Heart Failure Therapy in Patients with Advanced Cancer Receiving Specialized Palliative Care (EMPATICC trial)

Markus S. Anker[1,2,3,4], Amir A. Mahabadi[5], Matthias Totzeck[5], Mitra Tewes[6], Muhammad Shahzeb Khan[7,8,9], Raluca I. Mincu[5], Ulrike B. Hendgen-Cotta[5], Lars Michel[5], Baicy Mathew[6], Ophelia Drescher[10,11], Martin Schuler[10,11], Ulrich Keller[12,13,14,15], Kathrin Rieger[12], Johann Ahn[12], Lars Bullinger[12,13,14,15], Dominik P. Modest[12,14,15], Corinna Denecke[16], Lucie Kretzler[16], Luisa V. Ramer[16], Danara Krug[16], Ulf Landmesser[1,17,18], Lorenz Lehmann[19], Norbert Frey[19], Sven Bercker[20], Ulrich Laufs[21], Michael Böhm[22], Felix Mahfoud[23], Bela Merkely[24], Monika Diek[16,29], Javed Butler[8,25], Anja Veiser[26] Tim Heise [26], Martin Hellmich[27], Marius Placzek[27], Tim Friede[27,28], Stefan D. Anker[16], Tienush Rassaf[5]

Affiliations

[1] Charité – University Medicine Berlin corporate member of Free University Berlin and Humboldt-University Berlin, Berlin, Germany

[2] German Centre for Cardiovascular Research partner site Berlin and Berlin Institute of Health Center for Regenerative Therapies, Berlin, Germany

[3] Department of Cardiology, Angiology and Intensive Care Medicine CBF, German Heart Center Charité, Berlin, Germany

[4] School of Cardiovascular and Metabolic Health, University of Glasgow, United Kingdom

[5] West German Heart and Vascular Center, Clinic of Cardiology and Vascular Medicine, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

[6] Department of Palliative Medicine, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

[7] Baylor Scott and White Research Institute, Dallas, Texas, USA

[8] Baylor Scott and White The Heart Hospital-Plano, Plano, Texas, USA

[9] Department of Medicine, Baylor College of Medicine, Temple, Texas, USA

[10] West German Cancer Center, Department of Medical Oncology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany

© The Author(s) 2025. Published by Oxford University Press on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

[11] National Center for Tumor Diseases (NCT), NCT West, Essen, Germany
[12] Department of Hematology, Oncology and Tumor Immunology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany
[13] Max Delbrück Center, Berlin, Germany
[14] German Cancer Consortium (Deutsches Konsortium Für Translationale Krebsforschung, DKTK), Partner Site Berlin, Berlin, Germany
[15] National Center for Tumor Diseases (NCT), Partner Site, Berlin, Germany
[16] Department of Cardiology (CVK) of German Heart Center Charité; German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin, Berlin, Germany
[17] Department of Cardiology, Angiology and Intensive Care Medicine, Deutsches Herzzentrum der Charité, Charité-Universitätsmedizin Berlin, Berlin, Germany
[18] Friede Springer Cardiovascular Prevention Center at Charité, DZHK, Partner Site Berlin, Berlin Institute of Health, Berlin, Germany
[19] Department of Cardiology, Angiology, and Pneumology, Heidelberg University Hospital, Heidelberg, Germany; German Centre for Cardiovascular Research (DZHK), Heidelberg/Mannheim Partner Site, Germany
[20] Department of Anesthesiology and Critical Care Medicine, University Hospital Leipzig, Liebigstr. 20, 04103, Leipzig, Germany
[21] Clinic and Outpatient Clinic for Cardiology, University Hospital Leipzig, Leipzig, Germany
[22] Klinik für Innere Medizin III and HOMICAREM – Homburg Institute for CardioRenalMetabolic Medicine, Universitätsklinikum des Saarlandes, Saarland University, Kirrberger Str.1, 66421 Homburg/Saar, Germany
[23] Cardiology Department, University Hospital Basel, Basel, Switzerland
[24] Heart and Vascular Centre, Semmelweis University, Budapest, Hungary
[25] Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA
[26] Profil, Neuss, Germany
[27] University Medical Center Göttingen, Department of Medical Statistics, Göttingen, Germany
[28] DZHK (German Center for Cardiovascular Research), partner site Lower Saxony, Göttingen, Germany
[29] Department of Cardiology and Pneumology, University Medical Center Göttingen, Georg-August University, Göttingen, Germany

Corresponding Authors:
Markus S. Anker, MD
Charité - Campus Benjamin Franklin,
Hindenburgdamm 30, 12200 Berlin, Germany
Email: markus.anker@charite.de
Tel: +49-30-450 553092

AND

Tienush Rassaf, MD
West German Heart and Vascular Center
Clinic of Cardiology and Vascular Medicine
University Hospital Essen
University of Duisburg-Essen, Essen, Germany
Email: Tienush.rassaf@uk-essen.de
Phone: +49-201-723480

Word count (main text): 4237

Running title: Heart Failure Therapy in Advanced Cancer Patients

Presentations: This study will be presented at the European Society of Cardiology (ESC) Congress at Madrid, Spain, on 30th August 2025.

ABSTRACT (249 words)

Background and Aims: Advanced cancer may resemble a heart failure (HF)-like phenotype marked by cardiac wasting, dyspnoea, congestion, and/or physical dysfunction. The trial evaluated safety and efficacy of HF therapy among patients with advanced cancer receiving specialized palliative care to improve patients' self-care ability.

Methods: Patients with stage 4 solid tumours with a life expectancy of 1–6 months receiving specialized palliative care were enrolled. Patients were required to meet at least two cardiovascular risk criteria and at least one criterion for functional limitation. Participants were randomized 1:1 to receive optimised HF therapy (up to 4 drugs: sacubitril/valsartan, empagliflozin, ivabradine, ferric carboxymaltose) or placebo in a double-blind setting. The primary hierarchical endpoint included: (1) days alive and able to wash oneself, (2) ability to walk 4 m, (3) self-reported patient global assessment (PGA) of subjective well-being, during the 30-day placebo-controlled phase.

Results: In 5 centers, 93 patients were randomized. The primary endpoint did not differ between groups (win ratio 0.95, 95% confidence interval [CI] 0.57–1.58; P=0.83). Overall, mortality was 32% at 30 days (not different between groups). In patients alive at 30 days, HF therapy reduced N-terminal pro-B-type natriuretic peptide levels by 41% (P=0.040), increased left ventricular ejection fraction by 2.9% (P=0.036), and improved PGA scores (odds ratio 0.22, 95% CI 0.06–0.75; P=0.016).

Conclusions: In a population with advanced cancer receiving specialized palliative care and high early mortality, optimised HF therapy did not improve patients' self-care ability. Among survivors at 30 days, improvements in quality of life measures and cardiac biomarkers suggest potential benefit of individualized HF therapy, which is hypothesis generating and needs validation.

Keywords: Heart failure therapy, end-stage cancer, palliative care, cardiac wasting, clinical trial.

EudraCT Number: 2021-006994-48

NCT05636774

INTRODUCTION

Functional decline is a hallmark of disease progression in advanced cancer and is driven by multiple pathophysiological mechanisms, including inflammation, metabolic dysregulation, leading to progressive cardiac and skeletal muscle wasting.[1,2] Nearly half of all patients with cancer progress to palliative care, marked by a decline in physical function and increased dependence.[3] Combined effects of cancer progression and anticancer therapies may induce a heart failure (HF)–like phenotype, characterized by cardiac dysfunction, myocardial wasting, and disruption of cardiac homeostasis, including fibrosis and apoptosis, leading to congestion, dyspnoea, and impaired physical functioning.[4,5] Cardiac wasting in such patients significantly contributes to HF-like symptoms such as dyspnoea, fatigue, and functional decline, with up to 50% of the patients demonstrating evidence of myocardial atrophy.[6] This patient population is often characterized by advanced disease, significant functional decline, and a very limited life expectancy, posing considerable challenges for clinical trials seeking to establish clinical benefits statistically.

Most cardio-oncology trials have focused on preventing cardiotoxicity from chemotherapy, particularly from agents such as anthracyclines, tyrosine kinase inhibitors, and immunotherapies.[7–9] Despite the high burden of HF-like symptoms in advanced cancer, there remains a critical unmet need for studies investigating the efficacy of established HF therapies in improving cardiac function and reducing symptomatic burden in this highly vulnerable population receiving palliative care. The EMPATICC (EMPower the heArt of patients with TermInal Cancer using Cardiac medicines) trial – a randomised controlled trial evaluates the efficacy of an optimised HF regimen including sacubitril/valsartan, empagliflozin, ivabradine, and ferric carboxymaltose in patients with advanced cancer and some evidence of cardiac dysfunction. In this trial, we aim to investigate whether the optimised HF therapy can improve self-care ability, physical functioning, and overall quality of life in patients with advanced cancer receiving specialized palliative care.

METHODS

Study Design

EMPATICC (INCOR 1) was a multicentre, investigator-initiated, randomised, controlled, double-blind proof-of-concept trial involving patients with cancer receiving palliative care with a life expectancy of 1–6 months, alongside optimised analgesia. The study was conducted across five centres in Germany. All relevant institutional review boards approved the protocol. The protocol adhered to the principles of Good Clinical Practice and the Declaration of Helsinki. This study adhered to the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. Written informed consent was obtained from all patients. Safety was assessed in an ongoing manor by the study steering committee in a blinded setting. Assessment of mortality (and particularly early mortality) for safety was performed by an unblinded sponsor representative.

Participants

Eligible participants were adults aged 18 years or older with stage 4 solid cancer in a specialized palliative care setting, an expected survival time of 1–6 months, and optimised pain management. Patients were required to meet at least two cardiovascular risk criteria: heart rate ≥70 bpm, N-terminal pro-B-type natriuretic peptide (NT-proBNP) ≥600 pg/mL, elevated high-sensitivity troponin, left ventricular ejection fraction (LVEF) <55%, left ventricular mass loss >15%, transferrin saturation <20%, or moderate/high likelihood of HF with preserved ejection fraction. Additionally, at least one functional criterion had to be present: ≥6 s to walk 4 m, inability to wash for ≥3 days out of the last 7 days, or symptoms of dyspnoea at rest (New York Heart Association [NYHA] class IV symptoms). These pre-randomisation eligibility domains aimed to ensure that included patients exhibited both signs of HF progression and clinical frailty and were – in the view of the involved HF cardiologists – more likely to benefit from the therapy tested. The detailed eligibility criteria are shown in **Table S1** in the Supplementary Appendix.

Randomisation and masking

On Day 1, participants were randomised 1:1 to either the HF therapy group or the control group, initiating the 30-day treatment phase. An unblinded study team was responsible for treatment decisions and administration study drugs, ensuring the blinding of the group assignement for patients and the medical staff involved in patient care and study assessments. Participants, treating oncologists (who provided the background standard of care therapy), and outcome assessors remained blinded to treatment allocation throughout the trial, ensuring that patient management and endpoint assessment were not influenced by knowledge of therapy assignment. In addition, the monitors and dedicated study personnel for assessment of study outcomes were blinded. Hence, this study was performed in a double-blind setting.

Procedures

The intervention involved an optimised HF treatment regimen, including sacubitril/valsartan, empagliflozin, ivabradine, and intravenous ferric carboxymaltose. Each medication in the optimised HF treatment regimen was administered according to guidelines and approved dosages.[10] Selection of therapies was guided by prior clinical experience in this vulnerable population, with a focus on maintaining tolerability while addressing key pathophysiological targets. Details regarding medication and procedures have been published previously.[11] Sacubitril/valsartan was initiated at 24/26 mg twice daily, titrated up to 97/103 mg twice daily, being a well stablished and potent renin-angiotensin system inhibitor in HF therapy.[12] Ivabradine was prescribed for patients with a resting heart rate ≥75 bpm in sinus rhythm, starting at 5 mg twice daily and adjusted up to 7.5 mg twice daily. The intent was to lower the heart rate of the cancer patients, as is done in HF with reduced ejection fraction therapy, since elevated heart rate in cancer patients is a well-established risk factor for higher mortality.[13,14] Empagliflozin was administered at a standard dose of 10 mg once daily, as it had already shown great benefits for patients with HF across the spectrum of LVEF including in HF with preserved ejection fraction (HFpEF).[15] Patients with iron deficiency (transferrin saturation [TSAT] <20%) received

intravenous ferric carboxymaltose, with dosage calculated based on body weight and haemoglobin levels, administered in 0.9% sodium chloride solution, in an effort to restore iron storages of patients with iron deficiency. Since ferritin is also an acute phase protein which is very often elevated in cancer patients, we only used TSAT <20% for defining iron deficiency, being the main biomarker for defining iron deficiency in cancer patients.[16]

Dosing adjustments and administration were overseen by certified cardiologists. Since each patient only received the medication/matching placebo if the above-mentioned criteria were met, each patient received a somewhat individualized therapy. The treatment regimen was individualised according to the clinical profile of each patient and eligibility for the individual agents, with some patients receiving one drug, others a combination, and those meeting all relevant criteria receiving all four agents. Patients in the control group received one to three placebo pills (manufactured by Zentiva Pharma, Berlin) and/or saline infusions to maintain blinding; saline and ferric carboxymaltose infusions utilised black infusion sets wrapped in opaque foil for blinding. The number of patients receiving each drug (or their respective placebo) and their combinations is summarised in Supplementary **Table S2.**

A 30-day randomisation phase was followed by a 30-day open-label extension phase, during which all participants could receive optimized HF therapy. In-person assessments were conducted on Days 10, 20, and 30 during the randomised phase, and on Days 40, 50, and 60 during the extension phase.

Outcomes

The protocol pre-specified that in case of higher than expected drop-out numbers, a win ratio approach would be utilized. As 32% of study patients died within 30 days, this approach was selected by the blinded members of the steering committee. The primary hierarchical endpoint consisted of three components: (1) days alive and able to wash themselves (selected as step 1, as the washing ability endpoint was the corner stone of this trial in this population from the beginning of study planning), (2) the ability to walk 4 m, and (3) the self-reported patient global assessment (PGA) of subjective well-being during the 30-day placebo-controlled phase. The first component, "days alive

and able to wash themselves," was assessed over a 30±2-day period, with counts ranging from 0 to 32 days. The second component, "ability to walk 4 m", was assessed at the visits on Days 10, 20, and 30, with counts ranging from 0 to 3 visits. The third component, "self-reported PGA of subjective well-being", was assessed at the last common assessment visit where both patients were alive (Day 30, 20, or 10) using a 7-point Likert scale. The ability to wash was selected as the primary endpoint based on extensive personal and professional experiences, supported by discussions with oncologists, palliative care specialists, cardiologists, regulators, and patients, where it was consistently rated as a highly meaningful measure of dignity at the end of life. The relevance of this endpoint is also supported by data from 169 patients with cancer receiving palliative care, where self-reported ability to walk 4 m and to wash oneselves were independent predictors of survival and related to worsening functional status.[17] PGA was used due to feasibility in this frail oncology population and it has been successfully applied in other advanced disease settings.[18] Moreover, the composite endpoint accounts for potential attrition due to death.

For the first component, days alive and able to wash oneself, any form of washing (e.g., shower, bath, sink, or sponge bath [in the patients' bed]) qualified. The observation period extended up to Day 30 (±2 days), with scores ranging from 0 to 32. A "win" was determined if one patient had more days than the other, exceeding a 1-day difference (or an equivalent % difference). When both patients completed the study, only the shared observation period—determined by the shorter follow-up—was considered. The second component, ability to walk 4 m, was assessed at Days 10, 20, and 30. Patients were scored based on the number of visits where they could complete the walk (range 0–3). Gait speed was calculated, but those unable to walk or deceased were assigned a speed of zero. The third component, PGA of well-being, was measured on a 7-point Likert scale from "much worse" to "much improved" and evaluated at the last visit where both patients were alive. When patients were analysed for the secondary endpoint of PGA, deceased patients were assigned a score of 8 ("dead"). A higher PGA is considered a win only if it is better than "much worse" (i.e., with a score ≤6). Sensitivity analyses include reordering the hierarchy (e.g., prioritising survival or PGA) and

incorporating all-cause mortality as the top-ranked component, with longer survival considered a win if the difference exceeds one day.

Key secondary endpoints included the individual components of the primary endpoint, change in the overall health/quality of life (QoL) score (i.e. question 15) of the EORTC QLQ-C15-PAL questionnaire[10], and change in NT-proBNP during the 30-day intervention phase. In addition, 2D-echocardiography was performed at baseline and day 30 and 60 by staff blinded to the treatment allocation and that data are reported as per local readings.

Safety endpoints included all-cause mortality for 30 days (end of intervention phase) and 60 days (end of extension phase), as well as until the end of follow-up for survival of all patients (30 days after the last study visit of the last patient, i.e., until the end of February, 2025).

Statistical Analysis

The statistical analysis plan was signed on June 20, 2025, and the database was locked on July 8, 2025. This trial aimed to randomise a minimum of 72 patients (36 per group), with a final sample size of 93 completely randomised patients. The sample size calculation was based on a two-sided alpha level of 0.05 and 85% power.[19] Assuming 11±6 days (mean ± standard deviation [SD]) alive and able to wash themselves in the control group, the HF therapy was expected to improve this measure by 5 days. A probabilistic index of 0.278 indicated the likelihood of a patient in the HF therapy group having more days alive and being able to independently wash themselves than a patient in the control group.

If the primary hypothesis was rejected, five key secondary endpoints were tested hierarchically with multiplicity adjustment. First, the "washing days" component was tested at 5% significance. If significant, four additional secondary endpoints – days able to walk 4 meters, PGA, QoL (EORTC

QLQ-C15-PAL Q15), and NT-proBNP – were tested using the Hochberg procedure to control the familywise type I error rate.

The dataset for analysis included 90 patients for whom at least one data point for any primary or secondary endpoint was available after baseline, i.e. we use a modified intention to treat approach. Data for deceased or withdrawn patients were imputed based on the dependency of withdrawal on disease severity. In cases of withdrawal due to disease progression, worst-case values (e.g., PGA=7, walking speed = 0, no washing ability) were imputed for visits with missing data. The primary analysis used the win ratio approach without stratification. Finkelstein-Schoenfeld statistics, p-values, win ratio, win difference, win odds, and 95% confidence intervals (CI) were reported. Secondary analyses included win ratio for "days alive and able to wash". Walking ability was assessed via proportional odds logistic regression at Day 30, with non-ambulatory and deceased patients counted as unable to walk. Accumulated walking data from Days 10, 20, and 30 were modelled with ordinal outcomes ranging from 0–3; applying worst-case imputation as above. PGA was analysed using a mixed-effects proportional odds model with treatment, visit, treatment-by-visit interaction, and centre as fixed effects. Odds ratios (OR) and 95% CIs were calculated for Days 10, 20, and 30. EORTC QLQ-C15-PAL(q15) and NT-proBNP were analysed using mixed linear models for repeated measures (MMRM), with fixed effects for group, time, group-time interaction, baseline, and centre, assuming unstructured covariance. NT-proBNP was log-transformed. Least squares means (LSM) and between-group differences were reported with 95% CI.

Validated scales (ECOG) and other continuous outcomes (e.g., 4 m walking time) were analysed with MMRM. Ordinal outcomes like PGA were analysed using proportional odds models. All-cause mortality was analysed using Cox proportional hazards regression adjusted for centre. Hazard ratios (HR) with 95% CI were reported. The proportional hazards assumption was assessed via Schoenfeld residuals and time-by-treatment interaction testing. Kaplan-Meier survival curves with p-values from the Cox regression were used for group comparisons.

Subgroup analyses explored variations in outcomes based on sex, age, baseline self-care/mobility status/4m walking time, ECOG performance status, and BMI. These outcomes should be regarded as exploratory only, as the trial was not powered for these comparisons, and the small sample size (<100 randomised patients) with multiple testing increases the risk of over-interpretation. Sensitivity analyses explored robustness to fatal events, missing data, and withdrawal patterns. All statistical analyses were performed using R (R Core Team).

Organisational aspects

Principal investigators and representatives from BROST Stiftung designed the trial protocol. MSA, AAM, TF, SDA and TR had unrestricted access to the data and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. The first draft of the manuscript was written by MSA, AAM, and MSK, and all statistical analyses were performed by MP and MH. The manuscript was reviewed and edited by all co-authors.

RESULTS

Patient Population

Between December 2022 through November 2024, patients were screened on oncology wards and palliative care clinics of participating sites. For a total of 95 patients, inclusion and exclusion criteria are documented in the database, and for 93 patients the randomisation process was completed (distribution across centers: Essen: 56 patients, Berlin: 26, Heidelberg: 4, Leipzig: 4, Homburg: 3). A total of 46 patients were randomly assigned to the optimised HF therapy plus usual care and 47 to the control group (**Figure 1**). At baseline, 72% patients were on anti-cancer therapy. Of note, treatment with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitor was stopped shortly (i.e., within 2 days) before randomization in 27 participants) to allow for potential treatment with sacubitril/valsavartan. In addition, treatment with sodium-glucose co-transporter 2

inhibitors was stopped in 6 participants. While there were other changes in concomitant medication in a few more cases shortly before start of the study medication, these were initiated by the treating oncologists and related to the current clinical condition rather than to study medication.

The baseline characteristics of the patients are shown in **Table 1** and **Table S3** – the characteristics are indicative of a cohort of patients with advanced cancer (UICC stage 4) in palliative care. The details of the underlying cancer disease (all patients had solid cancers) are provided in **Table S4**. At screening, 68 (73%) had ability to walk 4 m, 39 (42%) reported inability to wash themselves for ≥3 of the past 7 days, 87 (94%) took ≥6.0 s to walk 4 m or had inability to walk 4 m at all and 36 (39%) had iron deficiency (TSAT <20%) (**Table 1**).

Primary Endpoint

Details on the treatment provided in actively treated patients are provided in **Table S5**. The primary hierarchical composite endpoint event did not differ significantly differ between groups (win ratio, 0.95; 95% CI 0.57–1.58; P = 0.83) (**Figure 2, Table 2, Graphical Abstract**). Prespecified subgroup analyses revealed no significant treatment-by-subgroup interactions when assessing interactions for men vs women, by age, body mass index and ECOG status and walking ability at baseline with P-interaction of 0.11 to 0.92 (**Table 1**). Sensitivity analyses, including those incorporating mortality as a first stage, excluding patients with study withdrawal unrelated to disease progression or restricted to survivors at Day 30, did not show a significant difference in the primary hierarchical composite endpoint (win ratio 1.03 to 1.07, all P ≥0.78, **Table S6**).

Secondary Endpoints

Results for days alive and able to wash oneself during 30 days follow-up (P = 0.87) and for the ability to walk 4 m (at visit D10, D20 and D30 – P = 0.34) were not different between for patients in the HF therapy group or control group (**Figure 3A** and **Figure 3B**). Also, self-reported PGA of well-being was not significantly different between groups (for results at Day 30: P=0.68, **Figure 3C**).

At day 30, self-reported overall QoL, assessed by Question 15 of the EORTC QLQ-C15-PAL, was not significantly different between the optimised HF therapy group and control group (LSM difference, 8.9; 95% CI -2.4 to 20.2; *P* = 0.12) (**Figure 3D**).

Analysing the changes in NT-proBNP levels from baseline to Day 30, NT-proBNP levels were found lowered by active therapy compared to control by 41% (LSM difference: -0.41; 95% CI -0.80 to -0.02; *P* = 0.040) (**Figure 4A**). Of note, this analysis was restricted to patients who were alive and had blood samples taken and analysed at the time of the visit (i.e. a total of 47 patients were included in the analysis at visit Day 30). Results were validated by assessing changes in LVEF, that revealed that LVEF increased from baseline to Day 30 in those alive at that visit (treatment estimate at day 30: +2.9% (95% CI 0.2% – 5.6%), p=0.036, **Figure 4B**).

All-cause Mortality

Of the 93 patients randomized, at day 30 and day 60, we observed 29 and 42 deaths, respectively, i.e. a mortality of 32% [95% CI 24-43%] and 47% [95%CI 38-58%], respectively. During the entire follow-up period available, 74 deaths were observed (12 months mortality 86% [95% CI 77-93%]). Cox proportional hazards analysis showed no difference between groups with a HR of 0.85 (95% CI 0.53–1.36; p=0.49) for HF therapy group vs control group (**Figure 5A** and **5B**).

Exploratory analysis

Because, no difference in mortality was observed, and as changes in NT-proBNP and LVEF suggested that active therapy was effective from a cardiovascular standpoint in survivors, we performed survivor analyses also for QoL-related secondary endpoints. In analyses restricted to patients who survived until Day 30, the HF therapy group demonstrated a significantly more favourable PGA at Day 30 compared to the control group (OR 0.22; 95% CI 0.06 - 0.75; P = 0.016,

Figure S1A). At day 30, the LSM difference for self-reported overall quality of life as assessed by EORTC QLQ-C15-PAL(q15) was 10.5 (95% CI, -0.9 to 21.9; P = 0.07, **Figure S1B**).

Treatment tolerability

In total, 28 adverse events of special interest occurred in 18 participants that were considered as possibly or probably related to study drug. However, 18 of these events occurred in placebo-treated patients. The remaining 10 events consisted of hypotension (6 events), dizziness, hypokalemia, hyperkalemia and deterioration of chronic renal failure (each 1 event). There were no discontinuations related to tolerability issues of the study medication.

DISCUSSION

In the EMPATICC trial, patients with advanced cancer in a specialized palliative care setting, treatment with an optimized heart failure regimen – variable combinations of up to four drugs – did not improve a hierarchical composite outcome focusing on survival together with self-care ability and walking ability. Also, the components of this hierarchical outcome measure were not affected positively, when studied in isolation. In patients who survived through 30 days, results suggest that optimized HF therapy was associated with improvements in cardiac function and QoL.

We recruited a population of patients with advanced cancer receiving specialised palliative care who showed symptomatic impairment and limited self-care ability as well as features of cardiac abnormalities. Around 72% of the patients were receiving ongoing anti-cancer therapy at baseline. Therefore, although patients were in a palliative care setting, the majority were still being actively treated for their malignancy, and not uniformly considered ‘terminal’ by their oncology teams.

Using a well-recognised score to assess likelihood of presence of HFpEF in patients with (presumed) cardiovascular disease, more than 80% of patients had intermediate or large likelihood of a diagnosis

of HFpEF at baseline (**Table S3**). Nevertheless, we would like to emphasise that there was no intend to select for presence of HFpEF per se, and no formal diagnosis of HFpEF was made in any patient. For instance, in a patient with intermediate likelihood this would require stress echocardiography and/or invasive haemodynamic assessments, which was not deemed appropriate for these patients.[32] This tool is not validated in advanced cancer. In many cases, elevated HFA-PEFF scores[32] were driven by increased NT-proBNP levels (>660 pg/mL), which contributed two points to the score. Median NT-proBNP values were between 600–800 pg/mL in both arms.

We selected a regimen tailored to patients with advanced cancer. Beta-blockers were avoided due to concerns for poor short-term quality of life responses, and mineralocorticoid receptor antagonists due to concerns for hyperkalemia. Sacubitril/valsartan was identified as the most effective renin-angiotensin system inhibitor; sodium-glucose co-transporter 2 inhibitor was used due to established cardio-kidney protective effects across the LVEF spectrum; ivabradine was used due to heart rate-reducing effects without the adverse effects of beta-blockers; and ferric carboxymaltose was used to address the frequent comorbidity of iron deficiency. Moreover, the choice of sacubitril/valsartan and ivabradine (not approved for HFpEF in Europe) was guided by the frequent presence of reduced systolic function in cancer patients with cardiac wasting cardiomyopathy[20], and presence of elevated heart rate with strong adverse prognostic meaning.[13] Furthermore, ivabradine has also shown benefit in a small study with patients with moderate to advanced HF.[21]

Many patients with increased heart rates and NT-proBNP levels, and somewhat reduced LVEF at baseline, and with presence of dyspnoea and very poor functional capacity, are indicative of possible presence of a HF like syndrome. However, the washing ability and 4 m walking ability dichotomous endpoints as used in the trial appear to be not sensitive to change in these patients, mostly at the end-of-life. Given a mortality rate of 32% at 30 days, the short remaining survival time of many patients appears to have dominated over the washing and walking ability assessments in this context. This is particularly seen in Figures 3A and 3B where extremes (i.e. to be able to wash one-selves most days or none, and the ability to walk 4 m on at all three assessment visits or none) dominated the observed

outcomes. Using such endpoints, it may be preferable to only include patients who are not able to walk 4 m and/or to include only patients who have specific problems with performing self-care activities. In addition, consistent daily documentation may be preferable for such activities.

We aimed to include in EMPATICC patients with advanced cancer with a life expectancy of 1-6 months at the time of inclusion. The observed mortality of 32% at day 30 and 47% at day 60 indicates to us that we did not achieve what we aimed for. Given the results particularly in those surviving at least 30 days, suggests that the aim was a correct one. This study shows that predicting survival times in advanced cancer receiving specialized palliative care is not easy and deaths might occur much faster and more often than anticipated. Developing better survival prediction models for patients with advanced cancer could be very beneficial for future clinical trials to be designed in this medical space.

The treatment did improve objective measures of cardiac function, i.e. plasma levels of natriuretic peptides and LVEF as assessed by echocardiography. Of note, these results are restricted to patients alive at the time of assessment. This and the finding of mortality rates in both treatment groups being identical at 30 and 60 days, prompted a survivor analysis of secondary endpoints related to QoL. Patients who were alive at day 30 and who had been randomized to active HF therapy expressed a 4.5 times higher likelihood of being 1 rank better in the PGA assessment score (p=0.04) (**Figure S1**). Also, the results of the overall health and quality of life score of the EORTC QLQ-C15-PAL questionnaire – showing an effect size of >10.0 in survivors (p=0.07) – suggest a positive clinically meaningful difference.[22] Based on these results, we hypothesise that patients with advanced cancer receiving specialized palliative care need to survive at least 30 days to be able to possibly derive benefit from optimized HF therapy. While treatment decisions at baseline cannot predict with certainty which patients will survive long enough to benefit, our findings suggest that a survival of at least 30 days may be a prerequisite for measurable improvements in QoL and cardiac function. This needs to be tested in future studies.

Prior studies in cardio-oncology have primarily focused on preventing cardiotoxicity related to cancer therapies and have largely excluded individuals receiving palliative care.[23,24] Evidence on the efficacy of guideline-directed HF therapy in this population is lacking. Current guidelines on palliative care at the end of life focus primarily on symptomatic treatment, e.g. shortness of breath, and only touch on causal therapies in passing.[25-27] Palliative care physicians often tend to discontinue some of medication towards end-of-life. The use of HF drugs is not common given the lack of evidence.[28] The literature on double-blind randomized clinical trials of patients with advanced cancer in specialized palliative care with very short expected survival times is scarce.[29,30] Importantly, EMPATICC shows that inter-disciplinary clinical trials with double-blind medication (of several drugs) in palliative care settings are possible. Screening failures were low with 93 randomized patients of 112 patients that were screened. Once patients were recruited, they tended to remain in the trial. With only 3 of 93 patients, withdrawal rates unrelated to disease progression were lower than expected.

While the EMPATICC trial focused on patients with stage 4 solid tumours, we acknowledge that other advanced diseases, including for instance haematological cancers[4] or chronic obstructive pulmonary disease[31], may also present with HF-like symptoms and benefit from similar therapeutic strategies. Future studies could explore these populations as well. In the present trial, we sought to maintain a relatively homogeneous disease background to optimise feasibility and clinical applicability, to ensure patients could provide informed consent, and to be able to complete the planned study assessments.

In this highly frail and functionally limited population of patients with advanced cancer receiving specialized palliative care, the EMPATICC trial did not demonstrate significant improvements patients' self-care and walking ability in the primary hierarchical endpoint that *de facto* also included all-cause mortality. In patients who survived through 30 days, the optimized HF therapy was associated with improvements in cardiac function and QoL. These findings suggest that, despite the challenges of late-stage disease, selected patients – with somewhat less poor prognosis than included here – may

derive meaningful benefit. Our results lead us to hypothesise that individualized HF therapy as part of appropriately timed, individualized palliative care strategies, is beneficial in patients with advanced cancer and an expected survival and treatment duration of at least 2-3 months or more. This will require confirmation in independent clinical trials.

Declarations

Disclosure of interest

MSK has received fees from Bayer and Novartis

TH institution received research funds from Adocia, Afon Technology, Astra Zeneca, Altimmune, Betagenon, Biocon, Bioton, Cass Pharmaceuticals, Civica Foundation, Corteria, Cytoki, Eli Lilly, Enyo Pharma, Gan&Lee Pharmaceuticals, Genova, Nanexa, Neodyne, Novo Nordisk, SamChunDang Pharm. Co., Spiden, Sun Pharma and Zealand Pharma. TH received speaker honoraria from Eli Lilly and Novo Nordisk. TH is a paid consultant to Gan&Lee Pharmaceuticals.

LB honoraria from AbbVie, Amgen, Astellas, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Gilead, Hexal, Janssen, Jazz Pharmaceuticals, Menarini, Novartis, Otsuka, Pfizer, Roche, and Sanofi; research funding from Bayer, Jazz Pharmaceuticals.

TR honoraria, lecture fees, and grant support from Edwards Lifesciences, AstraZeneca, BMS; Bayer, Novartis, Berlin Chemie, Daiicho-Sankyo, Boehringer Ingelheim, Novo Nordisk, Cardiac Dimensions, and Pfizer, all unrelated to this work. He is co-founder of Bimyo GmbH, a company that develops cardioprotective peptides, co-founder of Mycor GmbH, a company focusing on AI-based EKG-algorithms and co-founder of Yes2NO, developing nitric oxide-based treatments. TR is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation; RTG 2989, project number 517043330)

UL: Personal fees from Amgen, AstraZeneca, Bayer, Berlin-Chemie, Boehringer, Daiichi-Sankyo, Lilly, Novartis, Sanofi

MB is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation; TTR 219, project number 322900939) and reports personal fees from Amgen, Astra Zeneca, Bayer,

Boehringer Ingelheim, Cytokinetics, EDWARDS, Medtronic, Novartis, ReCor and Servier during the conduct of the study.

SDA reports grants and personal fees from Vifor and Abbott Laboratories, and personal fees for consultancies, trial committee work and/or lectures from Actimed, Alleviant, Astra Zeneca, Bayer, Berlin Heals, Boehringer Ingelheim, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Cytokinetics, Edwards, Impulse Dynamics, Lilly, Mankind Pharma, Medtronic, Novo Nordisk, Occlutech, Pfizer, Regeneron, Relaxera, Repairon, Scirent, Sensible Medical, Vectorious, Vivus, and V-Wave. Named co-inventor of two patent applications regarding MR-proANP (DE 102007010834 & DE 102007022367), but he does not benefit personally from the related issued patents.

JB: Consultant Abbott, Adaptyx, American Regent, Amgen, AskBio, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Cardiac Dimension, Cardior, CSL Vifor, CVRx, Cytokinetics, Daxor, Diastol, Edwards, Element Sciences, Faraday, Idorsia, Impulse Dynamics, Imbria, Innolife, Intellia, Inventiva, Levator, Lexicon, Eli Lilly, Mankind, Medtronic, Merck, New Amsterdam, Novartis, NovoNordisk, Pfizer, Pharmacosmos, Pharmain, Prolaio, Pulnovo, Regeneron, Renibus, Reprieve, Roche, Rycarma, Saillent, Salamandra, Salubris, SC Pharma, SQ Innovation, Secretome, Sequanna, Transmural, TekkunLev, Tenex, Tricog, Ultromic, Vera, Zoll

AAM: honoria and/or advisory boards: Amgen, Berlin Chemie, Daiichi Sankyo, Edwards, Novartis, Sanofi. Research funding: Daiichi Sankyo, Edwards, all outside the submitted work.

Co-founder of Mycor GmbH, a company focusing on AI-based EKG-algorithms.

MT is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation; RTG 2989, project number 517043330) and by the German Cancer Aid (Deutsche Krebshilfe). MT has received honoraria, lecture fees, and grant support from Edwards Lifesciences, AstraZeneca, BMS; Bayer, Novartis, Berlin Chemie, Daiicho-Sankyo, Boehringer Ingelheim, Novo Nordisk, all unrelated to this work.

MS is supported by the National Center of Tumor Diseases (NCT) West, and by an Oncology Center of Excellence support grant to the West German Cancer Center). He has received institutional research grants from AstraZeneca, Bristol Myers Squibb, and Johnson & Johnson, consulting fees, fees of CME presentations, and has participated on advisory boards for Amgen,

AstraZeneca, Bristol Myers Squibb, Gilead, GlaxoSmithKline, Immunocore, Johnson & Johnson, MSD, Novartis, Regeneron, Roche, and Sanofi.

All other authors declare no conflict of interest

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding

The trial was supported by an unrestricted grant from the BROST Stiftung to the Clinic of Cardiology and Vascular Medicine of the Universitätsmedizin Essen, Germany

Ethical approval

All relevant institutional review boards approved the protocol.

Pre-registered clinical trial number

EudraCT Number: 2021-006994-48

NCT05636774

Acknowledgements: The trial was supported by an unrestricted grant from the BROST Stiftung to the Clinic of Cardiology and Vascular Medicine of the Universitätsmedizin Essen, Germany

References:

1. Rausch V, Sala V, Penna F, Porporato PE, Ghigo A. Understanding the common mechanisms of heart and skeletal muscle wasting in cancer cachexia. *Oncogenesis 2020 10:1*. 2021;10: 1-13. doi:10.1038/s41389-020-00288-6
2. Peixoto da Silva S, Santos JMO, Costa e Silva MP, Gil da Costa RM, Medeiros R. Cancer cachexia and its pathophysiology: links with sarcopenia, anorexia and asthenia. *J Cachexia Sarcopenia Muscle*. 2020;11: 619. doi:10.1002/JCSM.12528
3. Anker MS, Rashid AM, Butler J, Khan MS. Cardiac wasting in patients with cancer. *Basic Res Cardiol*. 2024;120: 25. doi:10.1007/S00395-024-01079-5
4. Anker MS, Sanz AP, Zamorano JL, Mehra MR, Butler J, Riess H. et al. Advanced cancer is also a heart failure syndrome: a hypothesis. *Eur J Heart Fail*. 2021;23:140-144. doi:10.1002/ejhf.2071
5. Khan MS, Butler J, Khan LA, Anker MS. Advanced cancer as a heart failure like syndrome due to cardiac wasting cardiomyopathy: facts and numbers. *Global Cardiology*. 2024;2(4):e58. doi.org/10.4081/cardio.2024.58
6. Khan LA, Khan MS, Latif RU, Anker MS. Cardiac wasting in patients with advanced cancer: state of the art review. *Global Cardiology*. 2025;3(1):e65. doi:10.4081/cardio.2025.65
7. Camilli M, Cipolla CM, Dent S, Minotti G, Cardinale DM. Anthracycline Cardiotoxicity in Adult Cancer Patients: JACC: CardioOncology State-of-the-Art Review. *JACC CardioOncol*. 2024;6: 655-677. doi:10.1016/J.JACCAO.2024.07.016/SUPPL_FILE/MMC1.DOCX
8. Caspani F, Tralongo AC, Campiotti L, Asteggiano R, Guasti L, Squizzato A. Prevention of anthracycline-induced cardiotoxicity: a systematic review and meta-analysis. *Intern Emerg Med*. 2021;16: 477-486. doi:10.1007/S11739-020-02508-8,
9. de Baat EC, Mulder RL, Armenian S, Feijen EA, Grotenhuis H. Hudson M. et al. Dexrazoxane for preventing or reducing cardiotoxicity in adults and children with cancer receiving anthracyclines.

Cochrane Database of Systematic Reviews. 2022;2022(9). doi: 10.1002/14651858.CD014638.PUB2

10. Anker MS, Mahabadi AA, Totzeck M, Tewes M. Mincu R, Khan MS et al. Randomized investigation of heart failure therapy in patients at risk of cardiac wasting in patients with advanced cancer: rationale and design of the EMPATICC trial. *Eur J Heart Fail. 2025 (in press)*
11. Anker MS, Khan MS, Mahabadi AA, Totzeck M, Tewes M, Arshad MS et al. Optimized HF Therapy in Patients with Very Advanced Cancer in Palliative Care: the Dosing Strategies from EMPATICC Trial. *Global Cardiology. 2025 (in press)*
12. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014 Sep 11;371(11):993-1004. doi: 10.1056/NEJMoa1409077. Epub 2014 Aug 30. PMID: 25176015.
13. Anker MS, Ebner N, Hildebrandt B, Springer J, Sinn M, Riess H, et al. Resting heart rate is an independent predictor of death in patients with colorectal, pancreatic, and non-small cell lung cancer: results of a prospective cardiovascular long-term study. *Eur J Heart Fail*. 2016 Dec;18(12):1524-1534. doi: 10.1002/ejhf.670. PMID: 27910284.
14. Anker MS, Frey MK, Goliasch G, Bartko PE, Prausmüller S, Gisslinger H, et al. Increased resting heart rate and prognosis in treatment-naïve unselected cancer patients: results from a prospective observational study. *Eur J Heart Fail*. 2020 Jul;22(7):1230-1238. doi: 10.1002/ejhf.1782. Epub 2020 Mar 23. PMID: 32202022; PMCID: PMC7540544.
15. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al.; EMPEROR-Preserved Trial Investigators. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med*. 2021 Oct 14;385(16):1451-1461. doi: 10.1056/NEJMoa2107038. Epub 2021 Aug 27. PMID: 34449189.
16. Ludwig H, Evstatiev R, Kornek G, Aapro M, Bauernhofer T, Buxhofer-Ausch V, et al.. Iron metabolism and iron supplementation in cancer patients. *Wien Klin Wochenschr*. 2015 Dec;127(23-24):907-19. doi: 10.1007/s00508-015-0842-3. Epub 2015 Sep 15. Erratum in: Wien

Klin Wochenschr. 2015 Dec;127(23-24):920-1. doi: 10.1007/s00508-015-0893-5. PMID: 26373748; PMCID: PMC4679104.

17. Anker MS, Lena A, Roeland EJ, Porthun J, Schmitz S, Hadzibegovic S, et al. Patient-reported ability to walk 4 m and to wash: New clinical endpoints and predictors of survival in patients with pre-terminal cancer. J Cachexia Sarcopenia Muscle. 2023 Aug;14(4):1670-1681. doi: 10.1002/jcsm.13247.

18. Nikiphorou E, Radner H, Chatzidionysiou K, Desthieux C, Zabalan C, van Eijk-Hustings Y, et al. Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. Arthritis Res Ther. 2016 Oct 28;18(1):251. doi: 10.1186/s13075-016-1151-6.

19. Yu RX, Ganju J. Sample size formula for a win ratio endpoint. *Stat Med*. 2022;41: 950-963. doi:10.1002/SIM.9297

20. Lena A, Wilkenshoff U, Hadzibegovic S, Porthun J, Rösnick L, Fröhlich AK, et al. Clinical and Prognostic Relevance of Cardiac Wasting in Patients With Advanced Cancer. *J Am Coll Cardiol*. 2023 Apr 25;81(16):1569-1586. doi: 10.1016/j.jacc.2023.02.039.

21. De Ferrari GM, Mazzuero A, Agnesina L, Bertoletti A, Lettino M, Campana C, Schwartz PJ, Tavazzi L. Favourable effects of heart rate reduction with intravenous administration of ivabradine in patients with advanced heart failure. Eur J Heart Fail. 2008 Jun;10(6):550-5. doi: 10.1016/j.ejheart.2008.04.005.

22. Miyazaki K, Suzukamo Y, Ikenaga M, Ohsumi S, Saito M, Satomi E et al. . Interpretation of clinically meaningful change in cancer palliative care patients' quality of life: minimally important difference for EORTC QLQ-C15-PAL. *Journal of Patient-Reported Outcomes*. 2025;9:33. doi.org/10.1186/s41687-025-00858-5.

23. Sara JD, Kaur J, Khodadadi R, Rehman M, Lobo R., Chakrabarti S. et al. 5-fluorouracil and cardiotoxicity: a review. *Ther Adv Med Oncol*. 2018; 10:1758835918780140. doi:10.1177/1758835918780140

24. Curigliano G, Lenihan D, Fradley M, Ganatra S, Barac A., Blaes A. et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. *Annals of Oncology*. 2020; 31:171-190. doi: 10.1016/J.ANNONC.2019.10.023

25. Hui D, Maddocks M, Johnson MJ, Ekstrom M, Simon ST, Ogliari AC et al. Management of breathlessness in patients with cancer: ESMO Clinical Practice Guidelines†. *ESMO Open*. 2020;5(6):e001038. doi:10.1136/esmoopen-2020-001038

26. Albert RH. End-of-Life Care: Managing Common Symptoms. *Am Fam Physician*. 2017,95:356-361.

27. Sanders JJ, Temin S, Ghoshal A, Alesi ER, Ali ZV, Chauhan C, et al.. Palliative Care for Patients With Cancer: ASCO Guideline Update. *J Clin Oncol*. 2024;42:2336-57. doi: 10.1200/JCO.24.00542.

28. Elsten EECM, Pot IE, Geijteman ECT, Hedman C., van der Heide A., van der Kuy PHM. et al. Recommendations for Deprescribing of Medication in the Last Phase of Life: An International Delphi Study. *J Pain Symptom Manage*. 2024;68(5):443-455.e2. doi:10.1016/j.jpainsymman.2024.07.029

29. Thomas J, Karver S, Cooney GA, Chamberlain BH, Watt CK, Slatkin NE, et al.. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med*. 2008;358:2332-43. doi: 10.1056/NEJMoa0707377.

30. Yuan CS, Foss JF, O'Connor M, Osinski J, Karrison T, Moss J et al.. Methylnaltrexone for reversal of constipation due to chronic methadone use: a randomized controlled trial. *JAMA*. 2000;283:367-72. doi: 10.1001/jama.283.3.367.

31. Andreas S, Anker SD, Scanlon PD, Somers VK. Neurohumoral activation as a link to systemic manifestations of chronic lung disease. *Chest*. 2005 Nov;128(5):3618-24. doi: 10.1378/chest.128.5.3618.

32. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus

recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019 Oct 21;40(40):3297-3317. doi: 10.1093/eurheartj/ehz641..

Figure Legends

Figure 1. Consort flowchart

* 2 did not fulfill any group 2 inclusion criteria, 2 fulfilled no or only one of the group 1 inclusion criteria, 2 had life expectancy <1 month, 1 did not have solid cancer in UICC stage 4, 1 had an impaired neurological status, precluding the ability to walk, 1 had severe pulmonary embolism (PE) in the last 4 weeks

Figure 2. Win Ratio Analysis of Primary Hierarchical Composite Endpoint.

The win difference (95% CI) is -2.57% (-26.4% to 21.2%) comparing treatment versus control group.

Figure 3. Key secondary endpoints: (A) Percentage of days alive and able to wash oneself (N=87), (B) Times able to walk 4 meters during FU (0-3, N=90), (C) Patient Global Assessment at day 30 (N=85), and (D) EORTC QLQ-C15-PAL – change over time (MMRM, N_{BL}=90, N_{day10}=74, N_{day30}=58).

Figure 4. Trajectory of change from baseline in control and heart failure therapy groups in (A) log transformed NT-proBNP Least Squares Means (= key secondary endpoint, change over time) ($N_{baseline}$=90, N_{day10}=69, N_{day30}=47), and (B) left ventricular ejection fraction (change over time, $N_{baseline}$=90, N_{day30}=46, N_{day60}=30).

Figure 5. Kaplan-Meier Curves for All-Cause Mortality (A) at 60 Days of Follow-up, and (B) complete follow-up (until the end of all safety follow-up, i.e. 1 month after the last visit of the last patient)

Table 1. Baseline Characteristics of Patients

Characteristic	Heart Failure Therapy (N=46)	Placebo N=47)
Demographics		
Age	62.5 (55.0 - 69.0)	69.0 (61.0 - 77.0)
Sex (female)	20 (43.5%)	23 (48.9%)
Body Mass Index, kg/m^2	24.6 (21.8 - 29.0)	23.5 (21.5 - 30.0)
Vital Signs & Lab Parameters		
Systolic BP, mmHg	120.0 (109.0 - 140.0)	120.0 (110.0 - 138.0)
Diastolic BP, mmHg	71.0 (67.0 - 80.0)	71.0 (69.0 - 80.0)
Heart rate, bpm	90.0 (80.0 - 97.0)	89.0 (73.0 - 96.0)
NT-proBNP, pg/mL, median (IQR)	599.0 (309.0 - 1,159.0)	819.0 (305.0 - 3,509.0)
eGFR, mL/min/1.73m^2	61.5 (53.0 - 96.0)	66.7 (55.1 - 83.5)
Haemoglobin, g/dL	10.4 (9.0 - 11.5)	10.0 (8.9 - 11.4)
Transferrin Saturation (%) TSAT <20%	16 (34.8%)	20 (42.6%)
LVEF (%)	57.0 (52.0 - 63.0)	58.5 (53.0 - 64.0)
Co-morbidities		
Hypertension	30 (65.2%)	29 (61.7%)
Diabetes mellitus	15 (32.6%) (1 Type I, 14 Type II)	12 (25.5%) (0 Type I, 12 Type II)
Coronary artery disease	9 (19.6%)	6 (12.8%)
CKD (eGFR <60 mL/min/1.73m^2)	11 (31.4%)	11 (29.0%)
Anaemia	42 (91.3%)	39 (83.0%)
Baseline Medications		
Beta-blocker	19 (41.3%)	22 (46.8%)
ACE-I or ARB	13 (28.3%)	18 (38.3%)
Spironolactone	6 (13.0%)	9 (19.2%)
Loop diuretic	18 (39.1%)	18 (38.3%)
Ivabradine	0	0
SGLT2i	10 (21.7%)	3 (6.4%)
Anticoagulant	20 (43.5%)	19 (40.4%)
Antidepressants	11 (23.9%)	13 (27.7%)
Corticosteroids	13 (28.3%)	18 (38.3%)
Antiemetics	15 (32.6%)	20 (42.6%)
NSAIDs	14 (30.4%)	13 (27.7%)
Opioids	26 (56.5%)	26 (55.3%)
Anti-cancer therapy	36 (78.3%)	34 (72.3%)
Prior chemotherapy	35 (76.1%)	37 (78.7%)
Prior radiation therapy	21 (45.7%)	18 (38.3%)
Functional Status & Symptoms		
Dyspnoea at rest, n (%)	9 (19.6%)	15 (31.9%)
Was the subject able to walk 4 meters?, n (%)	33 (71.7%)	35 (74.5%)
1st measurement: Time to walk 4 meters	7.0 (6.0 - 10.0)	7.3 (6.0 - 10.0)
≥6.0 seconds to walk 4 meters / inability to walk inability to walk 4m at all, n (%)	44 (95.7%)	43 (91.5%)

Not being able to wash themselves in at least 3 of the last 7 days, n (%)	21 (45.7%)	18 (38.3%)
Peripheral leg oedema, n (%)	20 (43.5%)	21 (44.7%)
ECOG Performance Status ≥2	45 (97.8%)	46 (97.9%)

HF: Heart Failure; BP: Blood Pressure; bpm: beats per minute; NT-proBNP: N-terminal pro b-type Natriuretic Peptide; pg/mL: picograms per milliliter; IQR: Interquartile Range; eGFR: estimated Glomerular Filtration Rate (mL/min/1.73 m²); g/dL: grams per deciliter; TSAT: Transferrin Saturation; LVEF: Left Ventricular Ejection Fraction; CKD: Chronic Kidney Disease; ACE-I: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; ECOG: Eastern Cooperative Oncology Group Performance Status; dyspnoea: difficulty breathing.

Table 2. Primary and Secondary Endpoints

Endpoint	Win/odds ratio or LSM (95% CI)	P- value	
Primary Endpoint			
Hierarchical composite endpoint	0.95 (0.57 – 1.58)	0.83	
Secondary Endpoint			
Days alive and able to wash oneself	0.95 (0.51 – 1.76)	0.87	
4-meter walking ability	0.69 (0.32 – 1.49)	0.34	
PGA	0.77 (0.21 – 2.74)	0.68	
EORTC QLQ-C15-PAL overall health/QoL score	8.91 (-2.39 – 20.20)	0.12	
NT-proBNP	-0.41 (-0.80 – -0.02)	0.04	
Subgroup Analysis for the primary endpoint *			**P-interaction**
Male	0.71 (0.36 – 1.40)	0.32	0.21
Female	1.38 (0.62 – 3.03)	0.43	
Age <67 years	0.87 (0.40 – 1.89)	0.72	0.46

Age ≥67 years	1.30 (0.62 – 2.73)	0.49	
BMI <24 kg/m^2	0.84 (0.39 – 1.79)	0.65	0.92
BMI ≥24 kg/m^2	0.88 (0.43 – 1.80)	0.73	
Able to perform 4-m walking-test at BL – Yes	0.82 (0.46 – 1.47)	0.51	0.28
Able to perform 4-m walking-test at BL – No	1.72 (0.51 – 5.76)	0.38	
ECOG ≤2	0.53 (0.23 – 1.20)	0.13	0.11
ECOG ≥3	1.25 (0.63 – 2.48)	0.52	

EORTC QLQ-C15-PAL: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative care module; LS means: Least Square Means; SE: Standard Error; CI: Confidence Interval; NT-proBNP: N-terminal pro b-type Natriuretic Peptide; LS means with Time-Treatment Interaction: least square means calculated considering the interaction between time and treatment effects

*: The trial was not powered for subgroup analyses; results are exploratory and should be interpreted with caution.

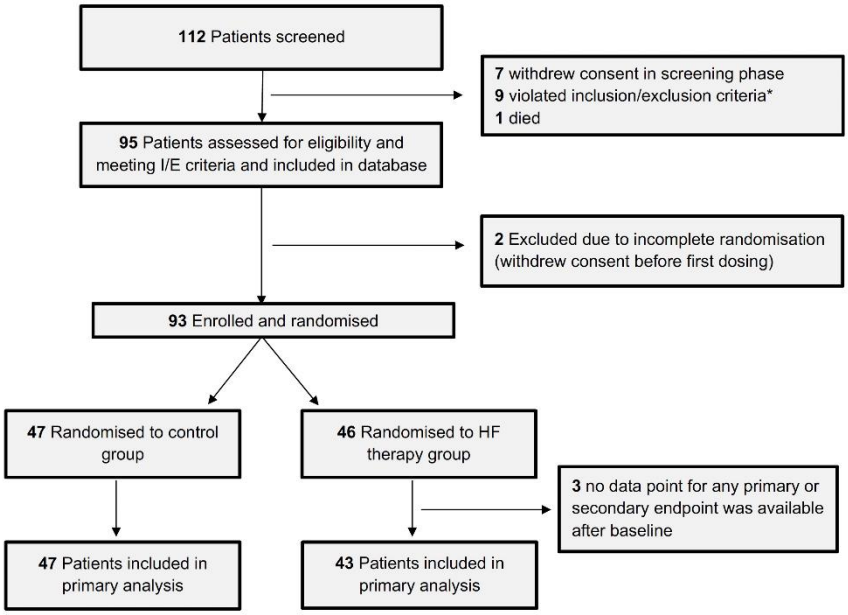
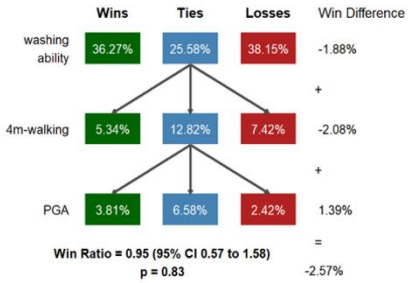


Figure 1
339x190 mm (DPI)



Primary Endpoint: Separate Stages

stage	wins	win_perc	losses	loss_perc	draws	draw_perc
1: washing	733	36.27	771	38.15	517	25.58
2: 4m-walking	108	5.34	150	7.42	259	12.82
3: PGA	77	3.81	49	2.42	133	6.58

Figure 2
339x190 mm (DPI)

Figure 3A
339x190 mm (DPI)

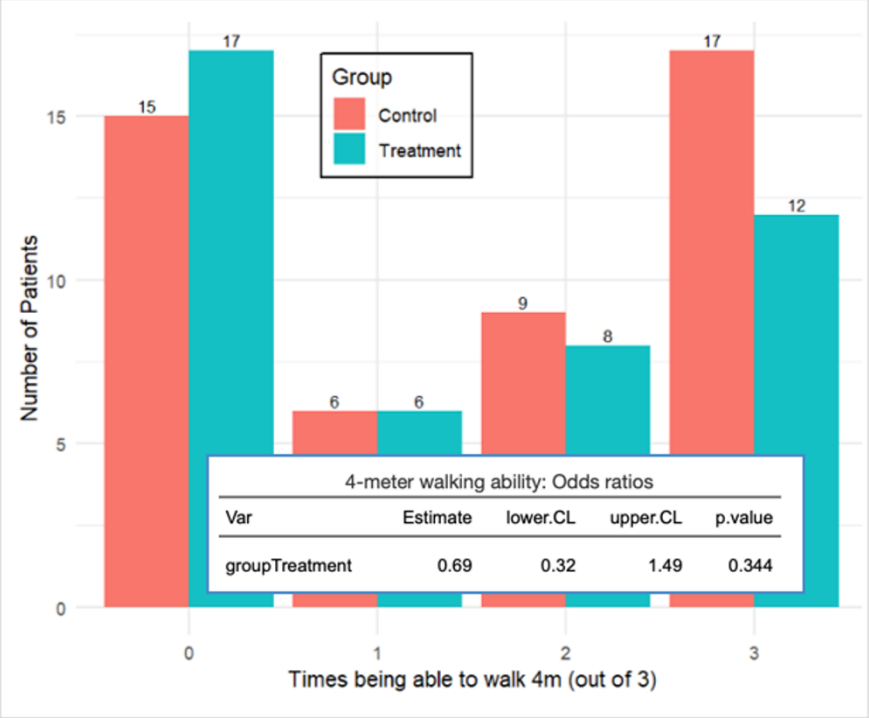


Figure 3B
339x190 mm (DPI)

Comparison	Estimate	lower.CL	upper.CL	p.value
Treatment Intervention Day 30 - Control Intervention Day 30	0.77	0.21	2.74	0.684

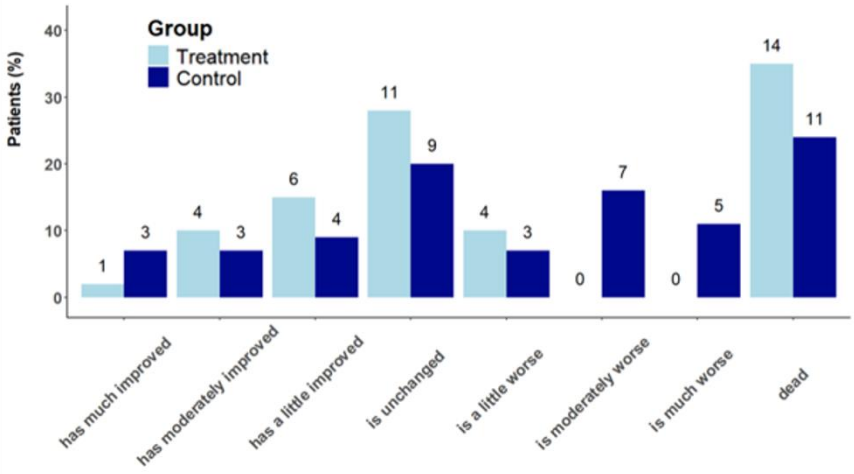


Figure 3C
339x190 mm (DPI)

EORTC15: Least square means with 95% CIs

group	VISIT	lsmean	SE	lower.CL	upper.CL
Control	Intervention Day 10	37.533	3.358	30.835	44.231
Treatment	Intervention Day 10	41.449	4.034	33.406	49.493
Control	Intervention Day 30	35.613	3.874	27.875	43.351
Treatment	Intervention Day 30	44.520	4.692	35.168	53.873

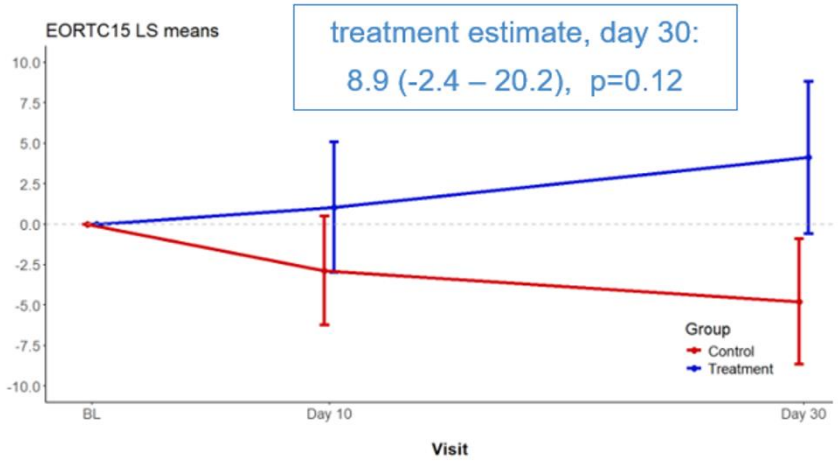


Figure 3D
339x190 mm (DPI)

NTproBNP: Geometric means with 95% CIs

group	VISIT	lsmean	lower.CL	upper.CL
Control	Intervention Day 10	0.820	0.622	1.082
Treatment	Intervention Day 10	0.563	0.400	0.791
Control	Intervention Day 30	1.026	0.712	1.480
Treatment	Intervention Day 30	0.619	0.397	0.966

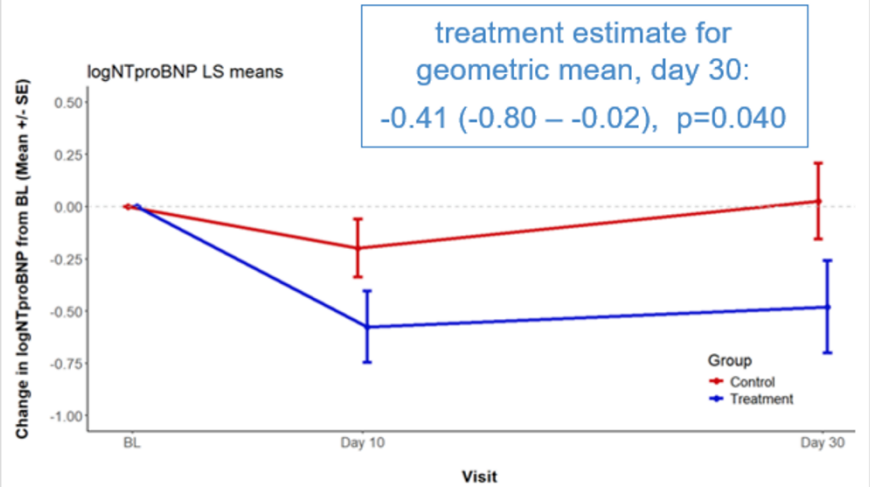


Figure 4A
339x190 mm (DPI)

LVEF differences to BL: Least square means with 95% CIs

group	VISIT	lsmean	SE	lower.CL	upper.CL
Control	Intervention Day 30	-0.985	0.905	-2.810	0.841
Treatment	Intervention Day 30	1.938	1.217	-0.516	4.392

LVEF differences to BL: Difference of least square means

contrast	estimate	SE	lower.CL	upper.CL	p.value
Treatment 30d - Control 30d	2.923	1.349	0.202	5.643	0.0359

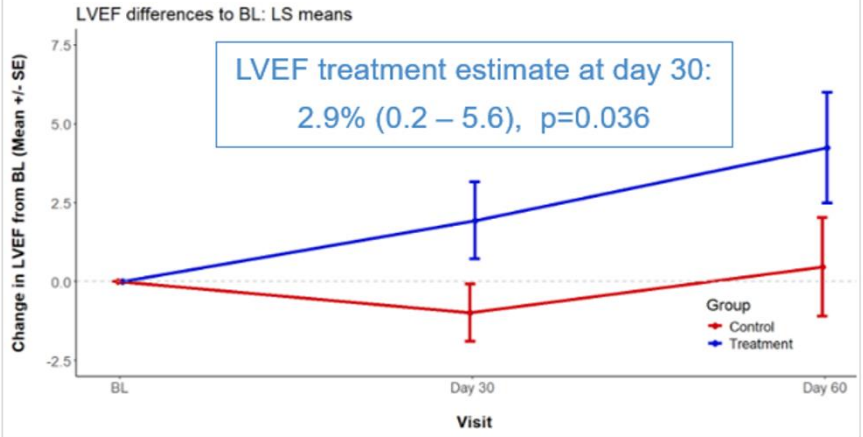


Figure 4B
339x190 mm (DPI)

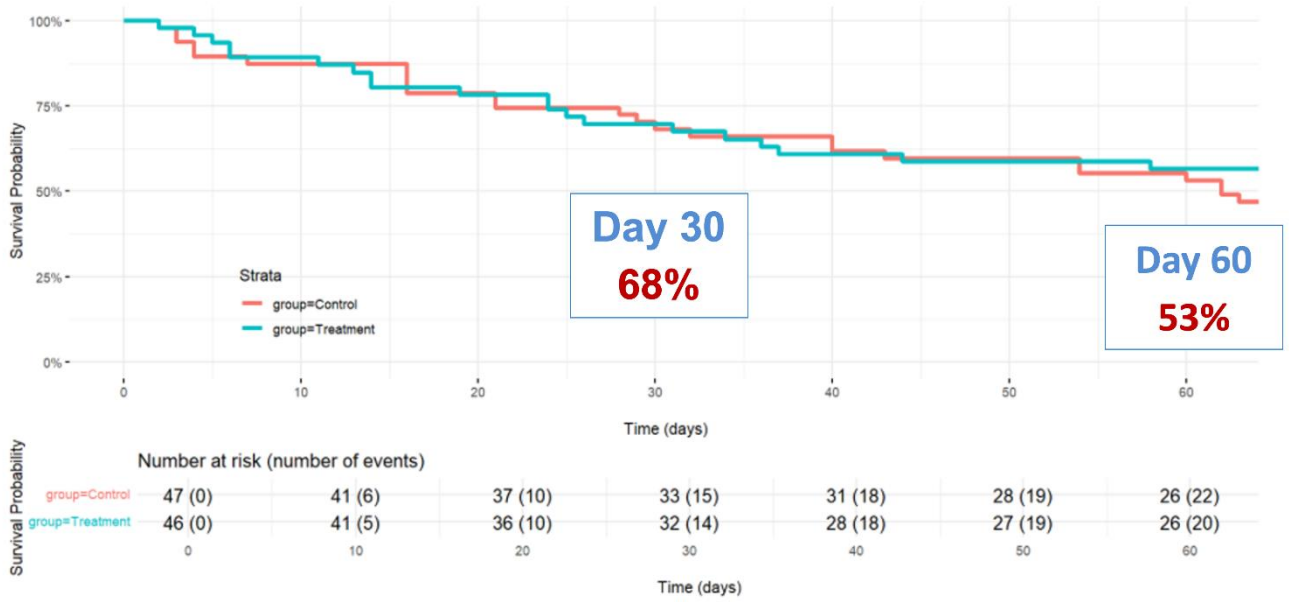


Figure 5A
339x190 mm (DPI)

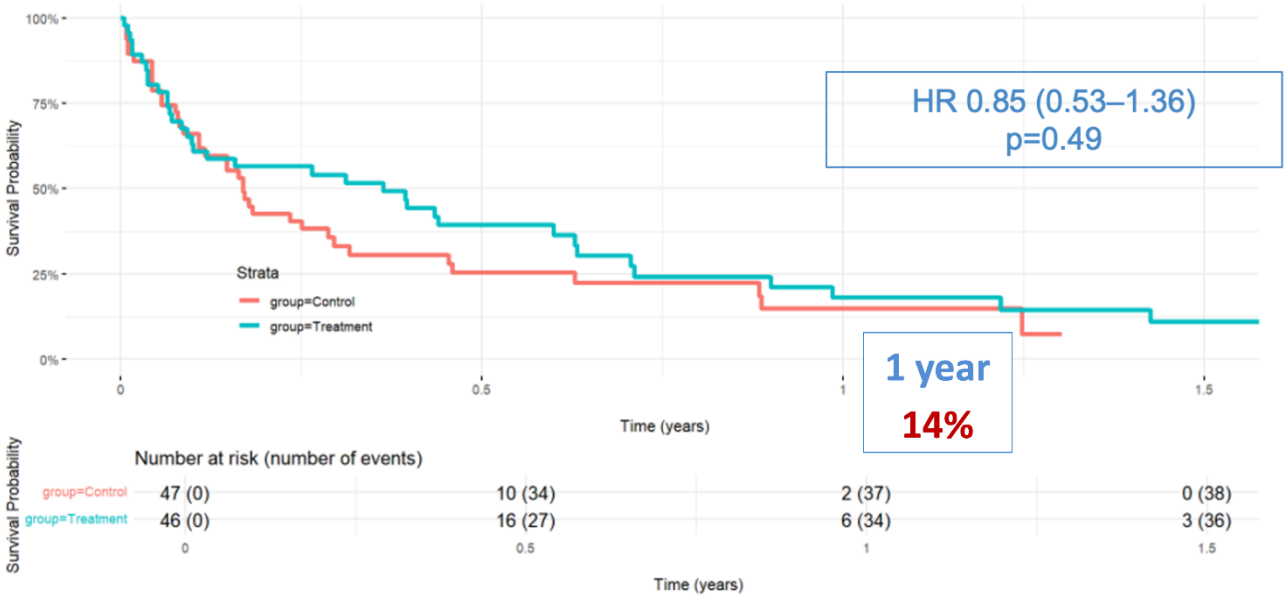


Figure 5B
339x190 mm (DPI)

Structured graphical abstract of EMPATICC

Key question

Can individualized heart failure (HF) therapy vs. placebo during 30-day follow-up improve self-care ability and quality of life (QoL) in patients with advanced cancer receiving specialized palliative care? Treatment components: sacubitril/valsartan, empagliflozin, ivabradine and intravenous iron (ferric carboxymaltose). Ninety patients studied.

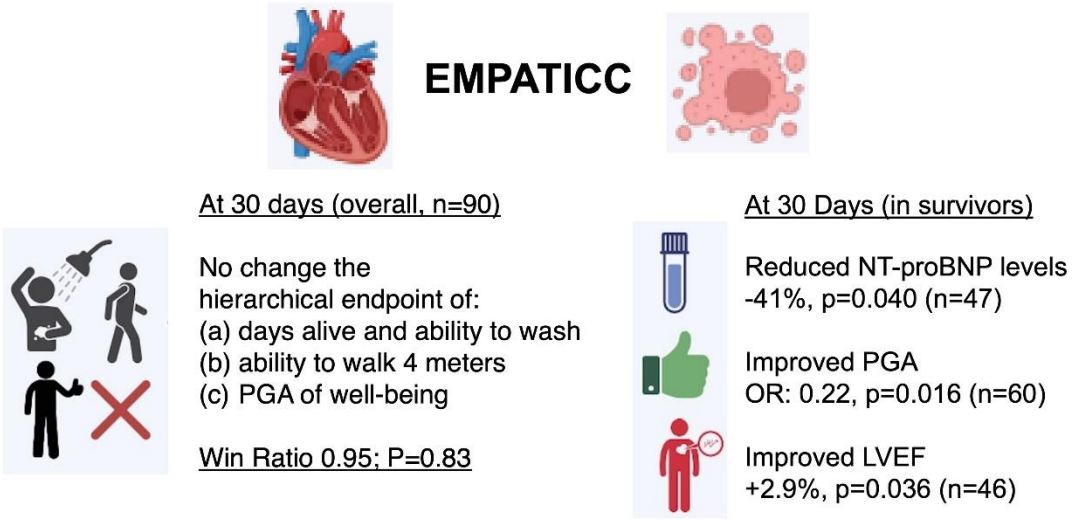
Key Finding

At 30 days, no overall improvement in hierarchical primary endpoint of being alive plus able to wash/walk 4 m/feeling better (patient global assessment [PGA]). Exploratory analysis in survivors (day 30): active treatment improves cardiac function (N-terminal pro-B-type natriuretic peptide, left ventricular ejection fraction) and QoL (PGA).

Take Home Message

Optimized HF therapy did not improve functional outcomes in a high-mortality advanced cancer population. Among survivors at 30 days, improvements in QoL measures and cardiac biomarkers suggest potential benefit of individualized HF therapy, which is hypothesis generating.

LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; PGA, patient global assessment



Structured Graphical Abstract
319x372 mm (DPI)