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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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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 an acute physical exercise realized immediately prior to immune-chemotherapy infusion in patients with mNSCLC and to examine the effects of this intervention 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 **** ****** 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 an acute physical exercise one hour prior to immune-chemotherapy infusion, and a home-based walking program with an activity tracker. The acute exercise consists in interval training at a submaximal intensity for 35 minutes. Clinical, physical, biological, and psychosocial parameters will be assessed at baseline, at 3 months and 6 months after study inclusion. Biological measures will include analyses of immune, inflammatory, metabolic, oxidative stress biomarkers and molecular profiling.

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

KEYWORDS: Non-small-cell lung cancer, Metastatic, Exercise, Immunotherapy, Chemotherapy, Immunology

Word count: 5181

Strengths and limitations of this study.

- This study is the first to assess the feasibility and effects of an acute physical exercise performed within one hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-based doublet) infusion in mNSCLC patients.
- Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption condition during a submaximal endurance test on a cycle-ergometer at baseline and this test will allow to individualize the intensity of the acute physical exercise program.
- The feasibility study assesses the acute physiological, immune, and metabolic response to an acute moderate physical exercise in patients with mNSCLC.

  The home-based walking program in the intervention arm aims to increase the level of physical activity in patients with mNSCLC and their cardiorespiratory fitness and physical capacity to perform acute physical exercise prior to chemo-immunotherapy infusion.
- The study concerns only one stage of lung cancer, participants must be eligible to immunotherapy and it's a study with a limited sample size (n=30).

INTRODUCTION

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

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

Immunomodulatory effects of acute physical exercise involve immune cell mobilization in blood like neutrophils, subsets of monocytes or lymphocytes involved in the host defence against tumours, seems to improve immunosurveillance (19). Acute physical exercise leads to a rapid increase in the mobilization of the peripheral activity of the sub-population of $CD56^{dim}$ NK cells during acute physical exercise of light to moderate intensity (20,21). A preclinical study reported that exercise training (voluntary running), through activation of epinephrine and IL-6, led to selective NK cell mobilization and limited tumour growth of several types of tumours (melanomas, liver, and lung mouse models) (22). In a recent study, the increase in PD-1+ CD8+ T cells was observed after a single exercise session (23). At the level of the adaptive immune system, acute exercise results in transient biphasic changes, i.e. increase of circulating lymphocytes during and immediately after exercise, followed by a transient decrease of blood lymphocytes below baseline level during recovery from exercise (1 hour), thought to be due to a redistribution of immune cells to peripheral tissues, including tumours, before return to basal level within few hours (22,24). Moreover, recent preclinical studies suggested that physical exercise performed during chemotherapy infusion may have additional physiological benefits such as increased blood flow leading to through improved intra-tumoral perfusion and enhanced drug delivery (25–27). However, most of the available evidence on the benefits of physical exercise in cancer patients has been observed in interventions performed either after the treatment or during the interval between the chemotherapy cycles. Only two studies have evaluated the feasibility of low-intensity physical exercises during the chemotherapy infusion without adverse events, interference with chemotherapy, or exacerbation in symptoms (28,29). Recently, it has been suggested in preclinical studies that exercise performed during chemotherapy infusion could lead to improve perfusion of solid tumours, mitigating tumour hypoxia, and enhancing drug delivery to tumours (25,26,30). Similarly, by its effect on immune regulation, physical exercise prior to infusion may potentiate the effect of the immunotherapy. Recent preclinical evidence has suggested a beneficial effect of exercise in addition to immunotherapy (anti–PD-1 immunotherapy) in a murine model of NSCLC, through increased necrosis and a decreased proliferative index of tumour cells (31).

Based on these findings, the main objective of ERICA (Exercise inteReaction Immunotherapy Chemotherapy and cAncer) feasibility study is to evaluate the feasibility of an intervention combining an acute exercise program performed immediately prior to immunotherapy and chemotherapy infusion (i.e. a combination of pembrolizumab and pemetrexed-cis- or carboplatin for non-squamous cell carcinoma or paclitaxel-carboplatin for squamous cell carcinoma) and a home-based walking program in first-line treatment of metastatic NSCLC patients. The secondary objectives are to evaluate the effects of the acute exercise before the first-line treatment combined with a home-based walking program on 1) physical fitness, 2) PA level and sedentary lifestyle, 3) psychosocial factors (HRQoL and fatigue), 4) sleep quality, 5) body composition, 6) sarcopenia, 7) treatment response, 8) treatment completion rate, 9) related treatment toxicities, and 10) progression-free survival. Furthermore, this feasibility study will generate data on the effect of this exercise intervention on immune, metabolic and inflammatory biomarkers as well as oxidative stress.

METHODS

STUDY DESIGN

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

Insert Figure 1

STUDY POPULATION

Inclusion criteria

Participants will have to meet all of the following eligibility criteria: 1) aged ≥ 18 and < 80 years; 2) diagnosed with a histologically confirmed metastatic NSCLC without EGFR mutation/ALK 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 carcinoma) in combination with pembrolizumab; 4) Eastern Co-operative Oncology Group (ECOG) performance status ≤ 2; 5) able to engage in PA attested by a medical certificate by an oncologist; and 6) provide a dated and signed informed consent form before study enrolment.

Exclusion criteria

Patients will not be eligible in at least one of the following cases: 1) bone metastases with risk of fractures or unconsolidated pathologic fractures; 2) contraindication to the physical exercise proposed in this study (e.g. orthopaedic disorder such as disabling coxarthrosis or gonarthrosis, central nervous system disorders); 3) history or co-existence of other primary cancer (except in situ cancer regardless of the site, and/or basal cell carcinoma, and/or non-lung cancer in complete remission for more than 5 years) ; 4) severe undernutrition defined according to the French National Authority for Health (i.e. for adults aged ≥18 years and < 70: Body Mass Index (BMI) ≤ 17, weight loss ≥ 10% in 1 month, ≥15% in 6 months, or ≥ 15% compared to the usual weight before the disease diagnosis, or serum albumin < 30 g/l; for adults aged ≥70 years: BMI < 18, weight loss ≥ 10% in 1 month or ≥15% in 6 months, or serum albumin < 30 g/l); 5) severe anaemia (haemoglobin ≤ 8 g/dl) in the past 30 days prior to enrolment; 6) history of cardiovascular disease or cardiovascular risk (i.e. chronic or poorly controlled coronary heart disease, peripheral arterial disease, cardiac arrhythmia, symptomatic heart disease, uncontrolled or untreated arterial hypertension, myocardial infarction diagnosed in the past 6 months, coronary angioplasty with or without stent implantation in the past 6 months, coronary artery bypass surgery in the past 12 months); 7) history of type 2 diabetes or glycated haemoglobin > 7% in the past 3 months prior to enrolment; 8) Stage IV Chronic obstructive pulmonary disease (forced expiratory volume in one second (FEV_1) < 30%).

RECRUITMENT

Participants will be recruited in ***, Lyon, France from December 2020. Eligible patients will be screened systematically based on electronical patient records during weekly multidisciplinary lung cancer board meetings. During a medical consultation before treatment initiation, an oncologist will propose the study to eligible patients and explain the study objectives and protocol. Once the written informed consent is signed, patients will undergo the following screening tests prior to inclusion: (1) clinical examination including assessing Performance Status (PS) and Blood Pressure, (2) echocardiography and electrocardiogram performed by a cardiologist, and (3) for patients with

diabetes, measurement of glycated haemoglobin. If these investigations confirm the patient's eligibility, the patient will be included in the study (D0). The end date for this study is planned in January 2023.

RANDOMIZATION

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

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

INTERVENTION

Treatment protocol

All patients in both exercise and control groups of this study will receive usual care and the same standard treatment protocol: pembrolizumab (200 mg) combined with carboplatin (AUC 5) plus pemetrexed (500 mg/m^2) with B9-B12 vitamin supplementation; carboplatin (AUC 6) plus paclitaxel (200 mg/m^2) every 3 weeks for 4 cycles; before pembrolizumab maintenance in squamous cell carcinoma or pembrolizumab plus pemetrexed maintenance for non-squamous cell carcinoma.

Physical Activity recommendations

Although there are no specific PA recommendations for patients with mNSCLC, all patients will be informed of the PA recommendations to be physically active as much as possible during the day, walking as much as possible and sitting as little as possible (WCRF, 2018). We have chosen to follow the recommendations of the Macmillan Cancer Support guide released in 2018, advising patients with bone metastases to have an active lifestyle on a daily basis and to maintain appropriate PA according

to their physical abilities (32). Several individual strategies will be proposed to patients (e.g., using stairs whenever possible, walking to local shops).

Nutritional recommendations

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

Exercise Group

Acute physical exercise protocol prior to immunotherapy and chemotherapy infusion

Patients in the "exercise" group will perform an acute physical exercise during hospitalization for treatment. It will be carried out 1 hour prior to the immunotherapy and chemotherapy infusion, on a cycle ergometer (Monark Ergomedic 939 Novo) for each of the 4 cycles of treatment foreseen. The physical exercise will be supervised by a qualified PA instructor. The physical exercise consists in a 35-min acute interval training and will be individualized based on the results of a submaximal endurance test performed on a cycle ergometer by each patient (described below) prior to treatment (D0). Following a five-minute warm-up at 60% of Ventilation Threshold 1 (VT1), the participant will carry out 5 sets, alternating periods of 3 minutes at 70-80% of VT1 with 3 minutes at 110-120% of VT1 (≥ 35 Revolutions Per Minute (RPM)). The acute exercise intensity will be programmed according to the load reached at VT1 during the cycle ergometer endurance submaximal test. Heart rate (HR), load, RPM, dyspnoea, and perception of effort on a Rating Perceived Exertion scale will be monitored. If the patient is no longer able to cycle at the load corresponding to 120% of his VT1, the PA instructor will decrease the load to 110% of VT1. In case of exercise-induced desaturation (≤ 4% of the measured value at rest or ≤ 93%), the PA instructor will stop the exercise until the resting oxygen saturation. In addition to detailed explanation by the qualified PA instructor, patients receive written support materials at baseline (D0).

Home-based walking program

During the 3-month intervention, between each treatment cycle (3 weeks), patients will follow a home-based walking program consisting of an individual goal of a number of steps per day. Each patient will receive a Fitbit® Inspire activity tracker with an instruction to wear it continuously during the intervention. They will be advised to achieve at least 6,000 daily steps which corresponds to a physically active lifestyle in a patient population (35). Ten days after each treatment cycle, the PA instructor will contact the patients by phone to assess and encourage adherence to the home-based walking program. Depending on the average number of steps performed in the past ten days, personalized objectives might be redefined to increase the target number of daily steps. For patients who reach more than 6,000 steps per day the initial target number of 6,000 steps will be increased by 30%. The target number of steps was set within a maximum of 7800 steps above the average number of steps in the previous week. Patients who do not reach 6,000 daily steps, will be advised to gradually increase the target number of steps per day according to the patient's abilities. Number of steps will be collected by regular sync with the mobile phone application (Fitbit®) of the activity tracker or by a step logbook.

EVALUATIONS

Modalities

The assessments in both groups will be performed before the first cycle of anti-neoplastic treatment (baseline, D0), at the end of the 4 cycles of treatment (M3), and at 6 months after study inclusion (M6).

DATA COLLECTION

Sociodemographic and clinical data

Sociodemographic and clinical data including gender, date of birth, living situation, employment status, lifestyle (alcohol consumption and smoking status) will be collected at baseline. All clinical data will be extracted from the participant's electronic medical records. The Response Evaluation Criteria In Solid

Tumours (RECIST) will be used for tumour assessments between the diagnosis and the end of the ERICA study.

Anthropometric data

Anthropometric data including body weight (kilogram), height (centimeter, cm), waist (cm) and hip (cm) circumference will be collected. Waist circumference will be measured around the abdomen midway between the last floating rib and the iliac crest. Hip circumference will be measured horizontally through the upper margin of the pubis. The body mass index is calculated as the body weight in kilograms divided by the square of the height in meters.

Physical fitness

Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption (VO_2) condition during a submaximal endurance test on a cycle-ergometer at baseline. This test will allow to individualize the intensity of the acute physical exercise program. Following a 5-minute warm-up at 20% of the participant's maximum theoretical load, watts will be increased by a constant amount of 5 watts each thirty seconds until VT1 will be reached. The PA instructor will ensure that the patient maintains a minimum pedalling frequency above 35 RPM throughout the test. HR, ventilation (VE), oxygen saturation (SaO_2), VO_2, and carbon dioxide production (VCO_2) will be measured by a gas analyser (MetaMax 3b, Cortex Biophysik, Leipzig, Germany) and continuously monitored. In addition, the perception of the difficulty and dyspnoea will be evaluated at the end of the test using the Borg Rating Perceived Exertion questionnaire(36). The PA instructor will stop the test when the patient exceeded his VT1. The test will end with a 6-minute recovery phase. The VT1 will be determined graphically when the ventilatory equivalent of oxygen (VE/VO_2) starts to increase and will be confirmed by Respiratory Exchange Ratio that strictly exceeds 1 (Wasserman method).

The lower strength muscular function will be evaluated by measuring the maximum isometric strength of the knee extensors (DFS II Series Digital; Force Gauges Chatillon, Largo, FL, USA). Participants will be

seated on a chair with the knee joint at 90°, arms crossed over the chest, and the dynamometer attached to the ankle. Participants were advised to stretch their leg as hard as possible within 3 seconds upon the instructor's signal. Only the dominant leg will be tested three times (with 2 minutes rest between each contraction), and the best performance will be considered.

The maximum isometric upper limb strength will be measured by a hand dynamometer (Jamar Plus Digital Hand Dynamometer, Patterson Medical, Huthwaite, United Kingdom) (37,38). Participants will be seated with their back straight and elbows bent at 90°. They will be asked to squeeze the handgrip as strongly as possible for five seconds to achieve maximum strength. Two measurements will be taken on each hand and the best performance will be recorded.

Physical activity level

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

Body composition and sarcopenia

Body composition and sarcopenia will be analysed using the Computed Tomography (CT) scans. CT scan cross-section at the level of the 3rd lumbar vertebra represents the method of choice for assessment of sarcopenia in the oncology setting given that CT scan as part of routine cancer diagnostic procedures is largely available (40). The thresholds for identifying muscle range from -29 to +150 HU,

subcutaneous and intramuscular adipose tissue from -190 to -30 HU, visceral adipose tissue from -150 to -50 HU and bone from +152 to 1000 HU (41–43). Skeletal muscle radiodensity (SMD) that represents muscle quality will be measured using the average radiation attenuation of the tissue in Hounsfield Units (HU). A low SMD is defined by values below the threshold of 37.8 HU. An estimate of lean body mass (LBM) will be calculated using the formula (LBM (kg) = [(L3 Muscle measured by CT (cm^2) × 0.3) + 6.06]) (44).

Nutrition

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

Health-related quality of life

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

Fatigue

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

Sleep quality

The perceived quality of sleep will be assessed by the Insomnia Severity Index which measures the severity of insomnia. The questionnaire consists of 7 items rated on a 5-point scale ranging from 0 ("none") to 4 ("very severe") (50,51). This self-questionnaire will evaluate the severity of the patient's sleep difficulties (initial, maintenance, and morning insomnia), the degree of sleep dissatisfaction, the level of interference with daily functioning, the degree of appearance of sleep difficulties, and the level of anxiety related to insomnia. The total score of the items varies between 0 and 28. A high score indicates greater sleep difficulties.

Social vulnerability

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

Biomarkers of the immune system, inflammation, sarcopenia, and oxidative stress

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

treatment (S3); in the control group: samples will be collected 40 minutes before the infusion of treatment (S1), just before the infusion of treatment (S2) and 12 hours after the start of treatment (S3). Blood test procedures will follow laboratory standards. Each blood sample will be collected in 3 x 10mL Ethylenediaminetetraacetic acid tubes and then centrifuged (10 minutes at 800G) within one hour (maintained at 4°C before and during centrifugation). After the centrifuge, plasma will be collected and aliquoted in 5 cryotubes of 1 mL and the Peripheral Blood Mononuclear Cell (PBMC) will be collected and aliquoted in 3 cryotubes (5 to 7 millions cells per tube). These cryotubes will be frozen at -80°C and stored in nitrogen at *** for the duration of the study. At the end of the study, biomarkers of immunity, sarcopenia, and inflammation will be analysed. We will measure i) immune biomarkers (NK cells, B lymphocytes, T lymphocytes, monocytes, sub-populations of dendritic cells on frozen PBMC); ii) plasma biomarkers of sarcopenia and inflammation (Myostatin, Activin, Cortisol, Tumor Necrosis Factor-α, Interferon-γ, Interleukine-1β, Interleukine-6, Follistatin, Growth Differentiation Factor 5, Bone morphogenetic protein 14, GDF15, IInterleukine-10, Interleukine-15, NH3, Aminogram, C-reactive protein, insulin); and iii) plasma oxidative stress (Superoxide dismutase, catalase, malondialdehyde, glutathione peroxidase, Xanthine Myeloperoxidase, and Xanthine oxidase). Finally, the blood samples will be also used to analyse the glucose (OneTouch Verio®) and lactate (LACTATE PRO II) metabolism by a mobile device. Patients will be asked to complete a questionnaire regarding the taking of antibiotics, anti-inflammatory, and antioxidants in the 48 hours prior to blood collection.

Toxicities

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

STATISTICAL ANALYSIS

SAMPLE SIZE

The main objective of the current study is to evaluate the feasibility of an acute physical exercise program performed prior to the infusion of treatments in mNSCLC patients, to assess if this planned exercise dose is safe and tolerable in this target patient population(53). In the context of a feasibility study without a concrete hypothesis and in absence of previous studies in this population, the sample size was defined empirically. Taking into account the number of mNSCLC patients who receive first line chemotherapy (i.e. pemetrexed-platinum or taxol-platinum) combined with Pembrolizumab each year in ***, we plan to include 30 patients over a 18 months period. This number will be sufficient to assess if the planned exercise dose is safe and tolerable in this target patient population, and the sample size falls within the range of sample sizes recommended in the literature for feasibility trials (54).

Although the main objective is to study the feasibility of physical exercise prior to the infusion of treatments, the evaluation of the biological objectives requires randomization to have reference measures. We have chosen to unbalance the randomization (2:1) so that more patients will benefit from the intervention proposed in the ERICA study.

STATISTICAL METHODS

All statistical analyses will be on an exploratory basis on all data from study subjects. Given the limited sample size, non-parametric tests will be performed. Qualitative data will be presented using their frequencies and percentages. Quantitative data will be presented using the number of observations, mean, standard deviation, median, minimum, and maximum. For both types of data, the number of missing data will be presented if necessary.

The feasibility of the ERICA study will be assessed at the end of the intervention (M3) in the exercise group only, according to the adherence rate by calculating the ratio of the number of acute physical exercise sessions performed to the number of acute physical exercise sessions planned before the

immunotherapy/chemotherapy. The safety will be assessed by the occurrence of adverse events related to the physical exercise intervention. The acceptability (i.e. the proportion of patients who accept to participate in the study among eligible patients) and the attrition (i.e. the proportion of patients who withdraw their participation from the study among patients initially enrolled) will be calculated. In the exercise group, the acceptability of the activity tracker, the observance of the home-walking program, and the safety of the intervention (the number, type, and timing of adverse events that occurred) will be assessed.

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

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

The results will allow to formulate the hypotheses and determine sample size for a subsequent multicenter randomized efficacy study.

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

DATA MONITORING

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

PATIENT AND PUBLIC INVOLVEMENT

Prior to the present study, we administrated a questionnaire to lung cancer patients to collect their experience and preferences in terms of physical activity to practice during cancer treatments. The results were used to develop the ERICA physical activity intervention. As it is a feasibility study, the

findings will be used to adjust the intervention if necessary for the purpose of an efficacy randomised controlled trial. Global findings will be disseminated to participants at the end of the study if they wish.

ETHICAL AND DISSEMINATION

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

DISCUSSION

To our knowledge, ERICA is the first study to assess the feasibility and effects of an acute physical exercise performed within one hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-based doublet) infusion in mNSCLC patients. Despite therapeutic advances, notably immunotherapy combined with chemotherapy, the prognosis of many patients with mNSCLC continues to be poor, and disease burden, cachexia, comorbidities, and treatment side effects lead to deconditioning and adversely affect exercise capacity in people with advanced NSCLC (17,58–61). Conversely, evidence from meta-analyses suggests that exercise training in patients with advanced lung cancer could be feasible and safe with no serious adverse events reported and may improve or avoid the decline of physical capacity (15,62). However, the evidence regarding the benefits of exercise in mNSCLC patients remains limited and there is a lack of widespread awareness of the benefits of maintaining physical activity in this particular population (61,63–65). Furthermore, the high prevalence of comorbidities in mNSCLC patients, which may be exacerbated by the direct and indirect effects of cancer treatment, led to exclude patients at risk of cardiovascular events from studies (i.e. history of cardiovascular disease; abnormal electrocardiogram and/or echocardiography) or undernutrition.

Based on preclinical evidence of exercise in modulating the efficacy of cancer therapy, the present study assesses the feasibility of acute exercise of submaximal intensity in the target population. Current evidence on the benefits of physical exercise in cancer patients mainly stems from interventions performed either between the chemotherapy cycles or after end of treatment. Yet, a

feasibility study in patients with various tumours, mostly breast cancer, reported that exercise (i.e. 20 min of supervised low-intensity cycling) during chemotherapy infusion appears to be safe and feasible (28). To prescribe a safe and efficacious intensity of acute exercise intervention, we decided to realize a submaximal cardiopulmonary exercise test with a continuous gas exchange analysis. Because of the comorbidities, the tumour location and the lack of information about high intensity exercise effects, the present study targets acute exercise of submaximal intensity.

Home-based exercises are a beneficial approach to reducing symptoms and improving exercise capacity as well as the quality of life in patients with NSCLC (66). The home-based walking program in the intervention arm aims to increase the level of physical activity in patients with mNSCLC and their cardiorespiratory fitness and physical capacity to perform acute physical exercise prior to chemo-immunotherapy infusion (15). Also, chronic exercise can favourably modulate inflammation and immune-related factors (67,68). Activity trackers are innovative tools increasingly used to promote an active lifestyle and to objectively measure the PA level of cancer patients (69–71). Trackers have been used in a randomized controlled trial to encourage patients with mNSCLC to maintain their PA by recommending a targeted number of steps (72). In a previous study by the team, the use of activity trackers have shown pertinent results in women with metastatic breast cancer (73,74). The combination of these two intervention modalities (acute exercise and unsupervised walking programme) allows us to offer an intervention adapted to this population in order to have sufficient physiological stimulation to observe changes in the immune system.

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

INNOVATION AND STUDY RELEVANCE

The ERICA study will provide clinical, physical, and psychosocial insights on the feasibility of acute exercise prior to first-line chemo-immunotherapy infusion in patients with mNSCLC. In particular, exploratory data on the safety and tolerability of the proposed exercise dose and schedule in the target patient population will be obtained. This feasibility study will further generate preliminary data on the acute physiological, immune, and metabolic response to the achieved exercise dose in patients with mNSCLC. The ERICA study will provide valuable information to design a large-scale adequately powered randomized controlled trial to assess the efficacy on clinically important endpoints (e.g. progression free survival) in patients with mNSCLC receiving first-line chemo-immunotherapy.

REFERENCES

1. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2018;29:iv192–237.

2. ASCO. Lung Cancer - Non-Small Cell - Statistics [Internet]. Cancer.Net. 2021 [cited 2021 Jul 3]. Available from: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics

3. Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non–Small-Cell Lung Cancer. JCO. 2020;JCO.19.03136.

4. Low JL, Walsh RJ, Ang Y, Chan G, Soo RA. The evolving immuno-oncology landscape in advanced lung cancer: first-line treatment of non-small cell lung cancer. Ther Adv Med Oncol [Internet]. 2019 [cited 2019 Nov 5];11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6716180/

5. Brahmer JR, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial. The Lancet Oncology. 2017 Dec;18(12):1600–9.

6. Polanski J, Jankowska-Polanska B, Rosinczuk J, Chabowski M, Szymanska-Chabowska A. Quality of life of patients with lung cancer. Onco Targets Ther. 2016;9:1023–8.

7. Camps C, del Pozo N, Blasco A, Blasco P, Sirera R. Importance of Quality of Life in Patients with Non–Small-Cell Lung Cancer. Clinical Lung Cancer. 2009;10(2):83–90.

8. Garassino MC, Gadgeel S, Esteban E, Felip E, Speranza G, Domine M, et al. Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Oncology. 2020;21(3):387–97.

9. Steffen McLouth LE, Lycan TW, Levine BJ, Gabbard J, Ruiz J, Farris M, et al. Patient-Reported Outcomes From Patients Receiving Immunotherapy or Chemoimmunotherapy for Metastatic Non–Small-Cell Lung Cancer in Clinical Practice. Clinical Lung Cancer. 2019;21(3):255-263.e4.

10. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126–31.

11. Hwang C-L, Yu C-J, Shih J-Y, Yang P-C, Wu Y-T. Effects of exercise training on exercise capacity in patients

with non-small cell lung cancer receiving targeted therapy. Support Care Cancer. 2012;20(12):3169–77.

12. Chen H-M, Tsai C-M, Wu Y-C, Lin K-C, Lin C-C. Effect of walking on circadian rhythms and sleep quality of patients with lung cancer: a randomised controlled trial. Br J Cancer. 2016;115(11):1304–12.

13. Dhillon HM, Bell ML, van der Ploeg HP, Turner JD, Kabourakis M, Spencer L, et al. Impact of physical activity on fatigue and quality of life in people with advanced lung cancer: a randomized controlled trial. Annals of Oncology. 2017;28(8):1889–97.

14. Zhang L-L, Wang S-Z, Chen H-L, Yuan A-Z. Tai Chi Exercise for Cancer-Related Fatigue in Patients With Lung Cancer Undergoing Chemotherapy: A Randomized Controlled Trial. Journal of Pain and Symptom Management. 2016;51(3):504–11.

15. Peddle-McIntyre CJ, Singh F, Thomas R, Newton RU, Galvão DA, Cavalheri V. Exercise training for advanced lung cancer. Cochrane Lung Cancer Group, editor. Cochrane Database of Systematic Reviews [Internet]. 2019 [cited 2019 Sep 17]; Available from: http://doi.wiley.com/10.1002/14651858.CD012685.pub2

16. Quist M, Adamsen L, Rørth M, Laursen JH, Christensen KB, Langer SW. The Impact of a Multidimensional Exercise Intervention on Physical and Functional Capacity, Anxiety, and Depression in Patients With Advanced-Stage Lung Cancer Undergoing Chemotherapy. Integr Cancer Ther. 2015;14(4):341–9.

17. Avancini A, Sartori G, Gkountakos A, Casali M, Trestini I, Tregnago D, et al. Physical Activity and Exercise in Lung Cancer Care: Will Promises Be Fulfilled? The Oncologist [Internet]. 2019;n/a(n/a). Available from: https://theoncologist.onlinelibrary.wiley.com/doi/abs/10.1634/theoncologist.2019-0463

18. Activité physique. Prévention et traitement des maladies chroniques Éditions EDP Sciences, janvier 2019, 824 pages, Collection Expertise collective ISBN 978-2-7598-2328-4 [Internet]. [cited 2021 Jul 4]. Available from: https://www.inserm.fr/sites/default/files/2019-02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf

19. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. J Sport Health Sci. 2019;8(3):201–17.

20. Bigley AB, Rezvani K, Chew C, Sekine T, Pistillo M, Crucian B, et al. Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells. Brain, Behavior, and Immunity. 2014;39:160–71.

21. Idorn M, Hojman P. Exercise-Dependent Regulation of NK Cells in Cancer Protection. Trends in Molecular Medicine. 2016;22(7):565–77.

22. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al. Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. Cell Metabolism. 2016;23(3):554–62.

23. Wadley AJ, Cullen T, Vautrinot J, Keane G, Bishop NC, Coles SJ. High intensity interval exercise increases the frequency of peripheral PD-1+ CD8+ central memory T-cells and soluble PD-L1 in humans. Brain, Behavior, & Immunity - Health. 2020;3:100049.

24. Pedersen BK, Hoffman-Goetz L. Exercise and the Immune System: Regulation, Integration, and Adaptation. Physiological Reviews. 2000;80(3):1055–81.

25. Wiggins JM, Opoku-Acheampong AB, Baumfalk DR, Siemann DW, Behnke BJ. Exercise and the Tumor Microenvironment: Potential Therapeutic Implications. Exercise and Sport Sciences Reviews. 2018;46(1):56–64.

26. McCullough DJ, Stabley JN, Siemann DW, Behnke BJ. Modulation of Blood Flow, Hypoxia, and Vascular Function in Orthotopic Prostate Tumors During Exercise. J Natl Cancer Inst [Internet]. 2014 [cited 2020 Jan 8];106(4). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3982888/

27. Schadler KL, Thomas NJ, Galie PA, Bhang DH, Roby KC, Addai P, et al. Tumor vessel normalization after aerobic exercise enhances chemotherapeutic efficacy. Oncotarget. 2016;7(40):65429–40.

28. Thomas VJ, Seet-Lee C, Marthick M, Cheema BS, Boyer M, Edwards KM. Aerobic exercise during chemotherapy infusion for cancer treatment: a novel randomised crossover safety and feasibility trial. Support Care Cancer. 2020;28(2):625–32.

29. Kerrigan K. A pilot study of aerobic exercise performed in breast cancer patients during chemotherapy infusion. | Journal of Clinical Oncology [Internet]. 2010 [cited 2020 Aug 11]. Available from: https://ascopubs.org/doi/10.1200/jco.2010.28.15_suppl.e19527

30. Ashcraft KA, Warner AB, Jones LW, Dewhirst MW. Exercise as Adjunct Therapy in Cancer. Seminars in Radiation Oncology. 2018;29(1):16–24.

31. Martín-Ruiz A, Fiuza-Luces C, Rincón-Castanedo C, Fernández-Moreno D, Martínez-Martínez E, Martín-Acosta P, et al. Benefits of exercise and immunotherapy in a murine model of human non–small-cell lung carcinoma. 2020;16.

32. Macmillan Cancer Support. Physical activity in patients with metastatic bone disease: Guidance for healthcare professionals. 2018 [Internet]. [cited 2021 Jul 4]. Available from: https://cdn.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/1784-10061/physical-activity-

for-people-with-metastatic-bone-disease-guidance-tcm9-326004

33. Senesse P, Bachmann P, Bensadoun RJ, Besnard I, Bourdel-Marchasson I, Bouteloup C, et al. Nutrition chez le patient adulte atteint de cancer : textes courts. Nutrition Clinique et Métabolisme. 2012;26(4):151–8.

34. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clinical Nutrition. 2017;36(1):11–48.

35. Tudor-Locke C, Craig CL, Aoyagi Y, Bell RC, Croteau KA, De Bourdeaudhuij I, et al. How many steps/day are enough? For older adults and special populations. Int J Behav Nutr Phys Act. 2011;8(1):80.

36. Borg G, Hassmén P, Lagerström M. Perceived exertion related to heart rate and blood lactate during arm and leg exercise. Europ J Appl Physiol. 1987;56(6):679–85.

37. Anand A, Gajra A. Hand Grip Dynamometry as Prognostic and Predictive Marker in Older Patients With Cancer. J Gerontol Geriatr Res [Internet]. 2018 [cited 2020 Jun 19];07(03). Available from: https://www.omicsonline.org/open-access/hand-grip-dynamometry-as-prognostic-and-predictive-marker-in-older-patients-with-cancer-2167-7182-1000471-102218.html

38. Trutschnigg B, Kilgour RD, Reinglas J, Rosenthall L, Hornby L, Morais JA, et al. Precision and reliability of strength (Jamar vs. Biodex handgrip) and body composition (dual-energy X-ray absorptiometry vs. bioimpedance analysis) measurements in advanced cancer patients. Appl Physiol Nutr Metab. 2008;33(6):1232–9.

39. Amireault S, Godin G, Lacombe J, Sabiston CM. The use of the Godin-Shephard Leisure-Time Physical Activity Questionnaire in oncology research: a systematic review. BMC Med Res Methodol [Internet]. 2015 [cited 2020 May 28];15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4542103/

40. Tosato M, Marzetti E, Cesari M, Savera G, Miller RR, Bernabei R, et al. Measurement of muscle mass in sarcopenia: from imaging to biochemical markers. Aging Clin Exp Res. 2017 Feb;29(1):19–27.

41. Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, et al. Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. Am J Clin Nutr. 1990 Aug;52(2):214–8.

42. Miller KD, Jones E, Yanovski JA, Shankar R, Feuerstein I, Falloon J. Visceral abdominal-fat accumulation associated with use of indinavir. Lancet. 1998 Mar 21;351(9106):871–5.

43. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol. 1998 Jul;85(1):115–22.

44. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise

approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997–1006.

45. Thibault R, Goujon N, Le Gallic E, Clairand R, Sébille V, Vibert J, et al. Use of 10-point analogue scales to estimate dietary intake: A prospective study in patients nutritionally at-risk. Clinical Nutrition. 2009;28(2):134–40.

46. Hjermstad MJ, Fossa SD, Bjordal K, Kaasa S. Test/retest study of the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire. JCO. 1995;13(5):1249–54.

47. Koller M, Shamieh O, Hjermstad MJ, Hornslien K, Young T, Chalk T, et al. Psychometric properties of the updated EORTC module for assessing quality of life in patients with lung cancer (QLQ-LC29): an international, observational field study. The Lancet Oncology. 2020;21(5):723–32.

48. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. European Journal of Cancer. 1994;30(5):635–42.

49. Weis J, Tomaszewski KA, Hammerlid E, Ignacio Arraras J, Conroy T, Lanceley A, et al. International Psychometric Validation of an EORTC Quality of Life Module Measuring Cancer Related Fatigue (EORTC QLQ-FA12). JNCI: Journal of the National Cancer Institute [Internet]. 2017 [cited 2020 May 28];109(5). Available from: https://academic.oup.com/jnci/article/doi/10.1093/jnci/djw273/2972669

50. Savard M-H, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer patients: INSOMNIA SEVERITY INDEX AND CANCER. Psycho-Oncology. 2005;14(6):429–41.

51. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: Psychometric Indicators to Detect Insomnia Cases and Evaluate Treatment Response. Sleep. 2011;34(5):601–8.

52. Sass C, Dupré C, Giordanella JP, Girard F, Guenot C, Labbe É, et al. Le score Epices : un score individuel de précarité. Construction du score et mesure des relations avec des données de santé, dans une population de 197 389 personnes. 2006;4.

53. Jones LW. Precision Oncology Framework for Investigation of Exercise As Treatment for Cancer. JCO. 2015;33(35):4134–7.

54. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. BMC Med Res Methodol. 2013;13(1):104.

55. R Core Team (2020). — European Environment Agency [Internet]. [cited 2021 Jul 4]. Available from: https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-development-core-team-2006

56. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics. 2009;42(2):377–81.

57. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. Journal of Biomedical Informatics. 2019;95:103208.

58. Jones LW. Physical Activity and Lung Cancer Survivorship. In: Courneya KS, Friedenreich CM, editors. Physical Activity and Cancer [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010 [cited 2021 Mar 28]. p. 255–74. (Recent Results in Cancer Research; vol. 186). Available from: http://link.springer.com/10.1007/978-3-642-04231-7_11

59. Quist M, Langer SW, Lillelund C, Winther L, Laursen JH, Christensen KB, et al. Effects of an exercise intervention for patients with advanced inoperable lung cancer undergoing chemotherapy: A randomized clinical trial. Lung Cancer. 2020;145:76–82.

60. Nadler M, Bainbridge D, Tomasone J, Cheifetz O, Juergens RA, Sussman J. Oncology care provider perspectives on exercise promotion in people with cancer: an examination of knowledge, practices, barriers, and facilitators. Support Care Cancer. 2017;25(7):2297–304.

61. Wilk M, Kepski J, Kepska J, Casselli S, Szmit S. Exercise interventions in metastatic cancer disease: a literature review and a brief discussion on current and future perspectives. BMJ Support Palliat Care. 2020;10(4):404–10.

62. Singh B, Spence R, Steele ML, Hayes S, Toohey K. Exercise for Individuals With Lung Cancer: A Systematic Review and Meta-Analysis of Adverse Events, Feasibility, and Effectiveness. Semin Oncol Nurs. 2020;36(5):151076.

63. Granger CL, Parry SM, Edbrooke L, Abo S, Leggett N, Dwyer M, et al. Improving the delivery of physical activity services in lung cancer: A qualitative representation of the patient's perspective. European Journal of Cancer Care. 2019;28(1):e12946.

64. Dittus KL, Gramling RE, Ades PA. Exercise interventions for individuals with advanced cancer: A systematic review. Preventive Medicine. 2017;104:124–32.

65. Heywood R, McCarthy AL, Skinner TL. Safety and feasibility of exercise interventions in patients with advanced cancer: a systematic review. Support Care Cancer. 2017 Oct;25(10):3031–50.

66. Yang M, Liu L, Gan C, Qiu L, Jiang X, He X, et al. Effects of home-based exercise on exercise capacity, symptoms, and quality of life in patients with lung cancer: A meta-analysis. European Journal of Oncology Nursing. 2020;49:101836.

67. Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour microenvironment. Nature Reviews Cancer. 2017;17(10):620–32.

68. Nieman DC, Lila MA, Gillitt ND. Immunometabolism: A Multi-Omics Approach to Interpreting the Influence of Exercise and Diet on the Immune System. Annu Rev Food Sci Technol. 2019;10:341–63.

69. Gresham G, Schrack J, Gresham LM, Shinde AM, Hendifar AE, Tuli R, et al. Wearable activity monitors in oncology trials: Current use of an emerging technology. Contemporary Clinical Trials. 2018;64:13–21.

70. Haberlin C, O'Dwyer T, Mockler D, Moran J, O'Donnell DM, Broderick J. The use of eHealth to promote physical activity in cancer survivors: a systematic review. Support Care Cancer. 2018;26(10):3323–36.

71. Turner RR, Steed L, Quirk H, Greasley RU, Saxton JM, Taylor SJ, et al. Interventions for promoting habitual exercise in people living with and beyond cancer. Cochrane Database Syst Rev [Internet]. 2018 [cited 2019 Oct 29];2018(9). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6513653/

72. Naito T, Mitsunaga S, Miura S, Tatematsu N, Inano T, Mouri T, et al. Feasibility of early multimodal interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer. J Cachexia Sarcopenia Muscle. 2019;10(1):73–83.

73. Delrieu L, Anota A, Trédan O, Freyssenet D, Maire A, Canada B, et al. Design and methods of a national, multicenter, randomized and controlled trial to assess the efficacy of a physical activity program to improve health-related quality of life and reduce fatigue in women with metastatic breast cancer: ABLE02 trial. BMC Cancer [Internet]. 2020 [cited 2021 Apr 15];20. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7333295/

74. Delrieu L, Martin A, Touillaud M, Pérol O, Morelle M, Febvey-Combes O, et al. Sarcopenia and serum biomarkers of oxidative stress after a 6-month physical activity intervention in women with metastatic breast cancer: results from the ABLE feasibility trial. Breast Cancer Res Treat [Internet]. 2021 [cited 2021 Jun 13]; Available from: https://link.springer.com/10.1007/s10549-021-06238-z

DECLARATIONS

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIAL

Not applicable

COMPETING INTERESTS

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

MG, OP, BF, VP, PM and MP designed the trial and obtained funding. MG, OP, BF, VP and MP developed the study protocol. BF, PM and MP contributed to the medical part of the protocol. MV, TW, CC and MCC brought their immunologic expertise. PS brought his biological expertise. MG, OP fulfilled administrative procedures for this project. MG, OP, BF and VP wrote this manuscript. All the authors reviewed and contributed to the final version of the manuscript.

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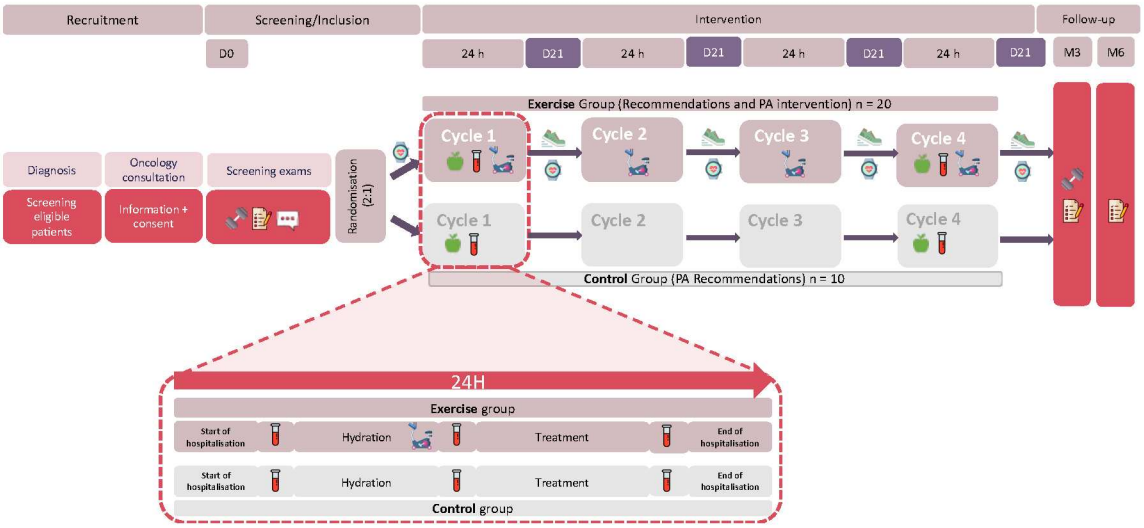
Figure 1: Flow chart of the ERICA study, France (original flow chart)


Recruitment
Screening/Inclusion
Intervention
Follow-up
D0
24 h
D21
24 h
D21
24 h
D21
24 h
D21
M3
M6
Exercise Group (Recommendations and PA intervention) n = 20
Diagnosis
Oncology consultation
Screening exams
Screening eligible patients
Information + consent
Randomisation (2:1)
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Control Group (PA Recommendations) n = 10
24H
Exercise group
Start of hospitalisation
Hydration
Treatment
End of hospitalisation
Start of hospitalisation
Hydration
Treatment
End of hospitalisation
Control group

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

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

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**
Methods: Participants, interventions, and outcomes			
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**
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**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**Line 188 to 241**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**N/A**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**Line 213 to 214** **Line 229 to 231** **Line 232 to 234**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	**Line 189 to 194**
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**
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**
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**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**Line 168 to 178**

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

		found, if not in the protocol	
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**Line 400 to 424**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**Line 400 to 424**
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**Line 426 to 429**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	**N/A** **no interim analyses are planned**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**Line 426 to 429**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**Line 432 to 434**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**Line 432 to 435**
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**N/A**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**Abstract : line 54** **Study population : line 149** **Recruitment: line 172-173**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**N/A**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality	**Line 434**

		before, during, and after the trial	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**Line 697**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**Line 428-429**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**N/A**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**line 54-55**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**line 54-55**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**N/A**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**Consent form, see supplementary file**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**Line 355 to 374**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" 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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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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ABSTRACT

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

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

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

KEYWORDS: Non-small-cell lung cancer, Metastatic, Exercise, Immunotherapy, Chemotherapy, Immunology

Word count: 5344

Strengths and limitations of this study.

- This study is the first to assess the feasibility effects of acute physical exercise performed within one hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-based doublet) infusion in mNSCLC patients.
- Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption condition during a submaximal endurance test on a cycle-ergometer at baseline and this test will allow individualisation of the intensity of the acute physical exercise program.
- The feasibility study assesses the acute physiological, immune, and metabolic response to a supervised acute moderate intensity physical exercise session in patients with mNSCLC.
  The unsupervised home-based walking program in the intervention arm aims to increase the level of physical activity in patients with mNSCLC and their cardiorespiratory fitness and physical capacity to perform acute physical exercise prior to chemo-immunotherapy infusion.
- The study concerns only one stage of lung cancer, participants must be eligible to immunotherapy and it's a study with a limited sample size (n=30).

INTRODUCTION

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

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

changes caused by acute exercise i.e., a single physical exercise bout, and cancer treatments(19). Immunomodulatory effects of acute physical exercise involve immune cell mobilisation in blood such as neutrophils, subsets of monocytes or lymphocytes involved in the host defence against tumours, seems to improve immunosurveillance (20). Acute physical exercise leads to a rapid increase in the mobilization of the peripheral activity of the sub-population of $CD56^{dim}$ NK cells during acute physical exercise of light to moderate intensity (21,22). A preclinical study reported that exercise training (voluntary running), through activation of epinephrine and IL-6, led to selective NK cell mobilization and limited tumour growth of several types of tumours (melanomas, liver, and lung mouse models) (23). In a recent study, the increase in PD-1+ CD8+ T cells was observed after a single exercise session (24). At the level of the adaptive immune system, acute exercise results in transient biphasic changes, i.e. increase of circulating lymphocytes during and immediately after exercise, followed by a transient decrease of blood lymphocytes below baseline level during recovery from exercise (1 hour), thought to be due to a redistribution of immune cells to peripheral tissues, including tumours, before return to basal level within a few hours (23,25). Moreover, recent preclinical studies suggested that physical exercise performed during chemotherapy infusion may have additional physiological benefits such as increase the blood flow leading to improved intra-tumoral perfusion and enhanced drug delivery (26–28). However, most of the available evidence on the benefits of physical exercise in cancer patients has been observed in interventions performed either after the treatment or during the interval between the chemotherapy cycles(29). Only two studies have evaluated the feasibility of low-intensity physical exercises during the chemotherapy infusion without adverse events, interference with chemotherapy, or exacerbation in symptoms (29,30). Recently, it has been suggested in preclinical studies that exercise performed during chemotherapy infusion could lead to improved perfusion of solid tumours, mitigating tumour hypoxia, and enhancing drug delivery to tumours (26,27,31). Similarly, by its effect on immune regulation, physical exercise prior to infusion may potentiate the effect of the immunotherapy. Recent preclinical evidence has suggested a beneficial effect of exercise

in addition to immunotherapy (anti–PD-1 immunotherapy) in a murine model of NSCLC, through increased necrosis and a decreased proliferative index of tumour cells (32).

Based on these findings, the main objective of the ERICA (Exercise inteReaction Immunotherapy Chemotherapy and cAncer) feasibility study is to evaluate the feasibility of a supervised acute physical exercise performed immediately prior to immunotherapy and chemotherapy infusion (i.e. a combination of pembrolizumab and pemetrexed-cis- or carboplatin for non-squamous cell carcinoma or paclitaxel-carboplatin for squamous cell carcinoma) in first-line treatment of metastatic NSCLC patients, and to assess if this planned exercise dose is safe and tolerable in this target patient population. The secondary objectives are to evaluate the effects of the supervised acute exercise before first-line treatment administration combined with an unsupervised home-based walking program, on 1) physical fitness, 2) PA level and sedentary lifestyle, 3) psychosocial factors (HRQoL and fatigue), 4) sleep quality, 5) body composition, 6) sarcopenia, 7) treatment response, 8) treatment completion rate, 9) related treatment toxicities, and 10) progression-free survival. Furthermore, this feasibility study will generate data on the effect of this exercise intervention on immune, metabolic, and inflammatory biomarkers as well as oxidative stress.

METHODS

STUDY DESIGN

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

Insert Figure 1

STUDY POPULATION

Inclusion criteria

Participants will have to meet all of the following eligibility criteria: 1) aged ≥ 18 and < 80 years; 2) diagnosed with a histologically confirmed metastatic NSCLC without EGFR mutation/ALK 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

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

Exclusion criteria

Patients will not be eligible in at least one of the following cases: 1) bone metastases with risk of fractures or unconsolidated pathologic fractures; 2) contraindication to the physical exercise proposed in this study (e.g. orthopaedic disorder such as disabling coxarthrosis or gonarthrosis, central nervous system disorders); 3) history or co-existence of other primary cancer (except in situ cancer regardless of the site, and/or basal cell carcinoma, and/or non-lung cancer in complete remission for more than 5 years) ; 4) severe undernutrition defined according to the French National Authority for Health (i.e. for adults aged ≥18 years and < 70: Body Mass Index (BMI) ≤ 17, weight loss ≥ 10% in 1 month, ≥15% in 6 months, or ≥ 15% compared to the usual weight before the disease diagnosis, or serum albumin < 30 g/l; for adults aged ≥70 years: BMI < 18, weight loss ≥ 10% in 1 month or ≥15% in 6 months, or serum albumin < 30 g/l) (33); 5) severe anaemia (haemoglobin ≤ 8 g/dl) in the past 30 days prior to enrolment; 6) history of cardiovascular disease or cardiovascular risk (i.e. chronic or poorly controlled coronary heart disease, peripheral arterial disease, cardiac arrhythmia, symptomatic heart disease, uncontrolled or untreated arterial hypertension, myocardial infarction diagnosed in the past 6 months, coronary angioplasty with or without stent implantation in the past 6 months, coronary artery bypass surgery in the past 12 months); 7) history of type 2 diabetes or glycated haemoglobin > 7% in the past 3 months prior to enrolment; 8) Stage IV Chronic obstructive pulmonary disease (forced expiratory volume in one second (FEV_1) < 30%).

RECRUITMENT

Participants will be recruited in Centre Léon Bérard, Lyon, France from December 2020. Eligible patients will be screened systematically based on electronic medical record during weekly multidisciplinary lung cancer board meetings, as seen in Figure 1. During a medical consultation before treatment initiation, an oncologist will propose the study to eligible patients and explain the study

objectives and protocol. Once the written informed consent is signed, patients will undergo the following screening tests prior to inclusion: (1) clinical examination including assessing Performance Status (PS) and Blood Pressure, (2) echocardiography and electrocardiogram performed by a cardiologist, and (3) for patients with diabetes, measurement of glycated haemoglobin. If these investigations confirm the patient's eligibility, the patient will be included in the study (D0). The end date for this study is planned in January 2023.

RANDOMIZATION

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

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

INTERVENTION

Treatment protocol

All patients in both exercise and control groups of this study will receive usual care and the same standard treatment protocol: pembrolizumab (200 mg) combined with carboplatin (AUC 5) plus pemetrexed (500 mg/m^2) with B9-B12 vitamin supplementation; carboplatin (AUC 6) plus paclitaxel (200 mg/m^2) every 3 weeks for 4 cycles; before pembrolizumab maintenance in squamous cell carcinoma or pembrolizumab plus pemetrexed maintenance for non-squamous cell carcinoma.

Physical Activity recommendations

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

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

Nutritional recommendations

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

Exercise Group

Acute physical exercise protocol prior to immunotherapy and chemotherapy infusion

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

Following a five-minute warm-up at 60% of Ventilation Threshold 1 (VT1), the participant will carry out 5 sets, alternating periods of 3 minutes at 70-80% of VT1 with 3 minutes at 110-120% of VT1 (≥ 35 Revolutions Per Minute (RPM)). The acute exercise intensity will be programmed according to the load reached at VT1 during the cycle ergometer endurance submaximal test. Heart rate (HR), load, RPM, dyspnoea, and perception of effort on a Borg-scale will be monitored. If the patient is no longer able to cycle at the load corresponding to 120% of his VT1, the clinical exercise physiologist will decrease the load to 110% of VT1. In case of exercise-induced desaturation (≥ 4% of the measured value at rest or ≤ 93%), the clinical exercise physiologist will stop the exercise until the rest value of oxygen

saturation. In addition to detailed explanation by the qualified clinical exercise physiologist, patients receive written support materials at baseline (D0).

Home-based walking program

During the 3-month intervention, between each treatment cycle (3 weeks), patients will follow an unsupervised home-based walking program consisting of an individual goal of a number of steps per day. Each patient will receive a Fitbit® Inspire activity tracker with an instruction to wear it continuously during the intervention. They will be advised to achieve at least 6,000 daily steps which corresponds to a physically active lifestyle in a patient population (37). Ten days after each treatment cycle, the clinical exercise physiologist will contact the patients by phone to assess and encourage adherence to the home-based walking program. Depending on the average number of steps performed in the past ten days, personalized objectives might be redefined to increase the target number of daily steps. For patients who reach more than 6,000 steps per day the initial target number of 6,000 steps will be increased by 30%. The target number of steps was set within a maximum of 7800 steps above the average number of steps in the previous week. Patients who do not reach 6,000 daily steps, will be advised to gradually increase the target number of steps per day according to the patient's abilities. Number of steps will be collected by regular sync with the mobile phone application (Fitbit®) of the activity tracker or by a step logbook.

EVALUATIONS

Modalities

The assessments of the repeated measures (PA level, anthropometric, HRQoL, fatigue, sleep quality, and sarcopenia) in both groups will be performed before the first cycle of anti-neoplastic treatment (baseline, D0), at the end of the 4 cycles of treatment (M3), and at 6 months after study inclusion (M6) (Table 1).

Table 1. Data collection schedule for the ERICA study

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

DATA COLLECTION

Sociodemographic and clinical data

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

Anthropometric data

Anthropometric data including body weight (kilogram), height (centimeter, cm), waist (cm) and hip (cm) circumference will be collected. Waist circumference will be measured around the abdomen midway between the last floating rib and the iliac crest. Hip circumference will be measured horizontally through the upper margin of the pubis. The body mass index is calculated as the body weight in kilograms divided by the square of the height in meters.

Physical fitness

Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption (VO_2) condition during a submaximal endurance test on a cycle-ergometer at baseline. This test will allow individualisation of the intensity of the acute physical exercise program. Following a 5-minute warm-up at 20% of the participant's maximum theoretical load**,** power will be increased by a constant amount of 5 watts each 30 seconds until VT1 will be reached. The clinical exercise physiologist will ensure that the patient maintains a minimum pedalling frequency above 35 RPM throughout the test. HR, ventilation (VE), oxygen saturation (SaO_2), VO_2, and carbon dioxide production (VCO_2) will be measured by a gas analyser (MetaMax 3b, Cortex Biophysik, Leipzig, Germany) and continuously monitored. In addition, the perception of the difficulty and dyspnoea will be evaluated at the end of the test using the Borg Rating Perceived Exertion questionnaire(38). The clinical exercise physiologist will stop the test when the patient exceeded the VT1. The test will end with a 6-minute recovery phase. The VT1 will be determined graphically when the ventilatory equivalent of oxygen (VE/VO_2) starts to increase and will be confirmed by Respiratory Exchange Ratio that strictly exceeds 1 (Wasserman method).

The lower body muscular strength will be evaluated by measuring the maximum isometric strength of the knee extensors (DFS II Series Digital; Force Gauges Chatillon, Largo, FL, USA). Participants will be seated on a chair with the knee joint at 90°, arms crossed over the chest, and the dynamometer attached to the ankle. Participants were advised to extend their leg as hard as possible within 3 seconds upon the instructor’s signal. Only the dominant leg will be tested three times (with 2 minutes rest between each contraction), and the best performance will be considered.

The maximum isometric upper limb strength will be measured by a hand dynamometer (Jamar Plus Digital Hand Dynamometer, Patterson Medical, Huthwaite, United Kingdom) (39,40,41). Participants will be seated with their back straight and elbows bent at 90°. They will be asked to squeeze the handgrip as strongly as possible for five seconds to achieve maximum strength. Two measurements will be taken on each hand and the best performance will be recorded.

Physical activity level

The PA level will be measured by the Godin Leisure-Time Physical Activity Questionnaire (GLTAPQ) (42). The GLTAPQ is a short, self-administered questionnaire with three questions designed to obtain information on the number of times an individual engages in low, moderate, and intense "leisure-time PA" periods of at least 15 minutes during a typical week. The score of the GSLTPAQ (Leisure Score Index, LSI) will be obtained by using the following formula: (light PA frequency × 3) + (moderate PA frequency × 5) + (vigorous PA frequency × 9). People with LSI ≥ 24 will be classified as active, while people with LSI ≤ 23 will be classified as insufficiently active (estimated energy expenditure < 14 Kcal/kg/week). The level of PA will be investigated by the change of a daily number of steps thanks to the activity tracker (only in the intervention group).

Body composition and sarcopenia

Body composition and sarcopenia will be analysed using the Computed Tomography (CT) scans. CT scan cross-section at the level of the 3rd lumbar vertebra represents the method of choice for assessment of sarcopenia in the oncology setting given that CT scan as part of routine cancer diagnostic procedures is largely available (43). The thresholds for identifying muscle range from -29 to +150 HU, subcutaneous and intramuscular adipose tissue from -190 to -30 HU, visceral adipose tissue from -150 to -50 HU and bone from +152 to 1000 HU (44–46). Skeletal muscle radiodensity (SMD) that represents muscle quality will be measured using the average radiation attenuation of the tissue in Hounsfield Units (HU). A low SMD is defined by values below the threshold of 37.8 HU. An estimate of lean body

mass (LBM) will be calculated using the formula (LBM (kg) = [(L3 Muscle measured by CT (cm^2) × 0.3) + 6.06]) (47).

Nutrition

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

Health-related quality of life

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

Fatigue

Fatigue will be assessed by the EORTC-QLQ module measuring cancer-related fatigue (EORTC QLQ-FA12) (52). This self-questionnaire includes 12 items that assess physical, cognitive, and emotional

fatigue related to cancer. Participants will respond on a Likert scale ranging from "not at all" to "a lot". All scores will be transformed into a scale from 0 to 100, with a higher score indicating a higher degree of fatigue.

Sleep quality

The perceived quality of sleep will be assessed by the Insomnia Severity Index which measures the severity of insomnia. The questionnaire consists of 7 items rated on a 5-point scale ranging from 0 ("none") to 4 ("very severe") (53,54). This self-questionnaire will evaluate the severity of the patient's sleep difficulties (initial, maintenance, and morning insomnia), the degree of sleep dissatisfaction, the level of interference with daily functioning, the degree of appearance of sleep difficulties, and the level of anxiety related to insomnia. The total score of the items varies between 0 and 28. A high score indicates greater sleep difficulties.

Social vulnerability

Social deprivation will be assessed using the EPICES score (Evaluation of Deprivation and Inequalities in Health Examination Centres) (55). The EPICES score will be obtained by adding up the points of the 11 binary questions ("Yes"/"No") of the self-questionnaire. This score ranges from 0 "no precariousness" to 100 "highest precariousness" with the threshold for deprivation at 30.

Biomarkers of the immune system, inflammation, sarcopenia, and oxidative stress

Blood samples will be collected during the first and last (forth) treatment cycle: in the exercise group, samples will be collected before exercise (S1), after exercise (S2), and 12 hours after the start of treatment (S3); in the control group: samples will be collected 40 minutes before the infusion of treatment (S1), just before the infusion of treatment (S2) and 12 hours after the start of treatment (S3). Blood test procedures will follow laboratory standards. Each blood sample will be collected in 3 x 10mL Ethylenediaminetetraacetic acid tubes and then centrifuged (10 minutes at 800G) within one

hour (maintained at 4°C before and during centrifugation). After the centrifuge, plasma will be collected and aliquoted in 5 cryotubes of 1 mL and the Peripheral Blood Mononuclear Cell (PBMC) will be collected and aliquoted in 3 cryotubes (5 to 7 millions cells per tube). These cryotubes will be frozen at -80°C and stored in nitrogen at the center for the duration of the study. At the end of the study, biomarkers of immunity, sarcopenia, and inflammation will be analysed. We will measure i) immune biomarkers (NK cells, B lymphocytes, T lymphocytes, monocytes, sub-populations of dendritic cells on frozen PBMC); ii) plasma biomarkers of sarcopenia and inflammation (Myostatin, Activin, Cortisol, Tumor Necrosis Factor-α, Interferon-γ, Interleukin-1β, Interleukin-6, Follistatin, Growth Differentiation Factor 5, Bone morphogenetic protein 14, GDF15, Interleukin-10, Interleukin-15, NH3, Aminogram, C-reactive protein, insulin); and iii) plasma oxidative stress (Superoxide dismutase, catalase, malondialdehyde, glutathione peroxidase, Xanthine Myeloperoxidase, and Xanthine oxidase). Finally, the blood samples will be also used to analyse the glucose (OneTouch Verio®) and lactate (LACTATE PRO II) metabolism by a mobile device. Patients will be asked to complete a questionnaire regarding the taking of antibiotics, anti-inflammatory, and antioxidants in the 48 hours prior to blood collection.

Toxicities

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

STATISTICAL ANALYSIS

SAMPLE SIZE

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

planned exercise dose is safe and tolerable in this target patient population(56). In the context of a feasibility study without a concrete hypothesis and in absence of previous studies in this population, the sample size was defined empirically. Taking into account the number of mNSCLC patients who receive first line chemotherapy (i.e. pemetrexed-platinum or taxol-platinum) combined with Pembrolizumab each year in Centre Léon Bérard (Lyon), we plan to include 30 patients over a 18 months period. This number will be sufficient to assess if the planned exercise dose is safe and tolerable in this target patient population, and the sample size falls within the range of sample sizes recommended in the literature for feasibility trials (57).

Although the main objective is to study the feasibility of physical exercise prior to the infusion of treatments, the evaluation of the biological objectives requires randomization to have reference measures. We have chosen to unbalance the randomization (2:1) so that more patients will benefit from the intervention proposed in the ERICA study.

STATISTICAL METHODS

All statistical analyses will be on an exploratory basis on all data from study subjects. Given the limited sample size, non-parametric tests will be performed. Qualitative data will be presented using their frequencies and percentages. Quantitative data will be presented using the number of observations, mean, standard deviation, median, minimum, and maximum. For both types of data, the number of missing data will be presented if necessary.

The feasibility of the ERICA study will be assessed at the end of the intervention (M3) in the exercise group only, according to the adherence rate by calculating the ratio of the number of acute physical exercise sessions performed to the number of acute physical exercise sessions planned before the immunotherapy/chemotherapy. The tolerability will be assessed by the relative dose intensity of exercise. The safety will be assessed by the occurrence of adverse events related to the physical exercise intervention. The acceptability (i.e. the proportion of patients who accept to participate in the

study among eligible patients) and the attrition (i.e. the proportion of patients who withdraw their participation from the study among patients initially enrolled) will be calculated. In the exercise group, the acceptability of the activity tracker, the observance of the home-walking program, and the safety of the intervention (the number, type, and timing of adverse events that occurred) will be assessed.

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

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

The results will allow to formulate the hypotheses and determine sample size for a subsequent multicenter randomized efficacy study.

Statistical analyses will be carried out using R statistical software (58).

DATA MONITORING

The database for clinical data will be managed using REDCap (Research Electronic Data Capture) (59,60) software hosted at CLB. The access to the database will be secured (personal ID and password required) with different levels of security depending on the role within the study. The investigator will have access to the final dataset.

PATIENT AND PUBLIC INVOLVEMENT

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

ETHICAL AND DISSEMINATION

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

DISCUSSION

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

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

a submaximal cardiopulmonary exercise test with a continuous gas exchange analysis. Because of the comorbidities, the tumour location and the lack of information about high intensity exercise effects, the present study targets acute exercise of submaximal intensity.

Home-based exercises are a beneficial approach to reducing symptoms and improving exercise capacity as well as the quality of life in patients with NSCLC (69). The unsupervised home-based walking program in the intervention arm aims to increase the level of physical activity in patients with mNSCLC and their cardiorespiratory fitness and physical capacity to perform acute physical exercise prior to chemo-immunotherapy infusion (15). Also, chronic exercise can favourably modulate inflammation and immune-related factors (19,70). Activity trackers are innovative tools increasingly used to promote an active lifestyle and to objectively measure the PA level of cancer patients (71–73). Trackers have been used in a randomized controlled trial to encourage patients with mNSCLC to maintain their PA by recommending a targeted number of steps (74). In a previous study by the team, the use of activity trackers have shown pertinent results in women with metastatic breast cancer (75,76). The combination of these two intervention modalities (acute exercise and unsupervised walking programme) allows us to offer an intervention adapted to this population in order to have sufficient physiological stimulation to observe changes in the immune system.

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

INNOVATION AND STUDY RELEVANCE

The ERICA study will provide clinical, physical, and psychosocial insights into the feasibility of acute exercise prior to first-line chemo-immunotherapy infusion in patients with mNSCLC. In particular, exploratory data on the safety and tolerability of the proposed exercise dose and schedule in the target

patient population will be obtained. This feasibility study will further generate preliminary data on the acute physiological, immune, and metabolic response to the achieved exercise dose in patients with mNSCLC. The ERICA study will provide valuable information to design a large-scale adequately powered randomized controlled trial to assess the efficacy on clinically important endpoints (e.g. progression free survival) in patients with mNSCLC receiving first-line chemo-immunotherapy.

REFERENCES

1. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2018;29:iv192–237.

2. ASCO. Lung Cancer - Non-Small Cell - Statistics [Internet]. Cancer.Net. 2021 [cited 2021 Jul 3]. Available from: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics

3. Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non–Small-Cell Lung Cancer. JCO. 2020;JCO.19.03136.

4. Low JL, Walsh RJ, Ang Y, Chan G, Soo RA. The evolving immuno-oncology landscape in advanced lung cancer: first-line treatment of non-small cell lung cancer. Ther Adv Med Oncol [Internet]. 2019 [cited 2019 Nov 5];11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6716180/

5. Brahmer JR, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial. The Lancet Oncology. 2017 Dec;18(12):1600–9.

6. Polanski J, Jankowska-Polanska B, Rosinczuk J, Chabowski M, Szymanska-Chabowska A. Quality of life of patients with lung cancer. Onco Targets Ther. 2016;9:1023–8.

7. Camps C, del Pozo N, Blasco A, Blasco P, Sirera R. Importance of Quality of Life in Patients with Non–Small-Cell Lung Cancer. Clinical Lung Cancer. 2009;10(2):83–90.

8. Garassino MC, Gadgeel S, Esteban E, Felip E, Speranza G, Domine M, et al. Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Oncology. 2020;21(3):387–97.

9. Steffen McLouth LE, Lycan TW, Levine BJ, Gabbard J, Ruiz J, Farris M, et al. Patient-Reported Outcomes From Patients Receiving Immunotherapy or Chemoimmunotherapy for Metastatic Non–Small-Cell Lung Cancer in Clinical Practice. Clinical Lung Cancer. 2019;21(3):255-263.e4.

10. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126–31.

11. Hwang C-L, Yu C-J, Shih J-Y, Yang P-C, Wu Y-T. Effects of exercise training on exercise capacity in

patients with non-small cell lung cancer receiving targeted therapy. Support Care Cancer. 2012;20(12):3169–77.

12. Chen H-M, Tsai C-M, Wu Y-C, Lin K-C, Lin C-C. Effect of walking on circadian rhythms and sleep quality of patients with lung cancer: a randomised controlled trial. Br J Cancer. 2016;115(11):1304–12.

13. Dhillon HM, Bell ML, van der Ploeg HP, Turner JD, Kabourakis M, Spencer L, et al. Impact of physical activity on fatigue and quality of life in people with advanced lung cancer: a randomized controlled trial. Annals of Oncology. 2017;28(8):1889–97.

14. Zhang L-L, Wang S-Z, Chen H-L, Yuan A-Z. Tai Chi Exercise for Cancer-Related Fatigue in Patients With Lung Cancer Undergoing Chemotherapy: A Randomized Controlled Trial. Journal of Pain and Symptom Management. 2016;51(3):504–11.

15. Peddle-McIntyre CJ, Singh F, Thomas R, Newton RU, Galvão DA, Cavalheri V. Exercise training for advanced lung cancer. Cochrane Lung Cancer Group, editor. Cochrane Database of Systematic Reviews [Internet]. 2019 [cited 2019 Sep 17]; Available from: http://doi.wiley.com/10.1002/14651858.CD012685.pub2

16. Quist M, Adamsen L, Rørth M, Laursen JH, Christensen KB, Langer SW. The Impact of a Multidimensional Exercise Intervention on Physical and Functional Capacity, Anxiety, and Depression in Patients With Advanced-Stage Lung Cancer Undergoing Chemotherapy. Integr Cancer Ther. 2015;14(4):341–9.

17. Avancini A, Sartori G, Gkountakos A, Casali M, Trestini I, Tregnago D, et al. Physical Activity and Exercise in Lung Cancer Care: Will Promises Be Fulfilled? The Oncologist [Internet]. 2019;n/a(n/a). Available from: https://theoncologist.onlinelibrary.wiley.com/doi/abs/10.1634/theoncologist.2019-0463

18. Activité physique. Prévention et traitement des maladies chroniques Éditions EDP Sciences, janvier 2019, 824 pages, Collection Expertise collective ISBN 978-2-7598-2328-4 [Internet]. [cited 2021 Jul 4]. Available from: https://www.inserm.fr/sites/default/files/2019-02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf

19. Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour microenvironment. Nature Reviews Cancer. 2017;17(10):620–32.

20. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. J Sport Health Sci. 2019;8(3):201–17.

21. Bigley AB, Rezvani K, Chew C, Sekine T, Pistillo M, Crucian B, et al. Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells. Brain, Behavior, and Immunity. 2014;39:160–71.

22. Idorn M, Hojman P. Exercise-Dependent Regulation of NK Cells in Cancer Protection. Trends in

Molecular Medicine. 2016;22(7):565–77.

23. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al. Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. Cell Metabolism. 2016;23(3):554–62.

24. Wadley AJ, Cullen T, Vautrinot J, Keane G, Bishop NC, Coles SJ. High intensity interval exercise increases the frequency of peripheral PD-1+ CD8+ central memory T-cells and soluble PD-L1 in humans. Brain, Behavior, & Immunity - Health. 2020;3:100049.

25. Pedersen BK, Hoffman-Goetz L. Exercise and the Immune System: Regulation, Integration, and Adaptation. Physiological Reviews. 2000;80(3):1055–81.

26. Wiggins JM, Opoku-Acheampong AB, Baumfalk DR, Siemann DW, Behnke BJ. Exercise and the Tumor Microenvironment: Potential Therapeutic Implications. Exercise and Sport Sciences Reviews. 2018;46(1):56–64.

27. McCullough DJ, Stabley JN, Siemann DW, Behnke BJ. Modulation of Blood Flow, Hypoxia, and Vascular Function in Orthotopic Prostate Tumors During Exercise. J Natl Cancer Inst [Internet]. 2014 [cited 2020 Jan 8];106(4). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3982888/

28. Schadler KL, Thomas NJ, Galie PA, Bhang DH, Roby KC, Addai P, et al. Tumor vessel normalization after aerobic exercise enhances chemotherapeutic efficacy. Oncotarget. 2016;7(40):65429–40.

29. Thomas VJ, Seet-Lee C, Marthick M, Cheema BS, Boyer M, Edwards KM. Aerobic exercise during chemotherapy infusion for cancer treatment: a novel randomised crossover safety and feasibility trial. Support Care Cancer. 2020;28(2):625–32.

30. Kerrigan K. A pilot study of aerobic exercise performed in breast cancer patients during chemotherapy infusion. | Journal of Clinical Oncology [Internet]. 2010 [cited 2020 Aug 11]. Available from: https://ascopubs.org/doi/10.1200/jco.2010.28.15_suppl.e19527

31. Ashcraft KA, Warner AB, Jones LW, Dewhirst MW. Exercise as Adjunct Therapy in Cancer. Seminars in Radiation Oncology. 2018;29(1):16–24.

32. Martín-Ruiz A, Fiuza-Luces C, Rincón-Castanedo C, Fernández-Moreno D, Martínez-Martínez E, Martín-Acosta P, et al. Benefits of exercise and immunotherapy in a murine model of human non–small-cell lung carcinoma. 2020;16.

33. Alexandre P. Haute Autorité de santé. 2019;142.

34. Macmillan Cancer Support. Physical activity in patients with metastatic bone disease: Guidance for healthcare professionals. 2018 [Internet]. [cited 2021 Jul 4]. Available from:

https://cdn.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/1784-10061/physical-activity-for-people-with-metastatic-bone-disease-guidance-tcm9-326004

35. Senesse P, Bachmann P, Bensadoun RJ, Besnard I, Bourdel-Marchasson I, Bouteloup C, et al. Nutrition chez le patient adulte atteint de cancer : textes courts. Nutrition Clinique et Métabolisme. 2012;26(4):151–8.

36. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clinical Nutrition. 2017;36(1):11–48.

37. Tudor-Locke C, Craig CL, Aoyagi Y, Bell RC, Croteau KA, De Bourdeaudhuij I, et al. How many steps/day are enough? For older adults and special populations. Int J Behav Nutr Phys Act. 2011;8(1):80.

38. Borg G, Hassmén P, Lagerström M. Perceived exertion related to heart rate and blood lactate during arm and leg exercise. Europ J Appl Physiol. 1987;56(6):679–85.

39. Kilgour RD, Vigano A, Trutschnigg B, Lucar E, Borod M, Morais JA. Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients. Support Care Cancer. 2013 Dec;21(12):3261–70.

40. Anand A, Gajra A. Hand Grip Dynamometry as Prognostic and Predictive Marker in Older Patients With Cancer. J Gerontol Geriatr Res [Internet]. 2018 [cited 2020 Jun 19];07(03). Available from: https://www.omicsonline.org/open-access/hand-grip-dynamometry-as-prognostic-and-predictive-marker-in-older-patients-with-cancer-2167-7182-1000471-102218.html

41. Trutschnigg B, Kilgour RD, Reinglas J, Rosenthall L, Hornby L, Morais JA, et al. Precision and reliability of strength (Jamar vs. Biodex handgrip) and body composition (dual-energy X-ray absorptiometry vs. bioimpedance analysis) measurements in advanced cancer patients. Appl Physiol Nutr Metab. 2008;33(6):1232–9.

42. Amireault S, Godin G, Lacombe J, Sabiston CM. The use of the Godin-Shephard Leisure-Time Physical Activity Questionnaire in oncology research: a systematic review. BMC Med Res Methodol [Internet]. 2015 [cited 2020 May 28];15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4542103/

43. Tosato M, Marzetti E, Cesari M, Savera G, Miller RR, Bernabei R, et al. Measurement of muscle mass in sarcopenia: from imaging to biochemical markers. Aging Clin Exp Res. 2017 Feb;29(1):19–27.

44. Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, et al. Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. Am J Clin Nutr. 1990 Aug;52(2):214–8.

45. Miller KD, Jones E, Yanovski JA, Shankar R, Feuerstein I, Falloon J. Visceral abdominal-fat accumulation associated with use of indinavir. Lancet. 1998 Mar 21;351(9106):871–5.

46. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol. 1998 Jul;85(1):115–22.

47. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997–1006.

48. Thibault R, Goujon N, Le Gallic E, Clairand R, Sébille V, Vibert J, et al. Use of 10-point analogue scales to estimate dietary intake: A prospective study in patients nutritionally at-risk. Clinical Nutrition. 2009;28(2):134–40.

49. Hjermstad MJ, Fossa SD, Bjordal K, Kaasa S. Test/retest study of the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire. JCO. 1995;13(5):1249–54.

50. Koller M, Shamieh O, Hjermstad MJ, Hornslien K, Young T, Chalk T, et al. Psychometric properties of the updated EORTC module for assessing quality of life in patients with lung cancer (QLQ-LC29): an international, observational field study. The Lancet Oncology. 2020;21(5):723–32.

51. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. European Journal of Cancer. 1994;30(5):635–42.

52. Weis J, Tomaszewski KA, Hammerlid E, Ignacio Arraras J, Conroy T, Lanceley A, et al. International Psychometric Validation of an EORTC Quality of Life Module Measuring Cancer Related Fatigue (EORTC QLQ-FA12). JNCI: Journal of the National Cancer Institute [Internet]. 2017 [cited 2020 May 28];109(5). Available from: https://academic.oup.com/jnci/article/doi/10.1093/jnci/djw273/2972669

53. Savard M-H, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer patients: INSOMNIA SEVERITY INDEX AND CANCER. Psycho-Oncology. 2005;14(6):429–41.

54. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: Psychometric Indicators to Detect Insomnia Cases and Evaluate Treatment Response. Sleep. 2011;34(5):601–8.

55. Sass C, Dupré C, Giordanella JP, Girard F, Guenot C, Labbe É, et al. Le score Epices : un score individuel de précarité. Construction du score et mesure des relations avec des données de santé, dans une population de 197 389 personnes. 2006;4.

56. Jones LW. Precision Oncology Framework for Investigation of Exercise As Treatment for Cancer. JCO. 2015;33(35):4134–7.

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

Cancer Care. 2019;28(1):e12946.

67. Dittus KL, Gramling RE, Ades PA. Exercise interventions for individuals with advanced cancer: A systematic review. Preventive Medicine. 2017;104:124–32.

68. Heywood R, McCarthy AL, Skinner TL. Safety and feasibility of exercise interventions in patients with advanced cancer: a systematic review. Support Care Cancer. 2017 Oct;25(10):3031–50.

69. Yang M, Liu L, Gan C, Qiu L, Jiang X, He X, et al. Effects of home-based exercise on exercise capacity, symptoms, and quality of life in patients with lung cancer: A meta-analysis. European Journal of Oncology Nursing. 2020;49:101836.

70. Nieman DC, Lila MA, Gillitt ND. Immunometabolism: A Multi-Omics Approach to Interpreting the Influence of Exercise and Diet on the Immune System. Annu Rev Food Sci Technol. 2019;10:341–63.

71. Gresham G, Schrack J, Gresham LM, Shinde AM, Hendifar AE, Tuli R, et al. Wearable activity monitors in oncology trials: Current use of an emerging technology. Contemporary Clinical Trials. 2018;64:13–21.

72. Haberlin C, O'Dwyer T, Mockler D, Moran J, O'Donnell DM, Broderick J. The use of eHealth to promote physical activity in cancer survivors: a systematic review. Support Care Cancer. 2018;26(10):3323–36.

73. Turner RR, Steed L, Quirk H, Greasley RU, Saxton JM, Taylor SJ, et al. Interventions for promoting habitual exercise in people living with and beyond cancer. Cochrane Database Syst Rev [Internet]. 2018 [cited 2019 Oct 29];2018(9). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6513653/

74. Naito T, Mitsunaga S, Miura S, Tatematsu N, Inano T, Mouri T, et al. Feasibility of early multimodal interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer. J Cachexia Sarcopenia Muscle. 2019;10(1):73–83.

75. Delrieu L, Anota A, Trédan O, Freyssenet D, Maire A, Canada B, et al. Design and methods of a national, multicenter, randomized and controlled trial to assess the efficacy of a physical activity program to improve health-related quality of life and reduce fatigue in women with metastatic breast cancer: ABLE02 trial. BMC Cancer [Internet]. 2020 [cited 2021 Apr 15];20. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7333295/

76. Delrieu L, Martin A, Touillaud M, Pérol O, Morelle M, Febvey-Combes O, et al. Sarcopenia and serum biomarkers of oxidative stress after a 6-month physical activity intervention in women with metastatic breast cancer: results from the ABLE feasibility trial. Breast Cancer Res Treat [Internet]. 2021 [cited 2021 Jun 13]; Available from: https://link.springer.com/10.1007/s10549-021-06238-z

DECLARATIONS

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIAL

Not applicable

COMPETING INTERESTS

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

MG, OP, BF, VP, PM and MP designed the trial and obtained funding. MG, OP, BF, VP, MP and LD developed the study protocol. BF, PM and MP contributed to the medical part of the protocol. MV, TW, CC and MCC brought their immunologic expertise. PS brought his biological expertise. MG, OP fulfilled administrative procedures for this project. MG, OP, BF and VP wrote this manuscript. All the authors reviewed and contributed to the final version of the manuscript.

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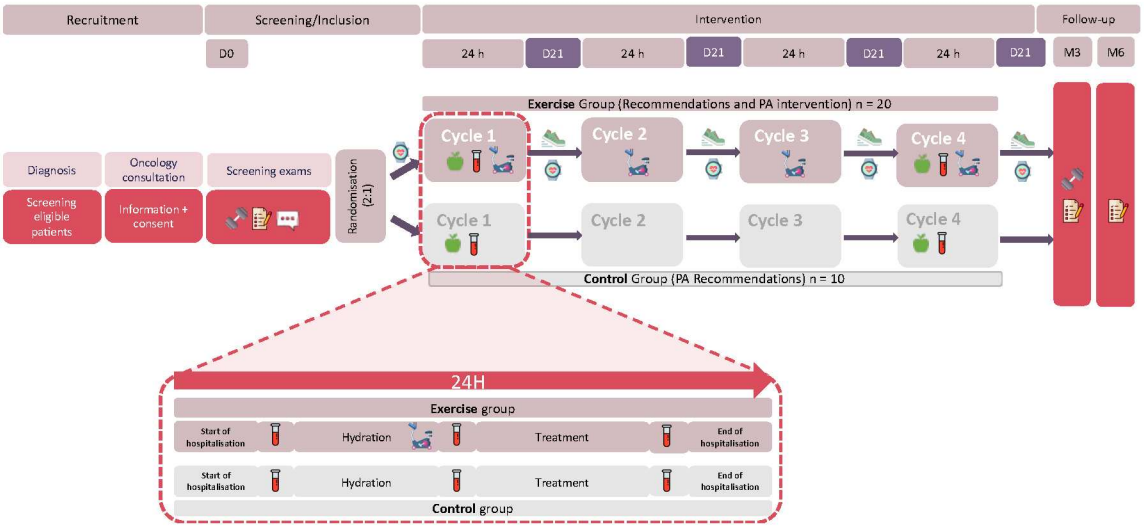
Figure 1: Flow chart of the ERICA study, France (original flow chart)


Recruitment
Screening/Inclusion
Intervention
Follow-up
D0
24 h
D21
24 h
D21
24 h
D21
24 h
D21
M3
M6
Exercise Group (Recommendations and PA intervention) n = 20
Diagnosis
Oncology consultation
Screening exams
Screening eligible patients
Information + consent
Randomisation (2:1)
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Control Group (PA Recommendations) n = 10
24H
Exercise group
Start of hospitalisation
Hydration
Treatment
End of hospitalisation
Start of hospitalisation
Hydration
Treatment
End of hospitalisation
Control group

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

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

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**
Methods: Participants, interventions, and outcomes			
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**
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**
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**
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**
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**
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**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**Page 7-8**

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

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

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**Page 28**
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**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**N/A**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**Page 2**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**Page 2**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**N/A**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**Consent form, see supplementary file**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**Page 15**

*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" license.

BMJ Open

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

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

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

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

KEYWORDS: Non-small-cell lung cancer, Metastatic, Exercise, Immunotherapy, Chemotherapy, Immunology

Word count: 5580

Strengths and limitations of this study.

- This study is the first to assess the feasibility effects of acute physical exercise performed within one hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-based doublet) infusion in mNSCLC patients.
- Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption condition during a submaximal endurance test on a cycle-ergometer at baseline and this test will allow individualisation of the intensity of the acute physical exercise program.
- The feasibility study assesses the acute physiological, immune, and metabolic response to a supervised acute moderate intensity physical exercise session in patients with mNSCLC. The unsupervised home-based walking program in the intervention arm aims to increase the level of physical activity in patients with mNSCLC and their cardiorespiratory fitness and physical capacity to perform acute physical exercise prior to chemo-immunotherapy infusion.
- The study concerns only one stage of lung cancer, participants must be eligible to immunotherapy and it's a study with a limited sample size (n=30).

INTRODUCTION

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

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

changes caused by acute exercise i.e., a single physical exercise bout, and cancer treatments(19). Immunomodulatory effects of acute physical exercise involve immune cell mobilisation in blood such as neutrophils, subsets of monocytes or lymphocytes involved in the host defence against tumours, seems to improve immunosurveillance (20). Acute physical exercise leads to a rapid increase in the mobilization of the peripheral activity of the sub-population of $CD56^{dim}$ NK cells during acute physical exercise of light to moderate intensity (21,22). A preclinical study reported that exercise training (voluntary running), through activation of epinephrine and IL-6, led to selective NK cell mobilization and limited tumour growth of several types of tumours (melanomas, liver, and lung mouse models) (23). In a recent study, the increase in PD-1+ CD8+ T cells was observed after a single exercise session (24)**.** At the level of the adaptive immune system, acute exercise results in transient biphasic changes, i.e. increase of circulating lymphocytes during and immediately after exercise, followed by a transient decrease of blood lymphocytes below baseline level during recovery from exercise (1 hour), thought to be due to a redistribution of immune cells to peripheral tissues, including tumours, before return to basal level within a few hours (23,25). Moreover, recent preclinical studies suggested that physical exercise performed during chemotherapy infusion may have additional physiological benefits such as increase the blood flow leading to improved intra-tumoral perfusion and enhanced drug delivery (26–28). However, to date, the optimal timing, duration and intensity of exercise that is feasible and produces clinically meaningful changes in tumour perfusion and immunmodulatory effects, needs to be determined (29). Most of the available evidence on the benefits of physical exercise in cancer patients has been observed in interventions performed either after the treatment or during the interval between the chemotherapy cycles(30). Only two studies have evaluated the feasibility of low-intensity physical exercises during the chemotherapy infusion without adverse events, interference with chemotherapy, or exacerbation in symptoms (30,31). Recently, it has been suggested in preclinical studies that exercise performed during chemotherapy infusion could lead to improved perfusion of solid tumours, mitigating tumour hypoxia, and enhancing drug delivery to tumours (26,27,32). Similarly, by its effect on immune regulation, physical exercise prior to infusion may

potentiate the effect of the immunotherapy. Recent preclinical evidence has suggested a beneficial effect of exercise in addition to immunotherapy (anti–PD-1 immunotherapy) in a murine model of NSCLC, through increased necrosis and a decreased proliferative index of tumour cells (33).

Based on these findings, the main objective of the ERICA (Exercise inteReaction Immunotherapy Chemotherapy and cAncer) feasibility study is to evaluate the feasibility of a supervised acute physical exercise performed immediately prior to immunotherapy and chemotherapy infusion (i.e. a combination of pembrolizumab and pemetrexed-cis- or carboplatin for non-squamous cell carcinoma or paclitaxel-carboplatin for squamous cell carcinoma) in first-line treatment of metastatic NSCLC patients, and to assess if this planned exercise dose is safe and tolerable in this target patient population. The secondary objectives are to evaluate the effects of the supervised acute exercise before first-line treatment administration combined with an unsupervised home-based walking program, on 1) physical fitness, 2) PA level and sedentary lifestyle, 3) psychosocial factors (HRQoL and fatigue), 4) sleep quality, 5) body composition, 6) sarcopenia, 7) treatment response, 8) treatment completion rate, 9) related treatment toxicities, and 10) progression-free survival. Furthermore, this feasibility study will generate data on the effect of this exercise intervention on immune, metabolic, and inflammatory biomarkers as well as oxidative stress.

METHODS

STUDY DESIGN

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

Insert Figure 1

STUDY POPULATION

Inclusion criteria

Participants will have to meet all of the following eligibility criteria: 1) aged ≥ 18 and < 80 years; 2) diagnosed with a histologically confirmed metastatic NSCLC without EGFR mutation/ALK 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 carcinoma) in combination with pembrolizumab; 4) Eastern Co-operative Oncology Group (ECOG) performance status ≤ 2; 5) able to engage in PA attested by a medical certificate by an oncologist; and 6) provide a dated and signed informed consent form before study enrolment.

Exclusion criteria

Patients will not be eligible in at least one of the following cases: 1) bone metastases with risk of fractures or unconsolidated pathologic fractures; 2) contraindication to the physical exercise proposed in this study (e.g. orthopaedic disorder such as disabling coxarthrosis or gonarthrosis, central nervous system disorders); 3) history or co-existence of other primary cancer (except in situ cancer regardless of the site, and/or basal cell carcinoma, and/or non-lung cancer in complete remission for more than 5 years) ; 4) severe undernutrition defined according to the French National Authority for Health (i.e. for adults aged ≥18 years and < 70: Body Mass Index (BMI) ≤ 17, weight loss ≥ 10% in 1 month, ≥15% in 6 months, or ≥ 15% compared to the usual weight before the disease diagnosis, or serum albumin < 30 g/l; for adults aged ≥70 years: BMI < 18, weight loss ≥ 10% in 1 month or ≥15% in 6 months, or serum albumin < 30 g/l) (34); 5) severe anaemia (haemoglobin ≤ 8 g/dl) in the past 30 days prior to enrolment; 6) history of cardiovascular disease or cardiovascular risk (i.e. chronic or poorly controlled coronary heart disease, peripheral arterial disease, cardiac arrhythmia, symptomatic heart disease, uncontrolled or untreated arterial hypertension, myocardial infarction diagnosed in the past 6 months, coronary angioplasty with or without stent implantation in the past 6 months, coronary artery bypass surgery in the past 12 months); 7) history of type 2 diabetes or glycated haemoglobin > 7% in the past 3 months prior to enrolment; 8) Stage IV Chronic obstructive pulmonary disease (forced expiratory volume in one second (FEV_1) < 30%).

RECRUITMENT

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

treatment initiation, an oncologist will propose the study to eligible patients and explain the study objectives and protocol. Once the written informed consent is signed, patients will undergo the following screening tests prior to inclusion: (1) clinical examination including assessing Performance Status (PS) and Blood Pressure, (2) echocardiography and electrocardiogram performed by a cardiologist, and (3) for patients with diabetes, measurement of glycated haemoglobin. If these investigations confirm the patient's eligibility, the patient will be included in the study (D0). The end date for this study is planned in January 2023.

RANDOMIZATION

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

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

INTERVENTION

Treatment protocol

All patients in both exercise and control groups of this study will receive usual care and the same standard treatment protocol: pembrolizumab (200 mg) combined with carboplatin (AUC 5) plus pemetrexed (500 mg/m^2) with B9-B12 vitamin supplementation; carboplatin (AUC 6) plus paclitaxel (200 mg/m^2) every 3 weeks for 4 cycles; before pembrolizumab maintenance in squamous cell carcinoma or pembrolizumab plus pemetrexed maintenance for non-squamous cell carcinoma.

Physical Activity recommendations

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

walking as much as possible and sitting as little as possible (WCRF, 2018). We have chosen to follow the recommendations of the Macmillan Cancer Support guide released in 2018, advising patients with bone metastases to have an active lifestyle on a daily basis and to maintain appropriate PA according to their physical abilities (35). Several individual strategies will be proposed to patients (e.g., using stairs whenever possible, walking to local shops).

Nutritional recommendations

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

Exercise Group

Acute physical exercise protocol prior to immunotherapy and chemotherapy infusion

Patients in the "exercise" group will perform a supervised acute physical exercise bout during hospitalization for treatment. It will be carried out within one hour prior to the immunotherapy and chemotherapy infusion, on a cycle ergometer (Monark Ergomedic 939 Novo) for each of the 4 cycles of treatment foreseen. The physical exercise will be supervised by a clinical exercise physiologist with experience in oncology. The physical exercise consists of a 35-min acute interval training, scheduled to terminate 15 minutes prior to infusion onset and will be individualized based on the results of a submaximal endurance test performed on a cycle ergometer by each patient (described below) prior to treatment (D0).

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

the load to 110% of VT1. In case of exercise-induced desaturation (≥ 4% of the measured value at rest or ≤ 93%), the clinical exercise physiologist will stop the exercise until the rest value of oxygen saturation. In addition to detailed explanation by the qualified clinical exercise physiologist, patients receive written support materials at baseline (D0).

Home-based walking program

During the 3-month intervention, between each treatment cycle (3 weeks), patients will follow an unsupervised home-based walking program consisting of an individual goal of a number of steps per day. Each patient will receive a Fitbit® Inspire activity tracker with an instruction to wear it continuously during the intervention. They will be advised to achieve at least 6,000 daily steps which corresponds to a physically active lifestyle in a patient population (38). Ten days after each treatment cycle, the clinical exercise physiologist will contact the patients by phone to assess and encourage adherence to the home-based walking program. Depending on the average number of steps performed in the past ten days, personalized objectives might be redefined to increase the target number of daily steps. For patients who reach more than 6,000 steps per day the initial target number of 6,000 steps will be increased by 30%. The target number of steps was set within a maximum of 7800 steps above the average number of steps in the previous week. Patients who do not reach 6,000 daily steps, will be advised to gradually increase the target number of steps per day according to the patient's abilities. Number of steps will be collected by regular sync with the mobile phone application (Fitbit®) of the activity tracker or by a step logbook.

EVALUATIONS

Modalities

The assessments of the repeated measures (PA level, anthropometric, HRQoL, fatigue, sleep quality, and sarcopenia) in both groups will be performed before the first cycle of anti-neoplastic treatment (baseline, D0), at the end of the 4 cycles of treatment (M3), and at 6 months after study inclusion (M6) (Table 1).

Table 1. Data collection schedule for the ERICA study

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

DATA COLLECTION

Sociodemographic and clinical data

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

Anthropometric data

Anthropometric data including body weight (kilogram), height (centimeter, cm), waist (cm) and hip (cm) circumference will be collected. Waist circumference will be measured around the abdomen midway between the last floating rib and the iliac crest. Hip circumference will be measured horizontally through the upper margin of the pubis. The body mass index is calculated as the body weight in kilograms divided by the square of the height in meters.

Physical fitness

Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption (VO_2) condition during a submaximal endurance test on a cycle-ergometer at baseline. This test will allow individualisation of the intensity of the acute physical exercise program. Following a 5-minute warm-up at 20% of the participant's maximum theoretical load**,** power will be increased by a constant amount of 5 watts each 30 seconds until VT1 will be reached. The clinical exercise physiologist will ensure that the patient maintains a minimum pedalling frequency above 35 RPM throughout the test. HR, ventilation (VE), oxygen saturation (SaO_2), VO_2, and carbon dioxide production (VCO_2) will be measured by a gas analyser (MetaMax 3b, Cortex Biophysik, Leipzig, Germany) and continuously monitored. In addition, the perception of the difficulty and dyspnoea will be evaluated at the end of the test using the Borg Rating Perceived Exertion questionnaire(39). The clinical exercise physiologist will stop the test when the patient exceeded the VT1. The test will end with a 6-minute recovery phase. The VT1 will be determined graphically when the ventilatory equivalent of oxygen (VE/VO_2) starts to increase and will be confirmed by Respiratory Exchange Ratio that strictly exceeds 1 (Wasserman method).

The lower body muscular strength will be evaluated by measuring the maximum isometric strength of the knee extensors (DFS II Series Digital; Force Gauges Chatillon, Largo, FL, USA). Participants will be seated on a chair with the knee joint at 90°, arms crossed over the chest, and the dynamometer attached to the ankle. Participants were advised to extend their leg as hard as possible within 3 seconds upon the instructor’s signal. Only the dominant leg will be tested three times (with 2 minutes rest between each contraction), and the best performance will be considered.

The maximum isometric upper limb strength will be measured by a hand dynamometer (Jamar Plus Digital Hand Dynamometer, Patterson Medical, Huthwaite, United Kingdom) (39,40,41). Participants will be seated with their back straight and elbows bent at 90°. They will be asked to squeeze the handgrip as strongly as possible for five seconds to achieve maximum strength. Two measurements will be taken on each hand and the best performance will be recorded. Hand grip strength is an easy and non-invasive method, well tolerated and routinely used in cancer patients to assess muscle strength and physical fitness.

Physical activity level

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

Lean body mass and sarcopenia

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

HU, subcutaneous and intramuscular adipose tissue from -190 to -30 HU, visceral adipose tissue from -150 to -50 HU and bone from +152 to 1000 HU (46–48). Skeletal muscle radiodensity (SMD) that represents muscle quality will be measured using the average radiation attenuation of the tissue in Hounsfield Units (HU). A low SMD is defined by values below the threshold of 37.8 HU. An estimate of lean body mass (LBM) will be calculated using the formula (LBM (kg) = [(L3 Muscle measured by CT (cm^2) × 0.3) + 6.06]) (49).

Nutrition

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

Health-related quality of life

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

Fatigue

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

Sleep quality

The perceived quality of sleep will be assessed by the Insomnia Severity Index which measures the severity of insomnia. The questionnaire consists of 7 items rated on a 5-point scale ranging from 0 ("none") to 4 ("very severe") (55,56). This self-questionnaire will evaluate the severity of the patient's sleep difficulties (initial, maintenance, and morning insomnia), the degree of sleep dissatisfaction, the level of interference with daily functioning, the degree of appearance of sleep difficulties, and the level of anxiety related to insomnia. The total score of the items varies between 0 and 28. A high score indicates greater sleep difficulties.

Social vulnerability

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

Biomarkers of the immune system, inflammation, sarcopenia, and oxidative stress

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

treatment (S3); in the control group: samples will be collected 40 minutes before the infusion of treatment (S1), just before the infusion of treatment (S2) and 12 hours after the start of treatment (S3). Blood test procedures will follow laboratory standards. Each blood sample will be collected in 3 x 10mL Ethylenediaminetetraacetic acid tubes and then centrifuged (10 minutes at 800G) within one hour (maintained at 4°C before and during centrifugation). After the centrifuge, plasma will be collected and aliquoted in 5 cryotubes of 1 mL and the Peripheral Blood Mononuclear Cell (PBMC) will be collected and aliquoted in 3 cryotubes (5 to 7 millions cells per tube). These cryotubes will be frozen at -80°C and stored in nitrogen at the center for the duration of the study. At the end of the study, biomarkers of immunity, sarcopenia, and inflammation will be analysed. We will measure i) immune biomarkers (NK cells, B lymphocytes, T lymphocytes, monocytes, sub-populations of dendritic cells on frozen PBMC); ii) plasma biomarkers of sarcopenia and inflammation (Myostatin, Activin, Cortisol, Tumor Necrosis Factor-α, Interferon-γ, Interleukin-1β, Interleukin-6, Follistatin, Growth Differentiation Factor 5, Bone morphogenetic protein 14, GDF15, Interleukin-10, Interleukin-15, NH3, Aminogram, C-reactive protein, insulin); and iii) plasma oxidative stress (Superoxide dismutase, catalase, malondialdehyde, glutathione peroxidase, Xanthine Myeloperoxidase, and Xanthine oxidase). Finally, the blood samples will be also used to analyse the glucose (OneTouch Verio®) and lactate (LACTATE PRO II) metabolism by a mobile device. Patients will be asked to complete a questionnaire regarding the taking of antibiotics, anti-inflammatory, and antioxidants in the 48 hours prior to blood collection.

Toxicities

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

STATISTICAL ANALYSIS

SAMPLE SIZE

The main objective of the current study is to evaluate the feasibility of an acute physical exercise program performed prior to the infusion of treatments in mNSCLC patients**,** and to assess if this planned exercise dose is safe and tolerable in this target patient population(58). In the context of a feasibility study without a concrete hypothesis and in absence of previous studies in this population, the sample size was defined empirically. Taking into account the number of mNSCLC patients who receive first line chemotherapy (i.e. pemetrexed-platinum or taxol-platinum) combined with Pembrolizumab each year in Centre Léon Bérard (Lyon), we plan to include 30 patients over a 18 months period. This number will be sufficient to assess if the planned exercise dose is safe and tolerable in this target patient population, and the sample size falls within the range of sample sizes recommended in the literature for feasibility trials (59).

Although the main objective is to study the feasibility of physical exercise prior to the infusion of treatments, the evaluation of the biological objectives requires randomization to have reference measures. We have chosen to unbalance the randomization (2:1) so that more patients will benefit from the intervention proposed in the ERICA study.

STATISTICAL METHODS

All statistical analyses will be on an exploratory basis on all data from study subjects. Given the limited sample size, non-parametric tests will be performed. Qualitative data will be presented using their frequencies and percentages. Quantitative data will be presented using the number of observations, mean, standard deviation, median, minimum, and maximum. For both types of data, the number of missing data will be presented if necessary.

The feasibility of the ERICA study will be assessed at the end of the intervention (M3) in the exercise group only, according to the adherence rate by calculating the ratio of the number of acute physical

exercise sessions performed to the number of acute physical exercise sessions planned before the immunotherapy/chemotherapy. The tolerability will be assessed by the relative dose intensity of exercise. The safety will be assessed by the occurrence of adverse events related to the physical exercise intervention. The acceptability (i.e. the proportion of patients who accept to participate in the study among eligible patients) and the attrition (i.e. the proportion of patients who withdraw their participation from the study among patients initially enrolled) will be calculated. In the exercise group, the acceptability of the activity tracker, the observance of the home-walking program, and the safety of the intervention (the number, type, and timing of adverse events that occurred) will be assessed.

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

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

The results will allow to formulate the hypotheses and determine sample size for a subsequent multicenter randomized efficacy study.

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

DATA MONITORING

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

PATIENT AND PUBLIC INVOLVEMENT

Prior to the present study, we administrated a questionnaire to lung cancer patients to collect their experience and preferences in terms of physical activity to practice during cancer treatments. The results were used to develop the ERICA physical activity intervention. As it is a feasibility study, the

findings will be used to adjust the intervention if necessary for the purpose of an efficacy randomised controlled trial. Global findings will be disseminated to participants at the end of the study if they wish.

ETHICAL AND DISSEMINATION

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

DISCUSSION

To our knowledge, ERICA is the first study to assess the feasibility and effects of acute physical exercise performed within one hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-based doublet) infusion in mNSCLC patients. Despite therapeutic advances, notably immunotherapy combined with chemotherapy, the prognosis of many patients with mNSCLC continues to be poor, and disease burden, cachexia, comorbidities, and treatment side effects lead to deconditioning and adversely affect exercise capacity in people with advanced NSCLC (17,63–66)**.** Conversely, evidence from meta-analyses suggests that exercise training in patients with advanced lung cancer could be feasible and safe with no serious adverse events reported and may improve or avoid the decline of physical capacity (15,67). However, the evidence regarding the benefits of exercise in mNSCLC patients remains limited and there is a lack of widespread awareness of the benefits of maintaining physical activity in this particular population (66,68–70). Furthermore, the high prevalence of comorbidities in mNSCLC patients, which may be exacerbated by the direct and indirect effects of cancer treatment, led to exclude patients at risk of cardiovascular events from studies (i.e. history of cardiovascular disease; abnormal electrocardiogram and/or echocardiography) or undernutrition.

Based on preclinical evidence of exercise in modulating the efficacy of cancer therapy, the present study assesses the feasibility of acute exercise of submaximal intensity in the target population. Current evidence on the benefits of physical exercise in cancer patients mainly stems from interventions performed either between the chemotherapy cycles or after end of treatment. Yet, a

feasibility study in patients with various tumours, mostly breast cancer, reported that exercise (i.e. 20 min of supervised low-intensity cycling) during chemotherapy infusion appears to be safe and feasible (30). To prescribe a safe and efficacious intensity of acute exercise intervention, we decided to realize a submaximal cardiopulmonary exercise test with a continuous gas exchange analysis. Because of the comorbidities, the tumour location, and the lack of information about high intensity exercise effects, the present study targets acute exercise of submaximal intensity.

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

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

INNOVATION AND STUDY RELEVANCE

The ERICA study will provide clinical, physical, and psychosocial insights into the feasibility of acute exercise prior to first-line chemo-immunotherapy infusion in patients with mNSCLC. In particular, exploratory data on the safety and tolerability of the proposed exercise dose and schedule in the target patient population will be obtained. This feasibility study will further generate preliminary data on the acute physiological, immune, and metabolic response to the achieved exercise dose in patients with mNSCLC. The ERICA study will provide valuable information to design a large-scale adequately powered randomized controlled trial to assess the efficacy on clinically important endpoints (e.g. progression free survival) in patients with mNSCLC receiving first-line chemo-immunotherapy.

DECLARATIONS

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIAL

Not applicable

COMPETING INTERESTS

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

MG, OP, BF, VP, PM and MP designed the trial and obtained funding. MG, OP, BF, VP, MP and LD developed the study protocol. BF, PM and MP contributed to the medical part of the protocol. MV, TW, CC and MCC brought their immunologic expertise. PS brought his biological expertise. MG, OP fulfilled administrative procedures for this project. MG, OP, BF and VP wrote this manuscript. All the authors reviewed and contributed to the final version of the manuscript.

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REFERENCES

1. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2018;29:iv192–237.

2. ASCO. Lung Cancer - Non-Small Cell - Statistics [Internet]. Cancer.Net. 2021 [cited 2021 Jul 3]. Available from: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics

3. Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non–Small-Cell Lung Cancer. JCO. 2020;JCO.19.03136.

4. Low JL, Walsh RJ, Ang Y, Chan G, Soo RA. The evolving immuno-oncology landscape in advanced lung cancer: first-line treatment of non-small cell lung cancer. Ther Adv Med Oncol [Internet]. 2019 [cited 2019 Nov 5];11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6716180/

5. Brahmer JR, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial. The Lancet Oncology. 2017 Dec;18(12):1600–9.

6. Polanski J, Jankowska-Polanska B, Rosinczuk J, Chabowski M, Szymanska-Chabowska A. Quality of life of patients with lung cancer. Onco Targets Ther. 2016;9:1023–8.

7. Camps C, del Pozo N, Blasco A, Blasco P, Sirera R. Importance of Quality of Life in Patients with Non–Small-Cell Lung Cancer. Clinical Lung Cancer. 2009;10(2):83–90.

8. Garassino MC, Gadgeel S, Esteban E, Felip E, Speranza G, Domine M, et al. Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Oncology. 2020;21(3):387–97.

9. Steffen McLouth LE, Lycan TW, Levine BJ, Gabbard J, Ruiz J, Farris M, et al. Patient-Reported Outcomes From Patients Receiving Immunotherapy or Chemoimmunotherapy for Metastatic Non–Small-Cell Lung Cancer in Clinical Practice. Clinical Lung Cancer. 2019;21(3):255-263.e4.

10. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126–31.

11. Hwang C-L, Yu C-J, Shih J-Y, Yang P-C, Wu Y-T. Effects of exercise training on exercise capacity in patients

with non-small cell lung cancer receiving targeted therapy. Support Care Cancer. 2012;20(12):3169–77.

12. Chen H-M, Tsai C-M, Wu Y-C, Lin K-C, Lin C-C. Effect of walking on circadian rhythms and sleep quality of patients with lung cancer: a randomised controlled trial. Br J Cancer. 2016;115(11):1304–12.

13. Dhillon HM, Bell ML, van der Ploeg HP, Turner JD, Kabourakis M, Spencer L, et al. Impact of physical activity on fatigue and quality of life in people with advanced lung cancer: a randomized controlled trial. Annals of Oncology. 2017;28(8):1889–97.

14. Zhang L-L, Wang S-Z, Chen H-L, Yuan A-Z. Tai Chi Exercise for Cancer-Related Fatigue in Patients With Lung Cancer Undergoing Chemotherapy: A Randomized Controlled Trial. Journal of Pain and Symptom Management. 2016;51(3):504–11.

15. Peddle-McIntyre CJ, Singh F, Thomas R, Newton RU, Galvão DA, Cavalheri V. Exercise training for advanced lung cancer. Cochrane Lung Cancer Group, editor. Cochrane Database of Systematic Reviews [Internet]. 2019 [cited 2019 Sep 17]; Available from: http://doi.wiley.com/10.1002/14651858.CD012685.pub2

16. Quist M, Adamsen L, Rørth M, Laursen JH, Christensen KB, Langer SW. The Impact of a Multidimensional Exercise Intervention on Physical and Functional Capacity, Anxiety, and Depression in Patients With Advanced-Stage Lung Cancer Undergoing Chemotherapy. Integr Cancer Ther. 2015;14(4):341–9.

17. Avancini A, Sartori G, Gkountakos A, Casali M, Trestini I, Tregnago D, et al. Physical Activity and Exercise in Lung Cancer Care: Will Promises Be Fulfilled? The Oncologist [Internet]. 2019;n/a(n/a). Available from: https://theoncologist.onlinelibrary.wiley.com/doi/abs/10.1634/theoncologist.2019-0463

18. Activité physique. Prévention et traitement des maladies chroniques Éditions EDP Sciences, janvier 2019, 824 pages, Collection Expertise collective ISBN 978-2-7598-2328-4 [Internet]. [cited 2021 Jul 4]. Available from: https://www.inserm.fr/sites/default/files/2019-02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf

19. Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour microenvironment. Nature Reviews Cancer. 2017;17(10):620–32.

20. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. J Sport Health Sci. 2019;8(3):201–17.

21. Bigley AB, Rezvani K, Chew C, Sekine T, Pistillo M, Crucian B, et al. Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells. Brain, Behavior, and Immunity. 2014;39:160–71.

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

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

third lumbar region in the assessment of sarcopenia. Critical Care. 2013 Nov 20;17(6):466.

45. Boutin RD, Yao L, Canter RJ, Lenchik L. Sarcopenia: Current Concepts and Imaging Implications. American Journal of Roentgenology. 2015 Sep;205(3):W255–66.

46. Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, et al. Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. Am J Clin Nutr. 1990 Aug;52(2):214–8.

47. Miller KD, Jones E, Yanovski JA, Shankar R, Feuerstein I, Falloon J. Visceral abdominal-fat accumulation associated with use of indinavir. Lancet. 1998 Mar 21;351(9106):871–5.

48. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol. 1998 Jul;85(1):115–22.

49. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997–1006.

50. Thibault R, Goujon N, Le Gallic E, Clairand R, Sébille V, Vibert J, et al. Use of 10-point analogue scales to estimate dietary intake: A prospective study in patients nutritionally at-risk. Clinical Nutrition. 2009;28(2):134–40.

51. Hjermstad MJ, Fossa SD, Bjordal K, Kaasa S. Test/retest study of the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire. JCO. 1995;13(5):1249–54.

52. Koller M, Shamieh O, Hjermstad MJ, Hornslien K, Young T, Chalk T, et al. Psychometric properties of the updated EORTC module for assessing quality of life in patients with lung cancer (QLQ-LC29): an international, observational field study. The Lancet Oncology. 2020;21(5):723–32.

53. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. European Journal of Cancer. 1994;30(5):635–42.

54. Weis J, Tomaszewski KA, Hammerlid E, Ignacio Arraras J, Conroy T, Lanceley A, et al. International Psychometric Validation of an EORTC Quality of Life Module Measuring Cancer Related Fatigue (EORTC QLQ-FA12). JNCI: Journal of the National Cancer Institute [Internet]. 2017 [cited 2020 May 28];109(5). Available from: https://academic.oup.com/jnci/article/doi/10.1093/jnci/djw273/2972669

55. Savard M-H, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer

patients: INSOMNIA SEVERITY INDEX AND CANCER. Psycho-Oncology. 2005;14(6):429–41.

56. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: Psychometric Indicators to Detect Insomnia Cases and Evaluate Treatment Response. Sleep. 2011;34(5):601–8.

57. Sass C, Dupré C, Giordanella JP, Girard F, Guenot C, Labbe É, et al. Le score Epices : un score individuel de précarité. Construction du score et mesure des relations avec des données de santé, dans une population de 197 389 personnes. 2006;4.

58. Jones LW. Precision Oncology Framework for Investigation of Exercise As Treatment for Cancer. JCO. 2015;33(35):4134–7.

59. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. BMC Med Res Methodol. 2013;13(1):104.

60. R Core Team (2020). — European Environment Agency [Internet]. [cited 2021 Jul 4]. Available from: https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-development-core-team-2006

61. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics. 2009;42(2):377–81.

62. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. Journal of Biomedical Informatics. 2019;95:103208.

63. Jones LW. Physical Activity and Lung Cancer Survivorship. In: Courneya KS, Friedenreich CM, editors. Physical Activity and Cancer [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010 [cited 2021 Mar 28]. p. 255–74. (Recent Results in Cancer Research; vol. 186). Available from: http://link.springer.com/10.1007/978-3-642-04231-7_11

64. Quist M, Langer SW, Lillelund C, Winther L, Laursen JH, Christensen KB, et al. Effects of an exercise intervention for patients with advanced inoperable lung cancer undergoing chemotherapy: A randomized clinical trial. Lung Cancer. 2020;145:76–82.

65. Nadler M, Bainbridge D, Tomasone J, Cheifetz O, Juergens RA, Sussman J. Oncology care provider perspectives on exercise promotion in people with cancer: an examination of knowledge, practices, barriers, and facilitators. Support Care Cancer. 2017;25(7):2297–304.

66. Wilk M, Kepski J, Kepska J, Casselli S, Szmit S. Exercise interventions in metastatic cancer disease: a literature review and a brief discussion on current and future perspectives. BMJ Support Palliat Care. 2020;10(4):404–10.

67. Singh B, Spence R, Steele ML, Hayes S, Toohey K. Exercise for Individuals With Lung Cancer: A Systematic Review and Meta-Analysis of Adverse Events, Feasibility, and Effectiveness. Semin Oncol Nurs. 2020;36(5):151076.

68. Granger CL, Parry SM, Edbrooke L, Abo S, Leggett N, Dwyer M, et al. Improving the delivery of physical activity services in lung cancer: A qualitative representation of the patient's perspective. European Journal of Cancer Care. 2019;28(1):e12946.

69. Dittus KL, Gramling RE, Ades PA. Exercise interventions for individuals with advanced cancer: A systematic review. Preventive Medicine. 2017;104:124–32.

70. Heywood R, McCarthy AL, Skinner TL. Safety and feasibility of exercise interventions in patients with advanced cancer: a systematic review. Support Care Cancer. 2017 Oct;25(10):3031–50.

71. Yang M, Liu L, Gan C, Qiu L, Jiang X, He X, et al. Effects of home-based exercise on exercise capacity, symptoms, and quality of life in patients with lung cancer: A meta-analysis. European Journal of Oncology Nursing. 2020;49:101836.

72. Nieman DC, Lila MA, Gillitt ND. Immunometabolism: A Multi-Omics Approach to Interpreting the Influence of Exercise and Diet on the Immune System. Annu Rev Food Sci Technol. 2019;10:341–63.

73. Gresham G, Schrack J, Gresham LM, Shinde AM, Hendifar AE, Tuli R, et al. Wearable activity monitors in oncology trials: Current use of an emerging technology. Contemporary Clinical Trials. 2018;64:13–21.

74. Haberlin C, O'Dwyer T, Mockler D, Moran J, O'Donnell DM, Broderick J. The use of eHealth to promote physical activity in cancer survivors: a systematic review. Support Care Cancer. 2018;26(10):3323–36.

75. Turner RR, Steed L, Quirk H, Greasley RU, Saxton JM, Taylor SJ, et al. Interventions for promoting habitual exercise in people living with and beyond cancer. Cochrane Database Syst Rev [Internet]. 2018 [cited 2019 Oct 29];2018(9). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6513653/

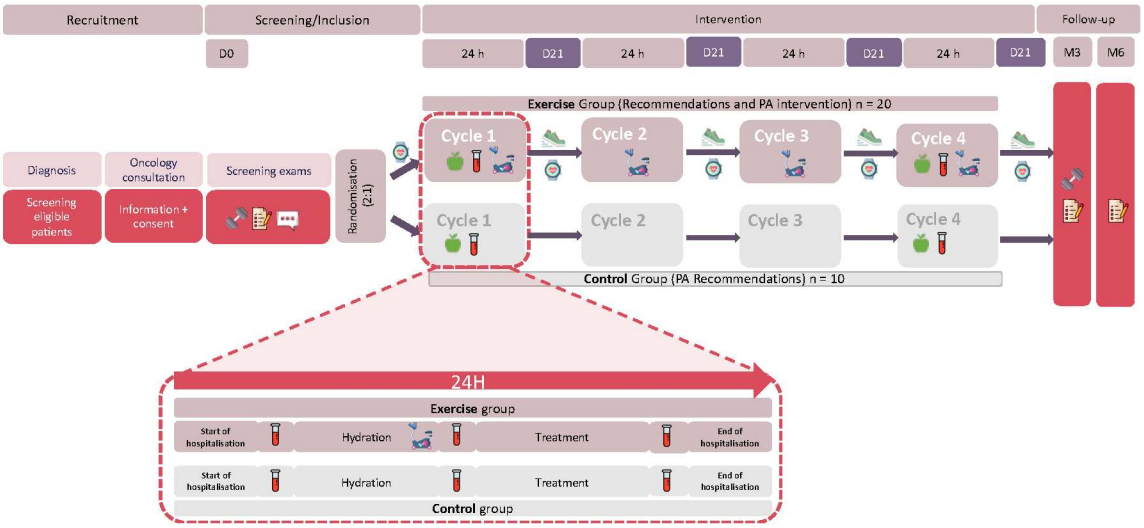
76. Naito T, Mitsunaga S, Miura S, Tatematsu N, Inano T, Mouri T, et al. Feasibility of early multimodal interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer. J Cachexia Sarcopenia Muscle. 2019;10(1):73–83.

77. Delrieu L, Anota A, Trédan O, Freyssenet D, Maire A, Canada B, et al. Design and methods of a national,

multicenter, randomized and controlled trial to assess the efficacy of a physical activity program to improve health-related quality of life and reduce fatigue in women with metastatic breast cancer: ABLE02 trial. BMC Cancer [Internet]. 2020 [cited 2021 Apr 15];20. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7333295/

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

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


Recruitment
Screening/Inclusion
Intervention
Follow-up
D0
24 h
D21
24 h
D21
24 h
D21
24 h
D21
M3
M6
Exercise Group (Recommendations and PA intervention) n = 20
Diagnosis
Oncology consultation
Screening exams
Screening eligible patients
Information + consent
Randomisation (2:1)
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Control Group (PA Recommendations) n = 10
24H
Exercise group
Start of hospitalisation
Hydration
Treatment
End of hospitalisation
Start of hospitalisation
Hydration
Treatment
End of hospitalisation
Control group

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

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

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**
Methods: Participants, interventions, and outcomes			
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**
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**
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**
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**
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**
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**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**Page 7-8**

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

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

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**Page 28**
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**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**N/A**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**Page 2**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**Page 2**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**N/A**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**Consent form, see supplementary file**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**Page 15**

*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" license.

BMJ Open

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

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

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

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

KEYWORDS: Non-small-cell lung cancer, Metastatic, Exercise, Immunotherapy, Chemotherapy, Immunology

Word count: 5580

Strengths and limitations of this study.

- This study is the first to assess the feasibility effects of acute physical exercise performed within one hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-based doublet) infusion in mNSCLC patients.
- Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption condition during a submaximal endurance test on a cycle-ergometer at baseline and this test will allow individualisation of the intensity of the acute physical exercise program.
- The feasibility study assesses the acute physiological, immune, and metabolic response to a supervised acute moderate intensity physical exercise session in patients with mNSCLC. The unsupervised home-based walking program in the intervention arm aims to increase the level of physical activity in patients with mNSCLC and their cardiorespiratory fitness and physical capacity to perform acute physical exercise prior to chemo-immunotherapy infusion.
- The study concerns only one stage of lung cancer, participants must be eligible to immunotherapy and it's a study with a limited sample size (n=30).

INTRODUCTION

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

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

changes caused by acute exercise i.e., a single physical exercise bout, and cancer treatments(19). Immunomodulatory effects of acute physical exercise involve immune cell mobilisation in blood such as neutrophils, subsets of monocytes or lymphocytes involved in the host defence against tumours, seems to improve immunosurveillance (20). Acute physical exercise leads to a rapid increase in the mobilization of the peripheral activity of the sub-population of $CD56^{dim}$ NK cells during acute physical exercise of light to moderate intensity (21,22). A preclinical study reported that exercise training (voluntary running), through activation of epinephrine and IL-6, led to selective NK cell mobilization and limited tumour growth of several types of tumours (melanomas, liver, and lung mouse models) (23). In a recent study, the increase in PD-1+ CD8+ T cells was observed after a single exercise session (24)**.** At the level of the adaptive immune system, acute exercise results in transient biphasic changes, i.e. increase of circulating lymphocytes during and immediately after exercise, followed by a transient decrease of blood lymphocytes below baseline level during recovery from exercise (1 hour), thought to be due to a redistribution of immune cells to peripheral tissues, including tumours, before return to basal level within a few hours (23,25). Moreover, recent preclinical studies suggested that physical exercise performed during chemotherapy infusion may have additional physiological benefits such as increase the blood flow leading to improved intra-tumoral perfusion and enhanced drug delivery (26–28). However, to date, the optimal timing, duration and intensity of exercise that is feasible and produces clinically meaningful changes in tumour perfusion and immunomodulatory effects, needs to be determined (29). Most of the available evidence on the benefits of physical exercise in cancer patients has been observed in interventions performed either after the treatment or during the interval between the chemotherapy cycles(30). Only two studies have evaluated the feasibility of low-intensity physical exercises during the chemotherapy infusion without adverse events, interference with chemotherapy, or exacerbation in symptoms (30,31). Recently, it has been suggested in preclinical studies that exercise performed during chemotherapy infusion could lead to improved perfusion of solid tumours, mitigating tumour hypoxia, and enhancing drug delivery to tumours (26,27,32). Similarly, by its effect on immune regulation, physical exercise prior to infusion may

potentiate the effect of the immunotherapy. Recent preclinical evidence has suggested a beneficial effect of exercise in addition to immunotherapy (anti–PD-1 immunotherapy) in a murine model of NSCLC, through increased necrosis and a decreased proliferative index of tumour cells (33).

Based on these findings, the main objective of the ERICA (Exercise inteReaction Immunotherapy Chemotherapy and cAncer) feasibility study is to evaluate the feasibility of a supervised acute physical exercise performed immediately prior to immunotherapy and chemotherapy infusion (i.e. a combination of pembrolizumab and pemetrexed-cis- or carboplatin for non-squamous cell carcinoma or paclitaxel-carboplatin for squamous cell carcinoma) in first-line treatment of metastatic NSCLC patients, and to assess if this planned exercise dose is safe and tolerable in this target patient population. The secondary objectives are to evaluate the effects of the supervised acute exercise before first-line treatment administration combined with an unsupervised home-based walking program, on 1) physical fitness, 2) PA level and sedentary lifestyle, 3) psychosocial factors (HRQoL and fatigue), 4) sleep quality, 5) body composition, 6) sarcopenia, 7) treatment response, 8) treatment completion rate, 9) related treatment toxicities, and 10) progression-free survival. Furthermore, this feasibility study will generate data on the effect of this exercise intervention on immune, metabolic, and inflammatory biomarkers as well as oxidative stress.

METHODS

STUDY DESIGN

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

Insert Figure 1

STUDY POPULATION

Inclusion criteria

Participants will have to meet all of the following eligibility criteria: 1) aged ≥ 18 and < 80 years; 2) diagnosed with a histologically confirmed metastatic NSCLC without EGFR mutation/ALK 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 carcinoma) in combination with pembrolizumab; 4) Eastern Co-operative Oncology Group (ECOG) performance status ≤ 2; 5) able to engage in PA attested by a medical certificate by an oncologist; and 6) provide a dated and signed informed consent form before study enrolment.

Exclusion criteria

Patients will not be eligible in at least one of the following cases: 1) bone metastases with risk of fractures or unconsolidated pathologic fractures; 2) contraindication to the physical exercise proposed in this study (e.g. orthopaedic disorder such as disabling coxarthrosis or gonarthrosis, central nervous system disorders); 3) history or co-existence of other primary cancer (except in situ cancer regardless of the site, and/or basal cell carcinoma, and/or non-lung cancer in complete remission for more than 5 years) ; 4) severe undernutrition defined according to the French National Authority for Health (i.e. for adults aged ≥18 years and < 70: Body Mass Index (BMI) ≤ 17, weight loss ≥ 10% in 1 month, ≥15% in 6 months, or ≥ 15% compared to the usual weight before the disease diagnosis, or serum albumin < 30 g/l; for adults aged ≥70 years: BMI < 18, weight loss ≥ 10% in 1 month or ≥15% in 6 months, or serum albumin < 30 g/l) (34); 5) severe anaemia (haemoglobin ≤ 8 g/dl) in the past 30 days prior to enrolment; 6) history of cardiovascular disease or cardiovascular risk (i.e. chronic or poorly controlled coronary heart disease, peripheral arterial disease, cardiac arrhythmia, symptomatic heart disease, uncontrolled or untreated arterial hypertension, myocardial infarction diagnosed in the past 6 months, coronary angioplasty with or without stent implantation in the past 6 months, coronary artery bypass surgery in the past 12 months); 7) history of type 2 diabetes or glycated haemoglobin > 7% in the past 3 months prior to enrolment; 8) Stage IV Chronic obstructive pulmonary disease (forced expiratory volume in one second (FEV_1) < 30%).

RECRUITMENT

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

treatment initiation, an oncologist will propose the study to eligible patients and explain the study objectives and protocol. Once the written informed consent is signed, patients will undergo the following screening tests prior to inclusion: (1) clinical examination including assessing Performance Status (PS) and Blood Pressure, (2) echocardiography and electrocardiogram performed by a cardiologist, and (3) for patients with diabetes, measurement of glycated haemoglobin. If these investigations confirm the patient's eligibility, the patient will be included in the study (D0). The end date for this study is planned in January 2023.

RANDOMIZATION

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

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

INTERVENTION

Treatment protocol

All patients in both exercise and control groups of this study will receive usual care and the same standard treatment protocol: pembrolizumab (200 mg) combined with carboplatin (AUC 5) plus pemetrexed (500 mg/m^2) with B9-B12 vitamin supplementation; carboplatin (AUC 6) plus paclitaxel (200 mg/m^2) every 3 weeks for 4 cycles; before pembrolizumab maintenance in squamous cell carcinoma or pembrolizumab plus pemetrexed maintenance for non-squamous cell carcinoma.

Physical Activity recommendations

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

walking as much as possible and sitting as little as possible (WCRF, 2018). We have chosen to follow the recommendations of the Macmillan Cancer Support guide released in 2018, advising patients with bone metastases to have an active lifestyle on a daily basis and to maintain appropriate PA according to their physical abilities (35). Several individual strategies will be proposed to patients (e.g., using stairs whenever possible, walking to local shops).

Nutritional recommendations

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

Exercise Group

Acute physical exercise protocol prior to immunotherapy and chemotherapy infusion

Patients in the "exercise" group will perform a supervised acute physical exercise bout during hospitalization for treatment. It will be carried out within one hour prior to the immunotherapy and chemotherapy infusion, on a cycle ergometer (Monark Ergomedic 939 Novo) for each of the 4 cycles of treatment foreseen. The physical exercise will be supervised by a clinical exercise physiologist with experience in oncology. The physical exercise consists of a 35-min acute interval training, scheduled to terminate 15 minutes prior to infusion onset and will be individualized based on the results of a submaximal endurance test performed on a cycle ergometer by each patient (described below) prior to treatment (D0).

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

the load to 110% of VT1. In case of exercise-induced desaturation (≥ 4% of the measured value at rest or ≤ 93%), the clinical exercise physiologist will stop the exercise until the rest value of oxygen saturation. In addition to detailed explanation by the qualified clinical exercise physiologist, patients receive written support materials at baseline (D0).

Home-based walking program

During the 3-month intervention, between each treatment cycle (3 weeks), patients will follow an unsupervised home-based walking program consisting of an individual goal of a number of steps per day. Each patient will receive a Fitbit® Inspire activity tracker with an instruction to wear it continuously during the intervention. They will be advised to achieve at least 6,000 daily steps which corresponds to a physically active lifestyle in a patient population (38). Ten days after each treatment cycle, the clinical exercise physiologist will contact the patients by phone to assess and encourage adherence to the home-based walking program. Depending on the average number of steps performed in the past ten days, personalized objectives might be redefined to increase the target number of daily steps. For patients who reach more than 6,000 steps per day the initial target number of 6,000 steps will be increased by 30%. The target number of steps was set within a maximum of 7800 steps above the average number of steps in the previous week. Patients who do not reach 6,000 daily steps, will be advised to gradually increase the target number of steps per day according to the patient's abilities. Number of steps will be collected by regular sync with the mobile phone application (Fitbit®) of the activity tracker or by a step logbook.

EVALUATIONS

Modalities

The assessments of the repeated measures (PA level, anthropometric, HRQoL, fatigue, sleep quality, and sarcopenia) in both groups will be performed before the first cycle of anti-neoplastic treatment (baseline, D0), at the end of the 4 cycles of treatment (M3), and at 6 months after study inclusion (M6) (Table 1).

Table 1. Data collection schedule for the ERICA study

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

DATA COLLECTION

Sociodemographic and clinical data

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

Anthropometric data

Anthropometric data including body weight (kilogram), height (centimeter, cm), waist (cm) and hip (cm) circumference will be collected. Waist circumference will be measured around the abdomen midway between the last floating rib and the iliac crest. Hip circumference will be measured horizontally through the upper margin of the pubis. The body mass index is calculated as the body weight in kilograms divided by the square of the height in meters.

Physical fitness

Cardiorespiratory fitness will be measured by evaluating the submaximal oxygen consumption (VO_2) condition during a submaximal endurance test on a cycle-ergometer at baseline. This test will allow individualisation of the intensity of the acute physical exercise program. Following a 5-minute warm-up at 20% of the participant's maximum theoretical load**,** power will be increased by a constant amount of 5 watts each 30 seconds until VT1 will be reached. The clinical exercise physiologist will ensure that the patient maintains a minimum pedalling frequency above 35 RPM throughout the test. HR, ventilation (VE), oxygen saturation (SaO_2), VO_2, and carbon dioxide production (VCO_2) will be measured by a gas analyser (MetaMax 3b, Cortex Biophysik, Leipzig, Germany) and continuously monitored. In addition, the perception of the difficulty and dyspnoea will be evaluated at the end of the test using the Borg Rating Perceived Exertion questionnaire(39). The clinical exercise physiologist will stop the test when the patient exceeded the VT1. The test will end with a 6-minute recovery phase. The VT1 will be determined graphically when the ventilatory equivalent of oxygen (VE/VO_2) starts to increase and will be confirmed by Respiratory Exchange Ratio that strictly exceeds 1 (Wasserman method).

The lower body muscular strength will be evaluated by measuring the maximum isometric strength of the knee extensors (DFS II Series Digital; Force Gauges Chatillon, Largo, FL, USA). Participants will be seated on a chair with the knee joint at 90°, arms crossed over the chest, and the dynamometer attached to the ankle. Participants were advised to extend their leg as hard as possible within 3 seconds upon the instructor’s signal. Only the dominant leg will be tested three times (with 2 minutes rest between each contraction), and the best performance will be considered.

The maximum isometric upper limb strength will be measured by a hand dynamometer (Jamar Plus Digital Hand Dynamometer, Patterson Medical, Huthwaite, United Kingdom) (39,40,41). Participants will be seated with their back straight and elbows bent at 90°. They will be asked to squeeze the handgrip as strongly as possible for five seconds to achieve maximum strength. Two measurements will be taken on each hand and the best performance will be recorded. Hand grip strength is an easy and non-invasive method, well tolerated and routinely used in cancer patients to assess muscle strength and physical fitness(42).

Physical activity level

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

Lean body mass and sarcopenia

Lean body mass and sarcopenia will be analysed using the Computed Tomography (CT) scans systematically available from routine care. CT scan cross-section at the level of the 3rd lumbar vertebra provides a reliable representation of the total body muscle mass and has therefore been widely adopted for the detection of sarcopenia in cancer patients and allows assessment without additional ionising radiation exposure given that CT scans as part of routine cancer diagnostic procedures is largely available(44,45). The thresholds for identifying muscle range from -29 to +150 HU,

subcutaneous and intramuscular adipose tissue from -190 to -30 HU, visceral adipose tissue from -150 to -50 HU and bone from +152 to 1000 HU (46–48). Skeletal muscle radiodensity (SMD) that represents muscle quality will be measured using the average radiation attenuation of the tissue in Hounsfield Units (HU). A low SMD is defined by values below the threshold of 37.8 HU. An estimate of lean body mass (LBM) will be calculated using the formula (LBM (kg) = [(L3 Muscle measured by CT (cm^2) × 0.3) + 6.06]) (49).

Nutrition

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

Health-related quality of life

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

Fatigue

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

Sleep quality

The perceived quality of sleep will be assessed by the Insomnia Severity Index which measures the severity of insomnia. The questionnaire consists of 7 items rated on a 5-point scale ranging from 0 ("none") to 4 ("very severe") (55,56). This self-questionnaire will evaluate the severity of the patient's sleep difficulties (initial, maintenance, and morning insomnia), the degree of sleep dissatisfaction, the level of interference with daily functioning, the degree of appearance of sleep difficulties, and the level of anxiety related to insomnia. The total score of the items varies between 0 and 28. A high score indicates greater sleep difficulties.

Social vulnerability

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

Biomarkers of the immune system, inflammation, sarcopenia, and oxidative stress

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

treatment (S3); in the control group: samples will be collected 40 minutes before the infusion of treatment (S1), just before the infusion of treatment (S2) and 12 hours after the start of treatment (S3). Blood test procedures will follow laboratory standards. Each blood sample will be collected in 3 x 10mL Ethylenediaminetetraacetic acid tubes and then centrifuged (10 minutes at 800G) within one hour (maintained at 4°C before and during centrifugation). After the centrifuge, plasma will be collected and aliquoted in 5 cryotubes of 1 mL and the Peripheral Blood Mononuclear Cell (PBMC) will be collected and aliquoted in 3 cryotubes (5 to 7 millions cells per tube). These cryotubes will be frozen at -80°C and stored in nitrogen at the center for the duration of the study. At the end of the study, biomarkers of immunity, sarcopenia, and inflammation will be analysed. We will measure i) immune biomarkers (NK cells, B lymphocytes, T lymphocytes, monocytes, sub-populations of dendritic cells on frozen PBMC); ii) plasma biomarkers of sarcopenia and inflammation (Myostatin, Activin, Cortisol, Tumor Necrosis Factor-α, Interferon-γ, Interleukin-1β, Interleukin-6, Follistatin, Growth Differentiation Factor 5, Bone morphogenetic protein 14, GDF15, Interleukin-10, Interleukin-15, NH3, Aminogram, C-reactive protein, insulin); and iii) plasma oxidative stress (Superoxide dismutase, catalase, malondialdehyde, glutathione peroxidase, Xanthine Myeloperoxidase, and Xanthine oxidase). Finally, the blood samples will be also used to analyse the glucose (OneTouch Verio®) and lactate (LACTATE PRO II) metabolism by a mobile device. Patients will be asked to complete a questionnaire regarding the taking of antibiotics, anti-inflammatory, and antioxidants in the 48 hours prior to blood collection.

Toxicities

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

STATISTICAL ANALYSIS

SAMPLE SIZE

The main objective of the current study is to evaluate the feasibility of an acute physical exercise program performed prior to the infusion of treatments in mNSCLC patients**,** and to assess if this planned exercise dose is safe and tolerable in this target patient population(58). In the context of a feasibility study without a concrete hypothesis and in absence of previous studies in this population, the sample size was defined empirically. Taking into account the number of mNSCLC patients who receive first line chemotherapy (i.e. pemetrexed-platinum or taxol-platinum) combined with Pembrolizumab each year in Centre Léon Bérard (Lyon), we plan to include 30 patients over a 18 months period. This number will be sufficient to assess if the planned exercise dose is safe and tolerable in this target patient population, and the sample size falls within the range of sample sizes recommended in the literature for feasibility trials (59).

Although the main objective is to study the feasibility of physical exercise prior to the infusion of treatments, the evaluation of the biological objectives requires randomization to have reference measures. We have chosen to unbalance the randomization (2:1) so that more patients will benefit from the intervention proposed in the ERICA study.

STATISTICAL METHODS

All statistical analyses will be on an exploratory basis on all data from study subjects. Given the limited sample size, non-parametric tests will be performed. Qualitative data will be presented using their frequencies and percentages. Quantitative data will be presented using the number of observations, mean, standard deviation, median, minimum, and maximum. For both types of data, the number of missing data will be presented if necessary.

The feasibility of the ERICA study will be assessed at the end of the intervention (M3) in the exercise group only, according to the adherence rate by calculating the ratio of the number of acute physical

exercise sessions performed to the number of acute physical exercise sessions planned before the immunotherapy/chemotherapy. The tolerability will be assessed by the relative dose intensity of exercise. The safety will be assessed by the occurrence of adverse events related to the physical exercise intervention. The acceptability (i.e. the proportion of patients who accept to participate in the study among eligible patients) and the attrition (i.e. the proportion of patients who withdraw their participation from the study among patients initially enrolled) will be calculated. In the exercise group, the acceptability of the activity tracker, the observance of the home-walking program, and the safety of the intervention (the number, type, and timing of adverse events that occurred) will be assessed.

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

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

The results will allow to formulate the hypotheses and determine sample size for a subsequent multicenter randomized efficacy study.

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

DATA MONITORING

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

PATIENT AND PUBLIC INVOLVEMENT

Prior to the present study, we administrated a questionnaire to lung cancer patients to collect their experience and preferences in terms of physical activity to practice during cancer treatments. The results were used to develop the ERICA physical activity intervention. As it is a feasibility study, the

findings will be used to adjust the intervention if necessary for the purpose of an efficacy randomised controlled trial. Global findings will be disseminated to participants at the end of the study if they wish.

ETHICAL AND DISSEMINATION

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

DISCUSSION

To our knowledge, ERICA is the first study to assess the feasibility and effects of acute physical exercise performed within one hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-based doublet) infusion in mNSCLC patients. Despite therapeutic advances, notably immunotherapy combined with chemotherapy, the prognosis of many patients with mNSCLC continues to be poor, and disease burden, cachexia, comorbidities, and treatment side effects lead to deconditioning and adversely affect exercise capacity in people with advanced NSCLC (17,63–66)**.** Conversely, evidence from meta-analyses suggests that exercise training in patients with advanced lung cancer could be feasible and safe with no serious adverse events reported and may improve or avoid the decline of physical capacity (15,67). However, the evidence regarding the benefits of exercise in mNSCLC patients remains limited and there is a lack of widespread awareness of the benefits of maintaining physical activity in this particular population (66,68–70). Furthermore, the high prevalence of comorbidities in mNSCLC patients, which may be exacerbated by the direct and indirect effects of cancer treatment, led to exclude patients at risk of cardiovascular events from studies (i.e. history of cardiovascular disease; abnormal electrocardiogram and/or echocardiography) or undernutrition.

Based on preclinical evidence of exercise in modulating the efficacy of cancer therapy, the present study assesses the feasibility of acute exercise of submaximal intensity in the target population. Current evidence on the benefits of physical exercise in cancer patients mainly stems from interventions performed either between the chemotherapy cycles or after end of treatment. Yet, a

feasibility study in patients with various tumours, mostly breast cancer, reported that exercise (i.e. 20 min of supervised low-intensity cycling) during chemotherapy infusion appears to be safe and feasible (30). To prescribe a safe and efficacious intensity of acute exercise intervention, we decided to realize a submaximal cardiopulmonary exercise test with a continuous gas exchange analysis. Because of the comorbidities, the tumour location, and the lack of information about high intensity exercise effects, the present study targets acute exercise of submaximal intensity.

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

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

INNOVATION AND STUDY RELEVANCE

The ERICA study will provide clinical, physical, and psychosocial insights into the feasibility of acute exercise prior to first-line chemo-immunotherapy infusion in patients with mNSCLC. In particular, exploratory data on the safety and tolerability of the proposed exercise dose and schedule in the target patient population will be obtained. This feasibility study will further generate preliminary data on the acute physiological, immune, and metabolic response to the achieved exercise dose in patients with mNSCLC. The ERICA study will provide valuable information to design a large-scale adequately powered randomized controlled trial to assess the efficacy on clinically important endpoints (e.g. progression free survival) in patients with mNSCLC receiving first-line chemo-immunotherapy.

DECLARATIONS

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIAL

Not applicable

COMPETING INTERESTS

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

MG, OP, BF, VP, PM and MP designed the trial and obtained funding. MG, OP, BF, VP, MP and LD developed the study protocol. BF, PM and MP contributed to the medical part of the protocol. MV, TW, CC and MCC brought their immunologic expertise. PS brought his biological expertise. MG, OP fulfilled administrative procedures for this project. MG, OP, BF and VP wrote this manuscript. All the authors reviewed and contributed to the final version of the manuscript.

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REFERENCES

1. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2018;29:iv192–237.

2. ASCO. Lung Cancer - Non-Small Cell - Statistics [Internet]. Cancer.Net. 2021 [cited 2021 Jul 3]. Available from: https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics

3. Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non–Small-Cell Lung Cancer. JCO. 2020;JCO.19.03136.

4. Low JL, Walsh RJ, Ang Y, Chan G, Soo RA. The evolving immuno-oncology landscape in advanced lung cancer: first-line treatment of non-small cell lung cancer. Ther Adv Med Oncol [Internet]. 2019 [cited 2019 Nov 5];11. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6716180/

5. Brahmer JR, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial. The Lancet Oncology. 2017 Dec;18(12):1600–9.

6. Polanski J, Jankowska-Polanska B, Rosinczuk J, Chabowski M, Szymanska-Chabowska A. Quality of life of patients with lung cancer. Onco Targets Ther. 2016;9:1023–8.

7. Camps C, del Pozo N, Blasco A, Blasco P, Sirera R. Importance of Quality of Life in Patients with Non–Small-Cell Lung Cancer. Clinical Lung Cancer. 2009;10(2):83–90.

8. Garassino MC, Gadgeel S, Esteban E, Felip E, Speranza G, Domine M, et al. Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet Oncology. 2020;21(3):387–97.

9. Steffen McLouth LE, Lycan TW, Levine BJ, Gabbard J, Ruiz J, Farris M, et al. Patient-Reported Outcomes From Patients Receiving Immunotherapy or Chemoimmunotherapy for Metastatic Non–Small-Cell Lung Cancer in Clinical Practice. Clinical Lung Cancer. 2019;21(3):255-263.e4.

10. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126–31.

11. Hwang C-L, Yu C-J, Shih J-Y, Yang P-C, Wu Y-T. Effects of exercise training on exercise capacity in

patients with non-small cell lung cancer receiving targeted therapy. Support Care Cancer. 2012;20(12):3169–77.

12. Chen H-M, Tsai C-M, Wu Y-C, Lin K-C, Lin C-C. Effect of walking on circadian rhythms and sleep quality of patients with lung cancer: a randomised controlled trial. Br J Cancer. 2016;115(11):1304–12.

13. Dhillon HM, Bell ML, van der Ploeg HP, Turner JD, Kabourakis M, Spencer L, et al. Impact of physical activity on fatigue and quality of life in people with advanced lung cancer: a randomized controlled trial. Annals of Oncology. 2017;28(8):1889–97.

14. Zhang L-L, Wang S-Z, Chen H-L, Yuan A-Z. Tai Chi Exercise for Cancer-Related Fatigue in Patients With Lung Cancer Undergoing Chemotherapy: A Randomized Controlled Trial. Journal of Pain and Symptom Management. 2016;51(3):504–11.

15. Peddle-McIntyre CJ, Singh F, Thomas R, Newton RU, Galvão DA, Cavalheri V. Exercise training for advanced lung cancer. Cochrane Lung Cancer Group, editor. Cochrane Database of Systematic Reviews [Internet]. 2019 [cited 2019 Sep 17]; Available from: http://doi.wiley.com/10.1002/14651858.CD012685.pub2

16. Quist M, Adamsen L, Rørth M, Laursen JH, Christensen KB, Langer SW. The Impact of a Multidimensional Exercise Intervention on Physical and Functional Capacity, Anxiety, and Depression in Patients With Advanced-Stage Lung Cancer Undergoing Chemotherapy. Integr Cancer Ther. 2015;14(4):341–9.

17. Avancini A, Sartori G, Gkountakos A, Casali M, Trestini I, Tregnago D, et al. Physical Activity and Exercise in Lung Cancer Care: Will Promises Be Fulfilled? The Oncologist [Internet]. 2019;n/a(n/a). Available from: https://theoncologist.onlinelibrary.wiley.com/doi/abs/10.1634/theoncologist.2019-0463

18. Activité physique. Prévention et traitement des maladies chroniques Éditions EDP Sciences, janvier 2019, 824 pages, Collection Expertise collective ISBN 978-2-7598-2328-4 [Internet]. [cited 2021 Jul 4]. Available from: https://www.inserm.fr/sites/default/files/2019-02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf

19. Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour microenvironment. Nature Reviews Cancer. 2017;17(10):620–32.

20. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. J Sport Health Sci. 2019;8(3):201–17.

21. Bigley AB, Rezvani K, Chew C, Sekine T, Pistillo M, Crucian B, et al. Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells. Brain, Behavior, and Immunity. 2014;39:160–71.

22. Idorn M, Hojman P. Exercise-Dependent Regulation of NK Cells in Cancer Protection. Trends in

Molecular Medicine. 2016;22(7):565–77.

23. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al. Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. Cell Metabolism. 2016;23(3):554–62.

24. Wadley AJ, Cullen T, Vautrinot J, Keane G, Bishop NC, Coles SJ. High intensity interval exercise increases the frequency of peripheral PD-1+ CD8+ central memory T-cells and soluble PD-L1 in humans. Brain, Behavior, & Immunity - Health. 2020;3:100049.

25. Pedersen BK, Hoffman-Goetz L. Exercise and the Immune System: Regulation, Integration, and Adaptation. Physiological Reviews. 2000;80(3):1055–81.

26. Wiggins JM, Opoku-Acheampong AB, Baumfalk DR, Siemann DW, Behnke BJ. Exercise and the Tumor Microenvironment: Potential Therapeutic Implications. Exercise and Sport Sciences Reviews. 2018;46(1):56–64.

27. McCullough DJ, Stabley JN, Siemann DW, Behnke BJ. Modulation of Blood Flow, Hypoxia, and Vascular Function in Orthotopic Prostate Tumors During Exercise. J Natl Cancer Inst [Internet]. 2014 [cited 2020 Jan 8];106(4). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3982888/

28. Schadler KL, Thomas NJ, Galie PA, Bhang DH, Roby KC, Addai P, et al. Tumor vessel normalization after aerobic exercise enhances chemotherapeutic efficacy. Oncotarget. 2016;7(40):65429–40.

29. Schumacher O, Galvão DA, Taaffe DR, Chee R, Spry N, Newton RU. Exercise modulation of tumour perfusion and hypoxia to improve radiotherapy response in prostate cancer. Prostate Cancer Prostatic Dis. 2021 Mar;24(1):1–14.

30. Thomas VJ, Seet-Lee C, Marthick M, Cheema BS, Boyer M, Edwards KM. Aerobic exercise during chemotherapy infusion for cancer treatment: a novel randomised crossover safety and feasibility trial. Support Care Cancer. 2020;28(2):625–32.

31. Kerrigan K. A pilot study of aerobic exercise performed in breast cancer patients during chemotherapy infusion. | Journal of Clinical Oncology [Internet]. 2010 [cited 2020 Aug 11]. Available from: https://ascopubs.org/doi/10.1200/jco.2010.28.15_suppl.e19527

32. Ashcraft KA, Warner AB, Jones LW, Dewhirst MW. Exercise as Adjunct Therapy in Cancer. Seminars in Radiation Oncology. 2018;29(1):16–24.

33. Martín-Ruiz A, Fiuza-Luces C, Rincón-Castanedo C, Fernández-Moreno D, Martínez-Martínez E, Martín-Acosta P, et al. Benefits of exercise and immunotherapy in a murine model of human non–small-cell lung carcinoma. 2020;16.

34. Alexandre P. Haute Autorité de santé. 2019;142.

35. Macmillan Cancer Support. Physical activity in patients with metastatic bone disease: Guidance for healthcare professionals. 2018 [Internet]. [cited 2021 Jul 4]. Available from: https://cdn.macmillan.org.uk/dfsmedia/1a6f23537f7f4519bb0cf14c45b2a629/1784-10061/physical-activity-for-people-with-metastatic-bone-disease-guidance-tcm9-326004

36. Senesse P, Bachmann P, Bensadoun RJ, Besnard I, Bourdel-Marchasson I, Bouteloup C, et al. Nutrition chez le patient adulte atteint de cancer : textes courts. Nutrition Clinique et Métabolisme. 2012;26(4):151–8.

37. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clinical Nutrition. 2017;36(1):11–48.

38. Tudor-Locke C, Craig CL, Aoyagi Y, Bell RC, Croteau KA, De Bourdeaudhuij I, et al. How many steps/day are enough? For older adults and special populations. Int J Behav Nutr Phys Act. 2011;8(1):80.

39. Borg G, Hassmén P, Lagerström M. Perceived exertion related to heart rate and blood lactate during arm and leg exercise. Europ J Appl Physiol. 1987;56(6):679–85.

40. Kilgour RD, Vigano A, Trutschnigg B, Lucar E, Borod M, Morais JA. Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients. Support Care Cancer. 2013 Dec;21(12):3261–70.

41. Anand A, Gajra A. Hand Grip Dynamometry as Prognostic and Predictive Marker in Older Patients With Cancer. J Gerontol Geriatr Res [Internet]. 2018 [cited 2020 Jun 19];07(03). Available from: https://www.omicsonline.org/open-access/hand-grip-dynamometry-as-prognostic-and-predictive-marker-in-older-patients-with-cancer-2167-7182-1000471-102218.html

42. Trutschnigg B, Kilgour RD, Reinglas J, Rosenthall L, Hornby L, Morais JA, et al. Precision and reliability of strength (Jamar vs. Biodex handgrip) and body composition (dual-energy X-ray absorptiometry vs. bioimpedance analysis) measurements in advanced cancer patients. Appl Physiol Nutr Metab. 2008;33(6):1232–9.

43. Amireault S, Godin G, Lacombe J, Sabiston CM. The use of the Godin-Shephard Leisure-Time Physical Activity Questionnaire in oncology research: a systematic review. BMC Med Res Methodol [Internet]. 2015 [cited 2020 May 28];15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4542103/

44. Binay Safer V, Safer U. Usefulness and limitations of single-slice computed tomography analysis at the third lumbar region in the assessment of sarcopenia. Critical Care. 2013 Nov 20;17(6):466.

45. Boutin RD, Yao L, Canter RJ, Lenchik L. Sarcopenia: Current Concepts and Imaging Implications.

American Journal of Roentgenology. 2015 Sep;205(3):W255–66.

46. Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, et al. Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. Am J Clin Nutr. 1990 Aug;52(2):214–8.

47. Miller KD, Jones E, Yanovski JA, Shankar R, Feuerstein I, Falloon J. Visceral abdominal-fat accumulation associated with use of indinavir. Lancet. 1998 Mar 21;351(9106):871–5.

48. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol. 1998 Jul;85(1):115–22.

49. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997–1006.

50. Thibault R, Goujon N, Le Gallic E, Clairand R, Sébille V, Vibert J, et al. Use of 10-point analogue scales to estimate dietary intake: A prospective study in patients nutritionally at-risk. Clinical Nutrition. 2009;28(2):134–40.

51. Hjermstad MJ, Fossa SD, Bjordal K, Kaasa S. Test/retest study of the European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire. JCO. 1995;13(5):1249–54.

52. Koller M, Shamieh O, Hjermstad MJ, Hornslien K, Young T, Chalk T, et al. Psychometric properties of the updated EORTC module for assessing quality of life in patients with lung cancer (QLQ-LC29): an international, observational field study. The Lancet Oncology. 2020;21(5):723–32.

53. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. European Journal of Cancer. 1994;30(5):635–42.

54. Weis J, Tomaszewski KA, Hammerlid E, Ignacio Arraras J, Conroy T, Lanceley A, et al. International Psychometric Validation of an EORTC Quality of Life Module Measuring Cancer Related Fatigue (EORTC QLQ-FA12). JNCI: Journal of the National Cancer Institute [Internet]. 2017 [cited 2020 May 28];109(5). Available from: https://academic.oup.com/jnci/article/doi/10.1093/jnci/djw273/2972669

55. Savard M-H, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer patients: INSOMNIA SEVERITY INDEX AND CANCER. Psycho-Oncology. 2005;14(6):429–41.

56. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: Psychometric Indicators to Detect Insomnia Cases and Evaluate Treatment Response. Sleep. 2011;34(5):601–8.

57. Sass C, Dupré C, Giordanella JP, Girard F, Guenot C, Labbe É, et al. Le score Epices : un score individuel de précarité. Construction du score et mesure des relations avec des données de santé, dans une population de 197 389 personnes. 2006;4.

58. Jones LW. Precision Oncology Framework for Investigation of Exercise As Treatment for Cancer. JCO. 2015;33(35):4134–7.

59. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. BMC Med Res Methodol. 2013;13(1):104.

60. R Core Team (2020). — European Environment Agency [Internet]. [cited 2021 Jul 4]. Available from: https://www.eea.europa.eu/data-and-maps/indicators/oxygen-consuming-substances-in-rivers/r-development-core-team-2006

61. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics. 2009;42(2):377–81.

62. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. Journal of Biomedical Informatics. 2019;95:103208.

63. Jones LW. Physical Activity and Lung Cancer Survivorship. In: Courneya KS, Friedenreich CM, editors. Physical Activity and Cancer [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010 [cited 2021 Mar 28]. p. 255–74. (Recent Results in Cancer Research; vol. 186). Available from: http://link.springer.com/10.1007/978-3-642-04231-7_11

64. Quist M, Langer SW, Lillelund C, Winther L, Laursen JH, Christensen KB, et al. Effects of an exercise intervention for patients with advanced inoperable lung cancer undergoing chemotherapy: A randomized clinical trial. Lung Cancer. 2020;145:76–82.

65. Nadler M, Bainbridge D, Tomasone J, Cheifetz O, Juergens RA, Sussman J. Oncology care provider perspectives on exercise promotion in people with cancer: an examination of knowledge, practices, barriers, and facilitators. Support Care Cancer. 2017;25(7):2297–304.

66. Wilk M, Kepski J, Kepska J, Casselli S, Szmit S. Exercise interventions in metastatic cancer disease: a literature review and a brief discussion on current and future perspectives. BMJ Support Palliat Care. 2020;10(4):404–10.

67. Singh B, Spence R, Steele ML, Hayes S, Toohey K. Exercise for Individuals With Lung Cancer: A Systematic Review and Meta-Analysis of Adverse Events, Feasibility, and Effectiveness. Semin Oncol Nurs. 2020;36(5):151076.

68. Granger CL, Parry SM, Edbrooke L, Abo S, Leggett N, Dwyer M, et al. Improving the delivery of physical activity services in lung cancer: A qualitative representation of the patient's perspective. European Journal of Cancer Care. 2019;28(1):e12946.

69. Dittus KL, Gramling RE, Ades PA. Exercise interventions for individuals with advanced cancer: A systematic review. Preventive Medicine. 2017;104:124–32.

70. Heywood R, McCarthy AL, Skinner TL. Safety and feasibility of exercise interventions in patients with advanced cancer: a systematic review. Support Care Cancer. 2017 Oct;25(10):3031–50.

71. Yang M, Liu L, Gan C, Qiu L, Jiang X, He X, et al. Effects of home-based exercise on exercise capacity, symptoms, and quality of life in patients with lung cancer: A meta-analysis. European Journal of Oncology Nursing. 2020;49:101836.

72. Nieman DC, Lila MA, Gillitt ND. Immunometabolism: A Multi-Omics Approach to Interpreting the Influence of Exercise and Diet on the Immune System. Annu Rev Food Sci Technol. 2019;10:341–63.

73. Gresham G, Schrack J, Gresham LM, Shinde AM, Hendifar AE, Tuli R, et al. Wearable activity monitors in oncology trials: Current use of an emerging technology. Contemporary Clinical Trials. 2018;64:13–21.

74. Haberlin C, O'Dwyer T, Mockler D, Moran J, O'Donnell DM, Broderick J. The use of eHealth to promote physical activity in cancer survivors: a systematic review. Support Care Cancer. 2018;26(10):3323–36.

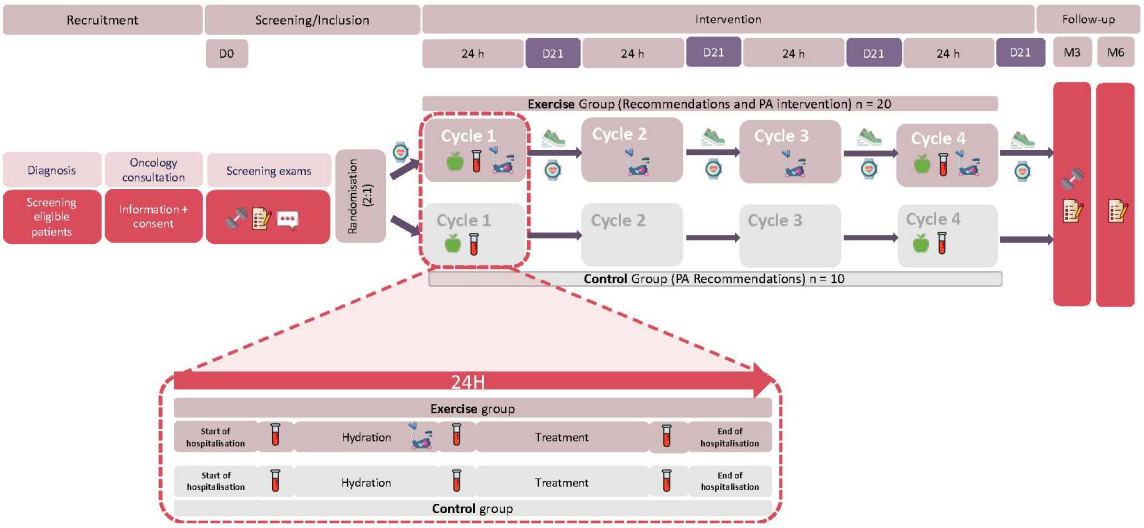
75. Turner RR, Steed L, Quirk H, Greasley RU, Saxton JM, Taylor SJ, et al. Interventions for promoting habitual exercise in people living with and beyond cancer. Cochrane Database Syst Rev [Internet]. 2018 [cited 2019 Oct 29];2018(9). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6513653/

76. Naito T, Mitsunaga S, Miura S, Tatematsu N, Inano T, Mouri T, et al. Feasibility of early multimodal interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer. J Cachexia Sarcopenia Muscle. 2019;10(1):73–83.

77. Delrieu L, Anota A, Trédan O, Freyssenet D, Maire A, Canada B, et al. Design and methods of a national, multicenter, randomized and controlled trial to assess the efficacy of a physical activity program to improve health-related quality of life and reduce fatigue in women with metastatic breast cancer: ABLE02 trial. BMC Cancer [Internet]. 2020 [cited 2021 Apr 15];20. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7333295/

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

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


Recruitment
Screening/Inclusion
Intervention
Follow-up
D0
24 h
D21
24 h
D21
24 h
D21
24 h
D21
M3
M6
Exercise Group (Recommendations and PA intervention) n = 20
Diagnosis
Oncology consultation
Screening exams
Screening eligible patients
Information + consent
Randomisation (2:1)
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Cycle 1
Cycle 2
Cycle 3
Cycle 4
Control Group (PA Recommendations) n = 10
24H
Exercise group
Start of hospitalisation
Hydration
Treatment
End of hospitalisation
Start of hospitalisation
Hydration
Treatment
End of hospitalisation
Control group

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

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

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**
Methods: Participants, interventions, and outcomes			
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**
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**
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**
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**
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**
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**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**Page 7-8**

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

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

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	**Page 28**
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**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**N/A**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**Page 2**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**Page 2**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**N/A**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**Consent form, see supplementary file**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	**Page 15**

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