Plan Overview

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Title: IMPACT OF ATORVASTATIN ON PROSTATE CANCER PROGRESSION AFTER INITIATION OF ANDROGEN DEPRIVATION THERAPY – LIPID METABOLISM AS A NOVEL BIOMARKER TO PREDICT PROSTATE CANCER PROGRESSION – PHASE 3, DOUBLE-BLIND RANDOMIZED CLINICAL TRIAL FINNPROSTATA XV/ESTO2

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Project abstract:

Local de novo production of cholesterol is abundant in prostate cancer (PCa) and important for cancer cell survival especially under androgen deprivation therapy (ADT). This likely provides novel opportunities to inhibit PCa progression, however serum lipidomic changes during ADT and development of ADT insensitivity, termed castration resistance (CR), have not been characterized. Concordantly, use of cholesterol-lowering statin drugs is associated with prolonged treatment response to ADT in advanced PCa and lowered risk of PCa death, but uncertainty lingers as no randomized clinical trials have been performed on the topic. The study objectives are: 1) Characterization of serum lipidomic changes during ADT to identify new biomarkers for disease progression and novel anticancer interventions. We evaluate lipidome in relation to cancer cell survival in hypoxic tumor microenvironment, evasion of antitumor immune response and occurrence of genetic modifications to improve understanding of disease progression and CR development, 2) Testing efficacy of cholesterol-targeted intervention with atorvastatin in delaying development of CR during ADT and reducing PCa mortality in a randomized, placebo-controlled clinical trial to test for efficacy in clinical PCa management, 3) Characterization of biomarkers to predict response to cholesterol-lowering atorvastatin treatment in PCa patients. A total of 400 men with PCa and starting permanent ADT will be recruited and randomized 1:1 to use daily either 80 mg of atorvastatin or placebo. Follow-up continues until development of CR or for a maximum of five years. After CR the participants are followed for PCa death. Serum lipidome is measured repeatedly during the study to observe changes preceding CR development. Tumor hypoxia and immune-cell infiltration in the primary tumor and metastases are repeatedly measured using PET scanning. Diagnostic prostatic biopsies will be genotyped and characterized to identify biomarkers predicting atorvastatin response. Characterizing role of serum lipidome in relation to tumor microenvironment and changes during ADT and CR progression will likely lead to new tools in personalized prostate cancer management and risk prediction. Further, the study will show whether efficacy of ADT in improving PCa survival can be enhanced with cholesterol-targeted intervention, cheap and well-tolerated atorvastatin.

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1. General description of data

1.1 What kinds of data is your research based on? What data will be collected, produced or reused? What file formats will the data be in? Additionally, give a rough estimate of the size of the data produced/collected.

Data collection in this study is based on clinical laboratory results, clinical treatments, symptoms, imaging results, quality of life questionnaire, PCa-specific survival and overall mortality which are collected during follow-up visits from patients' medical records and from Finnish registries. Also, genomic and metabolic data will be collected from gene and whole genome sequencing data, immunohistochemical staining and evaluation of lipid metabolisms. WHOQOL-BREF questionnaire is used to collect quality of life data. A closed cloud-based web-platform (RedCap) will be established on server maintained by the Tampere University, Finland and is used for collection and storage of the study data during trial. Study registry keeper is Pirkanmaa hospital district.

Collected samples are stored without personal indentifiers in freezers in Finlab laboratories. All data is added to database without personal identifiers. At the first entry each participant is given a study ID which is used to identified they through the follow-up. Clinician recruiting and treating the patient in study center has the key between study ID and personal identification number of the subject. Randomization into two groups is done by study coordinator (Aino Siltari) using online randomization platform. Only coordinator and study drugs manufacturer (Medfiles Oy) have access to the randomization key before the end of the study.

Data is collected using RedCap platform and stored in readme.txt, .xls, .sav and .sps file formats in study registry (administrator Pirkanmaa hospital district). Almost all collected data is from clinical records, thus data is sensitive.

Final recruitment target of the trial is 400 patients, thus, registry includes above mentioned data from that study population.

1.2 How will the consistency and quality of data be controlled?

External trained study monitors independent from the study sponsors ensure the data quality by making regular yearly check-up visits to participating study centers (monitoring of the study and collected data). Also, the study steering committee will monitor integrity of collected data in their meetings twice a year. Study steering committee includes principal clinicians from different study centers,

Almost all samples and measurements are done during clinical routine, thus, used methods are validated and reliable. Whole genome sequencing is done using commercial privet company, thus, quality of the data is monitored and recorded.

2. Ethical and legal compliance

2.1 What legal issues are related to your data management? (For example, GDPR and other legislation affecting data processing.)

Collected data consists of data from patients and is collected after subject has sign informed consent form. Data are collected and treated following national data protection act, regulation and law. All the data that are shared will be completely pseudonymized.

All data is added to database without personal identifiers. Only study ID of each patients is used to identify subjects. Only PI can give access to the study database which is protected by usernames and passwords. All persons who have access to data sign confidentially agreement and are trained how to handling sensitive data.

2.2 How will you manage the rights of the data you use, produce and share?

PI (who is also the sponsor of the study) and study steering committee owns all data.

There are no copyrights or other restrictions related the data. Opened data will be licensed using Creative commons -license.

3. Documentation and metadata

3.1 How will you document your data in order to make the data findable, accessible, interoperable and re-usable for you and others? What kind of metadata standards, README files or other documentation will you use to help others to understand and use your data?

All data is collected using web-based platform (RadCap) where units e.g. are clearly stated to make sure that the data is entered correctly. All clinical data is documented the same way as in normal routine clinical measurement results, thus, person who is aware of matter will understand the data e.g. abbreviations and units. Validated WHOQOL-BREF quality of life questionnaire is used and data is saved in the same format as in the original questionnaire.

If the data is shared, help to understand the data is offered by the study steering committee if needed.

Metadata will be available in Etsin, Open Science of Finland service. Project metadata is documented in readme files.

4. Storage and backup during the research project

4.1 Where will your data be stored, and how will the data be backed up?

Results of the measurements and study end-points will be stored in the Tampere University maintained server. A closed cloud-based web-platform (RedCap) will be established on server maintained by the Tampere University, Finland. For data protection, storage and pack up, annual fee is payed to the University to make sure that data is accurately stored and protected. Registry keeper is Pirkanmaa hospital district.

4.2 Who will be responsible for controlling access to your data, and how will secured access be controlled?

Access to the data is controlled by primary investigator Teemu Murtola. Secure access is controlled by Tampere University IT-service. Access to the data is protected by usernames and passwords.

5. Opening, publishing and archiving the data after the research project

5.1 What part of the data can be made openly available or published? Where and when will the data, or its metadata, be made available?

All results will be published in open access journals. Projects metadata will be available in the Etsin research data finder after study ends.

The anonymized dataset and statistical code will be made available by reasonable request directed at the trial steering board after the study ends.

5.2 Where will data with long-term value be archived, and for how long?

Long-term storage of the data is in Pirkanmaa hospital district managed register (register keeper Pirkanmaa hospital district).

6. Data management responsibilities and resources

6.1 Who (for example role, position, and institution) will be responsible for data management (i.e., the data steward)?

Study PI prof. Murtola will be responsible the whole data management and data management coordination with study steering committee during research project and after it.

Study coordinator is responsible to maintenance of RedCap web-based study platform during trial. External trained study monitors monitor quality of collected data in yearly checkups.

Annual fee is paid to the University for data protection, storage and pack ups. Study monitoring services of the data is bought from Tays Research, Development and Innovation Centre.

6.2 What resources will be required for your data management procedures to ensure that the data can be opened and preserved according to FAIR principles (Findable, Accessible, Interoperable, Re-usable)?

IT-department of Tampere University together with the study PI and co-ordinator ensure that FAIR principles are applied