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Development trends for new cancer therapeutics and vaccines

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Global commercial development of cancer treatments has dramatically increased over the past 15 years. To assess trends in the process, we analyzed data for 1111 candidates that entered clinical study during 1990–2006. Our results show that although the average number of therapeutic candidates entering clinical study per year more than doubled, the US approval success rate was low (8%) during the period. The therapeutics took seven years on average to go through the clinical and US approval phases, but cancer vaccines have yet to gain any US approvals. These results indicate that improvement in the efficiency of the development process for innovative cancer treatments is needed.

The 'war on cancer' initiated in the 1970s [1] was intended to foster development of innovative products, but progress has been slow. Research over the past three decades has revealed details of the biological basis of cancers, though it has also highlighted the complexity of the problem. Cancers are characterized by proliferation of malfunctioning cells that are involved in a complex series of interactions over time with their environment, including surrounding healthy cells and even components of the immune system [2]. Designing interventions is challenging because of the difficulty in differentiating healthy from cancerous cells.

The development of cancer therapeutics and vaccines has been stimulated by US government mechanisms intended to accelerate access to innovative treatments. For example, interventions can be designated as orphan drugs if the cancers they are designed to treat are rare. Accelerated approval and fast track designations are mechanisms used by the US Food and Drug Administration (FDA) to facilitate development of therapeutics that are treatments for serious or life-threatening diseases. In addition, priority review is available for candidates that are potentially significant improvements in disease treatment.

To assess the effects of efforts by the government and industry to bring innovative cancer therapeutics and vaccines to the US market, we evaluated data for 1111 candidates that entered commercially sponsored clinical study between 1990 and 2006 (Boxes 1 and 2). Of these, 920 were therapeutics and 191 were cancer vaccines. We examined the rate at which the candidates entered clinical studies and the types of candidates under investigation. We focused our examination of probabilities of approval success, and clinical and approval phase lengths on therapeutics because, till date, none of the cancer vaccines have been approved in the US. Our results show that industry is studying more candidates in the clinic than in the past, the average time to bring therapeutic products to market is lengthy (seven years) and that clinical and approval phase lengths are not greatly different when orphan, fast track or accelerated approval products are compared to nondesignated products. Our analysis indicates that success rates were low in all categories examined. Taken together, our results suggest that methods to improve the efficiency of the current development process for innovative cancer treatments are urgently needed.

Therapeutics and their targets

Evidence of the increasing focus on cancer therapeutics by the global pharmaceutical and biotechnology industry can be found in a number of new candidates entering clinical study each year. On average, the number more than doubled from 33 in the early-1990s to 75 in the mid-2000s. The actual number per year fluctuated somewhat over the period 1990–2006; the observed decrease in 2006 was within the range of historical year-to-year fluctuations and probably does not represent a downward trend (Figure 1).

The diverse nature of cancer is reflected in the wide array of candidates designed as interventions in the biological pathways leading to the diseases. The 920 candidates studied as cancer

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BOX 1

Inclusion/exclusion criteria

The following inclusion/exclusion criteria were used to compile the data set:

- 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.
- Clinical study was first initiated during the interval between 1 January 1990 and 31 December 2006. Candidates with investigational new drug (IND) application dates in late 1989 were included since the majority of their clinical development occurred in the 1990s.
- The candidate's activity was primarily directed against cancerous cells or 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 which had no inherent anticancer activity (e.g. radio- and chemosensitizers, detoxifying agents and 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 done during clinical development were for cancer indications. Candidates in clinical study primarily for noncancer indications were excluded even if some cancer studies were done. Products first marketed for noncancer indications but later studied for cancer (e.g. thalidomide) were excluded.
- Candidates studied for precancerous conditions (e.g. myelodysplastic syndrome) were included, but candidates for conditions involving noncancerous cellular proliferation (e.g. actinic keratoses, benign prostatic hyperplasia) were excluded.

BOX 2

Analysis criteria

Since it was founded in 1976, the Tufts Center for the Study of Drug Development has collected data on the clinical study and approval of therapeutics and vaccines. Data for cancer therapeutics and vaccines were collected by survey of pharmaceutical and biotechnology firms and from public documents (e.g. press releases, annual reports) and commercially available databases (IDdb3, IMS R&D Focus and PharmaProjects). Data were updated with all changes noted through 1 June 2007.

The data set comprised a total of 1111 cancer therapeutic or vaccine candidates that entered clinical study sponsored by commercial firms between January 1990 and December 2006. The exact years clinical study was initiated were not available for 31 (3%) of the candidates. These candidates, and an additional eight that had IND filing dates in late 1989, were not included in the data used for Figure 1. Most (83%) of the candidates were therapeutics. The status of the 920 therapeutic candidates was as follows: 478 were in clinical studies and not yet approved in any country (211 in Phase 1, 225 in Phase 2 and 42 in Phase 3), 5 were in US regulatory review, 32 were approved in the US and other countries (though one was later withdrawn), 20 were approved outside the US and 385 were discontinued. Products in Phase 1/2 were assigned to Phase 2 and products in Phase 2/3 were assigned to Phase 3.

Approval success calculations were based on data for candidates with known fates (US market approval or discontinuation). Percent completion was defined as the percent of products with a known fate in a given cohort. Clinical phase transition probabilities were calculated as follows: the number of products that completed a given phase (e.g. Phase 1) and entered the next (e.g. Phase 2) was divided by the difference between the number of products that entered the phase and those that were still in the phase at the time of the calculation. For these calculations, the 20 products marketed outside the US were considered to be in Phase 3. Transitions occurring between phases of clinical studies conducted worldwide were included.

The clinical phase was defined as the interval from the earliest of either the first IND application filing date or the date clinical study was first initiated to the date a marketing application was submitted to the US Food and Drug Administration (FDA). The clinical phase included any clinical development performed outside the USA before the first IND filing date. The approval phase was defined as the interval from the marketing application submission date to the first US approval date.

therapeutics were derived from a variety of sources, though half were chemically synthesized drugs (Figure 2). Synthetic candidates included traditional small molecule, peptide and oligonucleotide drugs, comprising 44, 3 and 3%, respectively, of the total data set. An additional 14% were either natural products, a traditional source of cancer drugs [3], or synthetic derivatives of natural products. Protein therapeutics comprised 26% of the total, and the majority of these (21%) were monoclonal antibodies. Candidates composed of recombinant plasmids or viral vectors, referred to collectively as gene therapy candidates, and biologics, including whole, modified cells or cell fragments and proteins from a natural source, were 5 and 4%, respectively, of the total data set. Interestingly, there was little change in this mixture of candidate types over time. The group of candidates entering clinical study during 1990–1997 had essentially the same composition of matter mixture as those entering clinical study during 1998–2006.

All cancer therapeutics are designed to interfere in some way with the functions of diseased cells. The intended result is typically inhibition of proliferation or destruction of tumor cells, or both. Data sufficient to broadly categorize modes of action were found for 95% of the synthetic and natural product candidates, which together comprised 599 therapeutics (65%) of the data set. The top two modes of action for these therapeutics were inhibition of protein kinases and interference with DNA replication. Protein kinase inhibition was the most common mode of action, with 113 candidates noted as targeting one or more kinases. The intended effect of the candidates varied with the specific signaling pathway that was interrupted, though most candidates inhibited angiogenesis, disrupted the cell cycle or induced apoptosis. A total of 105 candidates were categorized as affecting DNA replication. Typically these candidates either inhibited a DNA topoisomerase or affected DNA through alkylation or intercalation. The attention to protein kinase inhibition as a mode of action for cancer therapeutics is a recent phenomenon. While 60% of the candidates that affected DNA entered clinical study between 1990 and 1999, 78% of the protein kinase inhibitors entered clinical study during 2000–2006.

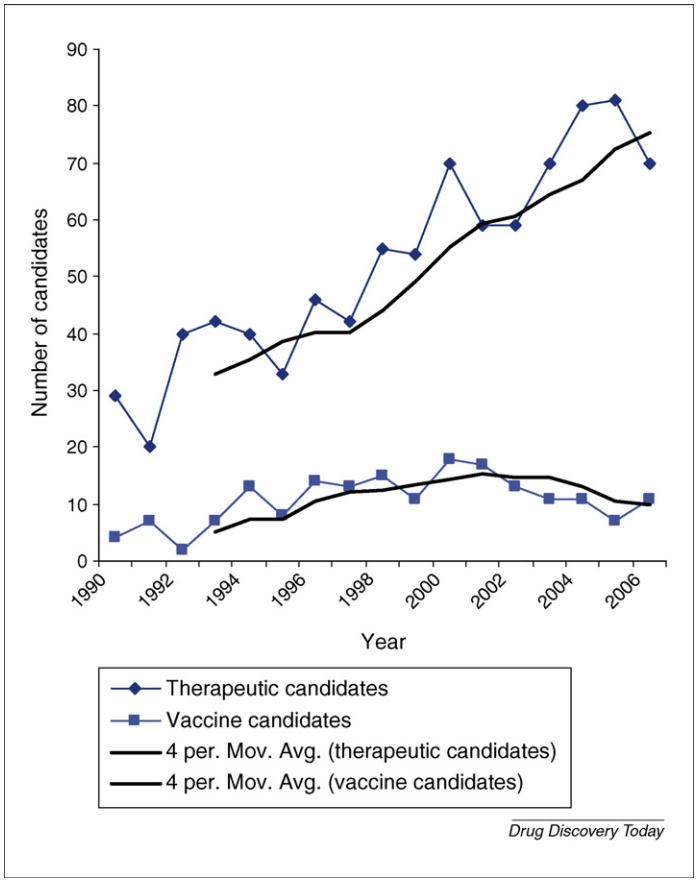

FIGURE 1

New cancer therapeutics and vaccines entering clinical study per year during 1990–2006.

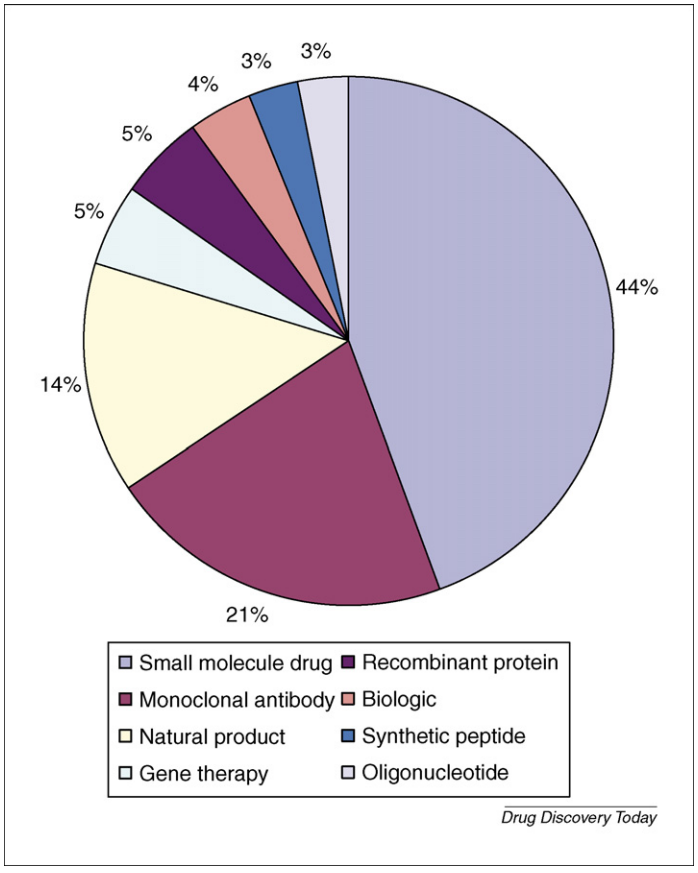

FIGURE 2

Composition of matter for cancer therapeutics in clinical study 1990–2006. *Note*: Percentages are rounded.

mAbs are attractive as cancer agents because they can be designed to selectively target cells and perform a variety of functions either as unmodified protein therapeutics or as conjugates. The majority (61%) of the anticancer mAbs in the data set were not modified and functioned either by activating immune system components against specific targets, or by performing actions such as blocking receptors or sequestering growth factors. The remaining mAbs were modified to carry molecules such as radiolabels, toxins or cytokines to targeted cancerous cells. Of the 190 mAbs in the data set, 30 (16%) carried radiolabels and 35 (18%) carried toxins to tumor cells. Historically, anticancer mAbs in the clinic have been designed against a wide variety of targets [4]. mAbs in the data set were specific for at least 76 different targets (targets for some mAbs have not been disclosed). The top three targets for the mAbs were epithelial cell adhesion molecule (EpCam; 11 mAbs), epidermal growth factor receptor (EGFR; 9 mAbs) and human epidermal growth factor receptor 2 (HER-2; 8 mAbs).

FDA designations of candidate therapeutics

FDA has a number of programs designed to encourage development of innovative candidates, especially those that might be improvements over existing treatments or that might satisfy unmet medical needs. The programs are intended to provide FDA's advice to companies as candidates move through the development process. Benefits of participation can begin at the preclinical phase and extend through the review period. As treatments for serious and potentially life-threatening diseases, some of which affect small number of people, cancer therapeutics are eligible for a number of these programs.

Two programs, orphan and fast track, are designed to provide assistance during the clinical phase of development. Orphan designation is available for treatments of rare diseases or conditions (those with a prevalence of less 200,000 patients in the US, or that affect more than 200,000, but for which there is no reasonable expectation that the costs for development would be recovered from US sales). Companies that develop orphan drugs are eligible for various incentives including seven years' marketing exclusivity (starting on the product's approval date), 50% tax credit for money spent on clinical studies done in the US for the orphan indication, protocol assistance and grants from the FDA, and a waiver of part or all user fees. While not commonly thought of as a disease affecting few people, cancer can be stratified into various tumor types, thus allowing some treatments to qualify as orphan drugs. Of the 920 therapeutics in the data set, 131 (14%) received US orphan designation.

Fast track designation has more obvious application to the development of cancer treatments because the fast track program focuses on therapeutics that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs. Benefits of the fast track program include an emphasis on close and early communication between companies and FDA during the preclinical and clinical phases. The

program also has some benefits that extend through the review phase (e.g. submission of sections of the application over a specified period of time, also referred to as 'rolling' submissions). Fast track designation has been available only since 1997, so evaluation of this variable focused on therapeutic candidates currently in clinical study. In addition, few candidates in Phase 1 had fast track designation, presumably because too little data on which to base a decision is available at that point. Of cancer therapeutics in Phase 2 or 3 studies, 41 (15%) have received US fast track designation.

Approval success probabilities for therapeutics

Attrition during the clinical phase is inevitable given the complex nature of both the science and business aspects of preclinical evaluation. Decisions to advance candidates into the clinic are based on *in vitro* data and on *in vivo* studies in animal models that do not exactly reproduce the human condition and so cannot be entirely predictive of either safety or efficacy in humans. Assumptions are also made about the stability of company strategic plans and program financing, though both can change during the clinical phase.

Probabilities of approval success are measures of the effectiveness of candidate preclinical evaluation. To assess these parameters, the probabilities of successfully proceeding through each clinical phase and FDA review were calculated according to the year that clinical study was initiated for all 920 candidates and also calculated separately for small molecule drugs and mAbs (Figure 3 and Table 1). For mAbs, values were calculated for the entire category, which included mAbs of all varieties (e.g. murine, chimeric, bispecific, etc.) and for humanized mAbs only. Probabilities for each category show a 'U'-shaped curve for the clinical phase corresponding to a high Phase 1 to 2 transition, a low Phase 2 to 3 transition and a moderate-to-high Phase 3 to FDA review transition. For all candidates that entered clinical study in the 1990–2006 period, the probabilities for transitioning from Phase 1 to 2, Phase 2 to 3, Phase 3 to FDA review and review to US approval were 78, 43, 52 and 89%, respectively. There was some variability in the transition probabilities when categories of therapeutics were compared, though only the differences in transitions after Phase 3 were notable.

An important point to note is that the categories encompassing the entire period 1990–2006 have high percentages of candidates still in clinical study (53% or greater). As a consequence, the calculated probability of success values will vary at least somewhat over time until fates for all candidates in the categories are known. The percentages of candidates with a known fate were higher when the categories were restricted to candidates that entered clinical study between 1990 and 1997. Phase transition probabilities were approximately the same for the early interval compared to the entire period, which suggests that these values have remained fairly consistent through the period examined. There was a notably low Phase 2 to 3 transition probability (27%) for the mAbs of all types of category because of discontinuation of murine, bispecific and IgM molecules, which comprised 67% of the mAb candidates that were discontinued at Phase 2 during 1990–1997.

Overall, the approval success rate for cancer therapeutics that entered clinical study between 1990 and 2006 was 8% (Table 1). There was some variation when values were calculated for separate categories of candidates. Using the data available till date,

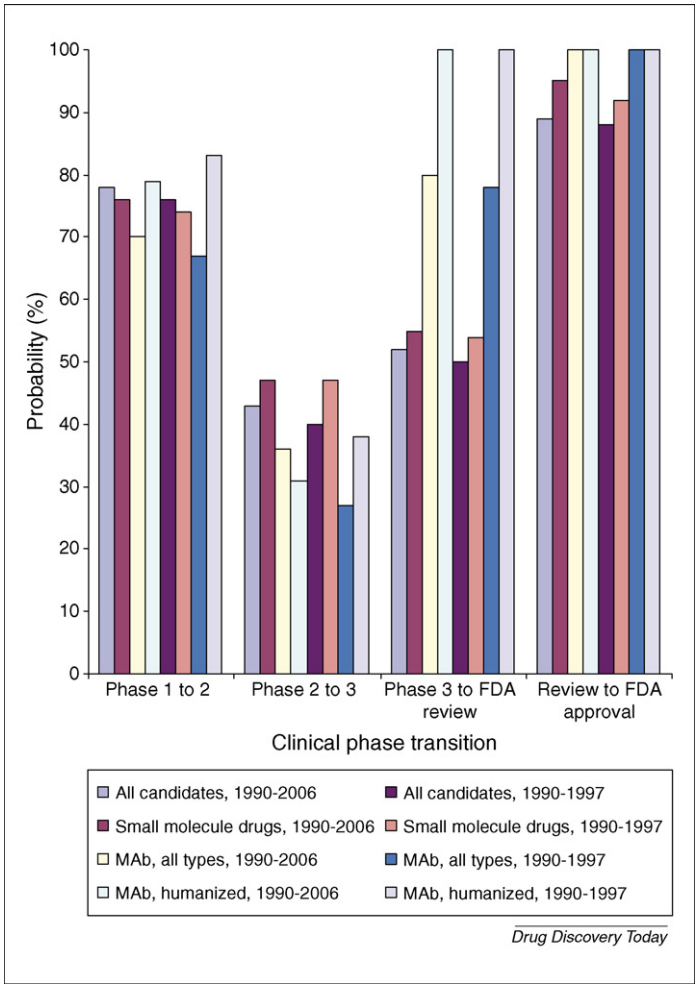

FIGURE 3

Clinical phase transition probabilities for cancer therapeutics.
Note: Candidates entered clinical study during 1990–2006.

humanized mAbs had the highest approval success rate (14%), though the rate decreased to 9% for the mAbs of all types of category. The latter category included murine mAbs, which have previously been reported to have low success rates [5,6]. Approval success rates increased when categories were restricted to candidates that entered clinical study between 1990 and 1997, though the increases were marginal for all categories except the humanized mAbs. For that period, the success rate for humanized mAbs was 30%, more than twice the rate for small molecule drugs (12%). It is important to note that the rate for humanized mAbs is based on data for only a small number of candidates. Relative to small molecule drugs, humanized mAbs entered clinical study in a ratio of approximately 1:8 during 1990–1997. This ratio decreased somewhat to 1:6 during 1998–2006.

Of the small molecule drugs, protein kinase inhibitors are currently the most successful. Small molecule protein kinase inhibitors entering clinical study during 1990–2006 have a 26% overall success rate so far (based on fates known for 28% of the candidates). Most (78%) entered clinical study during or after 2000, so analysis of data from an earlier period would not be useful. Again, it is important to note that calculated probability of success values will vary at least somewhat over time until fates for all candidates in the categories are known.

TABLE 1

Current approval success rates for cancer therapeutics

	Total number of candidates	Percent completion (%)	Number of US approved products[a]	Approval success rate[b] (%)
All candidates, 1990–2006	920	45	32	8
Small molecule drugs, 1990–2006	405	46	19	10
mAb, all types, 1990–2006	190	47	8	9
mAb, humanized, 1990–2006	59	37	3	14
All candidates, 1990–1997	306	78	22	9
Small molecule drugs, 1990–1997	134	77	12	12
mAb, all types, 1990–1997	62	84	7	13
mAb, humanized, 1990–1997	16	62.5	3	30

[a] As of 1 June 2007.
[b] Based on data for candidates with known fates (US approval or discontinuation); approval success rate will converge on the product of the phase transition probabilities as the percent completion goes to 100%.

Approved cancer therapeutics

Of 920 candidate therapeutics that entered clinical study between 1990 and 2006, a total of 32 have been approved in the US till date (Table 2). Slightly more than half (56%) were approved as orphan drugs, and nearly two-thirds of the total received fast track designation during their clinical phase. In addition, half received an accelerated approval, which indicates that the decision to approve the product was based on use of a surrogate endpoint or an effect on a clinical endpoint other than survival or irreversible morbidity, or that the product was approved with restrictions to assure safe use. Accelerated approvals were usually given because of the surrogate or clinical endpoint used in studies; only two, abarelix depot and lenalidomide, were given restricted approvals. All but three products received FDA priority review, which is given to treatments for serious or life-threatening diseases such as cancer. Designations listed here were given at or before the first FDA approval. Many of the 32 approved therapeutics have subsequently undergone additional clinical study and might have received additional designations (or approval) for other indications.

The mean clinical and approval phases for the 32 products were 74.4 and 9.8 months, respectively (Figure 4). Small molecule drugs went through both the clinical and approval phases somewhat faster than the average for all products while mAbs were slower. The latter result is at least partially because the mAb category included two radiolabeled products, ibritumomab tiuxetan and tositumomab-I131, that had lengthy clinical development and approval phases. To assess whether various FDA initiatives might have affected clinical and approval phase lengths, these phases were calculated for products that received US orphan or fast track designations, or accelerated approval. Orphan designation appeared to have little effect on the lengths of either phase. The mean clinical phase was 5% longer for orphan products compared to nonorphans (76.2 months versus 72.2 months), but the mean approval phase for orphan products was marginally shorter (9.5 months versus 10.2 months). By contrast, the mean clinical phase was 13% longer for fast track designated products compared to those without the designation, though the mean approval phase was shorter (8.2 months versus 12.7 months) for the fast track products. On average, products that received accelerated approval had a clinical phase 13% shorter than those that received a full approval, while the approval phases were marginally longer (10.1 months versus 9.5 months).

Notably, the mean approval time was 9.8 months for all 32 products though most (91%) were priority reviewed. FDA's current performance goal is to complete a time to first action on priority-reviewed products within six months for 90% of the applications submitted in FDA's fiscal year. However, the first action does not have to be approval and 10% of the reviews might take longer than six months even if the first action is an approval. Of the 29 priority-reviewed products, 15 (52%) were approved in six months or less, and an additional 2 products were approved in seven months or less.

Cancer vaccines

Vaccines for cancer represent an alternative approach to the use of therapeutics. In contrast to traditional vaccines that prevent disease, cancer vaccines enlist the patient's immune system to destroy existing cancer cells. While simple in concept, the development of products has proven difficult. Problems lie in eliciting sufficient, tumor-selective stimulation of an immune system that is already tolerant of cancer cells [2,7].

Commercially sponsored cancer vaccines first entered clinical studies in the early-1980s and so companies had at least some experience in the area by 1990. Since then, the rate of new candidates entering clinical study each year has been fairly steady, with a slight increase in the late-1990s to early-2000s (Figure 1). Cancer vaccines have entered clinical study in much lower numbers compared to therapeutics though. Overall, the number of cancer vaccine candidates is only one-fifth that of the therapeutics. Of the 191 cancer vaccines in the data set, 92 are currently in clinical study (32 at Phase 1, 48 at Phase 2 and 12 at Phase 3), 1 (sipuleucel-T) is in US regulatory review and 98 have been discontinued.

The cancer vaccines tended to be more complex in their composition of matter compared to the therapeutics. Candidates included one or more tumor-specific antigens and one or more immunostimulatory molecules. Cancer vaccines in the data set were classified by the composition of the antigen. By percentage, the top three types were biologic (40%), synthetic peptide (20%) and gene therapy (15%). The majority (70%) of the biologic cancer vaccines were cell-based; the cells were usually modified dendritic

TABLE 2

US approved[a] cancer therapeutics that entered clinical study during 1990–2006

Company[b]	Generic name	Trade name	Composition	Indication of first FDA approval	Review status	FDA designations	Year of first FDA approval
AstraZeneca	Anastrozole	Arimidex	SMD	Breast cancer	S	None	1995
Sanofi Aventis	Docetaxel	Taxotere	NP	Breast cancer	P	AA	1996
Genentech	Rituximab	Rituxan	mAb	Non-Hodgkin's lymphoma	P	O	1997
Novartis	Letrozole	Femara	SMD	Breast cancer	S	None	1997
Genentech	Trastuzumab	Herceptin	mAb	Breast cancer	P	FT	1998
Hoffmann LaRoche	Capecitabine	Xeloda	SMD	Breast cancer	P	AA	1998
Ligand Pharmaceuticals	Alitretinoin	Panretin	SMD	Cutaneous lesions in patients with AIDS-related Kaposi's sarcoma	P	O	1999
Ligand Pharmaceuticals	Bexarotene	Targretin	SMD	Cutaneous T-cell lymphoma	P	O	1999
Seragen	Denileukin diftitox	Ontak	rDNA	Cutaneous T-cell lymphoma	P	AA, O	1999
Cell Therapeutics	Arsenic trioxide	Trisenox	SMD	Acute promyelocytic leukemia	P	FT, O	2000
Wyeth	Gemtuzumab ozogamicin	Mylotarg	mAb	Acute myeloid leukemia	P	AA, O	2000
Novartis	Imatinib	Gleevec	SMD	Chronic myeloid leukemia	P	AA, FT, O	2001
AstraZeneca	Fulvestrant	Faslodex	SMD	Breast cancer	S	None	2002
BiogenIDEC	Ibritumomab tiuxetan	Zevalin	mAb	Non-Hodgkin's lymphoma	P	AA, FT, O	2002
AstraZeneca	Gefitinib	Iressa	SMD	Non-small cell lung cancer	P	AA, FT	2003
Corixa	Tositumomab-I131	Bexxar	mAb	Non-Hodgkin's lymphoma	P	FT, O	2003
Millennium	Bortezomib	Velcade	SMD	Multiple myeloma	P	AA, FT, O	2003
Praecis	Abarelix depot	Plenaxis	SP	Prostate cancer	P	AA	2003[c]
Genentech	Bevacizumab	Avastin	mAb	Colorectal cancer	P	FT	2004
Genzyme	Clofarabine	Clolar	SMD	Acute lymphoblastic leukemia	P	AA, FT, O	2004
ImClone Systems	Cetuximab	Erbitux	mAb	Colorectal cancer	P	AA, FT	2004
Eli Lilly & Co.	Pemetrexed	Alimta	SMD	Mesothelioma	P	FT, O	2004
OSI Pharmaceuticals	Erlotinib	Tarceva	SMD	Non-small cell lung cancer	P	FT	2004
BayerSchering	Sorafenib	Nexavar	SMD	Renal cell carcinoma	P	FT, O	2005
Celgene	Lenalidomide	Revlimid	SMD	Myelodysplastic syndrome	P	AA, FT, O	2005
GlaxoSmith Kline	Nelarabine	Arranon	SMD	T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma	P	AA, FT, O	2005
Amgen	Panitumumab	Vectibix	mAb	Colorectal cancer	P	AA, FT	2006
Bristol-Myers Squibb	Dasatinib	Sprycel	SMD	Chronic myeloid leukemia	P	AA, FT, O	2006
Merck & Company	Vorinostat	Zolinza	NP	Cutaneous T-cell lymphoma	P	FT, O	2006
Pfizer	Sunitinib malate	Sutent	SMD	Renal cell carcinoma, gastrointestinal stromal tumors	P	AA, FT	2006
GlaxoSmith Kline	Lapatinib	Tykerb	SMD	Breast cancer	P	FT	2007
Wyeth	Temsirolimus	Torisel	NP	Renal cell carcinoma	P	FT, O	2007

AA, accelerated approval; FT, fast track; mAb, monoclonal antibody; NP, natural product or derivative; O, US orphan; P, priority review; S, standard review; SP, synthetic peptide; SMD, small molecule drug.

[a] US approvals as of 1 June 2007 for 920 candidates that entered clinical study during 1990–2006; fates (approval or discontinuation) are known for 45% of these candidates.
[b] Company as listed in first FDA approval letter; updated to reflect current company name.
[c] Withdrawn from market in 2005.

or tumor cells. The gene therapy candidates were commonly plasmid or viral vectors encoding tumor-specific antigens with or without an additional encoded immunostimulatory molecule.

Cancer vaccines would seem to be as likely as therapeutics to have US orphan drug designation. However, this was not the case. Only 6% of the cancer vaccines received US orphan designations compared to 14% of therapeutics, implying that cancer vaccines have been developed less frequently for diseases affecting small numbers of patients than therapeutics. However, half the cancer vaccines in Phase 3 have been designated as US orphans. Cancer

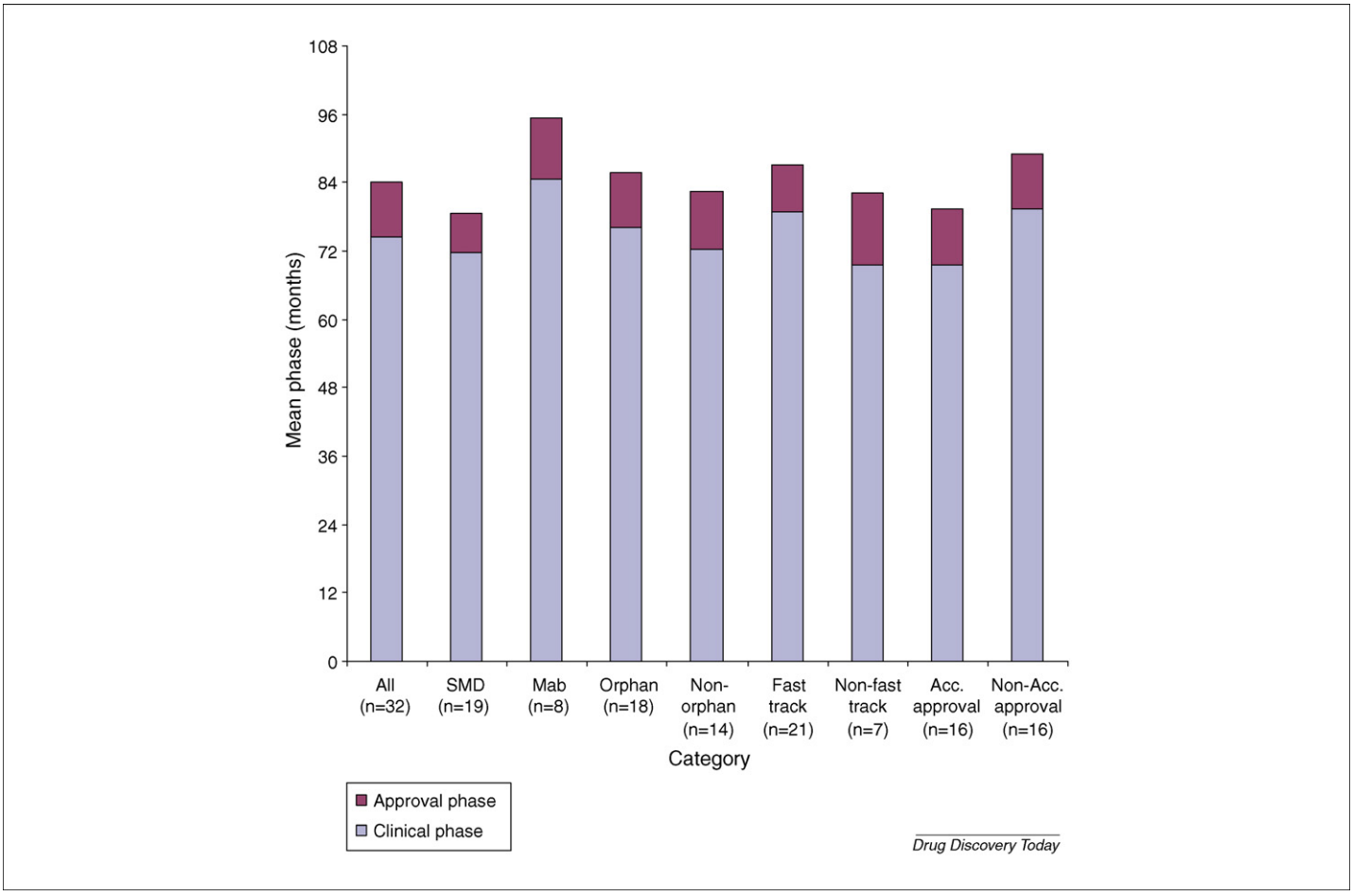

FIGURE 4

Mean clinical and approval phase lengths for US approved cancer therapeutics. US approvals as of 1 June 2007 for 920 candidates that entered clinical study during 1990–2006; fates (approval or discontinuation) are known for 45% of these candidates. *Note*: Four products approved before 1998 were excluded from the fast track versus nonfast track comparison.

vaccines have received fast track designation at approximately the same rate compared to the therapeutics. As was done for the therapeutics, this variable was considered for only those candidates currently in clinical study, and, as was observed for the therapeutics, few cancer vaccine candidates in Phase 1 had fast track designation. Of cancer vaccines in Phase 2 or 3, nine (18%) have received US fast track designation. Interestingly, these candidates are also clustered in late stage studies – 67% of the cancer vaccines in Phase 3 have fast track designations. Sipuleucel-T (Dendreon), which is currently undergoing FDA review, has a fast track designation.

The pace of clinical development for most cancer vaccines has been slow [8]. Of the 12 candidates currently in Phase 3, 7 (58%) entered clinical study at least a decade ago. The one candidate currently undergoing FDA review, sipuleucel-T provides an example of the promise and pitfalls of cancer vaccine development. Sipuleucel-T is an autologous treatment for advanced androgen-independent prostate cancer comprising peripheral blood mononuclear cells activated *in vitro* with a prostate antigen fused with an immune cell activator. The cancer vaccine was in clinical study for nearly ten years before the clinical studies data was submitted for FDA review in 2006 [9]. Data for two Phase 3 studies that included a total of 147 patients who received the treatment was provided to FDA. Both studies failed to meet the primary study endpoint of time to disease progression, but one showed an overall survival benefit of about four months. Though FDA's advisory committee recommended approval, FDA has requested additional data in support of an efficacy claim from an on-going study of sipuleucel-T. Interim survival results, which are due in 2008, might prove sufficient for FDA to approve the treatment.

Conclusion

The next decade will bring a continued focus on access to new cancer therapeutics in countries with aging populations such as the US, Europe and Japan, as well as in countries with emerging economies such as China and India. The pharmaceutical and biotechnology industries are dedicating resources to the challenge of developing innovative treatments, but assistance by government is needed to get products to market in a timely fashion. Increasing the number of candidates in clinical study will not result in increasing numbers of new products if the success rate declines. Government initiatives such as orphan drug and fast track programs are beneficial, though they do not necessarily reduce clinical or approval phase lengths below the average for products in any given category. The rationale for having such programs is not simply to reduce development time, but to prompt

companies to initiate the highly risky innovation process, especially for development of new products for serious or life-threatening diseases such as cancer.

Recent efforts by FDA and the National Institutes of Health (NIH) to assist companies in developing new cancer products might help bolster success rates and decrease development time. FDA has identified numerous opportunities to improve the efficiency of the innovation process [10]. Targeted areas relevant to cancer research include bioinformatics, biomarker development and streamlining clinical trials. In addition, the NIH's National Cancer Institute has a number of translational programs such as the Experimental Therapeutics program, which are designed to reduce development time by improving the amount and quality of the data used to evaluate candidates during the development process.

The biologic pathways that lead to cancer are complex, and characteristics of cancer cells and their metastatic cousins change over time. Improvements in the standard of care are incremental for many patients – new treatments might cause disease progression to be delayed for a few months. Yet progress is being made. If the current success rates remain constant, then the therapeutic candidates in clinical study might yield 40 new products that could be approved over the course of the next seven years. Some of the cancer vaccine candidates might also proceed to approval.

New targets for next generation cancer treatments are already being explored. For example, additional protein kinases have been newly implicated in cancer [11], and so research on new inhibitors holds promise in the future. Further progress will depend on the complex interactions between companies, FDA, physicians and patients that occur during the development and approval of cancer therapeutics and vaccines.

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