A Cancer Research UK Phase Ib trial to determine the safety, tolerability and immunogenicity of extended schedule vaccination with MVA-EBNA1/LMP2 in patients with Epstein Barr Virus positive nasopharyngeal carcinoma

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Background: Nasopharyngeal Carcinoma occurs worldwide but at high incidence throughout South East Asia, particularly among Chinese people. According to the Hong Kong Cancer Registry 2009 data NPC is the 6th most common cancer in men, with a median onset age of 53 years. In the United Kingdom (UK) it is a much rarer malignancy and only about 1 cancer out of every 1,250 cases diagnosed is an NPC. Although the incidence of NPC is relatively low in England and Wales, pockets of higher incidence are observed amongst those with a South Asian background. Immigrants from the Indian sub-continent, have a risk of death from cancer of the pharynx that is five times that of British natives.
NPC most often occurs within the lateral nasopharyngeal recess and may be well-differentiated, moderately-differentiated or undifferentiated. The undifferentiated form is the most common, and is the most strongly associated with Epstein Barr Virus positive (EBV+) infection.
Radiation therapy (RT) is the mainstay of treatment and is an essential component of curative-intent treatment of non-disseminated NPC. Stage I disease (tumour *in situ*) is treated by RT alone, while more advanced disease is treated by RT with concurrent chemotherapy. With disease free survival after 2 and 5 years being only 63% and 53% respectively and reported response rates to chemotherapy for metastatic or relapsed disease vary between 20-80% and progression within 8 months is typical. Distant metastases accounted for over 40% of failure events demonstrating a clear need for improved systemic adjuvant treatment for NPC. New salvage treatment modalities are needed; MVA-EBNA1/LMP2 vaccine may help fill this gap.

EBV and cancer
EBV is a ubiquitous human herpes virus carried as a persistent infection in most adult humans. EBV can exhibit various patterns of gene expression including entering complete replicative (or cell lytic) cycle in permissive environments yielding infectious virions..
EBV is present as a latent infection in approximately 200,000 new cases of cancer worldwide each year (Parkin 2006). NPC represents the largest burden of EBV+ disease in world health terms and is also the tumour in greatest need of new approaches to augment current therapies.
A study published in December 2011 estimated that out of a total of around 1,200 EBV+ cancers diagnosed that year in the UK a third were NPC. Nearly all cases of NPC (about 80,000) are EBV+ and the incidence in the Cantonese population of South East Asia is particularly high. The immunogenicity of EBV along with the prevalence of this infection in numerous disease states has made vaccination and immunotherapy against antigens expressed by this virus an attractive therapeutic target.

EBV immunotherapy
The successful use of adoptively transferred EBV-specific mixed helper and killer T cell populations to treat and prevent EBV+ cancer offers an important proof of principle for cancer immunotherapy against EBV+ targets. MVA-EBNA1/LMP2 vaccine is an immunotherapy based on recombinant Modified Vaccina Ankara (MVA) virus that has been constructed to express two antigens associated with EBV. It is anticipated that successful vaccination with MVA-EBNA1/LMP2 vaccine will provide patients with low volume EBV+ cancers an additional form of therapy for use in the adjuvant setting and as a second line therapy for patients with persistent disease or recurrence following maximum cytoreduction during first line chemotherapy and chemo-radiotherapy

Trial Design
This is a multi-centre, open-label, Phase Ib trial of the MVA-EBNA1/LMP2 vaccine in patients with NPC.

Treatment group and trial timelines
Approximately 18 patients with histologically confirmed EBV+ NPC will be recruited. It is expected that the trial will have a recruitment period of 24 months with an estimated total study duration of 48 months. Patients will

participate in the study for approximately 12 months from first vaccination. Survival data will be collected for all patients for up to two years from the final patient's first vaccination.

Administration schedule

Patients will receive up to four MVA-EBNA1/LMP2 vaccine cycles at a single fixed dose level of 5×108 plaque forming units (pfu). The first three vaccine cycles will be given at 3 weekly intervals, followed by a fourth cycle 12 weeks (±4 weeks) following the start of Cycle 3. MVA-EBNA/LMP2 vaccine will be administered by intra-dermal injection. To be eligible to receive the fourth vaccination patients must continue to meet all of the study eligibility criteria including blood parameters.

Trial Aim

The purpose of the proposed study is to further demonstrate the immunogenicity of MVA-EBNA1/LMP2 vaccination at the 5×108 pfu 3-weekly vaccination schedule and to extend the spectrum of vaccinated patients with NPC in the adjuvant setting and for those with low volume disease appropriate to the UK setting over and above the existing Phase I clinical trial data. Finally, the study aims to investigate the immune memory established by vaccination and establish if a vaccine boost after the initial three cycles might significantly amplify the duration of the immune response.

Inclusion and Exclusion Criteria

*Main Inclusion Criteria	*Main Exclusion Criteria
• Histologically confirmed nasopharyngeal carcinoma (NPC) in which the presence of EBV has been confirmed in the tumour by immunohistochemistry for viral antigens or EBV early RNA (EBER) fluorescent in situ hybridisation (FISH). • Patients in remission or with current disease for whom no standard therapy is currently appropriate or required. • Patients who have received primary treatment for their malignancy (radiotherapy ± chemotherapy) and up to one additional second-line course of therapy. • Life expectancy of at least 6 months. • World Health Organisation (WHO) performance status of 0 or 1 • Haematological and biochemical indices within the ranges shown below. These measurements must be performed within one week before the patient receives the first MVAEBNA1/LMP2 vaccination. Haemoglobin (Hb) ≥ 10.0 g/dL, lymphocyte count ≥ 0.5 x 10^9/L, absolute neutrophil count ≥ 1.0 x 10^9/L, platelet count ≥ 75 x 10^9/L, serum bilirubin ≤1.5 x upper limit of normal (ULN), alkaline phosphatase (ALP) and alanine aminotransferase (ALT) or aspartate • 18 years or over • Written (signed and dated) informed consent and be capable of cooperating with treatment and follow-up	• Radiotherapy, chemotherapy, endocrine therapy, immunotherapy or investigational medicinal products within 6 weeks prior to trial entry. • Patients who, in the opinion of the investigator and multidisciplinary team managing the patient, may require another oncological treatment within 14 weeks of the first vaccination. • Current active autoimmune disease requiring therapy • Current active eczema requiring therapy. • Allergy to eggs or egg products. • History of anaphylaxis or severe allergy to previous vaccinations or medications. • Previous splenectomy or splenic radiation, or with known splenic dysfunction. • Receiving current immunosuppressive medication including systemic use of corticosteroids. Prophylactic use of inhaled steroids is permitted. • Major thoracic or abdominal surgery from which the patient has not yet recovered. • At high medical risk because of non-malignant systemic disease including active uncontrolled infection. • Known to be serologically positive for hepatitis B, hepatitis C or human immunodeficiency virus (HIV). • Concurrent congestive heart failure, prior history of class III/ IV cardiac disease (New York Heart Association [NYHA]), prior history of cardiac ischaemia or prior history of cardiac arrhythmia. • Any other condition which in the Investigator's opinion would not make the patient a good candidate for the clinical trial. • Is a participant or plans to participate in another interventional clinical trial, whilst taking part in this Phase Ib study of MVAEBNA1/LMP2. Participation in an observational trial would be acceptable.

***N.B** Please note that this is **NOT** a full list of inclusion/ exclusion criteria. The full criteria can be found in the protocol.