Dear Mr. Banat,

In the following we would like to send you detailed information on a personalized anti-cancer vaccine. Individualized tumor neoantigen-targeting peptide vaccination is a promising approach tested in clinical trials. It serves as an additional treatment to conventional anti-tumor therapy and may be continued as a long-term therapy option.

The ultimate aim is to train and activate the immune system to recognize and destroy tumor cells.
Mutation-derived novel protein sequences (neoantigens) are presented on the surface of tumor cells via HLA molecules. The immune system has the ability to recognize these neoantigens as foreign structures and, as a consequence, specific immune cells (cytotoxic T cells) are activated to kill tumor cells.

Every single patient shows individual tumor-specific (somatic) mutations. Some of these mutations lead to novel protein sequences which are potentially immunogenic (neoantigens). To identify such tumorspecific mutations, exome analyses of DNA from tumor and blood (normal control) are performed using next-generation sequencing. At this stage you have already received a report of somatic tumor variants from us summarizing the therapeutically relevant mutations identified in your tumor.

Additionally, bioinformatic prediction algorithms are subsequently being used to identify those mutated peptides which are most probably presented on the cell surface of your tumor and have the potential to elicit an immune response. Standardized selection criteria are applied to select the most promising neoantigen-harboring peptides. You have already received the report with the selection of 19 peptides (neoantigens). All of those peptides will be included in your personalized peptide vaccine, depending on solubility. As solubility of peptides cannot be reliably predicted before synthesis, it cannot be guaranteed that all ordered peptides can be dissolved and included in the final vaccine. Peptides which have been proven problematic will be reported upon at vaccine release. Upon your agreement, the peptides will be chemically synthesized and formulated into an injectable vaccine. The whole process will take about 10 to 12 weeks, including quality control and release of the vaccine.

Peptide vaccines by themselves are in general weakly immunogenic. Hence, your personalized peptide vaccine is applied in combination with an adjuvant – typically a recombinant GM-CSF such as the FDA approved *Leukine*® – to increase stimulation of your immune system and will be injected subcutaneously. Repeated intradermal vaccinations will be performed in my practice regularly according to a fixed treatment plan. The plan includes a priming phase (4 vaccinations within 10 to 12 days) followed by another 23 vaccination sessions.

To the best of our knowledge and according to our experience, the treatment is well-tolerated. However, our personalized peptide vaccine must still be considered as an experimental therapeutic approach and hence its efficacy cannot be guaranteed.

In order to investigate the immunogenicity and potential beneficial effect of the vaccine, optional testing is possible (see below). Blood samples will be taken at your vaccination appointments - no extra visits are required. Please let us know during your first vaccination appointment in Germany if you opt for additional analysis.

- **Immune Monitoring**

  We investigate whether the vaccine peptides have activated and expanded neoantigen-specific immune cells (T cells).

  For this analysis, blood is collected at the first vaccination appointment and every 3 to 4 months thereafter. Immune cells (T cells and antigen presenting cells) are isolated and incubated with your personalized peptides. T cells specifically activated by a peptide will be identified by intracellular cytokine staining and FACS analysis. You will receive a report highlighting the vaccine peptides,

that induced a significant immune (T cell) response. This information can in turn be used to control the immunogenicity of the vaccination regime and to further adjust the treatment plan.

Taken together:
For the manufacture of a personalized tumor neoantigen-specific peptide vaccine the following steps have already been performed:

- Whole exome sequencing of tumor tissue and a normal sample (blood)
- Whole transcriptome sequencing of tumor tissue
- Identification of tumor-specific nonsynonymous mutations
  i.e. mutations that may lead to altered protein sequences
- Genotyping of HLA molecules
- Prediction of tumor-specific peptides which are most probably presented on the tumor cell surface by the patient-specific HLA molecules using novel bioinformatic algorithms
- Prediction which of these peptides can be synthesized and dissolved in an injectable solution
- Selection and recommendation of peptides which are predicted to elicit the most powerful immune response against the tumor, including compilation of report

Based on above described analyses, we offer the manufacturing of a personalized tumor neoantigen-specific peptide vaccine at a total price of:

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This offer includes:

- **Synthesis** of the desired number of tumor specific peptides

- **Preparation and quality control** of the injectable multi-peptide vaccine,
  i.e. 2 vaccine lots sufficient for about two years of treatment

- **27 vaccinations and adjuvant applications** in our practice,
  i.e. 4 injections (priming phase) followed by another 23 vaccination sessions

Optional additional analysis:

- **Immune Monitoring:**
  Measuring peptide-specific T cell responses including reporting:

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  Please note: The first immune monitoring analysis will require 2 time points to compare the immune response before and after vaccination.