

Original Paper

# Follow-Up of Cancer Patients Receiving Anti-PD-(L)1 Therapy Using an Electronic Patient-Reported Outcomes Tool (KISS): Prospective Feasibility Cohort Study

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## Abstract

**Background:** Immune checkpoint inhibitors (ICIs) have become a standard of care for various tumor types. Their unique spectrum of side effects demands continuous and long-lasting assessment of symptoms. Electronic patient-reported outcome (ePRO) follow-up has been shown to improve survival and quality of life of cancer patients treated with chemotherapy.

**Objective:** This study aimed to investigate whether ePRO follow-up of cancer patients treated with ICIs is feasible. The study analyzed (1) the variety of patient reported symptoms, (2) etiology of alerts, (3) symptom correlations, and (4) patient compliance.

**Methods:** In this prospective, one-arm, multi-institutional study, we recruited adult cancer patients whose advanced cancer was treated with anti-programmed cell death protein 1 (PD)- ligand (L)1 agents in outpatient settings. The ePRO tool consisted of a weekly questionnaire evaluating the presence of typical side effects, with an algorithm assessing the severity of the symptom according to National Cancer Institute Common Terminology Criteria for Adverse Events and an urgency algorithm sending alerts to the care team. A patient experience survey was conducted monthly. The patients were followed up to 6 months or until disease progression.

**Results:** A total of 889 symptom questionnaires was completed by 37 patients (lung cancer, n=15; melanoma, n=9; genitourinary cancer, n=9; head and neck cancer, n=4). Patients showed good adherence to ePRO follow-up. The most common grade 1 symptoms were fatigue (28%) and itching (13%), grade 2 symptoms were loss of appetite (12%) and nausea (12%), and grade 3-4 symptoms were cough (6%) and loss of appetite (4%). The most common reasons for alerts were loss of appetite and shortness of breath. In the treatment benefit analysis, positive correlations were seen between clinical benefit and itching as well as progressive disease and chest pain.

**Conclusions:** According to the results, ePRO follow-up of cancer patients receiving ICIs is feasible. ePROs capture a wide range of symptoms. Some symptoms correlate to treatment benefit, suggesting that individual prediction models could be generated.

**Trial Registration:** Clinical Trials Register, NCT3928938; <https://clinicaltrials.gov/ct2/show/NCT03928938>

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**KEYWORDS**

ePRO; immune checkpoint inhibitors; symptoms; side-effects; anti-PD-(L)1 therapy

## Introduction

Cancer patients experience a variety of symptoms derived from the malignancy itself as well as side effects of the given treatment. Many symptoms are left unnoticed due to factors such as limited symptom follow-up between prescheduled health care visits, nonsystematic evaluation of symptoms, and inadequate communication [1-7]. In general, worsening of symptoms indicates cancer progression or severe side effects of the treatment and is linked to poorer cancer survival [8].

Patient-reported outcomes (PROs) consist of health-related questionnaires completed by the patients themselves, which can capture symptoms and signs and their severity. Web-based reporting of PROs has many advantages compared to paper questionnaires such as reducing time to complete and overcoming geographic location limitations. Scheduled electronic patient-reported outcomes (ePROs) enable timely and continuous collection of symptoms in a cost-effective manner [9-14]. Furthermore, use of ePROs in cancer patient monitoring has shown impressive improvements in overall survival compared to standard follow-up [15,16]. In addition, ePROs can be coupled to an urgency algorithm, which sends an alert to the care unit upon report of severe or altering symptoms by a patient. This enables rapid reaction to and treatment of important medical events.

In the past 5 years, there has been significant advancement in the development of cancer immunotherapies with the introduction of immune checkpoint inhibitor (ICI) therapies such as anti-PD-(L)1 and anti-T-lymphocyte-associated protein 4 (CTLA-4) antibodies [17]. ICI therapies have become the most important medical therapies in many malignancies such as melanoma, non-small cell lung cancer, and urogenital cancers [18-27]. ICIs differ from traditional cancer therapies due to potentially severe side effects in all organs of the body and late timing of side effect occurrence [27-29]. Therefore, there is a need for comprehensive and ongoing assessment of symptoms.

Approximately 15% of patients receiving ICI monotherapies reportedly have severe grade 3-4 side effects, and about 30% have lower grade adverse events (AEs). Even life-threatening side effects can occur, but they can, in most cases, be managed with early detection, by delaying or stopping the ICI therapy, and with the initiation of immunosuppressive medication [30-32].

To our knowledge, this is the first prospective trial investigating ePROs in the follow-up of cancer patients receiving ICIs. The study aim was to investigate the feasibility of ePRO symptom follow-up and to analyze the spectrum of patient-reported symptoms, number and aetiology of urgency algorithm alerts, correlations between different symptoms and treatment benefit, and patient compliance.

## Methods

### Study Design and Participants

KISS was an investigator-initiated, multicenter, prospective, one-arm study, which was undertaken in 3 multidisease cancer centers in Finland. Patients were recruited during routine

doctors' appointments at study centers by study doctors. The inclusion criteria included advanced cancer to be treated with anti-PD-(L)1 in outpatient settings, initiation of anti-PD-(L)1 therapy had occurred  $\leq 2$  weeks prior to study recruitment, age  $\geq 18$  years, Eastern Cooperative Oncology Group  $\leq 3$ , and availability of internet access and email. Baseline information such as basic laboratory values, age, and gender were collected from electronic health care records. After providing written informed consent, study patients received a short (5-15 minutes) instruction on how to use the Kaiku software by a study physician. At the initiation of the treatment phase (within 0-2 weeks from the first anti-PD-(L)1 infusion) and weekly thereafter until treatment discontinuation or 6 months of follow-up, patients received an email notification to complete the baseline electronic symptom questionnaire of 17 questions. If a weekly symptom questionnaire was not completed on the day of email receipt, daily email reminders were sent for 6 days. In addition, patients were asked to fill in a monthly electronic patient experience survey until treatment discontinuation or 6 months of follow-up. The use of the ePRO tool was free of charge for the patients and study centers. Online technical support by Kaiku Health for the users was available from 8 am to 4 pm Monday to Friday. The investigators evaluated the treatment response according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria at 8-10 weeks after treatment initiation. Clinical benefit rate was selected as a benefit measure instead of objective response rate since (1) we had a small number of study subjects, (2) responses were analyzed only up to 12 weeks from inclusion, and (3) the correlation between clinical benefit and objective response rate is not as clearly defined with immunotherapies as with traditional cancer medications.

According to the protocol, study results were analyzed when the last included patient had 12 weeks of follow-up. The major endpoints of the study included (1) patient-reported symptoms and their severity; (2) number of triggered alerts by the ePRO tool and their correlation to treatment side effects, cancer progression, other medical events, or survival; (3) correlations between different symptoms and treatment side effects, cancer progression, other medical events, or survival; and (4) patient compliance using the patient experience survey and response rates to symptom questionnaires. Sample size was based on the estimation that 15% of patients receiving ICI monotherapies will experience severe (grade 3-4) side effects and about 30% will experience lower grade AE. In a 40-patient cohort, 3-6 patients will experience a severe immune-related AE. It was estimated that the expected study population is sufficient to evaluate the feasibility of the symptom questionnaire in detecting severe AEs. Questionnaires from several timepoints were estimated to be collected from 90% of the study population (~35 patients), which would enable a more comprehensive assessment of feasibility, patient experience, and correlation of ePRO changes to treatment response and survival.

All data collection was carried out according to national legislation and under permit from the medical director of each research center. The study was approved by the Pohjois-Pohjanmaan sairaanhoitopiiri (PPSHP) ethics committee (number 9/2017), Valvira (number 361), and Oulu University

Hospital Ethics Committee (9/2017). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

### ePRO Follow-Up

The Kaiku Health ePRO tool is a web-based solution scaled to be used easily on smartphones and home computers. The Kaiku Health immune-oncology module designed for the study consists of 17 questions. The symptoms selected for the Kaiku Health symptom tracking tool for cancer immunotherapy are based on the most common AEs that have occurred during clinical trials of anti-PD-1, anti-PD-L1, and anti-CTLA-4 monotherapies. The symptoms tracked by the instrument are potential signs and symptoms of immune-related AEs. The symptom selection was based on publications from the following clinical trials: CheckMate 017 (NCT01642004), CheckMate 026 (NCT02041533), CheckMate 057 (NCT01673867), CheckMate 066 (NCT01721772), CheckMate 067 (NCT01844505), KEYNOTE-010 (NCT01905657), and OAK (NCT02008227). Food and Drug Administration 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 the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) register by converting the description of a grading into patient-friendly language. Any criterion that would be impossible for patients to report has been excluded from the available questions. Developing the symptom questionnaire in this manner enabled self-reporting by patients and development of an algorithm that provides an assessment and approximation of the severity of each symptom according to NCI-CTCAE criteria. NCI-CTCAE grades the symptoms from 0 to 4: no (0), mild (1), moderate (2), severe (3), and life-threatening (4).

Questions assess the presence of blood in stool, blood in urine, blurred vision, chest pain, cough, loss of appetite, diarrhea, dizziness, fatigue, fever, headache, itching, nausea, pain in joints, rash, shortness of breath, stomach pain, and vomiting. Besides recording the presence of a symptom, a severity

algorithm that grades the symptom according to NCI-CTCAE was applied. The severity algorithm triggered an email alert to the study physician of the care unit based on preset limits (presence of a grade 3 or higher symptom or increase in symptom severity from grade 0 to 2). The patients were informed that the care unit would react to the alerts promptly within 3 days; thus, the ePRO follow-up was intended only for nonurgent communication, and in urgent matters, patients were advised to contact emergency care.

### Patient Experience Survey

Study participants were requested to reply to a monthly patient experience survey. The patient experience survey consisted of 6 yes/no or multiple-choice questions. The survey was developed by the investigators for the study and has not been previously validated.

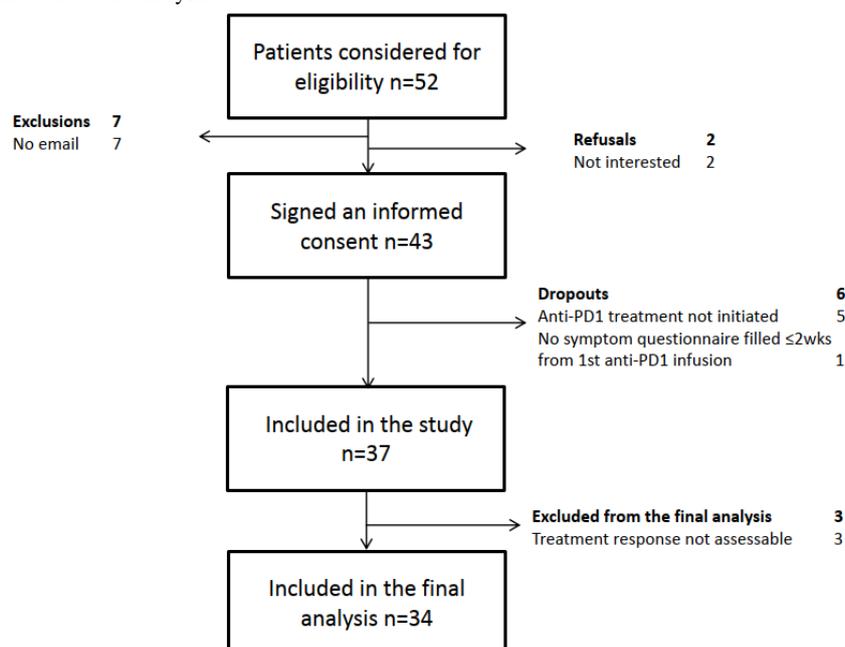
### Statistical Analysis

The analysis was carried out when the last patient included had 12 weeks of follow-up data available. Correlations of different patient-reported symptoms were analyzed using heat maps with Pearson product-moment correlation. In the heat map analysis, the intensity of the color signifies the level of correlation: red, negative correlation; blue, positive correlation. In other words, a large effect correlation was defined as 0.5; medium as 0.3, and small as 0.1 (absolute values).

## Results

### Study Accrual and Patient Characteristics

Patient recruitment took place between June 2017 and March 2019, and the last study patient visit was in June 2019. Anticipated recruitment for the study was 40 patients in 12 months, but due to a slow recruiting pace, the period was extended. Informed consent was provided by 43 patients, and analysis was limited to a total of 37 patients who had anti-PD(L)-1 therapy initiated and answered at least 2 symptom questionnaires (baseline and one following; [Figure 1](#)). No technical issues nor security breaches related to the web-based tool occurred during the study period.

**Figure 1.** Flowchart of patient accrual and analysis.

The median age of the study participants was 62 years (range 32-80 years). The majority of patients were male (27/37, 73%), and 5 patients had a history of an autoimmune disease, with hypothyroidism (4/5, 80%) being the most common. Tumor types

included lung cancer (15/37, 41%), melanoma (9/37, 24%), genitourinary (GU) cancer (9/37, 24%), and head and neck cancer (4/37, 11%), and 28 (28/37, 76%) patients had stage IV disease (Table 1).

**Table 1.** Patient demographics.

Characteristics	Results
Age (years), median	61.7
<b>Gender, n (%)</b>	
Male	27 (73)
Female	10 (27)
<b>Autoimmune disease, n (%)</b>	
Yes	5 (14)
No	32 (87)
<b>Tumor type, n (%)</b>	
Melanoma	9 (24)
Lung cancer	15 (41)
Genitourinary cancer	9 (24)
Head and neck	4 (11)
<b>Stage at diagnosis, n (%)</b>	
Stage III	9 (24)
Stage IV	28 (76)
<b>Eastern Cooperative Oncology Group ( ECOG), n (%)</b>	
0	20 (54)
1	15 (41)
2	2 (5)

### Patient-Reported Symptoms and Alerts

During the study, 889 completed symptom questionnaires were

registered. The range of answered questionnaires was 0.583-1.27 per patient per week, with high response rates throughout the complete follow-up period up to 24 weeks (Table 2).

**Table 2.** Average number of answered symptom questionnaires completed per patient per week, up to 24 weeks.

Week	Number of questionnaires per patient, mean
1	1.27
2	0.882
3	1.14
4	0.861
5	1.06
6	0.833
7	0.833
8	0.861
9	0.765
10	0.842
11	0.882
12	0.748
13	0.991
14	0.824
15	0.742
16	0.707
17	0.704
18	0.719
19	0.733
20	0.826
21	0.83
22	0.611
23	0.583
24	0.798

During the first 12 weeks of ePRO follow-up, the most common grade 1-2 symptoms were fatigue (346/889, 39%), cough (187/889, 21%), pain in joints (160/889, 18%), itching (151/889, 17%), loss of appetite (151/889, 17%), nausea (151/889, 17%),

and shortness of breath (133/889, 15%). The most common grade 3-4 symptoms were cough (53/889, 6%), loss of appetite (36/889, 4%), and nausea (36/889, 4%). None of the patients (0/37) reported blood in stool or hematuria (Table 3).

**Table 3.** Distribution of the severity of the reported symptoms according to all the answered symptom questionnaires (n=889) in weeks 1-12.

Symptom	Grade 0, %	Grade 1, %	Grade 2, %	Grades 3-4, %
Blood in stool	100	0	0	0
Blurred vision	96	0	4	0
Chest pain	94	4	1	1
Cough	74	12	9	6
Diarrhea	96	3	1	0
Dizziness	92	6	2	0
Fatigue	60	28	11	1
Fever	95	5	0	0
Headache	87	10	2	0
Hematuria	100	0	0	0
Itching	83	13	4	1
Loss of appetite	79	5	12	4
Nausea	94	5	12	4
Pain in joints	81	12	6	2
Rash	88	9	1	1
Shortness of breath	83	8	7	2
Stomach pain	94	3	2	1
Vomiting	98	2	0	0

Of the 391 answered symptom questionnaires during the first 12 weeks, the ePRO tool triggered 67 (67/391, 17.1%) alerts. The most common reasons for alerts were loss of appetite, shortness of breath, pain in joints, blurred vision, and cough. The treating physicians were asked to evaluate the etiology of

alerts by grading them to cancer, treatment, or unclear categories. Unclear reasons were the most common cause of alerts (38/67, 57%), followed by treatment (21/67, 31%) and cancer (8/67, 11%; [Table 4](#)).

**Table 4.** Etiology of the symptom questionnaire alerts (n=67).

Characteristics	n (%)
<b>Etiology</b>	
Unclear	38 (57)
Treatment	21 (31)
Cancer	8 (11)
<b>By symptom</b>	
Loss of appetite	32 (48)
Shortness of breath	31 (46)
Pain in joints	21 (31)
Blurred vision	17 (25)
Cough	16 (24)
Fatigue	15 (22)
Itching	12 (18)
Chest pain	9 (13)
Headache	8 (12)
Stomach pain	6 (9)
Rash	6 (9)
Nausea	5 (8)
Diarrhea	3 (5)
Dizziness	3 (5)

### Patient Compliance

Patient compliance was assessed every 4 weeks based on the electronic patient experience survey provided through Kaiku software. During the first 12 weeks, 31 patients replied to the survey, and analysis was limited to these. All the patients replied that using the Kaiku software was easy or very easy, and only

1 of 6 patients reported that they needed assistance using the software. Over 90% of the patients (29/31, 94%) reported that the questions were understandable. In addition, 90% of the patients (28/31, 90%) felt that the Kaiku ePRO follow-up improved their cancer care, and 95% (29/31) said they would recommend using it in the follow-up of cancer patients (Table 5).

**Table 5.** Kaiku Health patient experience survey results during the first 12 weeks of follow-up (n=31).

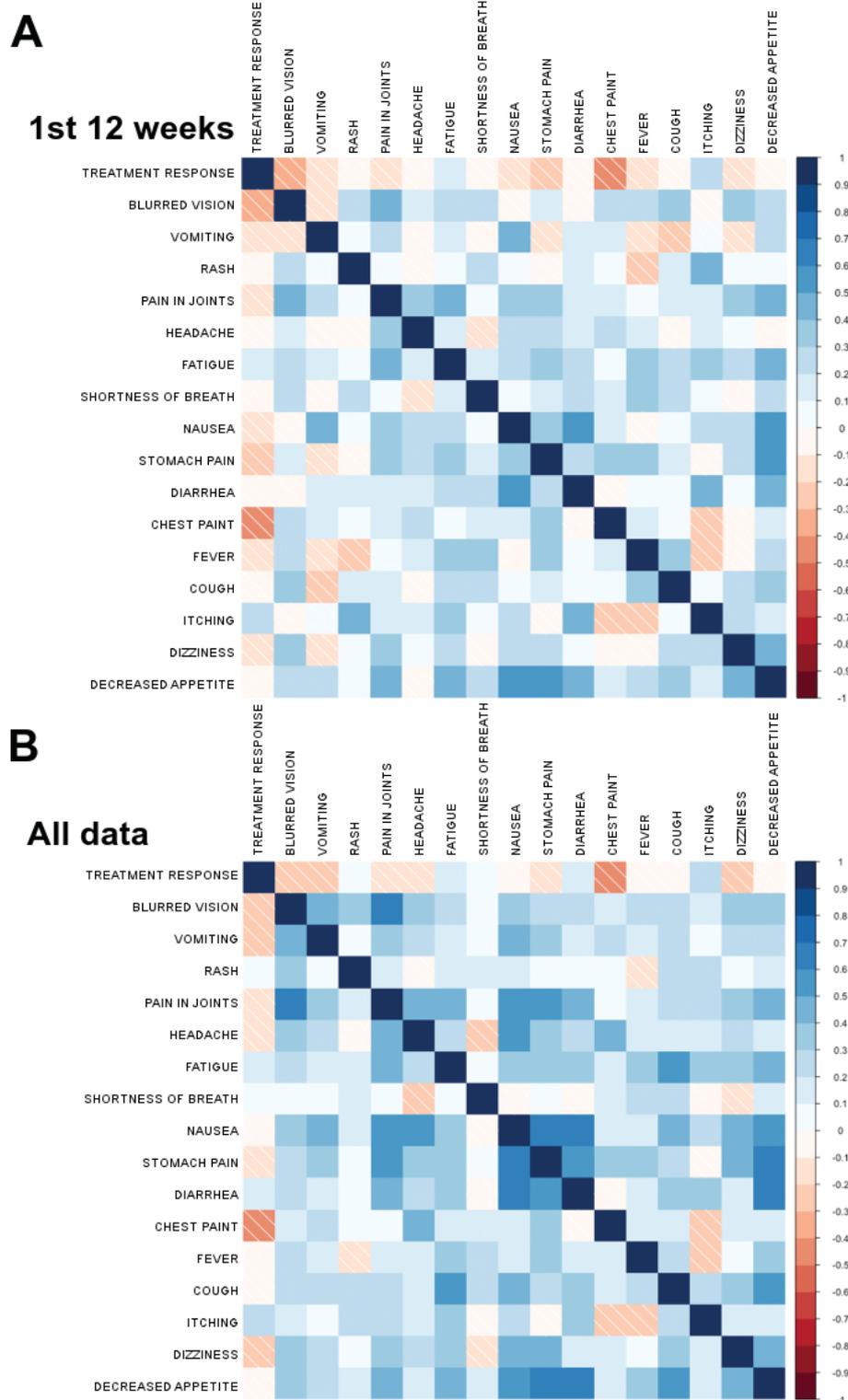
Survey questions	n (%)
<b>How easy or difficult is the use of the Kaiku Health application?</b>	
Very easy	15 (48)
Easy	16 (52)
Difficult	0
Very difficult	0
I cannot say	0
<b>Have you needed the help of another person to use the Kaiku Health application, not taking into account the training that you received at the health care unit?</b>	
Yes	5 (16)
No	26 (84)
<b>Were the questions in the symptom questionnaire in the Kaiku Health application understandable?</b>	
Totally agree	21 (68)
Partly agree	8 (26)
Partly disagree	2 (7)
Totally disagree	0
I cannot say	0
<b>Do you think that the use of the Kaiku Health application will improve the follow-up of your cancer treatment (compared to a situation where the application would not have been used)?</b>	
Yes	28 (90)
No	3 (10)
I cannot say	0
<b>Have you benefited from using the Kaiku Health application?</b>	
Yes	19 (61)
No	1 (3)
I cannot say	11 (36)
<b>Would you recommend the use of the Kaiku Health application in cancer care follow-up?</b>	
Yes	29 (94)
No	0
I cannot say	2 (7)

### Correlations Between Patient-Reported Symptoms and Treatment Benefit

Correlations between ePRO-collected symptoms were analyzed using heat maps. According to the results, the symptom correlations during the first 12 weeks and beyond were very

similar (Figure 2). During the first 12 weeks, large positive correlations were seen between nausea, diarrhea, loss of appetite, and vomiting; stomach pain and decreased appetite; and rash and itching. Only small negative correlations were detected between cough and vomiting, itching and chest pain, and itching and fever (Figure 2A).

**Figure 2.** Correlation analysis between different symptoms and treatment benefit (complete response, partial response, or stable disease as a best response) using heat maps during the (A) first 12 weeks of follow-up and (B) entire study. The color intensity signifies the correlation strength (0.5, large effect; 0.3, medium effect; 0.1, small effect): red, negative correlation; blue, positive correlation.



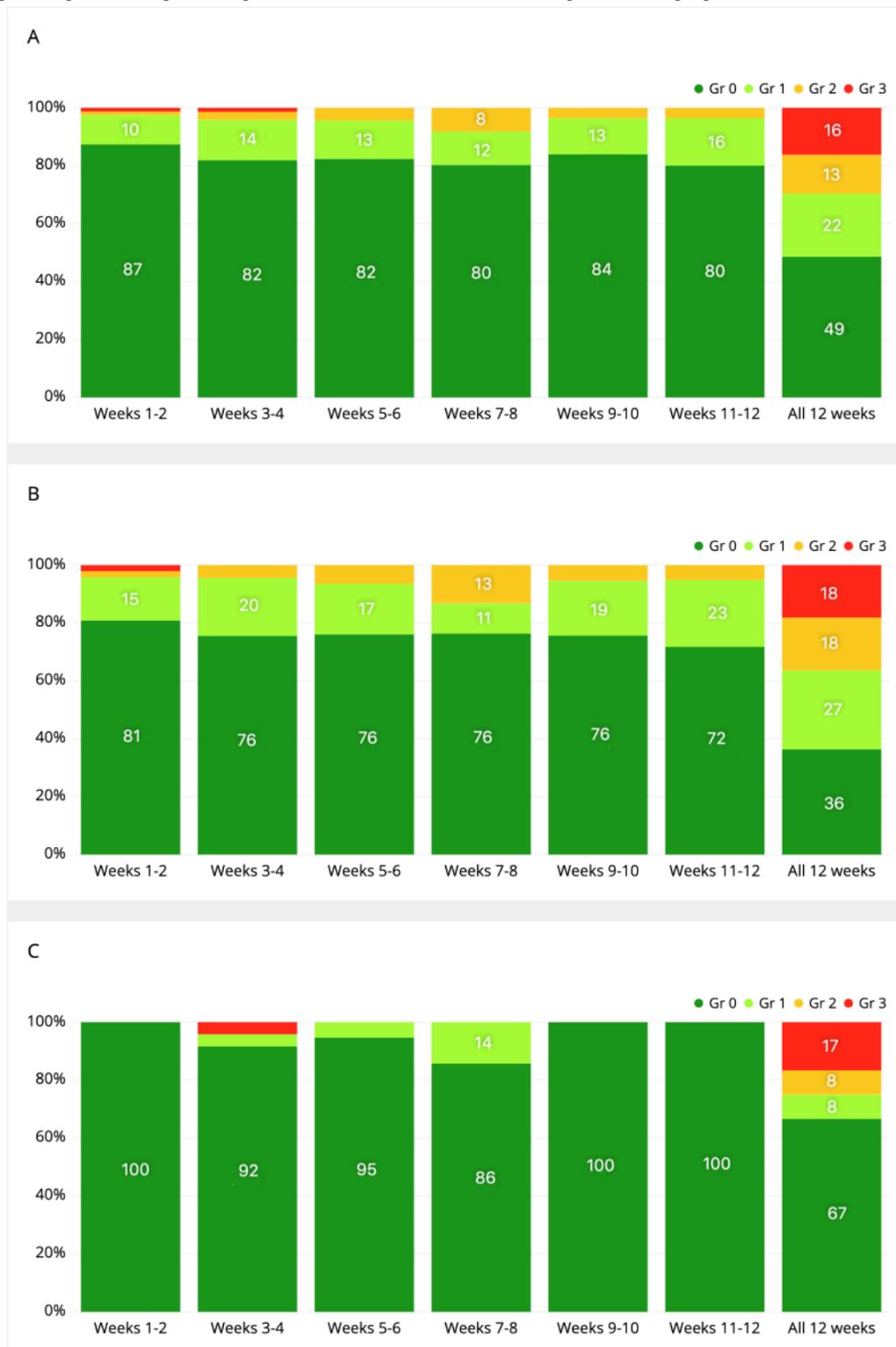
Of the 37 patients, 34 were evaluated for objective treatment response (RECIST 1.1) by the investigators and included in the treatment benefit analysis. Of the 34 patients, 22 (65%) patients had complete response (CR), partial response (PR), or stable disease (SD) as the best response, while 12 (12/34, 35%) patients had progressive disease (PD). The heat map analysis suggested a small positive correlation between clinical benefit (CR/PR/SD)

and itching (0.23 for the first 12 weeks, [Figure 2A](#); 0.25 for all data, [Figure 2B](#)) and medium correlations between PD and chest pain ( $-0.41$  for the first 12 weeks, [Figure 2A](#);  $-0.47$  for all data, [Figure 2B](#)). We further analyzed symptom progression and severity for itching and chest pain. During the first 12 weeks, 15-23% of the patients with clinical benefit reported itching, while the rate was much lower for patients with PD (0-14%;

Figure 3). Furthermore, the average grade was much higher for patients with clinical benefit (weeks 1-12, 0.26-0.37; all 12 weeks, 1.18) compared to patients with PD (weeks 1-12, 0-0.17; all 12 weeks, 0.75; Table 6). For the complete follow-up period, most of the patients with clinical benefit had itching (14/22, 64%), while this was much lower for patients with PD (4/12, 33%; Figure 3). The severity of itching for the patients with clinical benefit was mainly low grade (grade 1: 6/22, 27%; grade

2: 4/22, 18%; Figure 3). During the complete follow-up period, chest pain was much more common in patients with PD (7/12, 58%) than in the patients with clinical benefit (4/22, 18%; Figure 4). In the first 12 weeks, patients with PD had a tendency for gradually increasing average grades for chest pain; conversely, a continuing decrease in the average grade was seen for patients who responded to the therapy (Table 6).

Figure 3. Distribution of the symptom grades reported on the symptom questionnaires during the first 12 weeks for itching for (A) all patients, (B) patients with complete response (CR)/partial response (PR)/stable disease (SD), and (C) patients with progressive disease (PD).



**Table 6.** Average grade of itching and chest pain reported by patients.

Weeks	Itching			Chest pain		
	Entire sample (n=34)	CR <sup>a</sup> /PR <sup>b</sup> /SD <sup>c</sup> (n=22)	PD <sup>d</sup> (n=12)	Entire sample (n=34)	CR/PR/SD (n=22)	PD (n=12)
Weeks 1-2	0.16	0.26	0.00	0.06	0.09	0.04
Weeks 3-4	0.24	0.29	0.17	0.11	0.11	0.13
Weeks 5-6	0.22	0.30	0.05	0.06	0.04	0.11
Weeks 7-8	0.28	0.37	0.14	0.13	0.03	0.33
Weeks 9-10	0.20	0.30	0.00	0.07	0.00	0.22
Weeks 11-12	0.24	0.33	0.00	0.15	0.03	0.44
All 12 weeks	0.97	1.18	0.75	0.62	0.32	1.33

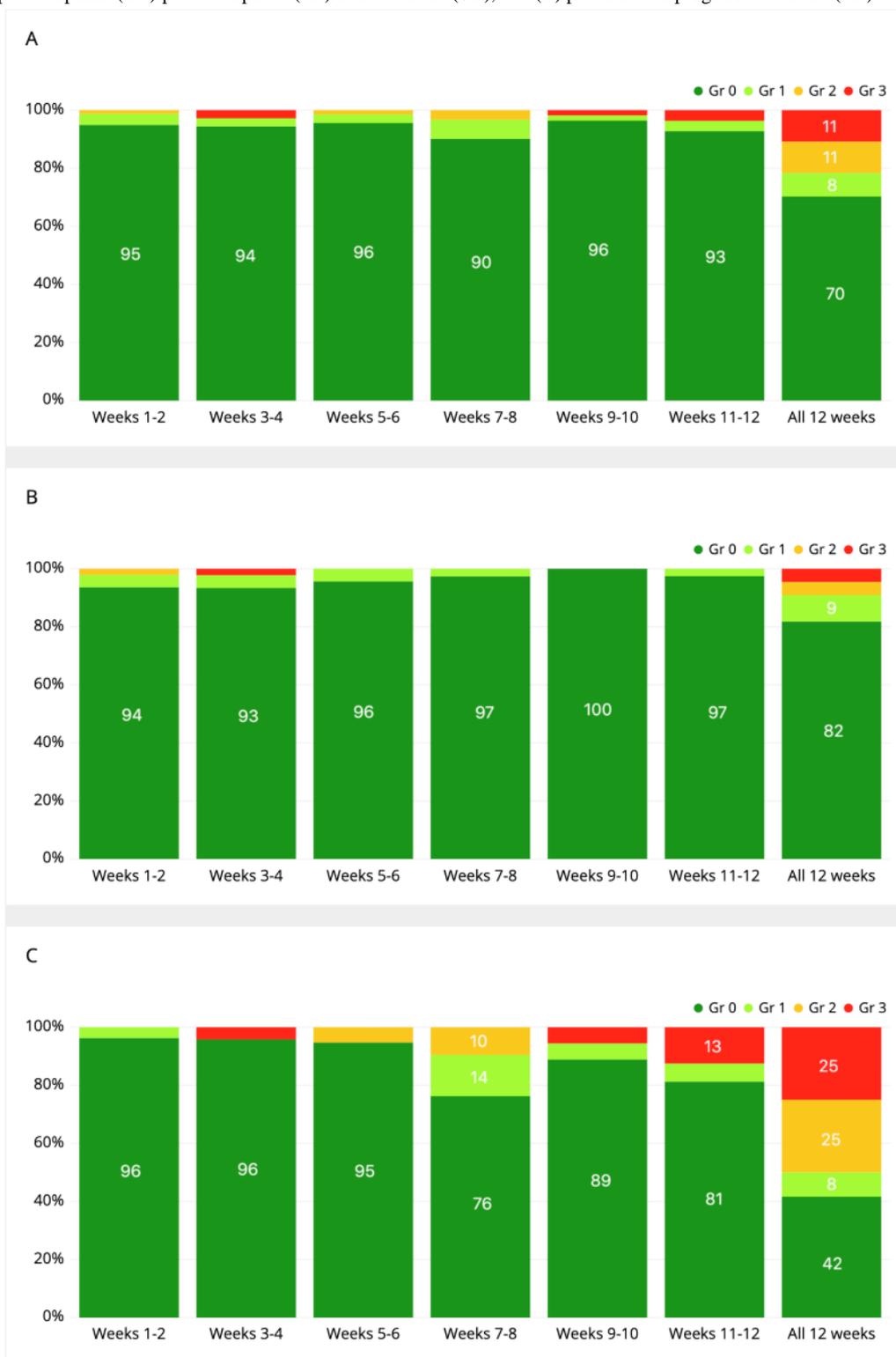
<sup>a</sup>CR: complete response.

<sup>b</sup>PR: partial response.

<sup>c</sup>SD: stable disease.

<sup>d</sup>PD: progressive disease.

**Figure 4.** Distribution of the symptom grades reported on the symptom questionnaires during the first 12 weeks for chest pain for (A) all patients, (B) patients with complete response (CR)/partial response (PR)/stable disease (SD), and (C) patients with progressive disease (PD).



## Discussion

According to previous studies, ePRO follow-up has improved survival and quality of life compared to routine surveillance when used with cancer patients receiving chemotherapy and lung cancer patients treated with curative intention [15,16]. However, the ePRO approach remains virtually unstudied in the context of cancer immunotherapies [33]. For optimal

follow-up of patients receiving ICIs, there is a need for comprehensive assessment, grading, and long-term surveillance of symptoms. ePROs could provide a cost-effective follow-up tool to meet these 3 requirements. We previously reported a retrospective pilot study of ePRO follow-up of cancer patients treated with ICIs [34]. To our knowledge, this study is the first prospective clinical trial investigating ePRO follow-up of cancer patients treated with anti-PD-(L)1 therapies.

In this study, we used an ePRO module with 17 questions and an algorithm grading the PROs according to NCI-CTCAE. The questionnaire was designed specifically for patients receiving ICIs based on the published side effect profile of these agents. The symptom variety based on patient reporting and the grading algorithm performed well, and the symptom data followed closely what has been reported in clinical trials investigating ICIs. A recent meta-analysis with more than 20,000 patients suggested that fatigue (18%), itching (11%), and diarrhea (9%) are the most common AEs reported in patients treated with anti-PD-(L)1 agents [35]. The incidence of AEs in clinical trials are generally lower than in our study, which might be related to better capture of patient-reported low-grade symptoms, which are often overlooked in physician-based AE reporting in clinical trials [36-42].

In the present study, the symptom questionnaire was also coupled to an urgency algorithm, which generated alerts in 17% of the answered questionnaires during the first 12 weeks. Loss of appetite and fatigue were among the most common symptoms generating alerts. These symptoms very rarely alter the cancer treatment, and symptomatic treatments are scarce. Furthermore, physicians determined that most of the alerts were caused by unclear reasons, which is probably related to the high frequency of symptoms with unclear etiology. Fine-tuning of the alerts to focus not only on the symptom grade but also the nature of the symptom could lower the number of alerts and staff workload without sacrificing the performance of ePROs.

Patient adherence to and experience with ePRO follow-up was found to be very good in this study. The patients were requested by email to complete symptom questionnaires weekly, and the number of completed questionnaires was very close to one per patient per week for the first 12 weeks. Based on the patient experience surveys, the system was easy to use, and patients felt that ePRO follow-up improved their cancer care, which is in line with previous studies [40,41].

Our previous retrospective study with patients treated with ICIs suggested that some ePRO-reported dermatological, gastrointestinal (GI), and pulmonary symptoms co-occur [34]. Similarly, we saw large positive correlations between treatment response and GI symptoms as well as between treatment response and dermatological symptoms. Furthermore, the data showed small negative correlations between pulmonary symptoms and some GI symptoms and between itching, pulmonary symptoms, and fever. In our previous retrospective study, which did not include data on the treatment responses,

we generated a hypothesis that GI and skin symptoms might be related to immune activation and treatment benefit, while pulmonary symptoms could signal tumor progression. Since this study also included data on treatment benefit, it enabled us to investigate our hypothesis. The results showed that there was a small positive correlation between treatment benefit (CR/PR/SD) and itching (ePRO) and between PD and chest pain (ePRO). Previous studies have linked autoimmune skin toxicity (rash) to PD-1 agent benefit [43-45]. Our results are hypothesis-generating while suggesting that ePRO-collected symptom data can mimic physician-assessed symptoms and correlate with treatment benefit. Furthermore, compared to physician-based AE reporting, it is possible that ePROs enable enhanced capturing of low-grade AEs without visible presentation such as itching and therefore facilitate predicting clinical treatment benefit.

ePROs enable cost-effective capture of symptoms and their change over long periods [46]. Changes over time might better predict treatment side effects and benefit than just a single presentation of a symptom. Furthermore, data from this study showed that early (in the first 12 weeks) changes in symptoms correlate with treatment benefit as well as symptoms from the whole follow-up period. This further highlights the possibility that early changes in symptoms predict outcomes. Large-scale symptom data coupled with treatment benefit and side effects could be used to build prediction models using artificial intelligence methods. These models could predict an individual's risk for symptom development, treatment-related side effects, and treatment benefit.

Our study has some limitations. The sample size is small (n=37); however, the size is typical for feasibility studies. The small sample size prevents us from making strong generalizations based on the data. The one-arm design of the study precludes comparison of the effectiveness of the intervention. However, we feel that our study is important since it lays the groundwork for future studies on the topic.

In conclusion, this study is the first reported prospective clinical trial investigating the use of ePROs in the follow-up of cancer patients treated with ICIs. The results of this study suggest that follow-up of cancer patients using ePROs is feasible, enabling comprehensive capturing of symptoms over long periods with good patient adherence and satisfaction. Moreover, some early patient-reported symptoms were found to correlate with treatment benefit suggesting that individual prediction models for treatment benefit could be generated.

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## Acknowledgments

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## Authors' Contributions

SI and JK contributed to the conception and design of the study; SI, JK, TA, PV, HV, TK, and JE acquired the data; TK and JE analyzed the data; and SI and JK interpreted the data. SI and JK contributed to the writing of the manuscript. All authors read and approved the final manuscript.

## Conflicts of Interest

SI and PV declare that they have no competing interests. TK, JE, and HV are employees of Kaiku Health, and HV owns stock in Kaiku Health. JK and TA are advisors for Kaiku Health.

## Multimedia Appendix 1

CONSORT EHEALTH checklist (V 1.6.1).

[\[PDF File \(Adobe PDF File\), 543 KB-Multimedia Appendix 1\]](#)

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## Abbreviations

**AE:** adverse event

**CTLA-4:** cytotoxic T-lymphocyte-associated protein 4

**CR:** complete response

**ECOG:** Eastern Cooperative Oncology Group

**ePRO:** electronic patient-reported outcome

**GI:** gastrointestinal

**ICI:** immune checkpoint inhibitor

**NCI-CTCAE:** National Cancer Institute Common Terminology Criteria for Adverse Events

**PD:** progressive disease

**PD-(L)1:** protein 1-ligand 1

**PR:** partial response

**PRO:** patient-reported outcome

**RECIST:** Response Evaluation Criteria in Solid Tumors

**SD:** stable disease

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