

BMJ Open 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 programme on clinical, physical, psychosocial and biological parameters.

Methods and analysis ERICA is a prospective, monocentric, randomised controlled, open-label feasibility study conducted at the Centre Léon Bérard Comprehensive Cancer Center (France). Thirty patients newly diagnosed with mNSCLC will be randomised (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-month programme consisting of a supervised acute physical exercise session prior to immune-chemotherapy infusion, and an unsupervised home-based walking programme with an activity tracker. The acute exercise consists of 35 min interval training at submaximal intensity scheduled to terminate 15 min 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, 8 December 2020). The study is registered on ClinicalTrials.gov (NCT number:NCT04676009) and is at the pre-results stage. All participants will sign an informed consent form. The

Strengths and limitations of this study

- This study is the first to assess the feasibility effects of acute physical exercise performed within 1 hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-based doublet) infusion in patients with metastatic non-small cell lung cancer (mNSCLC).
- 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 programme.
- 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 programme 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 chemoimmunotherapy infusion.
- The study concerns only one stage of lung cancer, participants must be eligible to immunotherapy and it is a study with a limited sample size (n=30).

findings will be disseminated in peer-reviewed journals and academic conferences.

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 ($\geq 50\%$ 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 first-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 $\geq 50\%$. 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, dyspnoea, 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 fitness¹⁰ have been widely demonstrated. In patients with lung cancer, 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 HRQoL¹⁵ and emotional well-being in patients with cancer.¹⁶ Several studies in patients with lung cancer 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, that is, 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 seem to improve immunosurveillance.²⁰ Acute physical exercise leads to a rapid increase in the mobilisation of the peripheral activity of the subpopulation 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 mobilisation 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, that is, 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 intratumoral 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 patients with cancer 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 (ie, a combination of pembrolizumab and pemetrexed-cisplatin or carboplatin for non-squamous cell carcinoma or paclitaxel-carboplatin for squamous cell carcinoma) in first-line treatment of patients with metastatic NSCLC 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 programme on (1) physical fitness, (2) PA level and sedentary lifestyle, (3) psychosocial factors (HRQoL and fatigue), (4) sleep quality, (5) body composition, (6) sarcopaenia, (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, randomised controlled, open-label feasibility study, conducted at

the Centre Léon Bérard Comprehensive Cancer Centre (Lyon, France).

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-cisplatin or carboplatin for non-squamous cell carcinoma or paclitaxel-carboplatin for squamous cell carcinoma) in combination with pembrolizumab; (4) Eastern Co-operative Oncology Group 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 pathological fractures; (2) contraindication to the physical exercise proposed in this study (eg, orthopaedic disorder such as disabling coxarthrosis or gonarthrosis, central nervous system disorders); (3) history or coexistence 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 (ie, for adults aged ≥ 18 years and < 70 : body mass index (BMI) ≤ 17 , weight loss $\geq 10\%$ in 1 month, $\geq 15\%$ in 6 months or $\geq 15\%$ compared with the usual weight before the disease diagnosis or serum albumin < 30 g/L; for adults aged ≥ 70 years: BMI < 18 , weight loss $\geq 10\%$ in 1 month or $\geq 15\%$ in 6 months or serum albumin < 30 g/L);³⁴ (5) severe anaemia (haemoglobin ≤ 80 g/L) in the past 30 days prior to enrolment; (6)

history of cardiovascular disease or cardiovascular risk (ie, 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 (FEV₁) $< 30\%$).

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 ECG 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.

Randomisation

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 programme with an

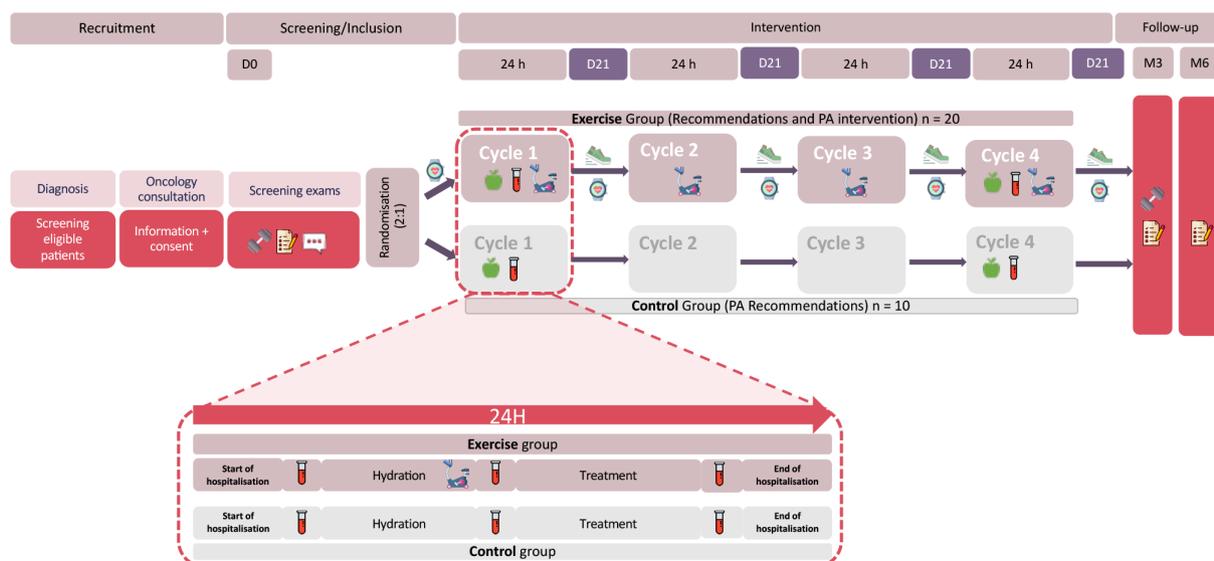


Figure 1 Flowchart of the ERICA study, France (original flowchart).

activity tracker or (ii) the control group to receive PA and nutrition recommendations only.

Randomisation 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/m²) with B9-B12 vitamin supplementation; carboplatin (AUC 6) plus paclitaxel (200 mg/m²) every 3 weeks for four 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 (WCRE, 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 (eg, using stairs whenever possible, walking to local shops).

Nutritional recommendations

All patients will receive nutritional recommendations during the first and fourth 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 hospitalisation for treatment. It will be carried out within 1 hour prior to the immunotherapy and chemotherapy infusion, on a cycle ergometer (Monark Ergonomic 939 Novo) for each of the four 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 min prior to infusion onset and will be individualised 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 5 min warm-up at 60% of ventilation threshold 1 (VT1), the participant will carry out five sets, alternating periods of 3 min at 70%–80% of VT1 with 3

min 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 programme 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 6000 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 programme. Depending on the average number of steps performed in the past 10 days, personalised objectives might be redefined to increase the target number of daily steps. For patients who reach more than 6000 steps per day, the initial target number of 6000 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 6000 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 sarcopaenia) in both groups will be performed before the first cycle of antineoplastic treatment (baseline, D0), at the end of the four cycles of treatment (M3) and at 6 months after study inclusion (M6) (table 1).

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

Table 1 Data collection schedule for the ERICA study

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

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 (kg), height (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 BMI is calculated as the body weight in kilograms divided by the square of the height in metres.

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

programme. Following a 5 min warm-up at 20% of the participant's maximum theoretical load, power will be increased by a constant amount of 5 W each 30 s 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 min 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, Florida, 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 s on the instructor's signal. Only the dominant leg will be tested three times (with 2 min 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).^{39–41} 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 5 s 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 patients with cancer 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 min 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 (LBM) and sarcopaenia will be analysed using the CT scans systematically available from routine care. CT scan cross-section at the level of the third lumbar vertebra provides a reliable representation of the total body muscle mass and has therefore been widely adopted for the detection of sarcopaenia in patients with cancer 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 Hounsfield Units (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

HU. A low SMD is defined by values below the threshold of 37.8 HU. An estimate of LBM will be calculated using the formula (LBM (kg) = [(L3 Muscle measured by CT (cm²)×0.3)+6.06]).⁴⁹

Nutrition

Dietary intake (24 hours 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 multidimensional HRQoL questionnaire designed for patients with cancer,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 patients with lung cancer 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 seven 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, sarcopaenia 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 min 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 3×10 mL Ethylenediaminetetraacetic acid tubes and then centrifuged (10 min at 800G) within 1 hour (maintained at 4°C before and during centrifugation). After the centrifuge, plasma will be collected and aliquoted in five cryotubes of 1 mL and the peripheral blood mononuclear cell (PBMC) will be collected and aliquoted in three cryotubes (5–7 million cells per tube). These cryotubes will be frozen at –80°C and stored in nitrogen at the centre for the duration of the study. At the end of the study, biomarkers of immunity, sarcopaenia and inflammation will be analysed. We will measure (i) immune biomarkers (NK cells, B lymphocytes, T lymphocytes, monocytes, subpopulations of dendritic cells on frozen PBMC); (ii) plasma biomarkers of sarcopaenia and inflammation (myostatin, activin, cortisol, tumour necrosis factor- α , interferon- γ , interleukin-1 β , 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 also be 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 \geq 3) will be noted according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) V.5.0. The number of rescheduled or cancelled treatment sessions and the relative dose intensity (RDI) of participants with grade \geq 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 programme performed prior to the infusion of treatments in patients with mNSCLC, 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 patients with mNSCLC who receive first-line chemotherapy (ie, pemetrexed-platinum or taxol-platinum) combined with Pembrolizumab each year in Centre Léon Bérard (Lyon), we plan to include 30 patients over a 18-month 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, SD, 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 RDI of exercise. The safety will be assessed by the occurrence of adverse events related to the physical exercise intervention. The acceptability (ie, the proportion of patients who accept to participate in the study among eligible patients) and the attrition (ie, 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 programme 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 sarcopaenia) 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 randomisation 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 multicentre randomised 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 patients with lung cancer to collect their experience and preferences in terms of PA to practice during cancer treatments. The results were used to develop the ERICA PA 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 1 hour prior to immunotherapy (pembrolizumab) and chemotherapy (platinum-based doublet) infusion in patients with mNSCLC. 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 patients with mNSCLC remains limited and there is a lack of widespread awareness of the benefits of maintaining PA in this particular population.^{66 68–70} Furthermore, the high prevalence of comorbidities in patients with mNSCLC, which may be exacerbated by the direct and indirect effects of cancer treatment, led to exclude patients at risk of cardiovascular events from studies (ie, history of cardiovascular disease; abnormal ECG 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 patients with cancer 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 (ie, 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 realise 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 programme in the intervention arm aims to increase the level of PA in patients with mNSCLC and their cardiorespiratory fitness and physical capacity to perform acute physical exercise prior to chemoimmunotherapy 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 patients with cancer.^{73–75} Trackers have been used in a randomised 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 chemoimmunotherapy 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 randomised controlled trial to assess the efficacy on clinically important endpoints (eg, progression-free survival) in patients with mNSCLC receiving first-line chemoimmunotherapy.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study involves human participants and was approved by Comité de protection des personnes Ile de France II, N°ID-RCB 20.09.04.65226. Participants gave informed consent to participate in the study before taking part.

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REFERENCES

- 1 Planchard D, Popat S, Kerr K, *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 [cited 2021 Jul 3]* 2021 <https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics>
- 3 Gadgeel S, Rodríguez-Abreu D, Speranza G, *et al*. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic Nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2020;38:1505–17. JCO.19.
- 4 Low JL, Walsh RJ, Ang Y, *et al*. The evolving immuno-oncology landscape in advanced lung cancer: first-line treatment of non-small cell lung cancer. *Ther Adv Med Oncol* 2019;11:1758835919870360 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6716180/>
- 5 Brahmer JR, Rodríguez-Abreu D, Robinson AG, *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. *Lancet Oncol* 2017;18:1600–9.
- 6 Polanski J, Jankowska-Polanska B, Rosinczuk J, *et al*. Quality of life of patients with lung cancer. *Onco Targets Ther* 2016;9:1023–8.
- 7 Camps C, del Pozo N, Blasco A, *et al*. Importance of quality of life in patients with non-small-cell lung cancer. *Clin Lung Cancer* 2009;10:83–90.
- 8 Garassino MC, Gadgeel S, Esteban E, *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. *Lancet Oncol* 2020;21:387–97.
- 9 Steffen McLouth LE, Lycan TW, Levine BJ, *et al*. Patient-Reported outcomes from patients receiving immunotherapy or chemoimmunotherapy for metastatic non-small-cell lung cancer in clinical practice. *Clin Lung Cancer* 2020;21:255–63.
- 10 Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 1985;100:126–31.
- 11 Hwang C-L, Yu C-J, Shih J-Y, *et al*. Effects of exercise training on exercise capacity in patients with non-small cell lung cancer receiving targeted therapy. *Support Care Cancer* 2012;20:3169–77.
- 12 Chen H-M, Tsai C-M, Wu Y-C, *et al*. Effect of walking on circadian rhythms and sleep quality of patients with lung cancer: a randomised controlled trial. *Br J Cancer* 2016;115:1304–12.
- 13 Dhillon HM, Bell ML, van der Ploeg HP, *et al*. Impact of physical activity on fatigue and quality of life in people with advanced lung cancer: a randomized controlled trial. *Ann Oncol* 2017;28:1889–97.
- 14 Zhang L-L, Wang S-Z, Chen H-L, *et al*. Tai chi exercise for cancer-related fatigue in patients with lung cancer undergoing chemotherapy: a randomized controlled trial. *J Pain Symptom Manage* 2016;51:504–11.
- 15 Peddle-McIntyre CJ, Singh F, Thomas R, *et al*. Exercise training for advanced lung cancer. *Cochrane Database Syst Rev* 2019;28 <http://doi.wiley.com/>
- 16 Quist M, Adamsen L, Rørth M, *et al*. 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;14:341–9.
- 17 Avancini A, Sartori G, Gkoutakos A. Physical activity and exercise in lung cancer care: will promises be fulfilled? *Oncologist* 2020;25:e555–69 <https://theoncologist.onlinelibrary.wiley.com/doi/abs/>
- 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]. Available: https://www.inserm.fr/sites/default/files/2019-02/Inserm_EC_2019_Activit%C3%A9PhysiqueMaladiesChroniques_Synthese.pdf

- 19 Koelwyn GJ, Quail DF, Zhang X, et al. Exercise-dependent regulation of the tumour microenvironment. *Nat Rev Cancer* 2017;17:620–32.
- 20 Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. *J Sport Health Sci* 2019;8:201–17.
- 21 Bigley AB, Rezvani K, Chew C, et al. Acute exercise preferentially redeploys NK-cells with a highly-differentiated phenotype and augments cytotoxicity against lymphoma and multiple myeloma target cells. *Brain Behav Immun* 2014;39:160–71.
- 22 Idorn M, Hojman P. Exercise-Dependent regulation of NK cells in cancer protection. *Trends Mol Med* 2016;22:565–77.
- 23 Pedersen L, Idorn M, Olofsson GH, et al. Voluntary running suppresses tumor growth through epinephrine- and IL-6-dependent NK cell mobilization and redistribution. *Cell Metab* 2016;23:554–62.
- 24 Wadley AJ, Cullen T, Vautrinot J, et al. High intensity interval exercise increases the frequency of peripheral PD-1+ CD8+ central memory T-cells and soluble PD-L1 in humans. *Brain Behav Immun Health* 2020;3:100049.
- 25 Pedersen BK, Hoffman-Goetz L. Exercise and the immune system: regulation, integration, and adaptation. *Physiol Rev* 2000;80:1055–81.
- 26 Wiggins JM, Opoku-Acheampong AB, Baumfalk DR, et al. Exercise and the tumor microenvironment: potential therapeutic implications. *Exerc Sport Sci Rev* 2018;46:56–64.
- 27 McCullough DJ, Stabley JN, Siemann DW, et al. Modulation of blood flow, hypoxia, and vascular function in orthotopic prostate tumors during exercise. *J Natl Cancer Inst* 2014;106:dju036 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3982888/>
- 28 Schadler KL, Thomas NJ, Galie PA, et al. Tumor vessel normalization after aerobic exercise enhances chemotherapeutic efficacy. *Oncotarget* 2016;7:65429–40.
- 29 Schumacher O, Galvão DA, Taaffe DR, et al. Exercise modulation of tumour perfusion and hypoxia to improve radiotherapy response in prostate cancer. *Prostate Cancer Prostatic Dis* 2021;24:1–14.
- 30 Thomas VJ, Seet-Lee C, Marthick M, et al. Aerobic exercise during chemotherapy infusion for cancer treatment: a novel randomised crossover safety and feasibility trial. *Support Care Cancer* 2020;28:625–32.
- 31 Kerrigan K. A pilot study of aerobic exercise performed in breast cancer patients during chemotherapy infusion. | Journal of Clinical Oncology [Internet], 2010. Available: https://ascopubs.org/doi/10.1200/jco.2010.28.15_suppl.e19527
- 32 Ashcraft KA, Warner AB, Jones LW, et al. Exercise as adjunct therapy in cancer. *Semin Radiat Oncol* 2019;29:16–24.
- 33 Martín-Ruiz A, Fiuzza-Luces C, Rincón-Castanedo C, et al. Benefits of exercise and immunotherapy in a murine model of human non-small-cell lung carcinoma. *Exerc Immunol Rev* 2020;26:100–15.
- 34 Haute Autorité de santé. Diagnostic de la dénutrition de l'enfant et de l'adulte : Méthode Recommandations pour la pratique clinique., 2019. Available: https://www.has-sante.fr/jcms/p_3118872/fr/diagnostic-de-la-denuitration-de-l-enfant-et-de-l-adulte [Accessed 29th March 2022].
- 35 Macmillan Cancer Support. Physical activity in patients with metastatic bone disease: Guidance for healthcare professionals [Internet], 2018. Available: <https://cdn.macmillan.org.uk/dfsmedia/1a6f23537f74519bb0cf14c45b2a629/1784-10061/physical-activity-for-people-with-metastatic-bone-disease-guidance-tcm9-326004> [Accessed cited 2021 Jul 4].
- 36 Senesse P, Bachmann P, Bensadoun RJ, et al. Nutrition chez le patient adulte atteint de cancer : textes courts. *Nutrition Clinique et Métabolisme* 2012;26:151–8.
- 37 Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. *Clin Nutr* 2017;36:11–48.
- 38 Tudor-Locke C, Craig CL, Aoyagi Y, et al. How many steps/day are enough? for older adults and special populations. *Int J Behav Nutr Phys Act* 2011;8:80.
- 39 Borg G, Hassmén P, Lagerström M. Perceived exertion related to heart rate and blood lactate during arm and leg exercise. *Eur J Appl Physiol Occup Physiol* 1987;56:679–85.
- 40 Kilgour RD, Viganò A, Trutschnigg B, et al. Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients. *Support Care Cancer* 2013;21:3261–70.
- 41 Anand A, Gajra A. Hand Grip Dynamometry as Prognostic and Predictive Marker in Older Patients With Cancer. J Gerontol Geriatr Res [Internet], 2018. Available: <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, 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;33:1232–9.
- 43 Amireault S, Godin G, Lacombe J, et al. The use of the Godin-Shephard leisure-time physical activity questionnaire in oncology research: a systematic review. *BMC Med Res Methodol* 2015;15:60 <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. *Crit Care* 2013;17:466.
- 45 Boutin RD, Yao L, Canter RJ, et al. Sarcopenia: current concepts and imaging implications. *AJR Am J Roentgenol* 2015;205:W255–66.
- 46 Heymsfield SB, Smith R, Aulet M, et al. Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. *Am J Clin Nutr* 1990;52:214–8.
- 47 Miller KD, Jones E, Yanovski JA, et al. Visceral abdominal-fat accumulation associated with use of indinavir. *Lancet* 1998;351:871–5.
- 48 Mitsiopoulos N, Baumgartner RN, Heymsfield SB, et al. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol* 1998;85:115–22.
- 49 Mourtzakis M, Prado CMM, Lieffers JR, et al. 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;33:997–1006.
- 50 Thibault R, Goujon N, Le Gallic E, et al. Use of 10-point analogue scales to estimate dietary intake: a prospective study in patients nutritionally at-risk. *Clin Nutr* 2009;28:134–40.
- 51 Hjermstad MJ, Fossa SD, Bjordal K, et al. Test/retest study of the European organization for research and treatment of cancer core quality-of-life questionnaire. *J Clin Oncol* 1995;13:1249–54.
- 52 Koller M, Shamieh O, Hjermstad MJ, 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. *Lancet Oncol* 2020;21:723–32.
- 53 Bergman B, Aaronson NK, Ahmedzai S, et al. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. *Eur J Cancer* 1994;30:635–42.
- 54 Weis J, Tomaszewski KA, Hammerlid E, 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* 2017;109 <https://academic.oup.com/jnci/article/doi/10.1093/jnci/djw273/2972669>
- 55 Savard M-H, Savard J, Simard S. Empirical validation of the insomnia severity index in cancer patients: insomnia severity index and cancer. *Psycho-Oncology* 2005;14:429–41.
- 56 Morin CM, Belleville G, Bélanger L, et al. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;34:601–8.
- 57 Sass C, Dupré C, Giordanella JP. 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. *Bulletin Epidemiologique Hebdomadaire* 2006;4:93–6 <https://bdsp-ehesp.inist.fr/vibad/index.php?action=getRecordDetail&idt=338168>
- 58 Jones LW. Precision oncology framework for investigation of exercise as treatment for cancer. *J Clin Oncol* 2015;33:4134–7.
- 59 Billingham SAM, 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;13:104.
- 60 R Core Team. European Environment Agency [Internet], 2020. Available: <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, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
- 62 Harris PA, Taylor R, Minor BL, et al. The REDCap Consortium: building an international community of software platform partners. *J Biomed Inform* 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 http://link.springer.com/10.1007/978-3-642-04231-7_11
- 64 Quist M, Langer SW, Lillelund C, 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, *et al.* Oncology care provider perspectives on exercise promotion in people with cancer: an examination of knowledge, practices, barriers, and facilitators. *Support Care Cancer* 2017;25:2297–304.
- 66 Wilk M, Kepski J, Kepska J, *et al.* Exercise interventions in metastatic cancer disease: a literature review and a brief discussion on current and future perspectives. *BMJ Support Palliat Care* 2020;10:404–10.
- 67 Singh B, Spence R, Steele ML, *et al.* Exercise for individuals with lung cancer: a systematic review and meta-analysis of adverse events, feasibility, and effectiveness. *Semin Oncol Nurs* 2020;36:151076.
- 68 Granger CL, Parry SM, Edbrooke L, *et al.* Improving the delivery of physical activity services in lung cancer: a qualitative representation of the patient's perspective. *Eur J Cancer Care* 2019;28:e12946.
- 69 Dittus KL, Gramling RE, Ades PA. Exercise interventions for individuals with advanced cancer: a systematic review. *Prev Med* 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;25:3031–50.
- 71 Yang M, Liu L, Gan C-E, *et al.* Effects of home-based exercise on exercise capacity, symptoms, and quality of life in patients with lung cancer: a meta-analysis. *Eur J Oncol Nurs* 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, *et al.* Wearable activity monitors in oncology trials: current use of an emerging technology. *Contemp Clin Trials* 2018;64:13–21.
- 74 Haberlin C, O'Dwyer T, Mockler D, *et al.* The use of eHealth to promote physical activity in cancer survivors: a systematic review. *Support Care Cancer* 2018;26:3323–36.
- 75 Turner RR, Steed L, Quirk H, *et al.* Interventions for promoting habitual exercise in people living with and beyond cancer. *Cochrane Database Syst Rev* 2018;9:CD010192 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6513653/>
- 76 Naito T, Mitsunaga S, Miura S, *et al.* Feasibility of early multimodal interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer. *J Cachexia Sarcopenia Muscle* 2019;10:73–83.
- 77 Delrieu L, Anota A, Trédan O, *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* 2020;20:622 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7333295/>
- 78 Delrieu L, Martin A, Touillaud M. 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* 2021;188:601–13. [cited 2021 Jun 13]; Available from <https://link.springer.com/10.1007/s10549-021-06238-z>