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

Karolinska Institutet

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 *PIK3CA, PIK3R1 IGF2, IGR2* and *PTEN*. Recently, acquired mutations in the *PIK3CA* gene were shown to potential predict benefit from treatment with ASA.[3-4] While patients whose tumors did not carry *PIK3CA* mutation had no benefit from ASA therapy, patients whose tumors carry *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.

Project	N	Patient inclusion	Collection/ follow-up	Analyses	Additional funding (in part or full)
ALASCCA	3,800	Completed	2016-2024	2022-2026	Swedish Research Council/Swedish Cancer Society/Private Donation
CITCCA	300	Ongoing	2021-2022	2021-2022	Private Donation/ Swedish Research Council/Swedish Cancer Society
The ALASCCA research platform (ARP)	4000+		2016-2026	2022-2040	Current funding
CRCBaSe	77,000 1,2 M	1995-2016	1995-2018	2019-	Swedish Cancer Society/Stockholm Cancer Society

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 personel, 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 safe 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:

1. Jaspersson KW et al, Hereditary and familial colon cancer. Gastroenterology 2010 Jun;138(6): 2044-2058. Doi: 10. 1053/j.gastro.2010.01.054.
2. Chan et al, Aspirin use and survival after diagnosis of colorectal cancer. JAMA. 2009 Aug 12;302(6):649-58. doi: 10. 1001/jama.2009.1112.
3. Liao X, Lochhead P, Nishihara R et al. Aspirin use, tumor PIK3CA mutation and colorectal cancer survival. NEJM 2012;367:1596-1606
4.Domingo E, Church DN, Sieber O et al. Evaluation of PIK3CA mutation as a predictor of benefit from nonsteroidal anti-inflammatory drug therapy in colorectal cancer. J Clin Oncol 2013;31:4297-4305.
5. LeCun, Y. *et al. Nature* **521,** 436–444 (2015).
6. Coudray, N. *et al. Nat. Med.* (2018). doi:10.1038/s41591-018-0177-5. 6. Kustanovich A, Schwartz R, Peretz T, et al: Life and death of circulating cell-free DNA. Cancer Biol Ther 20:1057-1067, 2019.
7.Wang Y, Li L, Cohen JD, et al: Prognostic Potential of Circulating Tumor DNA Measurement in Postoperative Surveillance of Nonmetastatic Colorectal Cancer. JAMA Oncol, 2019

Biography – Anna Martling

Anna Martling is a Professor of Surgery at Karolinska Institutet, Stockholm, Sweden. She defended her thesis on rectal cancer in 2003, became a board certified surgeon in 2004 and an associate professor of surgery in 2009. In 2014 Martling became full professor of surgery.

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

1. **Martling AL**, Holm T, Rutqvist L-E, Moran BJ, Heald RJ, Cedermark B. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm.
Lancet, 2000, vol 356, s 93-96. IF: 53.254.

2. **Martling A**, Holm T, Johansson H, Rutqvist L-E, Cedermark B. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma. Long-term follow-up of a population-based study.
Cancer, 2001, vol 92, s 896-902. IF: 5.238.

3. **Martling A**, Holm T, Rutqvist LE, Johansson H, Moran BJ, Heald RJ, Cedermark B. Impact of a surgical training programme on rectal cancer outcomes in Stockholm.
Br J of Surgery 2005, vol 92, s 225-229. IF: 5.433.

4. Genander M, Halford MM, Xu N-J, Eriksson M, Yu Z, Qiu Z, **Martling A**, Greicius G, Thakar S, Catchpole T, Chumley MJ, Zdunek S, Wang C, Holm T, Goff S, Pettersson S, Pestell RG, Henkemeyer M, Frisén J. Dissociation of EphB2 signaling pathways mediating progenitor cell proliferation and tumor suppression. ***Cell, Volume 139, Issue 4, 13 November 2009, p 679-692. IF: 31.398.***

5. Pettersson D, Cedermark B, Holm T, Radu C, Påhlman L, Glimelius B, **Martling A**. Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer.
Br J of Surgery 2010; 97:580-587. IF: 5.433.

6. Pettersson D, Holm T, Iversen H, Blomqvist L, Glimelius B, **Martling A.** Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer. ***Br J of Surg 2012 ;99:577-583. IF: 5.433.***

7. Segelman J, Granath F, Holm T, Machado M, Matheme H, **Martling A.** Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer- a populationbased study. ***Br J Surgery 2012;99: 699-705. IF: 5.433.***

8. Pettersson D, Glimelius B, Iversen H, Johansson H, Holm T, **Martling A**. Impaired postoperative leucocyte counts after preoperative radiotherapy for rectal cancer in the Stockholm III trial. ***Br J Surg. 2013 Jun;100(7):969-75. IF: 5.433.***

9. Kundu P, Genander M, Strååt K, Classon J, Björk J, **Martling A,** van Es J, Clevers H, Pettersson S, Frisén J. An EphB-Abl signaling pathway important for intestinal tumor initiation and growth. ***Sci Transl Med 1 April 2015:Vol 7(281):281. IF: 16.71.***

10. Pettersson D, Lörinc E, Holm T, Iversen H, Glimelius B, **Martling A**. Tumour regression in the randomized Stockholm III trial of radiotherapy regimens for rectal cancer. ***Br J Surg 2015 Jul;102(8):972-8. IF: 5.433.***

11. Breugom AJ, Bastiaannet E, Boelens PG, Iversen L.H, **Martling A**, Johansson R, Evans T, O'Brien K, Van Eycken L, Janciauskiene R, Liefers G.J, de Craen A.J.M, Cervantes A, Lemmens V.E.P.P, van de Velde C.J.H. Adjuvant chemotherapy and relative survival of patients with stage II colon cancer - a EURECCA international comparison between the Netherlands, Denmark, Sweden, England, Ireland, Belgium, and Lithuania. ***Eur J Cancer. 2016 Jun 11;63:110-117. IF: 7.191.***

12. **Martling A,** Smedby KE , Birgisson H, Olsson H, Granath F, Ekbom A, Glimelius B. Risk of second primary cancer in patients treated with radiotherapy for rectal cancer. ***Br J Surg. 2017 Feb;104(3):278-287. IF: 5.433.***

13. Erlandsson J, Holm T, Pettersson D, Berglund Å, Cedermark B, Johansson H, Machado M, Hjern F, Hallböök O, Syk I, Glimelius B, **Martling A**. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III) - a multicentre, randomised, non-blinded, phase 3, noninferiority trial. ***Lancet Oncol. 2017 Mar;18(3):336-346. IF: 36.421.***

14. Buchli C, **Martling A**, Al Abani M, Frödin J-E, Bottai M, Lax I, Arver S, Holm T. Risk of acute testicular failure after preoperative radiotherapy for rectal cancer: a prospective cohort study. ***Annals of Surg 2018 Volume 267;2; 326-331. IF: 9.203.***

15. van der Valk M.J.M. et al. and the **IWWD Consortium**. Registry of 1009 patients in the International Watch & Wait database (IWWD) for rectal cancer: Results of clinical complete responders. ***Lancet Oncology 2018 Jun 23;391(10139):25372545. IF: 36.421.***

16. **The PelvEx Collaborative Group**. Surgical and survival outcomes following pelvic exenteration for locally advanced primary rectal cancer: Results from an International collaboration. ***Ann Surg. 2019 Feb; 269(2):315-321. IF: 9.203.***

17. Ogura A, Konishi T, Cunningham C, Garcia-Aguilar J, Iversen H, Toda S, Lee IK, Lee HX, Uehara K, Lee P, Putter H, van de velde CJH, Beets GL, Rutten HJT, Kusters M, **On behalf of the Lateral Node Study Consortium.** Neoadjuvant (chemo)radiotherapy with TME only is not sufficient to prevent lateral local recurrence in enlarged nodes - results of the multi-center lateral node study with 1216 patients with low cT3/4 rectal cancer. ***J of Clin Oncol 2019 Jan 1;37(1):33-43. IF: 26.36.***

18. Segelman J, Buchli C, Svanström Röjvall A, Matthiessen P, Arver S, Bottai M,

Ahlberg M, Jasuja R, Flöter-Rådestad A, **Martling A**. Effect of radiotherapy for rectal cancer on ovarian androgen production.
Br J of Surg 2019 Feb;106(3):267-275. IF: 5.433

19. Erlandsson J, Pettersson D, Glimelius B, Holm T, **Martling A**. Postoperative complications in relation to overall treatment time after neo-adjuvant radiotherapy in patients with rectal cancer.
Br J Surg. 2019 Aug;106(9):1248-1256. IF: 5.572

20. Fernandez et al. and the **IWWD Consortium**. Conditional recurrence-free survival of clinical complete responders managed by watch and wait after neoadjuvant chemoradiotherapy for rectal cancer in the International Watch and Wait Database: a retrospective, international, multicenter registry study. ***Lancet Oncol. 2021 Jan,22(1):43-50. IF: 36.421.***

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
2003 PhD Thesis ”Rectal Cancer - Staging, Radiotherapy and Surgery”, Karolinska Institutet
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 (ASCRC)
2020 Member of International Surgical Group (ISG)
2021 Cancer researcher of the year, Swedish Cancer Society