Clinical Trial Protocol

Study

Follow-up of Cancer Patients Receiving Chemotherapy or Targeted Therapy by Electronic Patient Reported Outcomes-tool (ECHO)

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OUTLINE:

Study:	Follow-up of Cancer Patients Receiving Chemotherapy or Targeted Therapy by Electronic Patient Reported Outcomes-tool (ECHO)
Protocol version	1.1 28.2.2019
Sponsor	Jussi Koivunen, Oulu University Hospital
Indication	Cancer patients with breast, lung, colorectal or pancreatic cancer receiving chemotherapy or targeted therapy
Outcomes	Overall cohort: 1. Number of triggered alerts by the Kaiku Cancer medical therapy side-effects questionnaire and their correlation to treatment side-effects, cancer progression, other relevant medical events or survival 2. QoL of patients using Kaiku QLQ-C30 QoL questionnaire and its correlation to treatment side-effects, cancer progression, other relevant medical events or survival 3. Patient compliance using Kaiku Patient experience survey and response rates to symptom and QLQ-C30 questionnaires Additionally, in the CRC cohort: 1. Integration of laboratory values to patient reported symptoms when prescribing a new chemotherapy cycle 2. Phone calls related to chemotherapy prescribing 3. Unscheduled visits in oncology unit 4. Additional investigations in health care 5. ER visits 6. Additional days in hospitalization 7. Development of peripheral neurotoxicity 8. Amount of chemotherapy dose reductions 9. Number of delayed chemotherapy cycles 10. Usability experience of health care personnel
Study design	Prospective one arm study
Sample size	100 patients of which, 60 CRC patients which are expected to be recruited in 42 months
Criteria	**Inclusion criteria**: 1. Signed informed consent 2. Advanced breast, lung, colorectal or pancreatic cancer 3. Chemotherapy or targeted therapy initiated within +/- 2wks from signed consent 4. Age ≥18y 5. ECOG 0-2 6. CRC cohort: Adjuvant treatment, or first or second metastatic treatment line 7. Patient compliant with the study procedures **Exclusion criteria:** 8. Chemotherapy or targeted therapy iniated >2 wks prior to

	signed consent 9. General vulnerability affecting the participation in the trial 10. No internet access/email
Study procedures	Patient: 1. Fills 16 question Kaiku **Cancer medical treatment side-effects questionnaire** before initiation of the treatment or within 2 weeks and thereafter weekly up to disease progression or 24 weeks 2. Answers Kaiku **QLQ-C30 QoL questionnaire** before initiation of the treatment or within 2 weeks and thereafter every four weeks up to disease progression or 24 weeks 3. Answers **Patient Experience survey** every four weeks up to disease progression or 24 weeks Doctor/Nurse: 1. Fills Kaiku **baseline patient information** before the initiation of treatment or within 2 weeks 2. Fills Kaiku **follow-up information** 6-12 weeks frequency up to disease progression or 24 weeks 3. Fills **Survival follow-up information** after study closure Additionally, in the CRC cohort: 4. Evaluates patient reported symptoms and laboratory values before prescribing new chemotherapy cycle 5. Fills Kaiku **Chemotherapy follow-up information** before new chemotherapy cycle
Study end-points	Overall population: 1. Number of triggered alerts by Kaiku **Cancer medical treatment side-effects questionnaire** and their correlation to treatment side-effects, cancer progression, other medical events or survival 2. QoL of patients using Kaiku **QLQ-C30 questionnaire** and its correlation to treatment side-effects, cancer progression, other medical events or survival 3. Patient compliance using KaikuHealth e-questionnaire and response rates to symptom and QLQ-C30 questionnaires Additionally, in the CRC cohort: 4. Number of phone calls related to prescribing a new chemotherapy cycle per patient or treatment cycle 5. Unscheduled doctor appointments in oncology unit per patient or treatment cycle 6. ER visits per patient or treatment cycle 7. Days in hospitalization per patient or treatment cycle 8. Unscheduled medical investigations per patient or treatment cycle 9. Development of Grade 1 peripheral neurotoxicity per patients

	or treatment cycle and date 10. Development of peripheral neurotoxicity due to oxalplatin verus other chemotherapies 11. The number of chemotherapy dose reductions per patient or treatment cycle and date 12. The number of chemotherapy cycle delays per patient and date
Study course	After signing of the informed consent, patient is trained on use of Kaiku software. Patient answers questionnaires with 1-4 weeks frequency up to 24 weeks. Patients survival is followed after 24 weeks period. Study doctor/Nurse fills baseline information and thereafter follow-up information with 6-12 weeks frequency up to 24weeks, and **Chemotherapy follow-up information** at every new chemotherapy cycle up to 24 weeks and **Survival follow-up information** after study closure.
Study duration	1.12.2018 – 30.6.2021

AMENDMENTS

Amendment number	Amendment Date	Protocol version number	Amendment type	Amendment nature/purpose
1.	28.2.2019	1.1	Protocol change	• Establishment of colorectal cancer cohort • Adding new study end-points to CRC cohort • Integration of laboratory values to patient reported symptoms in CRC cohort • Update of statistical plan • Update of study duration and follow-up time

Table 1. Study procedures in overall population excluding CRC cohort

	Baseline	Cancer medical treatment duration or up to 24 weeks			Follow-up
Procedure	within -2vko - +2wks from cancer treatment initiation	1wks	4wks	6-12wks	
Written informed consent	X				
Kaiku Cancer medical treatment side-effects questionnaire[1,3]	X	X			
Kaiku QLQ-C30 QoL questionnaire[1,3]	X		X		
Kaiku Patient experience survey[1,3]				X	
Kaiku Patient baseline information[2]	X				
Kaiku follow-up information[2,3]				X	
Kaiku survival follow-up information[4]					X

(1) Patients fills

(2) Doctor/Nurse fills

(3) up to 24 weeks

(4) from electronic records at study closure

Table 2. Study procedures in CRC cohort

	Baseline	Chemotherapy duration or up to 24 wks				Follow-up
Procedure	within -2vko - +2wks from chemotherapy initiation	1wks	2-3wks	4wks	6-12wks	
Written informed consent	X					
Kaiku Cancer medical treatment side-effect questionnaire[1,3]	X	X				
Kaiku QLQ-C30 QoL questionnaire[1,3]	X			X		
Kaiku Patient experience survey[1,3]				X		
Kaiku Patient baseline information[2]	X					
Kaiku Chemotherapy follow-up information[2,3,4]			X			
Kaiku follow-up information[2,3]					X	
Kaiku survival follow-up information[5]						X
Health care user experience survey[2]				X		

(1) Patient fills

(2) Doctor/Nurse fills

(3) up to 24 weeks

(4) at every new chemotherapy cycle

(5) from electoronic records after study closure

TABLE OF CONTENTS PAGE

1.BACKGROUND

1.1. Chemotherapy and targeted therapies in cancer treatment

Cancer medical treatments aim to destroy mutated, malignant cells of the body. Even targeted cancer therapies have harmful effects on normal cells of the body. Selectivity of a drug is of importance from the point of side-effects. Unselectivity and wide side-effect spectrum are typical to traditional chemotherapies.

Traditional chemotherapy agents have narrow therapeutic levels. Therefore, grave side-effects are present even at therapeutic levels, typically. Most chemotherapy agents target rapidly dividing cells, and normal tissues like bone marrow and mucosa, in which cells proliferation is fast, are affected causing treatment related adverse events. Many traditional chemotherapy agents have multiple targets that widens the spectrum of side-effects. Typical side-effects of chemotherapy include neutropenia, oral cavity mucosal lesions, diarrhea and hair loss.

Targeted therapies are drugs designed to interfere with specific molecules necessary for tumor growth and progression, such as tyrosine-kinase inhibitors or monoclonal antibodies. Because of the more specific way of action, targeted therapies have less side-effects compared to chemotherapies. The more cancer specific mutation drug targets, the less adverse events exist. The selectivity of targeted therapies varies, and some of the adverse events are class specific. Typical side-effects include among others blood pressure rise and skin rash.

1.2. Study rationale

Patient reported outcomes (PROs) consist of health-related questionnaires filled by the patients themselves which can capture symptoms and signs and their severity. PROs can be captures by traditional paper questionnaires or by Web-based approaches. Web-based reporting of PROs has many advantages compared to paper questionnaires such as reducing timely and locational limitations. These advantages make web-based PRO capturing more likely to allow changes in symptoms or quality of life (QoL). Furthermore, web-based PROs can be coupled to urgency algorithm which sends an alert to the care unit on severe or altering symptoms of a patient. This enables rapid reaction and treatment of important medical events.

ePROs have been studied in oncological care. An American randomized study has investigated use of ePROs coupled with urgency algorithm in the follow-up of patients receiving chemotherapy as palliative treatment of multiple tumor types. Use of ePROs resulted in improvement of QoL, decreased ER visits, and improvement of overall survival. Another French study has investigated use of urgency algorithm coupled ePROs in follow-up of lung cancer patients compared to traditional follow-up with more frequent assessments using physician visits and scans. ePRO follow-up resulted in better QoL, improved ECOG status and more active cancer treatments at disease relapse, and improved survival
(1-7).

Before prescribing a new chemotherapy cycle peripheral blood samples are taken to evaluate e.g. total blood cell count which need to be in pre-defined limits. Furthermore, patient´s clinical status is evaluated by nurse based on phone calls. The manual evaluation of laboratory values is prone to human mistakes. In addition, symptom evaluation is seldom systematic and often timely limited to present situation. Computer assisted laboratory test evaluation, and structured and timely consistent symptom follow-up could improve safety of chemotherapy treatments, QoL of patients and health care resource allocation.

2. STUDY OBJECTIVES

Objectives:

1. The number of alerts triggered by Kaiku Cancer medical treatment side-effects questionnaire and their correlation to treatment side-effects, other relevant medical events, tumor progression, and survival.
2. Changes in Kaiku QLQ-C30 QoL questionnaire and their correlation to cancer treatment response, side-effects, other relevant medical event or survival
3. Patient compliance to Kaiku ePRO surveillance during treatment period according to response rates of Patient experience survey, Kaiku Cancer medical treatment side-effects questionnaire and Kaiku QLQ-C30 QoL questionnaire

In addition, in CRC cohort:

1. Integration of laboratory values to patient reported symptoms when prescribing a new chemotherapy cycle
2. Number of phone calls related to prescribing a new chemotherapy cycle
3. Unscheduled doctor appointments in oncology unit
4. ER visits
5. Days in hospitalization
6. Unscheduled investigations in health care
7. Development of peripheral neurotoxicity
8. The number of chemotherapy dose reductions
9. The number of chemotherapy delays
10. Health care user experience survey

3.STUDY DURATION

Patient recruiting started 1.12.2018 and is estimated last up to 30 months. The last visit of the last patient is estimated to happen 30.6.2021. The enrolment period is estimated to be 24 months. Survival data will also be collected at the study closure, and the collection of the survival data of a patient is limited to 12 months from the study entry.

4.PATIENT SELECTION

4.1. Patient population

Sample size of the study is 100 of which 60 are CRC patients, and study patients are expected to be recruited within 24 months.

4.2. Inclusion criteria

1. Written informed consent prior to any study procedure
2. Advanced breast, lung, colorectal, or pancreatiac cancer
3. New cancer medical treatment, chemotherapy or targeted therapy initiated within -/+ 2 weeks from signed consent
4. Age ≥18y
5. ECOG 0-2
6. CRC cohort: Patients with adjuvant treatment, or first or second line of treatment for metastatic disease
7. Patient compliant with study procedures

4.3. Exclusion criteria

1. Initiation of new cancer medical treatment > 2 wks from signed consent
2. Any medical condition that the Investigator considers significant to compromise the safety of the patient or that impairs the interpretation of study assessments
3. No internet access/email

5.STUDY NATURE

5.1. Study design

A prospective one arm multicenter observational trial.

5.2. Study procedures

See Tables 1 and 2 from pages six and seven.

5.2.1. Baseline

A signed informed consent from every patient must be present before any study procedures.

The parameters listed below are collected at baseline:

- Demographics (age, gender, weight, height)
- ECOG performance status
- Cancer medical treatment (drug, indication, day of the first infusion)
- Blood sampling to measure the following (blood cell counts: leucocytes, neutrophils, lymphocytes, thrombocytes; B-haemoglobin, P-creatinine, ALT, ALP, AST, bilirubin)
- Possible prior cancer medical treatment lines

- Kaiku Cancer medical treatment side-effects questionnaire and Kaiku QLQ-C30 QoL questionnaire filled ≤ 2weeks from 1st infusion or peroral drug dose

5.2.2. Treatment period

Study treatment period lasts the treatment phase of cancer medical treatment or up to 24 weeks.

The parameters listed below are collected during the treatment phase:

- 16 question Kaiku Cancer medical treatment side-effects questionnaire ≤2 weeks from the 1st infusion and weekly after that
- Kaiku QLQ-C30 QoL questionnaire ≤ 2weeks from the 1st infusion/per oral drug dose and every four weeks after that
- Kaiku Patient experience survey
- Kaiku follow-up information in 6-12 weeks cycle
    - Urgency algorithm alerts (grade, date, cause of the alert)
    - AE (type, date, related urgency alert if present)
    - Treatment of AE (type, date, treatment discontinuation)
    - Unscheduled appointments (ER, onkology unit, phone calls, type, date)
    - Treatment response (CR, PR, SD, PD, NE, date)
    - Treatment discontinuation (date, next treatment line)
    - Date of death

In addition, in CRC cohort:

- Kaiku Chemotherapy follow-up information at every new chemotherapy cycle
    - Phone calls to patient before new chemotherapy cycle (no/yes)
    - Unscheduled doctors' appointments in oncology unit (no/yes, amount)
    - Unscheduled health care investigations after during the last given chemotherapy cycle (no/yes, laboratory tests/radiological investigations/other)
    - Days in hospitalization during last given chemotherapy cycle (no/yes, in-ward treatment duration in days)
    - Has there been > 10% dose reduction in the next chemotherapy cycle compared to previous cycle, or has the treatment been de-intensified (no/yes)
    - Has the next chemotherapy cycle been delayed due to patients' laboratory values or symptoms (no/yes, duration in days)
    - Kaiku Follow-up information in 6-12wks cycle
    - ECOG (0-4)
    - Treatment related adverse events (no/yes, type, grade, date)
    - Treatment response (CR/PR/SD/PD/NE, date)
    - Possible discontinuation of treatment (no, yes, date, reason (cancer progression, side-effect, planned treatment duration, other), next treatment (cancer medical treatment, radiotherapy, other, no treatment), ECOG at the beginning of next treatment)

5.2.3. Follow-up period

Patient survival will be collected in the end of the follow-up period at study closure.

6. STUDY INSTRUMENTS

6.1 KaikuHealth questionnaires

Study patients will receive a short (5-15min) training on how to use Kaiku software by study physician or nurse. The training will include how the sign in to the system, login, navigation in Kaiku software, filling of ePRO questionnaires, function of urgency algorithms, messaging, and access email-address for technical assistance. Care unit will do the initial registration of the patient. KaikuHealth-service will send email reminders to fill in KaikuHealth questionnaires in prescheduled time line. First notification will be sent immediately when patient is registered to the study and weekly thereafter. If a patient doesn't fill an ePRO questionnaire promptly, an email remainder is sent three days later. If patient doesn't fill PRO questionnaire within six days, weekly PRO assessment will be missed, and notification of new PRO assessment period will be initiated with a new email notification seven days after previous. Patient data will stored on a server located in Finland. Anonymization will take place when data is analyzed.

KaikuHealth ePRO follow-up module consists of 16 symptom questionnaire which will assess both presence and severity of the symptom. The symptoms selected for the Kaiku Health symptom tracking tool for cancer medical treatment include typical side-effects of chemotherapy and targeted therapies. The questions for each symptom in the instrument were developed based on NCI-CTCAE v.4.03 register by converting the description of gradings into a patient-friendly language.

If algorithm analysis suggests a presence of grade 3 or higher symptom, alert will be sent to the care unit after which care unit contacts the patients and if necessary, further investigation and/or assessments will be ordered. It is recommended that care unit reacts to alerts promptly but no later than three days after an alert. Contact to the patient can be made by messaging properties of Kaiku software or phone call. Furthermore, patients are informed that Kaiku ePRO follow-up is intended for non-urgent manners.

7. MONITORING

Written informed consents are monitored by an independent single monitor in 12 months cycles.

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8.STATISTICAL PLAN

Due to the study nature (one-arm study) statistical plans are not calculated. Data analysis will be carried out when the length of follow-up time of the last recruited patient is at least six months. For the final analysis statistical methods will be redefined based on actual distributions. The data of CRC cohort will be analyzed separately from other cancer types of the overall population.

8.1. Study end-point analysis

The number of alerts generated by Kaiku Cancer medical treatment side-effect questionnaire will analyzed per patient or per treatment cycle in percentages in the overall population or based on stratification by indication (advanced disease or adjuvant treatment), cancer medical treatment (chemotherapy, other) or cancer type depending on final patient population.

The correlation of alerts triggered by Cancer medical treatment side-effect questionnaire to treatment side-effect, cancer progression, cancer relapse, other medical condition or survival will be analyzed with heat-map analysis or other valid statistical method.

The changes in QLQ-C30 QoL questionnaire will be analyzed at 3 and 6 months timepoints compared to baseline in the overall population or based on stratification by indication (advanced disease or adjuvant treatment), cancer medical treatment (chemotherapy, other) or cancer type depending on final patient population.

Patient compliance will be analyzed based on percentages of answers to Patient compliance survey in the overall population and/or in different timepoints. In addition, patient compliance will be analyzed based on answering rates to symptom and QoL questionnaires within 3 days from email reminder in percentages in the overall population and/or in different timepoints. Analysis can be made in the overall population or based on stratification by indication (advanced disease or adjuvant treatment), cancer medical treatment (chemotherapy, other) or cancer type depending on final patient population.

Health care personnel user experience will be analyzed based on answers to user experience survey in percentages in the overall population and/or in different timepoints.

Integration of laboratory values and symptom questionnaires will be analyzed as percentages of treatment cycles in three class: new chemotherapy cycle can be prescribed directly (≤grade 1 symptom and laboratory values within in limits), cycle prescribed after assessment of symptoms by study personnel (≥grade 2 symptoms and laboratory values within limits) and cycle delayed due to laboratory values outside

limits. Analysis can be made in the overall population or based on stratification by indication (advanced disease or adjuvant treatment), cancer medical treatment (chemotherapy, other) or cancer type depending on final patient population.
In addition, feasibility of integration of laboratory values and symptom questionnaires will be analyzed based on answering rates in percentages to health care personnel user experience survey.

The number of phone calls to patients are analyzed in percentages per patient or treatment cycle. Also, time to the first phone call to patient can be analyzed by Kaplan-Meier method. Analysis can be made in the overall population or based on stratification by indication (advanced disease or adjuvant treatment), cancer medical treatment (chemotherapy, other) or cancer type depending on final patient population.

The amount of unscheduled doctors' appointments in oncology unit will be analyzed in percentages per patient or treatment cycle. Also, time to the first unscheduled doctors' appointment can be analyzed by Kaplan-Meier method. Analysis can be made in the overall population or based on stratification by indication (advanced disease or adjuvant treatment), cancer medical treatment (chemotherapy, other) or cancer type depending on final patient population.

The amount of unscheduled ER visits will be analyzed in percentages per patient or treatment cycle. Also, time to the first unscheduled ER visit can be analyzed by Kaplan-Meier method. Analysis can be made in the overall population or based on stratification by indication (advanced disease or adjuvant treatment), cancer medical treatment (chemotherapy, other) or cancer type depending on final patient population.

Days in hospitalization will be analyzed in percentages per patient or treatment cycle. Also, time to the first in-ward phase can be analyzed by Kaplan-Meier method. Analysis can be made in the overall population or based on stratification by indication (advanced disease or adjuvant treatment), cancer medical treatment (chemotherapy, other) or cancer type depending on final patient population.

The amount of unscheduled medical interventions and investigation types will be analyzed in percentages and/or by type per patient or treatment cycle. Also, time to the first unscheduled medical intervention can be analyzed by Kaplan-Meier method. Analysis can be made in the overall population or based on stratification by indication (advanced disease or adjuvant treatment), cancer medical treatment (chemotherapy, other) or cancer type depending on final patient population.

Development of peripheral neurotoxicity is evaluated based on Kaiku Cancer medical treatment side-effect question of distinct symptom and its' severity in the latest symptom questionnaire filled before new treatment cycle and during the treatment period. Also, time to the development of neurotoxicity based on symptom questionnaires before new treatment cycle and its severity can be analyzed by Kaplan-Meier method. Analysis can be made in the overall population or based on stratification by indication (advanced disease or adjuvant treatment), cancer medical treatment (chemotherapy, other) or cancer type depending on final patient population.

The number of chemotherapy dose reductions (>10%) will be analyzed in percentages per patient of treatment cycle. Also, time to the first chemotherapy dose reduction (>10%) can be analyzed by Kaplan-Meier method. Analysis can be made in the overall population or based on stratification by indication (advanced disease or adjuvant treatment), cancer medical treatment (chemotherapy, other) or cancer type depending on final patient population.

The amount of chemotherapy cycle delays (> 2days) will be analyzed per patient or treatment cycle. Also, time to the first chemotherapy cycle delay (>2days) can be analyzed by Kaplan-Meier method. Analysis can be made in the overall population or based on stratification by indication (advanced disease or adjuvant treatment), cancer medical treatment (chemotherapy, other) or cancer type depending on final patient population.

8.2. Missing data

Patients who have filled at least to Kaiku Cancer medical treatment side-effects questionnaire will be included in the final analysis.

9.SIGNATURE

I promise to carry out investigation according to study protocol, good clinical practice and appropriate legislation.

Principal investigator and sponsor:

Place, date
Oulu, 13.5.2019

SIGNATURE

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Jussi Koivunen, adjuvant professor, medical oncologist
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