Development of precision guided treatment in patients with colorectal cancer - Creating the ALASCCA research platform (ARP)

Professor Anna Martling, Department of Molecular Medicine and Surgery
Development of precision guided treatment in patients with colorectal cancer - Creating the ALASCCA research platform (ARP)

Summary

Colorectal cancer (CRC) is the third most common cancer in Sweden. Treatment has improved, however 30-40% still suffer from severe relapses. For patients with relapse, treatments prolong survival but they cure only a small proportion. Thus, there is a need for improved treatments and predictive markers to reduce the risk of relapse. Our research program aims to develop precision guided treatment, increasing the chance of cure and to reduce side effects.

Parallel to the clinical trials below, we will create the ALASCCA Research Platform (ARP), which enriched by the already established Colorectal Cancer Data Base Sweden (CRCBaSe) will enable outstanding cutting edge translational, epidemiological and clinical research in the decades to come.

Background

CRC represents a model system for how mutations in cancer-associated genes accumulate during progression from adenoma to cancer. These mutations have been of great importance for the diagnosis of hereditary forms and to predict of treatment response. There are currently diagnostic markers for hereditary CRC and predictive markers for advanced disease, but a lack of markers to predict benefit from adjuvant therapy.

Low-dose acetylsalicylic acid (ASA) therapy both reduces the risk of developing CRC and reduces the incidence of adenomas. These findings have been confirmed in both animal studies and in human studies. ASA works by inhibiting the enzyme Cyclooxygenase-2 (COX-2) that is overexpressed in CRC. Several observational studies have also suggested that treatment with ASA after a CRC diagnosis improves disease-free and/or overall survival (OS)\(^2\). The PI3K pathway is frequently altered in CRC e.g. through mutations/inactivation of genes including \(\text{PIK3CA}, \text{PIK3R1 IGF2, IGR2 and PTEN}\). Recently, acquired mutations in the \(\text{PIK3CA}\) gene were shown to potential predict benefit from treatment with ASA.\(^3-4\) While patients whose tumors did not carry \(\text{PIK3CA}\) mutation had no benefit from ASA therapy, patients whose tumors carry \(\text{PIK3CA}\) mutations had an HR of 0.11-0.18 for CRC-specific death. These data, based on retrospective analyzes, require confirmation in prospective randomized trials to establish treatment recommendations with ASA in patients with CRC. The ALASCCA trial is a unique large (N=3,500), randomized biomarker driven trial powered for treatment recommendation change if successful.

Cell-free DNA, released from apoptotic cells, is present in plasma in healthy individuals. In patients with cancer, DNA fragments from cancer cells are continuously released into the bloodstream (ctDNA). ctDNA allows access to the cancer genome by simple blood draws and enables de novo detection of somatic alterations in advanced cancer. Recently, proof of concept studies have successfully applied ctDNA to monitor minimal residual disease (MRD), in localized breast, bladder and colorectal cancer.\(^6\) ctDNA measurements therefore has the potential to be an accurate and dynamic biomarker of MRD after surgery, however prospective studies of its clinical utility are currently lacking. In a recently published study, researchers from our group showed that 77% of patients with measurable levels of ctDNA in the blood (positive ctDNA) had recurrence of their disease while none of the patients without occurrence of ctDNA (negative ctDNA).\(^7\) Positive ctDNA preceded radiological findings of recurrence by 3-9 months. Furthermore, studies indicate that it can be possible to convert a patient with positive ctDNA to negative ctDNA with chemotherapy. The presence of ctDNA in a patient after surgery is likely a strong risk factor for recurrence of disease, which could enable early and more intense treatment to prevent relapse (CITCCA)
In addition, ALASCCA and CITCCA will enable us to create the world’s best characterized cohort of CRC patient. We are therefore, in parallel to conducting the trials, creating the ALASCCA research platform (ARP) that will include data from the 4000+ patients included in ALASCCA and CITCCA with complete and validated genomic profile, RNA and protein expression, clinical characteristics, treatment data and follow up. The ARP data will be further enhanced with outcome data from Colorectal Cancer Data Base Sweden (CRCBaSe), a database for clinical epidemiological CRC research that was launched by our group based on linkages between the Swedish Colorectal Cancer Register and nine other nationwide registries. We believe that ARP linked to CRCBaSe will be a major building block to future CRC translational clinical research and precision cancer medicine.

Planned projects during the next five years

Table 1: Overview of planned projects and the construction of two research platforms. Details on next step in each project provided below.

<table>
<thead>
<tr>
<th>Project</th>
<th>N</th>
<th>Patient inclusion</th>
<th>Collection/ follow-up</th>
<th>Analyses</th>
<th>Additional funding (in part or full)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALASCCA</td>
<td>3800</td>
<td>Completed</td>
<td>2016-2024</td>
<td>2022-2026</td>
<td>Swedish Research Council/Swedish Cancer Society/Private Donation</td>
</tr>
<tr>
<td>CITCCA</td>
<td>300</td>
<td>Ongoing</td>
<td>2021-2022</td>
<td>2021-2022</td>
<td>Private Donation/ Swedish Research Council/Swedish Cancer Society</td>
</tr>
<tr>
<td>The ALASCCA research platform (ARP)</td>
<td>4000+</td>
<td></td>
<td>2016-2026</td>
<td>2022-2040</td>
<td>Current funding</td>
</tr>
<tr>
<td>CRCBaSe</td>
<td>77000</td>
<td>1.2 M</td>
<td>1995-2016</td>
<td>1995-2018</td>
<td>Swedish Cancer Society/Stockholm Cancer Society</td>
</tr>
</tbody>
</table>

Adjuvant Low dose Aspirin in Colorectal Cancer (ALASCCA)
ALASCCA is the first randomized multicenter, placebo-controlled, biomarker-based study of adjuvant treatment with ASA in patients with CRC. Primary objective is to determine whether treatment with 160 mg ASA once daily for 3 years can improve disease-free survival in patients with somatic mutations in the PIK3 signaling pathway. Secondary endpoints are time to relapse, overall survival, safety and tolerability. 3,800 patients will be screened for mutations in the PIK3 signaling pathway and 600 patients with mutation will be randomized to daily intake of active drug or placebo for three years. Since March 2016 more than 32 hospitals have been recruiting patients in Sweden, Norway Denmark and Finland and in Q2 2021 patient inclusion was completed. Patients will now be followed for 3 years before primary endpoint is analysed.

Circulating Tumour DNA in Colorectal Cancer (CITCCA)
The purpose for the pilot study is to demonstrate the feasibility to perform prospective ctDNA profiling and to confirm previous studies regarding the presence of postoperative ctDNA in a large cohort of patients with CRC (n=300, stage I-III) using the already created infrastructure for clinical research built up for the ALASCCA study. If the pilot study proves to be successful, we plan in a second step to apply ctDNA profiling in a follow-up trial to ALASCCA to investigate if ctDNA-guided disease monitoring can be used to initiate, escalate or de-escalate adjuvant therapy. Our possibilities to carry out this study are unique through the existing national infrastructure with 32 centers, research nurses, research platforms and bioinformatics built up within the framework of the current ALASCCA study.
The ALASCCA research platform (ARP)
Based on the material collected in ALASCCA and CITCCA we will create the ARP, the world’s best characterized cohort of CRC patients (n=4000+) with open access to phenotype data and biobanked material. The work during the coming years includes database construction, bioinformatic organisation and processes set-up, biobanking and setting up processes for fair and transparent review and withdrawal processes.

Colorectal Cancer Data Base Sweden (CRCBaSe)
By use of the individually unique Swedish Personal Identity Number, the Swedish Colorectal Cancer Registry has been linked to the Swedish Cancer Registry, the Cause of Death Register, the Prescribed Drug Register, the National Patient Register, all held at the Centre for Epidemiology at the National Board of Health and Welfare, and the Register of the Total Population, the Longitudinal Integration Database for Health Insurance and Labor Market Studies and the Multi-Generation Register, held at Statistics Sweden. CRCBaSe consists of a unique database with over 77 000 cases of CRC with comprehensive data on inpatient and outpatient care, patterns of use of prescribed drugs and socioeconomic and familial factors. All individuals with CRC have six matched healthy controls resulting in the database consisting of 1.2 million individuals in total. Many topics in clinical CRC epidemiology will be investigated using CRCBaSe Sweden during coming years.

Motivation of funding of the project ARP
Funding of ARP would significantly accelerate our research further and create benefits to the patients. Also importantly, by long term investments in research platforms and clinical important studies, bolder research hypotheses will be possible to test. Funding of ARP will be used to establish the infrastructure around ARP by employing a data manager, 2 additional researchers (post doc-level) and a researcher with bioinformatic competence to the research group, to initiate and drive ARP and CRCBaSe for future cutting edge research within the field.

Time frame and estimated costs
Building and establishment of the technical infrastructure of the ARP platform is planned to start during the second half of 2021 and proceed during three years:
Q3 2021 – Recruitment of one data manager
Q4 2021/Q1 2022 – Recruitment of one bioinformatic researcher and one post-doc
Q3 2022 – Recruitment of the second post-doc

**Budget:** Salary costs for recruited personnel, 3-4 MSEK per year x 3 years.

Clinical impact and future potential
My research group has a very strong track record of translating study results to patient benefits, attributed to our integrated research structure in clinical practice, engagement in the Swedish National Guideline Group for CRC and to our research group’s extensive national and international network.

The ALASCCA study may lead to substantial changes in treatment strategies and significantly improve survival in a large group of patients by introducing a new indication of a well-proven, inexpensive drug with low toxicity. We see ALASCCA as a first proof-of-concept of how leveraging the knowledge of mutations in a specific signaling pathway could significantly reduce mortality. If proven successful, the study could potentially save 300-500 lives annually in Sweden. By conducting the CITCCA pilot study, we will be able to test the feasibility and logistics of measuring ctDNA in real life with provision of a response within 4-6 weeks after surgery, i.e. within the time set up for starting adjuvant treatments. In a second step, the main CITCCA study will investigate if ctDNA-guided disease monitoring can be used to escalate or de-escalate adjuvant therapy in high risk patients. By creating the research platforms in parallel to conducting the clinical trials, we will enable almost unlimited
opportunities for additional studies of signalling pathways and biomarkers and thereby lead to significant improvement of future prevention, diagnostics, and prognostics of CRC and important next step toward precision medicine.

**In summary**, the research planned for the next five years will putatively lead to high impact on patient outcome as well as build unique national research resources for future potential bold and cutting-edge studies of colorectal cancer.

**References:**
Biography – Anna Martling


Since 2008 she has been heading the research group and responsible for the research field of colorectal surgery with special focus on clinical, translational and epidemiological studies on colorectal cancer. A special interest of Martlings research group has been predictive and prognostic biomarkers, aspirin, radiotherapy, timing of surgery and development of new surgical techniques. Anna Martling has managed to fully integrate the work by the research group into the clinical department creating a unique creative and academic culture supporting high quality clinical research.

Her research has received numerous awards. In 2013, Anna Martling received the Swedish Surgical Society’s Great Research Prize. She is considered being a world leading expert in her field and is a frequent lecturer in Sweden and abroad. Professor Martling is chairman of the Swedish Colorectal Cancer Study Group, which is a national research network for colorectal cancer in Sweden.

Between 2015-2018 she has been the Chairman of the Program Committee of ESCP and responsible for the scientific program for the annual meeting. Since 2019 she holds the position as Dean at Karolinska Institutet, Stockholm.

Publications

20 Selected Publications by Anna Martling


Total number of publications: 122
H-index: 28 Sum of Times Cited: 3495

Curriculum Vitae

Name: Anna Martling
Office Address: D2:05; Karolinska University Hospital, 171 76 Stockholm
E-mail: anna.martling@ki.se
Dept. of Molecular Medicine and Surgery, Karolinska Institutet
Clinical affiliation: Theme Cancer, Division of Coloproctology, Karolinska University Hospital

Education:
1989-94 Medical School at Karolinska Institutet, MD
2004 Board Certified Surgeon

Qualification as Associate Professor: 2009, Surgery
Full Professor: 2014, Surgery

Current position:
2010- Senior Consultant Surgeon, Theme Cancer, Division of Coloproctology, Karolinska University Hospital. Clinical activity 30%.
2014 - Professor of Surgery, Karolinska Institutet
2019 - Dean Karolinska Institutet North

Distinctions and awards:
2003 Young Promising Researcher, Karolinska Institutet
2008-2014 Young Investigator Award, Swedish Cancer Society
2008, 2012, 2015, 2016 Six best papers award at the ESCP meeting
2013 Swedish Society of Surgery’s Major Research Price
2015 The Edward Wilson Lecture, Sydney, Australia
2016 The Lennander Lecture, Swedish Society of Medicine
2017 Marc-Claude Marti Lecture, Villars, Schweiz
2018 Hilda and Alfred Eriksson Prize, The Royal Swedish Academy of Science
2019 Tarmcancerpriset, ILCO
2019 Med dr Axel Hirsch Prize
2020 Honorary Fellowship of American Society of Colon and Rectal Surgeons (ASCRCL)
2020 Member of International Surgical Group (ISG)
2021 Cancer researcher of the year, Swedish Cancer Society