KEYS TO SLOW DOWN THE PROCESS OF CACHEXIA

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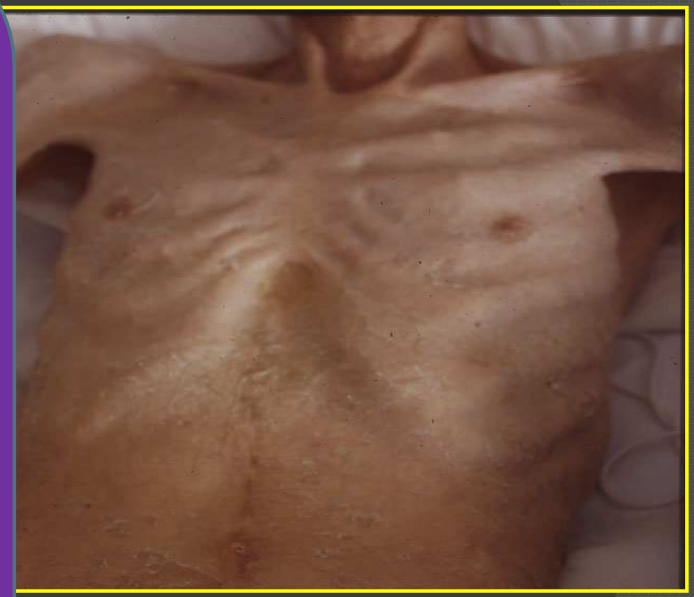
Division of hematology and medical oncology
Eda hospital

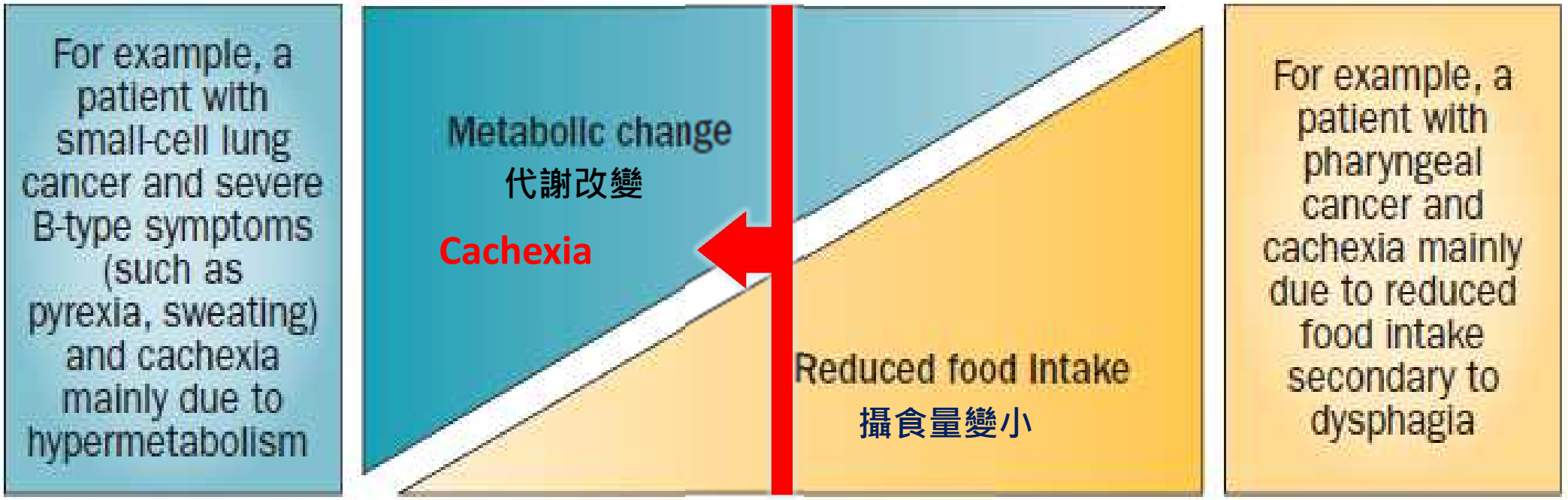
Cancer Anorexia-Cachexia Syndrome

4% weight lose: 2 year survival rate < 72%
3 year survival rate < 65%

Clin Geriatr Med 1997; 13:717-35
J Am Geriatr Soc 1995; 43:329-37



Dual Mechanisms of Cancer Cachexia



舉例：SCLC 及嚴重B型症狀
Pyrexia 發熱, sweating 發汗
cachexia mainly due to hyper-metabolism
惡病質主因為代謝速率高

舉例：pharyngeal cancer咽癌 cachexia mainly due to reduced food intake secondary to dysphagia
惡病質主因為吞嚥困難

Nat Rev Clin Oncol. 2013 Feb;10(2):90-9.

Energy metabolism in cachexia

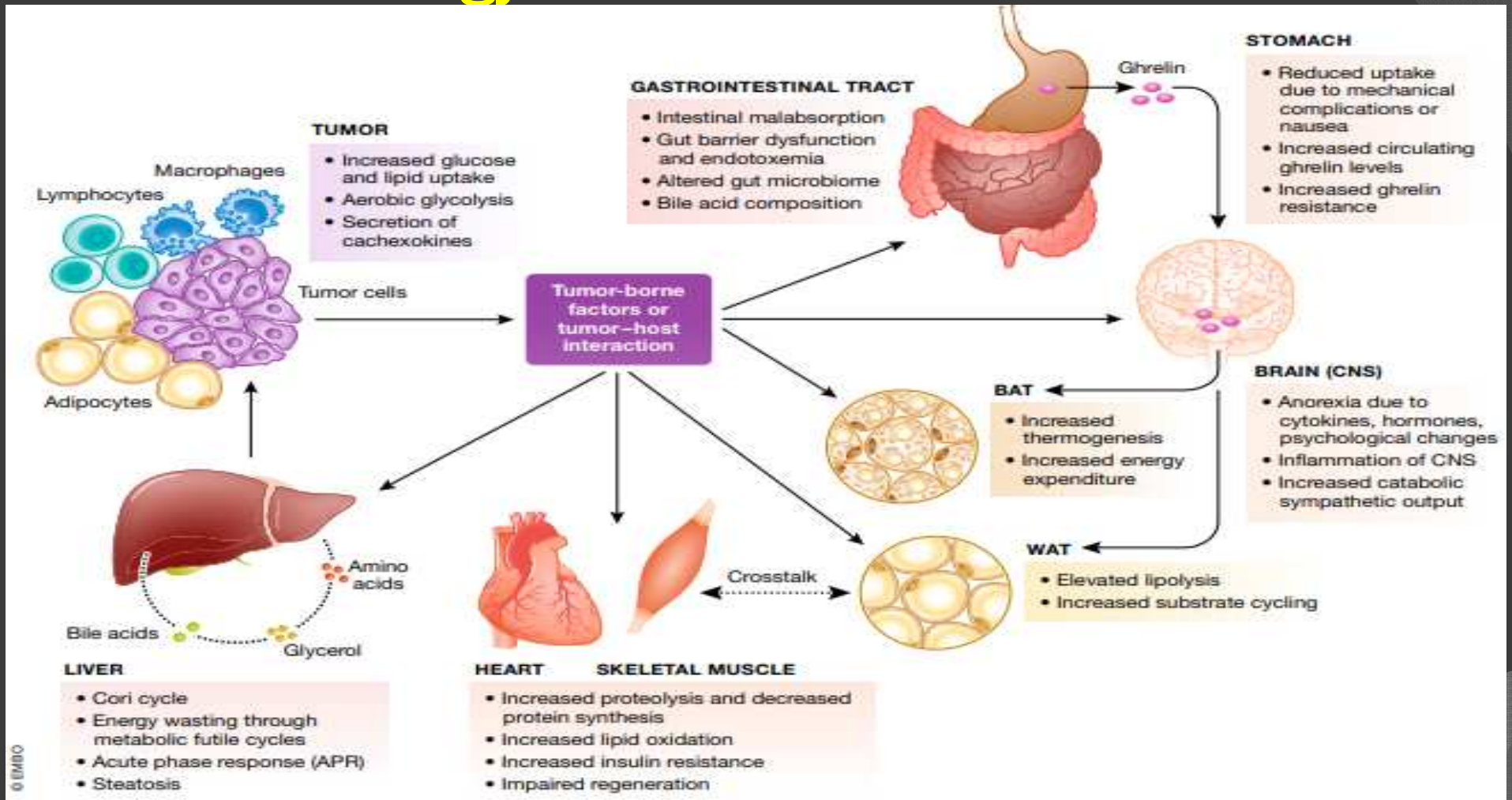
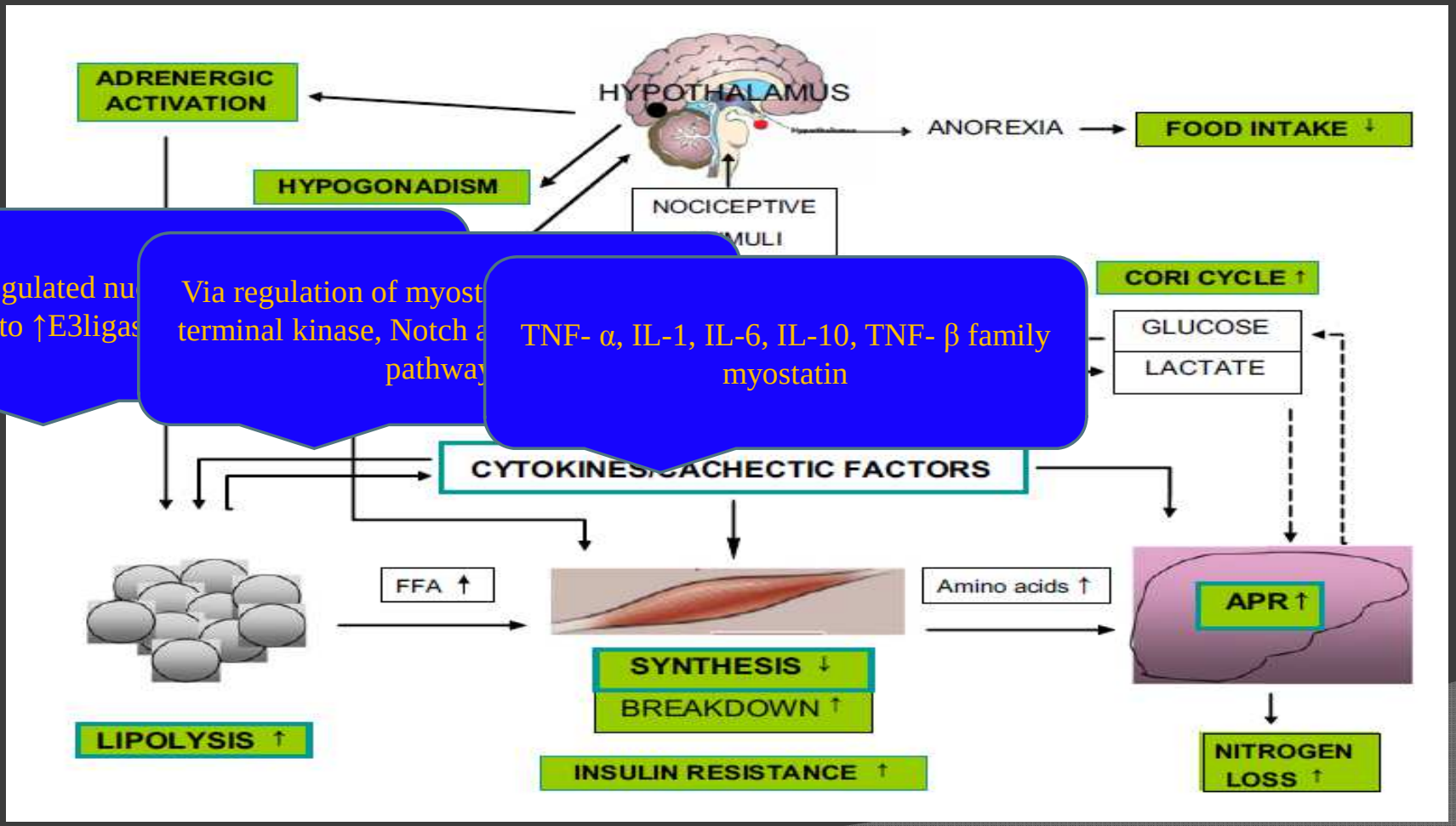


Figure 1. Overview of energy consuming processes in cachexia.

Tumor-secreted factors or tumor/host interactions reduce energy uptake and activate energy-wasting processes in different organ systems, acting on brain, CNS, adipose tissues, gastrointestinal system, liver, and muscles.

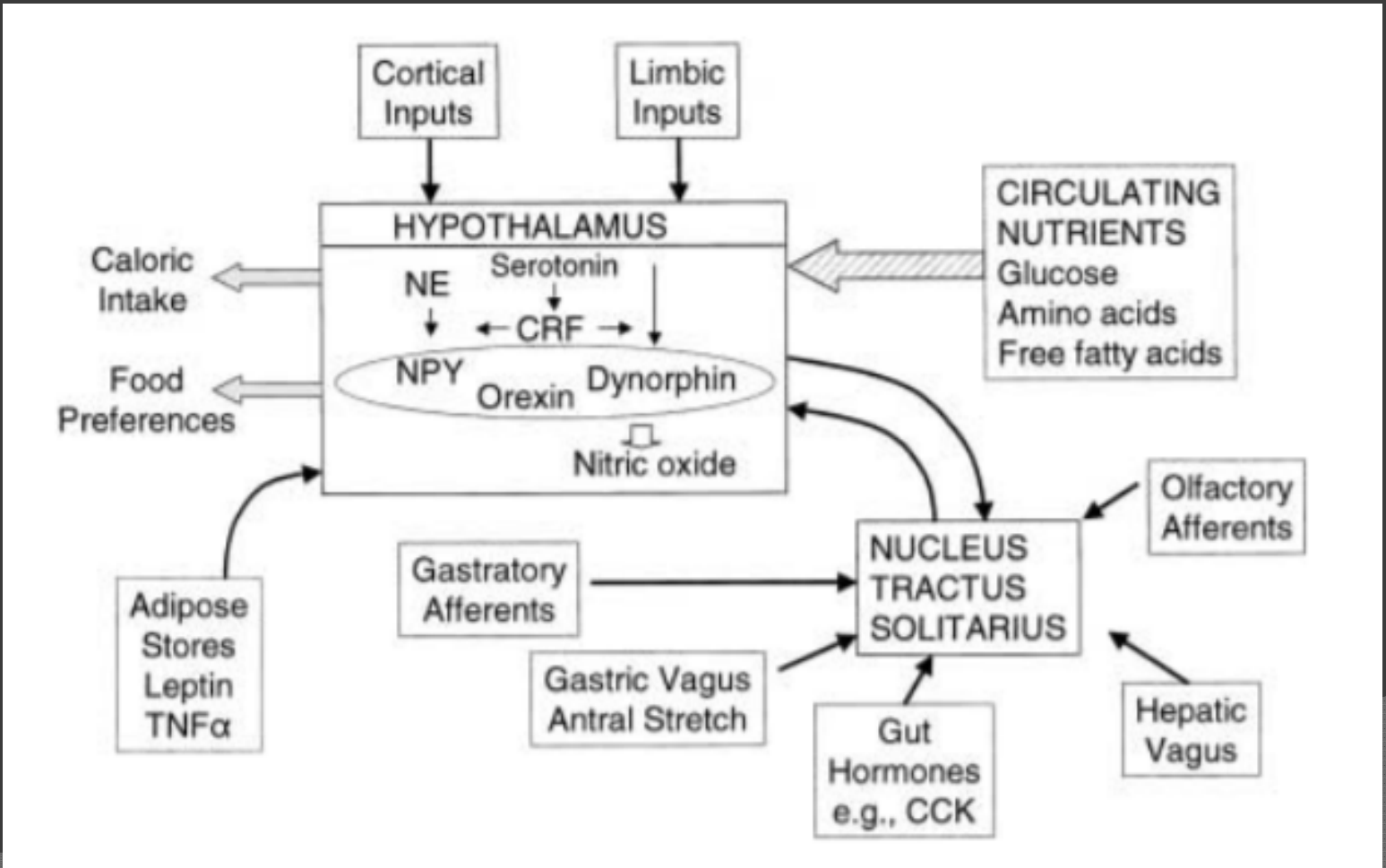
EMBO Rep. 2019 Apr;20(4):e47258.

Cachexia Mechanism

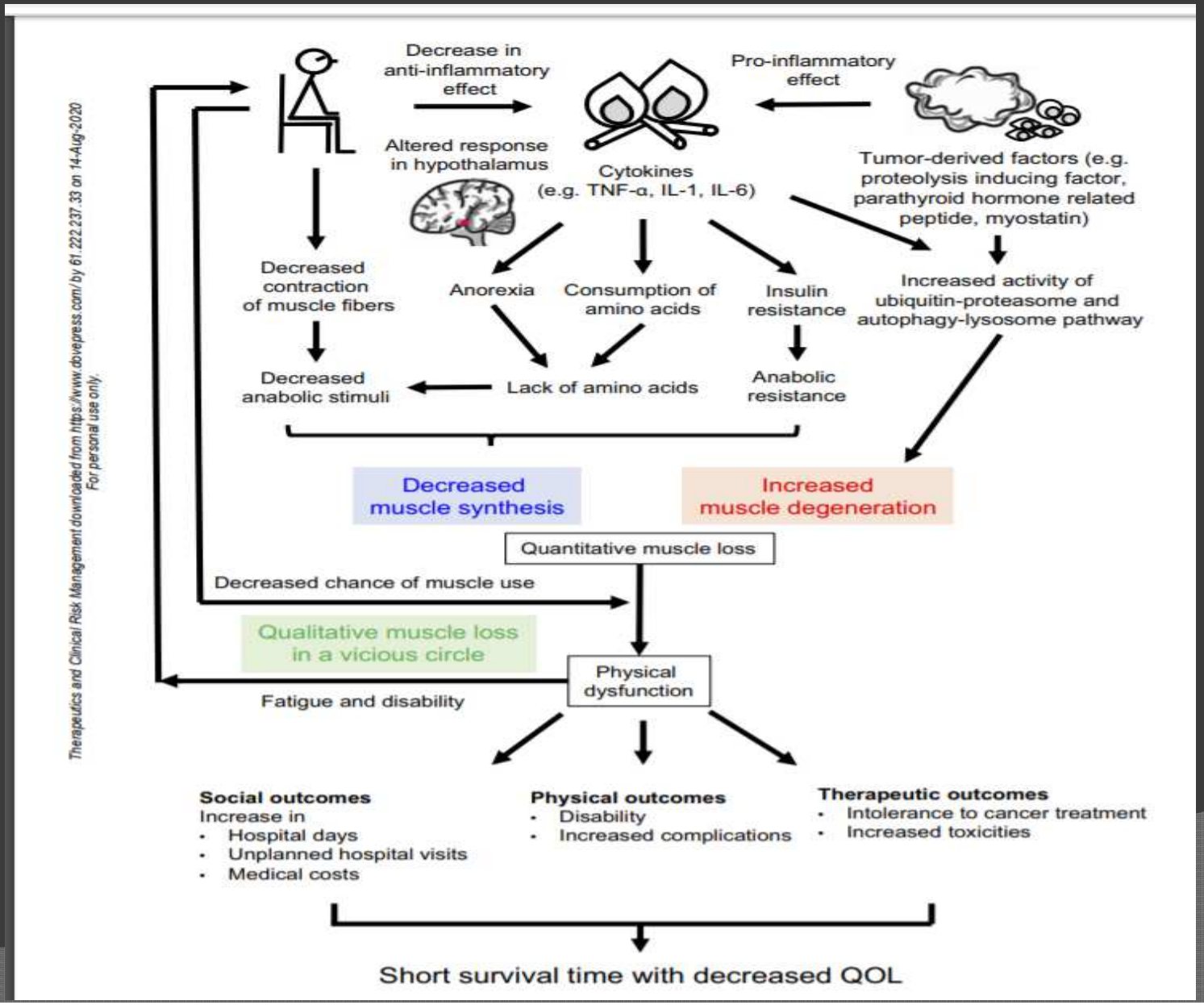


Cell metabolism 2012; 16:153-166

Regulate food intake in CNS

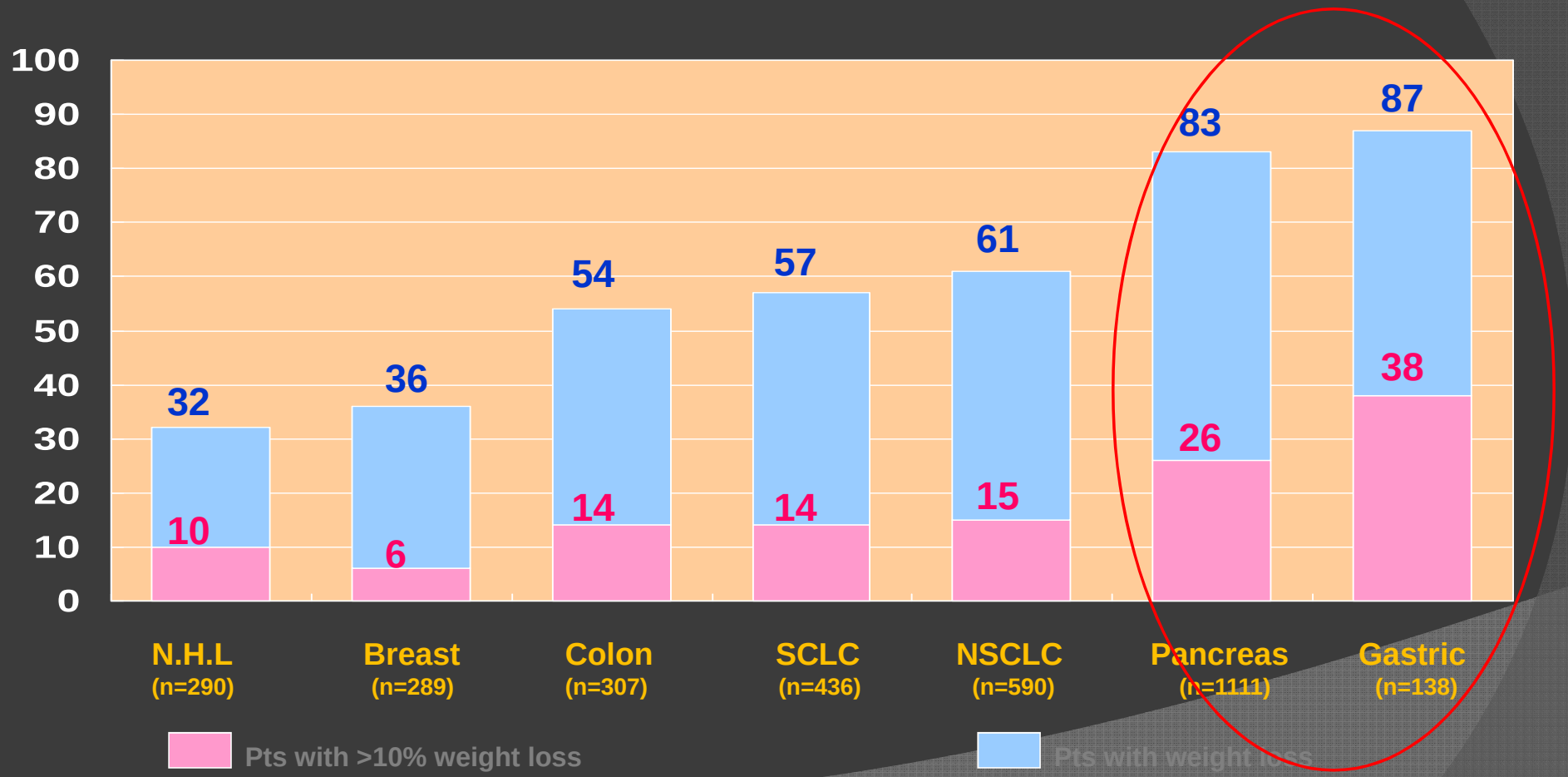


Journals of Gerontology 2001a; 56A (Special Issue II):81–88



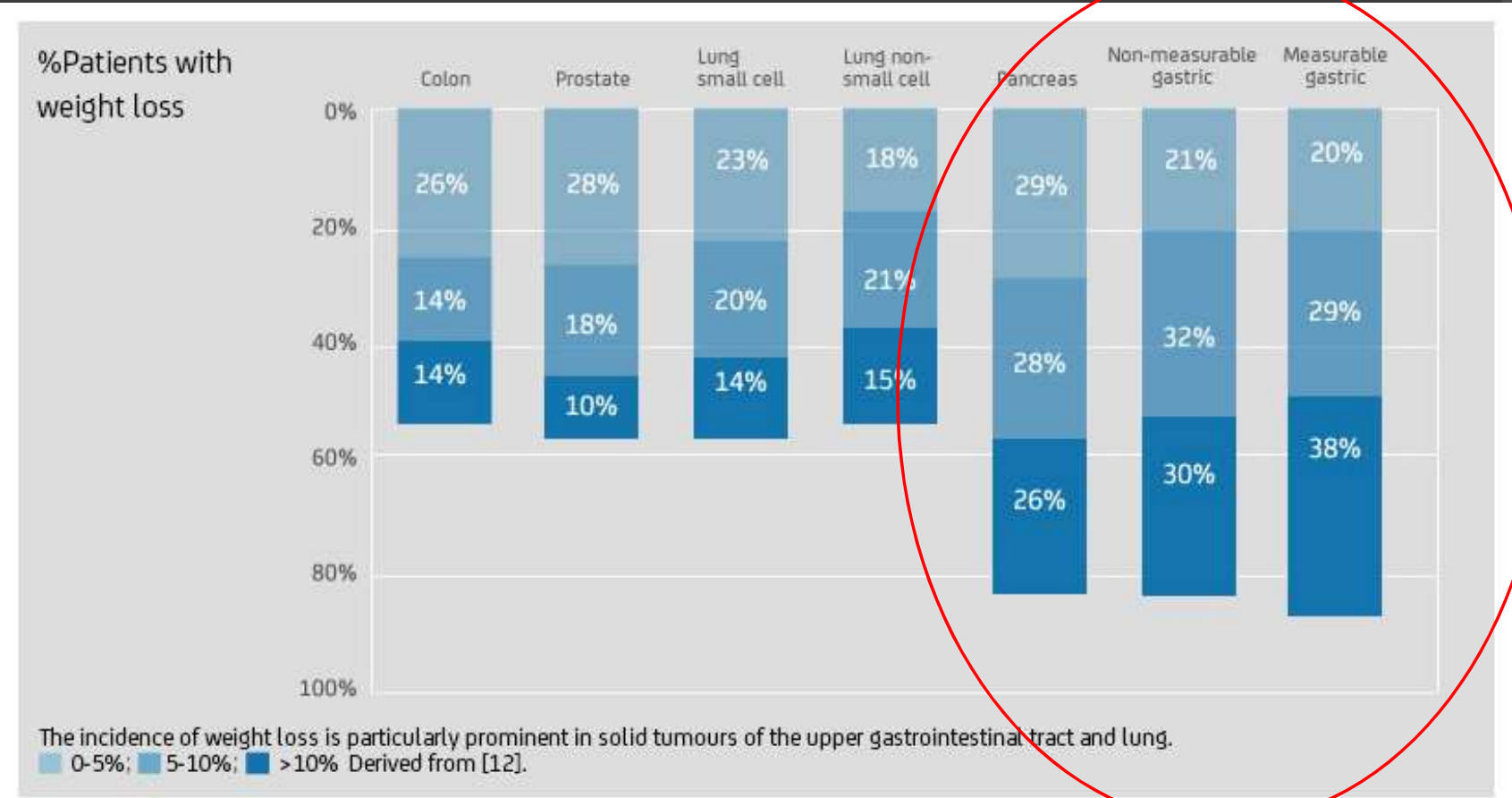
Therapeutics Clin Risk Management 2019; 15:1253-66

Incidence of Cancer Related Cachexia



DeWys et al: Am J Med 1980: 69:491

Incidence of cancer related cachexia



Tan BHL, et al; Curr Opin Clin Nutr Metab Care 2008;11(4):400-7

Incidence of Cancer Cachexia in cancer patient

Table 2: Proportion of cancer patients with cachexia by cancer type.

Cancer type	Cancer patients with cachexia ICD-9 code only	Cancer patients with any cachexia ICD-9 code	Cancer patients taking prescription medication indicative of cachexia	Cancer patients with ≥5% weight loss	Cancer patients with any one of the cachexia definitions
Breast, $n = 2112$	0.8%	3.1%	5.3%	18.6%	24.8%
Colorectal, $n = 905$	2.5%	6.1%	6.2%	16.4%	25.5%
Esophagus, $n = 117$	12.8%	20.5%	13.7%	16.2%	41.9%
Gastric, $n = 142$	8.4%	15.5%	19.0%	19.7%	41.5%
Head/neck, $n = 246$	6.1%	17.1%	6.1%	19.9%	37.0%
Liver, $n = 153$	3.3%	6.5%	3.9%	17.0%	24.2%
Lung, $n = 1291$	6.4%	9.7%	14.2%	15.2%	31.1%
Pancreas, $n = 221$	3.6%	7.2%	19.5%	12.7%	34.8%
Prostate, $n = 3354$	0.8%	3.2%	2.6%	11.0%	15.1%

Table 1 Incidence of weight loss in cancers of different sites (adapted, with permission, from ref 22).

Tumor site	Incidence of weight loss (%)
Pancreas	83
Gastric	83
Esophagus	79
Head and neck	72
Colorectal	55–60
Lung	50–66
Prostate	56
Breast	10–35
General cancer population	63

Cancer type (N)	Cachexia
Esophageal ca (117)	41.9%
Gastric ca (142)	41.5%
H&N ca (246)	37.0%
Pancreatic ca (221)	34.8%
Lung ca (1291)	31.1%

J Oncol. 2009;2009:693458

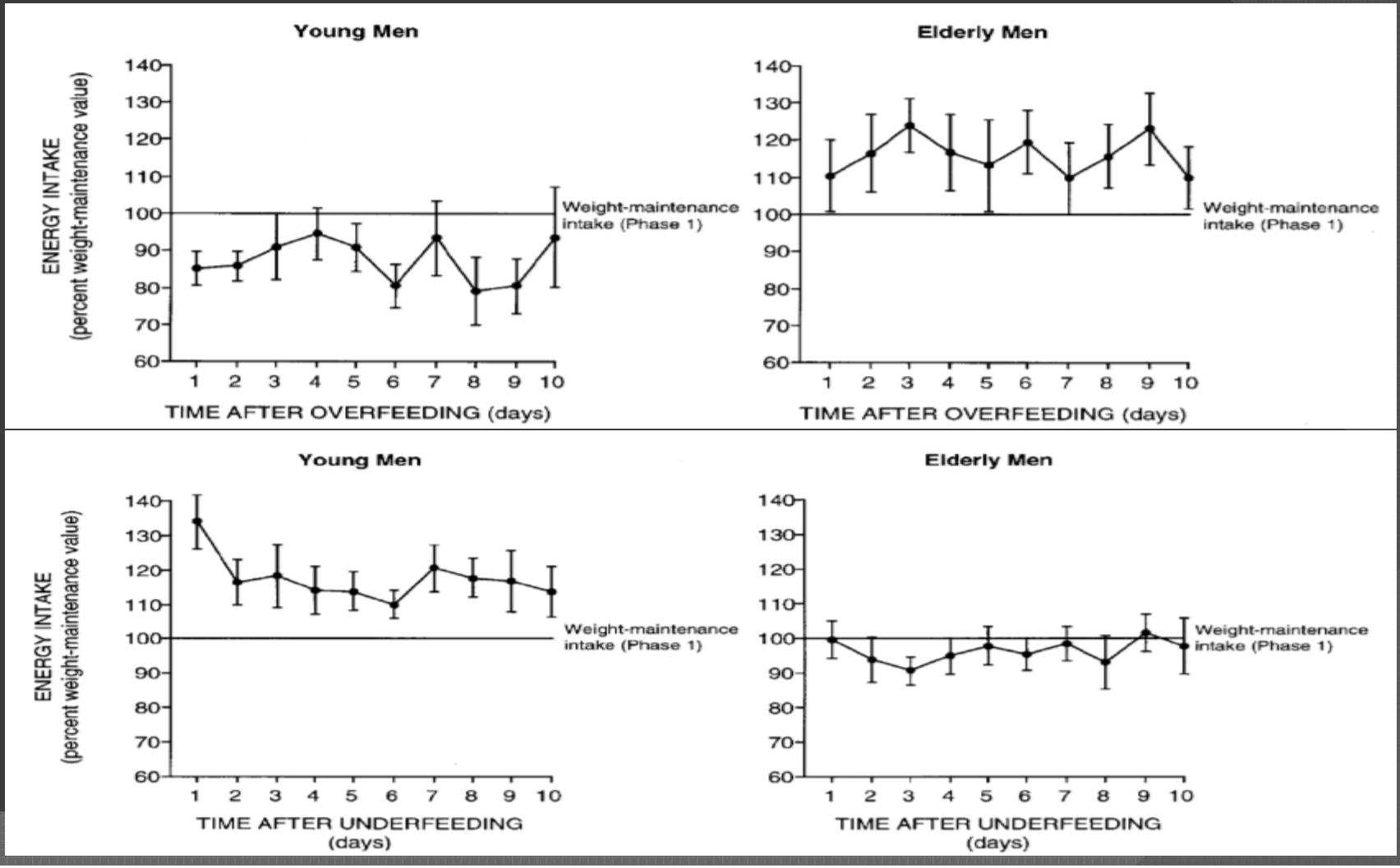
Laviano A et al. (2005). Nat Clin Pract Oncol 2: 158–165 10.1038/ncponc0112

Adapted, with permission from Laviano A and Meguid MM (1996). Nutrition 12: 358–371

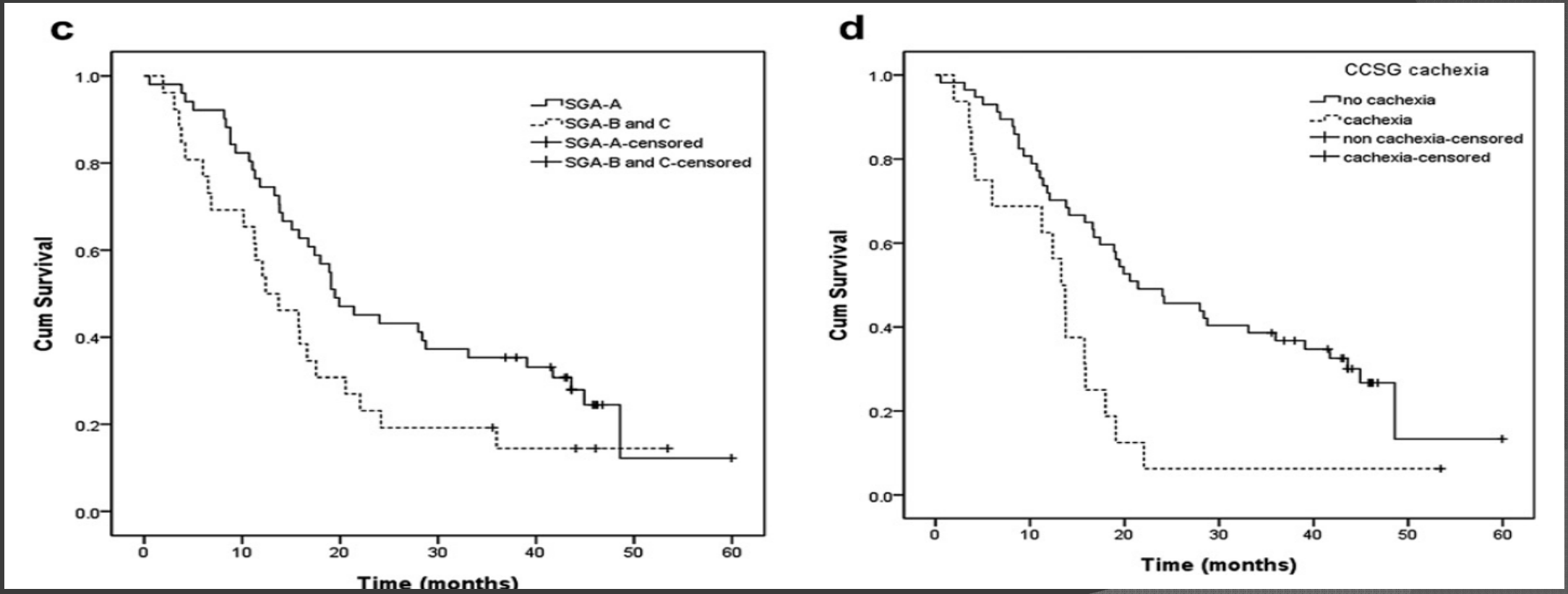
Age matter

overeat

undereat



Nutritional status, cachexia and survival



2002). c. Overall survival of patients with colorectal carcinoma stage IV ($N = 77$) with respect to the presence (dotted line, $N = 26$) or absence (solid line, $N = 51$) of malnutrition (SGA). d. Overall survival of patients with colorectal carcinoma stage IV ($N = 73$) with respect to the presence (dotted line, $N = 16$) or absence (solid line, $N = 57$) of cachexia defined by the Cancer Cachexia Study Group. e. Overall survival of patients with colorectal carcinoma stage IV ($N = 75$) with respect to the presence (dotted line, $N = 41$) or absence (solid

Clin Nutr. 2012 Jun 11:1~8

Weight Loss is Associated With Skeletal Muscle Loss

Study Design

- Lung Cancer Patients, N=6
- Control subjects of matching pre-illness weight

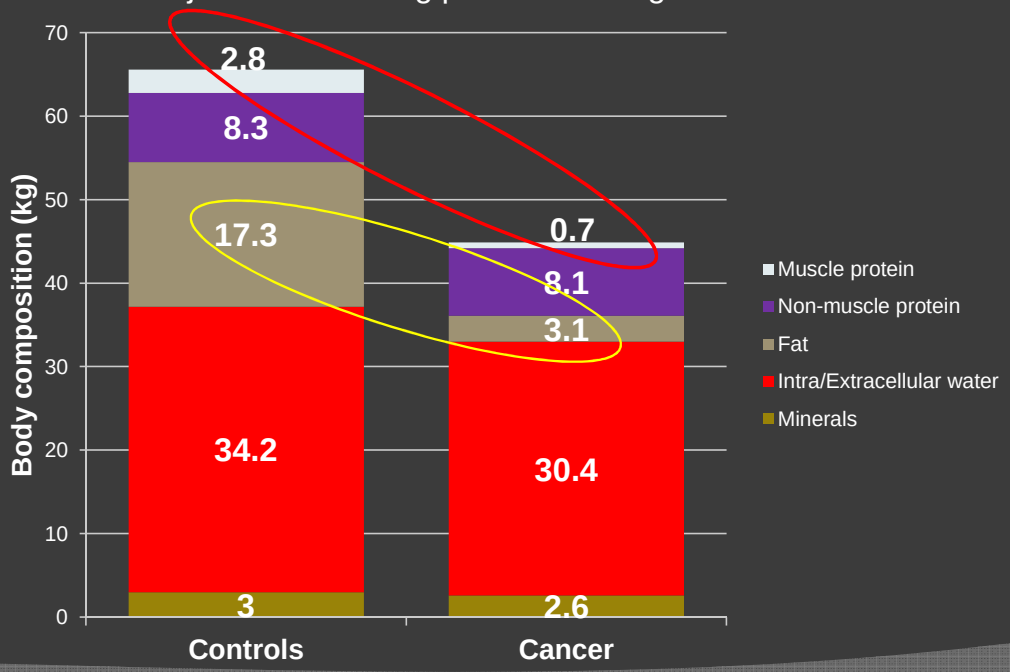


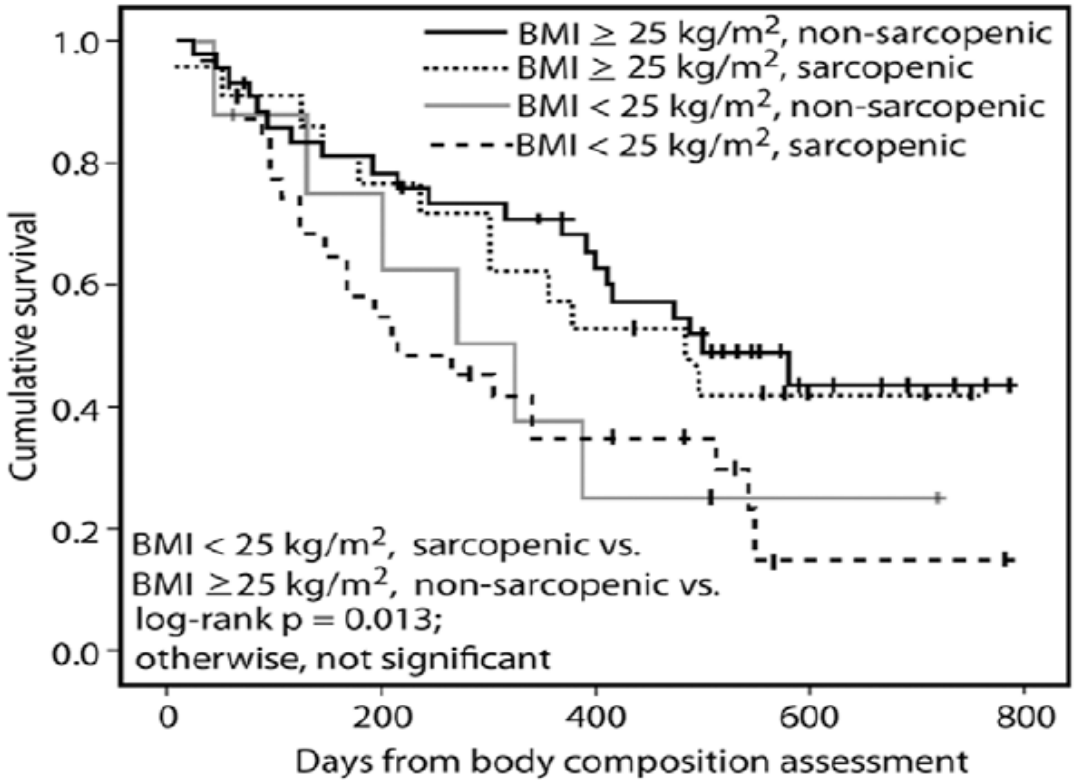
Chart adapted from Fearon K, *Proc. Nutr Soc.* 1992; 51: 251-265.

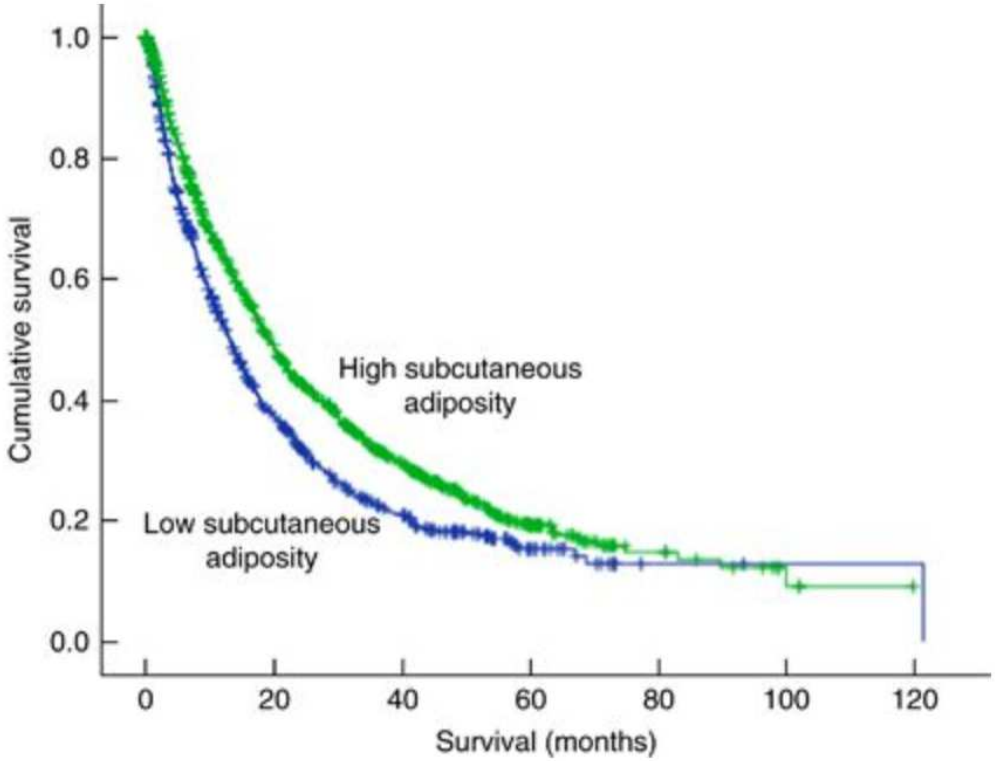
Patients had lost 30% of pre-illness stable weight

Skeletal muscle protein mass was 75% lower in cancer patients

Body fat was 82% lower in cancer patients

Sarcopenia, lipolysis and survival





124 advanced cancer patients

1473 GI and resp cancer;
273 metastatic RCC patients

PLoS ONE 2012; 7(1): e29330
British Journal of Cancer 2017;117:148–155

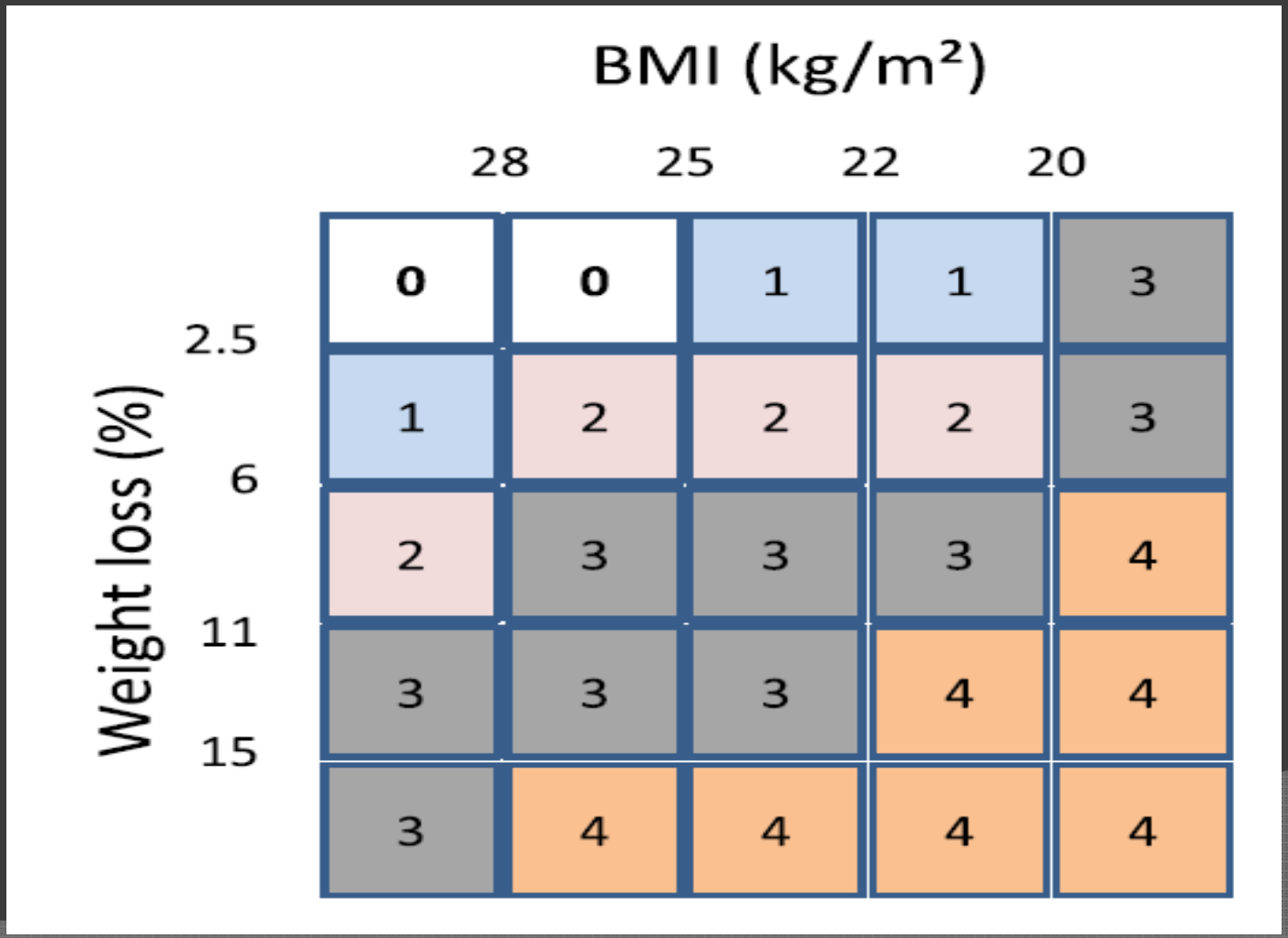
Table 3. Median Survival* and Univariate and Multivariate Analyses† for Predictors of Overall Survival

Characteristic	No. of Patients	No. of Deaths	Survival (months)		Univariate					Model One: Conventional					Model Two: Body Composition				
			Median	95% CI	Coefficient	SE	HR	95% CI	*P*	Coefficient	SE	HR	95% CI	*P*	Coefficient	SE	HR	95% CI	*P*
ECOG PS																			
0	299	164	26.1	20.5 to 31.7															
1	688	414	21.6	18.7 to 24.4	0.14	0.09	1.16	0.96 to 1.38	.119	0.33	0.09	1.39	1.16 to 1.68	< .001					
2	244	182	9.3	6.8 to 11.8	0.79	0.11	2.21	1.79 to 2.73	< .001	0.78	0.11	2.19	1.76 to 2.71	< .001					
3	222	190	4.5	2.8 to 6.2	1.29	0.11	3.64	2.94 to 4.49	< .001	1.23	0.11	3.41	2.75 to 4.23	< .001					
4	20	16	1.0	0.0 to 4.5	1.18	0.26	3.27	1.96 to 5.46	< .001	1.40	0.26	4.07	2.42 to 6.83	< .001					
BMI, kg/m^2																			
≥ 30.0	245	152	20.1	15.8 to 23.4															
25.0 to 29.9	511	313	18.8	15.6 to 22.1	−0.20	0.10	0.98	0.81 to 1.19	.844						−0.40	0.10	0.96	0.79 to 1.17	.691
20.0 to 24.9	536	366	15.2	13.1 to 17.3	0.19	0.10	1.21	1.00 to 1.45	.045						0.08	0.10	1.08	0.89 to 1.32	.425
< 20.0	181	135	11.5	8.8 to 14.1	0.45	0.12	1.56	1.25 to 1.99	< .001						0.32	0.13	1.38	1.07 to 1.78	.014
Weight loss, %																			
< 8	821	509	19.9	17.9 to 21.6															
≥ 8	652	457	12.7	11.0 to 14.4	0.31	0.06	1.36	1.20 to 1.54	< .001						0.22	0.07	1.25	1.10 to 1.43	.001
SMI																			
Nonsarcopenic	870	539	20.1	17.9 to 22.3															
Sarcopenic	603	427	13.0	11.1 to 14.8	0.29	0.06	1.34	1.18 to 1.52	< .001						0.18	0.07	1.20	1.04 to 1.37	.010
Muscle attenuation																			
Above threshold	686	400	19.9	17.0 to 22.7															
Below threshold	787	566	13.4	11.6 to 15.1	0.34	0.07	1.40	1.24 to 1.60	< .001						0.31	0.07	1.36	1.19 to 1.55	< .001
C statistic‡												0.73					0.92		
95% CI												0.67 to 0.79					0.88 to 0.95		

J Clin Oncol 2013; 31(12): 1539-47

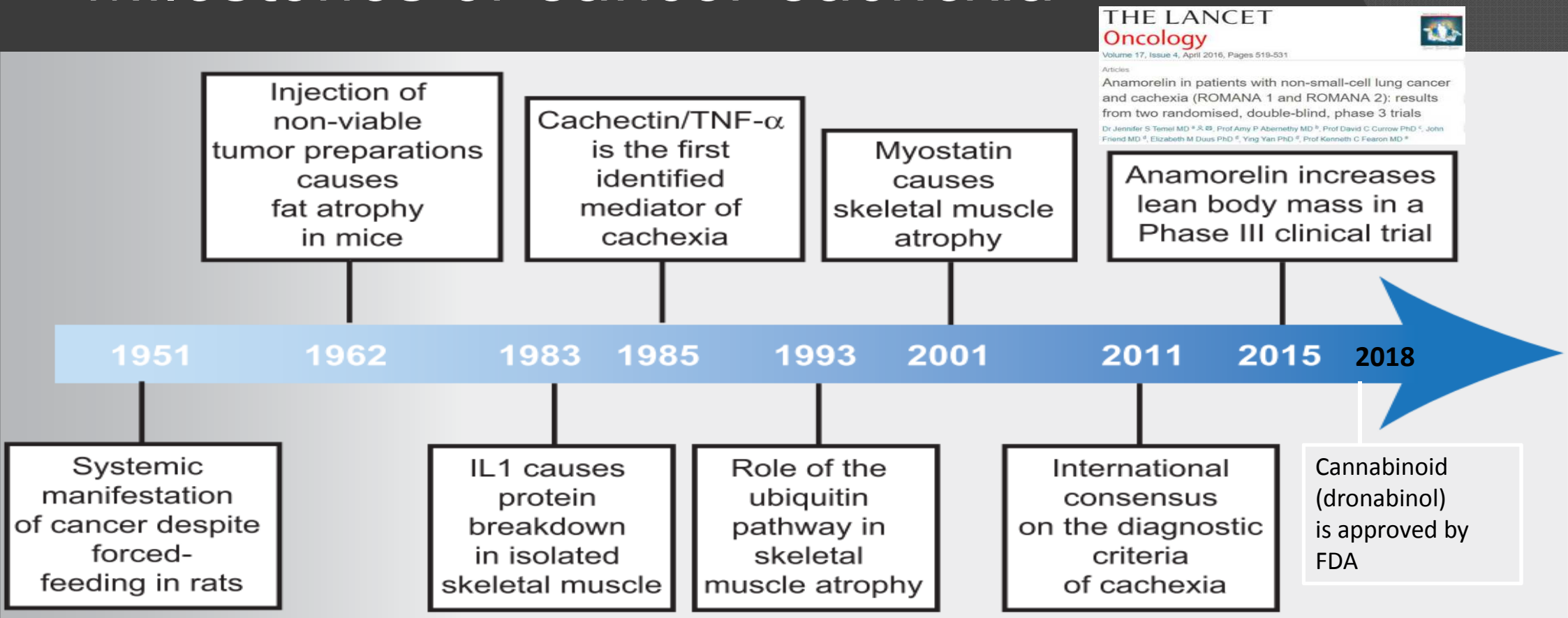
Cachexia related to survival

Grading schema to predict OS



Clin Nutrition 2017; 36:11-48

Milestones of Cancer Cachexia



1.Petruzzelli M. and Wagner EF. GENES & DEVELOPMENT 30:489–501(2016)
2.Drug Des Devel Ther. 2017; 11: 2325–2331.
3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018651s029lbl.pdf

Definition of Cancer Cachexia

--an international consensus

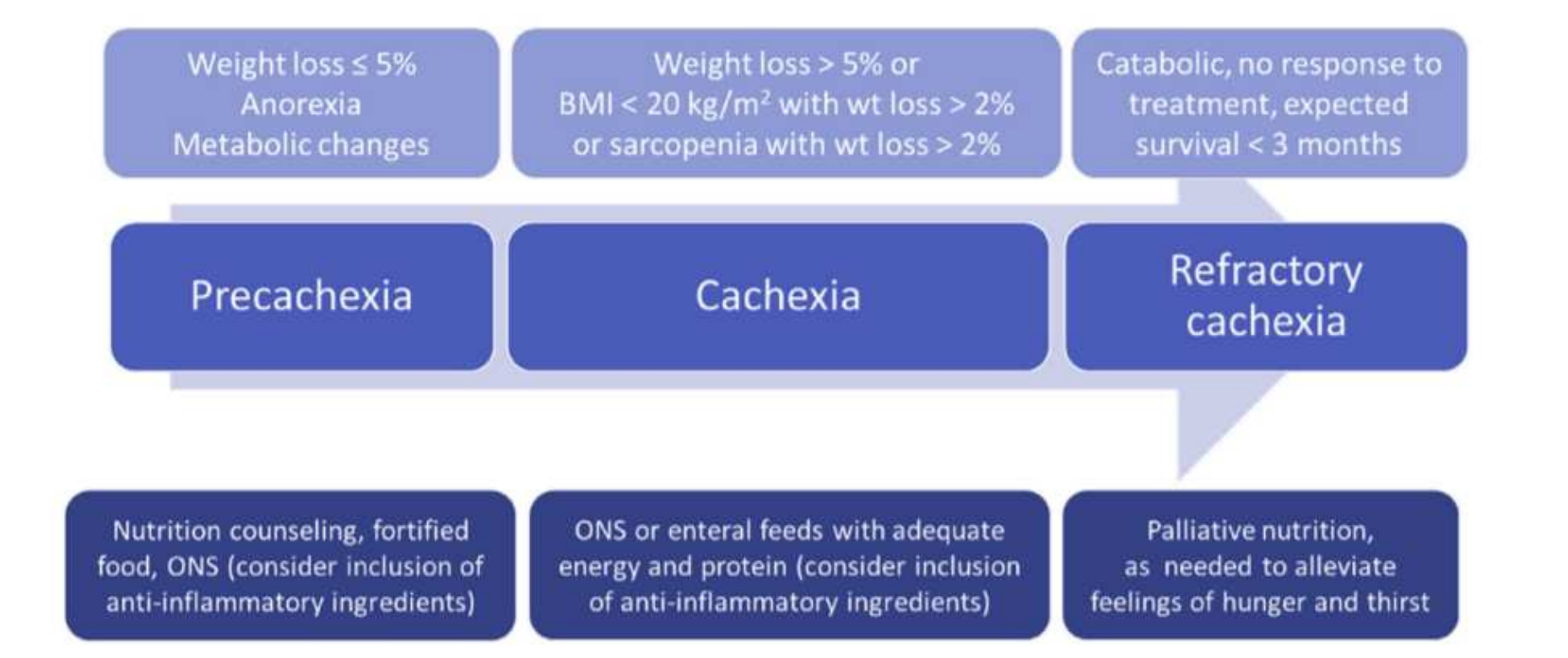
Panel: Diagnosis of Cancer Cachexia
• Weight loss >5% over past 6 months (in absence of simple starvation)
• BMI <20 and any degree of weight loss >2%
• Appendicular skeletal muscle index consistent with sarcopenia (males <7.26 kg/m^2; females <5.45 kg/m^2)* and any degree of weight loss >2%†

*Defined reference values (sex-specific) and standardised body composition measurements are essential to undertake assessment of skeletal muscle depletion. Although there is a paucity of reference values related to cancer-specific outcomes, a generally accepted rule is an absolute muscularity below the 5th percentile. This can be assessed as follows: mid upper-arm muscle area by anthropometry (men <32 cm^2, women <18 cm^2);31 appendicular skeletal muscle index determined by dual energy x-ray absorptiometry (men <7 · 26 kg/m^2; women <5 · 45 kg/m^2); lumbar skeletal muscle index determined by CT imaging (men <55 cm^2/m^2; women <39 cm^2/m^2);33 whole body fat-free mass index without bone determined by bioelectrical impedance (men <14 · 6 kg/m^2; women <11 · 4 kg/m^2).3

†A direct measure of muscularity is recommended in the presence of fluid retention, a large tumour mass, or obesity (overweight).

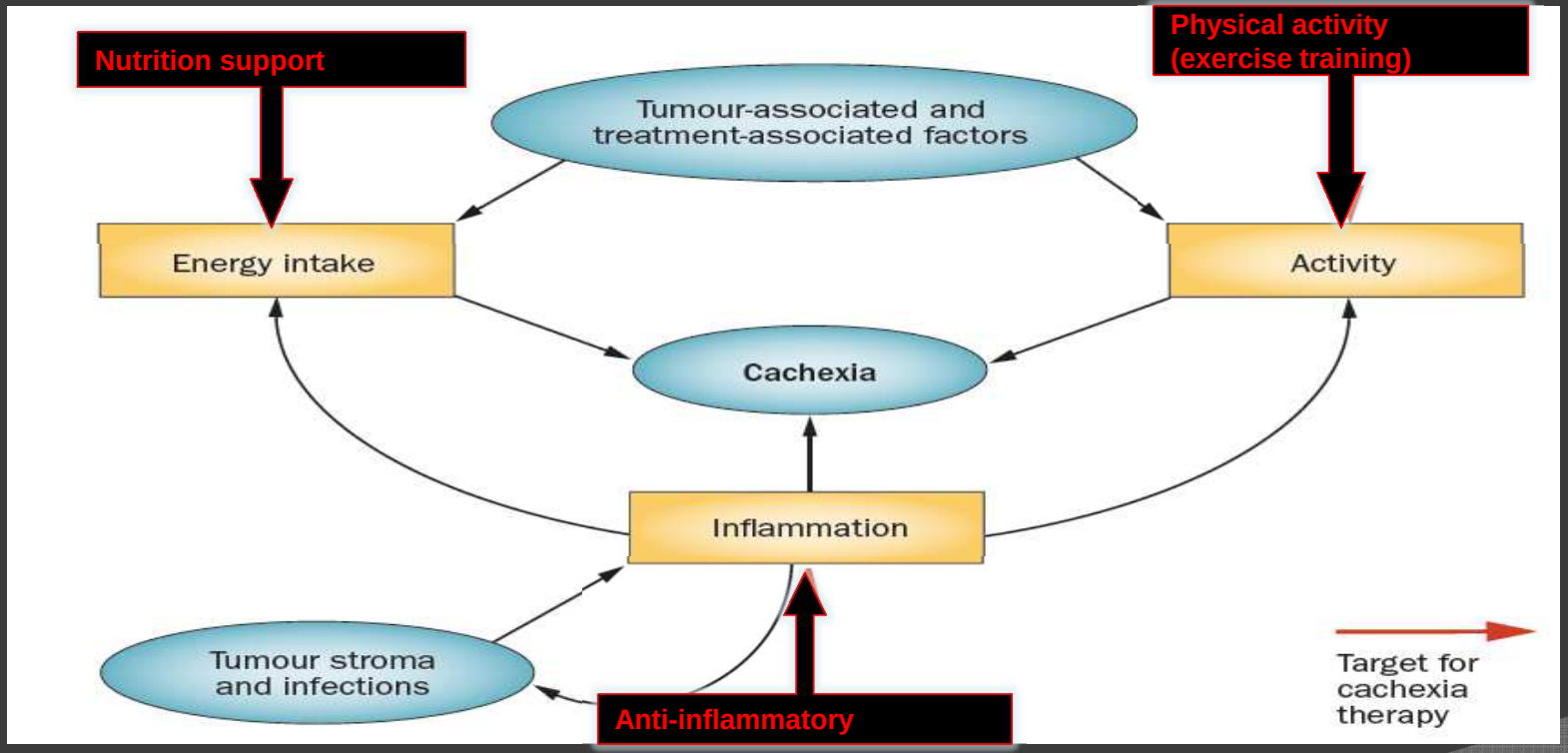
Fearon, K.et al. Lancet Oncol.12, 489-495 (2011)

When to interfere in cachexia status



Clin Nutrition 2017; 36:1187-96

Cachexia Treatment Choices



The combination of therapies promises a new era in supportive oncology, which could improve QOL and tolerance.

Nat Rev Clin Oncol. 2013 Feb;10(2):90-9.

Clinical Management of Cachexia

- Appetite stimulants
  - Corticosteroids
  - Progesterone analogs
  - (***Dual mechanism)***
  - Cannabinoids
  - Anamorelin hydrochloride
- Cytokine inhibitors
  - EPA (fish oil)
  - Thalidomide
  - Progesterone analogs
  - MABp1
- Increase lean body mass
  - anamorelin
  - enobosarm
  - progesterone analogs

- Anabolic Agents
  - Androgens
  - Growth hormones
- Miscellaneous
  - Insulin
  - Melatonin
  - Mirtazapine
  - Serotonin antagonists
  - Metoclopramide
  - Amino acid supplements
  - Combination therapy
  - **Majorly treat underlying illness…**

Steroid is only recommended for short life-expectancy patient

ASCO special articles

Management of Cancer Cachexia: ASCO Guideline

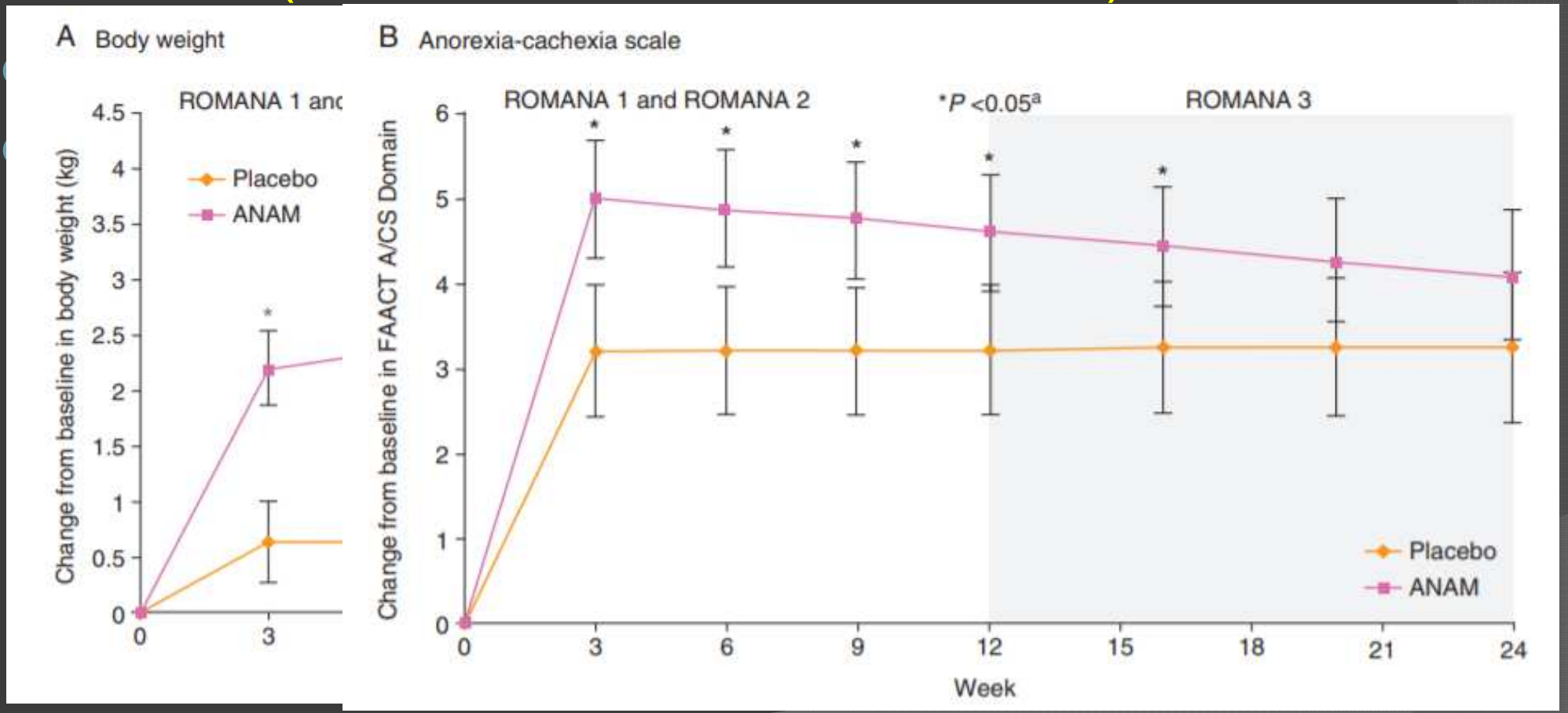
Eric J. Roeland, MD[1]; Kari Bohlke, ScD[2]; Vickie E. Baracos, PhD[3]; Eduardo Bruera, MD[4]; Egidio del Fabbro, MD[5]; Suzanne Dixon, MPH, MS, RD[6]; Marie Fallon, MD[7]; Jørn Herrstedt, MD, DMSci[8]; Harold Lau, MD[9]; Mary Platek, PhD, MS, RD[10]; Hope S. Rugo, MD[11]; Hester H. Schnipper, LICSW, BCD, OSW-C[12]; Thomas J. Smith, MD[13]; Winston Tan, MD[14]; and Charles L. Loprinzi, MD[15]

RECOMMENDATIONS Dietary counseling may be offered with the goals of providing patients and caregivers with advice for the management of cachexia. Enteral feeding tubes and parenteral nutrition should not be used routinely. In the absence of more robust evidence, no specific pharmacological intervention can be recommended as the standard of care; therefore, clinicians may choose not to prescribe medications specifically for the treatment of cancer cachexia. Nonetheless, when it is decided to trial a drug to improve appetite and/or improve weight gain, currently available pharmacologic interventions that may be used include progesterone analogs and short-term (weeks) corticosteroids.

NCCN guideline:life-expectancy: weeks to days, dexamethasone 4-8mg/d PO

Journal of Clinical Oncology 38, no. 21 (July 20, 2020) 2438-2453.

Anamorelin hydrochloride (ROMANA 1, 2 and 3 trials)



Ann Oncol 2017;28(8):1949-56

Anamorelin hydrochloride

Table 3. Summary of study drug-related TEAEs by system organ class and preferred term (safety population)

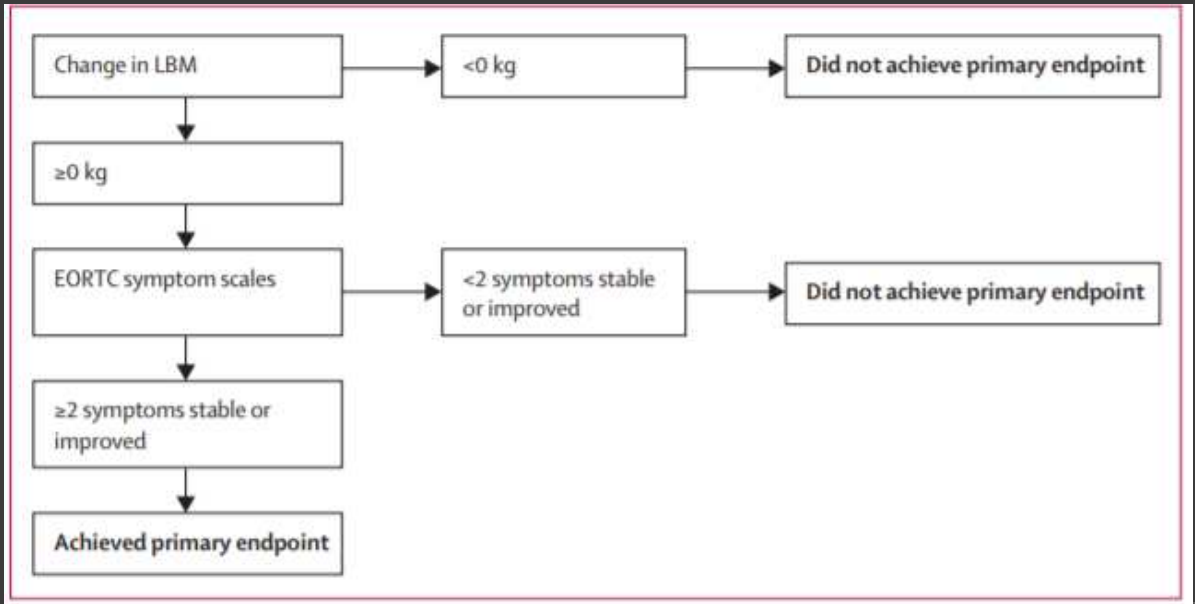
System organ class Preferred term	ROMANA 3 Anamorelin 100 mg (*n*=343) *n* (%)	 Placebo (*n*=167) *n* (%)
Patients with any drug-related TEAEs	12 (3.5)	2 (1.2)
Metabolism and nutrition disorders	5 (1.5)	0 (0.0)
Diabetes mellitus	1 (0.3)	0 (0.0)
Hyperglycemia	4 (1.2)	0 (0.0)
Gastrointestinal disorders	5 (1.5)	1 (0.6)
Dry mouth	0 (0.0)	1 (0.6)
Dyspepsia	1 (0.3)	0 (0.0)
Nausea	2 (0.6)	0 (0.0)
Vomiting	2 (0.6)	0 (0.0)
Skin and subcutaneous tissue disorders	3 (0.9)	0 (0.0)
Dermatitis bullous	1 (0.3)	0 (0.0)
Onychomadesis	1 (0.3)	0 (0.0)
Urticaria	1 (0.3)	0 (0.0)
General disorders and administration site conditions	1 (0.3)	1 (0.6)
Fatigue	0 (0.0)	1 (0.6)
Malaise	1 (0.3)	0 (0.0)
Immune system disorders	1 (0.3)	0 (0.0)
Allergic edema	1 (0.3)	0 (0.0)
Investigations	1 (0.3)	0 (0.0)
Increased γ-glutamyl transferase	1 (0.3)	0 (0.0)
Nervous system disorders	1 (0.3)	0 (0.0)
Headache	1 (0.3)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	1 (0.6)
Thrombocytopenia	0 (0.0)	1 (0.6)

TEAE, treatment-emergent adverse event (whether study drug-related to or not).

Ann Oncol 2017;28(8):1949-56

MABp 1

- A human IgG1 monoclonal antibody specific to human interleukin-1 α
- A phase 3 clinical trial in advanced colorectal cancer



Lancet Oncol 2017; 18: 192–201

MABp1 clinical outcomes

	MABp1 group		Placebo group (n=102)		Diffe (effe
	Number of patients	Achieved primary endpoint (%)	Number of patients	Achieved primary endpoint (%)	
ECOG performance status score					
1	170	57 (34%)	80	16 (20%)	14%
2	37	11 (30%)	22	3 (14%)	16%
Sex					
Female	79	24 (30%)	43	3 (7%)	23%
Male	128	44 (34%)	59	16 (27%)	7%
***KRAS* mutation status**					
Mutation	91	26 (29%)	56	10 (18%)	11%
Wild type	85	30 (35%)	37	6 (16%)	19%
Geographical region					
European Union	176	56 (32%)	91	16 (18%)	14%
ROW-CIS	31	12 (39%)	11	3 (27%)	11%

The sensitivity analysis showed a positive effect for MABp1 treatment in all cate numbers, not all differences were significant. ECOG=Eastern Cooperative Oncol Commonwealth of independent states, including Georgia and Russia.

***Table 2*: Stratified sensitivity analysis for patients who achieved the pr**

	MABp1 group (n=207)	Placebo group (n=102)	Difference (effect size)	p value	Relative risk (95% CI)
Lean body mass	105 (51%)	46 (45%)	6%	0·18	1·11 (0·89–1·39)
Pain	93 (45%)	45 (44%)	1%	0·45	1·01 (0·82–1·25)
Fatigue	94 (45%)	46 (45%)	0	0·48	1·0 (0·81–1·25)
Anorexia	114 (55%)	49 (48%)	7%	0·12	1·16 (0·91–1·47)

***Table 3*: Post-hoc analysis of patients who achieved the primary endpoint, by individual endpoint components**

	MABp1 group (n=207)	Placebo group (n=102)	p value
Interleukin 6 concentration (pg/mL)*	1·6 (1·9)	9·9 (2·7)	0·012
Platelet count (×10⁹/L)	14 (5)	40 (8)	0·0052
Global quality of life score	−2·36 (1·58)	−4·03 (2·27)	0·55
Physical function score	−5·11 (1·53)	−3·38 (2·19)	0·52
Role function score	−6·83 (2·12)	−7·83 (3·02)	0·79
Emotional function score	2·50 (1·64)	1·37 (2·34)	0·69
Social function score	−0·89 (2·14)	0·00 (3·06)	0·81

Data are mean (SD) *Four outlier values were removed from this analysis.

***Table 4*: Changes in pharmacodynamic outcomes from baseline from baseline to 8 weeks of treatment**

Lancet Oncol 2017; 18: 192–201

MABp1 adverse effects

	MABp1 group (n=207)		Placebo group (n=102)	
	Grade 1–2	Grade 3	Grade 1–2	Grade 3
Abdominal pain	31 (15%)	5 (2%)	10 (10%)	2 (2%)
Fatigue	21 (10%)	6 (3%)	6 (6%)	7 (7%)
Oedema, peripheral	24 (12%)	4 (2%)	5 (5%)	2 (2%)
Anaemia	13 (6%)	8 (4%)	2 (2%)	5 (5%)
Weight decreased	21 (10%)	0	8 (8%)	0
Constipation	21 (10%)	0	6 (6%)	0
Asthenia	17 (8 %)	2 (1%)	7 (7%)	3 (3%)
Nausea	18 (9%)	0	11 (11%)	1 (1%)

No patients had grade 4 events, and no patients died due to treatment.

***Table 6*: Treatment-emergent adverse events occurring in at least 10% of patients during the 8-week treatment period**

Lancet Oncol 2017; 18: 192–201

Enobosarm (POWER 1 and 2)

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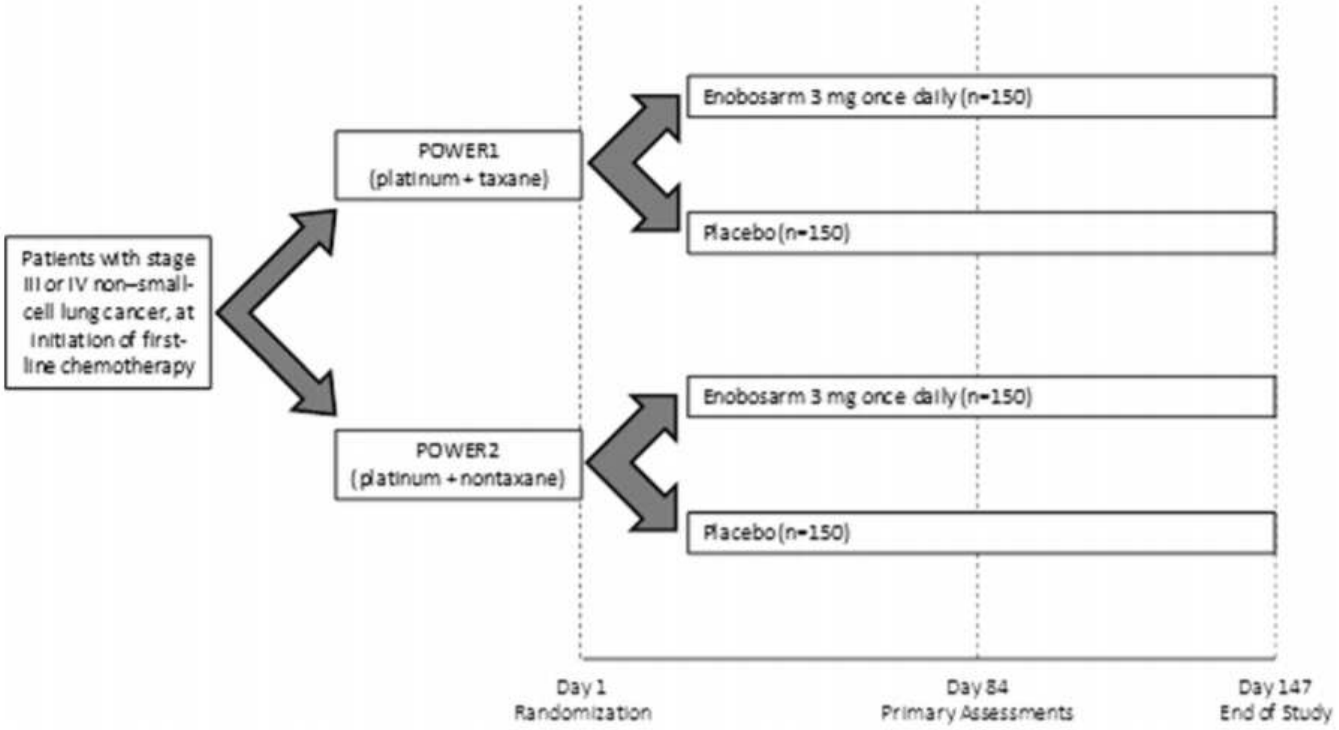


Fig. 1 POWER 1 and POWER 2 study design

Curr Oncol Rep (2016) 18: 37

Megestrol acetate發展歷程

- Megestrol acetate (MA) is a synthetic progestin

1963 Synthesized in England

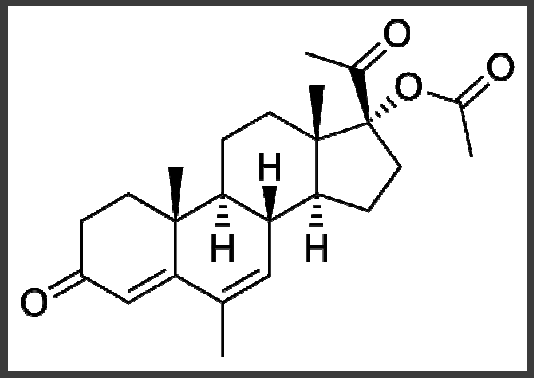
1964 Contraceptive

1967 Breast cancer and Endometrial cancer.

1993 Orexigenic (開胃) effect

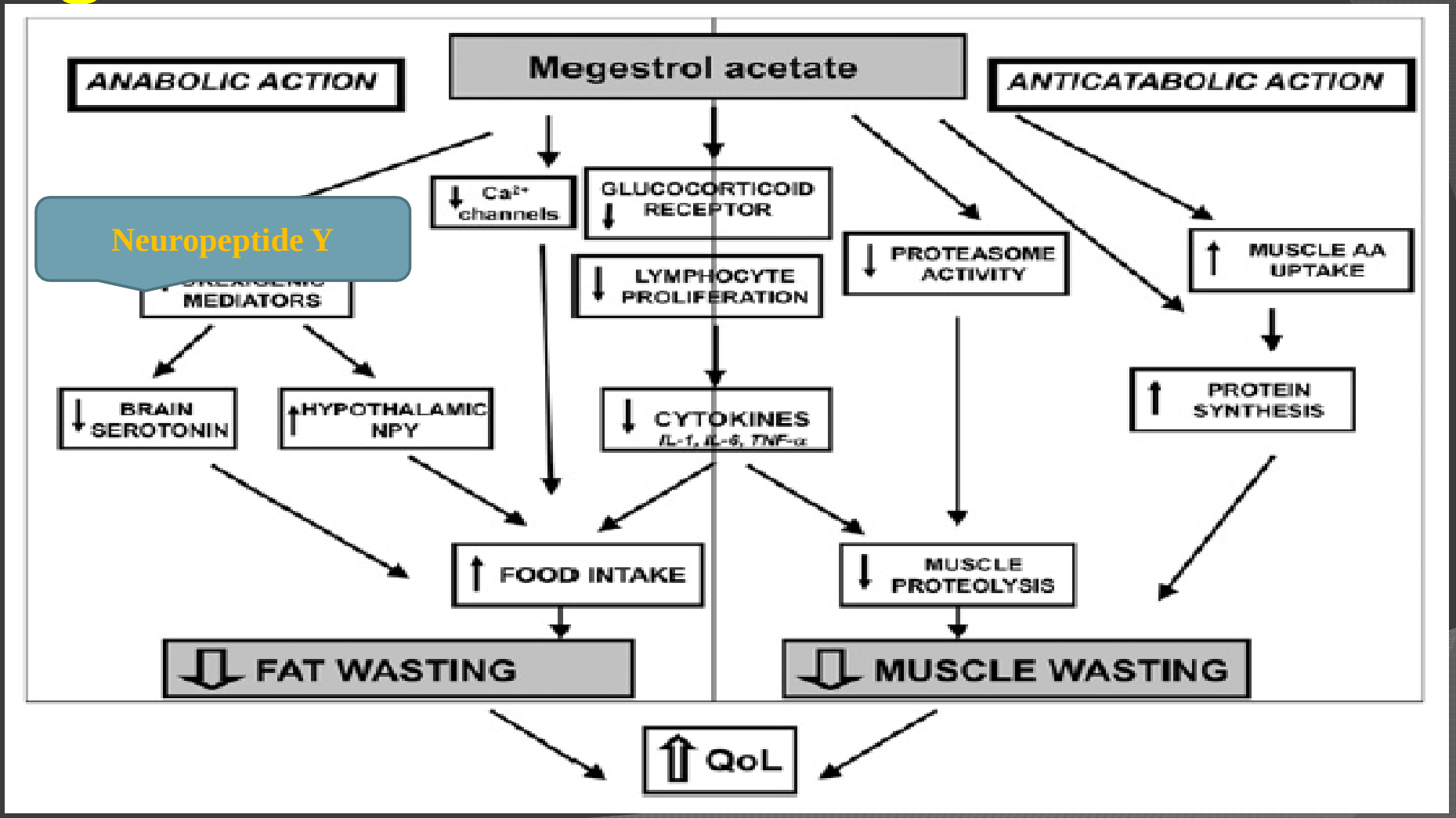
MA was approved by FDA

Indication: anorexia, cachexia, or weight loss due to unknown cause in AIDS patients.



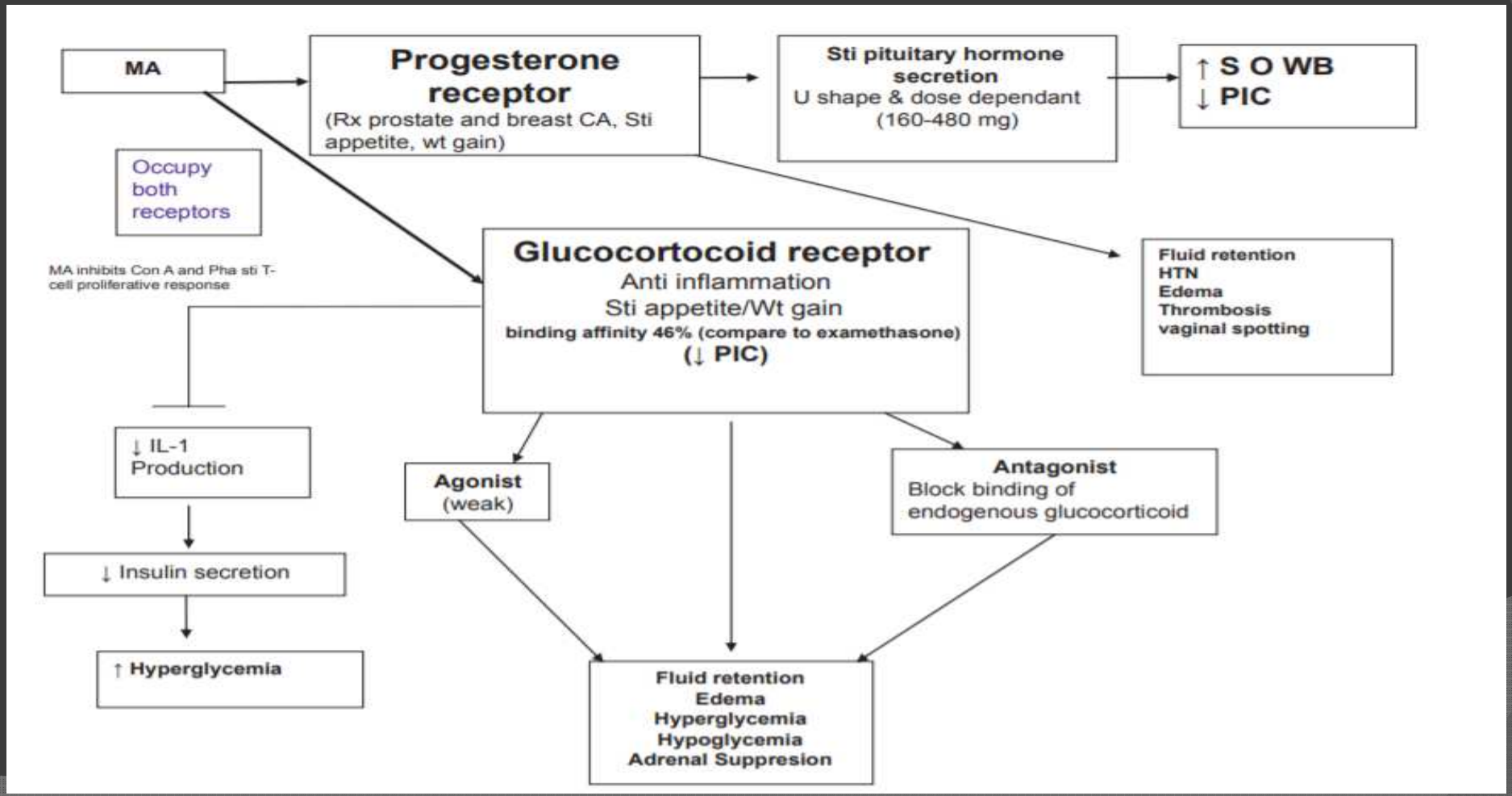
Now Majority of European countries have approved the indication of **ACS in AIDS and cancer patients**

Megestrol Acetate



Clinical Nutrition 2013:1-6

Megestrol acetate (MA) mechanism



Int J Nanomed 2006; 1(4):411-6

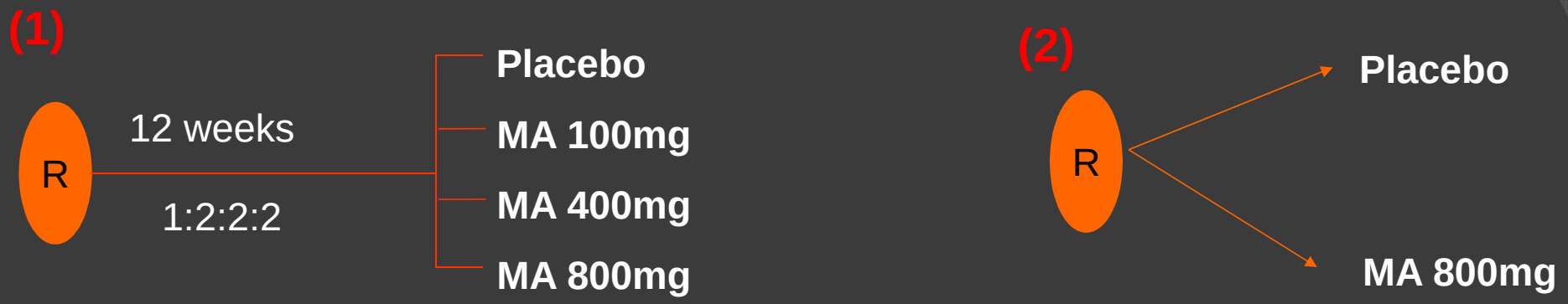
Pharmacokinetics

- Time to peak concentration: 3~5 hours (oral suspension)
- Metabolism site: LIVER, only 5%~8% of the dose of megestrol acetate results in metabolites.
- Eliminated in the URINE, t1/2=13~105 hours
- Bioavailability: NA

	Mean Cmax (ng/ml)	AUC (ng x hr/mL)	Median Tmax (hours)
10 cachectic males with acquired immunodeficiency syndrome received single oral doses of 800 mg/day for 21 days.	753 (+/- 529)	10476 (+/- 7788)	5
24 adults, HIV seropositive male subjects received 750 mg/day for 14 days.	490 (+/- 238)	6779 (+/- 3048)	3

From: Prod Info Megace® Oral Suspension,2001

Study for Optimal Dosage



- Randomized, double-blind,placebo-control trial
- **Endpoints :**
  - Primary : weight gain
  - Secondary : the changes in weight and body composition, caloric intake,sense of well-being, toxic effects and appetite.

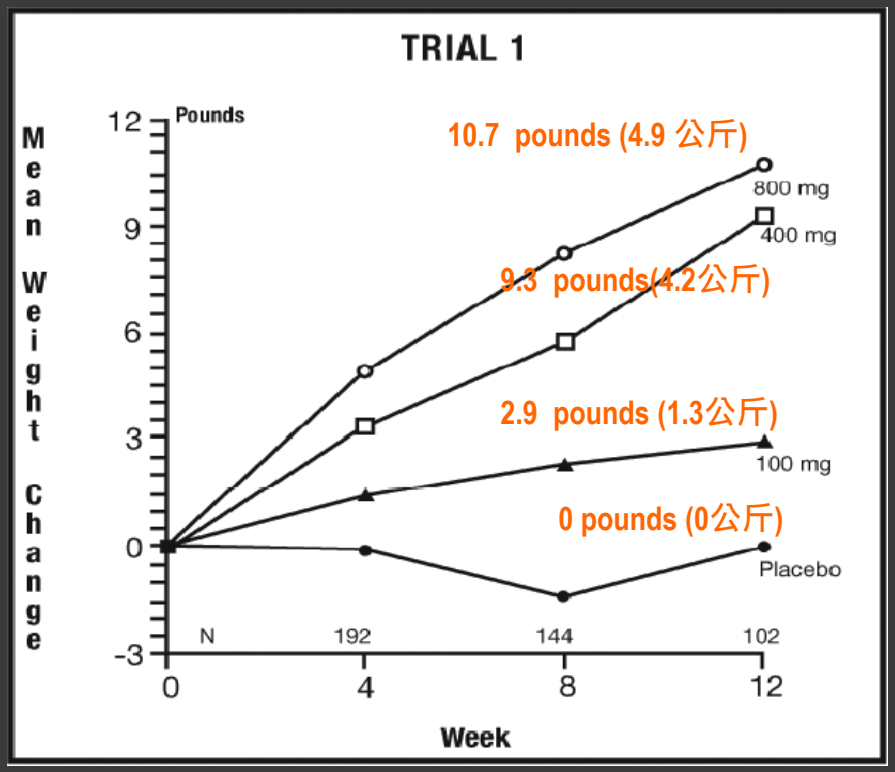
Annuals of Internal Medicine 1994; Volume 121, Number 6
Oncology 1994 ; 51 (suppl I):19-24

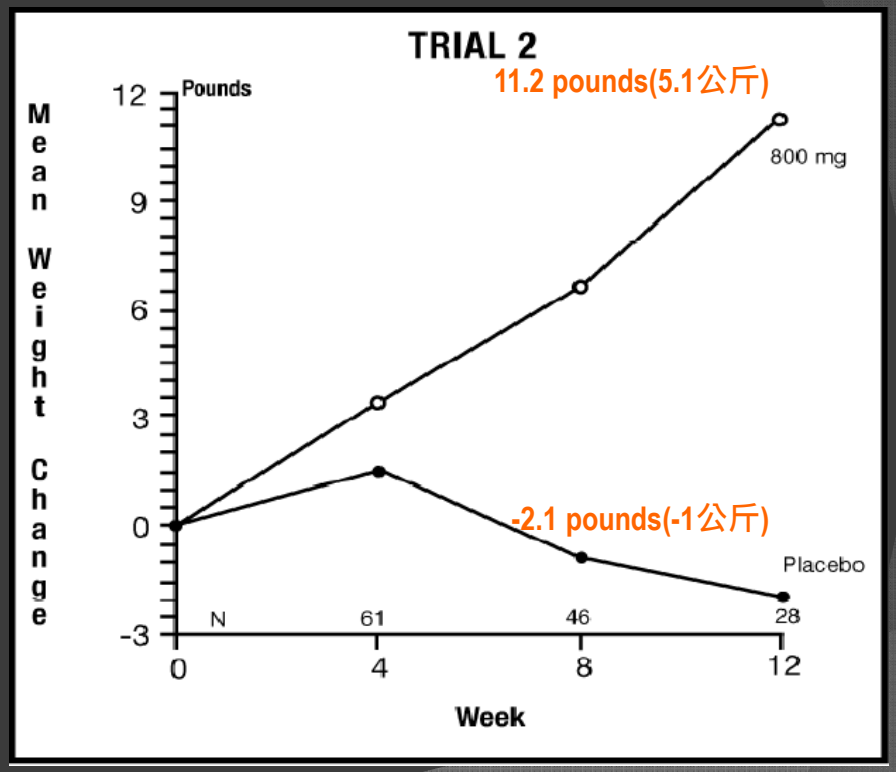
Change in Appetite

Treatment group	Patients with improved appetite at time of maximum weight change, %
Four-arm trial	
Placebo	50
Megace 100 mg	70.5
400 mg	71.7
800 mg	92.5**
Two-arm trial	
Placebo	48.3
Megace 800 mg	69.5*

Oncology 1994 ; 51 (suppl I):19-24

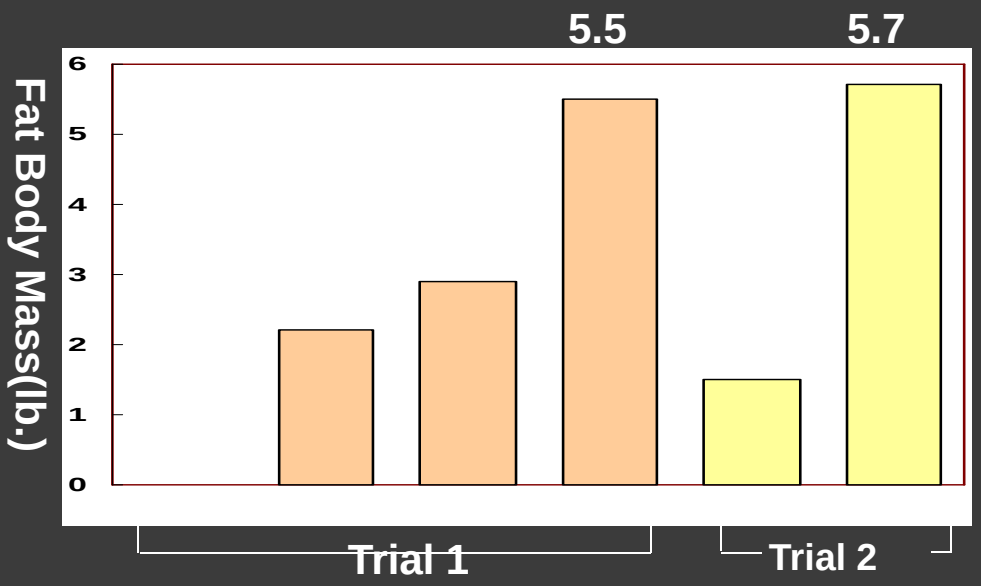
Weight Gain-1

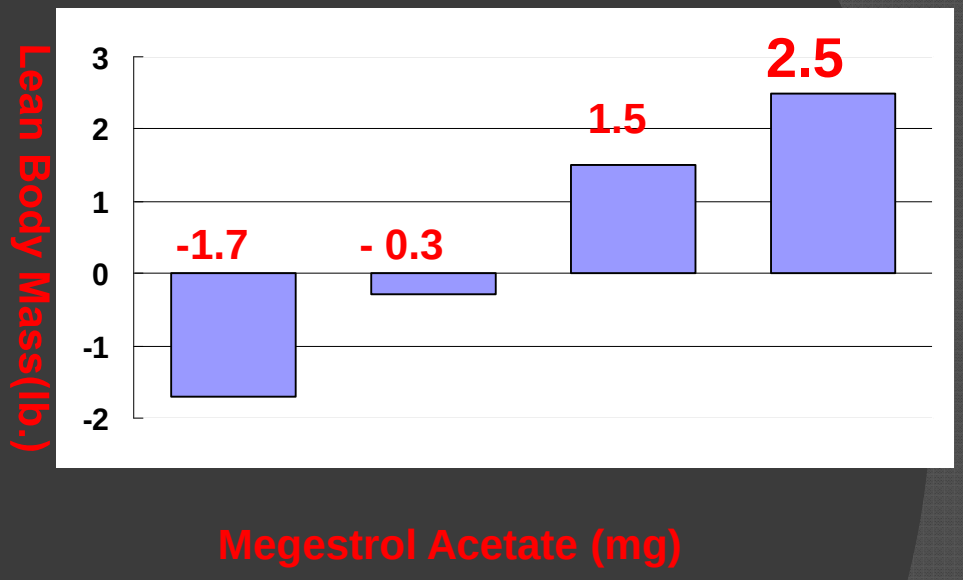




Prod Info Megace® Oral Suspension 2007 PDR@
Oncology 1994 ; 51 (suppl I):19-24

Mean Change in Body Composition



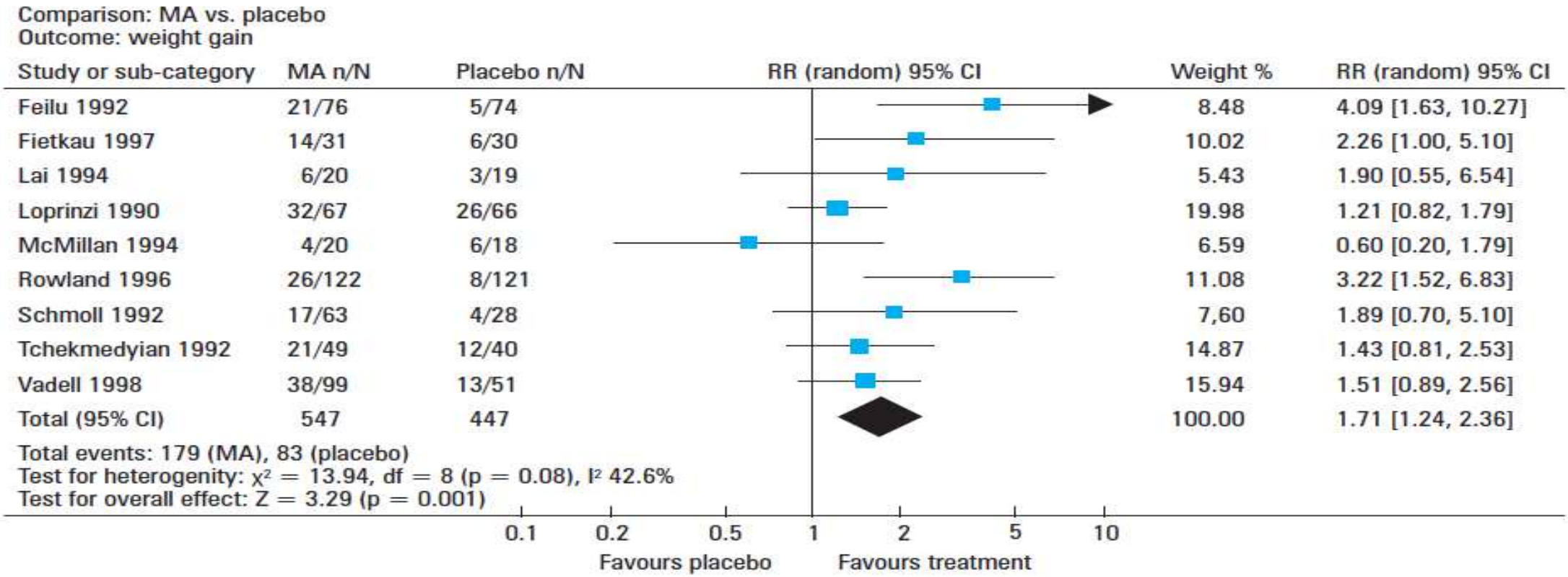


	0	100	400	800	0	800
Water (liters)	-1.3	-0.3	0	0	-0.1	-0.1

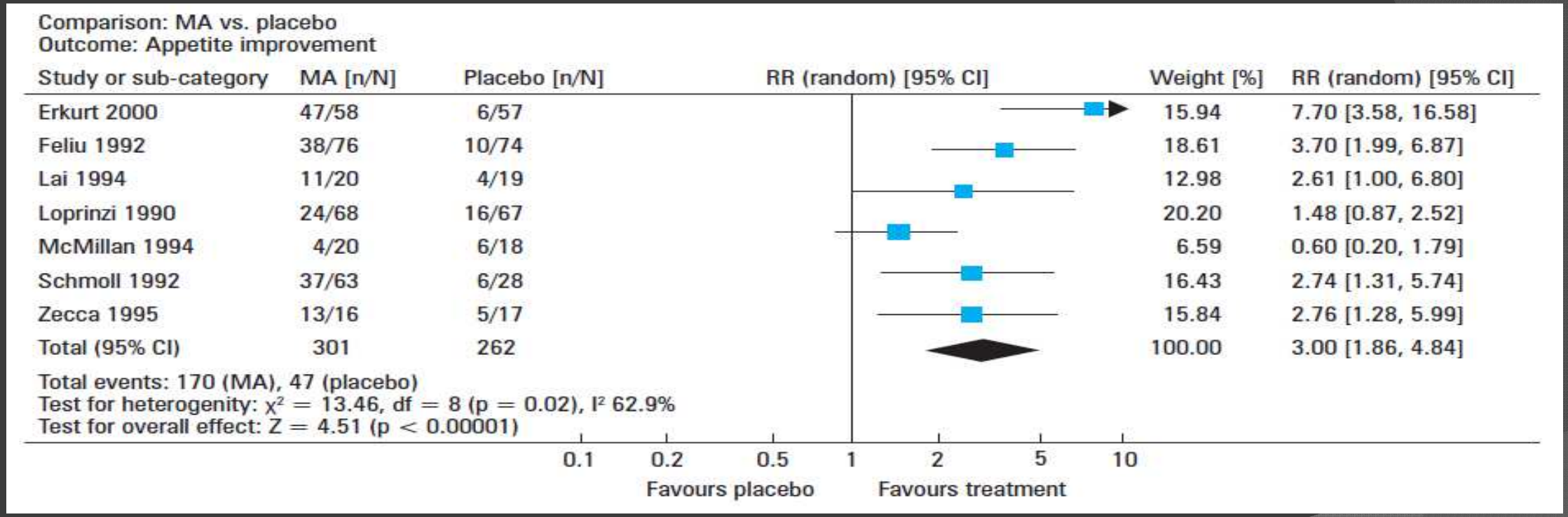
No statistically significant

Oncology 1994 ; 51 (suppl I):19-24

Megestrol increase body weight



Megestrol improved appetite



POLSKIE ARCHIWUM MEDYCYNY WEWNĘTRZNEJ 2008; 118 (11)

Safety

Adverse experience	Experiences, n			
	placebo	megestrol acetate, mg		
		100	400	800
	(n=86)	(n=82)	(n=75)	(n=127)
Deep-vein thrombosis	0	0	1(1.2)	0
Edema	7(8.2)	4(4.9)	9(12.0)	2(1.5)
Impotence	1(1.2)	3(3.7)	4(5.3)	11(8.7)
Rash	4(4.7)	6(7.3)	3(4.0)	9(7.1)

Values in parentheses are percentages

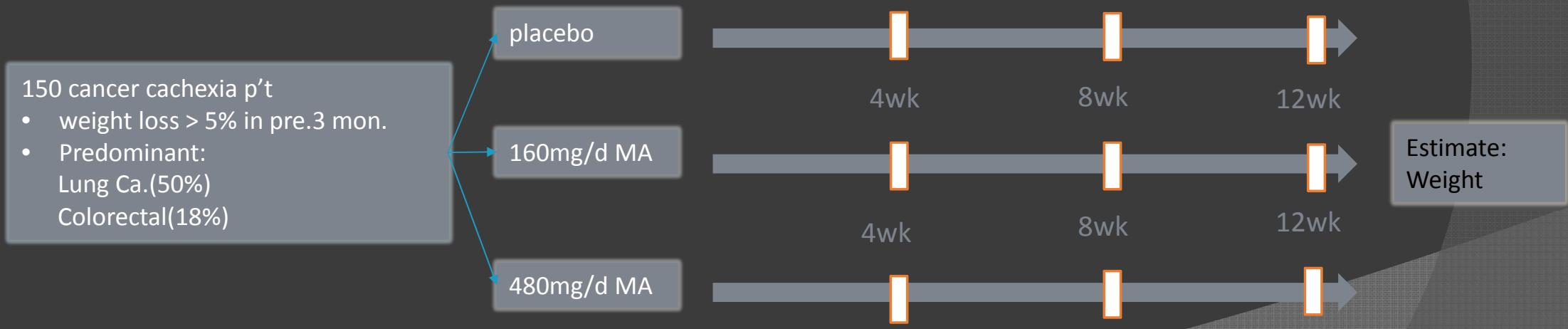
Oncology 1994 ; 51 (suppl I):19-24

Enough dose, Enough duration

[Articles]

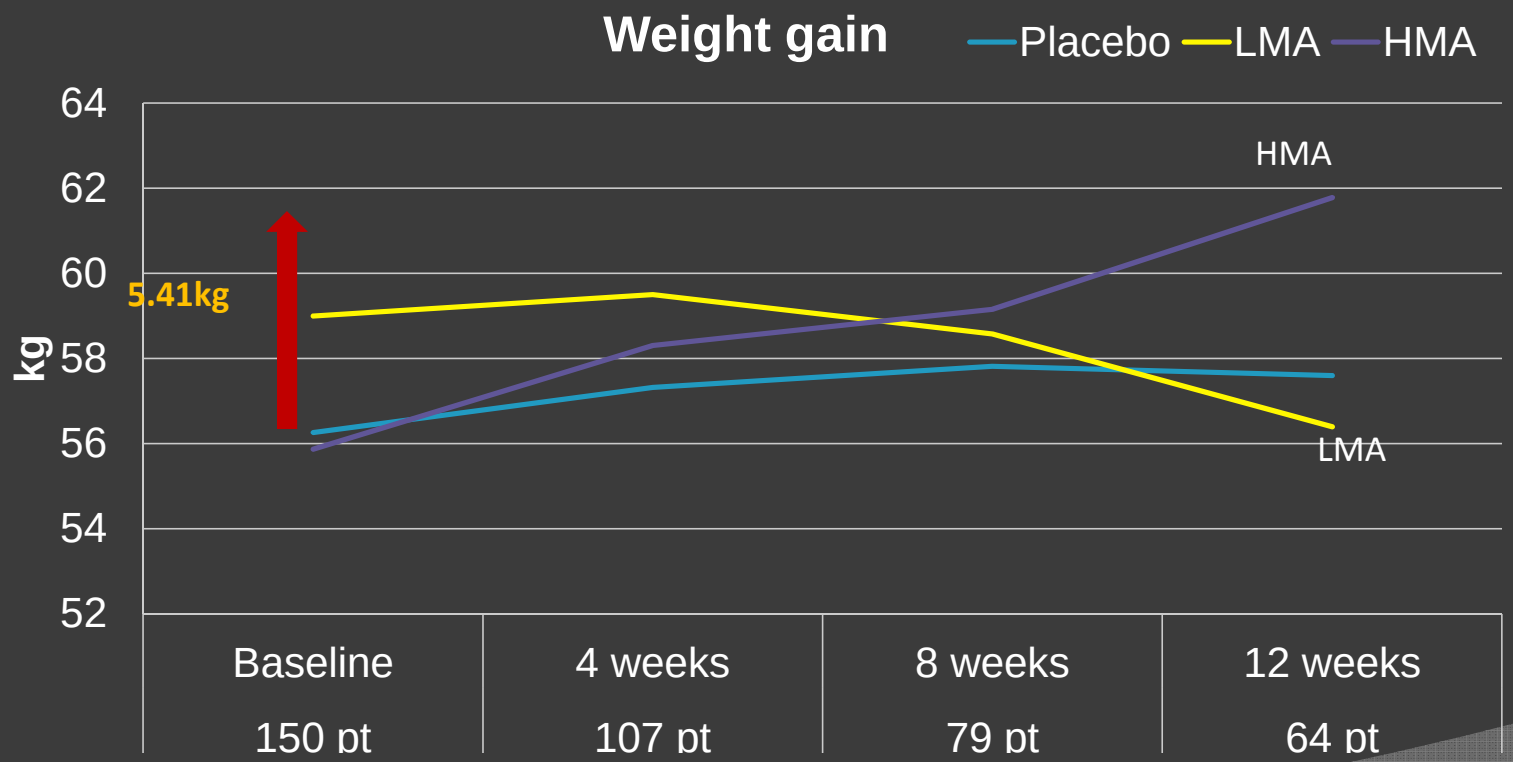
Anticachectic Efficacy of Megestrol Acetate at Different Doses and Versus Placebo in Patients With Neoplastic Cachexia

Vadell, Catalina M.D.; Segui, Miguel Angel M.D.; Gimenez-Arnau, Jose Maria M.D.; Morales, Serafin M.D.; Cirera, Luis M.D.; Bestit, Isabel M.D.; Batiste, Eduardo M.D.; Blanco, Remei M.D.; Jolis, Laura M.D.; Boleda, Montserrat M.D.; Anton, Isabel M.D.



Am J Clin Oncol.1998 Aug;21(4):347-51.

Enough dose, Enough duration



	Percentage of Weight gain at 12 weeks (%) (p<0.03)
Placebo	37%
LMA	38%
HMA	68%

2倍

HMA, megestrol acetate 480mg/d;
LMA, megestrol acetate 160mg/d;
*Mean Value, express in kg.

Am J Clin Oncol.1998 Aug;21(4):347-51.

Taiwanese local trial

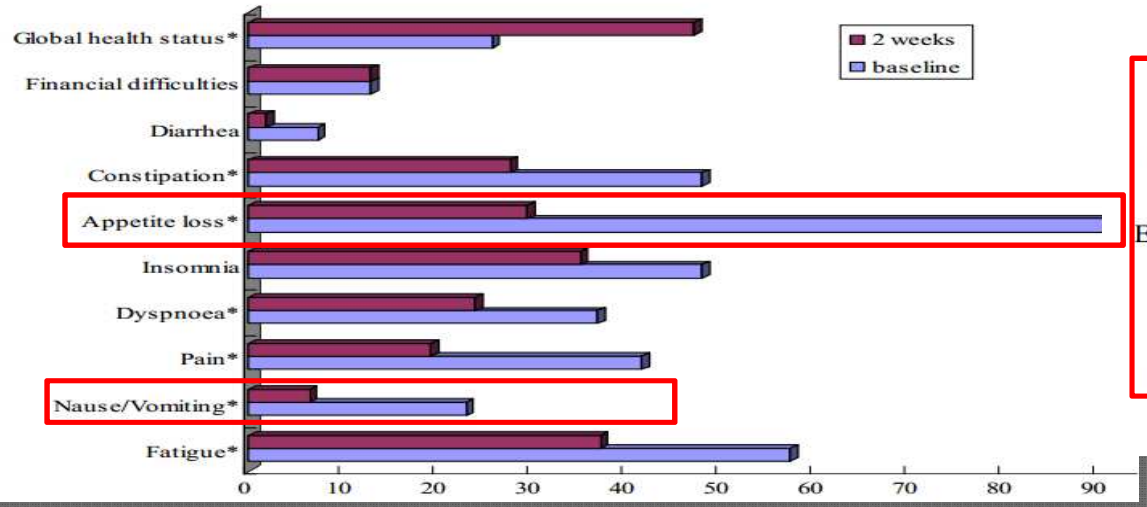
【Original Articles】

The Effect of Megestrol Acetate Oral Suspension on Appetite and Quality of Life in late-stage Cancer Patients

MA 12 c.c. per day (480 mg)

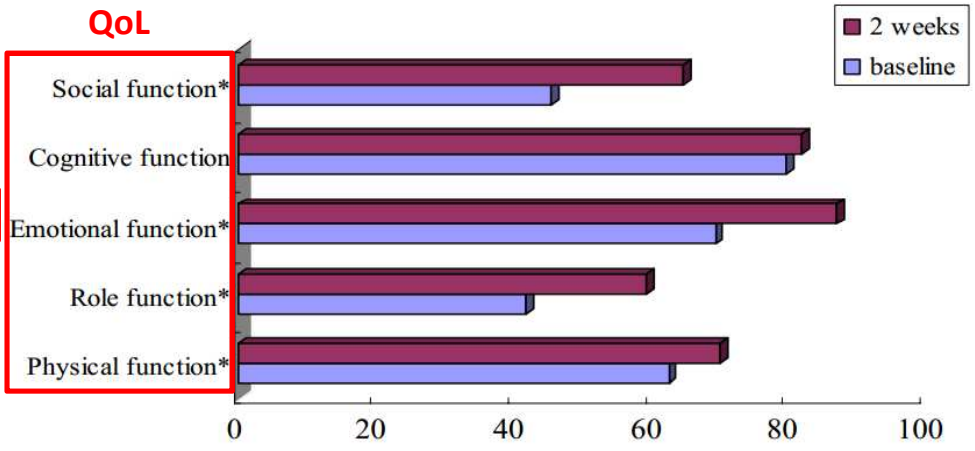
Ying-Yueh Tu[1] Yuen-Liang Lai[2,3]

(2) Global health status/financial difficulty/Symptom Scale/items



(1) Functional Scale (N=18)

QoL



Taiwan Journal of Hospice Palliative Care Vol.13 No.3 Aug. 2008

Table 2 Trials Of Multidrug Combinations In Patients With Cancer Cachexia

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

Notes: [a]Cachectic status was classified into precachecia, cachexia, refractory cachexia, or high risk for cachexia according to the consensus report.[4]

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

Compare with 5 different treatments

Parameter	Arm 3 L-carnitine Baseline	After treatment	p^a	Arm 4 thalidomide Baseline	After treatment	p^a	Arm 5 MA+EPA Baseline	After treatment	p^a
Primary endpoint									
LBM (kg)									
BIA ($n = 332$)	43.3 ± 8.6	44.6 ± 8.7	.952	43.5 ± 8.3	44.1 ± 8.7	.846	42.8 ± 8.1	44 ± 7.2	.609
DEXA ($n = 144$)	44.8 ± 9.8	45.2 ± 16.7	.980	45.3 ± 9.8	45.1 ± 9.3	.897	43.8 ± 9.4	44.9 ± 7.7	**.0148**
L3 CT ($n = 25$)									
Muscle mass (mm^2)	10,031 ± 3,833	10,477 ± 3,917	.148	11,419 ± 3,802	11,831 ± 3,074	.196	10,912 ± 3,304	11,504 ± 3,221	.084
Estimated LBM[b] (kg)	42.27 ± 29.5	43.5 ± 29.4	.058	42.4 ± 2.26	42.5 ± 9.1	.983	42.8 ± 8.1	45.4 ± 23.9	**.001**
REE (kcal/day)	1,286 ± 251	1,193 ± 324	.375	1,296 ± 445	1,169.9 ± 283	.486	1,227 ± 439	1,067.1 ± 181	**.044**
Fatigue (MFSI-SF score)	26.4 ± 23	26.1 ± 25	.801	24.2 ± 19.2	27.8 ± 24.6	.634	26.9 ± 16.8	20 ± 23.1	**.047**
Secondary endpoint									
Grip strength (kg)	25.9 ± 12.1	25.1 ± 11.9	.104	23.3 ± 9.4	29.1 ± 8.1	.086	27.2 ± 13.9	24.2 ± 7.2	.399
Appetite (VAS score)	5.1 ± 2.6	5.3 ± 3.1	.607	5 ± 2.5	5.3 ± 2.5	.351	5.1 ± 2.0	6.1 ± 1.5	**.00037**
IL-6 (pg/ml)	43.8 ± 42.2	31.6 ± 27.9	.663	40.8 ± 22.9	29.6 ± 25.9	**.0317**	41.4 ± 39.9	24.7 ± 23.4	**.0187**
TNF-α (pg/ml)	32.2 ± 32.3	37.5 ± 40.7	.240	30.8 ± 22.9	33.8 ± 30.8	.649	37.3 ± 35.8	22.5 ± 21.8	**.053**
ROS (FORT U)	449 ± 128	458 ± 138	.736	462 ± 138	378 ± 154	.696	497 ±121	445 ± 115	.262
GPx (IU/ml)	6,441 ± 4,012	7,107 ± 3,398	.383	7,046 ± 3,448	7,949 ± 3,669	.203	7,434 ± 3,125	6,676 ± 2,542	.816
EORTC QLQ-C30 (score)	55.2 ± 18.1	57.1 ± 21	.832	56.4 ± 19.3	60.3 ± 20	.188	56 ± 16.1	65.8 ± 18	.145
EQ-$5D_{index}$ (score)	0.5 ± 0.3	0.4 ± 0.5	.151	0.5 ± 0.4	0.5 ± 0.38	.599	0.5 ± 0.3	0.6 ± 0.4	.092
EQ-$5D_{VAS}$ (score)	45.3 ± 22.6	50 ± 26.8	.593	46.8 ± 21.7	48.8 ± 22.1	.712	51.7 ± 21.8	49.2 ± 18	.950
GPS	1.2 ± 0.76	0.9 ± 0.86	**.030**	1.3 ± 0.8	0.9 ± 0.8	**.006**	1.4 ± 0.7	0.9 ± 0.79	**.008**
ECOG PS score	1.88 ± 0.88	1.5 ± 0.9	**.0001**	1.7 ± 0.8	1.5 ± 0.8	**<.0001**	2 ± 0.6	1.5 ± 0.8	**<.0001**

The Oncologist 2010;15:200–211

NCCN Guidelines Recommendation

National Comprehensive Cancer Network®

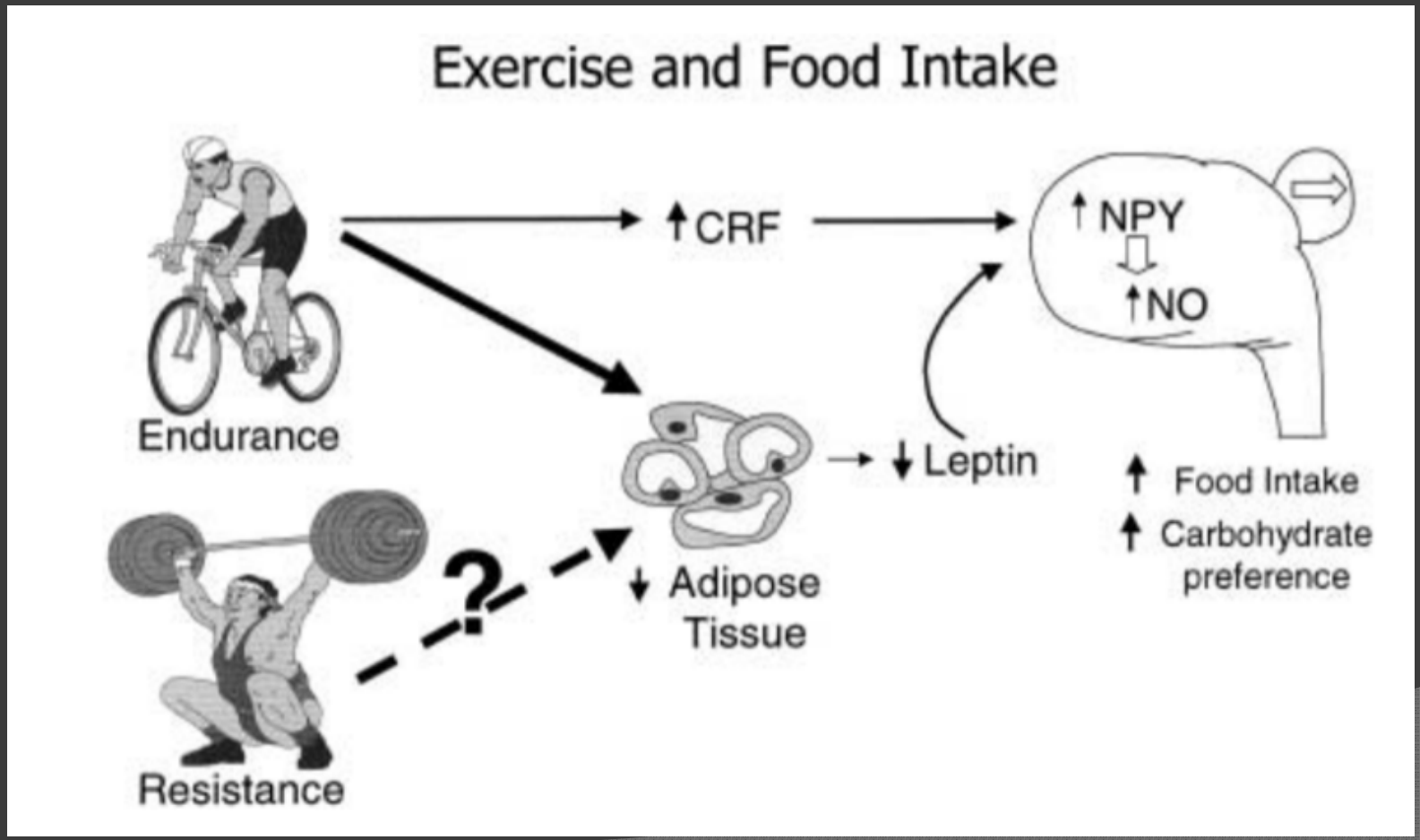
NCCN Guidelines Version 1.2020
Palliative Care

NCCN Guidelines Index
Table of Contents
Discussion

PALLIATIVE CARE DRUG APPENDIX

Condition	Recommended Agents and Dosage by Estimated Life Expectancy and Symptom Etiology
Dyspnea (PAL-11)	Life Expectancy: Years; Year to Months; and Months to Weeks • General: Morphine, 2.5–10 mg PO q2h PRN or 1–3 mg IV q2h PRN for opioid naïve, increase dose by 25% for non-opioid naïve ‣ For acute progressive dyspnea, or for patients who are not opioid naïve, more aggressive titration may be required • Anxiety: Lorazepam, 0.25–1 mg PO q4h PRN for benzodiazepine naïve
Dyspnea (PAL-12)	Life Expectancy: Weeks to Days (dying patient) • General: Morphine, 2.5–10 mg PO q2h PRN or 1–3 mg IV q2h PRN if opioid naïve, increase dose by 25% for non-opioid naïve ‣ For acute progressive dyspnea, or for patients who are not opioid naïve, more aggressive titration may be required • Anxiety: Lorazepam, 0.25–1 mg PO q4h PRN if benzodiazepine naïve • Fluid overload: Furosemide
Secretions (PAL-12)	• Excessive secretions: Scopolamine, 0.4 mg SC q4h PRN/1.5 mg patches, 1–3 patches q72h OR atropine, 1% ophthalmic solution 1–2 drops SL q4h PRN OR glycopyrrolate, 0.2–0.4 mg IV or SC q4h PRN
Anorexia/ Cachexia (PAL-13)	Life Expectancy: Years; Year to Months • Depression/anorexia: Mirtazapine, 7.5–30 mg PO QHS • Gastroparesis (early satiety): Metoclopramide 5–10 mg PO QID 30 min before meals and at bedtime • Low/no appetite: Megestrol acetate, 400–800 mg/d PO OR olanzapine, 5 mg/d PO
Anorexia/ Cachexia (PAL-14)	Life Expectancy: Months to Weeks; Weeks to Days (dying patient) • Low/no appetite: Megestrol acetate, 400–800 mg/d PO OR olanzapine, 5 mg/d PO OR dexamethasone, 4–8 mg/d PO OR consider cannabinoid • Depression: Mirtazapine, 7.5–30 mg PO QHS

Exercise increase appetite



Journals of Gerontology 2001a; 56A (Special Issue II):81–88

Take home message

- Cancer cachexia is a common syndrome in advance cancer patients
- Multiple factors, including change metabolism, decrease appetite and fat and muscle wasting
- Early intervention in precachexia status improve outcome
- Many pharmaceutical interventions including MA showed benefit in lean body mass increase, appetite increase and decrease anorexia.
- Enough dose and enough duration are important for MA supplement

THANK YOU FOR YOUR ATTENTION !!!