USZ Universitäts Spital Zürich

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Stadtspital Zürich

Malnutrition/Anorexia/Cachexia Sarcopenia/Fatigue…

David Blum

Overview

- Cancer Cachexia
- Treatment Principles
- Multimodal Treatment, MENAC: Results from ASCO
- New agents: Olanzapine, Mirtazapine, Cannabinoids?
- Palliation in Cachexia

Cancer-Cachexia

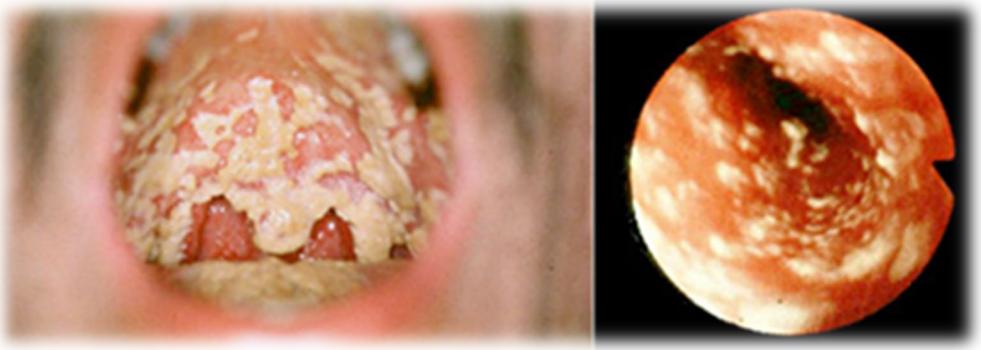
- A devastating syndrome characterized by anorexia, reduced nutritional intake, and systemic inflammation
- It leads to impaired function, worsened treatment response, poor quality of life, and shortened survival
- Overlap with other syndromes like malnutrition, sarcopenia, frailty, and asthenia
- No single agent treatment!

Importance of Early Screening

- Regularly assess symptoms and measure and record body weight, asses appetite and intake
- Weight loss is a predominant marker of cachexia
- Prevalence in various cancer types

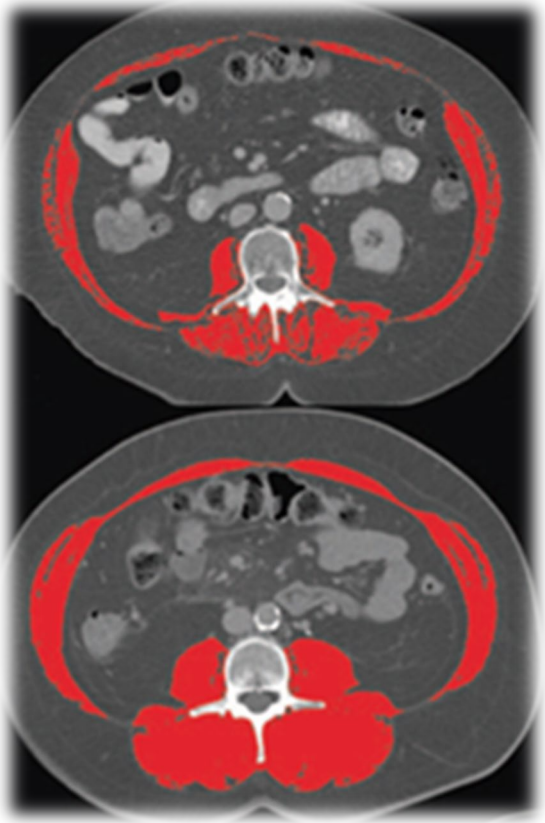
Proactive Treatment in High-Risk Cancers

- Starting interventions early in high-risk groups
- Goal to maintain or gain muscle mass
- Treat S-NIS like nausea, stomatitis, and pain



Sarcopenia in Cachexia

- Methods for early identification,
- including CT scans

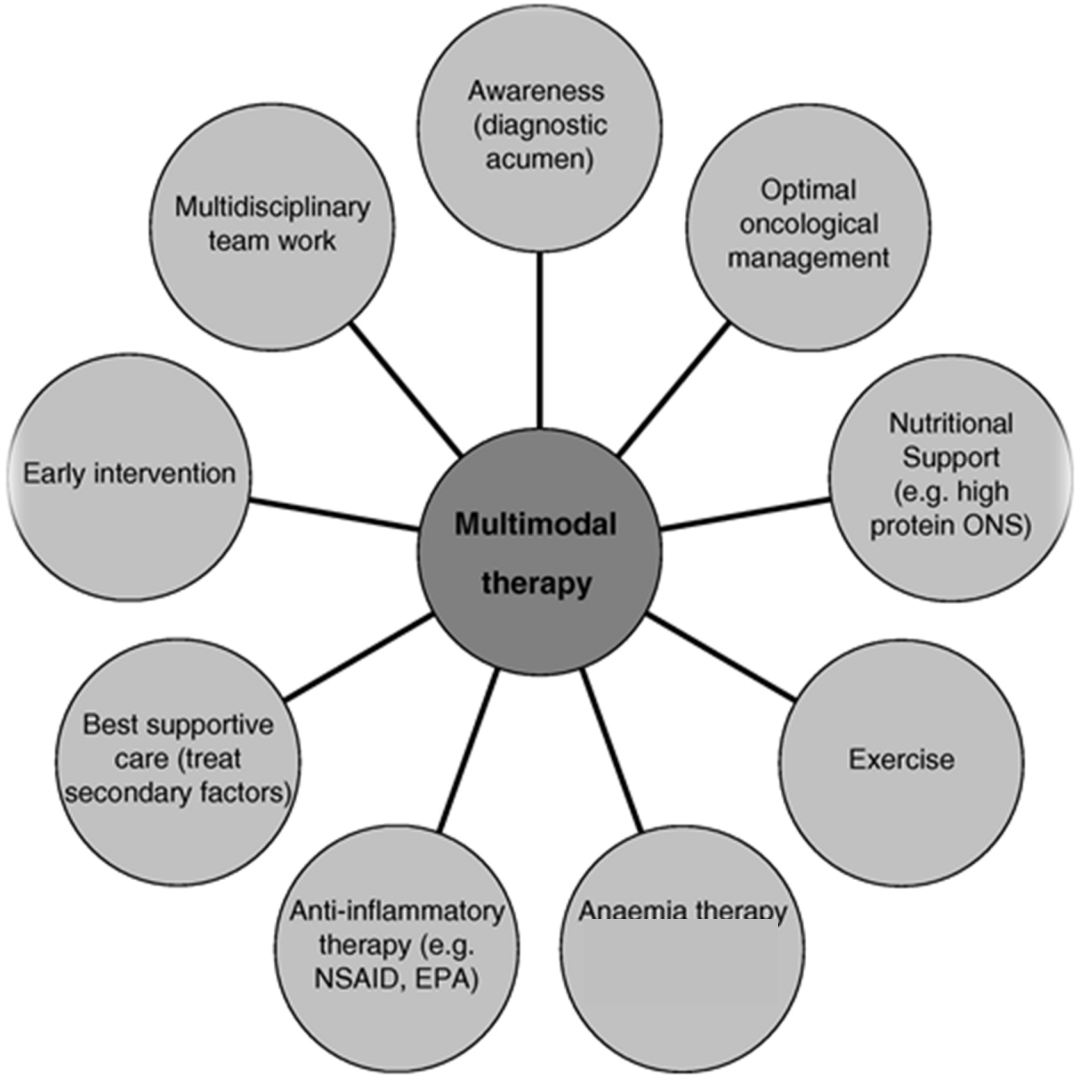


TIP: Assessing Functional & Inflammatory Status

- <u>Tools:</u>
  - ECOG-PS
  - mGPS

- Inflammation is a central driver in cachexia

Multimodal Therapy



2024 ASCO ANNUAL MEETING

MENAC - Multimodal, Exercise, Nutrition & Anti-inflammatories for Cachexia

An international, randomised, open-label trial in people with lung or pancreatic cancer

Tora S. Solheim, Barry J A Laird and Trude R. Balstad,
Guro Stene, Vickie Baracos, Asta Bye, Olav Dajani, Andrew Hendifar,
Florian Strasser, Martin Chasen, Matthew Maddocks, Melanie R. Simpson, Eva Skovlund, Garrett Griffiths,
Jonathan Hicks, Janet Graham, Fiona Kyle, Joanna Bowden
Marie Fallon and Stein Kaasa
(on behalf of the MENAC trial consortium)

WHAT IS A MULTIMODAL INTERVENTION?

- Intervention using ≥2 modalities
  - Pharmacological, nutritional, exercise, psychological/educational

Pictures: pixabay

MULTIMODAL INTERVENTION

Intervention		Target
Dietary counselling	→	Increase nutrition
Exercise (aerobic and resistance)	→	Muscle anabolism
Ibuprofen	→	Down regulate inflammatory response
Omega-3 oral nutritional supplements	→	Increase nutritional intake Down regulate inflammatory response
Systemic anti-cancer therapy	→	Treat the tumour

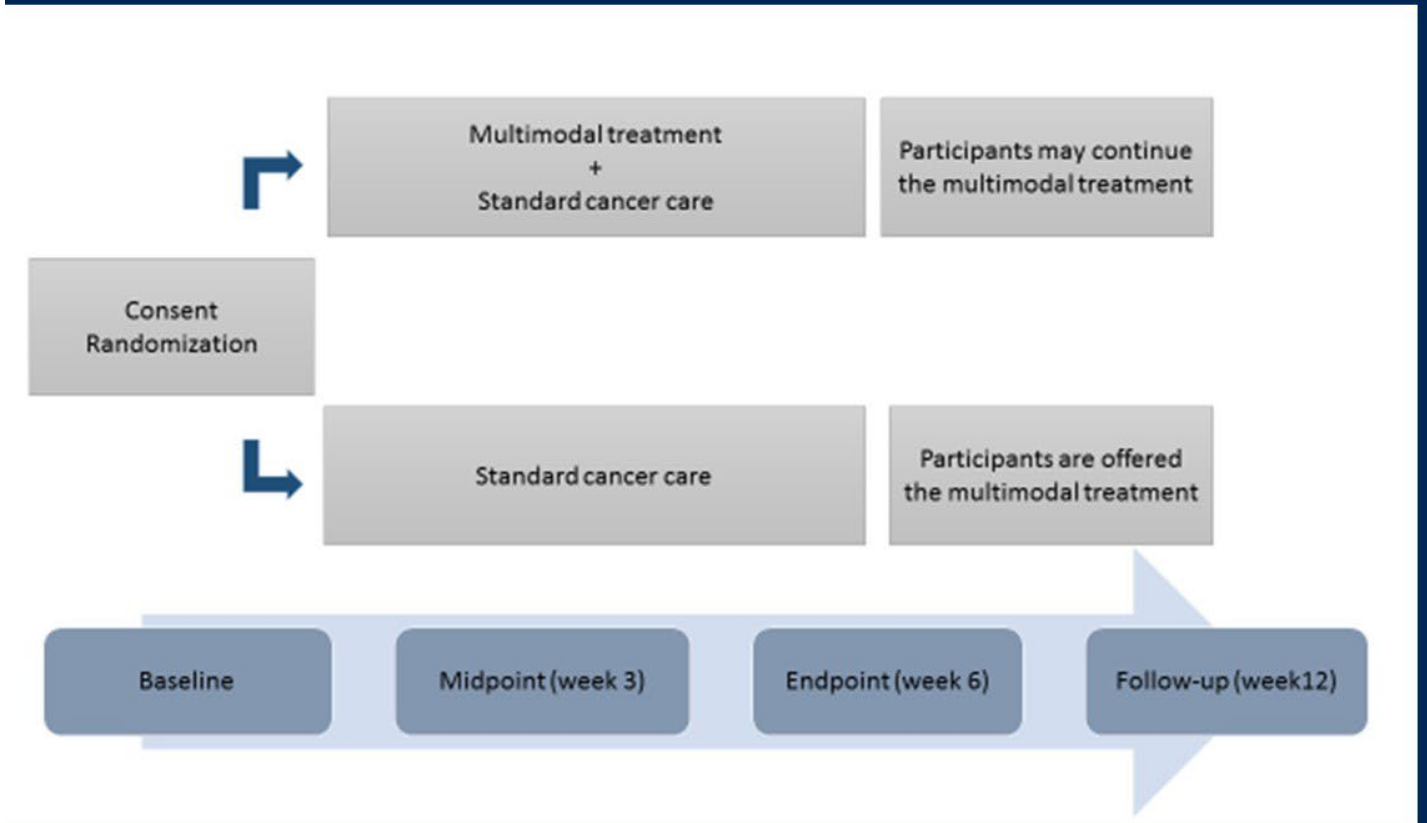
METHODS

- The MENAC trial was an investigator-initiated, multicentre, open-label, randomized phase III conducted at seventeen sites in five countries

- Patients with stage III or IV lung or pancreatic cancer receiving palliative SACT were randomly assigned (1:1)
  - Multimodal intervention: *nutritional counselling plus omega -3 ONS, physical exercise (endurance and strength) and ibuprofen in addition to standard cancer care*
  - Standard cancer care

ClinicalTrials.gov ID: NCT02330926

DESIGN



The primary objective of the MENAC trial was to prevent the development of cachexia and/or to attenuate cachexia progression in high risk patients

Primary outcome:

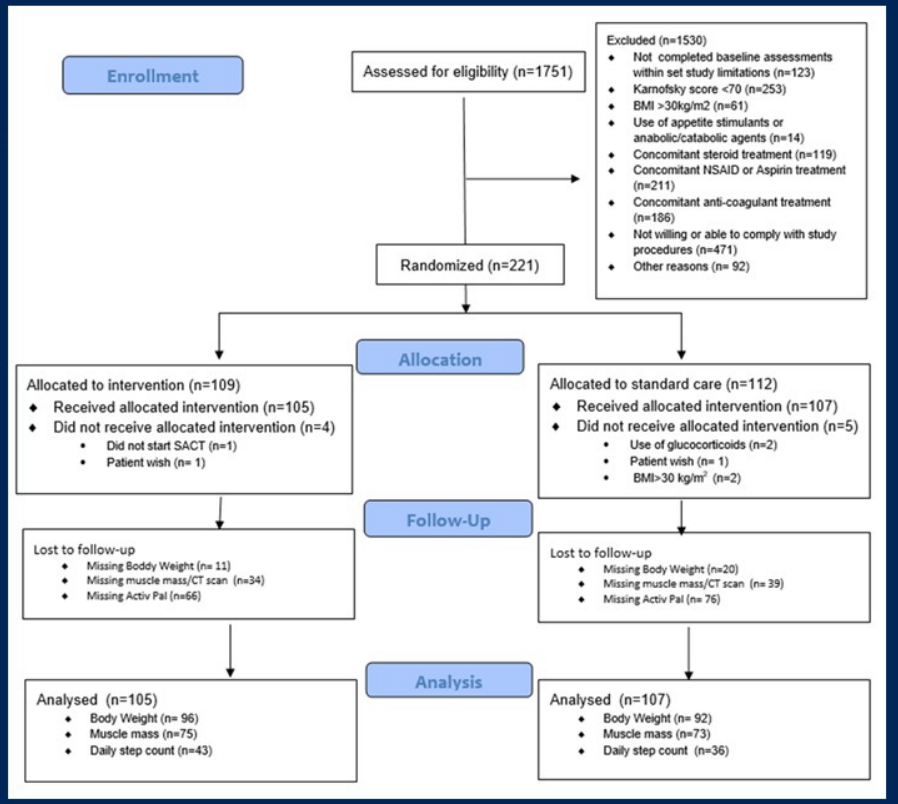
Difference in weight change as it is a key defining factor of cachexia, and is meaningful for both patients and clinicians

Secondary outcomes:

Difference in muscle mass assessed by CT scans, and physical activity assessed with ActivPal (average daily step)

RESULTS (1)

- Recruitment from May 2015 to February 2022
  - Randomized:
    - 105 intervention, 107 standard care
  - Lost to follow up:
    - 11 intervention, 20 standard care
  - Analyzed for primary endpoint
    - 96 intervention, 92 standard care

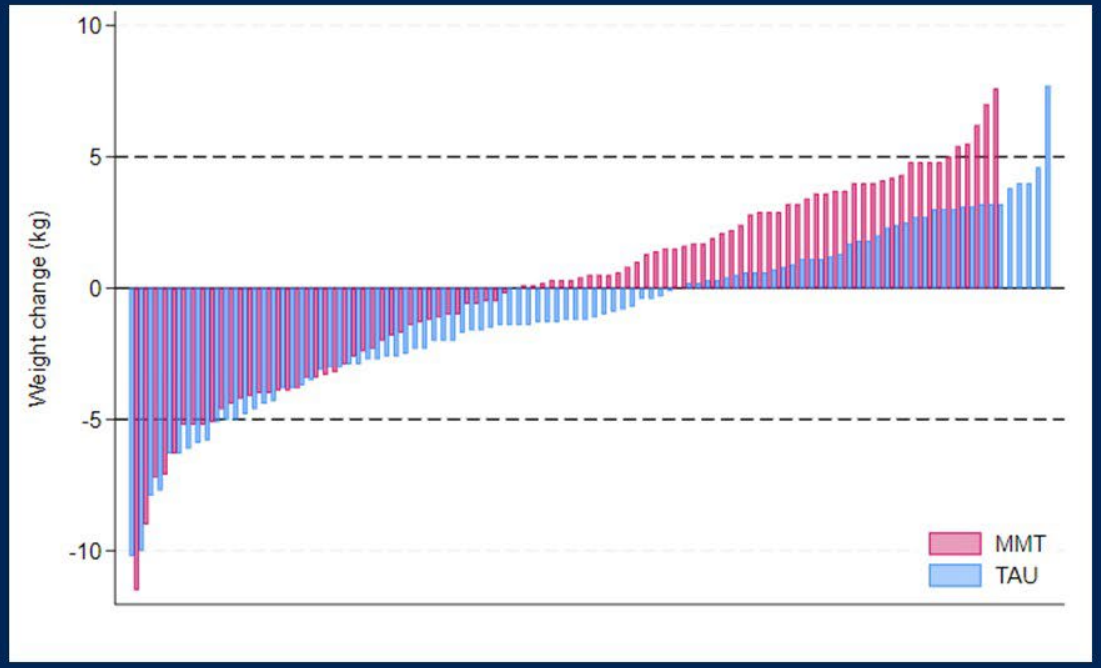


RESULTS (3)

- Primary endpoint:
  - Mean weight change [SD] 0.05 kg [3.8] MMT vs - 0.99 kg [3.2] control
    - mean difference in weight change between arms of -1.04kg, 95 % CI -2.02 to -0.06, p=0.04

- Secondary endpoints:
  - No difference in
    - muscle mass (mean change [SD] -6.5cm2 [10.1] MMT vs -6.3cm2 [11.9] control, p=0.93)
    - mean step counts [SD] (-377.7 [2075] MMT vs -458 [1858] control, p=0.89)
  - There were 28 and 24 reported SAEs in the intervention and control arm respectively, no SUSARs were reported

RESULTS (4)



CONCLUSIONS

- In patients with newly diagnosed NSCLC or PC, receiving SACT
  - the intervention stopped mean weight loss

- First large trial examining the multimodal hypothesis for cachexia
- Real world data in a pragmatic trial
  - On background of changing landscape of SACT
- Provides a background for optimal cachexia care to test new therapies

Maintaining Activity & Nutrition

- Encouraging daily physical activity
- Ensuring adequate nutrient and energy intake
    - Professional guidance and individualized motivation
- Include Nutritionist and Physiotherapy

Anorexia Therapy

Randomized Double-Blind Placebo-Controlled Study of Olanzapine for Chemotherapy-Related Anorexia in Patients With Locally Advanced or Metastatic Gastric, Hepatopancreaticobiliary, and Lung Cancer

Lakshmi Sandhya, MD[1]; Nirmala Devi Sreenivasan, MSc[1]; Luxitaa Goenka, MSc[1]; Biswajit Dubashi, MD, DM[1]; Smita Kayal, MD, DM[1]; Manikandan Solaiappan, MD[2]; Ramkumar Govindarajalou, MD[3]; Harichandrakumar KT, PhD, MSc[4]; and Prasanth Ganesan, MD, DM[1]

Published 28.03.2023 in Journal of Clinical Oncology

Rationale Olz

- Current therapy options for anorexia: dietary counseling, glucocorticoids
- **Olanzapine**:
  - antipsychotic agent
  - weight gain as side effect
  - Optional antiemetic therapy for chemotherapy-induced nausea (short duration)

ACUTE Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	5-HT$_3$ + DEX + NK$_1$ +/- OLZ*
High AC	5-HT$_3$ + DEX + NK$_1$ +/- OLZ*
Carboplatin	5-HT$_3$ + DEX + NK$_1$
Moderate (other than carboplatin)	5-HT$_3$ + DEX
Low	5-HT$_3$ or DEX or DOP
Minimal	No routine prophylaxis

5-HT$_3$ = serotonin$_3$ receptor antagonist	**DEX** = DEXAMETHASONE	**NK$_1$** = neurokinin$_1$ receptor antagonist such as APREPITANT or FOSAPREPITANT or ROLAPITANT or NEPA (combination of netupitant and palonosetron)	**OLZ** = OLANZAPINE	**DOP** = dopamine receptor antagonist

NOTE: If the NK$_1$ receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT$_3$ receptor antagonist.

*** OLZ:** Olanzapine may be added particularly if nausea is a concern.

Multinational Association of Supportive Care in Cancer

Supportive Care Makes Excellent Cancer Care Possible

MASCC WWW.MASCC.ORG ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Anthracycline-
Cyclophosphamide-

Objective

Can continuous, low-dose olanzapine improve appetite and weight gain among newly diagnosed patients with advanced lung and upper gastrointestinal cancer starting chemotherapy?

Design

Study design: Randomized, double-blinded, placebo-controlled

Patients: 124 patients with untreated, locally advanced, or metastatic gastric, hepatopancreaticobiliary (HPB), and lung cancers

Intervention: Standard of care* + Olanzapine 2.5mg/d

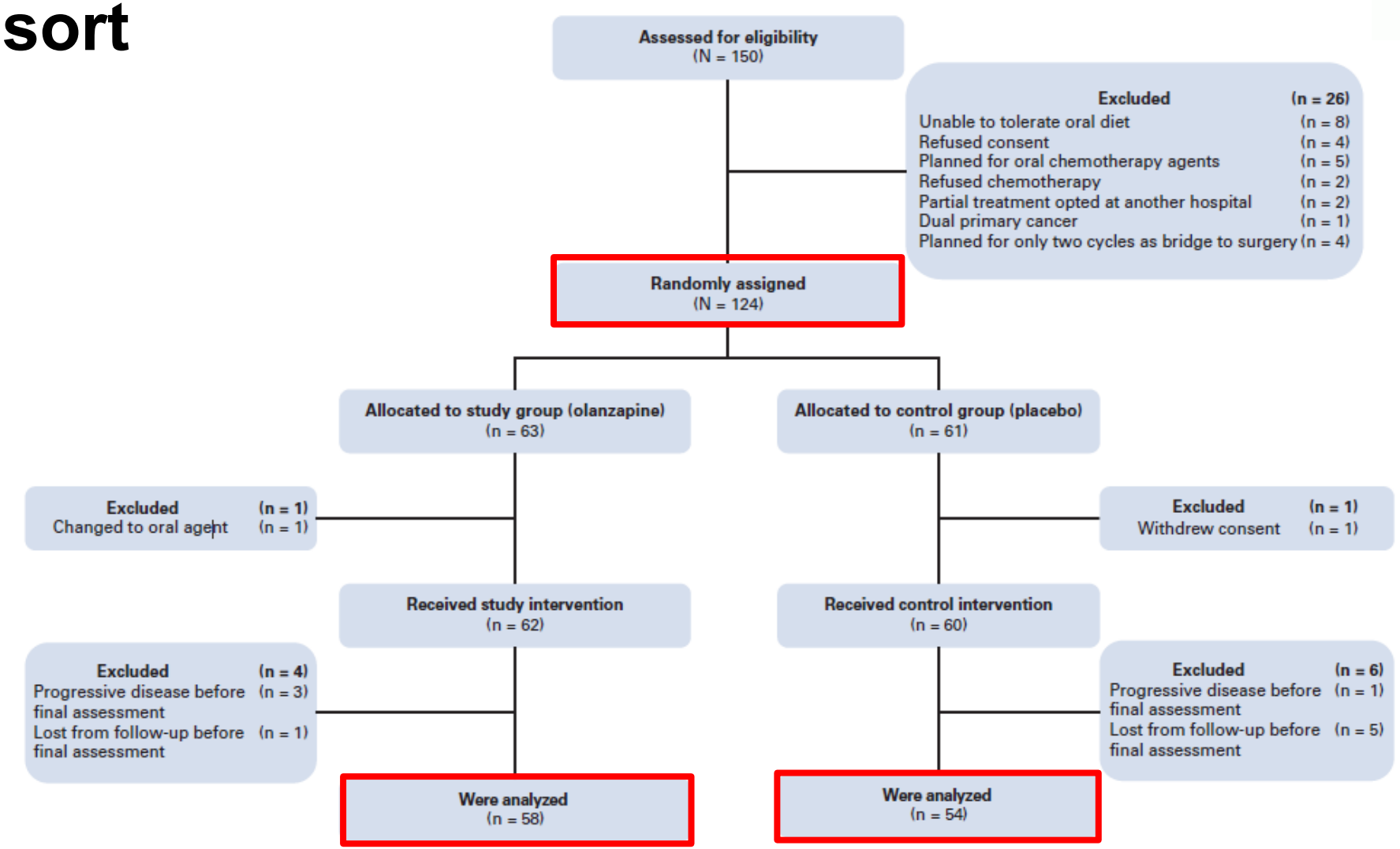
Control: Standard of care* + Placebo

Duration: 12 weeks

Assessments: baseline, at chemotherapy cycles, post-treatment

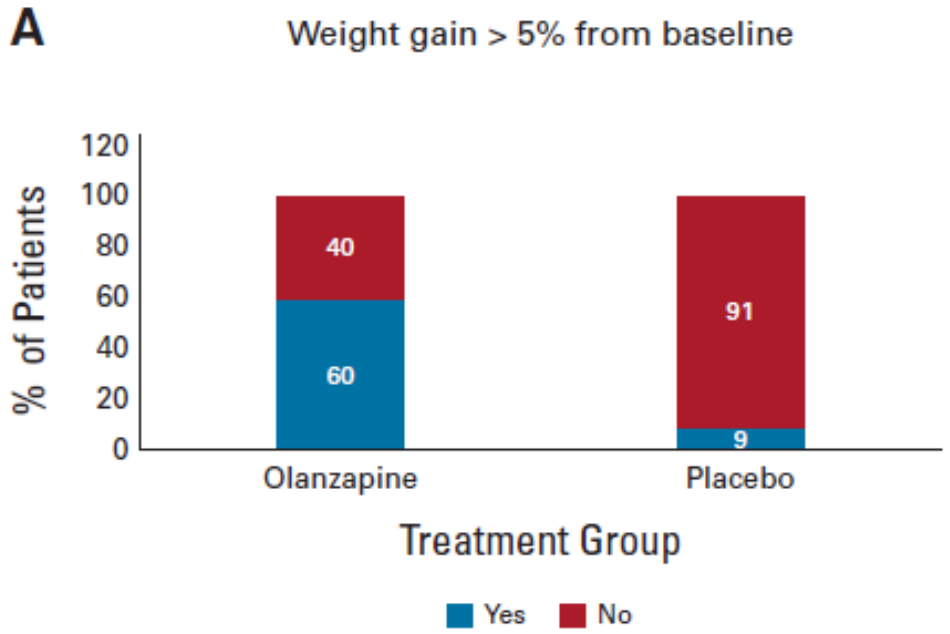
* chemotherapy + antiemetic therapy (Olanzapine 5mg/d day 1-4 + steroids) + dietary advice

Consort


Assessed for eligibility
(N = 150)
Excluded (n = 26)
Unable to tolerate oral diet (n = 8)
Refused consent (n = 4)
Planned for oral chemotherapy agents (n = 5)
Refused chemotherapy (n = 2)
Partial treatment opted at another hospital (n = 2)
Dual primary cancer (n = 1)
Planned for only two cycles as bridge to surgery (n = 4)
Randomly assigned
(N = 124)
Allocated to study group (olanzapine)
(n = 63)
Allocated to control group (placebo)
(n = 61)
Excluded (n = 1)
Changed to oral agent (n = 1)
Excluded (n = 1)
Withdrew consent (n = 1)
Received study intervention
(n = 62)
Received control intervention
(n = 60)
Excluded (n = 4)
Progressive disease before final assessment (n = 3)
Lost from follow-up before final assessment (n = 1)
Excluded (n = 6)
Progressive disease before final assessment (n = 1)
Lost from follow-up before final assessment (n = 5)
Were analyzed
(n = 58)
Were analyzed
(n = 54)

Results

- **Weight gain of >5%:** 60% (olanzapine) vs. 9% (placebo) (p<0.0001)



Results II

- **Weight gain of >5%:** 60% (olanzapine) vs. 9% (placebo) (p<0.0001)
- **Improvement in appetite:**
  - VAS: 43% (olanzapine) vs. 13% (placebo) (p<0.001)
  - FAACT ACS (scores ≥37*) after treatment : 22% (olanzapine) vs. 4% (placebo) (p=0.004)
- Improvement in nutrition score: 43% (olanzapine) vs. 9% (placebo) (p<0.0001)
- Improvement in QoL: 70% (olanzapine) vs. 50% (placebo) (p=0.003)

* cutoff of <37 was used to define anorexia

Results (III)

Side effects of trial drug: 13 (23%) (olanzapine) v. 8 (15%) (placebo), p=0.26

TABLE A2. Toxicities Attributed to Trial Drug

Variable	Olanzapine (n = 58)	Placebo (n = 54)	*P*
Any-grade toxicity present, No. (%)	13 (23)	8 (15)	.26
Hyperbilirubinemia/transaminitis, No.	3	1	
Constipation, No.	3	2	
Hyperglycemia, No.	4[a]	3	
Drowsiness, No.	2	1	
Headache, No.	1	1	
Suicidal tendencies, No.	0	0	
Cardiac complications, No.	0	0	
Grade 2 toxicity, No.	6	3	
Grade ≥3 toxicity, No.	1[b]	2[c]	

Discussion

- Appetite improvement and weight gain in patients receiving olanzapine → option for inexpensive and well-tolerated add-on therapy
- Olanzapine known as antiemetic drug, but longer time needed for weight gain
- Olanzapine was also associated with better nutrition, QOL, and less chemotherapy toxicity

Original Article

Mirtazapine in Cancer-Associated Anorexia and Cachexia: A Double-Blind Placebo-Controlled Randomized Trial

Catherine N. Hunter, MBBCh, MSc, Hesham H. Abdel-Aal, MBBCh, MSc, MD,
Wessam A. Elsherief, MBBCh, MSc, MD, Dina E. Farag, MBBCh, MSc, MD,
Nermine M. Riad, MBBCh, MSc, MD, and Samy A. Alsirafy, MBBCh, MSc, MD, DipPallMed
Palliative Medicine Unit, Kasr Al-Ainy Center of Clinical Oncology and Nuclear Medicine, Kasr Al-Ainy School of Medicine, Cairo University, Cairo, Egypt; Clinical and Chemical Pathology Department, Kasr Al-Ainy School of Medicine, Cairo University, Cairo, Egypt

Conclusion: Mirtazapine 15mg at night for 28 days is no better than placebo in improving the appetite of incurable solid tumor patients with cancer-associated anorexia and cachexia

JAMA Oncology | Original Investigation

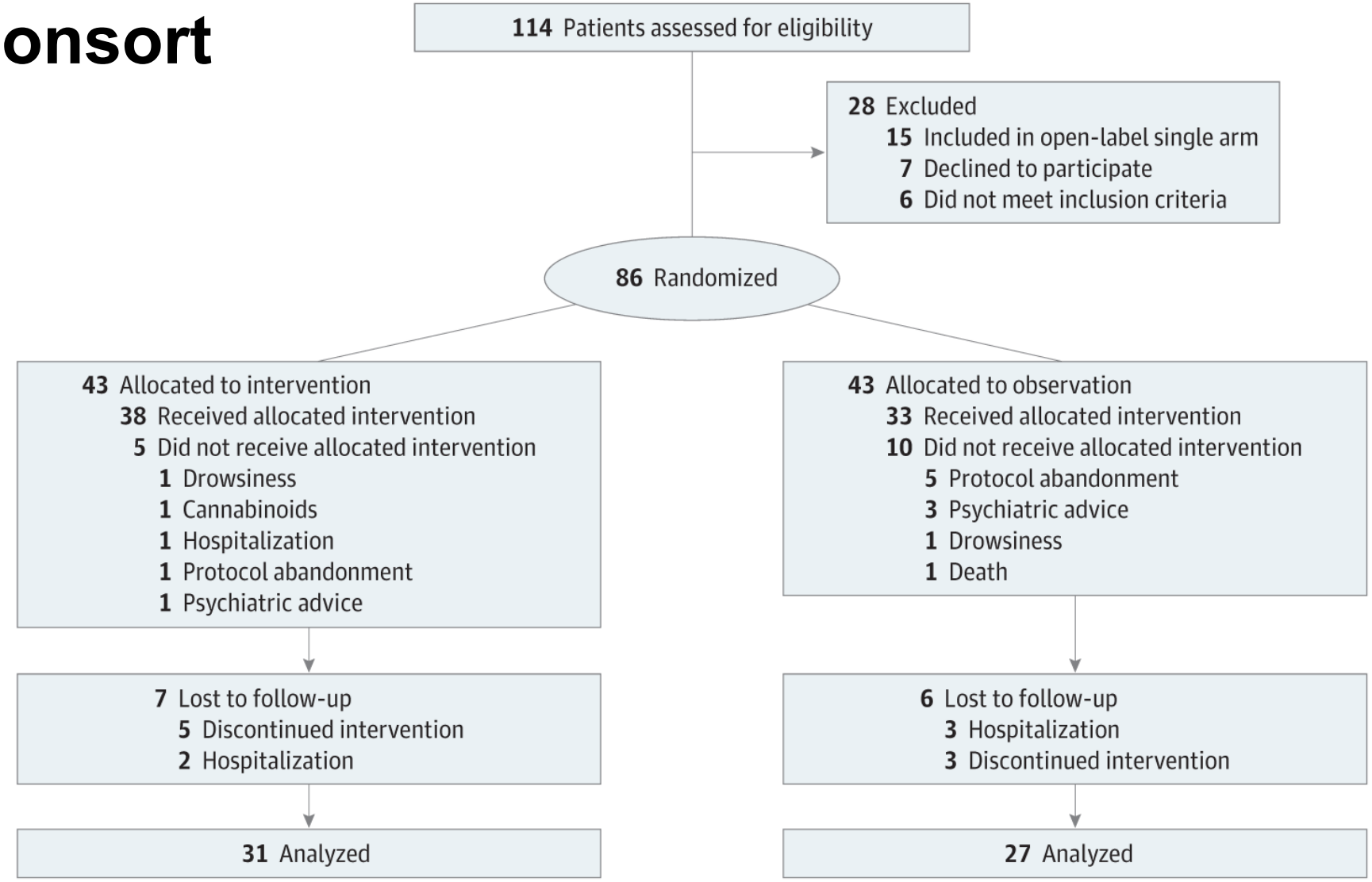
Mirtazapine as Appetite Stimulant in Patients With Non–Small Cell Lung Cancer and Anorexia

A Randomized Clinical Trial

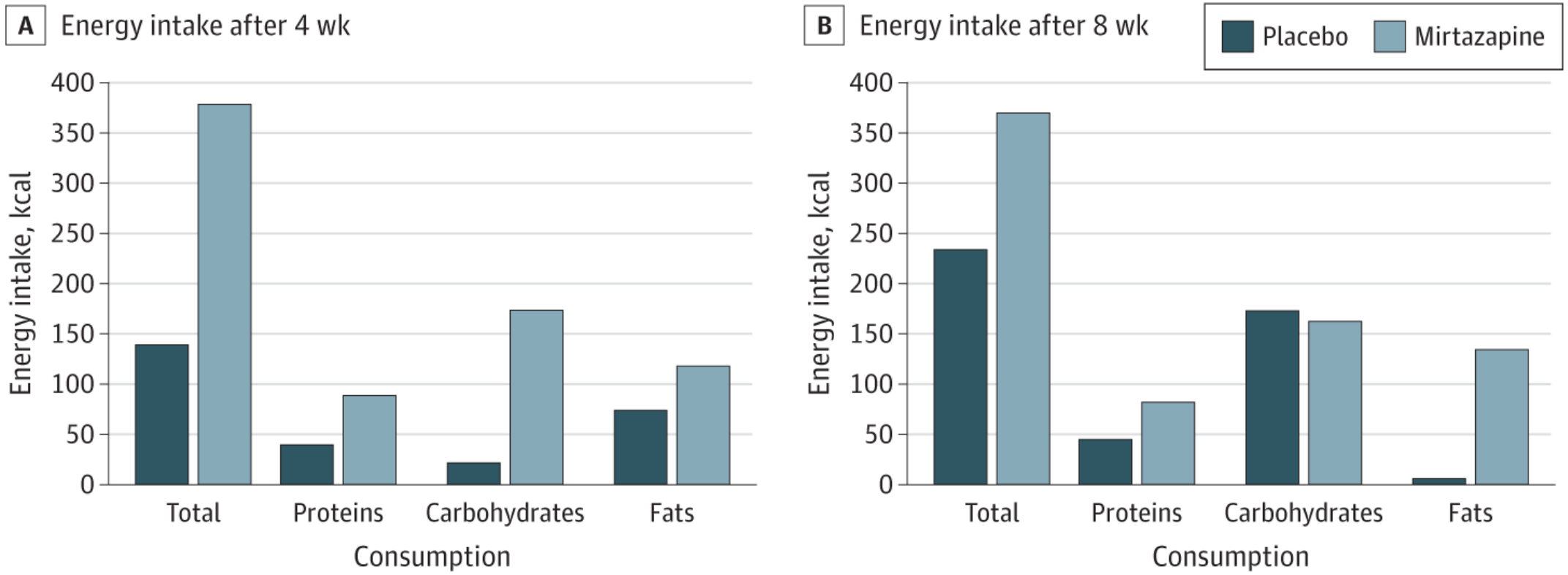
Oscar Arrieta, MD, MSc; Daniela Cárdenas-Fernández, BSD; Oscar Rodriguez-Mayoral, MD; Salvador Gutierrez-Torres, MD; Diana Castañares, MD; Diana Flores-Estrada, SW; Edgar Reyes, MD; Dennis López, MD; Pablo Barragán, MD; Pamela Soberanis Pina, MD; Andres F. Cardona, MD, MSc, PhD; Jenny G. Turcott, MSc, PhD

Interventions Patients were randomized in a 1:1 ratio to receive mirtazapine, 15 mg, or placebo for 2 weeks followed by a dose escalation to 30 mg until week 8 or placebo. Both groups received nutritional assessment and dietary advice.

Consort


114 Patients assessed for eligibility
28 Excluded
15 Included in open-label single arm
7 Declined to participate
6 Did not meet inclusion criteria
86 Randomized
43 Allocated to intervention
38 Received allocated intervention
5 Did not receive allocated intervention
1 Drowsiness
1 Cannabinoids
1 Hospitalization
1 Protocol abandonment
1 Psychiatric advice
43 Allocated to observation
33 Received allocated intervention
10 Did not receive allocated intervention
5 Protocol abandonment
3 Psychiatric advice
1 Drowsiness
1 Death
7 Lost to follow-up
5 Discontinued intervention
2 Hospitalization
6 Lost to follow-up
3 Hospitalization
3 Discontinued intervention
31 Analyzed
27 Analyzed

Results



In patients with advanced NSCLC and anorexia the addition of mirtazapine can improve energy consumption

Cannabis: A lot of activism and change of law…

Past: First large RCT

VOLUME 24 · NUMBER 21 · JULY 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

No differences in patients' appetite or QOL were found….

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

ORIGINAL REPORTS | Supportive Care and Quality of Life

Phase IIb Randomized, Placebo-Controlled, Dose-Escalating, Double-Blind Study of Cannabidiol Oil for the Relief of Symptoms in Advanced Cancer (MedCan1-CBD)

Janet Hardy, MD, FRACP[1,2]; Ristan Greer, PhD[2,3]; Georgie Huggett, BN[1]; Alison Kearney, FRACP[4,5]; Taylan Gurgenci, FRACGP[1,2]; and Phillip Good, PhD, FRACP[1,2,6]

Show Less

CONCLUSION CBD oil did not add value to the reduction in symptom distress provided by specialist palliative care
alone.

AES

Original Investigation

June 23/30, 2015

Cannabinoids for Medical Use

A Systematic Review and Meta-analysis

Penny F. Whiting, PhD[1,2,3]; Robert F. Wolff, MD[3]; Sohan Deshpande, MSc[3]; et al

» Author Affiliations | Article Information

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358

There was an increased risk of short-term AEs with cannabinoids, including serious AEs. Common AEs included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

TABLE 1. Targeted Therapeutic Trials in Cancer Cachexia

Therapeutic Target Area and Mechanism of Action	Compound/Route of Administration	Phase and Design	N	Population	Primary/Secondary Outcomes[a]	Study Start and Completion Dates[b]	Results	Clinical Trial No.
CNS—appetite/satiety/hypothalamic inflammation								
Melanocortin type 4 receptor antagonists	TCMCB07, SQ	I, randomized, double-blind, placebo-controlled	97	US, healthy volunteers	Safety/pharmacokinetics	July 12, 2022-	Recruiting	NCT05529849
Melanocortin type 4 receptor antagonists	PF-07258669, oral	I, randomized, double-blind, placebo-controlled	29	US, healthy volunteers				
Anti-GDF15	Ponsegromab (PF-06946860), SQ	II, randomized, double-blind, placebo-controlled	168	US, advanced cancers (NSCLC, pancreatic, CRC) with elevated GDF15 levels				
Anti-GDF15	Ponsegromab (PF-06946860), SQ	I, randomized, double-blind, placebo-controlled	63	US, healthy volunteers				
Anti-GDF15	Ponsegromab (PF-06946860), SQ	Pilot, randomized, double-blind, placebo-controlled	18	US and Canada, advanced cancers (NSCLC, pancreatic, CRC, prostate, breast, or ovarian)				
Anti-GDF15	Ponsegromab (PF-06946860), SQ	IB, nonrandomized	11	US, advanced cancers (NSCLC, pancreatic, CRC)				
Anti-GDF15	Ponsegromab (PF-06946860), SQ	I, randomized, double-blind, placebo-controlled	8	Japanese, healthy volunteers				
Anti-GDF15	NGM120, SQ	I, randomized, double-blind, placebo-controlled	92	Australia, healthy volunteers				
Anti-GDF15	NGM120, SQ	I/II, randomized, double-blind, placebo-controlled	75	US, advanced solid cancers	Safety/Bodyweight and Skeletal muscle index change	October 16, 2019-January 2025	Recruiting	NCT04068896
Anti-GDF15	AV380, IV and SQ	I, randomized, double-blind, placebo-controlled	56	US, healthy volunteers	Safety/pharmacokinetics and GDF15 levels by dose and serum level of AV380	February 22, 2021-January 2022	Active, not recruiting	NCT04815551
Anti-GDF15	CTL002, IV	I/II, nonrandomized	155	Europe, advanced cancers after progression on one previous anti-PD-1/PD-L1 treatment	Safety/change in appetite via questionnaire, BMI, and skeletal muscle index	December 9, 2020-May 31, 2025	Recruiting	NCT04725474
Ghrelin receptor agonist	Anamorelin, oral	III, randomized, double-blind, placebo-controlled	318	US and international, unresectable stage III or stage IV NSCLC	Weight change and 5-item Anorexia Symptom Subscale	December 18, 2018-January 31, 2023	Active, not recruiting	NCT03743064
Ghrelin receptor agonist	Anamorelin, oral	III, randomized, double-blind, placebo-controlled	316	US and international, unresectable stage III or stage IV NSCLC	Weight change and 5-item Anorexia Symptom Subscale	December 18, 2018-February 2023	Active, not recruiting	NCT03743051
Ghrelin receptor agonist	Anamorelin, oral	II, randomized, double-blind, placebo-controlled	100	US, locally advanced or metastatic pancreatic cancer	Weight change/5-item Anorexia Symptom Subscale, survival, and Fatigue Subscale	September 30, 2022-December 31, 2023	Recruiting	NCT04844970
Dopamine and serotonin receptor antagonist	Olanzapine, oral	III, randomized, open-label *v* megestrol	360	US, advanced solid or hematologic cancers	Change in appetite	October 15, 2021-December 2024	Recruiting	NCT04939090
Multimodality approach								
MENAC: anti-inflammatory, nutrient signaling, contractile work	Ibuprofen + ONS with EPA + nutritional counseling + exercise prescription	III, randomized, open-label *v* standard palliative care	240	US and international, advanced NSCLC or pancreas	Weight change	April 2015-September 2022	Active, not recruiting	NCT02330926
Nutrient signaling, anti-inflammatory	Arginine + omega-3 fatty acids	III, randomized, double-blind, placebo-controlled	200	US, bladder cancer	Postoperative complications/changes in body composition	February 21, 2019-May 1, 2026	Recruiting	NCT03757949
MIRACLE: anti-inflammatory, nutrient signaling, contractile work	Ibuprofen + omega-3 fatty acids + ONS + Bojungikki-tang + nutritional counseling + exercise prescription	II, randomized, open-label *v* standard palliative care	112	Korea, advanced NSCLC or GI cancers	Weight change and handgrip strength	January 31, 2020-June 30, 2022	Recruiting	NCT04907864
NEXTAC-III: ghrelin receptor agonist, nutrient signaling, contractile work	Anamorelin + nutritional counseling + home-based resistance training	II, randomized, open-label *v* SOC	90	Japan, advanced NSCLC or pancreas	Change in 6-minute walking distance	September 01, 2021-NP	Recruiting	jRCTs041210053

Abbreviations: BMI, body mass index; CRC, colorectal cancer; EPA, eicosapentaenoic acid; GDF, growth differentiation factor; IV, intravenous; JAK/STAT, Janus kinase-signal transducer and activator of transcription pathway; NP, not provided; NSCLC, non–small-cell lung cancer; ONS, oral nutritional supplement; QOL, quality of life; SOC, standard of care; SQ, subcutaneous.
[a]For phase I and II trials, select secondary outcomes focused on cachexia-related end points provided as available.
[b]For trials not completed, estimated study completion dates per ClinicalTrials.gov provided.

Current Therapeutic Targets
in Cancer Cachexia:
A Pathophysiologic Approach
Kadakia, Hamilton-Reeves, **Baracos**
American Society of Clinical Oncology
Educational Book 2023

The NEW ENGLAND JOURNAL of MEDICINE

Ponsegromab for Cancer Cachexia

A PLAIN LANGUAGE SUMMARY

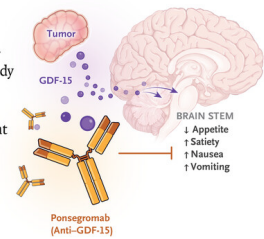
Based on the NEJM publication: Ponsegromab for the Treatment of Cancer Cachexia by J.D. Groarke et al. (published September 14, 2024)

In this trial, researchers examined the safety and efficacy of the monoclonal antibody ponsegromab for treating cancer cachexia.

Cachexia — also known as wasting syndrome — occurs commonly in patients with cancer and can lead to weight loss, muscle wasting, functional impairment, and reduced survival.

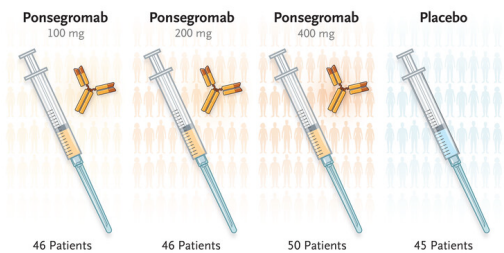
WHY WAS THE TRIAL DONE?

Pharmacologic treatment options for cancer cachexia are limited. Ponsegromab is a humanized monoclonal antibody that binds to growth differentiation factor 15 (GDF-15), a stress-induced cytokine implicated in the development of cachexia. In a small phase 1b study of ponsegromab, patients with cancer cachexia and an elevated circulating GDF-15 level had improved outcomes and few adverse events.



HOW WAS THE TRIAL CONDUCTED?

Adults with cancer cachexia and elevated serum GDF-15 levels were assigned to receive ponsegromab (100 mg, 200 mg, or 400 mg) or placebo, administered subcutaneously every 4 weeks for three doses. The primary end point was the change in body weight at 12 weeks.



PATIENTS

WHO

187 adults

Median age, 67 years

Men: 63%; Women: 37%

CLINICAL STATUS

Cachexia (involuntary weight loss of >5% within the previous 6 months or >2% with BMI <20)

Serum GDF-15 level of at least 1500 pg per milliliter

ECOG performance-status score of 3 or less (scale, 0 to 5, with higher numbers reflecting greater disability)

Life expectancy of at least 4 months

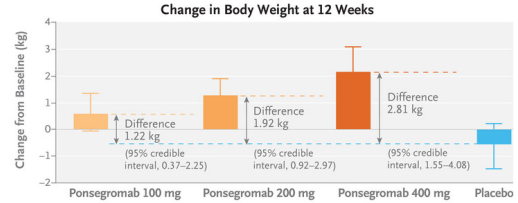
TRIAL DESIGN

- PHASE 2
- RANDOMIZED
- DOUBLE-BLIND
- PLACEBO-CONTROLLED
- DOSE-RANGING
- DURATION: 12 WEEKS
- LOCATION: 74 SITES IN 11 COUNTRIES

RESULTS

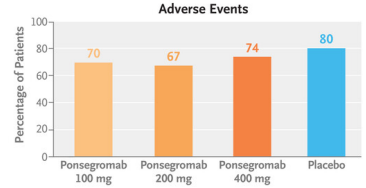
At 12 weeks, patients in the ponsegromab groups had significantly greater weight gain than those in the placebo group. Patients in the 400-mg ponsegromab group also had improvements in secondary end point measures of anorexia and cachexia symptoms, as well as physical activity, as compared with the placebo group.

Change in Body Weight at 12 Weeks

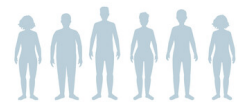


Adverse Events

The percentage of patients who reported adverse events of any cause was similar across groups.



CANCER TYPE



Non–small-cell lung cancer was the most prevalent cancer (40% of patients), followed by pancreatic cancer (32%) and colorectal cancer (29%).

LIMITATIONS AND REMAINING QUESTIONS

- Nearly all the patients in the trial were Asian or White.
- Although ponsegromab-mediated weight gain did not appear to be related to the magnitude of baseline GDF-15 elevation, larger studies are needed to evaluate a possible association.
- Missing data on physical activity level and gait for some patients may have limited detection of a treatment effect across the ponsegromab dose groups.

CONCLUSIONS

Among patients with cancer cachexia and an elevated GDF-15 level, the inhibition of GDF-15 with ponsegromab significantly increased body weight at 12 weeks, as compared with placebo.

LINKS: FULL ARTICLE | NEJM QUICK TAKE | EDITORIAL | SCIENCE BEHIND THE STUDY

FURTHER INFORMATION

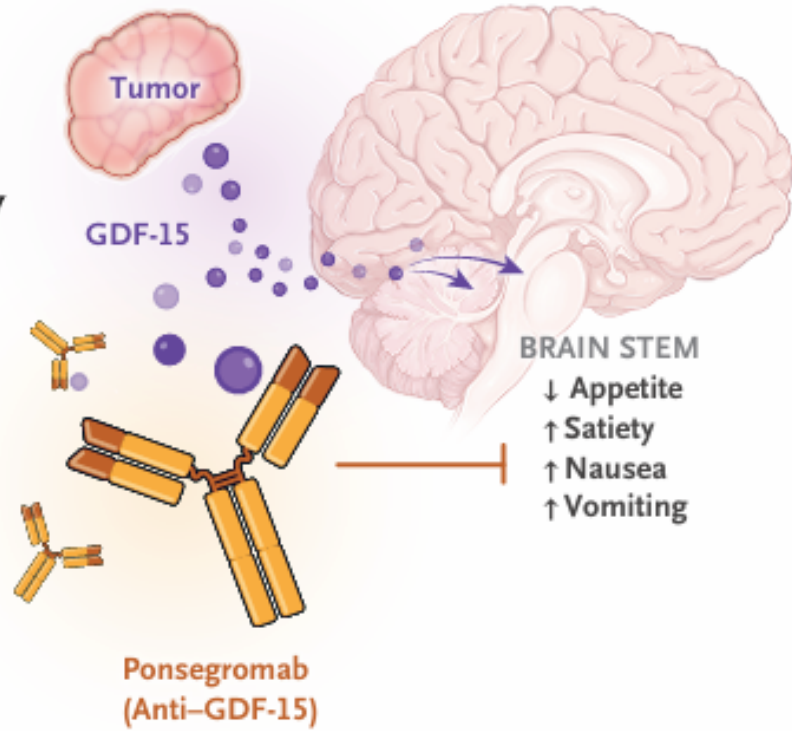
Trial registration: ClinicalTrials.gov number, NCT05546476

Trial funding: Pfizer

Full citation: Groarke JD, Crawford J, Collins SM, et al. Ponsegromab for the treatment of cancer cachexia. N Engl J Med 2024;391:2291-303. DOI: 10.1056/NEJMoa2409515

WHY WAS THE TRIAL DONE?

Pharmacologic treatment options for cancer cachexia are limited. Ponsegromab is a humanized monoclonal antibody that binds to growth differentiation factor 15 (GDF-15), a stress-induced cytokine implicated in the development of cachexia. In a small phase 1b study of ponsegromab, patients with cancer cachexia and an elevated circulating GDF-15 level had improved outcomes and few adverse events.



PATIENTS

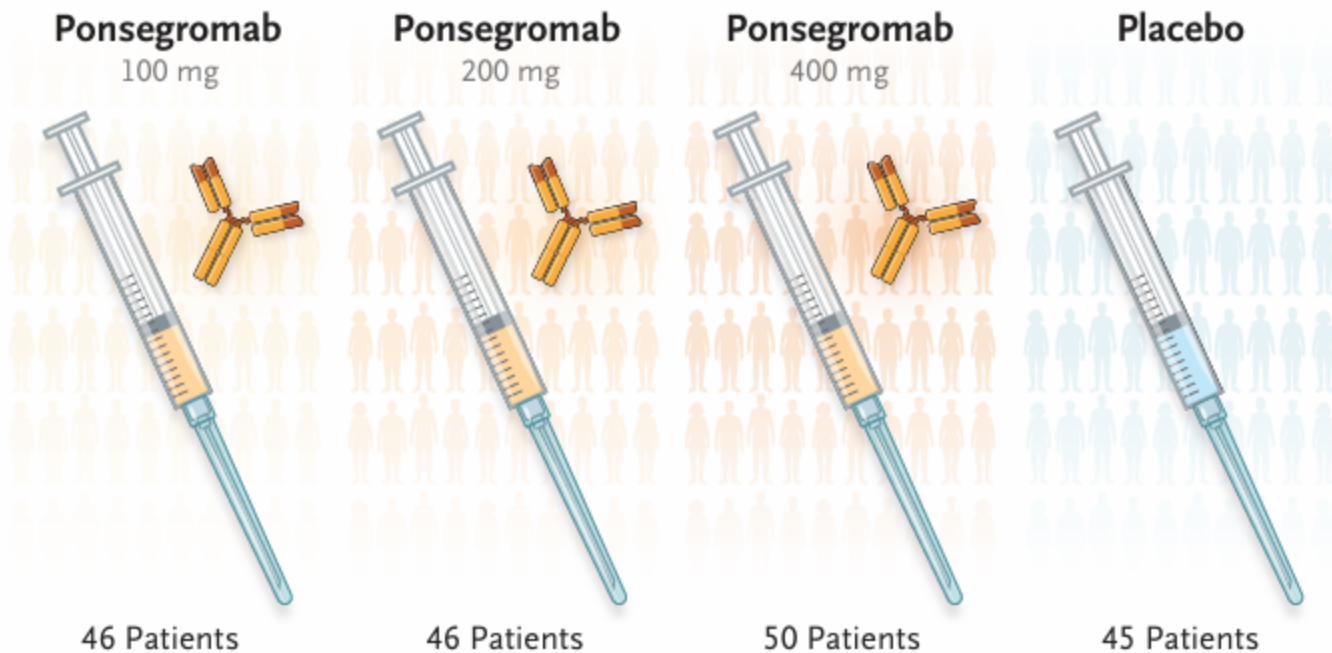
WHO	187 adults Median age, 67 years Men: 63%; Women: 37%
CLINICAL STATUS	Cachexia (involuntary weight loss of >5% within the previous 6 months or >2% with BMI <20) Serum GDF-15 level of at least 1500 pg per milliliter ECOG performance-status score of 3 or less (scale, 0 to 5, with higher numbers reflecting greater disability) Life expectancy of at least 4 months

TRIAL DESIGN

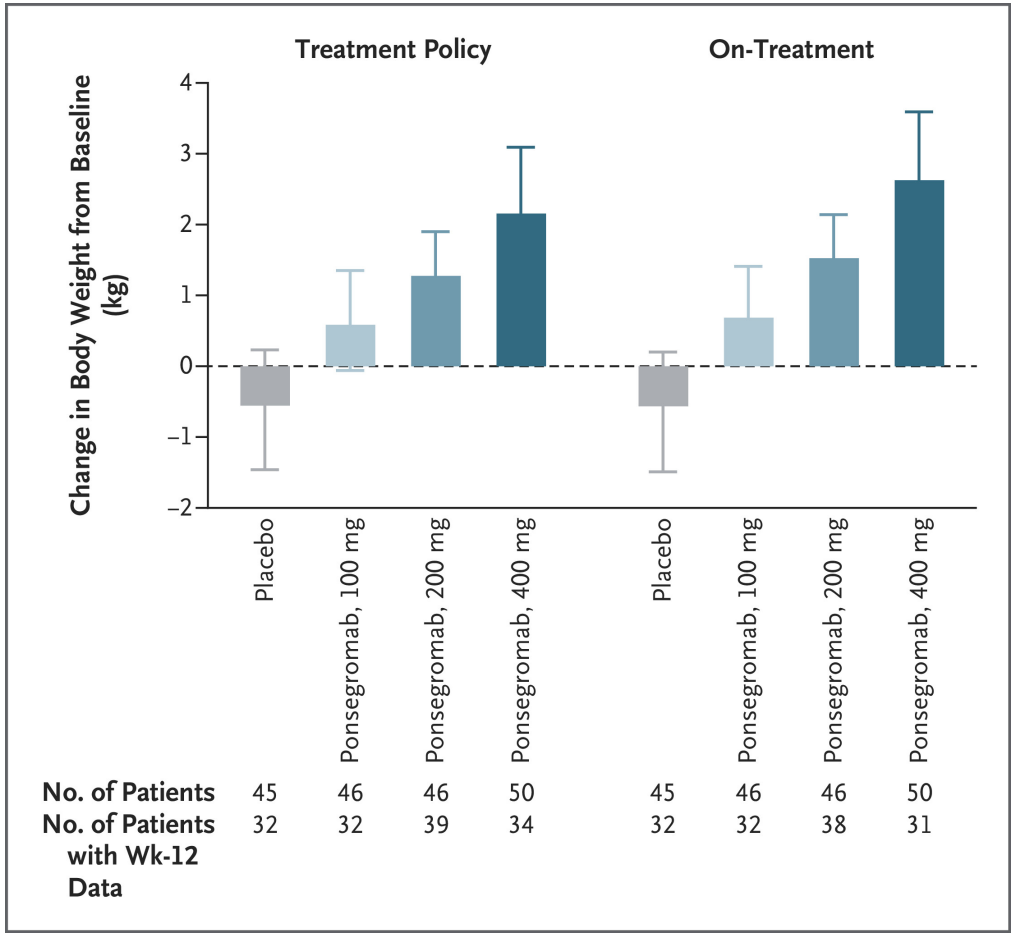
- PHASE 2
- RANDOMIZED
- DOUBLE-BLIND
- PLACEBO-CONTROLLED
- DOSE-RANGING
- DURATION: 12 WEEKS
- LOCATION: 74 SITES IN 11 COUNTRIES

HOW WAS THE TRIAL CONDUCTED?

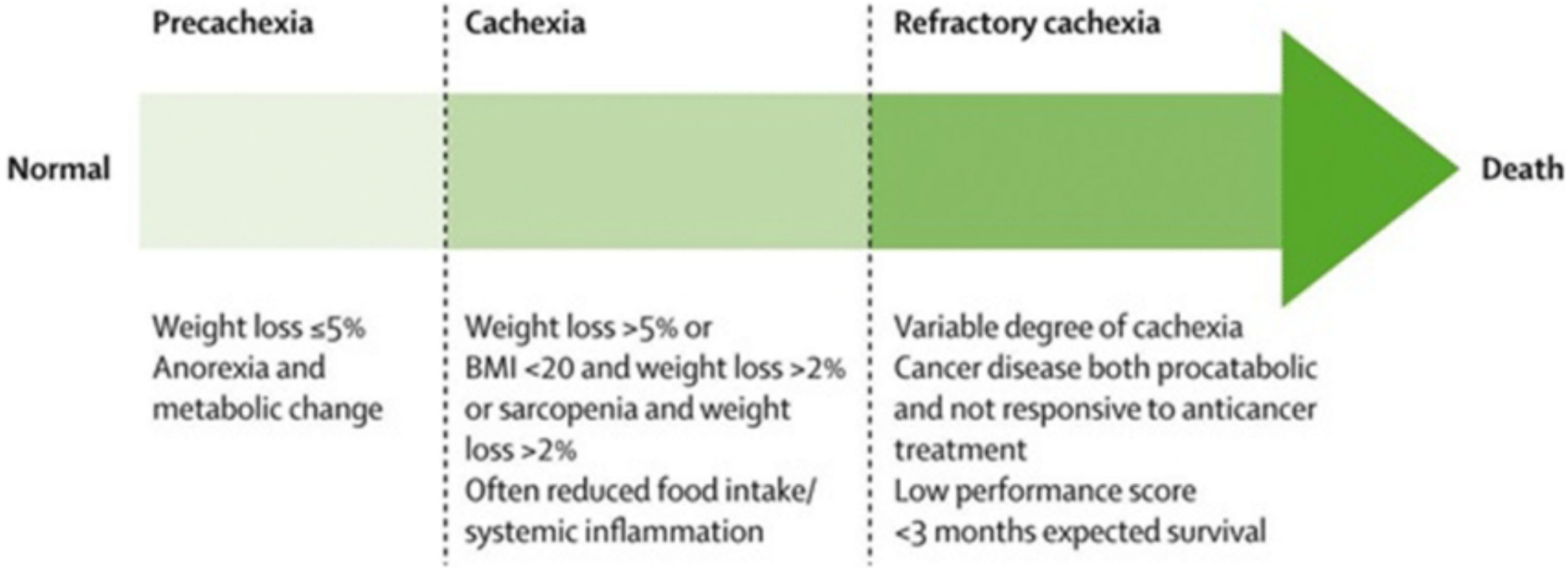
Adults with cancer cachexia and elevated serum GDF-15 levels were assigned to receive ponsegromab (100 mg, 200 mg, or 400 mg) or placebo, administered subcutaneously every 4 weeks for three doses. The primary end point was the change in body weight at 12 weeks.



Primary outcome



Cachexia Stages



Mitigating Cachexia-Related Distress

- Impact of cachexia on quality of life
- Education and psychosocial support
- Strategies for interdisciplinary team members to support self-management of cachexia-related problems

Palliation in Refractory Cachexia

- Challenges in diagnosing refractory cachexia
- Focus shifts to palliation in the refractory stage
- Symptom management and compassionate care is key

Conclusion

- Early identification
- Symptom control, nutrition and physical activity
- Stage adapted treatment
- Mitigate cachexia related distress

- Patient-centered care through multidisciplinary collaboration

- Cachexia remains underdiagnosed and undertreated

  Nutrition and exercise are key in early palliative care

- Happy to answer questions