APPLICANT/ COORDINATING INVESTIGATOR	Prof. Dr. Stefan Fröhling/Prof. Dr. Richard F. Schlenk National Center of Tumor diseases, Heidelberg
CONDITION	locally advanced/metastatic chordoma
OBJECTIVE(S)	Primary objective of this phase II trial is to gain first evidence of antitumor activity of palbociclib in adult patients with (locally) advanced or metastasized chordoma not amenable to curative treatment with surgery or radiotherapy. The primary endpoint is the disease control rate (DCR) after six cycles of palbociclib, which is defined as the presence of complete response (CR) or confirmed partial response (PR) or stable disease (SD) according to RECIST version 1.1. Secondary Objectives include: • Tumor Response rate (TRR) according to RECIST version 1.1 • Progression-free Survival (PFS) • Overall Survival (OS) • Safety/tolerability • Patient reported outcome including Quality of Life
INTERVENTION(S)	Palbociclib (CDK4/6-inhibition)
KEY EXCLUSION CRITERIA	• Prior treatment with palbociclib or known intolerance/allergy to the compound or any ingredient (acquired or hereditary). • Prior treatment with other CDK4/6 inhibitors • Co-therapy with strong/potent CYP3A inducers and/or inhibitors, (e.g., clarithromycin, indinavir, itraconazol, ketoconazol, lopinavir/ritonavir, nefazodon, nelfinavir, posaconazol, saquinavir, telaprevir, telithromycin, voriconazol, and St. John's Wort [Hypericum perforatum])) • Co-therapy with corticosteroidsabove 7.5 mg prednisolone/prednisone equivalent . • Organ insufficiency: creatinine clearance <30ml/min; total bilirubin >1.5x upper normal serum level; AST > upper normal serum level; abnormal blood counts; heart failure (New York Heart Association (NYHA) III/IV); uncontrolled hypertension; unstable angina; serious cardiac arrhythmia; severe obstructive or restrictive ventilation disorder • Clinical signs of active infection (>Grade 2 according to CTCAE version 5.0) • Patients with a "currently active" second malignancy other than non-melanoma skin cancer. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse within one year. • Severe neurologic or psychiatric disorder interfering with ability of giving informed consent • Known or suspected active alcohol or drug abuse • Known positivity for HIV, active HAV, HBV, or HCV infection • Cytopenia: platelets <100 G/l, neutrophils <1.0 G/l, hemoglobin <10.0 g/dl • Corrected QT interval (QTc_B) >470 msec (based on the mean value of triplicate ECGs), family or personal history of long or short QT syndrome, Brugada syndrome, or known history of QTc_B prolongation or Torsade de Pointes • Uncontrolled electrolyte disorders that can aggravate the effects of a QTc_B-prolonging drug (e.g., hypocalcemia, hypokalemia, hypomagnesemia) • Participation in other ongoing interventional clinical trials (according to AMG)within 4 weeks prior to study treatment.

KEY INCLUSION CRITERIA	• Patients with locally advanced or metastatic chordoma with confirmed diagnosis in a reference pathology (with immunohistology for epithelial membrane antigen, S100, Brachyury, INI-1). not amenable to curative treatment with surgery or radiotherapy. • At least one measurable tumor lesion according to RECIST 1.1 criteria • Loss of p16 determined immunohistochemically or CDKN2A/B genomically, presence of CDK4/6 and RB1 determined immunohistochemically or by RNA sequencing. • Age ≥ 18 years, no upper age limit • Availability of tissue blocks preferably not older than 12 months for immunohistologic assessment (if no adequate material is available, re-biopsy should be considered before entering the study) • • Non-pregnant and non-nursing. Women of child-bearing potential must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 72 hours prior to registration (WOCBP is defined as a sexually active mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 months). • Women of child-bearing potential must either commit to continued abstinence from heterosexual intercourse or use a highly effective method of birth control (e.g. double barrier contraceptive method (IUD, condome), tubal ligation, or partner's vasectomy) while on therapy and for 14 weeks after the last dose of therapy. Hormonal contraception alone is an inadequate method of birth control. Female patients must agree not to donate lactation during treatment and until 14 weeks after end of treatment. • Men must agree not to father a child and must use a latex condom during any sexual contact with WOCBP while receiving therapy and for 14 weeks after therapy is stopped, even if they have undergone successful vasectomy. Sperm donation is not permitted for the same time interval. • Signed written informed consent • Performance status ≤ 2 according to ECOG/WHO criteria • Ability of patient to understand the character and individual consequences of clinical trial
OUTCOME(S)	disease control rate (DCR) after six cycles of palbociclib
STUDY TYPE	Non-randomized, single-arm, open-label, multicenter phase II trial
STATISTICAL ANALYSIS	The study is a phase II trial with standard palbociclib dose of 125 mg once daily for 21 days in a 28-day cycle. The study needs 43 patients evaluable for the primary endpoint to complete. The sample size and power calculations were based on Simon's optimal two-stage design. The type I error was set at $\alpha = 0.05$, the type II error at $\beta = 0.2$. Here, the null hypothesis that the true response rate is less or equal to $p_0 = 0.1$ will be tested against a one-sided alternative, where the desirable level of response is 0.25. In the first stage, $n_1 = 18$ patients will be accrued. If there are $r_1 = 2$ or fewer responses in these 18 patients, the study will be stopped and the drug rejected. Otherwise, 25 additional patients will be accrued for a total of n = 43 patients. In the final analysis the null hypothesis will be rejected and the drug recommended for further development if 8 or more responses are observed in 43 patients.
SAMPLE SIZE	18 in the first stage 25 in the second stage (only if first stage was positive) Total sample size: minimum 18 patients; maximum 43 patients

TRIAL DURATION	Total trial duration: 48 months Duration of the clinical phase: 36 months
PARTICIPATING CENTERS	1. Universitätsklinikum Heidelberg, Prof. Dr. Richard Schlenk 2. Universitätsklinikum Essen, Dr. Rainer Hamacher 3. Universitätsklinikum Ulm, Dr. Verena Gaidzik
CURRENT NUMBER OF PATIENTS INCLUDED	22 (10 screening failures)