Peer Review File

Article Information: https://dx.doi.org/10.21037/TLCR-22-561

Round 1

Reviewer A

The authors have written a narrative review on cancer cachexia in patients with advanced non-small cell lung cancer. By writing a narrative review rather than a systematic review, the authors have the flexibility of providing a broader coverage of the topic, but at the same time without the detail that might be helpful in selected areas in the field of cancer cachexia, such as a deeper value of the biology or emerging therapeutic directions. With that said, the review does provide the reader with an overview of the topic of cachexia in lung cancer, specifically focusing on both components of pulmonary cachexia and cancer cachexia. In addition, the authors discuss the interplay of different factors impacting the appetite center, including GDF15, leptin, and ghrelin. They further focus on the approval of anamorelin in Japan and its potential impact on patients. Lastly, they focus on the need for standardization of biomarkers and future therapeutic development.

Specific comments:

In the last paragraph, beginning with Line 461, the authors discuss post-marketing surveillance of anamorelin in Japan, including a "clear difference between the effective and ineffective anamorelin patient groups". It is not clear to what the authors are referring. Furthermore, there is no reference for these statements which needs to be clarified. There is a minor typo at the end of Line 252.

Reply: We appreciate your valuable comments. As pointed out, we have revised the sentences and added a reference.

Changes in the text:

(Page 28, line 485) The action of anamorelin differs from patient to patient,

(Page 15, line 252-253) Japanese cachexia team prospectively observed untreated advanced NSCLC patients over

Reviewer B

In this article the authors describe the progress in the management of cancer cachexia in patients with non-small cell lung cancer. The article first introduces the various therapies available for NSCLC. This is followed by description of cachexia followed by brief presentation on mechanisms guiding cancer cachexia. Next the article goes more specific and sections are focused on respiratory disease and its impact on cachexia. A section focusses on ghrelin agonist identification and its use in preventing cachexia. The impact of cachexia on outcomes to different treatments is described and biomarkers of cachexia are also touched upon. The article is supported by 3 figures, 59 updated references and a table.

Specific comments:
Figures can be merged into 1 or 2 figures
In the introduction describing different NSCLC therapies, some description of recent KRAS pathway drugs (that received FDA approval) and the impact of cachexia on drug efficacy could be mentioned
The article should be carefully checked for typos
For example at several places there are extra commas and other similar punctuations on Page 10 and 11
This is a comprehensive article that will be well read by the audience. Minor revision will improve its quality further.

Reply: We are thankful for the valuable comments. As the reviewer recommended, we have merged the Figures into 2 Figures. We have added the information on KRAS inhibitors and the impact of cachexia on drug efficacy in the Introduction section. Also, we have carefully proofread the entire manuscript, including the extra commas and other similar punctuations on Pages 10 and 11.

Changes in the text:

(Page 4, lines 65–66), including novel molecular targeted therapy targeting KRAS G12C mutations (2). Therefore,

(Page 5, lines 78-79) Anamorelin continues to be used in daily clinical practice because of its therapeutic effects on cachexia.

Reviewer C
I think this review is well written. It focuses heavily on anamorelin and this is a therapy which is unlicenced outside of japan.

More needs to be made of the role of allied health professionals, specifically dietitians and physiotherapists, also the role of rehabilitation needs to be more formally acknowledged.

The role of pulmonary rehabilitation for copd should be commented on.

Reply: We are thankful for the important comments. As the reviewer pointed out, we have added more description and a reference regarding pulmonary rehabilitation for COPD.

Change in the text:
(Page 14, lines 233–243) Pulmonary rehabilitation and nutritional support constitute one of the standard interventions for patients with chronic lung disease. High intensity exercise training was shown to be effective in improving lower limb muscle strength and exercise performance in COPD patients with low muscle mass and moderate airflow obstruction. Specific nutritional supplementation showed additional effects on nutritional status,

inspiratory muscle strength, and physical activity (34). Despite proven physiological, symptom relief, psychosocial, and health economic benefits of pulmonary rehabilitation and nutritional support for patients with chronic respiratory diseases, these interventions are under-utilized worldwide. This is due to a lack of funding, resources, and reimbursement, as well as a lack of awareness and knowledge among healthcare professionals, payers, and patients.

As should the role of early palliative care and include the reference by temel et al 2010 in NEJM https://www.nejm.org/doi/pdf/10.1056/NEJMoa1000678

Reply: We appreciate your comment. As pointed out, we have added the indicated reference, as well as the role of early palliative care.

Change in the text:
(Page 16, lines 280–282) A previous clinical trial demonstrated that early palliative care led to significant improvements in both QOL and mood among patients with metastatic NSCLC (45).

I feel this review heavily focus's on anamorelin
I have attached the file with specific comments and possible references.

Reply: We thank the reviewer for the meaningful comments. We have responded to the specific comments, as follows:

Comment 1) As for delete “As”.

Reply: We have deleted the indicated word.

Change in the text: (Page 4, lines 63–66)
The prognosis of patients with advanced non-small cell lung cancer (NSCLC) is improving with advances in treatment, including novel molecular targeted therapy targeting KRAS G12C mutations(2). Therefore,

Comment 2) As for add the punctuation.

Reply: We have revised the sentences as pointed out by the reviewer.

Change in the text: (Pages 4–5, lines 67–70)
Inflammatory cytokines are produced by the immune system in response to factors produced by tumor cells. They play an important role in the pathogenesis of cancer cachexia, resulting in decreased appetite, abnormal energy metabolism, and skeletal muscle degeneration.

Comment 3) As for justify the use of this idiopathic pulmonary fibrosis as not directly relevant to lung cancer.

Reply: We are grateful for the reviewer's comment. We have deleted this keyword.

Comment 4) As for the word "structure of diseases"

Reply: As the reviewer pointed out, we have changed the word from "structure of disease" to "disease pattern."

Change in the text: (Page 7, lines 111–112)
Disease patterns have changed as medical advances have established effective treatments for many diseases.

Comment 5) As for add the width of targeted therapies available, e.g. ALK, ROS1, KRAS, MET/RET.

Reply: As the reviewer pointed out, we have revised the indicated sentences.

Change in the text: (Page 7, lines 119–120)
followed by the approval of the molecularly targeted drugs from 2013 for EGFR, ALK, ROS1, KRAS, MET, and RET,

Comment 6) As for long term survivors who are PDL1 high expressors on pembrolizumab.

Reply: We have added the sentence and the reference.

Change in the text: (Page 8, lines 127–129)
In addition, the 5-year survival rate for patients with treatment-naïve advanced NSCLC treated with pembrolizumab monotherapy was reported as 23.2% (11).

Comment 7) For "I dont think that anamorelin is directly relevant here. This sentence could be removed."

Reply: We have deleted the indicated sentence.

Comment 8) For "need to comment that the pathogenesis of cachexia is complex and not fully understood."

Reply: As the reviewer pointed out, we have added the sentence.

Change in the text: (Page 10, line 167)
The pathogenesis of cachexia is complex and not fully understood. At present,

Comment 9) For your comment "Do you mean 15% of patients with COPD have cachexia associated to COPD?"

Reply: We are grateful for your meaningful comment. We have added the following sentences and references.

Change in the text: (Page 13, lines 217–219)
The prevalence of cachexia in patients with COPD is relatively high, ranging from 5% to 15%. In addition, cachexia is known as an independent risk factor for mortality in COPD patients (27,29).

Comment 10) For your comment "need to talk about inflammatory scores/prognostic scores in this setting,…"

Reply: As the reviewer pointed out, we have added the following sentences and references to capture the issue of inflammatory scores/prognostic scores.

Change in the text: (Page 16, lines 272–275)
In addition, inflammatory/prognostic scores, such as modified Glasgow prognostic score, prognostic nutritional index, nutritional index, neutrophil/lymphocyte ratio, are associated with cancer cachexia (41) and prognosis of advanced NSCLC patients (42-44).

Comment 11) For your comment "need to comment on the fact that anamorelin has been licensed in other countries,…"

Reply: As the reviewer pointed out, we have added a description regarding the development of anamorelin.

Change in the text: (Page 18, lines 317–321)
However, it was not licensed in Europe and the US due to lack of adequate data on patient benefits and safety. Currently, two phase III SCALA studies on anamorelin are underway in the US, Europe, Russia, and Australia for treatment of malignancy-associated weight loss and anorexia in adult patients with advanced NSCLC (NCT03743051 and NCT03743064).

Comment 12) For your comment "need to acknowledge that nutritional need in this population is high…"

Reply: As the reviewer pointed out, we have added the following description and references on nutritional need.

Change in the text: (Page 22, lines 389–393)
Many NSCLC patients have a high symptom burden and are at risk of malnutrition prior to starting systemic anticancer therapy, suggesting that the improvement of nutritional conditions might enhance clinical outcomes (57). However, simple nutritional interventions did not improve clinical outcomes, including nutritional outcomes and QOL (58).

Reviewer D

The paper by Morita-Tanaka et al is a nicely written review about the basic science of cancer cachexia, and potential therapeutic targets that may be used for treatment. It is a clear and informative review which will add to the literature on this topic, and I do not have any major concerns about this paper. I do have a few minor suggestions:

- Lines 259-277: The authors focus on 2 studies from their group examining the link between cancer cachexia and poorer prognosis in patients treated with immunotherapy. Particularly since the methods discuss a comprehensive pubmed review, it would also be a good idea to include studies from other groups with similar findings, to show the broader applicability. For examples, Degens et al (PMID 33951326) Roch et al (PMID: 32200137), and Rounis et al (PMID: 34584855) are potential papers that could be included.

Reply:

As the reviewer recommended, we have added more information on the relationship between cachexia-sarcopenia and the poor outcomes of ICIs.

Changes in the text: (Page 15, lines 263–266)

Similarly, recent studies reported that advanced NSCLC patients with cancer cachexia-sarcopenia showed poor prognosis after treatment with immune checkpoint inhibitors (37-39).

- Lines 303-306: It would be clinically interesting to know what the average amount of weight gained in these trials was in kilograms, to understand how large of an effect was seen. How does this compare to the average weight gain with corticosteroids?

Reply: We have added information on weight gain by anamolerin. In contrast, as far as we know from previous studies, there are no reports of weight gain by corticosteroids.

Changes in the text: (Page 18, lines 309–312)

the change from baseline was 1.38 ± 0.18 kg and -0.17 ± 0.17 kg in the anamorelin and placebo groups, respectively (P<.0001). In addition, the LBM of anamorelin group increased one week after anamorelin treatment and it continued thereafter with no safety concern.

- Line 316-317: Can you specify which cardiac disease are contraindications? Is this just patients with a prior history of MI, or heart failure, or does it also include atrial fibrillation, valvular dysfunction, or hypertension?

Reply: We are grateful for the reviewer's comment. Nonclinical studies mentioned the occurrence of adverse cardiovascular events and cardiac disease. We have added this information to the section of "Lung cancer and cancer cachexia."

Changes in the text:

(Page 19, lines 323–325)

In terms of side effects, adverse cardiovascular events, such as first-degree atrioventricular block, tachycardia, and hypertension, have been reported. From the

results of nonclinical studies (48, 51),

(Page 19, lines 329-331)
cardiac diseases, such as congestive heart failure, myocardial infarction, and angina pectoris, as well as severe heart conduction disorders, including complete atrioventricular block.

- It would be interesting to include a paragraph discussing how anamorelin is currently being used in Japan. Since there is not yet data about whether the weight gain seen correlates with other outcomes such as survival or even quality of life, is it being routinely prescribed in Japan, is it too new to tell, or is its use mostly still limited to trials? What data or outcome measures would you want to see in order to be convinced that the increase in weight is clinically significant and/or valuable and that anamorelin should be routinely prescribed for patients with cancer cachexia?

Reply: Anamorelin is available for patients with cachexia in daily practice but is not routinely used in Japan. The Japanese Association of Supportive Care in Cancer formulated a guideline for proper use of anamorelin while considering precautions. We have added this information to the section "Lung cancer and cancer cachexia." Regarding the reviewer's comment on whether anamorelin should be routinely prescribed for patients with cancer cachexia, we agree that the usage of anamorelin should be incorporated into daily practice, but further evidence is warranted to reveal additional biomarkers for the selection of responders to anamorelin.

Changes in the text: (Pages19–20, lines 339–342)
The Japanese Association of Supportive Care in Cancer formulated a guideline for the proper use of anamorelin, considering the above precautions. Currently, anamorelin is available for patients with cachexia in daily practice but is not routinely used in Japan.

- In order to provide a complete picture, the authors should also include a paragraph discussing the regulatory status of anamorelin in Europe and the US. Anamorelin was not given approval in Europe as "the studies show a marginal effect of Adlumiz on lean body mass and no proven effect on hand grip strength or patients' quality of life. In addition, following an inspection at clinical study sites, CHMP considered that the safety data on the medicine had not been recorded adequately." (https://www.ema.europa.eu/en/medicines/human/EPAR/adlumiz). This should be discussed in the review to avoid confusion from readers from other countries.

Reply: We appreciate the reviewer for the important points. We have added more details on the current situation of anamorelin in Europe and the US, including two ongoing international clinical trials in the section "Development of novel therapeutic strategy with anamorelin for cancer cachexia."

Changes in the text: (Page18, lines 317–321)
However, it was not licensed in Europe and the US due to lack of adequate data on patient benefits and safety. Currently, two phase III SCALA studies on anamorelin are underway in the US, Europe, Russia, and Australia for treatment of malignancy-associated weight loss and

anorexia in adult patients with advanced NSCLC (NCT03743051 and NCT03743064).

- Line 404-406: would be helpful to include what the average weight or lean body mass change was in this study.

Reply: We appreciate the reviewer's suggestion. However, there is no information on the average weight or lean body mass change in this phase 3 study. We found the LBM data in the Phase1 study (reference 63) instead and have added the data as follows:

Changes in the text: (Page 24, lines 425–427)
They also reported that Bermekimab was well tolerated, with gains in LBM (1.0 ± 2.5 kg, mean 0.4 kg [SD: -0.5-2.6]) in patients with metastatic non-small cell lung cancer. (63)

Round 2

Reviewer A

The authors adequately addressed my comments

Reviewer B

Comments have been addressed

Reviewer C

Thank you for amending the paper, I think the changes improve the paper and clarify the context of anamorelin.

I am not sure that the section on pulmonary fibrosis, but this should not prevent publication.

Reply:

Comorbidity of IPF, a group of refractory interstitial pneumonia is one of the poor prognostic factors for advanced lung cancer. As with comorbidity of COPD, it has been suggested that chronic respiratory muscle fatigue by progression of IPF may exacerbate the pathophysiology of cachexia. Based on these findings, in this review article, pulmonary fibrosis was listed as one of the exacerbating factors for lung cancer with cachexia.

I would suggest adding 2 references to the section on blood biomarkers (line 273)

1. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer, Donald C McMillan, 2013, Cancer treatment reviews as it has been cited over 1,000 times.

Reply:

We appreciate for indicating the useful reference by McMillan DC. As the reviewer recommended, we added these reference in our review article (see Page 16, lines 272-275).

Changes in the text: (Line 272-275) In addition, inflammatory/prognostic scores, such as modified Glasgow prognostic score, prognostic nutritional index, nutritional index, and neutrophil/lymphocyte ratio, are associated with cancer cachexia (41)(42) and prognosis of advanced NSCLC patients (42-45).