Cancer vaccines – progress with Oncophage does not change the long, difficult road to success

LONDON, UK----15 April 2008----ExpertREACT. Recently, US-based Antigenics announced that Russian regulators had approved Oncophage (Vitespen), its therapeutic kidney cancer vaccine. Phase III data show that, in a subset of patients, Oncophage improved the rate of recurrence free survival when compared to controls. However, even with product approval obtained in Russia, Oncophage is still a long way from US-approval. Overall, **VacZine Analytics** believes Oncophage and Dendreon's Provenge provide a glimmer of hope but the widespread availability of effective cancer vaccines still remains a distant reality.

Cancer remains a major cause of illness and premature death. Incidence rates continue to rise as the global population steadily ages. The American Cancer Society (1) estimates that in 2008, there will be nearly 1.5 million new cases of cancer diagnosed in the US alone with the most prevalent being lung cancer (15%), prostate cancer (13%), breast cancer (13%), colon cancer (10%) and melanoma of the skin (5%) respectively. While the 5-year survival rates for prostate (99%) and breast cancer (89%) have increased dramatically since the 1970s, the survival rates for lung (16%) and colorectal (65%) cancer still remain poor.

In an effort to find an alternative means of combating cancer and diversify from traditional prophylactic vaccines various companies have attempted to develop cancer vaccines. Cancer vaccines generally contain proteins found on or produced by cancer cells and seek to increase the natural immune defenses of the body by stimulating antigen presenting (APCs) and T cells to increased tumour cell killing. There are numerous categories of cancer vaccines including peptide-based vaccines, heat shock protein (HSP) vaccines, DNA vaccines, antigen-presenting cell (APC) vaccines and whole cell vaccines. Conceptually cancer vaccines could be used with approved non-specific therapies which boost the immune system such as cytokines, Interleukins, Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) and Interferons (IFN-gamma and IFN-alpha).

VacZine Analytics estimates that around 150 separate organizations are actively pursuing cancer vaccine candidates with around 350 ongoing clinical trials (2). Unsurprisingly, competition is intense, with around 80 commercial companies active in the area. Those with products in late stage clinical development include AVAX Technologies, Bioven, Cell Genesys, Celldex Therapeutics, Dendreon, GlaxoSmithKline, Medarex, Merck KGaA, Pharmexa A/S ,Sanofi Pasteur/Oxford BioMedica, Transgene and Vical. In addition large number of academic institutions, governmental agencies, and other public and private research institutions are also involved. Overall, cancer vaccine programs are pursuing the majority of cancer tumor types with skin melanoma seemingly the most dominant target (~30% of programs).

Antigenic's Oncophage is a "personalized" patient-specific vaccine, combining heat shock protein (HSP) with purified tumor antigens. Once injected, the vaccine stimulates the body's defenses against cancer by increasing the response of the immune system to eliminate cancer cells.

The company started enrolling patients in the first clinical trial for Oncophage at Memorial Sloan-Kettering Cancer Center in New York, November 1997. Three years later, a Phase III international trial for non-metastatic renal cell carcinoma was initiated in 2000. In 2006, the company announced that Oncophage failed a late-stage trial in renal cell carcinoma patients at high risk of recurrence after surgery. However, after reanalysis of the data, Antigenics found that a subset of patients (stages I/II high-grade, III T1/2/3a low-grade) had better-prognosis and a decreased risk of disease recurrence.

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Antigenics has acknowledged that although subgroup analysis may support future clinical trial design, it will not support approval in the US. Further clinical studies must be conducted so delaying commercialization for several years, if at all. Antigenic plans to meet the FDA to enable a BLA based on the sub-set analysis coupled with commitments to conduct further clinical investigations. The company is also preparing to file for conditional authorization in Europe (H2 2008) for Oncophage as an adjuvant treatment for kidney cancer patients. Conditional authorization would allow for commercialization of Oncophage with post approval commitments that include annual regulatory evaluation until those commitments are fulfilled. Even with product approval obtained in Russia, the company still requires export clearance from the FDA before patient administration of Oncophage can begin.

Although Oncophage is highly patient- and tumor-specific, in commercial terms its main draw-back is a time-consuming (9 hrs per patient) and expensive production process. Indeed, a minimum of five to seven grams of tumor tissue is required to yield a sufficient amount of Oncophage for clinical use. Overall, it is estimated that the clinical development of Oncophage has taken approximately 12 years with a cost of around $400-450m.

Aside from logistical difficulties in producing Oncophage, the whole concept of developing a cancer vaccine still remains fraught with challenges both scientific and regulatory. **VacZine Analytics** estimates that a cancer vaccine may take as long as 7 years, and up to 12 years from certain indications, to move from Phase I trials to regulatory submission. This compares with around 5 years or less for a traditional vaccine approach for infectious diseases such as influenza. Additionally, both the FDA and European Medicines Agency have relatively little experience in reviewing patient-specific oncology therapies, which may lead to protracted approval process following submission.

While Antigenics has gained the first global approval for a cancer vaccine, US-based Dendreon appears likely to launch the first cancer vaccine in 2009 in the US market. Dendreon's Provenge has experienced a controversial and drawn-out route to potential approval for the treatment of prostate cancer. The company started Phase III recruitment in 1999, with a second study commencing in 2003. In 2005, the company announced that Provenge significantly improved survival in advanced prostate cancer (3). However, in 2007, the FDA delayed approval despite agreeing it was safe and effective. Provenge is now being further evaluated in an ongoing Phase III trial and the FDA will accept a positive interim or final analysis result, expected in the second half of 2009. **VacZine Analytics** believes Dendreon's challenge with Provenge is more appropriate case study than Oncophage. It shows that while the efficacy of new cancer vaccine is alluring, Western regulators are still hesitant to grant their approval.

References:

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3) Press release: Dendreon Announces Provenge Significantly Improves Survival In Men With Advanced Prostate Cancer, February 17, 2005. Available at: http://investor.dendreon.com/ReleaseDetail.cfm?ReleaseID=156146. Accessed April 2008.

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About VacZine Analytics:
VacZine Analytics is a new strategic research agency based in the United Kingdom. Its aim is to provide disease and commercial analysis for the vaccine industry and help build the case for developing new vaccines.