phase II trials within a two-year period

(61.4% vs. 45.3%). Moreover, if an early stage firm moves ahead into Phase II, the

clinical results of the trial are worse. In Phase II trials conducted by early stage firms, the

percentage of patients that exhibit some shrinkage of their tumors --- a key marker of

success of a Phase II trial --- is less than half that of trials conducted by mature firms (6%

vs. 12%). Given the poor performance of Phase II trials sponsored by early stage firms, it

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[2]Given the high costs of running Phase III trials --- the average cost is estimated by DiMasi et. al. (2003) at $86.3 million (deflated to 2000) --- we would expect few firms to take trials forward from Phase II to Phase III so that managers could mitigate the impact of abandonment on their human capital. Instead, we suspect that they would conduct more Phase II trials.

is not surprising that these firms are also less much less likely than mature firms to move into Phase III trials within a three-year period (13.6% vs. 34.9%). This difference is driven to a very large extent by early stage firms with large cash reserves. They bring 75.6% of their Phase I trials into Phase II, and have an even lower tumor response rate in Phase II (4% vs. 12% for mature firms). Only 3.2% of these early stage firms proceed to Phase III (i.e. once in 31 Phase II trials). The cash-poor early stage firms are only slightly more prone than mature firms to go from Phase I to Phase II, have somewhat worse clinical results in Phase II trials, and are less likely to proceed to Phase III.

These results point to agency problems in external capital markets that lead to over-investment. They suggest that internal capital markets play a role in mitigating these over-investment problems (Stein, 1997) and that financial constraints also limit the extent of over-investment (Jensen, 1986).

Our findings connect in important ways to three literatures. The first is the literature on the costs and benefits of internal capital markets. Most of this literature suggests that internal capital markets lead to investment inefficiencies due to cross-subsidization of divisions in low-growth industries by those in high growth industries (Scharfstein and Stein, 2000, Scharfstein, 1998, Shin and Stulz, 1998 and Rajan, Servaes and Zingales, 2001). Our findings point to an advantage of internal capital markets in line with the empirical work of Khanna and Tice (2001). They find that discount department store with no operations outside this sector were more prone to follow a stay-and-fight strategy against local-market entry by Wal-Mart, whereas more diversified firms tended to exit and focus their business in other areas. They argue that the stay-and-fight strategy was value reducing, but that focused firms --- in contrast to diversified firms --- chose

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this strategy because they had no place else to deploy their capital. Likewise, our early stage biopharmaceutical firms may have continued from Phase I to Phase II even in the face of poor clinical outcomes because they did not have an easy way to redeploy their financial and human capital.

This paper is also related to the literature on free cash flow and investment (Jensen, 1986) arguing that firms with large cash flows, cash reserves, or debt capacity, will tend to over-invest. There are many papers that try to test this hypothesis, but the ones closest to ours are the ones that look at investments at the project level. Lang, Stulz and Walkling (1991) find that the stock price reaction to the announcement of an acquisition is lower when bidding firms generate excess cash flow. More recently, Bertrand and Mullainathan (2003) find that firms with excess cash flow tend to bid more for oil and gas leases and that these leases are, on average, less productive.

Finally, our paper is related to the literature on the determinants of success in drug development. The closest link is to Danzon, Nicholson, and Pereira (2003) who estimate the effect of experience on the probability that firms move from one phase of clinical trials to the next. They find that small firms are slightly more likely than large firms to advance from Phase I to Phase II, and that the effect is reversed for Phase II to Phase III transitions. They interpret their findings as evidence that there is learning-by-doing in the management of clinical trials; however, our findings suggest that the higher Phase II success rates of large firms may not be the result of learning-by-doing but rather may be the result of agency problems at small firms that lead them to bring poor drug candidates into Phase II trials.[3]

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[3] Cockburn and Henderson (2001) examine the determinants of success at the level of a research program (e.g. cardiac and circulatory) rather than at the level of a particular drug candidate. They find that firms

The paper is organized as follows. The next section outlines a simple framework to structure our thinking about the agency problems that arise in biopharmaceutical firms. Section 3 outlines the construction of the database and Section 4 presents the results. Section 5 concludes.

2. A SIMPLE FRAMEWORK

This section outlines a simple framework for comparing the investment behavior of early-stage biopharmaceutical firms to that of mature biopharmaceutical firms. As noted in the Introduction, these firms make sizable investments in the clinical trials needed for regulatory approval of a drug. There are three phases of trials, each increasing in size and cost. We model the decision of whether to move forward from Phase I, the earliest and least expensive trial, to the next stage of clinical trials, Phase II, which are both larger and more costly.

Based on the outcome of the Phase I trial, the manager makes an assessment of the probability that the Phase II trial will be "successful," and that he will want to go forward to Phase III. We put successful in quotation marks because, in reality, success is not dichotomous; rather the outcome of a Phase II trial lies on a continuum and is often subject to different interpretations. However, for simplicity we suppose that if the trial is successful, further development of the drug has an expected discounted payoff of $X > 0$. If the trial is unsuccessful the expected payoff is zero. Let p_2 be the probability of success. Let I_2 be the cost of conducting a Phase II trial. Then, the first-best decision rule is to go forward with Phase II provided:

with a broader range of research program are more likely to end up with FDA-approved drugs. Given the different unit of analysis it is difficult to link their results to ours.

(1) $\qquad p_2X - I_2 \geq 0.$

The managers and researchers of early-stage firms might assess this differently than (1). We posit that these firms do not have credible alternative drug candidates in the pipeline so that if they do not move forward into Phase II they have two options. The first option is to liquidate the firm. If they liquidate the firm, they get some fraction, α, of the firm's liquidation value, A. However, their value outside the firm is less than their value inside the firm either because they have some firm-specific human capital or because they have general human capital that is better suited to the firm's needs than the average firm to which they would move. We denote this decrease in human capital Δh. Thus, the net payoff to the manager from liquidation is $\alpha A - \Delta h$. By contrast, if the firm continues to Phase II, the manager gets a fraction of the net present value plus the liquidation value, $\alpha(p_2X - I_2 + A)$. As a result, the managers will prefer continuation to liquidation if:

(2) $\qquad \alpha(p_2X - I_2) \geq -\Delta h.$

Inequality (2) implies that if the only option is liquidation, managers might choose to continue to Phase II even if it has negative net present value.

An alternative to liquidation is to begin another pre-clinical drug discovery program. Given that there is none in-house, this involves bringing one in from the outside. Finding one that has non-negative present value is by no means guaranteed. Moreover, even if one is found, it is unlikely that the human capital of the managers and researchers will be well-suited to the new drug development program. Thus, the net payoff to the manager from bringing a program in house is $\alpha A - \Delta v$, where Δv is the

human capital loss when outside projects are brought in house or the extent to which the new program has negative net present value.

The Phase II continuation condition can be written as:

(3) $\qquad \alpha(p_2X - I_2) \geq max(-\Delta h, -\Delta v)$

This means that on the margin, early-stage firms may continue a Phase II trial even if it has negative net present value.

The decision-making process in mature firms is different. First, one distinguishing feature of these firms is that they have a pipeline of viable drug candidates that can be rolled out for Phase I clinical trials. Second, unlike early stage firms, the key decision maker may be someone who is not involved in managing the drug candidate under consideration, but rather someone who manages a portfolio of drug candidates. Since his human capital is unlikely to be tied to the particular candidates being studied, he will only continue to Phase II if doing so has positive net present value, i.e., $p_2X - I_2 \geq 0$. This is the key idea underlying Stein's (1997) model showing the conditions under which internal capital markets lead to more efficient investments than external capital markets.

This simple framework generates two empirical predictions. From a comparison of (1) and (3) we get the first prediction.

Prediction 1: *Early stage firms will be more likely to advance from Phase I trials to Phase II trials.*

Holding X and I_2 fixed, a comparison of (1) and (3) implies that early stage firms that go ahead to Phase II, will do so, on average, at lower levels of p_2. This generates a second prediction:

Prediction 2: *Early stage firms will be more likely to fail in Phase II clinical trials.*

There are additional predictions if financial constraints are introduced into the model. These are most relevant for early stage firms, as mature firms have large cash flows from existing drugs on the market. If early stage firms do not have the financial resources to fund a Phase II trial, they will have to finance the trial by raising external capital. If the project has negative net present value this will be difficult or impossible to do. The firm will have to raise I_2 when it is worth $p_2X + A$. Thus, the firm will only be able to raise outside capital if $p_2X - I_2 > $ -A. If A is small, the firm will not be able to fund projects with significant negative net present value. Thus, we have our third and fourth predictions.

Prediction 3: *Early stage firms with low cash reserves will be less likely to advance from Phase I to Phase II trials than early stage firms with high cash reserves.*

Prediction 4: *Early stage firms with low cash reserves will be more likely to succeed in Phase II trials.*

If we find evidence confirming these predictions, we need to be careful about alternative explanations that could generate these findings. One possibility is that early stage firms undertake riskier projects --- those with higher values of X and lower values of p_2. This might be the case if early stage firms are founded by scientists exploring cutting edge technologies. However, if we can use proxies for X to control for the value of succeeding in Phase II, then we can alleviate this concern. This will be discussed in greater detail in Section 4

A second alternative interpretation of our findings is that early stage firms make efficient clinical trial continuation decisions according to (1), but that mature firms set a higher threshold for p_2 than that implied by (1). They might do this if they were financially constrained; however, it is hard to believe that mature firms with existing product revenues and cash flows would be more financially constrained than early stage firms with no products on the market. Another possibility is that mature firms have limited human capital, forcing them to choose between proceeding to Phase II and starting a new Phase I clinical trial.

To see this point, let V_1 be the expected net present value of starting a new Phase I clinical trial. If the firm continues to Phase II on the existing compound, then it must delay the new Phase I trial due to human capital constraints. At the completion of the Phase II trial, the firm can begin a new Phase I trial. The expected net present value of this drug compound is βV_1, where $\beta < 1$ is the discount factor for the relevant period of delay. Thus, the condition for the firm to go forward with the Phase II project is:

(4) $p_2 X - I_2 + \beta V_1 > V_1,$

which can be rewritten as

(4') $p_2 X - I_2 > (1 - \beta) V_1 > 0.$

Thus, human capital constrained mature firms would set a higher p_2 threshold than early stage firms with only one possible drug compound, no financial constraints, and no concerns about the adverse effects of liquidation on human capital.

There are two reasons to believe that this alternative explanation of the predictions is unlikely to be realistic. First, at the beginning of Phase I testing, the net present value, V_1, is very small (Myers and Howe, 1997). In this case, (4) is close to the

first-best continuation rule (1). Second, the existence of human capital constraints in mature firms does not explain Predictions 3 and 4. Thus, to generate our predictions one would need (a) financial capital constraints of early stage firms; (b) human capital constraints of mature firms; and (c) non-negligible Phase I valuations. This is possible but not, in our view, likely for a wide sample of firms.

3. DATA

As discussed in the Introduction, we compare the investment behavior of early stage biopharmaceutical firms (i.e. those with no product revenues) to the investment behavior of more established biopharmaceutical firms. After a drug compound has been identified through pre-clinical research, the biggest investments that biopharmaceutical firms make are the clinical trials they conduct to prove the safety and efficacy of the drug candidate. In particular, the FDA requires that before a drug is sold it must go through several rounds of clinical trials on human subjects. Phase I trials are typically conducted on fewer than 30 patients and are designed to determine a drug's safety. For most diseases, these trials are performed with healthy subjects, although cancer drug trials, the focus of our study, are conducted on subjects with the disease. DiMasi et. al. (2003), using a sample of 68 drug candidates undergoing trials at large biopharmaceutical firms between 1983 and 1994, estimate that the mean (median) out-of-pocket cost of a Phase I trial was $15.2 million ($13.9 million) deflated to 2000.

Phase II trials are larger and more costly than Phase I trials. They are conducted on as many as a few hundred subjects, use patients with the disease, and are designed to

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test both the safety and efficacy of the drug agent. The mean (median) cost of a Phase II trial in the DiMasi et. al. sample was $23.5 million ($17.0 million).

Finally, Phase III trials are typically very large studies, including possibly thousands of subjects. The mean (median) cost of a Phase III trial in the sample was $86.3 million ($62.0 million). After completing these trials, a drug sponsor can seek regulatory approval from the Food and Drug Administration by filing a New Drug Application (NDA)[4].

Our analysis focuses on clinical trials for the treatment of cancer. There are a few reasons why we restrict attention to cancer. First, one can only make meaningful comparisons of clinical outcomes within a disease class. The outcome of a clinical trial for lung cancer (e.g. tumor response) cannot easily be compared to the outcome of a clinical trial for hypertension (reduction in blood pressure). Second, in the case of cancer, there are relatively straightforward, measurable clinical outcomes such as tumor response. Third, as noted above, Phase I cancer trials include sick patients so that, in principle, efficacy can be measured at an early stage. We conjectured that Phase I cancer trials might result in more useful clinical information that could inform a decision to move to Phase II. (As we will soon see, this did not turn out to be the case.) Finally, cancer is the disease class with the largest number of clinical trials during the last decade.

3.1 Data Sources

The starting point for the construction of our sample is a database assembled by Roberts et. al. (2004) of the Phase I clinical oncology trials described in annual volumes

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[4] For certain classes of drugs, a drug's sponsor will file a Biological License Application, which is also evaluated by the FDA.

of *Papers/Proceedings of the American Society of Clinical Oncology* from 1990-2002.

Each year, the American Society of Clinical Oncology (ASCO) has an annual meeting for its members, mainly medical clinicians and researchers. Coinciding with the meeting, ASCO publishes (in hard copy and now on-line) a compilation of abstracts describing research in the field. It is standard for oncology research groups to submit abstracts describing their research. These abstracts are not peer-reviewed, and all submitted abstracts are published.

Roberts et. al. (2004) identify Phase I trials by searching all the abstracts that include in their title or in the abstract itself the words "Phase I", "Phase I/II", "dose-finding", "new", and "novel". From this list, they keep only the ones that indeed describe a Phase I clinical trial. They exclude abstracts that describe one or more of the following: combination trials (i.e. trials using multiple drug compounds); agents targeting pediatric cancers; agents that were previously reviewed by the FDA; radiation therapies or immuno-therapies; herbal medication; supportive care; and trials on non-human subjects. Although the purpose of their paper is quite different than ours, these exclusions make sense for us as well. It is very difficult to determine how successful a clinical trial is when a compound is tested in conjunction with another given that it is hard to determine the baseline response rate of the other compound. It also makes sense to exclude agents targeting pediatric cancers because the approval process for these drugs is quite different. Agents previously reviewed by the FDA add to the complexity of the data collection and therefore are excluded. The other trials are excluded because they are not drugs per se.

Table 1 details the annual number of abstracts describing Phase I oncology trials in the database and lists the annual number of abstracts excluded for each reason. The

main reason for exclusion is that the trial is a combination therapy. There are a total of 2,798 Phase I abstracts identified, but only 1,180 abstracts describe agents that meet the criteria. These 1,180 abstracts describe 575 unique drug agents. There are more abstracts than agents both because there are multiple abstracts published to describe a single trial, and because there are multiple Phase I trials on a single drug agent. Not surprisingly, there is a general increase over time in the number of abstracts and agents meeting the selection criteria.

The next step in the construction of our sample is to identify the organization sponsoring the trial. This information was collected from two commercial databases: Thomson's *Investigational Drug Database* (IDdb) and PJB Publications' *PharmaProjects*. These databases track compounds through their stages of development, from as early as pre-clinical laboratory studies to FDA approval. In addition to identifying the sponsoring organization, we also collected information on the timeline of development (including follow-on clinical trials in Phase II and Phase III) and the kinds of cancer these trials were targeting.[5] The *PharmaProjects* database also provides assessments --- developed by an in-house team of researchers and scientists --- of the novelty of the agent and its potential market size.

Of the 575 unique agents in the Roberts data, we can find 351 in one of these databases.   Sometimes multiple sponsors test a single agent for different indications. Since the unit of observation in our study will be agent/sponsor pairs, we end up with 377 unique agent/sponsor combinations. Note that if there is an alliance to develop a drug, we follow PharmaProjects in only counting the sponsor that developed the agent and is

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[5] Note that Phase I oncology trials do not typically target a specific cancer while Phase II trials do.

sponsoring the trial. There are several cases in which there are equal co-sponsors of the trials and we drop these from the sample. We have 175 unique sponsors in the sample.

The sponsors are a combination of public companies (62.3%), private companies (27.6%), universities and government agencies (10.1%). 58.9% of the Phase I trials are conducted by firms with headquarters in the United States. Many of the foreign companies in our sample, such as Novartis and Elan Pharmaceuticals, are listed on U.S. stock exchanges and have significant research operations in the U.S..

Our analysis centers on the 235 Phase I trials undertaken by the public firms in our database. We exclude the 65 drug candidates sponsored by private firms at this point because it is difficult to get balance sheet data on these firms, and because these firms raise issues, such as the role of venture capital, that are beyond the scope of this paper. We use Thomson Financial's Thomson Research (formerly Global Access) to find the tickers of the public companies, their IPO dates and financial details of the IPO. We merge it with Standard & Poor's Compustat, Compustat Canada, and Compustat Global Industrial/Commercial in order to get financial data about the public companies in our sample. For comparability, all the financial numbers are converted to U.S. Dollars and then adjusted to U.S. Dollars for the year 2000.

3.2 Information on Clinical Trials

Our study focuses on three elements: decision of the company to take the project forward from Phase I to Phase II; the clinical outcome of the Phase II study; and the decision to move from Phase II to Phase III. Table 3 shows the distribution of years from the first announcement of Phase I to the first announcement of Phase II. Since it takes

some time to start a new clinical phase, the many cases where the time to Phase II is one year or less, indicate that some or even all the preparations were undertaken *before* Phase I was finished, implying that the decision was taken with no real regard to the clinical data generated by Phase I.

As Table 3, Panel A indicates, the average time from the beginning of a Phase I trial to the beginning of the first Phase II trial is 25.3 months.   About 65% of the Phase 1 trials that move forward, do so within two years and 80% do so within three years (Table 3, Panel B).[6] This is about twice as long as the time between initiation of Phase I and Phase II trials reported in DiMasi et. al. (2003).

The mean time between initiation of the first Phase II trial and first Phase III trial is 27.1 months (Table 3, Panel A), with almost 60% moving forward within two years and 76% moving forward within three years (Table 3, Panel B). The mean length between trials is comparable to numbers reported in the DiMasi study.

Of course, not all trials move forward to the next phase. As Table 3 Panel C shows, 67% move forward from Phase I to Phase II as compared to 71% in the DiMasi study. Note however that our sample is right censored; for Phase I trials begun later in the sample, there are only a few years during which the trial could have moved forward. Given that the lion's share of Phase I trials move forward within three years, this right censuring of Phase II trials is not a major issue. Table 3, Panel C also shows that 32% of the trials that make it to Phase II, later move forward to Phase III. DiMasi's study finds

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[6] Based on this distribution, in some of our regression analyses we will look at the decision to move to Phase II within *two* years following the first announcement of Phase I.

that 44% of the Phase II trials move forward to Phase III. Here the right censuring might

be more of an issue, because the time between Phase 1 and Phase III is four to five years.[7]

Beginning in Phase II, drug candidates are tested for particular indications, e.g.,

lung cancer, liver cancer, or breast cancer. As Table 4, Panel A shows, 54% of the agents

are tested for two or more cancers, with the mean being 2.7 indications. In a majority of

cases (57%), sponsors only have one agent in clinical trials in our sample, while two

sponsors (Bristol Myers Squibb and Novartis) show up sixteen times. The average is 2.1

agents.

3.3 Information on Companies

Table 5 presents summary data (deflated to the year 2000) on the public

companies sponsoring the trials in the sample. On average, the public companies are very

large, with mean revenues of over $8 billion, mean assets of almost $11 billion, mean

cash of close to $2 billion and mean R&D of about $1 billion. The average market

capitalization is over $38 billion and mean Q is 10.2. On average, the firms were public

for almost 26 years before embarking on the Phase I trials in our sample.

These averages mask considerable heterogeneity in the data.   The 25th percentile

firm has revenues of only $9.5 million, cash of $41.4 million, R&D of $21.0 million and

a market capitalization of $202.7 million. As we have suggested, there are really two

types of firms that are undertaking clinical trials in oncology. One type is the mature

biopharmaceutical firm with sizable revenues, some (or many) drugs already on the

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[7]As our study will show, the Phase II to Phase III probabilities depend on the type of firm that is
undertaking the trial and the DiMasi study is restricted to mature biopharmaceutical firms. Also, the
transition probabilities and mean time between trials are very similar for public firms and the rest of the
sample.

market, and a portfolio of agents in clinical trials or in the laboratory. The other type of firm is an early stage biopharmaceutical, with no drugs on the market and a limited portfolio of agents (often only one) in clinical trials or in the laboratory.

Because we do not have direct information on drug revenues by company, our proxy for whether a firm is early stage is whether the firm has revenues less than $30 million deflated to 2000. The revenues of these firms typically come from two sources: milestone payments from other firms as part of alliances and contract R&D work. There are a few firms with revenues greater than $30 million, but less than $250 million. We found that these firms all had drugs that were on the market or about to be on the market, so we consider them mature firms.

Panels B and C of Table 5 break out the sample into mature and early stage firms. Fifty-nine percent of the Phase I trials are done by mature firms, and the remainder are done by early stage firms. Not surprisingly, the differences between these firms are very large in terms of cash, R&D, and market capitalization.

4. EMPIRICAL ANALYSIS

In this section we compare the decisions of early stage and mature firms to move forward in the clinical trials process.

4. 1 Basic Analysis

4.1.1 Phase I to Phase II Transition Probabilities. We start by estimating probit models of the decision to go from Phase I to Phase II within two years. We use a two-year cutoff on the Phase II decision for two reasons. One reason is that, without a cutoff, Phase I trials that were begun in the early part of the sample would be more likely to be

taken forward. If there is an over-representation of one type of firm in the early period, this would bias our findings. The second reason to use a time cutoff is to measure the aggressiveness with which firms move forward in the clinical trials process. Note that 69% of the agents that are taken forward to Phase II by the public companies are taken forward within two years. To avoid making seemingly arbitrary cutoffs, we will also estimate Cox proportional hazard models. This allows us to estimate the probability per year that a firm takes a trial forward.

The regressors in our model include a dummy variable that gets a value of 1 if the company that is developing the drug is an early stage biopharmaceutical firm, as well as a set of controls. These controls include the following: information on the clinical outcome at Phase I --- response rate and toxicity; whether the drug is a biologic (dummy = 1) or chemical (dummy = 0); whether the drug was sponsored at one point by the National Institutes of Health or any of its affiliate organizations; the novelty of the agent under investigation, and the potential market size of the drug.

Before getting to the regressions it is worth simply comparing the Phase II transition probabilities of the early stage and mature firms. Of the 139 agents sponsored by mature firms, 63 (45.3%) move from Phase I to Phase II within two years. By contrast, early stage firms are more prone to advance to Phase II; of the 96 agents sponsored by early stage firms, 59 (61.4%) move forward to Phase II within two years. This difference is statistically significant at the 1% confidence level.

The probit regressions in Table 6 show that this finding is robust to the inclusion of various controls. The numbers reported are marginal effect of a unit increase in the regressors; they are not coefficient estimates from the regression. The first column just

replicates the finding discussed above without the controls: the estimated marginal effect of the Early-Stage dummy is 0.161, indicating that early stage firms are 16.1% more likely than mature firms to move forward to Phase II.

The second column of Table 6 adds Phase I clinical data to the regression. Thus, an increase in the tumor response rate at Phase I from zero to 10% is predicted to increase the Phase II transition probability by 9.7%. This estimate is, however, statistically insignificant. This is true of the other regressors as well. Whether the drug candidate is a biologic agent or a chemical compound has a small, statistically insignificant effect. Prior NIH-sponsorship of research on the drug candidate appears to have a large estimated effect on the probability of moving forward, but here too the estimate is statistically insignificant.

One explanation of our findings might be that early stage firms try higher payoff strategies and are therefore more prone to move to Phase II. In the context of our model, this translates into a high X. One proxy for a high X is the market size of the disease class that the drug is targeting and the novelty of the therapeutic approach. Columns 3 and 4 of Table 6 add these variables to the regression, but their effects are not statistically significant. None of the controls alter the effect of the main variable of interest, the Early Stage dummy.

4.1.2 *Performance of Phase II Trials.* Prediction 2 suggests that early stage firms will be less successful than mature firms in Phase II trials. To test this prediction we collected data on the clinical outcomes of the Phase II trials from abstracts published in *Papers/Proceeding the American Society of Clinical Oncology*, the same source we used for information on the Phase I trials. We record the percentage of patients in a trial that

exhibit some tumor shrinkage. This is a key endpoint used by the industry to measure the

success of Phase II oncology trials. We have clinical data on a total of 201 Phase II trials.

These include multiple trials conducted on a single agent for different indications. We

are unable to find clinical information on a number of the trials that we know were

initiated either because the study was not completed or because the study abstract was

never published in *Papers/Proceedings*.

Table 7 presents summary information on the average tumor response rate

reported in the Phase II trials undertaken by the firms in our sample. On average, the

tumors of 9.5% of trial participants showed some response. Consistent with our

prediction, the table also shows that the response rate was nearly twice as high for the

mature firms (12.0%) as for the early stage firms (6.1%). The table also shows the

distribution of clinical trials across twelve different cancer types, with the most common

being respiratory, digestive, breast, and genital type cancers. There is no systematic

difference between mature and early stage firms in the distribution of trials across these

cancer types. The table also shows the percentage of patients in the trials who received

prior treatments for cancer. Again there is no difference between early stage and mature

firms.

Table 8 compares the Phase II response rates of early stage and mature firms in a

regression framework. The first column of the table restricts attention to the 108 Phase II

trials begun within two years of the initiation of the Phase I trial for which we also have

Phase II clinical data. This column includes no controls and simply documents that the

average response rate in these trials is 4.4% lower for early stage firms than for late stage

firms. The difference is not statistically significant. Including the controls in the

regression in the second column amplifies the difference; on average, early stage firms have a 6.4% lower response rate than mature firms. Evaluated at the means of the controls, this regression model predicts that the response rate of patients enrolled in Phase II trials of mature firms will be twice as likely to exhibit some tumor shrinkage as patients in Phase II trials of early stage firms. The third column of Table 8 shows that the estimated effect is similar if we include all Phase II trials, not just those begun within two years of Phase I initiation.

4.1.3 *Phase II to Phase III Transition Probabilities.* Another metric of whether Phase II trials were successful is whether firms proceed to Phase III trials. Before discussing the regressions, it is useful to compare the mean transition rates for the two sets of firms. Of the 63 drug candidates brought to Phase II by mature firms within two years, 22 (34.9%) are later brought to Phase III within three years. By contrast, only 8 (13.6%) of the 59 drug candidates brought to Phase II trials within two years by early stage firms are eventually brought to Phase III trials within three years. This 21.3% differential is highly statistically significant.

Table 9 presents the regression analysis. The first column simply replicates the comparison that we just presented. The other columns add the standard controls, but none is statistically significant and they do not affect the estimated effect of the Early Stage dummy.

4. 2 The Role of Financial Constraints in Early Stage Firms

The previous sub-section presents evidence that early stage firms are more prone than mature firms to move forward from Phase I to Phase II, to have lower response rates

in their Phase II trials, and to be less likely to move from Phase II to Phase III. Our model suggests that managers of early-stage firms are reluctant to pull the plug in early clinical trials even if doing so would be value maximizing. However, as Prediction 3 indicates, to the extent that the firm is financially constrained, this should put a limit on the ability of management to over-invest in Phase II trials and should lead to greater success at Phase II (Prediction 4).

To test these predictions, we need a measure of financial constraints. We define a financially constrained firm as an early stage firms with cash of less than $30 million (deflated to 2000). Our assumption is that all mature firms are financially *un*constrained, given that biopharmaceutical firms generate very large cash flows. Thus, the test really hinges on comparing the Phase I and Phase II decisions of constrained and unconstrained early stage firms.

A simple comparison of transition probabilities for early stage firms tells the basic story. Of the 96 Phase I trials conducted by early stage firms, 55 are conducted by financially constrained firms, and the remaining 41 are conducted by financially unconstrained firms. Out of the 55 Phase I trials conducted by constrained firms, 28 (50.9%) proceed to Phase II, whereas 31 (75.6%) out of the 41 Phase I trials conducted by the unconstrained firms proceed to Phase II. Thus, the Phase II transition probability for the constrained early-stage firms is only slightly higher than that of mature firms (45.3%), whereas the transition probability of the unconstrained firms is significantly higher than those of the constrained early stage firms and the mature firms. This result is reflected in the probit regressions in Table 10. As before, none of the controls is statistically significant nor do they impact the estimated effects of Early Stage dummies.

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Table 11 shows that the average response rate of patients in Phase II trials conducted by unconstrained early stage firms is particularly low. In the full model with controls, the response rate of these firms is 9.2% below that of mature firms; the response rate of early stage constrained firms is 4.7% below that of mature firms. This basic pattern is robust to including all Phase II trials, not just those begun within two years of Phase I initiations. The estimated effects for the early stage unconstrained firms are statistically significant. Evaluated at the means of the controls, they predicts that patients enrolled in trials conducted by mature firms will be more than three times as likely to show some tumor shrinkage as patients enrolled in a study conducted by unconstrained early stage firms.

The findings on the Phase II to Phase III transition are also very striking. Of the 28 Phase II trials conducted by constrained firms, 7 (25.0%) went on to Phase III; however, only 1 (3.2%) out of the 31 Phase II trials conducted by unconstrained firms went to Phase III. The Phase II success rate of the unconstrained firms is obviously much lower than that of the constrained firms and the mature firms (34.9%). The success rate of the early stage constrained firms is lower than that of the mature firms, but the difference is not statistically significant. Again, these finding are reflected in the probit regressions, which are presented in Table 12.

4.3 Estimating Proportional Hazard Models

As discussed above, our data is right censored, by which we mean that some drugs may eventually advance to Phase II or Phase III, but we do not yet observe that event. A Phase I trial begun in 2002 that has not yet transitioned to Phase II is not the same as a Phase I trial begun in 1994 that has not transitioned to Phase II. We dealt with this problem by counting as a Phase I to Phase II transition only those that occurred within two years. Likewise for Phase III transitions, we only counted those that occurred within three years of initiating Phase II. This approach has the added benefit of measuring how successful each phase was on the theory that trials that transition more quickly are probably more highly valued by their sponsors.

Another approach to dealing with right censoring is to use survival analysis. Survival analysis examines and models the time it takes for an event to occur. Here we use the Cox proportional hazard model, following the specification outlined in Cox (1975). A drug is assumed to have a certain probability of succeeding in each period. Success is defined as the event of moving from Phase I to Phase II. The instantaneous probability of success at any given time *t* is called the hazard rate, *h(t)*, defined as:

$$h(t) = \frac{\Pr obability\ of\ success\ between\ t\ and\ \Delta t}{\Pr obability\ of\ success\ for\ times \geq t}$$

The Cox model assumes that the hazard function has the functional form:

$$h(t) = h_0(t) \cdot e^{\beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_n x_n}$$

However, the model assumes no restriction on the function $h_0(t)$. Therefore, this model takes into account the possibility that an event has not occurred simply because it hasn't happened yet.

We report the results of our survival analysis in Table 13. We use the same controls as in the previous section. The numbers reported are hazard ratios. In column 1, the estimated effect of being an early stage company is large and statistically significant; it indicates that early stage firms have a 46.8% higher hazard of moving to Phase II than do mature firms. The second column reports results that break out financially constrained and unconstrained firms. Not surprisingly, the unconstrained firms have an even higher hazard ratio; they are 120% more likely to transitions from Phase I to Phase II. The increased hazard for the constrained firms is 10.9%, but it is statistically insignificant.

Columns 3 and 4 describe a similar analysis, this time on the probability of advancing from Phase II to Phase III. These results on Phase II to Phase III transitions are similar to those discussed earlier. The hazard ratio for the early stage firms is 0.519, indicating that their hazard is about half that of mature firms. This estimate is borderline statistically significant. The effects for the early stage unconstrained and early stage constrained firms are similar, though the former effect is closer to being statistically significant.

5. CONCLUSION

We show that early stage biopharmaceutical firms are more aggressive than mature biopharmaceutical firms in bringing their drug candidates forward from Phase I to Phase II clinical trials. However, the drug candidates they bring to Phase II appear to be less promising; conditional on making it to Phase II, patients in trials conducted by early stage firms are much less likely to show some tumor shrinkage and these agents are much less likely to advance to Phase III. These findings are driven to a great extent by the sub-

sample of early stage firms with large cash reserves. Our findings point to an agency problem between shareholders and managers of single-product early stage firms who are reluctant to pull the plug on their only viable drug candidates. We argue that the interests of managers of mature firms are more aligned with their shareholders. With their large portfolio of drug candidates, managers of these firms will not be reluctant to pull the plug on unpromising drug candidates because they have other ones they can easily bring to clinical trials. The findings appear to be consistent with the benefits of internal capital markets identified by Stein (1997).

There are a number of ways in which we hope to build on this research. First, it is worth investigating why there are such big differences in the behavior of early stage firms. A big part of answering this question is understanding why some firms have more cash on hand than others. One possibility is that firms are more prone to raise equity capital during periods when biopharmaceutical firms are more highly valued. These funds come with no strings attached and give managers considerable freedom in the conduct of clinical trials. By contrast, when market valuations in this sector are low, firms tend to rely more heavily on alliances in which control over clinical trials are shared by the firm and its alliance partner (Lerner, Shane and Tsai, 2003). Thus, understanding the role of the equity markets and alliances in the clinical trials process is very high on our research agenda.

Second, we have ignored differences that may exist in the drug development strategies of mature firms. Although our evidence suggests that having more drugs in the pipeline makes firms more selective on average and results in a higher Phase II success rate, the composition of this pipeline and the organizational structure of these firms could

have an effect on their decision making. For example, if cancer drugs are a large part of a company's overall portfolio, is it more or less selective in its decision to move forward to Phase II? Or if the drug candidate was acquired in a merger, how does it affect the transition probability?

Finally, it would be worth examining the 65 trials that are conducted by the private firms in our sample. We suspect that many of these firms are still being funded by venture capitalists. The staged nature of venture capital financing would likely put limits on the ability of early stage firms to move forward to Phase II without the consent of venture capitalists. Whether they end up being more successful is an open question.

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Table 1
Sample Construction: Identifying Phase I Clinical Trials

The initial sample summarized in this table is from Roberts et. al. (2004). It is constructed by searching for Phase I clinical trials listed in *Papers/Proceedings of the American Society of Clinical Oncology* from 1990-2002. For each year, the table list the number of abstracts identified, the number of abstracts eliminated from the sample for each of the main reasons described in the text, the number of abstracts meeting the selection criteria, and the number of unique drug agents meeting the selection criteria.

Year	Number of ASCO Abstracts	Radiation	Chemo-therapy	Pediatrics	Comb-ination Trials	Abstracts Meeting Selection Criteria	Number of Unique Agent Names
1990	28	0	0	0	14	14	14
1991	142	3	4	4	62	73	51
1992	172	6	9	6	87	71	38
1993	196	13	7	7	111	76	41
1994	240	11	16	13	123	89	33
1995	162	14	8	4	90	67	33
1996	162	10	8	5	92	59	29
1997	263	25	19	9	112	113	49
1998	296	22	8	9	159	115	64
1999	282	25	12	5	160	112	51
2000	261	20	8	7	141	109	51
2001	282	19	2	4	120	149	55
2002	312	27	8	7	156	133	66
Total	2798	195	109	80	1427	1180	575

Table 2
Sample Construction: Matching Clinical Trials to Firms

This table lists the number of compounds by year from the Roberts et. al. sample that can be found in Thomson's *Investigational Drug Database* (IDdb) and PJB Publications' *PharmaProjects*. Resulting in 351 unique agents. Twenty-six of these drugs were developed independently by two companies for different indications, resulting in 377 unique agent/company entities.

Year	Number of Unique Agent Names	Number of Unique Drugs	Number of Unique Agent/Research Entities	Percent of Sample
1990	14	12	**12**	3%
1991	51	19	**20**	5%
1992	38	18	**21**	6%
1993	41	21	**27**	7%
1994	33	21	**23**	6%
1995	33	23	**26**	7%
1996	29	22	**27**	7%
1997	49	35	**39**	10%
1998	64	47	**52**	14%
1999	51	33	**34**	9%
2000	51	43	**45**	12%
2001	55	26	**29**	8%
2002	66	15	**22**	6%
Total	575	351	**377**	**100%**

Table 3
Time between Clinical Trials

This table reports data on the time elapsed between the initiation of the first Phase I clinical trial and the initiation of the first Phase II clinical trial for a particular agent, as well as information on the time elapsed between Phase II and Phase III.

Panel A: Time Distribution between Clinical Phases (in months)

	Mean	Median	25%	75%	St. Dev.
Phase I to Phase II	25.27	19	11	32	21.71
Phase II to Phase III	27.12	18	12	38	23.78

Panel B: Time between Clinical Phases

Phase I to Phase II			Phase II to Phase III		
Years	Frequency	Percentage	Years	Frequency	Percentage
0-1	89	35.0%	0-1	18	21.7%
1-2	75	29.5%	1-2	30	36.1%
2-3	39	15.4%	2-3	13	15.7%
3-4	19	7.5%	3-4	8	9.6%
4-5	14	5.5%	4-5	7	8.4%
5-6	6	2.4%	5-6	3	3.6%
6-7	6	2.4%	6-7	1	1.2%
7-8	2	0.8%	7-8	1	1.2%
8-9	2	0.8%	8-9	1	1.2%
9-10	1	0.4%	9-10	0	0.0%
10-11	1	0.4%	10-11	1	1.2%
Total	254		Total	83	

Panel C: Percentage of the sample moving to the next clinical phase

	In 2 years	In 3 years	Ever
From Phase I to Phase II	43%	54%	67%
From Phase II to Phase III	19%	24%	32%

Table 3B
Time between Clinical Trials (Only public companies)

This table reports data on the time elapsed between the initiation of the first Phase I clinical trial and the initiation of the first Phase II clinical trial for a particular agent, as well as information on the time elapsed between Phase II and Phase III.

Panel A: Time Distribution between Clinical Phases (in months)

	Mean	Median	25%	75%	St. Dev.
Phase I to Phase II	22.32	18	11	27	16.97
Phase II to Phase III	26.60	17	12	36	23.32

Panel B: Time between Clinical Phases

Phase I to Phase II			Phase II to Phase III		
Years	**Frequency**	**Percentage**	**Years**	**Frequency**	**Percentage**
0-1	59	36.4%	0-1	10	20.0%
1-2	53	32.7%	1-2	20	40.0%
2-3	24	14.8%	2-3	8	16.0%
3-4	12	7.4%	3-4	4	8.0%
4-5	8	4.9%	4-5	3	6.0%
5-6	4	2.5%	5-6	3	6.0%
6-7	0	0.0%	6-7	1	2.0%
7-8	1	0.6%	7-8	0	0.0%
8-9	1	0.6%	8-9	0	0.0%
9-10	0	0.0%	9-10	0	0.0%
10-11	0	0.0%	10-11	1	2.0%
Total	**162**		**Total**	**50**	

Panel C: Percentage of the sample moving to the next clinical phase

	In 2 years	In 3 years	Ever
From Phase I to Phase II	48%	58%	69%
From Phase II to Phase III	19%	24%	31%

Table 4
Agents per Company and Indications per Agent

This table reports summary statistics of the number of drugs developed by companies and the number of indications (different types of cancer) investigated for each drug developed.

Panel A: Number of Agents per Sponsor

Number of drugs	Frequency	Percentage
1	103	57%
2	43	24%
3	13	7%
4	7	4%
5	4	2%
6	5	3%
7	0	0%
8	2	1%
9	0	0%
10	1	1%
11	0	0%
12	0	0%
13	1	1%
14	0	0%
15	0	0%
16	2	1%
Total	181	

Panel B: Number of Phase II Indications per Agent

Number of Indications	Frequency	Percentage
1	83	46%
2	31	17%
3	22	12%
4	14	8%
5	9	5%
6	9	5%
7	5	3%
8	3	2%
9	3	2%
14	1	1%
Total	180	

Table 5
Summary Statistics on Sample Companies

This table report summary statistics on the public companies in our sample. We use Standard & Poor's Compustat, Compustat Canada, and Compustat Global Industrial/Commercial. For comparability, all the financial numbers are converted to U.S. Dollars and then adjusted to U.S. Dollars of the year 2000. All the figures are in millions of Dollars. All the figures are for the year each drug went to phase I. Revenues, Assets, Cash, R&D, and Book Value are from the respective items in Compustat. Market Cap is the number of outstanding shares at the end of the calendar year multiplied by the share price at the end of the calendar year. Q is defined as the market value of equity the book value of assets less the book value of equity divided by the book value of assets.

Panel A reports the full sample, Panel B reports the sub-sample of mature firms, and Panel C reports the complimentary sub-sample of early-stage firms. We define an early stage firm as such as having revenues equal or lower than 30$m in year 2000 value.

Panel A: Full Sample

Statistics	Years Since Public	Revenues	Assets	Cash	R&D	Market Cap	Book Value	Q
Mean	25.8	8,116.9	10,964.5	1,947.0	1,003.9	38,635.2	5,282.3	10.2
Median	21.7	5,761.7	4,544.9	452.1	394.5	10,310.8	1,563.4	7.4
St. Dev.	22.7	9,766.1	13,531.1	3,257.8	1,228.8	54,844.1	7,001.9	10.5
1%	0.2	0.0	4.0	2.8	2.7	14.4	1.6	1.3
25%	4.2	9.5	57.5	41.4	21.0	202.7	45.7	4.4
75%	40.7	14,080.2	17,578.0	2,469.1	1,798.9	60,107.2	8,678.8	12.7
99%	73.4	33,822.0	45,561.8	12,959.5	4,879.3	246,316.3	26,140.6	64.4

Panel B: Mature Firms

Statistics	Years Since Public	Revenues	Assets	Cash	R&D	Market Cap	Book Value	Q
Mean	37.4	14,178.9	19,084.5	3,340.1	1,736.8	67,134.8	9,172.7	10.5
Median	37.9	13,488.5	16,543.5	2,184.0	1,635.0	55,626.0	7,344.0	8.1
St. Dev.	21.4	8,982.5	12,874.0	3,745.6	1,175.6	57,889.4	7,092.6	7.3
1%	1.0	89.1	114.5	73.8	15.0	932.6	93.8	2.4
25%	24.0	7,683.0	9,288.8	775.5	847.9	23,310.1	4,557.5	6.5
75%	56.3	18,216.0	29,971.0	3,836.8	2,445.9	92,310.5	11,913.0	13.7
99%	73.5	37,899.1	47,542.3	15,602.2	4,879.3	246,316.3	26,140.6	35.8

Panel C: Early Stage Firms

Statistics	Years Since Public	Revenues	Assets	Cash	R&D	Market Cap	Book Value	Q
Mean	10.2	10.7	106.3	84.1	23.9	404.0	78.9	9.7
Median	5.0	7.1	51.1	35.2	18.3	176.4	41.6	5.2
St. Dev.	12.9	11.6	156.9	142.1	26.3	581.4	120.3	13.8
1%	0.1	0.0	2.9	0.4	2.5	0.5	0.8	1.3
25%	1.3	1.8	24.9	17.8	10.4	72.4	18.1	3.0
75%	12.0	17.5	114.4	82.3	29.9	463.2	86.5	9.2
99%	42.4	28.1	793.7	788.5	223.5	2,893.8	541.4	74.2

Table 6
Probit Regression of the Probability of Moving from Phase I to Phase II

The model estimated is a probit model. The dependent variable is the probability of moving from phase I to phase II in the 2 years following phase I, thus it takes one of two values: 1 if the drug moved to phase II and 0 if not. We regress this probability on a dummy if the company is an early stage company (revenues less than 30$m). We control for clinical results and characteristics at phase I: Response Rate – the percentage of patients whose tumor shrank in the phase I trials. Toxicity – the percentage of patients who had a toxic reaction to the drug in the phase I trials. Biologic – a dummy variable that is equal to 1 if the drug is a biologic drug and is equal to 0 if it is a chemical drug. NIH sponsored – gets 1 if the National Institutes of Health (NIH) or any of its affiliate institutes such as the National Cancer Institute (NCI) sponsored the drug. We also control for the potential financial profit to be expected from the development of the drugs: Market size – We use 3 dummies whether the potential market size is up to 500$m, between 500 and 2000$m and more than 2000$m. Novelty of the drugs – We use two dummies whether the drug is a leading compound or an established strategy.

	(1)	(2)	(3)	(4)
Early Stage (dummy)	0.1613	0.1649	0.1615	0.1637
	(2.83)	(3.17)	(2.54)	(2.83)
Response Rate (percentage)		0.9721		1.0823
		(0.90)		(1.07)
Toxicity (percentage)		-4.9275		-5.1419
		-(0.57)		-(0.56)
Biologic (dummy)		-0.0274		-0.0204
		-(0.19)		-(0.13)
NIH Sponsored (dummy)		0.1929		0.2004
		(1.14)		(1.21)
Market Size - 500-2000$m (dummy)			0.0786	0.0746
			(0.50)	(0.46)
Market Size - 2000+$m (dummy)			0.0023	-0.0106
			(0.02)	-(0.08)
Low Novelty Drug (dummy)			0.1148	0.1226
			(1.28)	(1.43)
High Novelty Drug (dummy)			0.0378	0.0319
			(0.34)	(0.28)
Number of Observations	235	235	235	235

Note: We report the change in the probability for an infinitesimal change in each independent, continuous variable and, by default, the discrete change in the probability for dummy variables. In parenthesis are the z-stats calculated using White (1982) standard errors.

Table 7
Summary Statistics of Phase II Clinical Data

This table reports summary statistics on the clinical data collected from the *Papers/Proceedings of the American Society of Clinical Oncology* (ASCO) from 1990-2002. If a drug had more than one phase II we value weight the results by the number of effective patients in each clinical trial. We collect the data about each drug/indication, where we define 11 major indications based on the grouping of the *American Cancer Association*. Response Rate is the percentage of patients whose tumor shrank in the phase II trials. Previous treatments is the number of previous treatments the patients in the trial have had prior to joining the trial.

Panel A: Tumor Response Rates

Response Rate	Full Sample	Early Stage Companies	Mature Companies
Full Sample			
Mean	0.095	0.061	0.120
Median	0.040	0.030	0.065
Std	0.133	0.076	0.159
% Greater than 0	67%	65%	70%

Panel B: Phase II Indications

Indication	Full Sample	Early Stage Companies	Mature Companies
Bone	1%	1%	0%
Brain & Nervous systems	3%	3%	3%
Breast	14%	10%	17%
Digestive	20%	22%	18%
Genital	14%	14%	14%
Head and Neck	3%	3%	3%
Leukemia	1%	2%	0%
Lymphoma	6%	7%	5%
Respiratory	20%	21%	20%
Skin	7%	8%	6%
Urinary	10%	7%	12%
Other	1%	0%	1%

Panel C: Trial Patients with Previous Treatments

Previous Treatments	Full Sample	Early Stage Companies	Mature Companies
None	25.87%	25.58%	26.09%
1	21.39%	17.44%	24.35%
2	9.95%	10.47%	9.57%
2+	41.29%	46.51%	37.39%

Table 8
Regression of the Response Rate of Patients at the Phase 2 Clinical Trial

The dependent variable is the Response Rate - the percentage of patients whose tumor shrank in the phase II trials. This is the response rate for a certain drug for a certain indication. The data is gathered from ASCO Abstracts published. If more than one trial was undertaken for a certain indication, we aggregate them by value weighting by the number of patients. Different indications have different base line response rate. We thus control for each indication by adding indication dummies. We use the definition of indications of the American Cancer Society. We also control for the number of previous rounds of medication the patients were in. Columns (1) and (2) use the sub-sample of public firms that moved to phase II in 2 years or less as described in Table 6. Column (3) uses the full sample.

	(1)	(2)	(3)
Early Stage (dummy)	-0.0442	-0.0641	-0.0612
	-(1.56)	-(2.33)	-(3.53)
Indication Dummy - Bone			-0.0104
			-(0.09)
Indication Dummy - Brain & Nervous systems		0.0752	0.0400
		(0.92)	(0.79)
Indication Dummy - Breast		0.1440	0.1152
		(2.84)	(3.62)
Indication Dummy - Digestive		0.0398	0.0153
		(0.88)	(0.54)
Indication Dummy - Genital		0.0687	0.0411
		(1.34)	(1.34)
Indication Dummy - Head and Neck		0.0476	0.0220
		(0.69)	(0.44)
Indication Dummy - Leukemia		0.1876	0.1790
		(1.85)	(2.05)
Indication Dummy - Lymphoma		0.2719	0.2205
		(4.49)	(5.45)
Indication Dummy - Other		-0.0200	-0.0333
		-(0.15)	-(0.27)
Indication Dummy - Respiratory		0.0799	0.0718
		(1.75)	(2.56)
No Previous Treatments Dummy		0.0603	0.0645
		(1.45)	(2.54)
1 Previous Treatment Dummy		0.0461	0.0477
		(0.95)	(1.44)
2 Previous Treatments Dummy		0.0497	0.0427
		(1.38)	(1.96)
2+ Previous Treatments Dummy		-0.0917	-0.0275
		-(0.89)	-(0.43)
Number of Observations	108	108	201

Table 9
Probit Regressions of the Probability of Moving from Phase II to Phase III for the Drugs Candidates that Moved to Phase II

The model estimated is a probit model. The dependent variable is the probability of moving from phase II to phase III in the 3 years following phase I, thus it takes one of two values: 1 if the drug moved to phase II and 0 if not. We regress this probability on a dummy if the company is an early stage company (revenues less than 30$m). We control for clinical results and characteristics at phase I: Response Rate – the percentage of patients whose tumor shrank in the phase I trials. Toxicity – the percentage of patients who had a toxic reaction to the drug in the phase I trials. Biologic – a dummy variable that is equal to 1 if the drug is a biologic drug and is equal to 0 if it is a chemical drug. NIH sponsored – gets 1 if the National Institutes of Health (NIH) or any of its affiliate institutes such as the National Cancer Institute (NCI) sponsored the drug. We also control for the potential financial profit to be expected from the development of the drugs: Market size – We use 3 dummies whether the potential market size is up to 500$m, between 500 and 2000$m and more than 2000$m. Novelty of the drugs – We use two dummies whether the drug is a leading compound or an established strategy.

	(1)	(2)	(3)	(4)
Early Stage (dummy)	-0.2136	-0.2053	-0.1828	-0.1785
	-(2.79)	-(2.55)	-(2.31)	-(2.18)
Response Rate (percentage)		1.0384		1.0494
		(0.77)		(0.74)
Toxicity (percentage)				
Biologic (dummy)				
NIH Sponsored (dummy)				
Market Size - 500-2000$m (dummy)			0.1368	0.1178
			(0.57)	(0.42)
Market Size - 2000+$m (dummy)			0.0094	0.0012
			(0.04)	(0.00)
High Novelty Drug (dummy)			0.0532	0.0632
			(0.52)	(0.53)
Low Novelty Drug (dummy)			0.1316	0.1097
			(0.79)	(0.60)
Number of Observations	122	122	122	122

Note: We report the change in the probability for an infinitesimal change in each independent, continuous variable and, by default, the discrete change in the probability for dummy variables. In parenthesis are the z-stats calculated using White (1982) standard errors.

Table 10
Probit Regressions of the Probability of Moving from Phase I to Phase II

The model estimated is a probit model. The dependent variable is the probability of advancing from phase I to phase II in the 2 years following phase I, thus it takes one of two values: 1 if the drug moved to phase II and 0 if not. We define an early stage company as one that has revenues (deflated to the year 2000) of less than 30$m. We define a financially constrained company as one that has less than 30$m in cash and short-term investments (Deflated to the year 2000). We regress this probability on a dummy if the company is an early stage company and not financially constrained and on another dummy if it is an early stage company that is financially constrained. We control for clinical results and characteristics at phase I: Response Rate – the percentage of patients whose tumor shrank in the phase I trials. Toxicity – the percentage of patients who had a toxic reaction to the drug in the phase I trials. Biologic – a dummy variable that is equal to 1 if the drug is a biologic drug and is equal to 0 if it is a chemical drug. NIH sponsored – gets 1 if the National Institutes of Health (NIH) or any of its affiliate institutes such as the National Cancer Institute (NCI) sponsored the drug. We also control for the potential financial profit to be expected from the development of the drugs: Market size – We use 3 dummies whether the potential market size is up to 500$m, between 500 and 2000$m and more than 2000$m. Novelty of the drugs – We use two dummies whether the drug is a leading compound or an established strategy.

	(1)	(2)	(3)	(4)
Early Stage Financially Unconstrained (dummy)	0.3000	0.3165	0.3113	0.3295
	(4.11)	(4.50)	(3.88)	(4.34)
Early Stage Financially Constrained (dummy)	0.0557	0.0508	0.0427	0.0326
	(1.15)	(1.21)	(0.68)	(0.57)
Response Rate (percentage)		1.0887		1.2561
		(1.05)		(1.26)
Toxicity (percentage)		-7.6176		-8.0764
		-(0.87)		-(0.89)
Biologic (dummy)		-0.0398		-0.0335
		-(0.30)		-(0.23)
NIH Sponsored (dummy)		0.1930		0.2037
		(1.02)		(1.11)
Market Size - 500-2000$m (dummy)			0.0347	0.0246
			(0.20)	(0.14)
Market Size - 2000+$m (dummy)			-0.0601	-0.0793
			-(0.39)	-(0.49)
Low Novelty Drug (dummy)			0.1308	0.1441
			(1.33)	(1.51)
High Novelty Drug (dummy)			0.0413	0.0361
			(0.35)	(0.30)
Number of Observations	235	235	235	235

Note: We report the change in the probability for an infinitesimal change in each independent, continuous variable and, by default, the discrete change in the probability for dummy variables. In parenthesis are the z-stats calculated using White (1982) standard errors.

Table 11
Regression of the Response Rate of Patients at the Phase 2 Clinical Trial

The dependent variable is the Response Rate - the percentage of patients whose tumor shrank in the phase II trials. This is the response rate for a certain drug for a certain indication. The data is gathered from ASCO Abstracts published. If more than one trial was undertaken for a certain indication, we aggregate them by value weighting by the number of patients. Different indications have different base line response rate. We thus control for each indication by adding indication dummies. We use the definition of indications of the American Cancer Society. We also control for the number of previous rounds of medication the patients were in. Columns (1) and (2) use the sub-sample of public firms that moved to phase II in 2 years or less as described in Table 6. Column (3) uses the full sample.

	(1)	(2)	(3)
Early Stage Financially Unconstrained (dummy)	-0.0551	-0.0920	-0.0741
	-(1.42)	-(2.39)	-(3.38)
Early Stage Financially Constrained (dummy)	-0.0364	-0.0468	-0.0485
	-(1.07)	-(1.46)	-(2.23)
Indication Dummy - Bone			0.0021
			(0.02)
Indication Dummy - Brain & Nervous systems		0.0773	0.0363
		(0.95)	(0.71)
Indication Dummy - Breast		0.1447	0.1156
		(2.85)	(3.63)
Indication Dummy - Digestive		0.0390	0.0152
		(0.87)	(0.54)
Indication Dummy - Genital		0.0656	0.0396
		(1.28)	(1.29)
Indication Dummy - Head and Neck		0.0468	0.0190
		(0.68)	(0.38)
Indication Dummy - Leukemia		0.2162	0.1908
		(2.05)	(2.16)
Indication Dummy - Lymphoma		0.2712	0.2218
		(4.48)	(5.47)
Indication Dummy - Other		-0.0189	-0.0320
		-(0.14)	-(0.26)
Indication Dummy - Respiratory		0.0813	0.0706
		(1.78)	(2.52)
No Previous Treatments Dummy		0.0609	0.0613
		(1.47)	(2.40)
1 Previous Treatment Dummy		0.0526	0.0478
		(1.07)	(1.44)
2 Previous Treatments Dummy		0.0516	0.0413
		(1.43)	(1.89)
2+ Previous Treatments Dummy		-0.0895	-0.0250
		-(0.87)	-(0.40)
Number of Observations	108	108	201

Table 12
Probit Regressions of the Probability of Moving from Phase II to Phase III

The model estimated is a probit model. The dependent variable is the probability of advancing from phase II to phase III in the 3 years following phase II, thus it takes one of two values: 1 if the drug moved to phase II and 0 if not. We define an early stage company as one that has revenues (deflated to the year 2000) of less than 30$m. We define a financially constrained company as one that has less than 30$m in cash and short-term investments (Deflated to the year 2000). We regress this probability on a dummy if the company is an early stage company and not financially constrained and on another dummy if it is an early stage company that is financially constrained. We control for clinical results and characteristics at phase I: Response Rate – the percentage of patients whose tumor shrank in the phase I trials. Toxicity – the percentage of patients who had a toxic reaction to the drug in the phase I trials. Biologic – a dummy variable that is equal to 1 if the drug is a biologic drug and is equal to 0 if it is a chemical drug. NIH sponsored – gets 1 if the National Institutes of Health (NIH) or any of its affiliate institutes such as the National Cancer Institute (NCI) sponsored the drug. We also control for the potential financial profit to be expected from the development of the drugs: Market size – We use 3 dummies whether the potential market size is up to 500$m, between 500 and 2000$m and more than 2000$m. Novelty of the drugs – We use two dummies whether the drug is a leading compound or an established strategy.

	(1)	(2)	(3)	(4)
Early Stage Financially Unconstrained (dummy)	-0.2974	-0.3097	-0.2828	-0.2996
	-(3.28)	-(3.15)	-(3.40)	-(3.42)
Early Stage Financially Constrained (dummy)	-0.0762	-0.0765	-0.0450	-0.0418
	-(1.02)	-(0.92)	-(0.62)	-(0.51)
Response Rate (percentage)		0.7590		0.7334
		(0.62)		(0.59)
Toxicity (percentage)				
Biologic (dummy)				
NIH Sponsored (dummy)				
Market Size - 500-2000$m (dummy)			0.2397	0.2536
			(0.99)	(0.95)
Market Size - 2000+$m (dummy)			0.0733	0.0966
			(0.37)	(0.43)
Low Novelty Drug (dummy)			0.0293	0.0384
			(0.30)	(0.34)
High Novelty Drug (dummy)			0.0854	0.0709
			(0.57)	(0.43)
Number of Observations	122	122	122	122

Note: We report the change in the probability for an infinitesimal change in each independent, continuous variable and, by default, the discrete change in the probability for dummy variables. In parenthesis are the z-stats calculated using White (1982) standard errors.

Table 13
Cox Proportional Hazard Model

We use a Cox proportional hazard model, following the specification outlined in Cox (1975) as a methodology developed to analyze survival data. We do so in order to account for the possible right censoring in our data. A drug is assumed to have a certain probability of succeeding in each period. Success is defined as the event of moving from phase I to phase II, or the event of moving from phase II to phase III. The instantaneous probability of success at any given time t is called the hazard rate, $h(t)$, defined as:

$$h(t) = \frac{\Pr obability\ of\ success\ between\ t\ and\ \Delta t}{\Pr obability\ of\ success \geq t}$$

The Cox model assumes that the hazard function has a functional form, yet the model assumes no restriction on the function. Thus, the dependent variable is time to the defined outcome.
We use the same variables and controls as described the earlier tables.

	Advancing from phase I to phase II		Advancing from phase II to phase III	
	(1)	(2)	(3)	(4)
Early Stage (dummy)	1.4683		0.5186	
	(2.58)		-(1.85)	
Early Stage Financially Unconstrained (dummy)		2.2387		0.4761
		(4.35)		-(1.95)
Early Stage Financially Constrained (dummy)		1.1086		0.5635
		(0.71)		-(1.15)
Response Rate (percentage)	0.1059	0.1475	35.3132	34.7354
	-(1.28)	-(1.10)	(0.83)	(0.84)
Biologic (dummy)	0.9453	0.9838	0.3424	0.3482
	-(0.23)	-(0.07)	-(1.11)	-(1.11)
NIH Sponsored (dummy)	1.8910	1.9335		
	(1.40)	(1.38)		
Market Size - 500-2000$m (dummy)	1.4321	1.3593	0.4883	0.5072
	(0.72)	(0.58)	-(1.17)	-(1.11)
Market Size - 2000+$m (dummy)	1.3464	1.1752	0.4067	0.4241
	(0.74)	(0.37)	-(1.24)	-(1.13)
Low Novelty Drug (dummy)	1.5695	1.5108	2.6532	2.6357
	(1.67)	(1.35)	(2.02)	(2.02)
High Novelty Drug (dummy)	1.7850	1.8575	2.1317	2.1235
	(3.91)	(4.01)	(1.84)	(1.83)
Number of Observations	235	235	162	162

Note: We report the hazard rate for an infinitesimal change in time. In parenthesis are the z-stats calculated using White (1982) standard errors.