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Protocol of a prospective, multicentre phase I study to evaluate the safety, tolerability and preliminary efficacy of the bispecific PSMAxCD3 antibody CC-1 in patients with castration-resistant prostate carcinoma

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ABSTRACT

Introduction Prostate cancer is the second most common cancer in men worldwide. When the disease becomes resistant to androgen-deprivation therapy, treatment options are sparse. To address the high medical need in castration-resistant prostate cancer (CRPC), we generated a novel PSMAxCD3 bispecific antibody termed CC-1. CC-1 binds to prostate-specific membrane antigen that is expressed on prostate cancer cells and tumour vessels, thereby allowing a dual anticancer effect.

Methods and analysis This first in human clinical study is a prospective and multicentre trial which enrols patients with metastatic CRPC after failure of established third-line therapy. CC-1 is applied after prophylactic interleukin-6 receptor blockade with tocilizumab (once 8 mg/kg body weight). Each patient receives at least one cycle of CC-1 over a time course of 7 days in an inpatient setting. If clinical benefit is observed, up to five additional cycles of CC-1 can be applied. The study is divided in two parts: (1) a dose escalation phase with intraindividual dose increase from 28 µg to the target dose of 1156 µg based on a modified fast titration design by Simon *et al* to determine safety, tolerability and the maximum tolerated dose (MTD) as primary endpoints and (2) a dose expansion phase with additional 14 patients on the MTD level of part (1) to identify first signs of efficacy. Secondary endpoints compromise overall safety, tumour response, survival and a translational research programme with, among others, the analysis of CC-1 half-life, the induced immune response, as well as the molecular profiling in liquid biopsies.

Ethics and dissemination The PSMAxCD3 study was approved by the Ethics Committee of The University Hospital Tübingen (100/2019AMG1) and the Paul-Ehrlich-Institut (3684/02). Clinical trial results will be published in peer-reviewed journals.

Trial registration numbers ClinicalTrials.gov Registry (NCT04104607) and ClinicalTrials.eu Registry (EudraCT2019-000238-20).

Strengths and limitations of this study

- This first in human (FIH) study not only evaluates the clinical safety and maximum tolerated dose of a novel PSMAxCD3 antibody (CC-1) in prostate cancer, but will also unravel first signs of efficacy in a dose expansion cohort.
- The ethical dilemma for patients treated at early time points during dose escalation in FIH studies is addressed by rapid intrapatient dose escalation.
- The novel IgG-based format of CC-1 not only prolongs serum half-life but also reduces off-target T cell activation which, together with pre-emptive interleukin-6 receptor blockade using tocilizumab, results in fewer side effects and in turn allows for application of truly effective bispecific antibody doses.
- Close monitoring by Data Safety Monitoring Board to protect patients' interests and study safety.
- Development and first clinical application of the drug is exclusively financed by public resources.

INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide, with estimated 1 100 000 cases and 307 000 deaths in 2012.[1 2] Androgen-deprivation therapy is standard of care first-line therapy of advanced prostate cancer. However, frequently prostate carcinoma develops resistance to first-line therapy. Notably, most drugs established for treatment of these castration-resistant prostate carcinomas (CRPCs) (eg, abiraterone acetate, enzalutamide) still act on the androgen axis. Applied prior to or after treatment with chemotherapeutic agents (eg, docetaxel, cabazitaxel), these therapies slow down disease progression and improve survival to a moderate extent. Abiraterone resulted in a median overall survival (OS) benefit of 4.6 months post-docetaxel and of 4.4 months in

chemotherapy-naive patients.[3 4] Enzalutamide resulted in a median OS benefit of 4.8 months post-chemotherapy.[5] The chemotherapeutic agents docetaxel and cabazitaxel resulted in a median OS benefit of 2.4 months.[6 7] In case of progression/relapse, for example, abiraterone can be used after enzalutamid or after docetaxel and vice versa. Importantly, the best sequence of treatments has not been finally established, and any drug employed after the third line of treatment is associated with only limited clinical benefit.

Novel strategies have to be developed to address the medical need of this patient population. Of particular interest in this context are strategies to target the prostate-specific membrane antigen (PSMA), which is expressed, at least to some extent, in almost all patients (up to 98%) with a highly tumour-restricted expression pattern. Targeted radiotherapy approaches using for example, Lutetium-177-PSMA[8] showed efficacy and a tolerable toxicity profile on treatment of patients with metastatic disease. However, the duration of achieved responses is limited, and many patients do not at all benefit from this treatment option. Meanwhile, immunotherapy has become a mainstay of oncological treatment. Available strategies comprise immune checkpoint blocking antibodies (eg, nivolumab, pembrolizumab) that are approved for treatment of various solid tumours including non-small cell lung cancer, melanoma and renal cell carcinoma.[9–11] However, these checkpoint inhibitors have shown only limited efficacy in prostate cancer.[12] Other successful antibody-based strategies that mobilise T cells against cancer comprise bispecific antibodies (bsAbs) and chimeric antigen receptor T (CART) cells. The first stimulate the T cell receptor/CD3-complex with their effector part after binding their target antigen on tumour cells. The latter are functionally closely related to the bsAb, as CART cells can be considered as genetically modified T cells with an integrated bsAb (CD3 signalling unit anchored in the T cell).[13] The most advanced reagent in the class of bsAbs is the CD19xCD3 bsAb blinatumomab (Amgen) approved for treatment of acute lymphoblastic leukaemia in the bispecific single-chain (BiTE) format.[14 15] Like bsAb, CART cells are mainly established for treatment of lymphoid malignancies,[16] and so far both, bsAbs and CART cells, are less effective if applied against solid tumours compared with haematological malignancies.[17] In our view, a major problem is the lacking accessibility of solid tumours for the effector cells, be it for CART cells or bsAb-stimulated T cells.[18 19] Sustained therapeutic success of both, bsAb and CART cells are further limited by the severe side effects, in particular the potentially lethal cytokine-release syndrome (CRS) as most important group toxicity. At present, if CRS occurs, it is treated with interleukin-6 receptor (IL-6R) blockade using tocilizumab.[20]

We have developed an optimised bsAb with PSMAxCD3 specificity (CC-1) that, on application after pre-emptive IL-6R blockade holds promise to overcome the above described limitations. Of note, targeting PSMA with bsAbs not only holds promise to potentially induce more pronounced 'immediate effects' compared with PSMA-targeted radiotherapy, but may also stimulate immunological memory and thus mediate long-term efficacy.[21] In our first in human (FIH) study reported here, we evaluate CC-1 in patients with metastatic CRPC to determine overall safety and tolerability, as well as the maximum tolerated dose (MTD) and first signs of efficacy.

METHODS AND ANALYSIS

Properties of the bsAb CC-1

The bispecific PSMAxCD3 antibody CC-1 is an optimised IgG-like molecule (IgGsc format) with substantially improved serum half-life, especially when compared with the prototypical BiTE bsAb format. Specific modifications introduced in this proprietary format (disclosed patent application WO 2017/121905)[22] further reduce aggregation tendency and thus unspecific 'off-target' T cell activation and immunogenicity. Its target is, in prostate carcinoma, expressed on both, tumour cells and tumour vessels. Vascular expression is expected to facilitate access of immune effector cells to the tumour site. Notably, CC-1 binds a unique PSMA epitope which allows for such dual targeting not only in prostate carcinoma, but also in squamous cell carcinoma of the lung (data provided in the patent application).

Study design

This multicentre, open-label, FIH phase I dose escalation and dose expansion study is designed to gain evidence of the MTD of CC-1 on prophylactic IL6-R blockade. Moreover, with the dose expansion part we aim to achieve first evidence of efficacy with the MTD of CC-1 in adult patients with CRPC after third-line therapy for a subsequent phase II study. The study is entitled 'First in human study to evaluate the safety, tolerability and preliminary efficacy of the bispecific PSMAxCD3 antibody CC-1 in patients with castration-resistant prostate carcinoma' (short title: 'DKTK_PMO_1605') and will be conducted within the framework of the German Cancer Consortium (DKTK).

Study approach

This FIH study consists of two parts (figure 1): (1) a dose escalation part (patients n=10–72) comprising a dose escalation with prophylactic IL-6R blockade (8 mg/kg (body weight) tocilizumab) with intraindividual patient dose escalation (figure 2A–D) on CC-1-induced dose-limiting toxicity followed thereafter by a standard 3+3 dose escalation design without intra-individual dose escalation (figure 3). In case of no observed dose-limiting toxicity, the maximal dose is achieved after intrapatient and interpatient dose escalation after four patients (figure 2A–D). The dose escalation part is followed by (2) a dose expansion part with an additional cohort (n=14) receiving the defined MTD-level after pre-emptive tocilizumab application to refine/confirm the recommended phase II dose and to receive first signs of clinical efficacy (figure 2D).

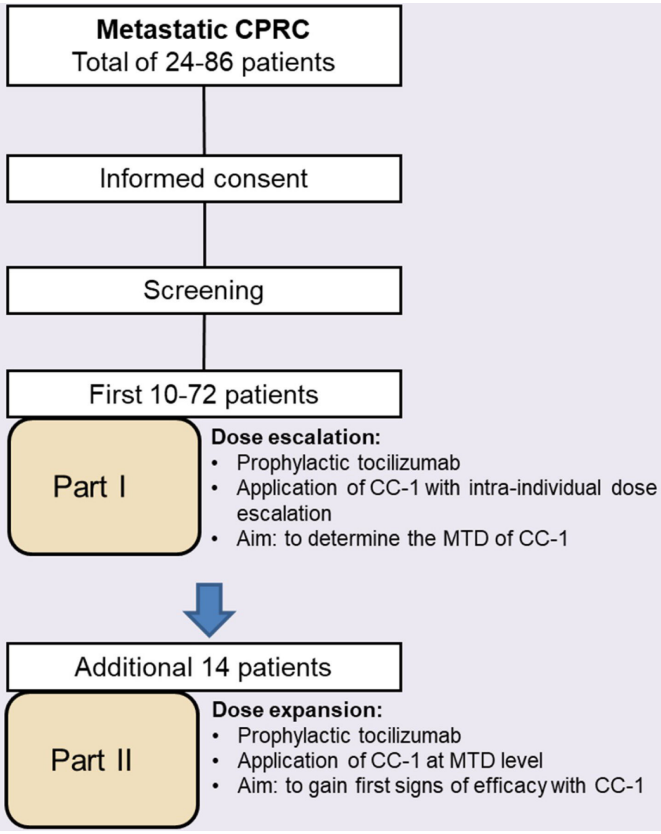

Figure 1 Study overview. CC-1, bispecific PSMAxCD3 antibody; CRPC, castration-resistant prostate carcinoma; MTD, maximum tolerated dose.

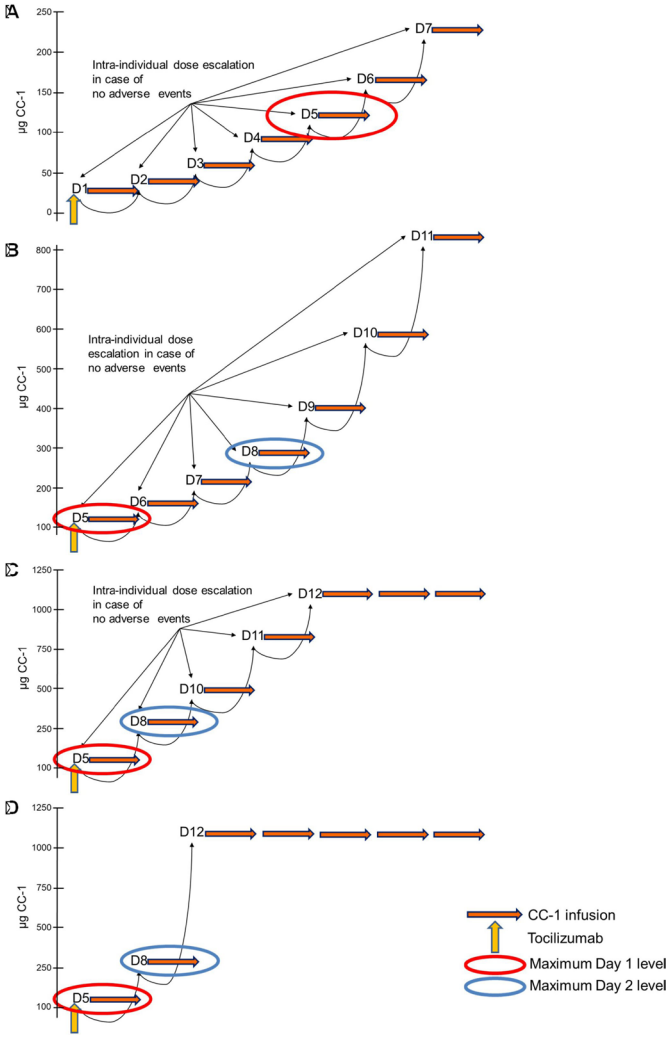

Figure 2 Dosing in different parts of CC-1 study. Part I: intraindividual dose escalation: tocilizumab (8 mg/kg body weight) is applied once as pretreatment >1 hour prior to the start of CC-1 infusion on day 1 of each cycle. CC-1 is administered as a 24-hour continuous intravenous infusion with escalated doses of CC-1. We perform a daily, intraindividual dose escalation to the next higher dose level. Dose escalations are depicted in the first patient (A), second (B), third (C). (D) Fourth to tenth patient of part I and part II: dose expansion at maximum tolerated dose (MTD): after pre-emptive interleukin-6 receptor blockade CC-1 is administered as a 24-hour continuous intravenous infusion started at the MTD dose level. The dose levels applied on day 1 and day 2 must not exceed 110 µg (maximum day 1 level) and 300 µg (maximum day 2 level), respectively. CC-1, bispecific PSMAxCD3 antibody.

Justification of starting and target dose

Definition of the starting dose (28 µg corresponding to 0.14 nmol) was based on preclinical data obtained with CC-1 and considerations taking into account available results of clinical studies with similar constructs. In vitro, CC-1 induced relevant T cell activation at concentrations of approximately 10 ng/mL. These data are provided in the investigators' brochure of the study and contained in a manuscript reporting the preclinical characterisation of CC-1 (Zekri *et al*, submitted). On application of the BiTE antibody blinatumomab, a 40 µg dose reportedly leads to serum concentrations in humans of approximately 1 ng/mL corresponding to 0.02 nm[23] which results in increased cytokine levels.[24] Due to the difference in molar weight between blinatumomab and CC-1, the molar dose of CC-1 is about four times lower than that of blinatumomab and thus four times lower molar serum concentrations will be achieved for CC-1 at identical 'mass dosing'. Considering the results of our preclinical analyses, this ensures a sufficient safety margin, in particular when treatment is started with 28 µg, that is, one dose level below 40 µg.

The target dose was determined based on in vivo dose titration studies in immunodeficient mice bearing large established tumours after adoptive transfer of human peripheral blood mononuclear cell. Based on dose titration experiments, it was concluded that application of approximately 1.2 mg via continuous infusion per day in humans would result in serum levels in the range of approximately 25–250 ng/mL, which in mice was sufficient to eliminate established tumours. It is envisaged that dose levels within this range will be sufficient to achieve significant antitumour activity in humans; taking into consideration the step-dosing approach described below, 1156 µg was chosen as maximum tested dose for the planned clinical study.

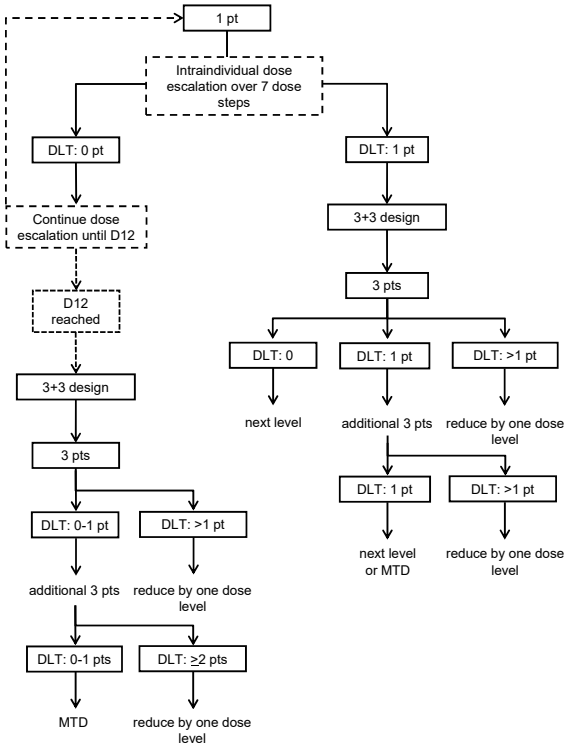

Figure 3 Flow chart of phase I design. In part of the phase I this is a dose escalation. Rather than the classical 3+3 design our escalation is intraindividual based in case no dose-limiting toxicity (DLT) occurs until maximum tolerated dose (MTD) is reached. If a DLT is reported, we will switch back to 3+3 design. D, dose level; pt, patient.

Inclusion criteria

Patients must meet the following criteria prior to treatment in the CC-1 study:

- Existence of a written informed consent.
- Patient is able to understand and comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations.
- CRPC after third-line therapy. Patients must be progressive prior to study enrolment, documented by either rising tumour marker or radiological assessment. Prior to study enrolment patients should have received chemotherapy and abiraterone or enzalutamide.
- Life expectance of >3 months.
- At least one measurable lesion that can be accurately assessed at baseline by CT or MRI and is suitable for repeated assessment.
- Eastern Cooperative Oncology Group Performance Status ≤2.
- Patient aged ≥18, no upper age limit.
- Male patients with partners of childbearing potential, who are sexually active, must agree to the use of two highly effective forms of contraception. This should be started from the signing of the informed consent and continue throughout period of taking study treatment for 3 months after last dose of study drug.
- Adequate bone marrow, renal and hepatic function defined by laboratory tests within 14 days prior to study treatment.

Exclusion criteria

Patients meeting any of the following criteria will not be considered for admission to the CC-1 study:

- Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer.
- Concurrent or previous treatment within 30 days in another interventional clinical trial with an investigational anticancer therapy.
- Persistent toxicity (≥2 grade according to Common Terminology Criteria for Adverse Events (CTCAE) V.5.0) caused by previous cancer therapy, excluding alopecia and neurotoxicity (≤2 grade).
- Clinical signs of active infection (>2 grade according to CTCAE V.5.0).
- History of HIV infection.
- Immunocompromised patients.
- Active or chronic viral hepatitis (hepatitis B or hepatitis C virus).
- History of autoimmune disease.
- History of relevant central nervous systems (CNS) pathology or current relevant CNS pathology (eg, seizure, paresis, aphasia, cerebrovascular ischaemia/haemorrhage, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis, coordination or movement disorder).
- Epilepsy requiring pharmacological treatment.
- Therapeutic anticoagulation therapy.
- Major surgery within 4 weeks of starting study treatment. Patients must have recovered from any effects of major surgery.
- Patients receiving any systemic chemotherapy or radiotherapy within 2 weeks prior to study treatment or a longer period depending on the defined characteristics of the agents used.
- Heart failure New York Heart Association III/IV.
- Severe obstructive or restrictive ventilation disorder.
- Known history of gastrointestinal perforation.
- Pre-existing human antihuman antibodies (HAHA).
- Known intolerance to CC-1, tocilizumab or other immunoglobulin drug products as well as hypersensitivity to any of the excipients present in the respective drug products (CC-1, tocilizumab).

Treatment/study distribution

As mentioned before, the study will be divided in two parts with similarly structured treatment cycles. Each cycle consists of 21 days, comprising 7 days (d1–7) of

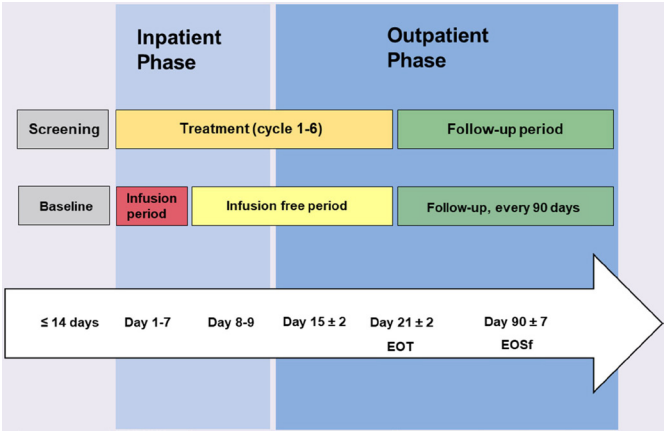

Figure 4 Study schedule. Screening: ≤14 days. Assessment of baseline values for imaging and quality of life; infusion period: days 1–7 (hospitalised as inpatient); on day 1 baseline assessment for prostate-specific antigen, cytokines and liquid biopsy, vital signs, concomitant medication, signs and symptoms of disease; infusion free period: days 8–9 no infusion, but still hospitalised as inpatient (discharge on day 9); day 9/10–21 (±2) outpatient; visit at day 15 (±2) and 21 (±2) (end of treatment/EOT); follow-up period: outpatient, visit at day 90 (±7) (end of safety follow-up, EOSf); after EOSf follow-up every 90 days (up to one 1 year, ongoing adverse events have to be followed to resolution).

CC-1 application as continuous infusion, followed by a treatment free period with appended close monitoring for safety (inpatient and outpatient monitoring). The duration of the trial for each patient is expected to be at least 3 months including the first treatment cycle of 21 days (end of treatment) and a follow-up visit on day 90 (end of safety follow-up (EOSf)). Thereafter, a continuous survival follow-up every 3 months is conducted for 1 year after EOSf (figure 4). In case of clinical benefit, additional CC-1 cycles may be applied. The estimated duration of the clinical phase is 30 months.

Dose escalation part

Tocilizumab (8 mg/kg body weight) is applied once as pretreatment >1 hour prior to the start of CC-1 infusion on day 1 of each cycle. CC-1 is administered as a 24-hour continuous intravenous infusion with escalated doses of CC-1 (absolute doses 28–1157 µg, table 1). To rapidly achieve effective CC-1 doses, we perform a daily, intraindividual dose escalation to the next higher dose level (figure 2A).

If no dose-limiting toxicity (DLT) is observed, the achieved dose (on day 7) minus one dose level is the day 1 starting dose of the next patient. In general, the dose levels applied on day 1 and day 2 must not exceed 110 µg (D5) and 300 µg (D8), respectively (table 1). Those dose levels were implemented as safety steps with the calculated (higher) dose level to be shifted to day 2 or day 3 accordingly (compare figure 2B).

For example, if the first patient accomplishes D7, the next patient receives on day 1 110 µg (D5) and continues with further dose escalation; if this patient reaches D11 without DLT, the next patient receives on day 1 and day 2 110 µg (D5) and 300 µg (D8), respectively before continuing with D10 and further escalation.

In case of observed DLT, the last tested dose according to schedule without observed DLT is applied to the next patient in a standard 3+3 dose-escalating design without intraindividual dose escalation until MTD is defined.

After completion of the cycle of the previous patient and prior to dosing of the next patient (until maximum dose level D12=1157 µg), approval by the Data Safety Monitoring Board (DSMB) is obtained. In case no DLT is observed, at least six patients are treated at the highest dose level before proceeding to the expansion cohort (figure 3).

Dose expansion part

After pre-emptive IL-6R blockade CC-1 is administered as a 24-hour continuous intravenous infusion started at the MTD dose level identified in the dose escalation part of the study. The dose levels applied on day 1 and day 2 must not exceed 110 µg and 300 µg, respectively, which are implemented as safety steps with the MTD dose level shifted to day 2 or day 3 accordingly (figure 2B). This may result in application of MTD dose level for 5 (or 6) days in each cycle.

Additional CC-1 treatment cycles

We implemented the option for additional CC-1 treatment cycles in order that patients at an early stage of clinical development, in addition to receiving intraindividual dose escalation, may achieve maximum personal benefit. If patients are considered to benefit from study treatment (indicated for example, by a prostate-specific antigen (PSA) drop of 20% from baseline on day 15 to enable early decision making with regard to potential benefits in light of the required hospitalisation to avoid undue burden for the patient), additional cycles of CC-1 may be applied to the same patient with the exact same dose schedule as in the previous cycle. Each patient may receive up to six cycles in total.

Endpoints of the study

The primary endpoints of the study are incidence and severity of adverse events (AEs) (CTCAE V.5.0) over 21

Table 1 Dose levels (D) from starting dose to maximum tested dose

Level	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12
Factor	–	√2	√2	√2	√2	√2	√2	√2	√2	√2	√2	√2
CC-1 dose (µg)	28	40	56	78	110	153	215	300	422	590	826	1157

days (ie, until end of first treatment cycle). Moreover, we report on DLT as important parameter to define MTD for the dose expansion part of the study. As part of a translational research programme, among others, the analysis of CC-1 half-life, the induced immune response as well as the molecular profiling in liquid biopsies, comprise the secondary endpoints and are:

- Safety (general): incidence and severity of AEs (CTCAE V.5.0).
- Immunogenicity: number and percentage of subjects who develop HAHA as compared with baseline.
- Cytokine induction: cytokine levels in serum.
- Pharmacokinetics: CC-1 serum concentrations.
- Antitumour activity: absolute changes from baseline in the tumour-marker (PSA) and objective tumour response assessed by response evaluation criteria in solid tumours (RECIST) on routine imaging.
- Survival: overall and progression free survival (absence of radiologically confirmed progression or death by any cause) evaluated by Kaplan-Meier method.
- Quality of life: overall quality of life scores (European Organization for Research and Treatment of Cancer core quality of life questionnaire).

Safety/DLT

Toxicity will be graded according to the National Cancer Institute CTCAE, V.5.0 and the CRS grading system by Lee *et al*.[25] All AEs and serious AEs will be documented and reported accordingly to good clinical practice guidelines. Furthermore, we will report on adverse events of special interest (AESIs), which include occurrence of allergic reaction, development of HAHA and CRS. These AESIs will be monitored closely and included in patient safety narrative reports to the DSMB.

DLT is defined as any grade ≥3 AE that the investigator considers to be at least possibly related to study treatment and occurring within the DLT safety period (from day 1 to 21) with few exceptions. In addition, since tocilizumab is given pre-emptively, the safety profile of tocilizumab is also considered. Remarkably, AEs occurring in the context of CRS are only considered as DLT, if the CRS grading is ≥3 according to Lee *et al*.[25]

Data Safety Monitoring Board

In the dose escalation part of the study, the DSMB receives patient safety narrative reports routinely after each patient in which dose has been escalated (assessment on day 21). After completion of the cycle of the previous patient, approval by the DSMB must be obtained prior to dosing of the next patient (until maximum dose level is reached). At maximum dose level of CC-1, the DSMB will receive a report routinely after the first three and second three (this is prior to start of the expansion part) treated patients. In addition, safety narrative reports are created on occurrence of DLT.

Sample size calculation

Depending on the occurrence of DLT in the dose escalation part, the patient number to define the MTD varies. A minimum number of 24 patients are treated, but potentially up to 86 patients may be included into the trial. Based on the broad range of dose levels to be tested (absolute doses of 28–1157 µg) and the employed intraindividual dose escalation (figure 2A), sample size may vary considerably dependent on CC-1-induced AEs. The dose escalation calculation is rule based on the titration design by Simon *et al*.[26] Once the maximum tested dose is reached, additional six patients are treated to define MTD (figure 3). Thus, the sample size varies in the dose escalation part of the study between n=10 patients required for definition of the MTD in the minimal and n=72 patients in the maximum case. Subsequently, a dose expansion part with 14 patients is foreseen to gain more information about the MTD level and to better define the recommended phase II dose of CC-1. Based on the planning, in total 20 patients will be treated at the MTD level, 6 patients from the dose escalation phase and 14 patients of the expansion cohort. Thus, we will be able to estimate within a single-stage phase II design an objective response defined as PSA drop ≥50% estimating P0 the maximum response proportion of a poor drug of ≤30% of the patients, and P1 the minimum response proportion of a good drug of ≥60% with a power of 80% and a type one error of 5%. To this aim we will need n=17 evaluable patients assuming a drop-out rate of 15% (n=3).

Estimation of sample size:

Minimum: (4 escalation+6 highest dose)+14 expansion-cohort=24 patients

Maximum: 12×6 escalation-cohort+14 expansion-cohort=86 patients

Patient and public involvement

CC-1 production (in accordance to good manufacturing practice) and trial conduct are exclusively funded by public resources without contribution of pharmaceutical industry or commercial organisations. Prior to approval of funding, proposals were peer reviewed in a competitive manner by the Helmholtz Validation Fund and the Joint Funding Program of the German Cancer Consortium.

Design of the clinical trial was done without support by patient representatives, but extensive efforts were undertaken to inform patients about the beginning of study recruitment.

Data handling and storage

All findings including clinical, radiological and laboratory data will be documented by the investigator or an authorised member of the study team in the electronic case report form. Investigators guarantee the privacy of patients and personal data are treated according to the European general data protection regulation (EU 2016/679) and the German law. The data will be stored for 25 years. All data entry, modification or deletion, will be recorded automatically in an electronic trail.

Monitoring of data will be conducted on a regular basis and prior to each safety report for DSMB.

ETHICS AND DISSEMINATION

The study will be performed in accordance with the Declaration of Helsinki and will comply to the International Conference on Harmonization and Good Clinical Practice. All possible treatments and examinations for CRPC are undertaken after obtaining written informed consent from (see online supplemental file) the patients by the treating physician. This trial is funded by research grants from the Helmholtz Validation Fund and the Joint Funding Program of the DKTK. The CC-1 study was approved by the Ethics Committee of the University and University Hospital Tübingen (100/2019AMG1) and the federal institute for biomedicine and vaccine, the Paul-Ehrlich-Institute, Germany (3684/02). During trial conduct, the responsible authorities will be informed on a regular basis about the progress of the trial. The results of this clinical trial results will be presented at relevant national and international meetings and published in peer-reviewed journals regardless of outcome. All planned publications will be reviewed by the principal investigator and the biostatistician prior to publication to avoid violation of patients' rights.

DISCUSSION

As of now, metastatic CRPC is an often rapidly progressive disease without curative treatment options. To address this high medical need, we here introduce a FIH study evaluating safety and efficacy of the bispecific PSMAxCD3 antibody CC-1 in patients with CRPC after failure of third-line therapy.

CC-1 is developed in a novel IgG-like format termed IgGsc to overcome several problems of so far available bsAb constructs: drawbacks in particular of bsAbs in the BiTE format are their low serum half-life (approximately 1 hour)[27] and aggregation tendency,[28] which necessitates cumbersome application protocols and results in off-target activation of T cells, respectively. Besides blinatumomab, this also holds true for the BiTE PSMAxCD3 bsAb developed by Amgen that presently is undergoing evaluation in phase I studies.[29] The IgGsc format of CC-1 not only allows for a longer serum half-life, but also has a lower aggregation tendency compared with the prototypical BiTe format, with accordingly reduced off-target T cell activation and thus fewer side effects[27 30 31] (Zekri *et al*, submitted). In addition, to achieve our superordinate goal, the safe application of sufficiently high bsAb doses which in turn shall facilitate better clinical efficacy, we will employ pre-emptive IL-6R blockade to prevent rather than to treat CRS. The prophylactic application of tocilizumab should abolish the clinical effects of CRS without impairing T cell antitumour reactivity.[32 33]

An additional advantage of CC-1 is that its target antigen PSMA is expressed on prostate carcinoma cells as well as on the tumour vessels of CRPC. Thereby, a dual mode of anticancer action is enabled: targeting the tumour vessels should allow for improved influx of T cells into the tumour via the damaged endothelial barrier followed by effective combating of the tumour cells themselves. Thereby we hope to overcome a critical factor that so far limits the success not only of bsAbs, but of T cell-based treatment of solid tumours in general.[18 19]

Taking into account the lack of effective treatment options and the dismal prognosis in the study patient population, the expected benefits of a CC-1 treatment with pre-emptive tocilizumab application in this clinical study outweigh the potential risks for the patients, especially since multiple risk mitigation measures have been implemented. The progress and safety data will be monitored by three independent experts (DSMB) and they will give approval/recommendations to the coordinating investigator/the sponsor whether to stop the trial or to change the trial protocol. In addition, the implemented intraindividual escalation of the applied CC-1 dose constitutes an additional hallmark for patients in this trial. Usually, early clinical trials study safety and tolerability of new drugs, with therapeutic benefit for patients accordingly being only of secondary interest. In our view, this constitutes an ethical dilemma, which we tried to resolve by our approach to rapidly increase CC-1 dose levels and thus reach doses levels that were preclinically effective already for the first patients treated. The concomitant prophylactic application of tocilizumab further supports the feasibility of the fast, intra-individual dose escalation and in turn the rapid evaluation of the MTD of CC-1 as first step. In case that no DLT is observed, already the fourth patient will receive the target dose. After six further patients that receive the maximum test dose, the dose escalation part would be completed, which constitutes an important particularity of our trial. The dose escalation phase is then followed by a dose expansion phase (also with prophylactic IL-6R blockade), as this approach has been shown to be efficient and beneficial for patients in early clinical trials.[34] Furthermore, in the expansion phase we plan to implement PSMA-positron emission tomography analysis to obtain reliable information on target antigen expression in patients undergoing analysis for efficacy, as reduction of PSMA expression on malignant cells reportedly occurs in a substantial proportion of patients over time.[35] Of note, even a few hundred molecules per cell suffice to render the malignant cells susceptible to T cell killing on bsAb treatment.

Notably, the development of CC-1 and the conduct of this trial are fully funded by public resources. This corresponds with our conviction that drug development, which nowadays almost exclusively is conducted by the pharmaceutical industry, should at least in part be reclaimed by academia as recently described elsewhere.[36]

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Contributors JSH, JSW, GJ, RFS and HRS designed the study protocol. MP and JK supervised production of CC-1 according to GMP and provided preclinical data to be provided to regulatory authorities. JSH, JSW, HRS and RFS initiated and conducted the clinical study. JSH, HRS and RFS wrote the paper. JSW, GJ, MP and JK contributed to manuscript preparation. All authors read, revised and approved the submitted manuscript.

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Competing interests GJ and HRS are listed as inventors on the patent application 'Novel PSMA binding antibody and uses thereof', EP16151281 and others, with the German Cancer Research Center (DKFZ), Heidelberg, Germany, as applicant. The other authors declare no competing interests.

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PSMAxCD3 DKTK_PMO_1605

Patient information

Lead Study Centre:
University Hospital Tübingen
CCU Translational Immunology

EudraCT-Nr. 2019-000238-20

First in man study to evaluate safety, tolerability and efficacy of the bispecific PSMAxCD3 antibody CC-1 in patients with castration resistant prostate cancer

(PSMAxCD3 in CRPC)

Dear patient,

we would like to ask you, if you are willing to participate in this clinical trial (study).

Clinical trials are necessary in order to gain insights into the efficacy and tolerance of medicinal products or to extend it.
Therefore the legislator stipulates in the German Medicines Act that new drugs must be clinically tested. The clinical trial that we are presenting to you here was evaluated - as the law requires - by an ethic committee and approved by the competent authority (Paul-Ehrlich institute). It will be approved in Tübingen and seven other German study centers. The study is initiated, organized and financed by the Clinical Cooperation Unit Translational Immunology at the DKTK (German Consortium for Translational Cancer Research) at the DKFZ partner site University Hospital Tübingen with the support of the Helmholtz. Sponsor of the study is the University Hospital of Tübingen.
The head of the clinical trial is Professor Dr. med. Helmut Salih (Contact: CCU Translational Immunology, University Hospital Tübingen, Tübingen, Germany)

Your participation in this clinical trial is voluntary. You will be enrolled in this trial if you give your consent in writing. Provided that you do not wish to participate in the clinical trial or later withdraw from it, you will not suffer any disadvantages as a result.

You have already been asked about the planned study. The following text should explain the goals and the process to you. Afterwards an investigator will like to have a clarifying conversation with you. Please do not hesitate to address all points that you do not understand. You will then be given sufficient time to think about your participation.

1. Why is this test performed?

Prostate carcinoma is the second most common male tumor worldwide. In the metastatic situation, an antiandrogenic therapy (hormone deprivation therapy) is used as first-line therapy. In many cases, despite this therapy disease will eventually relapse. In this situation, numerous substances were tested in clinical studies including abiraterone, an inhibitor of androgen biosynthesis, and enzalutamide, an inhibitor of the androgen receptor signaling pathway and chemotherapeutic drugs such as docetaxel or cabazitaxel. After a treatment with the above mentioned therapies currently no further established standard therapies are available.

In the present study, patients are treated after third-line therapy of a prostate carcinoma.

What are antibodies? How does the PSMAxCD3 antibody used work?
Antibodies are proteins of the body's own immune system (defense system of body). Our immune system produces antibodies that bind to certain target structures of for example, bacteria and viruses that invade the body and thereby eliminate the intruder. Modern medicine is now able to develop such substances and produce antibodies for therapeutic and diagnostic purposes. Since these are proteins, they cannot be taken like pills, but have to be administered as injections or infusions. Therapeutic antibodies have been available for many years and are very successfully used as standard therapy in the fight against diseases, for example for certain forms of cancer and inflammatory diseases such as rheumatism.

The investigational drug to be tested in our study, the PSMAxCD3 antibody CC-1, belongs to a new class of antibodies, the so-called bispecific antibodies. CC-1 is called bispecific because it can be delivered to two different targets simultaneously. On the one hand, it recognises tumor cells and also tumor vessel cells by the surface molecule PSMA. On the other hand, CC-1 binds to T cells, strong defense cells of the body's own immune system, and thereby brings them into the immediate proximity of tumor cells and tumor vessel cells enabling attacking PSMA-carrying cells. In this way CC-1 directs the immune system to the tumor cells and tumor vascular cells and helps to destroy them.

By activating the T cells, messenger substances of the immune system are released, which act similar to an inflammatory reaction and possible side effects can cause. To prevent or at least mitigate this, CC-1 is administered along with another antibody, tocilizumab. This "protective antibody" tocilizumab blocks the effect of a special messenger substance of immune system, which is essential for side effects of an activation of the immune system.

What is tocilizumab?
Tocilizumab (RoActemra®) is a drug that is known as interleukin-6- receptor (IL-6R) blocker and belongs to the monoclonal (=similar) antibodies. Interleukin-6 is a messenger substance of the immune system, which is essential involved in the development of inflammation. IL-6R blockers impede binding of interleukin-6 to its receptors (binding sites) on inflammatory cells in the tissue and in the blood and thus block the inflammation.

In which patients is tocilizumab currently used?
Tocilizumab is currently used for the treatment of rheumatoid arthritis, an autoimmune disease. In addition, the drug may be used for the therapy of cytokine release syndrome which will be discussed later (see also chapter 7).

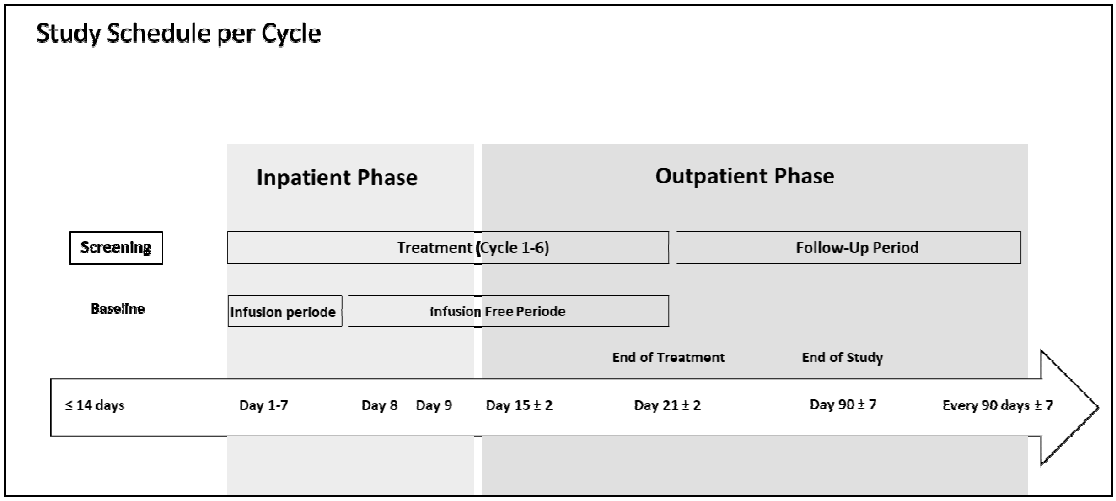
2. Will I receive the investigational product in any case?

Within the scope of this clinical trial, the bispecific antibody CC-1 is used in all patients tested, which means that you will receive the investigational product in any case.

3. Obtained all patients receive the same dose of antibody CC-1?

To determine the tolerability and to investigate the frequency and severity possible side effects of the investigational drug, the antibody CC-1 initially given in increasing doses (dose escalation phase of the study). If in the course of the study it is clear which dose of CC-1 is safe and well tolerated, all other patients receive the same dose of the antibody (dose expansion phase of the study). This is described in detail under point 4.

4. What is the course of the study and what do I have to consider when participating?

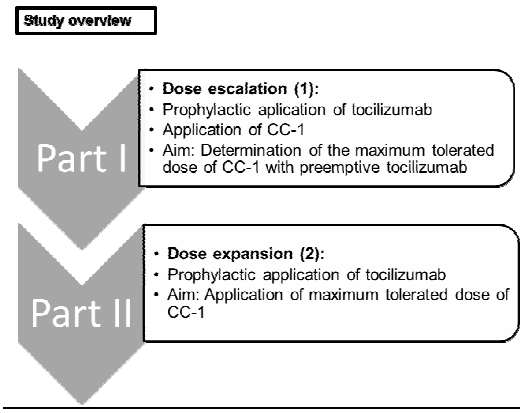


Screening phase:
If you wish to participate in the study and have signed the informed consent form, the screening phase will determine whether you can participate in the clinical trial or not.

During screening a detailed survey is conducted with regard to medical history, complaints, currently taken medication, a physical examination and a blood test including of tuberculosis, hepatitis (inflammation of the liver) B, C and HIV tests (AIDS test).
We would like to point out that according to the " Law on the prevention and control of infectious diseases in humans" (Infektionsschutzgesetz - IfSG § 6 "Meldepflichtige Krankheiten") there is a non-nominal laboratory obligation to report to the Robert Koch Institute, Berlin in the case of an infection with HIV, and in the case of illness with tuberculosis or hepatitis B and C a nominal obligation for the study doctor to report to the public health department.

The possibility of your participation in this clinical trial will depend on the results of these preliminary examinations. As a result, you may not be able to participate, even though you have decided to participate. At in this case we will discuss alternative therapy options with you, in the otherwise you enter the treatment phase.

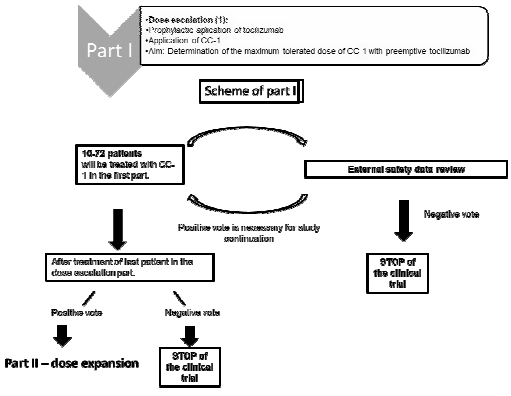
Treatment phase:



The aim of the therapy is to enable attacking of PSMA-carrying tumor cells and tumor vessel by the immune system, especially through so-called T cells. This study is primarily intended to verify the safety and tolerability of the PSMAxCD3 antibody CC-1 in humans. In addition, data on the distribution of CC-1 in the human body (pharmacokinetics) and the effect on the immune system as well as potential parameters for therapy response are collected. In addition, the quality of life under therapy, data on response to therapy and survival are assessed.
Antibody therapy (CC-1 and also the protective antibody tocilizumab) is administered via an arm vein or via a central access as an infusion.
In addition, in order to improve the tolerability of the antibody, you will be administered three concomitant drugs: paracetamol (500 mg, e.g. Benuron®) as an antipyretic, and ranitidine (50 mg, e.g. Ranitic®) and dimetinden (4 mg, e.g. Fenistil®) as drugs to prevent allergic reactions. These concomitant medications are usually also given as an infusion via a venous access. The study is divided into two sections. The allocation to the sections is made in chronological order. The treatment of each patient is adjusted based on the results of the previous treatments. Your doctor will inform you in which section of the study program you will be treated. For the period of administration of the study medication, you will be observed as an inpatient in hospital:

1. Escalation phase (10-72 patients):

You will be given 8 mg/kg body weight of the protective antibody tocilizumab prior to start of the study medication. The CC-1 antibody is then administered as a 24-hour infusion for 7 consecutive days and the dosage is initially increased each day until either side effects occur that prevent further increase or until the planned target dose is reached.
After treatment with the CC- 1 over a maximum of seven days, the therapy is terminated as planned and you will be discharged the following day, if your condition permits. In the following days, you must regularly check your body temperature and document them, for which you will receive a special diary (logbook). If a temperature rise above 38.5°C occurs, you must immediately contact your investigator/trial site. Assessment of body temperature has to be conducted until day 21. Afterwards, further visits to the doctor are necessary for at least one year.
After the planned target dose has been reached or if it is clear which dose is to be used, 6 patients will be equally treated with this dose. Thus, the maximum tolerated dose of CC-1 antibodies defined. If the dose identified as safely tolerated in previous patients is above a specified dose (110µg or 300µg), a so-called step-dosing is carried out for safety reasons: in each patient on the first day 110 µg and on the second day 300 µg CC-1 must not be exceeded.
During the initial phase of the dose increase, after treatment and follow-up of each patient considers all safety-relevant aspects and decided whether the trial could be continued. For this purpose an external data safety monitoring board evaluates side effects.
Your doctor will inform you about the doses of CC-1 with which you will be treated.



2. Expansion phase (14 patients):
After successful completion of the dose escalation phase described above, patients are included in the expansion phase. Here, 8 mg/kg body weight of the protective antibody tocilizumab will be administered prior to start of the study medication. If the determined dose is higher, the following is always performed: in each patient doses must not exceeding 110 µg CC-1 on the first day and 300 µg CC-1 on the second day, respectively, before the actual maximum tolerated dose is administered for five days. In this part of the study, the administration is also carried out as a 24-hour infusion. An external assessment and decision on the continuation or termination of the study will also be made immediately in this phase in case of unexpected side effects.
During the expansion phase, several patients can be treated. After treatment with the CC-1 antibody, you will be discharged on the following day as described above.

Follow-up phase:
After the final visit of the treatment phase, you will be further observed and, if necessary, treated within the framework of normal health care. The further course of your illness is documented during this time. If there are persistent side effects at the time of the end of treatment, we will monitor further developments in this regard.
Within the framework of the study, further visits every three months are planned for one year after the treatment phase (see diagram - timeline). Here again, a physical examination, blood sampling, a survey as well as documentation and observation of side effects are conducted.
If the disease shows a clear progression, an early study completion visit can be carried out at any time and immediately and study treatment can be terminated.
In all study phases, i.e. in the dose escalation phase and the dose expansion phase as well as in the follow-up phase, regular blood samples are taken at each visit to the physician to investigate the behavior of the active substance in the body (pharmacokinetics). Below is a list of the blood samples that are planned for the study.

Study related urine, blood and tissue samples up to day 90:

Sample	**sample quantity**
blood	Within the scope of the study at 13 visits to the doctor approx. 60 ml each
urine	Approx. 30 ml
Tissue sampling	A new tissue removal is not planned, but tumor tissue from a previous collection, if this is available

Thereafter, about 50 ml of blood will be drawn at each subsequent visit to the doctor within the scope of the study. Imaging is routinely scheduled first before starting therapy and three months after starting treatment. During additional cycles, imaging is performed every six to eight weeks.

Quality of life:
As part of the study, we also ask them to fill out questionnaires on quality of life on a regular basis. Each questionnaire usually takes 5-10 minutes. This will probably be 10 times over the planned duration of the study, so that a total of 50-100 minutes will be needed to complete the questionnaire.

It is important to know that if you participate in the trial, you will be taking additional/new medications (including over-the-counter) that the investigator is not aware of - except in emergencies - should only be taken after consultation with your investigator. If you are treated by other physicians, you must inform them of your participation in the trial.
Also, your investigator must be informed of any medical treatment you received by another doctor during the clinical trial. You will receive a study card, which you should always carry with you in case of emergency. Within the framework of the study, it is necessary to have a pass during the follow-up phase in the catchment area, i.e. within a radius of a 60-minute drive, of the treatment center.
This applies to the time until day 21 of the first cycle.

5. What is my personal benefit from participating in the study?

If you participate in the study, your disease may be reduced. However, since the efficacy of the investigational product has not yet been proven, your participation in this trial may also not have the desired effects. The study is primarily designed to test the safety and tolerability of the administered antibody. A comparison of possible benefits and risks is given in detail in chapter 8.

6. Do I have to participate in the study?

No. Participation in this study is completely voluntary. You have sufficient time to decide for or against participation. If you decide not to participate, you will of course still receive the best available treatment for your disease.
You may also withdraw your participation and stop the study at any time during the study without giving reasons. Terminating your participation in the study will not have any adverse consequences for your further treatment. In this case, your doctor will inform you about other suitable treatment options.
If you want to stop the study, you must inform your investigator or study staff. Your investigator will conduct a final examination. This is for your health safety.

7. What are the risks associated with participation in the study?

To date, there is no experience of side effects of the CC-1 antibody in humans; the present study is a first in man application study. The following information is therefore based on theoretical considerations, comparison with similar antibodies and results of laboratory tests.
Like any other drug and like food, PSMAxCD3 antibody CC-1 can cause allergic reactions, with symptoms such as burning, redness, itching and heat. Severe allergic reactions can in extreme cases cause a life-threatening state of shock. To detect such reactions in time, you will be closely monitored.

<u>What are the findings with other bispecific antibodies that are already being used in cancer patients?</u>
The only currently approved bispecific antibody is blinatumomab (Blincyto®) with CD19xCD3 specificity. Blinatumomab is used to treat adults with Philadelphia chromosome negative, relapsed (disease recurrence) or refractory (disease that does not respond to prior therapy) B-precursors of acute lymphocytic leukemia (ALL).
The prognosis of adults with ALL has been improved significantly in recent years. About 80 to 85 percent achieve a complete reduction of leukemia (full remission) under the first chemotherapy. However, the long-term survival rates are only 30 to 50 percent. Blinatumomab extends the survival time of patients with Philadelphia chromosome negative B cell progenitor ALL by more than three months compared to conventional chemotherapy.

<u>What side effects have occurred with Blinatumomab?</u>
In patients receiving blinatumomab, serious infections, including sepsis (blood poisoning and associated inflammatory response throughout the body), pneumonia, opportunistic infections (infections that occur only when the immune system is already severely weakened by another disease) and infections at catheter entry sites have been observed.
Other reported infections include inflammation of the nose, throat and nasal mucosa as well as sinusitis, infections of the upper respiratory tract, herpes virus infections, urinary tract infections, infections with staphylococci (a bacterium that can cause infections in different parts of the body) and conjunctivitis.
Other unexpected side effects without life-threatening character included a temporary increase in liver values, diarrhea, headache, short-term swelling of arms and legs, shortness of breath, constipation, disorders of blood salts, Insomnia, coughing, nausea, fever, shivering and stomach ache.

Other unexpected side effects without life-threatening character included a temporary increase in liver values, diarrhoea, headaches, short-term swelling of arms and legs, shortness of breath, constipation, disorders of blood salts, insomnia, coughing, nausea, fever, shivering and stomach ache. Life-threatening side effects of blinatumomab, in some cases, including fatal ones, have so far mainly been reported in connection with infections, especially in neutropenia or febrile neutropenia (reduced number of defense cells with or without fever), but also for the cytokine-releasing syndrome, the tumor lysis syndrome (rapid destruction of tumor cells, which leads kidney failure), brain dysfunction and pancreatitis.

Cytokine release syndrome - Serious complication:
The most likely side effect of the CC-1 antibody is an excessive activation of the immune system, which manifests itself in the form of a so-called cytokine release syndrome associated with fever and chills. The occurrence of this syndrome depends, among other things, on the amount of antibody administered and the amount of tumor tissue in the body.
The more tumor is found in the body and the higher the dose of CC-1 administered, the more likely the occurrence of a cytokine-release syndrome. In extreme cases, this reaction can be life-threatening (e.g. by impairing respiration, circulation and the central nervous system).
Based on the experience with other immune therapies, the administration of tocilizumab can be used to treat and possibly prevent the cytokine release syndrome. But the administration of concomitant drugs like tocilizumab are in turn themselves associated with potential risks. These concomitant drugs and their specific risks are, in contrast to those of CC-1, already well known and are described in detail below.

Risk of side effects:
The above mentioned possible side effects of blinatumomab could theoretically also occur when CC-1 is administered. However, other potentially life-threatening side effects not mentioned here cannot be ruled out, given the novelty of the treatment method.
It is therefore not possible to predict with certainty in advance how high the risk of a side effect will be for you. However, during the development and production of the PSMAxCD3 antibody CC-1, various intensive efforts were made to develop a low-risk drug and to improve known weaknesses of currently available therapies. To reduce the risk of possible serious side effects (in particular cytokine release syndrome) of therapy with CC-1, the antibody was built in an altered protein structure. These changes in the protein structure distinguish CC-1 from other antibodies such as blinatumumab. So a very specific effect is aimed to and compared to other bispecific antibodies, side effects are less likely to be expected.
Nevertheless, CC-1 also carries the risk of serious side effects, but these are not yet known as the antibody has not yet been tested in a human trial. On a theoretical comparison of the benefits and risks of CC-1 treatment based on these considerations is presented separately in Chapter 8.

Therapy monitoring and control during treatment with CC-1
Your doctors and the nursing team will monitor you closely during your participation in the study and, based on your state of health, will decide on possible preventive measures to avoid side effects or react early to side effects by using medication or other measures if necessary. In this context it may also be necessary to interrupt and/or reduce the dose or, if unavoidable to stop therapy.

Risks of measures required in the study (independent of CC-1)
Necessary measures such as inserting a venous catheter or taking blood samples can cause discomfort such as redness or pain or lead to a thrombosis (blockage of blood vessels by a blood clot). There is also a risk of infection at the injection site, inside the catheter or at its tip. There is also a risk of bleeding when puncturing tissues or vessels. Further risks are known to exist, especially when a central venous catheter is installed: Haematoma formation (bruising after vascular damage), malfunctions and in very rare cases thrombosis (blockage of blood vessels by a blood clot), thrombophlebitis (thrombosis with inflammation of the vessel wall), infection, injury to nerves and tendons, etc. Very rarely, it can lead to impairment of respiratory function up to respiratory arrest in response to a puncture if necessary, an anaesthetic used to relieve pain at the puncture site, so monitoring by the doctor, so that immediate countermeasures can be initiated if necessary. Extremely rarely, injuries to neighbouring organs (e.g. lungs) can occur.

Side effects of the accompanying medication

Adverse effects can occur during any treatment, including therapy with the accompanying drugs paracetamol, ranitidine, dimetinden and tocilizumab.

Most of the side effects mentioned in the package insert are rare, often only mild to moderate and easy to treat. Rarely serious side effects may lead to a permanent discontinuation of the therapy.

Side effects of concomitant drugs paracetamol[1], Ranitic[2], Fenistil[3] have been described:

- Very frequent (more than 10%): fatigue³
- Frequent (between 1 % and 10 %): drowsiness³, nervousness³
- Occasionally (between 0.1% and 1%): headache², fatigue², dizziness², abdominal pain², diarrhoea², constipation², nausea², temporary and reversible changes in liver function values², rash²
- Rare (between 0.01% and 0.1%): increase in liver values (liver transaminases¹), hypersensitivity reactions² (e.g. proliferation of red blood cells² (eosinophilia²), hives² (urticaria²), fever², drop in blood pressure², swelling of the skin²
(angioedema²), difficulty swallowing², cramping of the airway muscles² (bronchospasm²), chest pain², blurred vision² (reversible), vision, in which an altered adaptability of the refractive power (accommodation) seems to be the cause², acute inflammation of the skin² (erythema multiforme²), itching², joint pain² (arthralgia²), muscle pain² (myalgia²), increase in a renal breakdown product in blood² (plasma creatinine²), generally low; normalizes during treatment), agitation³, headache³, dizziness³, gastrointestinal complaints³, nausea³, dry mouth³, dry throat³, acute pancreatitis³ (pancreatitis²), inflammation of the liver² (hepatitis²) with or without jaundice (generally reversible)
- Very rare (< 1/10,000): changes in the blood count such as reduction of white blood cells (thrombocytopenia¹,², leukocytopenia²), very strong reduction of white blood cells¹,² (agranulocytosis¹,²), deficiency in all three cell lines of blood formation² (pancytopenia²), sometimes with bone marrow blockage (bone marrow hypoplasia/ -aplasia), bronchospasm¹ in persons with predisposition (analgesic-asthma), hypersensitivity reactions¹ (e.g. skin redness to urticaria¹, swelling of the skin (Quincke's edema¹, facial edema³, rash³), Swelling of the larynx³ (pharyngeal edema³), muscle cramps³, shortness of breath³, severe allergic reaction¹,² (anaphylactic shock¹,²), severe skin reactions¹ (e.g. drug-induced
Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, Acute Generalized Pustular Exanthema), agitation², reversible confusion², hallucinations², depression (predominantly in critically ill, elderly and renal patients), severe headache², reversible involuntary Movement disorders², tachycardia², slowed heartbeat² (bradycardia², AV block², asystole², vasculitis², increased hair loss², nephritis² (acute interstitial nephritis²), reversible impotence², chest pain²,
Changes in the breast² (e.g. gynecomastia, galactorrhea), reduced sexual desire² (loss of libido²)
- Not known (frequency cannot be estimated on the basis of available data): Respiratory distress² (dyspnoea²), pneumonia² (pneumonia²)

Side effects of the IL-6R blocker tocilizumab:

Since tocilizumab is a foreign protein for the body, allergic reactions can occur during or shortly after the therapy, which can rarely be severe and require medical treatment. These include allergic skin reactions, shortness of breath and circulatory reactions, up to a severe and possibly life-threatening severity.

However, during the infusion, a blood pressure-rise may occur. Since IL-6 contributes to the body's defence against infections, treatment with tocilizumab or subsequent infections may mainly affect the respiratory tract. Sometimes severe infections are also possible. You should therefore inform your doctor immediately of any signs of infection such as coughing, fever, malaise, poorly healing wounds, burning sensation when urinating, abdominal pain and diarrhoea, even in cases of doubt.

Your doctor must then decide whether further measures such as antibiotic treatment are required. Other possible side effects include an increase in liver values and acute damage to the liver, reduction of white blood cells and platelets and an increase in the blood lipid levels. For this reason regular laboratory checks are necessary. While having a serious infections with fever you must not receive tocilizumab. This also applies to newly occurring abdominal complaints, because under IL-6R blockade a slightly increased risk for intestinal inflammation (diverticulitis). A vaccination with live vaccines should not take place during

therapy. In the view of influence of tocilizumab on the immune system, theoretically an increased risk for the development of another tumor or an accelerated progression of the existing tumor can be assumed. However, in studies with many patients treated with tocilizumab for other diseases, no difference in the incidence of tumors compared to the untreated normal population has been demonstrated. Similarly, there is no firm evidence that existing prostate cancer could grow or spread more rapidly due to tocilizumab. Nevertheless, special attention will be paid to this aspect in the study. If new findings on the risk of tocilizumab arise during the study period, you will be informed accordingly.

Finally, it is important to remember that after the administration of tocilizumab, an infection can be hidden during the laboratory chemical diagnosis and therefore easily overlooked by the doctor. You should therefore inform every doctor that you have this have received medication. If necessary, they show him their patient ID card for this purpose.

Please inform the investigator's staff of any complaints, illnesses or injuries that occur during the course of the trial. If these are serious, please inform the staff of the trial site immediately after they occur, if necessary by telephone. You will find the telephone number on your patient identification card.
Note that any antibody therapy with its concomitant medication may cause fatigue or nausea and vomiting, this may indirectly affect the ability to actively participate in road traffic or to operate machinery.

8. Benefit-risk assessment

In this study, patients with refractory metastatic prostate carcinoma who are at risk from their disease or its progression are treated. In addition, the treatment methods currently available in this situation may have quite severe side effects. For example, if chemotherapy is initiated, there is a risk of changes in blood formation, infection, fatigue and exhaustion. Many patients also find the limited prospects of success of therapy that is still available a burden. Within the scope of this study, a new therapeutic approach is being tested, which aims at a targeted activation of the immune system against the tumor foci of prostate carcinoma. It is known from other diseases (e.g. acute lymphatic leukemia) that an activation of the immune system against the malignant cells improve the course of the disease.
The fact that in the example case of acute lymphatic leukemia, blinatumomab causes severe and potentially life-threatening side effects in some patients, in particular the cytokine release syndrome. This is explained in more detail in section 7. If a cytokine-release syndrome occurs, it is treated in particular by the use of the drug tocilizumab (IL-6R antibody). In our study, in which there is also a risk for the occurrence of a cytokine release syndrome, we will administer the protective antibody tocilizumab to each patient before administration of the antibody CC-1 for safety reasons, with the aim of keeping the risk of occurrence of a cytokine release syndrome as low as possible. As a result, even those patients who are initially enrolled in the study are treated with higher doses that may be more therapeutically. The protective antibody tocilizumab has been used for quite some time to treat diseases from the rheumatological field (rheumatoid arthritis) and is approved for this purpose. For your protection, you will be closely monitored during the inpatient stay. If during your stay despite administration of tocilizumab symptoms of cytokine release syndrome occur, you will be repeatedly treated with tocilizumab and other drugs.
If serious side effects should occur, one (also the safety and tolerability of the drug and the safety and tolerability of the drug independently assessed. Only when this assessment comes to the conclusion that continuation of the study is justified, it will be continued. This is intended to serve this purpose, to keep patient safety as high as possible and ensure that all current results obtained in the study are taken into account.

9. What other treatment options are available outside the study?

Currently, other available therapies are only used with little success in your stage of the disease. This is also a prerequisite for us to offer you the study with the CC-1 antibody.

10. Who may not participate in this clinical trial?

You may not participate in this clinical trial, if you are simultaneously participating in other clinical trials. In addition, you may not participate, if you have participated within the previous 30 days in a clinical trial investigating a targeted intervention or other anti-tumor therapy or if you have a history of gastrointestinal perforation (stomach or intestinal rupture).
If you are participating in this clinical trial, you and your partner reliable measures for contraception, e.g. oral (via the oral contraception ("pill")) plus condom or oral contraceptive plus diaphragm (vaginal pessary) or other medicinal contraception ("pill" as a patch) plus condom or diaphragm can be used. These are to be used up to six months after receipt the last administration of the test substance. You must use a barrier method (e.g. condom) of contraception during the clinical trial and for 6 months afterwards even if a vasectomy (sterilisation) was performed before. You are also not allowed to donate sperm during the trial and for 6 months afterwards. The reason for this is that it has not yet been clarified for the antibody CC-1 whether it can cause damage to the unborn child.

Please contact your investigator immediately, if your partner is pregnant or suspected of being pregnant. If she has become pregnant, your treatment with the PSMAxCD3 antibody CC-1 will be discontinued. Your observation will be continued and, in particular, information about your partner's well-being will be collected. The sponsor will ask your investigator for information about the outcome of the pregnancy.

11. Do I incur costs by participating in the clinical trial? Will I receive an expense allowance?

Your participation in this clinical trial will not result in any additional costs. An expense allowance is not paid, the travel costs are not reimbursed, but there is a commuting accident insurance.

12. Am I insured during the clinical trial?

In clinical trials, all study participants are insured in accordance with the German Drug Law. The scope of the insurance cover is determined by the insurance documents which you will receive.
If you suspect that your health has been damaged or existing conditions have been aggravated by your participation in the clinical trial, you must immediately inform the insurer directly, if necessary with the assistance of your investigator, in order not to activate your insurance cover. If your investigator supports you, you will receive a copy of the report. If you send your notification directly to the insurer please also inform your investigator. You must cooperate in clarifying cause or extent of any damage and do everything possible to avert and mitigate the damage.

During the duration of the clinical trial, you may receive other medical treatment - except in emergencies - only after prior consultation with the investigator. If emergency treatment is given, you must immediately inform the investigator.

13. Will I be informed of new findings during the clinical trial?

You will be informed of any new findings that become known in relation to this clinical trial that may be relevant to your willingness to continue participating. On this basis, you may then reconsider your decision to continue participating in this trial.

14. When am I excluded from the clinical trial?

You may terminate your participation at any time, even without giving reasons, without incurring any disadvantages in your further medical treatment. Further participation in the study is not advisable as the disease progresses, which is why participation ends after appropriate safety investigations.
Under certain circumstances, however, it is also possible that the investigator or sponsor may decide to terminate your participation in the trial prematurely without your influence on the decision. The reasons for this can be, for example:
-Their continued participation in the clinical trial is no longer medically justifiable;
-the entire clinical trial is discontinued
If you decide to withdraw prematurely from the trial or if your participation is terminated prematurely for any other of the above reasons, it is important for your own safety that you undergo a thorough final examination. The investigator will discuss with you how and where your further treatment will take place.

15. What happens to my data?

Your health data will be collected and processed in order to conduct this study. Your personal data includes, among other things, your name, your address, as well as sensitive personal data such as your medical history, findings and genetic data.
We ask you to give your consent before your personal data is used for this study. For the collection, storage, use and transfer of your data, your express consent is required by signing the informed consent form for data protection. Your consent is required to participate in the clinical trial.
We also ask you to give your consent to the use of your data for further research after the completion of this study. Your personal data will be processed and used for the following purposes, as described in the declaration of consent:
- For this clinical study (treatment of prostate carcinoma with a novel bispecific PSMAxCD3 antibodies First in human study to evaluate the safety, tolerability and preliminary efficacy of the bispecific PSMAxCD3 antibody CC-1 in patients with castration resistant prostate carcinoma, abbreviated: DKTK_PMO_1605),
- for further research by the test facility or with research partners of the test facility after completion of this study,
- to comply with the legal and regulatory obligations that apply to clinical trials under the legislation on medicinal products.

Your personal data will only be used as long as it is absolutely necessary. Under the european rules on archiving clinical trial documents this means at least 25 years.
Due to your treatment at the hospital (University Hospital Tübingen), your personal identifying data (e.g. surname, first name, address, date of birth) and illness data are in the electronic hospital systems recorded. In case of participation in this study so-called study pseudonyms and your data relevant to the study are transferred to the study's database.
Only authorized persons receive insight into the original data (e.g. medical records, health authorities, study monitors of the sponsor. The encryption key is only permitted for the following persons: examiner and his deputy and persons authorised by the investigator, sponsor staff (such as study monitors and auditors), regulatory authorities, which review study data and are responsible for the approval of new drugs.
Other institutions with which the clinical trial is jointly conducted, which are partners in other research projects or which conduct joint registry studies generally only receive your health data in pseudonymised shape. They must commit themselves in writing to keep your personal data safe.
Your personal data may be transferred to countries outside the European Union economic area. In some countries there may not be laws that provide the same level of data protection as within the European Union. In this case, the recipients of the data must have agreed on signing a data protection based on the

European level of data protection. Your personal data can be made anonymous. This means that you can no longer be associated with you. The anonymized information may be available for this study or, after completion of this study, for other purposes, including further research. The study results or other research results can only be published without mentioning your name (anonymized) for use in scientific journals or on conferences and/or on the Internet.

You have the right:
- to request information about the processing of your personal information
- to request a copy of your personal information
- to request that your personal data be corrected and/or deleted
- to pass on of the data provided by you in a form that is suitable for reuse to a third party (e.g. your family doctor).
- file a complaint with your local regulatory authority if your privacy rights are violated
- to claim compensation for any damage caused or suffered as a result of the unlawful processing of your personal information

You also have the right to withdraw your consent to participate in the clinical trial at any time. Your decision will not affect the further medical care you receive. If you revoke your consent to participate in the clinical trial, this will have the following consequences:
- You can then no longer participate in the study
- From the time of revocation, no further personal data may be collected about you
- Data that has already been collected up to the time of revocation may, in principle, be used further insofar as this is necessary due to legal requirements, for example to ensure that your interests worthy of protection are not impaired, the obligation to submit complete or to determine the effects of the medicinal product to be tested (see Section 40 (2a), No. 3, lit. a-c AMG).
- Data that has already been disclosed or published for research purposes cannot be withdrawn

If you withdraw your participation in the clinical trial, we will also immediately examine to what extent the data stored about you may still be required for the above-mentioned legally prescribed purposes. If these are not or no longer necessary, your personal data will be deleted immediately.
If you revoke your consent to the use of your personal information for further research, data already used for research purposes may be disclosed or published, shall not be withdrawn.
The head of the clinical trial and the respective investigators of the individual centers are responsible for data processing and compliance with the data protection regulations. If you have any complaints, you can contact the data protection officer of the University Hospital Tübingen, the data protection officer of your treating center or the respective responsible state data protection officer. You will find the contact information at the end of this information.
If you withdraw your participation in the study, you can demand that the data you have collected up to that point be deleted or immediately anonymised, as far as legally permissible.
The legal basis for the processing of your data is Section 40 Para. 2 a of the German Medicines Act, as well as your consent in accordance with Art. 6 Para. 1 lit a and Art. 9 Para. 2 lit a of the German Data Protection Act (DSGVO).

16. Collection, processing and scientific use of your data for further medical questions

If you agree to participate in this study, your data collected in this study may also be of considerable value for further medical questions. As mentioned at the beginning, this study is being conducted within the framework of the DKTK (German Consortium for Translational Cancer Research; https://dktk.dkfz.de/de/home). With this patient information we would also like to ask you to participate in a research project as a member or partner of the DKTK. In this consortium, top oncological centers throughout Germany are working together to achieve progress in the prevention, early detection, diagnosis and treatment of cancer patients.

In the course of your treatment at the hospital, you have already been given separate patient information (e.g. "Biomaterial and data in the research database and biobank"), which explains how your data and/or residual biomaterial stored or collected in the course of your treatment may be used for research. If you have not received these, simply contact us briefly.

In addition, in order to answer complex scientific questions, it is of great importance to use your data and residual biomaterial collected in the study to answer further scientific questions. For this purpose, your data may be passed on in pseudonymized form to the centers participating in the DKTK, their researchers and cooperating partners, and used for scientific questions and evaluations. Your data can also be pseudonymised and merged with data that is available about you within the hospital and in other hospitals, research institutions or registers.

What are the risks associated with this transfer of data?

In order to ensure the consolidation of your data, your identifying data (surname, first name, date of birth, address) are required. All data will only be stored in a protected database of the hospital and used for pseudonymisation electronically to a central unit of the DKTK (Clinical Communication Platform (CCP)), where they are deleted immediately after the pseudonym is created. It is a separate procedure for the use of your data for further scientific questions.

The more data are linked together, the more the risk statistically increases that your data can be assigned to you by unauthorized third parties, even if the personal identifying data are replaced by a pseudonym (re-identifiability risk). The legislator makes the misuse of your data fundamentally punishable.

Finally, we request your consent for the transfer and further scientific use of your data, which includes the following four aspects:

1. Transfer of the data in pseudonymised form to cooperation partners
2. Pseudonym generation using the separate pseudonymisation service
3. Transmission of the pseudonymised data from the study database to the treating hospital
4. Merging pseudonymised data with your pseudonymised data from databases of other research partners (e.g. other hospitals, institutes or registers)

Your consent is voluntary. You can revoke your consent to the further scientific use of your data at any time without giving reasons and without adverse consequences for you. This withdrawal for the use of your data for further scientific questions then relates to the four aspects mentioned above. Data that have already been merged or used for analyses cannot be deleted subsequently.
If deletion is not possible or not possible with reasonable technical effort, your data will be anonymised by deleting the pseudonyms assigned to you. Partners to whom pseudonymised data concerning your person has been transmitted will be informed of your revocation.

17. What happens to my blood samples / tissue samples / images with imaging techniques?

In order to determine the PSMA expression, tumor samples that were taken from you at an earlier point in time (e.g. when your disease was diagnosed) are used. Blood and urine from routine samples are analysed in the laboratory of the test center. At the University Hospital of Tübingen, the half-life of the CC-1 antibody in the blood is determined. Furthermore, an investigation of the development of human anti-human antibodies and an analysis of activation of immune cells and release of cytokines (messenger substances) after administration CC-1 will be assessed. At the DKFZ, the molecular genetic analysis of blood and, if necessary, tumor samples are made available.

Samples that are not currently required are stored for analysis at a later date. Your data and samples (blood samples as well as clinical data) can be used for possible future medical or pharmaceutical investigations and can be passed on to other investigators, for example for tests that are used to examine the immune response after antibody treatment in more detail. The exact questions cannot be specified at this time. All stored samples will also be pseudonymised. Afterwards the data set will be encoded and stored again. This double coding includes a identification of your person by unauthorized persons according to today's knowledge as far as possible. Only in this form biomaterials and data for research purposes are made available. The samples are considered a "donation".
All research projects in which biomaterial from this study could be used must first be reviewed and endorsed by a scientific panel of the study. Further research on these samples can only take place, if the project has been advised and approved by an ethics committee.

Biomaterials and data that have been passed on to third parties may only be used for the research purpose applied for and may not be passed on by the recipient for other purposes. Unused material will be returned or destroyed. Scientific publications of results will only be made anonymously, i.e. in a form that does not allow any conclusions about your person.
A prerequisite for the extraction and use of your biomaterials, including the associated personal data for research purposes, is your written consent. Your consent is voluntary and can be revoked at any time. If you withdraw your consent to participate in the study, you may request that all samples taken and identifiable without prior analysis will be destroyed. Data from analyses already performed cannot be removed. The results of all these analyses are collected for research purposes only and will not be stored in your medical records or given to you or the members of your family. The knowledge gained should improve the detection, treatment and prevention of diseases in the future.

18. What are my personal benefits of storing and analyzing samples?

Personally, you cannot expect any immediate health benefit or benefit from the analysis of your samples and data. The results are intended for research purposes only. A feedback of results from the analysis of the biomaterials is not intended. All current and future medical-scientific research projects aim to improve our understanding of disease development and diagnosis and, on this basis, to develop new improved treatment approaches.