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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  
8 26 symptoms linked to disease and treatment which may further impair the patient's overall condition.  
9  
10 27 In addition to its beneficial effects on quality of life and fatigue, physical exercise may improve  
11  
12 28 response to treatment, notably due to its known effects on the immune system. The ERICA study has  
13  
14 29 been designed to assess the feasibility of an acute physical exercise realized immediately prior to  
15  
16 30 immune-chemotherapy infusion in patients with mNSCLC and to examine the effects of this  
17  
18 31 intervention on clinical, physical, psycho-social and biological parameters.  
19

20  
21 32 **Methods and analysis.** ERICA is a prospective, monocentric, randomized controlled, open-label  
22  
23 33 feasibility study conducted at the \*\*\*\* \* Comprehensive Cancer Center (France). Thirty patients  
24  
25 34 newly diagnosed with mNSCLC will be randomized (2:1 ratio) to the “exercise” or the “control” group.  
26  
27 35 At baseline and during the last treatment cycle, participants in both groups will receive Physical Activity  
28  
29 36 recommendations, and two nutritional assessments and nutrition recommendations. In the exercise  
30  
31 37 group, participants will receive a 3-months program consisting of an acute physical exercise one hour  
32  
33 38 prior to immune-chemotherapy infusion, and a home-based walking program with an activity tracker.  
34  
35 39 The acute exercise consists in interval training at a submaximal intensity for 35 minutes. Clinical,  
36  
37 40 physical, biological, and psychosocial parameters will be assessed at baseline, at 3 months and 6  
38  
39 41 months after study inclusion. Biological measures will include analyses of immune, inflammatory,  
40  
41 42 metabolic, oxidative stress biomarkers and molecular profiling.  
42  
43  
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45

46 43 **Ethics and dissemination.** The study protocol was approved by the French ethics committee  
47  
48 44 (Comité de protection des personnes Ile de France II, N°ID-RCB 20.09.04.65226, 8<sup>th</sup> December  
49  
50 45 2020). The study is registered on ClinicalTrials.gov (NCT number: NCT04676009). All  
51  
52 46 participants will have to sign and date an informed consent form. The findings will be  
53  
54 47 disseminated in peer-reviewed journals and academic conferences.  
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3 48 **KEYWORDS:** Non-small-cell lung cancer, Metastatic, Exercise, Immunotherapy, Chemotherapy,  
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5 49 Immunology

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7  
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 performed within one hour prior to immunotherapy (pembrolizumab) and chemotherapy  
14 (platinum-based doublet) infusion in mNSCLC patients.  
15 53  
16  
17 54  
18  
19 55 • Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption  
20 condition during a submaximal endurance test on a cycle-ergometer at baseline and this test  
21 will allow to individualize the intensity of the acute physical exercise program.  
22 56  
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25  
26 58 • The feasibility study assesses the acute physiological, immune, and metabolic response to an  
27 acute moderate physical exercise in patients with mNSCLC.  
28 59  
29  
30 The home-based walking program in the intervention arm aims to increase the level of physical  
31 activity in patients with mNSCLC and their cardiorespiratory fitness and physical capacity to  
32 perform acute physical exercise prior to chemo-immunotherapy infusion.  
33 60  
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35 61  
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37 62  
38  
39 63 • The study concerns only one stage of lung cancer, participants must be eligible to  
40 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  
10 94 mobilization of the peripheral activity of the sub-population of CD56<sup>dim</sup> NK cells during acute physical  
11  
12 95 exercise of light to moderate intensity (20,21). A preclinical study reported that exercise training  
13  
14 96 (voluntary running), through activation of epinephrine and IL-6, led to selective NK cell mobilization  
15  
16 97 and limited tumour growth of several types of tumours (melanomas, liver, and lung mouse models)  
17  
18 98 (22). In a recent study, the increase in PD-1+ CD8+ T cells was observed after a single exercise session  
19  
20 99 (23). At the level of the adaptive immune system, acute exercise results in transient biphasic changes,  
21  
22  
23 100 i.e. increase of circulating lymphocytes during and immediately after exercise, followed by a transient  
24  
25 101 decrease of blood lymphocytes below baseline level during recovery from exercise (1 hour), thought  
26  
27 102 to be due to a redistribution of immune cells to peripheral tissues, including tumours, before return to  
28  
29 103 basal level within few hours (22,24). Moreover, recent preclinical studies suggested that physical  
30  
31 104 exercise performed during chemotherapy infusion may have additional physiological benefits such as  
32  
33 105 increased blood flow leading to through improved intra-tumoral perfusion and enhanced drug delivery  
34  
35 106 (25–27). However, most of the available evidence on the benefits of physical exercise in cancer  
36  
37 107 patients has been observed in interventions performed either after the treatment or during the  
38  
39 108 interval between the chemotherapy cycles. Only two studies have evaluated the feasibility of low-  
40  
41 109 intensity physical exercises during the chemotherapy infusion without adverse events, interference  
42  
43 110 with chemotherapy, or exacerbation in symptoms (28,29). Recently, it has been suggested in  
44  
45 111 preclinical studies that exercise performed during chemotherapy infusion could lead to improve  
46  
47 112 perfusion of solid tumours, mitigating tumour hypoxia, and enhancing drug delivery to tumours  
48  
49 113 (25,26,30). Similarly, by its effect on immune regulation, physical exercise prior to infusion may  
50  
51 114 potentiate the effect of the immunotherapy. Recent preclinical evidence has suggested a beneficial  
52  
53 115 effect of exercise in addition to immunotherapy (anti-PD-1 immunotherapy) in a murine model of  
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55 116 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  
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7 119 an acute exercise program performed immediately prior to immunotherapy and chemotherapy  
8  
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  $\geq 18$  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  $\leq 2$ ; 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  
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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  $\geq 18$  years and  $< 70$ : Body Mass Index (BMI)  $\leq 17$ , 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  $\geq 70$  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  $\leq 8$  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  
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35 159 3 months prior to enrolment; 8) Stage IV Chronic obstructive pulmonary disease (forced expiratory  
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37 160 volume in one second (FEV<sub>1</sub>)  $< 30\%$ ).  
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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  
48  
49 164 cancer board meetings. During a medical consultation before treatment initiation, an oncologist will  
50  
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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9

10 172

## 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  
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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  
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26 179 vs. female) and histology (squamous vs. non-squamous).  
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## 30 31 181 **INTERVENTION**

### 32 33 182 *Treatment protocol*

34  
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/m<sup>2</sup>) with B9-B12 vitamin supplementation; carboplatin (AUC 6) plus paclitaxel  
40  
41 186 (200 mg/m<sup>2</sup>) 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*

48  
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,  
52  
53 191 walking as much as possible and sitting as little as possible (WCRF, 2018). We have chosen to follow  
54  
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  
4  
5 195 stairs whenever possible, walking to local shops).

6  
7 196 *Nutritional recommendations*

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9  
10 197 All patients will receive nutritional recommendations during the 1<sup>st</sup> and 4<sup>th</sup> treatment cycle. The  
11  
12 198 nutritional recommendations and will include: energy intake of 30 kcal/kg body weight/day for  
13  
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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19 201

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21 202 **Exercise Group**

22  
23 203 *Acute physical exercise protocol prior to immunotherapy and chemotherapy infusion*

24  
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  
48  
49 216 decrease the load to 110% of VT1. In case of exercise-induced desaturation (≤ 4% of the measured  
50  
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  
6  
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  
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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  
20  
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  
24  
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  
28  
29 233 be collected by regular sync with the mobile phone application (Fitbit®) of the activity tracker or by a  
30  
31 234 step logbook.  
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39 236 **EVALUATIONS**

40  
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  
44  
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**

51  
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,  
55  
56 244 lifestyle (alcohol consumption and smoking status) will be collected at baseline. All clinical data will be  
57  
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*

11  
12 250 Anthropometric data including body weight (kilogram), height (centimeter, cm), waist (cm) and hip  
13  
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  
20 254 weight in kilograms divided by the square of the height in meters.  
21  
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23 255

24  
25 256 *Physical fitness*

26  
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).  
52  
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54  
55 270 The lower strength muscular function will be evaluated by measuring the maximum isometric strength  
56  
57 271 of the knee extensors (DFS II Series Digital; Force Gauges Chatillon, Largo, FL, USA). Participants will be  
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2  
3 272 seated on a chair with the knee joint at 90°, arms crossed over the chest, and the dynamometer  
4  
5 273 attached to the ankle. Participants were advised to stretch their leg as hard as possible within 3  
6  
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.  
19  
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23 281

#### 24 282 *Physical activity level*

25  
26  
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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48 292

#### 49 293 *Body composition and sarcopenia*

50  
51  
52 294 Body composition and sarcopenia will be analysed using the Computed Tomography (CT) scans. CT  
53  
54 295 scan cross-section at the level of the 3rd lumbar vertebra represents the method of choice for  
55  
56 296 assessment of sarcopenia in the oncology setting given that CT scan as part of routine cancer diagnostic  
57  
58 297 procedures is largely available (40). The thresholds for identifying muscle range from -29 to +150 HU,  
59  
60

1  
2  
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  
13 329 All scores will be transformed into a scale from 0 to 100, with a higher score indicating a higher degree  
14  
15 330 of fatigue.

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17 33118  
19 332 *Sleep quality*

20  
21 333 The perceived quality of sleep will be assessed by the Insomnia Severity Index which measures the  
22  
23 334 severity of insomnia. The questionnaire consists of 7 items rated on a 5-point scale ranging from 0  
24  
25 335 ("none") to 4 ("very severe") (50,51). This self-questionnaire will evaluate the severity of the patient's  
26  
27 336 sleep difficulties (initial, maintenance, and morning insomnia), the degree of sleep dissatisfaction, the  
28  
29 337 level of interference with daily functioning, the degree of appearance of sleep difficulties, and the level  
30  
31 338 of anxiety related to insomnia. The total score of the items varies between 0 and 28. A high score  
32  
33 339 indicates greater sleep difficulties.

34  
35 34036  
37 341 *Social vulnerability*

38  
39 342 Social deprivation will be assessed using the EPICES score (Evaluation of Deprivation and Inequalities  
40  
41 343 in Health Examination Centres) (52). The EPICES score will be obtained by adding up the points of the  
42  
43 344 11 binary questions ("Yes"/"No") of the self-questionnaire. This score ranges from 0 "no  
44  
45 345 precariousness" to 100 "highest precariousness" with the threshold for deprivation at 30.

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47 34648  
49 347 *Biomarkers of the immune system, inflammation, sarcopenia, and oxidative stress*

50  
51 348 Blood samples will be collected during the first and last (forth) treatment cycle: in the exercise group,  
52  
53 349 samples will be collected before exercise (S1), after exercise (S2), and 12 hours after the start of  
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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  
20 358 of immunity, sarcopenia, and inflammation will be analysed. We will measure i) immune biomarkers  
21  
22 359 (NK cells, B lymphocytes, T lymphocytes, monocytes, sub-populations of dendritic cells on frozen  
23  
24 360 PBMC); ii) plasma biomarkers of sarcopenia and inflammation (Myostatin, Activin, Cortisol, Tumor  
25  
26 361 Necrosis Factor- $\alpha$ , Interferon- $\gamma$ , Interleukine-1 $\beta$ , Interleukine-6, Follistatin, Growth Differentiation  
27  
28 362 Factor 5, Bone morphogenetic protein 14, GDF15, Interleukine-10, Interleukine-15, NH3, Aminogram,  
29  
30 363 C-reactive protein, insulin); and iii) plasma oxidative stress (Superoxide dismutase, catalase,  
31  
32 364 malondialdehyde, glutathione peroxidase, Xanthine Myeloperoxidase, and Xanthine oxidase). Finally,  
33  
34 365 the blood samples will be also used to analyse the glucose (OneTouch Verio®) and lactate (LACTATE  
35  
36 366 PRO II) metabolism by a mobile device. Patients will be asked to complete a questionnaire regarding  
37  
38 367 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  $\geq 3$ ) 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  $\geq 3$   
53  
54 373 toxicities related to chemotherapy and immunotherapy will be calculated as the ratio of "delivered"  
55  
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  
10 379 program performed prior to the infusion of treatments in mNSCLC patients, to assess if this planned  
11  
12 380 exercise dose is safe and tolerable in this target patient population(53). In the context of a feasibility  
13  
14 381 study without a concrete hypothesis and in absence of previous studies in this population, the sample  
15  
16 382 size was defined empirically. Taking into account the number of mNSCLC patients who receive first line  
17  
18 383 chemotherapy (i.e. pemetrexed-platinum or taxol-platinum) combined with Pembrolizumab each year  
19  
20 384 in \*\*\*, we plan to include 30 patients over a 18 months period. This number will be sufficient to assess  
21  
22  
23 385 if the planned exercise dose is safe and tolerable in this target patient population, and the sample size  
24  
25 386 falls within the range of sample sizes recommended in the literature for feasibility trials (54).  
26  
27  
28 387

29  
30 388 Although the main objective is to study the feasibility of physical exercise prior to the infusion of  
31  
32 389 treatments, the evaluation of the biological objectives requires randomization to have reference  
33  
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**  
42

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  
55  
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  
4  
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  
8  
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  
14  
15 408 that occurred) will be assessed.

16  
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).

23  
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.

34  
35  
36 417 Statistical analyses will be carried out using R statistical software (55).

#### 37 38 39 418 **DATA MONITORING**

40  
41 419 The database for clinical data will be managed using REDCap (Research Electronic Data Capture)  
42  
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**

51  
52 424 Prior to the present study, we administrated a questionnaire to lung cancer patients to collect their  
53  
54 425 experience and preferences in terms of physical activity to practice during cancer treatments. The  
55  
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.  
6

### 7 429 **ETHICAL AND DISSEMINATION**

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9  
10 430 The study protocol has been approved by a French ethics committee CPP Ile de France II (IDRCB:  
11  
12 431 20.09.04.65226) and the study database has been reported to the National Commission for Data  
13  
14 432 Protection and Liberties (CNIL; reference number: 2016177). The study has been registered at  
15  
16 433 reference number: NCT04676009.  
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### 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  
25  
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.  
53  
54 451 Current evidence on the benefits of physical exercise in cancer patients mainly stems from  
55  
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  
6  
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  
49  
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  
14  
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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3 690 **DECLARATIONS**

4  
5 691 **CONSENT FOR PUBLICATION**

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7 692 Not applicable

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10 693 **AVAILABILITY OF DATA AND MATERIAL**

11  
12 694 Not applicable

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14 695 **COMPETING INTERESTS**

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16 696 The authors declare no competing interests.

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19 697 **AUTHORS' CONTRIBUTIONS**

20  
21 698 MG, OP, BF, VP, PM and MP designed the trial and obtained funding. MG, OP, BF, VP and MP developed  
22  
23 699 the study protocol. BF, PM and MP contributed to the medical part of the protocol. MV, TW, CC and  
24  
25 700 MCC brought their immunologic expertise. PS brought his biological expertise. MG, OP fulfilled  
26  
27 701 administrative procedures for this project. MG, OP, BF and VP wrote this manuscript. All the authors  
28  
29 702 reviewed and contributed to the final version of the manuscript.

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31  
32 703 **FUNDING**

33  
34 704 The study was supported by Integrated Cancer Research Sites of Lyon : LYriCAN (LYon Recherche  
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37  
38 706 the Doctoral School EDISS ED 205 Sciences, Health, Interdisciplinary.

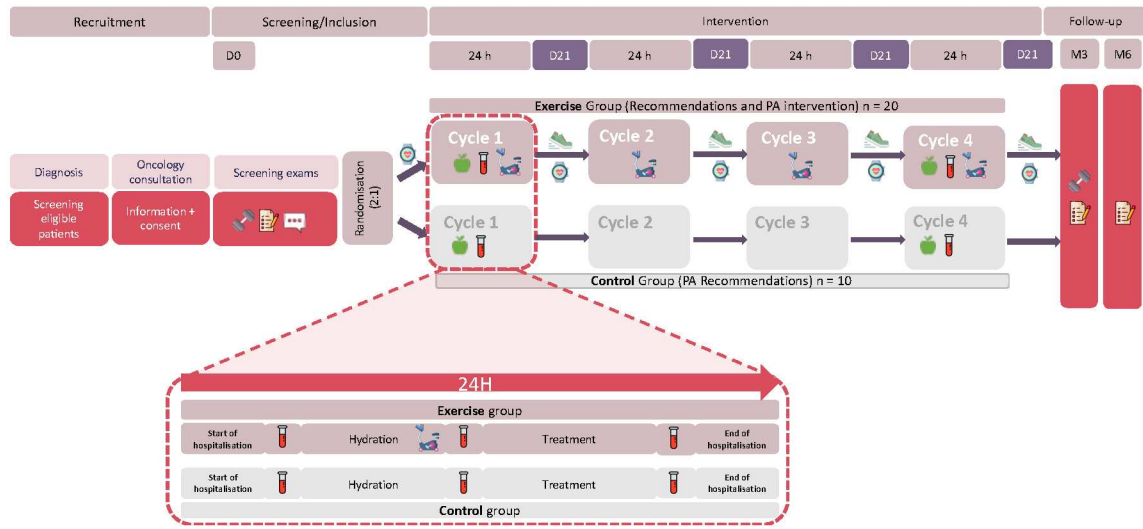
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41 707 **ACKNOWLEDGEMENTS**

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43 708 The authors would like to thank the LYriCAN for the funding for the biological analyses.

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48 710 **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	Line
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	<b>From line 1 to line 3</b>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<b>Abstract : Line 52-53; Methods : line 432-435</b>
	2b	All items from the World Health Organization Trial Registration Data Set	<b>N/A</b>
Protocol version	3	Date and version identifier	<b>Abstract : line 52 Declaration line 433</b>
Funding	4	Sources and types of financial, material, and other support	<b>Funding: line 706-708</b>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<b>Line : 4 to line 22; Author's contribution : line 700-704</b>
	5b	Name and contact information for the trial sponsor	<b>Line 23-25</b>
	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	<b>Funding : line 706-708</b>
	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)	<b>Data monitoring : line 426 to 429</b>
<b>Introduction</b>			
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	<b>Introduction : line 27 to 34</b>
	6b	Explanation for choice of comparators	<b>Line 123 to line 134</b>
Objectives	7	Specific objectives or hypotheses	<b>Line 123 to line 134</b>



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	<b>Methods: Participants, interventions, and outcomes</b>			
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	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Line 188 to 241
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)	Line 213 to 214 Line 229 to 231 Line 232 to 234
33 34 35		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

<b>Methods: Assignment of interventions (for controlled trials)</b>			
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	<b>Line 181 to 186</b>
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	<b>N/A</b>
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<b>Line 427 to 428</b>
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<b>N/A</b>
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<b>N/A</b>
<b>Methods: Data collection, management, and analysis</b>			
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	<b>Line 244 to 381</b>
	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	<b>Line 232 to 234</b>
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	<b>Line 427 to 429</b>
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be	<b>Line 400 to 424</b>

1		found, if not in the protocol	
2			
3	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<b>Line 400 to 424</b>
4			
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)	<b>Line 400 to 424</b>
6			
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9			
10	<b>Methods: Monitoring</b>		
11			
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			<b>Line 426 to 429</b>
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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			<b>N/A</b>
23			<b>no interim analyses are planned</b>
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			<b>Line 426 to 429</b>
27			
28			
29			
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			<b>Line 432 to 434</b>
32			
33			
34	<b>Ethics and dissemination</b>		
35			
36	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
37			<b>Line 432 to 435</b>
38			
39			
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			<b>N/A</b>
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			<b>Abstract : line 54</b>
48			<b>Study population : line 149</b>
49			<b>Recruitment: line 172-173</b>
50			
51			
52			
53		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
54			<b>N/A</b>
55			
56			
57	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality
58			<b>Line 434</b>
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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	<b>Line 697</b>
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	<b>Line 428-429</b>
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	<b>N/A</b>
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	<b>line 54-55</b>
	31b	Authorship eligibility guidelines and any intended use of professional writers	<b>line 54-55</b>
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<b>N/A</b>
<b>Appendices</b>			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<b>Consent form, see supplementary file</b>
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	<b>Line 355 to 374</b>

\*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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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 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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**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, 8<sup>th</sup> 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.



1  
2  
3 49 **KEYWORDS:** Non-small-cell lung cancer, Metastatic, Exercise, Immunotherapy, Chemotherapy,  
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5 50 Immunology

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7 51 **Word count:** 5344

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10 52 **Strengths and limitations of this study.**

- 11  
12  
13 53 • This study is the first to assess the feasibility effects of acute physical exercise performed  
14  
15 54 within one hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-  
16  
17 55 based doublet) infusion in mNSCLC patients.
- 18  
19 56 • Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption  
20  
21 57 condition during a submaximal endurance test on a cycle-ergometer at baseline and this test  
22  
23 58 will allow individualisation of the intensity of the acute physical exercise program.
- 24  
25 59 • The feasibility study assesses the acute physiological, immune, and metabolic response to a  
26  
27 60 supervised acute moderate intensity physical exercise session in patients with mNSCLC.
- 28  
29 61 The unsupervised home-based walking program in the intervention arm aims to increase the  
30  
31 62 level of physical activity in patients with mNSCLC and their cardiorespiratory fitness and  
32  
33 63 physical capacity to perform acute physical exercise prior to chemo-immunotherapy infusion.
- 34  
35 64 • The study concerns only one stage of lung cancer, participants must be eligible to  
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37 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

1  
2  
3 92 changes caused by acute exercise i.e., a single physical exercise bout, and cancer treatments(19).  
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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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9  
10 95 seems to improve immunosurveillance (20). Acute physical exercise leads to a rapid increase in the  
11  
12 96 mobilization of the peripheral activity of the sub-population of CD56<sup>dim</sup> NK cells during acute physical  
13  
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)  
19  
20  
21 100 (23). In a recent study, the increase in PD-1+ CD8+ T cells was observed after a single exercise session  
22  
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  
26  
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  
30  
31 105 basal level within a few hours (23,25). Moreover, recent preclinical studies suggested that physical  
32  
33 106 exercise performed during chemotherapy infusion may have additional physiological benefits such as  
34  
35 107 increase the blood flow leading to improved intra-tumoral perfusion and enhanced drug delivery (26–  
36  
37 108 28). However, most of the available evidence on the benefits of physical exercise in cancer patients  
38  
39 109 has been observed in interventions performed either after the treatment or during the interval  
40  
41 110 between the chemotherapy cycles(29). Only two studies have evaluated the feasibility of low-intensity  
42  
43 111 physical exercises during the chemotherapy infusion without adverse events, interference with  
44  
45 112 chemotherapy, or exacerbation in symptoms (29,30). Recently, it has been suggested in preclinical  
46  
47 113 studies that exercise performed during chemotherapy infusion could lead to improved perfusion of  
48  
49 114 solid tumours, mitigating tumour hypoxia, and enhancing drug delivery to tumours (26,27,31).  
50  
51 115 Similarly, by its effect on immune regulation, physical exercise prior to infusion may potentiate the  
52  
53 116 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).  
6  
7 119 Based on these findings, the main objective of the ERICA (Exercise inteReaction Immunotherapy  
8  
9 120 Chemotherapy and cAncer) feasibility study is to evaluate the feasibility of a supervised acute physical  
10  
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  
14  
15 123 or paclitaxel-carboplatin for squamous cell carcinoma) in first-line treatment of metastatic NSCLC  
16  
17 124 patients, and to assess if this planned exercise dose is safe and tolerable in this target patient  
18  
19 125 population. The secondary objectives are to evaluate the effects of the supervised acute exercise  
20  
21 126 before first-line treatment administration combined with an unsupervised home-based walking  
22  
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  
26  
27 129 completion rate, 9) related treatment toxicities, and 10) progression-free survival. Furthermore, this  
28  
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

137 *Insert Figure 1*

### 138 **STUDY POPULATION**

#### 139 *Inclusion criteria*

140 Participants will have to meet all of the following eligibility criteria: 1) aged  $\geq 18$  and  $< 80$  years; 2)  
141 diagnosed with a histologically confirmed metastatic NSCLC without EGFR mutation/ALK  
142 rearrangement; 3) eligible to receive first-line chemotherapy according to histology (pemetrexed-cis-  
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  $\leq 2$ ; 5) able to engage in PA attested by a medical certificate by an oncologist;  
6  
7 145 and 6) provide a dated and signed informed consent form before study enrolment.  
8  
9

#### 10 146 *Exclusion criteria*

11  
12 147 Patients will not be eligible in at least one of the following cases: 1) bone metastases with risk of  
13  
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  $\geq 18$  years and  $< 70$ : Body Mass Index (BMI)  $\leq 17$ , 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  $\geq 70$  years: BMI  $< 18$ , weight loss  $\geq 10\%$  in 1 month or  $\geq 15\%$  in 6 months, or  
29  
30 156 serum albumin  $< 30$  g/l) (33); 5) severe anaemia (haemoglobin  $\leq 8$  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  
39  
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  
43  
44 163 volume in one second (FEV<sub>1</sub>)  $< 30\%$ ).  
45  
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49

#### 50 164 **RECRUITMENT**

51  
52 165 Participants will be recruited in Centre Léon Bérard, Lyon, France from December 2020. Eligible  
53  
54 166 patients will be screened systematically based on electronic medical record during weekly  
55  
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  
6  
7 171 Status (PS) and Blood Pressure, (2) echocardiography and electrocardiogram performed by a  
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9  
10 172 cardiologist, and (3) for patients with diabetes, measurement of glycated haemoglobin. If these  
11  
12 173 investigations confirm the patient's eligibility, the patient will be included in the study (D0). The end  
13  
14 174 date for this study is planned in January 2023.

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## 18 176 **RANDOMIZATION**

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20  
21 177 At inclusion (D0), patients will be randomly assigned (ratio 2:1) to (i) the exercise group to receive PA  
22  
23 178 and nutrition recommendations; a supervised acute physical exercise prior each immuno-  
24  
25 179 chemotherapy infusion and an unsupervised home-based walking program with an activity tracker or  
26  
27  
28 180 (ii) the control group to receive PA and nutrition recommendations only.

29  
30 181 Randomization will be stratified using a dynamic minimization algorithm with two factors: sex (male  
31  
32 182 vs. female) and histology (squamous vs. non-squamous).

33  
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## 36 184 **INTERVENTION**

### 37 185 *Treatment protocol*

38  
39  
40 186 All patients in both exercise and control groups of this study will receive usual care and the same  
41  
42  
43 187 standard treatment protocol: pembrolizumab (200 mg) combined with carboplatin (AUC 5) plus  
44  
45 188 pemetrexed (500 mg/m<sup>2</sup>) with B9-B12 vitamin supplementation; carboplatin (AUC 6) plus paclitaxel  
46  
47 189 (200 mg/m<sup>2</sup>) every 3 weeks for 4 cycles; before pembrolizumab maintenance in squamous cell  
48  
49  
50 190 carcinoma or pembrolizumab plus pemetrexed maintenance for non-squamous cell carcinoma.

### 51 191 *Physical Activity recommendations*

52  
53  
54 192 Although there are no specific PA recommendations for patients with mNSCLC, all patients will be  
55  
56  
57 193 informed of the PA recommendations to be physically active as much as possible during the day,  
58  
59  
60 194 walking as much as possible and sitting as little as possible (WCRF, 2018). We have chosen to follow

1  
2  
3 195 the recommendations of the Macmillan Cancer Support guide released in 2018, advising patients with  
4  
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  
8  
9 198 stairs whenever possible, walking to local shops).

11  
12 199 *Nutritional recommendations*

13  
14 200 All patients will receive nutritional recommendations during the 1<sup>st</sup> and 4<sup>th</sup> treatment cycle. The  
15  
16 201 nutritional recommendations will include: energy intake of 30 kcal/kg body weight/day for patients  
17  
18 202 with BMI <30, or 25 kcal/kg body weight/day for patients with BMI ≥ 30, and protein intake of at least  
19  
20 203 1.2 g/kg body weight/day (35,36).

21  
22  
23 204 **Exercise Group**

24  
25 205 *Acute physical exercise protocol prior to immunotherapy and chemotherapy infusion*

26  
27 206 Patients in the "exercise" group will perform a supervised acute physical exercise bout during  
28  
29 207 hospitalization for treatment. It will be carried out 1 hour prior to the immunotherapy and  
30  
31 208 chemotherapy infusion, on a cycle ergometer (Monark Ergonomic 939 Novo) for each of the 4 cycles  
32  
33 209 of treatment foreseen. The physical exercise will be supervised by a clinical exercise physiologist with  
34  
35 210 experience in the oncology. The physical exercise consists of a 35-min acute interval training and will  
36  
37 211 be individualized based on the results of a submaximal endurance test performed on a cycle ergometer  
38  
39 212 by each patient (described below) prior to treatment (D0).

40  
41 213 Following a five-minute warm-up at 60% of Ventilation Threshold 1 (VT1), the participant will carry out  
42  
43 214 5 sets, alternating periods of 3 minutes at 70-80% of VT1 with 3 minutes at 110-120% of VT1 (≥ 35  
44  
45 215 Revolutions Per Minute (RPM)). The acute exercise intensity will be programmed according to the load  
46  
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  
50  
51 218 to cycle at the load corresponding to 120% of his VT1, the clinical exercise physiologist will decrease  
52  
53 219 the load to 110% of VT1. In case of exercise-induced desaturation (≥ 4% of the measured value at  
54  
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  
4  
5 222 receive written support materials at baseline (D0).

6  
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  
11  
12 225 unsupervised home-based walking program consisting of an individual goal of a number of steps per  
13  
14 226 day. Each patient will receive a Fitbit® Inspire activity tracker with an instruction to wear it continuously  
15  
16 227 during the intervention. They will be advised to achieve at least 6,000 daily steps which corresponds  
17  
18 228 to a physically active lifestyle in a patient population (37). Ten days after each treatment cycle, the  
19  
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  
25  
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  
29  
30 234 average number of steps in the previous week. Patients who do not reach 6,000 daily steps, will be  
31  
32 235 advised to gradually increase the target number of steps per day according to the patient's abilities.  
33  
34 236 Number of steps will be collected by regular sync with the mobile phone application (Fitbit®) of the  
35  
36 237 activity tracker or by a step logbook.  
37  
38  
39  
40  
41  
42

43 239 **EVALUATIONS**

44  
45 240 *Modalities*

46  
47  
48 241 The assessments of the repeated measures (PA level, anthropometric, HRQoL, fatigue, sleep quality,  
49  
50 242 and sarcopenia) in both groups will be performed before the first cycle of anti-neoplastic treatment  
51  
52 243 (baseline, D0), at the end of the 4 cycles of treatment (M3), and at 6 months after study inclusion (M6)  
53  
54 244 (Table 1).  
55  
56  
57  
58  
59  
60



245

246 Table 1. Data collection schedule for the ERICA study

	Screening	Inclusion D0	1 <sup>st</sup> cycle C1	4 <sup>th</sup> cycle C4	Month 3 M3	Month 6 M6
<b>Socio demographic and clinical data</b>						
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
<b>Physical evaluation</b>						
Anthropometrics		X			X	
Physical fitness ( <i>Cardiorespiratory fitness, strength tests</i> )		X			X	
<b>Self-reported outcomes</b>						
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	
<b>Biological assessments</b>						
Blood sample			X	X		
<b>Body composition</b>						
CT scan		X			X	X
<b>Exercise group</b>						
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.

254

255 *Anthropometric data*

1  
2  
3 256 Anthropometric data including body weight (kilogram), height (centimeter, cm), waist (cm) and hip  
4  
5 257 (cm) circumference will be collected. Waist circumference will be measured around the abdomen  
6  
7 258 midway between the last floating rib and the iliac crest. Hip circumference will be measured  
8  
9  
10 259 horizontally through the upper margin of the pubis. The body mass index is calculated as the body  
11  
12 260 weight in kilograms divided by the square of the height in meters.

13  
14 261

15  
16 262 *Physical fitness*

17  
18  
19 263 Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption ( $VO_2$ )  
20  
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  
28 267 of 5 watts each 30 seconds until VT1 will be reached. The clinical exercise physiologist will ensure that  
29  
30 268 the patient maintains a minimum pedalling frequency above 35 RPM throughout the test. HR,  
31  
32 269 ventilation (VE), oxygen saturation ( $SaO_2$ ),  $VO_2$ , and carbon dioxide production ( $VCO_2$ ) will be measured  
33  
34 270 by a gas analyser (MetaMax 3b, Cortex Biophysik, Leipzig, Germany) and continuously monitored. In  
35  
36  
37 271 addition, the perception of the difficulty and dyspnoea will be evaluated at the end of the test using  
38  
39 272 the Borg Rating Perceived Exertion questionnaire(38). The clinical exercise physiologist will stop the  
40  
41 273 test when the patient exceeded the VT1. The test will end with a 6-minute recovery phase. The VT1  
42  
43 274 will be determined graphically when the ventilatory equivalent of oxygen ( $VE/VO_2$ ) starts to increase  
44  
45 275 and will be confirmed by Respiratory Exchange Ratio that strictly exceeds 1 (Wasserman method).

46  
47  
48 276 The lower body muscular strength will be evaluated by measuring the maximum isometric strength of  
49  
50 277 the knee extensors (DFS II Series Digital; Force Gauges Chatillon, Largo, FL, USA). Participants will be  
51  
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  
57 280 seconds upon the instructor's signal. Only the dominant leg will be tested three times (with 2 minutes  
58  
59 281 rest between each contraction), and the best performance will be considered.

1  
2  
3 282 The maximum isometric upper limb strength will be measured by a hand dynamometer (Jamar Plus  
4  
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.  
13

14 287

#### 16 288 *Physical activity level*

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  
34  
35 297 the activity tracker (only in the intervention group).  
36  
37  
38

39 298

#### 41 299 *Body composition and sarcopenia*

43 300 Body composition and sarcopenia will be analysed using the Computed Tomography (CT) scans. CT  
44  
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,  
50  
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  
56  
57 307 Units (HU). A low SMD is defined by values below the threshold of 37.8 HU. An estimate of lean body  
58  
59  
60

1  
2  
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).

6  
7 310

8  
9  
10 311 *Nutrition*

11  
12 312 Dietary intake (24h recall, supplemented with patient preferences and habits), clinical (weight loss,  
13  
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).

19  
20  
21 316

22  
23 317 *Health-related quality of life*

24  
25 318 The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life  
26  
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  
34  
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  
42  
43 327 Life Questionnaire - Lung Cancer 13 (QLQ-LC13) (50,51). The QLQ-LC13 self-questionnaire is an  
44  
45 328 additional measure of the symptoms and side effects experienced by lung cancer patients who receive  
46  
47 329 non-surgical treatment.

48  
49  
50  
51 330

52  
53 331 *Fatigue*

54  
55 332 Fatigue will be assessed by the EORTC-QLQ module measuring cancer-related fatigue (EORTC QLQ-  
56  
57 333 FA12) (52). This self-questionnaire includes 12 items that assess physical, cognitive, and emotional  
58  
59  
60

1  
2  
3 334 fatigue related to cancer. Participants will respond on a Likert scale ranging from "not at all" to "a lot".  
4  
5 335 All scores will be transformed into a scale from 0 to 100, with a higher score indicating a higher degree  
6  
7 336 of fatigue.  
8  
9

10 337

11  
12 338 *Sleep quality*

13  
14 339 The perceived quality of sleep will be assessed by the Insomnia Severity Index which measures the  
15  
16 340 severity of insomnia. The questionnaire consists of 7 items rated on a 5-point scale ranging from 0  
17  
18 341 ("none") to 4 ("very severe") (53,54). This self-questionnaire will evaluate the severity of the patient's  
19  
20 342 sleep difficulties (initial, maintenance, and morning insomnia), the degree of sleep dissatisfaction, the  
21  
22 343 level of interference with daily functioning, the degree of appearance of sleep difficulties, and the level  
23  
24 344 of anxiety related to insomnia. The total score of the items varies between 0 and 28. A high score  
25  
26 345 indicates greater sleep difficulties.  
27  
28

29 346

30  
31  
32 347 *Social vulnerability*

33  
34 348 Social deprivation will be assessed using the EPICES score (Evaluation of Deprivation and Inequalities  
35  
36 349 in Health Examination Centres) (55). The EPICES score will be obtained by adding up the points of the  
37  
38 350 11 binary questions ("Yes"/"No") of the self-questionnaire. This score ranges from 0 "no  
39  
40 351 precariousness" to 100 "highest precariousness" with the threshold for deprivation at 30.  
41  
42

43 352

44  
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  
58  
59  
60

1  
2  
3 360 hour (maintained at 4°C before and during centrifugation). After the centrifuge, plasma will be  
4  
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  
8  
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- $\alpha$ , Interferon- $\gamma$ , Interleukin-1 $\beta$ , 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.  
31  
32  
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374

### 375 *Toxicities*

376 Severe treatment toxicities (grade  $\geq 3$ ) 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  $\geq 3$   
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  
10 389 receive first line chemotherapy (i.e. pemetrexed-platinum or taxol-platinum) combined with  
11  
12 390 Pembrolizumab each year in Centre Léon Bérard (Lyon), we plan to include 30 patients over a 18  
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  
20  
21 394

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

#### 33 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  
59  
60

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  
11  
12 416 The evolution of the different repeated measures (PA level, anthropometric, HRQoL, fatigue, sleep  
13  
14 417 quality, and sarcopenia) at inclusion, 3 and 6 months will be represented by graphs and compared by  
15  
16 418 non-parametric ANOVAs (performed on ranks).  
17  
18  
19 419 Progression-free survival will be measured from the date of randomization until the date of event  
20  
21 420 defined as either progression or death from any cause whichever occurs first. Participants with no  
22  
23 421 event at the time of the analysis will be censored at the date of the last available tumour assessment.  
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  
48  
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  
52  
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**

57  
58  
59  
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1  
2  
3 437 The study protocol has been approved by a French ethics committee CPP Ile de France II (IDRCB:  
4  
5 438 20.09.04.65226) and the study database has been reported to the National Commission for Data  
6  
7 439 Protection and Liberties (CNIL; reference number: 2016177). The study has been registered at  
8  
9  
10 440 reference number: NCT04676009.

## 11 12 13 441 **DISCUSSION**

14  
15 442 To our knowledge, ERICA is the first study to assess the feasibility and effects of acute physical exercise  
16  
17 443 performed within one hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-  
18  
19 444 based doublet) infusion in mNSCLC patients. Despite therapeutic advances, notably immunotherapy  
20  
21 445 combined with chemotherapy, the prognosis of many patients with mNSCLC continues to be poor, and  
22  
23 446 disease burden, cachexia, comorbidities, and treatment side effects lead to deconditioning and  
24  
25 447 adversely affect exercise capacity in people with advanced NSCLC (17,61–64). Conversely, evidence  
26  
27 448 from meta-analyses suggests that exercise training in patients with advanced lung cancer could be  
28  
29 449 feasible and safe with no serious adverse events reported and may improve or avoid the decline of  
30  
31 450 physical capacity (15,65). However, the evidence regarding the benefits of exercise in mNSCLC patients  
32  
33 451 remains limited and there is a lack of widespread awareness of the benefits of maintaining physical  
34  
35 452 activity in this particular population (64,66–68). Furthermore, the high prevalence of comorbidities in  
36  
37 453 mNSCLC patients, which may be exacerbated by the direct and indirect effects of cancer treatment,  
38  
39 454 led to exclude patients at risk of cardiovascular events from studies (i.e. history of cardiovascular  
40  
41 455 disease; abnormal electrocardiogram and/or echocardiography) or undernutrition.

42  
43 456 Based on preclinical evidence of exercise in modulating the efficacy of cancer therapy, the present  
44  
45 457 study assesses the feasibility of acute exercise of submaximal intensity in the target population.  
46  
47 458 Current evidence on the benefits of physical exercise in cancer patients mainly stems from  
48  
49 459 interventions performed either between the chemotherapy cycles or after end of treatment. Yet, a  
50  
51 460 feasibility study in patients with various tumours, mostly breast cancer, reported that exercise (i.e. 20  
52  
53 461 min of supervised low-intensity cycling) during chemotherapy infusion appears to be safe and feasible  
54  
55 462 (29). To prescribe a safe and efficacious intensity of acute exercise intervention, we decided to realize

1  
2  
3 463 a submaximal cardiopulmonary exercise test with a continuous gas exchange analysis. Because of the  
4  
5 464 comorbidities, the tumour location and the lack of information about high intensity exercise effects,  
6  
7 465 the present study targets acute exercise of submaximal intensity.  
8

9  
10 466 Home-based exercises are a beneficial approach to reducing symptoms and improving exercise  
11  
12 467 capacity as well as the quality of life in patients with NSCLC (69). The unsupervised home-based walking  
13  
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  
31  
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.  
35  
36  
37

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  
46  
47 483 study: larger sample size, multiple lung cancer stages, and to carry out the study in several hospital  
48  
49 484 institutions.  
50

#### 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  
55  
56 487 exercise prior to first-line chemo-immunotherapy infusion in patients with mNSCLC. In particular,  
57  
58 488 exploratory data on the safety and tolerability of the proposed exercise dose and schedule in the target  
59  
60

1  
2  
3 489 patient population will be obtained. This feasibility study will further generate preliminary data on the  
4  
5 490 acute physiological, immune, and metabolic response to the achieved exercise dose in patients with  
6  
7 491 mNSCLC. The ERICA study will provide valuable information to design a large-scale adequately  
8  
9  
10 492 powered randomized controlled trial to assess the efficacy on clinically important endpoints (e.g.  
11  
12 493 progression free survival) in patients with mNSCLC receiving first-line chemo-immunotherapy.  
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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  
22

23 713 developed the study protocol. BF, PM and MP contributed to the medical part of the protocol. MV,  
24

25 714 TW, CC and MCC brought their immunologic expertise. PS brought his biological expertise. MG, OP  
26

27 715 fulfilled administrative procedures for this project. MG, OP, BF and VP wrote this manuscript. All the  
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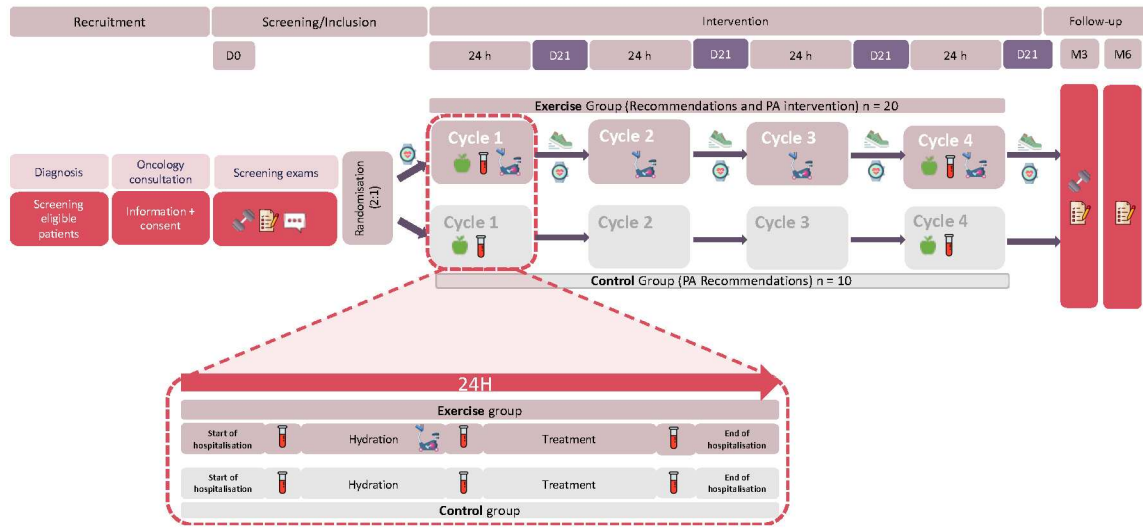
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48 724 **Figure 1:** Flow chart of the ERICA study, France (original flow chart)  
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	ItemNo	Description	Page
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	<b>Page 1</b>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<b>Abstract : page 2 Methods : page 18</b>
	2b	All items from the World Health Organization Trial Registration Data Set	<b>N/A</b>
Protocol version	3	Date and version identifier	<b>Abstract : page 2 Declaration line :page 18</b>
Funding	4	Sources and types of financial, material, and other support	<b>Funding: page 28</b>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<b>Page 1 Author's contribution : page 28</b>
	5b	Name and contact information for the trial sponsor	<b>Page 1</b>
	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	<b>Funding : page 28</b>
	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)	<b>Data monitoring : page 17</b>
<b>Introduction</b>			
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	<b>Introduction : page 2</b>
	6b	Explanation for choice of comparators	<b>Page 6</b>
Objectives	7	Specific objectives or hypotheses	<b>Page 6</b>

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	<b>Methods: Participants, interventions, and outcomes</b>			
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

<b>Methods: Assignment of interventions (for controlled trials)</b>			
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	<b>Page 8</b>
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	<b>N/A</b>
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<b>Page 17</b>
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<b>N/A</b>
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<b>N/A</b>
<b>Methods: Data collection, management, and analysis</b>			
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	<b>Page 10-16</b>
	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	<b>Page 10</b>
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	<b>Page 17</b>
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be	<b>Page 16-17</b>



1		found, if not in the protocol	
2			
3	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<b>Page 16-17</b>
4			
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)	<b>Page 16-17</b>
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10	<b>Methods: Monitoring</b>		
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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			<b>Page 17</b>
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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			<b>N/A</b>
23			<b>no interim analyses are planned</b>
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			<b>Page 17</b>
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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			<b>Page 18</b>
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34	<b>Ethics and dissemination</b>		
35			
36	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
37			<b>Page 18</b>
38			
39			
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			<b>N/A</b>
42			
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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			<b>Abstract : page 2</b>
48			<b>Study population : page 6</b>
49			<b>Recruitment: page 7-8</b>
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52		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
53			<b>N/A</b>
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56	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
57			<b>Page 17</b>
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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	<b>Appendices</b>			
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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Date Submitted by the Author:	15-Feb-2022
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<b>Primary Subject Heading</b>:	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**

4                   *Manon Gouez<sup>1,23</sup>, Olivia Pérol<sup>1,3</sup>, Maurice Pérol<sup>4</sup>, Christophe Caux<sup>5,6</sup>, Christine Ménétrier-Caux<sup>5,6</sup>,*  
5                   *Marine Villard<sup>7</sup>, Thierry Walzer<sup>7</sup>, Lidia Delrieu<sup>1,2</sup>, Pierre Saintigny<sup>5,8</sup>, Philippe Marijnen<sup>1</sup>, Vincent*  
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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.

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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.**

- 18  
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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  
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31 60 will allow individualisation of the intensity of the acute physical exercise program.
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34 61 • The feasibility study assesses the acute physiological, immune, and metabolic response to a  
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36 62 supervised acute moderate intensity physical exercise session in patients with mNSCLC.
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38 63 The unsupervised home-based walking program in the intervention arm aims to increase the  
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40 64 level of physical activity in patients with mNSCLC and their cardiorespiratory fitness and  
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42 65 physical capacity to perform acute physical exercise prior to chemo-immunotherapy infusion.
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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

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3 94 changes caused by acute exercise i.e., a single physical exercise bout, and cancer treatments(19).  
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5 95 Immunomodulatory effects of acute physical exercise involve immune cell mobilisation in blood such  
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7 96 as neutrophils, subsets of monocytes or lymphocytes involved in the host defence against tumours,  
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10 97 seems to improve immunosurveillance (20). Acute physical exercise leads to a rapid increase in the  
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12 98 mobilization of the peripheral activity of the sub-population of CD56<sup>dim</sup> NK cells during acute physical  
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14 99 exercise of light to moderate intensity (21,22). A preclinical study reported that exercise training  
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16 100 (voluntary running), through activation of epinephrine and IL-6, led to selective NK cell mobilization  
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18 101 and limited tumour growth of several types of tumours (melanomas, liver, and lung mouse models)  
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20 102 (23). In a recent study, the increase in PD-1+ CD8+ T cells was observed after a single exercise session  
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22 103 (24). At the level of the adaptive immune system, acute exercise results in transient biphasic changes,  
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24 104 i.e. increase of circulating lymphocytes during and immediately after exercise, followed by a transient  
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26 105 decrease of blood lymphocytes below baseline level during recovery from exercise (1 hour), thought  
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28 106 to be due to a redistribution of immune cells to peripheral tissues, including tumours, before return to  
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30 107 basal level within a few hours (23,25). Moreover, recent preclinical studies suggested that physical  
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32 108 exercise performed during chemotherapy infusion may have additional physiological benefits such as  
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34 109 increase the blood flow leading to improved intra-tumoral perfusion and enhanced drug delivery (26–  
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36 110 28). However, to date, the optimal timing, duration and intensity of exercise that is feasible and  
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38 111 produces clinically meaningful changes in tumour perfusion and immunomodulatory effects, needs to  
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40 112 be determined (29). Most of the available evidence on the benefits of physical exercise in cancer  
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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-  
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46 115 intensity physical exercises during the chemotherapy infusion without adverse events, interference  
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48 116 with chemotherapy, or exacerbation in symptoms (30,31). Recently, it has been suggested in  
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50 117 preclinical studies that exercise performed during chemotherapy infusion could lead to improved  
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52 118 perfusion of solid tumours, mitigating tumour hypoxia, and enhancing drug delivery to tumours  
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54 119 (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  
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5 121 effect of exercise in addition to immunotherapy (anti-PD-1 immunotherapy) in a murine model of  
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7 122 NSCLC, through increased necrosis and a decreased proliferative index of tumour cells (33).  
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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  
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14 125 exercise performed immediately prior to immunotherapy and chemotherapy infusion (i.e. a  
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16 126 combination of pembrolizumab and pemetrexed-cis- or carboplatin for non-squamous cell carcinoma  
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18 127 or paclitaxel-carboplatin for squamous cell carcinoma) in first-line treatment of metastatic NSCLC  
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20 128 patients, and to assess if this planned exercise dose is safe and tolerable in this target patient  
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23 129 population. The secondary objectives are to evaluate the effects of the supervised acute exercise  
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25 130 before first-line treatment administration combined with an unsupervised home-based walking  
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27 131 program, on 1) physical fitness, 2) PA level and sedentary lifestyle, 3) psychosocial factors (HRQoL and  
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29 132 fatigue), 4) sleep quality, 5) body composition, 6) sarcopenia, 7) treatment response, 8) treatment  
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31 133 completion rate, 9) related treatment toxicities, and 10) progression-free survival. Furthermore, this  
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33 134 feasibility study will generate data on the effect of this exercise intervention on immune, metabolic,  
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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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44 138 ERICA is a prospective, monocentric, randomized controlled, open-label feasibility study, conducted at  
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46 139 the Centre Léon Bérard Comprehensive Cancer Centre (Lyon, France).  
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49 140 *Insert Figure 1*

### 50 141 **STUDY POPULATION**

#### 51 142 *Inclusion criteria*

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54 143 Participants will have to meet all of the following eligibility criteria: 1) aged  $\geq 18$  and  $< 80$  years; 2)  
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56 144 diagnosed with a histologically confirmed metastatic NSCLC without EGFR mutation/ALK  
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58 145 rearrangement; 3) eligible to receive first-line chemotherapy according to histology (pemetrexed-cis-  
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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  $\leq 2$ ; 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  $\geq 18$  years and  $< 70$ : Body Mass Index (BMI)  $\leq 17$ , 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  $\geq 70$  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  $\leq 8$  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 (FEV<sub>1</sub>)  $< 30\%$ ).

#### 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  
172

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/m<sup>2</sup>) with B9-B12 vitamin supplementation; carboplatin (AUC 6) plus paclitaxel  
193 (200 mg/m<sup>2</sup>) 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 1<sup>st</sup> and 4<sup>th</sup> 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  
42  
43  
44  
45  
46  
47

## 48 244 **EVALUATIONS**

### 50 245 *Modalities*

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

250

251 Table 1. Data collection schedule for the ERICA study

	Screening	Inclusion D0	1 <sup>st</sup> cycle C1	4 <sup>th</sup> cycle C4	Month 3 M3	Month 6 M6
<b>Socio demographic and clinical data</b>						
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
<b>Physical evaluation</b>						
Anthropometrics		X			X	
Physical fitness ( <i>Cardiorespiratory fitness, strength tests</i> )		X			X	
<b>Self-reported outcomes</b>						
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	
<b>Biological assessments</b>						
Blood sample			X	X		
<b>Body composition</b>						
CT scan		X			X	X
<b>Exercise group</b>						
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

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  
28 272 of 5 watts each 30 seconds until VT1 will be reached. The clinical exercise physiologist will ensure that  
29  
30 273 the patient maintains a minimum pedalling frequency above 35 RPM throughout the test. HR,  
31  
32 274 ventilation (VE), oxygen saturation ( $SaO_2$ ),  $VO_2$ , and carbon dioxide production ( $VCO_2$ ) will be measured  
33  
34 275 by a gas analyser (MetaMax 3b, Cortex Biophysik, Leipzig, Germany) and continuously monitored. In  
35  
36 276 addition, the perception of the difficulty and dyspnoea will be evaluated at the end of the test using  
37  
38  
39 277 the Borg Rating Perceived Exertion questionnaire(39). The clinical exercise physiologist will stop the  
40  
41 278 test when the patient exceeded the VT1. The test will end with a 6-minute recovery phase. The VT1  
42  
43 279 will be determined graphically when the ventilatory equivalent of oxygen ( $VE/VO_2$ ) starts to increase  
44  
45 280 and will be confirmed by Respiratory Exchange Ratio that strictly exceeds 1 (Wasserman method).

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  
59 286 rest between each contraction), and the best performance will be considered.

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.

18 294

20 295 *Physical activity level*

22  
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).

41 305

43 306 *Lean body mass and sarcopenia*

45  
46  
47 307 Lean body mass and sarcopenia will be analysed using the Computed Tomography (CT) scans  
48  
49 308 systematically available from routine care. CT scan cross-section at the level of the 3rd lumbar vertebra  
50  
51 309 represents provides a reliable representation of the total body muscle mass and has therefore been  
52  
53 310 widely adopted for the detection of sarcopenia in cancer patients and allows assessment without  
54  
55 311 additional ionising radiation exposure given that CT scan as part of routine cancer diagnostic  
56  
57 312 procedures is largely available(44,45). The thresholds for identifying muscle range from -29 to +150  
58  
59  
60



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  $(LBM \text{ (kg)} = [(L3 \text{ Muscle measured by CT}$   
12  
13 318  $(\text{cm}^2) \times 0.3) + 6.06])$  (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.

1  
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 35537 356 *Social vulnerability*

38  
39 357 Social deprivation will be assessed using the EPICES score (Evaluation of Deprivation and Inequalities  
40  
41 358 in Health Examination Centres) (57). The EPICES score will be obtained by adding up the points of the  
42  
43 359 11 binary questions ("Yes"/"No") of the self-questionnaire. This score ranges from 0 "no  
44  
45 360 precariousness" to 100 "highest precariousness" with the threshold for deprivation at 30.

46  
47  
48 36149 362 *Biomarkers of the immune system, inflammation, sarcopenia, and oxidative stress*

50  
51 363 Blood samples will be collected during the first and last (forth) treatment cycle: in the exercise group,  
52  
53 364 samples will be collected before exercise (S1), after exercise (S2), and 12 hours after the start of

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- $\alpha$ , Interferon- $\gamma$ , Interleukin-1 $\beta$ , 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,  
32  
33 380 the blood samples will be also used to analyse the glucose (OneTouch Verio®) and lactate (LACTATE  
34  
35 381 PRO II) metabolism by a mobile device. Patients will be asked to complete a questionnaire regarding  
36  
37 382 the taking of antibiotics, anti-inflammatory, and antioxidants in the 48 hours prior to blood collection.  
38  
39  
40  
41  
42  
43  
44

383

#### 384 *Toxicities*

45  
46 385 Severe treatment toxicities (grade  $\geq 3$ ) will be noted according to the National Cancer Institute's  
47  
48 386 Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0. The number of rescheduled or  
49  
50 387 cancelled treatment sessions and the relative dose intensity (RDI) of participants with grade  $\geq 3$   
51  
52 388 toxicities related to chemotherapy and immunotherapy will be calculated as the ratio of "delivered"  
53  
54 389 to "expected" dose intensity.  
55  
56  
57  
58  
59  
60

1  
2  
3 391 **STATISTICAL ANALYSIS**

4  
5 392 **SAMPLE SIZE**

6  
7 393 The main objective of the current study is to evaluate the feasibility of an acute physical exercise  
8  
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,  
14  
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  
22  
23 401 tolerable in this target patient population, and the sample size falls within the range of sample sizes  
24  
25 402 recommended in the literature for feasibility trials (59).  
26  
27  
28  
29

30 403

31  
32 404 Although the main objective is to study the feasibility of physical exercise prior to the infusion of  
33  
34 405 treatments, the evaluation of the biological objectives requires randomization to have reference  
35  
36 406 measures. We have chosen to unbalance the randomization (2:1) so that more patients will benefit  
37  
38 407 from the intervention proposed in the ERICA study.  
39  
40

41 408

42  
43 409 **STATISTICAL METHODS**

44  
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.

54  
55  
56 415 The feasibility of the ERICA study will be assessed at the end of the intervention (M3) in the exercise  
57  
58 416 group only, according to the adherence rate by calculating the ratio of the number of acute physical  
59  
60

1  
2  
3 417 exercise sessions performed to the number of acute physical exercise sessions planned before the  
4  
5 418 immunotherapy/chemotherapy. The tolerability will be assessed by the relative dose intensity of  
6  
7 419 exercise. The safety will be assessed by the occurrence of adverse events related to the physical  
8  
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  
16  
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  
20  
21 426 quality, and sarcopenia) at inclusion, 3 and 6 months will be represented by graphs and compared by  
22  
23 427 non-parametric ANOVAs (performed on ranks).

24  
25  
26  
27 428 Progression-free survival will be measured from the date of randomization until the date of event  
28  
29 429 defined as either progression or death from any cause whichever occurs first. Participants with no  
30  
31 430 event at the time of the analysis will be censored at the date of the last available tumour assessment.  
32  
33 431 The results will allow to formulate the hypotheses and determine sample size for a subsequent  
34  
35 432 multicenter randomized efficacy study.

36  
37 433 Statistical analyses will be carried out using R statistical software (60).

#### 41 434 **DATA MONITORING**

42  
43 435 The database for clinical data will be managed using REDCap (Research Electronic Data Capture)  
44  
45 436 (61,62) software hosted at CLB. The access to the database will be secured (personal ID and password  
46  
47 437 required) with different levels of security depending on the role within the study. The investigator will  
48  
49 438 have access to the final dataset.

#### 50 439 **PATIENT AND PUBLIC INVOLVEMENT**

51  
52 440 Prior to the present study, we administrated a questionnaire to lung cancer patients to collect their  
53  
54 441 experience and preferences in terms of physical activity to practice during cancer treatments. The  
55  
56 442 results were used to develop the ERICA physical activity intervention. As it is a feasibility study, the  
57  
58  
59  
60

1  
2  
3 443 findings will be used to adjust the intervention if necessary for the purpose of an efficacy randomised  
4  
5 444 controlled trial. Global findings will be disseminated to participants at the end of the study if they wish.  
6

#### 7 445 **ETHICAL AND DISSEMINATION**

8  
9  
10 446 The study protocol has been approved by a French ethics committee CPP Ile de France II (IDRCB:  
11  
12 447 20.09.04.65226) and the study database has been reported to the National Commission for Data  
13  
14 448 Protection and Liberties (CNIL; reference number: 2016177). The study has been registered at  
15  
16 449 reference number: NCT04676009.  
17

#### 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  
23  
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  
27  
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  
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  
41  
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,  
45  
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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50  
51 465 Based on preclinical evidence of exercise in modulating the efficacy of cancer therapy, the present  
52  
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  
4  
5 470 min of supervised low-intensity cycling) during chemotherapy infusion appears to be safe and feasible  
6  
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  
17  
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  
21  
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  
27  
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  
31  
32 483 recommending a targeted number of steps (76). In a previous study by the team, the use of activity  
33  
34 484 trackers has shown pertinent results in women with metastatic breast cancer (77,78). The combination  
35  
36 485 of these two intervention modalities (acute exercise and unsupervised walking programme) allows us  
37  
38 486 to offer an intervention adapted to this population in order to have sufficient physiological stimulation  
39  
40 487 to observe changes in the immune system.

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42 488 The first challenge we need to overcome is that the study concerns only one stage of lung cancer and  
43  
44 489 participants must be eligible to immunotherapy. Next, we are looking at the intervention  
45  
46 490 reproducibility in other institutions. Finally, it is a feasibility study with a limited sample size (n=30).  
47  
48 491 We plan to conduct a randomised controlled trial to address the various limitations of the present  
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50 492 study: larger sample size, multiple lung cancer stages, and to carry out the study in several hospital  
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52 493 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  
11  
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.  
17  
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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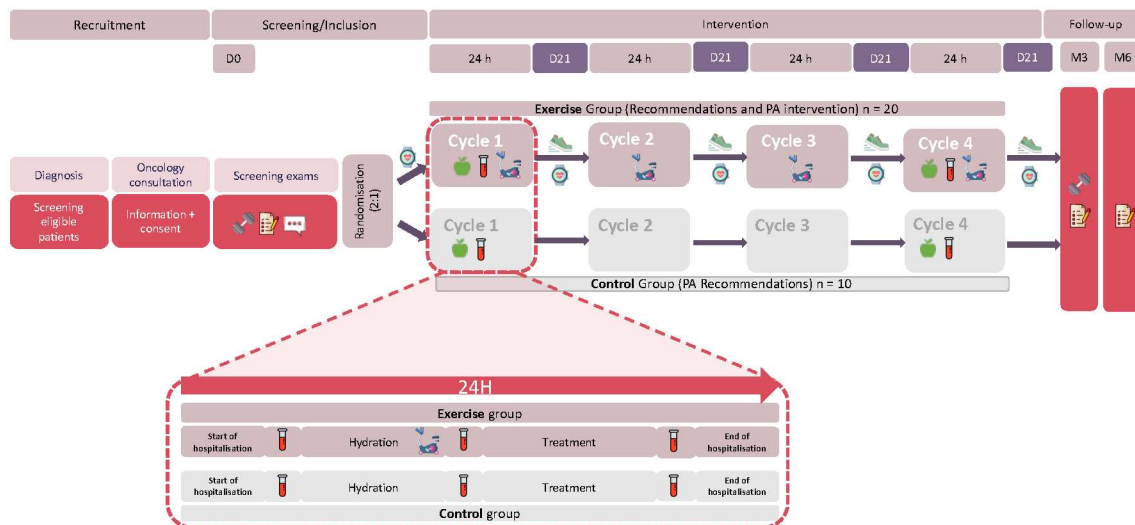


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24 737 **Figure 1:** Flow chart of the ERICA study, France (original flow chart)  
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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	ItemNo	Description	Page
<b>Administrative information</b>			
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
<b>Introduction</b>			
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	<b>Methods: Participants, interventions, and outcomes</b>			
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	<b>Methods: Assignment of interventions (for controlled trials)</b>			
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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	<b>Page 8</b>
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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	<b>N/A</b>
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<b>Page 17</b>
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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	<b>N/A</b>
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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	<b>N/A</b>
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32	<b>Methods: Data collection, management, and analysis</b>			
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	<b>Page 10-16</b>
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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	<b>Page 10</b>
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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	<b>Page 17</b>
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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	<b>Page 16-17</b>
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		found, if not in the protocol	
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<b>Page 16-17</b>
	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)	<b>Page 16-17</b>
<b>Methods: Monitoring</b>			
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	<b>Page 17</b>
	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	<b>N/A no interim analyses are planned</b>
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	<b>Page 17</b>
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<b>Page 18</b>
<b>Ethics and dissemination</b>			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<b>Page 18</b>
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)	<b>N/A</b>
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<b>Abstract : page 2 Study population : page 6 Recruitment: page 7-8</b>
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<b>N/A</b>
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	<b>Page 17</b>

1 2 3 4	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<b>Page 28</b>
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	<b>Page 18</b>
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	<b>N/A</b>
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	<b>Page 2</b>
22 23		31b	Authorship eligibility guidelines and any intended use of professional writers	<b>Page 2</b>
24 25 26 27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<b>N/A</b>
28	<b>Appendices</b>			
29 30 31 32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<b>Consent form, see supplementary file</b>
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	<b>Page 15</b>

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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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<b>Primary Subject Heading</b>:	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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**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-  
7  
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

16  
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  
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31 60 will allow individualisation of the intensity of the acute physical exercise program.
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34 61 • The feasibility study assesses the acute physiological, immune, and metabolic response to a  
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36 62 supervised acute moderate intensity physical exercise session in patients with mNSCLC.
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38 63 The unsupervised home-based walking program in the intervention arm aims to increase the  
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40 64 level of physical activity in patients with mNSCLC and their cardiorespiratory fitness and  
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42 65 physical capacity to perform acute physical exercise prior to chemo-immunotherapy infusion.
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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

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3 94 changes caused by acute exercise i.e., a single physical exercise bout, and cancer treatments(19).  
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5 95 Immunomodulatory effects of acute physical exercise involve immune cell mobilisation in blood such  
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7 96 as neutrophils, subsets of monocytes or lymphocytes involved in the host defence against tumours,  
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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<sup>dim</sup> 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  
55  
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57  
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60

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  
37  
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  $\geq 18$  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  $\leq 2$ ; 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  $\geq 18$  years and  $< 70$ : Body Mass Index (BMI)  $\leq 17$ , 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  $\geq 70$  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  $\leq 8$  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 (FEV<sub>1</sub>)  $< 30\%$ ).

#### 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  
172



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/m<sup>2</sup>) with B9-B12 vitamin supplementation; carboplatin (AUC 6) plus paclitaxel  
193 (200 mg/m<sup>2</sup>) 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 1<sup>st</sup> and 4<sup>th</sup> 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  
42  
43  
44  
45  
46  
47

## 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  
56 249 (Table 1).  
57  
58  
59  
60

250

251 Table 1. Data collection schedule for the ERICA study

	Screening	Inclusion D0	1 <sup>st</sup> cycle C1	4 <sup>th</sup> cycle C4	Month 3 M3	Month 6 M6
<b>Socio demographic and clinical data</b>						
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
<b>Physical evaluation</b>						
Anthropometrics		X			X	
Physical fitness ( <i>Cardiorespiratory fitness, strength tests</i> )		X			X	
<b>Self-reported outcomes</b>						
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	
<b>Biological assessments</b>						
Blood sample			X	X		
<b>Body composition</b>						
CT scan		X			X	X
<b>Exercise group</b>						
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

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  
28 272 of 5 watts each 30 seconds until VT1 will be reached. The clinical exercise physiologist will ensure that  
29  
30 273 the patient maintains a minimum pedalling frequency above 35 RPM throughout the test. HR,  
31  
32 274 ventilation (VE), oxygen saturation ( $SaO_2$ ),  $VO_2$ , and carbon dioxide production ( $VCO_2$ ) will be measured  
33  
34 275 by a gas analyser (MetaMax 3b, Cortex Biophysik, Leipzig, Germany) and continuously monitored. In  
35  
36 276 addition, the perception of the difficulty and dyspnoea will be evaluated at the end of the test using  
37  
38  
39 277 the Borg Rating Perceived Exertion questionnaire(39). The clinical exercise physiologist will stop the  
40  
41 278 test when the patient exceeded the VT1. The test will end with a 6-minute recovery phase. The VT1  
42  
43 279 will be determined graphically when the ventilatory equivalent of oxygen ( $VE/VO_2$ ) starts to increase  
44  
45 280 and will be confirmed by Respiratory Exchange Ratio that strictly exceeds 1 (Wasserman method).

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  
59 286 rest between each contraction), and the best performance will be considered.

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

#### 45 306 *Lean body mass and sarcopenia*

47 307 Lean body mass and sarcopenia will be analysed using the Computed Tomography (CT) scans  
48  
49 308 systematically available from routine care. CT scan cross-section at the level of the 3rd lumbar vertebra  
50  
51 309 provides a reliable representation of the total body muscle mass and has therefore been widely  
52  
53 310 adopted for the detection of sarcopenia in cancer patients and allows assessment without additional  
54  
55 311 ionising radiation exposure given that CT scans as part of routine cancer diagnostic procedures is  
56  
57 312 largely available(44,45). The thresholds for identifying muscle range from -29 to +150 HU,  
58  
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  
14 318  $6.06])$  (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.

1  
2  
3 339  
45 340 *Fatigue*

6  
7 341 Fatigue will be assessed by the EORTC-QLQ module measuring cancer-related fatigue (EORTC QLQ-  
8  
9 342 FA12) (54). This self-questionnaire includes 12 items that assess physical, cognitive, and emotional  
10  
11 343 fatigue related to cancer. Participants will respond on a Likert scale ranging from "not at all" to "a lot".  
12  
13 344 All scores will be transformed into a scale from 0 to 100, with a higher score indicating a higher degree  
14  
15 345 of fatigue.

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 35536  
37 356 *Social vulnerability*

38  
39 357 Social deprivation will be assessed using the EPICES score (Evaluation of Deprivation and Inequalities  
40  
41 358 in Health Examination Centres) (57). The EPICES score will be obtained by adding up the points of the  
42  
43 359 11 binary questions ("Yes"/"No") of the self-questionnaire. This score ranges from 0 "no  
44  
45 360 precariousness" to 100 "highest precariousness" with the threshold for deprivation at 30.

46  
47 36148  
49 362 *Biomarkers of the immune system, inflammation, sarcopenia, and oxidative stress*

50  
51 363 Blood samples will be collected during the first and last (forth) treatment cycle: in the exercise group,  
52  
53 364 samples will be collected before exercise (S1), after exercise (S2), and 12 hours after the start of



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- $\alpha$ , Interferon- $\gamma$ , Interleukin-1 $\beta$ , 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,  
32  
33 380 the blood samples will be also used to analyse the glucose (OneTouch Verio®) and lactate (LACTATE  
34  
35 381 PRO II) metabolism by a mobile device. Patients will be asked to complete a questionnaire regarding  
36  
37 382 the taking of antibiotics, anti-inflammatory, and antioxidants in the 48 hours prior to blood collection.  
38  
39  
40  
41  
42  
43  
44

383

#### 384 *Toxicities*

45  
46  
47 385 Severe treatment toxicities (grade  $\geq 3$ ) will be noted according to the National Cancer Institute's  
48  
49 386 Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0. The number of rescheduled or  
50  
51 387 cancelled treatment sessions and the relative dose intensity (RDI) of participants with grade  $\geq 3$   
52  
53 388 toxicities related to chemotherapy and immunotherapy will be calculated as the ratio of "delivered"  
54  
55 389 to "expected" dose intensity.  
56  
57  
58  
59  
60

1  
2  
3 391 **STATISTICAL ANALYSIS**  
4

5 392 **SAMPLE SIZE**  
6

7 393 The main objective of the current study is to evaluate the feasibility of an acute physical exercise  
8  
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,  
14  
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  
37  
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.  
54

55  
56 415 The feasibility of the ERICA study will be assessed at the end of the intervention (M3) in the exercise  
57  
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  
4  
5 418 immunotherapy/chemotherapy. The tolerability will be assessed by the relative dose intensity of  
6  
7 419 exercise. The safety will be assessed by the occurrence of adverse events related to the physical  
8  
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  
16  
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  
20  
21 426 quality, and sarcopenia) at inclusion, 3 and 6 months will be represented by graphs and compared by  
22  
23 427 non-parametric ANOVAs (performed on ranks).

24  
25  
26  
27 428 Progression-free survival will be measured from the date of randomization until the date of event  
28  
29 429 defined as either progression or death from any cause whichever occurs first. Participants with no  
30  
31 430 event at the time of the analysis will be censored at the date of the last available tumour assessment.  
32  
33  
34 431 The results will allow to formulate the hypotheses and determine sample size for a subsequent  
35  
36 432 multicenter randomized efficacy study.

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38  
39 433 Statistical analyses will be carried out using R statistical software (60).

#### 40 41 434 **DATA MONITORING**

42  
43 435 The database for clinical data will be managed using REDCap (Research Electronic Data Capture)  
44  
45 436 (61,62) software hosted at CLB. The access to the database will be secured (personal ID and password  
46  
47 437 required) with different levels of security depending on the role within the study. The investigator will  
48  
49 438 have access to the final dataset.

#### 50 51 439 **PATIENT AND PUBLIC INVOLVEMENT**

52  
53 440 Prior to the present study, we administrated a questionnaire to lung cancer patients to collect their  
54  
55 441 experience and preferences in terms of physical activity to practice during cancer treatments. The  
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57 442 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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9  
10 446 The study protocol has been approved by a French ethics committee CPP Ile de France II (IDRCB:  
11  
12 447 20.09.04.65226) and the study database has been reported to the National Commission for Data  
13  
14 448 Protection and Liberties (CNIL; reference number: 2016177). The study has been registered at  
15  
16 449 reference number: NCT04676009.  
17

#### 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  
23  
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  
27  
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  
39  
40 460 remains limited and there is a lack of widespread awareness of the benefits of maintaining physical  
41  
42 461 activity in this particular population (66,68–70). Furthermore, the high prevalence of comorbidities in  
43  
44 462 mNSCLC patients, which may be exacerbated by the direct and indirect effects of cancer treatment,  
45  
46 463 led to exclude patients at risk of cardiovascular events from studies (i.e. history of cardiovascular  
47  
48 464 disease; abnormal electrocardiogram and/or echocardiography) or undernutrition.  
49

50  
51 465 Based on preclinical evidence of exercise in modulating the efficacy of cancer therapy, the present  
52  
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.

14  
15  
16 475 Home-based exercises are a beneficial approach to reducing symptoms and improving exercise  
17  
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  
21  
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  
27  
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  
33  
34 484 trackers has shown pertinent results in women with metastatic breast cancer (77,78). The combination  
35  
36 485 of these two intervention modalities (acute exercise and unsupervised walking programme) allows us  
37  
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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42 488 The first challenge we need to overcome is that the study concerns only one stage of lung cancer and  
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44 489 participants must be eligible to immunotherapy. Next, we are looking at the intervention  
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46 490 reproducibility in other institutions. Finally, it is a feasibility study with a limited sample size (n=30).  
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48 491 We plan to conduct a randomised controlled trial to address the various limitations of the present  
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50 492 study: larger sample size, multiple lung cancer stages, and to carry out the study in several hospital  
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52 493 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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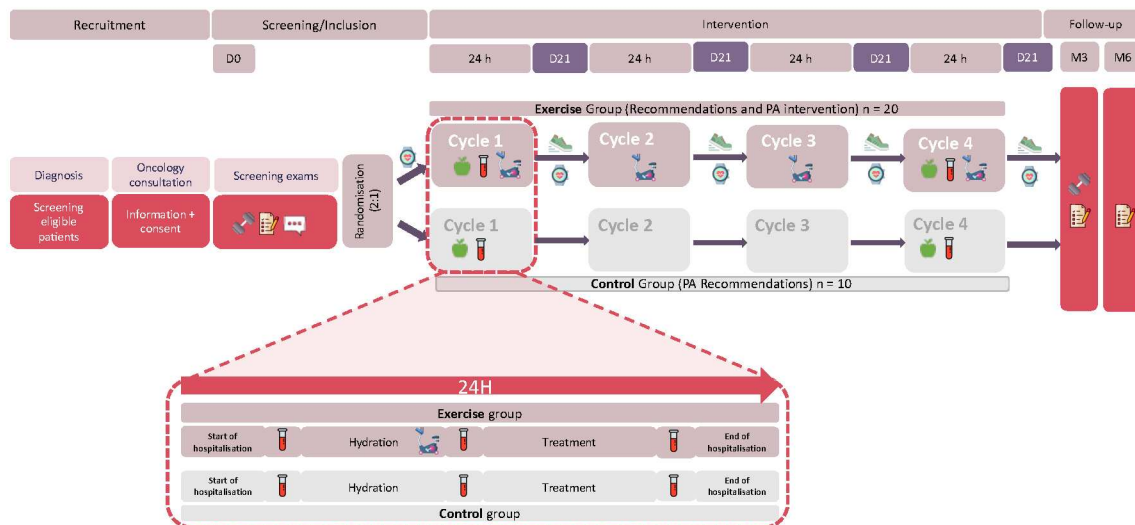
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740 **Figure 1:** Flow chart of the ERICA study, France (original flow chart)

For peer review only









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

Section/item	ItemNo	Description	Page
<b>Administrative information</b>			
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
<b>Introduction</b>			
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	<b>Methods: Participants, interventions, and outcomes</b>			
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

1	<b>Methods: Assignment of interventions (for controlled trials)</b>			
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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	<b>Page 8</b>
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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	<b>N/A</b>
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<b>Page 17</b>
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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	<b>N/A</b>
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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	<b>N/A</b>
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32	<b>Methods: Data collection, management, and analysis</b>			
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	<b>Page 10-16</b>
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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	<b>Page 10</b>
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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	<b>Page 17</b>
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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	<b>Page 16-17</b>
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		found, if not in the protocol	
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<b>Page 16-17</b>
	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)	<b>Page 16-17</b>
<b>Methods: Monitoring</b>			
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	<b>Page 17</b>
	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	<b>N/A no interim analyses are planned</b>
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	<b>Page 17</b>
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<b>Page 18</b>
<b>Ethics and dissemination</b>			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<b>Page 18</b>
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)	<b>N/A</b>
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<b>Abstract : page 2 Study population : page 6 Recruitment: page 7-8</b>
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<b>N/A</b>
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	<b>Page 17</b>

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	<b>Appendices</b>			
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.