

# 1 TRIAL OVERVIEW SAKK 08/15

<b>Sponsor:</b>	Swiss Group for Clinical Cancer Research (SAKK)
<b>Trial Title:</b>	PROMET - Multicenter, Randomized Phase II Trial of Salvage Radiotherapy +/- Metformin for Patients with Prostate Cancer after Prostatectomy
<b>Short Title / Trial ID:</b>	SAKK 08/15: PROMET
<b>Protocol Version and Date:</b>	Version 3.0, 17.01.2018
<b>Trial registration:</b>	EudraCT: 2016-003599-39 ClinicalTrials.gov: NCT02945813
<b>Trial category and Rationale</b>	The IMP (metformin) is a medication with marketing authorization in Switzerland and the European Union for the treatment of diabetes. In this trial, patients with prostate cancer will be treated with 850 mg BID metformin for 12 months. According to the Swiss HRA and its corresponding Ordinance KlinV/Oclin on clinical trials, this trial is classified as category B
<b>Clinical Phase:</b>	Clinical study phase II
<b>Background and Rationale:</b>	<p>The use of salvage radiation to the prostate bed has provided suboptimal results over the years. Dose escalation, prophylactic pelvic treatment and the use of systemic therapy (i.e. ADT) have been addressed in important phase III clinical trials.</p> <p>There is great interest in repurposing the commonly prescribed anti-diabetic drug metformin for cancer therapy. A substantial body of evidence based on laboratory and animal data supports that a specific interaction between metformin and radiation therapy exists through various mechanisms of action. Thus, metformin may represent an effective and inexpensive means to improve clinical outcomes with an optimal therapeutic ratio.</p> <p>PROMET is a follow-up study of the SAKK 09/10. The latter is a randomized phase III trial addressing dose-escalation to the prostate fossa of patients with biochemical relapse after prostatectomy. PROMET maintains similar inclusion criteria and endpoint definitions of the SAKK 09/10, therefore outcome data can be properly compared between these two studies.</p> <p>This is a multicenter, randomized, phase II study of SRT plus minus metformin. The study has 1:1 randomization and stratification variables include Gleason score, PSA at randomization, surgical margin status and ADT use.</p>
<b>Objective(s):</b>	The main objective of the trial is to explore the efficacy of SRT plus metformin compared to SRT in the endpoint of time to progression after prostatectomy failure.

<b>Endpoints:</b>	<p>The primary endpoint of the trial is: Time to progression (TTP)</p> <p>The secondary endpoints are:</p> <ul style="list-style-type: none"> <li>• Progression-free survival (PFS)</li> <li>• Undetectable PSA under normal testosterone levels</li> <li>• 50% PSA response</li> <li>• Clinical progression-free survival</li> <li>• Time to further anti-cancer systemic therapy</li> <li>• Prostate cancer-specific survival (PCSS)</li> <li>• Overall survival (OS)</li> <li>• Adverse events (AE)</li> </ul>
<b>Trial design:</b>	International multicenter, randomized phase II trial.
<b>Inclusion / Exclusion criteria:</b>	<p><b>Inclusion criteria</b></p> <ol style="list-style-type: none"> <li>1. Written informed consent according to ICH/GCP regulations before registration and prior to any trial specific procedures</li> <li>2. Histologically confirmed adenocarcinoma of the prostate without small cell features</li> <li>3. Tumor stage pT2a-3b, pN0 or cN0, M0, R0-1 resection margins, according to UICC TNM 2009 (see Appendix 1), Gleason score available</li> <li>4. Radical prostatectomy (RP) at least 12 weeks before registration</li> <li>5. PSA progression after RP defined as two consecutive rises with the final PSA &gt; 0.1 ng/mL or three consecutive rises. The first value must be measured earliest 4 weeks after RP</li> <li>6. PSA ≤ 2 ng/mL within 14 days prior to registration</li> <li>7. Age ≥ 18 years at time of registration</li> <li>8. WHO performance status 0-1 (see Appendix 2)</li> <li>9. Adequate hepatic function within 14 days prior to registration: bilirubin ≤ 1.5 x ULN (exception if Gilbert's syndrome ≤ 3 x ULN), AST and ALT ≤ 2.5 x ULN</li> <li>10. Adequate renal function within 14 days prior to registration: calculated corrected creatinine clearance ≥ 60 mL/min, according to the formula of corrected Cockcroft-Gault (see Appendix 3)</li> <li>11. Patient agrees not to father a child and to use effective contraceptive methods during salvage radiotherapy and until 6 months after the last fraction of radiotherapy</li> <li>12. Paraffin block of the surgical specimen containing representative tumor tissue and non-neoplastic prostatic tissue available for biobanking (see section 17).</li> </ol>

**Exclusion criteria**

1. Persistent PSA (> 0.4 ng/mL) 4 to 20 weeks after RP
2. Pelvic lymph node enlargement > 0.8 cm in short axis diameter (cN positive) assessed by mpMRI within 12 weeks prior to registration, unless the enlarged lymph node is sampled and negative.
3. Evidence of macroscopic local recurrence assessed by mpMRI within 12 weeks prior to registration as described in Appendix 6
4. Palpable prostatic fossa mass suggestive of recurrence, unless an ultrasound guided biopsy is negative for malignancy
5. Presence or history of prostate cancer metastases. In case of clinical suspicion (e.g. bone pain), imaging (e.g. bone scan, Choline-PET, PSMA-PET, whole body MRI) must be performed. The imaging method is at the discretion of the investigator
6. If PET/CT scan was performed, any metabolic uptake considered clinically suspicious for malignancy, unless biopsy proves to be negative
7. Previous hematologic or primary solid malignancy within 3 years prior registration with the exception of curatively treated localized non-melanoma skin cancer
8. Patients diagnosed with diabetes mellitus
9. Treatment with metformin within the last 3 months prior to registration
10. Prior pelvic radiotherapy
11. Hormonal treatment in the form of bilateral orchiectomy prior or following RP
12. Usage of products known to affect PSA levels within 4 weeks prior to start of trial treatment (see Appendix 4)
13. Bilateral hip prosthesis
14. Severe or active co-morbidity likely to impact on the advisability of salvage RT, e.g.:
  - a. History of inflammatory bowel disease or any malabsorption syndrome or conditions that would interfere with enteral absorption
  - b. Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration
  - c. Unstable angina, myocardial infarction and/or congestive heart failure requiring hospitalization within the last 6 months
  - d. Transmural myocardial infarction within the last 6 months
  - e. Chronic obstructive pulmonary disease (COPD) exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
15. Any condition associated with increased risk of *lactic acidosis* (e.g. alcohol abuse, congestive heart failure NYHA III or IV [see Appendix 5])
16. Clinically significant history of *liver disease* consistent with Child-Pugh Class B or C, including viral or hepatitis, current alcohol abuse, or cirrhosis

	<ol style="list-style-type: none"> <li>17. Any acute or chronic condition that could cause tissue hypoxia (e.g. cardiac or respiratory insufficiency, shock)</li> <li>18. Treatment with any experimental drug or participation within a clinical trial within 30 days prior to registration (exception: concurrent participation in the biobank study SAKK 63/12 is allowed)</li> <li>19. Any concomitant drug contraindicated for use with metformin according to the approved product information</li> <li>20. Known hypersensitivity to metformin or to any of its components</li> <li>21. Inability or unwillingness to swallow oral medication</li> <li>22. Any other serious underlying medical, psychiatric, psychological, familial or geographical condition, which in the judgment of the investigator may interfere with the planned staging, treatment and follow-up, affect patient compliance or place the patient at high risk from treatment-related complications.</li> <li>23. Dependency on the sponsor or the investigators (ICH/GCP E6(R2), guideline 1.61)</li> <li>24. Patients diagnosed with acute conditions that may alter the renal function</li> </ol>
<p><b>Measurements and procedures:</b></p>	<p>Patients will be randomized to either the treatment with metformin and salvage radiotherapy or to salvage radiotherapy only. The IMP metformin will be administered daily p.o. for 52 weeks. During the first four weeks, the dose is 850 mg daily, from the day 1 of week 5 until end of week 52, the dose is 1700 mg daily.</p> <p>At the beginning of the fifth week, the radiotherapy is started. It lasts for 7 weeks (5 x 2 Gy per week).</p> <p><b>Investigations before trial treatment phase</b></p> <p>Physical examinations, mpMRI of the pelvis, bone scan (in case of clinical suspicion only), digital rectal examination, blood analysis (hematology, hepatic and renal, metabolic parameters analysis (blood glucose, HbA1c, C-peptide), lipid profile (cholesterol, triglycerides, HDL, LDL), serum PSA, total testosterone.</p> <p><b>Investigations during trial treatment phase</b></p> <p>Planning CT scan; at day 1 and if screening done more than 7 days before registration: physical examinations, blood analysis (hepatic and renal); at day 1 of week 5: physical examinations, blood analysis (hepatic and renal), serum PSA, total testosterone, assessment of recurrences in case of suspected progression; at day 1 of weeks 13 and 25 and 37 physical examinations, blood analysis (hepatic and renal), serum PSA, total testosterone, assessment of recurrences (local, regional, distant); checking of patient compliance (diary) and recording of concomitant medication.</p> <p>If suspicion of clinical progression, digital rectal examination at day 1 of weeks 5, 13, 25, 37.</p>

	<p><b>At end of trial treatment phase</b></p> <p>Physical examinations, digital rectal examination (if suspected clinical progression), blood analysis (hematology, hepatic and renal, metabolic parameters analysis (blood glucose, HbA1c, C-peptide), lipid profile (cholesterol, triglycerides, HDL, LDL), serum PSA, total testosterone; checking of patient compliance (diary) and recording of concomitant medication, survival status and recording of further anti-cancer treatments, if any.</p> <p><b>During follow-up</b></p> <p>Digital rectal examination (if suspected clinical progression), serum PSA and total testosterone (only until biochemical progression), assessment of recurrences (local, regional, distant)</p> <p>All adverse events are collected throughout the trial treatment phase and only related to RT during the follow-up phase.</p>
<b>IMP / Intervention:</b>	<p>In this trial, patients after radical prostatectomy and biochemical progression are randomized to receive the following target dose:</p> <ul style="list-style-type: none"> <li>• Arm A: 70 Gy SRT plus 850 mg metformin BID</li> <li>• Arm B: 70 Gy SRT</li> </ul> <p>The total duration of the metformin treatment is 52 weeks. Treatment with metformin should be started within 14 days from randomization. SRT is started 4 weeks after the first dose of metformin (Arm A) / 4-6 weeks after randomization (Arm B).</p>
<b>Control Intervention:</b>	N/A
<b>Number of Participants with Rationale:</b>	It is planned to enroll a total of 170 patients (85 per treatment arm) in the trial. See statistical considerations for rationale.
<b>Trial Duration:</b>	<p>Start of the trial: Q3 2017</p> <p>End of accrual: Q1 2019</p> <p>End of trial treatment: Q1 2020</p> <p>Follow-up: 10 years after last RT fraction for each patient</p> <p>End of the trial: 2030</p>
<b>Schedule:</b>	<p>First-Participant-In: Q4 2017</p> <p>Last-Participant-Out: 2030 (planned)</p>
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<b>Investigator(s):</b>	Please refer to the participation list
<b>Study Site(s):</b>	International and multicenter with 26 participating sites foreseen (Switzerland: 13, France: 8, Germany: 5)
<b>Statistical Considerations:</b>	The sample size is based on the primary endpoint time to progression (TTP). Using a type I error of 5%, a power of 80%, 62 events will be needed to show superiority of the treatment arm under the alternative hypothesis that the hazard ratio (HR) is 0.65 (corresponding to a TTP at 18 months of 80% in the control arm and 86.5% in the treatment arm). The sample size needed is 170 patients (85 per arm). All efficacy endpoints will be analyzed based on the full analysis population. The treatment effect will be assessed using Cox regression models with the treatment arm as independent variable and the stratification factors as strata.
<b>GCP Statement:</b>	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.