## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | 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 |
| **AUTHORS** | Gouez, Manon; Pérol, Olivia; Pérol, Maurice; Caux, Christophe; Ménétrier-Caux, Christine; Villard, Marine; Walzer, Thierry; Delrieu, Lidia; Saintigny, Pierre; Marijnen, Philippe; Pialoux, Vincent; Fervers, Béatrice |

## VERSION 1 – REVIEW

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| **REVIEWER** | De Ruysscher, D<br>University Medical Center Maastricht |
| **REVIEW RETURNED** | 22-Sep-2021 |

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| **GENERAL COMMENTS** | This is a very well designed randomized trial protocol on a relevant topic. The results of the study may be practice-changing. The research group should be congratulated to embark this important study. |

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| **REVIEWER** | Voorn, M<br>VieCuri Medical Centre, Epidemiology |
| **REVIEW RETURNED** | 27-Oct-2021 |

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| **GENERAL COMMENTS** | The ERICA trial is designed to assess the feasibility of a multimodal rehabilitation and home-based<br>walking program in the first-line treatment of metastatic NSCLC patients immediately prior to the<br>infusion of immunochemotherapy for safety and tolerability of the proposed exercise dose. The<br>secondary objectives are to evaluate the effects of multimodal rehabilitation prior to first-line<br>treatment in combination with a home-based walking program on the effects on clinical, physical,<br>psychosocial and biological parameters: 1) physical fitness, 2) PA level and sedentary lifestyle , 3)<br>psychosocial factors (HRQoL and fatigue), 4) sleep quality, 5) body composition, 6) sarcopenia, 7)<br>treatment response, 8) treatment completion rate, 9) related treatment toxicities, and 10)<br>progression-free survival. Although this is a relevant topic with clinical relevance, there are some<br>major limitations.<br>Major limitations<br>Title and abstract<br>1. The aim in the abstract is not equal to the aim in the introduction, the main objective in the |

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| | statistical analysis (line 378), and the aim in the innovation and study relevance (line 478).<br>Methods<br>2. Patients with NSCLC often have comorbidities, whereas in this study these vulnerable<br>patients (patients <80 years of age, with ECOG ≤2, severe comorbidity, and undernutrition,<br>etcetera) are excluded. Also in the discussion section, the authors state that excluding<br>patients with comorbidity is a major limitation of previous studies. Therefore, I wonder why<br>these patients were excluded in this study. A good reflection of clinical practice would be to<br>divide high and low risk patients for complications. It is recommended to use the reference<br>of M.J.J. Voorn et al. (PMID: 33383208) for the relevance in the selection of high-risk<br>patients.<br>3. In this study protocol, patients undergo a standard dosage of physical exercises. Only the<br>number of steps are personalized. What is the added value of the use of the BORG-scale<br>during the CPET?<br>4. In addition, the Borg score is not used during training. Therefore, it is recommended to<br>describe the reason for not using the Borg score during training as well as how this can be a<br>possible limitation of the study.<br>5. Only at line 174 it becomes clear that patients also receive a nutritional intervention. This<br>should have been addressed earlier. Advice is to clarify this in the aim (multimodal program<br>instead of exercise program).<br>6. Patients only get physical training once every three weeks. I doubt that this is sufficient for<br>improving physical fitness? Please explain.<br>7. Strength tests are taken but no resistance exercise are performed. This is contradictory.<br>8. It is unclear when quality of life will be measured and how the data will be analysed. Within<br>patients or between groups?<br>9. It is unclear in the methods and statistical analyses which data is collected qualitatively and<br>quantitatively. Moreover, it seems odd that qualitative data will be presented as frequencies<br>and percentages.<br>10. The definition for feasibility is first described in line 399. Advice is to describe this earlier in<br>the methods section.<br>Minor limitations<br>Introduction:<br>11. It is unclear were the term "acute" refers to in the title, abstract and introduction. What does<br>it mean?<br>12. Line 108: insert reference. The terms advanced and metastatic are used interchangeably. It is<br>recommended to use the same term everywhere.<br>13. Write out all abbreviations in the introduction.<br>Methods:<br>1. Advice is to build up the methods based on the order in the aim. |

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| | 2. Line 149: insert reference.<br>3. Line 162: year 2020, so the study has already started?<br>4. Line 208: Exercise training is on VT1. It is explained later that a CPET is used. This should have<br>been mentioned earlier.<br>5. What is the background of the PA instructor?<br>6. Line 225: please decribe earlier that the program is partly supervised. |

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| **REVIEWER** | Newton, Robert<br>Edith Cowan University, Exercise Medicine Research Institute |
| **REVIEW RETURNED** | 04-Nov-2021 |

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| **GENERAL COMMENTS** | This proposed research study is timely in that there is growing evidence that exercise therapy performed acutely immediately prior to receipt of chemotherapy may be highly beneficial through a range of mechanisms. The proposed trial is appropriate and will lead to new knowledge in particular regarding the feasibility of implementing exercise medicine in the hospital setting prior to receiving systemic therapies.<br>Unfortunately, the manuscript includes a large number of grammatical and expression errors and lack of clarity. I have listed as many as I can in the specific comments below.<br>Throughout the manuscript it needs to be defined or corrected as to what a “PA instructor” actually is. Are the authors intending to involve an accredited exercise physiologist or clinical exercise physiologist or similar allied health professional or is the PA instructor a personal trainer or fitness instructor? Given the type, stage and treatment protocol of the patients being recruited I would suggest that a clinical exercise physiologist with experience in the oncology setting be involved in the research team to design, supervise and monitor the exercise intervention and physical fitness testing.<br>Given that sarcopenia and cachexia are highly prevalent in this patient population it is concerning that the exercise prescription consists entirely of aerobic endurance exercise which may actually exacerbate these two conditions. The authors should consider the addition of resistance training at least two sessions per week as per international guidelines to avoid the potential detrimental effects of the current exercise program which may further exacerbate energy deficit and muscle atrophy. I acknowledge that patients are being pre-screened for low body weight however the proposed exercise intervention over 12 weeks may actually push them into dangerously low muscle mass and overall body weight.<br>What is the justification for measuring upper and lower body muscle strength when the exercise intervention you have designed is unlikely to have any impact on these outcome measures and it is an additional test burden for the patients?<br>Specific comments<br>line 26 – suggest change to “of acute physical exercise therapy realised”<br>line 37 – suggest change to “consisting of an acute physical exercise session one hour prior”<br>line 39 – suggest change to “acute exercise consists of interval training”<br>line 40 – suggest change to “will be assessed at baseline, 3 months and 6 months after study inclusion”<br>line 52 – suggest change to “effects of acute physical exercise performed” |

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| | line 57 – suggest change to “will allow individualisation of the intensity”<br>line 59 – suggest change to “to an acute moderate intensity physical exercise session in patients”<br>line 79 – suggest change to “Principal reported symptoms and adverse effects from treatment are”<br>line 82 – PA needs to be defined before the abbreviation is used.<br>Line 84 – aerobic capacity and strength are two separate fitness qualities. Suggest change to “been shown to improve aerobic capacity (VO2peak), muscular strength, functional capacity”<br>line 91 – suggest change to “immune cell mobilisation in blood such as neutrophils”<br>line 103 – suggest change to “basal level within a few hours”<br>line 105 – suggest change to “increase the blood flow leading to improved”<br>line 111 – suggest change to “could lead to improved perfusion”<br>line 117 – is this how you wish to spell “inteRaction”?<br>Line 141 – do you mean physical activity or exercise? Suggest you check the WHO definitions as exercise is a subset of physical activity which is purposeful and planned. Physical activity is any movement that requires energy expenditure. All of the patients will be able to engage in physical activity of some sort but may not be able to perform your prescribed exercise program.<br>Line 158 – what is the rationale for excluding patients with type II diabetes?<br>Line 163 – the correct terminology is “electronic patient records”<br>line 168 - how useful is a resting electrocardiogram for assessing risk in patients commencing an exercise intervention trial? Have you considered an exercise stress test?<br>Line 198 – suggest change to “nutritional recommendations will include:”<br>line 204 – suggest change to “will perform an acute physical exercise bout during”<br>line 207 – what is a qualified PA instructor? Do you mean a clinical exercise physiologist, physical therapist or similar? Or is this a personal trainer or fitness instructor? Internationally the term PA instructor is unknown.<br>Line 207 – suggest change to physical exercise consists of a”<br>line 216 – do you mean more than or equal to 4% DECLINE of the measured value at rest?<br>Line 217 – until a resting oxygen saturation does what?<br>Line 230 – why are you using such a large increment of 30% in steps? Would it not be better to increment by say 10% and then evaluate more regularly?<br>Line 258 – suggest change to “test will allow individualisation of the intensity of”<br>line 260 – “watts” is the measurement unit of power so suggest you state more appropriately as “power will be increased by a constant amount of 5 W each 30 seconds”<br>line 262 – the submaximal cycle ergometers test is an excellent opportunity to also assess ECG under an exercise stress situation and I suggest that this be included.<br>Line 267 – “his” is not the appropriate term as you are including both males and females.<br>Line 270 – suggest change to “lower body muscular strength will be evaluated”<br>line 273 – the participants are not stretching their leg. I assume that you mean extend their knee? |

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| | Line 358 – Will you be assessing immunity to a particular disease or do you mean you will be assessing immune function? These are two quite different characteristics.<br>Line 362 – spelling of “interleukin 10”. Also for all the interleukins there is no “e” on the end of the word.<br>Line 435 – suggest change to “the feasibility and effects of acute physical exercise performed” |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

Dr. D De Ruysscher, University Medical Center Maastricht

Comments to the Author:

This is a very well designed randomized trial protocol on a relevant topic. The results of the study may be practice-changing. The research group should be congratulated to embark this important study.

Dear Dr De Ruysscher, the authors are grateful for your comment.

Reviewer: 2

Dr. M Voorn, VieCuri Medical Centre

Major limitations

Title and abstract

1. The aim in the abstract is not equal to the aim in the introduction, the main objective in the statistical analysis (line 378), and the aim in the innovation and study relevance (line 478).

The objectives have been homogeneised and revised accordingly in the following sections:

In abstract, changed to (page 2):

‘The ERICA study has been designed to assess the feasibility of an 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 exercise combined with a home walking program on clinical, physical, psycho-social and biological parameters.’

In introduction, changed to (page 6):

‘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.'

In Statistical analyses, change to (page 17):

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.

Innovation, changed to (page 20):

'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.'

Methods

2. Patients with NSCLC often have comorbidities, whereas in this study these vulnerable patients (patients <80 years of age, with ECOG ≤2, severe comorbidity, and undernutrition...) are excluded. Also in the discussion section, the authors state that excluding patients with comorbidity is a major limitation of previous studies. Therefore, I wonder why these patients were excluded in this study. A good reflection of clinical practice would be to divide high and low risk patients for complications.

We thank the reviewer for this pertinent comment. We fully agree that exercise interventions should be proposed to vulnerable patient populations. In line with this, our study targets patients with metastatic lung cancer that can present severe cancer-related symptoms and treatment-induced side effects. Yet, the limitations of the present study to stage IV NSCLC patients <80 years of age, with ECOG ≤2, is determined by the therapeutic indication of the immune-chemotherapy protocol following the KEYNOTE-189 Trial (see reference N°3 Gadgeel S, et al. JCO. 2020;JCO.19.03136).

It is recommended to use the reference of M.J.J. Voorn et al. (PMID: 33383208) for the relevance in

the selection of high-risk patients.

We thank the authors for this reference. This is a very pertinent review. Yet, the proposed reference focuses on the identification of stage I to III lung cancer patients at risk of postoperative complications, whereas the present study focuses on stage IV NSCLC patients receiving immune-chemotherapy andcapable to exercise safely at submaximal exercise levels.

3. In this study protocol, patients undergo a standard dosage of physical exercises. Only the number of steps are personalized. What is the added value of the use of the BORG-scale during the CPET?

In this study, both the number of steps as well as pre-treatment physical exercise sessions are personalized. As stated, page 9 (line 216-222), the latter is personalized based on the load achieved at VT1 during the submaximal endurance test (N.B. we don't use a CPET, we stop patients when they reach their VT1 (Schneider et al. Support Care Cancer (2020) 28:5521–5528).
The use of the Borg-scale during the different interventions in this study (endurance test and exercise sessions) is intended to measure the perceived physical activity intensity level by the patient (Borg Scale). We apply this scale before exercise, at the end of exercise and during recovery for all exercise sessions (page 11, line 271). The added value of using it during the endurance test is to familiarize the patient to evaluate his perception of the effort himself ("exercise anchoring procedure") and to directly control the intensity/cost of the exercise perceived by the patient. Therefore, the Borg scale is a valuable complementary measure in the assessment of effort and allows to adjust the load during the exercise sessions if necessary.

4. In addition, the Borg score is not used during training. Therefore, it is recommended to describe the reason for not using the Borg score during training as well as how this can be a possible limitation of the study.

The Borg scale is used before the start of exercise (rest), during exercise, at the end of exercise and after 3 minutes of stopping exercise.

This is now specified page 9, line 217: '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.'

5. Only at line 174 it becomes clear that patients also receive a nutritional intervention. This should have been addressed earlier. Advice is to clarify this in the aim (multimodal program instead of exercise program).

As specified in the abstract as well as line 180*, participants in both groups receive nutrition recommendations. This is in line with usual care at the Centre Léon Bérard Comprehensive Cancer center, and not part of the intervention assessed in the present study, and as such proposed to patients in both arms of the trial.

6. Patients only get physical training once every three weeks. I doubt that this is sufficient for improving physical fitness? Please explain.

The main objective of this study is to test the feasibility of an acute physical exercise performed one hour prior the immunotherapy and chemotherapy infusion. We hypothesize that through this intervention we will induce physiological transient effects such as hemodynamic variations, systemic activation of immune function cells and increased tumor perfusion as previously studied in mouse

models. We agree that this intervention is insufficient to improve physical fitness. Therefore, the intervention also involves a home walking program consisting of an individual goal of a daily number of steps to be performed by the patient. We have clarified this page 8 - line 177:

‘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.’

7. Strength tests are taken but no resistance exercise are performed. This is contradictory.

In this study, the strength tests are used to assess the general physical fitness of the patient before and after the 3 months of intervention. Assessment of muscular strength has been suggested as a useful indicator of functional fitness and health status, given its association with morbidity and mortality. This measure allows us to complete our sarcopenia and cachexia assessment (assessment of nutritional status, L3 CT scan, inflammatory biomarkers).

See reference N° 39: Trutschnigg et al. 2009. 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

We added the following reference (page 12, line 282)
Kilgour et al., 2013. Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients

8. It is unclear when quality of life will be measured and how the data will be analysed. Within patients or between groups?

Quality of life is assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30), a 30-item, self-administered questionnaire that evaluates a global quality-of-life domain, 5 functional domains (ie, physical, role, emotional, cognitive, and social), three symptom domains (ie, pain, fatigue, and nausea), and six single items (ie, dyspnea, insomnia, appetite loss, diarrhea, constipation, and financial impact). The score ranges from 0 to 100. (page 13-line 325).

It is specified page 10 -line 241 that” 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).”

We have now changed this to (page 10-line 241):
‘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).’
Furthermore, it is specified in the manuscript, page 17, line 417: “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).”

9. It is unclear in the methods and statistical analyses which data is collected qualitatively and quantitatively. Moreover, it seems odd that qualitative data will be presented as frequencies and percentages.

We added a table to summarize qualitative and quantitative outcome measures and data collection schedule (Table 1, page 10-line 244)

10. The definition for feasibility is first described in line 399. Advice is to describe this earlier in the methods section.

The notion of feasibility is introduced at the end of the introduction (page 6-line 120). The judgement criteria of the feasibility is specified in the statistical methods (page 16-line 407)

Minor limitations
Introduction:

1. It is unclear were the term "acute" refers to in the title, abstract and introduction. What does it mean?

“Acute exercise” has been defined as a single bout of exercise that triggers a physiological response at the whole-organism level (Koelwyn, 2017). In our study the acute exercise is defined as an intermittent physical exercise of 35 minutes at moderate intensity.

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.

We have specified this in the introduction (page 4 – line 97)
“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.”

2. Line 108: insert reference. The terms advanced and metastatic are used interchangeably. It is recommended to use the same term everywhere.

The population of interest of the present study are NSCLC patients at metastatic stage (IV) . They are designated as such in the study. Theterm ‘advanced’, is used in the Introduction and discussion, and designates stages III and IV lung cancer. The term is not used to designate the study population.

Reference added.(line 108) 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

3. Write out all abbreviations in the introduction.
Modified

Methods:
4. Advice is to build up the methods based on the order in the aim.
The methods section is built up as follows:
(1) Study population, inclusion and exclusion criteria
(2) Interventions common to both groups (treatment - physical activity recommendations - nutrition recommendations - and home exercise)
(3) Specific interventions for the exercise group: pre-treatment exercise and home walking program

5. Line 149: insert reference.
Added

6. Line 162: year 2020, so the study has already started?
The study protocol was approved by the French ethics committee December 15th 2020 and the first patient inclusion February 6th 2021.

7. Line 208: Exercise training is on VT1. It is explained later that a CPET is used. This should have been mentioned earlier.
We don't use a CPET but a submaximal endurance test. ◊ '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.' (page 9-line 213)

8. What is the background of the PA instructor?
We change for "clinical exercise physiologist". The clinical exercise physiologist, have a Master's degree specialized in physical activity in oncology.

9. Line 225: please describe earlier that the program is partly supervised.

We do not consider that the home walking program is supervised. Apart from phone calls there is no professional support during the walk program. Only pre-treatment physical exercise sessions are supervised during this study. We now specified systematically when the intervention is supervised or unsupervised throughout the article.
Reviewer: 3
Mr. Robert Newton, Edith Cowan University

Review of BMJ open – 2021 – 056819

General comments

Throughout the manuscript it needs to be defined or corrected as to what a "PA instructor" actually is. Are the authors intending to involve an accredited exercise physiologist or clinical exercise physiologist or similar allied health professional or is the PA instructor a personal trainer or fitness instructor? Given the type, stage and treatment protocol of the patients being recruited I would suggest that a clinical exercise physiologist with experience in the oncology setting be involved in the research team to design, supervise and monitor the exercise intervention and physical fitness testing.

We thank the author for the comment and modified for "clinical exercise physiologist".

Given that sarcopenia and cachexia are highly prevalent in this patient population it is concerning that the exercise prescription consists entirely of aerobic endurance exercise which may actually exacerbate these two conditions. The authors should consider the addition of resistance training at least two sessions per week as per international guidelines to avoid the potential detrimental effects of the current exercise program which may further exacerbate energy deficit and muscle atrophy. I acknowledge that patients are being pre-screened for low body weight however the proposed exercise intervention over 12 weeks may actually push them into dangerously low muscle mass and overall body weight.

The authors of this study are aware of the recommendations and doubt that this intervention will worsen sarcopenia and cachexia in patients. Moreover, the choice of the exercise program in this study was made in consultation with a medical team and exercise physiologists. Increasing the level of daily physical activity of these patients will improve their functional level. Furthermore, a recent study by the team showed that increasing the level of physical activity by an unsupervised home walking program in women with metastatic breast cancer increased the isometric quadriceps strength and the walking distance, and maintained muscle mass (Delrieu, 2018; Delrieu 2021). In addition, the authors pay attention to the nutritional follow-up of patients by qualified personnel.

Delrieu L, Pialoux V, Pérol O, Morelle M, Martin A, Friedenreich C, et al. Feasibility and health benefits of an individualized physical activity intervention in women with metastatic breast cancer: results of the ABLE single-arm Trial study (Preprint). JMIR MHealth UHealth. 2018;24 [cited 2019 Aug 2]; Available from: http://preprints.jmir.org/preprint/12306/accepted.
Delrieu L, Martin A, Touillaud M, Pérol O, Morelle M, Febvey-Combes O, Freyssenet D, Friedenreich C, Dufresne A, Bachelot T, Heudel PE, Trédan O, Crochet H, Bouhamama A, Pilleul F, Pialoux V, Fervers B. 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 Aug;188(3):601-613. doi: 10.1007/s10549-021-06238-z. Epub 2021 May 19. PMID: 34013451; PMCID: PMC8272711.

What is the justification for measuring upper and lower body muscle strength when the exercise intervention you have designed is unlikely to have any impact on these outcome measures and it is an additional test burden for the patients?

In this study, the strength tests are used to assess the general physical fitness of the patient before and after the 3 months of intervention. This measure allows us to complete our sarcopenia and cachexia assessment (assessment of nutritional status, L3 CT scan, inflammatory biomarkers). Kilgour et al., 2013. Handgrip strength predicts survival and is associated with markers of clinical and functional outcomes in advanced cancer patients

Specific comments
line 26 – suggest change to “of acute physical exercise therapy realised”
Modified (line 29)

line 37 – suggest change to “consisting of an acute physical exercise session one hour prior”
Modified

line 39 – suggest change to “acute exercise consists of interval training”
Modified

line 40 – suggest change to “will be assessed at baseline, 3 months and 6 months after study inclusion”
Modified

line 52 – suggest change to “effects of acute physical exercise performed”
Modified

line 57 – suggest change to “will allow individualisation of the intensity”
Modified

line 59 – suggest change to “to an acute moderate intensity physical exercise session in patients”
Modified

line 79 – suggest change to “Principal reported symptoms and adverse effects from treatment are”
Modified

line 82 – PA needs to be defined before the abbreviation is used.
Modified

Line 84 – aerobic capacity and strength are two separate fitness qualities. Suggest change to “been shown to improve aerobic capacity (VO2peak), muscular strength, functional capacity”
Modified

line 91 – suggest change to “immune cell mobilisation in blood such as neutrophils”
Modified

line 103 – suggest change to “basal level within a few hours”
Modified

line 105 – suggest change to “increase the blood flow leading to improved”
Modified

line 111 – suggest change to “could lead to improved perfusion”
Modified

line 117 – is this how you wish to spell “inteRaction”?
This is the study's acronym. Exercise inteReaction Immunotherapy Chemotherapy and cAncer

Line 141 – do you mean physical activity or exercise? Suggest you check the WHO definitions as exercise is a subset of physical activity which is purposeful and planned. Physical activity is any movement that requires energy expenditure. All of the patients will be able to engage in physical activity of some sort but may not be able to perform your prescribed exercise program.

The study proposes both. The 4 sessions of physical exercise pre-treatment, intermittent, of 35 minutes of intensity adapted to the load reached at SV1 for each patient. The criteria that would limit the patients are cardiac and respiratory limitations. The intensities proposed by the study are those from cardiac and respiratory rehabilitation programs.

It is possible that during the 3 months of the intervention, the cancer and its treatments reduce the physical capacities of the patients. For this reason, we encourage patients to stay active, through the home walking program, to maximize their chances of successfully completing the acute pre-treatment exercise.

In addition, the study excluded patients who were not able to perform the exercise at inclusion.

Line 158 – what is the rationale for excluding patients with type II diabetes?
We exclude the patients with uncontrolled type II diabetes *to reduce the risk of patients with delayed hypoglycemia following treatments andacute exercise.

Line 163 – the correct terminology is “electronic patient records”
Modified

line 168 - how useful is a resting electrocardiogram for assessing risk in patients commencing an exercise intervention trial? Have you considered an exercise stress test?

The resting electrocardiogram and cardiac ultrasound are part of the cardiological examination and help identify the risk of serious cardiovascular events. For our exercise intervention in our population of metastatic NSCLC patients the exercise stress test (CPET) is not useful. We do not require maximal exhaustion (to prescribe the target exercise intensity) which appears valuable in metastatic cancer who are not able or willing to spend maximal effort. (Schneider, 2020 ; HAS 2019 Guide de promotion, consultation et prescription médicale d'activité physique et sportive pour la santé chez les adultes)

Line 198 – suggest change to "nutritional recommendations will include:"
Modified

line 204 – suggest change to "will perform an acute physical exercise bout during"
Modified

line 207 – what is a qualified PA instructor? Do you mean a clinical exercise physiologist, physical therapist or similar? Or is this a personal trainer or fitness instructor? Internationally the term PA instructor is unknown.
Change to "a clinical exercise physiologist specialized in oncology".

Line 207 – suggest change to physical exercise consists of a"
Modified

line 216 – do you mean more than or equal to 4% DECLINE of the measured value at rest?
Modified

Line 217 – until a resting oxygen saturation does what?
Change to 'until the rest value of oxygen saturation'

Line 230 – why are you using such a large increment of 30% in steps? Would it not be better to increment by say 10% and then evaluate more regularly?
The increment of 30% of 6000 steps allow the patient to move from a low physical activity to a moderate physical activity levels (from 6000 to 7800 steps) (Delrieu, 2018).

Line 258 – suggest change to "test will allow individualisation of the intensity of"
Modified

line 260 – "watts" is the measurement unit of power so suggest you state more appropriately as "power will be increased by a constant amount of 5 W each 30 seconds"
Modified

line 262 – the submaximal cycle ergometers test is an excellent opportunity to also assess ECG under an exercise stress situation and I suggest that this be included.
The authors of the study consider this suggestion.

Line 267 – "his" is not the appropriate term as you are including both males and females.
Changed to 'The clinical exercise physiologist will stop the test when the patient exceeded their VT1'

Line 270 – suggest change to "lower body muscular strength will be evaluated"

Modified

line 273 – the participants are not stretching their leg. I assume that you mean extend their knee? Change to 'Participants were advised to extend their leg'

Line 358 – Will you be assessing immunity to a particular disease or do you mean you will be assessing immune function? These are two quite different characteristics.
Change to 'immune function'

Line 362 – spelling of "interleukin 10". Also for all the interleukins there is no "e" on the end of the word.
Modified

Line 435 – suggest change to "the feasibility and effects of acute physical exercise performed"
Modified

**VERSION 2 – REVIEW**

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| **REVIEWER** | Voorn, M<br>VieCuri Medical Centre, Epidemiology |
| **REVIEW RETURNED** | 04-Jan-2022 |

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| **GENERAL COMMENTS** | The comments of the reviewers have been well processed and substantiated. Thanks for this clear description. Good luck in conducting this interesting and important study. |

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| **REVIEWER** | Newton, Robert<br>Edith Cowan University, Exercise Medicine Research Institute |
| **REVIEW RETURNED** | 06-Jan-2022 |

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| **GENERAL COMMENTS** | What is the scientific rationale for participants completing the acute aerobic exercise session 1 hour prior to their infusion? Is the one hour from the start of the exercise session or is this one hour from the completion of the exercise session until infusion? Even if it is the former there is a 25 minute recovery period until they commence the infusion. Any transient perturbations of cardiovascular function and tissue perfusion will likely have returned to baseline by the time the patient receives the infusion. What then do you propose is the mechanism by which the acute aerobic exercise session will enhance the effectiveness of the infusion? As this is the underlying premise of your entire study you must provide scientific rationale as to the timing of the acute exercise bout.<br><br>You present quality evidence from the literature that an acute bout of exercise results in increased circulating lymphocytes with subsequent redistribution of immune cells including into tumour tissue. However, you failed to make the connection with why this acute exercise bout should be aligned in time with the infusion. The exercise could be done at any time and achieve the same immune and endocrine responses. The scientific framework for the studies is confusing in this regard and needs to be clarified and supported with scientific evidence as to this design.<br>You have provided a scientific rationale for aerobic exercise during immunotherapy and/or chemotherapy infusion with likely elevation of blood perfusion through the tumour resulting in higher concentrations of anti-cancer factors closer to the cancer cells. |

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| | This begs the question as to why you are scheduling the acute exercise session 1 hour before the patient commences infusion? Why not immediately before, or preferably as per the studies you reference, exercise during the infusion?<br>Why have you chosen a cycle ergometer test of cardiorespiratory capacity when your intervention is a walking program? I realise that you are using this to individualise workloads for the acute aerobic exercise session however you will have limited capacity to draw conclusions from any improvement or decline in cardiorespiratory fitness as a result of the chronic walking program.<br>Why have you chosen exercise recommendations for patients with bone metastases when this is an exclusion criteria for your study?<br>You are not assessing body composition but rather measuring muscle cross-sectional area and radio density at the third lumbar vertebra and then using this to estimate lean body mass. The title of this section should be changed to Lean body mass and sarcopenia and references to body composition removed.<br>What is your rationale for assessing muscle cross-sectional area and radio density at L3? If it is to determine if the walking program prevents or slows the development of sarcopenia common in these patients while undergoing this treatment then you need to present evidence that such an exercise intervention has any influence on muscle morphology in particular in the L3 region. Otherwise, you are subjecting the participants to ionising radiation which carries health risk for no reasonable purpose which is unethical human research.<br>Along the same lines, what is your ethical justification for performing strength tests on the participants? Where is the research evidence that your walking program as designed and implemented will have any influence on grip strength?<br>It is commendable that you have involved lung cancer patients in the design of the study to assess their preferences for physical activity during cancer treatment. However, your purpose is to determine the feasibility and effectiveness of an exercise intervention to alter morphological and physiological parameters and perhaps enhance effectiveness of systemic therapies yet you have chosen an exercise intervention (walking) which is unlikely to create sufficient perturbation within the participants to cause the adaptations you are seeking. If you asked patients whether they would prefer to receive chemotherapy or watch television as their treatment it is obvious what their response will be. Exercise as a medicine is no different, if we continue to choose exercise interventions which are “easy”, “unchallenging”, “pleasant” we will never advance the field because we are testing “medicines” and “therapies” that have no biological mechanism to alter the outcomes of interest. The patients you are recruiting are seriously ill and have very poor prognosis, surely they deserve an optimal exercise medicine prescription grounded in research evidence rather than simply a physical activity they enjoy?<br><br>Specific Comments<br>suggest change title to “The effect of acute aerobic exercise before…”<br>Line 38 - suggest change to “receive a 3-month program”<br>line 210 – suggest change to “experience in oncology”<br>line 475 – suggest change to “the use of activity trackers has shown pertinent” |

**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 3
Mr. Robert Newton, Edith Cowan University
Comments to the Author:
General comments

What is the scientific rationale for participants completing the acute aerobic exercise session 1 hour prior to their infusion? Is the one hour from the start of the exercise session or is this one hour from the completion of the exercise session until infusion? Even if it is the former there is a 25 minute recovery period until they commence the infusion. Any transient perturbations of cardiovascular function and tissue perfusion will likely have returned to baseline by the time the patient receives the infusion. What then do you propose is the mechanism by which the acute aerobic exercise session will enhance the effectiveness of the infusion? As this is the underlying premise of your entire study you must provide scientific rationale as to the timing of the acute exercise bout.
You present quality evidence from the literature that an acute bout of exercise results in increased circulating lymphocytes with subsequent redistribution of immune cells including into tumour tissue. However, you failed to make the connection with why this acute exercise bout should be aligned in time with the infusion. The exercise could be done at any time and achieve the same immune and endocrine responses. The scientific framework for the studies is confusing in this regard and needs to be clarified and supported with scientific evidence as to this design.
You have provided a scientific rationale for aerobic exercise during immunotherapy and/or chemotherapy infusion with likely elevation of blood perfusion through the tumour resulting in higher concentrations of anti-cancer factors closer to the cancer cells. This begs the question as to why you are scheduling the acute exercise session 1 hour before the patient commences infusion? Why not immediately before, or preferably as per the studies you reference, exercise during the infusion?

The authors thank the reviewer for the pertinent comments. The innovation of this study is the physical exercise performed by patients with metastatic NSCLC immediately prior to the administration of immunochemotherapy. The exercise consists of a 35-min acute interval training, scheduled to terminate 15 minutes prior to infusion onset. The 15 minutes to treatment start include time to return to the ward and time for the nurse to install the immunochemotherapy infusion.

Changes have been made accordingly :
● in the abstract : The acute exercise consists of 35 minutes interval training at submaximal intensity scheduled to terminate 15 minutes prior to infusion.
● In the main text (l.217) : ‘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). ‘

Tumor hypoxia in non–small cell lung cancer (NSCLC) is an important factor in treatment resistance and poor survival, and is associated with chemoresistance and impacts tumour-infiltrating lymphocytes (1,2). Evidence from pre-clinical studies suggests that acute exercise reduces tumor hypoxia through increased perfusion of the tumor tissue (3,4), and regular exercise may have the potential to improve tumor perfusion (5) and drug delivery as shown for mammary tumors (6). However, the duration of the exercise induced changes in tumor perfusion and the optimal timing of the bout of exercise, prior or during treatment administration, remain to be determined (1). Furthermore, recruitment of lymphocytes into tumors is critical for anti-tumor immunity and efficacious immunotherapy. Acute physical exercise has immunomodulatory effects involving changes in the quantity, composition, and function of immune cell types in both the circulation and certain tissus (4,7,8). The observed decline of circulating immune cells after cessation of exercise at any length, is suggested to reflect a redistribution of the mobilized NK cells to peripheral tissues (9). Furthermore,

multiple studies have shown that immunomodulatory effects, such as the natural killer cell cytolytic activity, persist a few hours and return to baseline afterwards (10–12). Yet, despite the extensive literature on the effect of acute exercise on the major cell types of the immune system, there is no exact consensus on the kinetics of these cells.
To date, it is unknown which exercise prescription, in terms of intensity and duration, would provide the most powerful stimulus that is both feasible and produces a clinically meaningful response (13). In this context, and in absence of any previous data of acute physical exercise performed in patients with metastatic NSCLC, we considered it necessary to provide data on the feasibility, safety and adherence to this intervention. Considering the concerns of the medical oncologists regarding the clinical status of the mNSCLC patients, it was decided to not to realize the effort during the administration of the treatments.
To be of note, a pre-clinical study conducted in parallel with the ERICA study assesses the effect of pre-injection exercise of immunochemotherapy on immune cell infiltrate and intratumoral hypoxia.

We have modified the introduction as follows (Line 112): 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 (1)

Why have you chosen a cycle ergometer test of cardiorespiratory capacity when your intervention is a walking program? I realize that you are using this to individualize workloads for the acute aerobic exercise session however you will have limited capacity to draw conclusions from any improvement or decline in cardiorespiratory fitness as a result of the chronic walking program.
We thank the reviewer for his comment. The cycle ergometer test has been chosen with respect to the primary objective of the study, i.e. physical exercise of a 35-min acute interval training performed on a cycle ergometer, and will allow us to individualize the training load of the acute physical activity on the ergometer. Moreover, the present study does not aim to assess the separate effect of the home-based walking program. Previous studies have demonstrated the capacity of a home-based walking program to increase the level of physical activity in cancer patients and their cardiorespiratory fitness and physical capacity, including patients with metastatic disease. The goal of the home walking program is to increase the physical activity level of patients with metastatic lung cancer with a target of at least 6000 steps per day, which corresponds to 1 hour of walking per day. The team has previously show the feasibility in women with metastatic breast cancer (Delrieu 2020, PMID: 32012082). Also, a role of regular physical exercise has been suggested to enhance tumor perfusion, oxygenation, and infiltration of immune cells (5). Therefore, the present study, in a secondary objective, assesses the combination of 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.

Why have you chosen exercise recommendations for patients with bone metastases when this is an exclusion criteria for your study?
As specified in the manuscript, bone metastases with risk of fractures or unconsolidated pathologic fractures are indeed exclusion criteria of the present study. Yet, bone metastases in patients with metastatic NSCLC are very frequent, and patients with stable bone metastases can be included into the study. Therefore, we have chosen exercise recommendations for patients with bone metastases.

You are not assessing body composition but rather measuring muscle cross-sectional area and radio density at the third lumbar vertebra and then using this to estimate lean body mass. The title of this section should be changed to Lean body mass and sarcopenia and references to body composition removed.
What is your rationale for assessing muscle cross-sectional area and radio density at L3? If it is to determine if the walking program prevents or slows the development of sarcopenia common in these

patients while undergoing this treatment then you need to present evidence that such an exercise intervention has any influence on muscle morphology in particular in the L3 region. Otherwise, you are subjecting the participants to ionising radiation which carries health risk for no reasonable purpose which is unethical human research.

Thanks for your suggestion, the section title has been changed. No additional examinations are performed, we recover the PET scans from the patient's usual care. In a previous study by the team, data suggest potential benefits of a walking program (similar to that of the present study) for maintenance of muscle mass in patients with metastatic breast cancer (14). Although some authors question the assessment of sarcopenia by body composition assessment at the 3rd lumbar vertebra, this method 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 (15,16). Indeed, sarcopenia is a generalized process in the whole body, the measurement of regional muscle mass does not always represent the totality of the muscles of the body. Thus, to eliminate the factors, and in order to keep the same value of the Hounsfield unit of the tissue all CT analysis must be done in the same CT scanners and only noncontrast-enhanced images must be evaluated to determine muscle mass.

We have made accordingly the following changes in the manuscript (Line 309):

- 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 (15,16)(43).

Along the same lines, what is your ethical justification for performing strength tests on the participants? Where is the research evidence that your walking program as designed and implemented will have any influence on grip strength?
Hand grip strength is widely used in patients with cancer to assess muscle strength and physical fitness (17–19). It has been proposed as a predictor of malnutrition in individuals with cancer and has been associated with cancer survival (2). Hand grip strength is an easy and non-invasive method that is well tolerated by cancer patients. In France, it is recommended as a routine test to assess muscle strength and physical fitness in cancer patients.
We specified accordingly in the manuscript (Line 294): 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.
It is commendable that you have involved lung cancer patients in the design of the study to assess their preferences for physical activity during cancer treatment.
However, your purpose is to determine the feasibility and effectiveness of an exercise intervention to alter morphological and physiological parameters and perhaps enhance effectiveness of systemic therapies yet you have chosen an exercise intervention (walking) which is unlikely to create sufficient perturbation within the participants to cause the adaptations you are seeking.

If you asked patients whether they would prefer to receive chemotherapy or watch television as their treatment it is obvious what their response will be. Exercise as a medicine is no different, if we continue to choose exercise interventions which are “easy”, “unchallenging”, “pleasant” we will never advance the field because we are testing “medicines” and “therapies” that have no biological mechanism to alter the outcomes of interest.
The patients you are recruiting are seriously ill and have very poor prognosis, surely they deserve an optimal exercise medicine prescription grounded in research evidence rather than simply a physical

activity they enjoy?

We fully agree with the reviewer that patients with cancer deserve an optimal exercise medicine prescription grounded in research evidence. Therefore, in the present study, instead of a standard exercise prescription, the exercise load at first ventilatory threshold intensity for patients with metastatic NSCLC (frequently presenting with limited physical fitness and comorbidities) is individualized based on the results of the submaximal endurance test using cycle ergometer; patients will also follow an individual goal of a number of daily steps in the home-based walking program. Therefore, we are not sure to well understand the comment referring to the choice of “easy”, “unchallenging”, “pleasant” exercise in our study. The mNSCLC patients clearly do not perceive the requested effort as “easy” and “unchallenging”.
Also, the home-walking program has previously shown significant improvements in the 6-minute walking distance test and isometric quadriceps strength (Delrieu 2020 PMID: 32012082). Moreover, current evidence shows that public and patient involvement in research has a positive effect on its quality and end-results; and involvement of cancer patients in all stages of research is strongly encouraged by the French Comprehensive Cancer Centers, including research performed on physical activity in the present team (20,21).

Specific Comments
suggest change title to “The effect of acute aerobic exercise before…” Modified
Line 38 - suggest change to “receive a 3-month program” Modified
line 210 – suggest change to “experience in oncology” Modified
line 475 – suggest change to “the use of activity trackers has shown pertinent” Modified

The authors are grateful for the suggestions and have made the necessary corrections.

**VERSION 3 – REVIEW**

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| **REVIEWER** | Newton, Robert<br>Edith Cowan University, Exercise Medicine Research Institute |
| **REVIEW RETURNED** | 22-Feb-2022 |

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| **GENERAL COMMENTS** | I am thankful to the authors for addressing my comments and concerns so thoughtfully and extensively. It is now much clearer as to the protocol being implemented. In particular it is critical that the authors have now specified that the acute exercise session will cease 15 minutes prior to the commencement of immunotherapy.<br>I have no further concerns or suggestions for improvement other than the small corrections to the text listed below.<br>Line 111 – spelling immunomodulatory<br>Line 309 – grammatical error. Suggest change to “vertebra provides a reliable representation”<br>Line 311 – suggest change to “given that CT scans as part” |

**VERSION 3 – AUTHOR RESPONSE**

Reviewer: 3

Mr. Robert Newton, Edith Cowan University

Comments to the Author:

I am thankful to the authors for addressing my comments and concerns so thoughtfully and extensively. It is now much clearer as to the protocol being implemented. In particular it is critical that the authors have now specified that the acute exercise session will cease 15 minutes prior to the commencement of immunotherapy.

I have no further concerns or suggestions for improvement other than the small corrections to the text listed below.

Line 111 – spelling immunomodulatory

Line 309 – grammatical error. Suggest change to “vertebra provides a reliable representation”

Line 311 – suggest change to “given that CT scans as part”