Clinical Trial Protocol

Study

Follow-up of Cancer Patients Receiving Immune Checkpoint Inhibitor Therapy by Electronic Patient Reported Outcomes-tool (KISS)

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OUTLINE:

Study:	Follow-up of Cancer Patients Receiving Immune Checkpoint Inhibitor Therapy by Electronic Patient Reported Outcomes-tool
Protocol version	11.2.2019
Sponsor	Jussi Koivunen, Oulu University Hospital
Indication	Cancer Patients Receiving Immune Checkpoint Inhibitor Therapy
Outcomes	1. Patient reported symptoms and their severity 2. Number of triggered alerts by the tool and their correlation to treatment side-effects, cancer progression, other medical events or survival 3. Correlation between different symptoms and to treatment side-effects, cancer progression, other medical events or survival 4. QoL of patients using QLQ-C30 and their correlation to treatment side-effects, cancer progression, other medical events or survival 5. Patient compliance using KaikuHealth e-questionnaire and response rates to symptom and QLQ-C30 questionnaires 6. Correlation of baseline laboratory values to treatment side-effects, cancer progression, other medical events or survival.
Study design	Prospective one-arm study
Study size	40 patients
Criteria	**Inclusion criteria**: 1. Signed informed consent 2. Advanced cancers 3. Immune checkpoint inhibitor therapy initiated within +/- 2wks 4. Age >18y 5. ECOG 0-3 6. Patient compliant with the study procedures **Exclusion criteria:** 1. Immune checkpoint inhibitor therapy initiated > 2wks ago 2. General vulnerability affecting the participation in the

	trial 3. No internet access
Study procedures	Patient: 1. Answers 17 question **Kaiku immunological 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 **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: 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
Study End-points	1. Patient reported symptoms and their severity 2. Number of triggered alerts by the tool and their correlation to treatment side-effects, cancer progression, other medical events or survival • Gr2 alerts • Gr3-4 alerts 3. Correlation between different symptoms and to treatment side-effects, cancer progression, other medical events or survival 4. QoL of patients using QLQ-C30 and their correlation to treatment side-effects, cancer progression, other medical events or survival 5. Patient compliance using KaikuHealth e-questionnaire and response rates to symptom and QLQ-C30 questionnaires 6. Correlation of baseline laboratory values to treatment side-effects, cancer progression, other medical events or survival.
Study course	After signing of the informed consent, patient is trained on use of Kaiku software. Patient answers questionnaires 1-4 week frequencies up to 24 weeks. Patients survival is followed after 24 week period. Study doctor fills baseline information and thereafter follow-up information 6-12week frequency up to 24weeks.

Sample size	Sample size of the study is 40 and study patients are expected to be recruited within 2 years.
Study time	Q2/2017-Q4/2019

Table 1. Study procedures

	Baseline	Immunological Therapy period			Follow-up
Schedule	≤ 2vk prior 1st immunological therapy infusion or ≤2vko after	Weekly	q4w	q6-12w	
Written Informed consent	X				
KaikuHealth immunological treatment side-effects questionnaire [1,3]	X	X			
KaikuHealth QLQ-C30[,3]	X		X		
KaikuHealth baseline patient information [2]	X				
KaikuHealth follow-up information [2,3]				X	
Patient survival follow-up[4]					X
Kaiku Patient experience questionnaire [1]			X		

(1) Patient fills

(2) Doctor fills

(3) Up to 24 wks

(4) Up to 12 mo

TABLE OF CONTENTS PAGE

AMENDMENTS

Amendment number	Amendment date	Protocol versio nro	Amendment type	Amendment nature/purpose
1.1	9.11.2017	1.1	Protocol change	Open form-question excluded from the side-effect questionnaire
1.12	23.11.2018	1.1	Patient Information and Informed Consent translation	Translation of patient documents to swedish and english.
1.2	28.1.2019	1.2	Protocol change	Study end-points, analysis of the results, side-effect questionnaire background and study duration were redefined

1. BACKGROUND

Immuno-oncological treatments

It has been known for years that immune system can resist or eradicate malignant tumors. However, efficient therapeutic approaches to enhance immune effect on tumors have been missing. In past five years, there has been huge development in cancer immunotherapies with introduction of immune checkpoint therapies such as PD-(L)1 and CTLA-4 antibodies. Immune checkpoint inhibitor therapies have become the most important therapies in many malignancies such as melanoma, non-small cell lung cancer, and urogenital cancers.

The effect of immune checkpoint inhibitors is mediated by inhibition of T-cell blocking which results in T-cell mediated cancer cell death. The side-effects of the immune checkpoint inhibitors also relate to the mechanism of action with activated T-cells attacking health tissues.

The side-effects of immune checkpoint inhibitors resemble autoimmune disease. The most common side-effects are skin rash, endocrine toxicity, gastrointestinal(GI) toxicity, hepatitis, pneumonitis, nephritis, and myositis. Some of the side-effects can be life-threating. In most cases however, early detection, delaying or stopping immune checkpoint therapy, and initiation of immunosuppressive medication (corticoids) can resolve or prevent further worsening of side-effect. As general rule, in the occurrence of NCI-CTCAE gr2 side-effects immune checkpoint inhibitor therapy is delayed until they resolve while in gr3-4 side-effects therapy is discontinued and corticoid therapy is initiated.

Timing of side-effects differs from traditional cancer therapy and they can occur from months to years after therapy initiation or after discontinuation of the therapy. Therefore, long-term follow-up of patients is warranted even after the therapy discontinuation.

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

Immune checkpoint inhibitors differ from traditional cancer therapies with potential severe side-effects rising from all the organs of the body and late timing of the side-effect occurrence. Therefore, there is a need for comprehensive and long-lasting assessment of symptoms. ePROs provide unique and cost-effective means to capture broad changes in patients' symptoms for extended time periods. Since ePRO follow-up has been shown to improve survival and QoL of lung cancer patients and cancer patients receiving chemotherapy, it is feasible to speculate that ePROs could also improve these in cancer patients receiving immune checkpoint inhibitors.

2. STUDY OBJECTIVES

Objectives:

1. Spectrum of patient reported symptoms and their severeness
2. Correlation of urgency algorithm alerts triggered by KaikuHealth immunological treatment side-effects questionnaire to investigator assessed iAEs, other relevant medical events, tumor progression, and survival
    a. Gr2 alarms
    b. Gr3-4 alarms
3. Correlation of PROs to investigator assessed iAEs, tumor progression, other relevant medical events and survival
4. Correlations between PROs
5. Changes in QoL according to KaikuHealth QLQ-C30 questionnaire and their correlation to immunological treatment response, AEs, other medical condition and survival
6. Patient compliance to Kaiku ePRO surveillance during treatment period according to response rates of Patient experience questionnaire, KaikuHealth

immunological treatment side-effects questionnaire and KaikuHealth QLQ-C30 questionnaire
7. Correlation of baseline laboratory values to iAE, tumor progression, other medical condition and survival

3. STUDY DURATION

Patient recruiting started 28.6.2017, and the last visit of the last study patient is estimated to happen in December 2019. The enrolment period is estimated to be 12 months. The study will consist a treatment phase, and a post-treatment period (up to 12months). Survival data will also be collected. The collection of the survival data of a patient is limited to 12 months from the study entry.

4. PATIENT SELECTION

Study population

Sample size of the study is 40 and study patients are expected to be recruited within 24 months.

Inclusion criteria

1. Written informed consent before any study procedures
2. Advanced cancer
3. Initiation of immune checkpoint inhibitor containing therapy ≤2 weeks from the 1sts infusion
4. Age ≥18
5. Performance status: ECOG 0-3
6. Patient is willing and able to comply with treatment and trial instructions

Exclusion criteria

1. Initiation of immune checkpoint inhibitor therapy >2 weeks prior to written informed 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 or email available

7. STUDY NATURE

Study form

A prospective one-arm multicenter observational study.

Study procedures

See Table 1 at page 5.

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, hight)
- ECOG performance status
- Type of immunological treatment (label, indication, day of the 1st infusion)
- Blood sampling to measure the following (blood cell counts: leucocytes, neutrophils, lymphocytes, thrombocytes; B-haemoglobin, P-creatinine, ALT, ALP, AST, bilirubin, P-LD, P-CRP)
- Prior autoimmune disease and their treatment
- KaikuHealth immunological treatment side-effects questionnaire and KaikuHealth QLQ-C30 questionnaire filled ≤ 2weeks from 1st infusion

Treatment period

Study treatment period lasts the treatment phase of immune checkpoint inhibitor or up to 24 weeks.

The parameters listed below are collected during the treatment phase:

- KaikuHealth immunological treatment side-effects questionnaire ≤2 weeks from the 1st infusion and weekly after that
    - Questionnaireof 17 questions assessing symptoms and their severeness
- KaikuHealth QLQ-C30 questionnaire ≤ 2weeks from the 1st infusion and every four weeks after that
- Kaiku patient experience questionnaire monthly
- KaikuHealth follow-up information in 6-12 weeks cycle
    - Urgency algorithm alerts (grade, date, cause of the alert)
    - irAE (type, date, related urgency alert if present)
    - Treatment of irAE (type, date)
    - Unscheduled health care contacts (ER, oncology department, appointments and phone calls, reason, date)
    - Treatment response (CR, PR, SD, PD, NE, date)
    - Date of death

Follow-up period

During follow-up period patient survival data will be collected from healthcare patient records or other electronical sources.

8. STUDY INSTRUMENTS

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 immunological treatment side-effects questionnaire

KaikuHealth ePRO follow-up module consists of 17 symptom questionnaire which will assess both presence and severity of the symptom. The symptoms selected for the Kaiku Health symptom tracking tool for cancer immunotherapy are based on the most common adverse events that have occurred during clinical trials of anti-PD1, anti-PDL1 and anti-CTLA4 immune checkpoint inhibitor monotherapies. The symptoms tracked by the instrument are potential signs and symptoms of immune-related adverse events. The symptom selection is based on the reported publications of following clinical trials: CheckMate 017, CheckMate 026, CheckMate 057, CheckMate 066, CheckMate 067, KEYNOTE-010, and OAK. FDA labels for Nivolumab, Pembrolizumab and Atezolizumab were also used in the symptom selection for the instrument. 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.

9. MONITORING

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

10. STATISTICAL PLAN

Power assessment

Due to the study nature (one-arm study) statistical plans are not calculated. Approximately 15% of patients receiving immune checkpoint inhibitor therapies have been reported to have severe grade 3-4 side-effects, and about 30% face lower grade adverse events. In a patient cohort of 40, three to six patients will experience a severe iAE. It is estimated that the expected study population is sufficient to evaluate the feasibility of the symptom questionnaire in detecting severe adverse events, and directing patients to further investigations. Questionnaires from several timepoints are estimated to be collected from 90% of study population (~35 patients) which will

enable a more comprehensive assessment of feasibility, patient experience and correlation of ePRO changes to treatment response and survival.

Data analysis

Data analysis will be carried out when the length of follow-up time of the last recruited patient is at least 12 weeks. For the final analysis statistical methods will be redefined based on actual distributions.

Safety assessment

The frequency of iAE not leading to Kaiku urgency alerts is the most important study related serious adverse event.

11. SIGNATURE

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

Principal investigator and sponsor:

Date

Oulu, 11.2.2019

Signature

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Jussi Koivunen, adjuvant professor, medical oncologist

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12. REFERENCES

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