Protocol Synopsis

Title	
	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
Phase	Phase I
Sponsor	University Hospital of Tübingen represented by Medical Director: Prof. Dr. med. M. Bamberg Director of Administration: G. Sonntag,
Coordinating Investigator (LKP)	Prof. Dr. Helmut R. Salih
Scientific coordinator	Prof. Dr. Gundram Jung
Financing	The trial is co-financed by funds of German Cancer Research Center, German Cancer Consortium and Helmholtz validation fund.
Indication	Castration resistant prostate cancer (CRPC) after third line therapy
Trial Population	
Inclusion Criteria	• 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 • 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 (ECOG) Performance Status ≤ 2 • Patient aged ≥ 18, no upper age limit • Male patients with partners of child-bearing 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 and for 3 months after the last dose of study drug. • Adequate bone marrow, renal, and hepatic function defined by laboratory tests within 14 days prior to study treatment: o Hemoglobin ≥ 10 g/dl o Neutrophil count ≥ 1,500/mm^3 o Platelet count ≥ 100,000/µl o Bilirubin ≤ 1.5 x upper limit of normal (ULN)

	○ ALT and AST ≤ 2.5 x ULN ○ Alkaline phosphatase ≤ 2.5 x ULN ○ PT-INR/PTT ≤ 1.5 x ULN ○ Creatine kinase ≤ 2.5 x ULN ○ Serum creatinine ≤ 1.5 mg/dl or creatinine clearance ≥ 60 ml/min
Exclusion Criteria	• 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 (≥Grade 2 according to Common Terminology Criteria for Adverse Events [CTCAE] version 5.0) caused by previous cancer therapy, excluding alopecia and neurotoxicity (≤ 2 grade) • Clinical signs of active infection (> grade 2 according to CTCAE version 5.0) • History of HIV infection • Immunocompromised patients • Viral active or chronic hepatitis (HBV or HCV) • History of autoimmune disease • History of relevant CNS pathology or current relevant CNS pathology (e.g. seizure, paresis, aphasia, cerebrovascular ischemia/hemorrhage, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, psychosis, coordination or movement disorder) • Epilepsy requiring pharmacologic 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 NYHA III/IV • Severe obstructive or restrictive ventilation disorder • Known history of GI-perforation • Pre-existing human anti-human 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)

Objectives		
	Primary Objective: • Dose escalation part: To define the maximum tolerated dose (MTD) of CC-1 and its overall safety profile under pre-emptive IL-6R blockade • Dose expansion: To define the recommended phase-II dose of CC-1 under pre-emptive IL-6R blockade	
	Secondary Objectives • To assess objective response to CC-1 in CRPC • To assess long-term safety and product specific safety • To assess clinical outcome • To define potential biomarkers in the study context • To assess pharmacokinetics of CC-1	
Trial Design	Open-label, multicenter dose escalation and dose expansion phase I trial, designed to gain evidence of maximally tolerated and recommended phase-II dose of CC-1 in adult patients with CRPC.	
Investigational Medicinal Products	CC-1	
Sample Size	A minimum number of 24 patients are treated, but potentially up to 86 patients may be included in the trial. The number depends on the occurrence of DLT in the dose escalation part. Dose escalation phase part: 10-72 patients Dose expansion phase: 14 additional patients	
Statistical Analysis	Summary statistics will be presented for each dosage level of CC-1 and for each cycle, toxicity, discontinuation and withdrawal from study treatment, as well as drop-out from the follow-up during the post-study phase. The assessment of safety will be based on the frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges and/or show prominent worsening from baseline during the study phase at each dose level.	
Trial Duration and Dates	Total trial duration:	39 months
	Duration of the clinical phase:	30 months
	First patient first visit (FPFV):	4th Quarter 2019
	Last patient first visit (LPFV):	4th Quarter 2021
	Last patient last visit (LPLV):	1st Quarter 2022
	Trial Report completed:	3rd Quarter 2022