

Scope of the contract

3.1

Erasmus MC is planning to conduct a dose-escalation Phase I/II clinical trial to evaluate neoantigen peptide-based cancer vaccines for the treatment of pancreatic ductal adenocarcinoma (PDAC). The primary objective will be to assess the maximum tolerated dose (MTD) and the associated safety profile, while secondary objectives will include the assessment of immunogenicity and radiographic response rates.

The study will comprise three dosage cohorts. Depending on observed toxicities, a minimum of three and a maximum of six patients will be included per cohort. The defined MTD cohort will be expanded with an additional six patients in whom a combination therapy will be evaluated. Due to the nature of this design, the total number of patients included in the trial will range from 6 to 24. For this trial, we require clinical-grade peptides that can be used as API to formulate the personalized investigational drug products in our institute.

3.2

PDAC remains one of the most formidable malignancies, characterised by a poor prognosis and limited therapeutic options. With an annually increasing incidence rate of 1.3%, PDAC is projected to become the second-leading cause of cancer-related death by 2030. Despite significant advancements in cancer therapies over the past decade, the overall survival (OS) rate for pancreatic cancer patients remains dismally low, with a 5-year OS of approximately 12%. Hence, developing more effective treatment options for PDAC is of critical importance.

Current treatment options for PDAC are limited and often ineffective in significantly improving long-term survival. The primary treatment approach for patients with resectable or borderline resectable PDAC is surgical resection, which is typically followed by adjuvant chemotherapy. For advanced or metastatic cases, systemic chemotherapy regimens such as FOLFIRINOX or gemcitabine with nab-paclitaxel remain the standard of care. However, these treatments are associated with significant toxicity and only marginal survival benefits. Emerging modalities, including targeted therapies and combination approaches, have yet to demonstrate substantial efficacy in PDAC.

Immunotherapy, which has transformed the treatment landscape for several cancers, has historically shown limited efficacy in PDAC. This is attributed to PDAC's highly immunosuppressive tumour microenvironment characteristic, which hinders immune system activation. Recent studies have highlighted the unique challenges in targeting PDAC with immune checkpoint inhibitors, such as PD-1/PD-L1 or CTLA-4 inhibitors, due to low tumour mutational burden and T-cell exclusion. However, advances in neoantigen-based immunotherapy offer a new avenue to overcome these barriers, holding potential where conventional immunotherapy has failed.

Neoantigens are mutated self-proteins which arise from genomic mutations during tumour cell development. The genomic mutations are often unique and, therefore, specific for each patient. They can even differ between tumour cells present in the same tumour. This, in turn, creates a unique, fingerprint-like, neoantigen landscape for each tumour. Their origin ensures that neoantigens are solely expressed in tumour cells and

are completely absent in healthy cells. This trait renders neoantigens a very promising candidate for immunotherapy, as targeting these would not target healthy cells, preventing the risk of off-target effects of the therapy.

Our Personalised Neoantigen Cancer Vaccine

We are developing a patient-tailored, personalised cancer vaccine which utilises neoantigens identified from the patient's tumour. The neoantigens are identified using advanced bioinformatic tools and verified for high immunogenicity. From the identified neoantigens, both short-sized (9-11 Amino Acids (AA)) and long-sized peptide (13-25 AA) sequences are designed and used as therapeutics. Hereby, this vaccine aims to elicit a robust and highly specific immune response, activating tumour-specific T cells to combat malignancy effectively.

The trial will encompass 6 to 24 patients, with each patient receiving treatment with up to 24 neoantigen peptides. The peptide sequences will range from 20 to 40 amino acids in length. In cases of a lower Tumour Mutational Burden (TMB), it is possible that fewer than 24 suitable neoantigens are identified for a given patient.

Consequently, a total of 6 to 576 neoantigen peptides will need to be manufactured for this trial. Each patient's peptides need to be produced individually and then pooled into a maximum of 4 pools, each containing up to 6 peptides. These pools must be sterile filtered and lyophilized (freeze-dried), and together constitute the Drug Substance (API) of the vaccine product.

For additional acceptance criteria on the API, please refer to the PvE/PvW documentation.

Turn-Around Times (TAT) are crucial for our product since they relate to personalised medicine, which must be administered to patients promptly to maximise the likelihood of a positive clinical response.

By preference, the API manufacturer additionally has the abilities/facilities to prepare the final Drug Product (DP, concerns sterile fill finish of the API in 2R glass vials) as our intent is to outsource these activities also.

We expect to include the patients in the trial in 24 months.