SAKK - SWISS GROUP FOR CLINICAL CANCER RESEARCH

Protocol SAKK 41/13-Aspirin
Adjuvant aspirin treatment in PIK3CA mutated colon cancer patients. A randomized, double-blinded, placebo-controlled, phase III trial.

Protocol version:	Version 4.0: amended version incl. amendments 1-3, 11.11.2021	
Activation date:	April 26, 2016	SNCTP No. SNCTP000001339 EudraCT No. 2015-001482-57

Study type:	Clinical trial with Investigational Medicinal Product (IMP)	
Categorization:	Risk category B according to the Human Research Act (HRA) and its ordinance KlinV/Oclin	

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Sponsor:	Swiss Group for Clinical Cancer Research Bern, Switzerland
Internet-based registration:	www.sakk.ch/edc

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CONFIDENTIALITY

PROTOCOL SIGN-OFF PAGE

SAKK 41/13-Aspirin. Adjuvant aspirin treatment in PIK3CA mutated colon cancer patients. A randomized, double-blinded, placebo-controlled, phase III trial.

The protocol SAKK 41/13-Aspirin was accepted by the SAKK Board on 28.01.2014 and has passed the recommended review process for SAKK trials.
The final protocol is dated 05.06.2015.
The amended version 4.0 of the protocol (including amendments 1-3) is dated 11.11.2021.

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Date: Nov. 15th, 2021 Signature:

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Date: 11.11.2021 Signature: S. Hayoz

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Date: 11.11.2021 Signature: Karin Rothg.

PROTOCOL SIGN-OFF PAGE PROTOCOL VERSION 4.0 FOR THE PRINCIPAL INVESTIGATOR

SAKK 41/13-Aspirin. Adjuvant aspirin treatment in PIK3CA mutated colon cancer patients. A randomized, double-blinded, placebo-controlled, phase III trial.

Principal Investigator in: _____

Having read and understood protocol version 4.0, I agree to conduct the trial as specified in the protocol, current version of the World Medical Association Declaration of Helsinki, the ICH-GCP guidelines and the local legally applicable requirements. Version 4.0 may only be implemented after the responsible ethics committee and the competent authority have accepted amendment 3.

Name: _____ Title: _____

Date: _____ Signature: _____

ABBREVIATIONS

AE	Adverse event
ASR	Annual safety report
CEA	Carcinoembryonic antigen
CI	Confidence interval
COX-2	Cyclooxygenase-2
CDM	Clinical Data Manager
CPM	Clinical Project Manager
CRA	Clinical Research Associate
CRF	Case report form
CRO	Clinical Research Organization
CSS	Cancer-specific survival
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DCN	Drug code number
DFS	Disease-free survival
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ESMO	European Society of Medical Oncology
EU	European Union
EudraCT	European Clinical Trials Database
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
HFV	Humanforschungsverordnung
HLA	Human leukocyte antigen
HR	Hazard ratio
HRA	Human Research Act
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product
KlinV	Verordnung über klinische Versuche in der Humanforschung
KOFAM	Koordinationsstelle Forschung am Menschen
MSI	Microsatellite instability
NCI	National Cancer Institute
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
OClin	Ordonnance sur les essais cliniques dans le cadre de la recherche sur l’être humain
ORH	Ordonnance relative à la recherche sur l'être humain
OTC	Over-the-counter
OS	Overall survival
PIK3CA	phosphatidylinositol-4,5-biphosphonate 3-kinase
PD	Progressive disease
PP	Per protocol
PQC	Product quality complaint

PS	Performance status
RSI	Reference safety information
SAE	Serious adverse event
SAKK	Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung
SAKK CC	SAKK Coordinating Center
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SDL	Source data location
SDV	Source data verification
SGG//SSG	Schweizerische Gesellschaft für Gastroenterologie/ Société Suisse de Gastroentérologie/ Società Svizzera di Gastroenterologia
SNCTP	Swiss National Clinical Trials Portal
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TTR	Time to recurrence
ULN	Upper limit of normal
UPN	Unique patient number
WHO	World Health Organization

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1 TRIAL OVERVIEW SAKK 41/13-ASPIRIN

SAKK 41/13-Aspirin. Adjuvant aspirin treatment in PIK3CA mutated colon cancer patients.
A randomized, double-blinded, placebo-controlled, phase III trial.

Sponsor: Swiss Group for Clinical Cancer Research (SAKK)

Trial registry No.: Swiss National Clinical Trial Portal (SNCTP): SNCTP000001339
Cancer Clinical Trials Registry (ClinicalTrials.gov): NCT02467582
European Clinical Trials Database (EudraCT): 2015-001482-57

Coordinating investigator: Prof. Dr. med. Ulrich Güller, Spital STS AG Thun, Switzerland

TRIAL TYPE AND CATEGORISATION

Clinical trial with IMP (including placebo as comparator).

Aspirin is a medication with marketing authorization in Switzerland and EU as an analgesic, anti-inflammatory and antipyretic drug and, at low dose, for the prevention and treatment of cardiovascular and cerebrovascular diseases. In this trial, low dose aspirin (i.e. 100 mg) will be used daily during 3 years for the adjuvant treatment of colon cancer. According to the Swiss HRA and its corresponding ordinance KlinV/Oclin on clinical trials, this trial is classified as category B.

OBJECTIVE

The trial objective is to demonstrate a statistically significant and clinically relevant disease-free survival benefit in stage II and III PIK3CA mutated colon cancer patients taking daily adjuvant aspirin for maximum 3 years.

ENDPOINTS

Primary endpoint:

- Disease-free survival (DFS)

Secondary endpoints:

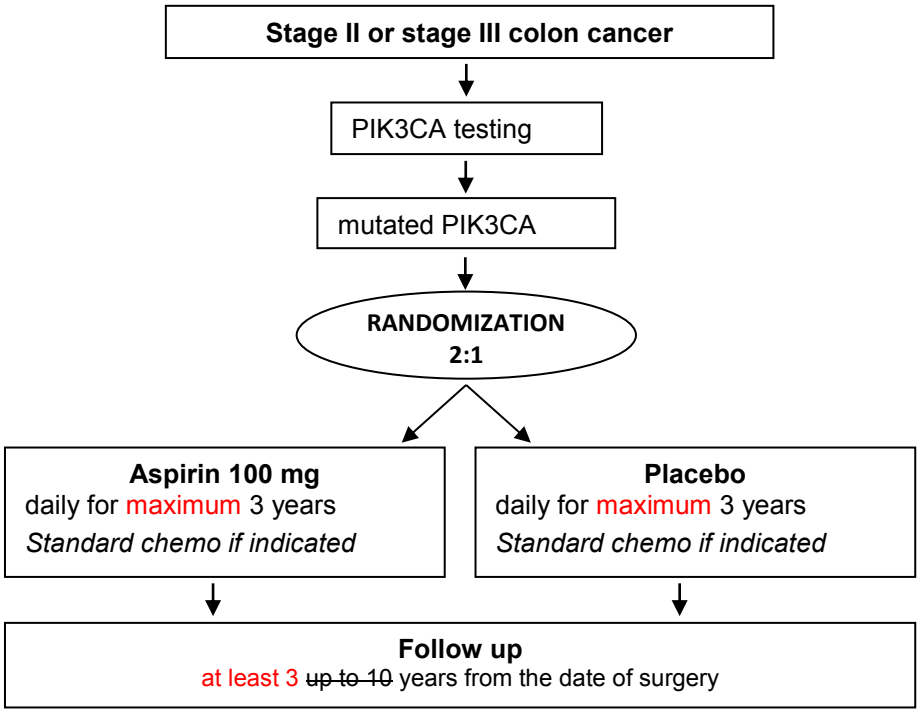
- Time to recurrence (TTR)
- Overall survival (OS)
- Cancer-specific survival (CSS)
- Adverse events (AEs)

Additional research questions:

Patient's tumor will be investigated for the identification of predictive and prognostic markers for the response to adjuvant therapy with aspirin and for the assessment of the biology of aspirin-mediated response.

TRIAL DESIGN

International, multicenter, randomized, double-blinded, placebo-controlled, phase III trial.



The concomitant use of adjuvant chemotherapy for stage III and high risk stage II colon cancer according to international treatment guidelines is allowed (chemotherapy regimens include intravenous 5-fluorouracil or oral capecitabine either alone or in combination with intravenous oxaliplatin).

SELECTION OF PATIENTS

Refer to section 6 for the full list of inclusion/exclusion criteria

- Histologically confirmed diagnosis of adenocarcinoma of the colon
- Stage II (pT3/T4 N0 cM0) or stage III (pTx pN+ cM0) disease
- Presence of predefined, activating PIK3CA mutation in exons 9 or 20
- Complete curative tumor resection (R0) within 14 weeks maximum before registration
- Adequate performance status (PS 0-2) and hematological values
- No multiple adenocarcinomas of the colon
- No rectal cancer
- No severe or uncontrolled cardiovascular disease
- No upper gastrointestinal bleeding within 12 months prior to registration; no bleeding disorder that is an absolute contraindication to the use of aspirin
- No regular intake of acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase (COX)-2 inhibitors
- No systemic rheumatic diseases or degenerative disorders affecting the musculoskeletal system with a relevant risk of requiring treatment with NSAIDs in the future
- No concurrent treatment with other experimental drugs, no administration of concomitant drugs contraindicated for use with the trial drug (the concomitant use of adjuvant chemotherapy for

stage III and high risk stage II colon cancer according to international treatment guidelines is allowed)

TRIAL DURATION

Duration of accrual: Initially planned 3 years, actual duration until premature closure of the trial (see section 5) 4.5 years

Duration of trial therapy (per patient): maximum 3 years (or until recurrence, death or consent withdrawal)

Duration of the follow-up (per patient): at least 3 years (from the date of surgery)

Duration of trial (in total): 7.5 years

The trial may be stopped early based on the results of two interim efficacy analyses or if new scientific data become available which change assessment of risk/benefit.

TRIAL SCHEDULE

Trial activation: Q2 2016

First patient in: Q2 2016

Last patient in: Q2 2019 (initially planned); Q4 2020 (after premature closure)

Last patient last treatment: Q2 2022 (initially planned); Q2 2021 (after premature closure)

Last patient last visit: Q2 2029 (initially planned); Q4 2023 (planned after premature closure)

TRIAL PRODUCT

Aspirin® (acetylsalicylic acid) is a salicylate drug that has analgesic, anti-inflammatory, antipyretic and antiplatelet properties. Aspirin is part of a group of medications called non-steroidal anti-inflammatory drugs, but differs from most other NSAIDs in the mechanism of action.
The comparator used in this trial is placebo, and both, aspirin or placebo are taken orally once daily.

TRIAL TREATMENT

Patients with resected colon cancer stage II or stage III bearing somatic mutations in exon 9 or 20 of PIK3CA will be 2:1 randomized to daily adjuvant aspirin 100 mg versus placebo for a maximum of 3 years or until disease recurrence, patient death or withdrawal of consent, whichever occurs first. Patients will be followed up for at least 3 years from the date of surgery.

The intake of aspirin or placebo is independent of adjuvant chemotherapy, and does not impact on the indication to give (or not to give) adjuvant chemotherapy.

MEASUREMENTS AND PROCEDURES

Following complete resection of their primary tumor, potentially eligible stage II or stage III colon cancer patients will undergo PIK3CA testing. Mutation screening will be performed centrally in archived formalin-fixed paraffin-embedded (FFPE) tumor tissue. Baseline assessments before trial treatment include clinical examination and blood testing for safety parameters and tumor marker. The trial therapy consists in daily aspirin (100 mg) or placebo *per os*.

The schedule of assessments during trial treatment and in the follow-up phase is in line with the guidelines from the Swiss Association for Gastroenterology (SGG/SSG) and the European Society of Medical Oncology (ESMO) for the follow-up of patients with colon cancer. Clinical examinations and carcinoembryonic antigen (CEA) measurements are to be performed every 3 months during the first 2 years following surgery, thereafter every 6 months until year 5. Bleeding-related adverse events potentially related to trial medication are to be recorded throughout trial treatment. Colonoscopy will be performed at year 1 and 4 following surgery, whereas computer tomography (CT) of the chest and abdomen are to be performed once a year. From year 6 to 10, disease and

survival status will be collected yearly. After recurrence, only survival status will be recorded for up to 10 years from surgery.

STATISTICAL CONSIDERATIONS

The sample size is based on the primary endpoint disease-free survival (DFS). Using a type I error of 5%, a power of 80% and a randomization ratio of 2:1, 43 events will be needed to show superiority of the aspirin arm under the alternative hypothesis that the hazard ratio (HR) is 0.456 (corresponding to a 3-year DFS of 70% in the placebo arm and 85% in the aspirin arm assuming constant hazards). The sample size needed is 185 patients (123 in the aspirin arm, 62 in placebo arm); the number needed to screen is estimated to be 1850 patients. All efficacy endpoints will be analyzed based on the full analysis population. The treatment effect will be assessed using Cox regression models with the treatment arm as independent variable and the stratification factors as strata.

GCP STATEMENT

This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH/GCP as well as Swiss and European legal and regulatory requirements.

2 INTRODUCTION AND BACKGROUND

2.1 Disease background

Colorectal cancer is the third most common malignancy for both women and men and is responsible for almost 10% of all cancer deaths [1]. Each year an estimated one million patients are diagnosed worldwide with colorectal cancer and about half will eventually die of it [2]. Particularly, the dramatic rise in the incidence of colorectal cancer in the 3rd, 4th and 5th decade is concerning [3]. Hence, colorectal cancer represents a tremendous public health problem.

2.2 Therapy background

Patients with stage II and III colorectal cancer usually undergo an oncologic resection including en bloc lymphadenectomy. Stage III patients (node-positive) generally receive adjuvant chemotherapy. Stage II (node-negative) colorectal cancer patients may receive adjuvant chemotherapy if high risk features are present (e. g. poor differentiation, lymphovascular invasion, perineural invasion, T4 tumor stage, ileus).

Despite complete removal and use of adjuvant chemotherapy, up to 25% of stage II patients [4] and up to 50% of stage III will suffer from recurrences [5, 6], which is associated with poor prognosis. This remains an unsettling problem for surgical and medical oncologists. Tremendous efforts have been undertaken to improve the prognosis of completely resected colon cancer patients. Indeed, several randomized controlled trials were performed adding irinotecan [7], vascular endothelial growth factor (VEGF)-A antibodies [8, 9] or epidermal growth factor receptor (EGFR) antibodies [10] to standard chemotherapy. However, all these efforts failed. Hence, there is a strong need for novel strategies to decrease the high recurrence rate in stage II and III colon cancer patients.

2.3 Rationale for performing the trial

Previous trials

Many observational and even randomized studies have provided evidence for a protective effect of aspirin on colorectal cancer. In a randomized, double-blinded trial 635 patients with previous colorectal cancer were allocated to aspirin 325 mg daily versus placebo. After a median follow-up of 12.8 months, one or more adenomas were found in 17% of patients in the aspirin group versus 27% in patients taking placebo (p=0.004) [11]. In the Nurses' Health Study, a prospective US cohort study, 27`077 patients were analyzed. After risk-adjusting in multivariable analyses, patients taking regular aspirin had a significantly lower risk of developing colorectal adenomas. Moreover, there was a clear association between higher daily aspirin doses and lower risk of colorectal adenomas [12].

In October 2012, a retrospective analysis based on 2 prospective cohort studies was published in the New England Journal of Medicine [13], which evaluated the effect of aspirin after diagnosis of colorectal cancer in relation to phosphatidylinositol-4,5-biphosphonate 3-kinase (PIK3CA)-mutational status. Patients with PIK3CA-mutated colorectal cancer taking aspirin had a large beneficial effect on both cancer-specific (hazard ratio (HR): 0.18; 95% confidence interval (CI) [0.05 - 0.60], p<0.001) and overall survival (HR: 0.57; 95% CI [0.33 - 0.94], p=0.01). The improvements of cancer-specific and overall survival were both statistically significant as well as clinically relevant. Conversely, no effect whatsoever was observed in patients with PIK3CA wild type.

In a recently published retrospective study based on prospective data [14] 896 patients after resection of colorectal cancer were analyzed for PIK3CA mutations. Patients with PIK3CA mutation taking regular low-dose aspirin were found to have a significantly lower risk of colorectal cancer recurrence (HR 0.11; 95% CI 0.001 - 0.832; p=0.027) compared to those not taking aspirin. Similarly to the publication by Liao et al. [13], no difference in recurrence-free survival was observed between patients who did and did not take aspirin in the PIK3CA wild type subset (HR: 0.92; 95% CI 0.60 - 1.42, p=0.71)

It is hypothesized that the inhibition of cyclooxygenase-2 (COX-2) through aspirin down regulates the PIK3CA signaling activity resulting in an inhibition of tumor cell proliferation [15]. COX-2 is an important mediator of prostaglandin E2 (PGE2) production, which has been demonstrated to

enhance tumor cell survival, angiogenesis and proliferation and reduce apoptosis [16]. Hence, the inhibition of COX-2 activity has a cytotoxic effect on gastric cancer cells, both in vivo and in vitro [16, 17].

Current trials

There are currently no randomized trials evaluating aspirin as an adjuvant treatment after resection of exclusively PIK3CA mutated colorectal cancer (website www.clinicaltrials.gov, last accessed on March 7th, 2015). One ongoing trial is currently randomizing stage II and III colorectal cancer patients to daily aspirin versus no aspirin (NCT00565708), but without selecting patients with exon 9 or 20 for PIK3CA mutations. In sharp contrast to this trial, which enrolls any patients with colorectal cancer, we plan to exclusively include colon cancer patients with a PIK3CA mutation and therefore prospectively address the question of a possible benefit of adjuvant aspirin for this patients group.

This trial

Although both studies mentioned above [13, 14] provide strong suggestive evidence for a very large protective effect of aspirin in PIK3CA mutated colorectal cancer patients, a potential selection bias in these retrospective analyses cannot be excluded with certainty. Therefore, these extremely interesting and intriguing findings need to be confirmed in a prospective trial to potentially change clinical practice. This trial was planned accordingly and prospectively investigates the role of aspirin in patients with confirmed PIK3CA mutation.

2.4 Choice of aspirin dosage

Patients will be treated with a daily dose of 100 mg of adjuvant aspirin or placebo in the frame of this trial.

Although there is suggestive evidence that the primary prevention of colorectal adenomas is more efficacious with higher dosages and longer durations of aspirin intake [12], the current state of knowledge suggests that low-dose, i.e. 100 mg of daily aspirin is equally efficient as 325 mg for the secondary prevention of the disease. The publication by Liao and colleagues suggesting a beneficial effect of aspirin to decrease recurrence rate in patients with colorectal cancer used 325 mg of aspirin daily [13], whereas patients received low-dose aspirin (≤100 mg/day) in the study by Domingo et al. [14]. Both studies presented a similarly low and statistically significant hazard ratio regarding disease-free and cancer-specific survival (HR of 0.11 and 0.18. respectively).

In a 3-arm randomized trial with 1`121 patients with prior colorectal adenomas, there was a lower rate of developing adenomas in patients taking low-dose aspirin (81 mg/day) compared to those taking 325 mg [18]. Furthermore, in a cohort of patients diagnosed with colorectal cancer selected from the Eindhoven Cancer registry, patients taking low-dose aspirin had a significantly reduced risk of overall- and cancer-specific survival [19].

The excellent side effect profile of aspirin has been extensively demonstrated. A meta-analysis of 24 randomized studies including almost 66`000 patients taking aspirin long-term showed that gastrointestinal hemorrhage occurred in 2.47% of patients taking long-term aspirin compared with 1.42% taking placebo [20]. In the ATT (antithrombotic trialists`) meta-analysis with over 110`000 patients, major gastrointestinal and extra-cranial bleeds occurred in 0.10% versus 0.07% per year [21]. As adverse events are dose dependent, we expect improved adherence to and reduced drop-out rate with the administration of 100 mg aspirin.

2.5 Choice of design and comparator

This is a randomized, placebo controlled, double-blinded, multicenter, phase III trial.

As aspirin is an easily available drug, the placebo-controlled, randomized trial design is of cardinal importance, as there might be a relevant contamination (e. g. patients in the control group switching to aspirin) if the trial were open-labeled.

Furthermore, since patients with PIK3CA mutation taking regular aspirin were found to have a significantly lower risk of colorectal cancer recurrence compared to those not taking aspirin in the two recently published retrospective studies [13, 14], the randomization ratio 2:1 was chosen to subject fewer patients to placebo.

This prospective randomized, double-blinded design will allow the immediate implementation of a new clinical practice, should the trial demonstrate the expected benefit of adjuvant aspirin for disease control.

2.6 Choice of study population

We will include stage II (pT3/T4 N0 cM0) and stage III (pTx pN+ cM0) PIK3CA mutated colon cancer patients after complete resection of the primary tumor. It must be emphasized that the aspirin intake – if the patient is randomized to the intervention arm – is independent of adjuvant chemotherapy and will not impact the indication to give (or not) adjuvant chemotherapy.

Rectal cancer patients will be excluded for the following two reasons: first, it is well known that the rate of PIK3CA mutation is relevantly lower in rectal cancer (approximately 8%) compared to colon cancer patients [22]. Therefore, the number needed to screen can be lowered by excluding rectal cancer patients. Second, rectal cancer patients are treated differently to colon cancer patients (e. g. neo-adjuvant radiation/chemo-radiation). Hence, including colon cancer patients only will result in a trial with a more homogeneous patient cohort.

In summary, this randomized controlled phase III multicenter trial investigates an interesting, novel and relevant research question in one of the most prevalent malignancies. The trial is ethical and feasible as the use of daily aspirin represents a simple and safe intervention.

If the trial confirms the protective effect of aspirin on PIK3CA mutated colorectal cancer patients, it would be a breakthrough in treating one of the most prevalent malignancies, result in a change of current clinical practice and lead to a huge benefit for our patients.

3 OBJECTIVES AND ENDPOINTS

3.1 Objective

The objective of the trial is to demonstrate a statistically significant and clinically relevant disease-free survival benefit in stage II and III PIK3CA mutated colon cancer patients taking daily adjuvant aspirin for a maximum of 3 years.

3.2 Endpoints

For definition of endpoints see section 13.

3.2.1 Primary endpoint

The primary endpoint of the trial is:

- Disease-free survival (DFS)

3.2.2 Secondary endpoints

Secondary endpoints of the trial are:

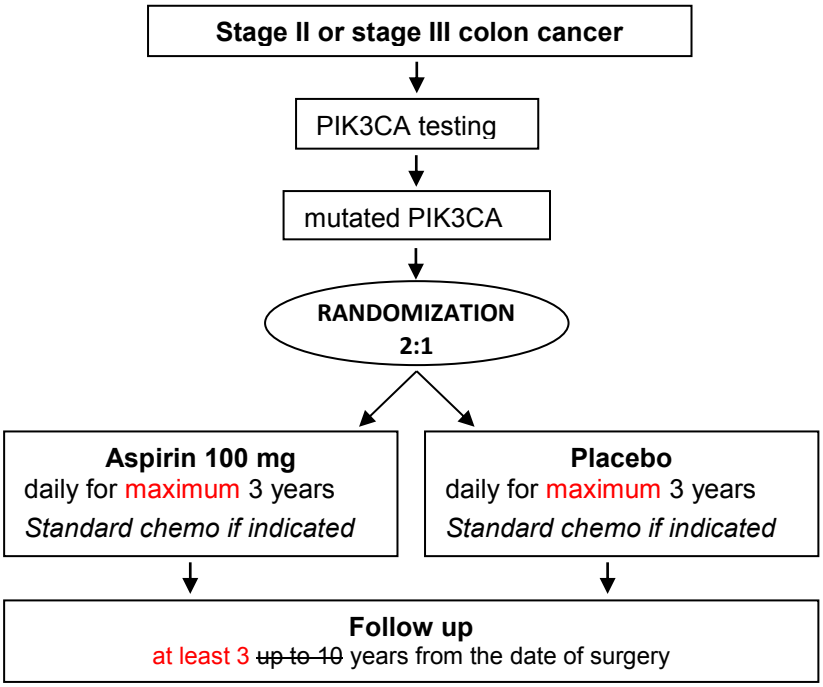
- Time to recurrence (TTR)
- Overall survival (OS)
- Cancer-specific survival (CSS)
- Adverse events (AEs)

3.3 Additional research questions

The patient's tumor samples will be investigated for the identification of predictive (e.g. COX-2 overexpression, human leukocyte antigen (HLA) class I antigen expression, germline genetics) and prognostic (including BRAF V600E mutations, tumoral microsatellite instability status (MSI)) factors for the response to adjuvant therapy with aspirin and for the assessment of the biology of aspirin-mediated response.

4 TRIAL DESIGN

This is an international, multicenter, randomized, double-blinded, placebo-controlled, phase III trial.



Initial design was that following complete resection of their primary tumor, potentially eligible stage II or stage III colon cancer patients will undergo central PIK3CA testing. Patients with somatic mutations will be 2:1 randomized to daily aspirin 100 mg versus placebo for a maximum of 3 years or until disease recurrence, patient death or withdrawal of consent, whichever occurs first. Patients will be followed up for at least 3 years from the date of surgery. However, the trial was prematurely closed for accrual and treatment, as described in chapter 5.

The intake of aspirin or placebo is independent of adjuvant chemotherapy, and does not impact on the indication to give (or not to give) adjuvant chemotherapy.

4.1 Methods of minimizing bias

4.1.1 Randomization and stratification

Patients are randomized in a 2:1 ratio to the aspirin or placebo arm using the minimization method with 80% allocation probability according to the stratification factors:

- Stage II versus stage III colon cancer
- Left versus right hemicolon
- PIK3CA mutation in exon 9 versus 20
- Country

A total of 185 patients (123 in the aspirin arm and 62 in the placebo group) were planned to be randomized.

Due to the premature closure for accrual of the trial, 113 patients were randomized.

4.1.2 Blinding

Patient randomization into the two treatment arms is double-blind. Neither the patient nor any of the investigators and other site personnel who are involved in the conduct of the trial or the analysis of the trial data have knowledge of the assigned treatment arm. This level of unblinding is maintained throughout the conduct of the trial unless there are compelling medical or safety reasons to alleviate the unblinding.

At SAKK CC, Clinical Research Associates (CRAs) performing source data verification and a designated Clinical Data Manager (CDM) remain blinded for the entire duration of the trial.

Blinding is performed by the authorized pre-wholesaler upon randomization of the patient (refer to section 7 for randomization/blinding procedures).

At the time point the trial treatment was prematurely stopped by the sponsor (see section 5), the site personnel was unblinded in order to inform the randomized patients about the treatment they had received. That allowed the patients to decide together with their treating investigator whether or not to continue aspirin treatment outside of the trial.

4.1.3 Other methods of minimizing bias

Patient compliance to trial treatment will be checked with the use of a patient diary. This diary will document the intake of the trial medication and the occasional intake of other medicinal products potentially interfering with COX-2 pathways, such as over-the-counter (OTC) acetylsalicylic acid containing products, NSAIDs or COX-2 inhibitors.

Measures to prevent contamination will include thorough information to the patient by means of the patient information sheet and the patient diary. Patients will be asked to consent in written to try to renounce to auto-medicate with OTC acetylsalicylic acid and other NSAIDs or COX-2 inhibitors during trial treatment, and preferentially use the permitted analgesics (paracetamol or metamizole).

5 TRIAL DURATION AND TERMINATION

The inclusion of patients has started in Q2 2016 and was planned to stop after the inclusion of 185 patients, which was initially expected in Q2 2019. Assuming a PIK3CA mutation rate of 17% based

on previous reports [13, 22], and some patients not being randomized into the trial due to patient's wish and eligibility criteria, the planned number of patients to be screened was 1850.

The trial may have been stopped prematurely based on the results of two interim efficacy analyses (see section 15, Statistical Considerations). In addition, accrual may have been interrupted and/or the trial may be stopped early if new scientific data become available which substantially change the benefit/risk ratio.

End of trial treatment was expected for Q2 2022.

In Q4 2020, the sponsor decided (due to financial reasons) to prematurely stop the accrual of the trial and the trial treatment at the next planned visit of each patient. Last patient, last treatment took place in Q2 2021, with the minority of accrued patients having reached the 3 years of treatment.

All patients randomized in Swiss sites will be followed-up for at least 3 years from the date of surgery until the last patient reaches the 3 years. The follow-up of patients randomized in foreign sites was stopped in Q2 2021 (after last patient, last treatment). Trial termination (last patient, last visit) was initially foreseen for Q2 2029, but is now foreseen in Q4 2023.

6 SELECTION OF PATIENTS

For timelines see chapter 12.

6.1 Inclusion criteria

To be eligible to enter this trial, patients must fulfill the following criteria.

6.1.1 Written informed consent according to ICH/GCP regulations before inclusion and prior to any trial-related investigations.

6.1.2 Histologically confirmed diagnosis of adenocarcinoma of the colon.

6.1.3 Stage II (pT3/T4 N0 cM0) or stage III (pTx pN+ cM0) colon cancer.

6.1.4 Availability of cancer tissue for central molecular testing.

6.1.5 Presence of predefined, activating PIK3CA mutation in exons 9 or 20 (centrally assessed, see section 17).

6.1.6 Complete resection of the primary tumor (R0) within 14 weeks maximum before registration.

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

6.1.8 Age ≥ 18 years.

6.1.9 Adequate hematological values: hemoglobin ≥ 80 g/L, platelets ≥ 50 x 10^9/L.

6.1.10 Adequate hepatic function: total bilirubin ≤1.5xULN, AST ≤2.5xULN, ALT ≤2.5xULN, AP ≤2.5xULN.

6.1.11 Calculated creatinine clearance > 30 mL/min, according to the formula of Cockcroft-Gault (see Appendix 2).

6.1.12 Women with child-bearing potential are using effective contraception (see 9.6), are not pregnant or lactating and agree not to become pregnant during trial treatment. A negative pregnancy test before inclusion (within 7 days) into the trial is required for all women with child-bearing potential.

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 Previous or concomitant malignancy within 3 years of registration, except for adequately treated cervical carcinoma in situ or localized non-melanoma skin cancer.

6.2.2 Multiple adenocarcinomas of the colon.

6.2.3 Rectal cancer (defined as distance from anal verge to proximal/oral tumor edge ≤15 cm).

6.2.4 Severe or uncontrolled cardiovascular disease (congestive heart failure NYHA III or IV (see Appendix 4), unstable angina pectoris, history of myocardial infarction) within three months prior to registration.

6.2.5 Systemic rheumatic diseases or degenerative disorders affecting the musculoskeletal system with a relevant risk of requiring treatment with NSAIDs in the future.

6.2.6 Comorbidities that require regular (i.e. more than 3x per month, any dose) intake of acetylsalicylic acid or other NSAIDs or COX-2 inhibitors.

6.2.7 Clinically relevant upper gastrointestinal bleeding within 12 months prior to registration.

6.2.8 Presence of any bleeding disorder that is an absolute contraindication to the use of aspirin.

6.2.9 General tendency to hypersensitivity and history of asthma triggered by salicylates or substances with a similar mechanism of action, and non-steroidal anti-inflammatory drugs in particular.

6.2.10 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. uncontrolled infection, active autoimmune disease, uncontrolled diabetes).

6.2.11 Concurrent treatment with other experimental drugs or treatment in an interventional clinical trial within 30 days prior to trial entry. Concomitant use of adjuvant chemotherapy for stage III and high risk stage II colon cancer according to international treatment guidelines is allowed (chemotherapy regimens include intravenous 5-fluorouracil or oral capecitabine either alone or in combination with intravenous oxaliplatin).

6.2.12 Psychiatric disorder precluding understanding of trial information, giving informed consent or interfering with compliance for oral drug intake.

6.2.13 Any familial, sociological or geographical condition potentially hampering proper staging and compliance with the trial protocol.

6.2.14 Known or suspected hypersensitivity to any component of the trial drug/placebo or any agent given in association with this trial.

6.2.15 Known galactose-1-phosphate uridyl transferase deficiency, UDP galactose 4 epimerase deficiency, galactokinase deficiency, Fanconi-Bickel syndrome, congenital lactase deficiency, or glucose-galactose malabsorption (due to the lactose-containing placebo).

6.2.16 Any concomitant drugs contraindicated for use with the trial drug according to the approved product information.

7 REGISTRATION AND RANDOMIZATION

7.1 Pre-registration procedure (PIK3CA mutation screening)

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

- Fill in the patient screening and enrollment list.
- Check the eligibility criteria.
- Obtain written informed consent from the patient for PIK3CA mutation testing. A separate information and consent form is designed for that purpose.
- Paraffin block of tumor tissue must be sent to Central Pathology for PIK3CA mutation analysis with enough time to allow registration within 14 weeks following surgery, together with a coded copy of the local pathology report and the “PIK3CA testing cover letter”. Ensure to use the pre-defined screening number in your correspondence (refer to the screening and enrollment list). See section 17.1 for details.

7.2 At registration and randomization

- Check the mutation status of PIK3CA centrally assessed.
- Obtain written informed consent from the patient for participation in the trial.
- When applicable: obtain written informed consent from the patient for translational research and banking of biological samples (on the corresponding trial-specific information and consent form).

Registration and randomization is done via Internet (www.sakk.ch/edc) or - only if this is not possible due to technical problems (e.g. unavailability of the EDC system) - by faxing the completed, dated and signed paper version of the eligibility CRF to the SAKK CC (Opening hours: Monday to Friday 8:00 a.m. to 5:00 p.m.).

SAKK Coordinating Center
Effingerstrasse 33
CH – 3008 Bern
Tel. +41 31 389 91 91

In order to receive authorization for online registration and data entry, sites must send a copy of the completed staff list (available on the SAKK portal) 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.

Randomization

Patient randomization is double-blind and is done by the site personnel during the online registration of the patient (on the same day as registration).

Upon randomization, a treatment arm is attributed by the system to each patient. The site and SAKK CC will receive a confirmation of randomization (without information on the ascribed treatment arm) by email. For patients enrolled in non-Swiss sites, the confirmation of randomization will also be sent to the relevant Cooperative Group or Clinical Research Organization responsible for local site management.

7.3 Blinding procedure and allocation of a drug code number (DCN)

Upon receipt of the automatic confirmation of randomization, SAKK CC informs the responsible pre-wholesaler of the UPN and the attributed treatment arm. Within 2 working days from randomization, the pre-wholesaler allocates one DCN to the corresponding patient and communicates this DCN to the site by fax or e-mail, with a copy to the SAKK CC. Thereafter, the SAKK CC provides the site with an unblinding scratch off card. **This card must be stored in the investigator's file**.

Refer to section 8.2.2 for the further management of DCN and the dispensing of trial medication.

Refer to section 7.5 below for unblinding procedures.

7.4 After randomization

- Report the medical history, baseline clinical and laboratory information, surgical therapy and tumor location, and baseline symptoms in the eCRFs.
- Update the screening and enrollment list.
- Fill in the patient identification list.
- Inform the central pathologist whether the patient consented to translational research/tumor tissue banking by completing the bottom part of the "PIK3CA screening results cover letter". Send the form per fax or email.

The certified copy of the signed Eligibility Form (printout of eCRF form ER) has to be sent to the responsible clinical project manager (CPM) by email or fax within one month after randomization. The original is kept in the investigator's file.

Trial therapy should be started within 14 days from randomization.

- Instruct the patient about the use of the patient diary.

7.5 Unblinding procedures

Unblinding during the conduct of the trial should be restricted to the cases where there are compelling medical or safety reasons to do so.

If unblinding is considered for non-emergency cases, the local investigator should contact the SAKK CC and the coordinating investigator immediately. Any reasons for unblinding – except for an emergency case – have to be discussed beforehand with the coordinating investigator or the Medical Advisor of the SAKK CC.

<u>For the case that emergency unblinding is necessary:</u>

A scratch off card is provided to the site by the SAKK CC for each patient after the initial DCN allocation (at the start of trial treatment). SAKK CC ensures the correct attribution of a card to each patient by double signatures and documentation.

Sites are responsible to store the card in the investigator's file. In case an investigator breaks the code of a patient, the SAKK CC has to be informed immediately. The investigator will be instructed to keep the information strictly confidential.

<u>Documentation of unblinding:</u>

Any breaking of the code (intentional and unintentional) must be reported and explained via EDC in the CRF "Unblinding" (UB), irrespective of the reason for its occurrence. The unblinding and reason for unblinding must be recorded.

At the time when the trial treatment was prematurely stopped by the sponsor in December 2020 (see section 5), all participating sites received the information about the allocated treatment arm of their

specific patients in order to inform them about the treatment they had received. That allowed the patients to decide together with their treating investigator whether or not to continue aspirin treatment outside of the trial. Since this general unblinding process involved all patients randomized to the trial, with the same date and reason for all of them, it must not be documented on the CRF UB via EDC.

8 DRUG SUPPLY AND HANDLING

8.1 Drugs in protocol

8.1.1 Investigational medicinal product (IMP)

In this trial the IMP is aspirin (including placebo as comparator).

Aspirin® is a medication with marketing authorization in Switzerland and EU as an analgesic, anti-inflammatory and antipyretic drug and, at low dose, for the prevention of cardiovascular and cerebrovascular diseases. In this trial, low dose aspirin (i.e. 100 mg) will be used for the adjuvant treatment of colon cancer.
The comparator used in this trial is placebo. Both aspirin® and placebo will be administered orally once daily (o.d.).

8.2 Drug supply and handling of aspirin and placebo

8.2.1 Drug supply

Aspirin and placebo are produced and supplied by Bayer and will be provided free of charge by the SAKK for all participating sites. The distribution will be managed by an authorized pre-wholesaler.

Aspirin and placebo will be supplied as film-coated tablets for oral intake in bottles of 100 tablets. The aspirin tablets contain 100 mg *Acidum acetylsalicylicum* per tablet. The placebo tablets are identical, but contain no active substance (*verum*).

SAKK CC will order the initial stock of IMP by the pre-wholesaler upon activation of the trial at the site and will reorder new trial medication for each site as soon as necessary.

8.2.2 DCN allocation and re-allocation

DCN allocation for newly registered patient:

Within 2 working days from randomization, the site is informed by fax or email of the DCN allocated to the randomized patient (see section 7.3). The allocated IMP bottle contains 100 tablets of trial medication.

DCN re-allocation at next visit

The site is responsible to request DCN re-allocation one week prior to the next visit of the patient.

Please fax or e-mail the duly filled “Demand of DCN re-allocation” form to the pre-wholesaler and SAKK CC (form is available for download from portal.sakk.ch (→Trials → SAKK 41/13-Aspirin). The site will be informed of the re-allocated DCN per fax or e-mail within 2 working days.

At the visits 24 and 30 months after surgery, the form “Demand of DCN reallocation after 2 years of trial treatment” should be used in order to get two DCNs allocated (since there will only be half-yearly visits during the third treatment year). In case a patient should have more frequent visits still in the third treatment year, it might also be continued to order only one DCN at a time by using the initial “Demand of DCN re-allocation” form.

The pre-wholesaler provides the SAKK CC monthly with an up-to-date list of all DCNs including their identification (aspirin or placebo), recipient site, and recipient UPN.

In case emergency unblinding is deemed necessary (only on the basis of compelling medical or safety reasons) the investigator breaks the code of the patient via the unblinding scratch off card (which is stored in the investigator’s file). Please refer to chapter 7.5 for details on unblinding procedures.

8.2.3 Labeling of aspirin and placebo

The trial medication will be labeled in all required local languages according to annex 13 from Eudralex GMP.

8.2.4 Handling and safety of aspirin and placebo

Trial medication is to be stored in a secure area at room temperature (15-25°C).

Please refer to the Swiss product information for detailed information on handling and safety of aspirin, available for download in English from the SAKK portal (https://portal.sakk.ch/ → Trials → SAKK 41/13-Aspirin → Documents).

8.2.5 Dispensing and accountability of aspirin and placebo

Trial medication will be given to the patient at each scheduled visit, i.e.

- every 3 months during the first 2 years of treatment (→ 1 bottle of IMP),
- every 6 months during the 3rd year of treatment (→ 2 bottles of IMP).

Trial medication must be dispensed in the original allocated IMP bottle with the label clearly visible. The UPN, the name and institution of the principal investigator as well as the dispensing date have to be written on the label of the IMP bottle before it is given to the patient.

IMP bottle(s) covering the treatment period between two visits will be provided to the patient at once. During the first two years patients will receive 1 bottle at each visit. During the third year patients will receive 2 bottles at each visit.

Patient diary: Patients must be instructed to note the date of IMP intake in a diary and to return empty, partly used or unused bottles of trial medication at each visit.

A patient diary covering a 3-month interval (to be used during year 1 and 2 of trial treatment) and a patient diary covering a 6-month interval (to be used during year 3 of trial treatment) were specifically designed for the trial. They are available for download from the trial-specific page on the SAKK portal.

Drug accountability: Sites must report the dispensing and return of the trial medication (including UPN, date, amount dispensed/returned, batch number). For that purpose, SAKK produced two drug inventory logs specific for this trial (aspirin/placebo inventory log; aspirin/placebo dispensing log per patient), which must be kept up-to-date.

Aspirin/placebo inventory logs are available on the SAKK portal (portal.sakk.ch → Members → Trials → Gastrointestinal Cancer → SAKK 41/13 → useful tools).

8.2.6 Unused aspirin and placebo

Unused or partly unused trial medication must be checked and reconciled with the patient diary.

In case aspirin or placebo is lost or damaged, its disposition must be documented in the source documents.

Unused, partly unused or expired trial medication has to be destroyed at the site according to local guidelines but only after the inspection of the CRA and receipt of instructions from SAKK CC. The destruction must be documented in an appropriate drug destruction certificate. Sites may use the local certificate or the trial-specific template provided by SAKK (available on the SAKK portal).

8.3 Product quality complaint handling

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical trials are crucial for the protection of patients, investigators and the sponsor, and are mandated by regulatory agencies worldwide.

8.3.1 Procedures

In case site staff identifies a potential product complaint situation, SAKK CC must be contacted immediately. In case a patient identifies a potential product complaint situation, the investigator must be contacted immediately, as outlined in the patient information and informed consent form.

PQCs must be forwarded within 24 hours to the SAKK CC (form available on portal.sakk.ch → Trials → SAKK 41/13 → useful tools). If the defect is combined with a SAE/SAR, the site staff must additionally report the event to SAKK CC according to the reporting timelines for SAEs (see chapter

11.5). A sample of the suspected product should be kept at the site in accordance with the storage instructions for further investigation if requested by SAKK CC, the pre-wholesaler or Bayer.

8.4 Other drugs for anticancer treatment outside protocol

In case standard adjuvant chemotherapy is administered concomitant to trial treatment, the treating physician must refer to the locally approved drug information and the respective country-specific guidelines for the use and handling of cytostatic compound(s).

Any potential interactions with the trial medication (aspirin or placebo) must be considered.

9 TRIAL TREATMENT

9.1 Treatment overview

Treatment consists of daily intake of 100 mg aspirin (experimental arm) or placebo (control arm) *per os*. Treatment duration is maximum 3 years from treatment start or until tumor recurrence, death, patient refusal or withdrawal by the physician, whichever occurs first. In Q4 2020, the sponsor decided to prematurely stop the accrual of the trial and the trial treatment at the next planned trial visit of each patient. Last patient, last treatment took place in Q2 2021.

9.2 Therapy with aspirin/placebo

Please refer to the Swiss product information for detailed information on handling and safety of aspirin, available for download in English from portal.sakk.ch (→ Trials → SAKK 41/13-Aspirin).

9.2.1 Administration and schedule

Aspirin or placebo is to be taken orally at a dose of 100 mg once daily, if possible before a meal, with some liquid. A time interval of 24 hours should occur between consecutive intakes. The omitted doses are not replaced (also in case of vomiting after the intake). No pre-medication or supportive medication is required.

No dose reduction of aspirin or placebo is allowed. Trial treatment may be temporarily discontinued in case of adverse events or surgery. Interruptions should be as short as possible. Please refer to 10.5 for more details.

9.2.2 Warnings and precautions

Caution should be applied in patients with asthma, allergic disease, impairment of hepatic or renal function (avoid if severe) and dehydration. Elderly patients may be more susceptible to potential adverse events of salicylates such as aspirin. Aspirin should be used with caution in patients with a history of peptic ulceration or coagulation abnormalities. Caution should also be used in patients with known glucose-6-phosphate-dehydrogenase (G6PD) deficiency as these patients may experience hemolytic anemia. Aspirin prolongs bleeding time, mainly by inhibiting platelet aggregation, and it should be discontinued several days before scheduled major surgical procedures (see also section 10.5).

Refer to the current Swiss product information for information on warnings and precautions, available for download in English from portal.sakk.ch (→Trials → SAKK 41/13-Aspirin).

9.2.3 Assessment of compliance

Patient compliance shall be assessed using a patient diary during trial treatment. This diary documents trial medication intake and deviations from the recommendations as outlined above.

The diary should also be used for the recording of co-medications that the patient may occasionally take during trial treatment, in particular OTC acetylsalicylic acid, other NSAIDs and COX-2 inhibitors.

The patient is requested to bring the diary at each visit. The completed diary has to be checked by the local trial staff in presence of the patient.

9.3 Treatments not permitted during trial treatment phase

The following treatments <u>are not permitted</u> during trial treatment with aspirin or placebo:

- Other investigational treatments

The following treatments <u>should be avoided</u> during trial treatment with aspirin or placebo **except if taken for acute reasons and as short as possible** (i.e. no more than 3x per month, any dose):

- acetylsalicylic acid (other than trial medication)
- other NSAIDs or COX-2 inhibitors such as diclofenac, mefenamic acid, ibuprofen, celecoxib, etc..

Preferred alternative treatments options: paracetamol or metamizole.

In case long-term use of acetylsalicylic acid, other NSAIDs or COX-2 inhibiting drugs is absolutely indicated (for whatever medical reason) trial treatment must be stopped. The patient may be unblinded if required for safety or medical reasons.

The patient will remain in the trial and the follow-up examinations will be performed as planned in this protocol (see section 12.3). If applicable, the unblinding and reason for unblinding must be recorded. Please refer to section 7.5 for unblinding procedures.

Of note: Surgical procedures are allowed during trial treatment. Trial medication (i.e. aspirin or placebo) should be discontinued and restarted as per local guidelines for aspirin.

9.4 Treatment duration

Patients will be transferred to the follow-up phase as soon as one of the following events occurs:

- treatment was completed as per protocol
- recurrence (must be confirmed by imaging)
- patient refusal (see 22.4 Premature withdrawal)
- withdrawal by the physician (see 22.4 Premature withdrawal)
- patient becomes pregnant
- premature trial closure by the sponsor (in Q4 2020, the sponsor decided to prematurely stop the accrual of the trial and the trial treatment due to financial reasons)

See section 12.3 for evaluations after treatment termination.

All patients randomized in Swiss sites will be followed-up for at least 3 years from the date of surgery. The follow-up of patients randomized in non-Swiss sites was prematurely stopped in Q2 2021.

9.5 Concomitant adjuvant chemotherapy

Adjuvant chemotherapy is given according to international treatment guidelines [23]. The choice of the individual chemotherapy regimen or the decision to do without adjuvant chemotherapy is at the discretion of the treating investigator.

Adjuvant chemotherapy may be started before or after trial entry. The administration of concomitant therapy will be recorded in the respective eCRF. Discontinuation or modification of any adjuvant chemotherapy given is allowed and will be recorded in the eCRF.

9.6 Precaution

The following precaution is valid for women taking part in a clinical trial:

Women with child-bearing potential who take part in this trial should use effective contraception during the duration of trial treatment. Effective contraceptives can be hormonal (e.g. contraceptive pill, injections, or implants) or mechanical (e.g. condom, intrauterine pessar, diaphragm, cervical cap or another device).

10 ADVERSE EVENT REPORTING, DOSE MODIFICATIONS AND SUPPORTIVE TREATMENT

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 AEs

Patients will be instructed by the investigator to report the occurrence of any AE.

The investigator assesses and records the specified AEs, grade 3 or higher (see section 10.2.1 below), observed during the AE reporting period (from registration until 30 days after the end of trial treatment). Ongoing AEs which are not resolved within 30 days after treatment termination need to be followed-up until resolution or sequelae.

10.2.1 List of AEs to be reported

The investigator must report AEs, grade ≥3, which are **possibly, probably or definitively related to the trial medication (aspirin/placebo)**. Particular attention should be made to **bleeding-related AEs**, including but not limited to:

- Gastrointestinal hemorrhage with loss of fresh blood per rectum
- Intracranial hemorrhage

AEs associated with concomitant adjuvant chemotherapy must not be reported.

10.2.2 Reporting procedure

AEs are coded with the National Cancer Institute (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 to trial treatment. The NCI CTCAE v4.0 (as pdf) as well as instructions on how to use the criteria can be found on http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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 eCRF 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, it exists for each of the 26 system organ classes (SOCs) the term ‘others’ 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 eCRFs. Abnormal laboratory values occurring outside of predefined assessment times or not specifically asked to be assessed by the protocol should be documented as AE if they are grade 3 or higher.
- Relationship of AEs to treatment is assessed using the following scale:

  1 Unrelated The adverse event is clearly not related to the trial treatment. The AE is completely independent of trial treatment and/or evidence exists that the event is definitely related to another etiology.

  2 Unlikely The adverse event is doubtfully related to the trial treatment. Temporal association between the AE and the trial treatment and the nature of the event is such that the trial treatment is not likely to have had any reasonable association with the observed illness/event (cause and effect relationship improbable but not impossible).

3 Possibly The adverse event may be related to the trial treatment. Less clear temporal association; other etiologies also possible.

4 Probably The adverse event is likely related to the trial treatment. Clear-cut temporal association and a potential alternative etiology are not apparent.

5 Definitively The adverse event is clearly related to the trial treatment. Clear-cut temporal association, and no other possible cause.

10.3 Aspirin-related adverse events

Aspirin has a very favorable adverse event profile. Nonetheless, special care should be taken in case of occurrence of bleeding events.

Please refer to the Swiss product information of aspirin for information concerning drug-related AEs (available for download in English from portal.sakk.ch (→Trials → SAKK 41/13-Aspirin).

10.4 Safety parameters

Aspirin/placebo should be used according to the published product information and in accordance with best clinical practice.

The following safety assessments must be performed at the indicated times as detailed in the schedule of assessments (see section 12):

- Assess signs and symptoms of bleeding disorders, including but not limited to: gastrointestinal hemorrhage with loss of fresh blood per rectum, intracranial hemorrhage.

10.5 General remarks on dose modifications and treatment interruption

No dose reduction of aspirin or placebo is allowed.

Trial treatment with aspirin or placebo may be temporarily discontinued in case of adverse events or surgery. Interruptions should be as short as possible. The omitted doses are not replaced.

- Trial treatment should be temporarily discontinued in case of an AE grade 3 or higher which is potentially related to aspirin/placebo.
- In case of AE grade 1 or 2, temporary interruption of trial treatment is at the discretion of the treating investigator.
- In case of chemotherapy-induced thrombocytopenia, aspirin/placebo should be discontinued if platelets are < 50 g/L and restarted when ≥ 50 g/L.
- In case of surgical procedures during trial treatment, aspirin/placebo should be discontinued and restarted as per local guidelines for aspirin.

The coordinating investigator must be contacted in case the treating physician has any doubts about trial treatment delays or discontinuation.

11 SAFETY REPORTING

11.1 Definition of serious adverse event (SAE)

SAE are any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect.

11.2 Definition of serious adverse reaction (SAR)

SARs are all SAEs considered to be possibly, probably or definitely related to the trial treatment.

11.3 Definition of suspected unexpected serious adverse reactions (SUSARs)

SUSARs are serious adverse reactions that are assessed as unexpected on the basis of the Swiss specific product information, which is the Reference Safety Information (RSI) in this trial (available for download in English from portal.sakk.ch (→Trials → SAKK 41/13-Aspirin).

11.4 Reporting of SAEs and pregnancy

11.4.1 SAEs during trial treatment

SAEs to be reported are any of the events **possibly, probably or definitively related to aspirin/placebo or to trial-specific procedures** (i.e. SARs), occurring between registration and up to 30 days after the end of trial treatment and additionally fulfilling the conditions listed in the following table:

SAE	Comments
Fatal	Events (possibly, probably or definitively related to aspirin/placebo or to trial-specific procedures) resulting in death.
Life-threatening	Events (possibly, probably or definitively related to aspirin/placebo or to trial-specific procedures) that put the patient at immediate risk of death. It does not include an event that, had it occurred in a more serious form, might have caused death.
Requires inpatient hospitalization	Events (possibly, probably or definitively related to aspirin/placebo or to trial-specific procedures) which require patient hospitalization for > 24 hours. Events not considered to be SAE are hospitalizations > 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) - PD
Prolongs hospitalization	Events (possibly, probably or definitively related to aspirin/placebo or to trial-specific procedures) which extend an existing hospitalization.
Disabling	Events (possibly, probably or definitively related to aspirin/placebo or to trial-specific procedures) leading to persistent or relevant disability or incapacity.
Secondary malignancy	Any new cancer other than a relapse of the current tumor.
Congenital anomaly	Birth defect in neonate/infant or stillbirth.
Other medically significant condition	Important AEs (possibly, probably or definitively related to aspirin/placebo or to trial-specific procedures) that are not immediately life-threatening or do not

	result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above.

11.4.2 SAEs after end of trial treatment

During the follow-up phase (starting 30 days after end of trial treatment), the following events have to be reported as SAE:

SAE	Comments
Fatal	Possibly, probably or definitely related to late effects of trial medication.
Life-threatening	Possibly, probably or definitely related to late effects of trial medication.
Disabling	Possibly, probably or definitely related to late effects of trial medication.
Secondary malignancy	Any new malignancy other than a relapse of the current tumor.
Congenital anomaly	Birth defect in neonate/infant or stillbirth.
Other medically significant condition	Possibly, probably or definitely related to late effects of trial medication.

11.4.3 Pregnancy

In the case of pregnancy occurring during trial treatment, the investigator must report it to the SAKK by completing the SAKK pregnancy reporting form. This form (available on the SAKK portal, Trials → SAKK 41/13-Aspirin → CRFs) has to be filled in immediately and faxed to the SAKK CC. The investigator shall ensure that the case is followed-up to the end of the pregnancy and supply a final report on the outcome to the SAKK CC. In addition, the investigator has to report any fetal anomaly, stillbirth or any other medicinal significant event concerning the pregnancy as SAE (see above 11.4.1 and 11.4.2).

11.5 Procedure for reporting individual SAEs by the investigator

Any SAE must be reported by submitting the completed **initial report** ~~section~~ of the trial-specific SAE form within **24 hours** of becoming aware of the event. This form can be downloaded from the SAKK portal (portal.sakk.ch → Trials → SAKK 41/13-Aspirin → CRFs).

Submission is done by sending the SAE form by email to: safety@sakk.ch.

The SAE outcome must be reported within 2 weeks after initial report by submitting the **follow-up** report (e.g. 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 to Bayer.

11.6 Reporting of individual SAEs and SUSARs by the sponsor

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

The SAKK CC will forward any SAE which is fatal and occurred at a Swiss site to the lead EC according to the Swiss HRA and its applicable ordinances.

The SAKK CC will report every SUSAR to all principal investigators, to the involved ECs, to Swissmedic and/or to the competent authorities of foreign countries (unless specified otherwise in the contract with a foreign site or foreign contract research organization (CRO), as specified in the Swiss HRA and the EU Clinical Directive 2001/20/EC. SUSARs occurring within CH or the EU will be entered into the Eudravigilance database by SAKK Safety Office within the required timeframe.

Additionally, SAKK CC will report SUSARs to Bayer.

11.7 Reporting of safety signals

In case the investigator receives external safety reports/letters related to the IMP, he/she must report to the sponsor within 7 days. The SAKK CC will forward these reports/letters to all investigators and to the local and lead ECs if applicable.

11.8 Periodic reporting on safety to principal investigators and regulatory authorities

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

A yearly Data Safety Update Report (DSUR) will be provided to the local investigators for filing in the investigator's file. The SAKK CC will submit the DSUR to the involved ECs, to Swissmedic, to the competent authorities of foreign countries and to Bayer. Since the trial has been closed in the foreign countries in Q3 2021 without further follow-up, the DSUR will be replaced by an Annual Safety Report (ASR) and will be submitted from 2022 onwards only to the Swiss local investigators, competent authorities, ECs and to Bayer.

12 EVALUATIONS AND INVESTIGATIONS BEFORE, DURING AND AFTER TRIAL TREATMENT

All assessments and investigations must be done within the defined time as indicated below.

An adaptable Excel schedule of assessments can be downloaded from the SAKK portal (portal.sakk.ch → Trials → SAKK 41/13-Aspirin → Documents → schedule of assessments).

12.1 Pretreatment evaluations and procedures

Informed consent for trial entry must be obtained before inclusion of the patient into the trial and prior to any trial-specific procedures (with the exception of the separately consented PIK3CA mutation analysis). Informed consent for PIK3CA mutation testing is obtained separately from and prior to the consent for trial entry.

Complete resection (R0) of the primary tumor must have been performed (max. 14 weeks prior to trial entry).

Stage II (pT3/T4 N0 cM0) or stage III (pTx pN+ cM0) and histologically diagnosis of adenocarcinoma of the colon must have been confirmed.

12.1.1 The following investigations have to be performed within 14 weeks before registration:

- Central PIK3CA mutation analysis (see section 17.1 for details on required material and logistics)

12.1.2 The following investigations have to be performed within 28 days before or on registration:

- Documentation of information on the patient, including ethnicity and risk factors
- Documentation of medical history, including baseline symptoms, surgical therapy, pre-surgery CEA, tumor history and location
- Physical examination, including assessment of WHO PS, weight and height
- Hematological values: hemoglobin, platelets
- Renal function: serum creatinine, calculated creatinine clearance (according to the formula of Cockcroft-Gault, see Appendix 2)
- Hepatic function: total bilirubin, ALT, AST, AP
- Pregnancy test for women with child-bearing potential (**within 7 days** prior randomization)
- Post-resection CEA level
- Assessment of all inclusion/exclusion criteria

Only for patients who consented to translational research:

- 5 ml EDTA-blood sample (see section 18.2 for details)

12.2 Evaluations during trial treatment

Trial treatment must start within 14 days following randomization.

OF NOTE: the time points of investigations and assessments refer to the **date of surgery** and not the date when the patient was randomized into the trial.

As such, the schedule of evaluations during the treatment and follow-up phases of the trial is according to the guidelines from the Swiss Association for Gastroenterology (SGG/SSG) & European Society of Medical Oncology (ESMO) for the follow-up of patients with colon cancer [24, 25]. Based on the recommendations of ESMO, clinical examinations and CEA measurements will be performed every 3 months during the first 24 months of evaluation as the vast majority of recurrences occur during the first 2 years after removal of the primary tumor. These examinations and any additional investigation upon suspected recurrence are not subjected to any limitation.

Table 2 below illustrates the time points of assessments in reference to the date of surgery versus the schedule of trial treatment.

Table 2: summary of assessments

Trial phase	*Adjuvant aspirin/placebo daily***										*Follow-up*			
Month after surgery*	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
Clinical examination and CEA level	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
AEs	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**				
Colonoscopy				**x**								**x**		
CT scan chest/abdomen				**x**				**x**		**x**		**x**		**x**

***Starting time point is date of colon cancer resection

****Adjuvant aspirin/placebo treatment is initiated within max. 16 weeks after colon cancer resection and is administered for 3 years from treatment start (or until tumor recurrence, death, patient refusal or withdrawal by the physician, whichever occurs first)

12.2.1 Year 1 and 2 following surgery

- Assessments to be done at 3*, 6, 9, 12, 15, 18, 21 and 24 months [± 2 weeks]
  - Clinical examination
  - Signs and symptoms of bleeding disorders, including but not limited to: gastrointestinal hemorrhage with loss of fresh blood per rectum, intracranial hemorrhage
  - Laboratory investigations (e.g. hemoglobin, platelets) only if clinically indicated
  - CEA level
    In case of significant increase compared to baseline (post-surgery): recurrence must be confirmed by colonoscopy or CT scan or other imaging technique
  - AEs (only while patient is under trial treatment)
    Only report AEs grade ≥ 3 potentially related to trial medication
  - Verify patient diary (i.e. patient's compliance to the protocol treatment & patient's intake of acetylsalicylic acid or other NSAIDs or COX-2 inhibitors beside trial treatment)
  - Collect information on concomitant anti-tumor adjuvant chemotherapy (e.g. regimen (doublet or monotherapy) versus no adjuvant chemotherapy, start/end date, etc.)

*) Note: If a patient is included into the trial later than three months after surgery, the visit at 3 months is omitted (and the first trial visit during treatment will take place 6 months after surgery).

- Assessments to be done at 12 and 24 months [± 2 weeks]
  - CT scan chest/abdomen (oral and i.v. contrast strongly recommended)

- Assessments to be done at 12 months [± 2 weeks]
  - Colonoscopy

12.2.2 Year 3 following surgery

- Assessments to be done at 30 and 36* months [± 1 month]
  - Clinical examination
  - Signs and symptoms of bleeding disorders, including but not limited to: gastrointestinal hemorrhage with loss of fresh blood per rectum, intracranial hemorrhage
  - Laboratory investigations (e.g. hemoglobin, platelets) only if clinically indicated
  - CEA level
    In case of significant increase compared to baseline (post-surgery): recurrence must be confirmed by colonoscopy or CT scan or other imaging technique
  - AEs (only while patient is under trial treatment)
    Only report AEs grade ≥ 3 potentially related to trial medication

- Verify patient diary (i.e. patient's compliance to the protocol treatment & patient's intake of acetylsalicylic acid or other NSAIDs or COX-2 inhibitors beside trial treatment)*
  *) Note: If a patient is still under trial treatment at month 36, the last patient diary verification will have to be done during the first follow-up visit at month 42.

- Assessments to be done at 36 months [± 1 month]
  - CT scan chest/abdomen (oral and i.v. contrast strongly recommended)

12.3 Evaluations in the follow-up phase

All patients randomized in Swiss sites will be followed-up for at least 3 years from the date of surgery (or until death, whichever occurs first), until the last patient completes the 3 years of follow-up from the date of surgery, which is expected in Q3 2024. The follow-up of patients randomized in non-Swiss sites was prematurely stopped in Q2 2021.

Evaluations in the follow-up phase will be different for disease-free patients and patients who experienced recurrence.

After a patient experienced recurrence, further treatment and investigation is up to the treating physician.

12.3.1 Patients without recurrence

Patients who completed trial treatment as per protocol (i.e. 3 years of treatment; for patients who stopped trial treatment earlier because of closure by the sponsor, please follow the instructions below under "Patients without recurrence who were transferred to the follow-up phase before completion of trial treatment")**:**

- Bi-yearly assessments at 42*, 48, 54, and 60 months after surgery [± 1 month]
  *) Note: If a patient is still under trial treatment at month 36, the last patient diary verification will have to be done during the first follow-up visit at month 42 (see section 12.2.2).
  - Clinical examination
  - CEA level
    In case of significant increase compared to baseline (post-surgery): recurrence must be confirmed by colonoscopy or CT scan or other imaging technique
  - Patient's intake of acetylsalicylic acid or other NSAIDs or COX-2 inhibitors

- Yearly assessments at 48 and 60 months after surgery [± 1 month]
  - CT scan chest/abdomen (oral and i.v. contrast strongly recommended)

- At 48 months only [± 1 month]
  - Colonoscopy

- From year 6 to 10 after surgery (yearly assessments at months 72, 84, 96, 108 and 120 after surgery [± 2 months])
  - Disease and survival status
  - Patient's intake of acetylsalicylic acid or other NSAIDs or COX-2 inhibitors

  This is performed with a phone call to the primary care physician.

Patients without recurrence who were transferred to the follow-up phase before completion of trial treatment (i.e. before 3 years of aspirin or placebo administration):

- Until and including year 3 (i.e. until 36 months after surgery)
  - Patients will be evaluated according to the schedule of assessments as described in section 12.2, with the exception of AEs and signs or symptoms of bleeding disorders (which do not need to be assessed)

- Bi-yearly assessments at 42, 48, 54, and 60 months after surgery [± 1 month]
  - Assessments as defined above

- From year 6 to 10 after surgery (yearly assessments at months 72, 84, 96, 108 and 120 after surgery [± 2 months])
  - Disease and survival status
  - Patient's intake of acetylsalicylic acid or other NSAIDs or COX-2 inhibitors

  This is performed with a phone call to the primary care physician.

12.3.2 Patients after recurrence

- Every year for at least 3 years from the date of surgery
  - Survival status

This is performed with a phone call to the primary care physician.

13 CRITERIA OF EVALUATION AND DEFINITION OF ENDPOINTS

13.1 Criteria of evaluation

The populations used for analysis will include the following:

- Full analysis population: the full analysis population is defined as all randomized patients who received at least one dose of aspirin/placebo excluding patients with major eligibility violations. Following the intention-to-treat principle, patients in this population will be analyzed according to the treatment they were randomized to.
- Per protocol (PP) population: the PP population is based on the full analysis population excluding patients with major protocol violations. All decisions to exclude patients from the PP population must be made by the coordinating investigator together with the trial team prior to the analysis, blinded to the treatment arm and without looking at any efficacy data. Patients in this population will be analyzed according to the actual treatment they received.
- Safety population: the safety population is defined as all patients who received any dose of aspirin/placebo. Patients will be analyzed according to the actual treatment they received.

13.2 Definition of Endpoints

13.2.1 Primary endpoint

The primary endpoint of this trial is DFS, defined as time from surgery until one of the following events, whichever comes first:

- recurrence
- second cancer
- death due to any reason

Patients not experiencing an event will be censored at the date of the last available tumor assessment.

13.2.2 Secondary endpoints

Time to recurrence

TTR will be calculated from surgery until recurrence or death due to colon cancer. Patients not experiencing an event or patients who died due to other reasons before experiencing an event will be censored at the date of the last available tumor assessment.

Overall survival

OS will be calculated from surgery until death from any cause. Patients not experiencing an event will be censored at the last date they were known to be alive.

Cancer-specific survival

CSS will be calculated from surgery until death due to colon cancer, whether due to the original tumor or to a second primary same cancer. Patients who died due to other reasons will be censored at the time of death. All other patients will be censored at the last date they were known to be alive.

Adverse events

AEs will be assessed according to NCI CTCAE v4.0.

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.

The CRFs have to be completed online (www.sakk.ch/edc) in a timely manner. The data should be entered into the electronic eCRFs within a month from the visit or medical examination. All eCRFs needed for the corresponding visit will be displayed automatically in the web-based electronic data capture (EDC) system for the SAKK 41/13-Aspirin trial.

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 certified copy of the signed form has to be sent to the responsible CPM by mail or fax within one month after the patient's inclusion.** The original signed form is kept at the site in the investigator's file.
- If it is not possible to enter the eligibility form online for technical reasons, complete the paper version of the eligibility CRF and fax it in due time to the SAKK CC, which will perform the registration/randomization of the patient (see also section 7.2).

SAE and pregnancy report forms:

- Trial-specific SAE report forms and trial-specific pregnancy report forms have to be submitted **by email** to the SAKK safety office within 24 hours of becoming aware of the SAE or pregnancy (see also section 11 for SAE reporting and pregnancy reporting). Originals of SAE and pregnancy 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
- drug inventory logs
- patient diary
- PIK3CA screening results cover letter

The source of original records and all data considered to be source data are defined in the SDL form (source data location form).

15 STATISTICAL CONSIDERATIONS

15.1 Sample size estimation

- Software package: East 6.2
- Number of treatment arms: 2
- Type of design: parallel design
- Trial intention: superiority
- Statistical test: One-sided log-rank test
- Null hypothesis: hazard ratio (HR) 1.0
- Alternative hypothesis: HR 0.456 (corresponding to a 3-year DFS of 70% in the placebo arm and 85% in the aspirin arm assuming constant hazards). This hazard ratio is based on the two published retrospective studies: The hazard ratio for cancer-specific survival in the study by Liao et al. [13] was 0.18, the hazard ratio in the study by Domingo et al. [14] for recurrence was 0.11. Therefore, the assumed hazard ratio of 0.456 in this trial represents a conservative estimate. The assumption of a 3-year DFS of 70% in the placebo arm was based on several studies [4, 13, 14, 26] as well as analyses of the SEER data base (http://seer.cancer.gov/data/) and analyses performed on data of the Cantonal Hospital St. Gallen.
- Type I error: 5%
- Power: 80%
- Randomization ratio: 2:1
- Number of interim analyses for the primary endpoint: Two
- Timing of interim analyses: after 25% (11) and 50% (22) of the events, the first is expected after approximately 2.4 years of accrual and the second after approximately 0.5 years of follow-up.
- Stopping boundary for benefit/futility: Lan-DeMets error spending function in spirit of the O'Brien & Fleming boundary [27, 28].
- Expected accrual rate: 60 patients per year
- Expected accrual time: 3 years
- Expected follow-up time until primary analysis: 3 years
- Expected proportion of lost to follow-up: 20%. This is based on various studies assessing aspirin intake [29-31].
- Required number of events: 43
- Sample size: 185 (123 in the aspirin group, 62 in placebo group)
- Number needed to screen: 1850 assuming 17% PIK3CA mutations in colorectal cancer patients; estimate of 17% is based on New England Journal of Medicine publication [13]. PIK3CA mutations in colorectal cancer patients are described between 15% and 20% in the literature. The rate of PIK3CA mutation is relevantly lower in rectal cancer (approximately 8%, [22]) compared to colon cancer. Therefore, by excluding rectal cancer patients, the estimate of a PIK3CA mutation rate of 17% is conservative. However, as not all the mutated patients will be included in the trial due to patient's wish, ineligibility discovered after PIK3CA screening, etc., it is assumed that 10% of all screened patients will be finally randomized in the trial.

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.

15.2 Interim efficacy analyses

Two interim efficacy analyses are planned, the first after 25% (11) of the events expected after approximately 2.4 years of accrual and the second after and 50% (22) of the events, expected after approximately 0.5 years of follow-up. The accrual will not be suspended while waiting for the interim results. In case of a higher accrual rate than expected, the time point and number of events for the interim analysis may be adapted accordingly. The critical values for early stopping will be obtained using the Lan-DeMets error spending function in spirit of the O'Brien & Fleming boundary.

The two interim analyses were planned to allow the trial to stop early if the beneficial effect of aspirin is higher than the HR of 0.45 that was assumed for the sample size calculations and is a conservative estimate compared to the results from the two published retrospective studies (HR 0.11 in Domingo et al [14] and HR 0.18 in Liao et al [13]).

At the first interim analysis stopping for efficacy would be possible with a HR of 0.11 or lower and at the second interim analysis with a HR of 0.34 or lower. The proportion of patients lost to follow-up without reaching the primary endpoint will be assessed at the first interim analysis and if it is higher than 20% the sample size may be re-estimated in order to reach the required number of events in a reasonable time.

The unblinded results of the interim efficacy analysis will be presented to an independent data monitoring committee (IDMC) appointed by the SAKK board. The SAKK board will decide on the continuation/modification/early stopping of the trial based on the recommendations of the IDMC.

15.3 Statistical analyses

The primary analysis will take place once the 43rd DFS event has taken place or at the latest after 3 years from the date of surgery of the last included patient.

All efficacy endpoints will be analyzed based on the full analysis population. Supportive analyses based on the PP population will be performed. All safety endpoints will be analyzed based on the safety population. Subgroup analyses for all stratification factors except country are planned for the primary endpoint. All time-to-event endpoints shall have the median value of each treatment group estimated using the Kaplan-Meier method, along with a 95% confidence interval. 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 regression models with the treatment arm as independent variable and the stratification factors as strata. Cox regression models will also be used to investigate the potential effects of other factors (e.g. chemotherapy given and concomitant therapy) on selected endpoints. Subgroup analyses may be performed for these factors. For the primary analysis, patients who were unblinded before experiencing an event will be censored at the date of the last available tumor assessment before unblinding. A supportive analysis will be performed in which the unblinding will not be considered.

Categorical variables will be summarized with frequency and percentage and may be compared between arms by chi-square tests or Fisher's exact tests. Continuous variables will be summarized using median and range and may be compared between arms by t-tests or Wilcoxon rank sum tests.

Laboratory values will be expressed as the absolute values and as grading according to NCI CTCAE v4.0 by treatment arm. AE grading shall be presented by type, grade, and relation showing frequency and percentage of the within-patient worst grades by treatment arms. In addition, grade ≥ 3 AEs and AEs with relation to treatment ≥ 3 will be summarized separately.

Full analysis details will be outlined in the statistical analysis plan (SAP).

15.4 Handling of missing data and drop-outs

No imputation of missing data will be performed. A row denoted "Missing" will be included in count tabulations if necessary to account for drop-outs and missing values. Patients lost to follow-up before reaching the primary endpoint will not be replaced.

16 QUALITY OF LIFE

Not applicable

17 PATHOLOGY

PIK3CA mutation testing will be performed centrally at the Institute of Pathology, Kantonsspital St. Gallen, Switzerland, in order to guarantee uniformity of the analysis methodology and to allow for a standardized examination of cancer tissues. Results will be available within 7 working days from receipt of the tumor block (see section 17.2 below for details).

17.1 Local pathology

17.1.1 Task of the local investigator

The local investigator at each participating site is responsible to inform the local pathologist about the protocol, the trial-specific investigations and the sample handling for central PIK3CA mutation testing and translational research/sample banking.

It is the task of the local investigator to determine the disease stage according to the TNM classification (7th edition, October 2009, see Appendix 1) and to order tumor blocks at the local pathology. **The investigator must ensure that informed consent for PIK3CA mutation analysis was obtained from the patient before ordering the pathology sample.**

17.1.2 Task of the local pathologist

The diagnosis of adenocarcinoma of the colon is performed locally. TNM classification has to be done according to the 7th edition, October 2009 (see Appendix 1).

Paraffin blocks with colon cancer tissues will be ordered by the local investigator from the local pathologist. The local pathologist should send the blocks to Central Pathology with enough time to allow registration within 14 weeks following surgery.

Patho/PIK3CA screening number:

The local pathologist (or investigator) must ensure to assign a pre-defined Patho/PIK3CA screening number to every patient undergoing central PIK3CA mutation analysis, based on the screening and enrollment list provided by SAKK CC (available for download from portal.sakk.ch → Trials → SAKK 41/13-Aspirin).

The Patho/PIK3CA screening number includes a site code which is specific for each participating site. The site code will be communicated to the site by SAKK CC prior to activation and can also be found on the SAKK webpage.

17.1.3 Required material for PIK3CA testing and translational research

The following material is required:

Tumor tissue:

- Paraffin block of the resection specimen with tumor tissue

Documents:

- A copy of the local pathology report (*patient information such as name and date of birth must be erased*), coded with the pre-defined Patho/PIK3CA screening number
- The completed “PIK3CA testing cover letter” provided on the SAKK portal (portal.sakk.ch → Trials → SAKK 41/13-Aspirin → useful tools)

Reconciliation listings:

The local pathologist (or investigator) will be requested to provide SAKK CC with the completed patient screening and enrollment list at regular intervals - in general, twice yearly - for the reconciliation of sample shipment to Central Pathology. Timing of reconciliation will be determined by the SAKK CC and communicated to the sites during trial conduct.

17.1.4 Labeling and handling

All material has to be clearly labeled with:

- SAKK 41/13
- Patho/PIK3CA screening number (since a UPN is not yet available)
- Sample ID of local pathology institute
- Site
- Sampling date

17.1.5 Shipment

Samples have to be sent to: Prof. Dr. Wolfram Jochum
Trial SAKK 41/13
Institute of Pathology
Kantonsspital St.Gallen
Rorschacher Strasse 95
CH – 9007 St. Gallen
Switzerland

The samples, including the associated documents, are to be sent by priority postal mail (e.g. *A-Post/Courrier A/Posta A* in Switzerland or equivalent postal delivery in EU).

17.2 Central PIK3CA mutation analysis

PIK3CA mutation screening is conducted centrally at the Institute of Pathology, Kantonsspital St. Gallen, using a validated assay. Testing includes PIK3CA exons 9/20 containing the somatic PIK3CA hotspot mutations of colon cancer (amino acid positions E542, E545, Q546, D549 and H1047) and any infrequent somatic mutation within both exons. The central pathologist will inform the referring site of the patient's PIK3CA mutation status within 7 working days from receipt of the tumor block, by faxing or emailing the completed "PIK3CA screening results cover letter" to the site and to the SAKK CC.

The central pathologist will be requested to send at regular intervals (in general twice yearly) a list of all analyzed samples to SAKK CC for information and reconciliation. Timing for the reconciliation will be determined by the SAKK CC and communicated to Central Pathology during trial conduct.

17.3 Pathology samples banking

In case the patient consented to the storage of the tumor material in the trial-associated Biobank, the paraffin blocks will be kept at the Institute of Pathology, Kantonsspital St.Gallen, for a maximum of 20 years, according to the trial-specific Biobank Regulation (see section 18.3 for further considerations and procedures with respect to sample banking).

Any diagnostic sample not used for translational research or banking will be destroyed by Central Pathology (unless the local pathologist requests the sample back).

18 TRANSLATIONAL RESEARCH

In Q4 2020, the sponsor decided to prematurely stop the accrual of the trial and the trial treatment due to financial reasons. As a consequence, it was decided not to continue with the translational research subproject with blood samples. All collected blood samples are to be destroyed. However, the biobank and translational research subproject of the tumor tissue samples will be continued.

The consent of the study patients for translational research with their clinical data and biological material, including the subprojects described in this section, will be obtained prior to patient's inclusion into the trial with the use of a separate information and consent form.

Participation in the translational aspects of the protocol is not mandatory. Patient refusal to participate in these ancillary substudies will not exclude them from participation in trial SAKK 41/13-Aspirin.

Any research question not included in the protocol has to be formulated in an amendment. This amendment has to consider the funding of the research and must be submitted to the SAKK Board and to the relevant Ethics Committees and regulatory authorities for authorization.

Participation in translational research is open to all patients in Switzerland and EU.

18.1 Rationale and aims

18.1.1 Tumoral expression of COX-2

Many observational and even randomized studies have provided evidence of a protective effect of aspirin on colorectal cancer [11, 12]. It is hypothesized that the inhibition of COX-2 – particularly prostaglandin E2 (PGE2) – by aspirin results in down-regulation of phosphoinositide-3-kinase (PI3K) activity in PIK3CA mutant cancers through activation of Tcf/Lef signaling [16, 32]. COX-2, the inducible isoform of cyclooxygenase, is overexpressed in human colorectal adenomas and adenocarcinomas [33]. COX-2 is the rate-limiting enzyme in the conversion of arachidonic acid into prostaglandin H2 (PGH2), which is then converted into prostaglandin E2 (PGE2) by prostaglandin E synthases. Microsomal prostaglandin E synthase 1 (mPGES-1) is the major isoform involved in promoting PGE2 production in inflammatory sites [34]. The COX-2/mPGES-1/PGE2 pathway is critical in potentiating colon carcinogenesis, and selective COX-2 inhibitors have been approved as adjunctive therapy for patients with familial polyposis [35]. COX-2 expression has also been studied in human colon cancer tissues, and it has been found that COX-2 expression is significantly more prevalent in left-sided colon cancers as compared to right-sided colon cancers (67% versus 33%, p=0.05) [36]. Most importantly, COX-2 overexpression was found to be an independent predictor of poor prognosis in 662 colon cancer patients stage I-IV from two independent prospective cohorts (the Nurses' Health Study and the Health Professionals Follow-up Study [37]). In this study, COX-2 overexpression as measured by immunohistochemistry was found in 83% of all tumors.

18.1.2 PI3K downstream signaling

In addition to inhibiting PGE2, aspirin has been shown to inhibit the serine/threonine kinase mechanistic target of rapamycin (mTOR), a downstream effector of the PI3K pathway by activation of adenosine monophosphate–activated protein kinase (AMPK) in colorectal cancer cells [38]. Signaling via mTOR controls cell survival and regulation of metabolism [39]. mTOR forms the catalytic core of 2 distinct complexes, mTORC1 and mTORC2, both containing mLST8 and DEPTOR proteins. In addition, mTORC1 consists of raptor and PRAS40, whereas mTORC2 includes rictor, mSIN1, and protor. mTORC1 integrates growth factor and nutrient signals to influence protein synthesis, growth, autophagy, and ribosomal biogenesis. The role of mTORC2 is less well defined, involving cell survival and cytoskeleton regulation. Furthermore, mTORC1 regulates mTORC2 through rictor phosphorylation by S6 kinase 1 (S6K1), adding further complexity to mTOR regulation [40]. Substantial evidence implicates dysregulated PI3K/mTOR signaling in cancer development, particularly colorectal cancer [41]. Mutations in PI3K signaling genes occur in up to 40% of colorectal carcinomas. Raptor, rictor, and mTOR itself are overexpressed in colorectal carcinomas [42]. The role of mTOR in cancer biology is strengthened by evidence that negative regulators of mTOR are tumor suppressors. Phosphatase and tensin homolog (PTEN), which down-regulates mTOR, is

inactivated in 30%–40% of colorectal carcinomas [43]. Unconstrained mTOR signaling, via effectors S6K1 and 4E-BP1, promotes tumor growth by enhancing translation and protein synthesis. Activation of the AMPK, a critical cellular energy sensor, leads to mTOR suppression. AMPK is activated by liver kinase B1 (LKB1), a tumor-suppressor gene inactivated by germline mutations in Peutz–Jeghers syndrome, a colorectal cancer susceptibility disorder [44].

18.1.3 Tumoral expression of HLA class I antigen

The metastatic potential of cancer cells that are shed into the bloodstream can be modified by environmental conditions, including platelets and bone marrow–derived cells in the vasculature [45]. Platelets are thought to protect disseminating tumor cells from natural killer cells, which preferentially recognize and eliminate cells with low or absent expression of HLA class I antigen. Therefore, the survival benefit associated with the use of low-dose aspirin after the diagnosis of colon cancer may be associated with tumors that exhibit altered expression of the HLA class I antigen. Reimers and colleagues studied tumor blocks from 999 patients with colon cancer surgically resected between 2002 and 2008 and receiving low-dose aspirin, and found that the overall survival benefit associated with aspirin was limited to tumors expressing HLA class I antigen (adjusted hazard ratio 0.65; 95% CI, 0.50-0.84; P = .001) [46]. Accordingly, any study exploring the effect of PIK3CA mutations on the survival benefit associated with the use of adjuvant aspirin in colon cancer patients should correct for tumor HLA class I expression.

18.1.4 Tumoral BRAF V600E mutations and microsatellite instability

In patients with stage III colon cancer, KRAS mutations are found in approximately 35% of patients, BRAF V600E mutations in 14% of patients, and mutations of KRAS and BRAF are nearly mutually exclusive [47]. KRAS mutations are more likely to be present in patients without a family history of colon cancer and never smokers. Tumors with KRAS mutations are less likely to have defective mismatch repair (dMMR) genes (odds ratio [OR] = 0.21; 95% confidence interval [CI] = 0.15 to 0.31; P < .001) and high-grade histology (OR = 0.73; 95% CI = 0.59 to 0.92; P < .001), but are more often right-sided [47]. Tumors with BRAF V600E mutations are more frequently found in patients who are aged 70 years or older (OR = 3.33; 95% CI = 2.50 to 4.42; P < .001) and current or former smokers (OR = 1.64; 95% CI = 1.26 to 2.14; P < .001), but less likely in non-whites and men. In the patient cohort form the PETACC-3 study, an adjuvant trial with 3,278 patients with stage II to III colon cancer, BRAF mutation was significantly associated with female sex (P = .017), and highly significantly associated with right-sided tumors, older age, high grade, and microsatellite instability (MSI)-high tumors (all $P < 10^{-4}$) [48]. Ogino and colleagues studied BRAF V600E mutations in 506 stage III colon cancer patients enrolled in the CALGB 89803 adjuvant study [49]. BRAF V600E mutational status was associated with inferior survival in stage III colon cancer. Compared with 431 BRAF wild-type patients, 75 BRAF-mutated patients experienced significantly worse overall survival (log-rank P = 0.015; multivariate HR = 1.66; 95% CI: 1.05-2.63). By assessing the combined status of BRAF mutational status and microsatellite instability, BRAF-mutated microsatellite stable (MSS) tumors had an unfavorable prognosis, whereas BRAF wild-type MSI-high tumor had a favorable prognosis, and BRAF-mutated MSI-high tumor and BRAF wild-type MSS tumor had an intermediate prognosis [49]. BRAF mutational status as well as MSI are hence important prognostic factors in stage II/III colon cancer and should be assessed in studies such as SAKK 41/13.

18.1.5 Germline genetics

Genetics in (fluoro)pyrimidine and folate metabolism have intensively been studied as potential predictors of the activity of 5FU-based chemotherapy in gastrointestinal malignancies. Key enzymes of the (fluoro)pyrimidine and folate metabolism are thymidylate synthase (TYMS) and methylene-tetrahydrofolate-reductase (MTHFR), respectively. Germline polymorphisms of both TYMS and MTHFR are potential predictive but also prognostic markers in patients with stage II-III colon cancer. Three polymorphisms in the TS untranslated regions (UTRs) have been identified. TS promoter–enhancer region (TSER) polymorphism (TS 2R/3R repeat) is a tandem repeat one, upstream of the TS translational start site, containing either double (2R) or triple (3R) repeats of 28-bp sequences. These tandem repeats have been found to be associated with the autoregulation of TS transcription and translation [50, 51]. More recently, additional functional variants within the 50-UTR region of the TS gene have been identified, and the TS 2R/3R repeat is now studied together with a G to C single nucleotide polymorphism within the second repeat of the 3R allele (TSER 3R G/C) [50]. In fact, the

TSER 3RC/3RC genotype caused a lower transcriptional activity of TS, comparable with the TS 2R/2R genotype. Another functional TS polymorphism is a 6-bp deletion/insertion within the 30-UTR region of the TS gene [52]. TS 1494del6 bp has been shown to decrease RNA stability, and thereby to influence TS mRNA and TS protein expression in vitro. Lurje and colleagues found the high-expression TYMS genotypes to be associated with an increased risk of tumor recurrence in 197 patients with stage II-III colon cancer [53]. Mutations in MTHFR were found to be prognostic in stage II-III colon cancer patients receiving adjuvant chemotherapy [54]. Various germline genetic polymorphisms have been found to potentially influence the response to aspirin treatment in cancer patients, including but not limited to polymorphisms within the interleukin (IL)-10 gene [55], variants within the COX genes, GPIIb/IIIA platelet receptors, collagen or ADP receptors [56] and polymorphic variants within the Catechol-O-Methyltransferase (COMPT) gene [57]. Germline genetics may play an important role as independent predictive and/or prognostic factors in patients with colon cancer receiving adjuvant chemotherapy and/or aspirin.

18.1.6 Objectives

The objective of the ancillary substudies of SAKK 41/13 is to explore individual patient's tumor tissue for important predictive (COX-2 overexpression by immunohistochemistry (IHC), HLA class I antigen expression, germline genetics) and prognostic (BRAF V600E mutations, tumoral MSI status) factors. This will allow to gain a comprehensive understanding of the therapeutic impact of low-dose aspirin in this group of patients.

Biobanks for tumor tissue will be implemented to permit future research on colon cancer.

18.2 Samples and schedule of sampling

- Archival **diagnostic tumor samples** of consented patients, which were sent to Central Pathology for PIK3CA mutation analysis, will be used for research projects (refer to section 17.1 for the logistics of tumor sample handling and shipment).
- In addition, **peripheral blood** (5 ml EDTA blood) was collected by venipuncture within 4 weeks prior to patient's inclusion into the trial.

No tube or shipping material will be provided by the SAKK CC. All sites have to use their own disposables.

18.2.1 Handling and labeling

Blood samples had to be clearly labeled with:

- SAKK 41/13
- Patient UPN
- Site
- Sampling date

and had to be stored at -20°C (alternatively, -80°C) at the site until shipment without prior centrifugation.

18.2.2 Shipment

Blood samples were supposed to be shipped IN BATCHES to:

PD. Dr. Dr. Markus Jörger
Trial SAKK 41/13
Medical Oncology, KSSG
Rorschacherstr. 95
CH – 9007 St. Gallen
Switzerland

In general, shipment will be made at the end of the accrual phase (unless otherwise specified in trial-specific agreements). Nevertheless, due to the premature stop of the trial, it was decided not to continue with the translational research subproject with blood samples. All collected blood samples are to be destroyed.

18.3 Sample biobanking

In case the patient agreed to the banking of tumor tissue, any residual histological sample or tumor tissue in excess will be stored for a maximum of 20 years at the Pathology Institute located at the Cantonal Hospital, St. Gallen, for future investigations in connection with colon cancer.

The banking of material must conform to the HRA and its corresponding ordinance HFV/ORH, and to the recommendations from the Swiss Ethics Committees on research involving humans. It is regulated by corresponding trial-specific Biobank Regulations. The patient will have no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the samples.

The patient retains the right to have their stored material irreversibly anonymized at any time by contacting the principal investigator according to the HRA and its applicable ordinances. The SAKK will be responsible for the anonymization of the sample(s) at the request of the patient. However, data which is already obtained from this material can be used for the intended analysis.

The SAKK will be responsible for the destruction of the sample(s) at the end of the storage period. The investigator will provide the sponsor with the required trial code and patient identification (UPN) so that any remaining sample can be located and destroyed.

Any new research on these samples that is not planned in this protocol must first be approved by the SAKK board and by the relevant Ethics committee.

Any diagnostic sample will be returned to the site in case of need for diagnostic purposes.

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 KlinV/Oclin and HFV/ORH and the requirements from the Swiss and European regulatory bodies [58-63].

The protocol, the patient information and consent form, as well as all other trial-related documents shall be submitted to all involved ECs and to the competent authorities 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 authorities with regard to the conduct of the trial will be made in written to the sponsor prior to trial initiation. Patient recruitment at a participating site can only take place after the site has been approved by the responsible regulatory bodies and has been officially opened for accrual by the SAKK CC.

Any substantial amendment to the protocol (except for safety reasons) can only be implemented at a site after obtaining written authorization by the corresponding regulatory bodies.

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

22.1 Risks/benefits

This trial investigates the use of adjuvant aspirin in patients with colon cancer following primary site surgery in a potentially curative setting. This treatment proposal is based on retrospective analyses which suggested a clinically relevant effect of using low-dose aspirin in patients carrying activating mutations of the PIK3CA gene in exons 9 and 20. On the one hand, aspirin is a very well-known drug, with minimal risk of adverse events at a daily dose of 100 mg. On the other site, the potential clinical benefit is very substantial, with a reduction of the risk of dying from colon cancer of roughly 70-80%. Therefore, the risk-benefit ratio is suggested to be very favorable in this group of patients.

22.2 Trial categorization

Clinical trial with IMP (including placebo as comparator).

Aspirin is a medication with marketing authorization in Switzerland and EU as an analgesic, anti-inflammatory and antipyretic drug and, at low dose, for the prevention of cardiovascular and cerebrovascular diseases. In this trial, low dose aspirin (i.e. 100 mg) will be used daily during a maximum of 3 years for the adjuvant treatment of colon cancer. According to the Swiss HRA and its corresponding ordinance KlinV/Oclin on clinical trials, this trial is classified as category B.

22.3 Patient information and informed consent

The informed consent procedure must conform to the Swiss law and 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 will be obtained twice:

For the pre-registration investigation of PIK3CA mutation status

- at screening and before any protocol-specific procedures for PIK3CA mutation analysis of the patient tumor material,

Only for patients with mutated PIK3CA

- before registration and prior to any protocol-specific procedures (except for the separately consented PIK3CA mutation analysis).

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. No inclusion of legally incompetent patients is permitted in this trial.

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 trial treatment for any reason and at any time. In that case, they will be transferred to the follow-up phase. Patients who decide to withdraw from the trial (i.e. refuse further data collection) 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.

Patients who withdraw from the trial have the right to know which treatment they received. However, every effort should be made to keep the patients who refuse further trial treatment without evidence of compelling medical or safety reason and accept further follow-up assessments and data collection (according to the protocol) blinded to the received treatment.

Patients may be withdrawn at any time from trial treatment at the discretion of the treating investigator due to an SAE or based on any other relevant medical condition. The investigator may unblind the patient in the case where there are compelling medical or safety reasons to do so. The patient will be transferred to the follow-up phase.

22.5 Patient information at trial unblinding

Upon trial unblinding each trial participant will be informed about the administered treatment.

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, Switzerland.

23.2 Monitoring and auditing

All source data must be accessible for auditing and monitoring. CRAs 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. Based on the risk analysis, low monitoring strategy has been chosen. The different monitoring activities as well as the frequency of the visits 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
- Validation of database and statistical analysis
- Quality control principles are implemented (randomization and blinding procedures require double signatures and are documented)
- On-site and central monitoring evaluates protocol compliance (SDV, verification of informed consent etc.) by personnel designated by the SAKK
- Data captured online is validated in real-time, yielding errors (for inacceptable data) and warnings (for possibly inconsistent data - these warnings may be overruled by the user)
- Audit trail of changes
- Medical data review is performed by the coordinating investigator or a delegated person (all CRFs will be reviewed and checked on medical content)
- Central management of deviations and implementation of corrective and preventive measures
- Independent data monitoring committee
- Central PIK3CA mutation screening
- Safety monitoring
- Accountability of IMP (aspirin or placebo) and patient diary
- 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 site documents, the SAKK CC - or the Cooperative Group or appointed CRO in EU (in agreement with the specificities defined in the contract with foreign sites and the Cooperative Group/appointed CRO) - will proceed with the submission to the relevant ECs and competent authorities.

Any site which is interested to participate in the trial but has not committed yet, is requested to contact the SAKK CC. The SAKK CC will evaluate the feasibility of the site participation and initiate the trial activation steps for the site if applicable.

The investigator is only allowed to screen and register patients into the trial after the involved ECs, Swissmedic or the responsible competent authorities in EU countries authorized the trial at the site and the SAKK CC 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 portal (portal.sakk.ch → Trials → SAKK 41/13-Aspirin → useful tools).

23.5.2 Useful tools

CRFs, drug order forms and accountability logs, documents required for EC approval, a schedule of assessments etc. can be downloaded from the SAKK portal (portal.sakk.ch → Trials → SAKK 41/13-Aspirin).

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, drug inventory and destruction logs, and all other information collected during the trial. These documents will be stored for at least 10 years in Switzerland (at least 15 years in EU countries) after the termination of the trial. The start and 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 for at least 10 years (respectively, 15 years in EU) after the termination of the trial. The data of patients who consented to the banking of their clinical data and their biological material may be used for additional investigations in the field of cancer. The banking of data must conform to the HRA and its corresponding ordinances, and to the recommendations from the Swiss Ethics Committees on research involving humans. The SAKK will be the exclusive owner of any data, discoveries, or derivative materials from the banked data. The patient will have no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the banked data.

The patient retains the right to have their recorded clinical data irreversibly anonymized at any time by contacting the principal investigator according to the HRA and its applicable ordinances. The SAKK will be responsible for the anonymization of the data at the request of the patient. However, data which is already obtained from this material can be used for the intended analysis

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 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 portal.sakk.ch (→ Trials → SAKK 41/13-Aspirin).

Separate trial-specific agreements will be issued for participating sites outside of Switzerland.

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 (if applicable) prior to implementation.

23.8.2 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 (if applicable).

23.8.3 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 DSUR. Non-substantial amendments which affect the evaluation of the competent authority have to be submitted to the CA as soon as possible.

23.9 Trial termination

The SAKK CC is responsible for submitting the information about trial termination to the national authorities according to local legislation (e.g. Switzerland, according to HRA).

24 PUBLICATION

The results of the trial will be published according to the current version of the SAKK publication guidelines (available on the SAKK portal). 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 registered 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 portal). 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 the locally applicable legislation. Patients must be informed of, and agree to, data and material transfer and handling, in accordance with the Swiss data protection law.

All information concerning the IMP supplied by Bayer in connection with this trial and not previously published is considered confidential and proprietary information.

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27 APPENDICES

Appendix 1 TNM Classification

According to UICC 2009 [64].

T - Primary tumor

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intraepithelial or invasion of lamina propria
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through the muscularis propria into the pericolorectal tissues
T4a Tumor penetrates to the surface of the visceral peritoneum
T4b Tumor directly invades or is adherent to other organs or structures

N - Regional lymph nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1-3 regional lymph nodes
N1a Metastasis in 1 regional lymph node
N1b Metastasis in 2-3 regional lymph nodes
N1c Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2 Metastasis in 4 or more lymph nodes
N2a Metastasis in 4-6 regional lymph nodes
N2b Metastasis in 7 or more regional lymph nodes

M - Distant metastasis

M0 No distant metastasis
M1 Distant metastasis
M1a Metastasis confined to 1 organ or site (e.g., liver, lung, ovary, non-regional node)
M1b Metastases in more than 1 organ/site or the peritoneum

Stage	T	N	M
0	Tis	N0	M0
I	T1, T2	N0	M0
II	T3, T4	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
III	Any T	N1, N2	M0
IIIA	T1, T2	N1	M0
	T1	N2a	M0
IIIB	T3-T4a	N1	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3, T4a	N2b	M0
	T4b	N1, N2	M0
IVA	Any T	Any N	M1a

IVB	Any T	Any N	M1b

Histopathological Grading

GX: The tumor grade cannot be identified.

G1: The cells look more like normal tissue cells (well differentiated).

G2: The cells are somewhat different (moderately differentiated).

G3: The cells look very unlike normal cells (poorly differentiated).

G4: The cells barely resemble normal cells (undifferentiated).

Appendix 2 Calculation of creatinine clearance

Creatinine clearance should be calculated according to the formula of Cockcroft-Gault [65].

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 [66].

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 New York Heart Association (NYHA) classification

according to the Criteria Committee of the New York Heart Association [67].

Class I 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.

Class II Patients have slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea or anginal pain.

Class III 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.

Class IV Patients are unable to carry out any physical activity without symptoms referred to above. Some Class IV patients may have symptoms at rest.