**Supplementary Materials**

**Supplementary Table 1:** Inclusion and exclusion criteria of the EMPATICC trial

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| **Inclusion Criteria:**  1. Signed and dated informed consent obtained before any trial-related activities. Trial-related activities are any procedures that would not have been done during normal management of the subject. 2. Age ≥18 years 3. Male or female subject with solid cancer in UICC stage 4 (in palliative care) 4. One to six months expected survival as assessed according to local standards 5. Patients under optimized pain management  6. Patients must be able to swallow tablets.  Group 1 criteria for inclusion (at least 2 need to be met): 7. Heart rate at rest >70 bpm 8. NT-proBNP ≥600 pg/mL 9. Elevated Troponin (>99th percentile of the respective high-sensitive test) 10. LVEF <55% 11. HFA-PEFF score29 with “intermediate” or large” likelihood  12. Evidence of LV mass reduction >15% since the start of cancer 13. Iron deficiency with TSAT <20%  Group 2 criteria for inclusion (at least 1 needs to be met): 14. 4m gait speed ≥6.0 seconds for 4m or not able to walk 4m at all 15. Not being able to wash themselves in at least 3 of the last 7 days 16. Presence of shortness of breath at rest (NYHA IV)  Requirement for inclusion: Fulfilled criteria 1-5 and at least two met criteria of Group 1 PLUS  at least one met criterion of Group 2. |
| **Exclusion Criteria:**  1. Ongoing hemodialysis 2. Patients currently on intravenous iron 3. Acute sepsis with at least 2 points at the qSOFA score.(36) The use of intravenous antibiotics is permitted in patients with a lower qSOFA score. 4. Ongoing acute exacerbation of COPD 5. Acute STEMI or severe PE or severe DVT (currently or in last 4 weeks) 6. Current uncontrolled cerebral metastasis 7. Impaired neurological status, precluding the ability to walk 8. Unable or unwilling to give written informed consent 9. Participation in other interventional trials using investigational products in randomised settings within the last 30 days |

UICC, Union internationale contre le cancer; NT-proBNP, N-terminal prohormone of b-type natriuretic peptide; LVEF, Left Ventricular Ejection Fraction; HFpEF, Heart Failure with Preserved Ejection Fraction; LV, Left Ventricular; TSAT, Transferrin Saturation; NYHA, New York Heart Association; qSOFA, Quick Sequential Organ Failure Assessment; COPD, Chronic Obstructive Pulmonary Disease; STEMI, ST-Elevation Myocardial Infarction; PE, Pulmonary Embolism; DVT, Deep Vein Thrombosis.

**Supplementary Table 2.** Active drug or placebo combinations provided to patients in the 30 day intervention phase(active drug or placebo had to be taken at least once at visit day 10, 20 or 30 to be include in a combination)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Treatment Group (n=46)** |  |  |  |  |
| Sacubitril/Valsartan | Empagliflozin | Ivabradine | IV iron | n (patients) |
| Y | Y | Y | N | 19 |
| Y | Y | Y | Y | 10 |
| Y | Y | N | N | 7 |
| Y | N | Y | N | 3 |
| N | Y | N | N | 2 |
| N | Y | Y | Y | 2 |
| N | N | Y | N | 1 |
| N | Y | Y | N | 1 |
| Y | N | Y | Y | 1 |
| **Placebo Group (n=47)** |  |  |  |  |
| Placebo white  (for Sacubitril/Valsartan) | Placebo blue  (for Empagliflozin) | Placebo pink  (for Ivabradine) | NaCl  for IV iron | n (patients) |
| Y | Y | Y | N | 21 |
| Y | Y | Y | Y | 13 |
| N | Y | Y | N | 4 |
| N | N | Y | N | 3 |
| Y | N | N | N | 2 |
| N | N | Y | Y | 1 |
| Y | N | Y | Y | 1 |
| N | Y | N | Y | 1 |
| Y | Y | N | N | 1 |

**Supplementary Table 3.** Frequency of meeting Group 1 inclusion criteria.

|  |  |  |
| --- | --- | --- |
| Group 1  Inclusion Criteria | HF Therapy group (%) | Control group (%) |
|  | **N=46** | **N=47** |
| Heart rate ≥75bpm | 40 (87.0) | 37 (78.7) |
| NT-proBNP ≥600 pg/mL | 20 (43.5) | 25 (53.2) |
| Elevated troponin | 16 (34.8) | 12 (25.5) |
| LVEF <55% | 20 (43.5) | 18 (38.3) |
| HFA-PEFF score with “intermediate” or large” likelihood | 38 (82.6) | 38 (80.9) |
| LV mass reduction >15% since start of cancer | 0 (0) | 2 (4.3) |
| Iron deficiency with TSAT <20% | 16 (34.8) | 20 (42.6) |
| Number of Group 1 Criteria Simultaneously Met |  |  |
| 2 | 15 (32.6) | 12 (25.5) |
| 3 | 11 (23.9) | 18 (38.3) |
| 4 | 14 (30.4) | 11 (23.4) |
| 5 | 5 (10.9) | 6 (12.7) |
| 6 | 1 (2.2) | 0 (0) |

**Supplementary Table 4.** Details on the underlying cancer diagnosis of patients included in EMPATICC.

1. **Summary of main cancer types:**

* GI cancer: 24 (26%)
* Lung cancer: 18 (19%)
* Melanoma: 8 (9%)
* Breast cancer: 7 (8%)
* Cancer of the kidney: 6 (6%)
* Prostate cancer: 5 (5%)
* Others: 25 (27%)

1. **Detailed listing of cancer entities**

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**Supplementary Table 5.** Drug treatment provided in the two treatment arms (i.e. for active and placebo therapy) in absolute numbers and as a proportion of patients alive at the time

|  |  |  |
| --- | --- | --- |
| **Treatment allocation** | **Day** | **n (%)** |
| **Active group Sacubitril/Valsartan** | 10 | 38 (84) |
|  | 20 | 25 (74) |
|  | 30 | 21 (72) |
| **Active group Ivabradine** | 10 | 34 (76) |
|  | 20 | 27 (79) |
|  | 30 | 22 (76) |
| **Active group Empagliflozin** | 10 | 39 (87) |
|  | 20 | 28 (82) |
|  | 30 | 23 (79) |
| **Active group iv FCM** | 10 | 11 (24) |
|  | 20 | 3 additional patients received FCM, i.e. 14 (41) |
|  | 30 | – |
| **Placebo group** | 10 | 47 (100) |
|  | 20 | 35 (97) |
|  | 30 | 31 (91) |

**Supplementary Table 6**

|  |  |  |
| --- | --- | --- |
| Sensitivity Analyses  For the primary endpoint |  |  |
| Primary hierarchical composite endpoint with only survivors at Day 30 | 1.07 (0.60 -1.92) | 0.82 |
| Primary hierarchical composite endpoint with mortality added as first stage | 1.03 (0.64 - 1.68) | 0.89 |
| Primary hierarchical composite endpoint with mortality added as first stage and drop withdrawals patients removed | 1.07 (0.65 - 1.76) | 0.78 |

**Figure S1.** Survivor analyses:Distribution of Patient Global Assessment at day 30 (Panel A, N=60) and Change in EORTC QLQ-C15-PAL global status / QoL score (Panel B, NBL=65, Nday10=64, Nday30=58) from baseline to day 30 in patients surviving to day 30 (N=65).

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