

The Ongoing Hopes and Challenges of Cancer

By Kuyler Doyle, Shelly Beer, and Philip Vorhies

As evidenced from Part 1 of this two part article, with lessons learned from the failed trials of the past, the significant number of cancer vaccine candidates in late-stage development is keeping hope alive for their market entry. However, challenges related to the commercialization of these products have yet to be resolved. Meeting the hurdles to gain approval from regulatory agencies is only one step towards getting cancer vaccines to market. Other challenges, as illustrated in Table 1, include company size, the complicated target market, manufacturing costs, and pricing and reimbursement.

Challenges to Commercialization

»» Company Size

Smaller companies, who historically have been leading the charge in cancer vaccine development, have limited resources with which to conduct clinical trials. As new trials are likely to become more complex due to the need to couple with other therapies, development costs will only rise, constraining their overall budgets. With the many failures associated with developing cancer vaccines, some venture capitalists have developed cold feet to fund early-stage companies. Further complicating the matter is the reduction in venture capital investments in biotechnology during the weakened economic climate.

»» Complicated and Potentially Small Target Market

Many targeted therapies on the market from large biotechnology companies have started with a niche target market but have gone on to become blockbusters through the ability to gain approvals for follow-on indications. As many cancer vaccines use antigens that are specific for a particular tumor, potential revenues are inherently restricted by market size and the willingness of stakeholders to pay a premium. Also, as tumors and immune systems are highly variable, clinical studies of some cancer vaccines have indicated that a subset of the patient population benefit from the vaccine. Restricting

Table 1. Commercialization Challenges

Challenge	Description	Possible Solution
Company Size	<ul style="list-style-type: none"> Limited financial resources for complex development programs and marketing Shortage of commercialization experience 	<ul style="list-style-type: none"> Partner with established and experienced company
Complicated and Potentially Small Target Market	<ul style="list-style-type: none"> Tumor antigen may be specific for limited cancer types, and individual variations may reduce market As new line of therapy, physicians may opt for standard of care over vaccine unless unresponsive to established treatments, where vaccine may be less effective 	<ul style="list-style-type: none"> Use biomarkers to find the right target population Investigate ability to delay recurrence from minimal recurrent disease or target very early stage disease
Manufacturing and Logistics	<ul style="list-style-type: none"> Biologics are expensive to produce and manufacturing changes need to be tested for bioequivalence Personalized vaccines lack economies of scale and face distribution challenges 	<ul style="list-style-type: none"> Standardize process as much and as early as possible Use adjuvants to allow for reduced quantity of antigen Look for logistics best practices in similar industries and seek assistance through partnering
Pricing and Reimbursement	<ul style="list-style-type: none"> Lack of precedent makes it difficult to establish initial market price Payers may resist prices and reimbursement in comparison with standard of care 	<ul style="list-style-type: none"> Develop and clearly communicate the value proposition to payers Justify the price

Vaccines

clinical trials to that subset may help get through regulatory hurdles, but a very small responsive population may render a cancer vaccine commercially non-viable if the vaccine has to be priced out of reasonable range.

» Manufacturing and Logistics

Cancer vaccines in development are derived from cellular material or proteins. As such, they are manufactured via biological processes that are costly and need to be tightly controlled for reproducibility. Immunostimulatory adjuvants—frequently included in vaccines to help break tolerance and boost the immune response—can help control manufacturing costs by minimizing quantity of antigen needed. However, as overstimulation of the immune system can lead to detrimental autoimmune responses, regulatory barriers have historically been high for adjuvants. Aluminum-based adjuvants have been approved for some time and are the most widely used adjuvant, although the type of immune response generated with their use would likely be ineffective in cancer vaccines. Regulatory approvals of new adjuvants have increased in recent years, but adjuvants are not approved alone and companies need to determine the appropriate compound and dose for their vaccines. In addition, use of newer adjuvants that stimulate the most effective immune response would require additional license agreements that will affect the bottom line where margins might already be tight.

Facing additional difficulties associated with their complex manufacturing processes are personalized vaccines. Logistics are clearly an issue as samples must travel from patient to laboratory and back while maintaining sterility. If the vaccine is derived from whole cell lysates from the patient's cancer cells, then that means the tumor must be operable and sufficiently large to extract and process. The need for sample or vaccine freezing during distribution to avoid breakdown or to inhibit possible microorganism growth adds further costs.

» Pricing and Reimbursement

Questions remain regarding the future pricing and reimbursement issues surrounding cancer vaccines. Since no therapeutic cancer vaccine is on the market in the United States, there is no precedent to help determine price or facilitate reimbursement. As a new category of therapy, it may take time to integrate into the current treatment landscape and be accepted by payers, especially for minimal residual disease where vaccines might be most efficacious in delaying or preventing recurrence.

Another remaining question will be how the company should price the product. Prophylactic vaccines are relatively inexpensive. Gardasil® is priced at \$125 per dose for a total of \$375 for the series, compared to the tens of thousands of dollars charged for targeted therapies against cancer. As cancer vaccines are biologics, they should theoretically be able to command a similar price. However, if the responsive target market is severely restricted by indication or sub-population, companies will need to charge a higher price to recover costs. Prices for personalized vaccines have been estimated to be anywhere in the \$20,000 to \$80,000 range for the series. As vaccines will likely be used with other expensive therapies, payers might push back on reimbursement and high prices without a very strong value proposition.

Recommendations for Development and Commercialization

There have been many challenges with the development of cancer vaccines, and many questions remain regarding their commercialization. To successfully market cancer vaccines, organizations need to have a deep understanding of the issues that led to repeated failures of predecessors and generate strategies to overcome them. **cont. on pg 10 >>**



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» Development

In general, cancer vaccines appear to be most successful in patients with minimal residual disease. The advantages of this patient population are that they have been exposed to fewer prior treatments, they typically have better immune status, and there is adequate time to evaluate efficacy before disease progression. On the downside, studying this patient population requires longer trials, larger sample sizes, challenging trial endpoints, and they may be less likely to participate since they have other options.

When possible, selection of a homogenous patient population should be considered when evidence suggests that it would provide a greater potential for efficacy and regulatory success. Tumor profile, immunological markers such as patient HLA, or other biomarkers may identify a subset of patients that are more likely to respond clinically.

Trials need to be designed with appropriate clinical endpoints for cancer vaccines. Endpoint criteria must be based upon solid evidence from earlier trials and use realistic expectations for what the product can achieve in the selected study population. Protocol developers need to move away from tumor sizing and toward incorporation of quality of life and survival into endpoints, even if the studies will take longer. Adding sufficient time allows for greater possibility of hitting target endpoints and also allows for the patient population to accumulate to supply ample statistical power. Additionally, more rigorous trial design needs to be employed in earlier stage trials to provide the ability to make clear go/no-go decisions and to reduce more costly failures in the later stages.

As the cancer vaccine alone may not be sufficient to eliminate the cancer, organizations have the option to also explore combination therapies in their development programs. Early studies suggest there could be potential

benefits through combination therapies with chemotherapy, hormone therapy, or drugs that can help break the immune tolerance. This realization may come too late for some of the vaccines that have been shelved after failure as monotherapy. One drawback of pursuing combination therapy studies is that combining cancer vaccines with other agents makes it challenging to demonstrate the contributions of each agent during clinical trials.

» Commercialization

Pharmaceutical companies are looking at biotechnology as the drugs of the future, and many now view therapeutic vaccines as a new niche category worth pursuing. Finding an experienced partner could help resolve issues with launch, manufacturing, adjuvants, and distribution. Recently, Celldex Therapeutics and Pfizer teamed up to develop the CDX-110 peptide antigen vaccine against glioblastoma. The deal provided Celldex with a \$40 million up-front fee, \$10 million in exchange for Pfizer equity, and the potential for \$390 million in milestone payments.

Organizations must work to find the best niche for their product. During cancer treatment, surgical procedures are able to remove a majority of the tumor, but the residual disease leads to recurrence, metastasis, and ultimately death of the patient. Systemic chemotherapy or hormone therapy can help with residual disease, but are limited by their lack of specificity and associated toxicities. Thus, there is a legitimate unmet need in this space. If cancer vaccines can demonstrate a greater efficacy for slowing or preventing recurrence, then organizations can embrace that

niche, accept development endpoints that may require longer trials, and work to demonstrate a clear value proposition that the vaccine will bring to the market. Where patient variation exists, the use of biomarkers will help define the target market with the greatest efficacy and justify premium pricing.

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Clearly, manufacturing and distribution models for off-the-shelf vaccines are more straightforward than personalized models and contain the potential for economies of scale. Standardizing manufacturing processes as much and as early as possible may help avoid later regulatory scrutiny. And, use of effective adjuvants could reduce the need for antigen, in addition to helping boost the immune response. Personalized vaccine models must work to maximize vaccine output per patient sample to reduce costs associated with multiple sample requirements, and need to minimize distribution complications such as the need to freeze the finished product. Logistics best practices from the diagnostics (centralized laboratory model) and blood industries need to be studied to develop the most economically feasible business model that meets regulatory standards.

Companies developing cancer vaccines need to consider the commercialization uncertainties when developing

clinical trial protocols. As there is no precedent for cancer vaccines in the market, clinical trials will need to be rigorous to firmly demonstrate the value proposition in relation to current standards of care that will allow access and reimbursement as well as justify the price. With ongoing discussions on pharmacoeconomics and the push for healthcare reform, cancer vaccines will need a solid data package to face pricing and reimbursement pressures from payers.

Outlook for Cancer Vaccines

Despite the many hurdles, the future of cancer vaccines looks hopeful. Big Pharma has developed a significant interest in the sector and many of the trends from ill-fated clinical trials have been subsequently righted. It is clear that there is still much to learn about the optimal use for cancer vaccines, but there is hope that the diverse ongoing development programs (Figure 1) will be able to find further niches that fill unmet needs. As the first rounds of clinical development data suggest, cancer vaccines will most likely be employed as complements to current therapies rather than replacements. There remain many different combination therapies, scheduling, and dosing regimens to investigate for potential synergies, including in combination with standard chemotherapeutic or hormone therapy, with agents that affect the immune response to either stimulate it or break tumor tolerance, or even with targeted therapies.

Additionally, initial commercialization of cancer vaccines will no doubt be a challenge. It will be essential for organizations to find resources with launch experience to help provide a clear value proposition that will allow adequate pricing and patient access. With several promising cancer vaccines in the pipeline, it appears that these much anticipated products may finally emerge on the market and provide another weapon in the fight against cancer.

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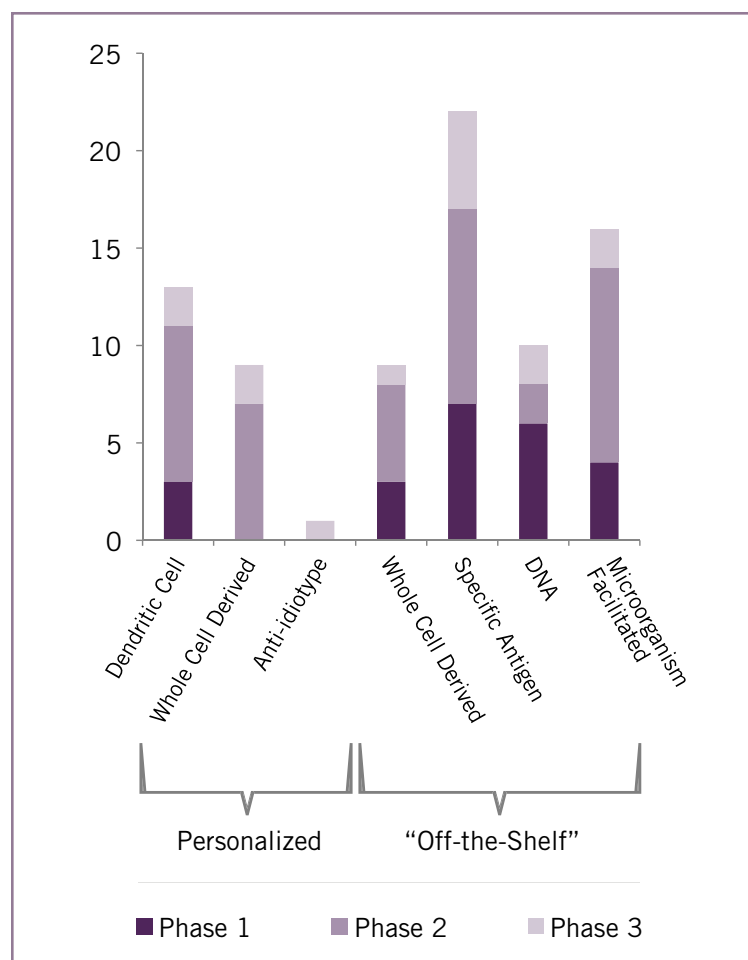


Figure 1. Types of Cancer Vaccines in Clinical Development

Source: Campbell Alliance.

