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Clinical Trial Note

Multicenter, open-label, randomized, controlled study to test the utility of electronic patient-reported outcome monitoring in patients with unresectable advanced cancers or metastatic/recurrent solid tumors

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Abstract

Electronic patient-reported outcome (ePRO) monitoring for patients undergoing cancer chemotherapy may provide qualified and early detection of adverse events or disease-related symptoms, leading to improved patient care. The aim of this study is to examine whether addition of ePRO monitoring to routine medical care contributes to improved overall survival and quality of life of cancer patients undergoing chemotherapy. Patients with unresectable advanced cancers or metastatic/recurrent solid tumors receiving systemic chemotherapy will be randomized to an ePRO monitoring group and a usual care group. The ePRO group will conduct weekly symptom monitoring using an electronic device after study enrollment until the end of the study. Monitoring results will be returned to medical personnel and used as information for patient care. The primary endpoints are overall survival and health related quality of life. The initial target sample size for the study was 1500 patients. However, due to delays in enrollment, the target was readjusted to 500 patients. Enrollment has been completed, and the study is now in the follow-up phase.

Keywords: electronic patient-reported outcomes monitoring; advanced cancers; systemic chemotherapy; randomized controlled study; quality of life; overall survival

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Background

Many solid tumors that develop distant metastasis or are locally unresectable are difficult to cure, and the goals of treatment are to prolong survival, alleviate symptoms, and maintain or improve health related quality of life (HRQoL). Many patients with such tumors experience physical symptoms related to the cancer lesion and psychological issues such as anxiety and depression. Simultaneously, they must endure the harsh reality of continuing treatment while facing adverse effects of the drug or radiation therapy for metastatic solid tumors. The impact of the lesions and the effects of treatment are assessed by healthcare professionals, and appropriate decisions on supportive and palliative care, dose reduction or cessation of drugs, and potential changes in treatment must be made accurately. However, adequate evaluation may not be possible during limited examination times that occur only once every few weeks. Moreover, previous studies have shown that healthcare professionals are not fully capturing the patients' self-perceived physical symptoms and psychological issues, leading to a phenomenon known as "under-reporting" [1–3].

To overcome this situation, there have been efforts in routine clinical practice to use patient-reported outcomes (PROs) and strive for improved health outcomes [4–6]. These studies have suggested benefits of incorporating PRO assessments into routine clinical practice, including improved patient satisfaction, enhanced patient-physician communication, early detection of serious adverse events, and improved outcomes. However, there are limitations in implementing traditional paper-pencil type PRO assessments in routine clinical practice, including time and resource constraints, recall bias and limited real-time monitoring [7]. To overcome these limitations, electronic PRO (ePRO) monitoring systems offer several advantages, including convenient and timely data collection through electronic devices, which allows patients to report symptoms in real-time and with reduced recall bias [7]. The reported data can also be automatically recorded, stored and analyzed, improving accuracy and completeness. Additionally, ePRO monitoring systems facilitate remote monitoring and enhance patient-provider communication, enabling healthcare providers to intervene promptly when needed and provide personalized care.

Several randomized trials have been conducted to evaluate the effectiveness of ePRO monitoring in cancer care [8]. These trials have found that ePRO monitoring can enhance patient satisfaction, improve healthcare provider-patient communication, and maintain or improve HRQoL. Furthermore, in recent years, randomized controlled trials (RCTs) of the effectiveness of ePRO monitoring in cancer patients undergoing chemotherapy have suggested the potential for extending overall survival (OS) [9–11]. These findings demonstrate the value of ePRO monitoring in improving patient outcomes and guiding clinical decision-making. However, the healthcare infrastructure varies significantly across regions, cultures, and countries. In Japan, the implementation of ePRO monitoring in cancer care has not been thoroughly investigated to determine its potential impact on improving patients' health outcomes. Therefore, the objective of this study is to examine the hypothesis that adding ePRO monitoring to routine care for patients with unresectable advanced cancers or metastatic/recurrent solid tumors receiving systemic drug therapy may be beneficial in extending OS and maintaining or improving HRQoL.

Methods/design

The aim of this study is to test the hypothesis that ePRO monitoring added to usual care helps to prolong OS and maintain or improve QOL in patients with unresectable advanced cancers or metastatic/recurrent solid tumors who are receiving systemic drug therapy.

Study design

This study is a multicenter, open-label, randomized controlled study. After written consent, subjects will be randomly assigned 1:1 to the ePRO monitoring group and the usual care group. The ePRO monitoring group will report symptoms once a week using a smartphone or tablet app, while the usual care group will undergo routine practice. Outcomes will be compared between the two groups. Research schema is shown in Fig. 1. This study is referred to as the PROMOTE Study. The study is registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN ID: 000042447) and ClinicalTrials.gov (NCT: 05931445).

Patients

Patients who meet all of the inclusion criteria and none of the exclusion criteria are potential subjects of the study. The key inclusion criteria are (i) an unresectable advanced/metastatic/recurrent solid tumor (breast cancer, lung cancer, gastric cancer, colorectal cancer, head and neck squamous cell carcinoma, liver cancer, cancer of the uterine body, and ovarian cancer), (ii) an expectation of treatment or observation at the study site for at least 6 months after enrollment, (iii) an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to2, (iv) systemic anticancer drug therapy (e.g. cytotoxic anticancer drugs, molecularly targeted agents, immune checkpoint inhibitors) with one or multiple drugs (outpatient drug therapy, in principle) at enrollment or scheduled within 1 month after enrollment, (v) able to operate an electronic device (some assistance may be required), (vi) aged 18 years or older at the time of informed consent, and (vii) written informed consent obtained directly from the potential subject. The key exclusion criteria are (i) fourth or subsequent drug therapy for an advanced/metastatic/recurrent solid tumor, (ii) participating in another study in which a PRO is used and results are sent back to healthcare providers, (iii) ongoing or planned radical radiotherapy, (iv) patients with breast cancer scheduled for or undergoing endocrine therapy or first-line anti-human epidermal growth factor receptor 2 (HER2) therapy, and (v) patients with liver cancer with Child-Pugh B/C liver function.

Randomization

Randomization will be performed centrally through an electronic data capture (EDC) system. For randomization, the EDC system utilizes a list of random numbers generated by the allocation manager at the data center using the Mersenne Twister algorithm. Since randomization is performed automatically in the EDC system immediately after patient enrollment, there is no opportunity for human intervention in the randomization process. The EDC system used in the study was developed in-house at the data center and is not a commercial product.

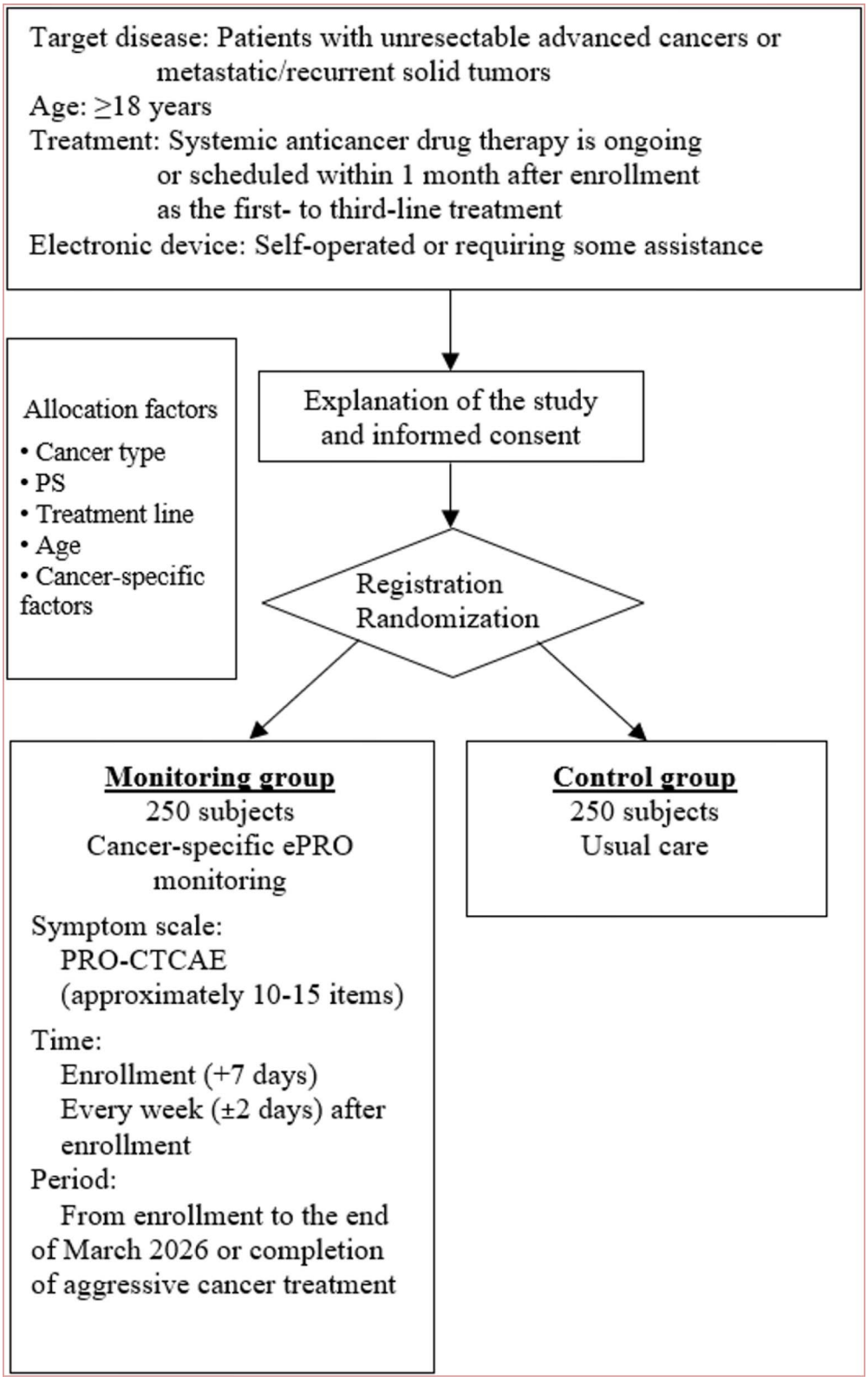

Figure 1. Research schema. Study subjects will be randomly assigned in a 1:1 ratio to an ePRO monitoring group and a control group that will receive routine care. In the ePRO monitoring group, patients will be monitored weekly using an electronic device for 10–15 symptoms extracted from the PRO-CTCAE.

During randomization, the subjects will first be stratified by cancer type (breast cancer vs. lung cancer vs. gastric cancer vs. colorectal cancer vs. head and neck squamous cell carcinoma vs. liver cancer vs. cancer of the uterine body vs. ovarian cancer). A minimization method using the following allocation factors will be performed in each stratum: (i) ECOG PS: 0 vs. 1 vs. 2, (ii) treatment line (ongoing or planned at enrollment): first-line vs. second-line vs. third-line treatment,

Table 1. Cancer-specific allocation factors.

Cancer type		Factor	Category
Breast cancer		Expression of estrogen receptor	Positive vs negative
		HER2	Positive vs negative
Lung Cancer		Lung cancer type	Driver mutation[a] translocation-positive non-small cell lung cancer vs driver mutation translocation-negative or -unknown non-small cell lung cancer vs small cell lung cancer.
Gastric cancer		HER2	Positive vs negative vs unknown
		MSI-H/MSS	MSI-H vs MSS vs unknown
Colorectal cancer		RAS mutation	Present vs absent vs unknown
		BRAF mutation	Present vs absent vs unknown
		MSI-H/MSS	MSI-H vs MSS vs unknown
Other	Head and neck squamous cell carcinoma	p16 staining (only for oropharyngeal cancer)	Positive vs negative vs unknown (oropharyngeal cancer with unknown p16 staining + non-oropharyngeal cancer)
	Liver cancer	Vascular invasion	Present vs absent
		Extrahepatic metastasis	Present vs absent

[a]Activating EGFR mutation, ALK fusion gene, ROS1 fusion gene, BRAF mutation, or MET skipping mutation. HER2: Human epidermal growth factor receptor 2; EGFR: Epidermal growth factor receptor; ALK: Anaplastic lymphoma kinase; ROS1: ROS proto-oncogene 1, receptor tyrosine kinase; BRAF: V-raf murine sarcoma viral oncogene homolog B; MET: MET proto-oncogene, receptor tyrosine kinase; MSH-H: High level microsatellite instability; MSS: Microsatellite stable; RAS: Ras oncogene.

(iii) age: <60 vs. ≥ 60 years, and (iv) cancer-specific allocation factors, as shown in Table 1.The minimization method used in the present study is not deterministic and includes a random component, the details of which are known only to the allocation manager at the data center and the trial statisticians.

Intervention

After enrollment in the study, the subjects will be provided with an anonymized ID and password. The ePRO monitoring group and usual care group will both download the study-specific app on their own mobile devices or on loaned research tablets. By entering the anonymized ID and password on the app's initial screen, users can gain access to input data. The app used in the ePRO monitoring group, namely "PromoSys", is equipped with a symptom monitoring feature, which allows participants to input their symptoms at registration and every week (± 2 days) until the end of the study. The monitoring scale is the Japanese version of the Patient-Reported Outcome-Common Terminology Criteria for Adverse Events (PRO-CTCAE) [12]. For each cancer type, ePRO monitoring items are extracted from the PRO-CTCAE based on the characteristics of the cancer and drug therapy, as described in Table 2. The PRO-CTCAE utilizes a Likert scale to assess severity, frequency, and interference in daily life (presence/absence or extent). The Likert scale uses five levels (none, mild, moderate, severe, very severe) to evaluate the degree of symptom severity for the past 7 days. Patients select the appropriate level for each symptom-related question based on their own experiences, thereby evaluating the severity of symptoms [13].

Subjects will be requested to respond at the scheduled date and time of the survey through e-mail and reminders. Response data from subjects will be transmitted to the data center and collected in the electronic data capture (EDC) system. The date and time of the response will also be recorded. The investigator or sub-investigator will confirm the response data before a medical examination. ePRO monitoring will be continuously performed throughout the study period until completion of aggressive cancer treatment (all treatments intended to reduce tumor burden, including drug therapy, surgery, and radiotherapy) or at the end of subject follow-up.

The alert threshold is set for each cancer. Any response with high severity in excess of the threshold will be conveyed to the study personnel at the study site through e-mail. Any action to be taken will be determined by the investigator or sub-investigator within 72 h, and the details will be entered into the EDC system. A flowchart of actions after alert notification is shown in Fig. 2.

Outcomes

The primary outcomes of this study are OS and HRQoL. OS is defined as the time from the day of enrollment in the study to the day of all-cause death. HRQoL will be evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) [14]. A comparison will be made based on the global health status score from registration up to the 24th week.

The secondary outcome measures include scores for each domain of the EORTC QLQ-C30, excluding the global health status score, quality-adjusted life year, at-home mortality, time from the end of the last drug therapy to death, unscheduled visits during drug therapy, relative dose intensity of drug therapy, total number of drug therapy regimens, incremental cost-effectiveness ratio, and patient-healthcare provider communication.

Survey

Information for patient demographics (age, sex, height/weight, cancer type, cancer-specific collection items, ECOG PS, and treatment line of drug therapy at enrollment) will be collected at enrollment. The evaluation of HRQoL will be conducted through the app for both groups, using the EORTC QLQ-C30, EuroQol 5-dimensions 5-levels (EQ-5D-5L) [15], and EORTC QLQ-COMU26 [16] as survey instruments. The EORTC QLQ-C30 will be assessed at enrollment (up to $+7$ days) and every 4 weeks (± 2 weeks) up to 24 weeks after the day of enrollment. The EQ-5D-5L will be assessed

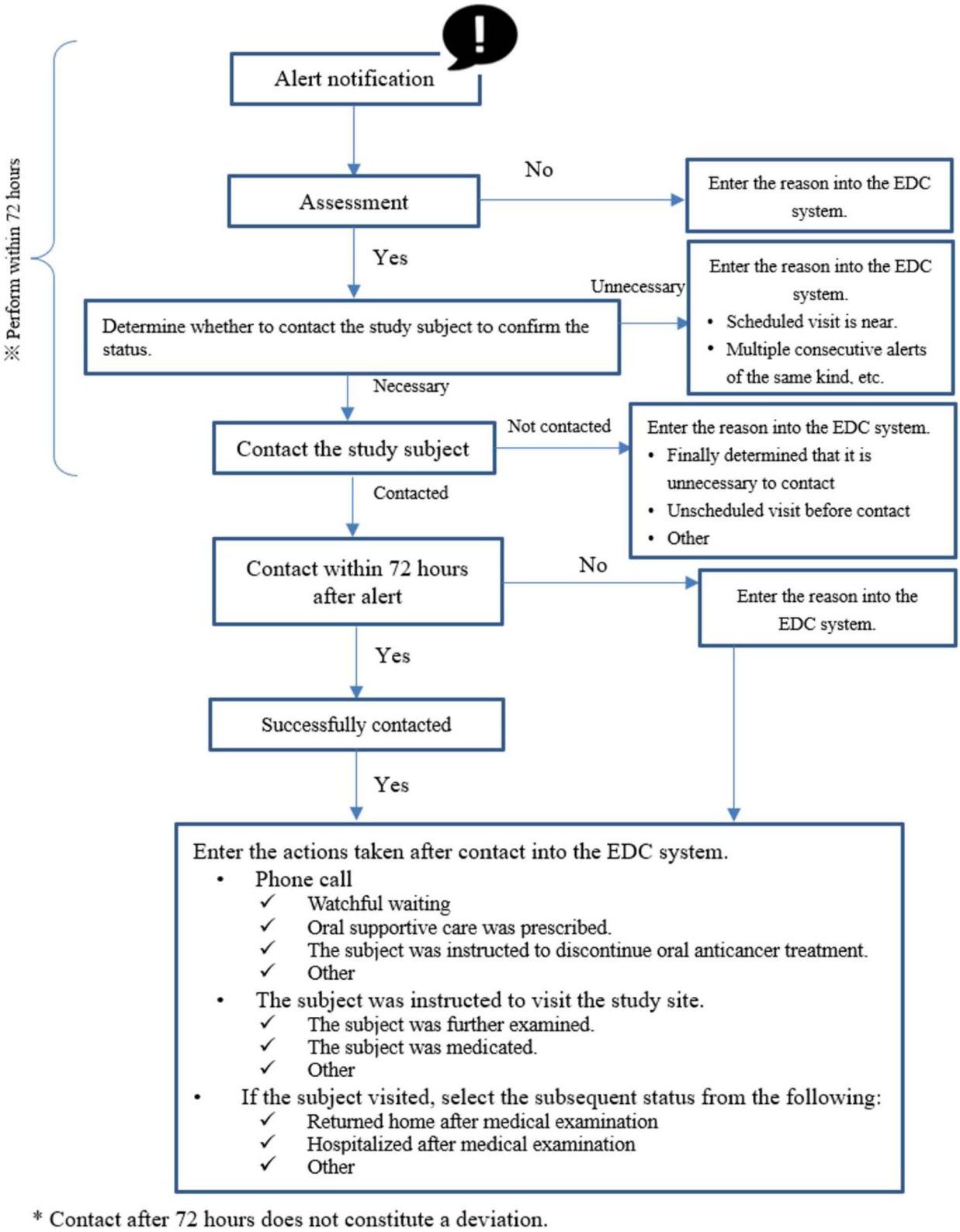

Figure 2. Flowchart of actions after alert notification. The alert threshold is set for each cancer. Any response with high severity in excess of the threshold will be conveyed to the study personnel at the study site through e-mail. Any action to be taken will be determined by the investigator or sub-investigator within 72 h. First, the medical provider determines the necessity of contacting the patient. If it is determined that this is unnecessary, the reason will be entered in the EDC system. If it is determined that contact is necessary, it will be recorded in the EDC whether or not contact was actually made, and if contact was made, the details of the instructions given to the patient will also be recorded.

Table 2. Cancer-specific electronic patient-reported outcome monitoring items.

Monitoring item	Breast cancer	Lung cancer	Gastric cancer	Colorectal cancer	Head and neck squamous cell carcinoma	Liver cancer	Cancer of the uterine body	Ovarian cancer
Abdominal bloating						×		×
Abdominal pain			×	×				
Anorexia	×	×	×	×	×	×	×	×
Anxiety	×						×	×
Atypical genital bleeding							×	
Constipation	×		×	×			×	×
Cough	×	×			×		×	×
Difficulty swallowing food					×			
Dry mouth						×		
Fatigue, tiredness, decreased energy	×	×			×	×	×	×
Hand and foot syndrome	×		×	×		×		
Having diarrhea	×		×	×	×		×	×
Hoarseness					×			
Insomnia	×					×	×	×
Limb numbness or tingling sensation	×							
Muscle pain						×		
Nausea	×		×	×	×		×	×
Pain	×	×	×	×	×		×	×
Rash						×		
Shortness of breath	×	×	×	×	×	×	×	×
Sore mouth and throat			×	×				
Swelling of arms or legs	×					×		
Vomiting	×		×	×	×		×	×
Wheezing		×	×	×	×			

at enrollment (up to +7 days) and every 4 weeks (±2 weeks) after the day of enrollment until death or termination in the study at the discretion of the investigator/sub-investigator. The EORTC QLQ-COMU26 will be assessed at enrollment (up to +7 days) and at 24 weeks (±2 weeks) after the day of enrollment.

An independent data monitoring committee (IDMC) consisting of experts independent of the study will be established. The IDMC will advise study representatives on continuation, suspension, or discontinuation of the study or changes in the study plan by evaluating the progress of the study and important endpoints.

Statistical analysis

In this study, OS and EORTC QLQ-C30 global health status score are both primary outcomes, and the utility of ePRO monitoring will be successfully verified if the between-group difference in at least one primary endpoint is statistically significant. Therefore, an adjustment needs to be made for multiple testing of the two primary endpoints. In addition, an interim analysis with early stopping for efficacy will be performed on OS. Therefore, an adjustment needs to be made for multiple testing for the interim and final analyses. Analysis of the primary endpoint described below is adjusted for multiple testing in a group sequential design using a graphical approach [17,18].

The OS rate and median OS will be estimated using the Kaplan–Meier method. The superiority of the monitoring group will be tested by stratified log-rank test and the hazard ratio for between-group difference and its 95% confidence interval (CI), and the 99% CI will be estimated by stratified Cox regression. Multiple factors are accounted for during randomization, and including all of them in the stratified analysis is not practical. Stratification variables in the stratified log-rank test and stratified Cox regression will be determined before the interim analysis and described in a statistical analysis plan (SAP). The between-group difference in OS will be tested at a two-sided significance level of 5% (one-sided significance level of 2.5%) if there is a statistically significant between-group difference in the EORTC QLQ-C30 global health status score, the other primary outcome described below, or at a two-sided significance level of 1% (one-sided significance level of 0.5%) if there is no statistically significant between-group difference. The rejection region used to determine superiority at the interim and final analyses will be derived from the α-spending function for O'Brien-Fleming type boundaries. The interim analysis will be conducted after the last enrolled patient has completed 24 weeks of follow-up.

For the EORTC QLQ-C30 global health status score, summary statistics of the score at each time point and summary statistics of the change from enrollment at each time point will be calculated. For the primary analysis, a linear mixed-effects model for repeated-measures will be fitted to the changes in score from enrollment at all time points up to 24 weeks to test the superiority of the ePRO monitoring group (two-sided significance level of 4% [one-sided significance level of 2%]) by estimating the between-group difference across all time points and its 95% (and 96%) CI, as well as the between-group difference at each time point and its 95% CI. The explanatory variables in the linear mixed-effects model are generally group, time point, group-by-time point interaction, global health status score at enrollment, and global health status score at enrollment-by-time point interaction. These

will be described in the SAP in more detail. For the secondary analysis, the proportion of subjects with improvement or deterioration of ≥ minimally important difference, as measured by the change from enrollment at each time point and the time to deterioration, will be compared between the groups.

Target sample size

In this study, OS and EORTC QLQ-C30 global health status score are both primary outcomes. Originally, the target sample size was calculated for OS, and the power was calculated for EORTC QLQ-C30 global health status score at the target sample size. With a hazard ratio for OS in the monitoring group versus the control group of 0.8, a median OS of 24 months in the control group, a power of 90%, a two-sided significance level of 4% (one-sided significance level of 2%), and one interim efficacy analysis, a total of 897 events in the two groups are required to demonstrate superiority in the log-rank test. This number is expected to be achieved if a total of 1434 potential subjects are constantly enrolled in the two groups over 30 months and then followed up for 24 months. A target sample size of 1500 subjects is determined to ensure the required power even if ∼5% of subjects are lost to follow-up. In this sample size, assuming that the between-group difference in mean change in global health status score at an arbitrary time point is five points with a standard deviation of 25 points, the power for demonstrating superiority at a two-sided significance level of 1% (one-sided significance level of 0.5%) will exceed 80% even with 20% of missing scores.

However, due to the slow rate of patient enrollment after the start of the study, the sample size was recalculated without viewing any outcome data. This sample size recalculation was not pre-planned before the study began. Although the original sample size was calculated to ensure the power for OS, the current target sample size was recalculated based on the EORTC QLQ-C30 global health status score, and the power for OS was assessed at the current target sample size. The two primary outcomes have not been changed since the study began.

The standard deviation for global health status scores at six time points over 6 months is assumed to be 25 points and the correlation coefficient among the time points to be 0.4. Analysis using a linear mixed-effect model for repeated-measures with a mean change in between-group difference of five points and a two-sided significance level of 4% (one-sided significance level of 2%) suggests that a sample size of 400 subjects can achieve 91% power to detect superiority [19,20]. To ensure 90% power even if data from 20% of the study subjects cannot be used in the analysis because of death or missing data, the target sample size was determined to be 500.

The power to detect superiority for OS, the other primary outcome, is estimated as follows, using the sample size of 500 and the registration and follow-up periods of this study. Assuming that median OS in the control group is 24 months, the two-sided significance level is 5% (one-sided significance level of 2.5%) on the assumption that the between-group difference in global health status score is significant, the interim analysis for efficacy is performed once, and 5% of the subjects are lost to follow-up, the power to detect superiority using a log-rank test is 49%, 70%, and 86% at hazard ratios of 0.8, 0.75, and 0.7, respectively. In randomized controlled studies testing the utility of ePRO monitoring, similar to the present study, the hazard ratios for OS have been reported to be 0.83 (95% CI: 0.70–0.99) and 0.59 (95% CI: 0.39–0.96) [10,11]. Based on these results, the hazard ratio can be estimated to be ∼0.8. The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) ver. 1.1 for therapies that are not likely to be curative with an endpoint of OS requires that, if median OS in the control group is 24 months, the hazard ratios should be ≤0.75 and ≤ 0.7 for clinical benefits of Grade 2 and Grade 3, respectively [21]. For these hazard ratios considered to show clinical benefit, the power is ensured. However, if a significant between-group difference in global health status score is not observed, the OS will be tested at a two-sided significant level of 1%, resulting in a decreased power (below 50% for hazard ratios of 0.8 and 0.75, and 68% for a hazard ratio of 0.7). The actual power for the OS analysis accounting for the result of global health status scores depends on the association between the global health status score and OS, which could not be reliably estimated in advance.

Study period

The registration period for the study is from the date of approval until 31 March 2024. The follow-up period extends until 31 March 2026. The overall study duration will continue until 31 March 2027.

Discussion

Two RCTs in patients with advanced cancer undergoing drug therapy have reported possible extension of OS through use of ePRO monitoring [9–11]. In a RCT reported in 2016 that examined the effectiveness of the Symptom Tracking and Reporting (STAR) system, an ePRO monitoring tool, in patients with solid cancer, the STAR group had significantly better HRQoL [9] and a significantly lower rate of emergency department visits. In a post hoc analysis, the median survival period was 31.2 months in the STAR group and 26.0 months for patients receiving standard care, indicating significantly improved survival in the STAR group [10]. In a larger RCT referred to as PRO-TECT, which utilized the same ePRO monitoring system, there were significant improvements in secondary outcome measures such as physical function, symptom control, and HRQoL [22].

In 2017, a randomized comparative trial was conducted to evaluate the utility of regular ePRO monitoring in patients with advanced lung cancer undergoing drug therapy [11]. The results showed a significant prolongation of OS in the ePRO monitoring group, with median survival of 19 months compared to 12 months in the control group. This could be attributed to several factors. In the ePRO monitoring group, changes in conditions were captured earlier, enabling timely interventions such as treatment modifications and palliative supportive care. Additionally, the ePRO monitoring group was able to address serious comorbidities unrelated to the primary disease, and there was a faster transition to palliative care, suggesting reduced continuation of futile treatment. Based on these findings, the clinical practice guidelines published by the European Society for Medical Oncology strongly recommend use of ePRO monitoring in cancer patients undergoing systemic drug therapy [23]. However, there is still limited evidence of the effectiveness of ePRO monitoring on OS during systemic drug therapy for patients with incurable cancer. This study is one of the few randomized controlled trials that set OS as the primary endpoint, and this

will make the results obtained from this study particularly valuable.

Author contributions

EI, KK, YK, NK, KK, NT, RT, AN, KN, YN, and KH developed and planned this trial and HM is the principle investigator of the study. HI, AG, KS, KM, TI, TS, YT, and TF are the investigative committee of the study, and reviewed the research plan, managed the research progress, and provided advice. TY and YH are the trial statisticians and are responsible for statistical planning and statistical analysis. NT and YH wrote the first draft of the manuscript. All authors commented on versions of the manuscript. All authors read and approved the final manuscript.

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This study will be conducted based on an agreement between the National Institute of Health Sciences (NIPH) and the Public Health Research Foundation (PHRF). Study-related funds required in the cooperative institution will be paid by the PHRF, which is the administrative office.

Competing interests

The authors declare that they have no competing interests.

Declarations

Ethics approval and consent to participate: This study will be performed in line with the principles of the Declaration of Helsinki. This study will be conducted with the approval of the Ethics Review Committee of the lead institution, Kobe University Hospital (Date 2021.3.8/No. A200016), as well as the approval of the Ethics Review Committees of all participating centers.

Consent to participate

Written informed consent will be obtained from all participants in the study.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

References

1. Basch E. The missing voice of patients in drug-safety reporting. *N Engl J Med* 2010;**362**:865–9. https://doi.org/10.1056/NEJMp0911494.
2. Fromme EK, Eilers KM, Mori M, Hsieh YC, Beer TM. How accurate is clinician reporting of chemotherapy adverse efects? A comparison with patient-reported symptoms from the quality-of life questionnaire C30. *J Clin Oncol* 2004;**22**:3485–90. https://doi.org/10.1200/JCO.2004.03.025.
3. Shimozuma K, Ohashi Y, Takeuchi A. *et al.* Feasibility and validity of the patient neurotoxicity questionnaire during taxane chemotherapy in a phase III randomized trial in patients with breast cancer: N-SAS BC 02. *Support Care Cancer* 2009;**17**:1483–91. https://doi.org/10.1007/s00520-009-0613-7.
4. Velikova G, Booth L, Smith AB. *et al.* Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. *J Clin Oncol* 2004;**22**:714–24. https://doi.org/10.1200/JCO.2004.06.078.
5. Detmar SB, Muller MJ, Schornagel JH, Wever LDV, Aaronson NK. Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. *JAMA* 2002;**288**:3027–34. https://doi.org/10.1001/jama.288.23.3027.
6. Greenhalgh J, Meadows K. The effectiveness of the use of patient-based measures of health in routine practice in improving the process and outcomes of patient care: a literature review. *J Eval Clin Pract* 1999;**5**:401–16. https://doi.org/10.1046/j.1365-2753.1999.00209.x.
7. Bannett AV, Jensen RE, Basch E. Electronic patient-reported outcome systems in oncology clinical practice. *CA Cancer J Clin* 2012;**62**:336–47. https://doi.org/10.3322/caac.21150.
8. Lu SC, Porter I, Valderas JM, Harrison CJ, Sidey-Gibbons C. Effectiveness of routine provision of feedback from patient reported outcome measurements for cancer care improvement: a systematic review and meta-analysis. *J Patient Rep Outcomes* 2023;**7**:54. https://doi.org/10.1186/s41687-023-00578-8.
9. Basch E, Deal AM, Kris MG. *et al.* Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. *J Clin Oncol* 2016;**34**:557–65. https://doi.org/10.1200/JCO.2015.63.0830.
10. Basch E, Deal AM, Dueck AC. *et al.* Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. *JAMA* 2017;**318**:197–8. https://doi.org/10.1001/jama.2017.7156.
11. Denis F, Lethrosne C, Pourel N. *et al.* Randomized trial comparing a web-mediated follow-up with routine surveillance in lung cancer patients. *J Natl Cancer Inst* 2017;**109**. https://doi.org/10.1093/jnci/djx029.
12. Miyaji T, Iioka Y, Kuroda Y. *et al.* Japanese translation and linguistic validation of the US National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *J Patient Rep Outcomes* 2017;**1**:8. https://doi.org/10.1186/s41687-017-0012-7.
13. Basch E, Reeve BB, Mitchell SA. *et al.* Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *J Natl Cancer Inst* 2014;**106**:dju244. https://doi.org/10.1093/jnci/dju244.
14. Aaronson NK, Ahmedzai S, Bergman B. *et al.* The European Organization for Research and Treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;**85**:365–76. https://doi.org/10.1093/jnci/85.5.365.
15. Shiroiwa T, Ikeda S, Noto S. *et al.* Comparison of value set based on DCE and/or TTO data: scoring for EQ-5D-5L health states in Japan. *Value Health* 2016;**19**:648–54. https://doi.org/10.1016/j.jval.2016.03.1834.
16. Arraras JI, Wintner LM, Sztankay M. *et al.* EORTC QLQ-COMU26: a questionnaire for the assessment of communication between patients and professionals. Phase III of the module development in ten countries. *Support Care Cancer* 2017;**25**:1485–94. https://doi.org/10.1007/s00520-016-3536-0.
17. Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. *Stat Biopharm Res* 2013;**5**:311–20. https://doi.org/10.1080/19466315.2013.807748.
18. Dmitrienko A, D'Agostino RB. Multiplicity considerations in clinical trials. *N Engl J Med* 2018;**378**:2115–22. https://doi.org/10.1056/NEJMra1709701.
19. Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European organisation for the research and treatment of cancer quality of life questionnaire core 30. *J Clin Oncol* 2011;**29**:89–96. https://doi.org/10.1200/JCO.2010.28.0107.

20. Musoro JZ, Coens C, Sprangers MAG. *et al.* Minimally important differences for interpreting EORTC QLQ-C30 change scores over time: a synthesis across 21 clinical trials involving nine different cancer types. *Eur J Cancer* 2023;**188**:171–82. https://doi.org/10.1016/j.ejca.2023.04.027.
21. Cherny NI, Dafni U, Bogaerts J. *et al.* ESMO-magnitude of clinical benefit scale version 1.1. *Ann Oncol* 2017;**28**:2340–66. https://doi.org/10.1093/annonc/mdx310.
22. Basch E, Schrag D, Henson S. *et al.* Effect of electronic symptom monitoring on patient-reported outcomes among patients with metastatic cancer: a randomized clinical trial. *JAMA* 2022;**327**:2413–22. https://doi.org/10.1001/jama.2022.9265.
23. Di Maio M, Basch E, Denis F. *et al.* The role of patient-reported outcome measures in the continuum of cancer clinical care: ESMO clinical practice guideline. *Ann Oncol* 2022;**33**:878–92. https://doi.org/10.1016/j.annonc.2022.04.007.

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Clinical Trial Note