

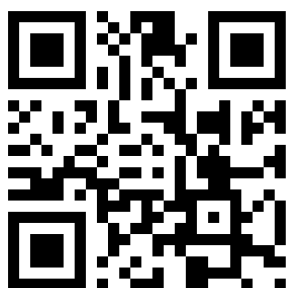
# Emerging Treatment Options For Cancer-Associated Cachexia: A Literature Review

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**Abstract:** Cachexia is a disease that has been recognized since antiquity; however, research in this area has recently increased. Promising new agents, including anamorelin hydrochloride, have been tested in large randomized controlled studies, and multidrug as well as multimodal approaches have been proposed as having the potential to improve outcomes in patients with cancer cachexia. However, standard treatment remains elusive. This review summarizes the current literature on treatment of cancer-associated cachexia, showing that there are challenges associated with conducting clinical trials in such patients. First, poor recruitment, retention, and compliance among cachectic patients cause research delays. Second, the lack of consensus regarding clinically meaningful endpoints impedes standardization of study designs and results. Further consideration is needed to identify the most suitable study design and endpoints, which can lead to the development of pharmacological and nonpharmacological interventions that improve patients' prognosis and outcomes.

**Keywords:** cancer cachexia, physical function, anamorelin, multimodal intervention

## Introduction

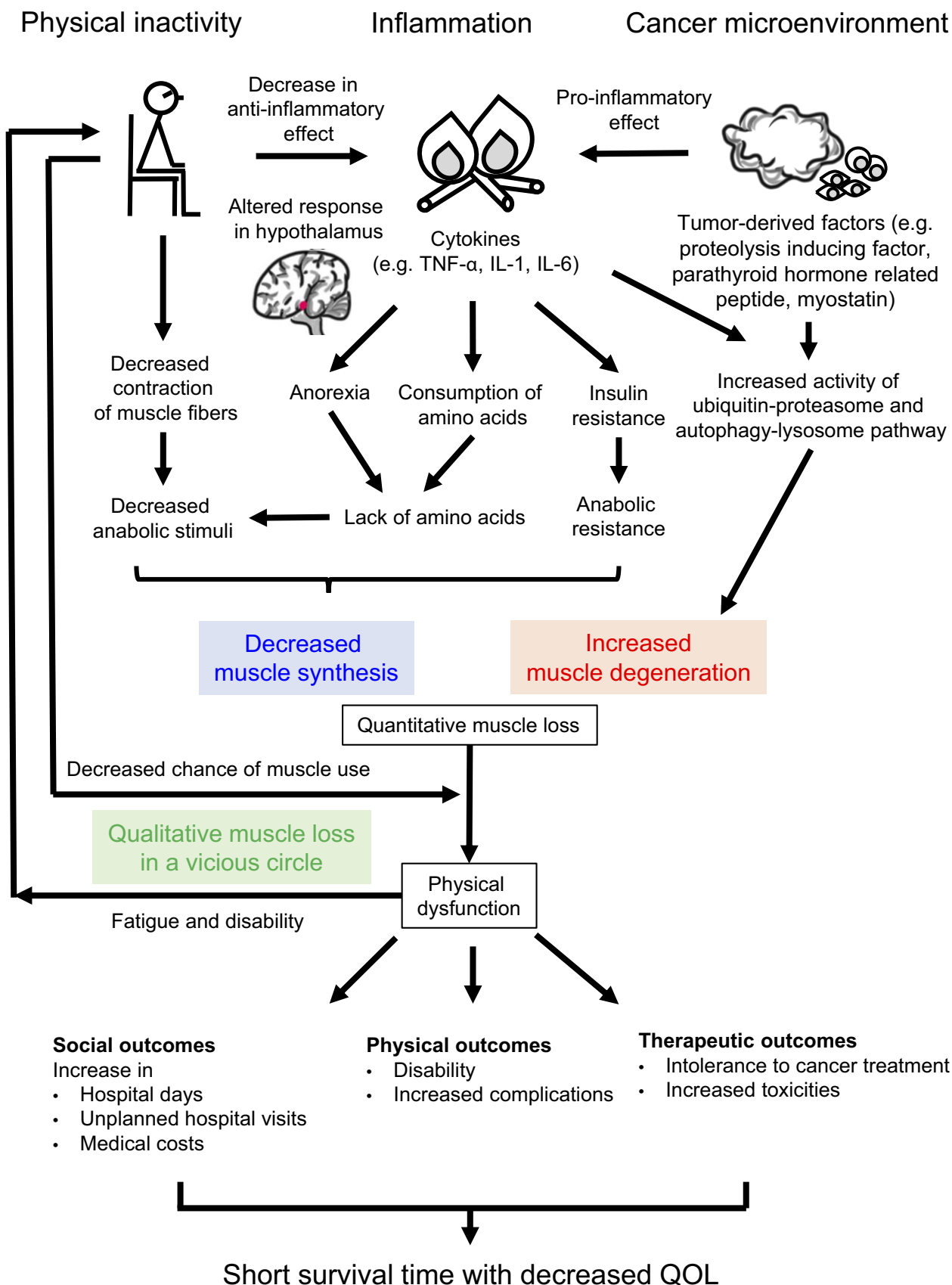
Cachexia is a wasting condition associated with chronic diseases that has been known since ancient time in Europe as well as East Asia.<sup>1</sup> In Greece, Hippocrates precisely described the core pathogenesis of cachexia already in the fourth century BC saying, "the flesh is consumed and becomes water." He considered cachexia as a sign of death.<sup>2</sup> The detrimental impact of cachexia on prognosis in cancer patients has been recognized since the early 20th century.<sup>3</sup> In 2011, the medical community achieved a landmark consensus on the diagnostic and staging criteria,<sup>4</sup> which have allowed cancer cachexia to be recognized based on few anthropometric measurements and a quick interview. However, in spite of considerable research efforts, there is still no standard treatment for cancer cachexia. This report aimed to review recent literatures on the development of therapeutic interventions for cancer cachexia to propose future research directions.

## Skeletal Muscle Metabolism And Clinical Outcomes In Cancer Cachexia

To understand the trends in emerging therapeutic interventions, examining the pathogenesis of cancer cachexia is essential. Cachexia involves multiple organs, including skeletal muscles, adipose tissues, and the digestive, immune, or central nervous system.<sup>5,6</sup> Among them, altered skeletal muscle metabolism might play the most important role in worsening clinical outcomes (Figure 1). The chronic systemic

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**Figure 1** Skeletal muscle metabolism and clinical outcomes in cancer cachexia.

**Abbreviations:** TNF, tumor necrosis factor; IL, interleukin; QOL, quality of life.

inflammation is provoked by the presence of tumor and its microenvironment.<sup>7</sup> Physical inactivity in cancer patients further increases systemic inflammation due to reduced anti-inflammatory effect of chronic exercise.<sup>8,9</sup> Infrequent contractions of skeletal muscles due to physical inactivity reduce anabolic stimuli for muscle protein synthesis in myocytes.<sup>10</sup> Relative shortage of amino acids in skeletal muscle restricted protein synthesis because amino acids are mainly consumed for production of acute phase protein in liver.<sup>11</sup> In addition, hypogonadism in male cancer patients,<sup>12</sup> and tissue resistance to ghrelin<sup>13,14</sup> and growth factors,<sup>15</sup> further impede muscle protein synthesis. Cytokines, including tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6, and IL-1 $\beta$ , induce insulin resistance in liver, skeletal muscle, and adipose tissue, which, in turn, produce anabolic resistance.<sup>16</sup> Increased levels of these cytokines<sup>17</sup> as well as the presence of ghrelin resistance<sup>14</sup> also affect hypothalamic appetite control and induce anorexia. At the same time, muscle degeneration is enhanced by the ubiquitin-proteasome or autophagy-lysosome pathways, which are induced by other pro-inflammatory mediators or tumor-derived factors. These factors might include IL-6, TNF- $\alpha$ , TNF-related weak inducer of apoptosis, parathyroid hormone-related peptide, or transforming growth factor- $\beta$  superfamily (e.g., activins and myostatin).<sup>5</sup> Overall, the physical dysfunction in cachectic patients might be caused by both quantitative<sup>18,19</sup> and qualitative<sup>20,21</sup> reduction in skeletal muscle, which, combined, further impede the patient's physical activity,<sup>22,23</sup> resulting in a vicious cycle (Figure 1). Over time, this means cachectic cancer patients often have a disability, require a longer hospital stay, and generate larger medical costs than patients without cachexia.<sup>24,25</sup> In addition, patients with cachexia are more susceptible to toxicity of chemotherapy<sup>26,27</sup> and often unable to complete planned chemotherapy cycles.<sup>28,29</sup> Consequently, the presence of cancer cachexia is associated with poor prognosis and low quality of life (QOL) from at the time of diagnosis,<sup>30</sup> through treatment<sup>31</sup> to near the end of the cancer trajectory.<sup>32</sup> As cachexia is a complex disease, each component of its pathogenesis is a potential target for interventions to improve outcomes. In addition, the multifactorial processes associated with cachexia suggest a need for multidrug or multimodal approaches to this condition.

## Methods

Randomized controlled trials and systematic reviews for therapeutic interventions for cancer cachexia were

identified by searching the PubMed using the following keywords in August 2019:

(cachexia[tiab] OR cachectic[tiab] OR Malnutrition[Mesh] OR malnutrition[tiab] OR 'muscle wasting'[tiab] OR 'muscular wasting'[tiab] OR 'Muscle Weakness'[Mesh] OR 'muscle weakness'[tiab] OR 'muscular weakness'[tiab] OR sarcopenia[tiab] OR 'Wasting syndrome'[MeSH:noexp] OR 'wasting syndrome'[tiab] OR 'weight loss'[tiab]) AND. (Neoplasms[MeSH] OR cancer[tiab] OR tumor[tiab] OR tumour[tiab] OR neoplas[tiab] OR malignan[tiab] OR carcinoma[tiab] OR adenocarcinoma[tiab] OR choriocarcinoma[tiab] OR leukemia[tiab] OR leukaemia[tiab] OR metastat[tiab] OR sarcoma[tiab] OR teratoma[tiab])

The pre-specified inclusion criteria were articles in the English language; studies involving adults. Studies on hematologic malignancies, surgically operable cancers, cancer survivors, or noncancer populations were excluded. Regarding pharmacological interventions, agents which have been tested in phase 3 randomized controlled trials were mainly chosen. Information for ongoing trials were collected from trial registration site, reports of regulatory authority, or publications for study protocol. Entry criteria, cachectic status of participants, concurrent treatments, types of intervention, efficacy, and major toxicities in each study were summarized. Cachectic status was classified according to the consensus report.<sup>4</sup>

## Results

### Pharmacological Interventions

Randomized controlled trials with agents such as corticosteroids,<sup>33</sup> progestins,<sup>34</sup> nonsteroidal anti-inflammatory drugs (NSAIDs),<sup>35</sup> thalidomide,<sup>36</sup> and eicosapentaenoic acids (EPA)<sup>37</sup> have been conducted to develop pharmacological interventions for cancer cachexia. Although each intervention improved some aspects of the condition, no reliable or clinically relevant effect on patient functioning or QOL was reported.<sup>38</sup> In addition, some agents were associated with risks that outweighed their benefits.<sup>39</sup> Previously reported treatment-associated complications included deep venous thrombosis or edema in progestins, glucose intolerance in corticosteroids, and gastrointestinal or renal toxicities in NSAIDs. As a result, no single agent was identified as a suitable standard treatment for cancer cachexia. However, recently, efforts have been made to develop novel agents or a way to combine available agents to improve treatment safety and effectiveness. Among various regimens, anamorelin hydrochloride,

MABp1, enobosarm, and several multidrug combinations were tested in the phase 3 randomized controlled trials. Subsequent candidate agents were also tested in the recent phase 2 trials, which include espendrol<sup>40</sup> (novel non-selective  $\beta$  blocker), testosterone,<sup>41</sup> nabilone<sup>42</sup> (cannabinoid), and LY2495655<sup>43</sup> (anti-myostatin antibody).

### Anamorelin Hydrochloride

Anamorelin is a novel, orally active, selective ghrelin receptor agonist with appetite-enhancing and anabolic activity.<sup>44</sup> It positively affects lean body mass (LBM) through increased secretion of the growth hormone, insulin-like growth factor 1, and insulin-like growth factor-binding protein 3 through activation of the ghrelin receptor. During phase 1 and 2 trials, anamorelin has been shown to enhance appetite and increase LBM, while maintaining a desirable tolerance profile (Table 1).<sup>45,46</sup> Moreover, in two phase 2 studies based in Japan, anamorelin (100 mg daily for 12 weeks) was associated with an increase in LBM, body weight, and appetite in patients who had advanced non-small-cell lung cancer (NSCLC) with cachexia.<sup>47,48</sup> Finally, two multinational phase 3 studies (ROMANA 1 and 2 trials) confirmed the effect of anamorelin (100 mg for 12 weeks) on increasing LBM and body weight, and improving anorexia/cachexia-specific QOL among patients with NSCLC and cachexia.<sup>49</sup> Subsequently, an extension study (ROMANA 3), involving participants who had completed the ROMANA 1 and 2 trials, assessed the safety and feasibility of prolonged use of anamorelin over 24 weeks.<sup>50</sup> Among the 345 patients who completed ROMANA 1 or 2 in the anamorelin group, 221 patients (64%) completed a 24-week of anamorelin 100 mg daily with a mean of 161.1 treatment days. Anamorelin was well tolerated and the incidence of treatment-related adverse events (AEs) was similar in the anamorelin (3.5%) and placebo (1.2%) groups without any grade  $\geq 3$  AEs. The most common treatment-related AEs in ROMANA 3 trial were hyperglycemia (1.2%), which is consistent with the results in ROMANA 1 (5.3%) and 2 (4.2%) trials. In addition, anamorelin, but not placebo, resulted in a progressive increase in body weight over the entire 24 weeks of the treatment period. Moreover, the alleviating effect of anamorelin on cachexia-related anorexia was maintained throughout the treatment period. Recently, anamorelin was further evaluated in patients with advanced gastrointestinal cancer and cachexia in a non-randomized single-arm study.<sup>51</sup> This study also showed a positive effect of anamorelin on LBM, body weight, and anorexia that was comparable to the

mentioned data in patients with lung cancer. Finally, two meta-analyses<sup>52,54</sup> also strongly supported the positive effect of anamorelin on LBM and body weight. However, in these studies, compared to placebo, anamorelin did not improve physical functions, measured with hand-grip strength<sup>44–50,52,53</sup> or a 6-min walk.<sup>48</sup>

### MABp1

MABp1 is a human IgG1 monoclonal antibody specific to human interleukin-1 $\alpha$ . In an open-label, phase 1 dose-escalation study, 52 patients with 18 types of refractory malignancies were enrolled.<sup>54</sup> MABp1 was well-tolerated and no dose-limiting toxicities were observed. For 30 patients whose data could be accessed, LBM increased by a mean of 1.02 kg during the 8-week treatment period. In a multinational double-blind, placebo-controlled phase 3 study, 333 patients with advanced colorectal cancer who have failed oxaliplatin- and irinotecan-based chemotherapy and had debilitating symptoms were randomly assigned to receive intravenous infusion of MABp1 (7.5 mg/kg) or placebo given every 2 weeks for 8 weeks until disease progression or unacceptable toxicity.<sup>55</sup> Concomitant chemotherapy and radiotherapy were restricted. A responder was defined as a patient having a stable or increased LBM, and maintenance or improvement in two of three other symptoms (pain, fatigue, or anorexia). In this trial, MABp1 was significantly associated with a higher response rate than placebo (33% vs 19%). However, there were no significant differences between the MABp1 and the placebo arms in the LBM or QOL change from baseline to week 8. Physical function was not measured. Twenty-six patients experienced treatment-related AEs including edema, nausea, and anemia. The majority were grade 1 or 2, and only few were grade 3, with no grade 4 or 5 cases included. However, there was an imbalance in infection-related AEs (11.6 vs 7.8%) and severe AEs (2.4 vs 0%) in the MABp1 and placebo arm, although these were reported as “not related” to treatment.<sup>56</sup> Furthermore, another phase 3 study was planned to compare overall survival between MABp1 and megestrol acetate (MA) in 656 patients with metastatic colorectal cancer and cachexia. However, the study was terminated early because the study crossed the prospective futility boundary of the primary endpoint.<sup>57</sup>

### Enobosarm

Enobosarm is an oral nonsteroidal selective androgen receptor modulator.<sup>58</sup> In a phase 2, double-blind, placebo-controlled study in healthy postmenopausal women

Table 1 Trials Of Anamorelin Hydrochloride In Patients With Cancer Cachexia

Publication	N	Study Population Cancer Types (Cachectic Status <sup>a</sup> )	Concurrent Cancer Treatment	Trial Arms (Intervention Period)	Major Outcomes For Anamorelin 1. Positive 2. Negative	Major Toxicity
Garcia et al, Support Care Cancer. 2013 <sup>45</sup>	16	Mixed advanced cancer (Cachexia)	Not specified or combined	Anamorelin vs placebo (3 days)	1. BW, Appetite 2. Food intake	Hyperglycemia
Garcia et al, Lancet Oncol. 2015 <sup>46</sup>	44	Mixed advanced cancer (Cachexia)	Not specified or combined	Anamorelin vs placebo (12 weeks)	1. LBM, BW, QOL 2. HGS	Not specified
Takayama et al, Support Care Cancer. 2016 <sup>47</sup>	181	Advanced NSCLC in Japanese (Cachexia)	Not specified or combined	Anamorelin vs placebo (12 weeks)	1. LBM, BW, PS, QOL, Anorexia 2. HGS	Nausea, Increased glycosylated hemoglobin
Temel et al, Lancet Oncol. 2016 (ROMANA 1 and 2) <sup>49</sup>	979	Advanced NSCLC (Cachexia)	Not specified or combined	Anamorelin vs placebo (12 weeks)	1. LBM, BW, Anorexia-cachexia symptoms 2. HGS, Fatigue	Not specified
Currow et al, Ann Oncol. 2017 (ROMANA 3) <sup>50</sup>	513	Advanced NSCLC: Completers of ROMANA 1 or 2 (Cachexia)	Not specified or combined	Anamorelin vs placebo (24 weeks)	1. BW, Anorexia-cachexia symptoms 2. HGS	Not specified
Katakami et al, Cancer. 2018 <sup>48</sup>	174	Advanced NSCLC in Japanese (Cachexia)	Not specified or combined	Anamorelin vs placebo (24 weeks)	1. LBM, BW, Anorexia 2. HGS, 6MWD, Fatigue	Arrhythmia, block, rash
Hamauchi et al, Cancer. 2019 <sup>51</sup>	50	Advanced gastrointestinal cancer in Japanese (Cachexia)	Not specified or combined	Anamorelin (12 weeks)	Single-arm study with pre-post comparison 1. LBM, BW, Appetite 2. Not specified	Not specified
Nishie et al, Lung Cancer. 2017 <sup>52</sup>	1641	Mixed advanced cancers in 6 RCTs for meta-analysis including reference 2, 3, 4, and 6 (Cachexia)	Not specified or combined	Anamorelin vs placebo (12 weeks)	In the meta-analysis, 1. LBM, BW, QOL 2. HGS, OS, Appetite	Not specified
Bai et al, Support Care Cancer. 2017 <sup>53</sup>	1168	Mixed advanced cancers in 4 RCTs for meta-analysis including reference 1, 2, 3, and 4 (Cachexia)	Not specified or combined	Anamorelin vs placebo (3 days or 12 weeks)	In the meta-analysis, 1. LBM, BW, QOL 2. HGS	Not specified

**Notes:** <sup>a</sup>Cachectic status was classified into precachexia, cachexia, refractory cachexia, or high risk for cachexia according to the consensus report.<sup>4</sup>

**Abbreviations:** BW, body weight; LBM, lean body mass; HGS, hand-grip strength; QOL, quality of life; NSCLC, non-small-cell lung cancer; PS, performance status; 6MWD, 6-min walk distance; RCT, randomized controlled trial; OS, overall survival.



and elderly men, enobosarm increased LBM with a clinically meaningful improvement in physical performance measured by the Stair Climb Test.<sup>59</sup> In a phase 2b, double-blind, placebo-controlled study, 159 patients with advanced cancer of different types and cachexia ( $\geq 2\%$  weight loss in the preceding 6 months) were randomized to receive enobosarm 1 mg, enobosarm 3 mg, or placebo for up to 113 days.<sup>60</sup> The primary endpoint was change in LBM from baseline. Both enobosarm arms significantly increased LBM compared to baseline; no improvement was observed in the placebo arm. In addition, performance on the Stair Climb Tests significantly improved in the enobosarm arms but not in the placebo arm. However, there was no significant difference in handgrip strength. No direct comparison between treatment arms was presented. No specific treatment-related or androgenic AEs were reported including negative effects on the prostate, virilization, or hirsutism. Finally, two large phase 3 studies (POWER 1 and 2 trials) enrolled 641 men or postmenopausal women with advanced NSCLC.<sup>61–63</sup> Patients were randomized at initiation of first-line chemotherapy based upon the planned chemotherapy regimen: platinum + taxane (POWER 1,  $n=321$ ) or platinum + non-taxane (POWER 2,  $n=320$ ) and received either enobosarm 3 mg or placebo for 5 months. The primary outcomes were the percentage of responders with stair climb power change  $\geq 10\%$  or LBM change  $\geq 10\%$  from baseline at day 84. Patient accrual and data collection were reportedly completed on May 2013.<sup>62,63</sup> However, the results have not been published to-date. Limited data from the POWER 1 trial are available from the trial registration site at the time of writing.<sup>62</sup> According to this data, the response rate in stair climb power was 29.4% (95% confidence interval [CI]: 22.4–37.1) in enobosarm and 24.2% (95% CI: 17.8–31.6) in the placebo group. The response rate in LBM was 41.9% (95% CI: 34.1–49.9) in enobosarm and 30.4% (95% CI: 23.4–38.2) in the placebo group. The final study results are currently awaited.

### Multidrug Combination

As shown in Figure 1, systemic inflammation is the central mechanism of cancer cachexia. Much effort has been made to develop multidrug combinations, including different types of anti-inflammatory agents, such as the MA, EPA, thalidomide, and NSAIDs (Table 2). In 2010, a large randomized phase 3 study showed that a combination of classic anticachectic medications is more effective than any one of these medications on its own.<sup>64</sup> A total of

332 patients with advanced cancer and cachexia were randomly assigned to one of the five treatment arms: (1) medroxyprogesterone (500 mg/day) or MA (320 mg/day); (2) EPA; (3) L-carnitine; (4) thalidomide; and (5) a combination of all agents. The primary endpoints were: an increase in LBM, a decrease in resting energy expenditure (REE), and decrease in fatigue. After two interim analyses, arms 1 and 2 were withdrawn due to significant inferiority for primary endpoints. A post hoc analysis showed a superiority of arm 5 over the others for all primary and secondary endpoints, including appetite, IL-6, Glasgow Prognostic Score (GPS), physical activity, and performance status. Several studies since have also reported that combination treatments are more effective than monotherapy.<sup>65,66</sup> For example, Wen et al reported results of a randomized controlled study comparing MA with MA + thalidomide for 8 weeks in 102 cachectic patients with advanced cancer.<sup>65</sup> The combination arm showed significantly greater improvements than the MA arm in body weight, hand grip strength, performance status, QOL, GPS, and fatigue. Toxicity was relatively negligible in both arms. Moreover, Macciò et al also reported the combination of MA + L-carnitine, celecoxib, and antioxidants was more effective than MA alone with respect to LBM, REE, fatigue, and global QOL in a randomized phase 3 study involving 104 patients with advanced gynecological tumor and cachexia.<sup>66</sup>

However, more is not always the better.<sup>67–69</sup> In a large randomized controlled study comparing EPA, MA, and EPA + MA for cachectic patients with advanced cancer, there was no significant difference between groups in body weight and appetite.<sup>67</sup> Madeddu et al reported that a two-drug combination of L-carnitine + celecoxib was non-inferior to a three-drug combination of L-carnitine + celecoxib + MA, with both arms showing a significant increase from baseline in LBM and physical performance.<sup>68</sup> In addition, Kouchaki et al recently reported that two-drug combination of MA + celecoxib was not superior to MA + placebo in a randomized phase 3 study of 96 patients with advanced gastrointestinal cancer and cachexia.<sup>69</sup> Differences in outcomes among these studies might depend on tumor types, concomitant treatments, or interactions between combined medications. Although the combination treatment, especially the MA-containing regimens, appears to have the most potential to alleviate signs and symptoms of cancer cachexia, no standard combination treatment has been established to-date.

Table 2 Trials Of Multidrug Combinations In Patients With Cancer Cachexia

Publication	N	Study Population Cancer Types (Cachectic Status <sup>a</sup> )	Concurrent Cancer Treatment	Trial Arms (Intervention Period)	Major Outcomes 1. Positive 2. Negative	Major Toxicity
Jatoi et al, J Clin Oncol. 2004 <sup>67</sup>	421	Mixed advanced cancer (Cachexia)	Not specified or combined	EPA vs MA vs MA + EPA (4 weeks)	In the MA containing regimens as compared with EPA 1. BW, Appetite 2. QOL, OS	Not specified
Mantovani et al, Oncologist. 2010 <sup>64</sup>	332	Mixed advanced cancer (Cachexia)	Not specified or combined	Progestational agent vs EPA vs L-Carnitine vs Thalidomide vs Combination of all agents (4 months)	In the combination arm as compared with other 4 arms 1. LBM, PS, GPS, REE, Fatigue, Appetite, Physical activity 2. QOL	Not specified
Wen et al, Chemotherapy. 2012 <sup>65</sup>	102	Mixed advanced cancer (Cachexia)	Not specified or combined	MA vs MA + Thalidomide (8 weeks)	In the combination arm as compared with MA 1. BW, HGS, PS, QOL, GPS, Fatigue 2. None	Not specified
Macciò et al, Gynecol Oncol. 2012 <sup>66</sup>	104	Advanced gynecological tumor (Cachexia)	Not specified or combined	MA vs MA + L-carnitine, celecoxib, and antioxidants (4 months)	In the combination arm as compared with MA 1. LBM, QOL, REE, Fatigue 2. PS, GPS, Appetite	Not specified
Madeddu et al, Clin Nutr. 2012 <sup>68</sup>	60	Mixed advanced cancer (Cachexia)	Not specified or combined	Arm 1 (L-carnitine + celecoxib) vs Arm 2 (L-carnitine + celecoxib + MA) (4 months)	In the arm 2 as compared with arm 1 1. None 2. LBM, BW, HGS, 6MWD, QOL, REE, Appetite, Fatigue	Not specified
Kouchaki et al, Support Care Cancer. 2018 <sup>69</sup>	90	Mixed gastrointestinal cancer (Cachexia)	Majority in chemotherapy	Arm 1 (MA + placebo) vs Arm 2 (MA + celecoxib) (2 months)	In the arm 2 as compared with arm 1 1. None 2. BW, QOL, HGS, Appetite, PS, GPS	Not specified

**Notes:** <sup>a</sup>Cachectic status was classified into precachexia, cachexia, refractory cachexia, or high risk for cachexia according to the consensus report.<sup>4</sup>

**Abbreviations:** EPA, eicosapentaenoic acid; MA, megestrol acetate; BW, body weight; QOL, quality of life; OS, overall survival; LBM, lean body mass; PS, performance status; GPS, Glasgow Prognostic Score; REE, resting energy expenditure; HGS, hand-grip strength; 6MWD, 6-min walk distance.

## Nonpharmacological Interventions

The consensus report on cancer cachexia proposed early introduction of combined nutritional, physical, and psychosocial interventions.<sup>4</sup> Following the publication of this consensus report, nonpharmacological interventions have been widely tested.<sup>1</sup> Moreover, many clinical trials selected study populations at an earlier stage of the cachexia and included patients with precachexia or those at high risk for cachexia. As a result, interventions tended to start earlier, alongside active cancer treatment.

### Monomodal Intervention

Although cancer cachexia cannot be treated with nutritional therapy alone,<sup>70,71</sup> optimum nutrition is an important part of any multimodal intervention aimed at increasing energy intake<sup>39</sup> and alleviating psychosocial stress.<sup>72</sup> In addition, nutritional supplements enriched with n-3 polyunsaturated fatty acids, such as EPA, might have benefits in cancer cachexia patients.<sup>73,74</sup> Furthermore, exercise might also be an important part of an anticachectic intervention. Physical inactivity in cancer patients may largely contribute to systemic inflammation and altered muscle metabolism. Exercise may improve muscle mass and strength, physical function, fatigue, and QOL in patients with advanced cancer.<sup>75–77</sup> Exercise may also directly prevent unfavorable consequences of cancer cachexia, including disability, which, overall, might prevent the effect of a vicious cycle described in the introduction to this review (Figure 1). However, evidence from well-designed clinical studies on exercise interventions for patients with cancer cachexia is limited.<sup>78</sup> Low recruitment, high attrition rate, and poor compliance with exercise interventions<sup>79,80</sup> are some of the challenges associated with clinical trials in cachectic patients with advanced cancer.

### Multimodal Intervention

At the time of writing, there is no standard multimodal intervention combining nutrition and exercise for patients with cancer cachexia (Table 3). However, Solheim et al<sup>81</sup> recently reported results of their multinational randomized phase 2 study (Pre-MENAC study) of multimodal intervention in patients who had advanced non-small-cell lung cancer and pancreatic cancer with or without cachexia. Their interventions consisted of nutritional counseling, exercise intervention, celecoxib, and supplements rich in EPA. The primary endpoint was feasibility. It took 30 months to recruit 46 patients; the recruitment rate was 11.5%. A total of 8% dropped out in the treatment arm.

Overall compliance was 76% for celecoxib, 60% for exercise, and 48% for supplements. However, compliance for combination of two or three treatments was only 20–48% or 12%, respectively, suggesting there is a trade-off between number of interventions and a level of compliance that can be expected. Nevertheless, the efficacy of this intervention is currently being tested in a large randomized controlled study (MENAC study), where body weight is the primary endpoint.<sup>82</sup> Meanwhile, Uster et al reported results of a single-center randomized controlled trial involving combined nutritional and exercise intervention for patients with advanced gastrointestinal or lung cancer with or without cachexia.<sup>83</sup> The aim of the trial was to assess any clinically relevant improvement to global QOL. It took 32 months to recruit 58 patients; the recruitment rate was 13.0%. The overall attrition rate was 14.2%, while 67% of the patients allocated to the intervention arm were compliant with the intervention. Although there was an increase in the amount of protein intake, there was no improvement in the global QOL, weight, fatigue, or physical function, including HGS, sit-to-stand test, and leg strength measures. These reports showcase the challenges associated with trial recruitment and achieving compliance with nutritional or exercise interventions in patients with advanced cancer.<sup>84</sup> The burden of multiple assessments, extra effort, and time spent on engaging with the intervention might have decreased compliance. Inclusion of patients at later disease stages may further limit the feasibility and efficacy of the potentially promising interventions.

To overcome these hurdles, another type of nonpharmacological multimodal intervention for cancer cachexia has been developed: The Nutrition and Exercise Treatment for Advanced Cancer (NEXTAC) program.<sup>85</sup> This program combined nutritional counseling, low-intensity home-based resistance training, and counseling focused on encouraging physical activity. It was designed to prevent disability in elderly patients at risk for cachexia, newly diagnosed with advanced NSCLC or pancreatic cancer, due to start systemic chemotherapy. Results of the Phase I feasibility study of this new intervention (NEXTAC-ONE) have already been reported.<sup>85</sup> It took 9 months to recruit 30 patients, and the recruitment rate was 63%. The attrition rate was 3%. Participants showed excellent attendance (96.7%) and compliance with each intervention ( $\geq 90\%$ ) in the program. The majority of patients also applied the insights from health education and changed their health-related behavior by, for example, increasing indoor or outdoor activity.<sup>86</sup> No severe



Table 3 Trials Of Multimodal Interventions For Patients With High-Risk For Cancer Cachexia

Publication	N	Study Population Cancer Types (Cachectic Status <sup>a</sup> )	Concurrent Cancer Treatment	Trial Arms (Intervention Period)	Major Outcomes 1. Positive 2. Negative	Major Toxicity (Compliance)
Solheim et al, J Cachexia Sarcopenia Muscle. 2017 (Pre-MENAC study) <sup>81</sup>	46	Advanced pancreatic or lung cancer (High-risk for cachexia)	Palliative chemotherapy	Exercise + Nutritional advice + ONS + NSAID vs Usual care ONS: Prosure <sup>®</sup> , rich in EPA (6 weeks)	In the multimodal intervention arm as compared with usual care arm 1. BW 2. LBM, HGS, 6MWD, Physical activity, Nutritional status, Fatigue, OS	Not specified (>50% compliance for all components was 12% (3/25) in the treatment arm)
Uster et al, Clin Nutr. 2018 <sup>83</sup>	58	Advanced gastrointestinal or lung cancer (High-risk for cachexia)	Not specified or combined	Exercise + Nutritional advice + ONS vs Usual care ONS: Protein-rich ONS (3 months)	In the multimodal intervention arm as compared with usual care arm 1. Nausea and vomiting, Protein intake 2. LBM, BW, HGS, 6MWD, sit-to-stand, leg strength, QOL	Not specified (Mean attendance of 67% in all sessions)
Solheim et al, BMJ Support Palliat Care. 2018 (MENAC study) <sup>82</sup> Trial registration: NCT02330926	240	Advanced pancreatic or lung cancer (High-risk for cachexia)	Not specified or combined	Exercise + Nutritional advice + ONS + NSAID vs Usual care ONS: Prosure <sup>®</sup> , rich in EPA (6 weeks)	Ongoing trial Status: Recruiting Start date: Jan 2015 Primary endpoint: BW Secondary endpoints: Muscle mass, Physical activity	
Hall et al, Pilot Feasibility Stud. 2018 <sup>88</sup>	40	Mixed advanced cancer (High-risk for cachexia)	Palliative care	Exercise + nutritional advice + ONS vs Usual care ONS: EPA-rich ONS (8 weeks)	Ongoing trial Status: on going Start date: Jan 2018 Primary endpoint: Compliance Secondary endpoints: BW, PS, 2-min walk test, Timed up and go test, QOL	
Miura et al, BMC Cancer. 2019 (NEXTAC-TWO study) <sup>87</sup> Trial registration: UMIN000028801	130	Elderly patients with advanced pancreatic or lung cancer (High-risk for cachexia)	Palliative chemotherapy	Exercise + Physical activity promotion + Nutritional advice + ONS vs Usual care ONS: Inner Power <sup>®</sup> , rich in branched chain amino acids (12 weeks)	Ongoing trial Status: On follow-up period until Mar 2021 (Enrollment completed) Start date: Nov 2017 Primary endpoint: Disability-free survival Secondary endpoints: BW, Muscle mass, HGS, SPPB, QOL	

**Notes:** <sup>a</sup>Cachectic status was classified into precachexia, cachexia, refractory cachexia, or high risk for cachexia according to the consensus report.<sup>4</sup>

**Abbreviations:** ONS, oral nutritional supplement; NSAID, nonsteroidal anti-inflammatory drug; EPA, eicosapentaenoic acid; BW, body weight; LBM, lean body mass; HGS, hand-grip strength; 6MWD, 6-min walk distance; OS, overall survival; QOL, quality of life; PS, performance status; SPPB, short physical performance battery.

AEs were reported. Subsequently, a prospective, multicenter, randomized phase 2 clinical study (NEXTAC-TWO) has been launched, aiming to increase disability-free survival in elderly patients with advanced cancer.<sup>87</sup> A total of 130 patients are planned to be randomized to usual care or usual care plus NEXTAC in a 1:1 ratio. It has been hypothesized that the NEXTAC prolongs disability-free survival by 4 months compared to the usual care (80% power). Other multimodal interventions in different tumor types and clinical setting are currently being tested.<sup>84,88</sup> The results of these ongoing studies are awaited because there was no report on nutrition/exercise interventions which definitively improved muscle mass or physical function in patients with cancer cachexia to-date. If one of these multimodal programs is shown as feasible and effective, it might be combined with newly emerging pharmacological interventions for cachexia to further improve functional prognosis and socioeconomic outcomes.

## Discussion

### Trial Challenges: Recruitment, Attrition, And Compliance

There are several challenges to conducting clinical studies of cancer cachexia. Trial recruitment is likely to be low,<sup>79–81</sup> compliance is likely to be low, and dropout rates are likely to be high in clinical trials of pharmacological<sup>89</sup> and non-pharmacological interventions.<sup>90</sup> These challenges are partially accounted for by the vulnerability of cachectic cancer patients. For example, Temel et al reported results of a feasibility study of structured, moderate-intensity exercise program for patients with advanced NSCLC.<sup>91</sup> Twenty-four percent of participants withdrew before attending any sessions; only 44% completed all planned study sessions. The reasons for withdrawal or noncompliance included deterioration of health status, feeling unwell, concerns about the amount of travel involved, and hospitalizations. As a result, it has been suggested that future trials in cancer cachexia patients should have less stringent entry criteria, and involve less exhaustive outcome measures.<sup>89</sup>

### Lack Of Widely Accepted Endpoints

Despite increase in the number and scope of cancer cachexia studies, the ultimate goal of these trials, and cancer cachexia care, remains to be established.<sup>1</sup> Selected endpoints, variables and measurements of interest, and statistical analyses used change, depending on the tested hypothesis, or preference of researchers or study sponsors. Such variation in endpoints decreases comparability of trial results and impede

standardization of study results. In addition, there is no consensus among researchers, pharmaceutical companies, and regulatory authorities regarding constitutes a “clinically relevant” outcome.<sup>92</sup> For example, although anamorelin has been associated with a significant increase in LBM, weight, and appetite among patients with advanced NSCLC,<sup>46–50</sup> the drug was refused marketing authorization by the European Medicines Agency (EMA) due to undesirable risk-benefit profile.<sup>93</sup> The EMA concluded that efficacy of anamorelin had not been established as there was only a marginal effect on LBM and no reliable and clinically relevant effect on patient functioning or QOL. A similar decision was made regarding MABp1. Although a well-designed phase 3 randomized controlled study met its primary endpoints,<sup>55</sup> a recent EMA opinion refused to authorize its marketing due to the lack of clear improvements in LBM or QOL, and risk of infection considered “unacceptable”.<sup>56</sup> Further regulatory review is pending in Europe. This regulatory reluctance to grant approval based on currently used endpoints suggests there is an urgent need to reconsider what is “clinically relevant” in cancer cachexia research and care, and meet the demands of patients, researchers, and regulatory authorities. Although concomitant improvement in skeletal muscle mass, physical function, QOL, and overall survival may be the “ideal” endpoint, these parameters do not always co-occur. For example, gain in LBM was not always associated with improvement in physical function<sup>46–49,60,66,94,95</sup> or QOL.<sup>60,64,95</sup> We have to determine the priority for outcomes among various endpoints used in the previous clinical studies including body weight, LBM, symptoms, physical functions, prognosis, or QOL.

## Limitation

This review has several limitations. First, the literature search was carried out using only PubMed. Second, a single reviewer (T.N.) carried out the selection of articles for inclusion. These drawbacks may result in a potential selection bias in the establishment of a reference list. Finally, information for ongoing trials was obtained from trial registration site, reports of regulatory authority, or publications for study protocol at the time of writing (Aug 2019). Based on these limitations, we should pay careful attention while interpreting the contents.

## Conclusion

Clinical trials evaluating treatments for cancer cachexia are increasing in number. Promising new agents, including anamorelin, MABp1, and enobosarm are being investigated.

Multidrug and multimodal approaches are expected to improve poor outcomes in patients with cancer cachexia. However, there are several challenges to conducting clinical trials and developing treatment standards in this area. The most meaningful endpoint of cachexia care might be prolonging active life with satisfying QOL. Although the established endpoint, such as body mass increase, might be an important outcome, it may not always contribute as a true endpoint. Thus, a novel study design and a high-priority endpoint are required before a combination of pharmacological and nonpharmacological interventions that improve functional patient outcomes can be delivered.

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