SAKK 41/14 ACTIVE-2

Physical activity in patients with metastatic colorectal cancer who receive palliative first-line chemotherapy. A randomized controlled phase III trial.

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Protocol Synopsis

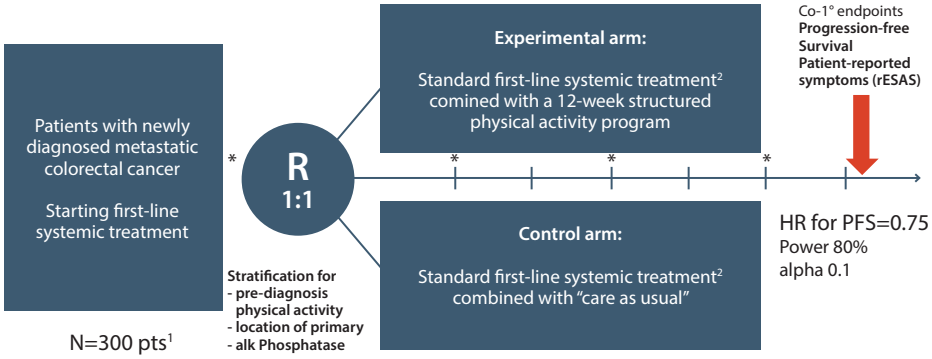
Indication:	Patients with metastatic colorectal cancer
Study design:	International, multicenter randomized open label trial
Planned sample size:	300 patients international
Duration:	First patient in (FPI): Q1 2016 Last patient in (LPI): Q4 2022 (expected) Last patient out (LPO): 2028 (expected))
Study medication:	Standard palliative chemotherapy + structured PA and pedometer
Status (March 2019):	11 patients (7 Kli. Wels, 4 PMU Salzburg) 68 patients (international)

Primary objective:
To assess whether a structured physical activity program (PA) during palliative chemotherapy improves progression-free survival (PFS) and/or patient-reported outcomes (ESAS-r-Edmonton Symptom Assessment System) in patients with metastatic colorectal cancer.

Primary Endpoints:
PFS, Patient-reported outcomes as measured by the ESAS-r

Secondary Endpoints:
Efficacy, Chemotherapy-related endpoints and toxicities, Patient-reported outcomes (PRO´s), Exercise endpoints

Study Design



*CT scan / MRI at baseline and every 12 weeks until progression in all patients
[1] Protocol amendment 2, June 2018, sample size changed from 524 to 300 pts
[2] Physician´s choice

All patients will undergo standard systemic therapy for metastatic colorectal cancer. Patients in the care-as-usual group are not actively encouraged to change their physical activity level e.g. to start a fitness program during chemotherapy.

The physical exercise ACTIVE-program describes a 12-week exercise program consisting of a combination of a bi-weekly aerobic exercise (cycle ergometer) supervised by a physical therapist and a self-paced increase in physical activity during daily life using a pedometer with a daily step goal as a motivational tool. The program will be individually tailored to each patient based on the training protocol and is aimed at increasing physical activity levels and cardiorespiratory fitness.

Measurements and procedures
For all patients irrespective of randomization every 12 weeks until PD: imaging of all affected body regions (CT or MRI), tumor marker (if elevated at baseline)

For all patients every 6 weeks until week 24 (total 4 time points): performance status, laboratory values, sit-to-stand test, patient reported outcomes questionnaires (ESAS-r, HADS, CASQ, distress thermometer, and GPAQ), dose modifications of chemo- and/or antibody therapy (y/n), of anti-diabetic drugs (y/n), of antihypertensive drugs (y/n); selected AEs.

Only for patients randomized to the PA arm: cycle ergometer stress test (HRmax) once before first supervised session; supervised sessions (physiotherapy): attended session (yes/no), if no, reason for not attending, session completed (yes/no), if no, reason for interruption; individual exercise: weekly diary filled in by patient including daily step count; SAEs related to exercise.

Amendment 2
Substantial changes to the previous protocol version:
- sample size: 300 patients instead of 524
- Patients can now be enrolled prior to start or within the first 3 weeks of systemic first-line therapy
- RAS status does not have to be known at time of inclusion
- Stress ergometry only in patients randomized to the movement arm
- No age limit upwards 18 years
- Former malignancy is not an exclusion criteria
- Simplification and clarification of assessments after the end of the training program until PD (until week 24 and after week 24)
- CT or MRI every 12 weeks until PD

Inclusion Criteria (selected)

- Patients with histologically or cytologically confirmed colorectal carcinoma (CRC) who start
  - palliative first-line systemic therapy for inoperable or metastatic disease
  - first-line "conversion"-therapy for borderline resectable metastatic disease and will be reassessed for metastasectomy after 3-4 months of systemic treatment
  Note: Patients can be included before the start or within the first three weeks of first-line systemic treatment.
- Patients who are diagnosed with metastatic disease and were initially treated with surgery and/or radiochemotherapy to the primary tumor are eligible (except if all disease sites/metastases have been removed)
- Patients who have been curatively treated with histologically or cytologically confirmed non-metastatic CRC previously and now relapse with metastatic disease are also eligible, irrespective of previous radiochemotherapy and/or adjuvant chemotherapy
- Patients must have measurable disease on CT scan or MRI to be performed within 6 weeks before randomization (measurability criteria according to RECIST 1.1, non-nodal lesions ≥10 mm, lymph nodes ≥15mm) OR evaluable disease i.e. patient with non-measurable metastases but elevated serum tumor marker (CEA at least >2xULN)

Exclusion Criteria (selected)

- Pre-existing severe medical conditions precluding participation in a physical activity program as determined by the local investigator. Such conditions include: chronic heart failure, recent myocardial infarction, unstable angina pectoris, clinically significant arrhythmias, uncontrolled hypertension with repeated systolic blood pressure above 160mmHg, and COPD
- Inability to ride a cycle ergometer e.g. for musculoskeletal reasons
- Patients in whom all CRC metastases have been removed surgically
- Any serious underlying medical condition (at the judgment of the investigator) which could impair the ability of the patient to participate in the trial (e.g. active autoimmune disease, uncontrolleddiabetes).

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An academic clinical trial by SAKK Swiss Group for Clinical Cancer Research (Study Chair: V. Hess), Bern, in cooperation with Arbeitsgemeinschaft medikamentöse Tumortherapie gemeinnützige GmbH, Clinical-Scientific Director: R. Greil

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