Die SAKK am ASCO-Jahrestreffen 2018

Die Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK) präsentierte am diesjährigen Jahrestreffen der ASCO – teilweise in Zusammenarbeit mit ausländischen onkologischen Studiengruppen – mehrere Abstracts klinischer (offener und abgeschlossener) Studien in Poster Sessions und in Oral Sessions. Wir stellen auf diesen Seiten die Abstracts in der englischen Originalversion mit den jeweiligen Ansprechpartnern zusammen.

Metastatic castration resistant prostate cancer (mCRPC)

A phase 2 trial of darolutamide maintenance therapy in patients with metastatic castration resistant prostate cancer (mCRPC) previously treated with AR targeting agents and non-progressive on a subsequent taxane (SAKK 08/16).

First author: PD Dr. med. Richard Cathomas, Kantonsspital Graubünden
Abstract # TPS5086 Poster Session

Background: Treatment with the AR targeting agents abiraterone or enzalutamide followed by a taxane is currently the most used treatment for men with mCRPC. Further treatment after response to chemotherapy is only indicated in case of disease progression, with limited treatment options available. Darolutamide is a second-generation oral androgen receptor antagonist which has demonstrated a good safety profile and antitumor activity in mCRPC. This trial evaluates whether the immediate use of darolutamide after successful chemotherapy can prolong radiographic progression-free survival (rPFS) compared to watchful waiting in patients with mCRPC.

Methods: This is a multicenter, randomized, double-blind, placebo-controlled phase 2 trial (NCT02933801) conducted in approximately 19 sites in Switzerland and Italy. Patients with mCRPC are required to have been previously treated with abiraterone and/or enzalutamide and have no evidence of disease progression on subsequent docetaxel or cabazitaxel. Patients (n = 88) will be randomized 1:1 to receive 600 mg darolutamide BID or placebo BID until disease progression. Patients will be stratified by country, WHO performance status (0, 1 vs 2), presence/absence of visceral metastases, enzalutamide vs abiraterone vs both prior to chemotherapy, and planned start of trial treatment after last taxane dose (< 35 days vs ≥35 days).
The primary endpoint is rPFS at 12 weeks after treatment initiation. The secondary endpoints are rPFS, time to PSA progression, time to symptomatic/clinical progression, event-free survival, overall survival, PSA response (30%, 50%, 90%, and best), duration of PSA response (50%), adverse events, and fatigue. The rPFS rate at 12 weeks after treatment initiation will be compared between the two treatment arms using a one-sided test statistic using the Kaplan–Meier method. Recruitment is ongoing, with the first patient randomized on 20.04.2017.

Clinical trial information: NCT02933801

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Non-small cell lung cancer (NSCLC) – Stage III

Multimodal treatment in operable stage III non-small cell lung cancer using the new TNM staging classification version 8: Long term results of a pooled analysis of three SAKK trials.

First author: PD Dr. med. Martin Früh, Kantonsspital St. Gallen
Abstract # 8531 Poster Session

Methods: Individual patient data of 368 patients from three very similarly designed trials (SAKK 16/96, SAKK 16/00 and SAKK 16/01) were pooled. Patients with operable stage III NSCLC received preoperative radiotherapy following three cycles of induction cisplatin/docetaxel (tri-modal) or neoadjuvant cisplatin/docetaxel alone (bi-modal). Factors associated with improved 5-year overall survival (OS) were evaluated using a logistic regression model.

Results: When applying the 8th TNM staging version, 162 patients moved from stage IIIA to IIIB and 5-and 10-year OS rates were 41% and 29% for stage IIIA and 35% and 27% for stage IIIB. When using the 6th version 5- and 10-year OS rates were 38% and 28% for stage IIIA and 36% and 24% for stage IIIB. Factors associated with improved 5-year-OS were age, R0 resection and pCR ($p = 0.043$, $p < 0.001$ and $p = 0.009$). There was no difference in the bi- vs. tri-modal group with regards to OS (median: 28 months [95% CI: 21-39 months] vs. 37 months [95% CI: 24-51 months], $p = 0.9$), event-free survival (median: 12 months [95% CI: 9-15 months] vs. 13 months [95% CI: 10-22 months], $p = 0.71$), local recurrence rate (48% vs 44%, $p = 0.61$), and pathologic complete remissions (pCR) rate (15% vs. 16% $p = 0.75$). R0 resection rates were lower in the bi-modal group (69% vs. 87%, $p < 0.001$).

Conclusions: Similarly favourable long term outcomes were observed when the 8th vs. 6th TNM classification was applied. With the exception of the excluded patients with T4
due to multiple lesions in different lobes, multimodality treatment decisions in operable stage III NSCLC can be based on the 8th TNM version in upcoming trials. Tri-modal therapy resulted in higher R0 resection rates but did not improve OS. Younger age, R0 resection and pCR were associated with improved 5-year survival.

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Metastatic castration resistant prostate cancer (mCRPC)

Investigation of metformin (MET) in patients with castration resistant prostate cancer (CRPC) in combination with enzalutamide (ENZ) vs. ENZ alone: A randomized, open label, phase 2 trial. SAKK 08/14 – IMPROVE.

First author: Dr. med. Christian Alexander Rothermundt, Kantonsspital St. Gallen
Abstract # TPS5086 Poster Session

Background: The current first-line treatment for patients with CRPC and disease progression is either treatment with abiraterone acetate/prednisone, ENZ, or treatment with docetaxel in more symptomatic patients. There is preclinical data on synergism of ENZ and the biguanide MET: studies on mice orthotopically implanted with ENZ-resistant cells demonstrated that the combination of ENZ and clomipramine or MET significantly reduced tumor growth compared to control groups. Rothermundt et al. previously reported favorable effects of single agent MET in a phase 2 trial: objective PSA responses, disease stabilization and improvement of metabolic endpoints in patients with CRPC. Therefore addition of MET to ENZ might have positive impact on tumor progression, on body composition and insulin sensitivity.

Methods: This is a prospective 1:1 randomized multicenter phase 2 trial.
Primary endpoint is disease control (DC) at 15 months. Progression is defined as having 2 of the following events: radiographic progression, symptomatic/clinical progression, or PSA progression. Secondary endpoints include overall response according to modified RECIST v1.1 and PCWG2 recommendations, event-free survival, adverse events, quality of life, pain and overall survival. Translation research comprises liquid biopsy, metabolomics, hyperglycemia, and pyruvate dehydrogenase substudies. Assuming a 20% difference in the DC rate at 15 months (50% vs. 70% in the combination arm) with alpha 0.10 and power 80%, 168 patients are required in total. Eligibility criteria are as follows: asymptomatic or minimally symptomatic mCPRC (adenocarcinoma) documented by imaging, ongoing androgen deprivation therapy (ADT) with GnRH agonists or antagonists or bilateral orchiectomy, total testosterone levels ≤ 1.7 nmol/L, tumor progression at the time of registration, no prior treatment for mCRPC other than ADT, no history of diabetes and metformin use, and adequate organ function.
Patients receive either ENZ 160mg qd in combination with MET 850mg bd or ENZ 160mg qd alone. 62 patients have been enrolled since accrual began in March, 2016.

Clinical trial information: NCT02640534

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Metastatic colorectal cancer

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

First author: Prof. Dr. med. Viviane Hess, Universitätsspital Basel
Abstract # TPS3621 Poster Session

Background: Exercise has become a main focus of basic and clinical research worldwide during the current pandemic of physical inactivity. A clear link between inactivity and cancer incidence/relapse has been established, particularly for colon cancer, the third most common cancer. However, whether exercise has an impact on disease course and survival in advanced disease is unknown. Exercise modifies key host factors that are determinants of chemotherapy efficacy such as metabolic and immunologic tumor microenvironment, drug tolerability and treatment adherence. Thus, we aim to assess whether a supervised exercise program concomitant to first-line palliative chemotherapy for patients with metastatic colorectal cancer (mCRC) enhances chemotherapy efficacy and, therefore, increases survival and decreases symptom burden as compared to patients treated with chemotherapy alone.

Methods: Patients with newly diagnosed mCRC are stratified (pre-diagnosis physical fitness, RAS-mutational status, primary tumor location, alkaline phosphatase levels) and randomly assigned to undergo standard systemic treatment and care-as-usual or standard systemic treatment combined with a 12-week structured physical activity (PA) program with twice weekly supervised, heart-rate guided interval training on a bike ergometer. Both groups undergo regular imaging with CT/MRI in order to assess the 1°endpoint of progression-free survival (PFS), i.e. the time between diagnosis and disease progression or death. Radiologists who are blinded to the group assignment will review imaging.
A total of 439 events occurring in 524 patients will be needed to show a clinically meaningful HR of 0.75 for PFS with 80% power and an α of 0.03.
Co-primary endpoint is self-reported symptom burden as measured by the revised Edmonton Symptom Assessment Scale (rESAS). 50 patients from 17 Swiss and Austrian Centers have been randomized. A planned feasibility analysis of the first 40 patients is ongoing.

Clinical trial information: NCT02597075

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Non-small cell lung cancer (NSCLC) – Stage III

Anti-PD-L1 antibody durvalumab (MEDI4736) in addition to neoadjuvant chemotherapy in patients with stage IIIA(N2) non-small cell lung cancer (NSCLC) – A multicenter single-arm phase II trial. (SAKK 16/14)

First author: PD Dr. med. et Dr. phil. Sacha Rothschild, Universitätsspital Basel
Abstract # TPS8584 Poster Session

Background: Improving the outcome of locally advanced non-small cell lung cancer (NSCLC) is one of the major challenges in thoracic oncology. Based on previous trials from the Swiss Group for Clinical Cancer Research (SAKK) neoadjuvant chemotherapy with 3 cycles of cisplatin/docetaxel is an accepted standard of care. Recently, the PACIFIC trial showed significantly improved progression-free survival (PFS) for durvalumab as consolidation therapy after definitive chemoradiotherapy in unresectable stage III NSCLC. Here, we give an update on the ongoing trial and present results from a predefined safety evaluation focusing on 30-day post-operative mortality rate.

Methods: This is a single-arm phase II clinical trial evaluating the addition of perioperative immunotherapy with durvalumab to the previously established standard of care for stage IIIA(N2) patients. Eligible patients must have pathologically proven NSCLC stage IIIA(N2) (T1-3 N2 M0) according to the 7th edition of the TNM classification, irrespective of histological subtype, genomic aberrations or PD-L1 expression status. Tumor tissue has to be available for the mandatory translational research. Patients whose tumor is deemed resectable at diagnosis receive 3 cycles of chemotherapy with cisplatin 100 mg/m^2 and docetaxel 85 mg/m^2 every three weeks followed by two cycles of durvalumab 750 mg every two weeks. Following surgery, patients will be treated with durvalumab 750 mg every two weeks for 12 months.
The primary endpoint of the trial is event-free survival at 12 months. Secondary endpoints include OS, objective response, nodal down-staging, complete resection, pattern of recurrence and toxicity. Additionally, a large translation research program accompanies the trial investigating potential predictive biomarkers of anti-PD-L1 therapy. Based on the protocol, a first safety evaluation has been done after the first 25 operated patients. This analysis demonstrated a 30-day post-operative mortality of less than 10%. According to the decision rule described in the protocol the trial thus shall continue as per protocol.

Clinical trial information: NCT02572843

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