Protocol Synopsis

Title
CDK4/6 inhibition in locally advanced/metastatic chordoma

Phase
Phase II

Sponsor
Heidelberg University Hospital
represented in law by its Commercial Director
Ms. Irmtraut Gürkan
Im Neuenheimer Feld 672, 69120 Heidelberg, Germany

Coordinating Investigator (CI, LKP)
Prof. Dr. med. Stefan Fröhling

Financing/ Status of the Sponsor
The trial will be co-financed by funds of NCT Heidelberg.
The study is supported by Pfizer Pharma GmbH. Study drug will be provided free-of-charge by Pfizer Pharma GmbH.

Indication
Chordoma (ICD-classification code: C41.0)

Trial Population
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) who have no response or have lost response to treatment with a tyrosine kinase inhibitor e.g. imatinib, lapatinib, erlotinib, sunitinib, sorafenib, etc.
- 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)
- No chemotherapy two weeks before study entry
- 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 begin one acceptable method of birth control (IUD, tubal ligation, or partner’s vasectomy) while on therapy and for three months 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 3 months 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 three months 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

Exclusion Criteria

- Prior treatment with palbociclib
- Organ insufficiency: creatinine > 1.5x upper normal serum level; bilirubin, AST, or AP >2.5x upper normal serum level; heart failure (New York Heart Association (NYHA) III/IV); uncontrolled hypertension; unstable angina; serious cardiac arrhythmia; severe obstructive or restrictive ventilation disorder
- Uncontrolled infection
- 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 least 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
- Uncontrolled CNS involvement (treatment for CNS involvement prior to inclusion is allowed)
- Cytopenia: platelets <100g/l, neutrophils <1.0g/l, hemoglobin <10.0g/dl
- corrected QT interval (QTc) >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 prolongation or Torsade de Pointes
- Uncontrolled electrolyte disorders that can aggravate the effects of a QTc-prolonging drug (e.g., hypocalcemia, hypokalemia, hypomagnesemia)
- Participation in other ongoing interventional clinical trials (according to AMG).

Objectives

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 refractory to treatment with tyrosine kinase inhibitors.

The primary endpoint is the disease control rate (DCR) after six cycles of palbociclib, which is defined as the presence of at least one confirmed complete response (CR) or confirmed
partial response (PR) or stable disease (SD) according to RECIST version 1.1.

Secondary Objectives include:
- Tumor Response (TR)
- Progression-free Survival (PFS)
- Overall Survival (OS)
- Safety/tolerability
- Quality of Life

Trial Design
Non-randomized, single-arm, open-label, multicenter phase II trial, designed to gain first evidence of antitumor activity of palbociclib in adult patients with (locally) advanced or metastatic chordoma. The primary endpoint is the disease control rate (DCR). A total of 18 (stage I) or 43 patients (stages I+II) evaluable for the primary outcome need to be treated guided by Simon's optimal two-stage design.

Investigational Medicinal Product(s)
Palbociclib (Ibrance®) 125 mg, 100 mg or 75 mg Capsule

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

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 (Simon, 1989). 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.

Trial Duration and Dates
Total trial duration: 48 months
Duration of the clinical phase: 36 months
First patient first visit (FPFV): 4 Quarter 2017
Last patient first visit (LPFV): 4 Quarter 2019
Last patient last visit (LPLV): 4 Quarter 2020
Trial Report completed: 4 Quarter 2021