SAKK - SWISS GROUP FOR CLINICAL CANCER RESEARCH

Protocol SAKK 41/14 ACTIVE-2
Physical activity program in patients with metastatic colorectal cancer who receive palliative first-line chemotherapy. A multicenter open label randomized controlled phase III trial

Activation date: January 29, 2016
SNCTP No. 000001495
EudraCT No. 2015-003733-10
Copyright © 2015 by SAKK

Study type: Other clinical trial (without medication, medical device, nor transplant)
Categorization: Risk category A according to the Human Research Act and its ordinance KlinV/Oclin

Coordinating Investigator: Prof. Dr. med. Viviane Hess
University Hospital Basel
Phone: +41 61 265 50 74
Fax: +41 61 265 50 16
viviane.hess@usb.ch

Supporting Coordinating Investigator: Dr. med. Benjamin Kasenda
University Hospital Basel
Phone: +41 61 265 50 74
Fax: +41 61 265 53 16
benjamin.kasenda@usb.ch

Supporting Coordinating Investigator: Dr. med. Ralph Winterhalder
Cantonal Hospital Lucerne
Phone: +41 41 205 58 75
Fax: +41 41 205 58 62
ralph.winterhalder@luks.ch

Supporting Coordinating Investigator: Prof. Dr. med. Josef Thaler
Klinikum Wels-Grieskirchen
Austria
Phone: +43 7242 415 34 51
Fax: +43 7242 415 3956
josef.thaler@klinikum-wegr.at

Statistician: Martin Bigler
SAKK CC, Bern
Phone: +41 31 389 93 54
martin.bigler@sakk.ch

Clinical Project Manager: Dr. Catherine Berset
SAKK CC, Bern
Phone: +41 31 389 92 18
catherine.berset@sakk.ch

Patient Reported Outcomes: Dr. Karin Ribi
SAKK CC, Bern
Phone: +41 31 389 93 88
karin.ribi@sakk.ch

Barbara Handschin, MSc
University Hospital Basel
Phone: +41 61 328 50 79
barbara.handschin@usb.ch
Clinical Research Associate: Dr. Katrin Lange
SAKK CC, Bern
Phone: +41 31 389 91 97
Katrin.lange@sakk.ch

Exercise program advisor: Dr. Ruud Knols
University Hospital Zurich
Phone: +41 44 255 88 09
ruud.knols@usz.ch

Internet-based registration: www.sakk.ch/edc

Fax-based registration and information:
SAKK CC
Effingerstrasse 40
CH – 3008 Bern
Phone: +41 31 389 91 91
Fax: +41 31 389 92 00
sakkcc@sakk.ch

Opening hours: Mon.-Fri. 8:00 a.m. to 5:00 p.m.

Website: www.sakk.ch

Protocol version 1.2: Amended version including Amendment 1, 05.12.2015
Original version v1.1: 11.11.2015

CONFIDENTIALITY
The information contained in this document is confidential and the property of SAKK (or “sponsor”). The information may not - in full or in part - be transmitted, reproduced, published, or disclosed to others than the applicable Competent Ethics Committees and Regulatory Authorities, and any other stakeholders without prior written authorization from the sponsor except to the extent necessary to obtain informed consent from those who will participate in the trial. The trial is performed along applicable transparency rules and is published on publicly available registries (e.g. KOFAM, clinicaltrials.gov)

The protocol SAKK 41/14 was accepted by the SAKK Board on 01.09.2015 and has passed the recommended review process for SAKK trials. The SAKK Board has been informed of non-substantial Amendment 1 on 13.01.2016.

The final protocol, version 1.1, is dated 11.11.2015. Version 1.2 including Amendment 1 is dated 05.12.2015.

SAKK Representative:
Name: Dr. Peter Brauchli, CEO
Date: 24.1.2016 Signature: [Signature]

Coordinating Investigator:
Name: Prof. Dr. med. Viviane Hess
Date: [Signature]

Trial Statistician:
Name: Martin Bigler
Date: 13.1.2016 Signature: [Signature]

Clinical Project Manager:
Name: Dr. Catherine Berset
Date: 13.1.2016 Signature: [Signature]

Head of Clinical Project Management:
Name: Christine Biaggi
Date: 14/01/2016 Signature: [Signature]

The protocol SAKK 41/14 was accepted by the SAKK Board on 01.09.2015 and has passed the recommended review process for SAKK trials. The SAKK Board has been informed of non-substantial Amendment 1 on 13.01.2016.
The final protocol, version 1.1, is dated 11.11.2015.
Version 1.2 including Amendment 1 is dated 05.12.2015.

SAKK Representative:
Name: Dr. Peter Brauchli, CEO

Date: __________________________ Signature: __________________________

Coordinating Investigator:
Name: Prof. Dr. med. Viviane Hess

Date: 14. Jan 2016 Signature: __________________________

Trial Statistician:
Name: Martin Bigler

Date: __________________________ Signature: __________________________

Clinical Project Manager:
Name: Dr. Catherine Berset

Date: __________________________ Signature: __________________________

Head of Clinical Project Management:
Name: Christine Biaggi

Date: __________________________ Signature: __________________________

Version 1.2, Amended Protocol including Amendment 1, 05.12.2015
SAKK 41/14 ACTIVE-2. PHYSICAL ACTIVITY IN PATIENTS WITH METASTATIC COLORECTAL CANCER WHO RECEIVE PALLIATIVE FIRST-LINE CHEMOTHERAPY. A MULTICENTER OPEN LABEL RANDOMIZED CONTROLLED PHASE III TRIAL.

Principal Investigator in: ______________________________________________________

Having read and understood protocol VERSION 1.2 of 05.12.2015, including Amendment 1, I agree to conduct the trial as specified in the protocol. As Amendment 1 is a non-substantial Amendment, the protocol version 1.2 shall be implemented immediately.

Name: ________________________ Title: ________________________

Date: ________________________ Signature: ________________________
ABBRVIATIONS

AE  Adverse event
BAG  Bundesamt für Gesundheit
BAM  binary alignment map
CI  Coordinating investigator
CPM  Clinical Project Manager
CR  Complete Response
CRF  Case report form
CT  Computed tomography
CTCAE  Common terminology criteria for adverse events
CV  Curriculum vitae
EC  Ethics Committee
ESAS-r  Edmonton Symptom Assessment System Revised
EU  European Union
EudraCT  European Clinical Trials Database
FDG  Fludeoxyglucose (18F)
GCP  Good Clinical Practice
HCPM  Head Clinical Project Management
HFV  Humanforschungsverordnung
HRA  Human research act
ICH  International Conference on Harmonization
IMP  Investigational medicinal product
KlinV  Verordnung über klinische Versuche in der Humanforschung
KOFAM  Koordinationsstelle Forschung am Menschen
LLN  Lower limit of normal
MD  Medical doctor
NCI  National Cancer Institute
OClin  Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain
Org LRH  Ordonnance d'organisation concernant la loi relative à la recherche sur l'être humain
ORH  Ordonnance relative à la recherche sur l'être humain
OS  Overall Survival
OV-HFG  Organisationsverordnung zum Humanforschungsgesetz
PA  Physical activity
PD  Progressive disease
PI  Principal investigator
PET  Positron emission tomography
PFS  Progression free survival
PR  Partial Response
PRO  Patient-reported outcome
PT  Physical therapist
RECIST  Response Evaluation Criteria in Solid Tumors
SAE  Serious adverse event
SADR  Serious adverse drug reaction
SAKK  Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung
SAKK CC  SAKK Coordinating Center
SD  Stable Disease
SDV  Source data verification  
SI    Sub-investigator   
SNCTP Swiss National Clinical Trials Portal  
SOC   System organ class  
SOP   Standard operating procedure  
STST  Sit-to-stand Test  
SUSAR Suspected unexpected serious adverse reaction  
SUVA  Schweizerische Unfallversicherungsanstalt  
TL    Target lesion  
TMF   Trial master file  
ULN   Upper limit of normal  
UPN   Unique patient number  
WHO   World Health Organization
**TABLE OF CONTENTS**

- **PROTOCOL SIGN-OFF PAGE**  
  Page 3

- **ABBREVIATIONS**  
  Page 5

- **TABLE OF CONTENTS**  
  Page 7

1. **TRIAL OVERVIEW SAKK 41/14**  
   Page 10

2. **INTRODUCTION AND BACKGROUND**  
   2.1 Disease background  
   2.2 Current evidence of physical activity interventions in cancer  
   2.3 Rationale for performing the trial  
   2.4 Choice of design and comparator  
   2.5 Choice of study population  
   Page 16

3. **OBJECTIVES AND ENDPOINTS**  
   3.1 Objective  
   3.2 Endpoints  
   Page 18

4. **TRIAL DESIGN**  
   4.1 Methods of minimizing bias  
   Page 19

5. **TRIAL DURATION AND TERMINATION**  
   Page 20

6. **SELECTION OF PATIENTS**  
   6.1 Inclusion criteria  
   6.2 Exclusion criteria  
   Page 21

7. **RANDOMIZATION**  
   7.1 Pre-randomization procedure  
   7.2 Randomization procedure  
   7.3 After randomization  
   Page 23

8. **DRUG SUPPLY AND HANDLING**  
   Page 24

9. **TRIAL INTERVENTION**  
   9.1 Intervention overview  
   9.2 Experimental intervention: Physical exercise ACTIVE-program  
   9.3 Control intervention: Care as usual  
   9.4 Duration of physical exercise intervention  
   9.5 Treatments not permitted during trial treatment phase  
   9.6 Precaution  
   Page 24

10. **ADVERSE EVENT REPORTING, PHYSICAL ACTIVITY INTENSITY MODIFICATION, DOSE MODIFICATIONS, AND SUPPORTIVE TREATMENT**  
    10.1 Definition of adverse event (AE)  
    10.2 Reporting of selected AEs  
    10.3 Safety parameters  
    10.4 Intensity modifications of PA and dose modifications  
    Page 32

11. **SAFETY REPORTING**  
    11.1 Definition of serious adverse event (SAE)  
    11.2 Definition of serious adverse reaction (SAR)  
    11.3 Definition of suspected unexpected serious adverse reactions (SUSARs)  
    11.4 Reporting of individual SAEs by the investigator  
    11.5 Reporting of individual SAEs by the sponsor  
    11.6 Periodic reporting on safety to principal investigators  
    Page 35
1 TRIAL OVERVIEW SAKK 41/14

SAKK 41/14 ACTIVE-2. Physical activity program in patients with metastatic colorectal cancer who receive palliative first-line chemotherapy. A multicenter open label randomized controlled phase III trial

Sponsor: Swiss Group for Clinical Cancer Research (SAKK)

Trial registry No.: Swiss National Clinical Trial Portal (SNCTP): 000001495
European Clinical Trials Database (EudraCT): 2015-003733-10
Cancer Clinical Trials Registry (ClinicalTrials.gov)

Coordinating investigator: Prof. Dr. med. Viviane Hess

TRIAL TYPE AND CATEGORISATION

Clinical trial with health intervention.
According to the Swiss HRA and its corresponding Ordinance KlinV/Oclin on clinical trials, this trial is classified as category A.

OBJECTIVE(S)

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

ENDPOINTS

Primary endpoints:
The co-primary endpoints are PFS and patient-reported symptoms as measured by the ESAS-r (Edmonton Symptom Assessment System revised).

Secondary endpoints:
Secondary endpoints of the trial are:
a) Efficacy
   • Overall Survival
   • Best Objective Response
   • Metastasectomy rate
b) Chemotherapy-related endpoints and toxicities
   • Selected Adverse Events (as defined in Section 10.2) including chemotherapy-induced polyneuropathy
   • Chemotherapy-completion-rate: absolute dose of chemotherapy applied in percentage of planned chemotherapy dose (only for first-line therapy)
   • Initiation or increase of anti-hypertensive drugs
   • Overall treatment utility (OTU)
c) Patient reported outcomes
   • Depression and anxiety as measured by the Hospital Anxiety and Depression Scale (HADS)
• Appetite as measured by the Cancer Appetite and Symptom Questionnaire (CASQ)
• General Distress as measured by a Distress thermometer
• Therapeutic relationship (patient – physical therapist) (intervention group only)

d) Exercise endpoints
• Exercise capacity as measured by the Sit-to-stand Test (STST)
• Self-reported physical activity as measured by the Global Physical Activity Questionnaire (GPAQ)
• Metabolic equivalent of task (MET)-hours per week (in intervention group only)
• Body mass index

Additional research questions:
In a translational research project potential mechanisms that link physical activity to tumor progression will be explored. Exercise-induced changes in the metabolic host-environment, more specifically in the insulin-PI3K-mTor signaling pathway, and function of the innate immune system (NK-cells) will be assessed in the MetACTIVE project.

TRIAL DESIGN

This is a multicenter randomized open label trial.

TRIAL DURATION

The inclusion of patients is planned to start in Q4 2015 and will stop after the inclusion of approximately 524 evaluable patients, which is expected in Q2 2021. The trial intervention lasts for 12 weeks. End of trial intervention is expected for Q3 2021. Patients will have a lifelong follow-up. Trial termination (last patient last visit) is expected to be in 2026.

SELECTION OF PATIENTS

• Patient with histologically or cytologically confirmed colorectal carcinoma (CRC) required to start palliative first-line systemic therapy for inoperable or metastatic disease.
• Patient has measurable disease on CT scan or MRI to be performed within 4 weeks before randomization (measurability criteria according to RECIST 1.1 [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).
• Cycle ergometer stress test (completed within 28 days before randomization) did not show any significant sign of ischemic heart disease or high-grade arrhythmias which preclude an exercise program
• No pre-existing severe medical conditions precluding participation in a physical activity program as determined by the local investigator. Such conditions include: chronic heart failure (greater than NYHA II see Appendices AAappendix 5), recent myocardial infarction (less than 3 months ago), unstable angina pectoris, clinically significant arrhythmias, uncontrolled hypertension with repeated systolic blood pressure above 160mmHg, and COPD (requiring oxygen supply or GOLD stadium greater than 2).
Accrual may be interrupted or the trial may be stopped early based on the results of an interim feasibility analysis (planned after the inclusion of 40 patients) or if new scientific data become available which change assessment of risk/benefit.

**TRIAL SCHEDULE**

- Planned trial activation: Q4 2015
- Planned first patient in: Q4 2015
- Planned feasibility analysis: Q3 2016
- Planned last patient in: Q2 2021
- Planned end of trial therapy: Q3 2021
- Planned last patient, last visit: 2026

**TRIAL TREATMENT**

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.

In addition to the supervised exercise program twice a week, patients of the intervention group are recommended to be physically active at home. Recommended activities of moderate intensity are: walking, climbing stairs, gardening, housekeeping, cycling, getting off the bus or tram earlier, walking in the park, the forest or with the dog, walking with a peer etc.

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.

**MEASUREMENTS AND PROCEDURES**

*Before trial intervention*

- Physical examination, blood analyses, radiological assessment of the metastatic disease, and Patient Reported Outcomes questionnaire (ESAS-r, HADS, CASQ, and Distress Thermometer).
- In addition, physical condition assessments: Saltin-Grimby Physical Activity Level Scale (SGPALS), Global Physical Activity Questionnaire (GPAQ), cycle ergometer stress test, Sit-to-stand Test (STST).

*During the trial intervention*

- Only for patients randomized to the PA arm: attended session (yes/no), if no, reason for not attending, session completed (yes/no), if no, reason for interruption.
- For all patients irrespective of randomization: physical examination, laboratory values, imaging of all affected body regions, tumor marker, exercise assessment with Sit-to-stand Test and GPAQ, Patient Reported Outcomes questionnaire (ESAS-r, HADS, CASQ, and Distress Thermometer).

*After the trial intervention*

- In the follow-up phase survival status and information whether PA started ("cross over") will be collected. The frequency of scans after documented first progression is at the discretion of the treating oncologist. All patients will have a lifelong follow-up.
STATISTICAL CONSIDERATIONS

The trial will have two co-primary endpoints, PFS and patient-reported symptoms.

**PFS:** 439 events in 524 patients will provide 80% power to detect a hazard ratio of 0.75 in favor of the intervention arm (improve in the median PFS from 9 to 12 months) at the $\alpha=0.03$ level.

**Patient-reported symptoms:** Simulations showed that we will have 80% power or more to detect a clinically meaningful difference of 7 points in favor of the intervention arm at the $\alpha=0.02$ level, if the within-patient standard deviation is not too high.

The trial will be *positive*, if the PFS analysis or the PRO analysis or both give a positive result. The overall type-I error probability will be $0.03 + 0.02 = 0.05$.

After inclusion of the 40th patient the feasibility assessment will consist of a descriptive analysis of patient characteristics, adherence to the training protocol, accrual data, dropout rate, and other data that are not related to the co-primary endpoints.

GCP STATEMENT

This trial will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as national legal and regulatory requirements.
2 INTRODUCTION AND BACKGROUND

2.1 Disease background

Colorectal cancer (CRC) is responsible for almost 10% of the total cancer burden (worldwide 1.23 million cases), after lung cancer (1.61 million) and breast cancer (1.38 million) [2]. About 20%–25% of patients with CRC have metastatic disease at time of diagnosis, and 20%–25% of patients will develop metastases later, resulting in a relatively high overall mortality rate of 40%–45%. At time of diagnosis of metastatic disease, standard of care chemotherapies are the 5-fluorouracil (5-FU) based regimens FOLFIRI (5-FU, irinotecan, and leucovorin), FOLFOX (5-FU, oxaliplatin, and leucovorin), or XELOX (capecitabine, oxaliplatin). These regimens are applied in combination with the epidermal growth factor antibodies cetuximab or panitumumab (depending on RAS mutation status) or the vascular epidermal growth factor antibody bevacizumab [3]. Other newer agents to inhibit tumor vascularisation and growth include regorafenib and aflibercept, which can also be combined with the aforementioned chemotherapy regimens. The median survival time in patients undergoing palliative chemotherapy in combination with modern antibodies or tyrosine-kinase inhibitors is around 20 months [4-7]. In some patients, elective resection of liver metastases can be considered, usually accompanied with neo-adjuvant and adjuvant chemotherapy [8].

2.2 Current evidence of physical activity interventions in cancer

Observational studies have linked physical inactivity with colon cancer incidence. Moreover, increased physical activity (PA) is associated with lower recurrence rates in observational studies of colon cancer patients after curative treatment [9-11]. Yet, contrary to cardiovascular medicine, increasing PA is not part of standard care for cancer patients. Several randomized trials have shown that increased PA during and after cancer treatment is feasible [12] and can lead to reduction of cancer-related fatigue, depression, anxiety [13], and improved quality of life [14, 15]. Importantly, in a recent randomized trial breast cancer patients who underwent a supervised exercise training during adjuvant chemotherapy suffered from significantly less side effects (nausea, vomiting) and needed less chemotherapy dose reductions than the control group with care as usual [16]. However, based on a recent Cochrane review, these already conducted trials were very heterogeneous regarding their patient populations and PA interventions, which make it difficult to generalize the results. Moreover, many trials were small and effect estimates were likely biased [17]. The impact of PA on cancer progression and survival is still unclear, because endpoints such as progression-free survival (PFS) have not systematically been investigated in a prospective randomized setting so far.

Below is a review of the so far published randomized clinical trial reports and protocols that were identified by a recent systematic Cochrane review [17] and an updated MEDLINE search for RCTs investigating PA in cancer patients. We focused on trials that primarily or partially included patients with advanced/metastatic disease of the colon.

Published randomized controlled trials

Oldervoll et al. reported a randomized controlled trial that specifically investigated the impact of a structured PA program in the palliative care setting [18]. Patients included in this trial mostly suffered from advanced or metastatic gastrointestinal cancer (32%) or breast cancer (22%). Other frequent diagnoses included lung cancer (16%) or urogenital cancer (13%). The PA intervention in this trial consisted of muscle strengthening and endurance training, which was conducted during the time of palliative treatment. Around 54% of patients were treated with palliative chemotherapy; other treatments included anti-hormonal therapy (19%) or radiotherapy (5.6%) only. The primary endpoint of this trial was physical fatigue. The authors calculated to include 77 participants per group to detect a two-point difference in the physical fatigue score (standard deviation, 4.4) with a significance level of 0.05 (two sided) and a power of 80%. Overall, 231 patients were included; 121 were randomized to the PA group and 110 to the care a usual group. There was no significant difference between the groups regarding the primary endpoint. However, patients from the PA...
group showed significant improvement regarding secondary endpoints such as physical performance and grip strength. The authors also reported that there was no difference between the two groups regarding overall survival (OS) [18] – importantly, the trial was neither powered to detect a survival difference nor was the population homogenous enough to compare survival times between groups (different diagnoses, different stages of disease, different treatment strategies).

Adamsen et al. reported the results from an RCT, which included 269 patients with various cancer diagnoses either in an adjuvant or palliative situation [19]. Most of them suffered from breast cancer (119 [44%], 99 without evidence of disease at baseline) or colorectal cancer (35 [13%], 23 without evidence for disease at baseline). Patients were randomized to a supervised exercise program (high intensity cardiovascular and resistance training, relaxation and body awareness training, massage) or to care as usual. The experimental intervention lasted for six weeks in addition to conventional care, mostly during active oncologic treatment. Adjusted for baseline score, disease, and demographic covariates, the intervention group showed an estimated improvement at six weeks for fatigue (primary endpoint) of 6.6 points (95% confidence interval 12.3 to 0.9, P=0.02). No data about PFS or OS were reported [19]. Furthermore, no subgroup analyses according to disease or stage of disease were reported.

**Planned randomized trials**

Several large randomized trials are planned or ongoing in the curative setting:

Courneya et al. published the protocol of the randomized Colon Health and Life-Long Exercise Change (CHALLENGE) trial [20]. It is designed to determine the effects of a structured PA intervention on outcomes for survivors of high-risk stage II or III colon cancer, who have completed adjuvant therapy within the previous 2–6 months. Overall 962 patients are planned to be included. The PA intervention will consist of a behavioural support program and supervised PA sessions delivered over a 3-year period, beginning with regular face-to-face sessions and tapering to less frequent face-to-face or telephone sessions. The primary endpoint is disease-free survival [20].

J. Thaler et al. are launching a large RCT within the Austrian Breast and Colorectal Cancer Study Group (ABCSG) in patients curatively treated for colon cancer: the primary hypothesis to be tested in 788 patients is whether a 1-year home-based individual exercise program after adjuvant chemotherapy for localized colorectal cancer improves disease-free survival as compared to care-as-usual (personal communication, ABCSG-C08). The ABCSG has just finished a pilot study (ABCSG-C07) to test feasibility of their exercise program.

In the palliative setting, there are no reports of randomized clinical trials with survival endpoints. There is one registered trial (Trials.gov Identifier:NCT00985400) from the MD Anderson Cancer center in patients with metastatic colorectal cancer, any line and independent of chemotherapy treatment: “Comparative Study of Oncologist Recommended, Home-Based Exercise Program and Relaxation Training for Physical Functioning and Symptom Control in Colon Cancer Patients (stage IV or recurrent)”.

In our own pilot study at the University Hospital Basel (submitted), we showed that in Swiss patients undergoing active treatment interest in a PA program is very high (30/38 patients showed interest) and a supervised aerobic PA program plus pedometer intervention is safe and feasible. Recruitment rate, with 10 patients in 6 weeks, was higher than for most interventional cancer trials. Important practical information was gained from this pilot study. It is essential to focus on individualized training (1:1 sessions). If appropriately informed, randomization between a PA intervention and “care as usual” seems feasible.

First evidence from an intervention trial that exercise might impact on survival comes from the START trial [21]. In an exploratory analysis 83% of the patients with breast cancer who underwent a supervised 12-week exercise program during adjuvant chemotherapy were alive and disease-free at 8 years compared to only 76% in the control group (HR, 0.68; 95% confidence interval (CI), 0.37–1.24; log-rank, P = 0.21). This trial was not designed and powered to show a meaningful difference in survival, but these results clearly warrant confirmation in a phase III trial.
2.3 Rationale for performing the trial

For any novel intervention to become part of what we recommend to our patients in clinical practice (standard treatment) it needs to reliably make a relevant difference for patients. Therefore, in evidence-based medicine, the pre-requisites are that a benefit on a clinically meaningful (i), objectively measurable standardized endpoint (ii) for the novel intervention as compared to the current standard has been shown in a well-defined population (iii) in a prospective, randomized, adequately powered trial (iv). While safety and feasibility as well as some improvements in fitness, fatigue and certain aspects of quality of life have been shown for physical activity in cancer patients during treatment, none of the pre-requisites above (i-iv) is fulfilled in the setting of patients with advanced colon cancer.

However, evidence, primarily from the adjuvant setting, that physical activity impacts on treatment tolerability [16] and tumor progression [21] is a strong enough rationale to now embark on this prospective trial. By assessing in a large randomized controlled trial whether a 12-week structured physical activity program during chemotherapy in patients with newly diagnosed colorectal cancer undergoing standard first-line chemotherapy improves progression-free survival as compared to standard first-line chemotherapy alone, all pre-requisites for a practice-changing intervention are met.

2.4 Choice of design and comparator

The hypothesis to be tested is whether a PA program in combination with standard first-line chemotherapy in patients with inoperable metastatic CRC improves treatment efficacy in terms of:
- progression-free survival (1° endpoint)
- patient-reported symptoms as reported with ESAS-r (1° patient-reported outcome)

A randomized phase III design was chosen in order to reach a rather definite conclusion on the efficacy endpoint. Progression-free survival (time from randomization to disease-progression or death) is a clinically meaningful and standardized efficacy outcome that serves as a very good surrogate for overall survival in patients with metastatic CRC [22]. There are numerous, recent large phase III trials using PFS as primary endpoint in this population that can serve as a reference for hypothesis formulation.

While survival time is important, quality of life is equally important in this palliative setting. Therefore a patient-reported outcome was chosen as co-primary endpoint. ESAS-r was specifically designed as a practical and simple tool for the palliative setting and covers the most relevant physical and psychological symptoms [23].

Since PA is not prescribed routinely to patients in this situation, the appropriate comparator (standard arm) is “standard first-line chemotherapy with care-as-usual”. Care-as-usual also entails maintaining usual (pre-diagnosis) physical activity, psychosocial support, and supportive care as commonly practiced at each site.

As a consequence of the design of the intervention and control groups, the mechanisms behind a potential benefit in efficacy of the intervention-arm can only be hypothesized based on secondary outcomes (treatment toxicity, dose density, etc.). This is, however, true with many new treatment approaches, where the mechanisms of action are often unknown: if a treatment works it will be used in routine practice exactly as within the trial, i.e. in this case the 12-week PA program will be “prescribed” together with standard first-line chemotherapy. To understand through which exact mechanism(s) the PA in combination with chemotherapy benefits patients, further trials, based on hypotheses from secondary outcomes of this trial, will be needed.

2.5 Choice of study population

The largest body of evidence that PA can impact on cancer outcome comes from patients with either breast or colon cancer [9-11]. Colorectal cancer is the third most common malignant disease in western countries with approx. 4000 new cases and 1200 deaths in Switzerland each year. Progress in this large population of patients is urgently needed; accrual seems feasible. Compared to breast cancer, first-line chemotherapy is fairly uniform, depending largely on the RAS-mutation...
status (a stratification factor). Also, PFS between the main groups of first-line chemotherapy (FOLFOX, FOLFIRI) is comparable [24]. It is also justified to focus on colorectal cancer patients, given that breast cancer patients are fairly over-represented in PA trials worldwide so far.
3 OBJECTIVES AND ENDPOINTS

3.1 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) in patients with metastatic colorectal cancer.

3.2 Endpoints
For definition of endpoints see section 13.

3.2.1 Primary endpoints
The co-primary endpoints are PFS and patient-reported symptoms as measured by the ESAS-r (Edmonton Symptom Assessment System revised).

3.2.2 Secondary endpoints
Secondary endpoints of the trial are:

Efficacy
- Overall Survival
- Best Objective Response
- Metastasectomy rate

Chemotherapy-related endpoints and toxicities
- Selected Adverse Events (as defined in Section 10.2) including chemotherapy-induced polyneuropathy
- Chemotherapy-completion-rate: absolute dose of chemotherapy applied in percentage of planned chemotherapy dose (only for first-line therapy) (See Section 13.2.2 for detailed description).
- Initiation or increase of anti-hypertensive drugs
- Overall treatment utility (OTU) [4] (further explanation see Section 13.2.2)

Patient reported outcomes (see Section 16.5 for detailed description)
- Depression and anxiety as measured by the Hospital Anxiety and Depression Scale (HADS) [25]
- Appetite as measured by the Cancer Appetite and Symptom Questionnaire (CASQ)
- General Distress as measured by a Distress thermometer
- Therapeutic relationship (patient – physical therapist) (in intervention group only)

Exercise endpoints
- Exercise capacity as measured by the Sit-to-stand Test (STST)
- Self-reported physical activity as measured by the Global Physical Activity Questionnaire (GPAQ)
- Metabolic equivalent of task (MET)-hours per week (in intervention group only)
- Body mass index

Translational studies see Section 18
4 TRIAL DESIGN

This is a multicenter randomized open label trial.

![Diagram of trial design]

**FIGURE 1:** Trial design. Patients with first diagnosis of metastatic colorectal cancer will be randomized in a 1:1 ratio to standard palliative chemotherapy or standard palliative chemotherapy plus a structured PA program and a daily step goal measured with pedometers. CRC=colorectal cancer; PA=physical activity.

4.1 Methods of minimizing bias

4.1.1 Randomization procedure

Patients will be allocated in a 1:1 ratio to the two treatment arms using the minimization method with a random component (80% allocation probability) to reduce predictability of allocation.

Randomization is stratified according to the following factors:

- Saltin-Grimby Physical Activity Level Scale (SGPALS, description see Section 12.1.1): group 1+2 (physically inactive and light physical activities) versus group 3+4 (moderate and vigorous physical activities)
- RAS status (see Section 12.1.1): mutated versus wild-type
- Location of the primary tumor: rectum versus left hemi-colon versus right hemi-colon
- Alkaline Phosphatase: normal vs >ULN

Randomization is done via internet ([www.sakk.ch/edc](http://www.sakk.ch/edc)).

4.1.2 Methods of minimizing bias

- Due to the nature of the treatment arms, neither patient nor the investigator can be blinded to the intervention.

  However, to minimize this bias, we have chosen an objective standardized endpoint, i.e. progression-free survival determined by progression on imaging (CT scan or MRI assessed in both groups regularly and at the same time points) according to RECIST criteria.

- The physical therapists, who conduct the PA program, are likely to be biased towards expecting a benefit of the intervention.

  To minimize this bias, the radiologists who determine the primary endpoint (PFS) will be blinded to the intervention. Other endpoints (STST, PROs) are assessed by the investigators (oncologist and site study team) who are not directly involved in administering the PA program. It is, however, not possible to blind the oncologist to the intervention.

- A placebo control for PA is not feasible. Sham-interventions such as regular meetings with a physical therapist to discuss matters unrelated to PA (weather etc.) (= unspecific control condition, [26]) do not seem appropriate for this patient population who just learned of a life-threatening disease and undergoes active chemotherapy. And, even though such an unspecific control condition can minimize some of the attention-bias between the arms, it will not be possible to blind the intervention.

**Attention bias**

The intervention group will receive additional attention and form a relationship with a physical therapist; this could have an impact by itself on the measured endpoints (=attention bias). To minimize this bias, one possibility would have been to introduce a sham intervention where the
participants receive the same amount of attention but without the physical activity program. However, we opted against this for feasibility reasons: since the current standard of care is no exercise (i.e. the control arm) we would have needed to introduce a third arm (sham-intervention) which would have inflated the patient numbers and the resources for this trial beyond what is feasible. Acknowledging that we will not be able to eliminate the attention bias has the following consequences: if the PA intervention proves beneficial, we will not know whether the effect is conveyed through PA or other factors such as psychological factors derived from additional attention. This does not imply, however, that the PA intervention (exactly as described in the protocol) should not become standard of care: for many standard medical interventions we do not know the exact mechanisms. However, we will be able to estimate the dimension of the therapeutic relationships from our patient-reported outcomes, which will allow formulating hypotheses to be tested in further trials.

**Bias through changed exercise behavior in control group ("Dilution" of intervention by increased PA in the control group)**

It is conceivable that patients randomized to the control group will start exercising more than they did before. Patients in the control group are allowed to exercise just as they did before participating in this trial (e.g. a life-long runner does not have to stop running). We deliberately do not measure the gold standard parameter of aerobic fitness (VO\textsubscript{2}max) nor do we document the physical activity of the patients in the control group (no patient diary, no pedometer), because this would change the exercise behavior in the control patients. There is ample evidence from controlled trials that physical parameters (VO\textsubscript{2} max, strength) are significantly increased by a PA program in cancer patients during treatment; we do not need to re-confirm these findings at the cost of introducing bias by a physically active control group. However, in order to assess how physical fitness evolves over time in both groups, and to allow for a conclusion whether an observed difference between groups is indeed portrayed via improved physical fitness, we have introduced the Sit-to-stand Test (STST). This test is a simple, standardized test for endurance and lower body strength that can be performed during a routine visit with the oncologist in all patients (at baseline, week 12, 18, 24 and 48). Also, physical activity will be assessed in a short questionnaire (GPAQ – Global Physical Activity Questionnaire) in all patients at baseline, week 6, 12, 18, 24 and 48 in all non-progressing patients. This will also give information whether patients in the intervention group stay physically active beyond the 12-week intervention.

### 5 TRIAL DURATION AND TERMINATION

The inclusion of patients is planned to start in Q4 2015 and will stop after the inclusion of approximately 524 evaluable patients, which is expected in Q2 2021. End of trial intervention is expected for Q3 2021.

Non-evaluable patients (see Section 13.1) will not be replaced.

For the co-primary endpoint PFS, patients will be followed until progression. Assessment of the co-primary endpoint ESAS-r (baseline, week 6, 12, 18, 24, 48) will also be stopped at progression.

For Overall survival, all patients will have a lifelong follow-up.

Trial termination (last patient last visit) is expected to be in 2026.

Accrual may be interrupted or the trial may be stopped early based on the results of an interim feasibility analysis (see section 15, Statistical Considerations) or if new scientific data become available which change assessment of risk/benefit.
6 SELECTION OF PATIENTS

6.1 Inclusion criteria

6.1.1 Written informed consent according to ICH/GCP regulations before randomization.

6.1.2 Patient with histologically or cytologically confirmed colorectal carcinoma (CRC) required to start palliative first-line systemic therapy for inoperable or metastatic disease. Patients who were diagnosed with histologically or cytologically confirmed non-metastatic CRC earlier and now relapsed with metastatic disease are also eligible, if any prior neo-adjuvant or adjuvant chemotherapy has been completed more than 4 months before inclusion into this trial.

6.1.3 Patient has measurable disease on CT scan or MRI to be performed within 4 weeks before randomization (measurability criteria according to RECIST 1.1 [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).

6.1.4 Command of written and spoken language allowing for informed consent and for filling in trial questionnaires.

6.1.5 Baseline patient-reported outcomes (PROs) have been completed.

6.1.6 WHO performance status 0-2 (see Appendix 3).

6.1.7 Age 18-75 (80) years (if WHO is 0-1 upper age limit is 80 years).

6.2 Exclusion criteria

Any potential patient who meets any of the following criteria has to be excluded from entering the trial.

6.2.1 Cycle ergometer stress test (completed within 28 days before trial start) shows significant signs of ischemic heart disease or high-grade arrhythmias, which preclude an exercise program.

6.2.2 Pre-existing severe medical conditions precluding participation in a physical activity program as determined by the local investigator. Such conditions include: chronic heart failure (greater than NYHA II see Appendices AAppendix 5), recent myocardial infarction (less than 3 months ago), unstable angina pectoris, clinically significant arrhythmias, uncontrolled hypertension with repeated systolic blood pressure above 160mmHg, and COPD (requiring oxygen supply or GOLD stadium greater than 2).

6.2.3 Inability to ride a cycle ergometer e.g. for musculoskeletal reasons.

6.2.4 Inability to perform 50 Watt on a cycle ergometer (during Cycle ergometer stress test), for any reason.

6.2.5 Patients who are a priori planned for curative surgery including metastasectomy. It is allowed to include patients for whom metastasectomy might be an option if chemotherapy induces a significant response.

6.2.6 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, uncontrolled diabetes).

6.2.7 Concurrent treatment in a trial with experimental drugs or other anti-cancer therapy, which are hypothesized to alter tumor progression. Participation in an observational trial or a translational trial is allowed.

6.2.8 Previous malignancy within 5 years with the exception of adequately treated cervical carcinoma in situ, localized non-melanoma skin cancer, superficial bladder cancer (non-muscle invasive disease), localized prostate cancer (T1-3).

6.2.9 Psychiatric disorder precluding understanding of trial information, giving informed consent, filling out PRO forms, or interfering with compliance.
6.2.10 Any psychological, familial, sociological or geographical condition potentially hampering proper compliance with the trial protocol.
7 RANDOMIZATION

7.1 Pre-randomization procedure

Prior to randomization, the following steps have to be performed:

- Fill in the patient screening and enrollment list
- Obtain written informed consent from the patient prior to any protocol-specific procedure
- Check the eligibility criteria (cave: in order to be eligible the patient must pass a physician-supervised cycle-ergometer test, see Section 12.1.1)
- Patient must fill in the baseline Patient Reported Outcomes questionnaire within 14 days prior to randomization
- Patient has to perform the Sit-to-stand Test within 28 days prior to randomization according to the trial protocol

7.2 Randomization procedure

Randomization is done via Internet www.sakk.ch/edc or - only if this is not possible - by faxing the completed, dated and signed form E to the SAKK CC (Opening hours: Monday to Friday 8:00 a.m. to 5:00 p.m.).

SAKK Coordinating Center
Effingerstrasse 40
CH – 3008 Bern
Tel. +41 31 389 91 91
Fax +41 31 389 92 00

In order to receive authorization for online randomization/data entry, sites must send a copy of the completed staff list (available on the SAKK website) to the SAKK CC. Login details for the EDC system will be sent to authorized persons within 2 working days.

The SAKK CC will be closed on the following days:

1st January 1st August (National holiday)*
2nd January 4th Monday of November, from 3:00 pm
Good Friday (Friday before Easter)* 24th December (from 12:00 noon)
Easter Monday 25th December
Ascension Thursday* 26th December
Whit Monday (Pentecost) 31st December (from 12:00 noon)

* The SAKK CC will close at 4:00 pm on weekdays before these holidays.

7.3 After randomization

Report the baseline clinical and laboratory information, baseline symptoms, PRO Questionnaires, Sit-to-stand-test score, and baseline tumor assessment in the CRFs.

Systemic therapy must start as soon as possible but at the latest within 14 days after randomization. The exercise intervention should start as close as possible to day 1 of cycle 1 of systemic therapy but at the latest within the first 3 weeks of systemic treatment.

Update the screening and enrollment list and fill in the patient identification list.

The signed Eligibility Form (printout of CRF form ER) has to be sent to the SAKK CC by mail or fax within one month after randomization.
8 DRUG SUPPLY AND HANDLING
The standard treatment applied in both arms must be prescribed and used in accordance with applicable clinical standards and the Swissmedic-approved product information.

9 TRIAL INTERVENTION

9.1 Intervention overview
The term ACTIVE-program describes a 12-week exercise program consisting of a combination of a bi-weekly supervised aerobic exercise (cycle ergometer) and a self-paced increase in physical activity during daily life using a pedometer with a daily step goal as a motivational tool. The ACTIVE-program was specifically designed for use in cancer patients during chemotherapy in a collaboration of the University of Basel, the University of Zurich, and the Memorial Sloan Kettering Cancer Center, USA [27, 28]. The ACTIVE-program has its own logo, designed by the renowned artist from Basel Louis Mermet.

The purpose of the logo is to give additional motivation to both participants and instructors to adhere to this specific training program by adding a sense of community.

The American College of Sports Medicine (ACSM) convened a panel of experts to review the available evidence supporting exercise prescription guidelines for cancer survivors [29, 30]. The panel concluded that cancer survivors should follow the 2008 Physical Activity Guidelines for Americans (≥ 150 minutes per week of moderate-intensity, or ≥ 75 minutes per week vigorous-intensity aerobic exercise or an equivalent combination of moderate and vigorous intensity aerobic exercise) for cancer survivors. Patients in this trial are not “survivors” but cancer patients undergoing treatment. They have, however, a median life expectancy of around 2 years and it has been shown that exercise in cancer patients undergoing treatment is safe. Therefore, similar exercise goals as for cancer survivors can be set.

To achieve 150 minutes of physical exercise per week by the end of the program, participants will be asked to exercise 2 x 45 minutes (including warm-up and cool-down) under supervision in the ambulatory hospital setting (90 minutes); this is the supervised aerobic exercise training program. In addition to the supervised training, each patient is motivated to be more active in everyday life, the so-called self-paced physical activity program.

9.2 Experimental intervention: Physical exercise ACTIVE-program
The ACTIVE-training program must start as close as possible to day 1 of cycle 1 of systemic treatment. If at all possible, the ACTIVE-program should start during the same week as systemic treatment. The ACTIVE-program needs to be started within 3 weeks of the start of systemic treatment.

9.2.1 Supervised aerobic exercise training program
The supervised exercise program will be performed twice a week for 12 weeks. Each patient will perform the exercise training on a cycle ergometer under supervision of a physical therapist at the study site. The training sessions will take place on nonconsecutive days.

The program will be individually tailored to each patient based on the training protocol (FIGURE 2) described below and is aimed at increasing cardiorespiratory fitness. Each patient’s HR_{max} will be taken from the cycle ergometer stress test and documented into the activity diary, so that the physical therapist can adjust the training program to each patient’s fitness. All exercise-training sessions will include a warm-up in the beginning and a cool down at the end.
Principles of exercise training, i.e. 1. specificity of the training program (form, dose, and intensity), 2. progression over time (introductory, intermediate, and optimization phase), 3. overload (80% - 85% of HR_{max}), 4. initial values (exercise history and cardio respiratory fitness state of the patient at baseline), 5. reversibility (modulation of the training intensity during chemotherapy side effects), will be respected and considered in the exercise program [31].

The supervised sessions are critical to maximize adherence (>80% of planned sessions) to the intervention both in terms of attendance and adherence to the prescription. Optimizing adherence is critical to ensure a robust test of aerobic training efficacy [29]. Research shows that interval training is perceived as more interesting and fun compared to continuous moderate training, which generally leads to a higher commitment and higher adherence rates [32]. Plus research (mostly with patients with chronic heart disease and patients with COPD) has shown that high-intensity interval training can be considered as safe as continuous moderate training and often leads to an even better increase of aerobic capacity [33-35].

The training plan is shown in **FIGURE 2** and is divided into three parts: 1) introductory phase, 2) intermediate phase, and 3) optimization phase. In the introductory phase light interval training is introduced, so that patients get used to the bike ergometer and experience different loads and paces. In the intermediate phase interval training with HR_{max} ≥ 85% will be introduced. In the optimization phase either 2 interval sessions or 1 interval session and 1 continuous moderate session can be performed.

The training plan is built up progressively. Over time warm-up minutes will be reduced (in addition to the general 2-3 min warm up and cool-down) from 8 min in the beginning to no additional warm-up starting at level 9. Over the time of the program, interval length will be increased and the recovery period will be decreased. The goal at the end of the program is to achieve a 1:1 ratio of interval time and recovery time (2 min at a workload of ≥ 85% of HR_{max}, followed by 2 min of active recovery at HR_{max} from 50 - 70%) or to be able to perform a continuous moderate training for 30 min at 75-80% HR_{max}. Each session will last ~30-32 min without the warm-up and cool-down-minutes. For the interval sessions recovery time can be individually adjusted to the patient’s fitness level and wellbeing (e.g. longer recovery period after the interval unit).
### Fig. 2 Supervised aerobic cycling exercise training – protocol

<table>
<thead>
<tr>
<th>Introductory Phase</th>
<th>Level 1 and 2:</th>
<th>Level 3 and 4:</th>
<th>The goal of this phase is:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1 – 4</td>
<td>Session 1, 2, 3 und 4:</td>
<td>Session 5, 6, 7 and 8:</td>
<td>patients get used to bike</td>
</tr>
<tr>
<td>(levels equal a week)</td>
<td>8 min @ 50-70% HR&lt;sub&gt;max&lt;/sub&gt; (~60% VO&lt;sub&gt;2max&lt;/sub&gt;)</td>
<td>6 min @ 50-70% HR&lt;sub&gt;max&lt;/sub&gt; (~60% VO&lt;sub&gt;2max&lt;/sub&gt;)</td>
<td>ergometer and exercise training</td>
</tr>
<tr>
<td>2 interval sessions/week</td>
<td>3 interval cycles:</td>
<td>4 interval cycles:</td>
<td>~ A light interval training will be</td>
</tr>
<tr>
<td></td>
<td>1 min @ ≥ 70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1 min @ ≥ 75% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>introduced</td>
</tr>
<tr>
<td></td>
<td>6 min recovery @ 50-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>5 min recovery @ 50-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>- patients can experience</td>
</tr>
<tr>
<td></td>
<td>Level 3 and 4:</td>
<td></td>
<td>different paces and work loads</td>
</tr>
<tr>
<td></td>
<td>Session 5, 6, 7 and 8:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 min @ 50-70% HR&lt;sub&gt;max&lt;/sub&gt; (~60% VO&lt;sub&gt;2max&lt;/sub&gt;)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 interval cycles:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 min @ ≥ 75% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 min recovery @ 50-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate Phase</td>
<td>Level 5:</td>
<td>Level 6:</td>
<td>A “real” interval training will be</td>
</tr>
<tr>
<td>Level 5 – 8</td>
<td>Session 9 und 10:</td>
<td>Session 11 und 12:</td>
<td>introduced in this phase with</td>
</tr>
<tr>
<td>2 interval sessions/week</td>
<td>4 min @ 65-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>4 min @ 65-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>HR&lt;sub&gt;max&lt;/sub&gt; ≥ 85% for the interval</td>
</tr>
<tr>
<td></td>
<td>4 interval cycles:</td>
<td>4 interval cycles:</td>
<td>unit</td>
</tr>
<tr>
<td></td>
<td>1 min @ ≥ 85% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>1 min @ ≥ 85% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>recovery time can be individually</td>
</tr>
<tr>
<td></td>
<td>5 min recovery @ 50-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>5 min recovery @ 50-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>adjusted to the</td>
</tr>
<tr>
<td>Optimization Phase</td>
<td>Level 7:</td>
<td>Level 8:</td>
<td>patient’s fitness level and</td>
</tr>
<tr>
<td>Level 9 – 12</td>
<td>Session 13 und 14:</td>
<td>Session 15 und 16</td>
<td>wellbeing (e.g. longer recovery</td>
</tr>
<tr>
<td>2 sessions/ week: either 2 interval</td>
<td>2 min @ 65-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>2 min @ 65-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>after the interval unit).</td>
</tr>
<tr>
<td></td>
<td>5 interval cycles:</td>
<td>5 interval cycles:</td>
<td>- Whole session length ~30-35</td>
</tr>
<tr>
<td></td>
<td>2 min @ ≥ 85% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>2 min @ ≥ 85% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>min</td>
</tr>
<tr>
<td></td>
<td>4 min recovery @ 50-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>4 min recovery @ 50-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Level 9 – 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interval Session 17 – 24:</td>
<td>Interval Session 17 – 24:</td>
<td>Interval Session: Goal is a 1:1</td>
</tr>
<tr>
<td></td>
<td>4 – 6 interval cycles:</td>
<td>Continuous moderate session 17 – 24:</td>
<td>ratio (2min ≥ 85% HR&lt;sub&gt;max&lt;/sub&gt;/ 2 min</td>
</tr>
<tr>
<td></td>
<td>2 min @ ≥ 85% HR&lt;sub&gt;max&lt;/sub&gt; (~≥ 80% VO&lt;sub&gt;2max&lt;/sub&gt;)</td>
<td>30 min @ 75%-80% HR&lt;sub&gt;max&lt;/sub&gt; (~75% VO&lt;sub&gt;2max&lt;/sub&gt;)</td>
<td>recovery. But length of recovery</td>
</tr>
<tr>
<td></td>
<td>2 min recovery @ 50%-70% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td></td>
<td>rate can be adjusted to individual</td>
</tr>
<tr>
<td></td>
<td>Continuous moderate session 17 – 24:</td>
<td></td>
<td>needs of patients.</td>
</tr>
<tr>
<td></td>
<td>30 min @ 75%-80% HR&lt;sub&gt;max&lt;/sub&gt; (~75% VO&lt;sub&gt;2max&lt;/sub&gt;)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR<sub>max</sub> = maximum heart rate as measured in the pre-treatment cycle ergometer stress test for each individual

The training protocol (FIGURE 2) is meant as a general guideline. The estimation of HR<sub>max</sub> values
in relation to VO₂\textsubscript{max} relies on the ACSM guidelines [36]. The training protocol is not stratified according to the SGPAL groups, but is based on pre-treatment HR\textsubscript{max}.

### 9.2.2 Adjustment of training intensity

Physical therapists can adjust the protocol according to the patient’s fitness level and wellbeing (including form of the day). Adjustments can be done by shortening the interval time or lengthening the recovery time. The Borg scale (Fig. 3) will guide these adjustments. The goal is to keep high adherence to the training sessions, therefore keeping the patients’ motivation high is important. For that reason, the program may be maintained at a level, in which patients still feel comfortable to sustain the program (or if patients experience treatment side effects).

During the entire training session the subjective wellbeing of each patient will be assessed by the Borg Rating of Perceived Exertion (RPE) Scale (BORG scale) at mid-time. The Borg Scale is a tool for estimating effort and exertion, breathlessness, and fatigue during physical work. [37, 38]

**Fig. 3 Modified Borg-Scale (in German and English)**

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>überhaupt keine Atemnot (nothing at all)</td>
</tr>
<tr>
<td>0.5</td>
<td>sehr sehr milde (knapp wahrnehmbar) (very, very slight shortness of breath)</td>
</tr>
<tr>
<td>1</td>
<td>sehr milde (very mild shortness of breath)</td>
</tr>
<tr>
<td>2</td>
<td>milde (mild shortness of breath)</td>
</tr>
<tr>
<td>3</td>
<td>mässig (moderate shortness of breath or breathing difficulty)</td>
</tr>
<tr>
<td>4</td>
<td>recht schwer (somewhat severe)</td>
</tr>
<tr>
<td>5</td>
<td>schwer (strong or hard breathing)</td>
</tr>
<tr>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>sehr schwer (severe shortness of breath or very hard breathing)</td>
</tr>
<tr>
<td>8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>sehr, sehr schwer (fast maximal) (extremely severe)</td>
</tr>
<tr>
<td>10</td>
<td>maximale Atemnot (Dyspnoe) (shortness of breath so severe you need to stop)</td>
</tr>
</tbody>
</table>

### 9.2.3 Interruption of the supervised training program

Breaks will happen and are allowed (e.g. due to chemotherapy complication such as neutropenic fever). When getting back into the program, the physical therapist will adjust the training according to the following guidelines:

- After an interruption up to 2 weeks: restart one level below the level before the break.
- After an interruption up to 4 weeks: restart 2 levels below the level before the break.
- After an interruption of more than 4 weeks: restart the training from level 1.
- If an interruption lasts more than 6 consecutive weeks or all interruptions together add up to more than 8 weeks the ACTIVE-program is stopped.

The physical therapist will adjust the pace of building back up into the training program in line with the patients’ fitness and wellbeing.

The total number of sessions will remain 24.

If a patient has disease progression during the ACTIVE-program, the patient is free to decide whether to finish the 12-week ACTIVE-program or not.
9.2.5 Discontinuation/Interruption of a supervised session due to side effects

The current exercise session should be discontinued if one of the following events occurs:

- Chest pain
- Enduring dizziness/fainting
- Vertigo
- Unexpected shortness of breath (“out of proportion” to the extent of exertion)
- Severe nausea/vomiting
- Acute pain (other than muscle soreness)
- Any unexpected exercise-induced event, that the supervising physical therapist judges as relevant or harmful

In case an exercise session had to be discontinued due to one of the above mentioned reasons, the physical therapist has to contact the treating oncologist (local PI or SI). For such an incident, the physical therapist receives the “ACTIVE emergency document” with the corresponding phone numbers of the emergency-oncologist for the study site. The contacted MD then decides whether the patient needs immediate medical care and whether the next session can be performed as planned or needs to be adjusted.

If a training session had to be discontinued only for a few minutes (e.g. dizziness), but was continued after a short break (e.g. dizziness resolved), physical therapists do not have to contact the treating oncologist. Physical therapists will document the session interruption and the reason in the corresponding training protocol under “comments”.

9.2.6 Timing of the supervised exercise sessions in relation to systemic treatment

As outlined above, the ACTIVE-program should start as close as possible but no later than 3 weeks after day 1 of cycle 1 of systemic treatment.

The two trainings sessions each week should be on non-consecutive days.

If patients receive a chemotherapy treatment with continuous infusional 5FU, this needs some logistic planning:

- If exercise sessions are only possible during the week (which might be the case at most sites) it might be possible to time the infusional 5FU during the weekend. If this is not possible, the first exercise session of the week might be in the morning of the same day as the start of infusional 5FU (before start of chemotherapy) and the second session towards the end of the week (after infusional 5FU). Supervised cycle ergometer training with a running 5FU-pump/infusion should be avoided, but can exceptionally take place if - according to the treating oncologist - the risk of cardiac complications is minimal, the patient is informed about the potentially increased risk of cardiac events and if at least one previous cycle of infusional 5FU has been administered without cardiac events.

- If a site offers supervised exercise sessions also on Saturdays or Sundays, infusional 5FU can be given during the week (after the first exercise session on Mon or Tue).

9.2.7 Self-paced physical activity program

In addition to the supervised exercise program twice a week, patients of the intervention group are encouraged to be physically active in their leisure time. This should include an aerobic component of moderate intensity in agreement with the participant's fitness and desires. Recommended activities are: walking, climbing stairs, gardening, housekeeping, cycling, getting off the bus or tram earlier, walking in the park, the forest or with the dog, walking with a peer etc. All patients in the exercise group will receive a pedometer to improve physical activity levels and motivation [28, 39].

The daily step target goal is set on 8500 steps per day (only on days without supervised exercise sessions). This is based on the experience with adjuvant breast cancer patients who achieved an average of 83% of the target of 10 000 steps [40]. To start off, each patient will define an individualized step goal together with the physical therapist depending on the fitness-level and wellbeing for each week. The step goal will gradually increase (plus ~ 500 steps a week) toward the 8500 steps a day. The step goal will be increased over the time of the program, so that patients
will get at least 150 minutes of physical activity into their week by the end of the program. If a patient already reaches the goal of 8500 steps a day, this step goal will be kept and the patient will be motivated to reach those 8500 steps as many times as possible. The step goal is meant for days without cycle ergometer training.

Each patient of the intervention group will receive an activity diary together with the pedometer. In the activity diary all activities will be logged (minutes per day) and rated regarding their intensity (mild, moderate, high). The achieved number of steps will be written down each day by the patients in the ACTIVE training diary. The activity diary will be checked and supervised on a weekly basis by the physical therapist. The physical therapist will also give some motivational advice to the patients if needed.

9.2.8 Mandatory equipment at each participating site

- Cycle ergometer (The CE-identification number (“CE-Kennzeichnung”, 4 digit number) of each ergometer used in the trial will have to be reported. If unknown, it can easily be asked from the manufacturer)
- Heart rate monitor (e.g.: polar watch)
- Emergency plan for cardiopulmonary resuscitation

9.2.9 Pedometer

Pedometer: A pedometer will be provided free of charge by SAKK for each patient in the intervention group. Pedometers are worn on 5 days a week (voluntary on the 2 days per week with supervised ergometer trainings) during the whole intervention period of 12 weeks. If a patient wants to wear the pedometer each day, even on ergometer training days, that is allowed too.

A pedometer is a simple device to monitor daily activities and steps. The main purpose of the pedometer in the ACTIVE-program is to motivate the participants to walk more during their daily activities in order to achieve a step goal. Unused pedometers will have to be returned to SAKK at the end of the enrollment period of the trial.

A pedometer is a type of motion sensor that is low-cost, unobtrusive, and accurate [41, 42]. According to the existing research on accuracy and validation of pedometers, the NEW-LIFESTYLES SW-200 Digiwalker Pedometer (DW) used in this trial is one of the most accurate in predicting steps, distance, and gross kilocalories for walking [41]. Prior research suggests to report pedometer data as steps [43] because it is the most accurate [42]. The SW-200 DW pedometer is simple and easy to use; it tracks the number of steps the participants take each day. The internal sensor mechanism uses a spring-suspended horizontal lever that moves up and down in response to the hip’s vertical accelerations. This movement opens and closes an electrical circuit: the lever arm makes an electrical contact (metal-on-metal), and a step is registered [44]. In general, pedometers tend to overestimate distance done at slower speeds and underestimate distance done at higher speeds [41]. DW Pedometer was one of the pedometers which gave mean values that were within ±1% of actual values at speeds of 80 m x min⁻¹ and above [41]. At slower speeds pedometers are not as accurate in step counting, but the DW pedometer showed acceptable accuracy at slower speeds and thus is a good choice for use in research [41] and the intramodel reliability for the DW was very high (>0.99) [42].

9.2.10 Staff requirement (ACTIVE-instructors)

The supervised exercise sessions will be performed at the participating sites under direct supervision of an exercise physiologist or physical therapist. 2 to 3 physical therapists (or equally qualified persons) per hospital are appointed to regularly supervise the training (=ACTIVE-instructors). Based on previous literature with structured exercise training during chemotherapy an adherence rate of ~70% is expected [19, 45]. Jones et al. 2010 states that with supervised exercise sessions, one could maximise adherence to > 80%, which is our goal [29].
9.2.11 Qualifications for ACTIVE-instructors and training of personnel

In order to qualify as an ACTIVE-instructor, instructors have to be either physical therapists (used throughout the text of this protocol), or similarly qualified staff (e.g. sports scientist including university students, medical students or MDs) who are specifically instructed by the study team for the ACTIVE-program and have to be proficient in cardio-pulmonary resuscitation (CPR). Education sessions for instructors will take place before the opening of the trial and 6-monthly thereafter. One-to-one educational sessions are provided for instructors who join the team in-between.

Each site has a local PI (oncologist of the study centre) and 2-3 appointed physical therapists (or equally qualified staff), who are specifically trained for the ACTIVE trial. All participating instructors have to be on the “staff list”.

Role of physical therapists (ACTIVE-instructors)

Each site will determine a supervising physical therapist and 1-2 deputies, who are trained as well. Physical therapists (PT) (or other qualified ACTIVE-instructors (see above)) perform the following tasks:

- The PT documents if the patient attended the training session or not. If not, the PT should call the patient and document the reason why the patient did not show up. In case there is a medical reason, the treating oncologist has to be informed (if not already involved).
- At the beginning of the training intervention, the PT instructs the participant on how the pedometer and activity diary are used and discusses individual strategies on how to best integrate physical activity into daily life with each participant. The PT has an important role in motivating the patient and keeping the process fun. During the intervention program, the PT will discuss with the patient regularly (each week) how the self-paced activities are going. If needed, the PT will give suggestions or ideas how physical activities at home could be increased (this can be done while the patient is on the cycle ergometer).
- Each week the PT will check the activity diary of the patient to see if steps and activities are written down. If not, the PT tries to motivate the patient to fill in the information, particularly the daily step count. If steps achieved are < 8500, the PT sets an individual step goal together with the patient (this can be done while the patient is on the cycle ergometer).

9.2.12 Setting of training

The supervised exercise sessions will be performed at the participating hospitals, primarily at the physical therapy department of the respective hospital.

9.3 Control intervention: Care as usual

All patients will undergo standard chemotherapy treatment for metastatic colorectal cancer. Care as usual is defined as following common practice of supportive care during palliative chemotherapy at each participating site according to the local guidelines. Patients in the care-as-usual group are not actively encouraged to change their physical activity level i.e. start a fitness program during chemotherapy. The above described structured physical exercise program (ACTIVE-program) can be offered to interested patients of the control group after the first tumor progression (PFS defining event).

Patients in the control arm will receive an information booklet with information on the ACTIVE study and general information on coping with cancer – topics include general recommendations concerning nutrition, treatment side effects and coping with fatigue.

9.4 Duration of physical exercise intervention

The PA intervention is planned for 12 weeks (2 sessions per week = 24 training sessions) during first-line systemic therapy (chemotherapy plus antibody). The physical activity program has to start as close as possible to day 1 of cycle 1 and within 3 weeks after the first day of systemic treatment. The PA intervention will be stopped if one of the following events occurs:
In case of progression of disease, the patient can decide whether to continue the PA program for the entire planned 12 weeks or not. All patients will be further assessed until progression (see Section 12.3 for evaluations after intervention termination). After progression patients will be followed up lifelong.

### 9.5 Treatments not permitted during trial treatment phase

Not applicable.

### 9.6 Precaution

For the trial specific intervention no additional safety precautions measures regarding contraception, pregnancy and breastfeeding are applicable. For the systemic standard therapy to treat the metastatic colorectal cancer it is referred to the Swissmedic-approved product information for safety precautions concerning contraception, pregnancy and breastfeeding, applicable for women with child-bearing potential and to men who take part in this trial.
10 ADVERSE EVENT REPORTING, PHYSICAL ACTIVITY INTENSITY MODIFICATION, DOSE MODIFICATIONS, AND SUPPORTIVE TREATMENT

Patients in this trial are treated with standard systemic first-line treatment with known and previously reported side effects. Since the systemic treatment is NOT the experimental intervention, only selected adverse events (below) that are related to systemic treatment, will be collected.

10.1 Definition of adverse event (AE)

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.

10.2 Reporting of selected AEs

All included patients will undergo standard palliative chemotherapy in combination with an antibody (depending on RAS mutation status and choice of the treating oncologist). Efficacy and safety profiles of these standardized treatments are well established and have comprehensively been investigated before [3, 5-7, 46]. Moreover, physical exercise interventions in cancer patients are also considered as safe interventions [12, 14, 17, 18]. The reason to document therapy-related AEs at all is to assess whether the PA program has an impact on the frequency and severity of the occurrence of typical therapy-related side-effects.

Patients will be instructed by the investigator to report the occurrence of any AE. The investigator assesses all AEs and records those which are listed below and are at least possibly related to the chemotherapy, the antibody treatment, or the PA, as defined below. The AE reporting period is from randomization until end of week 18 after randomization for all patients. In case the duration of the PA intervention is different from 12 weeks (shorter or longer because of delays) AEs will be assessed and recorded until 30 days after completion of the PA intervention.

Ongoing AEs need to be followed up until resolution or start of new line of therapy.

AEs are coded with the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0, and assigned a grade (from 1 = mild to 5 = death related to AE) as well as a relationship, separately to chemotherapy, antibody, and PA. The NCI CTCAE v4.0 (as pdf) as well as instructions on how to use the criteria can be found on:


Only the following AEs will be assessed and documented because they are typical side effects of the standard chemotherapy or antibody treatments:

1. Anemia (only AEs ≥ grade 3 will be documented)
2. Febrile neutropenia
3. Decreased neutrophil count (only AEs ≥ grade 3, i.e. < 1.0 \(10^9\)/L, will be documented)
4. Diarrhea (only AEs ≥ grade 3 will be documented)
5. Mucositis oral (only AEs ≥ grade 3 will be documented)
6. Vomiting (AEs ≥ grade 3 will be documented)
7. Palmar-plantar erythrodysesthesia syndrome (as a typical side effect of 5-FU or capecitabine, grade 1-3 will be documented)
8. Peripheral sensory neuropathy (as a typical side effect of oxaliplatin, only AE ≥ grade 2 will be documented)
9. Rash acneiform (as typical side effect of cetuximab/panitumumab therapy, only grade ≥3 will be documented)
If any other AEs occur, they only should be reported if grade ≥ 3 or if judged as clinically relevant (e.g. nose bleeding requiring tamponade) or lead to hospitalization and if related (possibly, probably, definitely) to chemotherapy, antibody, or PA intervention.

Note:
- Report the start and end date of the event and any changes in grading observed within the reporting period.
- Baseline symptoms will be recorded on the case report form (CRF) and will continue to be followed up during treatment.
- AEs are documented by the codes according to CTCAE v4.0. If none of the codes are applicable, the term ‘others’ exists for each of the 26 system organ classes (SOCs) to describe the AE. If the term ‘others’ is applicable, briefly describe the AE in a comprehensive and understandable manner.
- Laboratory values will be documented as absolute values on the CRFs. Out of range laboratory values occurring outside of predefined assessment times or any laboratory values not specifically asked to be assessed by the protocol should only be documented as AE if they are grade 3 or higher.
- Relationship of AEs is assessed separately to chemotherapy, antibody, and PA using the following scale:
  1. Unrelated: The adverse event is clearly not related to the chemotherapy, antibody, or PA. The AE is completely independent of chemotherapy, antibody, or PA and/or evidence exists that the event is definitely related to another etiology.
  2. Unlikely: The adverse event is doubtfully related to the chemotherapy, antibody, or PA. Temporal association between the AE and the chemotherapy, antibody, or PA and the nature of the event is such that the chemotherapy, antibody, or PA are not likely to have had any reasonable association with the observed illness/event (cause and effect relationship improbable but not impossible).
  3. Possible: The adverse event may be related to the chemotherapy, antibody, or PA. Less clear temporal association; other etiologies also possible.
  4. Probable: The adverse event is likely related to the chemotherapy, antibody, or PA. Clear-cut temporal association and a potential alternative etiology are not apparent.
  5. Definite: The adverse event is clearly related to the chemotherapy, antibody, or PA. Clear-cut temporal association and no other possible cause.

10.3 Safety parameters
Not applicable.
See stopping rules for PA training session (Section 9.2).

10.4 Intensity modifications of PA and dose modifications
Intensity of the structured PA intervention depends on the individual patient’s maximal heart rate (which is assessed in the cycle ergometer stress test) and will also be adjusted depending on the patient’s development of fitness over time during palliative treatment (see Section 9.2). Therefore, intensifications or modifications of training are highly individualized and rely on the interaction between the supervising physical therapist and the patient. In general, the patient should always be encouraged to try to follow the set limits of his/her individual training.

Because patients receive standard palliative treatments at the discretion of the treating oncologist and because those therapies are not subject of this trial, any dose modifications of the chosen chemotherapy are also decided by the treating oncologist. The same applies to supportive...
treatments including application of granulocyte stimulating factors, antibiotics, or provision of psycho-oncological support.
11 SAFETY REPORTING

11.1 Definition of serious adverse event (SAE)
A SAE includes any adverse event or reaction that is fatal or life-threatening, requires or prolongs hospitalization, is disabling, is a secondary malignancy or a congenital anomaly, or is another medically significant condition which may jeopardize the patient or may require intervention to prevent one of the other outcomes listed previously.
In this trial, only SARs are documented (see Section 11.2).

11.2 Definition of serious adverse reaction (SAR)
SARs are all SAEs for which a relationship (definitely, probably, possibly) to the trial intervention (PA program) cannot be excluded.

11.2.1 SARs during physical activity program
A SAR includes any of the events listed in the table below, that are possibly, probably, or definitely related to the PA and occurring between randomization and end of week 18 after randomization, for all patients undergoing the PA intervention. In case the duration of the PA intervention is different from 12 weeks (shorter or longer because of either early progression or delays) SARs will be assessed and recorded until 30 days after completion of the PA intervention.

Adverse events not related to the PA and AEs related to the systemic standard therapy to treat the metastatic colorectal cancer shall not be reported as SARs, even if they meet the seriousness criteria from the standard SAR definition (see below).

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal</td>
<td>Events resulting in death, possibly, probably or definitively related to the PA</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>Only events possibly, probably or definitively related to the PA. The patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death.</td>
</tr>
<tr>
<td>Requires inpatient hospitalization (&gt; 24 hours)</td>
<td>Only events possibly, probably or definitively related to the PA. Events not considered to be SAR are hospitalizations &gt; 24 hours and occurring under the following circumstances: - elective surgery (planned before entry into the trial) - part of the normal treatment or monitoring of the trial treatment - hospitalization for social reasons (e.g. in rehabilitation home)</td>
</tr>
<tr>
<td>Prolongs hospitalization</td>
<td>Prolongation of an existing hospitalization possibly, probably or definitively related to the PA</td>
</tr>
<tr>
<td>Disabling</td>
<td>Includes persistent or relevant disability or incapacity possibly, probably or definitively related to the PA</td>
</tr>
<tr>
<td>Secondary malignancy</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>Birth defect in neonate/infant or stillbirth possibly, probably or definitively related to the PA</td>
</tr>
<tr>
<td>Other medically significant condition</td>
<td>Only events possibly, probably or definitively related to the PA. Important AEs that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require</td>
</tr>
</tbody>
</table>
intervention to prevent one of the other outcomes listed above.

11.2.2 SARs after 18 weeks from randomization

The following events have to be reported as SAR:

<table>
<thead>
<tr>
<th>Event</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal</td>
<td>Possibly, probably or definitely related to (late effects) of the PA program</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>Possibly, probably or definitely related to (late effects) of the PA program</td>
</tr>
<tr>
<td>Disabling</td>
<td>Possibly, probably or definitely related to late effects of the PA program</td>
</tr>
<tr>
<td>Secondary malignancy</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Congenital anomaly</td>
<td>Birth defect in neonate/infant or stillbirth possibly, probably or definitively related to the PA</td>
</tr>
<tr>
<td>Other medically significant condition</td>
<td>Possibly, probably or definitely related to late effects of the PA program</td>
</tr>
</tbody>
</table>

11.2.3 Pregnancy

In the case of pregnancy occurring during the trial, recommendations from applicable clinical standards and Swissmedic-approved product information of the standard treatment must be followed.

11.3 Definition of suspected unexpected serious adverse reactions (SUSARs)

SUSARs are serious adverse drug reactions that are assessed as unexpected on the basis of the applicable Swiss product information.

11.4 Reporting of individual SAEs by the investigator

Any SAE related to the PA program must be reported by submitting the completed initial report using the trial-specific SAE form within 24 hours of becoming aware of the event. This form can be downloaded from the SAKK website (members section).

Submission is done by sending the SAE form by fax to:

SAKK Coordinating Center
Effingerstrasse 40
CH – 3008 Bern
Fax: +41 31 389 92 00

The SAE outcome must be reported within 2 weeks after initial report by submitting the follow-up report (i.e. initial SAE form, updated with follow-up information) to the SAKK CC as above. In case the SAE is reported as ongoing after 14 days, the follow-up report has to be submitted again with the final outcome.

The originals of the SAE forms (both initial and follow-up reports) are kept at the sites in the Investigator’s file. The SAKK CC will forward each individual SAE to the coordinating investigator and the supporting coordinating investigators.

The local investigator at a Swiss site is responsible to inform his/her local EC about all local SARs within 15 days, in accordance with the Swiss Human Research Act (HRA) and its applicable Ordinances.
The local investigator at a foreign site is requested to report local SAEs to the local EC according to the EU clinical Directive 2001/20/EC and applicable national law.

### 11.5 Reporting of individual SAEs by the sponsor

The SAKK CC ensures that all reporting requirements and timelines for reporting, as defined in the respective applicable national laws are followed.

The SAKK CC will forward any SAR which occurred at a Swiss site to the lead EC according to the Swiss Human Research Act (HRA) and its applicable Ordinances.

### 11.6 Periodic reporting on safety to principal investigators

The SAKK CC ensures that the reporting requirements and timelines for reporting, as defined in the respective applicable laws, are followed.

An ASR (annual safety report) listing all SARs which occurred at Swiss and foreign sites will be provided annually to each principal investigator (to be downloaded from www.sakk.ch, members section) and to the ECs.
12 EVALUATIONS AND INVESTIGATIONS BEFORE, DURING AND AFTER TRIAL TREATMENT

All assessments and investigations must be done within the defined time periods.
A schedule of assessments, treatments, and CRF completion is provided in Appendices A. An adaptable scheduler (MS Excel file) can be downloaded from the SAKK website.

12.1 Pretreatment evaluations and procedures

12.1.1 The following investigations have to be performed before randomization:
- Informed consent must be obtained before randomization and prior to any trial-specific procedure.
- Histological confirmation of CRC and confirmation of the metastatic stage by biopsy OR imaging (CT or MRI scan). In case of relapse from an initially localized CRC, no re-biopsy is needed (imaging sufficient), however, a biopsy result from the initial primary tumor is mandatory.
- RAS mutation status including KRAS, and NRAS mutation status (exons 2, 3, 4) assessed according to local practice.
- **Saltin-Grimby Physical Activity Level Scale (SGPALS):** The four-level Saltin-Grimby Physical Activity Scale was originally developed by Saltin and Grimby [47] and shows good reliability and validity [48] [49]. The SGPAL uses a single question: “How much do you move and exert yourself physically during leisure time? If your activity varies greatly between, for example summer and winter, try to estimate an average. The question concerns the last year”. Four options are given as possible answers, making up the four self-reported physical activity groups [49]:
  1. Physically inactive: Being almost completely inactive, reading, watching television, watching movies, using computers or doing other sedentary activities during leisure-time.
  2. Some light physical activity (LPA): Being physically active for at least four hours/week as riding a bicycle or walking to work, walking with the family, gardening, fishing, table tennis, bowling etc.
  3. Regular physical activity and training (moderate PA, MPA): Spending time on heavy gardening, running, swimming, playing tennis, badminton, calisthenics and similar activities, for at least 2 to 3 hours/week.
  4. Regular hard physical training for competition sports (vigorous PA, VPA): Spending time in running, orienteering, skiing, swimming, soccer, European handball etc. several times per week.
- Physical condition as evaluated by a **cycle ergometer stress test (under supervision of a physician).**

A bicycle ergometer should be used to perform the cycle ergometer stress test. The bicycle ergometer is a stationary exercise bike with an ergometer to measure the exercise capacity of a patient. The advantage of a cycling compared to treadmill testing is that there is less impact on joints, the cycle ergometer is less expensive, uses less space, and is less noisy than a treadmill. A major limitation of cycle ergometer testing is discomfort and fatigue of the quadriceps muscles that can limit test tolerance [50]. Differences in maximal responses between bicycle exercise and treadmill exercise are negligible [51]. Since all participants in the ACTIVE-program need to be able to use a bike ergometer (see Exclusion Criteria 6.2), treadmill stress test is not allowed as an alternative.

As for the protocol, patients will perform a bicycle ramp test (Schiller, CS-200, Baar, Switzerland). Based on age and functional health status we assume approx. 150 Watt as maximum capacity for this patient population. Therefore a pre-specified RAMP 150 will be used. With this the patient starts with a work load of 30 Watt. The work load will increase continuously by 12 Watt per minute until the patient reaches his maximum capacity.
Afterwards there will be 5 minutes of recovery with a work load of 25 Watt. The level of exertion will be assessed by using the Borg 6-20 scale [37] at peak exercise. Blood pressure is recorded every minute, 12-channel ECG needs to be monitored continuously by a physician experienced in recognizing ischemia-induced ECG-changes and arrhythmias and proficient in CPR. Duration of the stress test, achieved maximum power (peak) in Watts, and maximal heart rate will be recorded and used as basis for the training protocol (please insert these values in the patient’s activity diary after randomization).

12.1.2 The following investigations have to be performed within 28 days before randomization:

- Radiological assessment of the metastatic disease (contrast enhanced CT or MRI, chest and abdomen, the same method must be used for all assessments of an individual patient)
- Patient characteristics, medical history, including baseline symptoms, date of diagnosis of the malignancy, date of diagnosis of the metastatic stage, location of tumour sites, co-morbidities
- Concomittant anti-hypertensive and anti-diabetic medication
- Physical examination (lungs, heart, abdomen), including assessment of WHO performance status, weight, and height
- Blood pressure
- Hematological values: hemoglobin, total white blood cell count, neutrophils, lymphocytes, platelets
- Hepatic function: AP, AST, Serum Albumin, bilirubin
- Renal function: serum creatinine
- Tumor marker CEA
- Sit-to-stand Test: fitness baseline assessment (the instruction for the exact performance of the Sit-to-stand Test are provided in Appendices AAppendix 4)
- Planned chemotherapy scheme (according to Appendices AAppendix 6)

12.1.3 The following investigation has to be performed within 14 days before randomization:

- PROs: baseline assessment (the instruction for administration of PROs are provided in Appendices AAppendix 6)
- Baseline assessment of GPAQ
- BMI (body mass index) calculated from weight
- HbA1c

12.2 Evaluations during trial treatment

12.2.1 Physical therapist (during each training session)

Only applicable for patients being randomized to the PA arm. At each PA session the following has to be evaluated:

- Patient attended (yes/no). If no, reason for not attending
- Session completed (yes/no). If no, reason for interruption

Physical therapists will collect the activity diary on a weekly basis, discuss it with the patient, and determine the daily step goal. If the patient does not fill out the activity diary properly, the physical therapist will give some advice and motivation. After discussion, the completed pages (one page each week) of the activity diary will be handed over to the study team in the oncology department where it will be filed.
12.2.2 Oncology team
Applies to all patients irrespective of randomization. **On day one of each chemotherapy cycle** the following investigations have to be done:

- Physical examination (heart, lung, abdomen), WHO performance status, blood pressure, and weight.
- Laboratory values: full blood count (hemoglobin, total white blood cell count, neutrophils, lymphocytes, platelets), AP, AST, serum albumin, and serum creatinine.
- Documentation of chemotherapy drugs and biologicals with dose
- Imaging of all affected body regions with contrast enhanced CT or MRI every 8 weeks in the case of a 2-weekly regimen and every 9 weeks in the case of a 3-weekly regimen for one year and every 12 weeks thereafter until first PD. If chemotherapy is followed by a maintenance treatment with antibodies, imaging frequency during maintenance treatment is every 9 weeks. This frequency of imaging (i.e. every 3 or 4 cycles depending on the regimen) corresponds to standard assessments during palliative treatment. In case of clinical suspicion for progression, scans can be done as deemed appropriate by the treating oncologist. Images will be assessed according to RECIST 1.1 criteria locally.
- Documentation of metastasectomy
- Tumor marker at day 1 of each cycle for all patients with a baseline CEA value >2 x ULN
- Adverse events as defined in Section 10.2.

12.2.3 Study team
- Patient Reported Outcomes questionnaire (ESAS-r, HADS, CASQ, and Distress Thermometer): to be filled in **at week 6, 12, 18, 24, 48**
  PRO outcomes are extremely important in this trial, therefore missing data need to be avoided. If a patient misses an appointment or forgets to complete the questionnaires, please re-schedule and re-distribute the questionnaires as soon as possible or mail the questionnaires to the patient to be filled in at home. The patient then brings the completed questionnaires to the next appointment. For the quality of the trial it is ideal to have the PRO questionnaires completed exactly at the time points planned, but if this is not possible for any reason it is better to have a **late, completed questionnaire** than no questionnaire at all.
- GPAQ questionnaire **at week 6, 12, 18, 24, and 48**
- STST at week 12, 18, 24, and 48
- Activity diary (intervention group only): one page per week, **week 1-12**
  The study team will receive the completed pages of the activity diary (after the patient has discussed it with the physical therapist), take a look whether the activity diary has been filled out properly. If the patient does not fill out the activity diary properly, the study team can give some advice and motivation as well. A copy of the completed pages of the activity diary will be collected at the site and a copy will be sent to the University Hospital of Basel. The trial team at the University Hospital in Basel will convert the self-reported activities into MET hours/week (see Section 13.2.2)

12.3 Evaluations in the follow-up phase
Patients enter the follow-up phase after first progression. Patients who were in the control group will be asked whether they started the ACTIVE program after progression (“cross-over”). In the follow-up phase survival status and information whether PA started will be collected and the frequency of scans is at the discretion of the treating oncologist. All patients will have a lifelong follow-up.
13 CRITERIA OF EVALUATION AND DEFINITION OF ENDPOINTS

13.1 Criteria of evaluation

Patients shall be considered non-evaluable if they fail to meet the major eligibility criteria. It will be specified in the statistical analysis plan (SAP) which eligibility criteria are considered major. Unclear cases will be reviewed and judged by the trial team (CI, CPM, and statistician) together with the medical advisor and the HCPM. Such cases will be presented in a transparent manner as suggested by the CONSORT statement [52].

All other patients will be considered evaluable. Non-evaluable patients will not be replaced.

The populations used for analysis will include the following:

- Full analysis population: the full analysis population is defined as all evaluable patients. Patients in this population will be analyzed according to the treatment they were randomized to, irrespective of compliance to the PA intervention or chemotherapy (intention to treat).
- Per protocol (PP) population: the PP population is based on the full analysis population excluding patients with major protocol violations. Decisions to exclude patients from the PP population will be taken by the trial team together with the medical advisor and the HCPM, prior to the analysis and blinded to the treatment arm. Patients in this population will be analyzed according to the actual intervention they received.
- Safety population: The safety population will consist of all patients who attended at least one training session or received at least one dose of systemic treatment. Patients in the safety population will be analyzed according to the actual intervention they received.

Adverse events will be assessed using NCI CTCAE v4.0. Response will be assessed using RECIST v1.1 (see Appendices A).

13.2 Definition of Endpoints

13.2.1 Primary endpoints

The trial has two co-primary endpoints:

- Progression-free survival (PFS): PFS is defined as time between date of randomization and date of either of the following events: (i) disease progression (according to RECIST 1.1 criteria) with or without clinical signs of progression, (ii) clinical progression (including significant increase of tumor markers in case of unmeasurable disease) as judged by the treating oncologist irrespective of RECIST criteria, (iii) or death due to any cause.

Patients without event at the time of analysis will be censored at the date of their last tumor assessment showing non-progression.

Cases where progression was detected only by means of clinical progression (ii) will be reviewed centrally by the trial team together with the medical advisor and the HCPM in a blinded fashion.

- Patient-reported symptoms as measured by ESAS-r: The ESAS-r is a summary score ranging from 0 to 100 with lower scores representing better quality of life of the patients. For the primary analysis it will be examined at baseline and after weeks 6, 12, and 18 after randomization. For an exact definition see Section 16.5 (PRO).
13.2.2 Secondary endpoints

Efficacy endpoints

- **Overall survival**: time from randomization to date of death. Patients without event at the time of analysis will be censored at the date they were last known to be alive.

- **Best Objective Response**: best tumor response achieved during first-line systemic therapy according to RECIST criteria [1] (for definition of RECIST see Appendix 1). Only remission status achieved during first-line therapy will be considered.

- **Metastasectomy rate**: the proportion of patients having a metastasectomy with curative intent will be calculated.

Chemotherapy-related endpoints and toxicities

- **Selected adverse events** assessed according to NCI CTCAE v4.0 as specified in Section 10.2.

- **Chemotherapy-completion-rate**: The chemotherapy-completion-rate is defined as the total dose in mg which was applied divided by the total dose in mg which was initially planned according to the planned chemotherapy scheme. Absolute doses of chemotherapy agents applied will be collected after each chemotherapy cycle. The total planned dose will be derived based on the planned chemotherapy scheme which is specified at baseline incorporating weight or body surface.

- **Initiation or increase of anti-hypertensive drugs**: In the subgroup of patients who receive bevacizumab. The proportion of patients receiving new or increased doses of anti-hypertensive drugs will be calculated.

- **Overall treatment utility (OTU)**: Overall treatment (chemotherapy, antibodies, and PA) utility is a relatively novel clinical outcome measure incorporating objective and subjective measures of anticancer efficacy, tolerability, and acceptability condensed into a simple 3-point score [4]. The investigators of the MRC FOCUS2 trial developed OTU as a composite endpoint of treatment outcome to reflect both the doctor’s question: "In retrospect, am I glad I offered this treatment?"; and the patient’s question: “Am I glad I accepted the treatment?”. OTU combines clinical efficacy (“Is my patient alive without disease progression?”), clinical tolerability (“Did we avoid causing major harm?”), and patient opinion (“Was my treatment worthwhile and acceptable?”). The following criteria is used to score the OTU [4]:

  1. **Clinical benefit of treatment**
     a. Both no radiological progression (RECIST response or stable disease) **and** no clinical progression, as assessed by the treating oncologist.
     b. Either radiological progression (RECIST progressive disease) **or** clinical progression, as assessed by the treating oncologist.

  2. **T tolerability and acceptability of treatment (treatment = systemic treatment and PA program)**
     a. **All** of the following:
        - no AE that is fatal, life-threatening, requires inpatient hospitalization > 24 hours, prolonged hospitalization, leads to persistent disability or incapacity or any other medically significant condition attributed to treatment (treatment = systemic treatment or PA)
        - no episodes of grade ≥3 non-haematological toxicity
        - patient’s answer to the question "How much has your treatment interfered with your normal daily activities?" is **not** "Very much" (options: not applicable – not at all – a little – quite a bit – very much)
        - patient’s answer to "How worthwhile do you think your treatment has been?" is **not** "Not at all" (options: not applicable – not at all – a little – quite a bit – very much)
     b. **Any** of the following:
        - an AE that is fatal, life-threatening, requires inpatient hospitalization > 24 hours, prolonged hospitalization, leads to persistent disability or incapacity or any other
medically significant condition attributed to treatment (treatment = systemic treatment or PA)

- an episode of grade ≥3 non-haematological toxicity
- patient’s answer to "How much has your treatment interfered with your normal daily activities?" is "Very much"
- patient’s answer to “How worthwhile do you think your treatment has been?” is "Not at all"

**Scoring of Overall Treatment Utility**

<table>
<thead>
<tr>
<th>Good</th>
<th>Patient is alive and scores 1a/2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate</td>
<td>Patient is alive and scores 1a/2b or 1b/2a</td>
</tr>
<tr>
<td>Poor</td>
<td>Patient is alive and scores 1b/2b or patient is dead</td>
</tr>
</tbody>
</table>

Overall treatment utility (OTU) [4] will be evaluated at week 18 by the treating oncologist and the patient.

**Symptom control and Patient Reported Outcomes endpoints (for definition see Section 16.5)**

- Depression and anxiety as measured by HADS
- Appetite as measured by CASQ
- General Distress as measured by Distress Thermometer
- Therapeutic Relationship

**Exercise-endpoints:**

- **Exercise capacity as measured with the Sit-to-stand Test (STST):** The Sit-to-stand Test (STST) is a widely implemented measure of endurance and lower body muscular strength, in which participants have to stand up and sit down on a standard height chair (46 cm) as many times as possible within 1 minute in a self-selected pace [53]. The outcome measure is the number of times a participant can stand up and sit down completely in a minute. The exact description of the standardized procedure of the test can be found in the Appendices A. Research showed that the STST correlates with the 6 min walking test in healthy adults and therefore can be used as a submaximal exercise test comparable to the 6 min walking test [54]. The advantage of the STST is that the test is easy to perform, takes less time and needs minimal equipment. There are existing reference values for the STST in a European population [53]. STST will be evaluated in all patients at baseline, week 12, 18, 24, and 48 by a member of the study team of the study site.

- **Self-reported physical activity:** Self-reported physical activity as measured by the Global Physical Activity Questionnaire (GPAQ) [55, 56]. GPAQ will be completed by all patients at baseline, week 6, 12, 18, 24, and 48. The GPAQ version 2 consists of 16 questions about one’s physical activity in a typical week in 3 different domains, ‘Activity at work’, ‘Travel to and from places’, and ‘Recreational activities’, and in addition assesses ‘Sedentary behavior’. Study coordinators at the sites will transfer data from the paper form into the eCRF form. The analysis and the calculation of MET-min per week will be performed by the trial team and SAKK statistician according to the “GPAQ analysis guide” on the WHO website (http://www.who.int/chp/steps/GPAQ/en/). Compared to the International Physical Activity Questionnaire (IPAQ) [57], another well accepted and validated physical activity questionnaire, the GPAQ shows a moderate-to-good concurrent validity (r = 0.54) [55].

- **Metabolic equivalent of task (MET) hours/week (in the intervention group only):** One Metabolic Equivalent of Tasks (MET) is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5ml O₂ per kg body weight x min. The MET concept represents a simple, practical, and easily understood procedure for expressing the energy cost of physical
activities as a multiple of the resting metabolic rate [58]. To calculate the metabolic equivalent of task (MET) hours for each patient we will use the established coding scheme from the ‘2011 Compendium of Physical Activities: A Second Update of Codes and MET values’ [59]. The Compendium provides a five-digit coding scheme linking categories and types of physical activity with their respective MET intensity value [59]. The Compendium provides a comprehensive list of physical activities and their associated MET values [59]. The Compendium constantly incorporates updates of evidence-based research of new MET value data. As a user-friendly feature, the Compendium has a corresponding website with an easy interface to find specific activities with the corresponding MET value (https://sites.google.com/site/compendiumofphysicalactivities/). We will train students in psychology or sports science to calculate MET hours for each patient in a standardized way. They will analyze each patient’s activity diary and record the according MET hours for each week. To keep reliability as high as possible, patient diaries will be analyzed independently in duplicate by two students; disagreements will be resolved by discussion or third party adjudication. The final version will be considered for all further analyses. The MET hours/week will be assessed for the duration of the supervised exercise program i.e. during 12 weeks (+ delays). Analyses of the activity diaries will be performed at the University Hospital Basel.

- **Body mass index (BMI)** measured at baseline and week 18.
14 DOCUMENTATION

14.1 CRFs and reports

CRFs specifically created for this trial are used for documentation. It is very important to adhere to the schedule of visits prescribed in the protocol for all patients. All CRFs needed for the corresponding visit will be displayed automatically in the web-based electronic data capture (EDC) system for the SAKK trial 41/14.

The CRFs have to be completed online (www.sakk.ch/edc) in a timely manner. In general, the data should be entered into the CRFs within a month from the visit or medical examination.

Patient questionnaires are only available in paper form and calculated scores have to be entered into the online CRFs after the patient filled them out.

Sites must use a patient identification list in order to allow identification of a patient. This list must be kept at the site in the investigator's file.

14.2 Notes for special handling of CRFs

Eligibility CRF:

- The completed form ER in the web based EDC system has to be printed and signed by the investigator. A signed form (original or copy) has to be sent to SAKK CC by mail or fax within one month after registration. The original signed form or a copy thereof, in case the original was sent to SAKK CC, is kept at the site in the Investigator's file.
- If it is not possible to enter the eligibility form online, complete the paper CRF version and fax it before registration to the SAKK CC (see also Section 7).

Patient Reported Outcomes CRF:

- The paper CRF has to be completed by the patient. The CRF has to be entered via internet (www.sakk.ch/edc) into the EDC system by the site staff in a timely manner. The original forms are kept at the site in the Investigator's file.
- In addition, a copy of each form has to be sent by mail to the University of Basel within one month after the visit:
  
  Barbara Handschin  
  Medical Oncology  
  University Hospital Basel  
  Petersgraben 4  
  4031 Basel

- A copy of the patient training diary has to be sent to the University of Basel (to the address above)

SAE report forms:

- Trial-specific SAE report forms have to be submitted by fax to SAKK CC within 24 hours of becoming aware of the SAE (see also Section 11 for SAE reporting and pregnancy reporting). Originals of SAE reports are kept at the site in the Investigator’s file.

14.3 Source data

Additionally to other source data, the following data entered directly onto trial documents are considered to be source data:

- patient screening and enrollment list
- patient identification list
- Patient Reported Outcomes questionnaires
- ACTIVE training diary
- PT training session form
15 STATISTICAL CONSIDERATIONS (HYPOTHESIS)

15.1 Introduction

SAKK 41/14 is a multicenter, randomized phase III trial comparing standard palliative chemotherapy (standard arm) with standard palliative chemotherapy + structured PA and pedometer (intervention arm) in patients with metastatic CRC. The sample size is based on the primary endpoints PFS and patient-reported symptoms (ESAS-r).

The trial will be considered as positive, if either PFS or patient-reported symptoms or both of them give a positive result (in favor of the intervention arm) in the end. The PFS analysis will be performed with type-I error (α) of 0.03 and a power of 80%, for the patient-reported symptoms analysis the values are α=0.02 and power 80%. The overall type-I error probability is calculated as 0.03 + 0.02 = 0.05.

15.2 Sample size estimation

15.2.1 Progression-free survival

The sample size is based on the primary endpoint PFS. A randomized comparative design with two treatment arms will be applied. The calculation is based on a log-rank testing the following hypotheses on the hazard ratio (HR) between the two arms:

- \( H_0: HR = 1 \)
- \( H_A: HR ≠ 1 \)

The sample size was calculated based on the following assumptions:

- The median PFS in the standard arm is 9 months, the median PFS in the intervention arm is 12 months (HR = 0.75 in favor of the intervention arm).
- Type I error (α): two-sided 0.03
- Power: 80%
- Accrual rate: 8 patients per month
- Dropout rate (proportion of patients lost to follow-up for the primary endpoint): 5% at 9 months.
- No interim efficacy analyses will be performed.

The reference for these assumptions is [22].

With these assumptions, 439 events and a total sample size of \( N = 524 \) patients are required. The accrual duration is estimated to be 5.5 years. The primary analysis will be performed after the 439th PFS event has occurred (approximately after 5.7–6.0 years, follow-up time after last accrual: 0.2–0.5 years).

Note: These calculations are based on the formula for the log-rank test. Due to the asymptotic equivalence of the test statistic of the Cox regression model without covariates and the log-rank test statistics under the assumed model, the sample size calculation holds also true for the unadjusted Cox regression model. It can be expected that inclusion of the stratification factors in the analysis will further increase the power as compared to the above calculations that are based on the Cox regression model without covariates.

The sample size was calculated using EAST 6.3.

15.2.2 Patient-reported symptoms

Based on the empirical rule effect size (ERES) method of Sloan and Dueck (2004) [60], a medium clinically important difference is given by 8% of the total range of the scale. As we do not expect to include patients with a score of >70 points, the ERES method suggests a clinically important effect size of 8% of 70, i.e. around 6 points. If we look at the entire possible range (0-100), the clinically important effect size would be 8 points.
A nonparametric ANOVA model for longitudinal data, namely a F1-LD-F1 model, according to Brunner, Domhof and Langer [61] will be applied to model the course of the ESAS-r scores over time. The treatment arm will be the group factor and time the time factor. The main hypotheses are:

- \( H_0 \): there is no interaction of the treatment arm with the time
- \( H_A \): there is an interaction of the treatment arm with the time

I.e. the alternative hypothesis states that the course of the ESAS-r score is not the same in both treatment arms.

In the standard arm of the trial SAKK 95/06 (E-MOSAIC), the mean total score of the ESAS-r was 29 with a standard deviation of 12, ranging from 8 to 60. The mean difference of the ESAS-r score at week 6 minus the baseline ESAS-r score was approximately 0.8, with a standard deviation of 14. In our trial, however, we expect bigger differences between the treatment arms in favor of the intervention arm, and lower standard deviations, as the patients included are much fitter than the patients in the SAKK 95/06 trial.

Based on these assumptions, extensive simulations showed that the sample size of N=400 patients with complete data will provide enough power (at least 80%) to reject the null-hypothesis of no interaction between treatment arm and time at the \( \alpha = 0.02 \) level, if the effect on the ESAS-r score after week 18 is at least -7 points, and if the within-patient variation between two measurements is not too high (SD of difference between two measurements ≤ 8 points).

For the handling of missing data see section 15.6.

15.3 Interim efficacy analysis

No interim efficacy analysis will be performed.

15.4 Other interim analyses

After the inclusion of the 40th patient, a feasibility analysis will be performed. A report including patient characteristics, adherence to the training protocol, accrual data, dropout rate, and other related data will be created. This report will not include any results of the primary endpoints or of related secondary endpoints that could hint at results of the primary endpoints. The results will be published in a peer-reviewed journal. Based on this report, the trial team (coordinating investigator, clinical project manager, and statistician) together with the head clinical project management and the medical advisor will make a recommendation on the continuation of the trial. Probability of sufficient funding will also enter into consideration. If the recommendation is to stop the trial, the SAKK board has to approve this recommendation.

Furthermore, after inclusion of the 131st patient, the proportion of patients lost to follow-up before experiencing a PFS event will be estimated. If ≥ 12 out of these 131 patients are lost to follow-up, i.e. if the lower 95% confidence bound is > 5%, a sample size re-estimation may be done.

If the proportion of patients with missing ESAS-r data is high, alternative strategies for the primary PRO analysis may be defined.

15.5 Statistical analyses

The final analysis will take place once the 439th PFS event has taken place and after all patients have completed at least 18 weeks of the trial.

All efficacy endpoints will be analyzed based on the full analysis population and according to the intention-to-treat principle. Supportive analyses based on the per-protocol population will be performed. All safety and PRO endpoints will be analyzed based on the safety population.

The primary analysis of the endpoint PFS will be as follows: The HR and the corresponding two-sided 95% confidence interval (CI) will be calculated using a Cox proportional hazard model with the treatment arm as independent variable and the stratification factors as strata. The result will be considered positive, if there is a significant effect of treatment arm in favor of the intervention arm.
The median PFS and the corresponding 95% confidence intervals using the Kaplan-Meier method will be presented for each treatment arm.

Because of the non-blinded design of our trial, a potential influence of the relation between the supervising physical therapist team at the participating site and the patient on the primary endpoint (PFS) cannot be excluded. This influence may differ by participating physical therapist team. Therefore, we will investigate this potential bias using a hierarchical Cox regression model, with PFS as dependent variable, site as a random effect, and treatment assignment, age (as continuous variable), sex, RAS status (mutated versus not mutated), SGPALS group (1 & 2 versus 3 & 4), BMI (as continuous variable), location of the primary tumor (rectum versus left hemi-colon versus right hemi-colon), alkaline phosphatase (normal vs. >ULN), and diabetes (present versus absent) as fixed effects (independent variables). Results from this analysis will be considered exploratory in nature; however, if there are large discrepancies between this analysis and the main analysis, we will comprehensively discuss the consequences for our conclusions.

The primary analysis of the endpoint patient-reported symptoms will be a nonparametric ANOVA model for longitudinal data, namely a F1-LD-F1 model, according to Brunner, Domhof and Langer [61]. The result will be considered positive, if there is a significant interaction term of treatment arm and time (favoring the intervention arm). The primary analysis of the ESAS-r scores will be performed using the measurements until week 18. Supportive analyses using all measurements will be performed. For other analyses of PRO endpoints see section 16.6.

The effect of the number of attended training sessions and the therapeutic relationship on the PFS will be assessed in the intervention arm only and in an explorative way.

Secondary endpoints will be tested at a significance level of 0.05 without adjusting for multiple testing.

Generally for each categorical variable the results will be summarized by frequencies and percentages. For proportions, exact two-sided 95% CI will be presented for each treatment arm. To compare the arms logistic regression with baseline covariates such as age, sex, body mass index, SGPALS group (in categories of 1, 2, 3, and 4 with 1 as the reference group) and ECOG (0 versus >0), will be applied.

For each continuous variable the results will be summarized by median, minimum and maximum. To compare the arms, linear regression (covariates see above) will be applied. For endpoints which are evaluated at more than one time point, mixed models for repeated measurements will be applied.

All time-to-event endpoints shall have the median value of each treatment group estimated using the Kaplan-Meier method, along with a two-sided 95% CI. The number of events of each endpoint shall be presented descriptively by frequency and percentage by treatment arm. The treatment effect will be assessed using Cox proportional hazard models with the treatment arm as independent variable and the stratification factors as strata. The assumption of proportional hazards will be tested.

Adverse events (AEs) will be presented by type and grade in listing tables showing frequency and percentage of the within-patient worst grades by treatment arm. In addition, grade ≥ 3 AEs and AEs with relation to treatment ≥ 3 will be summarized separately.

SAEs will be fully listed. The number of SAEs per patient will be summarized using frequency and percentage. Frequencies and proportions of all reported AEs and SAEs will be presented (for definitions and grades of AEs collected see Sections 10.1 and 10.2).

Laboratory values will be expressed as the absolute values and as grading (ordinal categorical variables) according to NCI CTCAE v4.0.

Patient baseline characteristics at randomization will be presented in total and stratified by treatment assignment.

Adherence to the training protocol will be reported for the intervention arm only. The frequency of attended training sessions will be analysed both as a continuous variable as well as a categorical variable. The adherence to the exercise training of each patient in the PA group will be logged into the CRFs by the physical therapists. It will be assessed by the total number of sessions attended by the patient. Furthermore it will be categorized into the following groups: Fully completed (≥ 20 sessions attended), almost completed (≥ 16, but < 20 sessions attended), partly completed (≥ 12,
but < 16 sessions attended), and not completed (< 12 sessions attended). Adherence to exercise training will only be considered for the 12 weeks during first-line therapy (the planned time of exercise intervention including 24 planned sessions).

**Subgroup analyses for PFS and PROs**

We will consider self-reported baseline fitness (SGPALS group 1 & 2 versus 3 & 4) and the percentage achieved of the maximal heart rate (PMHR) during the cycle ergometer stress test (as continuous variable – a lower percentage expresses a lower fitness) as potential treatment effect modifiers regarding the primary endpoints PFS. We hypothesize that those patients with lower baseline fitness could benefit more from the PA intervention, because the various metabolic changes expected to control tumor growth have more potential to be increased in patients with a low baseline physical activity level compared to patients who are already more physically active. We will use the multivariable fractional polynomial interaction (MFPI) approach to investigate the treatment modifying effect of the PMHR adjusted for age, and sex [62, 63]. This approach avoids building cut-offs for an inherent continuous variable and therefore uses all power available in the dataset to investigate a potential interaction [64]. We will illustrate the potential interaction using a treatment effect function. In case the interaction is significant, we will categorize the PMHR variable into quartiles and plot corresponding Kaplan-Meier curves to check for any potential mis-modeling [65]. The potential interaction of self-reported baseline fitness with PFS will be investigated using a Cox regression model with an appropriate interaction term (treatment assignment x SGPALS group) adjusted for age, and sex. We will plot corresponding Kaplan-Meier curves to illustrate the subgroup effect.

The interaction effect of the following baseline variables with the treatment effect on PFS will be assessed using a Cox regression model:

- Baseline SGPALS (group 1+2 vs. group 3+4)
- RAS status (mutated versus wild-type)
- Location of the primary tumor (rectum versus left hemi-colon versus right hemi-colon)
- AP (normal vs. >ULN)
- Baseline ECOG (0 vs. >0)
- GPAQ at 12 weeks minus GPAQ at baseline (continuous)
- Baseline BMI (continuous)
- Therapy given (mono versus combination chemotherapy)
- Diabetes (present versus absent at baseline)
- Age at baseline (continuous)
- Sex

The model for the factors “therapy given” will be adjusted for ECOG and age. GPAQ will also be categorized into “inactive”, “moderately active” and “highly active” according to published guidelines.

Another Cox regression model for PFS will be calculated with treatment arm as independent factor, stratified for the biological agent given to the patient (none versus bevacizumab versus EGFR-inhibitor).

The primary analysis of the ESAS-r scores will be repeated separately for the subgroups created from the factors above (continuous variables will be dichotomized) except RAS status.

To explore the effect of the PA intervention on the secondary endpoint “initiation or increase of anti-hypertensive drugs” for patients receiving bevacizumab, a logistic regression analysis will be applied with treatment arm, administration of bevacizumab (yes/no) and the corresponding interaction term as well as diagnosis of high blood pressure at baseline (yes/no), sex and age as independent variables.

Full analysis details will be outlined in the statistical analysis plan (SAP).
15.7 Handling of missing data and drop-outs

A row denoted “Missing” will be included in count tabulations if necessary to account for drop-outs and missing values. As mentioned in Section 13.1, non-evaluable patients will not be replaced. For time to event endpoints such as PFS and OS, patients lost to follow-up will be censored as specified in section 13.2. For all other outcomes, we will check for the pattern of missing values and conduct multiple imputation techniques to impute missing values [66, 67]. The analyses based on the imputed datasets are considered as sensitivity analyses for all endpoints except the time-to-event endpoints. Frequencies and proportions of missing data will be reported for each individual outcome.

For the analysis of the ESAS-r score, the number of patients with missing data will be assessed before the analysis in a blinded fashion. The analysis based on the imputed dataset will be considered as primary analysis if less than 400 among the 524 patients (76%) have complete data (i.e. measured the ESAS-r score at each time point).

Other strategies might be used if the proportion of patients with missing data is high, such as restricting the primary analysis to 12 weeks instead of 18 weeks, or using mixed model approaches dealing with missing data.
16  PATIENT REPORTED OUTCOMES

16.1 Introduction

The main goal of this trial is to examine the effect of physical activity during chemotherapy on cancer progression and survival in patients with metastatic colorectal cancer. In such a palliative setting, the main focus for patients is to maintain or improve their quality of life [68]. A systematic review on symptom prevalence in patients with different incurable cancer types showed that about 50% of advanced cancer patients experience fatigue, pain, lack of energy, weakness, and loss of appetite [68], so an improvement in those symptoms is highly desirable.

Several studies and meta-analysis in cancer patients and cancer survivors have shown that physical activity leads to a reduction of those symptoms, especially fatigue [15, 19, 69-72], depression [15, 71], and anxiety [13] and to an improved wellbeing and quality of life [14, 73-75]. So far, there is no specific review on the effect of exercise on depression during chemotherapy.

Loss of appetite is very common in cancer patients and has a strong emotional and social impact on patients and family members [76]. The most effective treatment for cancer anorexia consists of pharmacological medications including progestagen, glucocorticoids, cannabinoids, and agents modulating serotonine synthesis [77]. The increase of physical activity is suggested as a core treatment concept for cachexic patients because it also leads to higher quality of life [78]. There is not much research examining the effect of exercise on loss of appetite in cancer patients and no research has been performed in a palliative setting so far. In a pilot randomized control trial, a web-based exercise and diet intervention program for breast cancer survivors demonstrated that the appetite loss score in the intervention group improved to a significantly greater degree compared to the control group [79].

Therefore, it is important to examine the impact of physical activity on patient-reported outcomes including pain, fatigue, appetite, depression, anxiety and wellbeing in this homogenous group of patients with metastatic colorectal cancer.

16.2 Objectives

16.2.1 Primary Objective

To compare changes in symptom-related PRO measured with the ESAS-r (revised Edmonton Symptom Assessment Scale) between the intervention and the control arm over time.

We hypothesize that the experimental intervention leads to a greater decrease in the overall ESAS-r score compared to the control intervention.

16.2.2 Secondary Objectives

To compare changes in Appetite, Anxiety/Depression, and Distress between the intervention and the control arms over time.

We hypothesize that the experimental intervention leads to a greater decrease in the overall depression/anxiety and distress score, and a greater increase in the appetite score compared to the control intervention.

16.3 Patient selection

All patients enrolled in this trial will complete all PRO questionnaires at the defined time points. There will be no patient selection within participating institutions.

16.4 Design

A longitudinal design is used. Patients are asked to complete a PRO questionnaire:

- at baseline (prior to randomization)
- at week 6, 12, 18, 24, and 48
PRO questionnaires have to be completed at the scheduled assessment time points until progression of disease, or consent withdrawal.

### 16.5 Assessment

#### Primary PRO Endpoint:

- **Symptom-related PRO**

  Symptom-related PRO will be assessed by the ESAS-r [80], a self-report tool of symptom intensity, developed for advanced cancer patients. It includes nine common symptoms experienced by patients with advanced cancer (pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, wellbeing, shortness of breath), with the option of adding one symptom important to the patient. The response format ranges from 0 (none, best) to 10 (worst), resulting in a summary score range from 0 to 100. It is designed to enable repeated quantitative measurements of multidimensional symptom intensity with minimal patient burden. The ESAS-r retains the core elements of the original version of the ESAS (nine common symptoms, option of adding a 10th symptom, 11-point numerical rating scales), with key revisions focusing on symptom assessment time frame, terminology, item order, and format [80]. Watanabe et al. 2012 demonstrated that patients found the ESAS-r to be significantly easier to understand and significantly more patients preferred the ESAS-r to the ESAS. The ESAS-r replaces the original version of ESAS [81].

#### Secondary PRO Endpoints:

- **Appetite (CASQ)**

  Appetite is measured by the Cancer Appetite and Symptom Questionnaire (CASQ) [82]. The CASQ is a specific screening tool for cancer patients and includes the following 12 items: appetite, satiety, hunger, enjoyment of food, number of meals, number of snacks, taste compared to pre-illness, taste changes, nausea, mood, energy level, and pain. The CASQ shows acceptable internal consistency with Cronbach α = 0.72 and test-retest reliability of 0.80 [82]. Answers are recorded on a 5-point scale and the score ranges between 0-48 with lower scores indicating greater symptom burden and/or poorer appetite [82].

- **Anxiety and Depression (HADS)**

  Anxiety and depression will be measured using the ‘Hospital Anxiety and Depression Scale’ (HADS), a well validated screening tool [83]. The HADS consists of 14 items; 7 belong to the depression subscale and 7 to the anxiety subscale. The HADS shows good psychometric properties with Cronbach’s Alpha = 0.80 for the anxiety and 0.81 for the depression-scale. Global test-retest reliability is acceptable and is 0.71 for both scales [25]. Each item of the HADS will be answered on a 4-point scale and asks the patient about the agreement to the statement or how often it applies (for example “most of the time, often, from time to time, not at all”). The scores will be summed up leading to a total score, with an increasing score representing increasing burden for the patient. The range lies between 0 (no depression or anxiety) to 21 (major depression or anxiety).

- **Distress**

  Overall distress will be assessed using the Distress Thermometer (DT) developed by the National Comprehensive Cancer Network [84]. It is a valid and reliable measure for screening psychological distress in cancer patients. The German version was adapted by Mehnert et al (2006) [85]. The question is answered on a 10-point score from ‘no distress’ (0) to ‘extreme distress’ (10). Same as in the ESAS-r a higher score means more distress. A score of 5 or higher at the DT visual analogue scale is recommended as a cut-off score for a clinically significant level of distress [85]. The Distress question will be added as a 10th question to the ESAS-r.
16.6 Statistical considerations

The primary PRO endpoint is the total score of the ESAS-r, a continuous score ranging from 0 to 100, with lower scores representing better PRO of the patients. It will be analyzed at baseline and at weeks 6, 12, and 18. For the main PRO analysis see section 15.5. Single items of the PRO questionnaires as well as secondary PRO endpoints will be analyzed descriptively. See also section 15.5. Full analysis details will be outlined in the SAP.

16.7 Data management

16.7.1 Timing requirements

All PRO questionnaires are to be completed during the patient’s visits at the hospital. The schedule of the PRO assessment must be followed as closely as possible. A completed baseline questionnaire is an eligibility criterion and has therefore to be completed before randomization. For the subsequent assessments, it is important that the PRO questionnaires are completed before any diagnostic procedures or communication of diagnostic or prognostic information to the patient, and before any treatment or supportive care measures.

PRO outcomes are extremely important in this trial, therefore missing data need to be avoided! If a patient misses an appointment or forgets to fill-in the questionnaires, please re-schedule and re-distribute the questionnaire as soon as possible. If necessary a time window of up to +/- 3 weeks of the scheduled time point will be allowed.

To ensure compliance with the protocol requirements, a scheduler with the dates of upcoming PRO assessments can be downloaded from the SAKK website (www.sakk.ch ➔ Members ➔ Trials ➔ Gastrointestinal ➔ SAKK 41/14).

16.7.2 Data collection and local data management

As part of the informed consent, the patients need to be informed that there will be repeated PRO assessments until disease progression. Detailed instructions are given in the guidelines for PRO Assessment (Appendices A Appendix 6). All questions in the questionnaires have to be answered. The completed PRO questionnaire has to be checked by the physician or study nurse while the patient is still present in the treating institution. If necessary, the patient should be asked to fill in missing answers.

Completed PRO questionnaires have to be entered via internet (www.sakk.ch/edc) in a timely manner. If a scheduled PRO assessment was not done, the reason for the missing (see respective codes on the PRO questionnaire) has to be entered into the system. Any questions regarding PRO questionnaires can be addressed to Barbara Handschin (barbara.handschin@usb.ch) or Karin Ribi (karin.ribi@ibcsg.org).
17 PATHOLOGY
Not applicable

18 TRANSLATIONAL RESEARCH
In translational research projects we will explore potential mechanisms that link physical activity to tumor progression. In the MetACTIVE project, exercise-induced changes in the innate immune system (NK-cells) and the metabolic host-environment, more specifically in the insulin-PI3K-mTor signaling pathway, will be assessed.
All translational research projects will be performed in Switzerland only.
After analysis, all samples used for translational research will be destroyed.

18.1 MetACTIVE project: metabolism (Aim 1) and NK cell function (Aim 2), in few selected sites only
This non-mandatory project will be performed in 3-4 sites in Switzerland with experience in PBMC preparation and handling. The consent of the patient will be obtained on a separate patient information sheet. The patient’s refusal to participate in the subproject will not be an exclusion criterion for the clinical trial.
A subgroup of max. 30 subjects from the main trial (15 from the exercise group and 15 from the control group) will be recruited for the MetACTIVE project. For logistic reasons of sample preparation (i.e. Peripheral Blood Mononuclear Cell (PBMC) isolation from whole blood with immediate cryopreservation) we will focus on subjects from three to four sites for this sub-study.

18.1.1 Background
Metabolism plays a major role in carcinogenesis and cancer progression. The central metabolic pathway involved in cancer cell growth is the PI3K-mTOR axis. 4EBP1 is the most prominent downstream effector of mTOR in cancer progression [86]. In selected cancers, activation of PI3K-mTOR signaling is sufficient to drive cancer development and progression (e.g. [87]). However, in most cancers, PI3K/mTOR signaling is not acting on its own but is rather part of a signaling network promoting cancer cell growth. In particular, the effects of diabetes and overweight on cancer incidence and prognosis are thought to be related to mTOR signaling [88]. Preliminary data also underline the role of mTOR and its antagonist AMPK as a link between exercise and cancer [89]. Inhibition of mTOR has been shown to be effective in treating renal cell, breast, and neuroendocrine cancers [90-92].
Exercise-induced changes in metabolism also affect lymphocyte function. The immune system aims to protect the organism from infections and malignancies using various mechanisms. Natural killer (NK) cells, part of the innate immune system, are a subset of cytotoxic and immune-modulatory lymphocytes able to readily lyse malignant or infected cells [93]. The second line of defense is formed by the adaptive immune system, including CD8 T cells and antibodies, that evolves to be highly specific for a tumor or a pathogen [94]. Both arms of the immune system contribute to tumor surveillance or removal and interventions to enhance their functions are being tested as potential cancer therapies [93-95].
Observational studies suggest better clinical outcomes in cancer patients with increased physical activity [9-11]. Modest physical exercise has been robustly linked to an enhanced adaptive immune response and the recruitment of innate effector cells, namely NK cells, to the peripheral blood [96, 97]. Moreover, in both healthy volunteers and cancer patients physical training induces enhanced NK cell function [96, 98-100]. Thus, analogous to current immune-modulatory approaches using tumor vaccines or drug-induced immune checkpoint blockade (PD1, CTLA4) [95, 101], exercise
might be an interesting, cheap, and simple immune-modulatory treatment modulator for cancer patients to enhance chemotherapy efficacy and prolong survival. We therefore assess the function of the innate immune system by assessing frequency and tumor-targeting functional activity of NK cells.

18.1.2 Aims

**Aim 1**: Based on the available evidence, we hypothesize that PI3K/mTOR and AMPK signaling may be altered in patients undergoing a structured exercise program and that this alteration may have an influence on the outcome of colorectal cancer patients. Therefore, in this trial, PI3K/mTOR signaling is assessed in all patients consenting to their participation in this translational part of the ACTIVE trial. As a surrogate for systemic PI3K/mTOR activity, we investigate PI3K/mTOR activity in peripheral leukocytes. Exercise alters the metabolic state of cells. As several metabolites are essential regulators and structural components of enzymes and factors involved in chromatin control, a direct signaling link between the metabolic state of a cell and regulatory features of gene expression is plausible [102]. Complementing the targeted characterization of the PI3K/mTOR signaling axis we thus will characterize the transcriptomes of PBMCs to identify relevant up and downregulated genes to construct gene ontology (GO) and pathway maps. Differential expression patterns identified should yield information on relevant gene classes and pathways involved in exposure to physical activity. While we will certainly apply whole-genome analyses (ChIP-seq) for histone modifications to be expected to be particularly relevant, the majority of epigenome analyses will rely on ChIP-qPCR experiments focusing on defined gene promoters and their regulatory regions.

**Aim 2**: We assess NK cell frequency in the peripheral blood (PBMCs) and NK cell tumor-targeting functional activity (degranulation and interferon gamma production) upon activation with a colon cancer cell line are established surrogates for anti-tumor activity of the innate immune system. Of note: In the setting of a large multicenter trial it is not possible to measure direct anti-tumor immune response in each patient, which would require repeated tumor biopsies and fresh tissue analyses. We therefore need to rely on surrogate outcomes. Furthermore, all analyses are exploratory analyses based on a feasible sample size given by the main trial.

18.1.3 Methods

Blood samples for Aim 1 and Aim 2 of this project will be taken at the same 4 time points. At each time point 4x7.5ml of EDTA blood will be used for IMMEDIATE PBMC preparation and freezing. After this immediate preparation of all 4 tubes, they all will be stored together at the center and shipped to Basel upon request of the SAKK CC.

Overview of procedures:
CAVE: it is important that the blood samples are drawn from fasting patients!

Blood samples (4x 7.5ml EDTA blood) will be drawn in fasting state at 4 time points:
- at baseline
- at week 6 (day 1 of week 7)
- at week 12 (day 1 of week 13)
- at week 48 in all non-progressed patients

Blood samples need to be prepared immediately (time-sensitive).
Sample preparation protocols will be provided in a separate study manual to the selected sites.

The blood samples will be analyzed at the Department of Biomedicine of the University Hospital of Basel in the Medical Oncology Laboratory (Andreas Wicki, Reto Ritschard) and the Immunobiology laboratory (Christoph Berger, Christoph Hess).

**Methods for Aim 1**: Activity of the PI3K/mTOR signaling axis is assessed using the PathScan® platform to measure pathway activation with phospho-specific antibodies. PBMCs will be prepared as described in the separate study manual. For RNA sequencing, total RNA will be isolated from approximately 2.5x10^6 cells using TRIzol reagent (Life Technologies...
Europe) and cleaned up with RNeasy Mini Kit (Qiagen). Genomic DNA will be removed from RNA samples by DNase treatment, followed by RNA quality assessment and quantitation on a fragment analyzer (Advanced Analytical Technologies). Purification of poly-A containing mRNA, mRNA fragmentation and cDNA library preparation for RNA sequencing will be performed using the TruSeq Stranded mRNA Sample Preparation kit (Illumina) according to the manufacturer's protocol. cDNA libraries will be sequenced on a NextSeq 500 or HiSeq2500 sequencing system (Illumina) at the Genomic Facility Basel using a single read sequencing approach. FastQC will be used to examine the quality of raw sequence data. The TopHat2 spliced alignment software and its underlying mapping engine Bowtie2 will be used to align the RNA sequencing reads to the human and mouse reference genome, respectively. Reads will be mapped against the reference genome based on Homo sapiens Ensembl GRCh37 gene annotations, thereby creating binary alignment map (BAM) files. BAM files will be sorted and indexed using the program SAMtools and then visualized in the UCSC Genome Browser.

To investigate and compare the transcriptome profiles of different cell conditions, the free open-source R language, Bioconductor software and particularly the DESeq2 tool will be used to perform a computational and statistical, count-based RNA sequencing differential expression analyses. Using transcript annotations from Ensembl, it will be counted how many reads map to each gene. Then DESeq2's differential expression pipeline comprising estimation of size factors, shrinkage estimation of dispersion for each gene and fitting a generalized linear model will be run on the obtained RNA sequencing data. Gene expression differences between the various conditions will be explored by methods for clustering and ordination, including principle components analysis, Euclidian sample distances calculation and hierarchical clustering of samples and genes. Differential expression between two different cell conditions will be considered statistically significant, if a gene's Benjamini-Hochberg adjusted p value is below 0.01. An enrichment analysis on sets of significantly downregulated or upregulated genes will be performed with MetaCore (Thomson Reuters), a software suite used for the functional analysis of next generation sequencing datasets. Overrepresentation and underrepresentation of gene ontology (GO) terms, metabolic networks, pathway maps and process networks will be identified in genes that are significantly differentially expressed between different conditions.

Chromatin immunoprecipitation followed by next-generation sequencing (ChIP-seq) will be done as described in [103]. In order to assure data comparability across ChIP-seq experiments, all chromatin samples will be taken from the same chromatin batch. Sequencing libraries will be prepared from immunoprecipitated DNA using the ChIP-seq DNA Sample Prep Kit (Illumina), including size selection of pre-amplified fragments on agarose gels. For quality control, the size distribution of the final libraries will be assayed on the Agilent BioAnalyzer 2100 using High Sensitivity DNA microfluidic chips. Each library will be sequenced for 36 cycles in a single-end run on the Illumina HiSeq sequencing system. The short reads will be aligned to the human or mouse reference genome using Bowtie. Merging and indexing of alignments will be done using SAMtools. Regions showing significantly enriched read coverage compared to input chromatin (also referred to as “peaks”) will be calculated using MACS.

Read coverage profiles will be calculated from aligned reads by shifting and extending reads according to the fitted MACS models. The distance calculation between peak intervals and transcription start sites (TSS) will be carried out using the R/Bioconductor package ChIPPeakAnno and basic R functions. Interval based co-localization analysis will be done by comparing MACS peak lists with BEDtools. The compilation of high-confidence factor sites will be constructed by intersecting peak lists using BEDTools too. Metagene profiles will be were created using the R/Bioconductor package GenomicRanges.

**Methods for Aim 2:**

PBMC analyses will only be done in sites with experience in PBMC preparation, storage, and shipment; those sites will be determined during the pre-study visit. PBMCs need to be prepared out of the blood samples at the site on the same day as the blood is drawn and immediately frozen down. Detailed instructions will be handed to the participating sites in a separate instruction manual. PBMC will be extracted using Ficoll and cryopreserved until used for the experiments. All subsequent experiments will be done in collaboration with Christoph Berger and Christoph Hess at the Department of Biomedicine, University Hospital Basel. Immunophenotyping will be performed...
using flow cytometry to quantify T-helper cells (CD3+CD4+), cytotoxic T cells (CD3+CD8+), B cells (CD3-CD19+) and NK cells (CD3-CD56+) amongst the live lymphocytes (FSC/SSC and live gate). NK cells will be activated by incubation with an EBV-transformed human lymphoblastoid cell line, a colon cancer cell line (DLD-1; ATCC® CCL-221™) or as a control with the same media without added other cells. NK cell degranulation (CD107a positive NK cells), as a marker of cytotoxicity, and IFNγ production will be assessed using intracellular cytokine staining in multicolor flow cytometry. NK cells will be identified as live CD3-CD19-CD14-CD56+CD16+ lymphocytes and the background controlled (i.e. subtraction of the NK degranulation of PBMC cultured in media alone) target specific response will be compared between subjects in the exercise group vs. control group [104].

18.1.4 Labeling and handling
No samples tubes will be provided by the SAKK CC. All sites have to use their own disposables. All material has to be clearly labeled (SAKK 41/14, UPN, year of birth site, date of sampling). Study-specific labels for the sample tubes and a study-specific form that needs to accompany the shipment of the samples will be provided at the initiation visit. The form will also be available on the SAKK website: www.sakk.ch → Members → Trials → Gastrointestinal Cancer → SAKK 41/14 → Useful tools.

18.1.5 Shipment
Samples have to be stored at -80°C until required by SAKK CC and sent altogether at once on dry ice by Swisspost/TNT using the form provided. Costs for shipment will be covered by SAKK. Samples will be sent (from Monday to Thursday) to:
Trial SAKK 41/14
Reto Ritschard
Department Biomedicine
Immuno-Oncology lab 416
University Hospital Basel
Hebelstrasse 20
4031 Basel
+41 (0)61 265 23 54

Complete address and shipment modalities are described in a separate “Useful tool” which will be available on the SAKK website: www.sakk.ch → Members → Trials → Gastrointestinal Cancer → SAKK 41/14 → useful tools

19 DIAGNOSTIC SUBSTUDY
Not applicable.

20 ECONOMIC EVALUATION
Not applicable.

21 INDEPENDENT RESPONSE REVIEW
Not applicable.
22 ETHICAL CONSIDERATIONS

This protocol was written and the trial will be carried out in accordance with the principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the applicable Swiss HRA and its associated Ordinances and the requirements from the Swiss and European regulatory bodies [105-110] [111].

The protocol, the patient information and consent form, as well as all other trial-related documents shall be submitted to all involved ECs in agreement with local legal requirements for formal authorization. Any amendment to the protocol or patient information and consent form will be submitted for authorization to these institutions.

The decision of the ECs and competent authority with regard to the conduct of the trial will be made in writing to the Sponsor prior to trial initiation. Any substantial amendment to the protocol (except for safety reasons) can only be implemented at a site after obtaining written authorization by the regulatory bodies. Before planning to enter any patients into this trial, the local investigator has to make sure that the trial has been authorized at their site by the involved ECs and competent authority. Patient recruitment can only take place after the site has officially been opened for accrual by the SAKK CC.

Sites in Switzerland have to adhere to the Swiss HRA and all applicable local regulatory guidelines. Sites in foreign countries have to adhere to national law and locally applicable regulatory guidelines.

22.1 Risks/benefits

In several controlled trials and in a meta-analysis [12] it has been shown that exercise during cancer treatment is safe. Exercise, however, puts the cardiovascular system under stress. To increase safety for participants it is mandatory for all patients to perform a cycle ergometer stress test up to maximal exhaustion under a physician's supervision. Only patients who do not show signs of cardiac ischemia or clinically relevant arrhythmia are eligible for the trial. Furthermore, during the supervised exercise program a person trained in cardio-pulmonary resuscitation (CPR) must be present (physical therapist). Thereby, the risks of the PA intervention are therefore minimal. Several trials have shown some benefit of exercise in cancer patients, mainly in terms of fatigue, anxiety and some aspects of quality of life. Therefore, it is conceivable that some patients might have some subjective benefit during the intervention. The data on benefit of exercise during palliative therapy is, however, not as compelling as to make it a standard intervention yet. Randomization to "care as usual" as control arm is therefore ethical as it represents the current standard.

22.2 Trial categorization

This is a clinical trial with health intervention.

According to the Swiss HRA and its corresponding Ordinance KlinV/Oclin on clinical trials, this trial is classified as category A, KlinV/Oclin (Art. 61).

22.3 Patient information and informed consent

The informed consent procedure must conform to the guidelines on GCP issued by ICH.

All patients will be informed of the aims and procedures of the trial, the possible AEs, how to react in case an AE occurs, and possible hazards to which they will be exposed. They will be informed as to the strict confidentiality of their patient data, but they need to know that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

The investigator must provide the patient with sufficient opportunity to consider whether or not to participate and minimize the possibility of coercion or undue influence. The information provided shall be in a language intelligible to the patient and may not include any content that appears to
waive any of the patient’s legal rights, or appears to release the investigator, the sponsor, or the institution from liability for negligence.

It will be emphasized that participation is voluntary and that the patient is allowed to refuse further participation in the trial whenever he/she wants. This will not prejudice the patient's subsequent care.

Informed consent shall be obtained on a written form approved by the local EC and signed and personally dated by the patient and the investigator. The patient information as well as a copy or original of the signed and dated informed consent will be handed to the patient.

In case new results become available that shift the risk/benefit ratio, the patient should re-consent.

Patients refusing to accept non-mandatory translational projects can nevertheless participate in the trial.

22.4 Premature withdrawal

Patients have the right to refuse further intervention for any reason and at any time. Patients who decide to withdraw from the trial will be informed that all data collected until the time point of their withdrawal will be used. For the patient’s security, a last examination should be performed. After patient’s withdrawal the patient’s data will be anonymized.

Patients may be withdrawn at any time from trial treatment at the discretion of the investigator due to a SAE, or based on any other relevant medical condition. The patient will then be transferred to the follow-up phase.
23 ADMINISTRATIVE CONSIDERATIONS

23.1 Insurance
The SAKK will indemnify patients for damages they have suffered as participants in the trial. For this purpose, SAKK has taken out a special insurance for clinical trials with Chubb Insurance Company of Europe SE, Zollikerstrasse 141, 8034 Zürich.

23.2 Monitoring and auditing
All source data must be accessible for auditing and monitoring. CRA and auditors will maintain patient confidentiality.

23.2.1 Monitoring strategy
This trial will be monitored. The SAKK is performing risk-adapted monitoring according to the concept developed by the ADAMON group [112]. Based on the risk analysis, low monitoring strategy has been chosen. The different monitoring activities as well as the frequency of the visit are described in a trial-specific monitoring plan.

23.2.2 Auditing/inspecting
Authorities have the right to perform inspections, and the SAKK has the right to perform on-site auditing during working hours upon reasonable prior notice.

23.3 Quality control and quality assurance
Several procedures ensure the quality of the trial in compliance with applicable regulatory requirements, GCP and the protocol:
- Written standard operating procedures are implemented
- Personnel involved in conducting the trial is qualified by education, training and experience
- An updated staff list must be kept at the site (template available on the SAKK website)
- Validation of database and statistical analysis
- Quality control principles are implemented
- On-site and/or central monitoring to evaluate protocol compliance (SDV, verification of informed consent etc.) by personnel designated by the SAKK
- Data captured online will be validated in real-time, yielding errors (for unacceptable data) and warnings (for possibly inconsistent data - these warnings may be overruled by the user).
- Audit trail of changes
- Medical data review by the coordinating investigator or a delegated person (all CRFs will be reviewed and checked on medical content)
- Safety monitoring
- Independent review of safety endpoints at the safety interim analysis
- Internal audit procedures

23.4 Trial activation procedure
The procedure for trial activation at a site is described in the final protocol letter, which is sent to the investigators who committed to participate in the trial. All participating investigators must follow the instructions given in this letter for the preparation of site documents. Upon receipt of the sites documents the SAKK CC will submit them to the involved ECs.

Any site which is interested to participate in the trial, but has not committed yet, has to contact the SAKK CC first.
The investigator will only be allowed to randomize patients into the trial after the ECs have authorized the trial at the site and the SAKK CC has opened the site for accrual.

23.5 Local trial records

23.5.1 Investigator’s file
All trial-related correspondence should be filed in the investigator’s file. A suggested table of contents (according to ICH E6, chapter 8) is provided on the SAKK website (Members → Trials → Gastrointestinal cancers → SAKK 41/14).

23.5.2 Useful tools
CRFs, documents required for EC approval, schedules of assessments etc. can be downloaded from the SAKK website (www.sakk.ch → Members → Trials → Gastrointestinal cancers → SAKK 41/14).

23.5.3 Record retention
The site will retain all essential documents according to ICH GCP. This includes copies of the patient trial records, which are considered as source data, patient informed consent statement, laboratory printouts, and all other information collected during the trial. These documents will be stored until at least 15 years after the termination of the trial. The end of this retention period will be communicated to the sites by the SAKK CC. For the patient trial records, which are entered into the EDC system, the sponsor guarantees the access and availability of the data at any time at least 15 years after the termination of the trial.

Longer retention may be required for foreign sites according to local applicable law.

In the event that the principal investigator retires or changes employment, custody of the records may be transferred to another competent person who will accept responsibility for those records. Written notice of such transfer will be given to the SAKK CC. The SAKK will notify the concerned regulatory authorities.

23.6 Trial registration
The SAKK will register the trial at www.clinicaltrials.gov and on the Swiss National Clinical Trials Portal (SNCTP) at www.kofam.ch. With the participation of sites in the EU it will also be registered with the EudraCT database (https://eudract.emea.europa.eu) of clinical trials.

23.7 Participation of local and foreign sites
A list of sites and investigators that have agreed to participate in the trial are given in a separate document which can be downloaded from www.sakk.ch (Members → Trials → Gastrointestinal cancers → SAKK 41/14).

23.8 Modifications of the protocol
23.8.1 Substantial amendment
Any amendment which may have an impact on the conduct of the trial, the potential benefit of the trial, or may affect patient safety, including changes of trial objectives, trial design, patient population, sample sizes, trial procedures, or significant administrative aspects. Such an amendment must be accepted by the SAKK Board and must have the authorization of the respective EC and competent authority prior to implementation.
23.8.3 Safety amendment
A safety amendment is a special kind of substantial amendment which is released when it is necessary to eliminate immediate hazards to trial participants. A safety amendment requires immediate implementation at local sites and is submitted in parallel for authorization to the ECs and the competent authority.

23.8.4 Non substantial amendment
Non-substantial amendments such as minor corrections and/or clarifications that have no effect on the way the trial is conducted have to be submitted to the ECs once a year, together with the submission of the annual data safety report. Non-substantial amendments which affect the evaluation of the competent authority have to be submitted to the CA as soon as possible.
24 PUBLICATION

The results of the trial will be published according to the current version of the SAKK publication
guidelines (available on the SAKK website). The SAKK publication guideline guarantees the
freedom of reporting of the participating physicians.

25 CONFIDENTIALITY

25.1 Copyright

The information contained in this protocol is copyright protected by the SAKK (Swiss Group for
Clinical Cancer Research). This information is given for the needs of the trial and must not be
disclosed to persons outside of the SAKK without prior written consent of the SAKK CC.

25.2 Confidentiality

Trial-related data of the patient will be provided in a coded manner to the SAKK CC. The names of
the patients will not be disclosed to the SAKK CC. A unique patient number (UPN) will be attributed
to each patient randomized into the trial.

Identification of patients must be guaranteed at the site. For this purpose, sites are requested to
use the patient screening and enrollment and the patient identification lists specifically produced for
the trial (available on the SAKK website). In order to avoid identification errors, the year of birth and
the UPN have to be provided on the CRFs. Patient confidentiality will be maintained according to
applicable legislation. Patients must be informed of, and agree to, data and material transfer and
handling, in accordance with Swiss data protection law.
26 REFERENCES


27 APPENDICES

Appendix 1  Tumor response assessment according to RECIST 1.1

All patients will be evaluated for response according to the revised Response Evaluation Criteria in Solid Tumors (RECIST v1.1) [1].

App 1.1  Methods of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

- **CT** is the best currently available and reproducible method to measure lesions selected for response assessment. CT should generally be performed using a ≤ 5 mm contiguous reconstruction algorithm. **MRI** is acceptable for certain situations.

- **Clinical lesions** will only be considered measurable when they are superficial (e.g. skin nodules) and ≥ 10 mm. In the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

- Lesions on **chest X-ray** are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

- **Ultrasound** is not useful in assessment of lesion size and should not be used as method of assessment.

- **FDG-PET** is generally not foreseen for regular response assessments. It may, however, be used to detect or confirm the appearance of new lesions. Attenuation correction CT scans performed as part of a **PET/CT** scan frequently show lower resolution; therefore, dedicated CT scans are preferred. However, if the site can demonstrate that the CT performed as part of a PET/CT is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast), then the CT portion of the PET/CT can be used for RECIST measurements.

App 1.2  Definition of measurability

Measurable disease is defined as the presence of at least one measurable lesion.

- **Measurable lesions:**
  - Non-nodal lesions that can be accurately measured in at least one dimension with longest diameter ≥ 10 mm using CT scan, assuming the slice thickness is ≤ 5 mm. As a general rule, the longest diameter must be at least twice the slice thickness of the imaging. In the case of chest X-ray, the lesion must be ≥ 20 mm. Clinically assessed lesions must be ≥ 10 mm.
  - Lymph nodes that can be accurately measured with a short axis of ≥ 15 mm using CT scan, assuming the slice thickness is ≤ 5 mm.

- **Non-measurable lesions:** all other lesions, i.e.:
  - small non-nodal lesions (longest diameter < 10 mm in CT scan)
  - small lymph nodes (short axis ≥ 10 and < 15 mm)
  - bone lesions
  - leptomeningeal disease
  - ascites
  - pleural/pericardial effusion
  - inflammatory breast disease
  - lymphangitis cutis/pulmonis
  - cystic lesions
  - tumor lesions situated in a previously irradiated area, or subjected to other locoregional therapy
abdominal masses/abdominal organomegaly identified by physical exam that are not measurable by reproducible imaging techniques

1 Lymph nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

2 Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

3 Cystic lesions thought to represent cystic metastases may be considered as measurable lesions. However, if non-cystic lesions are present, these are preferred as target lesions.

4 May be considered measurable if there has been demonstrated progression in the lesion.

App 1.3 Selection of lesions

Selection of target lesions

Measurable lesions up to a maximum of 5 lesions representative of all involved organs, and up to 2 per organ, should be identified as target lesions and measured and recorded at baseline. Target lesions (TL) should be selected on the basis of their size and their suitability for accurate repetitive measurements. A sum of diameters for all target lesions will be calculated and reported as the baseline sum of diameters. Lymph nodes selected as TL should always have the short axis recorded. All other lesions should always have their longest diameters recorded. This sum will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

Selection of non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, but the presence or absence of each should be noted throughout follow-up. It is possible to record multiple non-target lesions (NTL) as a single item on the CRF (e.g. "multiple liver metastases").

App 1.4 Evaluation of lesions

Evaluation of Target Lesions

All TL will be measured at each tumor assessment, and the sum of their diameters will be compared to previous assessments in order to assign the response status as specified below.

- Complete Response (CR): Disappearance of all TL. Lymph nodes selected as TL must each have reduction in the short axis to < 10 mm in order for the response to be considered complete.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of TL taking as reference the baseline sum of diameters.
- Progression (PD): At least a 20% increase in the sum of diameters of TL, taking as reference the smallest sum recorded on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Note: All TL, including lymph nodes, should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If the radiologist does not feel comfortable assigning an exact measure and reports a lesion as "too small to measure", a default value of 5 mm should be recorded. If a TL is thought likely to have disappeared, "0 mm" is noted.

Evaluation of Non-Target Lesions

- Complete Response (CR): Disappearance of all NTL; lymph nodes selected as NTL must be non-pathological in size (< 10 mm).
• Non-CR/non-PD: Persistence of one or more NTL (non-CR)
• Progression (PD): unequivocal progression of existing NTL. Unequivocal means: comparable in magnitude to the increase that would be required to declare PD for measurable disease or an overall substantial increase in tumor burden that merits treatment discontinuation.

**Determination of new lesions**
The appearance of any new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal, i.e. not attributable to differences in scanning technique or findings thought to represent something other than tumor. If a new lesion is equivocal, e.g. because of its small size, the patient will stay on treatment (if the decision on PD is based on this lesion only). If the repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the previous scan.

Lesions found in a new location not included in the baseline scan (e.g. brain metastases) are considered new lesions.

Note: the "re-appearance" of a previously "disappeared" target or non-target lesion does not in itself necessarily qualify as PD; this is the case only if the overall evaluation meets the PD criteria, or if the patient was previously in CR.

**Additional considerations**
• Tumor markers alone cannot be used to assess response. If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
• In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.
• The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

**App 1.5 Determination of overall response**
Based on the responses of TL, NTL, and the presence or absence of new lesions, the overall response will be determined at each tumor assessment, according to the table below:

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>CR</td>
<td>Not evaluated (NE)*</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD or not all evaluated*</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD or not all evaluated*</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>Not all evaluated</td>
<td>Non-PD</td>
<td>No</td>
<td>NE</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

* In selected circumstances, certain non-target organs may be evaluated less frequently. For instance, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Patients that have non-measurable disease only are evaluated for overall response as follows:

<table>
<thead>
<tr>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>Not evaluated (NE)</td>
<td>No</td>
<td>NE</td>
</tr>
</tbody>
</table>
Unequivocal PD | Yes or No | PD
---|---|---
Any | Yes | PD

**Note:** a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression, sometimes reported as “symptomatic deterioration”, is not a response outcome in itself. Every effort should be made to document objective progression even after discontinuation of treatment.

**App 1.6 Evaluation of best overall response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

In the case of stable disease, measurements must have met the SD criteria at least once after trial entry at a minimum interval of [6 to 8 weeks].

**App 1.7 Duration of response**

The duration of overall response is measured from the time measurement criteria are first met for CR/PR until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease is measured from the start of treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.
Appendix 2  Calculation of creatinine clearance
Creatinine clearance should be calculated according to the formula of Cockcroft-Gault [113].

Cockcroft-Gault formula:

\[
\text{Creatinine clearance (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (in kg)} \times \text{constant}}{\text{serum creatinine (in µmol/L)}}
\]

Constant is 1.04 for females and 1.23 for males

Appendix 3  WHO performance status
Performance status should be calculated according to the ECOG/WHO definition [114].

0  Fully active, able to carry on all pre-disease performance without restriction.
1  Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2  Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3  Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4  Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5  Dead.

Appendix 4  Sit-to-stand Test (STST)
The STST will be performed with a standard height (46 cm) chair without arm rests. The subjects hold their arms stationary by putting their hands on their hips. First the test will be demonstrated by a member of the study team and then performed once by the patient to see if everything is done correctly. Patients are asked to complete the sitting and standing positions as correctly and as fully without using the arms for support while rising and sitting down. When the patients are ready, they are instructed by the command “Go”, they stand upright and without delay sit down again, repeating the procedure as many times as possible in a 1 min period at a self-selected speed in which they feel safe and comfortable until they're asked to stop after the 1min period. Care is taken that the patient is doing the standing up to the full extent each time. The number of completed repetitions will be recorded. [54]
## Appendix 5  New York Heart Association (NYHA) classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Patients have cardiac disease but without significant limitations of physical activity. Ordinary activity does not cause undue fatigue, palpitations, dyspnea (shortness of breath), or anginal pain.</td>
</tr>
<tr>
<td>Class II</td>
<td>Patients have slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea or anginal pain.</td>
</tr>
<tr>
<td>Class III</td>
<td>Patients have marked limitations of physical activity. They are comfortable at rest, however less than ordinary physical activity results in fatigue, palpitations, dyspnea or anginal pain.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Patients are unable to carry out any physical activity without symptoms referred to above. Some Class IV patients may have symptoms at rest.</td>
</tr>
</tbody>
</table>

Source: The Criteria Committee of the New York Heart Association [115].
Appendix 6  Chemotherapy regimens

The local investigator is free to choose the first-line regimen for patients participating in this trial. Below is a list of the most commonly used regimens; particularly the first three regimens represent the current standard of care. If the local standard is a slightly different schedule, the investigator is allowed to use the local standard. If possible, the same local standard should be used for consecutive patients.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Irinotecan</th>
<th>Oxaliplatin</th>
<th>Leucovorin</th>
<th>5FU/capecitabine</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI (1)</td>
<td>180mg/m² d1</td>
<td>-</td>
<td>400mg/m²</td>
<td>bolus d1, 2400mg/m² over 46 hours</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>over 2</td>
<td>continuous infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>hours, d1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX (2)</td>
<td>-</td>
<td>85mg/m² d1</td>
<td>400mg/m²</td>
<td>bolus d1, 2400mg/m² over 46 hours</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>over 2</td>
<td>continuous infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>hours, d1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XELOX (3)</td>
<td>-</td>
<td>130mg/m² d1</td>
<td>-</td>
<td>Capcitabine 1000mg/m², orally</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>twice per day on days 1-14</td>
<td></td>
</tr>
<tr>
<td>Xeloda Mono (4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Capcitabine 1000mg/m², orally</td>
<td>Every 3 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>twice per day on days 1-14</td>
<td></td>
</tr>
<tr>
<td>FOLFOXIRI (5)</td>
<td>165mg/m² d1</td>
<td>85mg/m² d1</td>
<td>400mg/m²</td>
<td>3200mg/m² over 48 hours</td>
<td>Every two weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>over 2</td>
<td>continuous infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>hours, d1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1- Tournigand C JCO 2004; 22:229
2- Modified FOLFOX 6: Hochster HS JCO 2008; 26:3523 (other FOLFOX regimens are also allowed)
3- Goldberg R JCO 2004; 22:23
4- Cunningham D Lancet Oncol 2013; 14: 1077
5- Falcone A JCO 2007; 25:1670

First-line chemotherapy in patients with metastatic colorectal cancer (see list above) is combined with a biological at the local investigators’ choice.

The following dose/schedules are recommended:

- Bevacizumab  5mg/m² every two weeks or 7.5mg every three weeks OR
- Cetuximab (in ras-WT patients only) 400mg/m² loading dose d1, followed by 250mg/m² every week (or 500mg/m² every 2 weeks) OR
- Panitumumab (in ras-WT patients only) 9mg/kg every 3 weeks or 6mg/kg every 2 weeks

After 4-6 months of chemotherapy plus biological, the local investigator is free to either stop treatment until PD or to continue on a maintenance treatment with either the biological alone or with capecitabine+bevacizumab (Koopman M JCO2014; 32; suppl3; abstr LBA388).
Appendix 7 Guidelines for patient reported outcome assessments

A clinical research coordinator, nurse or physician should be designated to facilitate the patient’s self-completion of the patient reported outcome (PRO) questionnaires.

How should the PRO questionnaires be introduced?
The PRO assessment is an integral part of this trial. The patient should be informed about the purpose of the PRO questionnaires at the time of receiving information regarding the trial:

“We would like to learn about the patient’s subjective experience of disease and treatment. In order to evaluate this, we will ask you to fill in the PRO questionnaires repeatedly.”

Especially the first time (before randomization), it is very important that you take enough time to explain how to fill in the PRO questionnaires and make sure that the patient understands what she/he is expected to do.

Who should fill in the PRO questionnaires?
Every patient enrolled in this trial is expected to fill in the questionnaires. Patients must have a basic fluency in German, French or Italian.

When should the PRO questionnaires be filled in?
According to the schedule of assessment (Appendix 1) PRO questionnaires have to be completed:

- at baseline (prior to randomization)
- week 6, 12, 18, 24, and 48

Follow this schedule as closely as possible in accordance with the clinical visits of the patient.

It is important that the PRO questionnaires are completed prior to randomization, and always prior to any treatment administration or diagnostic procedures to prevent any confounding effect. Please note that only patients with completed baseline PRO questionnaires will be eligible for this trial.

Where should the PRO questionnaires be completed?
The PRO questionnaires have to be completed during the clinical visit. If, for administrative reasons, the questionnaires have not been presented to the patient, they may be mailed and filled in at home. Completed PRO forms have to be entered via internet (www.sakk.ch/edc) into the EDC system in a timely manner (see Section 14.2). For the quality of the trial it is ideal to have the PRO questionnaires completed exactly at the timepoints planned, but if this is not possible for some reason it is better to have a late, completed questionnaire than no questionnaire at all.

What if the patient asks for clarification with respect to the PRO questionnaires?
If a patient has difficulties in understanding particular words or instructions, please take enough time for clarification. Some patients may ask about the meaning of specific questions. If this happens, you can assist the patient by re-reading the question word by word. Please note: Patients should answer the questions based on what they think the question means.

What if the patient does not fill in a PRO questionnaire?
If the patient does not fill in a PRO questionnaire, please write the UPN, the date the PRO assessment should have been done, and the reason why it has not been completed on an empty form (refer to the corresponding codes on the form). All PRO forms have to be entered into the EDC system (see Section 14.2). A copy of each form has to be sent by mail to the University of Basel within one month after the visit (i.e. one month after it was completed). Any question regarding PRO assessment may be addressed to Barbara Handschin (barbara.handschin@usb.ch) or Karin Ribi (karin.ribi@ibcs.org; 031 389 93 91).
### Appendix 8  Schedule of assessments, treatments and documentation

An adaptable scheduler is available on the SAKK website ([www.sakk.ch](http://www.sakk.ch), members).

**SAKK 41/14 Schedule of assessments for patients undergoing a 2weekly chemotherapy regimen (e.g. FOLFOX, FOLFIRI)**

For patients undergoing a 3 weekly chemotherapy schedule (e.g. XelOx) use the other schedule of assessment for 3weekly regimens

Use this schedule for patients by changing the date in box D7. Excel will automatically calculate the subsequent dates.

In order to reschedule the dates after a delay, simply enter the new date for the visit into the corresponding box. The subsequent dates will then be recalculated accordingly.

#### Patient Information:
- **UPN:** 4114

#### Date of consultation

<table>
<thead>
<tr>
<th>Cycle</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>-28 to 0</td>
<td>-14 to 0</td>
<td>1</td>
<td>8</td>
<td>15</td>
<td>22</td>
<td>29</td>
<td>36</td>
<td>43</td>
<td>50</td>
<td>57</td>
<td>64</td>
</tr>
</tbody>
</table>

### Interventions

#### Pretreatment phase

- **Informed consent for trial participation and translational research**
- **Medical history (incl. baseline symptoms, previous therapies, location of tumor sites and TMM status), history of diabetes, arterial hypertension**
- **Physical examination (incl. WHO PS, blood pressure, weight, height only at baseline)**
- **Hematological values (leucocytes, ANC, lymphocytes, platelet count, hemoglobin), AST, AP, bilirubin, serum albumin; serum creatinine, CEA**
- **SGPALS**
- **HbA1c, weight (BMI)**
- **Blood sample for translational research (FASTING)**
- **Questionnaires on patient-reported outcomes**
- **Physical activity questionnaire GPAQ**
- **Sit-to-stand test**
- **Therapeutic relationship question (in intervention group only)**
- **Overall-Treatment-Utility Questionnaire**

#### Treatment phase

- **Assessment of anti-hypertensive drugs**
- **Assessment of anti-diabetic drugs**
- **Survival status**
- **Selected Adverse Events (AE) (see Protocol Chap. 10.2)**

**ACTIVE-Program in Arm A**

- **Informed consent for trial participation and translational research**
- **Medical history (incl. baseline symptoms, previous therapies, location of tumor sites and TMM status), history of diabetes, arterial hypertension**
- **Physical examination (incl. WHO PS, blood pressure, weight, height only at baseline)**
- **Hematological values (leucocytes, ANC, lymphocytes, platelet count, hemoglobin), AST, AP, bilirubin, serum albumin; serum creatinine, CEA**
- **SGPALS**
- **HbA1c, weight (BMI)**
- **Blood sample for translational research (FASTING)**
- **Questionnaires on patient-reported outcomes**
- **Physical activity questionnaire GPAQ**
- **Sit-to-stand test**
- **Therapeutic relationship question (in intervention group only)**
- **Overall-Treatment-Utility Questionnaire**

**Record throughout treatment phase (until 30 days after last drug administration or prior to start of subsequent anti-cancer therapy (whichever occurs first)).**

#### Notes:

a: The ACTIVE-program in the intervention group should be started as close as possible to day 1 of systemic treatment (at latest within the first 3 weeks) and takes 12 weeks (24 sessions).

b: Treatment phase designates the period where the patient receives active systemic treatment, including maintenance treatment if applicable (if maintenance treatment follows a 3weekly schedule switch to the schedule of assessment for 3weekly regimens).

c: Training sessions (incl attendance) and patient diary is documented/controlled by physical therapists.

d: assessment is done until PD: every 8 ± 1 weeks during the first year, then every 12 weeks until PD, use always the same modality i.e. either CT or MRI.

e: Body mass index (height in cm / (weight in kg)*2 ) will be calculated in all patients at baseline and at week 18.

f: Standardised sit-to-stand test is performed in all non-progressing patients at baseline, end of weeks 12, 18, 24 and 48.

i: Lab assessments correspond to the routine assessments (usually on day 1 of each cycle).

j: if patient takes part in translational project, this blood sampling is done in FASTING state (see f, and Chap. 18 of protocol).
SAKK 41/14 Schedule of assessments for patients undergoing a 3weekly chemotherapy regimen (e.g. XELOX)

(for patients undergoing a 2weekly chemotherapy schedule (e.g. FOLFOX) use the other schedule of assessment for 2weekly regimens)

This schedule for patients by changing the date in box D7. Excel will automatically calculate the subsequent dates.

In order to reschedule the dates after a delay, simply enter the new date for the visit into the corresponding box. The subsequent dates will then be recalculated accordingly.

Patient Information:  UPN 4114

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Week</td>
<td>-4 to 0</td>
<td>-2 to 0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Day</td>
<td>-28 to 0</td>
<td>-14 to 0</td>
<td>1</td>
<td>8</td>
<td>15</td>
<td>22</td>
<td>29</td>
<td>36</td>
<td>43</td>
<td>50</td>
<td>57</td>
<td>64</td>
<td>71</td>
<td>78</td>
<td>85</td>
<td>92</td>
<td>99</td>
<td>106</td>
<td>113</td>
<td>120</td>
</tr>
<tr>
<td>Intervention a</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Informed consent for trial participation and translational research</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Tumor assessment (CT or MRI) b</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Medical history (incl. baseline symptoms, previous therapies, location of tumor sites and TNM status), history of diabetes, arterial hypertension</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Physical examination (incl. WHO PS, blood pressure, weight, height only at baseline)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Hematological values (leucocytes, ANC, lymphocytes, platelet count, hemoglobin), AST, AP, bilirubin, serum albumin, serum creatinine, CEA c</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>SOPALS</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>HbA1c, weight (BMI) d</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Blood sample for translational research FASTING e</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Questionnaires on patient-reported outcomes f</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Physical activity questionnaire GPAQ</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Sit-to-stand test g</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Therapeutic relationship question (in intervention group only)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Overall-Treatment-Utility Questionnaire</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Assessment of anti-hypertensive drugs</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Assessment of anti-diabetic drugs</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Sunhel status</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Selected Adverse Events (AE) (see Protocol Chap. 10.2)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

a: The ACTIVE-program in the intervention group should be started as close as possible to day 1 of systemic treatment (at latest within the first 3 weeks) and takes 12 weeks (24 sessions)
b: Treatment phase designates the period where the patient receives active systemic treatment, including maintenance treatment if applicable (if maintenance treatment follows a 2weekly schedule switch to the schedule of assessment for 2weekly regimens)
c: Training sessions (incl attendance) and patient diary is documented/controlled by physiotherapists
d: assessment is done until PD: every 9 ± 1 weeks during the first year, then every 12 weeks until PD, use always the same modality i.e. either CT or MRI
f: Body mass index (height in cm / (weight in kg)*2 ) will be calculated in all patients at baseline and at week 18