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ORIGINAL ARTICLE

Significantly longer time to deterioration of quality of life due to CANKADO PRO-React eHealth support in HR+ HER2− metastatic breast cancer patients receiving palbociclib and endocrine therapy: primary outcome analysis of the multicenter randomized AGO-B WSG PreCycle trial

N. Harbeck[1,2*], P. A. Fasching[3], R. Wuerstlein[1,2], T. Degenhardt[1,4], D. Lüftner[5,6], R. E. Kates[2], J. Schumacher[7], P. Räth[7], O. Hoffmann[8], R. Lorenz[9], T. Decker[10], M. Reinisch[11,12], T. Göhler[13], P. Staib[14], O. Gluz[2], T. Schinköthe[15,16] & M. Schmidt[17], on behalf of the AGO-B WSG PreCycle investigators (see Appendix 1)

[1]Breast Center, Department of Obstetrics and Gynecology and CCC Munich LMU, University Hospital, Munich; [2]West German Study Group, Moenchengladbach; [3]University Hospital Erlangen, Obstetrics and Gynecology, Erlangen; [4]Hausarztpraxis Wolfratshausen, Wolfratshausen; [5]Immanuel Hospital Märkische Schweiz, Buckow; [6]Immanuel Hospital Rüdersdorf and Medical University of Brandenburg Theodor Fontane, Neuruppin; [7]palleos healthcare GmbH, Wiesbaden; [8]University Hospital Essen, Breast Center, Essen; [9]Studien GbR Braunschweig, Braunschweig; [10]Hematology/Oncology, Ravensburg; [11]Breast Center, Kliniken Essen-Mitte, Essen; [12]Department of Gynecology with Breast Center, Charité—Universitätsmedizin Berlin, Berlin; [13]Oncocenter Dresden, Dresden; [14]St.-Antonius Hospital gGmbH, Clinic for Hematology and Oncology, Eschweiler; [15]CANKADO Service GmbH, Kirchheim; [16]Research Center Smart Digital Health, University of the Bundeswehr, Neubiberg; [17]Department of Obstetrics and Gynecology, University Medical Center of the Johannes Gutenberg-University, Mainz, Germany

Available online 16 May 2023

Background: The multicenter, randomized, phase IV, intergroup AGO-B WSG PreCycle trial (NCT03220178) evaluated the impact of CANKADO-based electronic patient-reported outcome (ePRO) assessment on quality of life (QoL) in hormone receptor-positive, human epidermal growth factor receptor 2-negative locally advanced or metastatic breast cancer (MBC) patients receiving palbociclib and an aromatase inhibitor or palbociclib + fulvestrant. CANKADO PRO-React, a European Union-registered medical device, is an interactive autonomous application reacting to patient self-reported observations.

Patients and methods: Between 2017 and 2021, 499 patients (median age 59 years) from 71 centers were randomized (2 : 1, stratified by therapy line) between an active version of CANKADO PRO-React (CANKADO-active arm) and a version with limited functionality (CANKADO-inform arm). A total of 412 patients (271 CANKADO-active; 141 CANKADO-inform) were available for analysis of the primary endpoint, time to deterioration (TTD) of QoL [10-point drop on the Functional Assessment of Cancer Therapy—General (FACT-G) score], using an Aalen—Johansen estimator for cumulative incidence function of TTD DQoL (QoL deterioration) with 95% pointwise confidence intervals (CIs). Secondary endpoints included progression-free survival (PFS), overall survival (OS), and DQoL.

Results: In all patients [intention-to-treat (ITT)-ePRO], cumulative incidence of DQoL was significantly more favorable (lower) in the CANKADO-active arm (hazard ratio 0.698, 95% CI 0.506-0.963). Among first-line patients ($n = 295$), the corresponding hazard ratio was 0.716 (0.484-1.060; $P = 0.09$), and in second-line patients ($n = 117$) it was 0.661 (0.374-1.168; $P = 0.2$). Absolute patient numbers declined in later visits; FACT-G completion rates were 80% and higher until about visit 30. Mean FACT-G scores showed a steady decline from baseline and an offset in favor of CANKADO-active. No significant differences in clinical outcome were observed between arms: median PFS (ITT population) was 21.4 (95% CI 19.4-23.7) (CANKADO-active) and 18.7 (15.1-23.5) months (CANKADO-inform); median OS was not reached (CANKADO-active) and 42.6 months (CANKADO-inform).

Conclusions: PreCycle is the first multicenter randomized eHealth trial demonstrating a significant benefit for MBC patients receiving oral tumor therapy when using an interactive autonomous patient empowerment application.

Key words: metastatic breast cancer, eHealth, patient-reported outcome, quality of life, CDK4/6 inhibitor, endocrine therapy

*Correspondence to: Prof. Nadia Harbeck, Breast Center, Department of Obstetrics and Gynecology and CCC Munich LMU, University Hospital Munich, Marchioninistrasse 15, 81337 Munich, Germany. Tel: +49-89-4400-77581; Fax: +49-89-4400-77582

E-mail: nadia.harbeck@med.uni-muenchen.de (N. Harbeck).

INTRODUCTION

Metastatic breast cancer (MBC) is still considered an incurable disease.[1] Treatment aims are prolongation of survival and improvement or maintenance of quality of life (QoL) under therapy by sufficient control of cancer-related

symptoms.[2] QoL combines different aspects of individual personal health status.[3] It represents a multi-domain concept, which includes the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life. In MBC, more and more oral therapies have recently become available with the hope of providing therapeutic efficacy together with an easy integration of the cancer therapy into patients' routine daily activities. To date, regularly scheduled visits are used to ensure patient—physician communication and provide the treatment team with an overview of patients' symptoms and side-effects. However, there are significant discrepancies between patients' and physicians' perceptions of symptomatic toxicities.[4] For this reason, patient-reported outcomes (PROs) have become increasingly important and are now recommended by the ABC consensus.[1] Initial findings indicate that routine assessment may even be associated with improved survival.[5]

In a single-center cohort of metastatic cancer patients, Basch et al. were the first to show that electronic patient-reported symptom monitoring provides benefits compared to routine care not only for patient QoL, but also for patient outcome.[6] These beneficial effects were confirmed in advanced-stage lung cancer patients.[7] Both trials used a remote patient monitoring (RPM) system supervised by oncologists or a trained nurse with weekly PRO documentation.

CANKADO is a next-generation, interactive, autonomous patient empowerment application that works without any intervention by a health care professional (HCP) and can self-detect points in time to initiate symptom questionnaires. Patients are queried daily about their general health merely by a smiley slider, graphically based on the EuroQol Visual Analogue Scale (EQ-VAS).[8] Based on the documented longitudinal changes in the EQ-VAS value, the software selects the appropriate time to trigger a symptom questionnaire. Once symptoms and their grade of severity are documented, the system recommends to the patient whether and how urgently the treatment center should be contacted. In contrast to an RPM system, HCPs are not involved at any point in time until the patient contacts the center. The aim of CANKADO is thus to empower patients, prepare them better for the next contact with the treatment team, and initiate this contact when needed due to self-reported symptoms.

In hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) MBC, cyclin-dependent kinase 4/6 (CDK4/6) inhibitor-based therapy is now the standard of care,[1] as patient outcome has improved substantially with good QoL across all lines of therapy. This oral therapy has substantially changed management, since at present >80% of patients do receive a CDK4/6 inhibitor together with endocrine therapy (ET).[9] Palbociclib was the first approved CDK4/6 inhibitor worldwide and thus provided a good opportunity to test the benefits of eHealth-based therapy management under oral cancer therapy. The PreCycle trial aimed to investigate the impact of a next-generation, interactive, autonomous eHealth application on patient QoL as well as treatment efficacy of palbociclib-based therapy in the approved indications. Here, we report the results of the primary endpoint, time to deterioration (TTD) of patient QoL.

PATIENTS AND METHODS

Trial design

PreCycle (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.05.003) was a multicenter, randomized, parallel-group, phase IV clinical trial with 71 study sites in Germany. The trial was approved by all relevant competent authorities and an independent ethics committee. It is registered at EudraCT (2016-004191-22).

Eligible patients had histologically or cytologically proven diagnosis of HR+ HER2− locally advanced or metastatic breast cancer and were either candidates to receive palbociclib in combination with aromatase inhibitor (first line) or candidates to receive palbociclib in combination with fulvestrant (later lines) for their locally advanced or metastatic disease. All anticancer treatments used in this study were approved drugs and therapy is in accordance with national treatment guidelines. Further details of trial design, treatment, and planned exploratory analyses were previously reported.[10]

PreCycle compared two different kinds of eHealth support and documentation of patient-reported QoL data. CANKADO-active (intervention arm) is a fully functional CANKADO-based eHealth treatment support service, including documentation of daily drug intake, daily documentation of daily general health, symptoms, feedback functions (PRO-React), and on-site Functional Assessment of Cancer Therapy—Breast (FACT-B) surveys. CANKADO-inform (control arm) is an eHealth service comprising only personal login and documentation of daily drug intake, on-site FACT-B surveys, but no symptom documentation and no feedback functions. For determination of primary and secondary endpoints, all patients filled out the FACT-B questionnaire [which included Functional Assessment of Cancer Therapy—General (FACT-G)] on-site on day 1 of every planned trial visit during the active treatment phase.

Patients in CANKADO-active were prompted to fill out the EQ-VAS instrument every day. An additional symptom questionnaire was triggered [Triggered Symptoms Questionnaire (TSQ)] if the system identified an unexpected change in the longitudinal EQ-VAS values. The TSQ contained 13 symptoms (fatigue, fever, night sweats, shortness of breath, bleeding, loss of appetite, stomatitis, nausea, vomiting, diarrhea, hair loss, visual disturbances, skin changes) and one additional question about self-administered medication changes, which included nutrition supplements. All answer options were categorized according to Common Terminology Criteria for Adverse Events (CTCAE). Before the start of the study, a response matrix was developed, based on which patients were given recommendations on how urgently to clarify their observations with the supervising centers. There were three categories of recommendations: (level 1) address own observations at the next scheduled visit; (level 2) contact the center

promptly; or (level 3) contact the center today or visit the emergency department. No recommendations were made when the app was first used, as this was considered a baseline determination. The centers did not receive alert messages at any time.

Patients were to receive study treatment together with the assigned ePRO assessment until any of the following: investigator-assessed disease progression, unacceptable toxicity, death, or withdrawal of consent. Patients discontinuing the active treatment phase (i.e. due to progression or patient's decision) entered a follow-up phase, comprising collection of further progression and new anticancer therapy data once a year up to 48 months after randomization.

The study was prematurely terminated by the sponsor because of the coronavirus disease 2019 (COVID-19) pandemic after 52 months on 7 December 2021.

Statistical analysis

The primary objective of PreCycle was to test the hypothesis of superiority regarding 'time to deterioration' (TTD) of QoL for CANKADO-active compared to CANKADO-inform with 2 : 1 randomization. The event 'deterioration of QoL' (DQoL) was defined as a 10-point drop on FACT-G total score (score range 0-108, a higher score means better QoL)[11] from baseline, unless a recovery is achieved at the subsequent visit. Sample size estimation utilized results of the PALOMA-1 and -3 palbociclib registration trials[12,13] as previously reported,[10] resulting in recruitment target $n = 960$. The trial was stratified by therapy line (first/later). The test was calibrated with respect to an alternative hypothesis that asserts a hazard ratio of 0.8 favoring CANKADO-active, corresponding to a superior median TTD of ∼4 months in first line and ∼2 months in later lines. Efficacy results are reported based on the intention-to-treat (ITT)-PRO population (assessable randomized patients).

Event and censoring dates are defined using the latest observable FACT-G score in the respective patient dataset. Patient data are also considered to be censored if either two or more consecutive 28-day palbociclib cycle visits took place without FACT-G application. This criterion is appropriate to censor potential cases of failure to observe DQoL events during such intervals. The effect of interest addresses the dynamic end of therapy events using a 'while on treatment' strategy.[14] Consequently, documented therapy discontinuation for any reason, including death and disease progression (which were not prospectively included within the primary endpoint definition), is considered a competing event.[15] This procedure further allows to distinguish true ('administrative') censoring from events such as therapy discontinuation that preclude the event of interest (DQoL). Accordingly, the Aalen–Johansen estimator[16] was used to estimate the cumulative incidence functions of TTD and therapy discontinuation with 95% pointwise confidence intervals (CIs). The primary objective was tested using the score function in a Cox regression model (cause-specific hazard for DQoL), stratified by therapy line, and using the Breslow likelihood for handling ties. Median follow-up was estimated by the inverse Kaplan–Meier method (counting both event types as 'censored').

As per protocol, FACT-B questionnaire was requested from patients during all visits at the clinical site, including unscheduled visits related to study assessments, toxicities, or similar observations. The primary analysis is consequently based on the full CANKADO QoL dataset, including unscheduled visits.

Secondary trial endpoints reported here included progression-free survival (PFS) and overall survival (OS); safety-related endpoints such as cumulative incidence of serious adverse events (SAEs) will be reported elsewhere.

Computations were carried out using the statistical software R (version 4.2.0, R Core Team, Vienna, Austria).

RESULTS

As shown in the Consolidated Standards of Reporting Trials (CONSORT) diagram (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.05.003), a total of 499 patients were randomized in 71 centers between August 2017 and June 2021 (331 in CANKADO-active versus 169 in CANKADO-inform); the reduction from the target of 960 patients occurred because of the COVID-19 pandemic-related termination of the trial. The ITT-PRO population (randomized patients available for analysis of primary endpoint) comprised $n = 412$ patients (271 CANKADO-active; 141 CANKADO-inform). Table 1 shows their baseline characteristics by arm. The proportion of later-line patients was slightly lower than expected in CANKADO-active; the proportion of postmenopausal patients was slightly higher in CANKADO-inform. Median follow-up was 20 months in CANKADO-active and 18 months in CANKADO-inform (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2023.05.003).

There were 95/271 (35.1%) DQoL events in CANKADO-active versus 63/141 (44.7%) in CANKADO-inform (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.05.003). The hazard ratio for TTD in CANKADO-active versus CANKADO-inform was 0.698 (95% CI 0.506-0.963; $P = 0.03$) by stratified univariable Cox regression. Hence, the primary objective of the PreCycle trial, superiority of the CANKADO-active arm concerning TTD, was achieved.

The corresponding cumulative incidence functions for DQoL by arm are shown in Figure 1 for the ITT-PRO population. In first-line patients ($n = 295$), the hazard ratio was 0.716 (95% CI 0.484-1.060; $P = 0.09$); in later-line patients ($n = 117$) it was 0.661 (95% CI 0.374-1.168; $P = 0.2$). The corresponding cumulative incidence functions are shown in Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2023.05.003.

The cumulative incidence function for therapy discontinuation (any cause) as a competing event (Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2023.05.003) to DQoL shows similar characteristics in

Table 1. Baseline patient and disease characteristics by arm for the ITT-PRO analysis set

Parameter	Level		Arm		Overall
			CANKADO-active	CANKADO-inform	
N (population)			271	141	412
Menopausal status	Postmenopausal	Count (%)	203 (74.91)	121 (85.82)	324 (78.64)
	Pre-/perimenopausal	Count (%)	68 (25.09)	20 (14.18)	88 (21.36)
HR status	Positive[a]	Count (%)	271 (100.00)	141 (100.00)	412 (100.00)
HER2 status	Negative[b]	Count (%)	271 (100.00)	141 (100.00)	412 (100.00)
Disease status	Locally advanced	Count (%)	14 (5.17)	9 (6.38)	23 (5.58)
	Metastatic	Count (%)	257 (94.83)	132 (93.62)	389 (94.42)
Therapy line	First	Count (%)	203 (74.91)	92 (65.25)	295 (71.60)
	Later	Count (%)	68 (25.09)	49 (34.75)	117 (28.40)
Age		Mean (years)	58.1	60.6	59.0
		Range (years)	31-81	36-81	31-84

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor status; IHC, immunohistochemistry; ISH, *in situ* hybridization; ITT, intention-to-treat; PR, progesterone receptor; PRO, patient-reported outcome.
[a]ER >1% and/or PR >1%.
[b]HER2 by IHC 0, 1+, or 2+/ISH negative.

CANKADO-active and CANKADO-inform, with strongly overlapping CIs.

The time sequence of FACT-G scores relative to baseline is shown in Figure 2. Mean changes decline roughly monotonically in both arms, with an offset in favor of the CANKADO-active arm, consistent with the analysis of TTD.

EQ-VAS mean scores and completion rates (with 95% CI) in the CANKADO-active arm are shown in Figure 3. A declining trend of completion rates over time appears until about day 750, while mean EQ-VAS scores among those in the assessable population appear to remain roughly constant. Both curves may be affected by survivor bias, since patients leaving the EQ-VAS assessable population could be more likely to have lower scores or to omit completion.

A total of 2944 TSQs were triggered, corresponding to a mean of 8.9 TSQ per patient. In 2449 cases, at least one symptom was recorded (83.2%). The mean number of documented symptoms was 3.0. In 54.4% of all cases, patients received level 1, in 40.5% level 2, and in 5.1% level 3 recommendations. The most frequently reported SAEs regarding System Organ Class were 'infections and infestations', 'gastrointestinal disorders', and 'general disorders and administration site conditions'.

PFS and OS curves are shown in Figure 4. Median PFS was 21.4 months (19.4-23.7 months) in the CANKADO-active arm versus 18.7 months (15.1-23.5 months) in the CANKADO-inform arm; 24-month PFS rates were 41.6% (95% CI 35.5% to 48.8%) versus 39.2% (95% CI 31.1% to

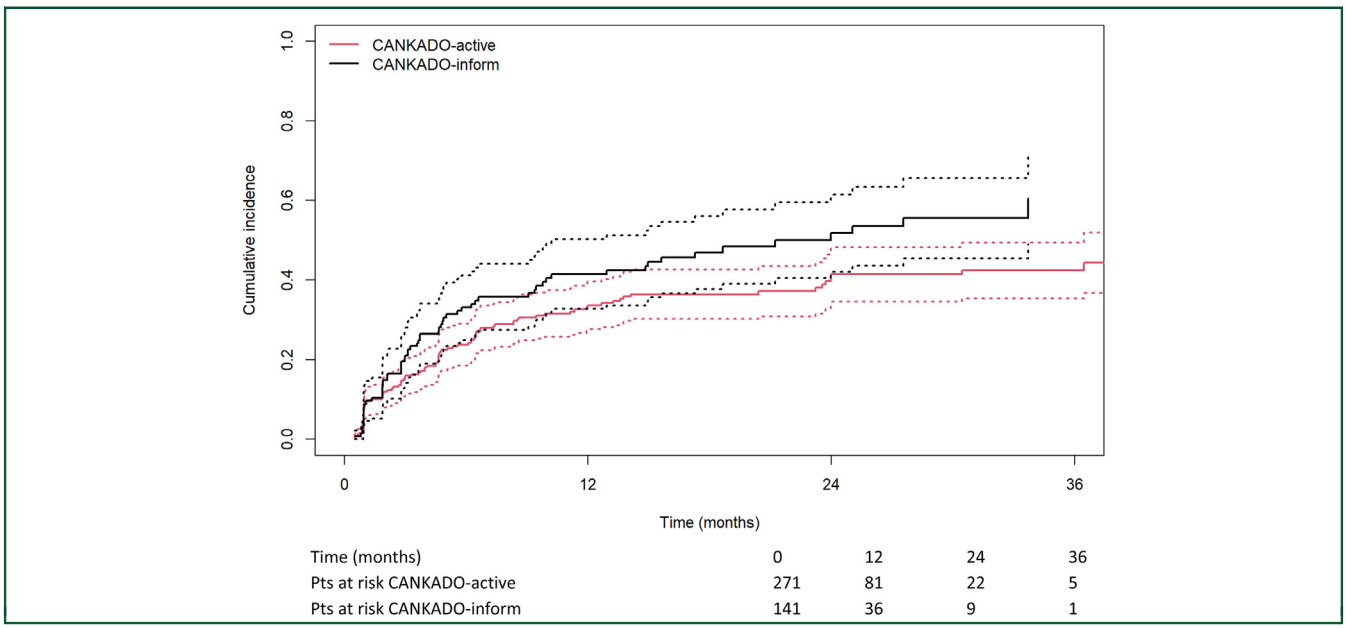

Figure 1. Cumulative incidence of DQoL in the ITT-PRO population. The cumulative incidence of DQoL in the ITT-PRO population is presented with 95% confidence intervals (dotted lines). Horizontal axis is time in months to deterioration; vertical axis is estimated cumulative probability of a DQoL event, taking censoring and competing events into account. Table under the panel indicates the number of patients at risk.
DQoL, deterioration of quality of life; ITT, intention-to-treat; PRO, patient-reported outcome.

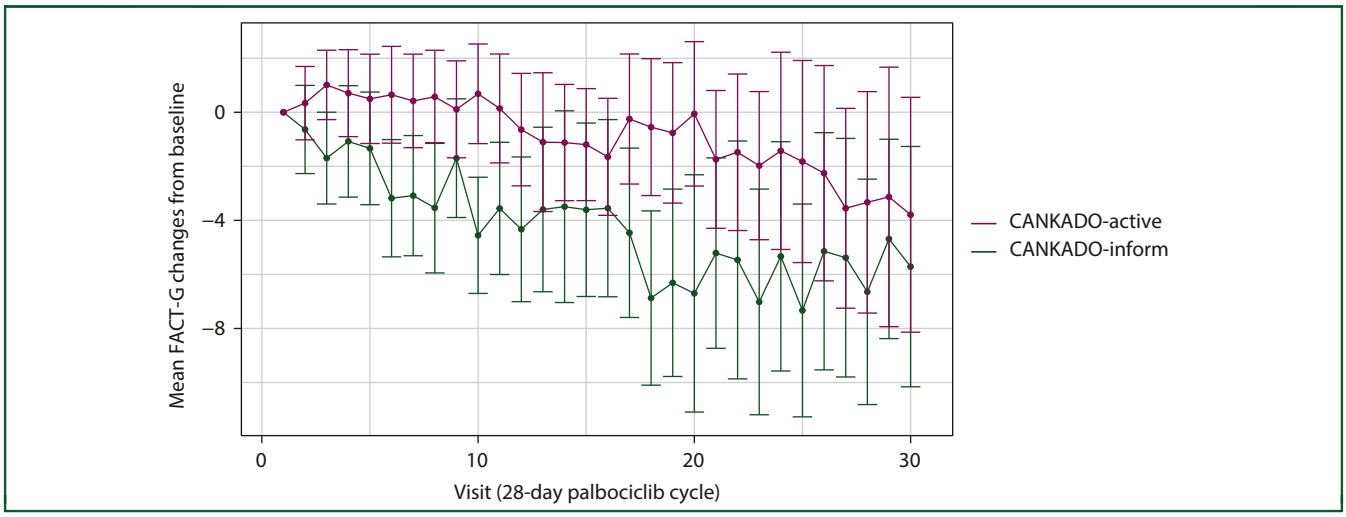

Figure 2. Mean FACT-G changes from baseline, ITT-PRO population. Mean FACT-G changes from baseline in the ITT-PRO population with 95% error bars by normal approximation. The figure is cropped at 30 weeks due to small sample size.
FACT-G, Functional Assessment of Cancer Therapy—General; ITT, intention-to-treat; PRO, patient-reported outcome.

49.4%), respectively. Median OS was not reached in CANKADO-active and was 42.6 months in CANKADO-inform; 24-month OS rates were 75.1% (69.6% to 81.0%) in CANKADO-active versus 72.1% (64.4% to 80.7%) in CANKADO-inform; the wide CIs result from censoring.

Treatment characteristics including median relative dose intensity, postponement, interruption, and dose reduction rates were similar in the two arms (Table 2).

DISCUSSION

The multicenter randomized AGO-B WSG PreCycle trial has reached its primary endpoint, showing significantly longer TTD of QoL with an autonomous eHealth support application in advanced or metastatic HR+ HER2− breast cancer treated with ET + palbociclib. The improvement corresponds to a hazard ratio of ∼0.7 in favor of the CANKADO-active arm.

Patient reporting of symptoms may differ substantially from clinician reporting.[17] ePRO assessment thus provides a continuous as well as more reliable picture of patient well-being and may thus serve as the basis of therapy management in oncology.[18]

In contrast to other cancer types, in HR+ HER2− MBC, QoL is usually very good during first-line therapy, and addition of palbociclib to letrozole maintains health-related QoL in this setting. In the palbociclib phase III trials,[13,19] improvement of QoL by adding palbociclib to ET could only be observed in later-line trials.[20,21] Therefore, our observed improvement in TTD of QoL by the autonomous eHealth system CANKADO already in the first line is quite remarkable. Considering that improving QoL is one of the most important goals in MBC, our results by a non-drug intervention are highly encouraging. The central innovation in CANKADO's approach is that it is an interactive, autonomous system that operates entirely without

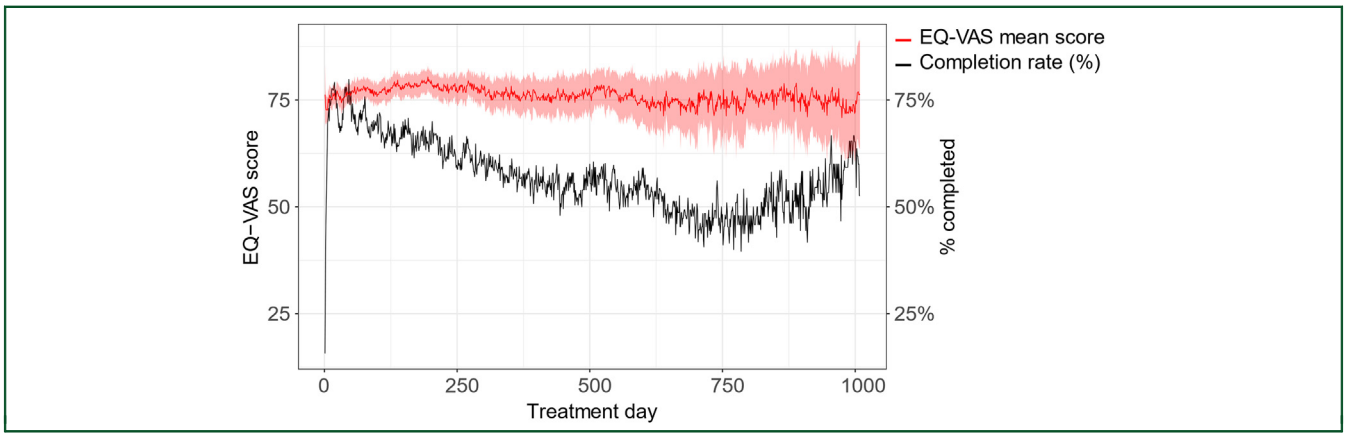

Figure 3. EQ-VAS and completion rates during palbociclib exposure in the EQ-VAS assessable population of the CANKADO-active arm. EQ-VAS mean score with 95% confidence intervals and completion rates during palbociclib exposure in the EQ-VAS assessable population of the CANKADO-active arm by day (up to 1000) since randomization are presented. EQ-VAS records the respondents' self-rated health on a vertical, visual analog scale from 0 to 100 where the endpoints are labeled 'best imaginable health state' (100) and 'worst imaginable health state' (0). Note, measurements after day 1000 are omitted due to low patient counts and completion rates. Confidence intervals are shown only if more than nine patients were observable at a particular time point.
EQ-VAS, EuroQol Visual Analogue Scale; QoL, quality of life.

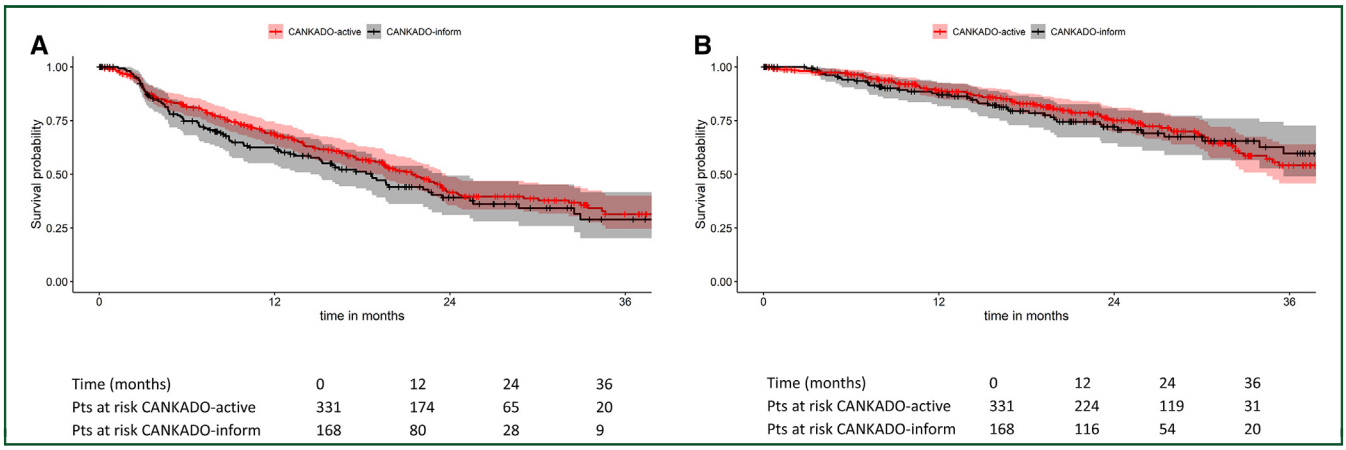

Figure 4. PFS (A) and OS (B) in the ITT population by arm. Tables under the panels indicate the number of patients at risk.
ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival.

remote patient monitoring (RPM). Thus, the decision to contact the center for an unscheduled visit comes exclusively from patient empowerment. There is no additional workload on the centers due to RPM within the application.

Our findings from a randomized trial in MBC using this interactive autonomous eHealth system are consistent with those of the PRO-TECT trial, which randomized 1191 cancer patients from community oncology practices to remote electronic symptom monitoring with PRO surveys versus routine care. In the PRO group, significant improvements in mean changes on the European Organization for Research and Treatment (EORTC) quality of life questionnaire (QLQ-C30) from baseline to 3 months were observed for physical function, symptom control, and QoL.[22]

In a prior single-center study, Basch and co-workers found that electronic symptom self-reporting significantly improved not only QoL but also OS in 766 patients with advanced solid tumors who received outpatient chemotherapy.[6,23] In our breast cancer cohort, continuous eHealth-based symptom reporting did not significantly affect patient survival but maintained QoL for a longer period, with a significant extension of TTD compared to routine care (even including digital disease information). A possible explanation for the difference in survival results observed in a mixed metastatic cohort[6] or in later-line lung cancer[7] may be the long disease control and survival in our breast cancer-only collective, which is consistent with the long survival times observed today in HR+ HER2− MBC.

In the PRO-TECT trial, user perception by the medical staff of an electronic patient-reported symptom monitoring during cancer care was very favorable: 75% of the nurses reported this to be helpful for patient care, and 65% of the physicians used the information to guide patient discussions.[24]

In Germany, the Digital Healthcare Act came into effect in December 2019, regulating the use of digital health applications (DIGA) in routine clinical care. Applications with demonstrated benefit for patients can be prescribed by physicians and reimbursed by insurance companies. Other European countries such as Belgium or France are currently exploring similar legislative initiatives and thus providing clinicians and patients with quality-assured frameworks for integrating eHealth applications into routine care. In the evaluation of positive impacts of DIGAs in Germany, improvements in QoL are considered the most positive effect and benefit of such an application.

The PreCycle trial has several strengths and limitations. Limitations include the fact that fewer patients were enrolled than originally planned since the trial needed to be stopped early due to the COVID-19 pandemic. A major strength is that PreCycle enrolled a homogeneous patient population, even including first-line patients. Furthermore, PreCycle is—to our knowledge—the first randomized trial demonstrating benefit of an interactive autonomous patient empowerment application on QoL in MBC patients during oral cancer therapy. Integration of such applications into routine oncology care holds the promise of patient empowerment. Moreover, capturing patient well-being under systemic treatment in a continuous manner may open new strategies for therapy management. In the ongoing OMCAT registry (NCT04531995), intelligent learning and knowledge engineering procedures will utilize electronically captured PRO data to provide high-quality event prediction algorithms for early side-effect detection with the goal of avoiding higher-grade side-effects under systemic cancer therapy.

Table 2. Treatment characteristics by arm in the safety population (all patients who received at least one dose of palbociclib)

	CANKADO-active (n = 311)	CANKADO-inform (n = 161)
Median relative dose intensity (%)	96.7	93.9
Treatment postponement (%)	60.1	57.1
Treatment interruption (%)	37.1	42.2
Dose reduction (%)	41.2	47.8

Data were available for 472/479 patients in the safety population.

https://doi.org/10.1016/j.annonc.2023.05.003

In conclusion, the AGO-B WSG PreCycle trial has demonstrated, for the first time, substantial benefits of an interactive, autonomous patient empowerment application regarding QoL of MBC patients during oral cancer therapy. These findings support further investigation of eHealth applications in different treatment settings of breast cancer as well as in other tumor types and support the use of quality-assured applications in routine care.

ACKNOWLEDGEMENTS

The PreCycle protocol was developed by TDeg, REK, and NH in cooperation with the ECCO-AACR-EORTC-ESMO Workshop on Methods in Clinical Cancer Research (MCCR) 2016. The authors are grateful for the continued support of the trial conduct by palleos healthcare and iOMEDICO and the financial trial support by Pfizer.

FUNDING

This work was supported by Pfizer (no grant number).

DISCLOSURE

NH reported honoraria for lectures and/or consulting from Amgen, AstraZeneca, Daiichi Sankyo, EPG Communication, Gilead, Lilly, MEDSCAPE, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, Sanofi, Seagen, Springer, Viatris, Zuelligpharma; all outside the submitted work, and co-director position at West German Study Group (WSG). PAF reported personal fees for advisory board from Agendia, AstraZeneca, Daiichi Sankyo, Eisai, Hexal, Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi Aventis, Seagen; personal fees for invited speaker from AstraZeneca, Daiichi Sankyo, Eisai, Gilead, Lilly, Merck, Sharp & Dohme, Novartis, Seagen; personal fees for medical writing support from Roche; non-financial support to the institution from BioNTech, Cepheid, all outside the submitted work; non-financial interests: member for Arbeitsgemeinschaft für Gynäkologische Onkologie, ASCO, Deutsche Gesellschaft für Senologie, Translational Research in Oncology. TDec reported personal fees from Adboards, Novartis, and iOMEDICO. OG reported consulting fees from Daiichi Sankyo, BMS, Genomic Health/Exact Sciences, Lilly, MSD, Novartis, Pfizer, Roche, Seagen, Pierre Fabre, Gilead, Molecular Health; honoraria from Genomic Health/Exact Sciences, Eisai, Roche, BMS, Pfizer, Novartis, NanoString Technologies, Agendia, AstraZeneca; travel support from Roche, Daiichi Sankyo, all outside of the submitted work; co-director position at West German Study Group (WSG). OH reported personal fees for advisory boards, lectures, and congress and travel expense support from Roche, Novartis, MSD, Pfizer, Astra Zeneca, Daichii-Sankyo, Hexal, Riemser Pharma, BMS, Gilead, Lilly, and Seagen; expert by the Deutsche Krebsgesellschaft and expert in court; PI of breast cancer studies at the Department of Gynecology and Obstetrics, University Hospital of Essen, Germany. DL reported honoraria from Amgen, Astra Zeneca, Daiichi Sankyo, Eli Lilly, Gilead, GSK, Loreal, Novartis, Pfizer, Seagen; consulting or advisory role from Amgen, AstraZeneca, Daiichi Sankyo, Eli Lilly, Gilead, GSK, Loreal, Novartis, Pfizer, Seagen; speakers' bureau from Amgen, Astra Zeneca, Daiichi Sankyo, Eli Lilly, Gilead, GSK, Loreal, Novartis, Pfizer, Seagen; research funding from Novartis; experts testimony from Amgen, AstraZeneca, Daiichi Sankyo, Eli Lilly, Gilead, GSK, Loreal, Novartis, Pfizer, Seagen; travel, accommodation, expenses from Amgen, AstraZeneca, Daiichi Sankyo, Eli Lilly, Gilead, GSK, Loreal, Novartis, Pfizer, Seagen. MR reported personal fees from MSD, AstraZeneca, Roche, Somatex, Daiichi Sankyo; personal fees and non-financial support from Lilly, Novartis, Pfizer, Seagen, outside the submitted work. MS reported grants or contracts to the institution from AstraZeneca, BioNTech, Eisai, German Breast Group, Genentech, Novartis, Pantarhei Bioscience, Pfizer, Pierre Fabre, Roche; consulting fees from AstraZeneca, BioNTech, Eisai, Daiichi Sankyo, Lilly, MSD, Novartis, Pantarhei Bioscience, Pfizer, Pierre Fabre, Roche, Seagen; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AstraZeneca, Novartis, Pfizer, Roche, Seagen; support for attending meetings and/or travel from Pfizer, Roche; patents planned, issued, or pending: EP 2951317 B1, EP 2390370 B1; personal fees for participation on a Data Safety Monitoring Board or Advisory Board from AstraZeneca, BioNTech, Eisai, Daiichi Sankyo, Eisai, Lilly, Novartis, Pantarhei Bioscience, Pfizer, Pierre Fabre, Roche, Seagen. PS reported honoraria from Abbvie, Amgen, AstraZeneca, BMS, MSD Oncology, Pfizer, Merck Serono, Roche, Novartis; consulting or advisory role from Abbvie, Amgen, AstraZeneca, BMS; speakers' bureau from Abbvie, Amgen, AstraZeneca, BMS, Roche, Pfizer; research funding from Abbvie, BMS, Novartis, Roche; travel, accommodations, expenses from Abbvie, AstraZeneca; other from Abbvie, Amgen, BMS, Eisai, Incyte, Ipsen, Gilead Sciences, AstraZeneca, Janssen Oncology, Lilly Medical, Merck Serono, MSD Oncology, Pfizer, Roche, Novartis, Takeda. RW reported advisor, consultant, speaker, and travel grant from Agendia, Amgen, Aristo, AstraZeneca, BMS, Clovis Oncology, Daiichi Sankyo, Eisai, Exact Sciences, Gilead, Glaxo Smith Kline, Hexal, Lilly, Medstrom Medical, MSD, Mundipharma, Mylan, Nanostring, Novartis, Odonate, Paxman, palleos healthcare, Pfizer, Pierre Fabre, PINK, PumaBiotechnology, Riemser, Roche, Sandoz/Hexal, Sanofi Genzyme, Seattle Genetics /Seagen, Stemline, Tesaro Bio, Teva, Veracyte, Viatris; other from FOMF, Aurikamed, Clinsol, Pomme Med, medconcept, MCI. REK reported honoraria from West German Study Group (WSG) and honoraria to an immediate family member for lectures and/or consulting from Amgen, AstraZeneca, Daiichi Sankyo, EPG Communication, Gilead, Lilly, MEDSCAPE, MSD, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, Sanofi, Seagen, Springer, Viatris, Zuelligpharma. TS reported employment, leadership, and stock or other ownership by CANKADO GmbH. All other authors have declared no conflicts of interest.

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Appendix 1. Lists of PreCycle investigators who are collaborators (non-author contributors) and should be searchable on PubMed

Name of the investigator	Affiliations
Dirk Günter Kieback	Ev.-Luth. Diakonissenanstalt zu Flensburg Frauenklinik, Flensburg, Germany
Marion Tina van Mackelenbergh	Universitätsklinikum Schleswig-Holstein (UKSH), Campus Kiel, Klinik für Gynäkologie und Geburtshilfe Studienzentrale Gynäkologische Onkologie (SGO), Kiel, Germany
Carsten Hielscher	G.SUND Gynäkologie Kompetenzzentrum, Stralsund, Germany
Mustafa Celalettin Ugur	Agaplesion Diakonieklinikum Hamburg Frauenklinik, Brustzentrum u. Gyn. Tumorzentrum, Hamburg, Germany
Christoph Uleer	Gyn.-onkologische Gemeinschaftspraxis Dres. Med. Christoph Uleer/Jasmin Y. Pourfard Klinische Studien, Hildesheim, Germany
Mark-Oliver Zahn	MVZ Onkologische Kooperation Harz Hämatologie und Internistische Onkologie, Goslar, Germany
Ralf Meyer	Onkologisch-Hämatologische Schwerpunktpraxis, Bremen, Germany
Susanne Kraudelt	Altmark Klinikum gGmbH Klinik für Frauenheilkunde, Salzwedel, Germany
Andrea Stefek	Johanniter-Krankenhaus Genthin-Stendal GmbH Klinik für Frauenheilkunde und Geburtshilfe, Stendal, Germany
Daniel Pink	HELIOS Klinikum Bad Saarow Klinik für Hämatologie, Onkologie und Palliativmedizin, Bad Saarow, Germany
Marianne Just	Onkologische Schwerpunktpraxis, Bielefeld, Germany
Hans-Christian Kolberg	Marienhospital Bottrop gGmbH Klinik für Frauenheilkunde, Bottrop, Germany
Tanja Fehm	Universitätsklinikum Düsseldorf Klinik für Frauenheilkunde und Geburtshilfe, Düsseldorf, Germany
Wolfram Malter	Klinik für Frauenheilkunde Uniklinik Köln CIO Studienzentrale, Köln, Germany
Mathias Warm	Kliniken der Stadt Köln Brustzentrum Holweide, Köln, Germany
Helmut Forstbauer	Praxisnetzwerk Hämatologie und intern. Onkologie,Troisdorf, Germany
Dirk Behringer	Augusta-Kranken-Anstalt GmbH Klinik für Hämatologie und Onkologie, Bochum, Germany
Anke Wortmann	MVZ Kloster Paradiese GbR Onkologiezentrum, Soest, Germany
Joachim Rom	Klinikum Frankfurt-Höchst Klinik für Gynäkologie, Frankfurt, Germany
Antje Lehnert	St. Josefs-Hospital Frauenklinik, Wiesbaden, Germany
Sven Ackermann	Klinikum Darmstadt GmbH Frauenklinik, Darmstadt, Germany
Dagmar Guth	Frauenheilkunde und Geburtshilfe Gynäkologische Onkologie, Plauen, Germany
Eike Simon	Kreiskrankenhaus Torgau Gynäkologie/Geburtshilfe, Torgau, Germany
Jan Dünnebacke	Katholisches Klinikum Koblenz-Montabaur Marienhof Koblenz, Germany
Arnd Hönig	Marienhaus Klinikum Mainz GmbH Abteilung für Frauenheil-kunde und Geburtshilfe, Mainz, Germany
Peter Ehscheidt	MVZ Hämatologie/Onkologie Neuwied GmbH, Neuwied, Germany
Karsten Gnauert	Ostalb-Klinikum Brustzentrum, Aalen, Germany
Thorsten Kühn	Klinikum Esslingen Klinik für Frauenheilkunde und Geburtshilfe, Esslingen a. N., Germany
Ekkehard von Abel	Stauferklinikum, gynäkologische Onkologie, Mutlangen, Germany
Andreas Hartkopf	Universitäts-Frauenklinik Tübingen Department für Frauengesundheit, Tübingen, Germany
Ulrich Karck	Klinikum Stuttgart Frauenklinik Olgahospital, Stuttgart, Germany
Martina Negwer	Klinikum am Steinenberg Frauenklinik, Reutlingen, Germany
Jürgen Wacker	Fürst-Stirum-Klinik Frauenklinik, Bruchsal, Germany
Manfred Welslau	MVZ am Klinikum/Onkologie phase drei Hämato-Onkologischer Studienkreis am Klinikum Aschaffenburg, Aschaffenburg, Germany
Jaqueline Sagasser	Klinikum Augsburg Frauenklinik ZK, Augsburg, Germany
Bernhard Heinrich	Hämatologische Onkologische Praxis, Augsburg, Germany
Cosima Brucker	Klinikum Nürnberg Klinik für Frauenheilkunde, Nürnberg, Germany
Heribert Stauder	Krankenhaus "Barmherzige Brüder" Klinik für Onkologie und Hämatologie, Regensburg, Germany
Isolde Gröll	Praxis und Tagesklinik für gynäkologische Onkologie, Ebersberg, Germany
Ricardo Felberbaum	Klinikverbund Kempten Oberallgäu gGmbH Gynäkologie, Kempten (Allgäu), Germany

Continued

Appendix 1. Continued

Name of the investigator	Affiliations
Milos Popovic	Klinikum Bayreuth GmbH Frauenklinik, Bayreuth, Germany
Dirk-Toralf Baerens	Gynäko-Onkologische Praxis, Ilsede, Germany
Ulrike Söling	Hämato-Onkologisches Zentrum Kassel MVZ GmbH, Kassel, Germany
Matthias Zaiss	Praxis für interdisziplinäre Onkologie und Hämatologie, Freiburg, Germany
Jaqueline Rauh	GIM-Gemeinschaftspraxis Innere Medizin, Witten, Germany
Thomas Fietz	Schwerpunktpraxis für Hämatologie und Intrenistische Onkologie Gastroenterologie, Singen, Germany
Jan Schröder	Praxis für Hämatologie und Onkologie, Mülheim a.d.Ruhr, Germany
Hermann Voß	MVZ des Städtischen Klinikums Dessau GmbH, Dessau-Roßlau, Germany
Johannes Mohm	Gemeinschaftspraxis Dr. med. J. Mohm und Dr. G. Prange-Krex Fachärzte für Innere Medizin und Hämatologie und Onkologie, Dresden, Germany
Ute Neef	Gemeinschaftspraxis für Innere Medizin, Hämatologie, Onkologie, Gastroenterologie, Halle (Saale), Germany
Lorenz Rieger	ÜBAG Medizinisches Versorgungszentrum Dr. Vehling-Kaiser GmbH, Landshut, Germany
Andrea Distelrath	Praxisgemeinschaft für Onkologie und Urologie, Wilhemshaven, Germany
Arnd Nusch	Praxis für Hämatologie und internistische Onkologie, Velbert, Germany
Burkhard Schmidt	Hämato-Onkologische Überörtliche Gemeinschaftspraxis Pasing und Fürstenfeldbruck, München, Germany
Kerstin Lüdtke-Heckenkamp	MVZ II der Niels Stensen Kliniken, Zentrum für Hämatologie und Onkologie, Georgsmarienhütte, Germany
Michael Berghorn	Allgemeines Krankenhaus Celle MVZ (Gynäkologische Onkologie), Celle, Germany
Steffi Busch	Dr. Busch MVZ GmbH Gynäkologisch-onkologische Schwerpunktpraxis, Mühlhausen, Germany
Caroline Schock	Ambulantes Therapiezentrum Hämatologie/Onkologie, Offenburg, Germany
Michael Metz	OSP Göttingen Dres. Meyer/Ammon/Metz, Göttingen, Germany
Andreas Lorenz	Frauenarztpraxis Dr. Lorenz, Hildburghausen, Germany
Jens Uhlig	Praxis Dr. med. Jens Uhlig, Naunhof, Germany
Burkhard Otremba	Onkologische Praxis Oldenburg, Oldenburg, Germany