## V. Synopsis

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| Sponsor | University Hospital Tuebingen |
| Title | iVAC-XS15-CLL01: Personalized multi-peptide vaccination in combination with the TLR1/2 ligand XS15 in CLL patients undergoing ibrutinib-based regimes. |
| Short Title and<br><br>Internal Study Code | iVAC-XS15-CLL01 |
| EudraCT-Number<br><br>ID number study Register | 2020-002367-65<br><br>iVAC-XS15-CLL01 |
| Clinical Trials | XXX |
| Coordinating Investigator | PD Dr. med. Juliane Walz |
| Study Design: | Phase I open label interventional clinical trial |
| Number of Patients | 20 |
| Patient Population | Chronic lymphocytic leukemia (CLL) under ibrutinib treatment |
| Length of Study/ Time Lines | Total trial duration: 3 years<br>Duration for individual patient: Study treatment: 4 month<br>Follow-up: 6 month<br>Number of visits: 6<br>FSI (First Subject In): 09/2020<br>LSI (Last Subject In): 05/2022<br>LSO (Last Subject Out): 09/2023<br>DBL (Data Base Lock): 11/2023<br>Statistical Analyses Completed: 01/2024<br>Trial Report Completed: 04/2024 |

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| Aim of the Study | The aim of this study is to evaluate the efficiency along with safety and toxicity of a personalizied multi-peptide vaccine in combination with the TLR1/2 ligand XS15 in CLL patients undergoing ibrutinib-based regimes. |

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| Objectives | Primary objective:<br>• To assess immunogenicity in terms of induction of peptide specific T-cell responses<br>• To assess safety and toxicity of the peptide vaccine in combination with the TLR1/2 ligand XS15 and Montanide ISA 51 VG in CLL patients undergoing ibrutinib-based regimes<br><br>Secondary objective:<br>• To assess efficacy of peptide vaccine in combination with XS15<br>• To evaluate progression free survival<br>• To evaluate qualitiy of life during study treatment<br>• To assess lymphocyte subsets during vaccination<br>• To characterize the T-cell response after vaccination<br>Exploratory objective:<br>• To evaluate overall survival, disease free survival and remission status<br>• To correlate inducability of immune responses with clinical, biological and mass spectrometry-based patient characteristics |

Inclusion Criteria

- Documented diagnosis of CLL according to IWCLL guidelines.

**For screening phase:**

- CLL that warrants treatment (according to modified criteria for initiation of therapy[1]):
    - Massive (i. e., lower edge of spleen ≥6 cm below the left costal margin), progressive, or symptomatic splenomegaly, or
    - Massive (i. e., ≥10 cm in the longest diameter), progressive, or symptomatic lymphadenopathy, or
    - Progressive lymphocytosis in the absence of infection, with an increase in blood ALC ≥50% over a 2-month period or lymphocyte doubling time of <6 months (as long as initial ALC was ≥30,000/L), or
    - Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy, or
    - Constitutional symptoms, defined as any one or more of the following disease-related symptoms or signs occurring in the absence of evidence of infection:
        - Unintentional weight loss of ≥ 10% within the previous 6 months, or
        - Significant fatigue (≥Grade 2), or
        - Fevers > 38.0°C for ≥2 weeks, or
        - Night sweats for > 1 month.
- Planned initiation of a ibrutinib-based regime (monotherapy or combination therapy (e.g. with anti-CD20 antibody))

**For vaccination phase:**

- Ongoing ibrutinib therapy.
- Achievement of a response (at least PR according to iWCLL guidelines[1]) under current treatment.
- MRD (minimal residual disease) positivity (CLL cells in peripheral blood ≥ $10^{-4,}$ determined by flow cytometry, Labor Kiel, Prof. Brüggemann).
- Negative SARS-CoV-2 test (as long as WHO declares pandemic spread of SARS-CoV-2)
- Ibrutinib treatment of at least 6 months and not longer than 8 months.
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- HLA typing positive for any of the following HLA alleles: HLA-A*02, A*24, B*07.
- Ability to understand and voluntarily sign an informed consent form.
- Ability to adhere to the study visit schedule and other protocol requirements
- Age ≥ 18 years at the time of signing the informed consent form.
- Eastern Cooperative Oncology Group (ECOG) performance status score of ≤ 2.
- Negative serological Hepatitis B test or negative PCR in case of positive serological test without evidence of an active infection, negative testing of Hepatitis C RNA, negative HIV test within 6 weeks prior to study inclusion.
- Female patients of childbearing potential (FCBP) and male volunteers with partners of child bearing potential, who are sexually active must agree to the use of two effective forms (at least one highly effective method) of contraception. This should be started from the signing of the informed consent and continue throughout period of study
- Postmenopausal or evidence of non-childbearing status. For FCBP: negative urine or serum pregnancy test within 14 days prior to study treatment. Postmenopausal or evidence of non-childbearing status is defined as:
    - Amenorrhoeic for 1 year or more following cessation of exogenous hormonal treatments
    - Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post menopausal range for women under 50

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| Exclusion Criteria | • Pregnant or lactating females.<br>• Treatment regimes without ibrutinib<br>• Ibrutinib-related side effect > CTC grade 2 (CTCAE V5.0 (Appendix 14.1))<br>• Participation in any clinical study or having taken any investigational therapy, which would interfere with the studys primary and secondary end points within 2 weeks prior to screening.<br>• Prior history of malignancies, other than CLL, unless the subject has been free of the disease for ≥ 5 years. Exceptions include the following:<br>  ○ Basal cell carcinoma of the skin<br>  ○ Carcinoma in situ of the cervix<br>  ○ Carcinoma in situ of the breast<br>  ○ Incidental histological finding of prostate cancer (TNM stage of T1a or T1b)<br>• Disease transformation (active) (i.e., Richter's syndrome, prolymphocytic leukemia).<br>• Autoimmune hemolysis or immune thrombocytopenia caused by CLLAny immunosuppressive treatment not related to CLL except corticosteroids.<br>• Pre-existing auto-immune disease except for Hashimoto thyroiditis and mild (not requiring immunosuppressive treatment) psoriasis<br>• Chronic lung disease requiring drug treatment |

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| Statistics, Safety Variables and Stopping Rules | As usual in early phase 1 and 2 studies, statistical planning is designed as such that a statistically reasoned decision for or against a subsequent phase 3 study can be made. The sample size of the study was chosen based on the assumption that, in the case of peptide specific immune response induction in ≤ 30% of the patients, the therapy concept is extended with a probability of at most 5% (type one error, one-sided). On the other hand, in the case of peptide specific immune response induction in ≥ 60% of the patients, the therapy concept should be followed with a probability of at least 80% (power).<br><br>With a sample size of n = 20 patients, this means that at least 10 patients must have an immune response, so that the therapy concept is evaluated in a randomized phase 3 study. The exact power is 87%, the exact type 1 error is 4.8% (calculations based on the binomial distribution with n = 20, p = 0.3 or p = 0.6, k <10 or k ≥ 10).<br><br>The safety and toxicity of the personalized multi-peptide vaccine in combination with the TLR1/2 ligand XS15 in CLL patients undergoing ibrutinib treatment will be determined based on the Common Terminology Criteria for Adverse Events (CTCAE V 5.0 (Appendix 14.1)) and assessed in a descriptive manner. |

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| Study Intervention/ Study Medication<br><br>Description of the Medical Product/Medical Device | Peptide vaccine: Multi-peptide vaccine cocktails consisting of 300µg each of 3 HLA class I and 3 HLA class II-restricted CLL-associated peptides and 2 HLA class II-restricted control peptides. The HLA class I-restricted peptides for each patient will be selected individually based on the patient-individual HLA allotypes and HLA ligandome analysis of CLL cells from a premanufactured warehouse consisting of 9 different HLA class I peptides restricted to 3 of the most common HLA class I allotypes (A*02, A*24, B*07). The 5 HLA class II peptides will be administered to each patient. Peptides are synthesized in the GMP-certified Wirkstoffpeptidlabor at the University of Tübingen (Prof. Stefan Stevanovic) and will be formulated at the GMP-Center of the University Hospital Tübingen. These warehouse peptides comprise the most frequently detected CLL-associated antigens identified in our previous experimental and clinical studies.<br><br>Peptides will be administered subcutaneously (s.c.) together with the novel TLR1/2 ligand XS15 emulsified in Montanide ISA 51 VG as adjuvant.<br><br>Vaccination will take place every 4 weeks. A total of three vaccinations are planned.<br><br>Treatment schedule:<br><br>Peptide vaccination will take place in CLL patients that achieved at least a partial remission with detectable MRD after at least 6 and less than 9 months of an ibrutinib-based treatment regime. MRD will be determined by flow cytometry. MRD positivity is defined as > $10^{-4}$ CLL cells in peripheral blood or bone marrow. Patients will receive either ibrutinib monotherapy or combinational therapy before study treatment. Vaccination will be done under ibrutinib monotherapy (i.e. after the end of e.g. anti-CD20 treatment, if applicable). |

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| Participating Centers | Clinical Collaboration Unit Translational Immunology, Department of Internal Medicine, University Hospital Tübingen<br>Robert-Bosch-Krankenhaus, Stuttgart |
| GCP-compliance | This study will be conducted according to GCP and ICH guidelines |
| Financing | This study is financed by an AKF grant and Cluster of Excellence iFIT (EXC2180) of the University Tuebingen |