Scientific Abstract

BN ImmunoTherapeutics (BNIT) is developing poxviral based therapeutic vaccination strategies for cancer therapy. In this application, BNIT is proposing clinical evaluation of an attenuated pox viral vector which encodes two separate prostate tissue antigens for treatment of recurrent and androgen refractory prostate cancer. It is anticipated that induction of immune responses to these prostate proteins will help delay progression of disease.

BNIT is using MVA-BN®, a well-characterized clonal strain of modified vaccinia virus Ankara (MVA) as a vector. MVA-BN is being developed by Bavarian Nordic A/S as a safe third generation smallpox vaccine. MVA was derived by attenuation of vaccinia Ankara by culture in chicken embryo fibroblasts and has deleted 15 Kb from its genome and the virus no longer replicates in human cells. MVA-BN® is a clonally derived isolate which has been safe and immunogenic in rodent and primate models. MVA-BN® has also been administered safely to approximately 1500 individuals in nine clinical studies, including over 200 HIV+ patients. MVA-BN®-derived vectors encoding heterologous antigens are being developed for use as vaccines for infectious diseases such as HIV, measles, and RSV. In addition, BNIT is also developing a breast cancer therapy based on the same MVA-BN® vector. MVA-BN®-HER2 contains the extracellular domain of the growth factor receptor Her2, is targeted for the Her2 positive subset of breast cancer patients. MVA-BN®-HER2 has recently completed NIH OBA RAC review (BB-IND 13211; OBA Protocol 0701-824 submitted by Dr A. Guardino), and is currently in clinical trials.

The MVA-BN®-PRO comprises the highly attenuated non-replicating vaccinia virus, MVA-BN®, engineered to encode prostate specific antigen (PSA) and prostatic acid phosphatase (PAP). It is anticipated that upon treatment, cells that take-up MVA-BN®-PRO in situ will produce PSA and PAP. Because MVA-BN® is a non-replicative and non-integrating virus; the production of human antigens will be transient only. However, when combined with the highly immunogenic properties of viral infection with MVA-BN®, it is expected to result in the induction of a robust and comprehensive immune response capable of eliminating PSA and/or PAP-positive prostate cells.

The clinical trial BNIT-PR-001 is an open-label, multi-center, Phase I dose finding trial in 18 men with androgen-insensitive prostate cancer. At time of enrollment, patients will have PSA recurrence after failing treatment with androgen deprivation therapy. The trial will consist of treatment with subcutaneous injections of MVA-BN®-PRO, at various doses (3 dose levels 1, 2, or 4 $x10^8$ $TCID_{50}$) at monthly intervals for three vaccinations. If well tolerated patients are eligible for retreatment with a further series of three vaccinations at same dose level. This is then followed by a 1-year observational follow-up phase. The primary objective of the trial is to evaluate the safety and tolerability of repeat administration regimens of MVA-BN®-PRO for the treatment of androgen-insensitive prostate cancer. The secondary objective is to evaluate the ability of MVA-BN®-PRO to generate humoral and cellular immune responses to prostate antigens. Additionally, an exploratory objective will be to evaluate the anti-tumor activity of MVA-BN®-PRO.

Clinical trials of a previous pox viral strategy have shown promise in prostate cancer. A prime boost strategy using vaccinia-PSA followed by fowlpox-PSA has shown relative safety as well as survival prolongation in a Phase II trial. In addition, a PAP antigen based, autologous antigen presenting cell strategy has been evaluated in a Phase III trial, also showing relative safety as well as prolongation of survival. The BNIT strategy is to combine both antigens in the MVA-BN® vector to enhance the immunogenic effect and to help override self and tumor tolerance mechanisms as well as mitigate development of tumor resistance.