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The effect of acute physical exercise before immunotherapy and chemotherapy infusion in patients with metastatic non-small-cell lung cancer: Protocol for the ERICA feasibility trial

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1 **The effect of acute physical exercise before immunotherapy and**
2 **chemotherapy infusion in patients with metastatic non-small-cell lung cancer:**
3 **Protocol for the ERICA feasibility trial**

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2
3 24 **ABSTRACT**
4

5 25 **Introduction.** Patients with metastatic Non-Small Cell Lung Cancer (mNSCLC) suffer from numerous
6
7 symptoms linked to disease and treatment which may further impair the patient's overall condition.
8
9
10 27 In addition to its beneficial effects on quality of life and fatigue, physical exercise may improve
11
12 response to treatment, notably due to its known effects on the immune system. The ERICA study has
13
14 been designed to assess the feasibility of an acute physical exercise realized immediately prior to
15
16 immune-chemotherapy infusion in patients with mNSCLC and to examine the effects of this
17
18 intervention on clinical, physical, psycho-social and biological parameters.
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21

22 32 **Methods and analysis.** ERICA is a prospective, monocentric, randomized controlled, open-label
23
24 feasibility study conducted at the **** * Comprehensve Cancer Center (France). Thirty patients
25
26 newly diagnosed with mNSCLC will be randomized (2:1 ratio) to the "exercise" or the "control" group.
27
28 At baseline and during the last treatment cycle, participants in both groups will receive Physical Activity
29
30 recommendations, and two nutritional assessments and nutrition recommendations. In the exercise
31
32 group, participants will receive a 3-months program consisting of an acute physical exercise one hour
33
34 prior to immune-chemotherapy infusion, and a home-based walking program with an activity tracker.
35
36 The acute exercise consists in interval training at a submaximal intensity for 35 minutes. Clinical,
37
38 physical, biological, and psychosocial parameters will be assessed at baseline, at 3 months and 6
39
40 months after study inclusion. Biological measures will include analyses of immune, inflammatory,
41
42 metabolic, oxidative stress biomarkers and molecular profiling.
43
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46 43 **Ethics and dissemination.** The study protocol was approved by the French ethics committee
47
48 (Comité de protection des personnes Ile de France II, N°ID-RCB 20.09.04.65226, 8th December
49
50 2020). The study is registered on ClinicalTrials.gov (NCT number: NCT04676009). All
51
52 participants will have to sign and date an informed consent form. The findings will be
53
54 disseminated in peer-reviewed journals and academic conferences.
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3 48 **KEYWORDS:** Non-small-cell lung cancer, Metastatic, Exercise, Immunotherapy, Chemotherapy,
4
5 49 Immunology

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8 50 **Word count:** 5181

9
10 51 **Strengths and limitations of this study.**

- 11
12 52 • This study is the first to assess the feasibility and effects of an acute physical exercise
13
14 53 performed within one hour prior to immunotherapy (pembrolizumab) and chemotherapy
15
16 54 (platinum-based doublet) infusion in mNSCLC patients.
- 17
18 55 • Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption
19
20 56 condition during a submaximal endurance test on a cycle-ergometer at baseline and this test
21
22 57 will allow to individualize the intensity of the acute physical exercise program.
- 23
24 58 • The feasibility study assesses the acute physiological, immune, and metabolic response to an
25
26 59 acute moderate physical exercise in patients with mNSCLC.
- 27
28 60 The home-based walking program in the intervention arm aims to increase the level of physical
29
30 61 activity in patients with mNSCLC and their cardiorespiratory fitness and physical capacity to
31
32 62 perform acute physical exercise prior to chemo-immunotherapy infusion.
- 33
34 63 • The study concerns only one stage of lung cancer, participants must be eligible to
35
36 64 immunotherapy and it's a study with a limited sample size (n=30).
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65 INTRODUCTION

66 Non-small cell lung cancer (NSCLC) accounts for approximately 80-90% of lung cancers (1,2). More than
67 half of NSCLC are diagnosed at advanced stages due to their asymptomatic nature at early stage
68 explaining their poor survival. The development of immunotherapy in first-line therapy with anti-PD-1
69 and anti-PD-L1 has changed the first line treatment algorithm of advanced NSCLC (1). The anti-PD-1
70 pembrolizumab and cemiplimab clearly improve the overall survival in NSCLC with high PD-L1
71 expression ($\geq 50\%$ of tumour cells) in comparison with cytotoxic chemotherapy. Combinations of anti-
72 PD(L)-1 to platinum-based chemotherapy are superior to chemotherapy alone, independently of PD-
73 L1 level of expression. They represent the 1st line gold-standard when PD-L1 is expressed in less than
74 50% of tumour cells and might reduce the risk of early disease progression in comparison with
75 pembrolizumab when PD-L1 $\geq 50\%$. Immunotherapy has significantly improved the prognosis of
76 patients with mNSCLC and has led to prolonged remissions in some patients especially for non-
77 squamous cell carcinoma in the KEYNOTE-189 trial (3,4). Despite these therapeutic advances,
78 metastatic lung cancer has a negative impact on patients' physical, psychological, and social
79 functioning including health-related quality of life (HRQoL) (5–7). Most of reported symptoms and
80 adverse effects from treatment are fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite
81 loss, and financial concerns (8,9).

82 Benefits of physical exercise defined as planned, structured, repeated, and purposeful PA to improve
83 physical fitness (10) have been widely demonstrated. In lung cancer patients, physical exercise has
84 been shown to improve aerobic capacity (VO_{2peak} and strength), functional capacity (11), sleep quality
85 (12), PA level (13), some fatigue domains (14), anxiety, disease-specific global health-related quality of
86 life (15) and emotional well-being in cancer patients (16). Several studies in lung cancer patients have
87 reported the potential of physical exercise to limit or even reverse some of the adverse effects induced
88 by the disease and its treatment (17). While regular PA is recommended in patients with cancer, no
89 specific recommendations exist for patients with lung cancer or metastatic disease (18). In addition,
90 few studies have examined the interactions between acute exercise and cancer treatments.

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3 91 Immunomodulatory effects of acute physical exercise involve immune cell mobilization in blood like
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5 92 neutrophils, subsets of monocytes or lymphocytes involved in the host defence against tumours,
6
7 93 seems to improve immunosurveillance (19). Acute physical exercise leads to a rapid increase in the
8
9 94 mobilization of the peripheral activity of the sub-population of CD56^{dim} NK cells during acute physical
10
11 95 exercise of light to moderate intensity (20,21). A preclinical study reported that exercise training
12
13 96 (voluntary running), through activation of epinephrine and IL-6, led to selective NK cell mobilization
14
15 97 and limited tumour growth of several types of tumours (melanomas, liver, and lung mouse models)
16
17 98 (22). In a recent study, the increase in PD-1+ CD8+ T cells was observed after a single exercise session
18
19 99 (23). At the level of the adaptive immune system, acute exercise results in transient biphasic changes,
20
21 100 i.e. increase of circulating lymphocytes during and immediately after exercise, followed by a transient
22
23 101 decrease of blood lymphocytes below baseline level during recovery from exercise (1 hour), thought
24
25 102 to be due to a redistribution of immune cells to peripheral tissues, including tumours, before return to
26
27 103 basal level within few hours (22,24). Moreover, recent preclinical studies suggested that physical
28
29 104 exercise performed during chemotherapy infusion may have additional physiological benefits such as
30
31 105 increased blood flow leading to through improved intra-tumoral perfusion and enhanced drug delivery
32
33 106 (25–27). However, most of the available evidence on the benefits of physical exercise in cancer
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35 107 patients has been observed in interventions performed either after the treatment or during the
36
37 108 interval between the chemotherapy cycles. Only two studies have evaluated the feasibility of low-
38
39 109 intensity physical exercises during the chemotherapy infusion without adverse events, interference
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41 110 with chemotherapy, or exacerbation in symptoms (28,29). Recently, it has been suggested in
42
43 111 preclinical studies that exercise performed during chemotherapy infusion could lead to improve
44
45 112 perfusion of solid tumours, mitigating tumour hypoxia, and enhancing drug delivery to tumours
46
47 113 (25,26,30). Similarly, by its effect on immune regulation, physical exercise prior to infusion may
48
49 114 potentiate the effect of the immunotherapy. Recent preclinical evidence has suggested a beneficial
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51 115 effect of exercise in addition to immunotherapy (anti-PD-1 immunotherapy) in a murine model of
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53 116 NSCLC, through increased necrosis and a decreased proliferative index of tumour cells (31).
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3 117 Based on these findings, the main objective of ERICA (Exercise inteReaction Immunotherapy
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5 118 Chemotherapy and cAncer) feasibility study is to evaluate the feasibility of an intervention combining
6
7 119 an acute exercise program performed immediately prior to immunotherapy and chemotherapy
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9 120 infusion (i.e. a combination of pembrolizumab and pemetrexed-cis- or carboplatin for non-squamous
10
11 121 cell carcinoma or paclitaxel-carboplatin for squamous cell carcinoma) and a home-based walking
12
13 122 program in first-line treatment of metastatic NSCLC patients. The secondary objectives are to evaluate
14
15 123 the effects of the acute exercise before the first-line treatment combined with a home-based walking
16
17 124 program on 1) physical fitness, 2) PA level and sedentary lifestyle, 3) psychosocial factors (HRQoL and
18
19 125 fatigue), 4) sleep quality, 5) body composition, 6) sarcopenia, 7) treatment response, 8) treatment
20
21 126 completion rate, 9) related treatment toxicities, and 10) progression-free survival. Furthermore, this
22
23 127 feasibility study will generate data on the effect of this exercise intervention on immune, metabolic
24
25 128 and inflammatory biomarkers as well as oxidative stress.

129 **METHODS**

130 **STUDY DESIGN**

131 ERICA is a prospective, monocentric, randomized controlled, open-label feasibility study, conducted at
132 the ***** Comprehensive Cancer Centre (***) (*****).

133 *Insert Figure 1*

134 **STUDY POPULATION**

135 *Inclusion criteria*

136 Participants will have to meet all of the following eligibility criteria: 1) aged ≥ 18 and < 80 years; 2)
137 diagnosed with a histologically confirmed metastatic NSCLC without EGFR mutation/ALK
138 rearrangement; 3) eligible to receive first-line chemotherapy according to histology (pemetrexed-cis-
139 or carboplatin for non-squamous cell carcinoma or paclitaxel-carboplatin for squamous cell
140 carcinoma) in combination with pembrolizumab; 4) Eastern Co-operative Oncology Group (ECOG)
141 performance status ≤ 2 ; 5) able to engage in PA attested by a medical certificate by an oncologist;
142 and 6) provide a dated and signed informed consent form before study enrolment.

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3 143 *Exclusion criteria*
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5 144 Patients will not be eligible in at least one of the following cases: 1) bone metastases with risk of
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7 145 fractures or unconsolidated pathologic fractures; 2) contraindication to the physical exercise proposed
8
9
10 146 in this study (e.g. orthopaedic disorder such as disabling coxarthrosis or gonarthrosis, central nervous
11
12 147 system disorders); 3) history or co-existence of other primary cancer (except in situ cancer regardless
13
14 148 of the site, and/or basal cell carcinoma, and/or non-lung cancer in complete remission for more than
15
16 149 5 years) ; 4) severe undernutrition defined according to the French National Authority for Health (i.e.
17
18 150 for adults aged ≥ 18 years and < 70 : Body Mass Index (BMI) ≤ 17 , weight loss $\geq 10\%$ in 1 month, $\geq 15\%$
19 151 in 6 months, or $\geq 15\%$ compared to the usual weight before the disease diagnosis, or serum albumin
20
21 152 < 30 g/l; for adults aged ≥ 70 years: BMI < 18 , weight loss $\geq 10\%$ in 1 month or $\geq 15\%$ in 6 months, or
22
23 153 serum albumin < 30 g/l); 5) severe anaemia (haemoglobin ≤ 8 g/dl) in the past 30 days prior to
24
25 154 enrolment; 6) history of cardiovascular disease or cardiovascular risk (i.e. chronic or poorly controlled
26
27 155 coronary heart disease, peripheral arterial disease, cardiac arrhythmia, symptomatic heart disease,
28
29 156 uncontrolled or untreated arterial hypertension, myocardial infarction diagnosed in the past 6 months,
30
31 157 coronary angioplasty with or without stent implantation in the past 6 months, coronary artery bypass
32
33 158 surgery in the past 12 months); 7) history of type 2 diabetes or glycated haemoglobin $> 7\%$ in the past
34
35 159 3 months prior to enrolment; 8) Stage IV Chronic obstructive pulmonary disease (forced expiratory
36
37 160 volume in one second (FEV₁) $< 30\%$).
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43 161 **RECRUITMENT**
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45 162 Participants will be recruited in ***, Lyon, France from December 2020. Eligible patients will be
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47 163 screened systematically based on electronical patient records during weekly multidisciplinary lung
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49 164 cancer board meetings. During a medical consultation before treatment initiation, an oncologist will
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51 165 propose the study to eligible patients and explain the study objectives and protocol. Once the written
52
53 166 informed consent is signed, patients will undergo the following screening tests prior to inclusion: (1)
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55 167 clinical examination including assessing Performance Status (PS) and Blood Pressure, (2)
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57 168 echocardiography and electrocardiogram performed by a cardiologist, and (3) for patients with
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3 169 diabetes, measurement of glycated haemoglobin. If these investigations confirm the patient's
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5 170 eligibility, the patient will be included in the study (D0). The end date for this study is planned in
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7 171 January 2023.
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11 12 173 **RANDOMIZATION**

13
14 174 At inclusion (D0), patients will be randomly assigned (ratio 2:1) to (i) the exercise group to receive PA
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16 175 and nutrition recommendations; an acute physical exercise prior each immuno-chemotherapy infusion
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18 176 and a home-based walking program with an activity tracker or (ii) the control group to receive PA and
19
20 177 nutrition recommendations only.
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24 178 Randomization will be stratified using a dynamic minimization algorithm with two factors: sex (male
25
26 179 vs. female) and histology (squamous vs. non-squamous).
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30 31 181 **INTERVENTION**

32 33 182 *Treatment protocol*

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35 183 All patients in both exercise and control groups of this study will receive usual care and the same
36
37 184 standard treatment protocol: pembrolizumab (200 mg) combined with carboplatin (AUC 5) plus
38
39 185 pemetrexed (500 mg/m²) with B9-B12 vitamin supplementation; carboplatin (AUC 6) plus paclitaxel
40
41 186 (200 mg/m²) every 3 weeks for 4 cycles; before pembrolizumab maintenance in squamous cell
42
43 187 carcinoma or pembrolizumab plus pemetrexed maintenance for non-squamous cell carcinoma.
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46 47 188 *Physical Activity recommendations*

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49 189 Although there are no specific PA recommendations for patients with mNSCLC, all patients will be
50
51 190 informed of the PA recommendations to be physically active as much as possible during the day,
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53 191 walking as much as possible and sitting as little as possible (WCRF, 2018). We have chosen to follow
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55 192 the recommendations of the Macmillan Cancer Support guide released in 2018, advising patients with
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57 193 bone metastases to have an active lifestyle on a daily basis and to maintain appropriate PA according
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3 194 to their physical abilities (32). Several individual strategies will be proposed to patients (e.g., using
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5 195 stairs whenever possible, walking to local shops).

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7 196 *Nutritional recommendations*

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10 197 All patients will receive nutritional recommendations during the 1st and 4th treatment cycle. The
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12 198 nutritional recommendations and will include: energy intake of 30 kcal/kg body weight/day for
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14 199 patients with BMI <30, or 25 kcal/kg body weight/day for patients with BMI ≥ 30, and protein intake
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16 200 of at least 1.2 g/kg body weight/day (33,34).

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21 202 **Exercise Group**

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23 203 *Acute physical exercise protocol prior to immunotherapy and chemotherapy infusion*

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25 204 Patients in the "exercise" group will perform an acute physical exercise during hospitalization for
26
27 205 treatment. It will be carried out 1 hour prior to the immunotherapy and chemotherapy infusion, on a
28
29 206 cycle ergometer (Monark Ergomedic 939 Novo) for each of the 4 cycles of treatment foreseen. The
30
31 207 physical exercise will be supervised by a qualified PA instructor. The physical exercise consists in a 35-
32
33 208 min acute interval training and will be individualized based on the results of a submaximal endurance
34
35 209 test performed on a cycle ergometer by each patient (described below) prior to treatment (D0).

36
37 210 Following a five-minute warm-up at 60% of Ventilation Threshold 1 (VT1), the participant will carry out
38
39 211 5 sets, alternating periods of 3 minutes at 70-80% of VT1 with 3 minutes at 110-120% of VT1 (≥ 35
40
41 212 Revolutions Per Minute (RPM)). The acute exercise intensity will be programmed according to the load
42
43 213 reached at VT1 during the cycle ergometer endurance submaximal test. Heart rate (HR), load, RPM,
44
45 214 dyspnoea, and perception of effort on a Rating Perceived Exertion scale will be monitored. If the
46
47 215 patient is no longer able to cycle at the load corresponding to 120% of his VT1, the PA instructor will
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49 216 decrease the load to 110% of VT1. In case of exercise-induced desaturation (≤ 4% of the measured
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51 217 value at rest or ≤ 93%), the PA instructor will stop the exercise until the resting oxygen saturation. In
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53 218 addition to detailed explanation by the qualified PA instructor, patients receive written support
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55 219 materials at baseline (D0).
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3 220 *Home-based walking program*
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5 221 During the 3-month intervention, between each treatment cycle (3 weeks), patients will follow a
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7 222 home-based walking program consisting of an individual goal of a number of steps per day. Each
8
9 223 patient will receive a Fitbit® Inspire activity tracker with an instruction to wear it continuously during
10
11 224 the intervention. They will be advised to achieve at least 6,000 daily steps which corresponds to a
12
13 225 physically active lifestyle in a patient population (35). Ten days after each treatment cycle, the PA
14
15 226 instructor will contact the patients by phone to assess and encourage adherence to the home-based
16
17 227 walking program. Depending on the average number of steps performed in the past ten days,
18
19 228 personalized objectives might be redefined to increase the target number of daily steps. For patients
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21 229 who reach more than 6,000 steps per day the initial target number of 6,000 steps will be increased by
22
23 230 30%. The target number of steps was set within a maximum of 7800 steps above the average number
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25 231 of steps in the previous week. Patients who do not reach 6,000 daily steps, will be advised to gradually
26
27 232 increase the target number of steps per day according to the patient's abilities. Number of steps will
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29 233 be collected by regular sync with the mobile phone application (Fitbit®) of the activity tracker or by a
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31 234 step logbook.
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39 236 **EVALUATIONS**

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41 237 *Modalities*
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43 238 The assessments in both groups will be performed before the first cycle of anti-neoplastic treatment
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45 239 (baseline, D0), at the end of the 4 cycles of treatment (M3), and at 6 months after study inclusion (M6).
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50 241 **DATA COLLECTION**

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52 242 *Sociodemographic and clinical data*
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54 243 Sociodemographic and clinical data including gender, date of birth, living situation, employment status,
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56 244 lifestyle (alcohol consumption and smoking status) will be collected at baseline. All clinical data will be
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58 245 extracted from the participant's electronic medical records. The Response Evaluation Criteria In Solid
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3 246 Tumours (RECIST) will be used for tumour assessments between the diagnosis and the end of the ERICA
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5 247 study.
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10 249 *Anthropometric data*

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12 250 Anthropometric data including body weight (kilogram), height (centimeter, cm), waist (cm) and hip
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14 251 (cm) circumference will be collected. Waist circumference will be measured around the abdomen
15
16 252 midway between the last floating rib and the iliac crest. Hip circumference will be measured
17
18 253 horizontally through the upper margin of the pubis. The body mass index is calculated as the body
19
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21 254 weight in kilograms divided by the square of the height in meters.
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25 256 *Physical fitness*

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27 257 Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption (VO_2)
28
29 258 condition during a submaximal endurance test on a cycle-ergometer at baseline. This test will allow to
30
31 259 individualize the intensity of the acute physical exercise program. Following a 5-minute warm-up at
32
33 260 20% of the participant's maximum theoretical load, watts will be increased by a constant amount of 5
34
35 261 watts each thirty seconds until VT1 will be reached. The PA instructor will ensure that the patient
36
37 262 maintains a minimum pedalling frequency above 35 RPM throughout the test. HR, ventilation (VE),
38
39 263 oxygen saturation (SaO_2), VO_2 , and carbon dioxide production (VCO_2) will be measured by a gas
40
41 264 analyser (MetaMax 3b, Cortex Biophysik, Leipzig, Germany) and continuously monitored. In addition,
42
43 265 the perception of the difficulty and dyspnoea will be evaluated at the end of the test using the Borg
44
45 266 Rating Perceived Exertion questionnaire(36). The PA instructor will stop the test when the patient
46
47 267 exceeded his VT1. The test will end with a 6-minute recovery phase. The VT1 will be determined
48
49 268 graphically when the ventilatory equivalent of oxygen (VE/VO_2) starts to increase and will be confirmed
50
51 269 by Respiratory Exchange Ratio that strictly exceeds 1 (Wasserman method).
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55 270 The lower strength muscular function will be evaluated by measuring the maximum isometric strength
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57 271 of the knee extensors (DFS II Series Digital; Force Gauges Chatillon, Largo, FL, USA). Participants will be
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1
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3 272 seated on a chair with the knee joint at 90°, arms crossed over the chest, and the dynamometer
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5 273 attached to the ankle. Participants were advised to stretch their leg as hard as possible within 3
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7 274 seconds upon the instructor's signal. Only the dominant leg will be tested three times (with 2 minutes
8
9 275 rest between each contraction), and the best performance will be considered.

10 276 The maximum isometric upper limb strength will be measured by a hand dynamometer (Jamar Plus
11
12 277 Digital Hand Dynamometer, Patterson Medical, Huthwaite, United Kingdom) (37,38). Participants will
13
14 278 be seated with their back straight and elbows bent at 90°. They will be asked to squeeze the handgrip
15
16 279 as strongly as possible for five seconds to achieve maximum strength. Two measurements will be taken
17
18 280 on each hand and the best performance will be recorded.
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24 282 *Physical activity level*

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27 283 The PA level will be measured by the Godin Leisure-Time Physical Activity Questionnaire (GLTAPQ)
28
29 284 (39). The GLTAPQ is a short, self-administered questionnaire with three questions designed to obtain
30
31 285 information on the number of times an individual engages in low, moderate, and intense "leisure-time
32
33 286 PA" periods of at least 15 minutes during a typical week. The score of the GSLTPAQ (Leisure Score
34
35 287 Index, LSI) will be obtained by using the following formula: (light PA frequency × 3) + (moderate PA
36
37 288 frequency × 5) + (vigorous PA frequency × 9). People with LSI ≥ 24 will be classified as active, while
38
39 289 people with LSI ≤ 23 will be classified as insufficiently active (estimated energy expenditure < 14
40
41 290 Kcal/kg/week). The level of PA will be investigated by the change of a daily number of steps thanks to
42
43 291 the activity tracker (only in the intervention group).
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49 293 *Body composition and sarcopenia*

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52 294 Body composition and sarcopenia will be analysed using the Computed Tomography (CT) scans. CT
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54 295 scan cross-section at the level of the 3rd lumbar vertebra represents the method of choice for
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56 296 assessment of sarcopenia in the oncology setting given that CT scan as part of routine cancer diagnostic
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58 297 procedures is largely available (40). The thresholds for identifying muscle range from -29 to +150 HU,
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3 298 subcutaneous and intramuscular adipose tissue from -190 to -30 HU, visceral adipose tissue from -150
4
5 299 to -50 HU and bone from +152 to 1000 HU (41–43). Skeletal muscle radiodensity (SMD) that represents
6
7 300 muscle quality will be measured using the average radiation attenuation of the tissue in Hounsfield
8
9 301 Units (HU). A low SMD is defined by values below the threshold of 37.8 HU. An estimate of lean body
10
11 302 mass (LBM) will be calculated using the formula $(LBM \text{ (kg)} = [(L3 \text{ Muscle measured by CT (cm}^2) \times 0.3) +$
12
13 303 $6.06])$ (44).

304

305 *Nutrition*

306 Dietary intake (24h recall, supplemented with patient preferences and habits), clinical (weight loss,
307 BMI), and biological (albumin and CRP) parameters will be assessed by clinical dietitians affiliated with
308 the study. The dietician will use the SEFI® (Score d'Evaluation Facile des Ingesta EPA). The score ranges
309 from 0 to 10. Patients with a SEFI score below 7 will be identified as at risk of undernutrition (45).

310

311 *Health-related quality of life*

312 The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life
313 Questionnaire (QLQ-C30) is a validated multi-dimensional HRQoL questionnaire designed for cancer
314 patients (46), consisting of 30 items to assess five domains of functioning (physical, role, emotional,
315 cognitive, and social), one domain of overall quality of life, three domains of symptoms (pain, fatigue,
316 and nausea), and six single items (dyspnoea, insomnia, anorexia, diarrhoea, constipation, and financial
317 impact). Participants will respond on a Likert scale ranging from "not at all" to "a lot". All scores will be
318 transformed into a scale from 0 to 100 according to the performance of the EORTC scoring manual
319 (47). A high score represents better functioning, better overall quality of life, and lower symptom
320 burden. Quality of life specific to lung cancer will be assessed by the 13-item module: the Quality of
321 Life Questionnaire - Lung Cancer 13 (QLQ-LC13) (47,48). The QLQ-LC13 self-questionnaire is an
322 additional measure of the symptoms and side effects experienced by lung cancer patients who receive
323 non-surgical treatment.

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3 3244
5 325 *Fatigue*

6
7 326 Fatigue will be assessed by the EORTC-QLQ module measuring cancer-related fatigue (EORTC QLQ-
8
9 327 FA12) (49). This self-questionnaire includes 12 items that assess physical, cognitive, and emotional
10
11 328 fatigue related to cancer. Participants will respond on a Likert scale ranging from "not at all" to "a lot".
12
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14 329 All scores will be transformed into a scale from 0 to 100, with a higher score indicating a higher degree
15
16 330 of fatigue.

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19 33120
21 332 *Sleep quality*

22
23 333 The perceived quality of sleep will be assessed by the Insomnia Severity Index which measures the
24
25 334 severity of insomnia. The questionnaire consists of 7 items rated on a 5-point scale ranging from 0
26
27 335 ("none") to 4 ("very severe") (50,51). This self-questionnaire will evaluate the severity of the patient's
28
29 336 sleep difficulties (initial, maintenance, and morning insomnia), the degree of sleep dissatisfaction, the
30
31 337 level of interference with daily functioning, the degree of appearance of sleep difficulties, and the level
32
33 338 of anxiety related to insomnia. The total score of the items varies between 0 and 28. A high score
34
35 339 indicates greater sleep difficulties.

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39 34040
41 341 *Social vulnerability*

42
43 342 Social deprivation will be assessed using the EPICES score (Evaluation of Deprivation and Inequalities
44
45 343 in Health Examination Centres) (52). The EPICES score will be obtained by adding up the points of the
46
47 344 11 binary questions ("Yes"/"No") of the self-questionnaire. This score ranges from 0 "no
48
49 345 precariousness" to 100 "highest precariousness" with the threshold for deprivation at 30.

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52 34653
54 347 *Biomarkers of the immune system, inflammation, sarcopenia, and oxidative stress*

55
56 348 Blood samples will be collected during the first and last (forth) treatment cycle: in the exercise group,
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58 349 samples will be collected before exercise (S1), after exercise (S2), and 12 hours after the start of
59
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3 350 treatment (S3); in the control group: samples will be collected 40 minutes before the infusion of
4
5 351 treatment (S1), just before the infusion of treatment (S2) and 12 hours after the start of treatment
6
7 352 (S3). Blood test procedures will follow laboratory standards. Each blood sample will be collected in 3 x
8
9
10 353 10mL Ethylenediaminetetraacetic acid tubes and then centrifuged (10 minutes at 800G) within one
11
12 354 hour (maintained at 4°C before and during centrifugation). After the centrifuge, plasma will be
13
14 355 collected and aliquoted in 5 cryotubes of 1 mL and the Peripheral Blood Mononuclear Cell (PBMC) will
15
16 356 be collected and aliquoted in 3 cryotubes (5 to 7 millions cells per tube). These cryotubes will be frozen
17
18 357 at -80°C and stored in nitrogen at *** for the duration of the study. At the end of the study, biomarkers
19
20
21 358 of immunity, sarcopenia, and inflammation will be analysed. We will measure i) immune biomarkers
22
23 359 (NK cells, B lymphocytes, T lymphocytes, monocytes, sub-populations of dendritic cells on frozen
24
25 360 PBMC); ii) plasma biomarkers of sarcopenia and inflammation (Myostatin, Activin, Cortisol, Tumor
26
27 361 Necrosis Factor- α , Interferon- γ , Interleukine-1 β , Interleukine-6, Follistatin, Growth Differentiation
28
29 362 Factor 5, Bone morphogenetic protein 14, GDF15, Interleukine-10, Interleukine-15, NH3, Aminogram,
30
31 363 C-reactive protein, insulin); and iii) plasma oxidative stress (Superoxide dismutase, catalase,
32
33 364 malondialdehyde, glutathione peroxidase, Xanthine Myeloperoxidase, and Xanthine oxidase). Finally,
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35 365 the blood samples will be also used to analyse the glucose (OneTouch Verio®) and lactate (LACTATE
36
37 366 PRO II) metabolism by a mobile device. Patients will be asked to complete a questionnaire regarding
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39 367 the taking of antibiotics, anti-inflammatory, and antioxidants in the 48 hours prior to blood collection.
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369 *Toxicities*

47
48 370 Severe treatment toxicities (grade ≥ 3) will be noted according to the National Cancer Institute's
49
50 371 Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0. The number of rescheduled or
51
52 372 cancelled treatment sessions and the relative dose intensity (RDI) of participants with grade ≥ 3
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54 373 toxicities related to chemotherapy and immunotherapy will be calculated as the ratio of "delivered"
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56 374 to "expected" dose intensity.
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3 376 **STATISTICAL ANALYSIS**

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5 377 **SAMPLE SIZE**

6
7 378 The main objective of the current study is to evaluate the feasibility of an acute physical exercise
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9 379 program performed prior to the infusion of treatments in mNSCLC patients, to assess if this planned
10 380 exercise dose is safe and tolerable in this target patient population(53). In the context of a feasibility
11
12 381 study without a concrete hypothesis and in absence of previous studies in this population, the sample
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14 382 size was defined empirically. Taking into account the number of mNSCLC patients who receive first line
15
16 383 chemotherapy (i.e. pemetrexed-platinum or taxol-platinum) combined with Pembrolizumab each year
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18 384 in ***, we plan to include 30 patients over a 18 months period. This number will be sufficient to assess
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20 385 if the planned exercise dose is safe and tolerable in this target patient population, and the sample size
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22 386 falls within the range of sample sizes recommended in the literature for feasibility trials (54).
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30 388 Although the main objective is to study the feasibility of physical exercise prior to the infusion of
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32 389 treatments, the evaluation of the biological objectives requires randomization to have reference
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34 390 measures. We have chosen to unbalance the randomization (2:1) so that more patients will benefit
35
36 391 from the intervention proposed in the ERICA study.
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41 393 **STATISTICAL METHODS**

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43 394 All statistical analyses will be on an exploratory basis on all data from study subjects. Given the limited
44
45 395 sample size, non-parametric tests will be performed. Qualitative data will be presented using their
46
47 396 frequencies and percentages. Quantitative data will be presented using the number of observations,
48
49 397 mean, standard deviation, median, minimum, and maximum. For both types of data, the number of
50
51 398 missing data will be presented if necessary.
52
53

54 399 The feasibility of the ERICA study will be assessed at the end of the intervention (M3) in the exercise
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56 400 group only, according to the adherence rate by calculating the ratio of the number of acute physical
57
58 401 exercise sessions performed to the number of acute physical exercise sessions planned before the
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3 402 immunotherapy/chemotherapy. The safety will be assessed by the occurrence of adverse events
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5 403 related to the physical exercise intervention. The acceptability (i.e. the proportion of patients who
6
7 404 accept to participate in the study among eligible patients) and the attrition (i.e. the proportion of
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9 405 patients who withdraw their participation from the study among patients initially enrolled) will be
10
11 406 calculated. In the exercise group, the acceptability of the activity tracker, the observance of the home-
12
13 407 walking program, and the safety of the intervention (the number, type, and timing of adverse events
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15 408 that occurred) will be assessed.

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17
18 409 The evolution of the different repeated measures (PA level, anthropometric, HRQoL, fatigue, sleep
19
20 410 quality, and sarcopenia) at inclusion, 3 and 6 months will be represented by graphs and compared by
21
22 411 non-parametric ANOVAs (performed on ranks).

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24
25 412 Progression-free survival will be measured from the date of randomization until the date of event
26
27 413 defined as either progression or death from any cause whichever occurs first. Participants with no
28
29 414 event at the time of the analysis will be censored at the date of the last available tumour assessment.
30
31 415 The results will allow to formulate the hypotheses and determine sample size for a subsequent
32
33 416 multicenter randomized efficacy study.

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36 417 Statistical analyses will be carried out using R statistical software (55).

37 38 39 418 **DATA MONITORING**

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41 419 The database for clinical data will be managed using REDCap (Research Electronic Data Capture)
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43 420 (56,57) software hosted at ***. The access to the database will be secured (personal ID and password
44
45 421 required) with different levels of security depending on the role within the study. The investigator will
46
47 422 have access to the final dataset.

48 49 50 423 **PATIENT AND PUBLIC INVOLVEMENT**

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52 424 Prior to the present study, we administrated a questionnaire to lung cancer patients to collect their
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54 425 experience and preferences in terms of physical activity to practice during cancer treatments. The
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56 426 results were used to develop the ERICA physical activity intervention. As it is a feasibility study, the
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3 427 findings will be used to adjust the intervention if necessary for the purpose of an efficacy randomised
4
5 428 controlled trial. Global findings will be disseminated to participants at the end of the study if they wish.
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7 429 **ETHICAL AND DISSEMINATION**

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10 430 The study protocol has been approved by a French ethics committee CPP Ile de France II (IDRCB:
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12 431 20.09.04.65226) and the study database has been reported to the National Commission for Data
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14 432 Protection and Liberties (CNIL; reference number: 2016177). The study has been registered at
15
16 433 reference number: NCT04676009.
17

18 19 20 434 **DISCUSSION**

21
22 435 To our knowledge, ERICA is the first study to assess the feasibility and effects of an acute physical
23
24 436 exercise performed within one hour prior to immunotherapy (pembrolizumab) and chemotherapy
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26 437 (platinum-based doublet) infusion in mNSCLC patients. Despite therapeutic advances, notably
27
28 438 immunotherapy combined with chemotherapy, the prognosis of many patients with mNSCLC
29
30 439 continues to be poor, and disease burden, cachexia, comorbidities, and treatment side effects lead to
31
32 440 deconditioning and adversely affect exercise capacity in people with advanced NSCLC (17,58–61).
33
34 441 Conversely, evidence from meta-analyses suggests that exercise training in patients with advanced
35
36 442 lung cancer could be feasible and safe with no serious adverse events reported and may improve or
37
38 443 avoid the decline of physical capacity (15,62). However, the evidence regarding the benefits of exercise
39
40 444 in mNSCLC patients remains limited and there is a lack of widespread awareness of the benefits of
41
42 445 maintaining physical activity in this particular population (61,63–65). Furthermore, the high prevalence
43
44 446 of comorbidities in mNSCLC patients, which may be exacerbated by the direct and indirect effects of
45
46 447 cancer treatment, led to exclude patients at risk of cardiovascular events from studies (i.e. history of
47
48 448 cardiovascular disease; abnormal electrocardiogram and/or echocardiography) or undernutrition.
49
50 449 Based on preclinical evidence of exercise in modulating the efficacy of cancer therapy, the present
51
52 450 study assesses the feasibility of acute exercise of submaximal intensity in the target population.
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54 451 Current evidence on the benefits of physical exercise in cancer patients mainly stems from
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56 452 interventions performed either between the chemotherapy cycles or after end of treatment. Yet, a
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3 453 feasibility study in patients with various tumours, mostly breast cancer, reported that exercise (i.e. 20
4
5 454 min of supervised low-intensity cycling) during chemotherapy infusion appears to be safe and feasible
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7 455 (28). To prescribe a safe and efficacious intensity of acute exercise intervention, we decided to realize
8
9 456 a submaximal cardiopulmonary exercise test with a continuous gas exchange analysis. Because of the
10
11 457 comorbidities, the tumour location and the lack of information about high intensity exercise effects,
12
13 458 the present study targets acute exercise of submaximal intensity.

14
15
16 459 Home-based exercises are a beneficial approach to reducing symptoms and improving exercise
17
18 460 capacity as well as the quality of life in patients with NSCLC (66). The home-based walking program in
19
20 461 the intervention arm aims to increase the level of physical activity in patients with mNSCLC and their
21
22 462 cardiorespiratory fitness and physical capacity to perform acute physical exercise prior to chemo-
23
24 463 immunotherapy infusion (15). Also, chronic exercise can favourably modulate inflammation and
25
26 464 immune-related factors (67,68). Activity trackers are innovative tools increasingly used to promote an
27
28 465 active lifestyle and to objectively measure the PA level of cancer patients (69–71). Trackers have been
29
30 466 used in a randomized controlled trial to encourage patients with mNSCLC to maintain their PA by
31
32 467 recommending a targeted number of steps (72). In a previous study by the team, the use of activity
33
34 468 trackers have shown pertinent results in women with metastatic breast cancer (73,74). The
35
36 469 combination of these two intervention modalities (acute exercise and unsupervised walking
37
38 470 programme) allows us to offer an intervention adapted to this population in order to have sufficient
39
40 471 physiological stimulation to observe changes in the immune system.

41
42 472 The first challenge we need to overcome is that the study concerns only one stage of lung cancer and
43
44 473 participants must be eligible to immunotherapy. Next, we are looking at the intervention
45
46 474 reproducibility in other institutions. Finally, it is a feasibility study with a limited sample size (n=30).
47
48 475 We plan to conduct a randomised controlled trial to address the various limitations of the present
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50 476 study: larger sample size, multiple lung cancer stages, and to carry out the study in several hospital
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52 477 institutions.

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59 478 **INNOVATION AND STUDY RELEVANCE**
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3 479 The ERICA study will provide clinical, physical, and psychosocial insights on the feasibility of acute
4
5 480 exercise prior to first-line chemo-immunotherapy infusion in patients with mNSCLC. In particular,
6
7 481 exploratory data on the safety and tolerability of the proposed exercise dose and schedule in the target
8
9 482 patient population will be obtained. This feasibility study will further generate preliminary data on the
10
11 483 acute physiological, immune, and metabolic response to the achieved exercise dose in patients with
12
13 484 mNSCLC. The ERICA study will provide valuable information to design a large-scale adequately
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15 485 powered randomized controlled trial to assess the efficacy on clinically important endpoints (e.g.
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17 486 progression free survival) in patients with mNSCLC receiving first-line chemo-immunotherapy.
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487 **REFERENCES**

- 488 1. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung
489 cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*.
490 2018;29:iv192–237.
- 491 2. ASCO. Lung Cancer - Non-Small Cell - Statistics [Internet]. *Cancer.Net*. 2021 [cited 2021 Jul 3]. Available
492 from: <https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics>
- 493 3. Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, et al. Updated Analysis From
494 KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic
495 Nonsquamous Non–Small-Cell Lung Cancer. *JCO*. 2020;JCO.19.03136.
- 496 4. Low JL, Walsh RJ, Ang Y, Chan G, Soo RA. The evolving immuno-oncology landscape in advanced lung
497 cancer: first-line treatment of non-small cell lung cancer. *Ther Adv Med Oncol* [Internet]. 2019 [cited 2019 Nov
498 5];11. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6716180/>
- 499 5. Brahmer JR, Rodríguez-Abreu D, Robinson AG, Hui R, Csósz T, Fülöp A, et al. Health-related quality-of-
500 life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a
501 multicentre, international, randomised, open-label phase 3 trial. *The Lancet Oncology*. 2017 Dec;18(12):1600–9.
- 502 6. Polanski J, Jankowska-Polanska B, Rosinczuk J, Chabowski M, Szymanska-Chabowska A. Quality of life of
503 patients with lung cancer. *Onco Targets Ther*. 2016;9:1023–8.
- 504 7. Camps C, del Pozo N, Blasco A, Blasco P, Sirera R. Importance of Quality of Life in Patients with Non–
505 Small-Cell Lung Cancer. *Clinical Lung Cancer*. 2009;10(2):83–90.
- 506 8. Garassino MC, Gadgeel S, Esteban E, Felip E, Speranza G, Domine M, et al. Patient-reported outcomes
507 following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated,
508 metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised,
509 placebo-controlled, phase 3 trial. *The Lancet Oncology*. 2020;21(3):387–97.
- 510 9. Steffen McLouth LE, Lycan TW, Levine BJ, Gabbard J, Ruiz J, Farris M, et al. Patient-Reported Outcomes
511 From Patients Receiving Immunotherapy or Chemoimmunotherapy for Metastatic Non–Small-Cell Lung Cancer
512 in Clinical Practice. *Clinical Lung Cancer*. 2019;21(3):255-263.e4.
- 513 10. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and
514 distinctions for health-related research. *Public Health Rep*. 1985;100(2):126–31.
- 515 11. Hwang C-L, Yu C-J, Shih J-Y, Yang P-C, Wu Y-T. Effects of exercise training on exercise capacity in patients

- 1
2
3 516 with non-small cell lung cancer receiving targeted therapy. *Support Care Cancer*. 2012;20(12):3169–77.
4
5 517 12. Chen H-M, Tsai C-M, Wu Y-C, Lin K-C, Lin C-C. Effect of walking on circadian rhythms and sleep quality
6
7 518 of patients with lung cancer: a randomised controlled trial. *Br J Cancer*. 2016;115(11):1304–12.
8
9 519 13. Dhillon HM, Bell ML, van der Ploeg HP, Turner JD, Kabourakis M, Spencer L, et al. Impact of physical
10
11 520 activity on fatigue and quality of life in people with advanced lung cancer: a randomized controlled trial. *Annals*
12
13 521 *of Oncology*. 2017;28(8):1889–97.
14
15 522 14. Zhang L-L, Wang S-Z, Chen H-L, Yuan A-Z. Tai Chi Exercise for Cancer-Related Fatigue in Patients With
16
17 523 Lung Cancer Undergoing Chemotherapy: A Randomized Controlled Trial. *Journal of Pain and Symptom*
18
19 524 *Management*. 2016;51(3):504–11.
20
21 525 15. Peddle-McIntyre CJ, Singh F, Thomas R, Newton RU, Galvão DA, Cavalheri V. Exercise training for
22
23 526 advanced lung cancer. Cochrane Lung Cancer Group, editor. *Cochrane Database of Systematic Reviews*
24
25 527 [Internet]. 2019 [cited 2019 Sep 17]; Available from: <http://doi.wiley.com/10.1002/14651858.CD012685.pub2>
26
27 528 16. Quist M, Adamsen L, Rørth M, Laursen JH, Christensen KB, Langer SW. The Impact of a Multidimensional
28
29 529 Exercise Intervention on Physical and Functional Capacity, Anxiety, and Depression in Patients With Advanced-
30
31 530 Stage Lung Cancer Undergoing Chemotherapy. *Integr Cancer Ther*. 2015;14(4):341–9.
32
33 531 17. Avancini A, Sartori G, Gkoutakos A, Casali M, Trestini I, Tregnago D, et al. Physical Activity and Exercise
34
35 532 in Lung Cancer Care: Will Promises Be Fulfilled? *The Oncologist* [Internet]. 2019;n/a(n/a). Available from:
36
37 533 <https://theoncologist.onlinelibrary.wiley.com/doi/abs/10.1634/theoncologist.2019-0463>
38
39 534 18. *Activité physique. Prévention et traitement des maladies chroniques* Éditions EDP Sciences, janvier
40
41 535 2019, 824 pages, Collection Expertise collective ISBN 978-2-7598-2328-4 [Internet]. [cited 2021 Jul 4]. Available
42
43 536 from: [https://www.inserm.fr/sites/default/files/2019-](https://www.inserm.fr/sites/default/files/2019-02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf)
44
45 537 [02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf](https://www.inserm.fr/sites/default/files/2019-02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf)
46
47 538 19. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. *J*
48
49 539 *Sport Health Sci*. 2019;8(3):201–17.
50
51 540 20. Bigley AB, Rezvani K, Chew C, Sekine T, Pistillo M, Crucian B, et al. Acute exercise preferentially redeploys
52
53 541 NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple
54
55 542 myeloma target cells. *Brain, Behavior, and Immunity*. 2014;39:160–71.
56
57 543 21. Idorn M, Hojman P. Exercise-Dependent Regulation of NK Cells in Cancer Protection. *Trends in Molecular*
58
59 544 *Medicine*. 2016;22(7):565–77.

- 1
2
3 545 22. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al. Voluntary Running
4 546 Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution.
5 547 Cell Metabolism. 2016;23(3):554–62.
6
7
8
9 548 23. Wadley AJ, Cullen T, Vautrinot J, Keane G, Bishop NC, Coles SJ. High intensity interval exercise increases
10 549 the frequency of peripheral PD-1+ CD8+ central memory T-cells and soluble PD-L1 in humans. *Brain, Behavior, &*
11 550 *Immunity - Health*. 2020;3:100049.
12
13
14
15 551 24. Pedersen BK, Hoffman-Goetz L. Exercise and the Immune System: Regulation, Integration, and
16 552 Adaptation. *Physiological Reviews*. 2000;80(3):1055–81.
17
18
19 553 25. Wiggins JM, Opoku-Acheampong AB, Baumfalk DR, Siemann DW, Behnke BJ. Exercise and the Tumor
20 554 Microenvironment: Potential Therapeutic Implications. *Exercise and Sport Sciences Reviews*. 2018;46(1):56–64.
21
22
23 555 26. McCullough DJ, Stabley JN, Siemann DW, Behnke BJ. Modulation of Blood Flow, Hypoxia, and Vascular
24 556 Function in Orthotopic Prostate Tumors During Exercise. *J Natl Cancer Inst [Internet]*. 2014 [cited 2020 Jan
25 557 8];106(4). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3982888/>
26
27
28
29 558 27. Schadler KL, Thomas NJ, Galie PA, Bhang DH, Roby KC, Addai P, et al. Tumor vessel normalization after
30 559 aerobic exercise enhances chemotherapeutic efficacy. *Oncotarget*. 2016;7(40):65429–40.
31
32
33 560 28. Thomas VJ, Seet-Lee C, Marthick M, Cheema BS, Boyer M, Edwards KM. Aerobic exercise during
34 561 chemotherapy infusion for cancer treatment: a novel randomised crossover safety and feasibility trial. *Support*
35 562 *Care Cancer*. 2020;28(2):625–32.
36
37
38
39 563 29. Kerrigan K. A pilot study of aerobic exercise performed in breast cancer patients during chemotherapy
40 564 infusion. | *Journal of Clinical Oncology [Internet]*. 2010 [cited 2020 Aug 11]. Available from:
41 565 https://ascopubs.org/doi/10.1200/jco.2010.28.15_suppl.e19527
42
43
44
45 566 30. Ashcraft KA, Warner AB, Jones LW, Dewhirst MW. Exercise as Adjunct Therapy in Cancer. *Seminars in*
46 567 *Radiation Oncology*. 2018;29(1):16–24.
47
48
49
50 568 31. Martín-Ruiz A, Fiuza-Luces C, Rincón-Castanedo C, Fernández-Moreno D, Martínez-Martínez E, Martín-
51 569 Acosta P, et al. Benefits of exercise and immunotherapy in a murine model of human non–small-cell lung
52 570 carcinoma. 2020;16.
53
54
55
56 571 32. Macmillan Cancer Support. Physical activity in patients with metastatic bone disease: Guidance for
57 572 healthcare professionals. 2018 [Internet]. [cited 2021 Jul 4]. Available from:
58 573 <https://cdn.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/1784-10061/physical-activity->

- 1
2
3 574 for-people-with-metastatic-bone-disease-guidance-tcm9-326004
4
5 575 33. Senesse P, Bachmann P, Bensadoun RJ, Besnard I, Bourdel-Marchasson I, Bouteloup C, et al. Nutrition
6
7 576 chez le patient adulte atteint de cancer : textes courts. *Nutrition Clinique et Métabolisme*. 2012;26(4):151–8.
8
9 577 34. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition
10
11 578 in cancer patients. *Clinical Nutrition*. 2017;36(1):11–48.
12
13 579 35. Tudor-Locke C, Craig CL, Aoyagi Y, Bell RC, Croteau KA, De Bourdeaudhuij I, et al. How many steps/day
14
15 580 are enough? For older adults and special populations. *Int J Behav Nutr Phys Act*. 2011;8(1):80.
16
17 581 36. Borg G, Hassmén P, Lagerström M. Perceived exertion related to heart rate and blood lactate during
18
19 582 arm and leg exercise. *Europ J Appl Physiol*. 1987;56(6):679–85.
20
21 583 37. Anand A, Gajra A. Hand Grip Dynamometry as Prognostic and Predictive Marker in Older Patients With
22
23 584 Cancer. *J Gerontol Geriatr Res* [Internet]. 2018 [cited 2020 Jun 19];07(03). Available from:
24
25 585 [https://www.omicsonline.org/open-access/hand-grip-dynamometry-as-prognostic-and-predictive-marker-in-](https://www.omicsonline.org/open-access/hand-grip-dynamometry-as-prognostic-and-predictive-marker-in-older-patients-with-cancer-2167-7182-1000471-102218.html)
26
27 586 [older-patients-with-cancer-2167-7182-1000471-102218.html](https://www.omicsonline.org/open-access/hand-grip-dynamometry-as-prognostic-and-predictive-marker-in-older-patients-with-cancer-2167-7182-1000471-102218.html)
28
29 587 38. Trutschnigg B, Kilgour RD, Reinglas J, Rosenthal L, Hornby L, Morais JA, et al. Precision and reliability of
30
31 588 strength (Jamar vs. Biodex handgrip) and body composition (dual-energy X-ray absorptiometry vs. bioimpedance
32
33 589 analysis) measurements in advanced cancer patients. *Appl Physiol Nutr Metab*. 2008;33(6):1232–9.
34
35 590 39. Amireault S, Godin G, Lacombe J, Sabiston CM. The use of the Godin-Shephard Leisure-Time Physical
36
37 591 Activity Questionnaire in oncology research: a systematic review. *BMC Med Res Methodol* [Internet]. 2015 [cited
38
39 592 2020 May 28];15. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4542103/>
40
41 593 40. Tosato M, Marzetti E, Cesari M, Saveria G, Miller RR, Bernabei R, et al. Measurement of muscle mass in
42
43 594 sarcopenia: from imaging to biochemical markers. *Aging Clin Exp Res*. 2017 Feb;29(1):19–27.
44
45 595 41. Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, et al. Appendicular skeletal muscle
46
47 596 mass: measurement by dual-photon absorptiometry. *Am J Clin Nutr*. 1990 Aug;52(2):214–8.
48
49 597 42. Miller KD, Jones E, Yanovski JA, Shankar R, Feuerstein I, Falloon J. Visceral abdominal-fat accumulation
50
51 598 associated with use of indinavir. *Lancet*. 1998 Mar 21;351(9106):871–5.
52
53 599 43. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of
54
55 600 skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol*.
56
57 601 1998 Jul;85(1):115–22.
58
59 602 44. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise

- 1
2
3 603 approach to quantification of body composition in cancer patients using computed tomography images acquired
4
5 604 during routine care. *Appl Physiol Nutr Metab*. 2008;33(5):997–1006.
6
7 605 45. Thibault R, Goujon N, Le Gallic E, Clairand R, Sébille V, Vibert J, et al. Use of 10-point analogue scales to
8
9 606 estimate dietary intake: A prospective study in patients nutritionally at-risk. *Clinical Nutrition*. 2009;28(2):134–
10
11 607 40.
12
13 608 46. Hjermstad MJ, Fossa SD, Bjordal K, Kaasa S. Test/retest study of the European Organization for Research
14
15 609 and Treatment of Cancer Core Quality-of-Life Questionnaire. *JCO*. 1995;13(5):1249–54.
16
17 610 47. Koller M, Shamieh O, Hjermstad MJ, Hornslien K, Young T, Chalk T, et al. Psychometric properties of the
18
19 611 updated EORTC module for assessing quality of life in patients with lung cancer (QLQ-LC29): an international,
20
21 612 observational field study. *The Lancet Oncology*. 2020;21(5):723–32.
22
23 613 48. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement
24
25 614 to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. *European Journal*
26
27 615 *of Cancer*. 1994;30(5):635–42.
28
29 616 49. Weis J, Tomaszewski KA, Hammerlid E, Ignacio Arraras J, Conroy T, Lanceley A, et al. International
30
31 617 Psychometric Validation of an EORTC Quality of Life Module Measuring Cancer Related Fatigue (EORTC QLQ-
32
33 618 FA12). *JNCI: Journal of the National Cancer Institute [Internet]*. 2017 [cited 2020 May 28];109(5). Available from:
34
35 619 <https://academic.oup.com/jnci/article/doi/10.1093/jnci/djw273/2972669>
36
37 620 50. Savard M-H, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer
38
39 621 patients: INSOMNIA SEVERITY INDEX AND CANCER. *Psycho-Oncology*. 2005;14(6):429–41.
40
41 622 51. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: Psychometric Indicators to
42
43 623 Detect Insomnia Cases and Evaluate Treatment Response. *Sleep*. 2011;34(5):601–8.
44
45 624 52. Sass C, Dupré C, Giordanella JP, Girard F, Guenot C, Labbe É, et al. Le score Epices : un score individuel
46
47 625 de précarité. Construction du score et mesure des relations avec des données de santé, dans une population de
48
49 626 197 389 personnes. 2006;4.
50
51 627 53. Jones LW. Precision Oncology Framework for Investigation of Exercise As Treatment for Cancer. *JCO*.
52
53 628 2015;33(35):4134–7.
54
55 629 54. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being
56
57 630 undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC*
58
59 631 *Med Res Methodol*. 2013;13(1):104.

- 1
2
3 632 55. R Core Team (2020). — European Environment Agency [Internet]. [cited 2021 Jul 4]. Available from:
4
5 633 [https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-](https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-development-core-team-2006)
6
7 634 [development-core-team-2006](https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-development-core-team-2006)
8
9 635 56. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture
10
11 636 (REDCap)—A metadata-driven methodology and workflow process for providing translational research
12
13 637 informatics support. *Journal of Biomedical Informatics*. 2009;42(2):377–81.
14
15 638 57. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O’Neal L, et al. The REDCap consortium: Building
16
17 639 an international community of software platform partners. *Journal of Biomedical Informatics*. 2019;95:103208.
18
19 640 58. Jones LW. Physical Activity and Lung Cancer Survivorship. In: Courneya KS, Friedenreich CM, editors.
20
21 641 Physical Activity and Cancer [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010 [cited 2021 Mar 28].
22
23 642 p. 255–74. (Recent Results in Cancer Research; vol. 186). Available from: [http://link.springer.com/10.1007/978-](http://link.springer.com/10.1007/978-3-642-04231-7_11)
24
25 643 [3-642-04231-7_11](http://link.springer.com/10.1007/978-3-642-04231-7_11)
26
27 644 59. Quist M, Langer SW, Lillelund C, Winther L, Laursen JH, Christensen KB, et al. Effects of an exercise
28
29 645 intervention for patients with advanced inoperable lung cancer undergoing chemotherapy: A randomized clinical
30
31 646 trial. *Lung Cancer*. 2020;145:76–82.
32
33 647 60. Nadler M, Bainbridge D, Tomasone J, Cheifetz O, Juergens RA, Sussman J. Oncology care provider
34
35 648 perspectives on exercise promotion in people with cancer: an examination of knowledge, practices, barriers, and
36
37 649 facilitators. *Support Care Cancer*. 2017;25(7):2297–304.
38
39 650 61. Wilk M, Kepski J, Kepska J, Casselli S, Szmit S. Exercise interventions in metastatic cancer disease: a
40
41 651 literature review and a brief discussion on current and future perspectives. *BMJ Support Palliat Care*.
42
43 652 2020;10(4):404–10.
44
45 653 62. Singh B, Spence R, Steele ML, Hayes S, Toohey K. Exercise for Individuals With Lung Cancer: A Systematic
46
47 654 Review and Meta-Analysis of Adverse Events, Feasibility, and Effectiveness. *Semin Oncol Nurs*.
48
49 655 2020;36(5):151076.
50
51 656 63. Granger CL, Parry SM, Edbrooke L, Abo S, Leggett N, Dwyer M, et al. Improving the delivery of physical
52
53 657 activity services in lung cancer: A qualitative representation of the patient’s perspective. *European Journal of*
54
55 658 *Cancer Care*. 2019;28(1):e12946.
56
57 659 64. Dittus KL, Gramling RE, Ades PA. Exercise interventions for individuals with advanced cancer: A
58
59 660 systematic review. *Preventive Medicine*. 2017;104:124–32.

- 1
2
3 661 65. Heywood R, McCarthy AL, Skinner TL. Safety and feasibility of exercise interventions in patients with
4
5 662 advanced cancer: a systematic review. *Support Care Cancer*. 2017 Oct;25(10):3031–50.
6
7 663 66. Yang M, Liu L, Gan C, Qiu L, Jiang X, He X, et al. Effects of home-based exercise on exercise capacity,
8
9 664 symptoms, and quality of life in patients with lung cancer: A meta-analysis. *European Journal of Oncology*
10
11 665 *Nursing*. 2020;49:101836.
12
13 666 67. Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour
14
15 667 microenvironment. *Nature Reviews Cancer*. 2017;17(10):620–32.
16
17 668 68. Nieman DC, Lila MA, Gillitt ND. Immunometabolism: A Multi-Omics Approach to Interpreting the
18
19 669 Influence of Exercise and Diet on the Immune System. *Annu Rev Food Sci Technol*. 2019;10:341–63.
20
21 670 69. Gresham G, Schrack J, Gresham LM, Shinde AM, Hendifar AE, Tuli R, et al. Wearable activity monitors in
22
23 671 oncology trials: Current use of an emerging technology. *Contemporary Clinical Trials*. 2018;64:13–21.
24
25 672 70. Haberlin C, O'Dwyer T, Mockler D, Moran J, O'Donnell DM, Broderick J. The use of eHealth to promote
26
27 673 physical activity in cancer survivors: a systematic review. *Support Care Cancer*. 2018;26(10):3323–36.
28
29 674 71. Turner RR, Steed L, Quirk H, Greasley RU, Saxton JM, Taylor SJ, et al. Interventions for promoting habitual
30
31 675 exercise in people living with and beyond cancer. *Cochrane Database Syst Rev* [Internet]. 2018 [cited 2019 Oct
32
33 676 29];2018(9). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6513653/>
34
35 677 72. Naito T, Mitsunaga S, Miura S, Tatematsu N, Inano T, Mouri T, et al. Feasibility of early multimodal
36
37 678 interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer. *J Cachexia Sarcopenia*
38
39 679 *Muscle*. 2019;10(1):73–83.
40
41 680 73. Delrieu L, Anota A, Trédan O, Freyssenet D, Maire A, Canada B, et al. Design and methods of a national,
42
43 681 multicenter, randomized and controlled trial to assess the efficacy of a physical activity program to improve
44
45 682 health-related quality of life and reduce fatigue in women with metastatic breast cancer: ABLE02 trial. *BMC*
46
47 683 *Cancer* [Internet]. 2020 [cited 2021 Apr 15];20. Available from:
48
49 684 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7333295/>
50
51 685 74. Delrieu L, Martin A, Touillaud M, Pérol O, Morelle M, Febvey-Combes O, et al. Sarcopenia and serum
52
53 686 biomarkers of oxidative stress after a 6-month physical activity intervention in women with metastatic breast
54
55 687 cancer: results from the ABLE feasibility trial. *Breast Cancer Res Treat* [Internet]. 2021 [cited 2021 Jun 13];
56
57 688 Available from: <https://link.springer.com/10.1007/s10549-021-06238-z>
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3 690 **DECLARATIONS**

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5 691 **CONSENT FOR PUBLICATION**

6
7 692 Not applicable

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10 693 **AVAILABILITY OF DATA AND MATERIAL**

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12 694 Not applicable

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14 695 **COMPETING INTERESTS**

15
16 696 The authors declare no competing interests.

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18 697 **AUTHORS' CONTRIBUTIONS**

19
20 698 MG, OP, BF, VP, PM and MP designed the trial and obtained funding. MG, OP, BF, VP and MP developed
21
22 699 the study protocol. BF, PM and MP contributed to the medical part of the protocol. MV, TW, CC and
23
24 700 MCC brought their immunologic expertise. PS brought his biological expertise. MG, OP fulfilled
25
26 701 administrative procedures for this project. MG, OP, BF and VP wrote this manuscript. All the authors
27
28 702 reviewed and contributed to the final version of the manuscript.

29
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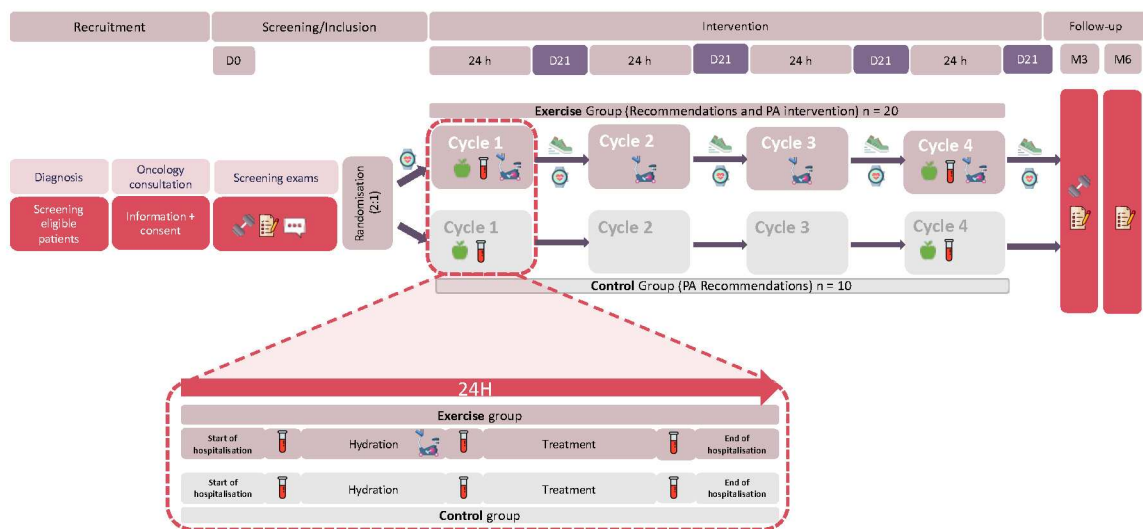
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38 707 **ACKNOWLEDGEMENTS**

39
40 708 The authors would like to thank the LYriCAN for the funding for the biological analyses.

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47 710 **Figure 1:** Flow chart of the ERICA study, France (original flow chart)

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Line
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	From line 1 to line 3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract : Line 52-53; Methods : line 432-435
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	Abstract : line 52 Declaration line 433
Funding	4	Sources and types of financial, material, and other support	Funding: line 706-708
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Line : 4 to line 22; Author's contribution : line 700-704
	5b	Name and contact information for the trial sponsor	Line 23-25
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Funding : line 706-708
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Data monitoring : line 426 to 429
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction : line 27 to 34
	6b	Explanation for choice of comparators	Line 123 to line 134
Objectives	7	Specific objectives or hypotheses	Line 123 to line 134

1 2 3 4 5 6 7	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Line 137
8	Methods: Participants, interventions, and outcomes			
9 10 11 12 13	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Line 137 to 138 Line 169
14 15 16 17 18	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Line 142 to 167
19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Line 188 to 241
		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Line 213 to 214 Line 229 to 231 Line 232 to 234
		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Line 189 to 194
36 37 38 39 40 41 42 43 44 45	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Line 243 to 281
46 47 48 49 50 51	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Line 244 to 246
52 53 54 55 56 57	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Line 384 to 393
58 59 60	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Line 168 to 178

Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Line 181 to 186
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Line 427 to 428
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Line 244 to 381
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Line 232 to 234
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Line 427 to 429
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be	Line 400 to 424

1		found, if not in the protocol	
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3	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Line 400 to 424
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5	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Line 400 to 424
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10	Methods: Monitoring		
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12	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
13			Line 426 to 429
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21		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
22			N/A
23			no interim analyses are planned
24			
25	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
26			Line 426 to 429
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30	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
31			Line 432 to 434
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34	Ethics and dissemination		
35			
36	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
37			Line 432 to 435
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40	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
41			N/A
42			
43			
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45			
46	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
47			Abstract : line 54
48			Study population : line 149
49			Recruitment: line 172-173
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53		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
54			N/A
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57	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality
58			Line 434
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		before, during, and after the trial	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Line 697
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Line 428-429
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	line 54-55
	31b	Authorship eligibility guidelines and any intended use of professional writers	line 54-55
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Consent form, see supplementary file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Line 355 to 374

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

The effect of acute physical exercise before immunotherapy and chemotherapy infusion in patients with metastatic non-small-cell lung cancer: Protocol for the ERICA feasibility trial

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Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Oncology, Immunology (including allergy), Pharmacology and therapeutics
Keywords:	CHEMOTHERAPY, IMMUNOLOGY, Adult oncology < ONCOLOGY, Respiratory tract tumours < ONCOLOGY, SPORTS MEDICINE



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ABSTRACT

Introduction. Patients with metastatic Non-Small Cell Lung Cancer (mNSCLC) suffer from numerous symptoms linked to disease and treatment which may further impair the patient's overall condition. In addition to its beneficial effects on quality of life and fatigue, physical exercise may improve response to treatment, notably due to its known effects on the immune system. The ERICA study has been designed to assess the feasibility of a supervised acute physical exercise therapy realised immediately prior to first line immune-chemotherapy infusion in patients with mNSCLC. Secondary objectives are to examine the effects of this acute physical exercise combined with an unsupervised home walking program on clinical, physical, psycho-social and biological parameters.

Methods and analysis. ERICA is a prospective, monocentric, randomized controlled, open-label feasibility study conducted at the Centre Léon Bérard Comprehensive Cancer Center (France). Thirty patients newly diagnosed with mNSCLC will be randomized (2:1 ratio) to the "exercise" or the "control" group. At baseline and during the last treatment cycle, participants in both groups will receive Physical Activity recommendations, and two nutritional assessments and nutrition recommendations. In the exercise group, participants will receive a 3-months program consisting of a supervised acute physical exercise session one hour prior to immune-chemotherapy infusion, and an unsupervised home-based walking program with an activity tracker. The acute exercise consists of interval training at a submaximal intensity for 35 minutes. Clinical, physical, biological, and psychosocial parameters will be assessed at baseline, 3 months and 6 months after study inclusion. Biological measures will include analyses of immune, inflammatory, metabolic, oxidative stress biomarkers and molecular profiling.

Ethics and dissemination. The study protocol was approved by the French ethics committee (Comité de protection des personnes Ile de France II, N°ID-RCB 20.09.04.65226, 8th December 2020). The study is registered on ClinicalTrials.gov (NCT number: NCT04676009). All participants will have to sign and date an informed consent form. The findings will be disseminated in peer-reviewed journals and academic conferences.

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3 49 **KEYWORDS:** Non-small-cell lung cancer, Metastatic, Exercise, Immunotherapy, Chemotherapy,
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5 50 Immunology
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8 51 **Word count:** 5344
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10 52 **Strengths and limitations of this study.**
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13 53 • This study is the first to assess the feasibility effects of acute physical exercise performed
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15 54 within one hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-
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17 55 based doublet) infusion in mNSCLC patients.
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19 56 • Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption
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21 57 condition during a submaximal endurance test on a cycle-ergometer at baseline and this test
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23 58 will allow individualisation of the intensity of the acute physical exercise program.
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25 59 • The feasibility study assesses the acute physiological, immune, and metabolic response to a
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27 60 supervised acute moderate intensity physical exercise session in patients with mNSCLC.
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30 61 The unsupervised home-based walking program in the intervention arm aims to increase the
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32 62 level of physical activity in patients with mNSCLC and their cardiorespiratory fitness and
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34 63 physical capacity to perform acute physical exercise prior to chemo-immunotherapy infusion.
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37 64 • The study concerns only one stage of lung cancer, participants must be eligible to
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39 65 immunotherapy and it's a study with a limited sample size (n=30).
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66 INTRODUCTION

67 Non-small cell lung cancer (NSCLC) accounts for approximately 80-90% of lung cancers (1,2). More than
68 half of NSCLC are diagnosed at advanced stages due to their asymptomatic nature at early stage
69 explaining their poor survival. The development of immunotherapy in first-line therapy with anti-PD-1
70 and anti-PD-L1 has changed the first line treatment algorithm of advanced NSCLC (1). The anti-PD-1
71 pembrolizumab and cemiplimab clearly improve the overall survival in NSCLC with high PD-L1
72 expression ($\geq 50\%$ of tumour cells) in comparison with cytotoxic chemotherapy. Combinations of anti-
73 PD(L)-1 to platinum-based chemotherapy are superior to chemotherapy alone, independently of PD-
74 L1 level of expression. They represent the 1st line gold-standard when PD-L1 is expressed in less than
75 50% of tumour cells and might reduce the risk of early disease progression in comparison with
76 pembrolizumab when PD-L1 $\geq 50\%$. Immunotherapy has significantly improved the prognosis of
77 patients with mNSCLC and has led to prolonged remissions in some patients especially for non-
78 squamous cell carcinoma in the KEYNOTE-189 trial (3,4). Despite these therapeutic advances,
79 metastatic lung cancer has a negative impact on patients' physical, psychological, and social
80 functioning including health-related quality of life (HRQoL) (5–7). Principal reported symptoms and
81 adverse effects from treatment are fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite
82 loss, and financial concerns (8,9).

83 Benefits of physical exercise defined as planned, structured, repeated, and purposeful Physical Activity
84 (PA) to improve physical fitness (10) have been widely demonstrated. In lung cancer patients, physical
85 exercise has been shown to improve aerobic capacity (VO_{2peak}), muscular strength, functional capacity
86 (11), sleep quality (12), PA level (13), some fatigue domains (14), anxiety, disease-specific global
87 health-related quality of life (15) and emotional well-being in cancer patients (16). Several studies in
88 lung cancer patients have reported the potential of physical exercise to limit or even reverse some of
89 the adverse effects induced by the disease and its treatment (17). While regular PA is recommended
90 in patients with cancer, no specific recommendations exist for patients with lung cancer or metastatic
91 disease (18). In addition, few studies have examined the interactions between transient physiological

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3 92 changes caused by acute exercise i.e., a single physical exercise bout, and cancer treatments(19).
4
5 93 Immunomodulatory effects of acute physical exercise involve immune cell mobilisation in blood such
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7 94 as neutrophils, subsets of monocytes or lymphocytes involved in the host defence against tumours,
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10 95 seems to improve immunosurveillance (20). Acute physical exercise leads to a rapid increase in the
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12 96 mobilization of the peripheral activity of the sub-population of CD56^{dim} NK cells during acute physical
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14 97 exercise of light to moderate intensity (21,22). A preclinical study reported that exercise training
15
16 98 (voluntary running), through activation of epinephrine and IL-6, led to selective NK cell mobilization
17
18 99 and limited tumour growth of several types of tumours (melanomas, liver, and lung mouse models)
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21 100 (23). In a recent study, the increase in PD-1+ CD8+ T cells was observed after a single exercise session
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23 101 (24). At the level of the adaptive immune system, acute exercise results in transient biphasic changes,
24
25 102 i.e. increase of circulating lymphocytes during and immediately after exercise, followed by a transient
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27 103 decrease of blood lymphocytes below baseline level during recovery from exercise (1 hour), thought
28
29 104 to be due to a redistribution of immune cells to peripheral tissues, including tumours, before return to
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32 105 basal level within a few hours (23,25). Moreover, recent preclinical studies suggested that physical
33
34 106 exercise performed during chemotherapy infusion may have additional physiological benefits such as
35
36 107 increase the blood flow leading to improved intra-tumoral perfusion and enhanced drug delivery (26–
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38 108 28). However, most of the available evidence on the benefits of physical exercise in cancer patients
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41 109 has been observed in interventions performed either after the treatment or during the interval
42
43 110 between the chemotherapy cycles(29). Only two studies have evaluated the feasibility of low-intensity
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45 111 physical exercises during the chemotherapy infusion without adverse events, interference with
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47 112 chemotherapy, or exacerbation in symptoms (29,30). Recently, it has been suggested in preclinical
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49 113 studies that exercise performed during chemotherapy infusion could lead to improved perfusion of
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51 114 solid tumours, mitigating tumour hypoxia, and enhancing drug delivery to tumours (26,27,31).
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54 115 Similarly, by its effect on immune regulation, physical exercise prior to infusion may potentiate the
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57 116 effect of the immunotherapy. Recent preclinical evidence has suggested a beneficial effect of exercise
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3 117 in addition to immunotherapy (anti-PD-1 immunotherapy) in a murine model of NSCLC, through
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5 118 increased necrosis and a decreased proliferative index of tumour cells (32).
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7 119 Based on these findings, the main objective of the ERICA (Exercise inteReaction Immunotherapy
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9 120 Chemotherapy and cAncer) feasibility study is to evaluate the feasibility of a supervised acute physical
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11 121 exercise performed immediately prior to immunotherapy and chemotherapy infusion (i.e. a
12
13 122 combination of pembrolizumab and pemetrexed-cis- or carboplatin for non-squamous cell carcinoma
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15 123 or paclitaxel-carboplatin for squamous cell carcinoma) in first-line treatment of metastatic NSCLC
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17 124 patients, and to assess if this planned exercise dose is safe and tolerable in this target patient
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19 125 population. The secondary objectives are to evaluate the effects of the supervised acute exercise
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21 126 before first-line treatment administration combined with an unsupervised home-based walking
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23 127 program, on 1) physical fitness, 2) PA level and sedentary lifestyle, 3) psychosocial factors (HRQoL and
24
25 128 fatigue), 4) sleep quality, 5) body composition, 6) sarcopenia, 7) treatment response, 8) treatment
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27 129 completion rate, 9) related treatment toxicities, and 10) progression-free survival. Furthermore, this
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29 130 feasibility study will generate data on the effect of this exercise intervention on immune, metabolic,
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31 131 and inflammatory biomarkers as well as oxidative stress.
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132 **METHODS**

133 **STUDY DESIGN**

134 ERICA is a prospective, monocentric, randomized controlled, open-label feasibility study, conducted at
135 the Centre Léon Bérard Comprehensive Cancer Centre (Lyon, France).
136

136 *Insert Figure 1*

137 **STUDY POPULATION**

138 *Inclusion criteria*

139 Participants will have to meet all of the following eligibility criteria: 1) aged ≥ 18 and < 80 years; 2)
140 diagnosed with a histologically confirmed metastatic NSCLC without EGFR mutation/ALK
141 rearrangement; 3) eligible to receive first-line chemotherapy according to histology (pemetrexed-cis-
142 or carboplatin for non-squamous cell carcinoma or paclitaxel-carboplatin for squamous cell

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3 143 carcinoma) in combination with pembrolizumab; 4) Eastern Co-operative Oncology Group (ECOG)
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5 144 performance status ≤ 2 ; 5) able to engage in PA attested by a medical certificate by an oncologist;
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7 145 and 6) provide a dated and signed informed consent form before study enrolment.
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10 146 *Exclusion criteria*

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12 147 Patients will not be eligible in at least one of the following cases: 1) bone metastases with risk of
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14 148 fractures or unconsolidated pathologic fractures; 2) contraindication to the physical exercise proposed
15
16 149 in this study (e.g. orthopaedic disorder such as disabling coxarthrosis or gonarthrosis, central nervous
17
18 150 system disorders); 3) history or co-existence of other primary cancer (except in situ cancer regardless
19
20 151 of the site, and/or basal cell carcinoma, and/or non-lung cancer in complete remission for more than
21
22 152 5 years) ; 4) severe undernutrition defined according to the French National Authority for Health (i.e.
23
24 153 for adults aged ≥ 18 years and < 70 : Body Mass Index (BMI) ≤ 17 , weight loss $\geq 10\%$ in 1 month, $\geq 15\%$
25
26 154 in 6 months, or $\geq 15\%$ compared to the usual weight before the disease diagnosis, or serum albumin
27
28 155 < 30 g/l; for adults aged ≥ 70 years: BMI < 18 , weight loss $\geq 10\%$ in 1 month or $\geq 15\%$ in 6 months, or
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30 156 serum albumin < 30 g/l) (33); 5) severe anaemia (haemoglobin ≤ 8 g/dl) in the past 30 days prior to
31
32 157 enrolment; 6) history of cardiovascular disease or cardiovascular risk (i.e. chronic or poorly controlled
33
34 158 coronary heart disease, peripheral arterial disease, cardiac arrhythmia, symptomatic heart disease,
35
36 159 uncontrolled or untreated arterial hypertension, myocardial infarction diagnosed in the past 6 months,
37
38 160 coronary angioplasty with or without stent implantation in the past 6 months, coronary artery bypass
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40 161 surgery in the past 12 months); 7) history of type 2 diabetes or glycated haemoglobin $> 7\%$ in the past
41
42 162 3 months prior to enrolment; 8) Stage IV Chronic obstructive pulmonary disease (forced expiratory
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44 163 volume in one second (FEV₁) $< 30\%$).
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50 164 **RECRUITMENT**

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52 165 Participants will be recruited in Centre Léon Bérard, Lyon, France from December 2020. Eligible
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54 166 patients will be screened systematically based on electronic medical record during weekly
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56 167 multidisciplinary lung cancer board meetings, as seen in Figure 1. During a medical consultation before
57
58 168 treatment initiation, an oncologist will propose the study to eligible patients and explain the study
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3 169 objectives and protocol. Once the written informed consent is signed, patients will undergo the
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5 170 following screening tests prior to inclusion: (1) clinical examination including assessing Performance
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7 171 Status (PS) and Blood Pressure, (2) echocardiography and electrocardiogram performed by a
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10 172 cardiologist, and (3) for patients with diabetes, measurement of glycated haemoglobin. If these
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12 173 investigations confirm the patient's eligibility, the patient will be included in the study (D0). The end
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14 174 date for this study is planned in January 2023.

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18 176 **RANDOMIZATION**

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21 177 At inclusion (D0), patients will be randomly assigned (ratio 2:1) to (i) the exercise group to receive PA
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23 178 and nutrition recommendations; a supervised acute physical exercise prior each immuno-
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25 179 chemotherapy infusion and an unsupervised home-based walking program with an activity tracker or
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28 180 (ii) the control group to receive PA and nutrition recommendations only.

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30 181 Randomization will be stratified using a dynamic minimization algorithm with two factors: sex (male
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32 182 vs. female) and histology (squamous vs. non-squamous).

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36 184 **INTERVENTION**

37 185 *Treatment protocol*

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40 186 All patients in both exercise and control groups of this study will receive usual care and the same
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43 187 standard treatment protocol: pembrolizumab (200 mg) combined with carboplatin (AUC 5) plus
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45 188 pemetrexed (500 mg/m²) with B9-B12 vitamin supplementation; carboplatin (AUC 6) plus paclitaxel
46
47 189 (200 mg/m²) every 3 weeks for 4 cycles; before pembrolizumab maintenance in squamous cell
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50 190 carcinoma or pembrolizumab plus pemetrexed maintenance for non-squamous cell carcinoma.

51 191 *Physical Activity recommendations*

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54 192 Although there are no specific PA recommendations for patients with mNSCLC, all patients will be
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57 193 informed of the PA recommendations to be physically active as much as possible during the day,
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60 194 walking as much as possible and sitting as little as possible (WCRF, 2018). We have chosen to follow

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3 195 the recommendations of the Macmillan Cancer Support guide released in 2018, advising patients with
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5 196 bone metastases to have an active lifestyle on a daily basis and to maintain appropriate PA according
6
7 197 to their physical abilities (34). Several individual strategies will be proposed to patients (e.g., using
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9 198 stairs whenever possible, walking to local shops).

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12 199 *Nutritional recommendations*

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14 200 All patients will receive nutritional recommendations during the 1st and 4th treatment cycle. The
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16 201 nutritional recommendations will include: energy intake of 30 kcal/kg body weight/day for patients
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18 202 with BMI <30, or 25 kcal/kg body weight/day for patients with BMI ≥ 30, and protein intake of at least
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20 203 1.2 g/kg body weight/day (35,36).

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23 204 **Exercise Group**

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25 205 *Acute physical exercise protocol prior to immunotherapy and chemotherapy infusion*

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27 206 Patients in the "exercise" group will perform a supervised acute physical exercise bout during
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29 207 hospitalization for treatment. It will be carried out 1 hour prior to the immunotherapy and
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31 208 chemotherapy infusion, on a cycle ergometer (Monark Ergonomic 939 Novo) for each of the 4 cycles
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33 209 of treatment foreseen. The physical exercise will be supervised by a clinical exercise physiologist with
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35 210 experience in the oncology. The physical exercise consists of a 35-min acute interval training and will
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37 211 be individualized based on the results of a submaximal endurance test performed on a cycle ergometer
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39 212 by each patient (described below) prior to treatment (D0).

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41 213 Following a five-minute warm-up at 60% of Ventilation Threshold 1 (VT1), the participant will carry out
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43 214 5 sets, alternating periods of 3 minutes at 70-80% of VT1 with 3 minutes at 110-120% of VT1 (≥ 35
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45 215 Revolutions Per Minute (RPM)). The acute exercise intensity will be programmed according to the load
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47 216 reached at VT1 during the cycle ergometer endurance submaximal test. Heart rate (HR), load, RPM,
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49 217 dyspnoea, and perception of effort on a Borg-scale will be monitored. If the patient is no longer able
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51 218 to cycle at the load corresponding to 120% of his VT1, the clinical exercise physiologist will decrease
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53 219 the load to 110% of VT1. In case of exercise-induced desaturation (≥ 4% of the measured value at
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55 220 rest or ≤ 93%), the clinical exercise physiologist will stop the exercise until the rest value of oxygen
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3 221 saturation. In addition to detailed explanation by the qualified clinical exercise physiologist, patients
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5 222 receive written support materials at baseline (D0).
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7 223 *Home-based walking program*

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10 224 During the 3-month intervention, between each treatment cycle (3 weeks), patients will follow an
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12 225 unsupervised home-based walking program consisting of an individual goal of a number of steps per
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14 226 day. Each patient will receive a Fitbit® Inspire activity tracker with an instruction to wear it continuously
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16 227 during the intervention. They will be advised to achieve at least 6,000 daily steps which corresponds
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18 228 to a physically active lifestyle in a patient population (37). Ten days after each treatment cycle, the
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20 229 clinical exercise physiologist will contact the patients by phone to assess and encourage adherence to
21
22 230 the home-based walking program. Depending on the average number of steps performed in the past
23
24 231 ten days, personalized objectives might be redefined to increase the target number of daily steps. For
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26 232 patients who reach more than 6,000 steps per day the initial target number of 6,000 steps will be
27
28 233 increased by 30%. The target number of steps was set within a maximum of 7800 steps above the
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30 234 average number of steps in the previous week. Patients who do not reach 6,000 daily steps, will be
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32 235 advised to gradually increase the target number of steps per day according to the patient's abilities.
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34 236 Number of steps will be collected by regular sync with the mobile phone application (Fitbit®) of the
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36 237 activity tracker or by a step logbook.
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43 239 **EVALUATIONS**

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45 240 *Modalities*

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48 241 The assessments of the repeated measures (PA level, anthropometric, HRQoL, fatigue, sleep quality,
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50 242 and sarcopenia) in both groups will be performed before the first cycle of anti-neoplastic treatment
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52 243 (baseline, D0), at the end of the 4 cycles of treatment (M3), and at 6 months after study inclusion (M6)
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54 244 (Table 1).
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246 Table 1. Data collection schedule for the ERICA study

	Screening	Inclusion D0	1 st cycle C1	4 th cycle C4	Month 3 M3	Month 6 M6
Socio demographic and clinical data						
Screening tests (<i>PS, blood Pressure, echocardiography, electrocardiogram</i>)	X					
Sociodemographic data (<i>gender, date of birth, living situation, employment status, lifestyle</i>)		X			X	X
Clinical data		X			X	X
Severe treatment toxicities (grade \geq 3) (<i>NCI-CTCAE</i>)			Continuously		X	
Tumour response (<i>RECIST</i>)		X			X	X
Physical evaluation						
Anthropometrics		X			X	
Physical fitness (<i>Cardiorespiratory fitness, strength tests</i>)		X			X	
Self-reported outcomes						
Physical activity level (<i>GODIN</i>)		X				X
Quality of life (<i>QLQ-C30, QLQ-LC13</i>)		X				X
Dietary intake (<i>24h recall</i>)			X	X		
Fatigue (<i>QLQ-FA12</i>)		X				X
Sleep quality (<i>ISI</i>)		X				X
Social deprivation (<i>EPICES</i>)		X				X
Acceptability ERICA					X	
Biological assessments						
Blood sample			X	X		
Body composition						
CT scan		X			X	X
Exercise group						
Steps per day			Continuously		X	
Number of acute physical exercise sessions			Continuously		X	

247 **DATA COLLECTION**248 *Sociodemographic and clinical data*

249 Sociodemographic and clinical data including gender, date of birth, living situation, employment status,
 250 lifestyle (alcohol consumption and smoking status) will be collected at baseline. All clinical data will be
 251 extracted from the participant's electronic medical record. The Response Evaluation Criteria In Solid
 252 Tumours (RECIST) will be used for tumour assessments between the diagnosis and the end of the ERICA
 253 study.

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255 *Anthropometric data*

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2
3 256 Anthropometric data including body weight (kilogram), height (centimeter, cm), waist (cm) and hip
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5 257 (cm) circumference will be collected. Waist circumference will be measured around the abdomen
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7 258 midway between the last floating rib and the iliac crest. Hip circumference will be measured
8
9 259 horizontally through the upper margin of the pubis. The body mass index is calculated as the body
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11 260 weight in kilograms divided by the square of the height in meters.
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16 262 *Physical fitness*

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19 263 Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption (VO_2)
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21 264 condition during a submaximal endurance test on a cycle-ergometer at baseline. This test will allow
22
23 265 individualisation of the intensity of the acute physical exercise program. Following a 5-minute warm-
24
25 266 up at 20% of the participant's maximum theoretical load, power will be increased by a constant amount
26
27 267 of 5 watts each 30 seconds until VT1 will be reached. The clinical exercise physiologist will ensure that
28
29 268 the patient maintains a minimum pedalling frequency above 35 RPM throughout the test. HR,
30
31 269 ventilation (VE), oxygen saturation (SaO_2), VO_2 , and carbon dioxide production (VCO_2) will be measured
32
33 270 by a gas analyser (MetaMax 3b, Cortex Biophysik, Leipzig, Germany) and continuously monitored. In
34
35 271 addition, the perception of the difficulty and dyspnoea will be evaluated at the end of the test using
36
37 272 the Borg Rating Perceived Exertion questionnaire(38). The clinical exercise physiologist will stop the
38
39 273 test when the patient exceeded the VT1. The test will end with a 6-minute recovery phase. The VT1
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41 274 will be determined graphically when the ventilatory equivalent of oxygen (VE/VO_2) starts to increase
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43 275 and will be confirmed by Respiratory Exchange Ratio that strictly exceeds 1 (Wasserman method).
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48 276 The lower body muscular strength will be evaluated by measuring the maximum isometric strength of
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50 277 the knee extensors (DFS II Series Digital; Force Gauges Chatillon, Largo, FL, USA). Participants will be
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52 278 seated on a chair with the knee joint at 90°, arms crossed over the chest, and the dynamometer
53
54 279 attached to the ankle. Participants were advised to extend their leg as hard as possible within 3
55
56 280 seconds upon the instructor's signal. Only the dominant leg will be tested three times (with 2 minutes
57
58 281 rest between each contraction), and the best performance will be considered.
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3 282 The maximum isometric upper limb strength will be measured by a hand dynamometer (Jamar Plus
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5 283 Digital Hand Dynamometer, Patterson Medical, Huthwaite, United Kingdom) (39,40,41). Participants
6
7 284 will be seated with their back straight and elbows bent at 90°. They will be asked to squeeze the
8
9
10 285 handgrip as strongly as possible for five seconds to achieve maximum strength. Two measurements
11
12 286 will be taken on each hand and the best performance will be recorded.
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16 288 *Physical activity level*

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18
19 289 The PA level will be measured by the Godin Leisure-Time Physical Activity Questionnaire (GLTAPQ)
20
21 290 (42). The GLTAPQ is a short, self-administered questionnaire with three questions designed to obtain
22
23 291 information on the number of times an individual engages in low, moderate, and intense "leisure-time
24
25 292 PA" periods of at least 15 minutes during a typical week. The score of the GSLTPAQ (Leisure Score
26
27 293 Index, LSI) will be obtained by using the following formula: (light PA frequency × 3) + (moderate PA
28
29 294 frequency × 5) + (vigorous PA frequency × 9). People with LSI ≥ 24 will be classified as active, while
30
31 295 people with LSI ≤ 23 will be classified as insufficiently active (estimated energy expenditure < 14
32
33 296 Kcal/kg/week). The level of PA will be investigated by the change of a daily number of steps thanks to
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35 297 the activity tracker (only in the intervention group).
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41 299 *Body composition and sarcopenia*

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43 300 Body composition and sarcopenia will be analysed using the Computed Tomography (CT) scans. CT
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45 301 scan cross-section at the level of the 3rd lumbar vertebra represents the method of choice for
46
47 302 assessment of sarcopenia in the oncology setting given that CT scan as part of routine cancer diagnostic
48
49 303 procedures is largely available (43). The thresholds for identifying muscle range from -29 to +150 HU,
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51 304 subcutaneous and intramuscular adipose tissue from -190 to -30 HU, visceral adipose tissue from -150
52
53 305 to -50 HU and bone from +152 to 1000 HU (44–46). Skeletal muscle radiodensity (SMD) that represents
54
55 306 muscle quality will be measured using the average radiation attenuation of the tissue in Hounsfield
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57 307 Units (HU). A low SMD is defined by values below the threshold of 37.8 HU. An estimate of lean body
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3 308 mass (LBM) will be calculated using the formula $(LBM \text{ (kg)} = [(L3 \text{ Muscle measured by CT (cm}^2) \times 0.3) +$
4
5 309 $6.06])$ (47).

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10 311 *Nutrition*

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12 312 Dietary intake (24h recall, supplemented with patient preferences and habits), clinical (weight loss,
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14 313 BMI), and biological (albumin and CRP) parameters will be assessed by clinical dietitians affiliated with
15
16 314 the study. The dietician will use the SEFI® (Score d'Evaluation Facile des Ingesta EPA). The score ranges
17
18 315 from 0 to 10. Patients with a SEFI score below 7 will be identified as at risk of undernutrition (48).

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23 317 *Health-related quality of life*

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25 318 The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life
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27 319 Questionnaire (QLQ-C30) is a validated multi-dimensional HRQoL questionnaire designed for cancer
28
29 320 patients (49), consisting of 30 items to assess five domains of functioning (physical, role, emotional,
30
31 321 cognitive, and social), one domain of overall quality of life, three domains of symptoms (pain, fatigue,
32
33 322 and nausea), and six single items (dyspnoea, insomnia, anorexia, diarrhoea, constipation, and financial
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35 323 impact). Participants will respond on a Likert scale ranging from "not at all" to "a lot". All scores will be
36
37 324 transformed into a scale from 0 to 100 according to the performance of the EORTC scoring manual
38
39 325 (50). A high score represents better functioning, better overall quality of life, and lower symptom
40
41 326 burden. Quality of life specific to lung cancer will be assessed by the 13-item module: the Quality of
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43 327 Life Questionnaire - Lung Cancer 13 (QLQ-LC13) (50,51). The QLQ-LC13 self-questionnaire is an
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45 328 additional measure of the symptoms and side effects experienced by lung cancer patients who receive
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47 329 non-surgical treatment.

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53 331 *Fatigue*

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55 332 Fatigue will be assessed by the EORTC-QLQ module measuring cancer-related fatigue (EORTC QLQ-
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57 333 FA12) (52). This self-questionnaire includes 12 items that assess physical, cognitive, and emotional
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3 334 fatigue related to cancer. Participants will respond on a Likert scale ranging from "not at all" to "a lot".
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5 335 All scores will be transformed into a scale from 0 to 100, with a higher score indicating a higher degree
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7 336 of fatigue.
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11 338 *Sleep quality*

12 339 The perceived quality of sleep will be assessed by the Insomnia Severity Index which measures the
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14 340 severity of insomnia. The questionnaire consists of 7 items rated on a 5-point scale ranging from 0
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16 341 ("none") to 4 ("very severe") (53,54). This self-questionnaire will evaluate the severity of the patient's
17
18 342 sleep difficulties (initial, maintenance, and morning insomnia), the degree of sleep dissatisfaction, the
19
20 343 level of interference with daily functioning, the degree of appearance of sleep difficulties, and the level
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22 344 of anxiety related to insomnia. The total score of the items varies between 0 and 28. A high score
23
24 345 indicates greater sleep difficulties.
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31 347 *Social vulnerability*

32 348 Social deprivation will be assessed using the EPICES score (Evaluation of Deprivation and Inequalities
33
34 349 in Health Examination Centres) (55). The EPICES score will be obtained by adding up the points of the
35
36 350 11 binary questions ("Yes"/"No") of the self-questionnaire. This score ranges from 0 "no
37
38 351 precariousness" to 100 "highest precariousness" with the threshold for deprivation at 30.
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45 353 *Biomarkers of the immune system, inflammation, sarcopenia, and oxidative stress*

46
47 354 Blood samples will be collected during the first and last (forth) treatment cycle: in the exercise group,
48
49 355 samples will be collected before exercise (S1), after exercise (S2), and 12 hours after the start of
50
51 356 treatment (S3); in the control group: samples will be collected 40 minutes before the infusion of
52
53 357 treatment (S1), just before the infusion of treatment (S2) and 12 hours after the start of treatment
54
55 358 (S3). Blood test procedures will follow laboratory standards. Each blood sample will be collected in 3 x
56
57 359 10mL Ethylenediaminetetraacetic acid tubes and then centrifuged (10 minutes at 800G) within one
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3 360 hour (maintained at 4°C before and during centrifugation). After the centrifuge, plasma will be
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5 361 collected and aliquoted in 5 cryotubes of 1 mL and the Peripheral Blood Mononuclear Cell (PBMC) will
6
7 362 be collected and aliquoted in 3 cryotubes (5 to 7 millions cells per tube). These cryotubes will be frozen
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9
10 363 at -80°C and stored in nitrogen at the center for the duration of the study. At the end of the study,
11
12 364 biomarkers of immunity, sarcopenia, and inflammation will be analysed. We will measure i) immune
13
14 365 biomarkers (NK cells, B lymphocytes, T lymphocytes, monocytes, sub-populations of dendritic cells on
15
16 366 frozen PBMC); ii) plasma biomarkers of sarcopenia and inflammation (Myostatin, Activin, Cortisol,
17
18 367 Tumor Necrosis Factor- α , Interferon- γ , Interleukin-1 β , Interleukin-6, Follistatin, Growth Differentiation
19
20 368 Factor 5, Bone morphogenetic protein 14, GDF15, Interleukin-10, Interleukin-15, NH3, Aminogram, C-
21
22 369 reactive protein, insulin); and iii) plasma oxidative stress (Superoxide dismutase, catalase,
23
24 370 malondialdehyde, glutathione peroxidase, Xanthine Myeloperoxidase, and Xanthine oxidase). Finally,
25
26 371 the blood samples will be also used to analyse the glucose (OneTouch Verio®) and lactate (LACTATE
27
28 372 PRO II) metabolism by a mobile device. Patients will be asked to complete a questionnaire regarding
29
30 373 the taking of antibiotics, anti-inflammatory, and antioxidants in the 48 hours prior to blood collection.
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374

375 *Toxicities*

376 Severe treatment toxicities (grade ≥ 3) will be noted according to the National Cancer Institute's
377 Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0. The number of rescheduled or
378 cancelled treatment sessions and the relative dose intensity (RDI) of participants with grade ≥ 3
379 toxicities related to chemotherapy and immunotherapy will be calculated as the ratio of "delivered"
380 to "expected" dose intensity.

381

382 **STATISTICAL ANALYSIS**

383 **SAMPLE SIZE**

384 The main objective of the current study is to evaluate the feasibility of an acute physical exercise
385 program performed prior to the infusion of treatments in mNSCLC patients, and to assess if this

1
2
3 386 planned exercise dose is safe and tolerable in this target patient population(56). In the context of a
4
5 387 feasibility study without a concrete hypothesis and in absence of previous studies in this population,
6
7 388 the sample size was defined empirically. Taking into account the number of mNSCLC patients who
8
9 389 receive first line chemotherapy (i.e. pemetrexed-platinum or taxol-platinum) combined with
10
11 390 Pembrolizumab each year in Centre Léon Bérard (Lyon), we plan to include 30 patients over a 18
12
13
14 391 months period. This number will be sufficient to assess if the planned exercise dose is safe and
15
16 392 tolerable in this target patient population, and the sample size falls within the range of sample sizes
17
18 393 recommended in the literature for feasibility trials (57).
19
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22
23 395 Although the main objective is to study the feasibility of physical exercise prior to the infusion of
24
25 396 treatments, the evaluation of the biological objectives requires randomization to have reference
26
27 397 measures. We have chosen to unbalance the randomization (2:1) so that more patients will benefit
28
29 398 from the intervention proposed in the ERICA study.
30
31

32 399

34 400 **STATISTICAL METHODS**

35
36 401 All statistical analyses will be on an exploratory basis on all data from study subjects. Given the limited
37
38 402 sample size, non-parametric tests will be performed. Qualitative data will be presented using their
39
40 403 frequencies and percentages. Quantitative data will be presented using the number of observations,
41
42 404 mean, standard deviation, median, minimum, and maximum. For both types of data, the number of
43
44 405 missing data will be presented if necessary.
45
46

47
48 406 The feasibility of the ERICA study will be assessed at the end of the intervention (M3) in the exercise
49
50 407 group only, according to the adherence rate by calculating the ratio of the number of acute physical
51
52 408 exercise sessions performed to the number of acute physical exercise sessions planned before the
53
54 409 immunotherapy/chemotherapy. The tolerability will be assessed by the relative dose intensity of
55
56 410 exercise. The safety will be assessed by the occurrence of adverse events related to the physical
57
58 411 exercise intervention. The acceptability (i.e. the proportion of patients who accept to participate in the
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1
2
3 412 study among eligible patients) and the attrition (i.e. the proportion of patients who withdraw their
4
5 413 participation from the study among patients initially enrolled) will be calculated. In the exercise group,
6
7 414 the acceptability of the activity tracker, the observance of the home-walking program, and the safety
8
9 415 of the intervention (the number, type, and timing of adverse events that occurred) will be assessed.

10 416 The evolution of the different repeated measures (PA level, anthropometric, HRQoL, fatigue, sleep
11
12 417 quality, and sarcopenia) at inclusion, 3 and 6 months will be represented by graphs and compared by
13
14 418 non-parametric ANOVAs (performed on ranks).

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18 419 Progression-free survival will be measured from the date of randomization until the date of event
19
20 420 defined as either progression or death from any cause whichever occurs first. Participants with no
21
22 421 event at the time of the analysis will be censored at the date of the last available tumour assessment.

23
24
25 422 The results will allow to formulate the hypotheses and determine sample size for a subsequent
26
27 423 multicenter randomized efficacy study.

28
29
30 424 Statistical analyses will be carried out using R statistical software (58).

31 32 425 **DATA MONITORING**

33
34 426 The database for clinical data will be managed using REDCap (Research Electronic Data Capture)
35
36 427 (59,60) software hosted at CLB. The access to the database will be secured (personal ID and password
37
38 428 required) with different levels of security depending on the role within the study. The investigator will
39
40 429 have access to the final dataset.

41 42 43 430 **PATIENT AND PUBLIC INVOLVEMENT**

44
45 431 Prior to the present study, we administrated a questionnaire to lung cancer patients to collect their
46
47 432 experience and preferences in terms of physical activity to practice during cancer treatments. The
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49 433 results were used to develop the ERICA physical activity intervention. As it is a feasibility study, the
50
51 434 findings will be used to adjust the intervention if necessary for the purpose of an efficacy randomised
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53 435 controlled trial. Global findings will be disseminated to participants at the end of the study if they wish.

54 55 56 436 **ETHICAL AND DISSEMINATION**

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3 437 The study protocol has been approved by a French ethics committee CPP Ile de France II (IDRCB:
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5 438 20.09.04.65226) and the study database has been reported to the National Commission for Data
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7 439 Protection and Liberties (CNIL; reference number: 2016177). The study has been registered at
8
9 440 reference number: NCT04676009.

441 **DISCUSSION**

442 To our knowledge, ERICA is the first study to assess the feasibility and effects of acute physical exercise
443 performed within one hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-
444 based doublet) infusion in mNSCLC patients. Despite therapeutic advances, notably immunotherapy
445 combined with chemotherapy, the prognosis of many patients with mNSCLC continues to be poor, and
446 disease burden, cachexia, comorbidities, and treatment side effects lead to deconditioning and
447 adversely affect exercise capacity in people with advanced NSCLC (17,61–64). Conversely, evidence
448 from meta-analyses suggests that exercise training in patients with advanced lung cancer could be
449 feasible and safe with no serious adverse events reported and may improve or avoid the decline of
450 physical capacity (15,65). However, the evidence regarding the benefits of exercise in mNSCLC patients
451 remains limited and there is a lack of widespread awareness of the benefits of maintaining physical
452 activity in this particular population (64,66–68). Furthermore, the high prevalence of comorbidities in
453 mNSCLC patients, which may be exacerbated by the direct and indirect effects of cancer treatment,
454 led to exclude patients at risk of cardiovascular events from studies (i.e. history of cardiovascular
455 disease; abnormal electrocardiogram and/or echocardiography) or undernutrition.

456 Based on preclinical evidence of exercise in modulating the efficacy of cancer therapy, the present
457 study assesses the feasibility of acute exercise of submaximal intensity in the target population.
458 Current evidence on the benefits of physical exercise in cancer patients mainly stems from
459 interventions performed either between the chemotherapy cycles or after end of treatment. Yet, a
460 feasibility study in patients with various tumours, mostly breast cancer, reported that exercise (i.e. 20
461 min of supervised low-intensity cycling) during chemotherapy infusion appears to be safe and feasible
462 (29). To prescribe a safe and efficacious intensity of acute exercise intervention, we decided to realize

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2
3 463 a submaximal cardiopulmonary exercise test with a continuous gas exchange analysis. Because of the
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5 464 comorbidities, the tumour location and the lack of information about high intensity exercise effects,
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7 465 the present study targets acute exercise of submaximal intensity.
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10 466 Home-based exercises are a beneficial approach to reducing symptoms and improving exercise
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12 467 capacity as well as the quality of life in patients with NSCLC (69). The unsupervised home-based walking
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14 468 program in the intervention arm aims to increase the level of physical activity in patients with mNSCLC
15
16 469 and their cardiorespiratory fitness and physical capacity to perform acute physical exercise prior to
17
18 470 chemo-immunotherapy infusion (15). Also, chronic exercise can favourably modulate inflammation
19
20 471 and immune-related factors (19,70). Activity trackers are innovative tools increasingly used to promote
21
22 472 an active lifestyle and to objectively measure the PA level of cancer patients (71–73). Trackers have
23
24 473 been used in a randomized controlled trial to encourage patients with mNSCLC to maintain their PA by
25
26 474 recommending a targeted number of steps (74). In a previous study by the team, the use of activity
27
28 475 trackers have shown pertinent results in women with metastatic breast cancer (75,76). The
29
30 476 combination of these two intervention modalities (acute exercise and unsupervised walking
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32 477 programme) allows us to offer an intervention adapted to this population in order to have sufficient
33
34 478 physiological stimulation to observe changes in the immune system.
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38
39 479 The first challenge we need to overcome is that the study concerns only one stage of lung cancer and
40
41 480 participants must be eligible to immunotherapy. Next, we are looking at the intervention
42
43 481 reproducibility in other institutions. Finally, it is a feasibility study with a limited sample size (n=30).
44
45 482 We plan to conduct a randomised controlled trial to address the various limitations of the present
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47 483 study: larger sample size, multiple lung cancer stages, and to carry out the study in several hospital
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49 484 institutions.
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51 52 485 **INNOVATION AND STUDY RELEVANCE**

53
54 486 The ERICA study will provide clinical, physical, and psychosocial insights into the feasibility of acute
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56 487 exercise prior to first-line chemo-immunotherapy infusion in patients with mNSCLC. In particular,
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58 488 exploratory data on the safety and tolerability of the proposed exercise dose and schedule in the target
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3 489 patient population will be obtained. This feasibility study will further generate preliminary data on the
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5 490 acute physiological, immune, and metabolic response to the achieved exercise dose in patients with
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7 491 mNSCLC. The ERICA study will provide valuable information to design a large-scale adequately
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10 492 powered randomized controlled trial to assess the efficacy on clinically important endpoints (e.g.
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12 493 progression free survival) in patients with mNSCLC receiving first-line chemo-immunotherapy.
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For peer review only

494 **REFERENCES**

- 495 1. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung
496 cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*.
497 2018;29:iv192–237.
- 498 2. ASCO. Lung Cancer - Non-Small Cell - Statistics [Internet]. Cancer.Net. 2021 [cited 2021 Jul 3].
499 Available from: <https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics>
- 500 3. Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, et al. Updated Analysis
501 From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated
502 Metastatic Nonsquamous Non–Small-Cell Lung Cancer. *JCO*. 2020;JCO.19.03136.
- 503 4. Low JL, Walsh RJ, Ang Y, Chan G, Soo RA. The evolving immuno-oncology landscape in advanced
504 lung cancer: first-line treatment of non-small cell lung cancer. *Ther Adv Med Oncol* [Internet]. 2019 [cited 2019
505 Nov 5];11. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6716180/>
- 506 5. Brahmer JR, Rodríguez-Abreu D, Robinson AG, Hui R, Csósz T, Fülöp A, et al. Health-related quality-
507 of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024):
508 a multicentre, international, randomised, open-label phase 3 trial. *The Lancet Oncology*. 2017 Dec;18(12):1600–
509 9.
- 510 6. Polanski J, Jankowska-Polanska B, Rosinczuk J, Chabowski M, Szymanska-Chabowska A. Quality of
511 life of patients with lung cancer. *Onco Targets Ther*. 2016;9:1023–8.
- 512 7. Camps C, del Pozo N, Blasco A, Blasco P, Sirera R. Importance of Quality of Life in Patients with Non–
513 Small-Cell Lung Cancer. *Clinical Lung Cancer*. 2009;10(2):83–90.
- 514 8. Garassino MC, Gadgeel S, Esteban E, Felip E, Speranza G, Domine M, et al. Patient-reported outcomes
515 following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated,
516 metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised,
517 placebo-controlled, phase 3 trial. *The Lancet Oncology*. 2020;21(3):387–97.
- 518 9. Steffen McLouth LE, Lycan TW, Levine BJ, Gabbard J, Ruiz J, Farris M, et al. Patient-Reported
519 Outcomes From Patients Receiving Immunotherapy or Chemoimmunotherapy for Metastatic Non–Small-Cell
520 Lung Cancer in Clinical Practice. *Clinical Lung Cancer*. 2019;21(3):255-263.e4.
- 521 10. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions
522 and distinctions for health-related research. *Public Health Rep*. 1985;100(2):126–31.
- 523 11. Hwang C-L, Yu C-J, Shih J-Y, Yang P-C, Wu Y-T. Effects of exercise training on exercise capacity in

- 1
2
3 524 patients with non-small cell lung cancer receiving targeted therapy. *Support Care Cancer*. 2012;20(12):3169–77.
- 4
5 525 12. Chen H-M, Tsai C-M, Wu Y-C, Lin K-C, Lin C-C. Effect of walking on circadian rhythms and sleep
6
7 526 quality of patients with lung cancer: a randomised controlled trial. *Br J Cancer*. 2016;115(11):1304–12.
- 8
9 527 13. Dhillon HM, Bell ML, van der Ploeg HP, Turner JD, Kabourakis M, Spencer L, et al. Impact of physical
10
11 528 activity on fatigue and quality of life in people with advanced lung cancer: a randomized controlled trial. *Annals*
12
13 529 *of Oncology*. 2017;28(8):1889–97.
- 14
15 530 14. Zhang L-L, Wang S-Z, Chen H-L, Yuan A-Z. Tai Chi Exercise for Cancer-Related Fatigue in Patients
16
17 531 With Lung Cancer Undergoing Chemotherapy: A Randomized Controlled Trial. *Journal of Pain and Symptom*
18
19 532 *Management*. 2016;51(3):504–11.
- 20
21 533 15. Peddle-McIntyre CJ, Singh F, Thomas R, Newton RU, Galvão DA, Cavalheri V. Exercise training for
22
23 534 advanced lung cancer. Cochrane Lung Cancer Group, editor. *Cochrane Database of Systematic Reviews* [Internet].
24
25 535 2019 [cited 2019 Sep 17]; Available from: <http://doi.wiley.com/10.1002/14651858.CD012685.pub2>
- 26
27 536 16. Quist M, Adamsen L, Rørth M, Laursen JH, Christensen KB, Langer SW. The Impact of a
28
29 537 Multidimensional Exercise Intervention on Physical and Functional Capacity, Anxiety, and Depression in Patients
30
31 538 With Advanced-Stage Lung Cancer Undergoing Chemotherapy. *Integr Cancer Ther*. 2015;14(4):341–9.
- 32
33 539 17. Avancini A, Sartori G, Gkoutakos A, Casali M, Trestini I, Tregnago D, et al. Physical Activity and
34
35 540 Exercise in Lung Cancer Care: Will Promises Be Fulfilled? *The Oncologist* [Internet]. 2019;n/a(n/a). Available
36
37 541 from: <https://theoncologist.onlinelibrary.wiley.com/doi/abs/10.1634/theoncologist.2019-0463>
- 38
39 542 18. *Activité physique. Prévention et traitement des maladies chroniques* Éditions EDP Sciences, janvier 2019,
40
41 543 824 pages, Collection Expertise collective ISBN 978-2-7598-2328-4 [Internet]. [cited 2021 Jul 4]. Available from:
42
43 544 [https://www.inserm.fr/sites/default/files/2019-](https://www.inserm.fr/sites/default/files/2019-02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf)
44
45 545 [02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf](https://www.inserm.fr/sites/default/files/2019-02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf)
- 46
47 546 19. Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour
48
49 547 microenvironment. *Nature Reviews Cancer*. 2017;17(10):620–32.
- 50
51 548 20. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system.
52
53 549 *J Sport Health Sci*. 2019;8(3):201–17.
- 54
55 550 21. Bigley AB, Rezvani K, Chew C, Sekine T, Pistillo M, Crucian B, et al. Acute exercise preferentially
56
57 551 redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and
58
59 552 multiple myeloma target cells. *Brain, Behavior, and Immunity*. 2014;39:160–71.
- 60
553 22. Idorn M, Hojman P. Exercise-Dependent Regulation of NK Cells in Cancer Protection. *Trends in*

- 1
2
3 554 Molecular Medicine. 2016;22(7):565–77.
4
5 555 23. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al. Voluntary Running
6
7 556 Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution.
8
9 557 Cell Metabolism. 2016;23(3):554–62.
10
11 558 24. Wadley AJ, Cullen T, Vautrinot J, Keane G, Bishop NC, Coles SJ. High intensity interval exercise
12
13 559 increases the frequency of peripheral PD-1+ CD8+ central memory T-cells and soluble PD-L1 in humans. *Brain,*
14
15 560 *Behavior, & Immunity - Health.* 2020;3:100049.
16
17 561 25. Pedersen BK, Hoffman-Goetz L. Exercise and the Immune System: Regulation, Integration, and
18
19 562 Adaptation. *Physiological Reviews.* 2000;80(3):1055–81.
20
21 563 26. Wiggins JM, Opoku-Acheampong AB, Baumfalk DR, Siemann DW, Behnke BJ. Exercise and the Tumor
22
23 564 Microenvironment: Potential Therapeutic Implications. *Exercise and Sport Sciences Reviews.* 2018;46(1):56–64.
24
25 565 27. McCullough DJ, Stabley JN, Siemann DW, Behnke BJ. Modulation of Blood Flow, Hypoxia, and
26
27 566 Vascular Function in Orthotopic Prostate Tumors During Exercise. *J Natl Cancer Inst [Internet].* 2014 [cited 2020
28
29 567 Jan 8];106(4). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3982888/>
30
31 568 28. Schadler KL, Thomas NJ, Galie PA, Bhang DH, Roby KC, Addai P, et al. Tumor vessel normalization
32
33 569 after aerobic exercise enhances chemotherapeutic efficacy. *Oncotarget.* 2016;7(40):65429–40.
34
35 570 29. Thomas VJ, Seet-Lee C, Marthick M, Cheema BS, Boyer M, Edwards KM. Aerobic exercise during
36
37 571 chemotherapy infusion for cancer treatment: a novel randomised crossover safety and feasibility trial. *Support*
38
39 572 *Care Cancer.* 2020;28(2):625–32.
40
41 573 30. Kerrigan K. A pilot study of aerobic exercise performed in breast cancer patients during chemotherapy
42
43 574 infusion. | *Journal of Clinical Oncology [Internet].* 2010 [cited 2020 Aug 11]. Available from:
44
45 575 https://ascopubs.org/doi/10.1200/jco.2010.28.15_suppl.e19527
46
47 576 31. Ashcraft KA, Warner AB, Jones LW, Dewhirst MW. Exercise as Adjunct Therapy in Cancer. *Seminars*
48
49 577 *in Radiation Oncology.* 2018;29(1):16–24.
50
51 578 32. Martín-Ruiz A, Fiuza-Luces C, Rincón-Castanedo C, Fernández-Moreno D, Martínez-Martínez E,
52
53 579 Martín-Acosta P, et al. Benefits of exercise and immunotherapy in a murine model of human non–small-cell lung
54
55 580 carcinoma. 2020;16.
56
57 581 33. Alexandre P. Haute Autorité de santé. 2019;142.
58
59 582 34. Macmillan Cancer Support. Physical activity in patients with metastatic bone disease: Guidance for
60
583 healthcare professionals. 2018 [Internet]. [cited 2021 Jul 4]. Available from:

- 1
2
3 584 [https://cdn.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/1784-10061/physical-activity-for-](https://cdn.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/1784-10061/physical-activity-for-people-with-metastatic-bone-disease-guidance-tcm9-326004)
4
5 585 [people-with-metastatic-bone-disease-guidance-tcm9-326004](https://cdn.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/1784-10061/physical-activity-for-people-with-metastatic-bone-disease-guidance-tcm9-326004)
6
7 586 35. Senesse P, Bachmann P, Bensadoun RJ, Besnard I, Bourdel-Marchasson I, Bouteloup C, et al. Nutrition
8
9 587 chez le patient adulte atteint de cancer : textes courts. *Nutrition Clinique et Métabolisme*. 2012;26(4):151–8.
10
11 588 36. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on
12
13 589 nutrition in cancer patients. *Clinical Nutrition*. 2017;36(1):11–48.
14
15 590 37. Tudor-Locke C, Craig CL, Aoyagi Y, Bell RC, Croteau KA, De Bourdeaudhuij I, et al. How many
16
17 591 steps/day are enough? For older adults and special populations. *Int J Behav Nutr Phys Act*. 2011;8(1):80.
18
19 592 38. Borg G, Hassmén P, Lagerström M. Perceived exertion related to heart rate and blood lactate during arm
20
21 593 and leg exercise. *Europ J Appl Physiol*. 1987;56(6):679–85.
22
23 594 39. Kilgour RD, Vigano A, Trutschnigg B, Lucar E, Borod M, Morais JA. Handgrip strength predicts survival
24
25 595 and is associated with markers of clinical and functional outcomes in advanced cancer patients. *Support Care*
26
27 596 *Cancer*. 2013 Dec;21(12):3261–70.
28
29 597 40. Anand A, Gajra A. Hand Grip Dynamometry as Prognostic and Predictive Marker in Older Patients With
30
31 598 Cancer. *J Gerontol Geriatr Res [Internet]*. 2018 [cited 2020 Jun 19];07(03). Available from:
32
33 599 [https://www.omicsonline.org/open-access/hand-grip-dynamometry-as-prognostic-and-predictive-marker-in-](https://www.omicsonline.org/open-access/hand-grip-dynamometry-as-prognostic-and-predictive-marker-in-older-patients-with-cancer-2167-7182-1000471-102218.html)
34
35 600 [older-patients-with-cancer-2167-7182-1000471-102218.html](https://www.omicsonline.org/open-access/hand-grip-dynamometry-as-prognostic-and-predictive-marker-in-older-patients-with-cancer-2167-7182-1000471-102218.html)
36
37 601 41. Trutschnigg B, Kilgour RD, Reinglas J, Rosenthal L, Hornby L, Morais JA, et al. Precision and reliability
38
39 602 of strength (Jamar vs. Biodex handgrip) and body composition (dual-energy X-ray absorptiometry vs.
40
41 603 bioimpedance analysis) measurements in advanced cancer patients. *Appl Physiol Nutr Metab*. 2008;33(6):1232–
42
43 604 9.
44
45 605 42. Amireault S, Godin G, Lacombe J, Sabiston CM. The use of the Godin-Shephard Leisure-Time Physical
46
47 606 Activity Questionnaire in oncology research: a systematic review. *BMC Med Res Methodol [Internet]*. 2015 [cited
48
49 607 2020 May 28];15. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4542103/>
50
51 608 43. Tosato M, Marzetti E, Cesari M, Saveria G, Miller RR, Bernabei R, et al. Measurement of muscle mass
52
53 609 in sarcopenia: from imaging to biochemical markers. *Aging Clin Exp Res*. 2017 Feb;29(1):19–27.
54
55 610 44. Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, et al. Appendicular skeletal muscle
56
57 611 mass: measurement by dual-photon absorptiometry. *Am J Clin Nutr*. 1990 Aug;52(2):214–8.
58
59 612 45. Miller KD, Jones E, Yanovski JA, Shankar R, Feuerstein I, Falloon J. Visceral abdominal-fat
60
613 613 accumulation associated with use of indinavir. *Lancet*. 1998 Mar 21;351(9106):871–5.

- 1
2
3 614 46. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation
4 615 of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol*.
5 616 1998 Jul;85(1):115–22.
- 6
7
8 617 47. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise
9 618 approach to quantification of body composition in cancer patients using computed tomography images acquired
10 619 during routine care. *Appl Physiol Nutr Metab*. 2008;33(5):997–1006.
- 11
12
13 620 48. Thibault R, Goujon N, Le Gallic E, Clairand R, Sébille V, Vibert J, et al. Use of 10-point analogue scales
14 621 to estimate dietary intake: A prospective study in patients nutritionally at-risk. *Clinical Nutrition*. 2009;28(2):134–
15 622 40.
- 16
17
18 623 49. Hjermstad MJ, Fossa SD, Bjordal K, Kaasa S. Test/retest study of the European Organization for
19 624 Research and Treatment of Cancer Core Quality-of-Life Questionnaire. *JCO*. 1995;13(5):1249–54.
- 20
21
22 625 50. Koller M, Shamieh O, Hjermstad MJ, Hornslien K, Young T, Chalk T, et al. Psychometric properties of
23 626 the updated EORTC module for assessing quality of life in patients with lung cancer (QLQ-LC29): an
24 627 international, observational field study. *The Lancet Oncology*. 2020;21(5):723–32.
- 25
26
27 628 51. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular
28 629 supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials.
29 630 *European Journal of Cancer*. 1994;30(5):635–42.
- 30
31
32 631 52. Weis J, Tomaszewski KA, Hammerlid E, Ignacio Arraras J, Conroy T, Lanceley A, et al. International
33 632 Psychometric Validation of an EORTC Quality of Life Module Measuring Cancer Related Fatigue (EORTC QLQ-
34 633 FA12). *JNCI: Journal of the National Cancer Institute [Internet]*. 2017 [cited 2020 May 28];109(5). Available
35 634 from: <https://academic.oup.com/jnci/article/doi/10.1093/jnci/djw273/2972669>
- 36
37
38 635 53. Savard M-H, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer
39 636 patients: INSOMNIA SEVERITY INDEX AND CANCER. *Psycho-Oncology*. 2005;14(6):429–41.
- 40
41
42 637 54. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: Psychometric Indicators to
43 638 Detect Insomnia Cases and Evaluate Treatment Response. *Sleep*. 2011;34(5):601–8.
- 44
45
46 639 55. Sass C, Dupré C, Giordanella JP, Girard F, Guenot C, Labbe É, et al. Le score Epices : un score individuel
47 640 de précarité. Construction du score et mesure des relations avec des données de santé, dans une population de 197
48 641 389 personnes. 2006;4.
- 49
50
51 642 56. Jones LW. Precision Oncology Framework for Investigation of Exercise As Treatment for Cancer. *JCO*.
52 643 2015;33(35):4134–7.
- 53
54
55
56
57
58
59
60

- 1
2
3 644 57. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being
4
5 645 undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC*
6
7 646 *Med Res Methodol.* 2013;13(1):104.
- 8
9 647 58. R Core Team (2020). — European Environment Agency [Internet]. [cited 2021 Jul 4]. Available from:
10
11 648 [https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-development-](https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-development-core-team-2006)
12
13 649 [core-team-2006](https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-development-core-team-2006)
- 14
15 650 59. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture
16
17 651 (REDCap)—A metadata-driven methodology and workflow process for providing translational research
18
19 652 informatics support. *Journal of Biomedical Informatics.* 2009;42(2):377–81.
- 20
21 653 60. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O’Neal L, et al. The REDCap consortium:
22
23 654 Building an international community of software platform partners. *Journal of Biomedical Informatics.*
24
25 655 2019;95:103208.
- 26
27 656 61. Jones LW. Physical Activity and Lung Cancer Survivorship. In: Courneya KS, Friedenreich CM, editors.
28
29 657 *Physical Activity and Cancer* [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010 [cited 2021 Mar
30
31 658 28]. p. 255–74. (Recent Results in Cancer Research; vol. 186). Available from:
32
33 659 http://link.springer.com/10.1007/978-3-642-04231-7_11
- 34
35 660 62. Quist M, Langer SW, Lillelund C, Winther L, Laursen JH, Christensen KB, et al. Effects of an exercise
36
37 661 intervention for patients with advanced inoperable lung cancer undergoing chemotherapy: A randomized clinical
38
39 662 trial. *Lung Cancer.* 2020;145:76–82.
- 40
41 663 63. Nadler M, Bainbridge D, Tomasone J, Cheifetz O, Juergens RA, Sussman J. Oncology care provider
42
43 664 perspectives on exercise promotion in people with cancer: an examination of knowledge, practices, barriers, and
44
45 665 facilitators. *Support Care Cancer.* 2017;25(7):2297–304.
- 46
47 666 64. Wilk M, Kepski J, Kepska J, Casselli S, Szmit S. Exercise interventions in metastatic cancer disease: a
48
49 667 literature review and a brief discussion on current and future perspectives. *BMJ Support Palliat Care.*
50
51 668 2020;10(4):404–10.
- 52
53 669 65. Singh B, Spence R, Steele ML, Hayes S, Toohey K. Exercise for Individuals With Lung Cancer: A
54
55 670 Systematic Review and Meta-Analysis of Adverse Events, Feasibility, and Effectiveness. *Semin Oncol Nurs.*
56
57 671 2020;36(5):151076.
- 58
59 672 66. Granger CL, Parry SM, Edbrooke L, Abo S, Leggett N, Dwyer M, et al. Improving the delivery of physical
60
673 activity services in lung cancer: A qualitative representation of the patient’s perspective. *European Journal of*

- 1
2
3 674 Cancer Care. 2019;28(1):e12946.
- 4
5 675 67. Dittus KL, Gramling RE, Ades PA. Exercise interventions for individuals with advanced cancer: A
6
7 676 systematic review. *Preventive Medicine*. 2017;104:124–32.
- 8
9 677 68. Heywood R, McCarthy AL, Skinner TL. Safety and feasibility of exercise interventions in patients with
10
11 678 advanced cancer: a systematic review. *Support Care Cancer*. 2017 Oct;25(10):3031–50.
- 12
13 679 69. Yang M, Liu L, Gan C, Qiu L, Jiang X, He X, et al. Effects of home-based exercise on exercise capacity,
14
15 680 symptoms, and quality of life in patients with lung cancer: A meta-analysis. *European Journal of Oncology*
16
17 681 *Nursing*. 2020;49:101836.
- 18
19 682 70. Nieman DC, Lila MA, Gillitt ND. Immunometabolism: A Multi-Omics Approach to Interpreting the
20
21 683 Influence of Exercise and Diet on the Immune System. *Annu Rev Food Sci Technol*. 2019;10:341–63.
- 22
23 684 71. Gresham G, Schrack J, Gresham LM, Shinde AM, Hendifar AE, Tuli R, et al. Wearable activity monitors
24
25 685 in oncology trials: Current use of an emerging technology. *Contemporary Clinical Trials*. 2018;64:13–21.
- 26
27 686 72. Haberin C, O’Dwyer T, Mockler D, Moran J, O’Donnell DM, Broderick J. The use of eHealth to promote
28
29 687 physical activity in cancer survivors: a systematic review. *Support Care Cancer*. 2018;26(10):3323–36.
- 30
31 688 73. Turner RR, Steed L, Quirk H, Greasley RU, Saxton JM, Taylor SJ, et al. Interventions for promoting
32
33 689 habitual exercise in people living with and beyond cancer. *Cochrane Database Syst Rev* [Internet]. 2018 [cited
34
35 690 2019 Oct 29];2018(9). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6513653/>
- 36
37 691 74. Naito T, Mitsunaga S, Miura S, Tatematsu N, Inano T, Mouri T, et al. Feasibility of early multimodal
38
39 692 interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer. *J Cachexia Sarcopenia*
40
41 693 *Muscle*. 2019;10(1):73–83.
- 42
43 694 75. Delrieu L, Anota A, Trédan O, Freyssenet D, Maire A, Canada B, et al. Design and methods of a national,
44
45 695 multicenter, randomized and controlled trial to assess the efficacy of a physical activity program to improve health-
46
47 696 related quality of life and reduce fatigue in women with metastatic breast cancer: ABLE02 trial. *BMC Cancer*
48
49 697 [Internet]. 2020 [cited 2021 Apr 15];20. Available from:
50
51 698 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7333295/>
- 52
53 699 76. Delrieu L, Martin A, Touillaud M, Pérol O, Morelle M, Febvey-Combes O, et al. Sarcopenia and serum
54
55 700 biomarkers of oxidative stress after a 6-month physical activity intervention in women with metastatic breast
56
57 701 cancer: results from the ABLE feasibility trial. *Breast Cancer Res Treat* [Internet]. 2021 [cited 2021 Jun 13];
58
59 702 Available from: <https://link.springer.com/10.1007/s10549-021-06238-z>
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3 704 **DECLARATIONS**
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5 705 **CONSENT FOR PUBLICATION**
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7 706 Not applicable
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10 707 **AVAILABILITY OF DATA AND MATERIAL**
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12 708 Not applicable
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14 709 **COMPETING INTERESTS**
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16 710 The authors declare no competing interests.
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19 711 **AUTHORS' CONTRIBUTIONS**
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21 712 MG, OP, BF, VP, PM and MP designed the trial and obtained funding. MG, OP, BF, VP, MP and LD
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23 713 developed the study protocol. BF, PM and MP contributed to the medical part of the protocol. MV,
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25 714 TW, CC and MCC brought their immunologic expertise. PS brought his biological expertise. MG, OP
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27 715 fulfilled administrative procedures for this project. MG, OP, BF and VP wrote this manuscript. All the
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29 716 authors reviewed and contributed to the final version of the manuscript.
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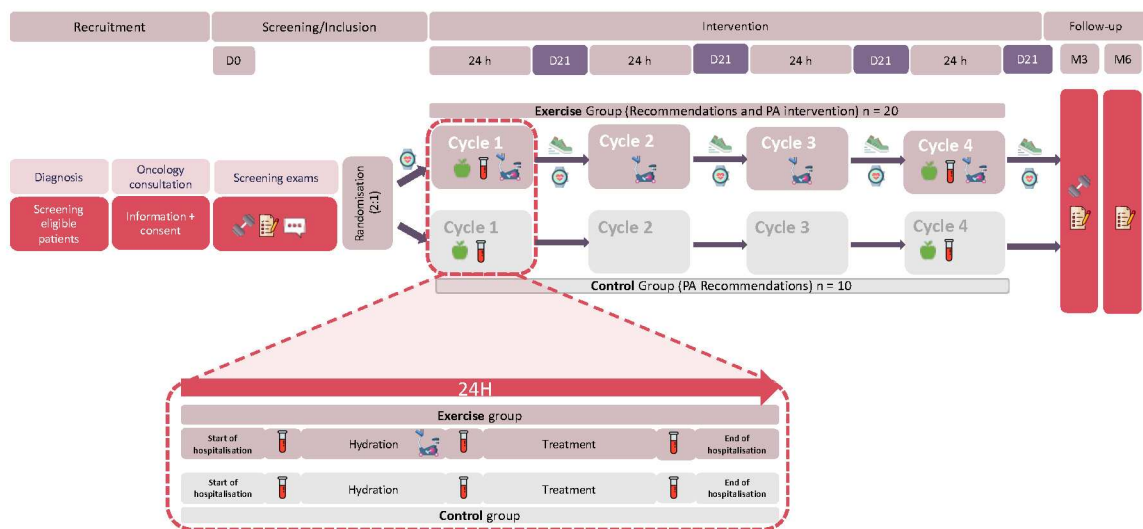
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41 721 **ACKNOWLEDGEMENTS**
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43 722 The authors would like to thank the LYriCAN for the funding for the biological analyses.
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48 724 **Figure 1:** Flow chart of the ERICA study, France (original flow chart)
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract : page 2 Methods : page 18
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	Abstract : page 2 Declaration line :page 18
Funding	4	Sources and types of financial, material, and other support	Funding: page 28
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1 Author's contribution : page 28
	5b	Name and contact information for the trial sponsor	Page 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Funding : page 28
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Data monitoring : page 17
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction : page 2
	6b	Explanation for choice of comparators	Page 6
Objectives	7	Specific objectives or hypotheses	Page 6

1 2 3 4 5 6 7	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 6
8	Methods: Participants, interventions, and outcomes			
9 10 11 12 13	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 6 Page 7
14 15 16 17 18	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 6-7
19 20 21 22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 8-10
23 24 25 26 27		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
28 29 30 31 32		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 9-10
33 34 35		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 8
36 37 38 39 40 41 42 43 44 45	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 10-16
46 47 48 49 50 51	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 10
52 53 54 55 56 57	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 16
58 59 60	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 7-8

Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 17
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 10-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be	Page 16-17

		found, if not in the protocol	
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 16-17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 16-17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A no interim analyses are planned
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Abstract : page 2 Study population : page 6 Recruitment: page 7-8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 17

1 2 3 4	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 28
5 6 7 8	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 18
9 10 11 12	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
13 14 15 16 17 18 19 20 21	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 2
22 23		31b	Authorship eligibility guidelines and any intended use of professional writers	Page 2
24 25 26 27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
28	Appendices			
29 30 31 32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Consent form, see supplementary file
33 34 35 36 37	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Page 15

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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

The effect of acute aerobic exercise before immunotherapy and chemotherapy infusion in patients with metastatic non-small-cell lung cancer: Protocol for the ERICA feasibility trial

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Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Oncology, Immunology (including allergy), Pharmacology and therapeutics
Keywords:	CHEMOTHERAPY, IMMUNOLOGY, Adult oncology < ONCOLOGY, Respiratory tract tumours < ONCOLOGY, SPORTS MEDICINE



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The effect of acute aerobic exercise before immunotherapy and chemotherapy infusion in patients with metastatic non-small-cell lung cancer:

Protocol for the ERICA feasibility trial

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1
2
3 24 **ABSTRACT**
4

5 25 **Introduction.** Patients with metastatic Non-Small Cell Lung Cancer (mNSCLC) suffer from
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8 26 numerous symptoms linked to disease and treatment which may further impair the patient's
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10 27 overall condition. In addition to its benefits on quality of life and fatigue, physical exercise may
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12 28 improve treatment response, notably due to its known effects on the immune system. The
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14 29 ERICA study is designed to assess the feasibility of a supervised acute physical exercise therapy
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16 30 realised immediately prior immune-chemotherapy infusion in patients with mNSCLC.
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18 31 Secondary objectives will examine the effects of acute exercise combined with an
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20 32 unsupervised home-walking program on clinical, physical, psycho-social and biological
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22 33 parameters.
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27 34 **Methods and analysis.** ERICA is a prospective, monocentric, randomized controlled, open-
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29 35 label feasibility study conducted at the Centre Léon Bérard Comprehensive Cancer Center
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31 36 (France). Thirty patients newly diagnosed with mNSCLC will be randomized (2:1 ratio) to the
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33 37 “exercise” or the “control” group. At baseline and during the last treatment cycle, participants
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35 38 in both groups will receive Physical Activity recommendations, and two nutritional
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37 39 assessments. In the exercise group, participants will receive a 3-months program consisting of
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39 40 a supervised acute physical exercise session prior to immune-chemotherapy infusion, and an
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41 41 unsupervised home-based walking program with an activity tracker. The acute exercise
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43 42 consists of 35 minutes interval training at submaximal intensity scheduled to terminate 15
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45 43 minutes prior to infusion. Clinical, physical, biological, and psychosocial parameters will be
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47 44 assessed at baseline, 3 and 6 months after inclusion. Biological measures will include immune,
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56 46 **Ethics and dissemination.** The study protocol was approved by the French ethics committee
57
58 47 (Comité de protection des personnes Ile de France II, N°ID-RCB 20.09.04.65226, 8th December
59
60

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3 48 2020). The study is registered on ClinicalTrials.gov (NCT number:NCT04676009). All
4
5
6 49 participants will sign an informed consent form. The findings will be disseminated in peer-
7
8 50 reviewed journals and academic conferences.

9
10 51 **KEYWORDS:** Non-small-cell lung cancer, Metastatic, Exercise, Immunotherapy, Chemotherapy,
11
12 52 Immunology

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14
15 53 **Word count:** 5580

16
17 54 **Strengths and limitations of this study.**

- 18
19
20 55 • This study is the first to assess the feasibility effects of acute physical exercise performed
21
22 56 within one hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-
23
24 57 based doublet) infusion in mNSCLC patients.
- 25
26
27 58 • Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption
28
29 59 condition during a submaximal endurance test on a cycle-ergometer at baseline and this test
30
31 60 will allow individualisation of the intensity of the acute physical exercise program.
- 32
33
34 61 • The feasibility study assesses the acute physiological, immune, and metabolic response to a
35
36 62 supervised acute moderate intensity physical exercise session in patients with mNSCLC.
- 37
38 63 The unsupervised home-based walking program in the intervention arm aims to increase the
39
40 64 level of physical activity in patients with mNSCLC and their cardiorespiratory fitness and
41
42 65 physical capacity to perform acute physical exercise prior to chemo-immunotherapy infusion.
- 43
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45 66 • The study concerns only one stage of lung cancer, participants must be eligible to
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47 67 immunotherapy and it's a study with a limited sample size (n=30).
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68 INTRODUCTION

69 Non-small cell lung cancer (NSCLC) accounts for approximately 80-90% of lung cancers (1,2). More than
70 half of NSCLC are diagnosed at advanced stages due to their asymptomatic nature at early stage
71 explaining their poor survival. The development of immunotherapy in first-line therapy with anti-PD-1
72 and anti-PD-L1 has changed the first line treatment algorithm of advanced NSCLC (1). The anti-PD-1
73 pembrolizumab and cemiplimab clearly improve the overall survival in NSCLC with high PD-L1
74 expression ($\geq 50\%$ of tumour cells) in comparison with cytotoxic chemotherapy. Combinations of anti-
75 PD(L)-1 to platinum-based chemotherapy are superior to chemotherapy alone, independently of PD-
76 L1 level of expression. They represent the 1st line gold-standard when PD-L1 is expressed in less than
77 50% of tumour cells and might reduce the risk of early disease progression in comparison with
78 pembrolizumab when PD-L1 $\geq 50\%$. Immunotherapy has significantly improved the prognosis of
79 patients with mNSCLC and has led to prolonged remissions in some patients especially for non-
80 squamous cell carcinoma in the KEYNOTE-189 trial (3,4). Despite these therapeutic advances,
81 metastatic lung cancer has a negative impact on patients' physical, psychological, and social
82 functioning including health-related quality of life (HRQoL) (5–7). Principal reported symptoms and
83 adverse effects from treatment are fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite
84 loss, and financial concerns (8,9).

85 Benefits of physical exercise defined as planned, structured, repeated, and purposeful Physical Activity
86 (PA) to improve physical fitness (10) have been widely demonstrated. In lung cancer patients, physical
87 exercise has been shown to improve aerobic capacity (VO_{2peak}), muscular strength, functional capacity
88 (11), sleep quality (12), PA level (13), some fatigue domains (14), anxiety, disease-specific global
89 health-related quality of life (15) and emotional well-being in cancer patients (16). Several studies in
90 lung cancer patients have reported the potential of physical exercise to limit or even reverse some of
91 the adverse effects induced by the disease and its treatment (17). While regular PA is recommended
92 in patients with cancer, no specific recommendations exist for patients with lung cancer or metastatic
93 disease (18). In addition, few studies have examined the interactions between transient physiological

1
2
3 94 changes caused by acute exercise i.e., a single physical exercise bout, and cancer treatments(19).
4
5 95 Immunomodulatory effects of acute physical exercise involve immune cell mobilisation in blood such
6
7 96 as neutrophils, subsets of monocytes or lymphocytes involved in the host defence against tumours,
8
9 97 seems to improve immunosurveillance (20). Acute physical exercise leads to a rapid increase in the
10
11 98 mobilization of the peripheral activity of the sub-population of CD56^{dim} NK cells during acute physical
12
13 99 exercise of light to moderate intensity (21,22). A preclinical study reported that exercise training
14
15 100 (voluntary running), through activation of epinephrine and IL-6, led to selective NK cell mobilization
16
17 101 and limited tumour growth of several types of tumours (melanomas, liver, and lung mouse models)
18
19 102 (23). In a recent study, the increase in PD-1+ CD8+ T cells was observed after a single exercise session
20
21 103 (24). At the level of the adaptive immune system, acute exercise results in transient biphasic changes,
22
23 104 i.e. increase of circulating lymphocytes during and immediately after exercise, followed by a transient
24
25 105 decrease of blood lymphocytes below baseline level during recovery from exercise (1 hour), thought
26
27 106 to be due to a redistribution of immune cells to peripheral tissues, including tumours, before return to
28
29 107 basal level within a few hours (23,25). Moreover, recent preclinical studies suggested that physical
30
31 108 exercise performed during chemotherapy infusion may have additional physiological benefits such as
32
33 109 increase the blood flow leading to improved intra-tumoral perfusion and enhanced drug delivery (26–
34
35 110 28). However, to date, the optimal timing, duration and intensity of exercise that is feasible and
36
37 111 produces clinically meaningful changes in tumour perfusion and immunomodulatory effects, needs to
38
39 112 be determined (29). Most of the available evidence on the benefits of physical exercise in cancer
40
41 113 patients has been observed in interventions performed either after the treatment or during the
42
43 114 interval between the chemotherapy cycles(30). Only two studies have evaluated the feasibility of low-
44
45 115 intensity physical exercises during the chemotherapy infusion without adverse events, interference
46
47 116 with chemotherapy, or exacerbation in symptoms (30,31). Recently, it has been suggested in
48
49 117 preclinical studies that exercise performed during chemotherapy infusion could lead to improved
50
51 118 perfusion of solid tumours, mitigating tumour hypoxia, and enhancing drug delivery to tumours
52
53 119 (26,27,32). Similarly, by its effect on immune regulation, physical exercise prior to infusion may
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3 120 potentiate the effect of the immunotherapy. Recent preclinical evidence has suggested a beneficial
4
5 121 effect of exercise in addition to immunotherapy (anti-PD-1 immunotherapy) in a murine model of
6
7 122 NSCLC, through increased necrosis and a decreased proliferative index of tumour cells (33).
8
9
10 123 Based on these findings, the main objective of the ERICA (Exercise inteReaction Immunotherapy
11
12 124 Chemotherapy and cAncer) feasibility study is to evaluate the feasibility of a supervised acute physical
13
14 125 exercise performed immediately prior to immunotherapy and chemotherapy infusion (i.e. a
15
16 126 combination of pembrolizumab and pemetrexed-cis- or carboplatin for non-squamous cell carcinoma
17
18 127 or paclitaxel-carboplatin for squamous cell carcinoma) in first-line treatment of metastatic NSCLC
19
20 128 patients, and to assess if this planned exercise dose is safe and tolerable in this target patient
21
22
23 129 population. The secondary objectives are to evaluate the effects of the supervised acute exercise
24
25 130 before first-line treatment administration combined with an unsupervised home-based walking
26
27 131 program, on 1) physical fitness, 2) PA level and sedentary lifestyle, 3) psychosocial factors (HRQoL and
28
29 132 fatigue), 4) sleep quality, 5) body composition, 6) sarcopenia, 7) treatment response, 8) treatment
30
31 133 completion rate, 9) related treatment toxicities, and 10) progression-free survival. Furthermore, this
32
33 134 feasibility study will generate data on the effect of this exercise intervention on immune, metabolic,
34
35 135 and inflammatory biomarkers as well as oxidative stress.
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40 136 **METHODS**

41 137 **STUDY DESIGN**

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43
44 138 ERICA is a prospective, monocentric, randomized controlled, open-label feasibility study, conducted at
45
46
47 139 the Centre Léon Bérard Comprehensive Cancer Centre (Lyon, France).
48

49 140 *Insert Figure 1*

50 141 **STUDY POPULATION**

51 142 *Inclusion criteria*

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53
54 143 Participants will have to meet all of the following eligibility criteria: 1) aged ≥ 18 and < 80 years; 2)
55
56 144 diagnosed with a histologically confirmed metastatic NSCLC without EGFR mutation/ALK
57
58 145 rearrangement; 3) eligible to receive first-line chemotherapy according to histology (pemetrexed-cis-
59
60

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2
3 146 or carboplatin for non-squamous cell carcinoma or paclitaxel-carboplatin for squamous cell
4
5 147 carcinoma) in combination with pembrolizumab; 4) Eastern Co-operative Oncology Group (ECOG)
6
7 148 performance status ≤ 2 ; 5) able to engage in PA attested by a medical certificate by an oncologist;
8
9 149 and 6) provide a dated and signed informed consent form before study enrolment.

150 *Exclusion criteria*

151 Patients will not be eligible in at least one of the following cases: 1) bone metastases with risk of
152 fractures or unconsolidated pathologic fractures; 2) contraindication to the physical exercise proposed
153 in this study (e.g. orthopaedic disorder such as disabling coxarthrosis or gonarthrosis, central nervous
154 system disorders); 3) history or co-existence of other primary cancer (except in situ cancer regardless
155 of the site, and/or basal cell carcinoma, and/or non-lung cancer in complete remission for more than
156 5 years) ; 4) severe undernutrition defined according to the French National Authority for Health (i.e.
157 for adults aged ≥ 18 years and < 70 : Body Mass Index (BMI) ≤ 17 , weight loss $\geq 10\%$ in 1 month, $\geq 15\%$
158 in 6 months, or $\geq 15\%$ compared to the usual weight before the disease diagnosis, or serum albumin
159 < 30 g/l; for adults aged ≥ 70 years: BMI < 18 , weight loss $\geq 10\%$ in 1 month or $\geq 15\%$ in 6 months, or
160 serum albumin < 30 g/l) (34); 5) severe anaemia (haemoglobin ≤ 8 g/dl) in the past 30 days prior to
161 enrolment; 6) history of cardiovascular disease or cardiovascular risk (i.e. chronic or poorly controlled
162 coronary heart disease, peripheral arterial disease, cardiac arrhythmia, symptomatic heart disease,
163 uncontrolled or untreated arterial hypertension, myocardial infarction diagnosed in the past 6 months,
164 coronary angioplasty with or without stent implantation in the past 6 months, coronary artery bypass
165 surgery in the past 12 months); 7) history of type 2 diabetes or glycated haemoglobin $> 7\%$ in the past
166 3 months prior to enrolment; 8) Stage IV Chronic obstructive pulmonary disease (forced expiratory
167 volume in one second (FEV₁) $< 30\%$).

168 **RECRUITMENT**

169 Participants will be recruited in Centre Léon Bérard, Lyon, France from December 2020. Eligible
170 patients will be screened systematically based on electronic medical record during weekly
171 multidisciplinary lung cancer board meetings, as seen in Figure 1. During a medical consultation before

1
2
3 172 treatment initiation, an oncologist will propose the study to eligible patients and explain the study
4
5 173 objectives and protocol. Once the written informed consent is signed, patients will undergo the
6
7 174 following screening tests prior to inclusion: (1) clinical examination including assessing Performance
8
9
10 175 Status (PS) and Blood Pressure, (2) echocardiography and electrocardiogram performed by a
11
12 176 cardiologist, and (3) for patients with diabetes, measurement of glycated haemoglobin. If these
13
14 177 investigations confirm the patient's eligibility, the patient will be included in the study (D0). The end
15
16 178 date for this study is planned in January 2023.

179

180 **RANDOMIZATION**

181 At inclusion (D0), patients will be randomly assigned (ratio 2:1) to (i) the exercise group to receive PA
182 and nutrition recommendations; a supervised acute physical exercise prior each immuno-
183 chemotherapy infusion and an unsupervised home-based walking program with an activity tracker or
184 (ii) the control group to receive PA and nutrition recommendations only.

185 Randomization will be stratified using a dynamic minimization algorithm with two factors: sex (male
186 vs. female) and histology (squamous vs. non-squamous).

187

188 **INTERVENTION**

189 *Treatment protocol*

190 All patients in both exercise and control groups of this study will receive usual care and the same
191 standard treatment protocol: pembrolizumab (200 mg) combined with carboplatin (AUC 5) plus
192 pemetrexed (500 mg/m²) with B9-B12 vitamin supplementation; carboplatin (AUC 6) plus paclitaxel
193 (200 mg/m²) every 3 weeks for 4 cycles; before pembrolizumab maintenance in squamous cell
194 carcinoma or pembrolizumab plus pemetrexed maintenance for non-squamous cell carcinoma.

195 *Physical Activity recommendations*

196 Although there are no specific PA recommendations for patients with mNSCLC, all patients will be
197 informed of the PA recommendations to be physically active as much as possible during the day,

1
2
3 198 walking as much as possible and sitting as little as possible (WCRF, 2018). We have chosen to follow
4
5 199 the recommendations of the Macmillan Cancer Support guide released in 2018, advising patients with
6
7 200 bone metastases to have an active lifestyle on a daily basis and to maintain appropriate PA according
8
9 201 to their physical abilities (35). Several individual strategies will be proposed to patients (e.g., using
10
11 202 stairs whenever possible, walking to local shops).

14 203 *Nutritional recommendations*

16 204 All patients will receive nutritional recommendations during the 1st and 4th treatment cycle. The
17
18 205 nutritional recommendations will include: energy intake of 30 kcal/kg body weight/day for patients
19
20 206 with BMI <30, or 25 kcal/kg body weight/day for patients with BMI ≥ 30, and protein intake of at least
21
22 207 1.2 g/kg body weight/day (36,37).

25 208 **Exercise Group**

27 209 *Acute physical exercise protocol prior to immunotherapy and chemotherapy infusion*

30 210 Patients in the "exercise" group will perform a supervised acute physical exercise bout during
31
32 211 hospitalization for treatment. It will be carried out within one hour prior to the immunotherapy and
33
34 212 chemotherapy infusion, on a cycle ergometer (Monark Ergonomic 939 Novo) for each of the 4 cycles
35
36 213 of treatment foreseen. The physical exercise will be supervised by a clinical exercise physiologist with
37
38 214 experience in oncology. The physical exercise consists of a 35-min acute interval training, scheduled to
39
40 215 terminate 15 minutes prior to infusion onset and will be individualized based on the results of a
41
42 216 submaximal endurance test performed on a cycle ergometer by each patient (described below) prior
43
44 217 to treatment (D0).

47 218 Following a five-minute warm-up at 60% of Ventilation Threshold 1 (VT1), the participant will carry out
48
49 219 5 sets, alternating periods of 3 minutes at 70-80% of VT1 with 3 minutes at 110-120% of VT1 (≥ 35
50
51 220 Revolutions Per Minute (RPM)). The acute exercise intensity will be programmed according to the load
52
53 221 reached at VT1 during the cycle ergometer endurance submaximal test. Heart rate (HR), load, RPM,
54
55 222 dyspnoea, and perception of effort on a Borg-scale will be monitored. If the patient is no longer able
56
57 223 to cycle at the load corresponding to 120% of his VT1, the clinical exercise physiologist will decrease
58
59
60

1
2
3 224 the load to 110% of VT1. In case of exercise-induced desaturation ($\geq 4\%$ of the measured value at
4
5 225 rest or $\leq 93\%$), the clinical exercise physiologist will stop the exercise until the rest value of oxygen
6
7 226 saturation. In addition to detailed explanation by the qualified clinical exercise physiologist, patients
8
9 227 receive written support materials at baseline (D0).

12 228 *Home-based walking program*

14 229 During the 3-month intervention, between each treatment cycle (3 weeks), patients will follow an
15
16 230 unsupervised home-based walking program consisting of an individual goal of a number of steps per
17
18 231 day. Each patient will receive a Fitbit® Inspire activity tracker with an instruction to wear it continuously
19
20 232 during the intervention. They will be advised to achieve at least 6,000 daily steps which corresponds
21
22 233 to a physically active lifestyle in a patient population (38). Ten days after each treatment cycle, the
23
24 234 clinical exercise physiologist will contact the patients by phone to assess and encourage adherence to
25
26 235 the home-based walking program. Depending on the average number of steps performed in the past
27
28 236 ten days, personalized objectives might be redefined to increase the target number of daily steps. For
29
30 237 patients who reach more than 6,000 steps per day the initial target number of 6,000 steps will be
31
32 238 increased by 30%. The target number of steps was set within a maximum of 7800 steps above the
33
34 239 average number of steps in the previous week. Patients who do not reach 6,000 daily steps, will be
35
36 240 advised to gradually increase the target number of steps per day according to the patient's abilities.
37
38 241 Number of steps will be collected by regular sync with the mobile phone application (Fitbit®) of the
39
40 242 activity tracker or by a step logbook.
41
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48 244 **EVALUATIONS**

49 245 *Modalities*

50 246 The assessments of the repeated measures (PA level, anthropometric, HRQoL, fatigue, sleep quality,
51
52 247 and sarcopenia) in both groups will be performed before the first cycle of anti-neoplastic treatment
53
54 248 (baseline, D0), at the end of the 4 cycles of treatment (M3), and at 6 months after study inclusion (M6)
55
56
57 249 (Table 1).
58
59
60

250

251 Table 1. Data collection schedule for the ERICA study

	Screening	Inclusion D0	1 st cycle C1	4 th cycle C4	Month 3 M3	Month 6 M6
Socio demographic and clinical data						
Screening tests (<i>PS, blood Pressure, echocardiography, electrocardiogram</i>)	X					
Sociodemographic data (<i>gender, date of birth, living situation, employment status, lifestyle</i>)		X			X	X
Clinical data		X			X	X
Severe treatment toxicities (grade ≥ 3) (<i>NCI-CTCAE</i>)			Continuously		X	
Tumour response (<i>RECIST</i>)		X			X	X
Physical evaluation						
Anthropometrics		X			X	
Physical fitness (<i>Cardiorespiratory fitness, strength tests</i>)		X			X	
Self-reported outcomes						
Physical activity level (<i>GODIN</i>)		X				X
Quality of life (<i>QLQ-C30, QLQ-LC13</i>)		X				X
Dietary intake (<i>24h recall</i>)			X	X		
Fatigue (<i>QLQ-FA12</i>)		X				X
Sleep quality (<i>ISI</i>)		X				X
Social deprivation (<i>EPICES</i>)		X				X
Acceptability ERICA					X	
Biological assessments						
Blood sample			X	X		
Body composition						
CT scan		X			X	X
Exercise group						
Steps per day			Continuously		X	
Number of acute physical exercise sessions			Continuously		X	

252 **DATA COLLECTION**

253 *Sociodemographic and clinical data*

254 Sociodemographic and clinical data including gender, date of birth, living situation, employment status,
 255 lifestyle (alcohol consumption and smoking status) will be collected at baseline. All clinical data will be
 256 extracted from the participant's electronic medical record. The Response Evaluation Criteria In Solid
 257 Tumours (RECIST) will be used for tumour assessments between the diagnosis and the end of the ERICA
 258 study.

259

260 *Anthropometric data*

1
2
3 261 Anthropometric data including body weight (kilogram), height (centimeter, cm), waist (cm) and hip
4
5 262 (cm) circumference will be collected. Waist circumference will be measured around the abdomen
6
7 263 midway between the last floating rib and the iliac crest. Hip circumference will be measured
8
9 264 horizontally through the upper margin of the pubis. The body mass index is calculated as the body
10
11 265 weight in kilograms divided by the square of the height in meters.
12
13
14 266

15
16 267 *Physical fitness*

17
18
19 268 Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption (VO_2)
20
21 269 condition during a submaximal endurance test on a cycle-ergometer at baseline. This test will allow
22
23 270 individualisation of the intensity of the acute physical exercise program. Following a 5-minute warm-
24
25 271 up at 20% of the participant's maximum theoretical load, power will be increased by a constant amount
26
27 272 of 5 watts each 30 seconds until VT1 will be reached. The clinical exercise physiologist will ensure that
28
29 273 the patient maintains a minimum pedalling frequency above 35 RPM throughout the test. HR,
30
31 274 ventilation (VE), oxygen saturation (SaO_2), VO_2 , and carbon dioxide production (VCO_2) will be measured
32
33 275 by a gas analyser (MetaMax 3b, Cortex Biophysik, Leipzig, Germany) and continuously monitored. In
34
35 276 addition, the perception of the difficulty and dyspnoea will be evaluated at the end of the test using
36
37 277 the Borg Rating Perceived Exertion questionnaire(39). The clinical exercise physiologist will stop the
38
39 278 test when the patient exceeded the VT1. The test will end with a 6-minute recovery phase. The VT1
40
41 279 will be determined graphically when the ventilatory equivalent of oxygen (VE/VO_2) starts to increase
42
43 280 and will be confirmed by Respiratory Exchange Ratio that strictly exceeds 1 (Wasserman method).
44
45
46
47

48 281 The lower body muscular strength will be evaluated by measuring the maximum isometric strength of
49
50 282 the knee extensors (DFS II Series Digital; Force Gauges Chatillon, Largo, FL, USA). Participants will be
51
52 283 seated on a chair with the knee joint at 90°, arms crossed over the chest, and the dynamometer
53
54 284 attached to the ankle. Participants were advised to extend their leg as hard as possible within 3
55
56 285 seconds upon the instructor's signal. Only the dominant leg will be tested three times (with 2 minutes
57
58 286 rest between each contraction), and the best performance will be considered.
59
60

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2
3 287 The maximum isometric upper limb strength will be measured by a hand dynamometer (Jamar Plus
4
5 288 Digital Hand Dynamometer, Patterson Medical, Huthwaite, United Kingdom) (39,40,41). Participants
6
7 289 will be seated with their back straight and elbows bent at 90°. They will be asked to squeeze the
8
9
10 290 handgrip as strongly as possible for five seconds to achieve maximum strength. Two measurements
11
12 291 will be taken on each hand and the best performance will be recorded. Hand grip strength is an easy
13
14 292 and non-invasive method, well tolerated and routinely used in cancer patients to assess muscle
15
16 293 strength and physical fitness.

18 294

21 295 *Physical activity level*

23 296 The PA level will be measured by the Godin Leisure-Time Physical Activity Questionnaire (GLTAPQ)
24
25 297 (43). The GLTAPQ is a short, self-administered questionnaire with three questions designed to obtain
26
27 298 information on the number of times an individual engages in low, moderate, and intense "leisure-time
28
29 299 PA" periods of at least 15 minutes during a typical week. The score of the GSLTPAQ (Leisure Score
30
31 300 Index, LSI) will be obtained by using the following formula: (light PA frequency × 3) + (moderate PA
32
33 301 frequency × 5) + (vigorous PA frequency × 9). People with LSI ≥ 24 will be classified as active, while
34
35 302 people with LSI ≤ 23 will be classified as insufficiently active (estimated energy expenditure < 14
36
37 303 Kcal/kg/week). The level of PA will be investigated by the change of a daily number of steps thanks to
38
39 304 the activity tracker (only in the intervention group).

43 305

46 306 *Lean body mass and sarcopenia*

48 307 Lean body mass and sarcopenia will be analysed using the Computed Tomography (CT) scans
49
50 308 systematically available from routine care. CT scan cross-section at the level of the 3rd lumbar vertebra
51
52 309 represents provides a reliable representation of the total body muscle mass and has therefore been
53
54 310 widely adopted for the detection of sarcopenia in cancer patients and allows assessment without
55
56 311 additional ionising radiation exposure given that CT scan as part of routine cancer diagnostic
57
58 312 procedures is largely available(44,45). The thresholds for identifying muscle range from -29 to +150

1
2
3 313 HU, subcutaneous and intramuscular adipose tissue from -190 to -30 HU, visceral adipose tissue from
4
5 314 -150 to -50 HU and bone from +152 to 1000 HU (46–48). Skeletal muscle radiodensity (SMD) that
6
7 315 represents muscle quality will be measured using the average radiation attenuation of the tissue in
8
9 316 Hounsfield Units (HU). A low SMD is defined by values below the threshold of 37.8 HU. An estimate of
10
11 317 lean body mass (LBM) will be calculated using the formula (LBM (kg) = [(L3 Muscle measured by CT
12
13 318 (cm²) × 0.3) + 6.06]) (49).

319

320 *Nutrition*

321 Dietary intake (24h recall, supplemented with patient preferences and habits), clinical (weight loss,
322 BMI), and biological (albumin and CRP) parameters will be assessed by clinical dietitians affiliated with
323 the study. The dietician will use the SEFI® (Score d'Evaluation Facile des Ingesta EPA). The score ranges
324 from 0 to 10. Patients with a SEFI score below 7 will be identified as at risk of undernutrition (50).

325

326 *Health-related quality of life*

327 The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life
328 Questionnaire (QLQ-C30) is a validated multi-dimensional HRQoL questionnaire designed for cancer
329 patients (51), consisting of 30 items to assess five domains of functioning (physical, role, emotional,
330 cognitive, and social), one domain of overall quality of life, three domains of symptoms (pain, fatigue,
331 and nausea), and six single items (dyspnoea, insomnia, anorexia, diarrhoea, constipation, and financial
332 impact). Participants will respond on a Likert scale ranging from "not at all" to "a lot". All scores will be
333 transformed into a scale from 0 to 100 according to the performance of the EORTC scoring manual
334 (52). A high score represents better functioning, better overall quality of life, and lower symptom
335 burden. Quality of life specific to lung cancer will be assessed by the 13-item module: the Quality of
336 Life Questionnaire - Lung Cancer 13 (QLQ-LC13) (52,53). The QLQ-LC13 self-questionnaire is an
337 additional measure of the symptoms and side effects experienced by lung cancer patients who receive
338 non-surgical treatment.

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2
3 3394
5 340 *Fatigue*

6
7 341 Fatigue will be assessed by the EORTC-QLQ module measuring cancer-related fatigue (EORTC QLQ-
8 342 FA12) (54). This self-questionnaire includes 12 items that assess physical, cognitive, and emotional
9
10 343 fatigue related to cancer. Participants will respond on a Likert scale ranging from "not at all" to "a lot".
11
12 344 All scores will be transformed into a scale from 0 to 100, with a higher score indicating a higher degree
13
14 345 of fatigue.

15
16
17 34618
19 347 *Sleep quality*

20
21 348 The perceived quality of sleep will be assessed by the Insomnia Severity Index which measures the
22
23 349 severity of insomnia. The questionnaire consists of 7 items rated on a 5-point scale ranging from 0
24
25 350 ("none") to 4 ("very severe") (55,56). This self-questionnaire will evaluate the severity of the patient's
26
27 351 sleep difficulties (initial, maintenance, and morning insomnia), the degree of sleep dissatisfaction, the
28
29 352 level of interference with daily functioning, the degree of appearance of sleep difficulties, and the level
30
31 353 of anxiety related to insomnia. The total score of the items varies between 0 and 28. A high score
32
33 354 indicates greater sleep difficulties.

34
35
36
37 35538
39 356 *Social vulnerability*

40
41 357 Social deprivation will be assessed using the EPICES score (Evaluation of Deprivation and Inequalities
42
43 358 in Health Examination Centres) (57). The EPICES score will be obtained by adding up the points of the
44
45 359 11 binary questions ("Yes"/"No") of the self-questionnaire. This score ranges from 0 "no
46
47 360 precariousness" to 100 "highest precariousness" with the threshold for deprivation at 30.

48
49
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51 36152
53 362 *Biomarkers of the immune system, inflammation, sarcopenia, and oxidative stress*

54
55 363 Blood samples will be collected during the first and last (forth) treatment cycle: in the exercise group,
56
57 364 samples will be collected before exercise (S1), after exercise (S2), and 12 hours after the start of
58
59
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2
3 365 treatment (S3); in the control group: samples will be collected 40 minutes before the infusion of
4
5 366 treatment (S1), just before the infusion of treatment (S2) and 12 hours after the start of treatment
6
7 367 (S3). Blood test procedures will follow laboratory standards. Each blood sample will be collected in 3 x
8
9
10 368 10mL Ethylenediaminetetraacetic acid tubes and then centrifuged (10 minutes at 800G) within one
11
12 369 hour (maintained at 4°C before and during centrifugation). After the centrifuge, plasma will be
13
14 370 collected and aliquoted in 5 cryotubes of 1 mL and the Peripheral Blood Mononuclear Cell (PBMC) will
15
16 371 be collected and aliquoted in 3 cryotubes (5 to 7 millions cells per tube). These cryotubes will be frozen
17
18 372 at -80°C and stored in nitrogen at the center for the duration of the study. At the end of the study,
19
20 373 biomarkers of immunity, sarcopenia, and inflammation will be analysed. We will measure i) immune
21
22 374 biomarkers (NK cells, B lymphocytes, T lymphocytes, monocytes, sub-populations of dendritic cells on
23
24 375 frozen PBMC); ii) plasma biomarkers of sarcopenia and inflammation (Myostatin, Activin, Cortisol,
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26 376 Tumor Necrosis Factor- α , Interferon- γ , Interleukin-1 β , Interleukin-6, Follistatin, Growth Differentiation
27
28 377 Factor 5, Bone morphogenetic protein 14, GDF15, Interleukin-10, Interleukin-15, NH3, Aminogram, C-
29
30 378 reactive protein, insulin); and iii) plasma oxidative stress (Superoxide dismutase, catalase,
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32 379 malondialdehyde, glutathione peroxidase, Xanthine Myeloperoxidase, and Xanthine oxidase). Finally,
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34 380 the blood samples will be also used to analyse the glucose (OneTouch Verio®) and lactate (LACTATE
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36 381 PRO II) metabolism by a mobile device. Patients will be asked to complete a questionnaire regarding
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38 382 the taking of antibiotics, anti-inflammatory, and antioxidants in the 48 hours prior to blood collection.
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384 *Toxicities*

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46 385 Severe treatment toxicities (grade ≥ 3) will be noted according to the National Cancer Institute's
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48 386 Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0. The number of rescheduled or
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50 387 cancelled treatment sessions and the relative dose intensity (RDI) of participants with grade ≥ 3
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52 388 toxicities related to chemotherapy and immunotherapy will be calculated as the ratio of "delivered"
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54 389 to "expected" dose intensity.
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3 391 **STATISTICAL ANALYSIS**
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5 392 **SAMPLE SIZE**
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7 393 The main objective of the current study is to evaluate the feasibility of an acute physical exercise
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9 394 program performed prior to the infusion of treatments in mNSCLC patients, and to assess if this
10
11 395 planned exercise dose is safe and tolerable in this target patient population(58). In the context of a
12
13 396 feasibility study without a concrete hypothesis and in absence of previous studies in this population,
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15 397 the sample size was defined empirically. Taking into account the number of mNSCLC patients who
16
17 398 receive first line chemotherapy (i.e. pemetrexed-platinum or taxol-platinum) combined with
18
19 399 Pembrolizumab each year in Centre Léon Bérard (Lyon), we plan to include 30 patients over a 18
20
21 400 months period. This number will be sufficient to assess if the planned exercise dose is safe and
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23 401 tolerable in this target patient population, and the sample size falls within the range of sample sizes
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25 402 recommended in the literature for feasibility trials (59).
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32 404 Although the main objective is to study the feasibility of physical exercise prior to the infusion of
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34 405 treatments, the evaluation of the biological objectives requires randomization to have reference
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36 406 measures. We have chosen to unbalance the randomization (2:1) so that more patients will benefit
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38 407 from the intervention proposed in the ERICA study.
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43 409 **STATISTICAL METHODS**
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45 410 All statistical analyses will be on an exploratory basis on all data from study subjects. Given the limited
46
47 411 sample size, non-parametric tests will be performed. Qualitative data will be presented using their
48
49 412 frequencies and percentages. Quantitative data will be presented using the number of observations,
50
51 413 mean, standard deviation, median, minimum, and maximum. For both types of data, the number of
52
53 414 missing data will be presented if necessary.
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56 415 The feasibility of the ERICA study will be assessed at the end of the intervention (M3) in the exercise
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58 416 group only, according to the adherence rate by calculating the ratio of the number of acute physical
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3 417 exercise sessions performed to the number of acute physical exercise sessions planned before the
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5 418 immunotherapy/chemotherapy. The tolerability will be assessed by the relative dose intensity of
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7 419 exercise. The safety will be assessed by the occurrence of adverse events related to the physical
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9 420 exercise intervention. The acceptability (i.e. the proportion of patients who accept to participate in the
10
11 421 study among eligible patients) and the attrition (i.e. the proportion of patients who withdraw their
12
13 422 participation from the study among patients initially enrolled) will be calculated. In the exercise group,
14
15 423 the acceptability of the activity tracker, the observance of the home-walking program, and the safety
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17 424 of the intervention (the number, type, and timing of adverse events that occurred) will be assessed.
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19 425 The evolution of the different repeated measures (PA level, anthropometric, HRQoL, fatigue, sleep
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21 426 quality, and sarcopenia) at inclusion, 3 and 6 months will be represented by graphs and compared by
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23 427 non-parametric ANOVAs (performed on ranks).

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27 428 Progression-free survival will be measured from the date of randomization until the date of event
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29 429 defined as either progression or death from any cause whichever occurs first. Participants with no
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31 430 event at the time of the analysis will be censored at the date of the last available tumour assessment.
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33 431 The results will allow to formulate the hypotheses and determine sample size for a subsequent
34
35 432 multicenter randomized efficacy study.

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37 433 Statistical analyses will be carried out using R statistical software (60).

41 434 **DATA MONITORING**

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43 435 The database for clinical data will be managed using REDCap (Research Electronic Data Capture)
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45 436 (61,62) software hosted at CLB. The access to the database will be secured (personal ID and password
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47 437 required) with different levels of security depending on the role within the study. The investigator will
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49 438 have access to the final dataset.

50 439 **PATIENT AND PUBLIC INVOLVEMENT**

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52 440 Prior to the present study, we administrated a questionnaire to lung cancer patients to collect their
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54 441 experience and preferences in terms of physical activity to practice during cancer treatments. The
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56 442 results were used to develop the ERICA physical activity intervention. As it is a feasibility study, the
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3 443 findings will be used to adjust the intervention if necessary for the purpose of an efficacy randomised
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5 444 controlled trial. Global findings will be disseminated to participants at the end of the study if they wish.
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7 445 **ETHICAL AND DISSEMINATION**

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10 446 The study protocol has been approved by a French ethics committee CPP Ile de France II (IDRCB:
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12 447 20.09.04.65226) and the study database has been reported to the National Commission for Data
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14 448 Protection and Liberties (CNIL; reference number: 2016177). The study has been registered at
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16 449 reference number: NCT04676009.
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18 19 20 450 **DISCUSSION**

21
22 451 To our knowledge, ERICA is the first study to assess the feasibility and effects of acute physical exercise
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24 452 performed within one hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-
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26 453 based doublet) infusion in mNSCLC patients. Despite therapeutic advances, notably immunotherapy
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28 454 combined with chemotherapy, the prognosis of many patients with mNSCLC continues to be poor, and
29
30 455 disease burden, cachexia, comorbidities, and treatment side effects lead to deconditioning and
31
32 456 adversely affect exercise capacity in people with advanced NSCLC (17,63–66). Conversely, evidence
33
34 457 from meta-analyses suggests that exercise training in patients with advanced lung cancer could be
35
36 458 feasible and safe with no serious adverse events reported and may improve or avoid the decline of
37
38 459 physical capacity (15,67). However, the evidence regarding the benefits of exercise in mNSCLC patients
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40 460 remains limited and there is a lack of widespread awareness of the benefits of maintaining physical
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42 461 activity in this particular population (66,68–70). Furthermore, the high prevalence of comorbidities in
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44 462 mNSCLC patients, which may be exacerbated by the direct and indirect effects of cancer treatment,
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46 463 led to exclude patients at risk of cardiovascular events from studies (i.e. history of cardiovascular
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48 464 disease; abnormal electrocardiogram and/or echocardiography) or undernutrition.
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51 465 Based on preclinical evidence of exercise in modulating the efficacy of cancer therapy, the present
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53 466 study assesses the feasibility of acute exercise of submaximal intensity in the target population.
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55 467 Current evidence on the benefits of physical exercise in cancer patients mainly stems from
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57 468 interventions performed either between the chemotherapy cycles or after end of treatment. Yet, a
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3 469 feasibility study in patients with various tumours, mostly breast cancer, reported that exercise (i.e. 20
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5 470 min of supervised low-intensity cycling) during chemotherapy infusion appears to be safe and feasible
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7 471 (30). To prescribe a safe and efficacious intensity of acute exercise intervention, we decided to realize
8
9 472 a submaximal cardiopulmonary exercise test with a continuous gas exchange analysis. Because of the
10
11 473 comorbidities, the tumour location, and the lack of information about high intensity exercise effects,
12
13 474 the present study targets acute exercise of submaximal intensity.

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15
16 475 Home-based exercises are a beneficial approach to reducing symptoms and improving exercise
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18 476 capacity as well as the quality of life in patients with NSCLC (71). The unsupervised home-based walking
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20 477 program in the intervention arm aims to increase the level of physical activity in patients with mNSCLC
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22 478 and their cardiorespiratory fitness and physical capacity to perform acute physical exercise prior to
23
24 479 chemo-immunotherapy infusion (15). Also, chronic exercise can favourably modulate inflammation
25
26 480 and immune-related factors (19,72). Activity trackers are innovative tools increasingly used to promote
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28 481 an active lifestyle and to objectively measure the PA level of cancer patients (73–75). Trackers have
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30 482 been used in a randomized controlled trial to encourage patients with mNSCLC to maintain their PA by
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32 483 recommending a targeted number of steps (76). In a previous study by the team, the use of activity
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34 484 trackers has shown pertinent results in women with metastatic breast cancer (77,78). The combination
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36 485 of these two intervention modalities (acute exercise and unsupervised walking programme) allows us
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38 486 to offer an intervention adapted to this population in order to have sufficient physiological stimulation
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40 487 to observe changes in the immune system.

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43 488 The first challenge we need to overcome is that the study concerns only one stage of lung cancer and
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45 489 participants must be eligible to immunotherapy. Next, we are looking at the intervention
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47 490 reproducibility in other institutions. Finally, it is a feasibility study with a limited sample size (n=30).
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49 491 We plan to conduct a randomised controlled trial to address the various limitations of the present
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51 492 study: larger sample size, multiple lung cancer stages, and to carry out the study in several hospital
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53 493 institutions.

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59 494 **INNOVATION AND STUDY RELEVANCE**

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3 495 The ERICA study will provide clinical, physical, and psychosocial insights into the feasibility of acute
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5 496 exercise prior to first-line chemo-immunotherapy infusion in patients with mNSCLC. In particular,
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7 497 exploratory data on the safety and tolerability of the proposed exercise dose and schedule in the target
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10 498 patient population will be obtained. This feasibility study will further generate preliminary data on the
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12 499 acute physiological, immune, and metabolic response to the achieved exercise dose in patients with
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14 500 mNSCLC. The ERICA study will provide valuable information to design a large-scale adequately
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16 501 powered randomized controlled trial to assess the efficacy on clinically important endpoints (e.g.
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18 502 progression free survival) in patients with mNSCLC receiving first-line chemo-immunotherapy.
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23 504 **DECLARATIONS**

25 505 **CONSENT FOR PUBLICATION**

27 506 Not applicable

30 507 **AVAILABILITY OF DATA AND MATERIAL**

32 508 Not applicable

34 509 **COMPETING INTERESTS**

36 510 The authors declare no competing interests.

39 511 **AUTHORS' CONTRIBUTIONS**

41 512 MG, OP, BF, VP, PM and MP designed the trial and obtained funding. MG, OP, BF, VP, MP and LD
42
43 513 developed the study protocol. BF, PM and MP contributed to the medical part of the protocol. MV,
44
45 514 TW, CC and MCC brought their immunologic expertise. PS brought his biological expertise. MG, OP
46
47
48 515 fulfilled administrative procedures for this project. MG, OP, BF and VP wrote this manuscript. All the
49
50 516 authors reviewed and contributed to the final version of the manuscript.

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55
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57
58
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524 **REFERENCES**

- 525 1. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung
526 cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*.
527 2018;29:iv192–237.
- 528 2. ASCO. Lung Cancer - Non-Small Cell - Statistics [Internet]. *Cancer.Net*. 2021 [cited 2021 Jul 3]. Available
529 from: <https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics>
- 530 3. Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, et al. Updated Analysis From
531 KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic
532 Nonsquamous Non–Small-Cell Lung Cancer. *JCO*. 2020;JCO.19.03136.
- 533 4. Low JL, Walsh RJ, Ang Y, Chan G, Soo RA. The evolving immuno-oncology landscape in advanced lung
534 cancer: first-line treatment of non-small cell lung cancer. *Ther Adv Med Oncol* [Internet]. 2019 [cited 2019 Nov
535 5];11. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6716180/>
- 536 5. Brahmer JR, Rodríguez-Abreu D, Robinson AG, Hui R, Csósz T, Fülöp A, et al. Health-related quality-of-
537 life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a
538 multicentre, international, randomised, open-label phase 3 trial. *The Lancet Oncology*. 2017 Dec;18(12):1600–9.
- 539 6. Polanski J, Jankowska-Polanska B, Rosinczuk J, Chabowski M, Szymanska-Chabowska A. Quality of life of
540 patients with lung cancer. *Onco Targets Ther*. 2016;9:1023–8.
- 541 7. Camps C, del Pozo N, Blasco A, Blasco P, Sirera R. Importance of Quality of Life in Patients with Non–
542 Small-Cell Lung Cancer. *Clinical Lung Cancer*. 2009;10(2):83–90.
- 543 8. Garassino MC, Gadgeel S, Esteban E, Felip E, Speranza G, Domine M, et al. Patient-reported outcomes
544 following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated,
545 metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised,
546 placebo-controlled, phase 3 trial. *The Lancet Oncology*. 2020;21(3):387–97.
- 547 9. Steffen McLouth LE, Lycan TW, Levine BJ, Gabbard J, Ruiz J, Farris M, et al. Patient-Reported Outcomes
548 From Patients Receiving Immunotherapy or Chemoimmunotherapy for Metastatic Non–Small-Cell Lung Cancer
549 in Clinical Practice. *Clinical Lung Cancer*. 2019;21(3):255-263.e4.
- 550 10. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and
551 distinctions for health-related research. *Public Health Rep*. 1985;100(2):126–31.
- 552 11. Hwang C-L, Yu C-J, Shih J-Y, Yang P-C, Wu Y-T. Effects of exercise training on exercise capacity in patients

- 1
2
3 553 with non-small cell lung cancer receiving targeted therapy. *Support Care Cancer*. 2012;20(12):3169–77.
4
5 554 12. Chen H-M, Tsai C-M, Wu Y-C, Lin K-C, Lin C-C. Effect of walking on circadian rhythms and sleep quality
6
7 555 of patients with lung cancer: a randomised controlled trial. *Br J Cancer*. 2016;115(11):1304–12.
8
9 556 13. Dhillon HM, Bell ML, van der Ploeg HP, Turner JD, Kabourakis M, Spencer L, et al. Impact of physical
10
11 557 activity on fatigue and quality of life in people with advanced lung cancer: a randomized controlled trial. *Annals*
12
13 558 of *Oncology*. 2017;28(8):1889–97.
14
15 559 14. Zhang L-L, Wang S-Z, Chen H-L, Yuan A-Z. Tai Chi Exercise for Cancer-Related Fatigue in Patients With
16
17 560 Lung Cancer Undergoing Chemotherapy: A Randomized Controlled Trial. *Journal of Pain and Symptom*
18
19 561 *Management*. 2016;51(3):504–11.
20
21 562 15. Peddle-McIntyre CJ, Singh F, Thomas R, Newton RU, Galvão DA, Cavalheri V. Exercise training for
22
23 563 advanced lung cancer. Cochrane Lung Cancer Group, editor. *Cochrane Database of Systematic Reviews*
24
25 564 [Internet]. 2019 [cited 2019 Sep 17]; Available from: <http://doi.wiley.com/10.1002/14651858.CD012685.pub2>
26
27 565 16. Quist M, Adamsen L, Rørth M, Laursen JH, Christensen KB, Langer SW. The Impact of a Multidimensional
28
29 566 Exercise Intervention on Physical and Functional Capacity, Anxiety, and Depression in Patients With Advanced-
30
31 567 Stage Lung Cancer Undergoing Chemotherapy. *Integr Cancer Ther*. 2015;14(4):341–9.
32
33 568 17. Avancini A, Sartori G, Gkoutakos A, Casali M, Trestini I, Tregnago D, et al. Physical Activity and Exercise
34
35 569 in Lung Cancer Care: Will Promises Be Fulfilled? *The Oncologist* [Internet]. 2019;n/a(n/a). Available from:
36
37 570 <https://theoncologist.onlinelibrary.wiley.com/doi/abs/10.1634/theoncologist.2019-0463>
38
39 571 18. *Activité physique. Prévention et traitement des maladies chroniques* Éditions EDP Sciences, janvier
40
41 572 2019, 824 pages, Collection Expertise collective ISBN 978-2-7598-2328-4 [Internet]. [cited 2021 Jul 4]. Available
42
43 573 from: [https://www.inserm.fr/sites/default/files/2019-](https://www.inserm.fr/sites/default/files/2019-02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf)
44
45 574 [02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf](https://www.inserm.fr/sites/default/files/2019-02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf)
46
47 575 19. Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour
48
49 576 microenvironment. *Nature Reviews Cancer*. 2017;17(10):620–32.
50
51 577 20. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. *J*
52
53 578 *Sport Health Sci*. 2019;8(3):201–17.
54
55 579 21. Bigley AB, Rezvani K, Chew C, Sekine T, Pistillo M, Crucian B, et al. Acute exercise preferentially redeploys
56
57 580 NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple
58
59 581 myeloma target cells. *Brain, Behavior, and Immunity*. 2014;39:160–71.

- 1
2
3 582 22. Idorn M, Hojman P. Exercise-Dependent Regulation of NK Cells in Cancer Protection. *Trends in Molecular*
4
5 583 *Medicine*. 2016;22(7):565–77.
6
7 584 23. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al. Voluntary Running
8
9 585 Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution.
10
11 586 *Cell Metabolism*. 2016;23(3):554–62.
12
13 587 24. Wadley AJ, Cullen T, Vautrinot J, Keane G, Bishop NC, Coles SJ. High intensity interval exercise increases
14
15 588 the frequency of peripheral PD-1+ CD8+ central memory T-cells and soluble PD-L1 in humans. *Brain, Behavior, &*
16
17 589 *Immunity - Health*. 2020;3:100049.
18
19 590 25. Pedersen BK, Hoffman-Goetz L. Exercise and the Immune System: Regulation, Integration, and
20
21 591 Adaptation. *Physiological Reviews*. 2000;80(3):1055–81.
22
23 592 26. Wiggins JM, Opoku-Acheampong AB, Baumfalk DR, Siemann DW, Behnke BJ. Exercise and the Tumor
24
25 593 Microenvironment: Potential Therapeutic Implications. *Exercise and Sport Sciences Reviews*. 2018;46(1):56–64.
26
27 594 27. McCullough DJ, Stabley JN, Siemann DW, Behnke BJ. Modulation of Blood Flow, Hypoxia, and Vascular
28
29 595 Function in Orthotopic Prostate Tumors During Exercise. *J Natl Cancer Inst [Internet]*. 2014 [cited 2020 Jan
30
31 596 8];106(4). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3982888/>
32
33 597 28. Schadler KL, Thomas NJ, Galie PA, Bhang DH, Roby KC, Addai P, et al. Tumor vessel normalization after
34
35 598 aerobic exercise enhances chemotherapeutic efficacy. *Oncotarget*. 2016;7(40):65429–40.
36
37 599 29. Schumacher O, Galvão DA, Taaffe DR, Chee R, Spry N, Newton RU. Exercise modulation of tumour
38
39 600 perfusion and hypoxia to improve radiotherapy response in prostate cancer. *Prostate Cancer Prostatic Dis*. 2021
40
41 601 Mar;24(1):1–14.
42
43 602 30. Thomas VJ, Seet-Lee C, Marthick M, Cheema BS, Boyer M, Edwards KM. Aerobic exercise during
44
45 603 chemotherapy infusion for cancer treatment: a novel randomised crossover safety and feasibility trial. *Support*
46
47 604 *Care Cancer*. 2020;28(2):625–32.
48
49 605 31. Kerrigan K. A pilot study of aerobic exercise performed in breast cancer patients during chemotherapy
50
51 606 infusion. | *Journal of Clinical Oncology [Internet]*. 2010 [cited 2020 Aug 11]. Available from:
52
53 607 https://ascopubs.org/doi/10.1200/jco.2010.28.15_suppl.e19527
54
55 608 32. Ashcraft KA, Warner AB, Jones LW, Dewhirst MW. Exercise as Adjunct Therapy in Cancer. *Seminars in*
56
57 609 *Radiation Oncology*. 2018;29(1):16–24.
58
59 610 33. Martín-Ruiz A, Fiuza-Luces C, Rincón-Castanedo C, Fernández-Moreno D, Martínez-Martínez E, Martín-

- 1
2
3 611 Acosta P, et al. Benefits of exercise and immunotherapy in a murine model of human non–small-cell lung
4
5 612 carcinoma. 2020;16.
6
7 613 34. Alexandre P. Haute Autorité de santé. 2019;142.
8
9 614 35. Macmillan Cancer Support. Physical activity in patients with metastatic bone disease: Guidance for
10
11 615 healthcare professionals. 2018 [Internet]. [cited 2021 Jul 4]. Available from:
12
13 616 <https://cdn.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/1784-10061/physical-activity->
14
15 617 [for-people-with-metastatic-bone-disease-guidance-tcm9-326004](https://cdn.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/1784-10061/physical-activity-for-people-with-metastatic-bone-disease-guidance-tcm9-326004)
16
17 618 36. Senesse P, Bachmann P, Bensadoun RJ, Besnard I, Bourdel-Marchasson I, Bouteloup C, et al. Nutrition
18
19 619 chez le patient adulte atteint de cancer : textes courts. *Nutrition Clinique et Métabolisme*. 2012;26(4):151–8.
20
21 620 37. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition
22
23 621 in cancer patients. *Clinical Nutrition*. 2017;36(1):11–48.
24
25 622 38. Tudor-Locke C, Craig CL, Aoyagi Y, Bell RC, Croteau KA, De Bourdeaudhuij I, et al. How many steps/day
26
27 623 are enough? For older adults and special populations. *Int J Behav Nutr Phys Act*. 2011;8(1):80.
28
29 624 39. Borg G, Hassmén P, Lagerström M. Perceived exertion related to heart rate and blood lactate during
30
31 625 arm and leg exercise. *Europ J Appl Physiol*. 1987;56(6):679–85.
32
33 626 40. Kilgour RD, Vigano A, Trutschnigg B, Lucar E, Borod M, Morais JA. Handgrip strength predicts survival
34
35 627 and is associated with markers of clinical and functional outcomes in advanced cancer patients. *Support Care*
36
37 628 *Cancer*. 2013 Dec;21(12):3261–70.
38
39 629 41. Anand A, Gajra A. Hand Grip Dynamometry as Prognostic and Predictive Marker in Older Patients With
40
41 630 Cancer. *J Gerontol Geriatr Res* [Internet]. 2018 [cited 2020 Jun 19];07(03). Available from:
42
43 631 <https://www.omicsonline.org/open-access/hand-grip-dynamometry-as-prognostic-and-predictive-marker-in->
44
45 632 [older-patients-with-cancer-2167-7182-1000471-102218.html](https://www.omicsonline.org/open-access/hand-grip-dynamometry-as-prognostic-and-predictive-marker-in-older-patients-with-cancer-2167-7182-1000471-102218.html)
46
47 633 42. Trutschnigg B, Kilgour RD, Reinglas J, Rosenthal L, Hornby L, Morais JA, et al. Precision and reliability of
48
49 634 strength (Jamar vs. Biodex handgrip) and body composition (dual-energy X-ray absorptiometry vs. bioimpedance
50
51 635 analysis) measurements in advanced cancer patients. *Appl Physiol Nutr Metab*. 2008;33(6):1232–9.
52
53 636 43. Amireault S, Godin G, Lacombe J, Sabiston CM. The use of the Godin-Shephard Leisure-Time Physical
54
55 637 Activity Questionnaire in oncology research: a systematic review. *BMC Med Res Methodol* [Internet]. 2015 [cited
56
57 638 2020 May 28];15. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4542103/>
58
59 639 44. Binay Safer V, Safer U. Usefulness and limitations of single-slice computed tomography analysis at the

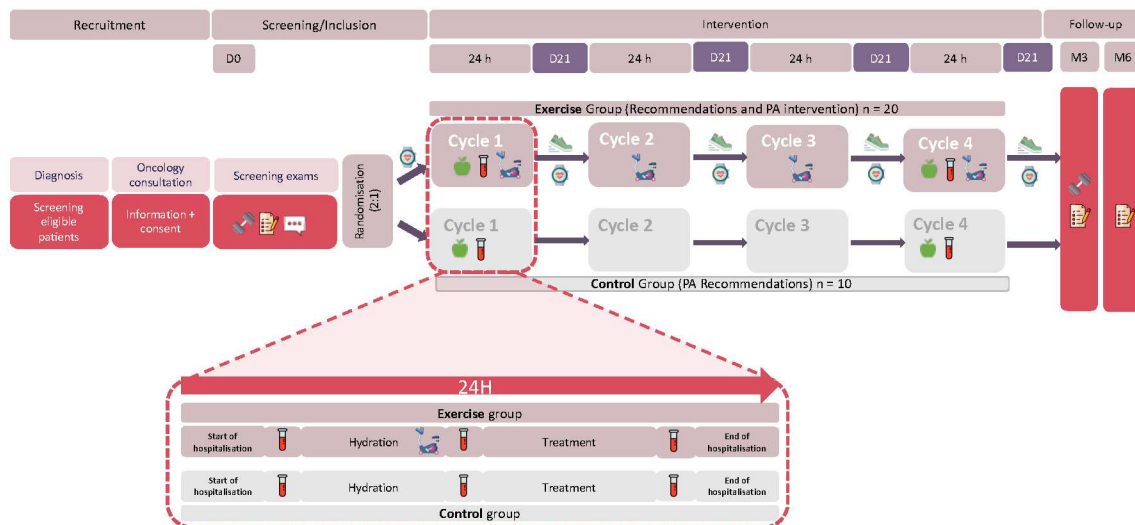
- 1
2
3 640 third lumbar region in the assessment of sarcopenia. *Critical Care*. 2013 Nov 20;17(6):466.
- 4
5 641 45. Boutin RD, Yao L, Canter RJ, Lenchik L. Sarcopenia: Current Concepts and Imaging Implications. *American*
6
7 642 *Journal of Roentgenology*. 2015 Sep;205(3):W255–66.
- 8
9 643 46. Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, et al. Appendicular skeletal muscle
10
11 644 mass: measurement by dual-photon absorptiometry. *Am J Clin Nutr*. 1990 Aug;52(2):214–8.
- 12
13 645 47. Miller KD, Jones E, Yanovski JA, Shankar R, Feuerstein I, Falloon J. Visceral abdominal-fat accumulation
14
15 646 associated with use of indinavir. *Lancet*. 1998 Mar 21;351(9106):871–5.
- 16
17 647 48. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of
18
19 648 skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol*.
20
21 649 1998 Jul;85(1):115–22.
- 22
23 650 49. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise
24
25 651 approach to quantification of body composition in cancer patients using computed tomography images acquired
26
27 652 during routine care. *Appl Physiol Nutr Metab*. 2008;33(5):997–1006.
- 28
29 653 50. Thibault R, Goujon N, Le Gallic E, Clairand R, Sébille V, Vibert J, et al. Use of 10-point analogue scales to
30
31 654 estimate dietary intake: A prospective study in patients nutritionally at-risk. *Clinical Nutrition*. 2009;28(2):134–
32
33 655 40.
- 34
35 656 51. Hjermstad MJ, Fossa SD, Bjordal K, Kaasa S. Test/retest study of the European Organization for Research
36
37 657 and Treatment of Cancer Core Quality-of-Life Questionnaire. *JCO*. 1995;13(5):1249–54.
- 38
39 658 52. Koller M, Shamieh O, Hjermstad MJ, Hornslien K, Young T, Chalk T, et al. Psychometric properties of the
40
41 659 updated EORTC module for assessing quality of life in patients with lung cancer (QLQ-LC29): an international,
42
43 660 observational field study. *The Lancet Oncology*. 2020;21(5):723–32.
- 44
45 661 53. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement
46
47 662 to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. *European Journal*
48
49 663 *of Cancer*. 1994;30(5):635–42.
- 50
51 664 54. Weis J, Tomaszewski KA, Hammerlid E, Ignacio Arraras J, Conroy T, Lanceley A, et al. International
52
53 665 Psychometric Validation of an EORTC Quality of Life Module Measuring Cancer Related Fatigue (EORTC QLQ-
54
55 666 FA12). *JNCI: Journal of the National Cancer Institute [Internet]*. 2017 [cited 2020 May 28];109(5). Available from:
56
57 667 <https://academic.oup.com/jnci/article/doi/10.1093/jnci/djw273/2972669>
- 58
59 668 55. Savard M-H, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer

- 1
2
3 669 patients: INSOMNIA SEVERITY INDEX AND CANCER. *Psycho-Oncology*. 2005;14(6):429–41.
4
5 670 56. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: Psychometric Indicators to
6
7 671 Detect Insomnia Cases and Evaluate Treatment Response. *Sleep*. 2011;34(5):601–8.
8
9 672 57. Sass C, Dupré C, Giordanella JP, Girard F, Guenot C, Labbe É, et al. Le score Epices : un score individuel
10
11 673 de précarité. Construction du score et mesure des relations avec des données de santé, dans une population de
12
13 674 197 389 personnes. 2006;4.
14
15 675 58. Jones LW. Precision Oncology Framework for Investigation of Exercise As Treatment for Cancer. *JCO*.
16
17 676 2015;33(35):4134–7.
18
19 677 59. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being
20
21 678 undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC*
22
23 679 *Med Res Methodol*. 2013;13(1):104.
24
25 680 60. R Core Team (2020). — European Environment Agency [Internet]. [cited 2021 Jul 4]. Available from:
26
27 681 [https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-](https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-development-core-team-2006)
28
29 682 [development-core-team-2006](https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-development-core-team-2006)
30
31 683 61. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture
32
33 684 (REDCap)—A metadata-driven methodology and workflow process for providing translational research
34
35 685 informatics support. *Journal of Biomedical Informatics*. 2009;42(2):377–81.
36
37 686 62. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O’Neal L, et al. The REDCap consortium: Building
38
39 687 an international community of software platform partners. *Journal of Biomedical Informatics*. 2019;95:103208.
40
41 688 63. Jones LW. Physical Activity and Lung Cancer Survivorship. In: Courneya KS, Friedenreich CM, editors.
42
43 689 *Physical Activity and Cancer* [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010 [cited 2021 Mar 28].
44
45 690 p. 255–74. (Recent Results in Cancer Research; vol. 186). Available from: [http://link.springer.com/10.1007/978-](http://link.springer.com/10.1007/978-3-642-04231-7_11)
46
47 691 [3-642-04231-7_11](http://link.springer.com/10.1007/978-3-642-04231-7_11)
48
49 692 64. Quist M, Langer SW, Lillielund C, Winther L, Laursen JH, Christensen KB, et al. Effects of an exercise
50
51 693 intervention for patients with advanced inoperable lung cancer undergoing chemotherapy: A randomized clinical
52
53 694 trial. *Lung Cancer*. 2020;145:76–82.
54
55 695 65. Nadler M, Bainbridge D, Tomasone J, Cheifetz O, Juergens RA, Sussman J. Oncology care provider
56
57 696 perspectives on exercise promotion in people with cancer: an examination of knowledge, practices, barriers, and
58
59 697 facilitators. *Support Care Cancer*. 2017;25(7):2297–304.

- 1
2
3 698 66. Wilk M, Kepski J, Kepska J, Casselli S, Szmit S. Exercise interventions in metastatic cancer disease: a
4
5 699 literature review and a brief discussion on current and future perspectives. *BMJ Support Palliat Care*.
6
7 700 2020;10(4):404–10.
- 8
9 701 67. Singh B, Spence R, Steele ML, Hayes S, Toohey K. Exercise for Individuals With Lung Cancer: A Systematic
10
11 702 Review and Meta-Analysis of Adverse Events, Feasibility, and Effectiveness. *Semin Oncol Nurs*.
12
13 703 2020;36(5):151076.
- 14
15 704 68. Granger CL, Parry SM, Edbrooke L, Abo S, Leggett N, Dwyer M, et al. Improving the delivery of physical
16
17 705 activity services in lung cancer: A qualitative representation of the patient's perspective. *European Journal of*
18
19 706 *Cancer Care*. 2019;28(1):e12946.
- 20
21 707 69. Dittus KL, Gramling RE, Ades PA. Exercise interventions for individuals with advanced cancer: A
22
23 708 systematic review. *Preventive Medicine*. 2017;104:124–32.
- 24
25 709 70. Heywood R, McCarthy AL, Skinner TL. Safety and feasibility of exercise interventions in patients with
26
27 710 advanced cancer: a systematic review. *Support Care Cancer*. 2017 Oct;25(10):3031–50.
- 28
29 711 71. Yang M, Liu L, Gan C, Qiu L, Jiang X, He X, et al. Effects of home-based exercise on exercise capacity,
30
31 712 symptoms, and quality of life in patients with lung cancer: A meta-analysis. *European Journal of Oncology*
32
33 713 *Nursing*. 2020;49:101836.
- 34
35 714 72. Nieman DC, Lila MA, Gillitt ND. Immunometabolism: A Multi-Omics Approach to Interpreting the
36
37 715 Influence of Exercise and Diet on the Immune System. *Annu Rev Food Sci Technol*. 2019;10:341–63.
- 38
39 716 73. Gresham G, Schrack J, Gresham LM, Shinde AM, Hendifar AE, Tuli R, et al. Wearable activity monitors in
40
41 717 oncology trials: Current use of an emerging technology. *Contemporary Clinical Trials*. 2018;64:13–21.
- 42
43 718 74. Haberlin C, O'Dwyer T, Mockler D, Moran J, O'Donnell DM, Broderick J. The use of eHealth to promote
44
45 719 physical activity in cancer survivors: a systematic review. *Support Care Cancer*. 2018;26(10):3323–36.
- 46
47 720 75. Turner RR, Steed L, Quirk H, Greasley RU, Saxton JM, Taylor SJ, et al. Interventions for promoting habitual
48
49 721 exercise in people living with and beyond cancer. *Cochrane Database Syst Rev* [Internet]. 2018 [cited 2019 Oct
50
51 722 29];2018(9). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6513653/>
- 52
53 723 76. Naito T, Mitsunaga S, Miura S, Tatematsu N, Inano T, Mouri T, et al. Feasibility of early multimodal
54
55 724 interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer. *J Cachexia Sarcopenia*
56
57 725 *Muscle*. 2019;10(1):73–83.
- 58
59 726 77. Delrieu L, Anota A, Trédan O, Freyssenet D, Maire A, Canada B, et al. Design and methods of a national,

1
2
3 727 multicenter, randomized and controlled trial to assess the efficacy of a physical activity program to improve
4
5 728 health-related quality of life and reduce fatigue in women with metastatic breast cancer: ABLE02 trial. BMC
6
7 729 Cancer [Internet]. 2020 [cited 2021 Apr 15];20. Available from:
8
9 730 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7333295/>
10
11 731 78. Delrieu L, Martin A, Touillaud M, Pérol O, Morelle M, Febvey-Combes O, et al. Sarcopenia and serum
12
13 732 biomarkers of oxidative stress after a 6-month physical activity intervention in women with metastatic breast
14
15 733 cancer: results from the ABLE feasibility trial. Breast Cancer Res Treat [Internet]. 2021 [cited 2021 Jun 13];
16
17 734 Available from: <https://link.springer.com/10.1007/s10549-021-06238-z>
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24 737 **Figure 1:** Flow chart of the ERICA study, France (original flow chart)
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract : page 2 Methods : page 18
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	Abstract : page 2 Declaration line :page 18
Funding	4	Sources and types of financial, material, and other support	Funding: page 28
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1 Author's contribution : page 28
	5b	Name and contact information for the trial sponsor	Page 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Funding : page 28
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Data monitoring : page 17
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction : page 2
	6b	Explanation for choice of comparators	Page 6
Objectives	7	Specific objectives or hypotheses	Page 6

1 2 3 4 5 6 7	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 6
8	Methods: Participants, interventions, and outcomes			
9 10 11 12 13	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 6 Page 7
14 15 16 17 18	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 6-7
19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 8-10
11b		Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A	
11c		Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 9-10	
11d		Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 8	
36 37 38 39 40 41 42 43 44 45	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 10-16
46 47 48 49 50 51	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 10
52 53 54 55 56 57	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 16
58 59 60	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 7-8

1	Methods: Assignment of interventions (for controlled trials)			
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3	Allocation:			
4	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 8
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14	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 17
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
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28		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
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32	Methods: Data collection, management, and analysis			
33	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 10-16
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44		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 10
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49	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 17
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57	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be	Page 16-17
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		found, if not in the protocol	
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 16-17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 16-17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A no interim analyses are planned
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Abstract : page 2 Study population : page 6 Recruitment: page 7-8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 17

1 2 3 4	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 28
5 6 7 8	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 18
9 10 11 12	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
13 14 15 16 17 18 19 20 21	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 2
22 23		31b	Authorship eligibility guidelines and any intended use of professional writers	Page 2
24 25 26 27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
28	Appendices			
29 30 31 32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Consent form, see supplementary file
33 34 35 36 37	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Page 15

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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

BMJ Open

The effect of acute aerobic exercise before immunotherapy and chemotherapy infusion in patients with metastatic non-small-cell lung cancer: Protocol for the ERICA feasibility trial

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Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Oncology, Immunology (including allergy), Pharmacology and therapeutics
Keywords:	CHEMOTHERAPY, IMMUNOLOGY, Adult oncology < ONCOLOGY, Respiratory tract tumours < ONCOLOGY, SPORTS MEDICINE



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1 **The effect of acute aerobic exercise before immunotherapy and**
2 **chemotherapy infusion in patients with metastatic non-small-cell lung cancer:**
3 **Protocol for the ERICA feasibility trial**

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ABSTRACT

Introduction. Patients with metastatic Non-Small Cell Lung Cancer (mNSCLC) suffer from numerous symptoms linked to disease and treatment which may further impair the patient's overall condition. In addition to its benefits on quality of life and fatigue, physical exercise may improve treatment response, notably due to its known effects on the immune system. The ERICA study is designed to assess the feasibility of a supervised acute physical exercise therapy realised immediately prior immune-chemotherapy infusion in patients with mNSCLC. Secondary objectives will examine the effects of acute exercise combined with an unsupervised home-walking program on clinical, physical, psycho-social and biological parameters.

Methods and analysis. ERICA is a prospective, monocentric, randomized controlled, open-label feasibility study conducted at the Centre Léon Bérard Comprehensive Cancer Center (France). Thirty patients newly diagnosed with mNSCLC will be randomized (2:1 ratio) to the "exercise" or the "control" group. At baseline and during the last treatment cycle, participants in both groups will receive Physical Activity recommendations, and two nutritional assessments. In the exercise group, participants will receive a 3-months program consisting of a supervised acute physical exercise session prior to immune-chemotherapy infusion, and an unsupervised home-based walking program with an activity tracker. The acute exercise consists of 35 minutes interval training at submaximal intensity scheduled to terminate 15 minutes prior to infusion. Clinical, physical, biological, and psychosocial parameters will be assessed at baseline, 3 and 6 months after inclusion. Biological measures will include immune, inflammatory, metabolic, oxidative stress biomarkers and molecular profiling.

Ethics and dissemination. The study protocol was approved by the French ethics committee (Comité de protection des personnes Ile de France II, N°ID-RCB 20.09.04.65226, 8th December

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3 48 2020). The study is registered on ClinicalTrials.gov (NCT number:NCT04676009). All
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6 49 participants will sign an informed consent form. The findings will be disseminated in peer-
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8 50 reviewed journals and academic conferences.

9
10 51 **KEYWORDS:** Non-small-cell lung cancer, Metastatic, Exercise, Immunotherapy, Chemotherapy,
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12 52 Immunology

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15 53 **Word count:** 5580

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17 54 **Strengths and limitations of this study.**

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20 55 • This study is the first to assess the feasibility effects of acute physical exercise performed
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22 56 within one hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-
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24 57 based doublet) infusion in mNSCLC patients.
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27 58 • Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption
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29 59 condition during a submaximal endurance test on a cycle-ergometer at baseline and this test
30
31 60 will allow individualisation of the intensity of the acute physical exercise program.
- 32
33
34 61 • The feasibility study assesses the acute physiological, immune, and metabolic response to a
35
36 62 supervised acute moderate intensity physical exercise session in patients with mNSCLC.
- 37
38 63 The unsupervised home-based walking program in the intervention arm aims to increase the
39
40 64 level of physical activity in patients with mNSCLC and their cardiorespiratory fitness and
41
42 65 physical capacity to perform acute physical exercise prior to chemo-immunotherapy infusion.
- 43
44
45 66 • The study concerns only one stage of lung cancer, participants must be eligible to
46
47 67 immunotherapy and it's a study with a limited sample size (n=30).
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68 INTRODUCTION

69 Non-small cell lung cancer (NSCLC) accounts for approximately 80-90% of lung cancers (1,2). More than
70 half of NSCLC are diagnosed at advanced stages due to their asymptomatic nature at early stage
71 explaining their poor survival. The development of immunotherapy in first-line therapy with anti-PD-1
72 and anti-PD-L1 has changed the first line treatment algorithm of advanced NSCLC (1). The anti-PD-1
73 pembrolizumab and cemiplimab clearly improve the overall survival in NSCLC with high PD-L1
74 expression ($\geq 50\%$ of tumour cells) in comparison with cytotoxic chemotherapy. Combinations of anti-
75 PD(L)-1 to platinum-based chemotherapy are superior to chemotherapy alone, independently of PD-
76 L1 level of expression. They represent the 1st line gold-standard when PD-L1 is expressed in less than
77 50% of tumour cells and might reduce the risk of early disease progression in comparison with
78 pembrolizumab when PD-L1 $\geq 50\%$. Immunotherapy has significantly improved the prognosis of
79 patients with mNSCLC and has led to prolonged remissions in some patients especially for non-
80 squamous cell carcinoma in the KEYNOTE-189 trial (3,4). Despite these therapeutic advances,
81 metastatic lung cancer has a negative impact on patients' physical, psychological, and social
82 functioning including health-related quality of life (HRQoL) (5–7). Principal reported symptoms and
83 adverse effects from treatment are fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite
84 loss, and financial concerns (8,9).

85 Benefits of physical exercise defined as planned, structured, repeated, and purposeful Physical Activity
86 (PA) to improve physical fitness (10) have been widely demonstrated. In lung cancer patients, physical
87 exercise has been shown to improve aerobic capacity (VO_{2peak}), muscular strength, functional capacity
88 (11), sleep quality (12), PA level (13), some fatigue domains (14), anxiety, disease-specific global
89 health-related quality of life (15) and emotional well-being in cancer patients (16). Several studies in
90 lung cancer patients have reported the potential of physical exercise to limit or even reverse some of
91 the adverse effects induced by the disease and its treatment (17). While regular PA is recommended
92 in patients with cancer, no specific recommendations exist for patients with lung cancer or metastatic
93 disease (18). In addition, few studies have examined the interactions between transient physiological

1
2
3 94 changes caused by acute exercise i.e., a single physical exercise bout, and cancer treatments(19).
4
5 95 Immunomodulatory effects of acute physical exercise involve immune cell mobilisation in blood such
6
7 96 as neutrophils, subsets of monocytes or lymphocytes involved in the host defence against tumours,
8
9
10 97 seems to improve immunosurveillance (20). Acute physical exercise leads to a rapid increase in the
11
12 98 mobilization of the peripheral activity of the sub-population of CD56^{dim} NK cells during acute physical
13
14 99 exercise of light to moderate intensity (21,22). A preclinical study reported that exercise training
15
16 100 (voluntary running), through activation of epinephrine and IL-6, led to selective NK cell mobilization
17
18 101 and limited tumour growth of several types of tumours (melanomas, liver, and lung mouse models)
19
20 102 (23). In a recent study, the increase in PD-1+ CD8+ T cells was observed after a single exercise session
21
22 103 (24). At the level of the adaptive immune system, acute exercise results in transient biphasic changes,
23
24 104 i.e. increase of circulating lymphocytes during and immediately after exercise, followed by a transient
25
26 105 decrease of blood lymphocytes below baseline level during recovery from exercise (1 hour), thought
27
28 106 to be due to a redistribution of immune cells to peripheral tissues, including tumours, before return to
29
30 107 basal level within a few hours (23,25). Moreover, recent preclinical studies suggested that physical
31
32 108 exercise performed during chemotherapy infusion may have additional physiological benefits such as
33
34 109 increase the blood flow leading to improved intra-tumoral perfusion and enhanced drug delivery (26–
35
36 110 28). However, to date, the optimal timing, duration and intensity of exercise that is feasible and
37
38 111 produces clinically meaningful changes in tumour perfusion and immunomodulatory effects, needs to
39
40 112 be determined (29). Most of the available evidence on the benefits of physical exercise in cancer
41
42 113 patients has been observed in interventions performed either after the treatment or during the
43
44 114 interval between the chemotherapy cycles(30). Only two studies have evaluated the feasibility of low-
45
46 115 intensity physical exercises during the chemotherapy infusion without adverse events, interference
47
48 116 with chemotherapy, or exacerbation in symptoms (30,31). Recently, it has been suggested in
49
50 117 preclinical studies that exercise performed during chemotherapy infusion could lead to improved
51
52 118 perfusion of solid tumours, mitigating tumour hypoxia, and enhancing drug delivery to tumours
53
54 119 (26,27,32). Similarly, by its effect on immune regulation, physical exercise prior to infusion may
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1
2
3 120 potentiate the effect of the immunotherapy. Recent preclinical evidence has suggested a beneficial
4
5 121 effect of exercise in addition to immunotherapy (anti-PD-1 immunotherapy) in a murine model of
6
7 122 NSCLC, through increased necrosis and a decreased proliferative index of tumour cells (33).
8
9
10 123 Based on these findings, the main objective of the ERICA (Exercise inteReaction Immunotherapy
11
12 124 Chemotherapy and cAncer) feasibility study is to evaluate the feasibility of a supervised acute physical
13
14 125 exercise performed immediately prior to immunotherapy and chemotherapy infusion (i.e. a
15
16 126 combination of pembrolizumab and pemetrexed-cis- or carboplatin for non-squamous cell carcinoma
17
18 127 or paclitaxel-carboplatin for squamous cell carcinoma) in first-line treatment of metastatic NSCLC
19
20 128 patients, and to assess if this planned exercise dose is safe and tolerable in this target patient
21
22
23 129 population. The secondary objectives are to evaluate the effects of the supervised acute exercise
24
25 130 before first-line treatment administration combined with an unsupervised home-based walking
26
27 131 program, on 1) physical fitness, 2) PA level and sedentary lifestyle, 3) psychosocial factors (HRQoL and
28
29 132 fatigue), 4) sleep quality, 5) body composition, 6) sarcopenia, 7) treatment response, 8) treatment
30
31 133 completion rate, 9) related treatment toxicities, and 10) progression-free survival. Furthermore, this
32
33 134 feasibility study will generate data on the effect of this exercise intervention on immune, metabolic,
34
35 135 and inflammatory biomarkers as well as oxidative stress.
36
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38
39

40 136 **METHODS**

41 137 **STUDY DESIGN**

42
43
44 138 ERICA is a prospective, monocentric, randomized controlled, open-label feasibility study, conducted at
45
46
47 139 the Centre Léon Bérard Comprehensive Cancer Centre (Lyon, France).
48

49 140 *Insert Figure 1*

50 141 **STUDY POPULATION**

51 142 *Inclusion criteria*

52
53
54 143 Participants will have to meet all of the following eligibility criteria: 1) aged ≥ 18 and < 80 years; 2)
55
56 144 diagnosed with a histologically confirmed metastatic NSCLC without EGFR mutation/ALK
57
58 145 rearrangement; 3) eligible to receive first-line chemotherapy according to histology (pemetrexed-cis-
59
60

1
2
3 146 or carboplatin for non-squamous cell carcinoma or paclitaxel-carboplatin for squamous cell
4
5 147 carcinoma) in combination with pembrolizumab; 4) Eastern Co-operative Oncology Group (ECOG)
6
7 148 performance status ≤ 2 ; 5) able to engage in PA attested by a medical certificate by an oncologist;
8
9 149 and 6) provide a dated and signed informed consent form before study enrolment.

12 150 *Exclusion criteria*

14 151 Patients will not be eligible in at least one of the following cases: 1) bone metastases with risk of
15
16 152 fractures or unconsolidated pathologic fractures; 2) contraindication to the physical exercise proposed
17
18 153 in this study (e.g. orthopaedic disorder such as disabling coxarthrosis or gonarthrosis, central nervous
19
20 154 system disorders); 3) history or co-existence of other primary cancer (except in situ cancer regardless
21
22 155 of the site, and/or basal cell carcinoma, and/or non-lung cancer in complete remission for more than
23
24 156 5 years) ; 4) severe undernutrition defined according to the French National Authority for Health (i.e.
25
26 157 for adults aged ≥ 18 years and < 70 : Body Mass Index (BMI) ≤ 17 , weight loss $\geq 10\%$ in 1 month, $\geq 15\%$
27
28 158 in 6 months, or $\geq 15\%$ compared to the usual weight before the disease diagnosis, or serum albumin
29
30 159 < 30 g/l; for adults aged ≥ 70 years: BMI < 18 , weight loss $\geq 10\%$ in 1 month or $\geq 15\%$ in 6 months, or
31
32 160 serum albumin < 30 g/l) (34); 5) severe anaemia (haemoglobin ≤ 8 g/dl) in the past 30 days prior to
33
34 161 enrolment; 6) history of cardiovascular disease or cardiovascular risk (i.e. chronic or poorly controlled
35
36 162 coronary heart disease, peripheral arterial disease, cardiac arrhythmia, symptomatic heart disease,
37
38 163 uncontrolled or untreated arterial hypertension, myocardial infarction diagnosed in the past 6 months,
39
40 164 coronary angioplasty with or without stent implantation in the past 6 months, coronary artery bypass
41
42 165 surgery in the past 12 months); 7) history of type 2 diabetes or glycated haemoglobin $> 7\%$ in the past
43
44 166 3 months prior to enrolment; 8) Stage IV Chronic obstructive pulmonary disease (forced expiratory
45
46 167 volume in one second (FEV₁) $< 30\%$).

52 168 **RECRUITMENT**

54 169 Participants will be recruited in Centre Léon Bérard, Lyon, France from December 2020. Eligible
55
56 170 patients will be screened systematically based on electronic medical record during weekly
57
58 171 multidisciplinary lung cancer board meetings, as seen in Figure 1. During a medical consultation before
59
60

1
2
3 172 treatment initiation, an oncologist will propose the study to eligible patients and explain the study
4
5 173 objectives and protocol. Once the written informed consent is signed, patients will undergo the
6
7 174 following screening tests prior to inclusion: (1) clinical examination including assessing Performance
8
9
10 175 Status (PS) and Blood Pressure, (2) echocardiography and electrocardiogram performed by a
11
12 176 cardiologist, and (3) for patients with diabetes, measurement of glycated haemoglobin. If these
13
14 177 investigations confirm the patient's eligibility, the patient will be included in the study (D0). The end
15
16 178 date for this study is planned in January 2023.

179

180 **RANDOMIZATION**

181 At inclusion (D0), patients will be randomly assigned (ratio 2:1) to (i) the exercise group to receive PA
182 and nutrition recommendations; a supervised acute physical exercise prior each immuno-
183 chemotherapy infusion and an unsupervised home-based walking program with an activity tracker or
184 (ii) the control group to receive PA and nutrition recommendations only.

185 Randomization will be stratified using a dynamic minimization algorithm with two factors: sex (male
186 vs. female) and histology (squamous vs. non-squamous).

187

188 **INTERVENTION**

189 *Treatment protocol*

190 All patients in both exercise and control groups of this study will receive usual care and the same
191 standard treatment protocol: pembrolizumab (200 mg) combined with carboplatin (AUC 5) plus
192 pemetrexed (500 mg/m²) with B9-B12 vitamin supplementation; carboplatin (AUC 6) plus paclitaxel
193 (200 mg/m²) every 3 weeks for 4 cycles; before pembrolizumab maintenance in squamous cell
194 carcinoma or pembrolizumab plus pemetrexed maintenance for non-squamous cell carcinoma.

195 *Physical Activity recommendations*

196 Although there are no specific PA recommendations for patients with mNSCLC, all patients will be
197 informed of the PA recommendations to be physically active as much as possible during the day,

1
2
3 198 walking as much as possible and sitting as little as possible (WCRF, 2018). We have chosen to follow
4
5 199 the recommendations of the Macmillan Cancer Support guide released in 2018, advising patients with
6
7 200 bone metastases to have an active lifestyle on a daily basis and to maintain appropriate PA according
8
9 201 to their physical abilities (35). Several individual strategies will be proposed to patients (e.g., using
10
11 202 stairs whenever possible, walking to local shops).

203 *Nutritional recommendations*

16 204 All patients will receive nutritional recommendations during the 1st and 4th treatment cycle. The
17
18 205 nutritional recommendations will include: energy intake of 30 kcal/kg body weight/day for patients
19
20 206 with BMI <30, or 25 kcal/kg body weight/day for patients with BMI ≥ 30, and protein intake of at least
21
22 207 1.2 g/kg body weight/day (36,37).

208 **Exercise Group**

209 *Acute physical exercise protocol prior to immunotherapy and chemotherapy infusion*

29
30 210 Patients in the "exercise" group will perform a supervised acute physical exercise bout during
31
32 211 hospitalization for treatment. It will be carried out within one hour prior to the immunotherapy and
33
34 212 chemotherapy infusion, on a cycle ergometer (Monark Ergonomic 939 Novo) for each of the 4 cycles
35
36 213 of treatment foreseen. The physical exercise will be supervised by a clinical exercise physiologist with
37
38 214 experience in oncology. The physical exercise consists of a 35-min acute interval training, scheduled to
39
40 215 terminate 15 minutes prior to infusion onset and will be individualized based on the results of a
41
42 216 submaximal endurance test performed on a cycle ergometer by each patient (described below) prior
43
44 217 to treatment (D0).

47
48 218 Following a five-minute warm-up at 60% of Ventilation Threshold 1 (VT1), the participant will carry out
49
50 219 5 sets, alternating periods of 3 minutes at 70-80% of VT1 with 3 minutes at 110-120% of VT1 (≥ 35
51
52 220 Revolutions Per Minute (RPM)). The acute exercise intensity will be programmed according to the load
53
54 221 reached at VT1 during the cycle ergometer endurance submaximal test. Heart rate (HR), load, RPM,
55
56 222 dyspnoea, and perception of effort on a Borg-scale will be monitored. If the patient is no longer able
57
58 223 to cycle at the load corresponding to 120% of his VT1, the clinical exercise physiologist will decrease
59
60

1
2
3 224 the load to 110% of VT1. In case of exercise-induced desaturation ($\geq 4\%$ of the measured value at
4
5 225 rest or $\leq 93\%$), the clinical exercise physiologist will stop the exercise until the rest value of oxygen
6
7 226 saturation. In addition to detailed explanation by the qualified clinical exercise physiologist, patients
8
9 227 receive written support materials at baseline (D0).

12 228 *Home-based walking program*

14 229 During the 3-month intervention, between each treatment cycle (3 weeks), patients will follow an
15
16 230 unsupervised home-based walking program consisting of an individual goal of a number of steps per
17
18 231 day. Each patient will receive a Fitbit® Inspire activity tracker with an instruction to wear it continuously
19
20 232 during the intervention. They will be advised to achieve at least 6,000 daily steps which corresponds
21
22 233 to a physically active lifestyle in a patient population (38). Ten days after each treatment cycle, the
23
24 234 clinical exercise physiologist will contact the patients by phone to assess and encourage adherence to
25
26 235 the home-based walking program. Depending on the average number of steps performed in the past
27
28 236 ten days, personalized objectives might be redefined to increase the target number of daily steps. For
29
30 237 patients who reach more than 6,000 steps per day the initial target number of 6,000 steps will be
31
32 238 increased by 30%. The target number of steps was set within a maximum of 7800 steps above the
33
34 239 average number of steps in the previous week. Patients who do not reach 6,000 daily steps, will be
35
36 240 advised to gradually increase the target number of steps per day according to the patient's abilities.
37
38 241 Number of steps will be collected by regular sync with the mobile phone application (Fitbit®) of the
39
40 242 activity tracker or by a step logbook.
41
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48 244 **EVALUATIONS**

49 245 *Modalities*

50 246 The assessments of the repeated measures (PA level, anthropometric, HRQoL, fatigue, sleep quality,
51
52 247 and sarcopenia) in both groups will be performed before the first cycle of anti-neoplastic treatment
53
54 248 (baseline, D0), at the end of the 4 cycles of treatment (M3), and at 6 months after study inclusion (M6)
55
56
57 249 (Table 1).
58
59
60

250

251 Table 1. Data collection schedule for the ERICA study

	Screening	Inclusion D0	1 st cycle C1	4 th cycle C4	Month 3 M3	Month 6 M6
Socio demographic and clinical data						
Screening tests (<i>PS, blood Pressure, echocardiography, electrocardiogram</i>)	X					
Sociodemographic data (<i>gender, date of birth, living situation, employment status, lifestyle</i>)		X			X	X
Clinical data		X			X	X
Severe treatment toxicities (grade ≥ 3) (<i>NCI-CTCAE</i>)			Continuously		X	
Tumour response (<i>RECIST</i>)		X			X	X
Physical evaluation						
Anthropometrics		X			X	
Physical fitness (<i>Cardiorespiratory fitness, strength tests</i>)		X			X	
Self-reported outcomes						
Physical activity level (<i>GODIN</i>)		X				X
Quality of life (<i>QLQ-C30, QLQ-LC13</i>)		X				X
Dietary intake (<i>24h recall</i>)			X	X		
Fatigue (<i>QLQ-FA12</i>)		X				X
Sleep quality (<i>ISI</i>)		X				X
Social deprivation (<i>EPICES</i>)		X				X
Acceptability ERICA					X	
Biological assessments						
Blood sample			X	X		
Body composition						
CT scan		X			X	X
Exercise group						
Steps per day			Continuously		X	
Number of acute physical exercise sessions			Continuously		X	

252 **DATA COLLECTION**

253 *Sociodemographic and clinical data*

254 Sociodemographic and clinical data including gender, date of birth, living situation, employment status,
 255 lifestyle (alcohol consumption and smoking status) will be collected at baseline. All clinical data will be
 256 extracted from the participant's electronic medical record. The Response Evaluation Criteria In Solid
 257 Tumours (RECIST) will be used for tumour assessments between the diagnosis and the end of the ERICA
 258 study.

259

260 *Anthropometric data*

1
2
3 261 Anthropometric data including body weight (kilogram), height (centimeter, cm), waist (cm) and hip
4
5 262 (cm) circumference will be collected. Waist circumference will be measured around the abdomen
6
7 263 midway between the last floating rib and the iliac crest. Hip circumference will be measured
8
9
10 264 horizontally through the upper margin of the pubis. The body mass index is calculated as the body
11
12 265 weight in kilograms divided by the square of the height in meters.
13

14 266

16 267 *Physical fitness*

18
19 268 Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption (VO_2)
20
21 269 condition during a submaximal endurance test on a cycle-ergometer at baseline. This test will allow
22
23 270 individualisation of the intensity of the acute physical exercise program. Following a 5-minute warm-
24
25 271 up at 20% of the participant's maximum theoretical load, power will be increased by a constant amount
26
27 272 of 5 watts each 30 seconds until VT1 will be reached. The clinical exercise physiologist will ensure that
28
29 273 the patient maintains a minimum pedalling frequency above 35 RPM throughout the test. HR,
30
31 274 ventilation (VE), oxygen saturation (SaO_2), VO_2 , and carbon dioxide production (VCO_2) will be measured
32
33 275 by a gas analyser (MetaMax 3b, Cortex Biophysik, Leipzig, Germany) and continuously monitored. In
34
35 276 addition, the perception of the difficulty and dyspnoea will be evaluated at the end of the test using
36
37 277 the Borg Rating Perceived Exertion questionnaire(39). The clinical exercise physiologist will stop the
38
39 278 test when the patient exceeded the VT1. The test will end with a 6-minute recovery phase. The VT1
40
41 279 will be determined graphically when the ventilatory equivalent of oxygen (VE/VO_2) starts to increase
42
43 280 and will be confirmed by Respiratory Exchange Ratio that strictly exceeds 1 (Wasserman method).
44
45

46
47
48 281 The lower body muscular strength will be evaluated by measuring the maximum isometric strength of
49
50 282 the knee extensors (DFS II Series Digital; Force Gauges Chatillon, Largo, FL, USA). Participants will be
51
52 283 seated on a chair with the knee joint at 90°, arms crossed over the chest, and the dynamometer
53
54 284 attached to the ankle. Participants were advised to extend their leg as hard as possible within 3
55
56 285 seconds upon the instructor's signal. Only the dominant leg will be tested three times (with 2 minutes
57
58 286 rest between each contraction), and the best performance will be considered.
59
60

1
2
3 287 The maximum isometric upper limb strength will be measured by a hand dynamometer (Jamar Plus
4
5 288 Digital Hand Dynamometer, Patterson Medical, Huthwaite, United Kingdom) (39,40,41). Participants
6
7 289 will be seated with their back straight and elbows bent at 90°. They will be asked to squeeze the
8
9
10 290 handgrip as strongly as possible for five seconds to achieve maximum strength. Two measurements
11
12 291 will be taken on each hand and the best performance will be recorded. Hand grip strength is an easy
13
14 292 and non-invasive method, well tolerated and routinely used in cancer patients to assess muscle
15
16 293 strength and physical fitness(42).

18 294

21 295 *Physical activity level*

23 296 The PA level will be measured by the Godin Leisure-Time Physical Activity Questionnaire (GLTAPQ)
24
25 297 (43). The GLTAPQ is a short, self-administered questionnaire with three questions designed to obtain
26
27 298 information on the number of times an individual engages in low, moderate, and intense "leisure-time
28
29 299 PA" periods of at least 15 minutes during a typical week. The score of the GSLTPAQ (Leisure Score
30
31 300 Index, LSI) will be obtained by using the following formula: (light PA frequency × 3) + (moderate PA
32
33 301 frequency × 5) + (vigorous PA frequency × 9). People with LSI ≥ 24 will be classified as active, while
34
35 302 people with LSI ≤ 23 will be classified as insufficiently active (estimated energy expenditure < 14
36
37 303 Kcal/kg/week). The level of PA will be investigated by the change of a daily number of steps thanks to
38
39 304 the activity tracker (only in the intervention group).

43 305

46 306 *Lean body mass and sarcopenia*

47
48 307 Lean body mass and sarcopenia will be analysed using the Computed Tomography (CT) scans
49
50 308 systematically available from routine care. CT scan cross-section at the level of the 3rd lumbar vertebra
51
52 309 provides a reliable representation of the total body muscle mass and has therefore been widely
53
54 310 adopted for the detection of sarcopenia in cancer patients and allows assessment without additional
55
56 311 ionising radiation exposure given that CT scans as part of routine cancer diagnostic procedures is
57
58 312 largely available(44,45). The thresholds for identifying muscle range from -29 to +150 HU,
59
60

1
2
3 313 subcutaneous and intramuscular adipose tissue from -190 to -30 HU, visceral adipose tissue from -150
4
5 314 to -50 HU and bone from +152 to 1000 HU (46–48). Skeletal muscle radiodensity (SMD) that represents
6
7 315 muscle quality will be measured using the average radiation attenuation of the tissue in Hounsfield
8
9 316 Units (HU). A low SMD is defined by values below the threshold of 37.8 HU. An estimate of lean body
10
11 317 mass (LBM) will be calculated using the formula $(LBM \text{ (kg)} = [(L3 \text{ Muscle measured by CT (cm}^2) \times 0.3) +$
12
13 318 $6.06])$ (49).

319

320 *Nutrition*

321 Dietary intake (24h recall, supplemented with patient preferences and habits), clinical (weight loss,
322 BMI), and biological (albumin and CRP) parameters will be assessed by clinical dietitians affiliated with
323 the study. The dietician will use the SEFI® (Score d'Evaluation Facile des Ingesta EPA). The score ranges
324 from 0 to 10. Patients with a SEFI score below 7 will be identified as at risk of undernutrition (50).

325

326 *Health-related quality of life*

327 The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life
328 Questionnaire (QLQ-C30) is a validated multi-dimensional HRQoL questionnaire designed for cancer
329 patients (51), consisting of 30 items to assess five domains of functioning (physical, role, emotional,
330 cognitive, and social), one domain of overall quality of life, three domains of symptoms (pain, fatigue,
331 and nausea), and six single items (dyspnoea, insomnia, anorexia, diarrhoea, constipation, and financial
332 impact). Participants will respond on a Likert scale ranging from "not at all" to "a lot". All scores will be
333 transformed into a scale from 0 to 100 according to the performance of the EORTC scoring manual
334 (52). A high score represents better functioning, better overall quality of life, and lower symptom
335 burden. Quality of life specific to lung cancer will be assessed by the 13-item module: the Quality of
336 Life Questionnaire - Lung Cancer 13 (QLQ-LC13) (52,53). The QLQ-LC13 self-questionnaire is an
337 additional measure of the symptoms and side effects experienced by lung cancer patients who receive
338 non-surgical treatment.

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2
3 3394
5 340 *Fatigue*

6
7 341 Fatigue will be assessed by the EORTC-QLQ module measuring cancer-related fatigue (EORTC QLQ-
8 342 FA12) (54). This self-questionnaire includes 12 items that assess physical, cognitive, and emotional
9
10 343 fatigue related to cancer. Participants will respond on a Likert scale ranging from "not at all" to "a lot".
11
12 344 All scores will be transformed into a scale from 0 to 100, with a higher score indicating a higher degree
13
14 345 of fatigue.

15
16
17 34618
19 347 *Sleep quality*

20
21 348 The perceived quality of sleep will be assessed by the Insomnia Severity Index which measures the
22
23 349 severity of insomnia. The questionnaire consists of 7 items rated on a 5-point scale ranging from 0
24
25 350 ("none") to 4 ("very severe") (55,56). This self-questionnaire will evaluate the severity of the patient's
26
27 351 sleep difficulties (initial, maintenance, and morning insomnia), the degree of sleep dissatisfaction, the
28
29 352 level of interference with daily functioning, the degree of appearance of sleep difficulties, and the level
30
31 353 of anxiety related to insomnia. The total score of the items varies between 0 and 28. A high score
32
33 354 indicates greater sleep difficulties.

34
35
36
37 35538
39 356 *Social vulnerability*

40
41 357 Social deprivation will be assessed using the EPICES score (Evaluation of Deprivation and Inequalities
42
43 358 in Health Examination Centres) (57). The EPICES score will be obtained by adding up the points of the
44
45 359 11 binary questions ("Yes"/"No") of the self-questionnaire. This score ranges from 0 "no
46
47 360 precariousness" to 100 "highest precariousness" with the threshold for deprivation at 30.

48
49
50
51 36152
53 362 *Biomarkers of the immune system, inflammation, sarcopenia, and oxidative stress*

54
55 363 Blood samples will be collected during the first and last (forth) treatment cycle: in the exercise group,
56
57 364 samples will be collected before exercise (S1), after exercise (S2), and 12 hours after the start of
58
59
60

1
2
3 365 treatment (S3); in the control group: samples will be collected 40 minutes before the infusion of
4
5 366 treatment (S1), just before the infusion of treatment (S2) and 12 hours after the start of treatment
6
7 367 (S3). Blood test procedures will follow laboratory standards. Each blood sample will be collected in 3 x
8
9 368 10mL Ethylenediaminetetraacetic acid tubes and then centrifuged (10 minutes at 800G) within one
10
11 369 hour (maintained at 4°C before and during centrifugation). After the centrifuge, plasma will be
12
13 370 collected and aliquoted in 5 cryotubes of 1 mL and the Peripheral Blood Mononuclear Cell (PBMC) will
14
15 371 be collected and aliquoted in 3 cryotubes (5 to 7 millions cells per tube). These cryotubes will be frozen
16
17 372 at -80°C and stored in nitrogen at the center for the duration of the study. At the end of the study,
18
19 373 biomarkers of immunity, sarcopenia, and inflammation will be analysed. We will measure i) immune
20
21 374 biomarkers (NK cells, B lymphocytes, T lymphocytes, monocytes, sub-populations of dendritic cells on
22
23 375 frozen PBMC); ii) plasma biomarkers of sarcopenia and inflammation (Myostatin, Activin, Cortisol,
24
25 376 Tumor Necrosis Factor- α , Interferon- γ , Interleukin-1 β , Interleukin-6, Follistatin, Growth Differentiation
26
27 377 Factor 5, Bone morphogenetic protein 14, GDF15, Interleukin-10, Interleukin-15, NH3, Aminogram, C-
28
29 378 reactive protein, insulin); and iii) plasma oxidative stress (Superoxide dismutase, catalase,
30
31 379 malondialdehyde, glutathione peroxidase, Xanthine Myeloperoxidase, and Xanthine oxidase). Finally,
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33 380 the blood samples will be also used to analyse the glucose (OneTouch Verio®) and lactate (LACTATE
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35 381 PRO II) metabolism by a mobile device. Patients will be asked to complete a questionnaire regarding
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37 382 the taking of antibiotics, anti-inflammatory, and antioxidants in the 48 hours prior to blood collection.
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384 *Toxicities*

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47 385 Severe treatment toxicities (grade ≥ 3) will be noted according to the National Cancer Institute's
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49 386 Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0. The number of rescheduled or
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51 387 cancelled treatment sessions and the relative dose intensity (RDI) of participants with grade ≥ 3
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53 388 toxicities related to chemotherapy and immunotherapy will be calculated as the ratio of "delivered"
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55 389 to "expected" dose intensity.
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3 391 **STATISTICAL ANALYSIS**
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5 392 **SAMPLE SIZE**
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7 393 The main objective of the current study is to evaluate the feasibility of an acute physical exercise
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9 394 program performed prior to the infusion of treatments in mNSCLC patients, and to assess if this
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11 395 planned exercise dose is safe and tolerable in this target patient population(58). In the context of a
12
13 396 feasibility study without a concrete hypothesis and in absence of previous studies in this population,
14
15 397 the sample size was defined empirically. Taking into account the number of mNSCLC patients who
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17 398 receive first line chemotherapy (i.e. pemetrexed-platinum or taxol-platinum) combined with
18
19 399 Pembrolizumab each year in Centre Léon Bérard (Lyon), we plan to include 30 patients over a 18
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21 400 months period. This number will be sufficient to assess if the planned exercise dose is safe and
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23 401 tolerable in this target patient population, and the sample size falls within the range of sample sizes
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25 402 recommended in the literature for feasibility trials (59).
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32 404 Although the main objective is to study the feasibility of physical exercise prior to the infusion of
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34 405 treatments, the evaluation of the biological objectives requires randomization to have reference
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36 406 measures. We have chosen to unbalance the randomization (2:1) so that more patients will benefit
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38 407 from the intervention proposed in the ERICA study.
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43 409 **STATISTICAL METHODS**
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45 410 All statistical analyses will be on an exploratory basis on all data from study subjects. Given the limited
46
47 411 sample size, non-parametric tests will be performed. Qualitative data will be presented using their
48
49 412 frequencies and percentages. Quantitative data will be presented using the number of observations,
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51 413 mean, standard deviation, median, minimum, and maximum. For both types of data, the number of
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53 414 missing data will be presented if necessary.
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56 415 The feasibility of the ERICA study will be assessed at the end of the intervention (M3) in the exercise
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58 416 group only, according to the adherence rate by calculating the ratio of the number of acute physical
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3 417 exercise sessions performed to the number of acute physical exercise sessions planned before the
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5 418 immunotherapy/chemotherapy. The tolerability will be assessed by the relative dose intensity of
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7 419 exercise. The safety will be assessed by the occurrence of adverse events related to the physical
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9 420 exercise intervention. The acceptability (i.e. the proportion of patients who accept to participate in the
10
11 421 study among eligible patients) and the attrition (i.e. the proportion of patients who withdraw their
12
13 422 participation from the study among patients initially enrolled) will be calculated. In the exercise group,
14
15 423 the acceptability of the activity tracker, the observance of the home-walking program, and the safety
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17 424 of the intervention (the number, type, and timing of adverse events that occurred) will be assessed.
18
19 425 The evolution of the different repeated measures (PA level, anthropometric, HRQoL, fatigue, sleep
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21 426 quality, and sarcopenia) at inclusion, 3 and 6 months will be represented by graphs and compared by
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23 427 non-parametric ANOVAs (performed on ranks).

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27 428 Progression-free survival will be measured from the date of randomization until the date of event
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29 429 defined as either progression or death from any cause whichever occurs first. Participants with no
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31 430 event at the time of the analysis will be censored at the date of the last available tumour assessment.
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33 431 The results will allow to formulate the hypotheses and determine sample size for a subsequent
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35 432 multicenter randomized efficacy study.

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37 433 Statistical analyses will be carried out using R statistical software (60).
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39 434 **DATA MONITORING**

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41 435 The database for clinical data will be managed using REDCap (Research Electronic Data Capture)
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43 436 (61,62) software hosted at CLB. The access to the database will be secured (personal ID and password
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45 437 required) with different levels of security depending on the role within the study. The investigator will
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47 438 have access to the final dataset.

48 439 **PATIENT AND PUBLIC INVOLVEMENT**

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50 440 Prior to the present study, we administrated a questionnaire to lung cancer patients to collect their
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52 441 experience and preferences in terms of physical activity to practice during cancer treatments. The
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54 442 results were used to develop the ERICA physical activity intervention. As it is a feasibility study, the
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3 443 findings will be used to adjust the intervention if necessary for the purpose of an efficacy randomised
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5 444 controlled trial. Global findings will be disseminated to participants at the end of the study if they wish.
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7 445 **ETHICAL AND DISSEMINATION**

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10 446 The study protocol has been approved by a French ethics committee CPP Ile de France II (IDRCB:
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12 447 20.09.04.65226) and the study database has been reported to the National Commission for Data
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14 448 Protection and Liberties (CNIL; reference number: 2016177). The study has been registered at
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16 449 reference number: NCT04676009.
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18 19 20 450 **DISCUSSION**

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22 451 To our knowledge, ERICA is the first study to assess the feasibility and effects of acute physical exercise
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24 452 performed within one hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-
25
26 453 based doublet) infusion in mNSCLC patients. Despite therapeutic advances, notably immunotherapy
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28 454 combined with chemotherapy, the prognosis of many patients with mNSCLC continues to be poor, and
29
30 455 disease burden, cachexia, comorbidities, and treatment side effects lead to deconditioning and
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32 456 adversely affect exercise capacity in people with advanced NSCLC (17,63–66). Conversely, evidence
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34 457 from meta-analyses suggests that exercise training in patients with advanced lung cancer could be
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36 458 feasible and safe with no serious adverse events reported and may improve or avoid the decline of
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38 459 physical capacity (15,67). However, the evidence regarding the benefits of exercise in mNSCLC patients
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40 460 remains limited and there is a lack of widespread awareness of the benefits of maintaining physical
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42 461 activity in this particular population (66,68–70). Furthermore, the high prevalence of comorbidities in
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44 462 mNSCLC patients, which may be exacerbated by the direct and indirect effects of cancer treatment,
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46 463 led to exclude patients at risk of cardiovascular events from studies (i.e. history of cardiovascular
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48 464 disease; abnormal electrocardiogram and/or echocardiography) or undernutrition.
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52 465 Based on preclinical evidence of exercise in modulating the efficacy of cancer therapy, the present
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54 466 study assesses the feasibility of acute exercise of submaximal intensity in the target population.
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56 467 Current evidence on the benefits of physical exercise in cancer patients mainly stems from
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58 468 interventions performed either between the chemotherapy cycles or after end of treatment. Yet, a
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3 469 feasibility study in patients with various tumours, mostly breast cancer, reported that exercise (i.e. 20
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5 470 min of supervised low-intensity cycling) during chemotherapy infusion appears to be safe and feasible
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7 471 (30). To prescribe a safe and efficacious intensity of acute exercise intervention, we decided to realize
8
9 472 a submaximal cardiopulmonary exercise test with a continuous gas exchange analysis. Because of the
10
11 473 comorbidities, the tumour location, and the lack of information about high intensity exercise effects,
12
13 474 the present study targets acute exercise of submaximal intensity.

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16 475 Home-based exercises are a beneficial approach to reducing symptoms and improving exercise
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18 476 capacity as well as the quality of life in patients with NSCLC (71). The unsupervised home-based walking
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20 477 program in the intervention arm aims to increase the level of physical activity in patients with mNSCLC
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22 478 and their cardiorespiratory fitness and physical capacity to perform acute physical exercise prior to
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24 479 chemo-immunotherapy infusion (15). Also, chronic exercise can favourably modulate inflammation
25
26 480 and immune-related factors (19,72). Activity trackers are innovative tools increasingly used to promote
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28 481 an active lifestyle and to objectively measure the PA level of cancer patients (73–75). Trackers have
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30 482 been used in a randomized controlled trial to encourage patients with mNSCLC to maintain their PA by
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32 483 recommending a targeted number of steps (76). In a previous study by the team, the use of activity
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34 484 trackers has shown pertinent results in women with metastatic breast cancer (77,78). The combination
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36 485 of these two intervention modalities (acute exercise and unsupervised walking programme) allows us
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38 486 to offer an intervention adapted to this population in order to have sufficient physiological stimulation
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40 487 to observe changes in the immune system.

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43 488 The first challenge we need to overcome is that the study concerns only one stage of lung cancer and
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45 489 participants must be eligible to immunotherapy. Next, we are looking at the intervention
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47 490 reproducibility in other institutions. Finally, it is a feasibility study with a limited sample size (n=30).
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49 491 We plan to conduct a randomised controlled trial to address the various limitations of the present
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51 492 study: larger sample size, multiple lung cancer stages, and to carry out the study in several hospital
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53 493 institutions.

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59 494 **INNOVATION AND STUDY RELEVANCE**
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3 495 The ERICA study will provide clinical, physical, and psychosocial insights into the feasibility of acute
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5 496 exercise prior to first-line chemo-immunotherapy infusion in patients with mNSCLC. In particular,
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7 497 exploratory data on the safety and tolerability of the proposed exercise dose and schedule in the target
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9 498 patient population will be obtained. This feasibility study will further generate preliminary data on the
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11 499 acute physiological, immune, and metabolic response to the achieved exercise dose in patients with
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13 500 mNSCLC. The ERICA study will provide valuable information to design a large-scale adequately
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15 501 powered randomized controlled trial to assess the efficacy on clinically important endpoints (e.g.
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17 502 progression free survival) in patients with mNSCLC receiving first-line chemo-immunotherapy.
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23 504 **DECLARATIONS**

25 505 **CONSENT FOR PUBLICATION**

27 506 Not applicable

30 507 **AVAILABILITY OF DATA AND MATERIAL**

32 508 Not applicable

34 509 **COMPETING INTERESTS**

36 510 The authors declare no competing interests.

39 511 **AUTHORS' CONTRIBUTIONS**

41 512 MG, OP, BF, VP, PM and MP designed the trial and obtained funding. MG, OP, BF, VP, MP and LD
42
43 513 developed the study protocol. BF, PM and MP contributed to the medical part of the protocol. MV,
44
45 514 TW, CC and MCC brought their immunologic expertise. PS brought his biological expertise. MG, OP
46
47 515 fulfilled administrative procedures for this project. MG, OP, BF and VP wrote this manuscript. All the
48
49 516 authors reviewed and contributed to the final version of the manuscript.

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524 **REFERENCES**

- 525 1. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung
526 cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*.
527 2018;29:iv192–237.
- 528 2. ASCO. Lung Cancer - Non-Small Cell - Statistics [Internet]. Cancer.Net. 2021 [cited 2021 Jul 3].
529 Available from: <https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics>
- 530 3. Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, et al. Updated Analysis
531 From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated
532 Metastatic Nonsquamous Non–Small-Cell Lung Cancer. *JCO*. 2020;JCO.19.03136.
- 533 4. Low JL, Walsh RJ, Ang Y, Chan G, Soo RA. The evolving immuno-oncology landscape in advanced
534 lung cancer: first-line treatment of non-small cell lung cancer. *Ther Adv Med Oncol* [Internet]. 2019 [cited 2019
535 Nov 5];11. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6716180/>
- 536 5. Brahmer JR, Rodríguez-Abreu D, Robinson AG, Hui R, Csósz T, Fülöp A, et al. Health-related quality-
537 of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024):
538 a multicentre, international, randomised, open-label phase 3 trial. *The Lancet Oncology*. 2017 Dec;18(12):1600–
539 9.
- 540 6. Polanski J, Jankowska-Polanska B, Rosinczuk J, Chabowski M, Szymanska-Chabowska A. Quality of
541 life of patients with lung cancer. *Onco Targets Ther*. 2016;9:1023–8.
- 542 7. Camps C, del Pozo N, Blasco A, Blasco P, Sirera R. Importance of Quality of Life in Patients with Non–
543 Small-Cell Lung Cancer. *Clinical Lung Cancer*. 2009;10(2):83–90.
- 544 8. Garassino MC, Gadgeel S, Esteban E, Felip E, Speranza G, Domine M, et al. Patient-reported outcomes
545 following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated,
546 metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised,
547 placebo-controlled, phase 3 trial. *The Lancet Oncology*. 2020;21(3):387–97.
- 548 9. Steffen McLouth LE, Lycan TW, Levine BJ, Gabbard J, Ruiz J, Farris M, et al. Patient-Reported
549 Outcomes From Patients Receiving Immunotherapy or Chemoimmunotherapy for Metastatic Non–Small-Cell
550 Lung Cancer in Clinical Practice. *Clinical Lung Cancer*. 2019;21(3):255-263.e4.
- 551 10. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions
552 and distinctions for health-related research. *Public Health Rep*. 1985;100(2):126–31.
- 553 11. Hwang C-L, Yu C-J, Shih J-Y, Yang P-C, Wu Y-T. Effects of exercise training on exercise capacity in

- 1
2
3 554 patients with non-small cell lung cancer receiving targeted therapy. *Support Care Cancer*. 2012;20(12):3169–77.
- 4
5 555 12. Chen H-M, Tsai C-M, Wu Y-C, Lin K-C, Lin C-C. Effect of walking on circadian rhythms and sleep
6
7 556 quality of patients with lung cancer: a randomised controlled trial. *Br J Cancer*. 2016;115(11):1304–12.
- 8
9 557 13. Dhillon HM, Bell ML, van der Ploeg HP, Turner JD, Kabourakis M, Spencer L, et al. Impact of physical
10
11 558 activity on fatigue and quality of life in people with advanced lung cancer: a randomized controlled trial. *Annals*
12
13 559 *of Oncology*. 2017;28(8):1889–97.
- 14
15 560 14. Zhang L-L, Wang S-Z, Chen H-L, Yuan A-Z. Tai Chi Exercise for Cancer-Related Fatigue in Patients
16
17 561 With Lung Cancer Undergoing Chemotherapy: A Randomized Controlled Trial. *Journal of Pain and Symptom*
18
19 562 *Management*. 2016;51(3):504–11.
- 20
21 563 15. Peddle-McIntyre CJ, Singh F, Thomas R, Newton RU, Galvão DA, Cavalheri V. Exercise training for
22
23 564 advanced lung cancer. *Cochrane Lung Cancer Group*, editor. *Cochrane Database of Systematic Reviews* [Internet].
24
25 565 2019 [cited 2019 Sep 17]; Available from: <http://doi.wiley.com/10.1002/14651858.CD012685.pub2>
- 26
27 566 16. Quist M, Adamsen L, Rørth M, Laursen JH, Christensen KB, Langer SW. The Impact of a
28
29 567 Multidimensional Exercise Intervention on Physical and Functional Capacity, Anxiety, and Depression in Patients
30
31 568 With Advanced-Stage Lung Cancer Undergoing Chemotherapy. *Integr Cancer Ther*. 2015;14(4):341–9.
- 32
33 569 17. Avancini A, Sartori G, Gkoutakos A, Casali M, Trestini I, Tregnago D, et al. Physical Activity and
34
35 570 Exercise in Lung Cancer Care: Will Promises Be Fulfilled? *The Oncologist* [Internet]. 2019;n/a(n/a). Available
36
37 571 from: <https://theoncologist.onlinelibrary.wiley.com/doi/abs/10.1634/theoncologist.2019-0463>
- 38
39 572 18. *Activité physique. Prévention et traitement des maladies chroniques* Éditions EDP Sciences, janvier 2019,
40
41 573 824 pages, Collection Expertise collective ISBN 978-2-7598-2328-4 [Internet]. [cited 2021 Jul 4]. Available from:
42
43 574 [https://www.inserm.fr/sites/default/files/2019-](https://www.inserm.fr/sites/default/files/2019-02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf)
44
45 575 [02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf](https://www.inserm.fr/sites/default/files/2019-02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf)
- 46
47 576 19. Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour
48
49 577 microenvironment. *Nature Reviews Cancer*. 2017;17(10):620–32.
- 50
51 578 20. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system.
52
53 579 *J Sport Health Sci*. 2019;8(3):201–17.
- 54
55 580 21. Bigley AB, Rezvani K, Chew C, Sekine T, Pistillo M, Crucian B, et al. Acute exercise preferentially
56
57 581 redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and
58
59 582 multiple myeloma target cells. *Brain, Behavior, and Immunity*. 2014;39:160–71.
- 60
583 22. Idorn M, Hojman P. Exercise-Dependent Regulation of NK Cells in Cancer Protection. *Trends in*

- 1
2
3 584 Molecular Medicine. 2016;22(7):565–77.
4
5 585 23. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al. Voluntary Running
6
7 586 Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution.
8
9 587 Cell Metabolism. 2016;23(3):554–62.
10
11 588 24. Wadley AJ, Cullen T, Vautrinot J, Keane G, Bishop NC, Coles SJ. High intensity interval exercise
12
13 589 increases the frequency of peripheral PD-1+ CD8+ central memory T-cells and soluble PD-L1 in humans. Brain,
14
15 590 Behavior, & Immunity - Health. 2020;3:100049.
16
17 591 25. Pedersen BK, Hoffman-Goetz L. Exercise and the Immune System: Regulation, Integration, and
18
19 592 Adaptation. Physiological Reviews. 2000;80(3):1055–81.
20
21 593 26. Wiggins JM, Opoku-Acheampong AB, Baumfalk DR, Siemann DW, Behnke BJ. Exercise and the Tumor
22
23 594 Microenvironment: Potential Therapeutic Implications. Exercise and Sport Sciences Reviews. 2018;46(1):56–64.
24
25 595 27. McCullough DJ, Stabley JN, Siemann DW, Behnke BJ. Modulation of Blood Flow, Hypoxia, and
26
27 596 Vascular Function in Orthotopic Prostate Tumors During Exercise. J Natl Cancer Inst [Internet]. 2014 [cited 2020
28
29 597 Jan 8];106(4). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3982888/>
30
31 598 28. Schadler KL, Thomas NJ, Galie PA, Bhang DH, Roby KC, Addai P, et al. Tumor vessel normalization
32
33 599 after aerobic exercise enhances chemotherapeutic efficacy. Oncotarget. 2016;7(40):65429–40.
34
35 600 29. Schumacher O, Galvão DA, Taaffe DR, Chee R, Spry N, Newton RU. Exercise modulation of tumour
36
37 601 perfusion and hypoxia to improve radiotherapy response in prostate cancer. Prostate Cancer Prostatic Dis. 2021
38
39 602 Mar;24(1):1–14.
40
41 603 30. Thomas VJ, Seet-Lee C, Marthick M, Cheema BS, Boyer M, Edwards KM. Aerobic exercise during
42
43 604 chemotherapy infusion for cancer treatment: a novel randomised crossover safety and feasibility trial. Support
44
45 605 Care Cancer. 2020;28(2):625–32.
46
47 606 31. Kerrigan K. A pilot study of aerobic exercise performed in breast cancer patients during chemotherapy
48
49 607 infusion. | Journal of Clinical Oncology [Internet]. 2010 [cited 2020 Aug 11]. Available from:
50
51 608 https://ascopubs.org/doi/10.1200/jco.2010.28.15_suppl.e19527
52
53 609 32. Ashcraft KA, Warner AB, Jones LW, Dewhirst MW. Exercise as Adjunct Therapy in Cancer. Seminars
54
55 610 in Radiation Oncology. 2018;29(1):16–24.
56
57 611 33. Martín-Ruiz A, Fiuza-Luces C, Rincón-Castanedo C, Fernández-Moreno D, Martínez-Martínez E,
58
59 612 Martín-Acosta P, et al. Benefits of exercise and immunotherapy in a murine model of human non–small-cell lung
60
613 613 carcinoma. 2020;16.

- 1
2
3 614 34. Alexandre P. Haute Autorité de santé. 2019;142.
- 4
5 615 35. Macmillan Cancer Support. Physical activity in patients with metastatic bone disease: Guidance for
6
7 616 healthcare professionals. 2018 [Internet]. [cited 2021 Jul 4]. Available from:
8
9 617 [https://cdn.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/1784-10061/physical-activity-for-](https://cdn.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/1784-10061/physical-activity-for-people-with-metastatic-bone-disease-guidance-tcm9-326004)
10
11 618 [people-with-metastatic-bone-disease-guidance-tcm9-326004](https://cdn.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/1784-10061/physical-activity-for-people-with-metastatic-bone-disease-guidance-tcm9-326004)
- 12
13 619 36. Senesse P, Bachmann P, Bensadoun RJ, Besnard I, Bourdel-Marchasson I, Bouteloup C, et al. Nutrition
14
15 620 chez le patient adulte atteint de cancer : textes courts. *Nutrition Clinique et Métabolisme*. 2012;26(4):151–8.
- 16
17 621 37. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on
18
19 622 nutrition in cancer patients. *Clinical Nutrition*. 2017;36(1):11–48.
- 20
21 623 38. Tudor-Locke C, Craig CL, Aoyagi Y, Bell RC, Croteau KA, De Bourdeaudhuij I, et al. How many
22
23 624 steps/day are enough? For older adults and special populations. *Int J Behav Nutr Phys Act*. 2011;8(1):80.
- 24
25 625 39. Borg G, Hassmén P, Lagerström M. Perceived exertion related to heart rate and blood lactate during arm
26
27 626 and leg exercise. *Europ J Appl Physiol*. 1987;56(6):679–85.
- 28
29 627 40. Kilgour RD, Vigano A, Trutschnigg B, Lucar E, Borod M, Morais JA. Handgrip strength predicts survival
30
31 628 and is associated with markers of clinical and functional outcomes in advanced cancer patients. *Support Care*
32
33 629 *Cancer*. 2013 Dec;21(12):3261–70.
- 34
35 630 41. Anand A, Gajra A. Hand Grip Dynamometry as Prognostic and Predictive Marker in Older Patients With
36
37 631 Cancer. *J Gerontol Geriatr Res* [Internet]. 2018 [cited 2020 Jun 19];07(03). Available from:
38
39 632 [https://www.omicsonline.org/open-access/hand-grip-dynamometry-as-prognostic-and-predictive-marker-in-](https://www.omicsonline.org/open-access/hand-grip-dynamometry-as-prognostic-and-predictive-marker-in-older-patients-with-cancer-2167-7182-1000471-102218.html)
40
41 633 [older-patients-with-cancer-2167-7182-1000471-102218.html](https://www.omicsonline.org/open-access/hand-grip-dynamometry-as-prognostic-and-predictive-marker-in-older-patients-with-cancer-2167-7182-1000471-102218.html)
- 42
43 634 42. Trutschnigg B, Kilgour RD, Reinglas J, Rosenthal L, Hornby L, Morais JA, et al. Precision and reliability
44
45 635 of strength (Jamar vs. Biodex handgrip) and body composition (dual-energy X-ray absorptiometry vs.
46
47 636 bioimpedance analysis) measurements in advanced cancer patients. *Appl Physiol Nutr Metab*. 2008;33(6):1232–
48
49 637 9.
- 50
51 638 43. Amireault S, Godin G, Lacombe J, Sabiston CM. The use of the Godin-Shephard Leisure-Time Physical
52
53 639 Activity Questionnaire in oncology research: a systematic review. *BMC Med Res Methodol* [Internet]. 2015 [cited
54
55 640 2020 May 28];15. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4542103/>
- 56
57 641 44. Binay Safer V, Safer U. Usefulness and limitations of single-slice computed tomography analysis at the
58
59 642 third lumbar region in the assessment of sarcopenia. *Critical Care*. 2013 Nov 20;17(6):466.
- 60
643 45. Boutin RD, Yao L, Canter RJ, Lenchik L. Sarcopenia: Current Concepts and Imaging Implications.

- 1
2
3 644 American Journal of Roentgenology. 2015 Sep;205(3):W255–66.
4
5 645 46. Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, et al. Appendicular skeletal muscle
6
7 646 mass: measurement by dual-photon absorptiometry. *Am J Clin Nutr.* 1990 Aug;52(2):214–8.
8
9 647 47. Miller KD, Jones E, Yanovski JA, Shankar R, Feuerstein I, Falloon J. Visceral abdominal-fat
10
11 648 accumulation associated with use of indinavir. *Lancet.* 1998 Mar 21;351(9106):871–5.
12
13 649 48. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation
14
15 650 of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol.*
16
17 651 1998 Jul;85(1):115–22.
18
19 652 49. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise
20
21 653 approach to quantification of body composition in cancer patients using computed tomography images acquired
22
23 654 during routine care. *Appl Physiol Nutr Metab.* 2008;33(5):997–1006.
24
25 655 50. Thibault R, Goujon N, Le Gallic E, Clairand R, Sébille V, Vibert J, et al. Use of 10-point analogue scales
26
27 656 to estimate dietary intake: A prospective study in patients nutritionally at-risk. *Clinical Nutrition.* 2009;28(2):134–
28
29 657 40.
30
31 658 51. Hjermstad MJ, Fossa SD, Bjordal K, Kaasa S. Test/retest study of the European Organization for
32
33 659 Research and Treatment of Cancer Core Quality-of-Life Questionnaire. *JCO.* 1995;13(5):1249–54.
34
35 660 52. Koller M, Shamieh O, Hjermstad MJ, Hornslien K, Young T, Chalk T, et al. Psychometric properties of
36
37 661 the updated EORTC module for assessing quality of life in patients with lung cancer (QLQ-LC29): an
38
39 662 international, observational field study. *The Lancet Oncology.* 2020;21(5):723–32.
40
41 663 53. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular
42
43 664 supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials.
44
45 665 *European Journal of Cancer.* 1994;30(5):635–42.
46
47 666 54. Weis J, Tomaszewski KA, Hammerlid E, Ignacio Arraras J, Conroy T, Lanceley A, et al. International
48
49 667 Psychometric Validation of an EORTC Quality of Life Module Measuring Cancer Related Fatigue (EORTC QLQ-
50
51 668 FA12). *JNCI: Journal of the National Cancer Institute [Internet].* 2017 [cited 2020 May 28];109(5). Available
52
53 669 from: <https://academic.oup.com/jnci/article/doi/10.1093/jnci/djw273/2972669>
54
55 670 55. Savard M-H, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer
56
57 671 patients: INSOMNIA SEVERITY INDEX AND CANCER. *Psycho-Oncology.* 2005;14(6):429–41.
58
59 672 56. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: Psychometric Indicators to
60
673 673 Detect Insomnia Cases and Evaluate Treatment Response. *Sleep.* 2011;34(5):601–8.

- 1
2
3 674 57. Sass C, Dupré C, Giordanella JP, Girard F, Guenot C, Labbe É, et al. Le score Epices : un score individuel
4
5 675 de précarité. Construction du score et mesure des relations avec des données de santé, dans une population de 197
6
7 676 389 personnes. 2006;4.
- 8
9 677 58. Jones LW. Precision Oncology Framework for Investigation of Exercise As Treatment for Cancer. *JCO*.
10
11 678 2015;33(35):4134–7.
- 12
13 679 59. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being
14
15 680 undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC*
16
17 681 *Med Res Methodol*. 2013;13(1):104.
- 18
19 682 60. R Core Team (2020). — European Environment Agency [Internet]. [cited 2021 Jul 4]. Available from:
20
21 683 [https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-development-](https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-development-core-team-2006)
22
23 684 [core-team-2006](https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-development-core-team-2006)
- 24
25 685 61. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture
26
27 686 (REDCap)—A metadata-driven methodology and workflow process for providing translational research
28
29 687 informatics support. *Journal of Biomedical Informatics*. 2009;42(2):377–81.
- 30
31 688 62. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O’Neal L, et al. The REDCap consortium:
32
33 689 Building an international community of software platform partners. *Journal of Biomedical Informatics*.
34
35 690 2019;95:103208.
- 36
37 691 63. Jones LW. Physical Activity and Lung Cancer Survivorship. In: Courneya KS, Friedenreich CM, editors.
38
39 692 *Physical Activity and Cancer* [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010 [cited 2021 Mar
40
41 693 28]. p. 255–74. (Recent Results in Cancer Research; vol. 186). Available from:
42
43 694 http://link.springer.com/10.1007/978-3-642-04231-7_11
- 44
45 695 64. Quist M, Langer SW, Lillelund C, Winther L, Laursen JH, Christensen KB, et al. Effects of an exercise
46
47 696 intervention for patients with advanced inoperable lung cancer undergoing chemotherapy: A randomized clinical
48
49 697 trial. *Lung Cancer*. 2020;145:76–82.
- 50
51 698 65. Nadler M, Bainbridge D, Tomasone J, Cheifetz O, Juergens RA, Sussman J. Oncology care provider
52
53 699 perspectives on exercise promotion in people with cancer: an examination of knowledge, practices, barriers, and
54
55 700 facilitators. *Support Care Cancer*. 2017;25(7):2297–304.
- 56
57 701 66. Wilk M, Kepski J, Kepska J, Casselli S, Szmít S. Exercise interventions in metastatic cancer disease: a
58
59 702 literature review and a brief discussion on current and future perspectives. *BMJ Support Palliat Care*.
60
703 2020;10(4):404–10.

- 1
2
3 704 67. Singh B, Spence R, Steele ML, Hayes S, Toohey K. Exercise for Individuals With Lung Cancer: A
4
5 705 Systematic Review and Meta-Analysis of Adverse Events, Feasibility, and Effectiveness. *Semin Oncol Nurs*.
6
7 706 2020;36(5):151076.
8
9 707 68. Granger CL, Parry SM, Edbrooke L, Abo S, Leggett N, Dwyer M, et al. Improving the delivery of physical
10
11 708 activity services in lung cancer: A qualitative representation of the patient's perspective. *European Journal of*
12
13 709 *Cancer Care*. 2019;28(1):e12946.
14
15 710 69. Dittus KL, Gramling RE, Ades PA. Exercise interventions for individuals with advanced cancer: A
16
17 711 systematic review. *Preventive Medicine*. 2017;104:124–32.
18
19 712 70. Heywood R, McCarthy AL, Skinner TL. Safety and feasibility of exercise interventions in patients with
20
21 713 advanced cancer: a systematic review. *Support Care Cancer*. 2017 Oct;25(10):3031–50.
22
23 714 71. Yang M, Liu L, Gan C, Qiu L, Jiang X, He X, et al. Effects of home-based exercise on exercise capacity,
24
25 715 symptoms, and quality of life in patients with lung cancer: A meta-analysis. *European Journal of Oncology*
26
27 716 *Nursing*. 2020;49:101836.
28
29 717 72. Nieman DC, Lila MA, Gillitt ND. Immunometabolism: A Multi-Omics Approach to Interpreting the
30
31 718 Influence of Exercise and Diet on the Immune System. *Annu Rev Food Sci Technol*. 2019;10:341–63.
32
33 719 73. Gresham G, Schrack J, Gresham LM, Shinde AM, Hendifar AE, Tuli R, et al. Wearable activity monitors
34
35 720 in oncology trials: Current use of an emerging technology. *Contemporary Clinical Trials*. 2018;64:13–21.
36
37 721 74. Haberlin C, O'Dwyer T, Mockler D, Moran J, O'Donnell DM, Broderick J. The use of eHealth to promote
38
39 722 physical activity in cancer survivors: a systematic review. *Support Care Cancer*. 2018;26(10):3323–36.
40
41 723 75. Turner RR, Steed L, Quirk H, Greasley RU, Saxton JM, Taylor SJ, et al. Interventions for promoting
42
43 724 habitual exercise in people living with and beyond cancer. *Cochrane Database Syst Rev* [Internet]. 2018 [cited
44
45 725 2019 Oct 29];2018(9). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6513653/>
46
47 726 76. Naito T, Mitsunaga S, Miura S, Tatematsu N, Inano T, Mouri T, et al. Feasibility of early multimodal
48
49 727 interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer. *J Cachexia Sarcopenia*
50
51 728 *Muscle*. 2019;10(1):73–83.
52
53 729 77. Delrieu L, Anota A, Trédan O, Freyssenet D, Maire A, Canada B, et al. Design and methods of a national,
54
55 730 multicenter, randomized and controlled trial to assess the efficacy of a physical activity program to improve health-
56
57 731 related quality of life and reduce fatigue in women with metastatic breast cancer: ABLE02 trial. *BMC Cancer*
58
59 732 [Internet]. 2020 [cited 2021 Apr 15];20. Available from:
60 733 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7333295/>

1
2
3 734 78. Delrieu L, Martin A, Touillaud M, Pérol O, Morelle M, Febvey-Combes O, et al. Sarcopenia and serum
4
5 735 biomarkers of oxidative stress after a 6-month physical activity intervention in women with metastatic breast
6
7 736 cancer: results from the ABLE feasibility trial. *Breast Cancer Res Treat* [Internet]. 2021 [cited 2021 Jun 13];
8
9 737 Available from: <https://link.springer.com/10.1007/s10549-021-06238-z>

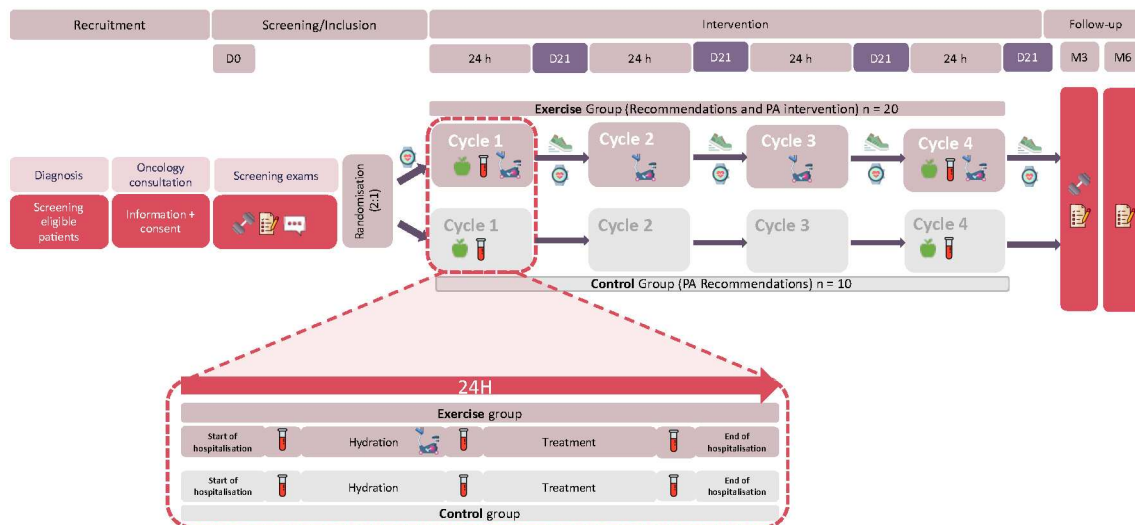
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15 740 **Figure 1:** Flow chart of the ERICA study, France (original flow chart)

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For peer review only





SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract : page 2 Methods : page 18
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	Abstract : page 2 Declaration line :page 18
Funding	4	Sources and types of financial, material, and other support	Funding: page 28
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1 Author's contribution : page 28
	5b	Name and contact information for the trial sponsor	Page 1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Funding : page 28
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Data monitoring : page 17
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction : page 2
	6b	Explanation for choice of comparators	Page 6
Objectives	7	Specific objectives or hypotheses	Page 6

1 2 3 4 5 6 7	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 6
8	Methods: Participants, interventions, and outcomes			
9 10 11 12 13	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 6 Page 7
14 15 16 17 18	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 6-7
19 20 21 22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 8-10
23 24 25 26 27		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
28 29 30 31 32		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 9-10
33 34 35		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 8
36 37 38 39 40 41 42 43 44 45	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 10-16
46 47 48 49 50 51	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Page 10
52 53 54 55 56 57	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 16
58 59 60	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 7-8

Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 17
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 10-16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be	Page 16-17

		found, if not in the protocol	
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 16-17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Page 16-17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Page 17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A no interim analyses are planned
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Page 17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 18
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Abstract : page 2 Study population : page 6 Recruitment: page 7-8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 17

1 2 3 4	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 28
5 6 7 8	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 18
9 10 11 12	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
13 14 15 16 17 18 19 20 21	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Page 2
22 23		31b	Authorship eligibility guidelines and any intended use of professional writers	Page 2
24 25 26 27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
28	Appendices			
29 30 31 32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Consent form, see supplementary file
33 34 35 36 37	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Page 15

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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.