Author’s response to reviews

Title: Impact of AferBio® on Quality of Life and Chemotherapy Toxicity in Advanced Lung Cancer Patients (AFERBIO study): protocol study for a phase II randomized controlled trial

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To

Editor-in-Chief

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Impact of AferBio® on Quality of Life and Chemotherapy Toxicity in Advanced Lung Cancer Patients (AFERBIO study): protocol study for a phase II randomized controlled trial
Dear Editor

First, we would like to thank the reviewers for their careful review of our manuscript. Below are our point-by-point responses to the concerns. Changes are highlighted in gray color within the manuscript text.

Reviewer 1: I would advise to add the following paper:


Response: Thanks for suggesting such an interesting reference. It was added as suggested (please see below).

Background section, lines 82-84:

In patients with lung cancer, nutritional status is inversely correlated with pain, anxiety and depression scores, highlighting the need for early supportive psychotherapy or interventions focused on nutrition aspects[16].

Reviewer 2:

The major points that needed to be addressed are detailed below:

1. Introduction part: Lack of their conclusion which will very important to readers to follow

Response: The text was modified accordingly.
Previous text: Therefore, the present study aim to assess the impact of a novel food supplement on HRQOL and reduction of treatment-related complications in patients with advanced lung cancer beginning palliative chemotherapy treatment. The AferBio® is already available for commercialization, but has not yet been duly tested in cancer patients.

New text: The AferBio® is already available for commercialization, but has not yet been duly tested in cancer patients. Therefore, the present study aim to assess the impact of this novel food supplement on HRQOL and reduction of treatment-related complications in patients with advanced lung cancer beginning palliative chemotherapy treatment. This trial tests the hypothesis that patients receiving AferBio will have fewer adverse events and infectious complications during treatment compared with patients receiving placebo, leading to better quality of life and fewer treatment delays. If intervention proves successful, we will have a new supportive product to be used as adjuvant of chemotherapy in patients with advanced lung cancer.

2. In Methods/Design:

2.1 NSCLC cancer patients with stage IIIB or IV will need combination treatment without mono-chemotherapy. In case with mono-chemotherapy design, why did the authors select docetaxel without other NSCLC drugs?

Response: We agree with the reviewer that there are other chemotherapy regimens including combinations of chemotherapy. Considering the very different toxicity profiles between the different drugs, in the non-randomized phase of the study, we chose to evaluate only those submitted to docetaxel monotherapy. In the randomized phase, we will include patients undergoing other treatments as well (researcher's choice). At our Hospital, the institutional protocol includes mono-chemotherapy with docetaxel, gemcitabine and vinorelbine in the second line or more for the treatment of Stage IIIB or IV NSCLC.

3. In Data collection, how about further analysis?

How can we further do with "blood collection, toxicity assessment and response evaluation" as mentioned by the authors?

Response: After criticism from the reviewer, we realized that the text was unclear. The blood collection in the present study is only to check for toxicity, since we did not plan to collect biological samples for future molecular analyzes. Thus, to make the text clearer, we excluded the text "collect blood samples" (please see below).

In Abstract section, lines 40-42:
Each evaluation will include the following: HRQOL (EORTC QLQ-C30, LC13 and IQualiV-Lung), ECOG-PS, anthropometric measurements, blood collection, toxicity assessment and response evaluation.

Regarding toxicity and response evaluation, some modifications were conducted in order to make the manuscript clearer for the readers.

In the Methods Section, lines 198-200, the text was rewritten:

Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, will guide the evaluation of oncological status related to the response to chemotherapy as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD).

Lines 216-219:

The number of patients with toxicity ≥ grade 3, hospitalization, infections, use of antimicrobials, febrile neutropenia, adherence to the investigational product/placebo, dose reduction above 20 %, and response rates (clinical benefit) will be compared among groups by the chi-square test (or Fisher’s exact test).

Clinical benefit rate will be considered the percentage of patients who have achieved CR, PR and SD.

4. This whole manuscript also has several major issues, especially about academic language.

Response: the whole manuscript was reviewed by a researcher fluent in English to fit to the academic language

5. Importantly, in Discussion part,
The authors mentioned about some case studies which are related to AferBio® with Ref # 37 and Ref # 38 as shown in their manuscript.

However, both titles of these Refs are not in international language (English).

The Reviewer could not find paper as Ref # 37.

About Ref # 38, whole manuscript was not written in English.

Taken together, it will be extremely hard to evaluate this manuscript version.

Response: I understand the reviewer. However, some work has been published only in Portuguese language, since AferBio was originally developed in Brazil. In order to improve this issue, we translated the reference text into English (between brackets) and include another reference in English and openly available at NCBI database.

Discussion Section, lines 231-233:

Previous text: Studies have been conducted to assess the possible effects of AferBio® in animals and humans. One study was performed using rats, that were fed with the product for 90 days, and there were no signs of systemic toxicity, and in general, the organs were preserved[37]. Another study assessed the cytotoxic activity of an AferBio® extract in several human tumor cell lines that were cultivated and replicated under sterile conditions. In those analyses, a concentration of 25 µg/mL inhibited growth in colon and lung cell lines[38].

Next text: Studies have been conducted to assess the possible effects of AferBio® in animals and humans. One study was performed using rats, that were fed with the product for 90 days, and there were no signs of systemic toxicity, and in general, the organs were preserved[37]. Another study assessed the cytotoxic activity of an AferBio® extract in several human tumor cell lines that were cultivated and replicated under sterile conditions. In those analyses, a concentration of 25 µg/mL inhibited growth in colon and lung cell lines[38]. Additionally, a promising anti-inflammatory activity of AferBio was verified in a study using a rat inflammatory model. In this study, wistar rats were fed the AferBio product (900mg / kg / day) for 30 days before the induction of inflammation and for another 6 days; significant effects in both acute and chronic models of inflammation were observed (REF).

The minor point that needed to be addressed are detailed below

6. The authors did not carefully follow BMC Cancer reference style

Response: All refs were adequated according to BMC Cancer reference style
Ref# 2 was updated without modifying the citation in the text

With kindly regards,

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