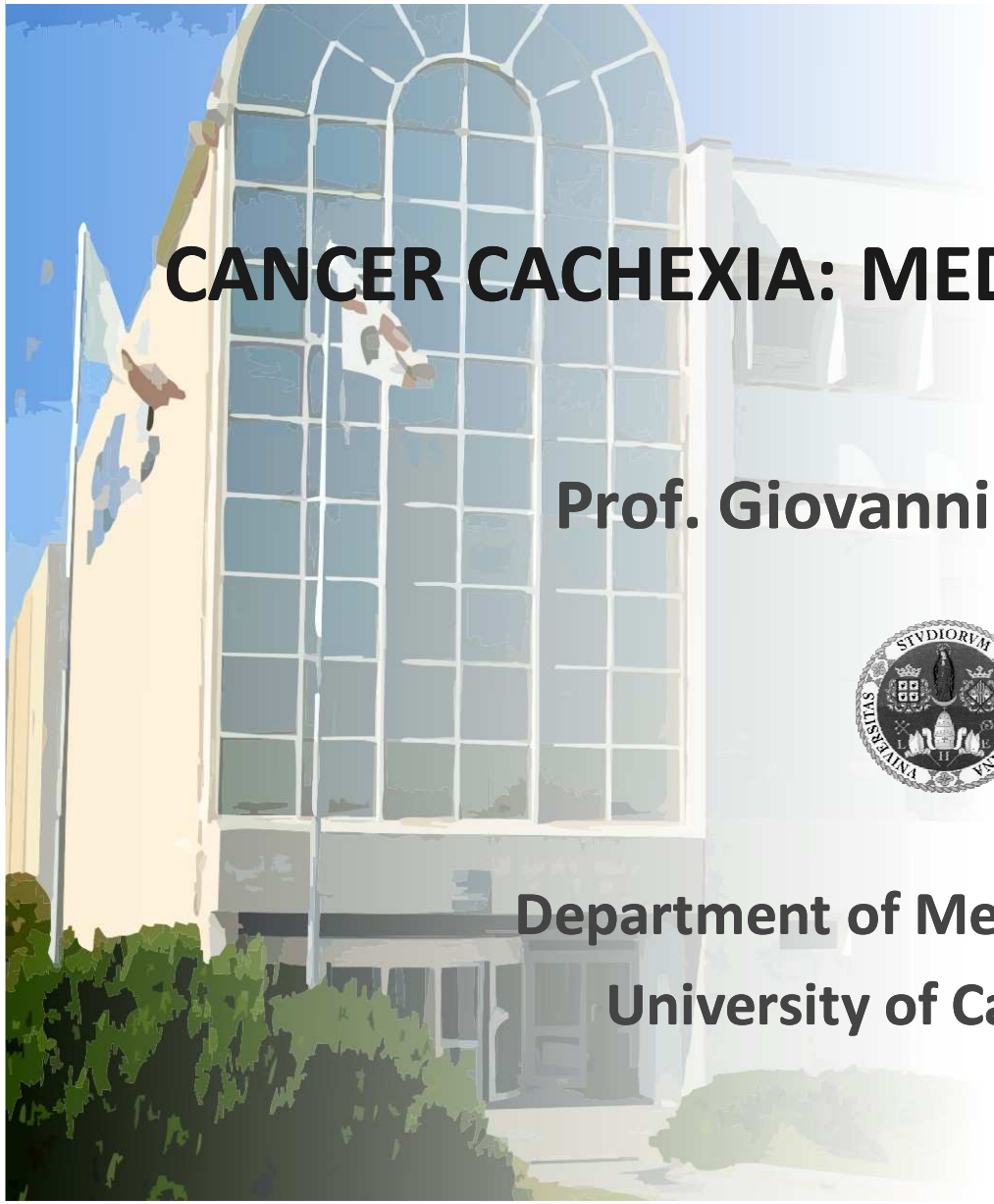
ESMO SYMPOSIUM

Cancer and Nutrition

Zurich, Switzerland

20–21 March 2009

ESMO Symposium | Zurich, 20–21 March 2009



CANCER CACHEXIA: MEDICAL MANAGEMENT

Prof. Giovanni Mantovani

Department of Medical Oncology

University of Cagliari, Italy

DEFINITION OF CACHEXIA

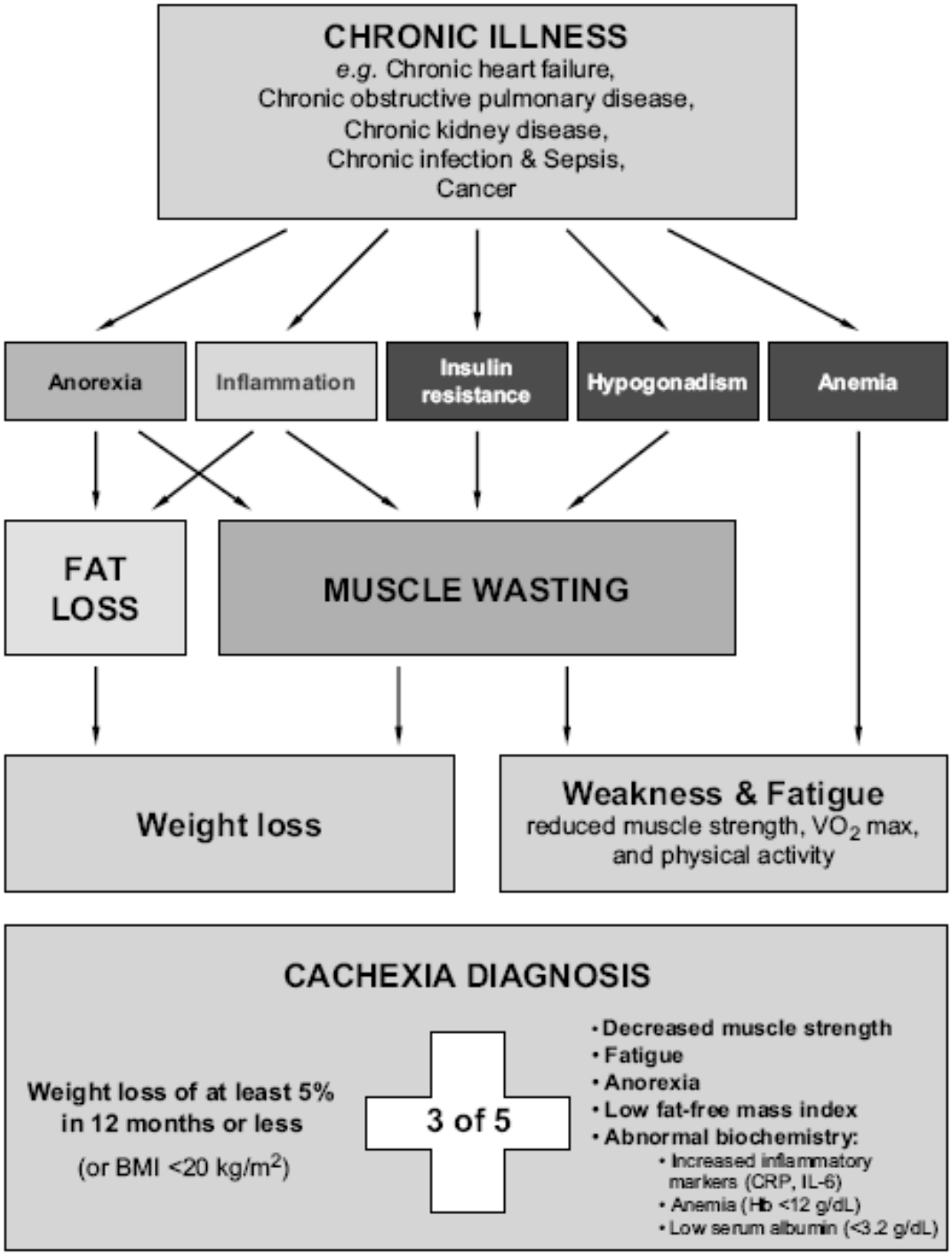
Cachexia, is a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass.

The prominent clinical feature of cachexia is weight loss in adults (corrected for fluid retention) or growth failure in children (excluding endocrine disorders).

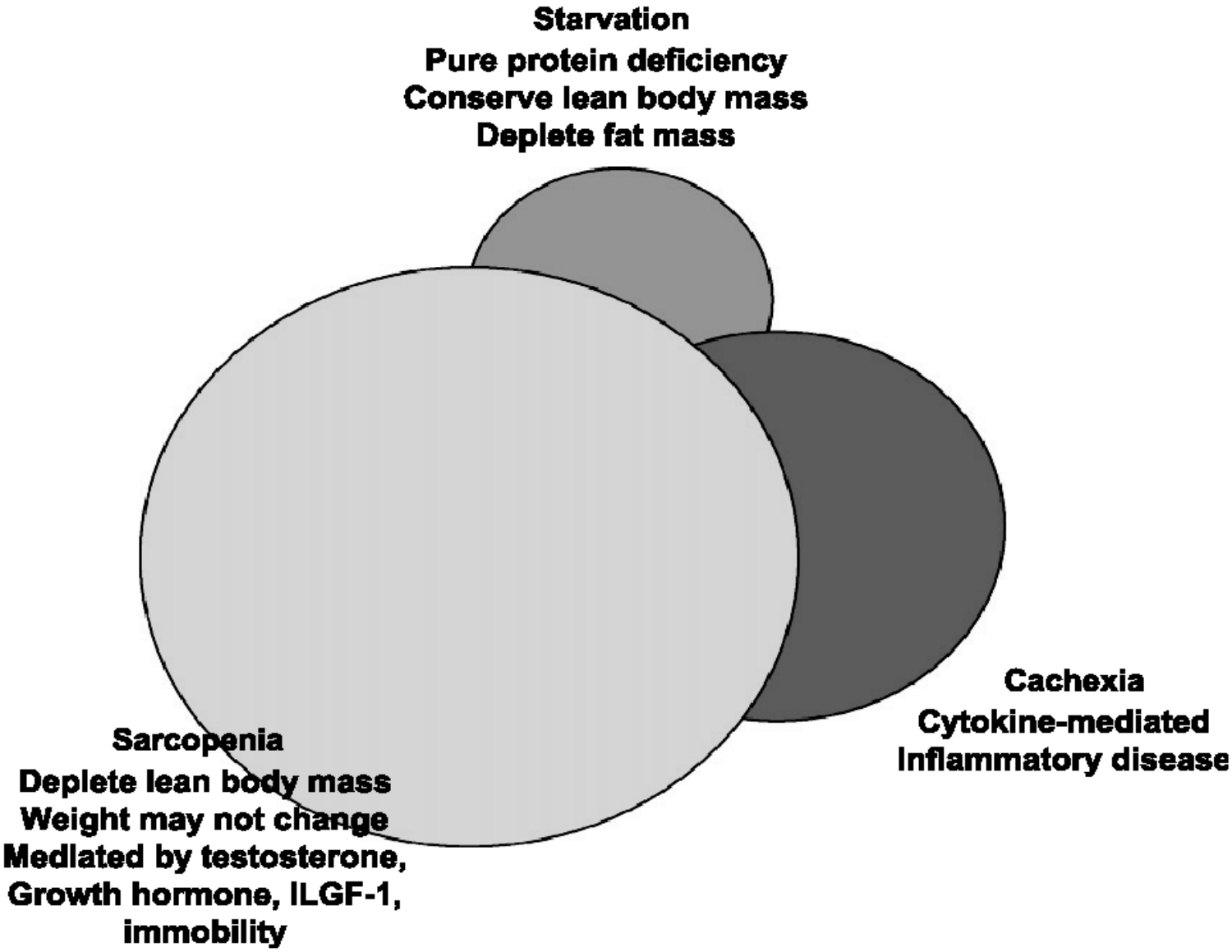
Anorexia, inflammation, insulin resistance and increased muscle protein breakdown are frequently associated with cachexia.

Cachexia is distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption and hyperthyroidism and is associated with increased morbidity

Cachexia: a new definition. Clin Nutr 2008; 27: 793-799

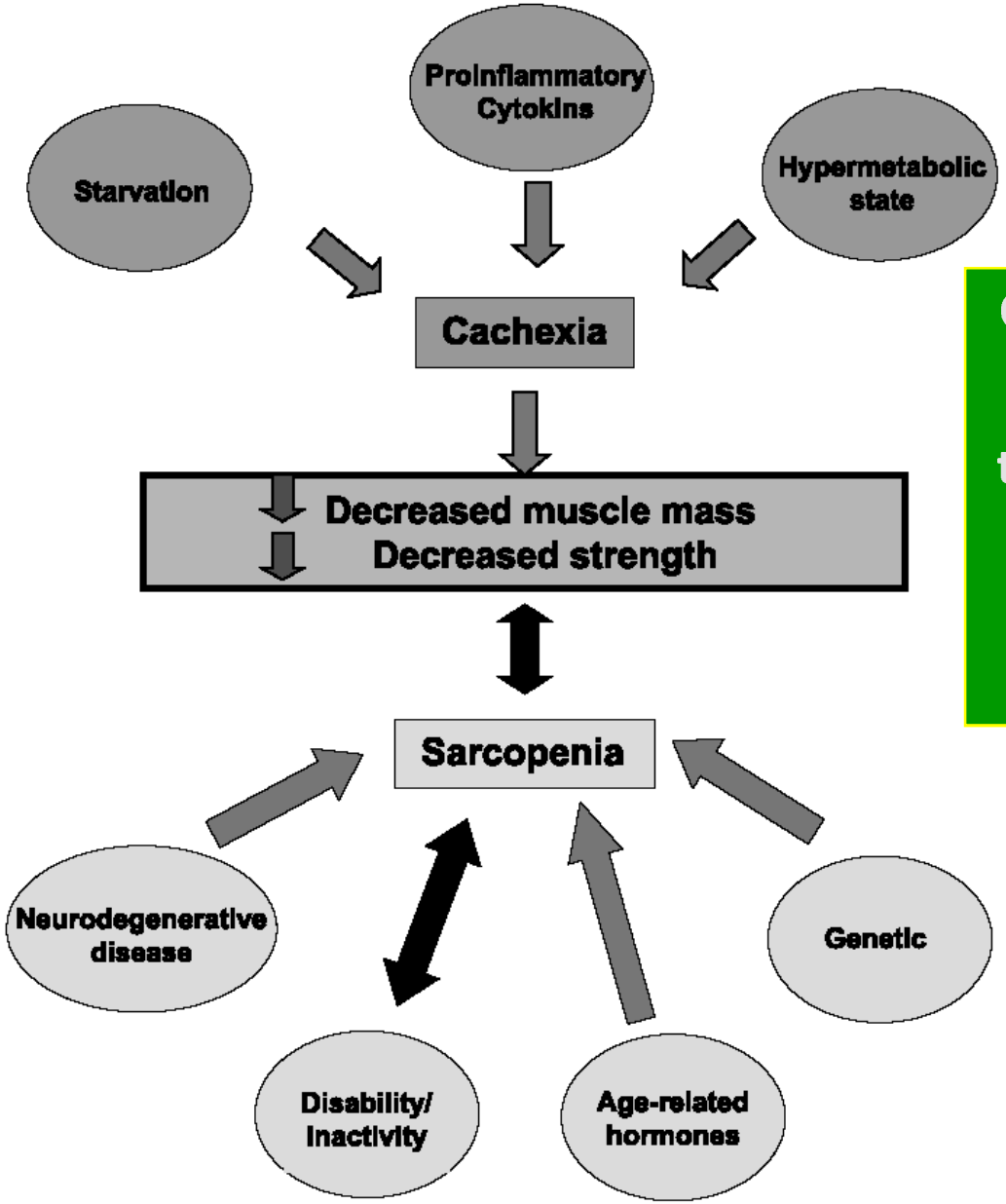

CHRONIC ILLNESS
e.g. Chronic heart failure,
Chronic obstructive pulmonary disease,
Chronic kidney disease,
Chronic infection & Sepsis,
Cancer
Anorexia
Inflammation
Insulin resistance
Hypogonadism
Anemia
FAT LOSS
MUSCLE WASTING
Weight loss
Weakness & Fatigue
reduced muscle strength, VO2 max, and physical activity
CACHEXIA DIAGNOSIS
Weight loss of at least 5% in 12 months or less
(or BMI <20 kg/m2)
3 of 5
• Decreased muscle strength
• Fatigue
• Anorexia
• Low fat-free mass index
• Abnormal biochemistry:
• Increased inflammatory markers (CRP, IL-6)
• Anemia (Hb <12 g/dL)
• Low serum albumin (<3.2 g/dL)

CAUSES OF BODY WEIGHT LOSS



Thomas DR. Clinical Nutrition 2007; 26:389

MECHANISMS OF AGE-RELATED MUSCLE WASTING



Cachexia defines a distinct clinical syndrome where

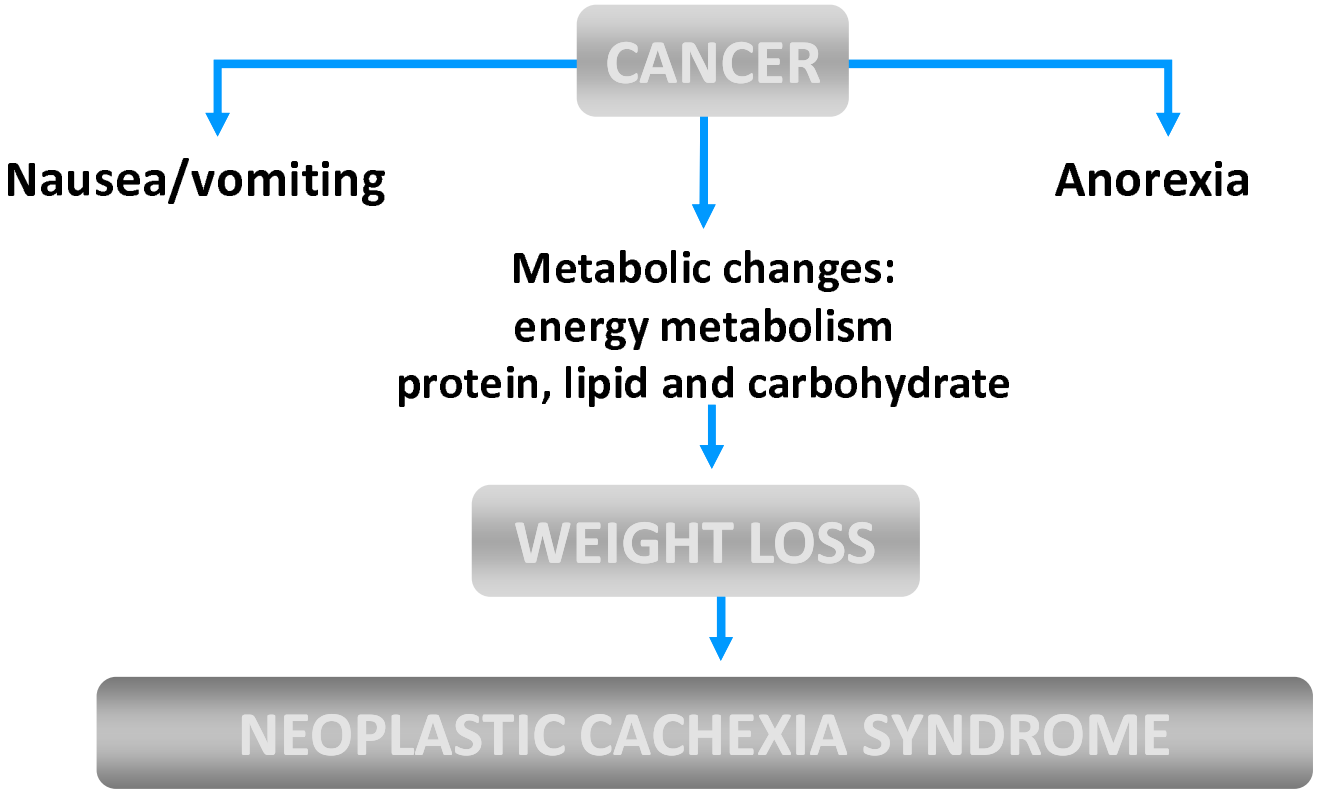
the activation of proinflammatory cytokines

has a direct effect on muscle metabolism and anorexia

Thomas DR. Clinical Nutrition 2007; 26:389

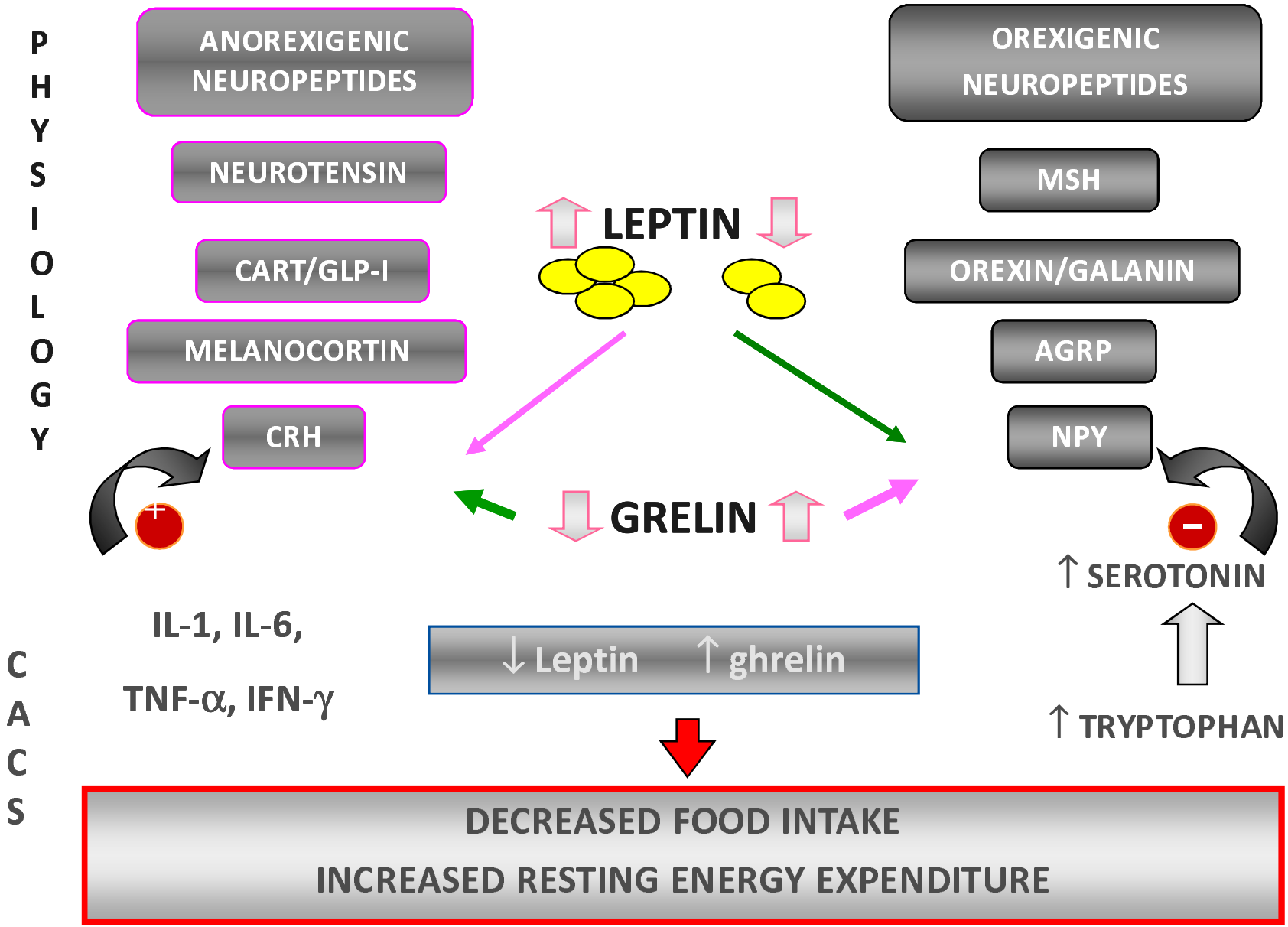
PATHOGENESIS OF CACS

Cancer-induced cachexia is invariably associated with the presence and growth of tumor

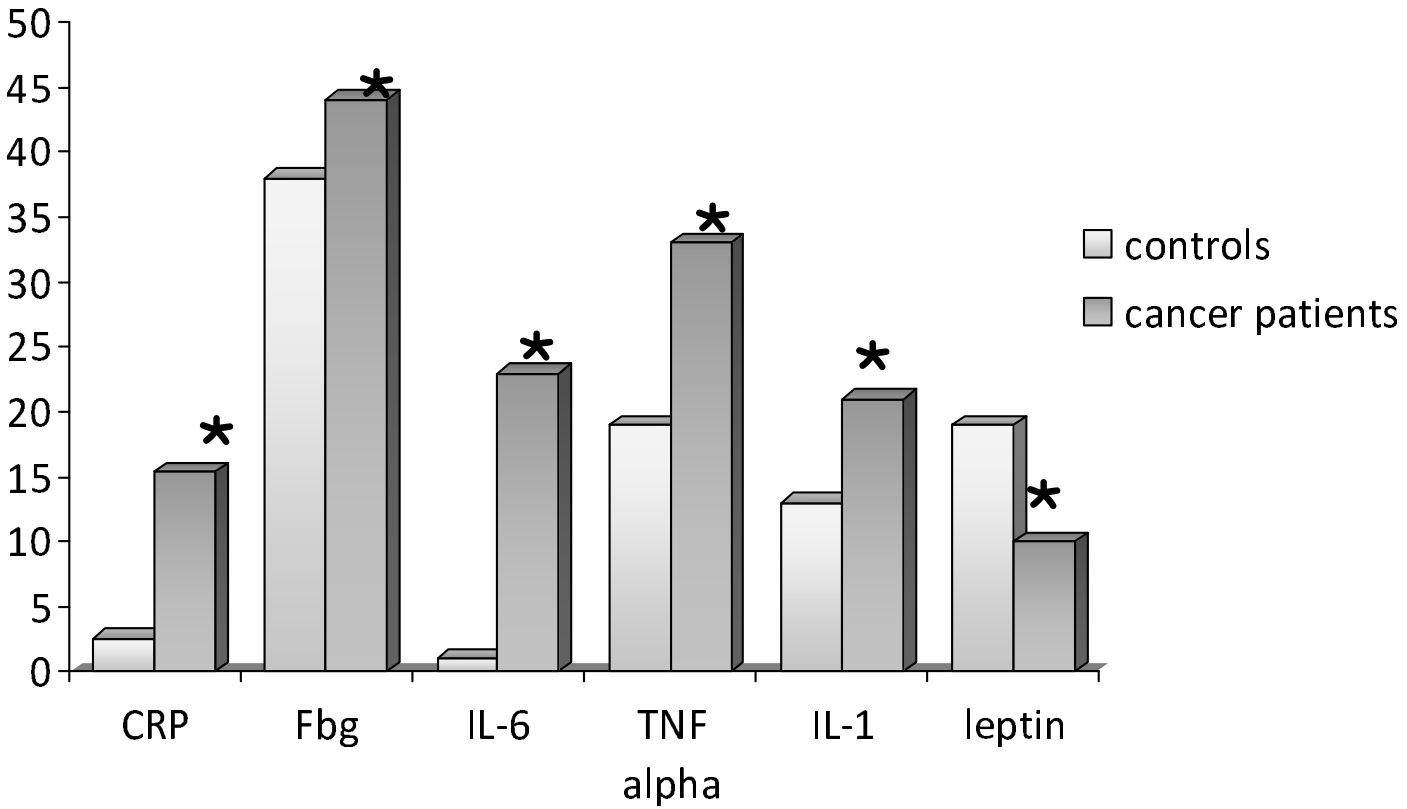


In addition, the competition for nutrients between tumor and host leads to an accelerated starvation state characterised by severe metabolic disturbances and hypermetabolism resulting in an increased energetic inefficiency

HYPOTHALAMIC NEUROPEPTIDE CIRCUITRY IN CACS



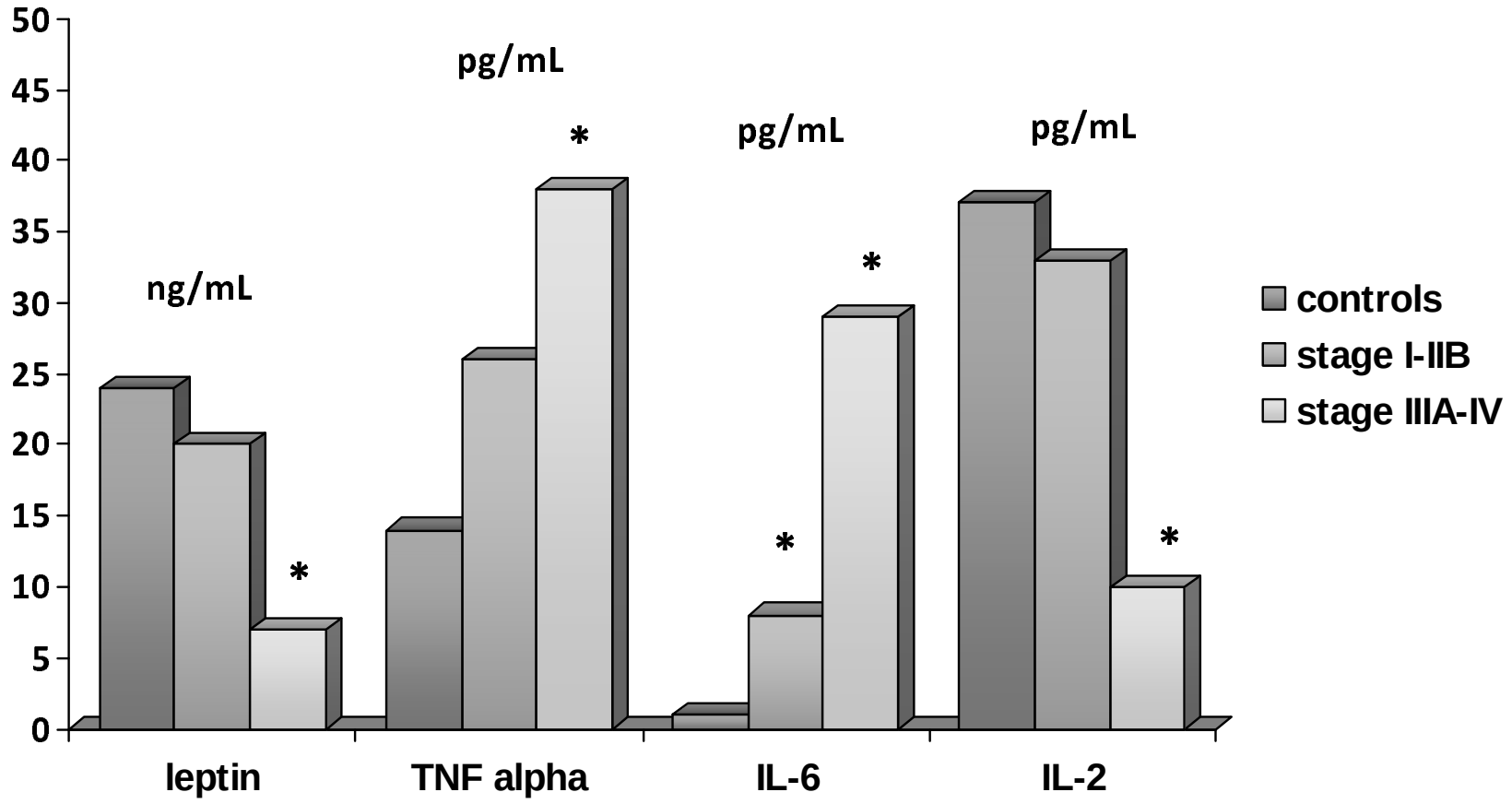
Levels of c-reactive protein, fibrinogen, proinflammatory cytokines and leptin in advanced cancer patients



*** p<0.005 in comparison to controls**

Mantovani G, et al. J Mol Med 2000; 78: 554-561

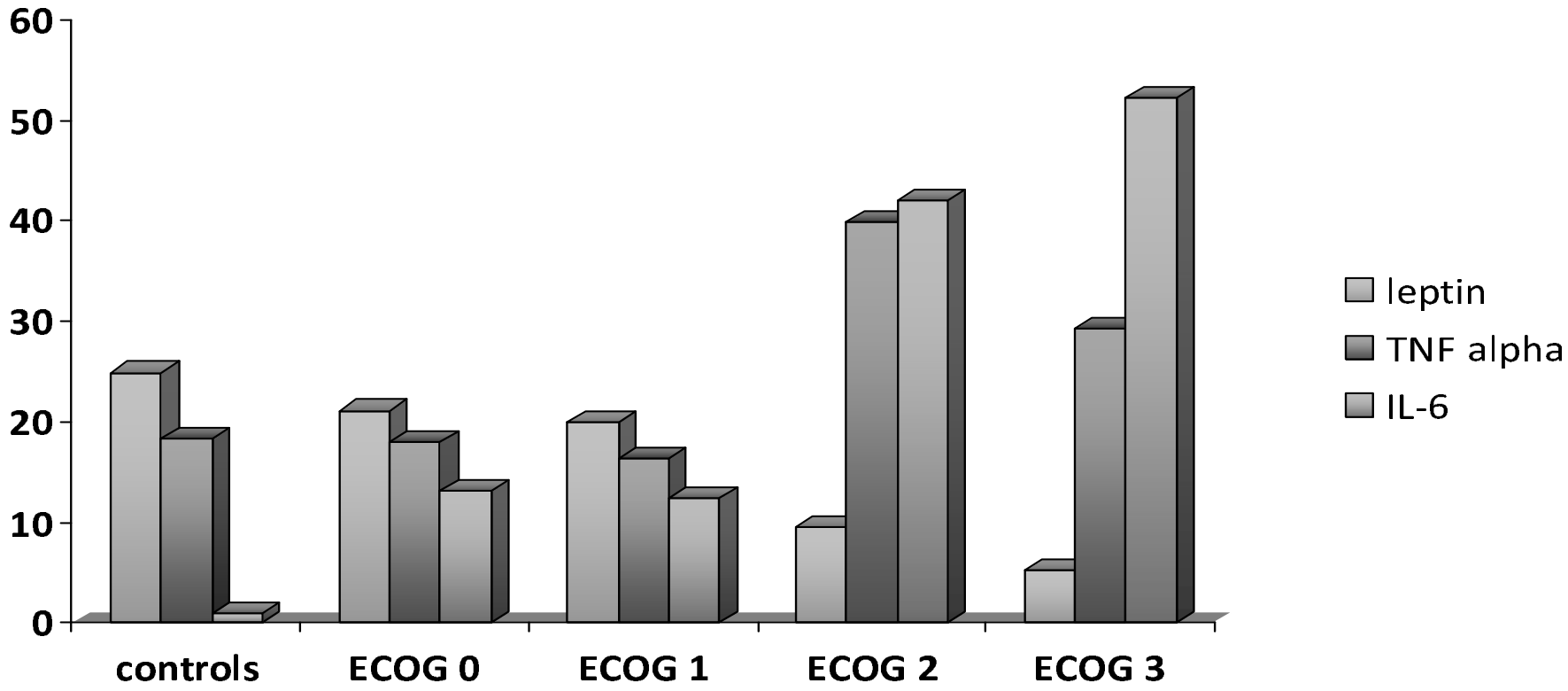
Serum levels of leptin, proinflammatory cytokines and IL-2 in cancer patients according to stage



* p<0.05 in comparison to controls

Mantovani G, et al. J Mol Med 2001;79:406-414

Serum levels of leptin and proinflammatory cytokines in a population of cancer patients according to performance status



Lowest ECOG PS (2 and 3) are associated with lowest levels of leptin and highest levels of proinflammatory cytokines (expecially IL-6)

Mantovani G, et al. J Mol Med 2000; 78: 554-561

MANAGEMENT OF CANCER CACHEXIA

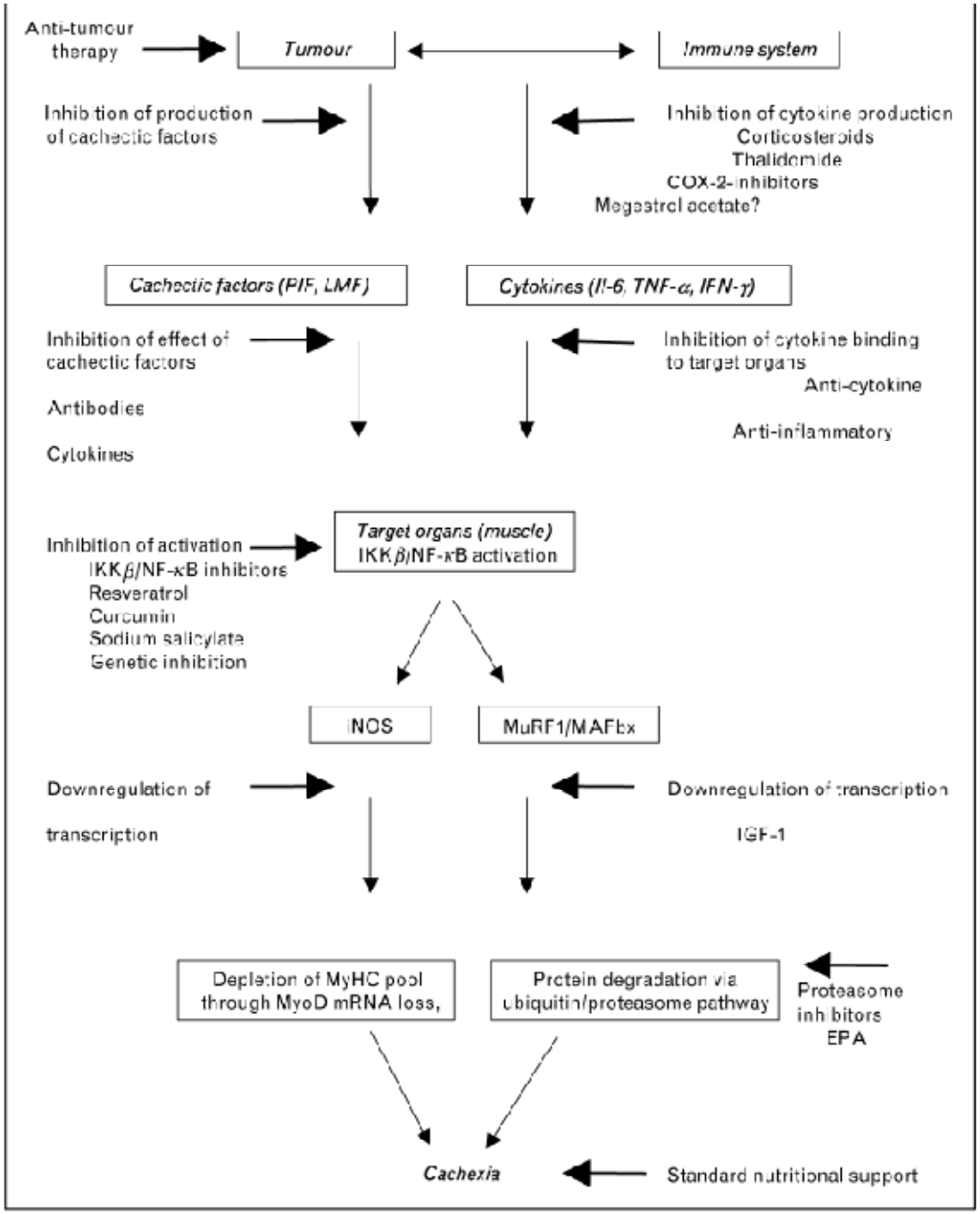
The best management of cancer cachexia is to cure the cancer, as this will completely reverse the cachexia syndrome. Unfortunately, this remains an infrequent achievement in adults with advanced solid tumours.

The second option would be to increase nutritional intake, but a large number of randomized controlled trials of nutritional intervention did not show a significant benefit with regard to weight change or quality of life.

These results have led to attempts to manipulate the process of cachexia with a variety of pharmacological agents, with the main purpose of providing symptomatic improvement.

To date, however, despite several years of co-ordinated efforts in basic and clinical research, practice guidelines for the prevention and treatment of cancer-related muscle wasting are lacking, mainly because of the multifactorial pathogenesis of the syndrome

Boddaert MA et al Curr Opin Oncol 2006;18:335-340



CACS pathophysiology and potential therapeutic targets

From Boddaert MA et al
Curr Opin Oncol 2006;18:335-340

MANAGING CANCER-RELATED ANOREXIA/CACHEXIA

Ineffective treatments

- Cyproheptadine
- Hydrazine
- Metoclopramide
- Pentoxifylline

Drugs commonly used

- Progestagens: Megestrol acetate/Medroxyprogesterone acetate
- Corticosteroids

Drugs with a strong rationale that failed or did not show univocal results in clinical trials

- Omega-3 Fatty Acids
- Cannabinoids (dronabinol)
- Bortezomib

Emerging drugs with some effective results but still under clinical evaluation

- Thalidomide
- Ghrelin
- COX-2 inhibitors
- Insulin
- BCAA
- oxandrolone

Future trends

- Melanocortin antagonist
- b_2 agonists (formoterol)
- Anti Myostatin
- Anti IL-6
- SARMs

Mantovani G et al, Drugs 2001; 61, 499-514

EFFECTIVE TREATMENTS
Progestagens

Progestagens, medroxyprogesterone acetate and megestrol acetate, are currently considered the best available treatment option for CACS and they are approved in Europe for treatment of cancer- and AIDS- related cachexia

However, progestational agents are nonetheless limited in their ability to treat cancer cachexia. Fewer than 30% of patients treated with megestrol acetate experience short-term appetite stimulation, and although weight and appetite improve, there is no demonstrated improvement in quality of life or survival.

Simons JP et al. Cancer 1998; 82:553
Jatoi A, et al. J Clin Oncol 2002; 20:567
Jatoi A, et al. J Clin Oncol 2004;22:2469

Cytokine involvement in cancer anorexia/cachexia: role of megestrol acetate and medroxyprogesterone acetate on cytokine downregulation and improvement of clinical symptoms

This paper describes a series of experimental and clinical studies showing that:

1) high serum levels of some cytokines, including IL-1, IL-6, and TNF, are present in advanced-stage cancer patients, particularly those with CACS;
2) megestrol acetate (MA) has a beneficial therapeutic effect on CACS symptoms, such as appetite, body weight, and quality-of-life;
3) MA downregulates the synthesis and release of cytokines and relieves the symptoms of CACS;
4) cytokines play a key role in the onset of CACS;
5) medroxyprogesterone acetate (MPA) reduces the in vitro production of cytokines and serotonin (5-hydroxytryptamine, 5-HT) by peripheral blood mononuclear cells (PBMC) of cancer patients;
6) MA and MPA reduce the cisplatin-induced 5-HT release in vitro from PBMC of cancer patients.

Crit Rev Oncog. 1998;9(2):99-106

MEGESTROL ACETATE IN NEOPLASTIC ANOREXIA/CACHEXIA: CLINICAL EVALUATION AND COMPARISON WITH CYTOKINE LEVELS IN PATIENTS WITH HEAD AND NECK CARCINOMA TREATED WITH NEOADJUVANT CHEMOTHERAPY.

PATIENTS

From April **1993** to February 1994, 11 male patients with head and neck cancer in advanced stage were enrolled in the study:

- **Mean age 57.8 years, range 43-69 years**
- **Karnofsky performance status (PS) 90 to 100**
- **Weight decrease >10% of the ideal or customary body weight**

TREATMENT PLAN

MEGESTROL ACETATE (MA) at a dose of 320 mg/day.
The MA dose ranged from 160 to 320 mg/day, based on clinical response.

❑ 10 patients were treated with MA in the interval between chemotherapeutic cycles starting from the third day after the end of cycle until the day before the next cycle (days 8 to 21) for a total of 3 consecutive cycles

❑ 1 patient was treated with MA during definitive loco-regional radiation therapy administered at the end of primary chemotherapy

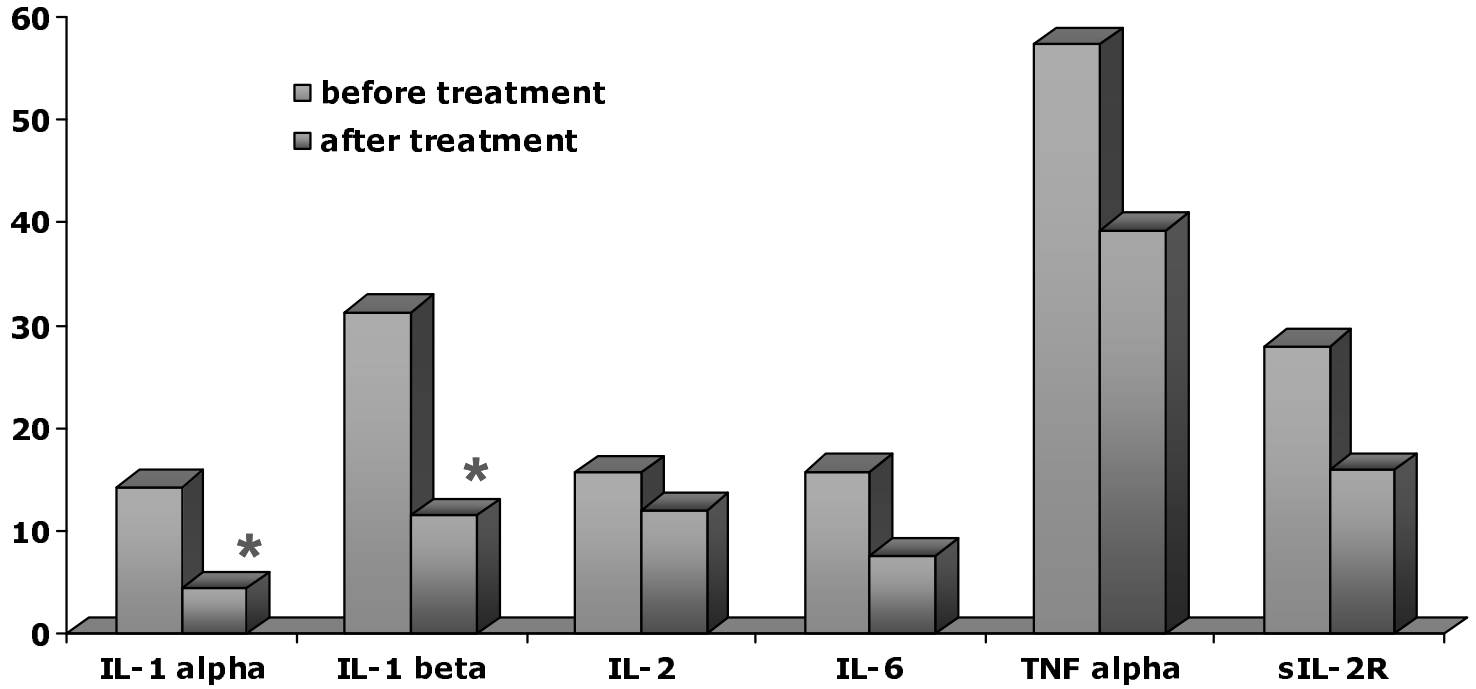
Mantovani, G et al. Int J Clin Lab Res. 1995;25:135-41

EVALUATION OF CLINICAL PARAMETERS IN PATIENTS TREATED WITH CHEMOTHERAPY AND MA

	Pretreatment Mean (range)	Post-treatment Mean (range)	Mean increase %
Weight (Kg)	47.3 (34-63)	53.6 (29-70)	+13.2
Appetite	6.3 (2-9)	8.7 (6-10)	+38.6
PSK	96.7 (90-100)	94.4 (50-100)	- 2.3
Spitzer's QLI	6.4 (5-9)	8.8 (6-10)	+ 36.2

Mantovani, G et al. Int J Clin Lab Res. 1995;25:135-41

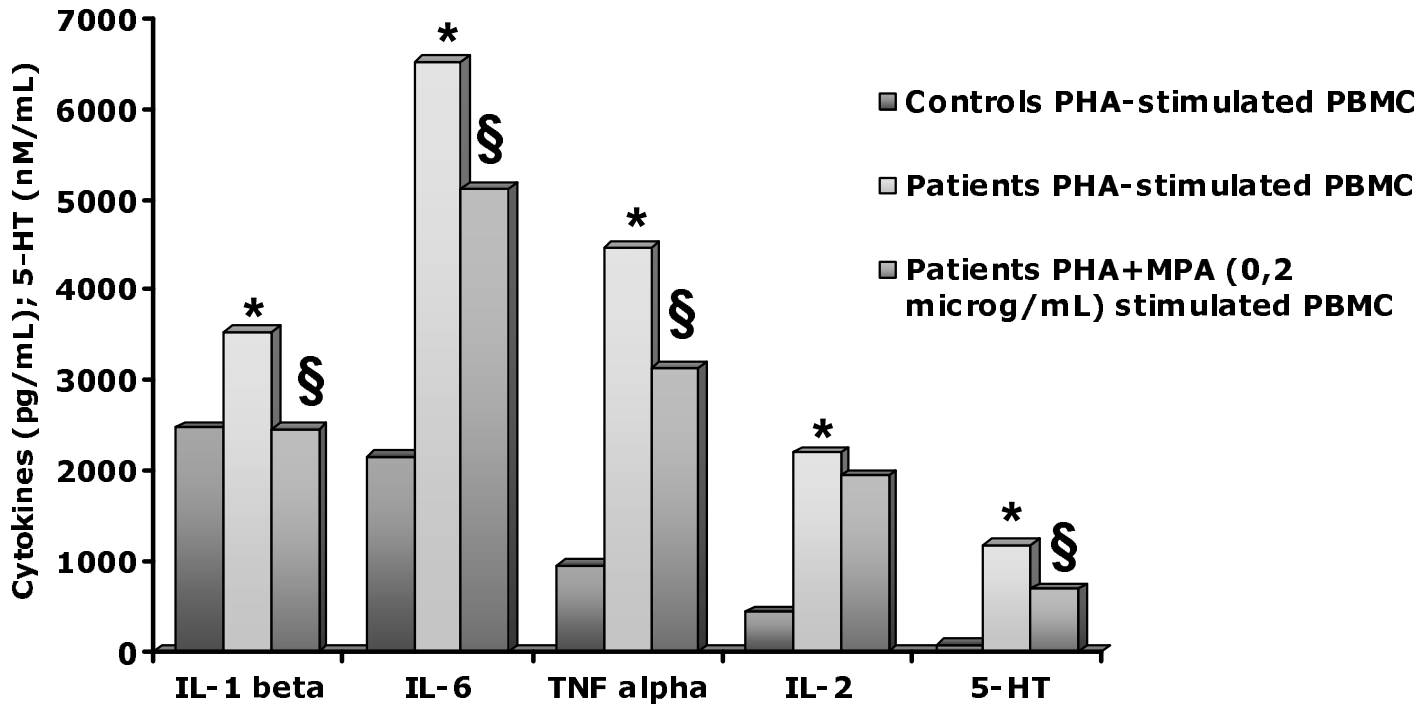
SERUM LEVELS OF IL-1 α, IL-1β, IL-2, IL-6, TNF α AND sIL-2R IN CANCER PATIENTS BEFORE AND AFTER CHEMOTHERAPY + MA TREATMENT



Results are expressed as mean values. *p<0.05 as calculated with Student's t test in comparison to controls. N.S. non significant

Mantovani, G et al. Int J Clin Lab Res. 1995;25:135-41

Medroxyprogesterone acetate reduces the in vitro production of cytokines and serotonin involved in anorexia/cachexia and emesis by PBMC of cancer patients.



Results are expressed as mean values. *p<0.05, calculated with Student's t test versus controls. §p<0.05, calculated with Student's t test versus PHA-stimulated patients PBMC

Eur J Cancer 33; 602-607, 1997

Effects of Medroxyprogesterone Acetate on Food Intake, Body Composition, and Resting Energy Expenditure in Patients with Advanced, Nonhormone-Sensitive Cancer

A Randomized, Placebo-Controlled Trial

METHODS. Fifty-four patients with non–hormone-sensitive cancer, generally characterized by substantial weight loss and hypermetabolism, received either MPA, 500 mg, or placebo twice daily for 12 weeks (double-blind study). Food intake was measured by dietary history, body composition was assessed by deuterium dilution (fat mass, fat-free mass), and REE was obtained by indirect calorimetry.

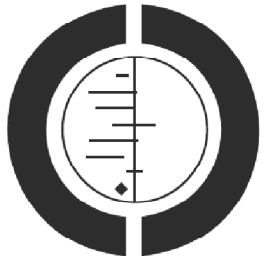
RESULTS. Compared with placebo, 12 weeks of MPA led to an increase in energy intake (between-group difference, 426 kcal/day; $P = 0.01$) that was significantly associated ($r = 0.68$, $P = 0.003$) with an increase in fat mass (between-group difference, 2.5 kg; $P = 0.009$). Fat-free mass was not significantly influenced. REE increased during MPA treatment: at 6 weeks, the between-group difference in change was 135 kcal/day ($P = 0.009$); after 12 weeks, this difference was 93 kcal/day ($P = 0.07$).

Simons JP, et al Cancer 1998; 82:553

Megestrol acetate for treatment of anorexia-cachexia syndrome (Review)

Berenstein EG, Ortiz Z.

***Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD004310**



Thirty trials were included in the original review, four new trials were identified for this update, but only two met the inclusion criteria (4123 + 703 patients). Twenty-two trials compared MA at different doses with placebo; five compared different doses of MA versus other drugs; two compared MA with other drugs and placebo; and five compared different doses of MA.

For all patient conditions, metaanalysis showed a benefit of MA compared with placebo, particularly with regard to appetite improvement and weight gain in cancer patients.
Analysing quality of life, clinical and statistical heterogeneity was found and discussed. There was insufficient information to define the optimal dose of MA.

CONCLUSIONS: This review demonstrates that MA improves appetite and weight gain in patients with cancer. No overall conclusion about Quality of Life (QoL) could be drawn due to heterogeneity.

Megestrol acetate Nanocrystal Oral Suspension

Megestrol acetate Nanocrystal Oral Suspension was designed to optimize drug delivery and improve bioavailability enhancing the performance of drugs with poor water solubility.

By rapidly increasing plasma MA concentrations, this formulation may have the potential to produce a more rapid clinical response.

It was approved by FDA for the treatment of AIDS-related cachexia and it is under evaluation for approval in cancer cachexia.

Biodrugs 2005;19(3):179-87

EFFECTIVE TREATMENTS
Corticosteroids

Among orexigenic agents, corticosteroids are widely used.
In randomized controlled studies, they have been shown to improve appetite and quality of life compared with placebo [*Mortel CG, Cancer 1974; Willox JC BMJ 1984*].
Megestrol acetate and corticosteroids seem equally effective, although for long-term use, corticosteroids have more side effects [*Loprinzi J Clin Oncol 1999*]: protein breakdown, insulin resistance, water retention and adrenal suppression.

Therefore steroids are not suitable for long-term use, and tend to be used during the pre-terminal phase of a patient illness.

Drugs with a strong rationale that have failed or have not shown univocal results in clinical trials so far

Drugs capable of inhibiting:

- the synthesis and/or release of cytokines
  (EPA, melatonin, cyclo-oxygenase-2 inhibitors and thalidomide)
- the cytokine action
  [anti-cytokine antibodies, anti-inflammatory cytokines (interleukin-12, interleukin-15)]
- the proteasome activity
  (bortezomib)

These drugs have been tested in experimental models of cachexia, with some positive results.

Unfortunately, most clinical trials in humans have provided limited and disappointing results.

Boddaert MA et al Curr Opin Oncol 2006;18:335-340

Effect of a protein and energy dense n-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial

K C H Fearon, M F von Meyenfeldt, A G W Moses, R van Geenen, A Roy, D J Gouma, A Giacosa, A Van Gossum, J Bauer, M D Barber, N K Aaronson, A C Voss, M J Tisdale

Gut 2003;**52**:1479–1486

Aim:

N-3 fatty acids, especially eicosapentaenoic acid (EPA), may possess anticachectic properties. This trial compared **a protein and energy dense supplement enriched with n-3 fatty acids and antioxidants (experimental: E)** with an **isocaloric isonitrogenous control supplement (C**) for their effects on weight, lean body mass (LBM), dietary intake, and quality of life in cachectic patients with advanced pancreatic cancer.

Methods:

A total of 200 patients (**95 E; 105 C**) were randomised to consume two cans/day of the E or C supplement (480 ml, 620 kcal, 32 g protein ¡ 2.2 g EPA) for eight weeks in a multicentre, randomised, double blind trial.

Gut 2003;**52**:1479–1486

Results:
At enrolment, patients' mean rate of weight loss was 3.3 kg/month. Intake of the supplements (E or C) was below the recommended dose (2 cans/day) and averaged 1.4 cans/day. Over eight weeks, patients in both groups stopped losing weight (Dweight E: 20.25 kg/month versus C: 20.37 kg/month; p = 0.74) and LBM (DLBM E: +0.27 kg/month versus C: +0.12 kg/month; p = 0.88) to an equal degree (change from baseline E and C, p,0.001). In view of evident non-compliance in both E and C groups, correlation analyses were undertaken to examine for potential dose-response relationships.

E patients demonstrated significant correlations between their supplement intake and weight gain (r = 0.50, p,0.001) and increase in LBM (r = 0.33, p = 0.036). Such correlations were not statistically significant in C patients. The relationship of supplement intake with change in LBM was significantly different between E and C patients (p = 0.043). Increased plasma EPA levels in the E group were associated with weight and LBM gain (r = 0.50, p,0.001; r = 0.51, p = 0.001). **Weight gain was associated with improved quality of life (p,0.01) only in the E group.**

Conclusion:
Intention to treat group comparisons indicated that at the mean dose taken, enrichment with n-3 fatty acids did not provide a therapeutic advantage and that both supplements were equally effective in arresting weight loss.

Post hoc dose-response analysis suggests that if taken in sufficient quantity, only the n-3 fatty acid enriched energy and protein dense supplement results in net gain of weight, lean tissue, and improved quality of life. Further trials are required to examine the potential role of n-3 enriched supplements in the treatment of cancer cachexia.

Gut 2003;**52**:1479–1486

An Eicosapentaenoic Acid Supplement Versus Megestrol Acetate Versus Both for Patients With Cancer-Associated Wasting: A North Central Cancer Treatment Group and National Cancer Institute of Canada Collaborative Effort

Aminah Jatoi, Kendrith Rowland, Charles L. Loprinzi, Jeff A. Sloan, Shaker R. Dakhil, Neil MacDonald, Bruno Gagnon, Paul J. Novotny, James A. Mailliard, Teresita L.L. Bushey, Suresh Nair, and Brad Christensen

J Clin Oncol 2004; 22:2469

Patients and Methods

Four hundred twenty-one assessable patients with cancer-associated wasting were randomly assigned to an EPA supplement 1.09 g administered bid plus placebo; MA liquid suspension 600 mg/d plus an isocaloric, isonitrogenous supplement administered twice a day; or both. Eligible patients reported a 5-lb, 2-month weight loss and/or intake of less than 20 calories/kg/d.

Table 2. Maximum Weight Gain Over Baseline

Maximal Weight Gain Over Baseline (physician-reported)	% EPA-Treated Patients (n = 141)*	% Megestrol Acetate–Treated Patients (n = 140)	P†	% EPA Supplement + Megestrol Acetate–Treated Patients (n = 140)	P†
0%	63	61		55	
1%-4%	22	11	.24	20	.69
5%-9%	9	10		14	
10% or more‡	6	18		11	

Abbreviation: EPA, eicosapentaenoic acid.
*Data are reported as the percentage of patients in each treatment arm.
†Compared with 10% + weight gain category with megestrol acetate.
‡For 10% or more weight gain, there was a statistically significant difference between groups ($P = .01$).

An Eicosapentaenoic Acid Supplement Versus Megestrol Acetate Versus Both for Patients With Cancer-Associated Wasting: A North Central Cancer Treatment Group and National Cancer Institute of Canada Collaborative Effort

Aminah Jatoi, Kendrith Rowland, Charles L. Loprinzi, Jeff A. Sloan, Shaker R. Dakhil, Neil MacDonald, Bruno Gagnon, Paul J. Novotny, James A. Mailliard, Teresita L.L. Bushey, Suresh Nair, and Brad Christensen

J Clin Oncol 2004; 22:2469

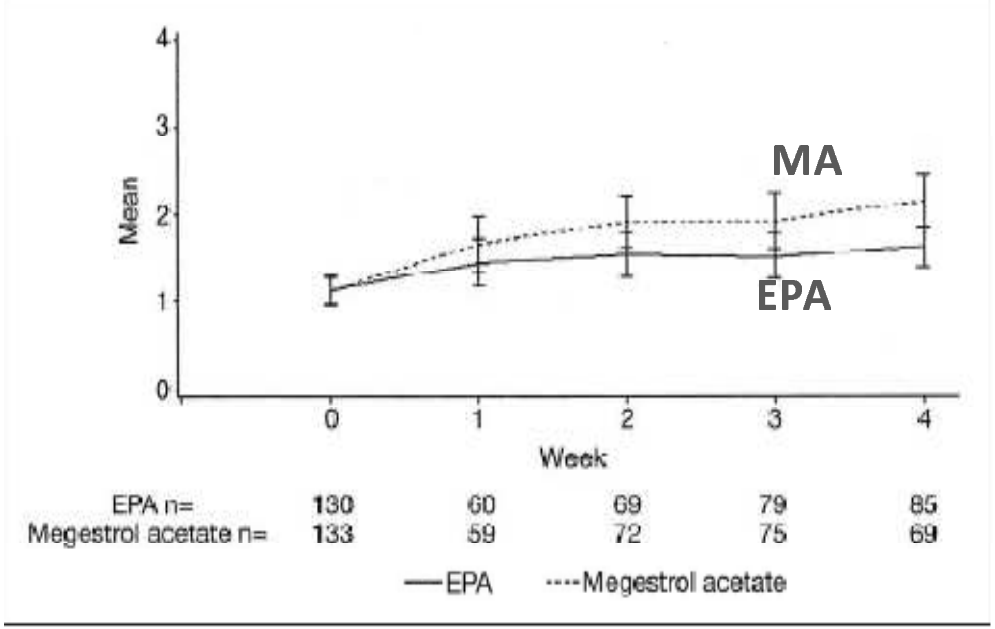


Fig 1. Serial assessment of appetite with the Functional Assessment of Anorexia/Cachexia Therapy suggested that single-agent megestrol acetate provided better appetite stimulation compared with the eicosapentaenoic acid (EPA) supplement. Graph shows mean scores with 95% CIs.

In conclusion,
this EPA supplement,
either alone
or in combination with MA,
does not improve weight or appetite
more than MA alone

Double-Blind, Placebo-Controlled, Randomized Study of Eicosapentaenoic Acid Diester in Patients With Cancer Cachexia

Kenneth C.H. Fearon, Matthew D. Barber, Alastair G. Moses, Sam H. Ahmedzai, Gillian S. Taylor, Michael J. Tisdale, and Gordon D. Murray

ABSTRACT

Purpose
Eicosapentaenoic acid (EPA) has been proposed to have specific anticachectic effects. This trial compared EPA diethyl ester with placebo in cachectic cancer patients for effects on weight and lean body mass.

Patients and Methods
Five hundred eighteen weight-losing patients with advanced gastrointestinal or lung cancer were studied in a multicenter, double-blind, placebo controlled trial. Patients were randomly assigned to receive a novel preparation of pure EPA at a dose of 2 g or 4 g daily or placebo (2g EPA, n = 175; 4 g EPA, n = 172; placebo, n = 171). Patients were assessed at 4 weeks and 8 weeks.

Results
The groups were well balanced at baseline. Mean weight loss at baseline was 18% (n = 518). Over the 8-week treatment period, both intention-to-treat analysis and per protocol analysis revealed no statistically significant improvements in survival, weight, or other nutritional variables. There was, however, a trend in favor of EPA with analysis of the primary end point, weight, at 8 weeks showing a borderline, nonsignificant treatment effect ($P = .066$). Relative to placebo, mean weight increased by 1.2 kg with 2 g EPA (95% CI, 0 kg to 2.3 kg) and by 0.3 kg with 4g EPA (−0.9 kg to 1.5 kg).

Conclusion
The results indicate no statistically significant benefit from single agent EPA in the treatment of cancer cachexia. Future studies should concentrate on other agents or combination regimens.

J Clin Oncol 24:3401-3407.

THE COCHRANE COLLABORATION®

Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia (Review)

Dewey A, Baughan C, Dean TP, Higgins B, Johnson I

OBJECTIVES → To evaluate the effectiveness and safety of EPA in relieving symptoms associated with the cachexia syndrome in patients with advanced cancer.

SELECTION CRITERIA → Studies were included in the review if they assessed oral EPA compared with placebo or control in randomised controlled trials of patients with advanced cancer and either a clinical diagnosis of cachexia or self-reported weight loss of 5% or more.

DATA COLLECTION AND ANALYSIS → Both methodological quality evaluation of potential trials and data extraction were conducted by two independent review authors.

Cochrane Database Syst Rev. 2007 Jan 24;(1):CD004597

THE COCHRANE COLLABORATION®

MAIN RESULTS

Five trials (involving 587 patients) met the inclusion criteria. Three trials compared EPA at different doses with placebo with two outcomes, nutritional status and adverse events comparable across two of the three included trials. In addition, two trials compared different doses of EPA with an active matched control. It was possible to compare the outcomes of weight, quality of life and adverse events across these two trials. There were insufficient data to define the optimal dose of EPA.

AUTHORS' CONCLUSIONS

There were insufficient data to establish whether oral EPA was better than placebo. Comparisons of EPA combined with a protein energy supplementation versus a protein energy supplementation (without EPA) in the presence of an appetite stimulant (Megestrol Acetate)

provided no evidence that EPA improves symptoms associated with the cachexia syndrome often seen in patients with advanced cancer.

Cochrane Database Syst Rev. 2007 Jan 24;(1):CD004597

Dronabinol Versus Megestrol Acetate Versus Combination Therapy for Cancer-Associated Anorexia: A North Central Cancer Treatment Group Study

By Aminah Jatoi, Harold E. Windschitl, Charles L. Loprinzi, Jeff A. Sloan, Shaker R. Dakhil, James A. Mailliard, Sarode Pundaleeka, Carl G. Kardinal, Tom R. Fitch, James E. Krook, Paul J. Novotny, and Brad Christensen

PATIENTS AND METHODS: **Four hundred sixty-nine** assessable advanced cancer patients were randomized to (1) **oral megestrol acetate** 800 mg/d liquid suspension plus placebo, (2) **oral dronabinol** 2.5 mg twice a day plus placebo, **or (3) both agents.**

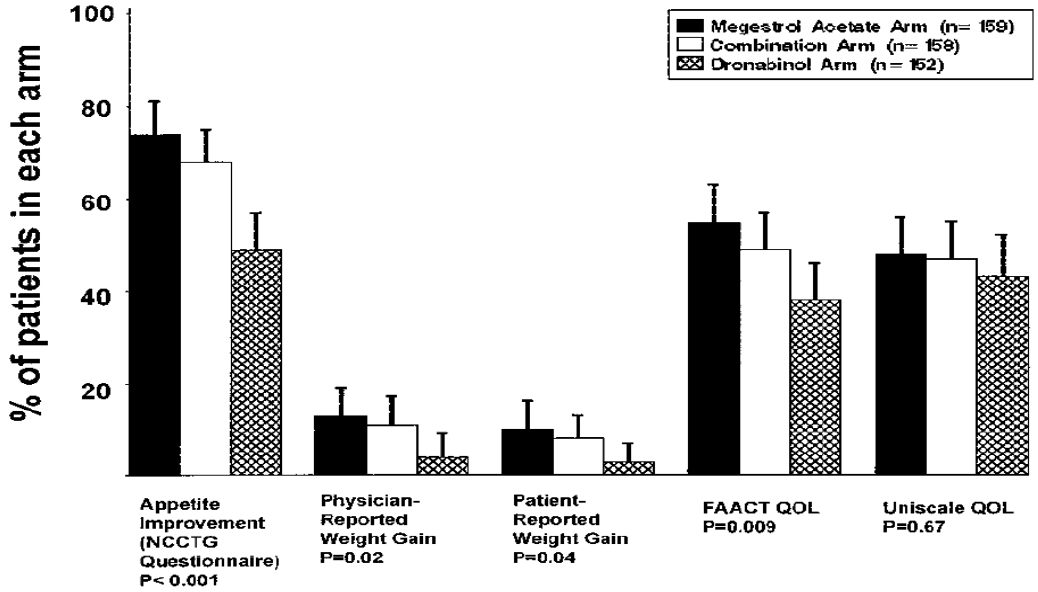


Fig 1. Megestrol acetate improved (1) appetite, (2) physician-reported weight, (3) patient-reported weight, and (4) FAACT QOL score (Fisher's exact test, $P < .001$, .02, .04, and .009, respectively). The UNISCALE found no significant differences in QOL. Bars represent 95% confidence intervals.

A greater percentage of megestrol acetate-treated patients reported appetite improvement and weight gain compared with dronabinol-treated patients. Combination treatment resulted in no significant differences in appetite or weight compared with megestrol acetate alone

J Clin Oncol 2002; 20: 567-573

Comparison of Orally Administered Cannabis Extract and Delta-9-Tetrahydrocannabinol in Treating Patients With Cancer-Related Anorexia-Cachexia Syndrome: A Multicenter, Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial From the Cannabis-In-Cachexia-Study-Group

Florian Strasser, Diana Luftner, Kurt Possinger, Gernot Ernst, Thomas Ruhstaller, Winfried Meissner, You-Dschun Ko, Martin Schnelle, Marcus Reif, and Thomas Cerny

J Clin Oncol 2006; 24:3394-3400

Adult patients with advanced cancer, CACS, weight loss (5% over 6 months), and ECOG performance status 2 were randomly assigned (2:2:1) to receive CANNABIS EXTRACT (CE, i.e. 2.5 mg THC and 1 mg cannabidiol) or delta-9-tetrahydrocannabinol (THC 2.5 mg) or placebo orally, twice daily for 6 weeks.

Of 289 patients screened, 243 were randomly assigned and 164 completed treatment.

Intent-to treat analysis showed no significant differences between the three arms for appetite, QOL, or cannabinoid-related toxicity.
An independent data review board recommended termination of recruitment because of insufficient differences between study arms.

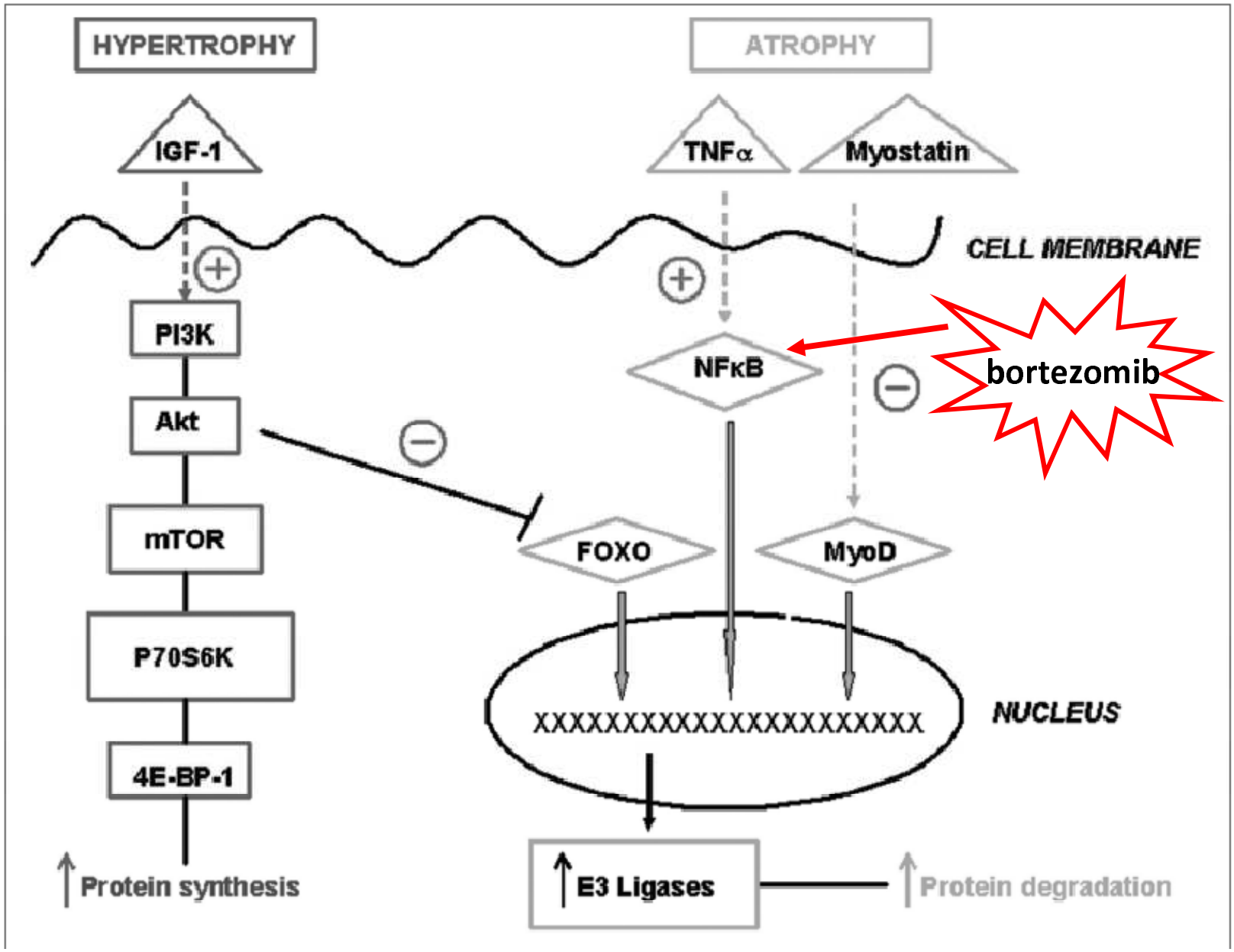
Conclusion: CE at the oral dose administered was well tolerated by these patients with CACS. No differences in patients' appetite or QOL were found either between CE, THC, and placebo or between CE and THC at the dosages investigated

BORTEZOMIB

With regard to the pharmacological inhibition of proteasome activity, a drug like bortezomib could be of future interest for the management of cachexia.

Despite rat studies demonstrating significant reduction in denervation-induced muscle atrophy following bortezomib administration, **preliminary studies in human patients with metastatic pancreatic cancer have demonstrated an insignificant impact on weight loss.**

INTRACELLULAR SIGNALLING PATHWAYS INVOLVED IN SKELETAL MUSCLE WASTING



Is bortezomib, a proteasome inhibitor, effective in treating cancer-associated weight loss? Preliminary results from the North Central Cancer Treatment Group.

Jatoi A, et al Supportive Care Cancer 2005;13:381

This study is a subanalysis from two prior antineoplastic trials in patients with adenocarcinoma of the pancreas. The first included 46 patients with metastatic pancreatic cancer treated with **single-agent bortezomib (intravenous doses of 1.5 or 1.3 mg/m2 on days 1, 4, 8, and 11 of a 21-day cycle).** The second included 42 patients with pancreatic cancer treated with single-agent octreotide (200 or 500 microg subcutaneously three times a day).

RESULTS: FACT-C data suggested stable appetite, but high patient dropout rates invite caution in interpretation. For example, in response to "I have a good appetite," mean scores for bortezomib-treated patients were 45 at baseline (n=42), 45 at the end of cycle 1 (n=26), and 44 at the end of cycle 2 (n=9). In contrast, weight data appeared more straightforward to interpret: direct comparisons of mean change in weight from baseline between bortezomib- and octreotide-treated patients showed no significant differences between groups.

CONCLUSIONS: These preliminary results suggest that bortezomib shows negligible favorable effects on cancer-associated weight loss in patients with metastatic pancreatic cancer. We conclude that further study of bortezomib specifically in this setting and for this indication is not warranted.

A multicenter, phase II study of infliximab – *an anti TNF-alpha moAb* - plus gemcitabine in pancreatic cancer cachexia

Wiedenmann B, et al. J Support Oncol 2008 ;6:18-25

This multicenter, phase II, placebo-controlled study randomized 89 patients with stage II-IV pancreatic cancer and cachexia to receive either placebo or 3 mg/ kg or 5 mg/kg of infliximab at weeks 0, 2, and 4 and then every 4 weeks to week 24; patients also received 1,000 mg/m2 of gemcitabine weekly from weeks 0-6 and then for 3 of every 4 weeks until their disease progressed.

The primary endpoint was change in lean body mass (LBM) at 8 weeks from baseline; major secondary endpoints included overall survival, progression-free survival, Karnofsky performance status, and 6-minute walk test distance. In addition, quality of life was measured.

The mean change in LBM at 8 weeks was +0.4 kg for patients receiving placebo, +0.3 kg for those receiving 3 mg/kg of infliximab, and +1.7 kg for those receiving 5 mg/kg of infliximab. No statistically significant differences in LBM or secondary endpoints were observed among the groups. Safety findings were similar in all groups.

Adding infliximab to gemcitabine to treat cachexia in advanced pancreatic cancer patients was not associated with statistically significant differences in safety or efficacy when compared with placebo.

EMERGING DRUGS WITH SOME EFFECTIVE RESULTS

BUT STILL UNDER CLINICAL EVALUATION

- ❑ THALIDOMIDE
- ❑ CELECOXIB
- ❑ GHRELIN
- ❑ INSULIN
- ❑ BRANCHED CHAIN AMINO ACIDS
- ❑ OXANDROLONE
- ❑ OLANZAPINE

GUT ONLINE

Thalidomide in the treatment of cancer cachexia: a randomised placebo controlled trial

J N Gordon, T M Trebble, R D Ellis, H D Duncan, T Johns and P M Goggin

Gut 2005;54;540-545

Methods: Fifty patients with advanced pancreatic cancer who had lost at least 10% of their body weight were randomised to receive thalidomide 200 mg daily or placebo for 24 weeks in a single centre, double blind, randomised controlled trial. The primary outcome was change in weight and nutritional status.

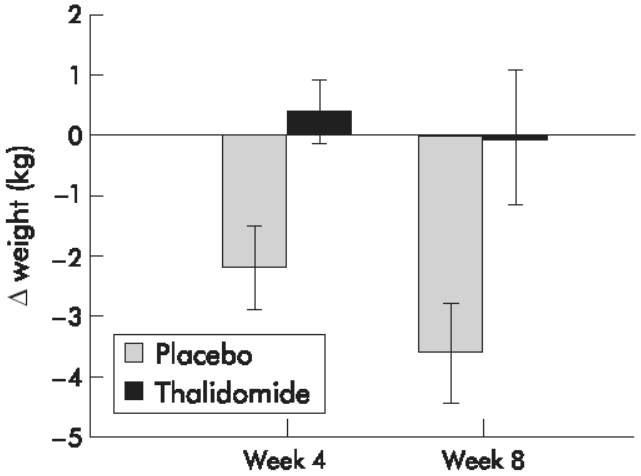


Figure 2 Change in weight in pancreatic cancer patients randomised to either thalidomide (n = 17, week 4; n = 12, week 8) or placebo (n = 16, week 4; n = 8, week 8). Differences between groups: p = 0.005 at four weeks and p = 0.034 at eight weeks.

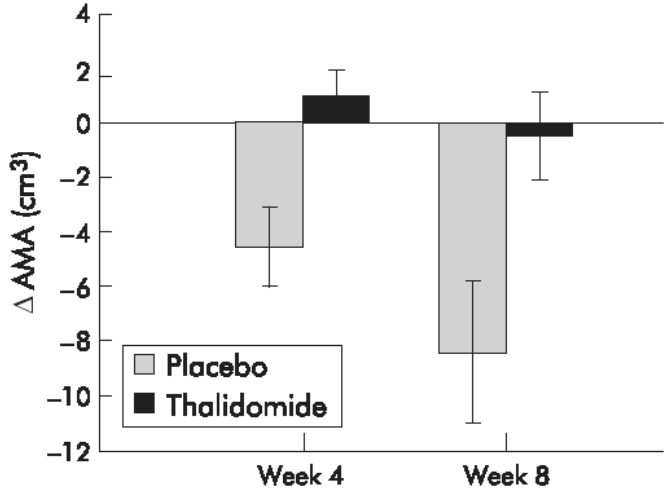


Figure 3 Change in bone free arm muscle area (AMA) in pancreatic cancer patients randomised to either thalidomide (n = 17, week 4; n = 12, week 8) or placebo (n = 16, week 4; n = 8, week 8). Differences between groups: p = 0.002 at four weeks and 0.014 at eight weeks.

RESULTS OF A PILOT STUDY OF THE EFFECTS OF CELECOXIB ON CANCER CACHEXIA IN PATIENTS WITH CANCER OF THE HEAD, NECK, AND GASTROINTESTINAL TRACT

Victor Lai, MD,[1] Jonathan George, BA,[1] Luther Richey, BA,[1] Hong J. Kim, MD,[2,3]
Trinitia Cannon, MD,[4] Carol Shores, MD, PhD,[3,4] Marion Couch, MD, PhD[2,3,4]

Head and neck 2008;30:67-74

Eleven cachectic patients with head and neck or gastrointestinal cancer were randomly assigned to receive placebo or celecoxib for 21 days while awaiting the initiation of cancer therapy. Body composition, resting energy expenditure, QOL, physical function, and inflammatory markers were measured on days 1 and 21.

Results. Patients receiving celecoxib experienced statistically significant increases in weight and body mass index (BMI), while patients receiving placebo experienced weight loss and a decline in BMI. Patients receiving celecoxib also had increases in QOL scores.

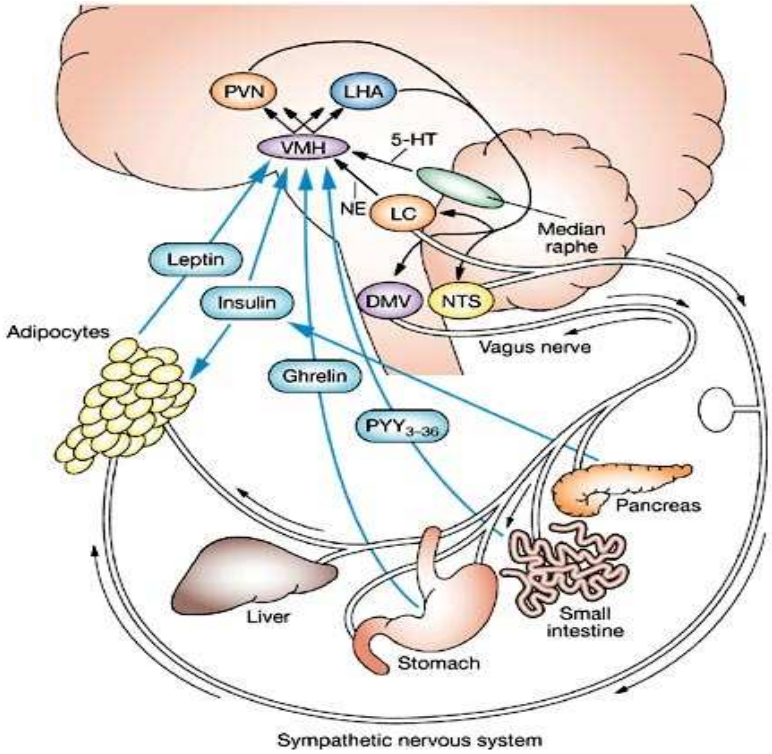
CONCLUSIONS
Cachectic patients receiving celecoxib gained weight, experienced increased BMI, and demonstrated improved QOL scores. Compliance was good and no adverse events were seen.

GHRELIN MIMETIC WITH OREXIGENIC AND ANABOLIC ACTIVITY

Recently, much research interest has focused on ghrelin, a 28 amino-acid peptide produced by the P/D1 cells of the stomach.

Not only does ghrelin stimulate GH secretion (via the GH secretagogue-1a (GHS-1a) receptor), but it also promotes food intake (via the orexigenic NPY system) and decreases sympathetic nerve activity.

Synthetic human ghrelin has been shown to improve muscle wasting and functional capacity in patients with cardiopulmonary-associated cachexia, and to improve energy intake in anorexic cancer patients.



GHRELIN MIMETIC WITH OREXIGENIC AND ANABOLIC ACTIVITY

Based on these animal studies and short-term human trials, there appears to be much promise for the use of ghrelin and GHS-R agonists for the treatment of cachexia caused by multiple underlying conditions.

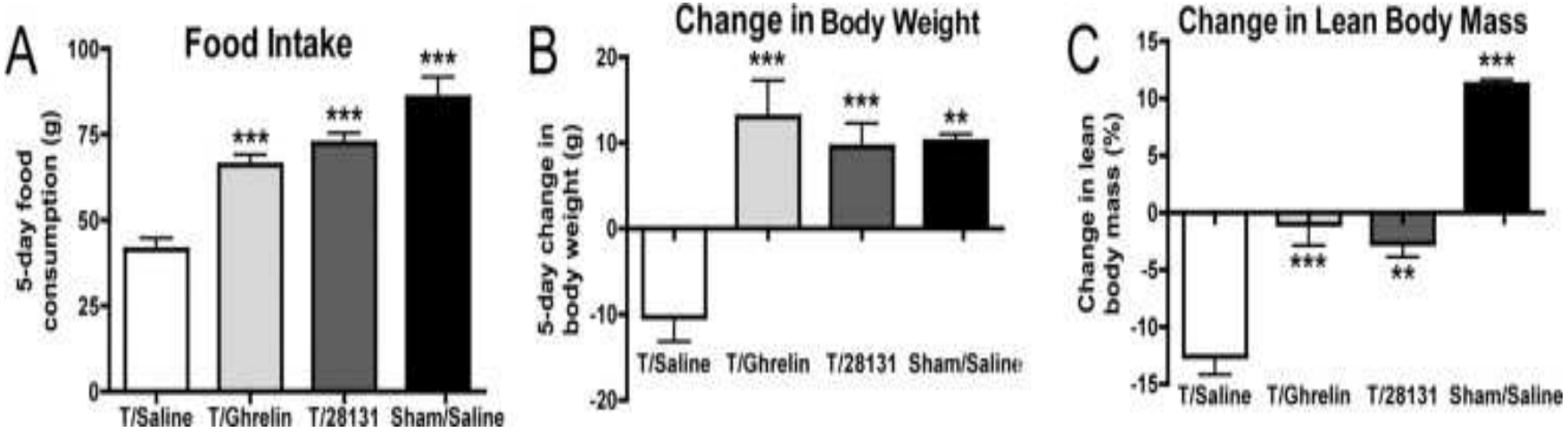
Significant questions remain to be answered, however, before its widespread use, most prominently whether the gains produced by GHS-R agonists maintain safety and efficacy with long-term use in human disease.

Clearly, more long-term research is needed.

Deboer MD. Nutrition 2008; 24:806-14

Emergence of ghrelin as a treatment for cachexia syndromes

Deboer MD. Nutrition 2008; 24:806-14



Administration of ghrelin and a GHS-R agonist (BIM-28131) to rats that had been implanted with a syngenic sarcoma known to cause cachexia via an osmotic mini-pump, delivering 500 nmol/kg of medication as a continuous infusion resulted in an improvement of:

- food intake (A)

- body weight (B)

- lean body mass (C)

Administration of ghrelin to humans with cachexia has shown not univocal efficacy in increasing food intake with single dose intravenous administration

(Strasser et al Br J Cancer 2008; Neary et al. J Clin Endocrinol Metab 2004)

Safety, tolerability and pharmacokinetics of intravenous ghrelin for cancer-related anorexia/cachexia: a randomised, placebo-controlled, double-blind, double-crossover study

Strasser F, et al. Br J Cancer 2008;98:300

Twenty-one adult patients were randomised to receive ghrelin on days 1 and 8 and placebo on days 4 and 11 or vice versa, given intravenously over a 60-min period before lunch: 10 received 2 mg kg1 (lower-dose) ghrelin; 11 received 8 mg kg1 (upper-dose) ghrelin.

Nutritional intake and eating-related symptoms, measured to explore preliminary efficacy, did not differ between ghrelin and placebo.

Ghrelin is well tolerated and safe in patients with advanced cancer. For safety, tolerance, and patient preference for treatment, no difference was observed between the lower- and upper-dose group.

Ghrelin Increases Energy Intake in Cancer Patients with Impaired Appetite: Acute, Randomized, Placebo-Controlled Trial

NICOLA M. NEARY, CAROLINE J. SMALL, ALISON M. WREN, JENNIFER L. LEE, MARALYN R. DRUCE, CARLO PALMIERI, GARY S. FROST, MOHAMMAD A. GHATEI, R. CHARLES COOMBES, AND STEPHEN R. BLOOM

J Clin Endocrinol Metab 89: 2832–2836, 2004

An acute, randomized, placebo-controlled, cross-over clinical trial to determine whether ghrelin (5 pmol/kg/min for 180 min i.c.) stimulates appetite in cancer patients with anorexia. Seven cancer patients who reported loss of appetite were recruited from oncology clinics at Charing Cross Hospital.

A marked increase in energy intake was observed with ghrelin infusion compared with saline control, and every patient reported food intake increase
The meal appreciation score was greater by 28.8% with ghrelin treatment.

No side effects were observed.

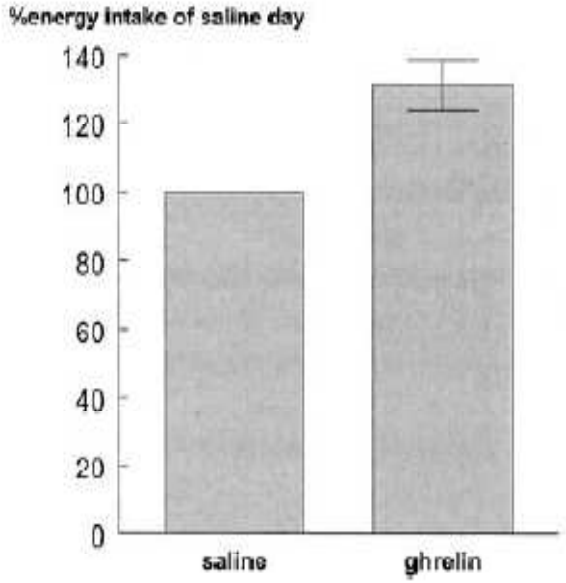


FIG. 1. Percentage increase in energy intake from a buffet meal after ghrelin compared with saline infusion.

A phase II randomized, placebo-controlled, double-blind study of the efficacy and safety of RC-1291 (RC) for the treatment of cancer cachexia

Garcia et al . Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings
Part I. Vol 25, No. 18S , 2007: 9133

GHS-R agonist RC-1291 (Anamorelin; Saphire Therapeutics, Bridgewater, NJ), a small-molecule orally active compound, was administered in a randomized, placebo-controlled trial over a 12-wk period to subjects with a variety of cancers (predominantly lung cancer).

Over this 12-wk course, RC-1291 produced an improvement in total body mass and a trend towards increased lean mass.
A measurement of quality of life—an important consideration for any late-term cancer treatment—was unchanged between the groups receiving RC-1291 and placebo.

Insulin Treatment in Cancer Cachexia: Effects on Survival, Metabolism, and Physical Functioning

Kent Lundholm,[1] Ulla Körner,[1] Lena Gunnebo,[1] Petra Sixt-Ammilon,[2] Marita Fouladiun,[1] Peter Daneryd,[1] and Ingvar Bosaeus[2]

Clin Cancer Res 2007;13:2699

Experimental Design: One hundred and thirty-eight unselected patients with mainly advanced gastrointestinal malignancy were randomized to receive insulin (0.11 ± 0.05 units/kg/d) plus best available palliative support [anti-inflammatory treatment (indomethacin), prevention of anemia (recombinant erythropoietin), and specialized nutritional care (oral supplements + home parenteral nutrition)] according to individual needs. Control patients received the best available palliative support according to the same principles. Health-related quality of life, food intake, resting energy expenditure, body composition, exercise capacity, metabolic efficiency during exercise, and spontaneous daily physical activity as well as blood tests were evaluated during follow-up (30-824 days) according to intention to treat.

Results: Patient characteristics at randomizations were almost identical in study and control groups. Insulin treatment for 193 ± 139 days (mean ± SD) significantly stimulated carbohydrate intake, decreased serum-free fatty acids, increased whole body fat, particularly in trunk and leg compartments, whereas fat-free lean tissue mass was unaffected. Insulin treatment improved metabolic efficiency during exercise, but did not increase maximum exercise capacity and spontaneous physical activity. Tumor markers in blood (CEA, CA-125, CA 19-9) did not indicate the stimulation of tumor growth by insulin; a conclusion also supported by improved survival of insulin-treated patients ($P < 0.03$).

Conclusion: Insulin is a significant metabolic treatment in multimodal palliation of weight-losing cancer patients.

Effect of branched-chain amino acids on muscle atrophy in cancer cachexia

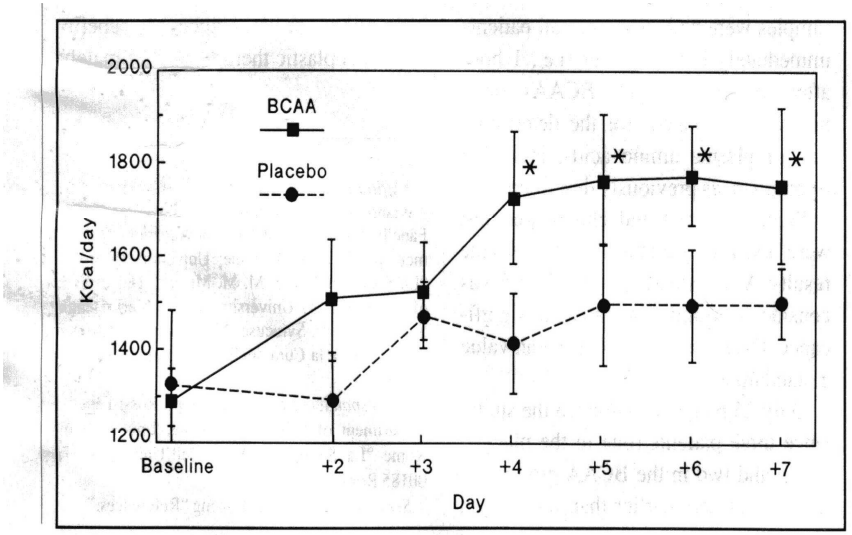
Helen L. ELEY, Steven T. RUSSELL and Michael J. TISDALE[1]

Biochem. J. (2007) 407, 113–120

Branched-chain amino acids are neutral amino acids with interesting and clinically relevant metabolic effects. By interfering with brain serotonergic activity and by inhibiting the overexpression of critical muscular proteolytic pathways, branched-chain amino acids have been shown to induce beneficial metabolic and clinical effects under different pathological conditions.

Their potential role as antianorexia and anticachexia agents was proposed many years ago, but only recent experimental studies and clinical trials have tested their ability to stimulate food intake and counteract muscle wasting in anorectic, weight-losing patients.

Laviano A, et al. Branched-chain amino acids: the best compromise to achieve anabolism? Curr Opin Clin Nutr Metab Care. 2005;8:408-14



Journal of the National Cancer Institute, Vol. 88, No. 8, April 17, 1996

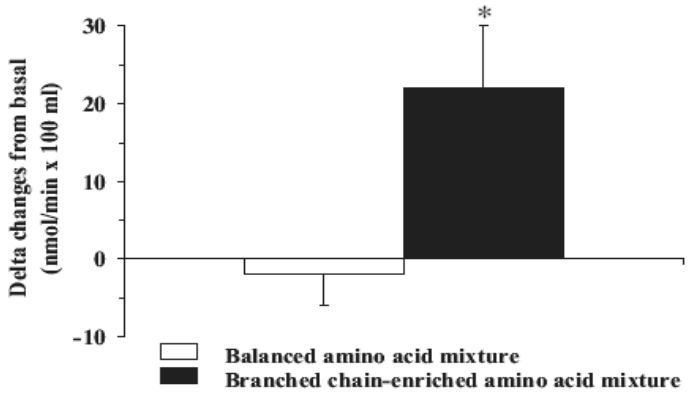


Fig. 1. Delta changes from basal leg muscle phenylalanine rate of disappearance to protein synthesis after infusions of the balanced (white bar) and branched-chain–enriched (black bar) amino acid mixtures. $^{*}P < 0.05$ branched-chain–enriched versus balanced amino acid infusion.

Biolo G et al, Nutrition 2006; 22:475-482

Excerpta Medica

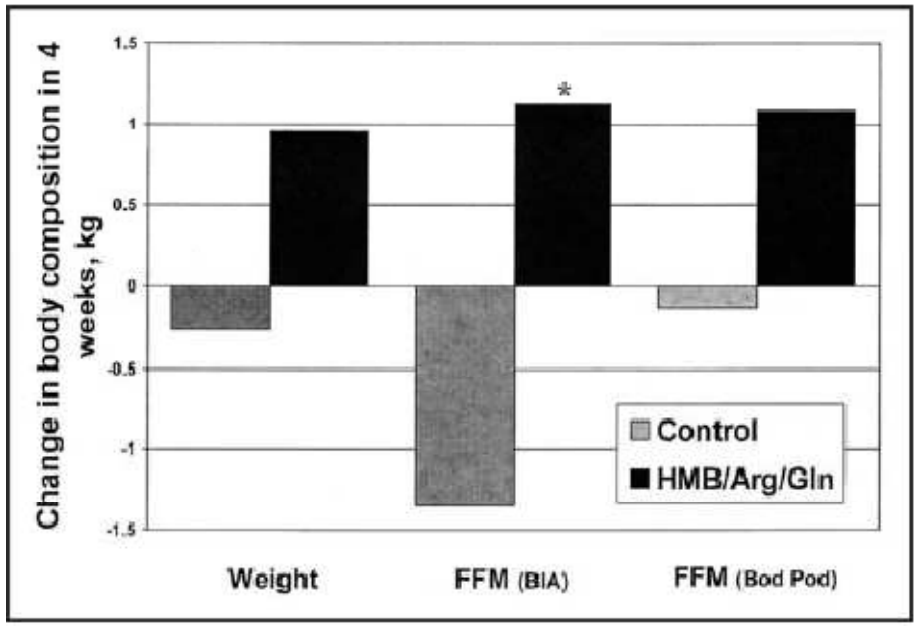
The American Journal of Surgery 183 (2002) 471–479

The American Journal of Surgery

Reversal of cancer-related wasting using oral supplementation with a combination of β-hydroxy-β-methylbutyrate, arginine, and glutamine

Patricia Eubanks May, M.D.[a,b,*], Annabel Barber, M.D.[b], James T. D'Olimpio, M.D.[c], Ann Hourihane, N.P.[c], Naji N. Abumrad, M.D.[c]

Patients with solid tumors who had demonstrated a weight loss of at least 5% were randomly assigned in a double-blind fashion to either an isonitrogenous control mixture of nonessential amino acids or an experimental treatment containing -hydroxy--methylbutyrate (3 g/d), L-arginine (14 g/d), and L-glutamine (14 g/d [HMB/Arg/Gln]).



The mixture of HMB/Arg/Gln was effective in increasing FFM of advanced (stage IV) cancer. The exact reasons for this improvement will require further investigation, but could be attributed to the observed effects of HMB on slowing rates of protein breakdown.

Recent issues form ASCO 2008

G. J. Lesser, D. Case, F. Ottery, R. McQuellon, J. K. Choksi, G. Sanders, R. Rosdhal, E. G. Shaw, Wake Forest

A phase III randomized study comparing the effects of oxandrolone (Ox) and megestrol acetate (Meg) on lean body mass (LBM), weight (wt) and quality of life (QOL) in patients with solid tumors and weight loss receiving chemotherapy.

J Clin Oncol 26: 2008 (May 20 suppl; abstr 9513)

Methods: prospective, randomized phase 3 trial comparing the effects of Ox (10mg bid) and MA (800mg qd) on weight, body composition and QOL in adult pts with solid tumors and weight loss receiving chemotherapy. The primary outcome was LBM after 12 weeks of drug therapy. Secondary outcomes included wt, fat mass, and QOL.

Results: 155 pts were randomized and the study has been completed. At 12 weeks, significant changes from baseline were observed for weight (lbs) (Ox -3.4 vs MA +5.8, $p<.001$) and fat mass (Ox -4.89 vs MA +2.68, $p<.001$).

Conclusions: Pts treated with Ox still lost weight but experienced an increase in LBM, a reduction in fat mass and reduced self-reported anorectic symptoms. MA therapy was associated with an increase in weight and fat mass, minimal change in LBM and improved appetite. The complementary effects of the two agents on appetite, overall weight gain and LBM suggest that their combination may result in optimal effects in a similar pt population.

Recent issues form ASCO 2008

F. Braiteh, S. Dalal, A. Khuwaja, H. David, E. Bruera, R. Kurzrock

Phase I pilot study of the safety and tolerability of olanzapine (OZA) for the treatment of cachexia in patients with advanced cancer

***J Clin Oncol* 26: 2008 (May 20 suppl; abstr 20529)**

Background: Olanzapine (OAZ), an atypical neuroleptic with safe therapeutic window for several psychotic diseases, induces significant weight gain positive metabolic gains.
To explore if OAZ can improve cachexia in pts with advanced cancer, we are investigating its safety and tolerability, its effects on weight and nutrition, and the outcome of serum metabolic and inflammatory factors.

Methods: Enrolled eligible pts received daily oral OAZ, starting at a dose of 2.5 mg (6-pts/cohort, dose-escalation at of 5, 7.5, 10, 12.5, and 15 mg).
Results: To date, 14 pts with advanced cancer tumor referred to the Phase I Clinic have been enrolled at 2.5, 5 and 7.5 mg/m2 dose-levels.

Conclusions: Our preliminary data suggest that lower doses of OAZ are very well tolerated with promising clinical activity on weight, nutrition and function in pts with cachexia. ELISA assays of the inflammatory and metabolic factors are in progress. The trial is currently accruing at a dose-level of daily 7.5 mg.

Studies demonstrating effect of drugs on single symptoms of cachexia

Fatigue

Barton DL, et al. Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 9001

Participants were randomized to receive, in a double blind manner, placebo, 750 mg/d, 1,000 mg/d or 2,000 mg/d of American Ginseng in BID dosing for 8 weeks.

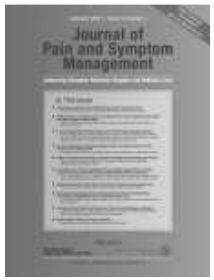
<u>Conclusion:</u> This randomized pilot trial provided data to suggest that American Ginseng doses of 1000-2000 mg/d may be effective for alleviating cancer related fatigue.

Therefore, further study of American Ginseng in cancer survivors appears warranted.

COMBINED APPROACH

From all the data presented, one can speculate that one single therapy may not be completely successful in the treatment of cachexia. From this point of view, treatments involving different combinations are more likely to be successful.

From: Argiles J, et al. Drug Discovery Today 2008; 13:72-78



Effects of Celecoxib, Medroxyprogesterone, and Dietary Intervention on Systemic Syndromes in Patients with Advanced Lung Adenocarcinoma: A Pilot Study

Leandro C.A. Cerchietti, MD, Alfredo H. Navigante, MD, PhD, Guillermo D. Peluffo, MS, Miriam J. Diament, MS, Isabel Stillitani, MS, Slobodanka A. Klein, MS, and Maria E. Cabalar, MD

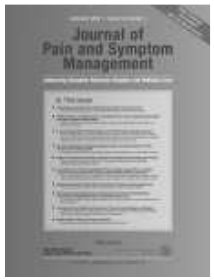
Supportive Care Division (L.C.A.C., A.H.N.), Translational Research Unit (L.C.A.C.), Internal Medicine Department (A.H.N., M.E.C.), and Experimental Cancer Department (G.D.P., M.J.D., I.S., S.A.K.), Angel H. Roffo Cancer Institute, University of Buenos Aires, Buenos Aires, Argentina

Systemic syndromes characterized by a persistent activity of circulating mediators (cytokines) are frequently present with advanced cancer. We grouped under the general heading of "Systemic Immune-Metabolic Syndrome (SIMS)" a particular variety of distressing systemic syndrome characterized by dysregulation of the psycho-neuro-immune-endocrine homeostasis, with overlapping clinical manifestations.

SIMS may include cachexia, anorexia, nausea, early satiety, fatigue, tumor fever, cognitive changes and superinfection. The aim of this study was to ameliorate some of the SIMS symptoms in a homogeneous group of lung adenocarcinoma patients using a multitargeted therapy.

Fifteen patients with evidence of SIMS were studied.

SIMS was defined as the presence of weight loss, anorexia, fatigue performance status ≥ 2 and acute-phase protein response.



Patients received medroxyprogesterone (MPA) (500 mg twice daily), celecoxib (200 mg twice daily), plus oralfood supplementation for 6 weeks.

After treatment, 13 patients either had stable weight (±1%) or had gained weight. There were significant differences in improvement of bodyweight-change rate, nausea, early satiety, fatigue, appetite and performance status.

Patients who had any kind of lung infection showed higher levels of IL-10 compared to non-infected patients ($P = 0.039$).

Our results suggest that patients with advanced lung adenocarcinoma, treated with MPA, celecoxib and dietary intervention, might have considerable improvement in certain SIMS outcomes.

This multitargeted symptomatic approach deserves further study.

Effects of Eicosapentaenoic and Docosahexaenoic n-3 Fatty Acids From Fish Oil and Preferential Cox-2 Inhibition on Systemic Syndromes in Patients With Advanced Lung Cancer

Leandro C.A. Cerchietti, Alfredo H. Navigante, and Monica A. Castro

NUTRITION AND CANCER 2007; *59*, 14–20

A cohort of 22 patients with advanced lung cancer and SIMS were randomly assigned to receive either fish oil, 2 g tid, plus placebo capsules bid (n = 12) or fish oil, 2 g tid, plus celecoxib 200 mg bid (n = 10). All patients in both groups received oral food supplementation.

After 6 wk of treatment, patients receiving fish oil + placebo or fish oil + celecoxib showed significantly more appetite, less fatigue, and lower C-reactive protein (C-RP) values than their respective baselines values ($P < 0.02$ for all the comparisons). Additionally, patients in the fish oil + celecoxib group also improved their body weight and muscle strength compared to baseline values ($P < 0.02$for all the comparisons).

Comparing both groups, patients receiving fish oil + celecoxib showed significantly lower C-RP levels ($P = 0.005$, t-test), **improved muscle strength** ($P = 0.002$, t-test) and body weight ($P=0.05$, t-test) than patients receiving fish oil + placebo.

The addition of celecoxib improved the control of the acute phase protein response, total body weight, and muscle strength.

Cancer-related anorexia/cachexia syndrome and oxidative stress: an innovative approach beyond current treatment

Giovanni Mantovani, Clelia Madeddu, Antonio Macciò, Giulia Gramignano, Maria Rita Lusso, Elena Massa, Giorgio Astara and Roberto Serpe

Department of Medical Oncology, University of Cagliari, Italy

Cancer Epidemiol Biomarkers and Prev 2004; 13:1651-1659 Cancer Epidemiol Biomarkers and Prev 2006; 15:1030-1034

Aim of the study was **to test the EFFICACY AND SAFETY**

-clinical response

- improvement of nutritional and functional variables
- changes of laboratory variables (as indicators of CACS/OS)
- and improvement of quality of life (QL).

of an integrated treatment based on diet, p.o. pharmaconutritional support, and drugs in a population of advanced cancer patients with CACS/OS.

The **ultimate goa**l of our study should be that of translating the results obtained on CACS/OS symptoms found in advanced cancer patients into a prevention trial in a population of individuals at risk of developing CACS/OS

The trial design was:

AN OPEN NON RANDOMIZED PHASE II STUDY

On the basis of the Simon two-stage design for phase II studies, the treatment has to be considered effective if at least 18/34 patients demonstrate a response in the first stage, while in the second stage

21/39 patients should demonstrate a response.

Mantovani G, et al Cancer Epidemiol, Biomarkers and Prev, 2004; 13:1651-9 and 2006;15:1030-4

Patient eligibility criteria

- **18 to 80 years old**
- **Histologically confirmed tumors of any site**
- **Patients with the following nutritional characteristics:**
  - ***1) patients who had lost at least 5% of ideal or pre-illness body weight in the last 3 months (clinical CACS);***
  - ***2) and/or with abnormal values of proinflammatory cytokines, ROS and antioxidant enzymes predictive of the onset of CACS.***
- **Patients with a life expectancy > 4 months.**

Patient exclusion criteria

- **Pregnancy**
- **Significant comorbidities**
- **Impaired food intake due to mechanical obstruction**
- **Medical treatments inducing significant changes of patient metabolism or body weight such as enteral or parenteral nutrition, corticosteroids, insulin.**

Patients could be treated with either antineoplastic therapy with palliative intent or supportive care

Treatment plan

On the basis of several of our previously published studies and our clinical experience we have developed an innovative approach which consists of an integrated nutritional and pharmacological treatment:

1. **Diet with high poliphenols content (400 mg) obtained by alimentary sources (onions, apples, oranges, red wine, or green tea) or supplemented by tablets per os;**
2. **Pharmaco-nutritional support enriched with n-3 PUFA containing EPA and DHA;**
3. **Oral progestagen: medroxyprogesterone acetate 500 mg/day;**
4. **Antioxidant treatment with alpha lipoic acid 300 mg/day + carboxycysteine lysine salt 2.7 g/day + vitamin E 400 mg/day + vitamin A 30000 IU + vitamin C 500 mg/day.**
5. **Selective COX-2 inhibitor: Celecoxib 200 mg/day orally**

The planned treatment duration is 16 weeks.

Mantovani G, et al Cancer Epidemiol, Biomarkers and Prev, 2004; 13:1651-9 and 2006;15:1030-4

RATIONALE FOR AGENT SELECTION

1. **The polyphenols, in particular quercetin have been included for their high activity as antioxidants.**
2. **The oral dietary supplement has the objective to integrate the energetic/proteic intake with the supplementation of n-3 PUFA, which are able to inhibit cytokine production (TNFa).**
3. **The treatment with medroxyprogesterone acetate has the objective to inhibit the cytokine production and to act positively on patients cenestesis: our previous experimental and clinical experience with MPA supports this choice.**
4. **The selected antioxidant treatment has been demonstrated effective in reducing blood levels of ROS and increasing blood levels of physiological antioxidant enzymes in a series of our published papers.**
5. **The COX-2 selective inhibitor Celecoxib has been chosen for its ability, demonstrated both in experimental and in clinical studies, to inhibit cancer-related inflammatory mediators (PGE2), angiogenesis and therefore cancer progression as well as CACS causal factors.**

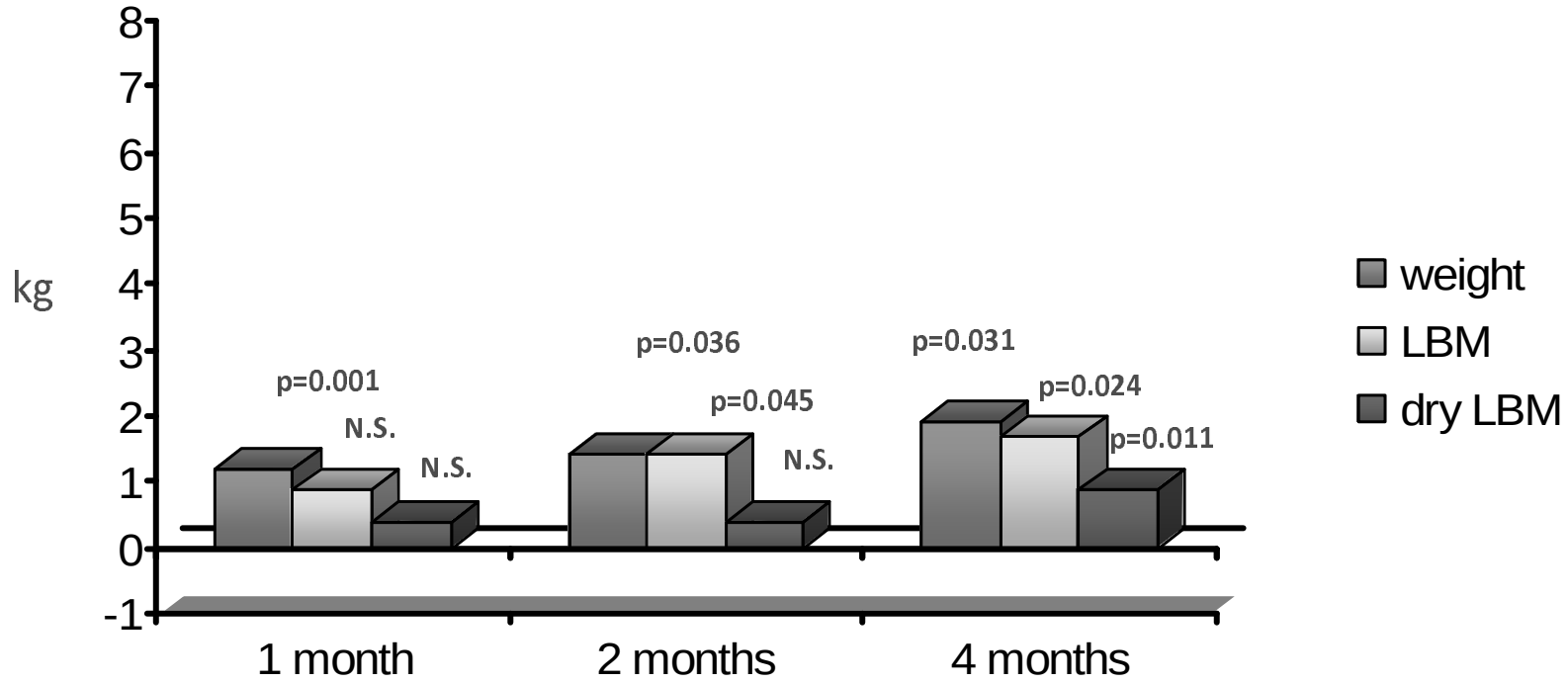
PATIENT CHARACTERISTICS

	N°	%
Patients evaluable	39	
M/F: 23/16		
Mean age 58.9 y, range 42-78		
Mean weight 55.8 kgs, range 36-76		
Body mass index (weight in kg/height in m^2)		
<18.5	9	23.1
18.5-25	25	64.1
>25	5	12.8
Stage		
IIIA	1	2.6
IV	38	97.4
Performance Status (ECOG)		
ECOG 0	2	5.1
ECOG 1	27	69.2
ECOG 2	10	25.7

Mantovani G, et al Cancer Epidemiol, Biomarkers and Prev, 2004, 13:1651-9 and 2006,15:1030-4

Body weight and lean body mass (LBM) changes after 1, 2 and 4 months of treatment

39 patients were evaluable after 1 , 2 and 4 months of treatment

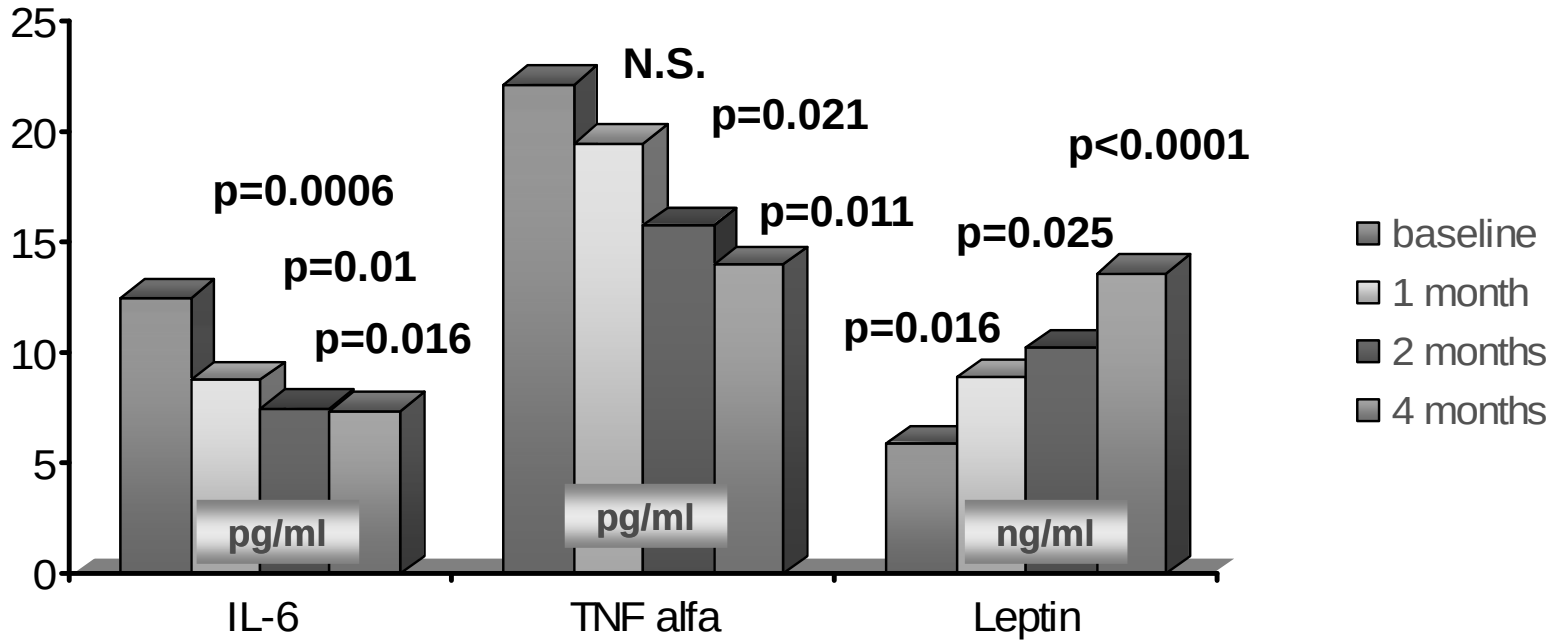


Bars represent the mean increase in comparison to baseline (0). Significance was evaluated by Student' s t - test for paired data. N.S., not significant

Mantovani G, et al Cancer Epidemiol, Biomarkers and Prev, 2004; 13:1651-9 and 2006;15:1030-4

Proinflammatory cytokines and leptin before and after 1, 2 and 4 months of treatment

39 patients were evaluable after 1 , 2 and 4 months of treatment



Results are expressed as mean values. Significance was calculated by Student' t test for paired data. N.S. non significant

Mantovani G, et al Cancer Epidemiol, Biomarkers and Prev, 2004; 13:1651-9 and 2006;15:1030-4

EVALUATION OF APPETITE AND QUALITY OF LIFE AFTER 1 , 2 AND 4 MONTHS OF TREATMENT

Questionnaire	baseline	1 month	2 months	4 months
VAS-APPETITE	5.5± 2.5	6.6 ± 2.2*	6.8 ± 1.9*	7.0 ± 1.6*
EORTC-QLQ C30	66 ± 16.4	72.4 ± 15.6*	71.8± 14.6*	70.9 ± 14.6*
EQ-5D index	0.50 ± 0.4	0.58 ± 0.4	0.56 ± 0.4	0.59 ± 0.4
EQ-5D vas	49.4 ± 21.4	58.9 ± 22.7*	58.6± 20.6*	58.7± 19.4 *
MFSI-SF	20.1 ± 22.1	14.4 ±20.3	11.8 ± 17.2*	10.8 ± 14.4*

Results are expressed as mean score ± SD. Significance was calculated in comparison to baseline by Student's t-test for paired data. * $p<0.05$

Mantovani G, et al Cancer Epidemiol, Biomarkers and Prev, 2004, 13:1651-9 and 2006,15:1030-4

ASSESSMENT OF "RESPONDERS" AND "NON RESPONDERS"

The conclusive analysis on 39 patients who completed the treatment showed
17 patients "responders"
and **5 "high responders"**
According to the Simon's design, 22/39 "responders" patients demonstrated the efficacy of treatment.

In conclusion, the treatment has demonstrated to be **EFFECTIVE** as for:

increase of body weight
- **increase of lean body mass**
- decrease of proinflammatory cytokines
- improvement of quality of life parameters
- amelioration of fatigue symptom

The treatment has demonstrated to be **SAFE** with good compliance of patients.

Mantovani G, et al Cancer Epidemiol, Biomarkers and Prev, 2004, 13:1651-9 and 2006,15:1030-4

ELSEVIER

Nutrition 24 (2008) 305–313

NUTRITION

www.elsevier.com/locate/nut

Applied nutritional investigation

Randomized phase III clinical trial of five different arms of treatment for patients with cancer cachexia: interim results

Giovanni Mantovani, M.D.[a,*], Antonio Macciò, M.D.[a], Clelia Madeddu, M.D.[a], Giulia Gramignano, M.D.[a], Roberto Serpe, B.Sc.[a], Elena Massa, M.D.[a], Mariele Dessì, M.D.[a], Francesca Maria Tanca, M.D.[a], Eleonora Sanna, M.D.[a], Laura Deiana, M.D.[a], Filomena Panzone, M.D.[a], Paolo Contu, M.D.[b], and Carlo Floris, M.D.[c]

[a] *Department of Medical Oncology, University of Cagliari, Cagliari, Italy*
[b] *Department of Hygiene and Public Health, University of Cagliari, Cagliari, Italy*
[c] *Division of Medical Oncology 2, Ospedale Oncologico Regionale "Businco", Cagliari, Italy*

Manuscript received April 24, 2007; accepted December 13, 2007.

AIM OF THE STUDY:

to establish which was the most effective and safest treatment able to improve the identified "key" variables (primary endpoints) of CACS/OS: increase of LBM, decrease of REE, increase of total daily physical activity, decrease of IL-6 and TNF-alpha and improvement of fatigue.
Eligibility and exclusion criteria are the same of the phase II study

TREATMENT PLAN

All patients included in the study were given as basic treatment:

poliphenols (300 mg/day) obtained from alimentary sources (onions, apples, oranges, red wine 150 ml, green tea) or supplemented by tablets (Quercetix, Elbea Pharma, 1 tablet 300 mg/day) + antioxidant agents alpha lipoic acid 300 mg/day (included in the Quercetix tablet) + carbocysteine 2.7 g/day (Fluifort, Dompè, 1 sachet/day) + Vitamin E 400 mg /day (Sursum, Abiogen, 1 tablet/day) + Vitamin A 30000 IU and Vitamin C 500 mg/day (Trocaflu, Laborest, 2 sachets/day), all orally.

Patients were then randomised to one of the following 5 arms of treatment:

Arm 1. Medroxyprogesterone acetate (MPA) 500 or Megestrol Acetate (MA) 320mg/day.

Arm 2. Pharmaco-nutritional support containing EPA, 2-3 cartons/day

Arm 3. L-carnitine 4 g/day.

Arm 4. Thalidomide 200 mg/day

Arm 5. MPA or MA + Pharmaco-nutritional support + L-carnitine + Thalidomide

The planned treatment duration is 16 weeks.

RATIONALE FOR AGENT SELECTION

L-carnitine is crucial for cell energy metabolism. It was found to be effective in improving fatigue as well as appetite and LBM in one of our recently published studies (Gramigano G et al, Nutrition. 2006 22:136-45).

Thalidomide has multiple immunomodulatory and antiinflammatory properties; its inhibitory effect on TNF-alpha and IL-6 production may be responsible for its anticachectic activity.

PRIMARY EFFICACY ENDPOINTS

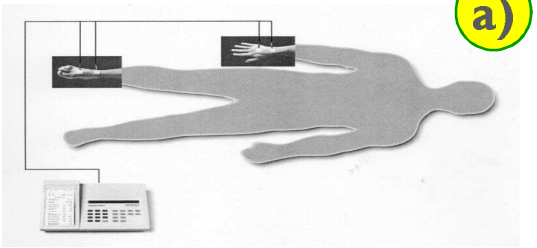
Nutritional/Functional:

- lean body mass by bioimpedentiometry (a) and DEXA (b);

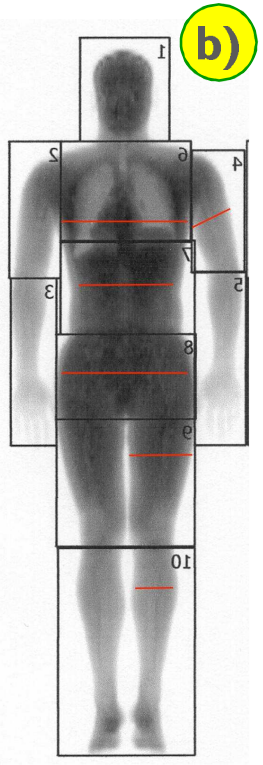
-resting energy expenditure by

indirect calorimetry (c)

a)



b)



c)

d)

- total daily physical activity and related energy expenditure (d)

Laboratory: - proinflammatory cytokines IL-6 and TNFalpha;

Quality of Life: - fatigue assessed by Multidimensional Fatigue Symptom Inventory Short Form (MFSI-SF)

STATISTICAL ANALYSIS

- Hypothesizing a difference between arms of 20%, considering an alpha type error of 0.05 and a beta type error of 0.20, 95 patients will be enrolled for each arm for a total of 475 patients.
- The efficacy for the primary endpoints of each arm versus the other ones will be made comparing the arms by the ANOVA t-test for repeated measures for the "key variables".
- Moreover, benefits obtained by the patients enrolled in each arm will be evaluated using the paired Student's t test.
- Survival (overall survival and progression-free survival) will be evaluated starting from the date of enrollment in the study using the Kaplan-Meier method.

Interim analyses were planned every 100 randomized patients to test the efficacy (primary efficacy endpoints) and the toxicity of the different arms of treatment

INTERIM ANALYSIS – January 2007

A first interim analysis was carried out on 125 patients. The ANOVA test comparing the different treatment arms (for changes between baseline and post- treatment values) showed::

- a significant improvement of REE score in favor of arm 5 versus arm 2;
- a significant improvement of MFSI-SF score in favor of arm 1, 3 and 5 versus arm 2.

A significant difference (worsening of the primary endpoints LBM, REE and MFSI-SF) of arm 2 versus arms 3, 4 and 5 was observed on the basis of the t-test for changes.

Consequently, arm 2 was withdrawn from the study.

INTERIM ANALYSIS – October 2007

PRIMARY EFFICACY ENDPOINTS

The interim analysis after the enrollment of 204 patients showed :

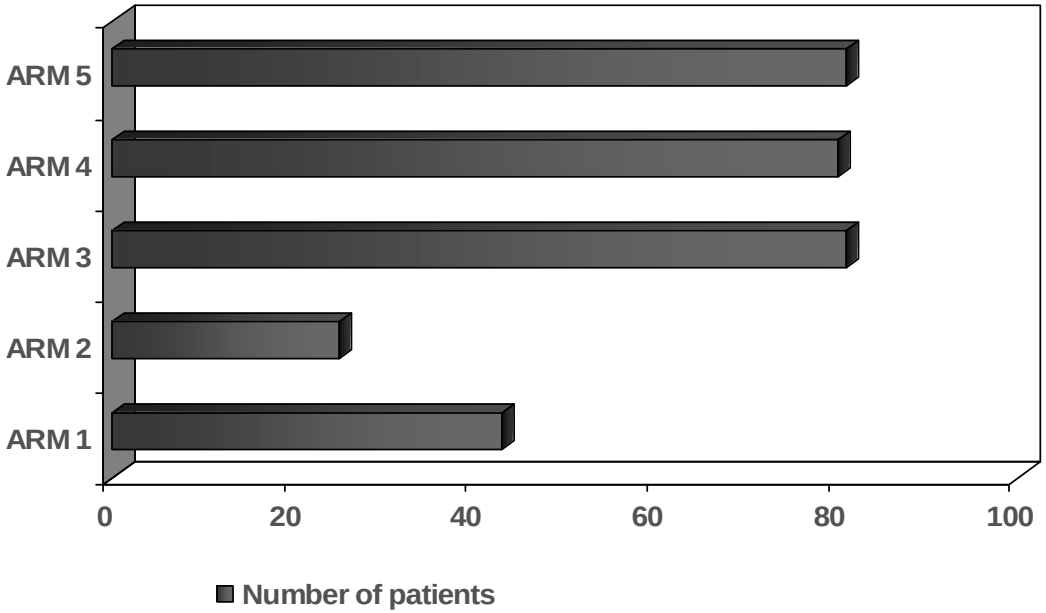
- a significant improvement of fatigue in arm 3 and 5
- a significant decrease of IL-6 in favor of arm 3
- a significant decrease of TNF alpha in favor of arm 3

The interim analysis showed that arm 1 is inferior to the others as for primary efficacy endpoints.

Consequently, arm 1 was withdrawn from the study

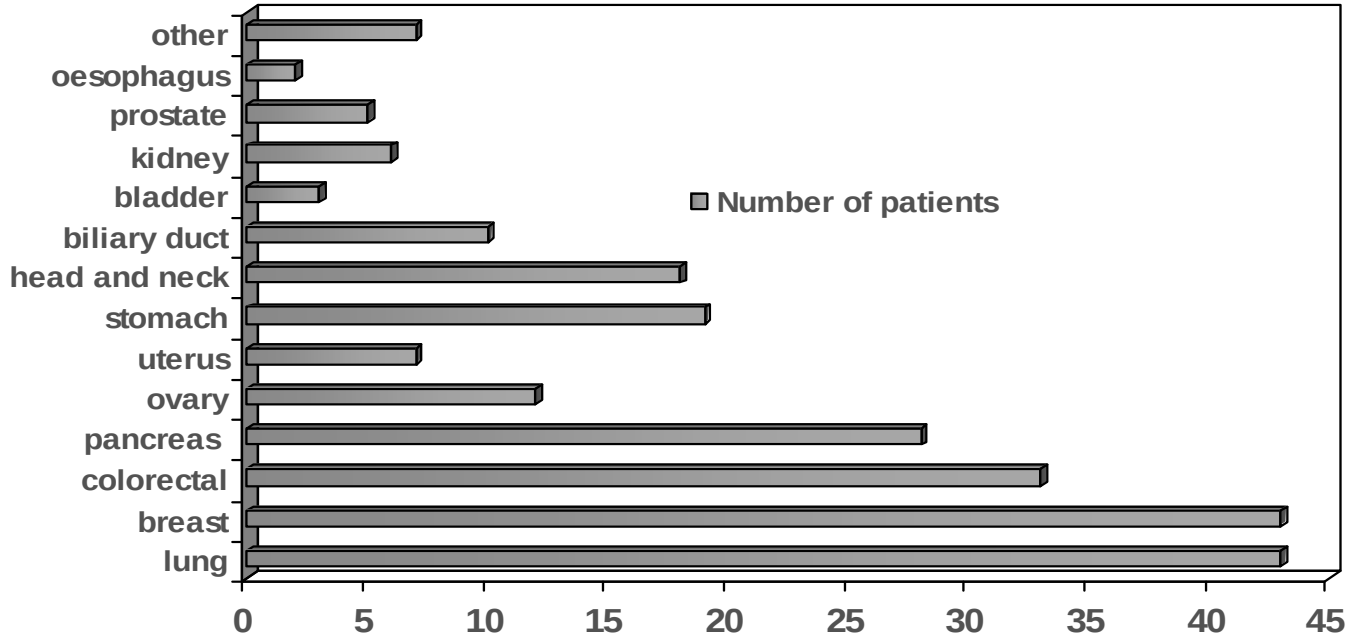
Patient characteristics

	No.	%
Patients enrolled from April 2005 to February 2009	**332**	
Patients evaluable	**287**	
M/F: 168/119		
Mean age 62.4 y, range 30-84		
Mean weight 56.4 kgs, range 34-90		
Body mass index (kg/m^2)		
<18.5	**54**	**18.8**
18.5-25	**209**	**72.8**
>25	**24**	**8.4**
Stage		
III	**13**	**4.5**
IV	**274**	**95.5**
Performance Status (ECOG)		
ECOG 0	**9**	**3.1**
ECOG 1	**146**	**50.9**
ECOG 2	**118**	**41.1**
ECOG 3	**14**	**4.9**

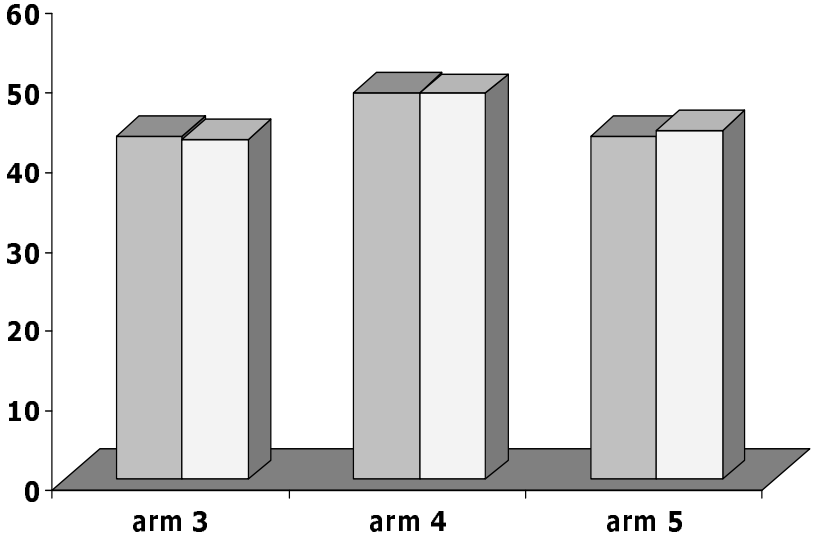


Randomization

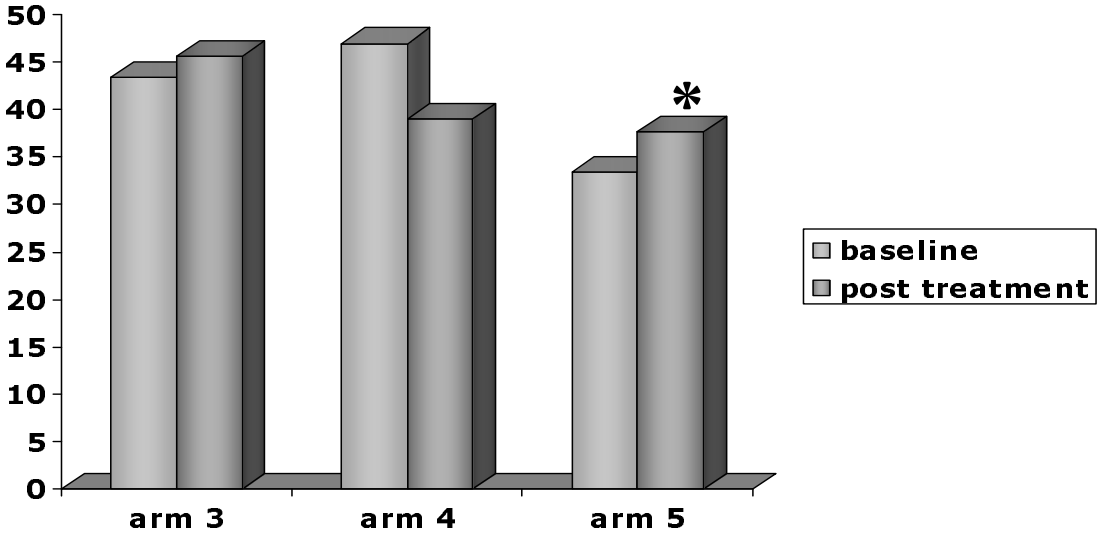
Patient characteristics: tumor sites



Results update-February 2009
Changes of LBM by arm of treatment

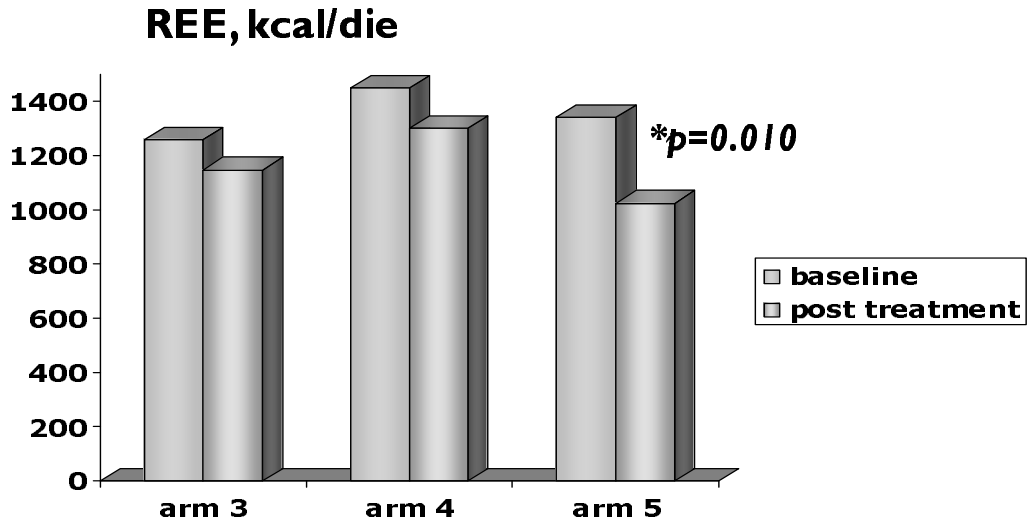


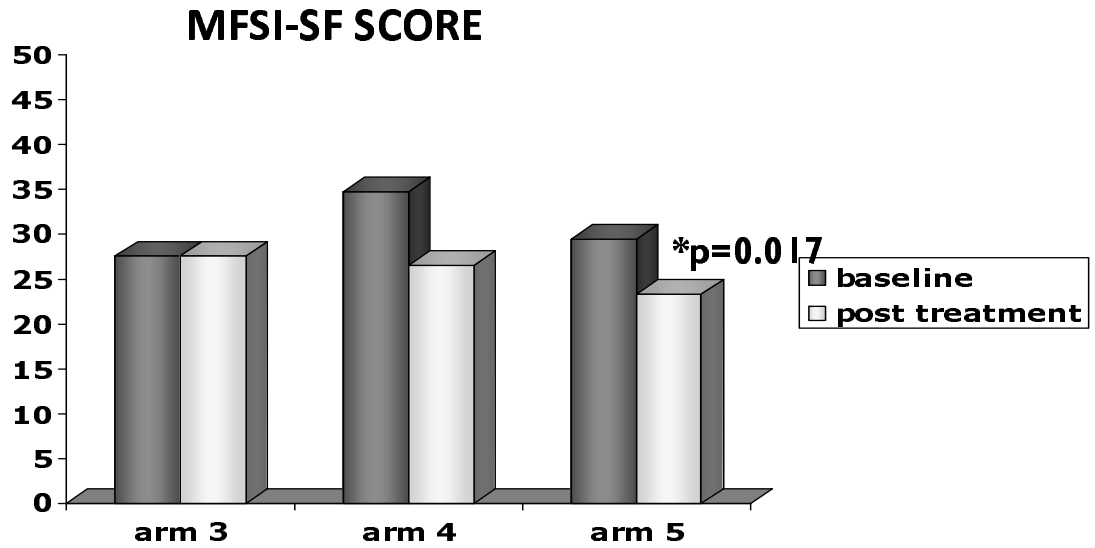
Lean body mass (kg) by BIA did not show a significant difference in any arm of treatment



LBM by DEXA (97 patients) showed a significant improvement only in arm 5.
* $p<0.05$

Results update-February 2009
Changes of REE and Fatigue (MFSI-SF) by arm of treatment
No. 287 patients

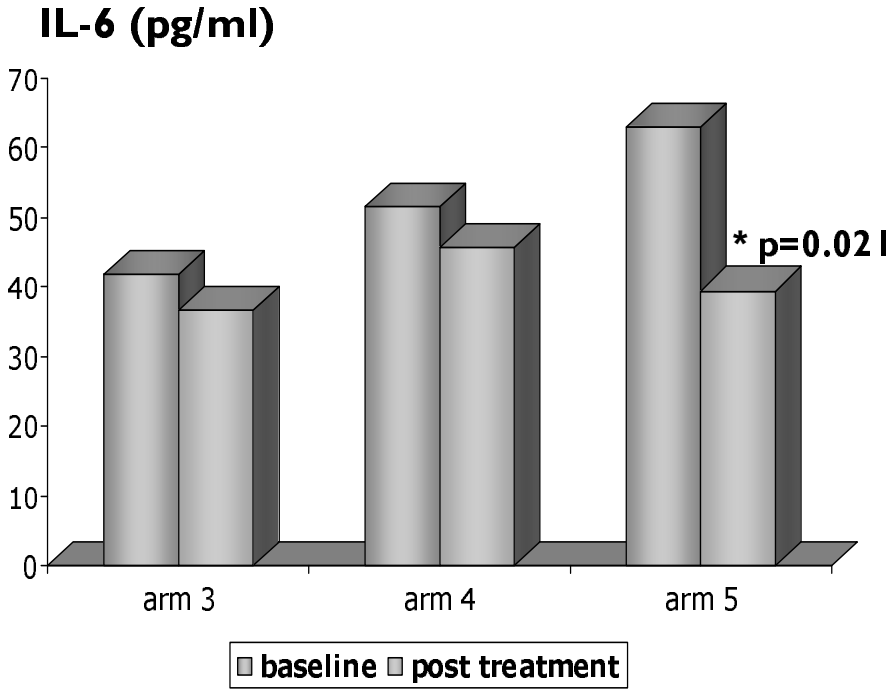


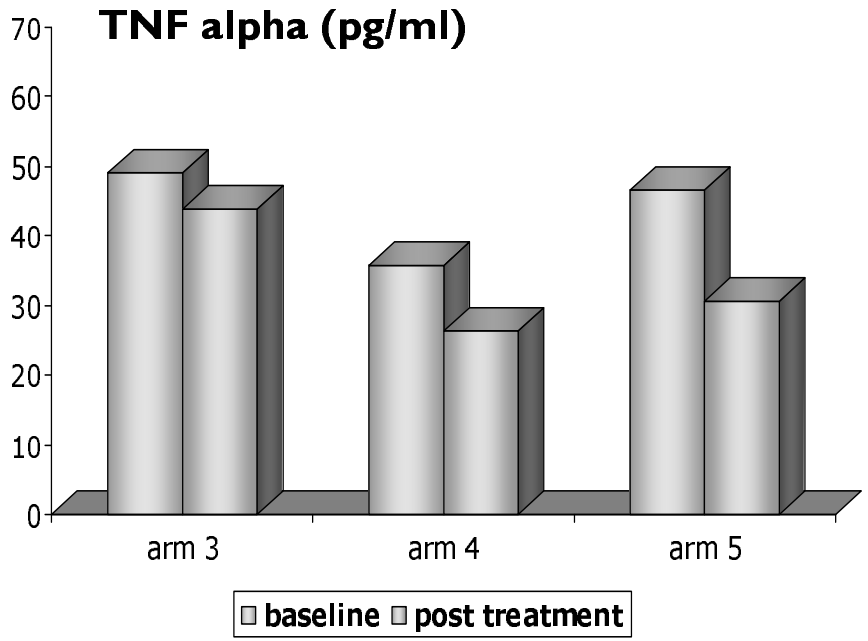


Patients in arm 5 showed a significant decrease of resting energy expenditure assessed by indirect calorimetry and fatigue assessed by MFSI- SF score.

*p<0.05 versus baseline.

Results update- February 2009
Changes of IL-6 and TNF-alpha by arm of treatment
No. 287 patients





IL-6 decreased significantly in arm 5

***p<0.05 post-treatment values vs pre-treatment values.**

CONCLUSION

The interim results seem to suggest that the most effective treatment for cancer patients with CACS/OS is the combination regimen (arm 5).

The study is still in progress.

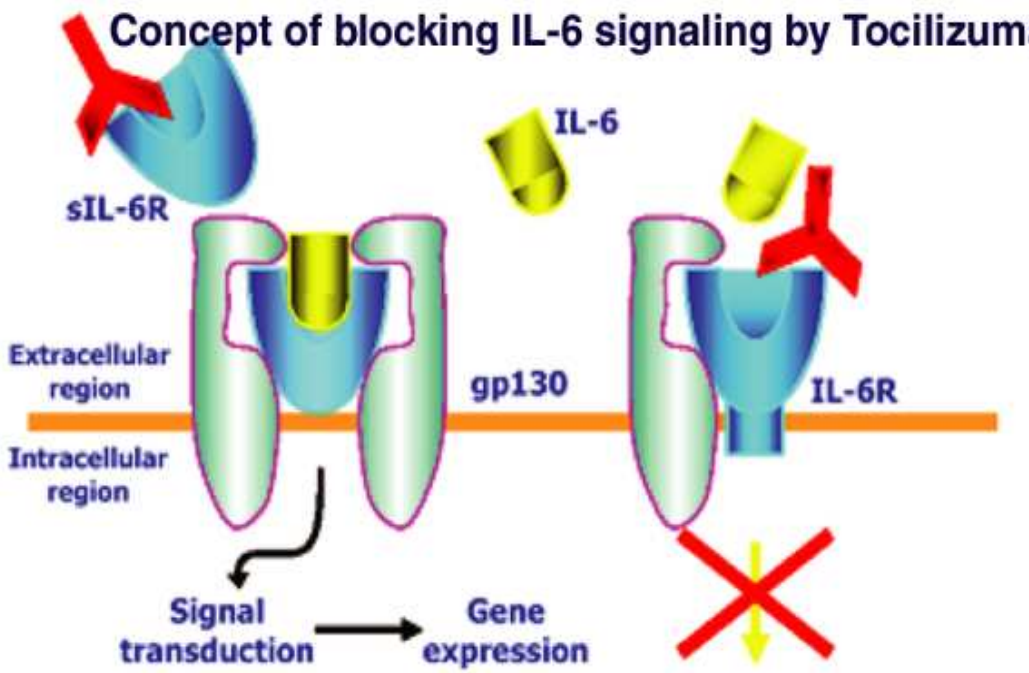
The final results are expected in June 2009

FUTURE TRENDS

Presently there is not a consolidated treatment for cancer cachexia.
As progestagens and corticosteroids are obsolete drugs and considering that anti-TNF-alpha monoclonal antibody (infliximab) was shown to be ineffective, research interest is currently shifting towards the use of different approaches addressing the potential targets involved in the pathophysiology of cachexia

Current new trends include

ANTI-IL-6 HUMANIZED MONOCLONAL ANTIBODY



In murine models IL-6 antagonists appear to inhibit cancer cachexia

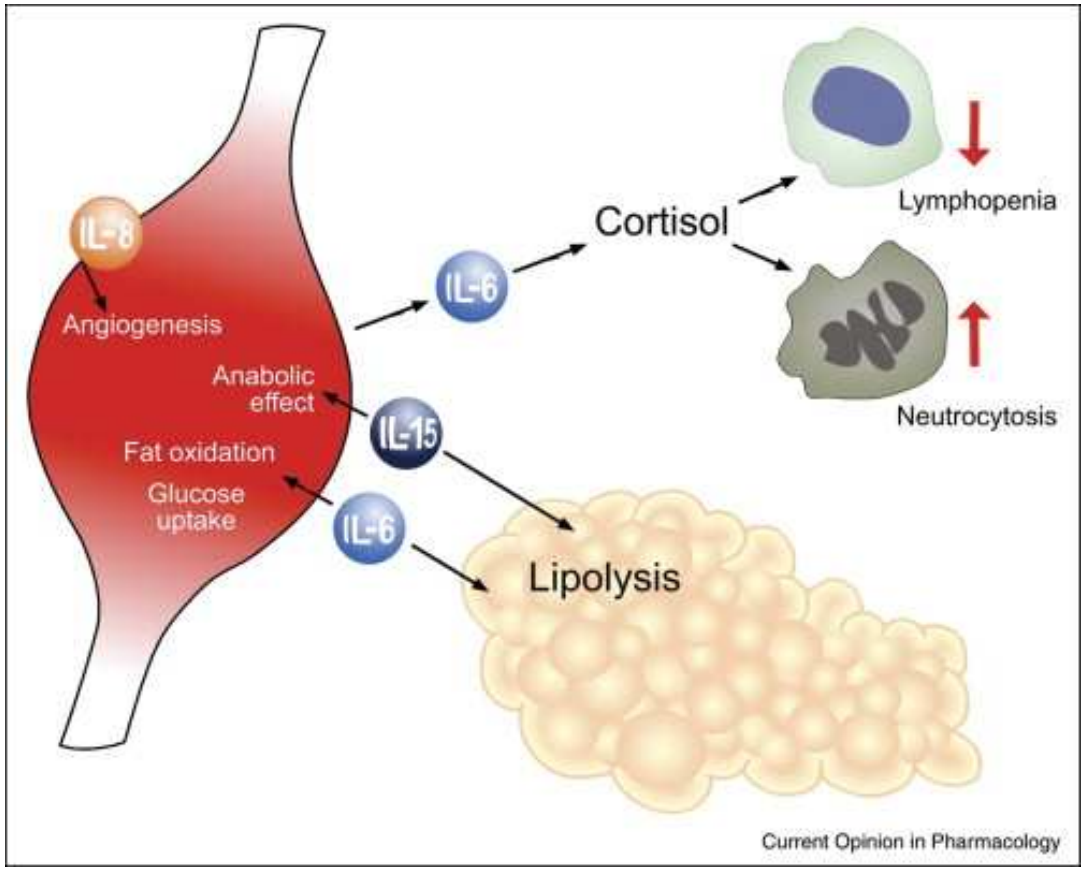
Trikha M, Corringham R, Klein B, Rossi JF. Clin Cancer Res. 2003; 9:4653-65

Interleukin-15 is able to suppress the increased DNA fragmentation associated with muscle wasting in tumour-bearing rats

Figueras M, et al. FEBS Lett. 2004 Jul 2;569(1-3):201-6

A schematic representation of anabolic effects of interleukin-15

From Current Opinion in Pharmacology 2008; 8: 346-351

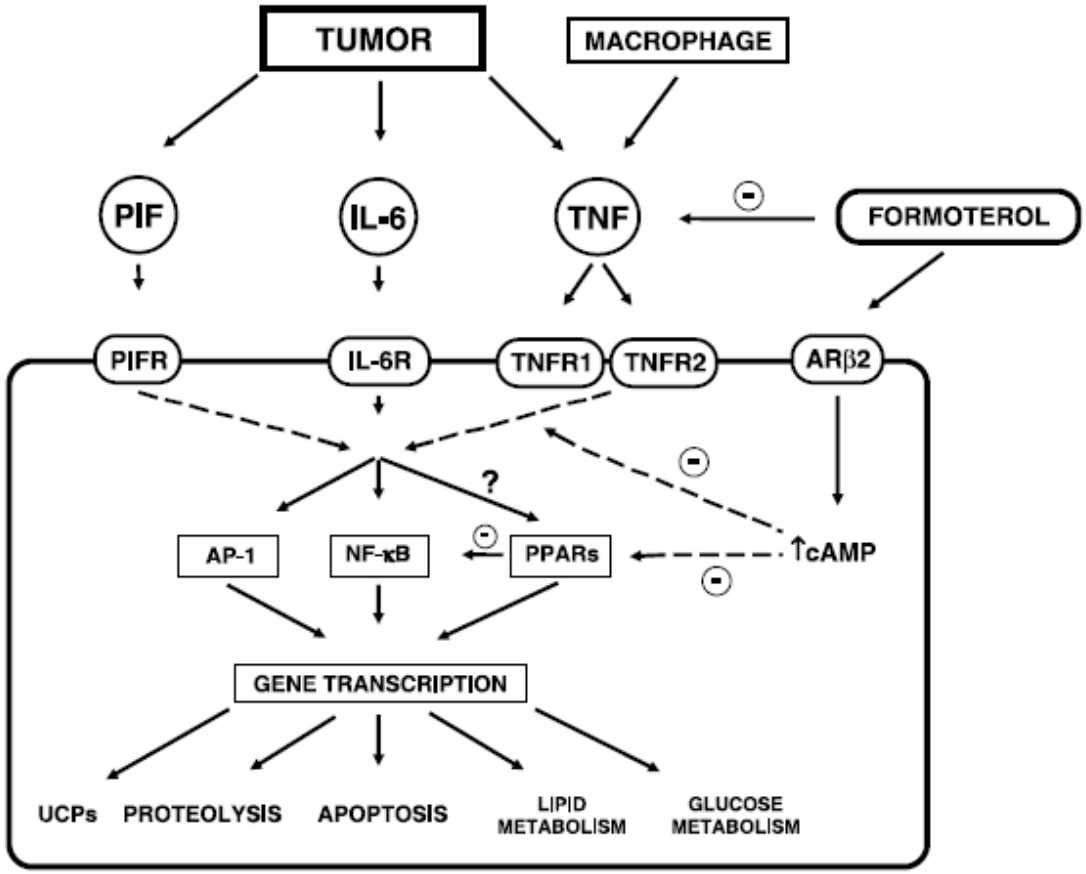


Interleukin (IL)-15, a cytokine expressed in skeletal muscle, has been shown to have muscle anabolic effects in vitro and to slow muscle wasting in rats with cancer cachexia.

Harcourt LJ, et al. Am J Pathol. 2005 ;166:1131-41

Are Peroxisome Proliferator-Activated Receptors Involved in Skeletal Muscle Wasting during Experimental Cancer Cachexia? Role of β_2-Adrenergic Agonists

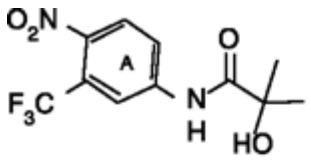
Gemma Fuster, Sílvia Busquets, Elisabet Ametller, Mireia Olivan, Vanessa Almendro, Cibely Cristine Fontes de Oliveira, Maite Figueras, Francisco J. López-Soriano, and Josep M. Argilés



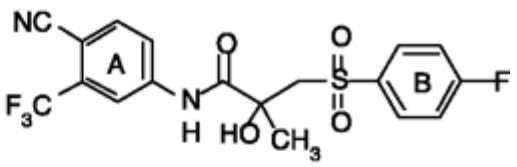
Formoterol, a β2-adrenergic agonist, is a very efficient agent preventing muscle weight loss in tumor-bearing rats

Current new trends include

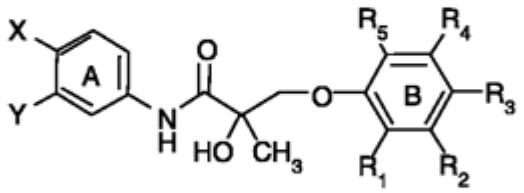
NON STEROIDAL SELECTIVE ANDROGEN RECEPTOR MODULATORS (SARMS)



Hydroxyflutamide



Bicalutamide



Aryl Propionamide Ligands

X = NO_2 / CN / Halogen, etc.
Y = CH_3 / Halogen, etc.
R_1 ~ R_5 = H / Halogen etc.

Recently, several promising androgen analogues have been developed, as potential selective androgen receptor modulators (SARMs), which claim to preferentially act on skeletal muscle.
They bind to the androgen receptor (AR) with high affinity and exert strong pharmacological activity in selective tissues. However, the mechanism for this selectivity is not well understood.

In cellular and animal models, androgen activated AR modulates myoblasts proliferation, promotes sexual dimorphic muscle development, and alters muscle fiber type. In the clinical setting, administration of anabolic androgens can decrease cachexia and speed wound healing.

Ostarine increases lean body mass and improves physical performance in healthy elderly subjects: Implications for cancer cachexia patients.

Evans W, et al. Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 9119

A new class of non-steroidal selective androgen receptor modulators (SARMs) is being developed for use in cancer cachexia.

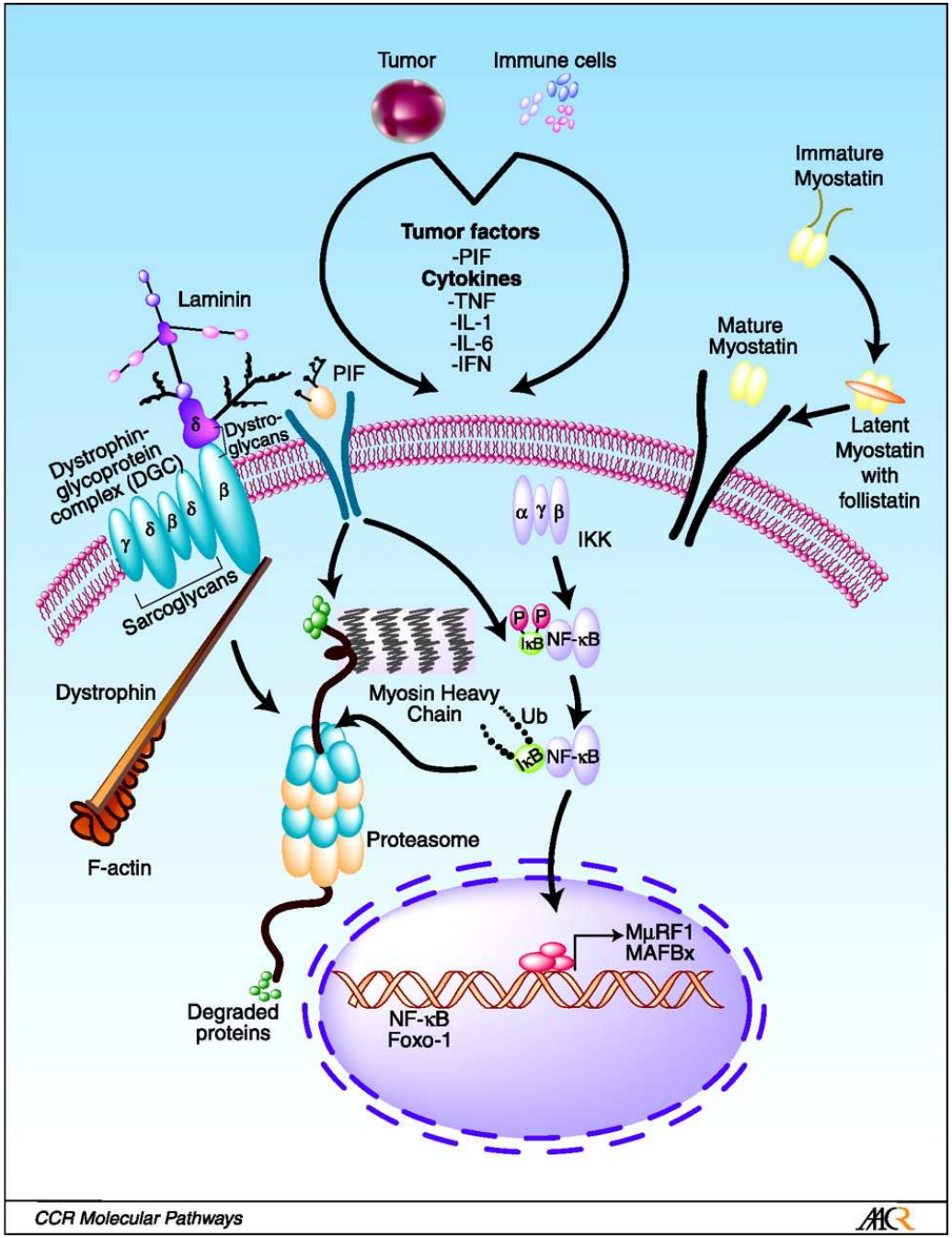
SARMs are designed to have predominately anabolic activity in muscle and bone with minimal androgenic effects in most other tissues.

We conducted a randomized phase II proof of concept study of ostarine, the first-in-class SARM, in healthy postmenopausal women and elderly men prior to intitiating a phase II study in cancer patients.

Methods: **Sixty elderly men (mean age 66 years) and 60 postmenopausal women (mean age 63 years) were randomly assigned to ostarine 0.1, 0.3, 1 mg, 3 mg or placebo for three months. The primary end point was change from baseline to three months in total lean body mass (LBM) measured by dual energy x-ray absorptiometry (DXA).**

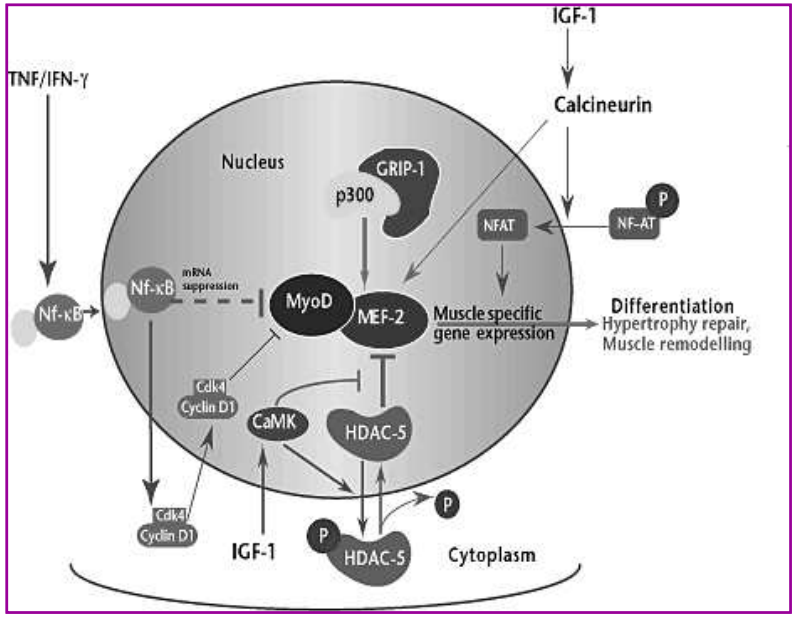
Conclusions: **Ostarine improves LBM and physical performance in healthy older men and women. Ostarine had no unwanted androgenic side effects. A phase II study is planned to evaluate the safety and efficacy of ostarine in patients with cancer cachexia.**

Emerging signaling pathways in cancer cachexia



❑ ANTI MYOSTATIN

Myostatin has been implicated in several forms of muscle wasting, including cancer cachexia. Anti-myostatin strategies are, therefore, promising and should be considered in future clinical trials involving cachectic patients

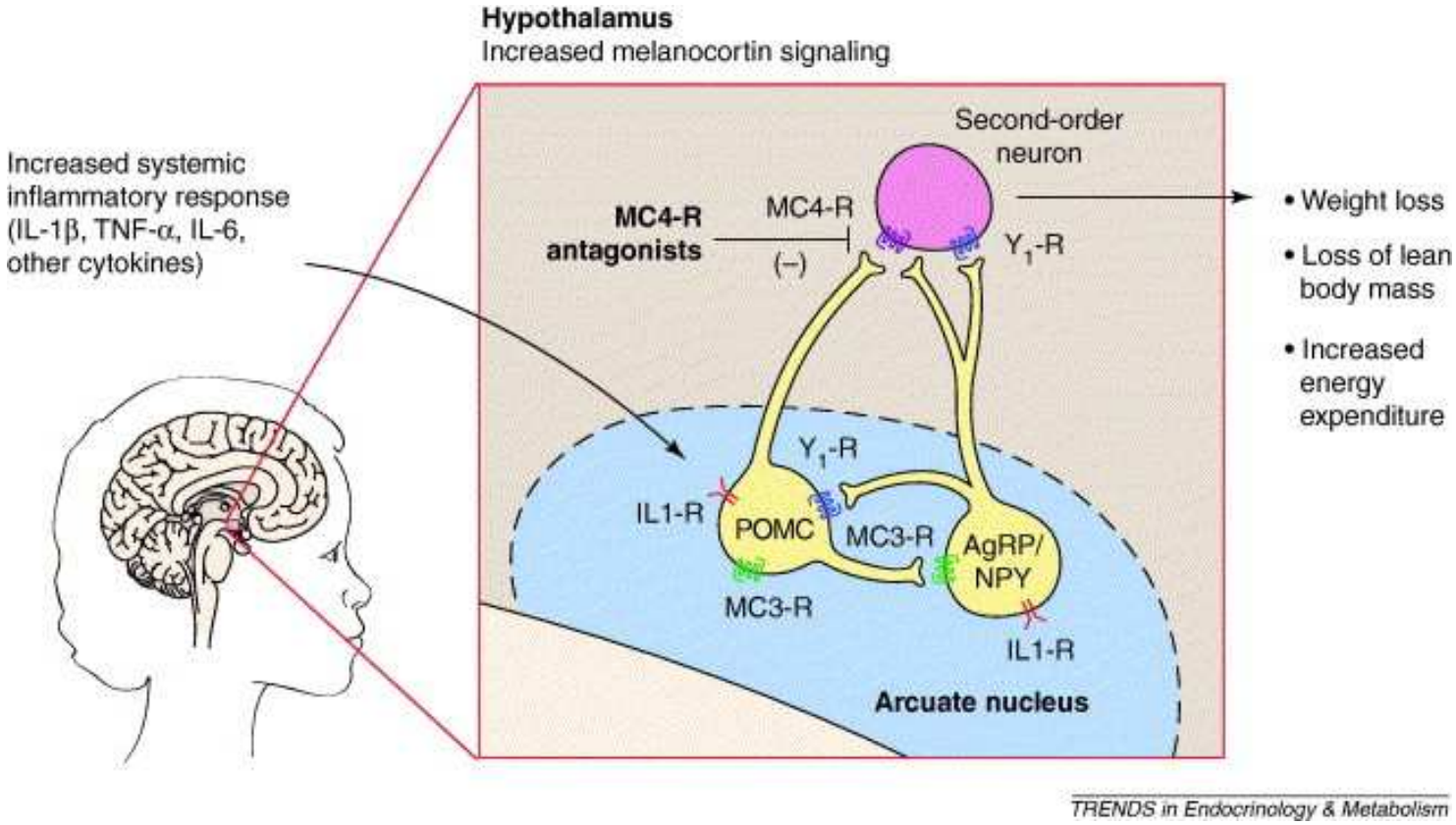


Clinical Cancer Research 13; 1356-1361, 2007

MELANOCORTIN RECEPTOR ANTAGONISTS

AS POTENTIAL THERAPEUTICS IN CANCER CACHEXIA

Foster AC, et al. Current Topics in Medicinal Chemistry, 2007, *7,* 1147-1152



Recent experiments have shown that blockade of melanocortin signaling using antagonists to the melanocortin MC4 receptor attenuates disease-associated anorexia and wasting in rodent models of cancer and renal failure.

DeBoer MD and Marks DL. Trends in Endocrinology and Metabolism 2006; 17:199-204

Why is progress in treatment of cancer cachexia so slow?

Kathryn Senior, Lancet Oncology 2007; 8:671-672

"In the last decade, very little progress has been made towards treating a condition that leads directly to 30% of cancer deaths and affects half of all cancer patients during the course of their disease", Thomas Adrian

"At present there is no agreed management for cachexia… indeed there is no internationally agreed definition of cachexia", Ken Fearon

"Although patients and families care a great deal about the impact of cachexia, the oncology profession seemingly does not respond." Ian Mc Donald

"I do not know of any FDA approved drugs for cancer cachexia", Marion Couch.

Biomarkers for cancer cachexia: is there also a genetic component to cachexia?

B. H. L. Tan · D. A. C. Deans · R. J. E. Skipworth · J. A. Ross · K. C. H. Fearon

Support Care Cancer (2008) 16:229–234

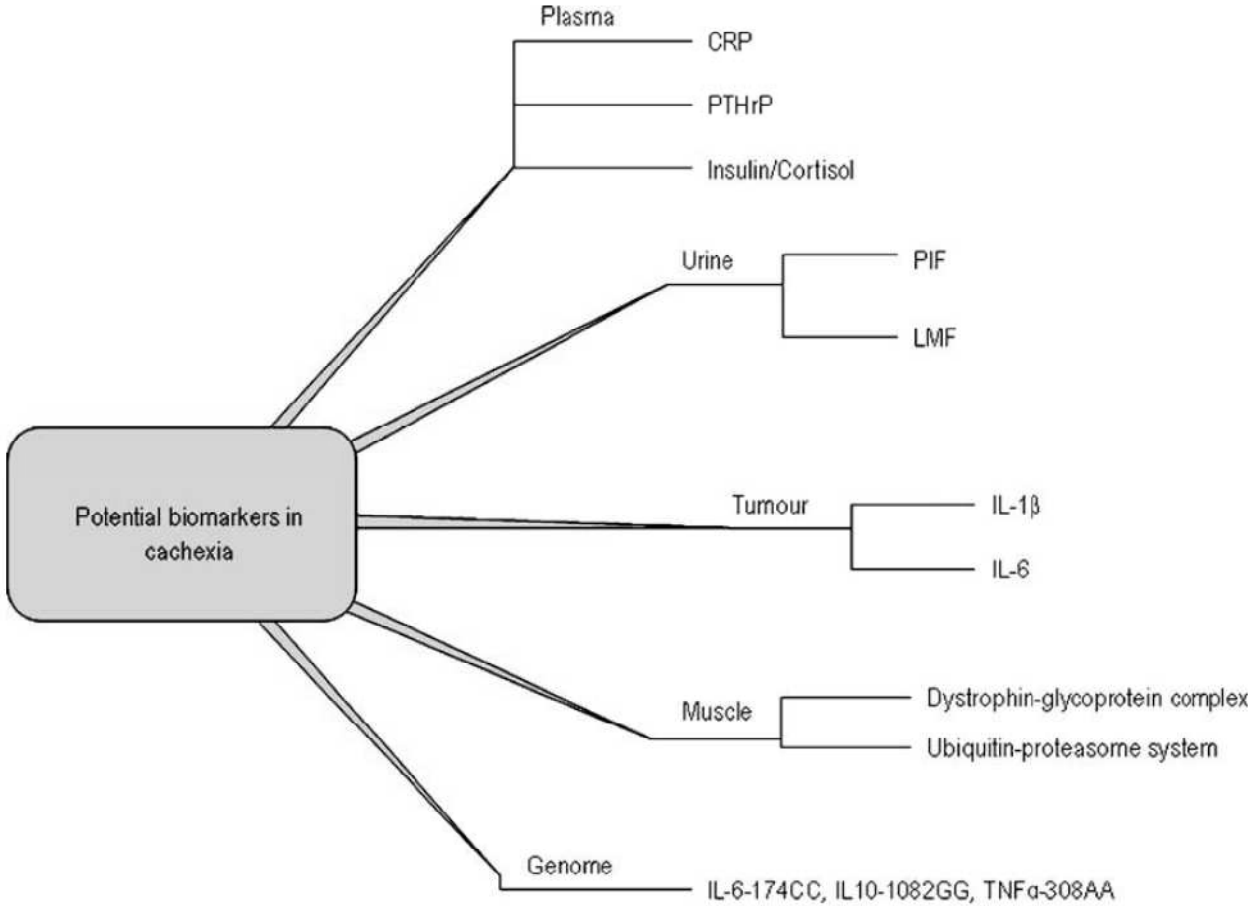


Fig. 1 Potential biomarkers for the development of cancer cachexia

Predictive or early biomarkers of cachexia could be developed, which would aid in the selection of patients for early therapeutic intervention.

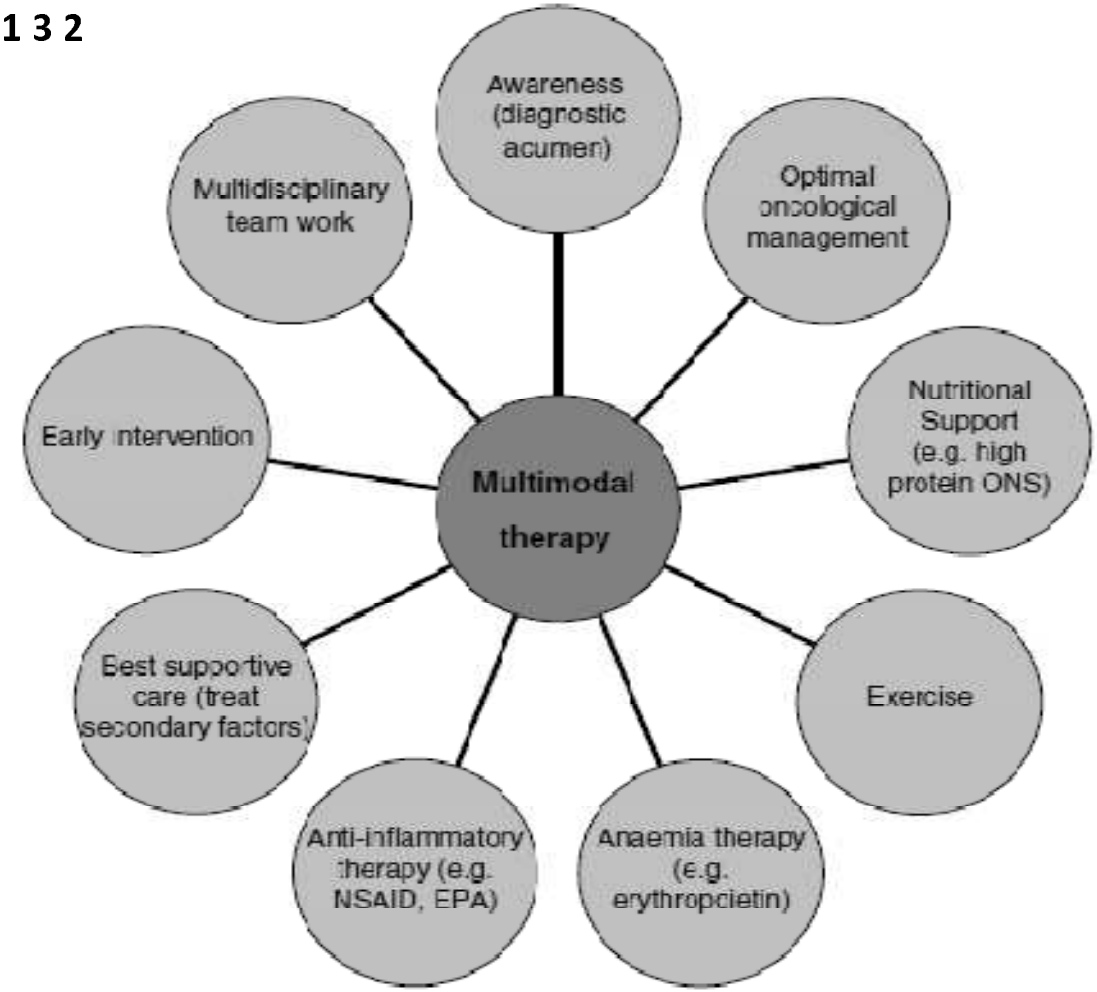
Cancer cachexia: Developing multimodal therapy for a multidimensional problem

K.C.H. Fearon*

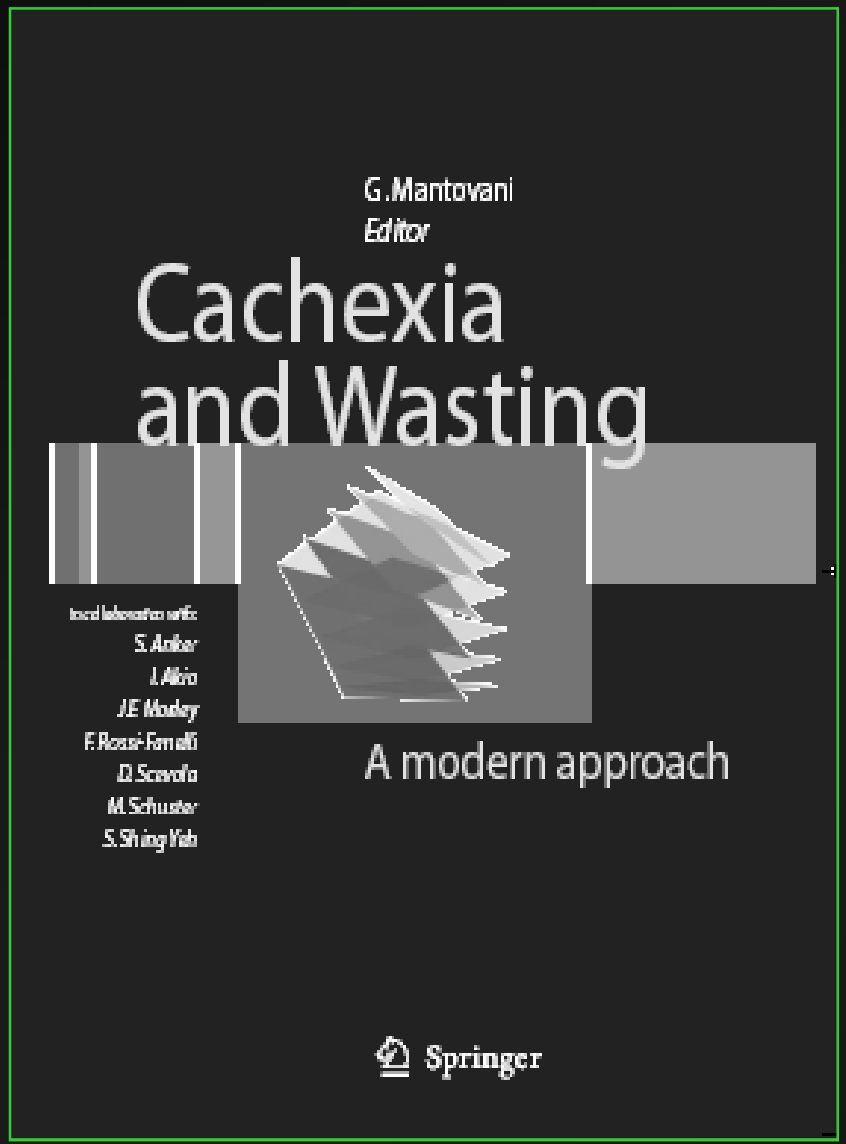
Eur J Cancer 2008; 44: 1124–1132

Multimodal approaches that address these key issues can stabilise and even improve the nutritional status, function and quality of life of at least a proportion of advanced cancer patients.

The current evidence-base justifies new enthusiasm for the design of complex intervention studies in the management of cancer cachexia.



Cachexia and Wasting. A modern approach. Springer, July 2006



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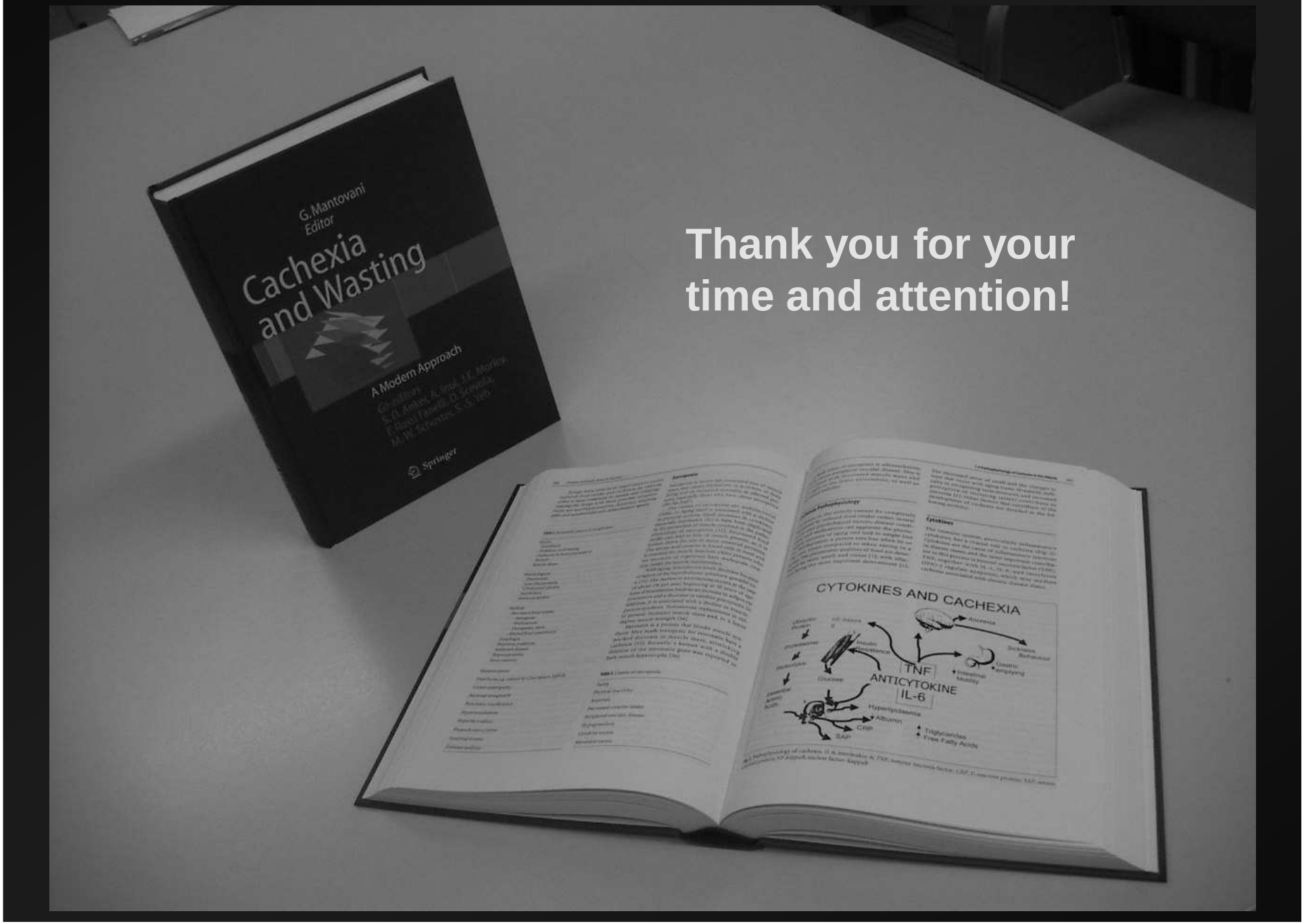

Thank you for your time and attention!

Thank you for your attention!

University Hospital
Chair of Medical Oncology
University of Cagliari - Italy

Prof. Giovanni Mantovani

and

Dr. Clelia Madeddu, M.D.
Dr. Elena Massa, M.D.
Dr. Giorgio Astara, M.D.
Dr. Mariele Dessì, M.D.
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Dr. Federica Saba, M.D.
Dr. Valeria Cherchi, M.D.
Dr. Filomena Panzone, M.D.
Dr. Antonino Zarzana, M.D.
Dr. Laura Spano, M.D.