Summary of study protocol

<table>
<thead>
<tr>
<th>Title of application:</th>
<th>Orteronel maintenance therapy in patients with metastatic castration resistant prostate cancer and non-progressive disease after first line chemotherapy with docetaxel: a multicenter randomized double-blind placebo controlled phase III trial</th>
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<tbody>
<tr>
<td>Protocol no.:</td>
<td>SAKK 08/11</td>
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<td>Applicant:</td>
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<td>Other employees:</td>
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Background:
In metastatic castration-resistant carcinoma of the prostate (progression during antihormonal therapy) the standard first-line treatment consists of chemotherapy with docetaxel. This can significantly prolong survival while preserving the quality of life (1). At the end of chemotherapy, the patient is regularly monitored and, in the event of disease progression, receives second-line treatment with an androgen synthesis blocker (abiraterone) or a new chemotherapeutic agent (cabazitaxel), as reported in recent studies. These treatments likewise prolong survival (2, 3). Nevertheless, renewed tumor progression occurs in the further course of the disease.
Besides abiraterone, the new medicines orteronel (TAK-700) also inhibits testosterone production (4). Orteronel is currently the subject of a large international Phase III study in patients with metastatic carcinoma of the prostate and progression of disease following docetaxel. Initial results have shown that orteronel effectively inhibits testosterone synthesis and, in contrast to abiraterone, has fewer side effects.

Hypothesis:
Studies in other types of cancer have shown that good results with prolonged overall survival can be achieved through so-called maintenance therapy, i.e. through the early use of effective and well-tolerated medicines after stabilization of a cancer as a result of first-line therapy (5, 6). Maintenance therapy could also prolong the time to progression in patients with cancer of the prostate and consequently should also be studied in this indication.

Aim of this study:
The aim of the study is to establish whether early use of the testosterone synthesis blocker orteronel prolongs the time to disease progression in patients with metastatic prostate cancer that has at least been stabilized by means of first-line chemotherapy with docetaxel. The study is further intended to examine whether the quality of life of patients can be preserved for longer as a result of this treatment.

Primary endpoint:
The primary endpoint is event-free survival. An event is defined as ONE of the following:
- Progression of tumor manifestations observed in imaging and symptomatic progression
- Progression of tumor manifestations observed in imaging and PSA (prostate-specific antigen) progression
- PSA progression and symptomatic progression
- Death from any cause

Secondary endpoints:
- Side effects of treatment
- PSA response rates (decrease by 30%, 50% and 90%; best response)
- Duration of PSA response (50%)
- Time to PSA progression
- Time to progression of tumor manifestations in imaging
• Quality of life and pain response
• Overall survival

**Study design:**
International multicenter randomized Phase III study: placebo-controlled, double-blind.

**Inclusion and exclusion criteria for trial subjects:**

**Inclusion criteria:**
- Written consent
- Male patient ≥ 18 years
- WHO performance status ≤ 2
- Adenocarcinoma of the prostate
- Castration resistance, i.e. tumor progression despite medical or surgical castration
- Metastatic disease, radiographically documented
- Testosterone ≤ 50 ng/dL
- Regression or stabilization of disease (according to PSA and imaging results) during chemotherapy with a total dose of at least 300mg/m² docetaxel
- Non-surgically castrated patients agree to continue taking GnRH analogs during the study
- PSA ≥ 2 ng/mL, potassium ≥ 3.5 mmol/L, neutrophils ≥ 1.5 x 10⁹/L, platelets ≥ 100 x 10⁹/L
- Normal kidney and liver function
- Start of study treatment within 3-6 weeks of receiving the last dose of docetaxel
- Echocardiography showing ejection fraction >50% or normal values according to local standard
- Completed questionnaire for quality of life
- Patient is able and willing to take the drug
- Geographic proximity and compliance of the patient allow participation in the study and aftercare
- Even if the patient has been surgically sterilized, adequate contraceptive precautions must be taken for the duration of therapy and for at least 4 months afterwards

**Exclusion criteria:**
- Prior therapy with aminoglutethimide, ketoconazole, orteronel, abiraterone or other modern CYP17 inhibitors
- Prior chemotherapy for prostate cancer within 12 months before inclusion in the study except for docetaxel
- Retreatment with docetaxel after interruption of > 5 weeks
- Long-term corticosteroid therapy with a daily dose of > 10 mg prednisone (or equivalent)
- Known hypersensitivity to orteronel
- The patient has received another experimental treatment within the last 30 days
- Detection of small-cell carcinoma in histology
- Radiotherapy less than 2 weeks before the start of the study treatment
- Known metastases in the CNS or spinal canal
- Spinal cord compression
- Diagnosis or treatment of other malignant tumor within the last 2 years (except basal cell carcinoma, squamous cell carcinoma or in situ malignancies)
- History of myocardial infarction, unstable angina pectoris, symptomatic ischemic heart disease, arrhythmias of ≥ grade 3 or thromboembolic events within the last 6 months before the start of study treatment. Chronic atrial fibrillation during oral anticoagulant therapy is permitted.
- Heart failure NYHA III-IV
- ECG abnormalities: Q-wave infarction (unless identified more than 6 months ago); QTc interval > 460msec
- Uncontrolled arterial hypertension despite adequate medication: blood pressure > 160 mmHg systolic and 90 mmHg diastolic
- Likely inability of the patient (e.g. as the result of a psychiatric disorder) to understand information on the study, to give informed consent, to comply with the protocol, to complete the questionnaires on quality of life and to cooperate with the study doctor and hospital staff.
- Known gastrointestinal disease that impairs oral ingestion of medicines.
- Known active hepatitis B or C, life-threatening disease unrelated to cancer, any severe medical or mental disorder that, in the view of the investigator, makes participation in the study impossible

**Study procedure (study-specific/non-specific examinations)**

Before inclusion in the study, the patient receives detailed verbal and written information. Study-specific examinations are only carried out after written informed consent. On successful inclusion in the study, all patients undergo a centralized double-blind procedure randomizing them to the treatment arm or the placebo arm. Each patient then receives orteronel or placebo daily until progression (as defined above), the occurrence of intolerable side effects or withdrawal of consent.

Examinations **not specific** to the study:
- Computed tomography and bone scintigraphy before inclusion and every 12 weeks during the study until progression
- Physical examination and history-taking
- Blood sample to assess blood count, kidney and liver function, PSA and testosterone
- Check-ups with blood samples every 4 weeks until progression; during the first 8 weeks two additional examinations after 2 and 6 weeks

Examinations **specific** to the study:
- Echocardiography (ultrasound of the heart) before the start of study treatment and then every 24 weeks until progression
- ECG before the start of study treatment and then every 12 weeks until progression; additional ECG on day 1 of cycles 1 and 2
- Questionnaire on quality of life and use of pain-killers
- Collection of urine samples before the start of study treatment and after 12 weeks (optional)

**Study medicines:**

Orteronel inhibits cytochrome P17 lyase, an important enzyme in androgen synthesis. The inhibition takes place not only in the testes, but above all in the adrenals, prostate and tumor cells. This enables a highly effective reduction of testosterone production that should lead to a decrease in tumor growth and thus to a prolonged time to progression.

During the study, patients take 300 mg orteronel or placebo twice daily. Studies to date have shown that orteronel is well tolerated. Severe side effects did occur only in a few cases. The main side effects are tiredness, nausea, constipation, diarrhea and headache.

**Statistical analysis concept:**

The aim is to achieve an improvement in event-free survival from 4 months for patients receiving placebo to 6.67 months for patients receiving orteronel. The type I error stands at 5% and power at 90%. Overall, 96
patients in each arm (total 192 patients) with a total of 163 events are needed to achieve this. Randomization is carried out 1:1. Every year about 100 patients are included, so the period of inclusion amounts to about 2 years. The duration of the study (last patient, last treatment) is estimated at 4 years.

Justification of patient number:
The number of 192 patients derives from the statistical calculations to prove the expected advantage with regard to prolonged event-free survival with statistical significance.

Risks/stresses/inconvenience:
If the patient receives the treatment with orteronel, the above-mentioned side effects constitute a conceivable stress. In the case of a response, however, prolonged event-free survival and improved quality of life can be expected. If the patient is randomized to the placebo arm, no stresses or risks are to be expected by comparison with the current standard care (wait-and-watch approach). In the event of disease progression, patients in both treatment arms receive the best therapy for their particular cases.

References: