
HRVATSKO DRUŠTVO ZA SUPLEMENTACIJU U MEDICINI
Hotel Sheraton,
Zagreb
22.-25.10.2026.
JESENSKA AKADEMIJA SUPLEMENTACIJE U MEDICINI
Utjecaj malnutricije i kaheksije na ishode liječenja onkološkog bolesnika
Prof. dr. sc. Antonio Juretić, Onkologija KB Dubrava

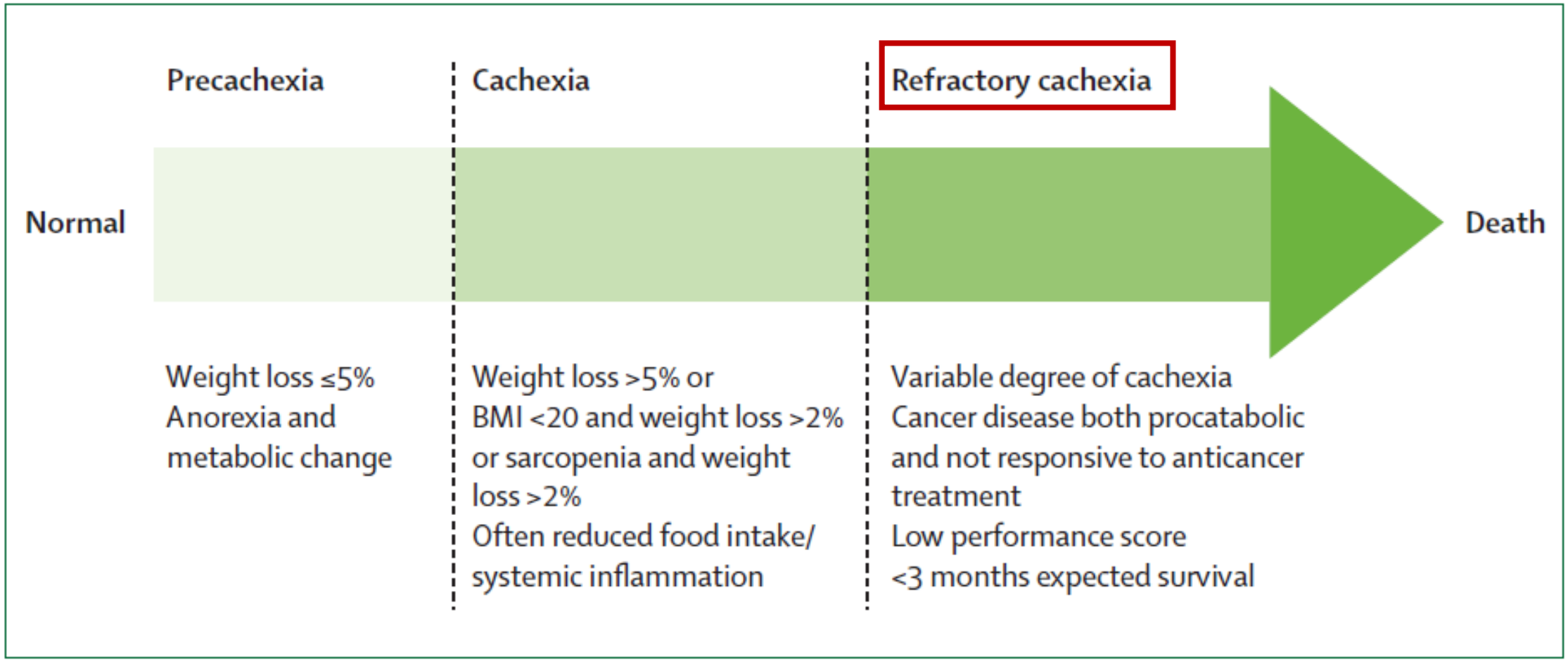
# Tumorska kaheksija i anoreksija: izgled bolesnika
## vlastite slike





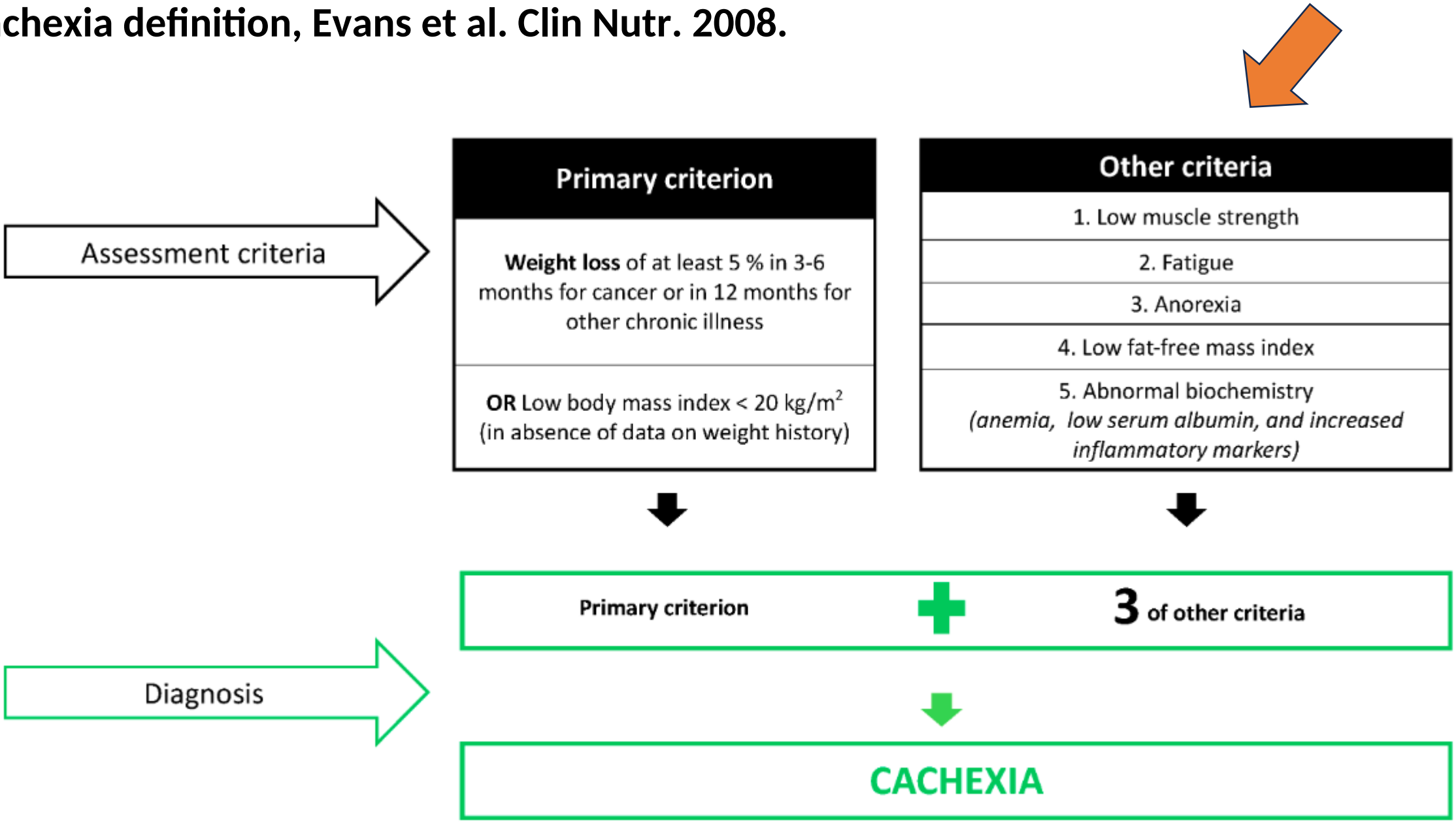
# Definicija kaheksije > „radna-opisna” definicija, klinički nevoljni gutitak težine i apetita

## „no robust biomarkers to identify those precachectic patients ..... „



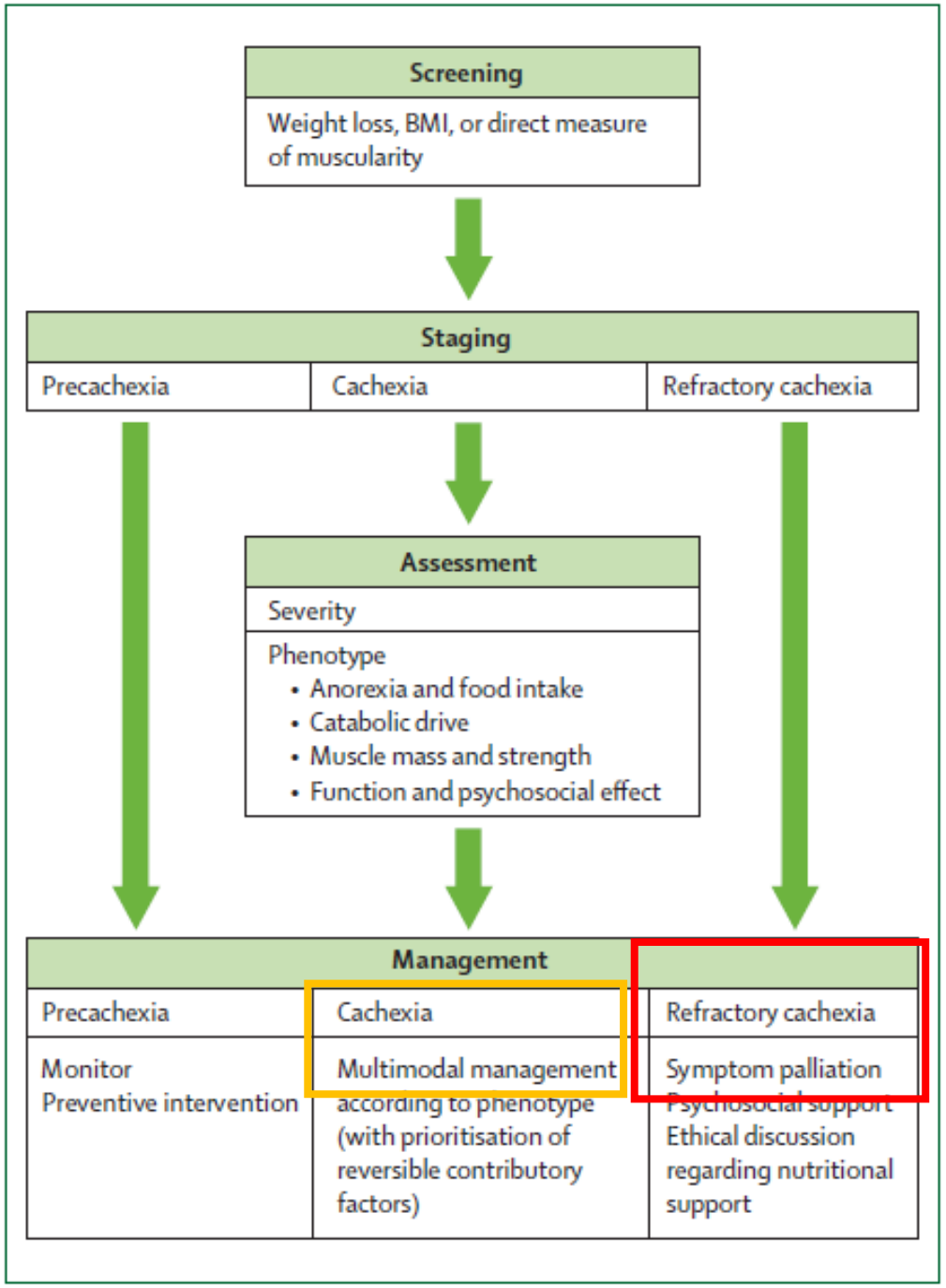

**Fearon K**, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S, Baracos VE. Definition and classification of **cancer cachexia**: an international consensus. **Lancet Oncol. 2011** May;12(5):489-95. doi: 10.1016/S1470-2045(10)70218-7. Epub 2011 Feb 4. PMID: 21296615.

# Cachexia definition, Evans et al. Clin Nutr. 2008.




Evans WJ, Morley JE, Argilés J, et al. Cachexia: a new definition. **Clin Nutr. 2008** Dec;27(6):793-9. doi: 10.1016/j.clnu.2008.06.013. Epub 2008 Aug 21. PMID: 18718696.

# Algoritam zbrinjavanja tumorske kaheksije




**Fearon K** et al. Definition and classification of cancer cachexia: an international consensus. **Lancet Oncol. 2011** May;12(5):489-95. doi: 10.1016/S1470-2045(10)70218-7. Epub 2011 Feb 4. PMID: 21296615.

# Osnovne kliničke karakteristike kaheksije u onkoloških bolesnika

- Uznapredovala tumorska bolest u bolesnika u liječenih (> u progresiji) ili u neliječenih
- Gubitak apetita
- Gubitak težine
- Gubitak mišične snage, zamor, slabost
- **Pogoršanje kvalitete života**
- **Nepodnošenje onkološkog liječenja, odgađanje, nuspojave**
- **Povišena smrtnost**

# Osnovne kliničke karakteristike kaheksije u onkoloških bolesnika

- **Sistemna bolest – bolest cijelog organizma**
- Multiorganska zahvaćenost
- Paraneoplastični sindrom
- Različit stupanj učestalosti u raznih vrsta tumora
  - Rak pluća i gušterače **vs.** melanom, rak dojke
- Povišena vrijednost proinflamatornih citokina - sustavno upalno stanje
- **Metabilizam pomaknut u smjeru kataboličkih procesa**
  - Lipoliza i proteoliza
  - Prevladaju katabolički hormoni
  - U hipotalamusu u centru za hranjenje pomak u smjeru **anoreksije**

# Razmatranje patogeneze i liječenja

- U različitih karcinoma različitost u pojedinim molekularnim alteracijama
- **Nije dovoljno gledati samo odnos unosa i potrošnje kalorija**
- **Masno tkivo (WAT i BAT)**:
  - Nije samo skladište energije
  - **Regulatorna uloga** putem adipokina na metabolizam, upalne procese i apetit
- **Aminokiseline (AA) i proteini**:
  - Supstrat za biološke strukture, enzime, mišiće (motori za pokretanje)
  - EAAs: **signalna/regulatorna uloga** (metabokini)
  - Energetski supstrat: deaminacija AA i proteoliza > glukoneogeneza i ketogeneza

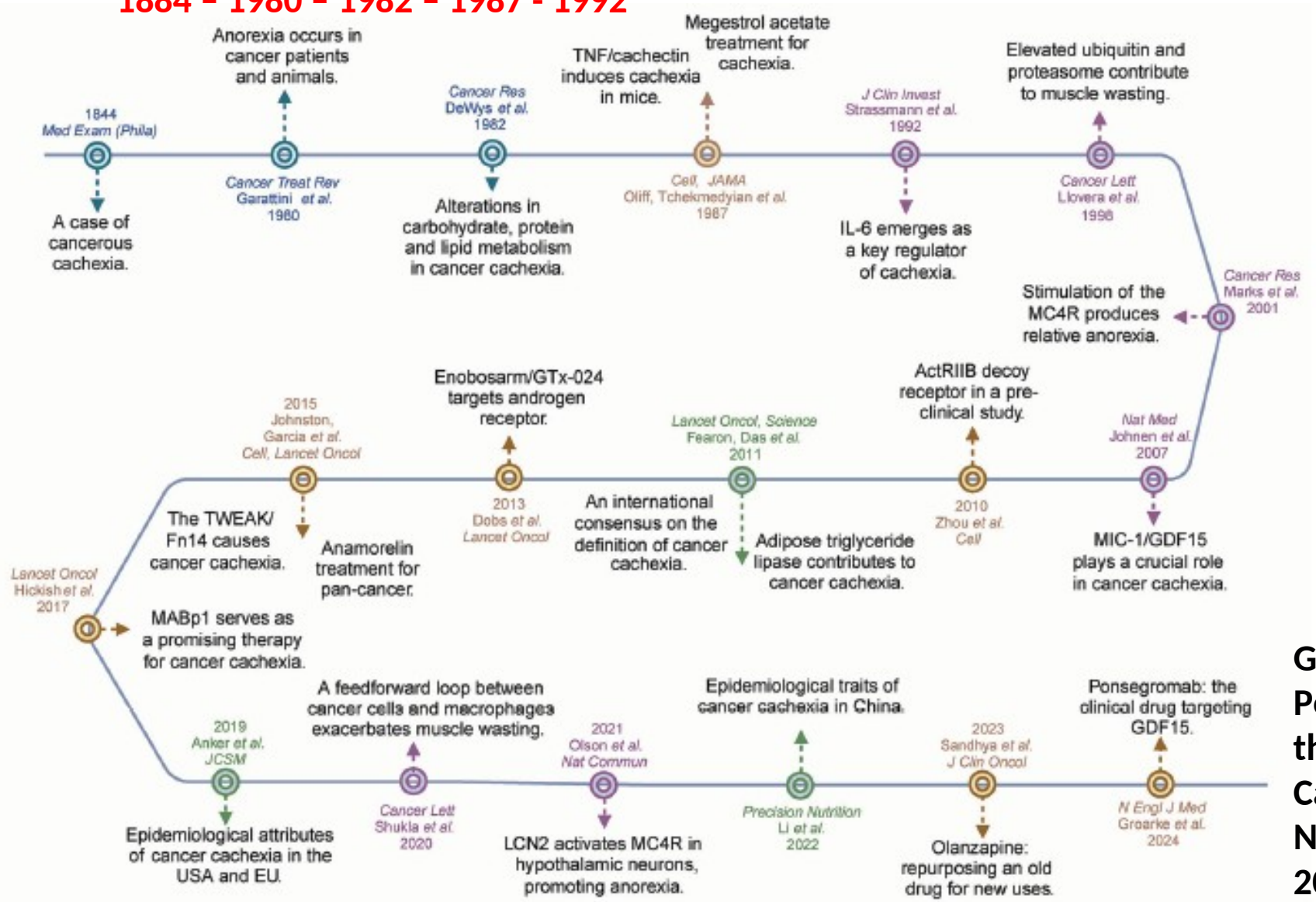
# Razmatranje patogeneze i liječenja

- **Proupalni citokini**: TNF-alfa, IL-6, IL-1b, TGF-15, ……
  - aktivacija  transkripcijskih faktora (NF-kB, STAT3) i UPS-a.
- **Hormoni**:
  - anabolički: inzulin, testosteron, hormon rasta
  - katabolički i hormoni stresa: kortizol, kateholamini, glukagon
    - Rezistencija na inzulin, glikogenoliza, proteoliza, glukoneogeneza, lipoliza
- **Sastav tijela**:
  - lean body mass (fat-free mass), sadržaj mišića, sadržaj masnog tkiva
    - bioelectric impendance
- **Mišična snaga**:
  - mjerenje

# Vremenski slijed i ključne etape u proučavanju tm. kaheksije

**Hipokrat iz 3. i 4. stoljeća pr. Kr.**

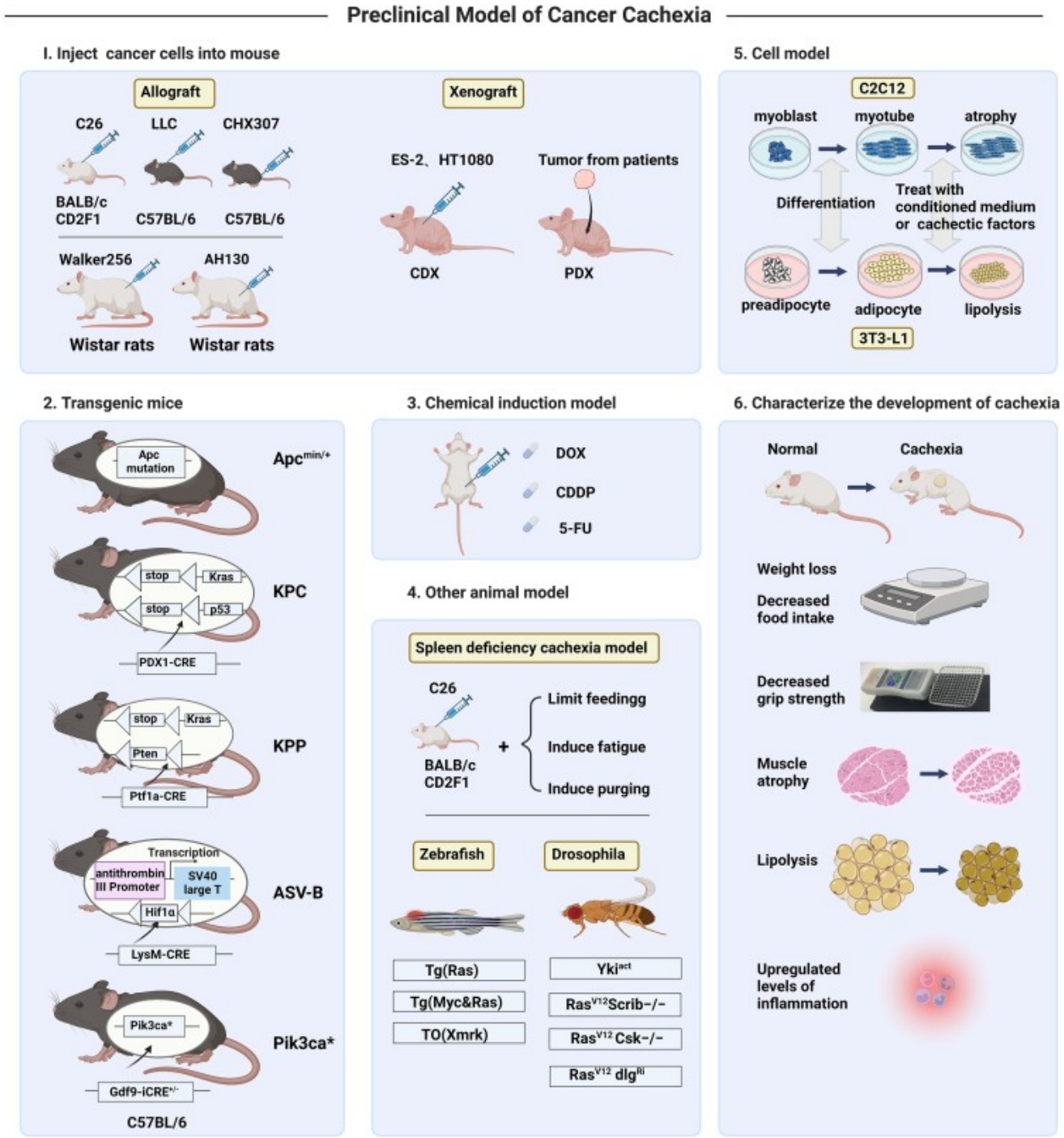
**1884 – 1980 – 1982 – 1987 - 1992 TNFa and Megestrol acetate; IL-6**




**Groarke JD et. al. Ponsegromab for the Treatment of Cancer Cachexia. N Engl J Med. 2024**

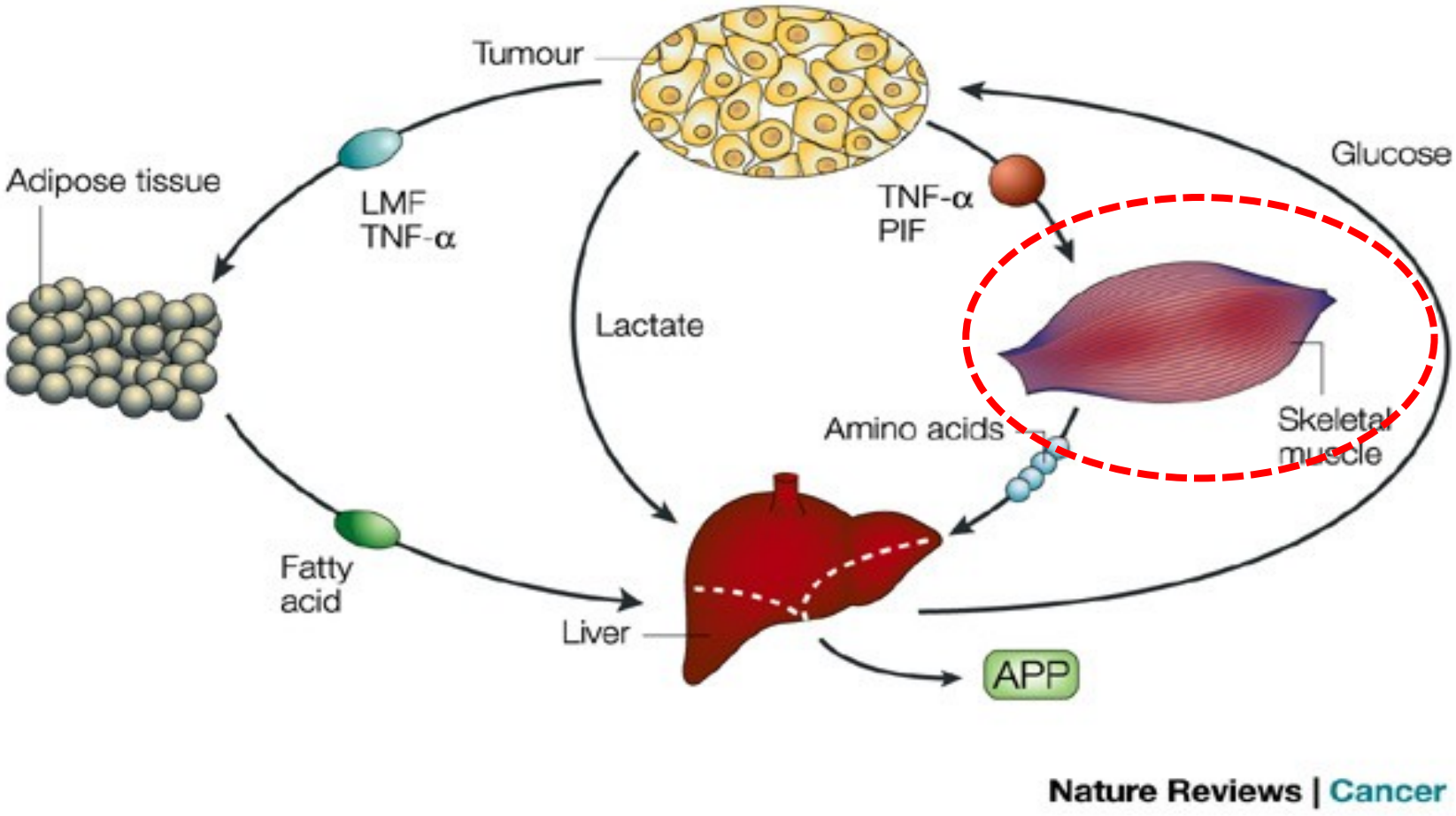
Tan Y, Xue R, Pan Y, He Z, Hu X, Li Y, Li K, Zhang X, Bian XW, Wang B. Cancer cachexia: molecular basis and therapeutic advances. Signal Transduct Target Ther. 2026 Jan 13;11(1):16. doi: 10.1038/s41392-025-02331-7. PMID: 41526343; PMCID: PMC12795897.

# Various preclinical model of cancer cachexia




Li L, Wazir J, Huang Z, Wang Y, Wang H. A comprehensive review of animal models for cancer cachexia: Implications for translational research. Genes Dis. 2023 Sep 13;11(6):101080. doi: 10.1016/j.gendis.2023.101080. PMID: 39220755; PMCID: PMC11364047.

# Kaheksija: složeni metabolički poremećaji + anoreksija

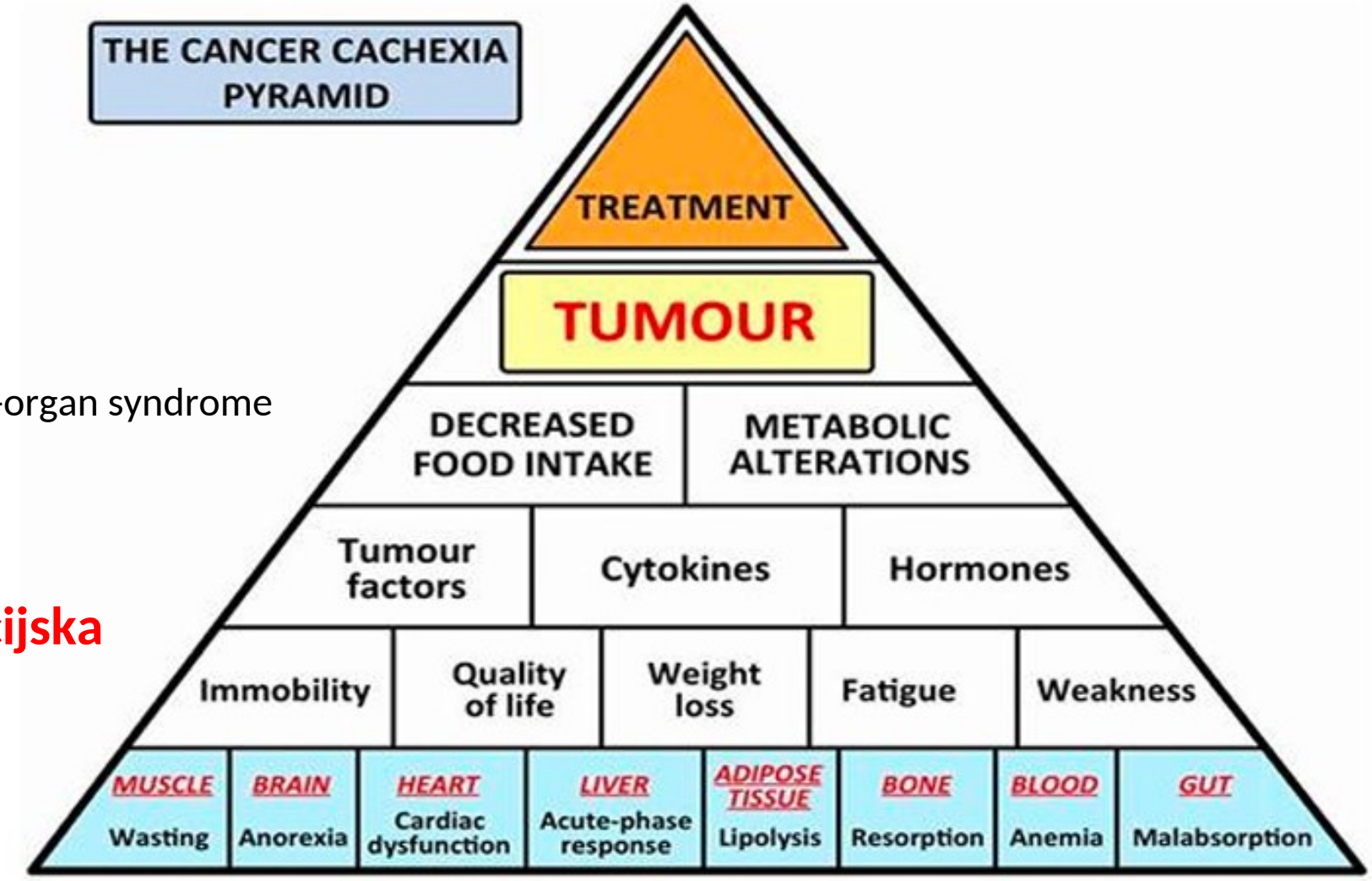



Tisdale MJ. Cachexia in cancer patients. Nat Rev Cancer. 2002 Nov;2(11):862-71. doi: 10.1038/nrc927. PMID: 12415256.

# Piramida tm. kaheksije koja prikazuje to stanje kao multiorganski sindrom

multi-organ syndrome

**Multiorganska i multifunkcijska pogođenost**




Singh AV, Ahmad F, Neem SS. Cancer chemotherapy-induced cachexia: the orphan disease .IJPSR 2025; 16 (9): 2430-41. DOI: 10.13040/IJPSR.0975-8232.16(9).

# Važnost ranog prepoznavanje tm. kaheksije i anoreksije ?

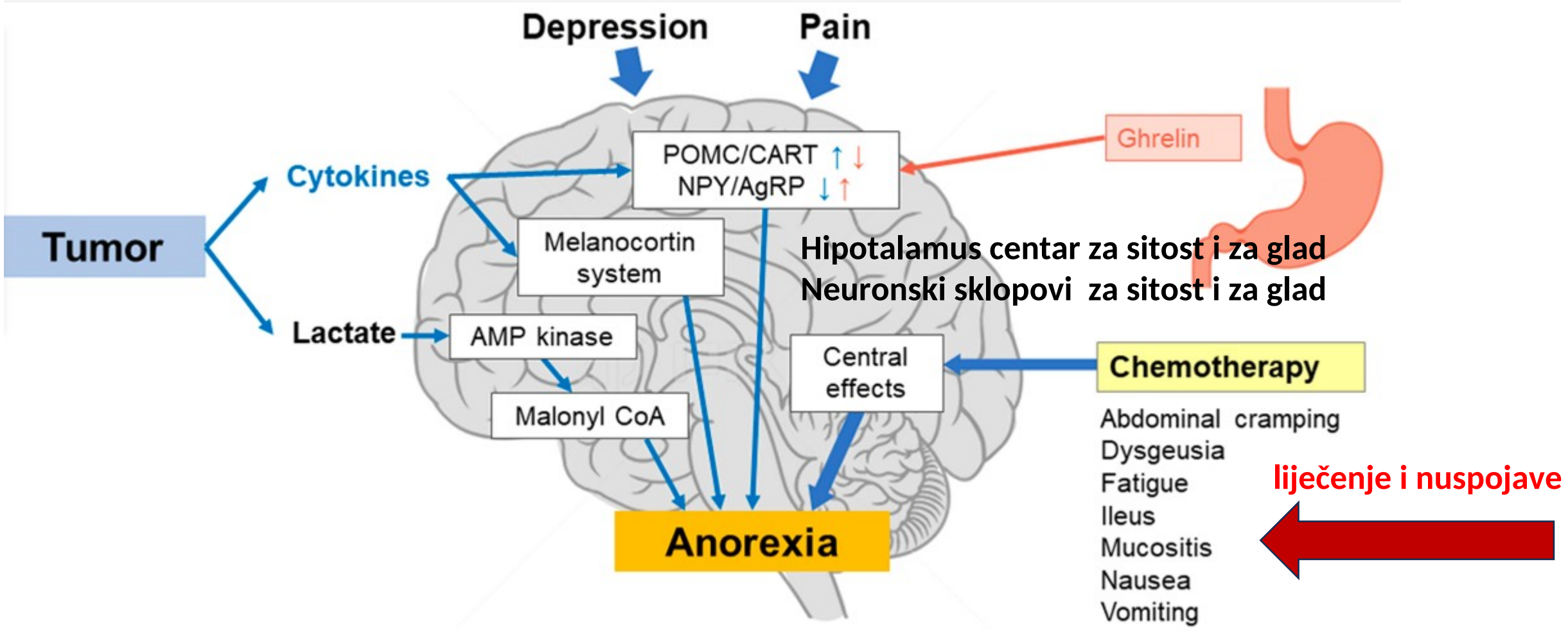
vlastite slike

**> uspješnije liječenje, manje nuspojava**



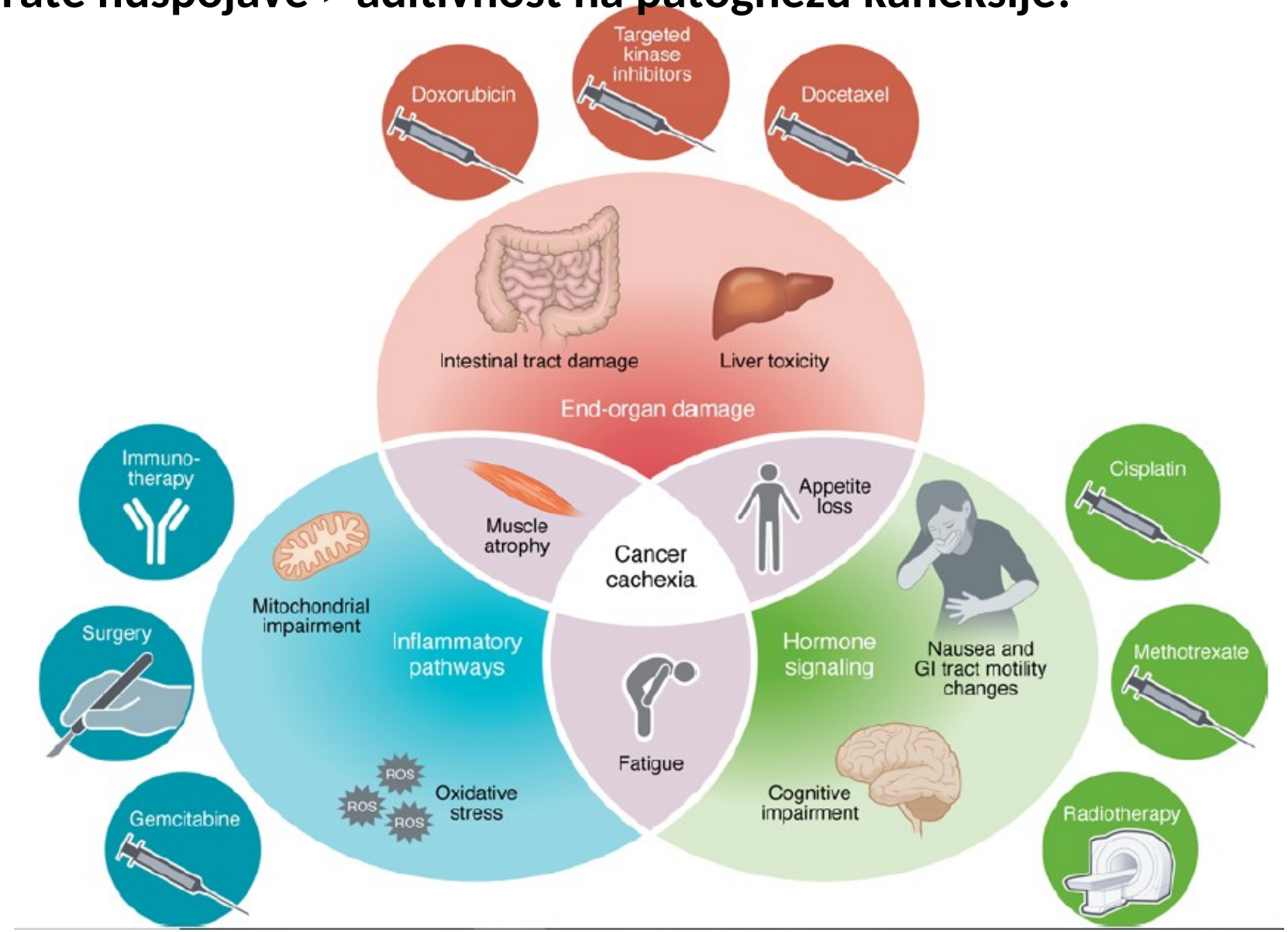


# Onkološki bolesnik i liječenje i nuspojave ?



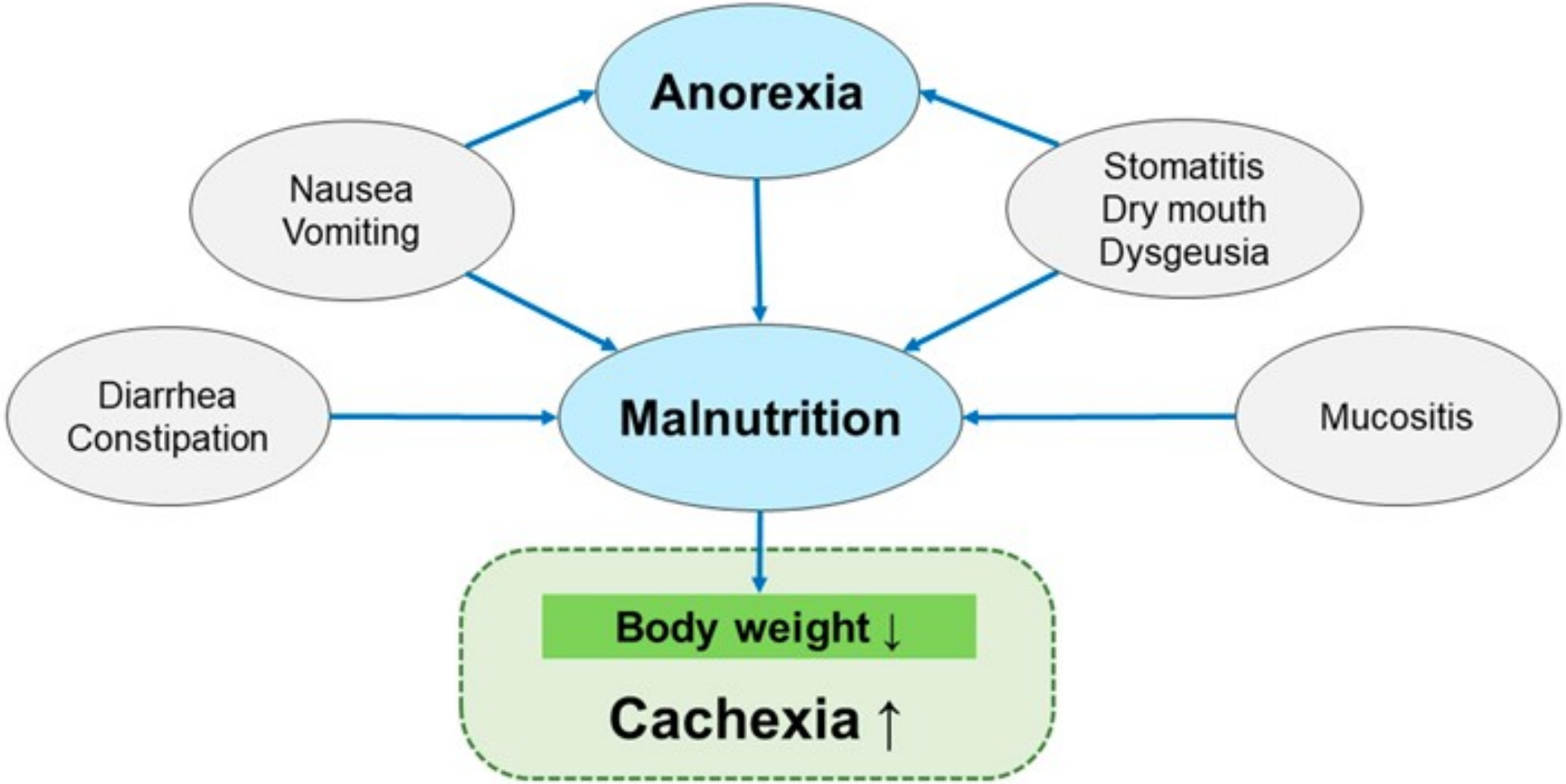

Takahashi S, Matsumoto K, Ohba K, Nakano Y, Miyazawa Y, Kawaguchi T. The Incidence and Management of Cancer-Related Anorexia During Treatment with Vascular Endothelial Growth Factor Receptor-Tyrosine Kinase Inhibitors. Cancer Manag Res. 2023 Sep 22;15:1033-1046. doi: 10.2147/CMAR.S417238. PMID: 37771675; PMCID: PMC10522463.

# Onkološko liječenje s pratećim nuspojavama
# Svaki th. modalitet prate nuspojave > aditivnost na patognezu kaheksije!



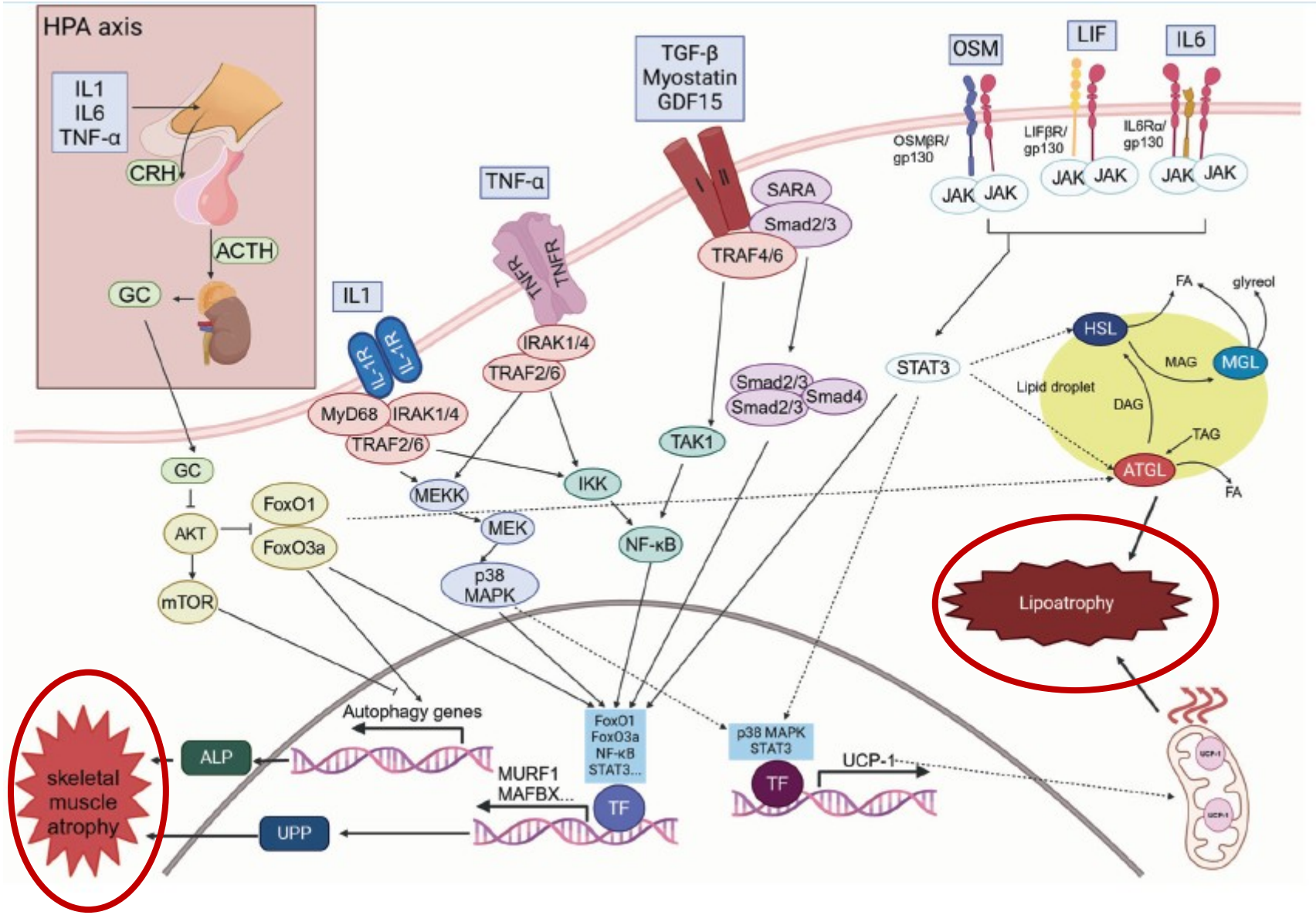

Thakir TM, Wang AR, Decker-Farrell AR, Ferrer M, Guin RN, Kleeman S, Levett L, Zhao X, Janowitz T. Cancer therapy and cachexia. J Clin Invest. 2025 Aug 1;135(15):e191934. doi: 10.1172/JCI191934. PMID: 40759570; PMCID: PMC12321403.

# „Jednostavnije” nuspojave onkološkog liječenja > anoreksija, malnutricija > kaheksija



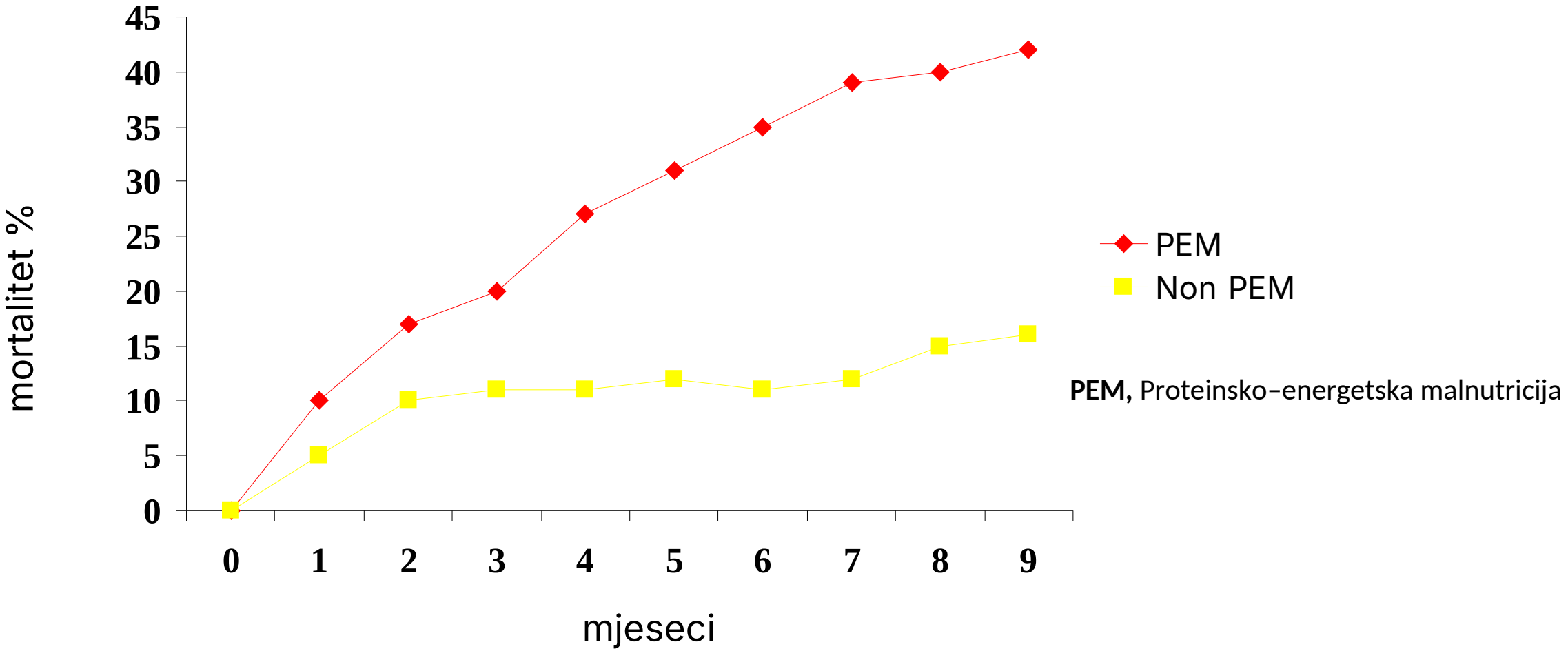

Takahashi S, Matsumoto K, Ohba K, Nakano Y, Miyazawa Y, Kawaguchi T. The Incidence and Management of Cancer-Related Anorexia During Treatment with Vascular Endothelial Growth Factor Receptor-Tyrosine Kinase Inhibitors. Cancer Manag Res. 2023 Sep 22;15:1033-1046. doi: 10.2147/CMAR.S417238. PMID: 37771675; PMCID: PMC10522463.

# Složeniji uvid: molekularna zbivanja s posljedicom razgradnje mišića i masti




Tan Y, Xue R, Pan Y, He Z, Hu X, Li Y, Li K, Zhang X, Bian XW, Wang B. Cancer cachexia: molecular basis and therapeutic advances. Signal Transduct Target Ther. 2026 Jan 13;11(1):16. doi: 10.1038/s41392-025-02331-7. PMID: 41526343; PMCID: PMC12795897.

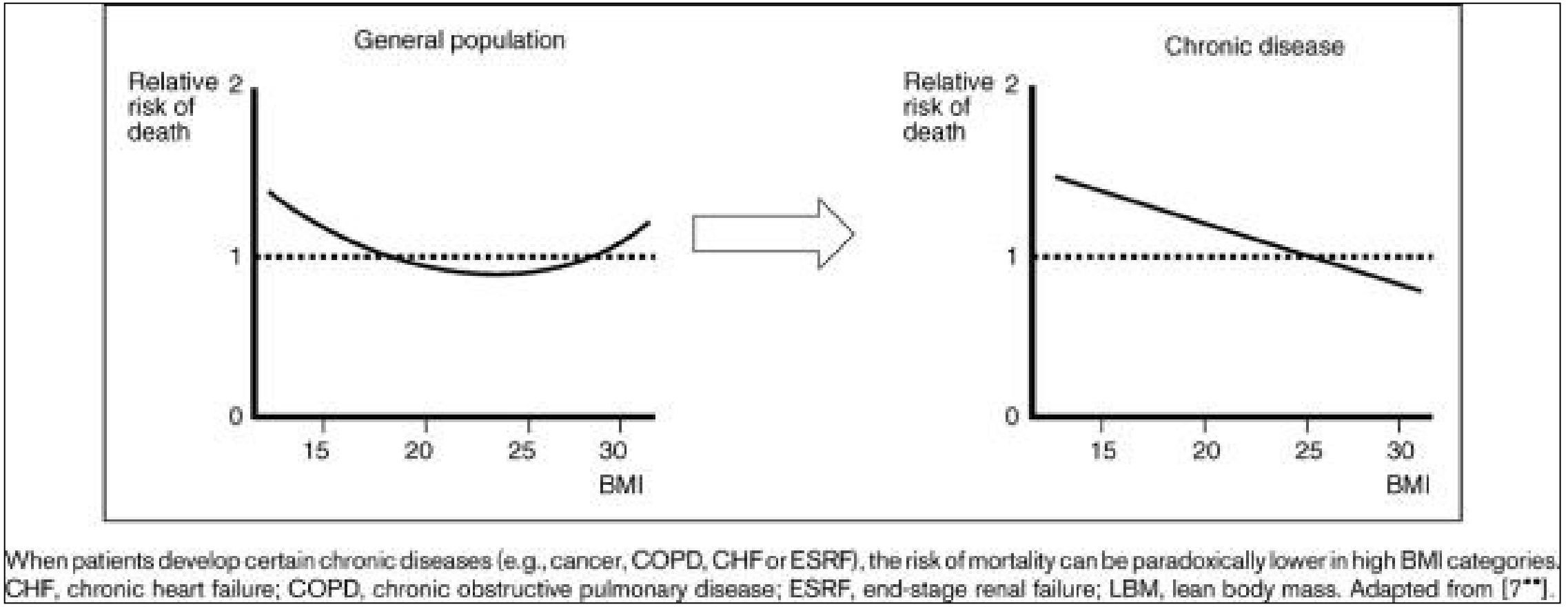
# Malnutricija i mortalitet




**PEM,** Proteinsko–energetska malnutricija

Cederholm T, Jägrén C, Hellström K. Outcome of protein-energy malnutrition in elderly medical patients. Am J Med. 1995 Jan;98(1):67-74. doi: 10.1016/S0002-9343(99)80082-5. PMID: 7825621.

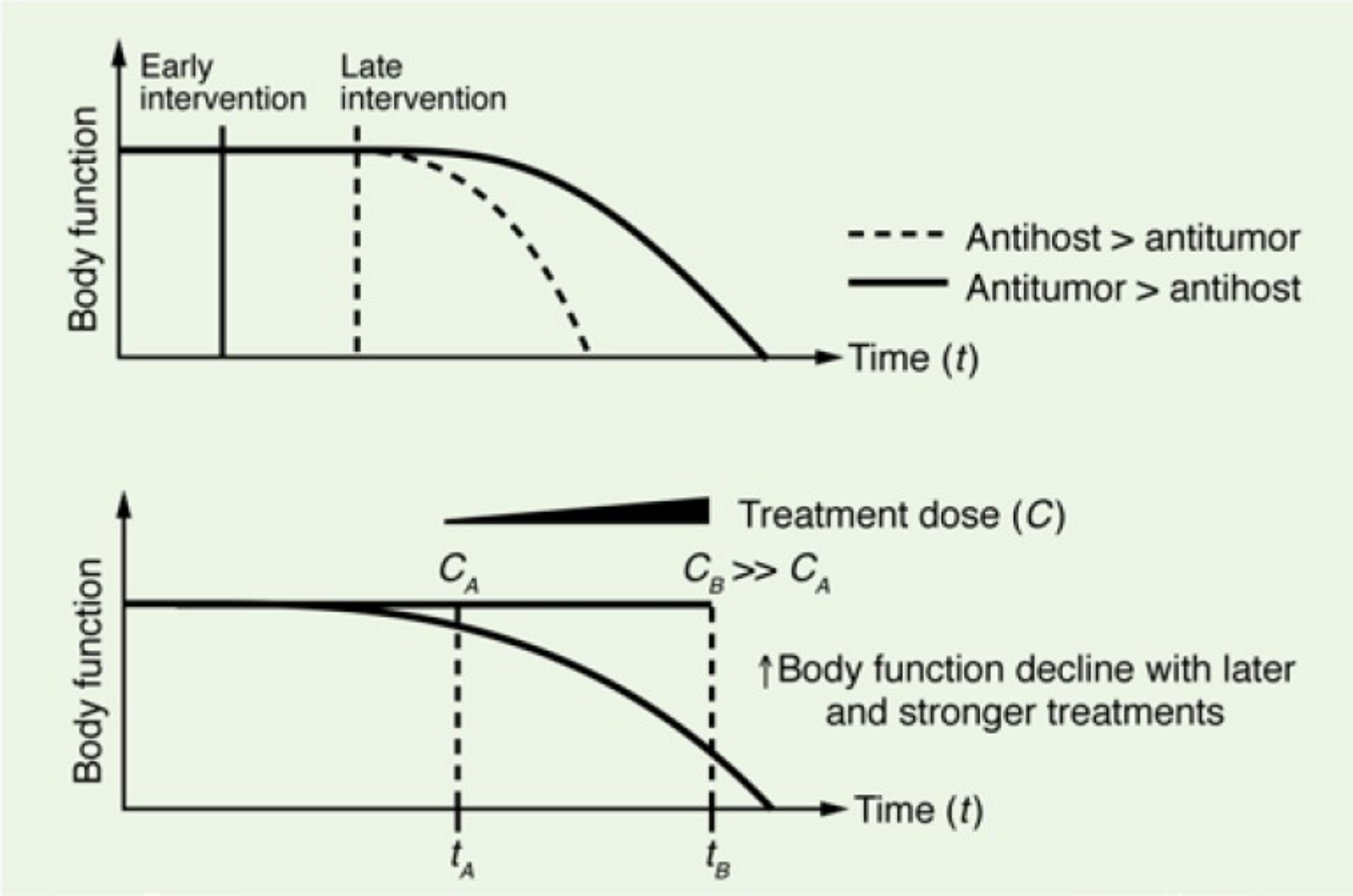
# Paradoks čimbenika rizika – važnost ishranjenosti kod kroničnih bolesti




When patients develop certain chronic diseases (e.g., cancer, COPD, CHF or ESRF), the risk of mortality can be paradoxically lower in high BMI categories. CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; ESRF, end-stage renal failure; LBM, lean body mass. Adapted from [7••].

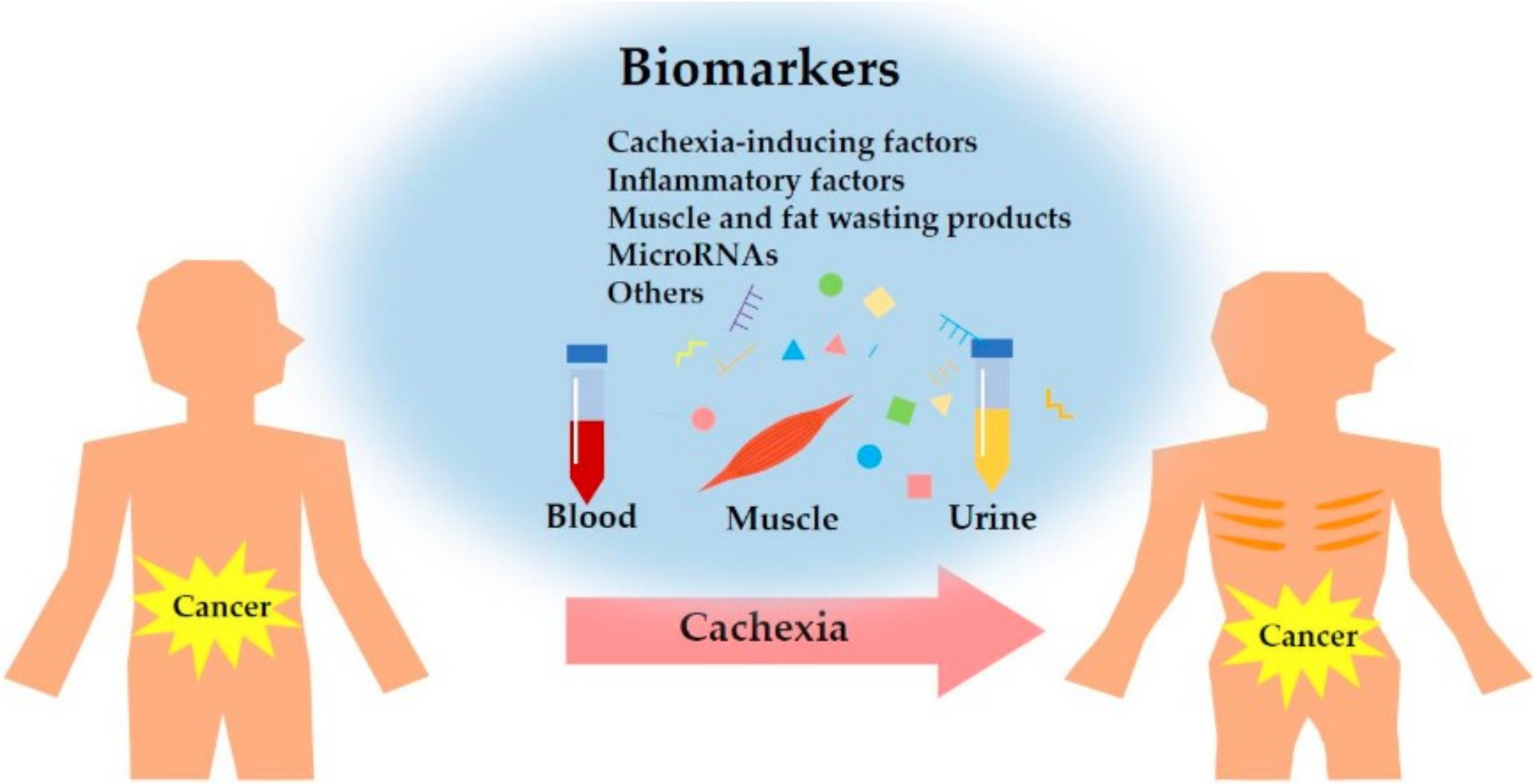
Tan BH, Fearon KC. Cachexia: prevalence and impact in medicine. Curr Opin Clin Nutr Metab Care. 2008 Jul;11(4):400-7. doi: 10.1097/MCO.0b013e328300ecc1. PMID: 18541999.

# Važnost primjerenosti onkološkog liječenja na ishod i kaheksiju – oprez!




Thakir TM, Wang AR, Decker-Farrell AR, Ferrer M, Guin RN, Kleeman S, Levett L, Zhao X, Janowitz T. Cancer therapy and cachexia. J Clin Invest. 2025 Aug 1;135(15):e191934. doi: 10.1172/JCI191934. PMID: 40759570; PMCID: PMC12321403.

# Definitivna potreba ranog prepoznavanja tm. kaheksije: biomarkeri ?

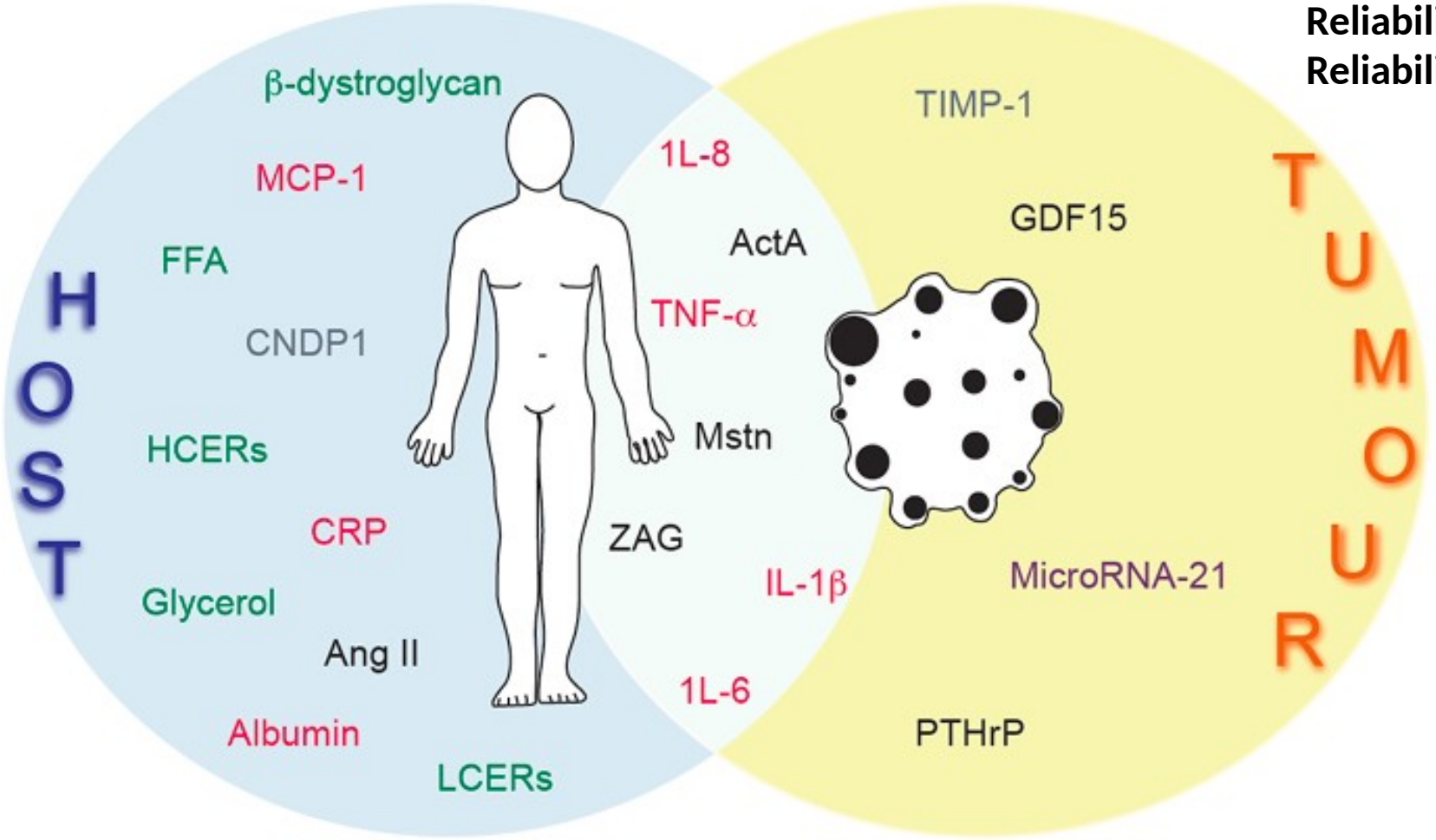



Cao Z, Zhao K, Jose I, Hoogenraad NJ, Osellame LD. Biomarkers for Cancer Cachexia: A Mini Review. Int J Mol Sci. 2021 Apr 26;22(9):4501. doi: 10.3390/ijms22094501. PMID: 33925872; PMCID: PMC8123431.

# Stanično porijeklo biomarkera

## Niti jedan pojedinačni biomarker nije dovoljan!

**Biomarkers ?**
**Availability of testing**
**Validated status**
**Reliability**
**Reliability in all patients and cancers**




Cao Z, Zhao K, Jose I, Hoogenraad NJ, Osellame LD. Biomarkers for Cancer Cachexia: A Mini Review. Int J Mol Sci. 2021 Apr 26;22(9):4501. doi: 10.3390/ijms22094501. PMID: 33925872; PMCID: PMC8123431.

## Sažetak potencijalnih biomarkera

## Niti jedan pojedinačni biomarker nije dovoljan!

**Table 1.** Summary of potential biomarkers.

| Origin | Potential Biomarkers [1] |
|---|---|
| Cachexia-inducing factors | ActA, MSTN, GDF15, PTHrP, ZAG, Ang II, MURF-1, Atrogin-1 |
| Inflammatory factors | TNF-α, IL-6, IL-1β, IL-8, MCP-1, CRP, Albumin |
| Muscle and fat wasting products | β-dystroglycan, Glycerol, FFA, HCERs, LCERs |
| MicroRNAs | MicroRNA-21, MicroRNA-203, MicroRNA-130a |
| Other factors | CNDP1, TIMP-1 |

[1] ActA (Activin A), MSTN (Myostatin), GDF15 (Growth/differentiation factor 15), PTHrP (Parathyroid Hormone release Peptide), ZAG (Zinc-α2-glycoprotein), Ang II (Angiotensin II), MURF-1 (muscle RING-finger protein-1), MCP-1 (Monocyte chemoattractant protein-1), CRP (C-reactive protein), FFA (Free fatty acid), HCERs (Hexosyl-ceramides), LCERs (Lactosyl-ceramides), CNDP1 (Carnosine dipeptidase 1), TIMP-1 (Tissue inhibitor of metalloproteinases-1).

Neshan M, Tsilimigras DI, Han X, Zhu H, Pawlik TM. Molecular Mechanisms of Cachexia: A Review. Cells. 2024 Jan 29;13(3):252. doi: 10.3390/cells13030252. PMID: 38334644; PMCID: PMC10854699.

# Ponsegromab, GDF-15 i tm. kaheksija, Groarke JD et al, NEJM 2024.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 19/26, 2024 VOL. 391 NO. 24

Ponsegromab for the Treatment of Cancer Cachexia

John D. Groarke, M.B., B.Ch., M.P.H., Jeffrey Crawford, M.D., Susie M. Collins, M.Sc.,

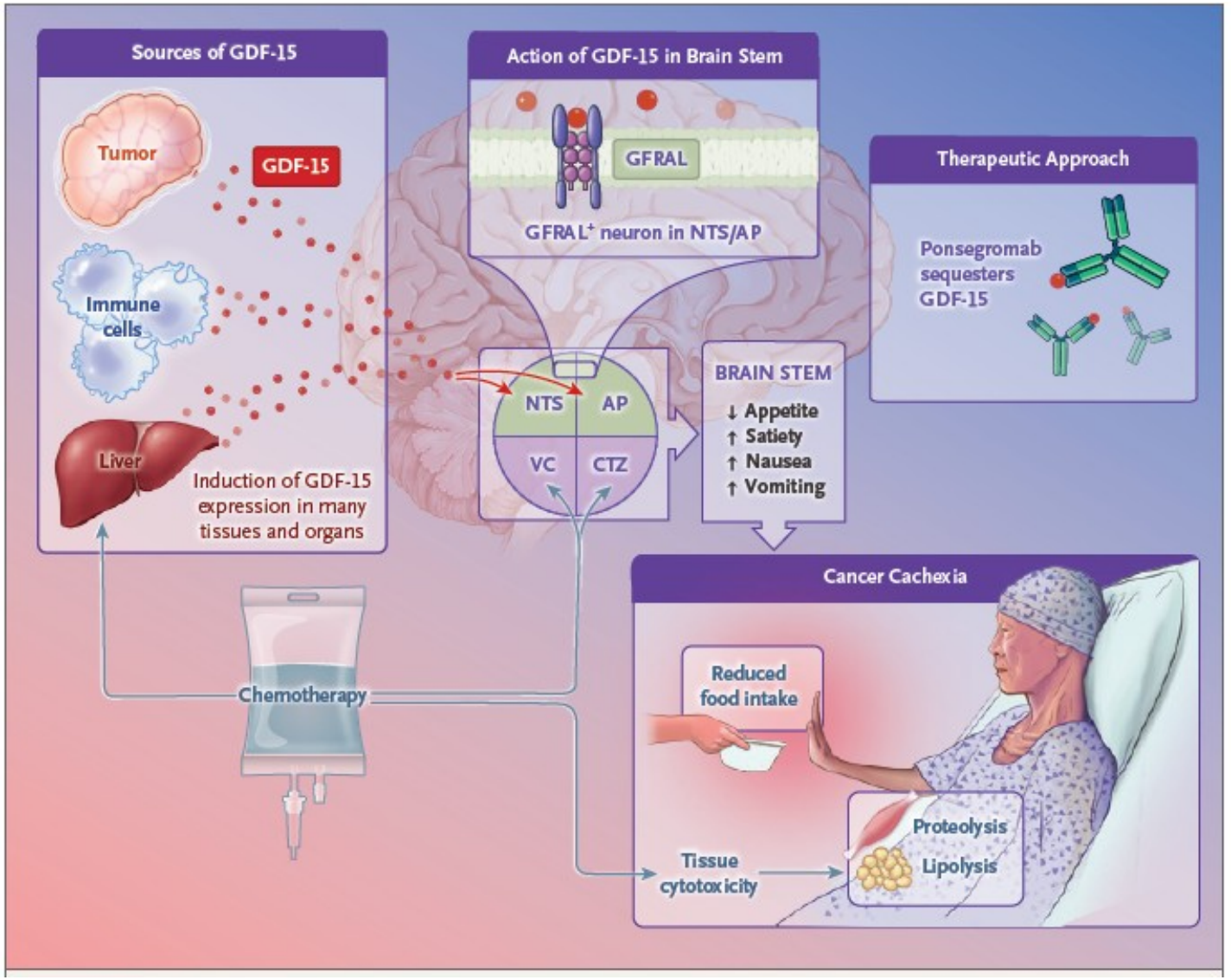
**GDF-15**: growth differentiation factor 15 is a circulating cytokine.

METHODS:

**- phase 2, 12-week trial.**

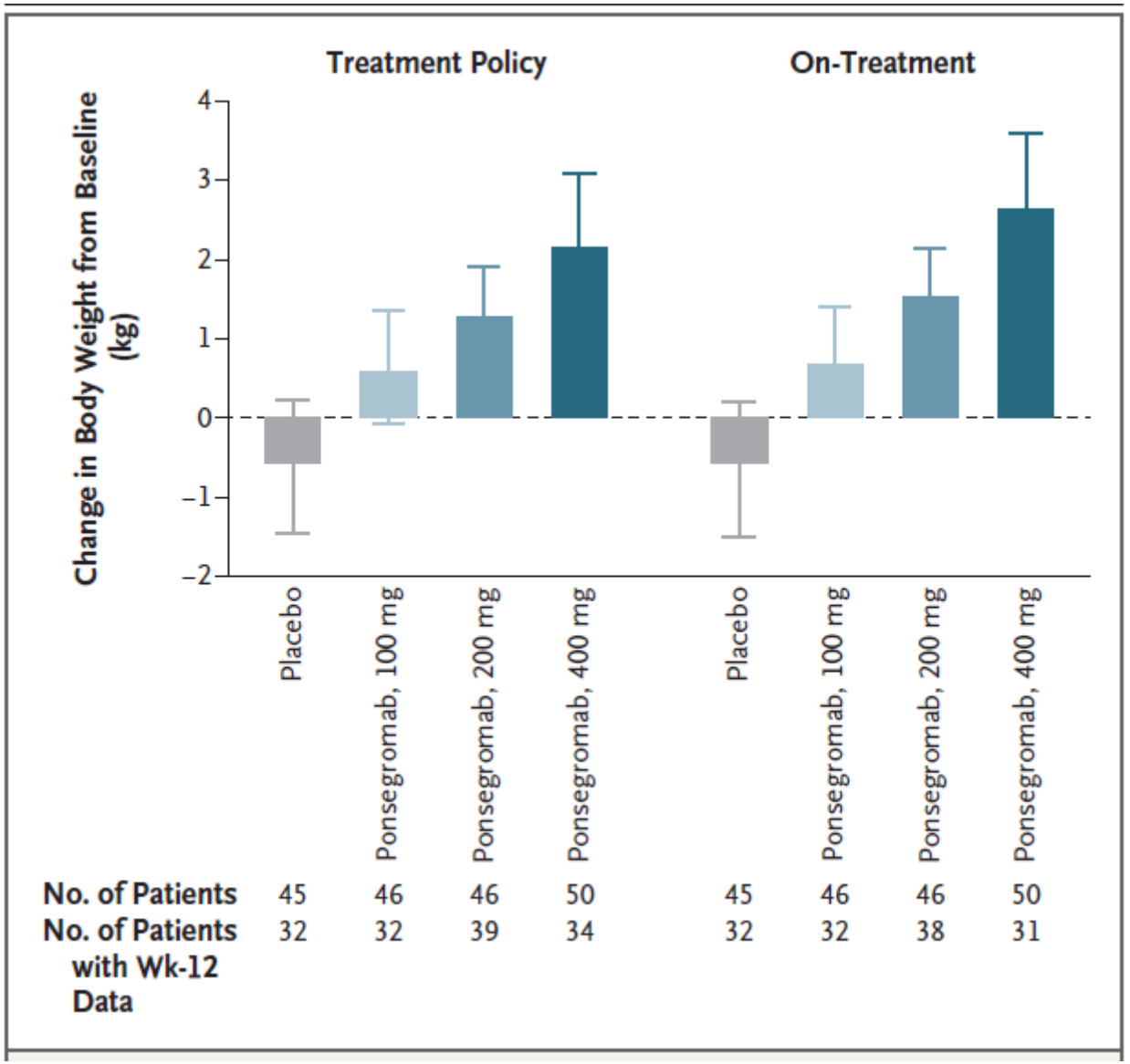
- patients with cancer cachexia and an elevated serum **GDF-15 level (≥1500 pg per milliliter**) in a 1:1:1:1 ratio to receive **ponsegromab** at a dose of 100 mg, 200 mg, or 400 mg or to receive placebo, administered subcutaneously every 4 weeks for three doses.

**- The primary end point was the change from baseline in body weight at 12 weeks. Key secondary end points were appetite and cachexia symptoms, digital measures of physical activity, and safety.**




Baracos VE. Cancer Cachexia and the Brain Stem. N Engl J Med. 2024 Dec 19;391(24):2373-2376. doi: 10.1056/NEJMe2411334. PMID: 39693548.

# Ponsegromab rezultati: promjena tjelesne težine u odnosu na početnu vrijednost nakon 12 tjedana




CONCLUSIONS:
Among patients with cancer cachexia and elevated GDF-15 levels, the inhibition of GDF-15 with ponsegromab **resulted in increased weight gain and overall activity level and reduced cachexia symptoms**, findings that confirmed the role of GDF-15 as a driver of cachexia. (ClinicalTrials.gov number, NCT05546476.)

**Groarke JD**, Crawford J, Collins SM, Lubaczewski S, Roeland EJ, Naito T, Hendifar AE, Fallon M, Takayama K, Asmis T, Dunne RF, Karahanoglu I, Northcott CA, Harrington MA, Rossulek M, Qiu R, Saxena AR. **Ponsegromab** for the Treatment of Cancer Cachexia. **N Engl J Med. 2024** Dec 19;391(24):2291-2303. doi: 10.1056/NEJMoa2409515. Epub 2024 Sep 14. PMID: 39282907.

# **Osvrt**: Ponsegromab for the Treatment of Cancer Cachexia. N Engl J Med. 2024.

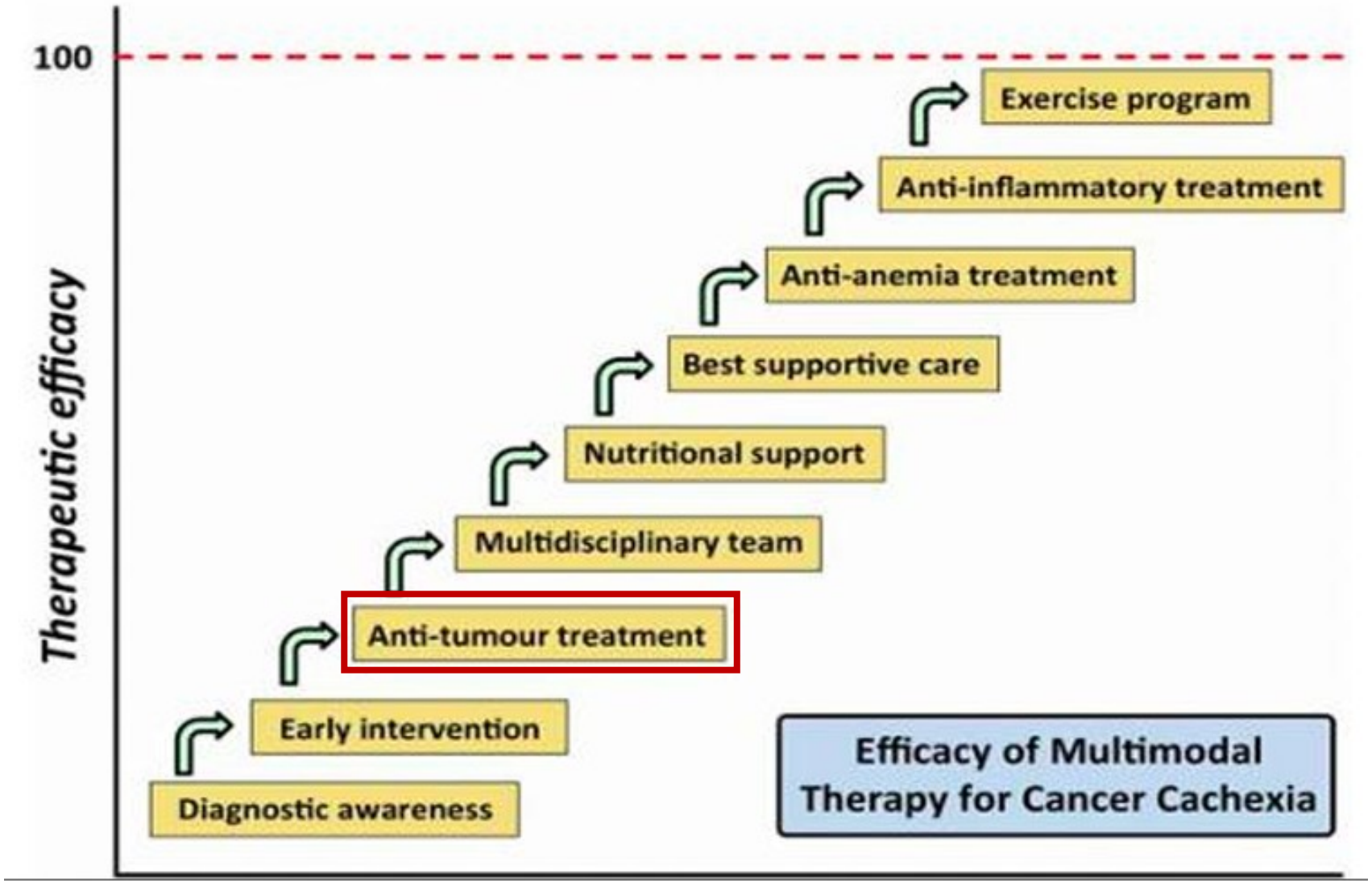
- Liječenje na temelju biomarkera GDF-15!
  - GDF-15 **vs.** multifaktorijalnost patogeneze kaheksije i multifaktorijalnost citokina!
  - Vremenska primjena ponsegrumaba (u studiji 3 mj.), što i kako nakon toga?

- Farmakoekonomika?
  - Ponsegromab **vs.** megestrol acetat, pripravci s omega-3 m. kiselinama

# Liječenje kaheksije u zaključku: rano uočavanje i multimodalni pristup (za sada suportivno)

**Liječenje kaheksije?**
**Multimodalno**
**Općenito:**
**kalorijska suplementacija**
**glukokortikoidi**
**megestrol acetat**
**kanabis**
**vježbanje**
**antipsihotik olanzapin**
**antidepresiv mirtazapin**

**Farmakološko ciljano spec.:**
**omega-3 m. kis (EPA, DHA)**
**celecoxib – inhibitor COX-2**
**talidomid**
**anamorelin – grelin mimetic**
**infliksimab > anti-TNFa**
**tocilizumab > anti-IL-6**
**ponsegromab > anti-TGF 15**




Singh AV, Ahmad F, Neem SS. Cancer chemotherapy-induced cachexia: the orphan disease .IJPSR 2025; 16 (9): 2430-41. DOI: 10.13040/IJPSR.0975-8232.16(9).