18th World Congress on Gastrointestinal Cancer, ESMO, Barcelona
29. June 2016, 15:30-15:50, CCIB
Nutritional support in gastrointestinal cancer

Cancer cachexia and sarcopenia in GI Cancer: mechanism and ways to interfere with it

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MASCC Working Group Nutrition and Cachexia, Co-Chair
Society **C**achexia **W**asting **S**arcopenia, Board

Disclosure Slide (last *1 year*)

Unrestricted industry-grants for clinical research

Helsinn: for Palliative Research Center, MENAC trial & other cachexia-related work (50'000 $ 2015, for 1-3 years)

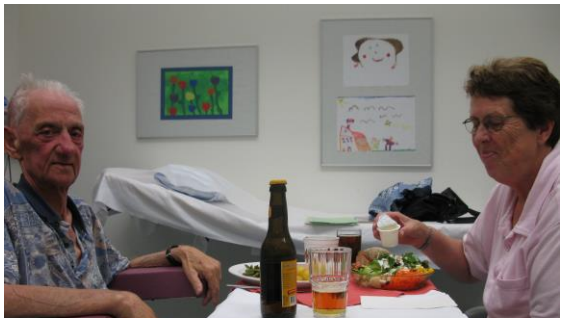
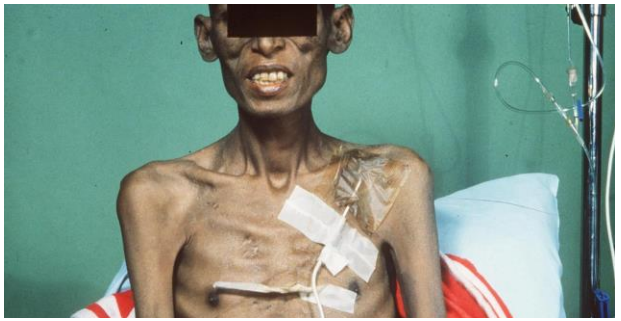
Participation in *company-lead* clinical cachexia trials

***Punctual* Advisorship** (Boards, Expert meetings)

Amgen, Celgene, Danone, Helsinn (ca 8000 $), Mundipharma (7000 $ 2016), Novartis, Ono, Vifor

No: Mono-sponsored industry-controlled Sattelite meetings

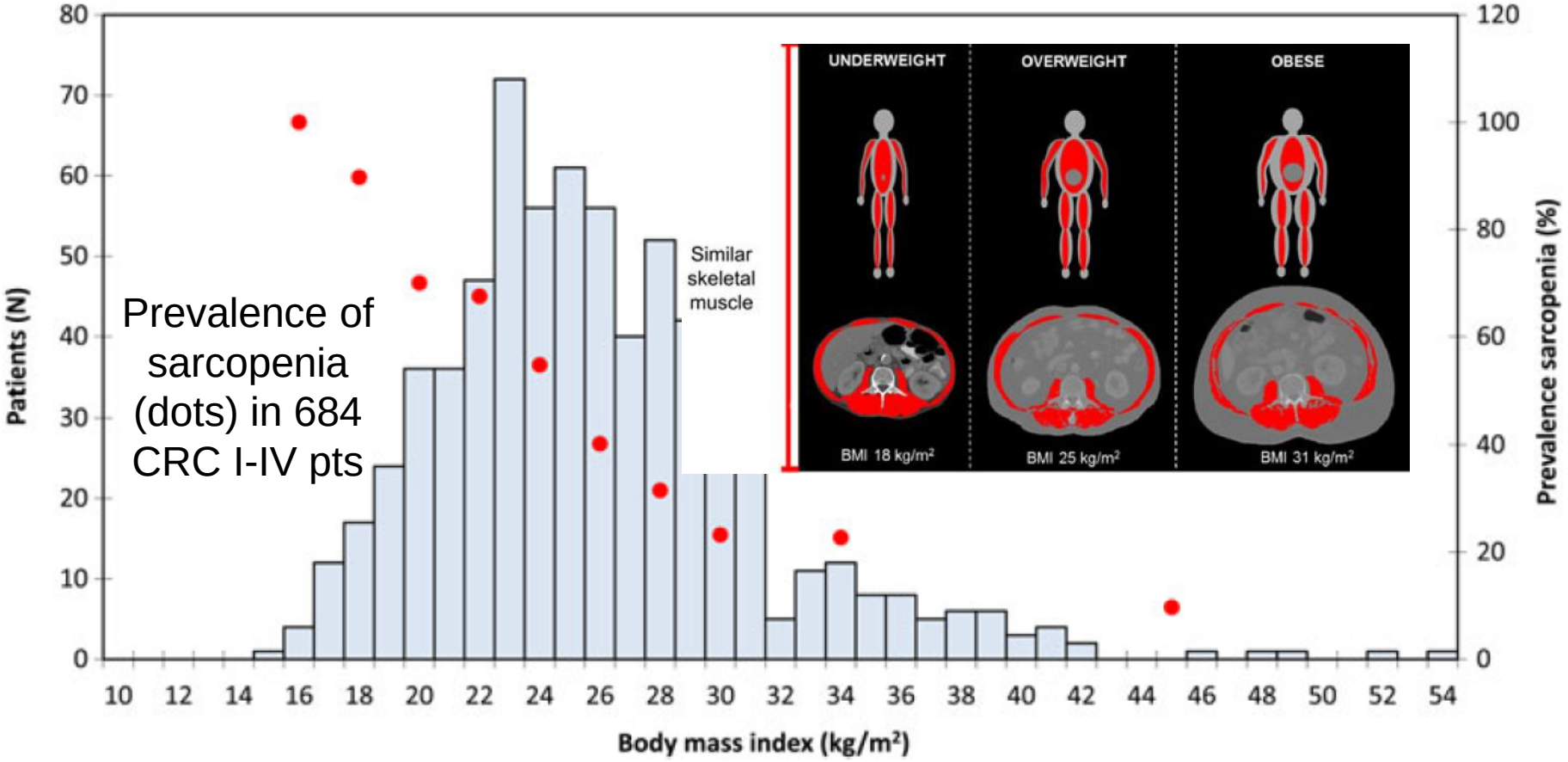
No: Personal financial interest (stocks, private use of honoraria, ...)

Precachexia	Cachexia	Refractory cachexia
Weight loss ≤ 5% Anorexia and metabolic change	Weight loss > 5% or BMI < 20 and weight loss > 2% or sarcopenia and weight loss > 2% Often reduced food intake/ systemic inflammation	Variable degree of cachexia Cancer disease both procatabolic and not responsive to anticancer treatment **Performance Status low ([2],3,4)** **Close to End of life**

Conceptual Framework: Fearon K & Strasser F, et al. Definition and classification of cancer cachexia, an international consensus. Lancet Oncol 2011;12(5):489-95

How often do I see (as GI oncologist) a patient with cancer cachexia or sarcopenia?

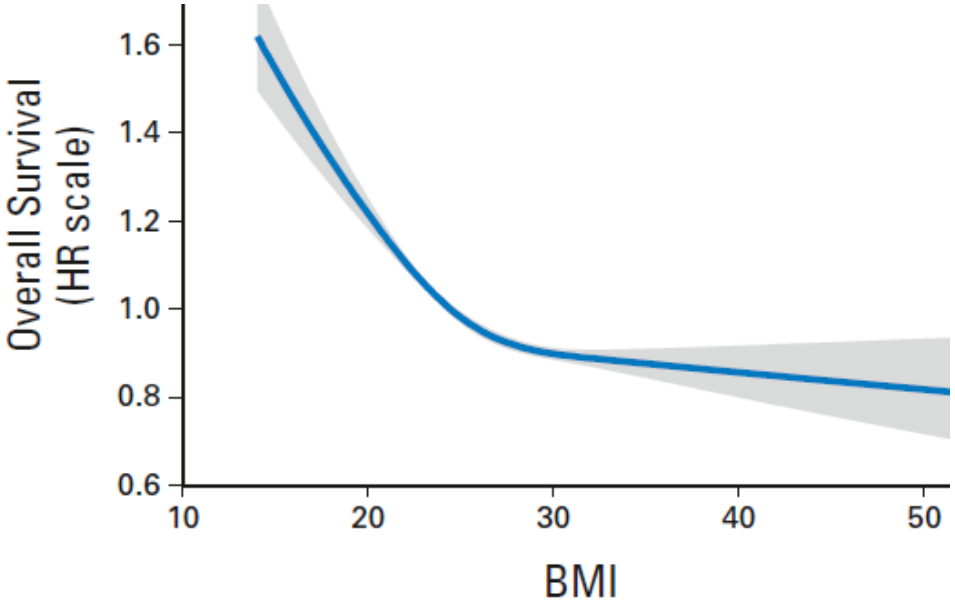


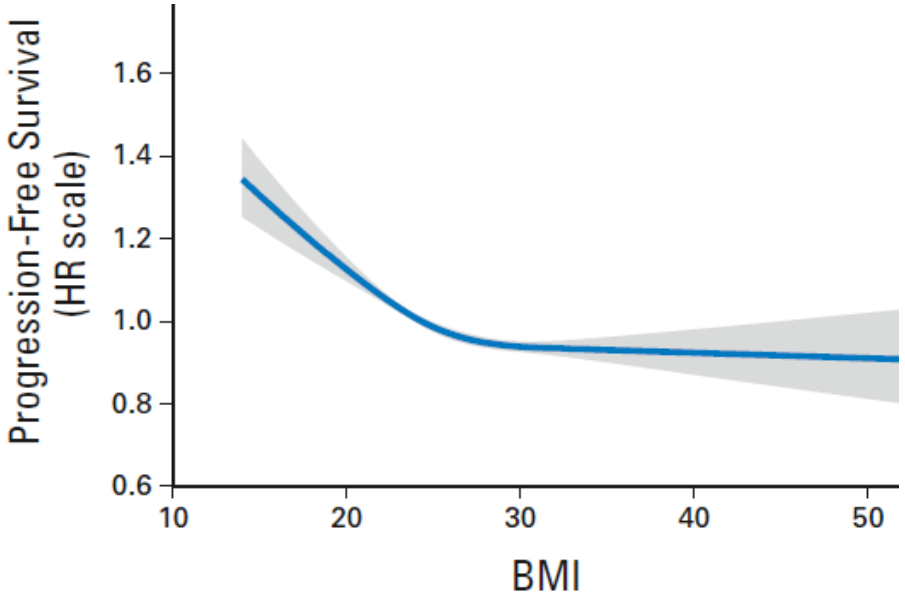
Sarcopenia in CRC pts having BMI 24: 55%

Prado CM et al. Proc Nutr Soc 2016;75:188–198

Why does it matter that my patient has cancer cachexia or sarcopenia?

21’149 mCRC patients from 39 intl ARCAD[1] clinical trials (1997-2012)[2]





Survival is heavily affected
Obesity paradox

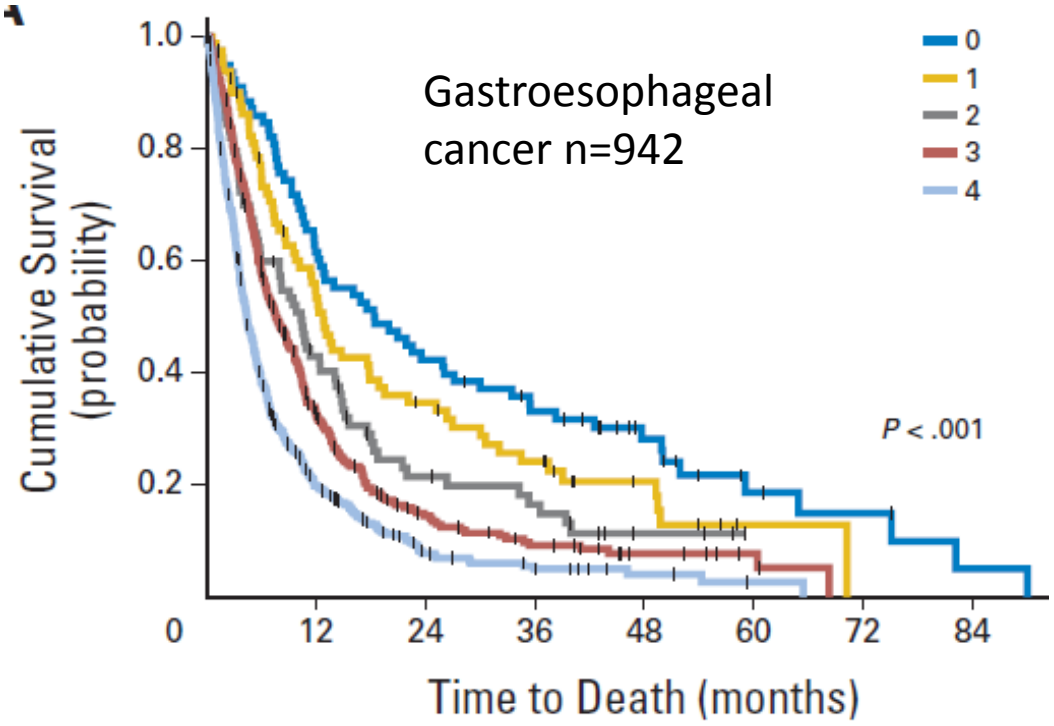
1 de Gramont A et al. J Clin Oncol 2010;28:527-530
2 Renfro LA et al. J Clin Oncol 2016;4:144-150

Cancer-Associated Weight Loss: Survival, Grading System

Weight Loss (%) \ BMI (kg/m²)	28	25	22	20
2.5	0	0	1	1	3
6	1	2	2	2	3
11	2	3	3	3	4
15	3	3	3	4	4
	3	4	4	4	4

Weight Loss (%) \ BMI (kg/m²)	28	25	22	20	
2.5	21.5	19.9	15.7	13.5	8.4	17.3
6	14.2	11.9	10.5	10.6	7.8	11.3
11	10.7	9.2	6.8	6.7	4.7	7.5
15	8.1	8.1	6.2	5.4	4.4	6.2
	7.1	4.8	4.7	3.7	4.1	4.4
	13.1	10.2	8.1	6.1	4.7	Overall

8160 cancer pts, multivariable analysis (age, sex, cancer site, stage, PS). Independent validation sample 2963 pts
Survival mts depends both on WL% and BMI



Martin L et al. J Clin Oncol 2015;33:90-99

Anorexia & cachexia are frequent most severe symptoms

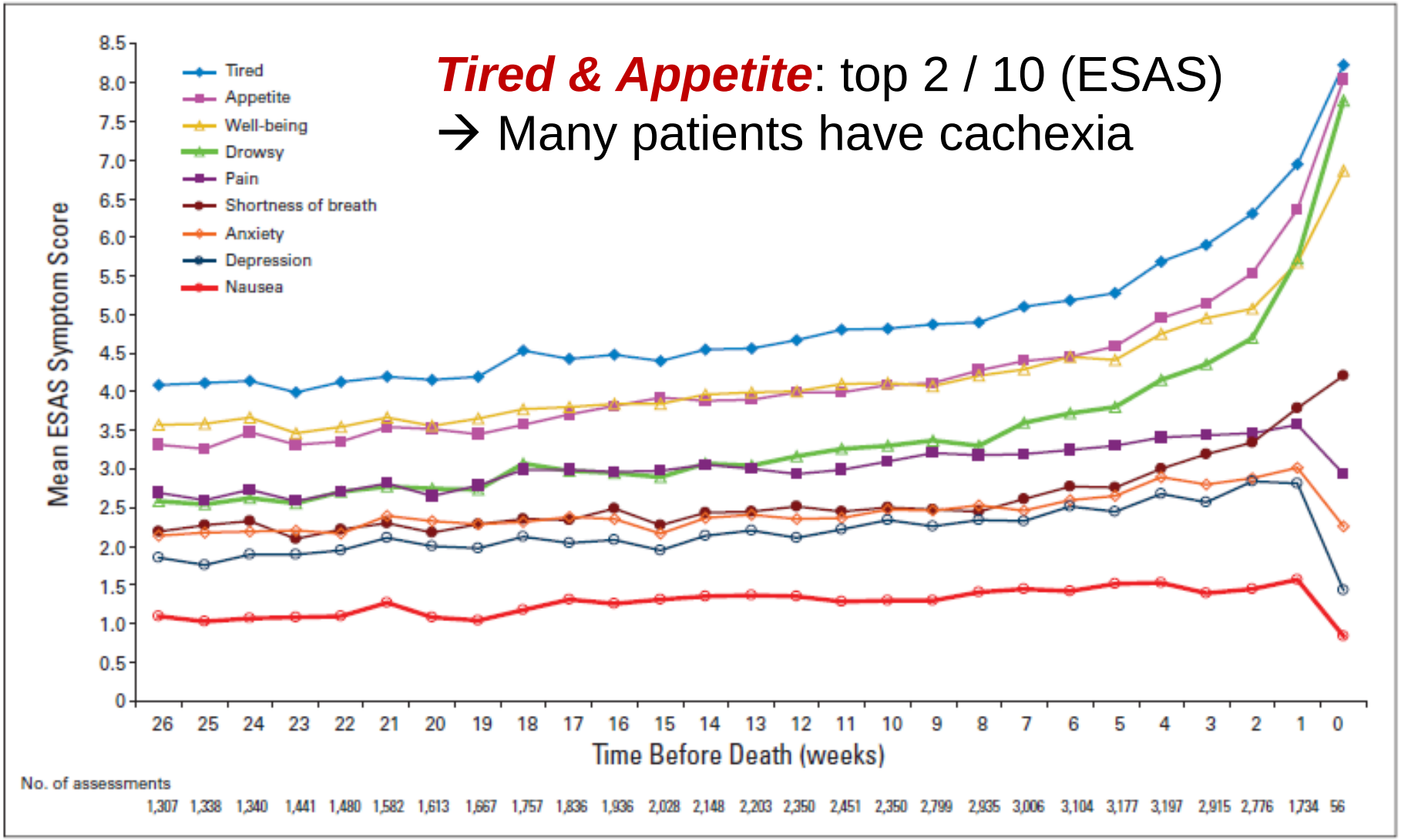
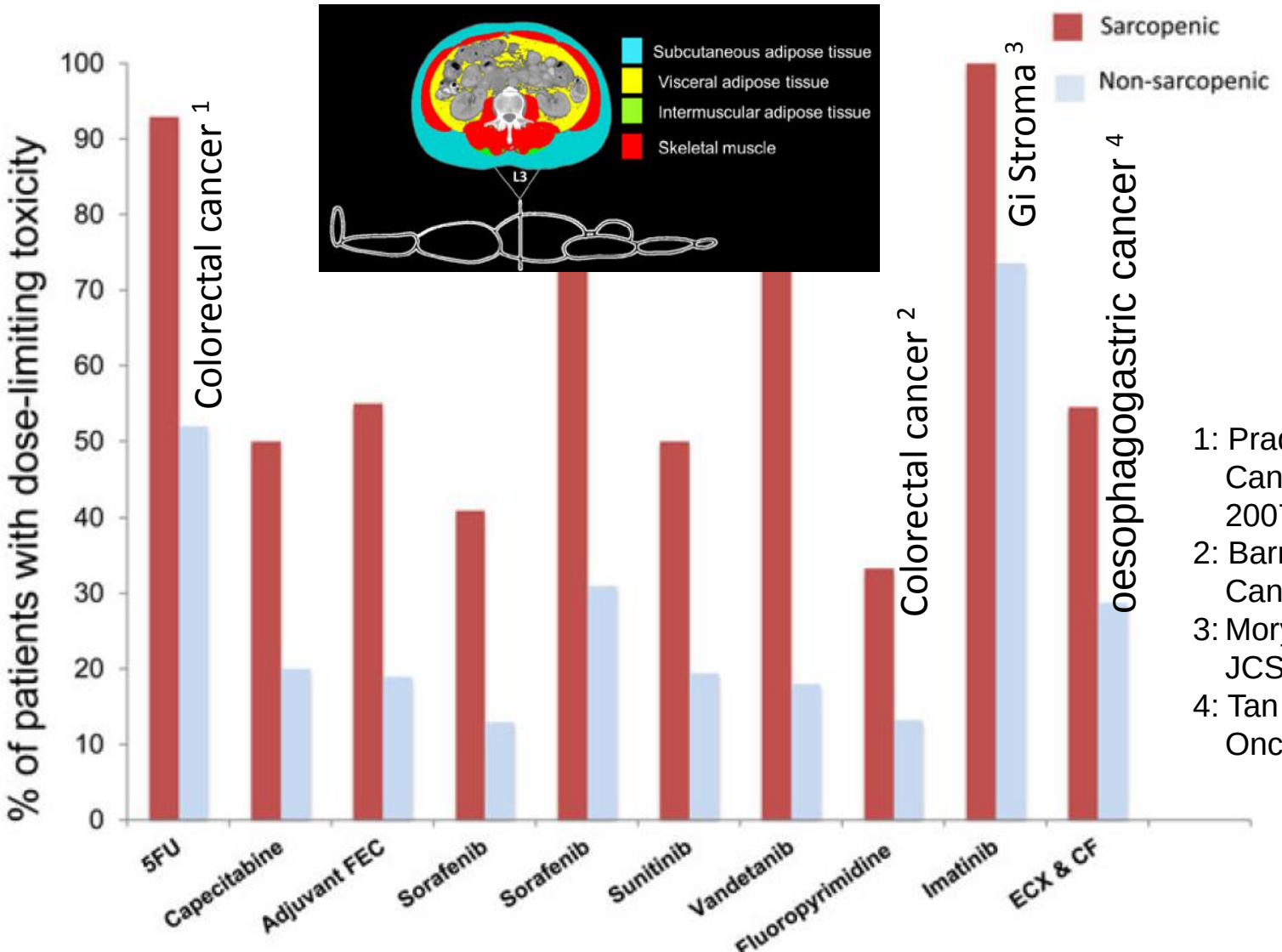


Fig 2. Mean Edmonton Symptom Assessment System (ESAS) symptom scores over time. Number of assessments is maximum number available among all nine symptoms. Missing ESAS values for a given symptom were not included when calculating the mean.

Seow H, et al. J Clin Oncol 2011:1151-8

Sarcopenia is associated with anticancer tx toxicity

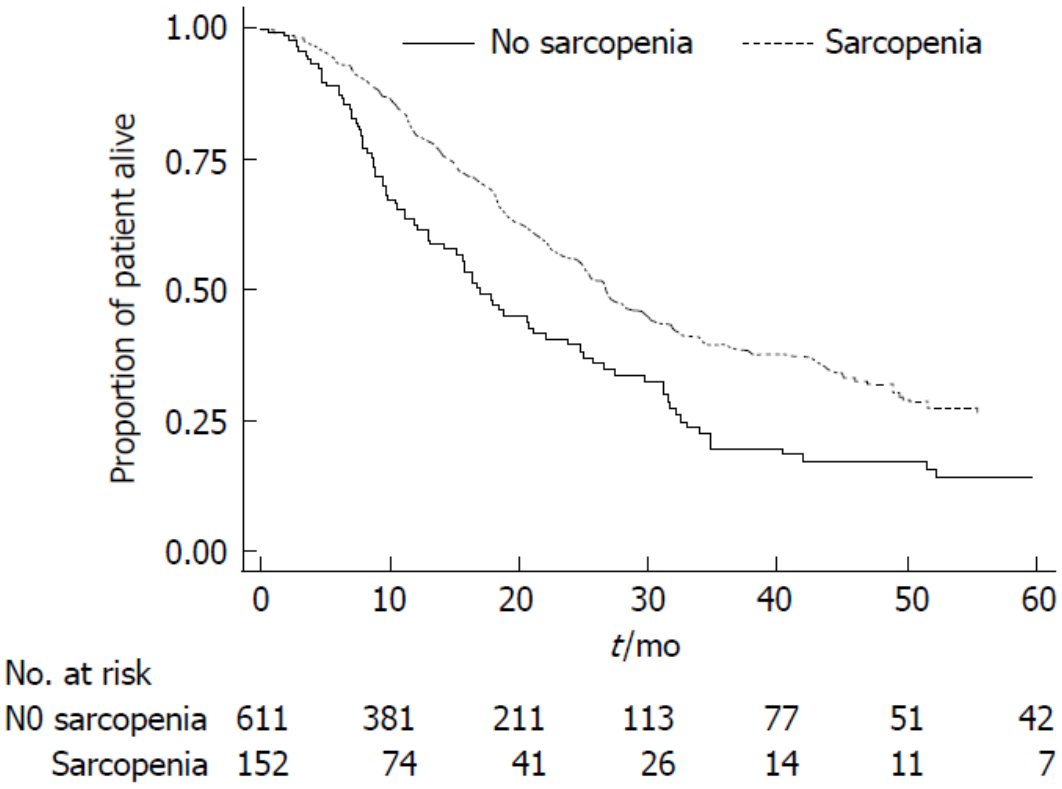


1: Prado CM et al. Clin Cancer Res 2007;13,3264–8
2: Barret M et al. Nutr Cancer 2014;66: 583–9
3: Moryoussef F et al. JCSM 2015;6,343–50
4: Tan BH et al. Eur J Surg Oncol 2015; 41, 333–8

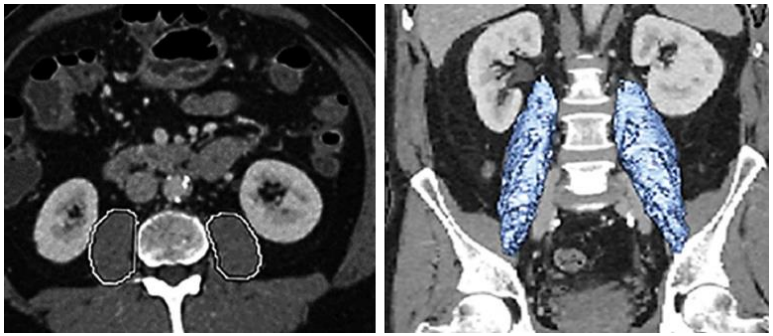
Prado CM et al. Proc Nutr Soc 2016;75:188–198

Kantonsspital St.Gallen

Sarcopenia, or wasting of lean muscle mass: emerging important metric of frailty ("**morphometric age**"), associated with peri-operative outcomes and survival



3-dimensional psoas volume-sarcopenia (not area): independent risk factor of postoperative complications (OR = 1.69), survival (OR = 1.46) (both $P < 0.05$)



Amini N et al. J Gastrointest Surg 2015; **19**: 1593-1602
Wagner D et al. World J Gastrointest Surg 2016; 8: 27-40

What is sarcopenia?

Sarcopenia is the loss of muscle mass due to many causes

Hypogonadism

Physical inactivity

Corticosteroids

Thyroid dysfunction

Age-related*

- *Less muscle stem cell response to acute resistance exercise*
- *Same Type I, less Type II fibres*
- *myogenic program reduced*
- *impaired induction of MyoD in Pax7 cells*

Cachexia

* McKay B etz al. FASEB J 2012;(26):2509–2521
Joseph AM et al. Aging Cell 2012; 11: 801–809

What is cancer cachexia?

Cancer cachexia is a multifactorial syndrome defined by a ongoing loss of skeletal muscle mass that cannot be *fully* reversed by conventional nutritional support and leads to progressive functional impairment.
Its pathophysiology is characterized
by negative protein and negative energy balance driven by a variable combination of reduced food intake and abnormal metabolism[1,2]

1: Fearon K & Strasser F, et al. Lancet Oncol 2011 ;12:489-95
2: Argilés JM et al. J Am Med Dir Assoc 2010;11:229-30

Molecular pathways leading to loss of skeletal muscle mass in cancer cachexia

Critical remark: Results from animal studies are only partially translatable to humans

+ role confirmed in few studys
++ role confirmed in many studys
+/– role not confirmed/inconsistent results

TNF-α	++	+/–
	Yoshida hepatoma/sarcoma, LLC, Leydig cell tumor, Morris hepatoma	Various types of solid tumors
TRAF-6	+	+
	LLC	Gastric cancer
IL-6	++	+/–
	C26, Morris hepatoma, ApcMin/+	Various types of solid tumors
IL-1	+	+/–
	Methylcholanthrene-induced Sarcoma, Prostate ADK	Various types of solid tumors
INF-γ	+	+/–
	MAC16	Various types of solid tumors
Myostatin/ TGF-ß	++	+
	C26, MAC16	Gastric cancer
PIF	+	+/–
	MAC16	GIT cancers
Angiotensin II	+	+
	C26	NSCLC, congestive heart failure
Ubiquitin-Proteasome system	++	+
	C26, Yoshida hepatoma, LLC	GIT cancers
Autophagy-lysosomal system	+	+
	C26, Yoshida hepatoma, LLC	Lung cancer
IGF-1/Pi3K/Akt/mTOR	+/–	+/–
	C26, ApcMin/+	Various types of solid tumors
MRFs (Myo D, Pax7)	+	+
	C26	Pancreatic cancer

Mueller et al. BMC Cancer (2016) 16:75

Molecular pathways leading to loss of skeletal muscle mass in cancer cachexia

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<u>Inflammation</u>
TNF-receptor adaptor protein
<u>Muscle</u>
MRF muscle growth and regeneration factor

TNF-α	++	+/–
	Yoshida hepatoma/sarcoma, LLC, Leydig cell tumor, Morris hepatoma	Various types of solid tumors
TRAF-6	+	+
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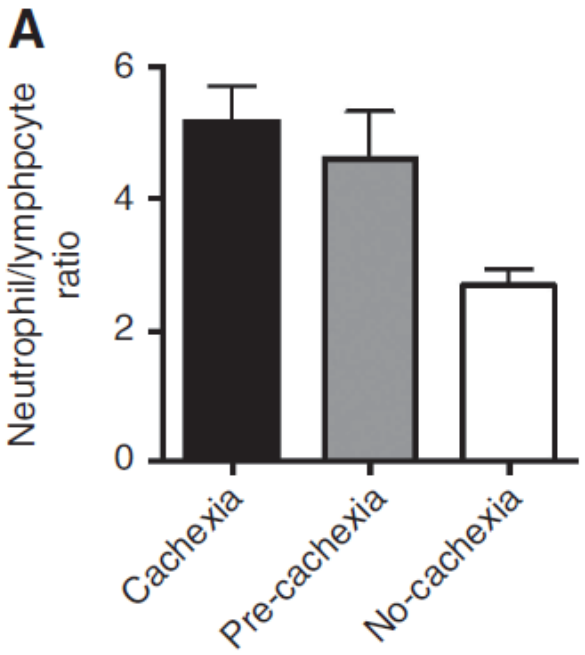
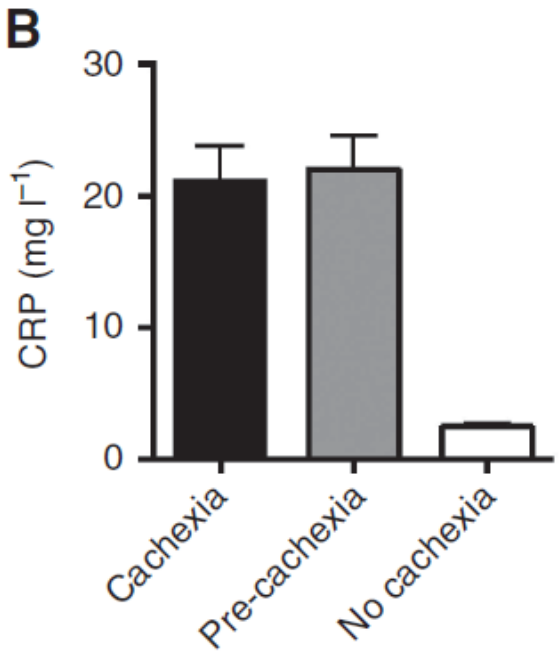
Mueller et al. BMC Cancer (2016) 16:75

Inflammatory drivers of cancer cachexia

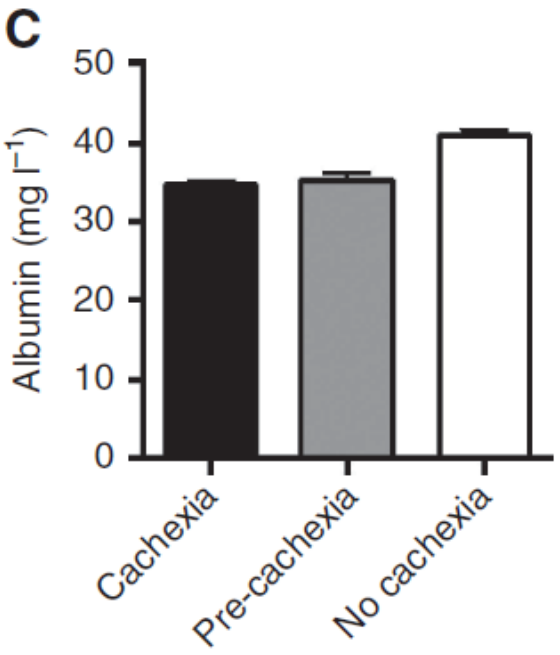
122 newly diagnosed cancer pts (stages III & IV), prior any treatment
46.7% > 5% weight lost, 61.5% CRP level > 5mg/dl, 65.6% sarcopenia
50.8% cachectic, 28.7% pre-cachectic



P *vs* C	NS
C *vs* N	*P*= 0.02
N *vs* P	NS



P *vs* C	NS
C *vs* N	*P*<0.0001
N *vs* P	*P*<0.0001



P vs C	NS
C vs N	*P*=0.0027
N vs P	*P*=0.01

Penafuerte CA et al. BJC 2016;114:680–687

Inflammatory drivers of cancer cachexia

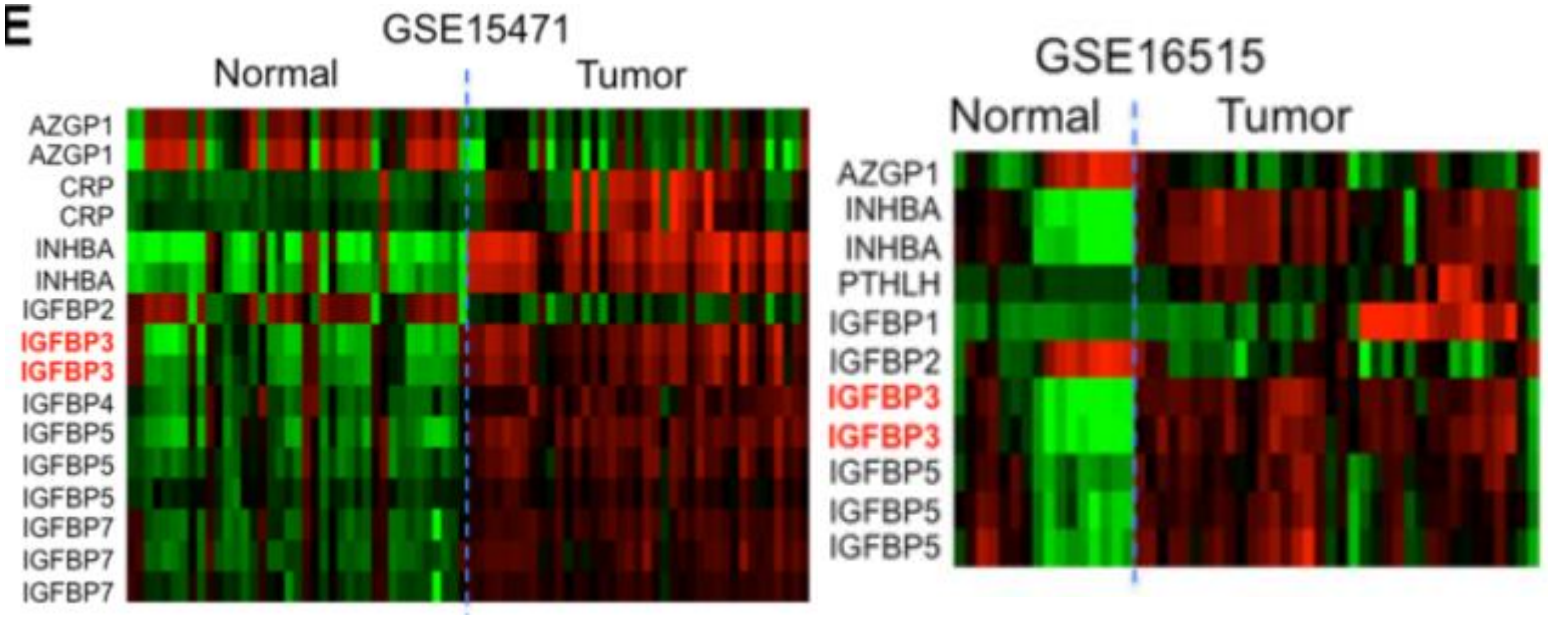
	Cachexia status		
Biomarkers	**Cachexia**	**Pre-cachexia**	**No cachexia**
ANC/neutrophil proteases	+ + + + +	+ +	+
Ang II	+ + + + +	+ + + + +	+
TGFβ1	+ + + + +	+ + + + +	+
IL-8	+ + + + +	+	+
IL-6	+ + + + +	+ +	+
CRP	+ + + + +	+ + + + +	+

Abbreviations: ANC = absolute neutrophil count; Ang II = angiotensin II; CRP = C-reactive protein; IL-6 = interleukin-6; IL-8 = interleukin-8; TGFβ1 = transforming growth factor β1. ANC and plasma levels of neutrophil-derived proteases, Ang II, CRP, TGFβ1, IL-6 and IL-8 in pre-cachectic and cachectic patients. + *vs* + means no significant, + *vs* + + and + + *vs* + + + means increase, but no significant; and + *vs* + + + means significant.

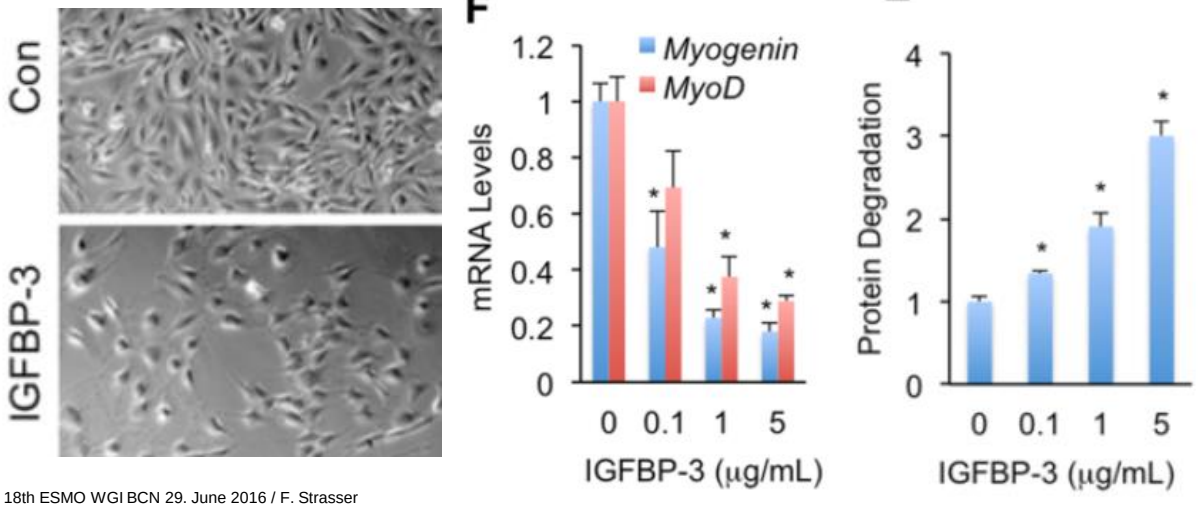
Measuring inflammation is relevant in clinical practice

Penafuerte CA et al. BJC 2016;114:680–687

Pancreatic cancer derived IGFBP-3 contributes to muscle wasting



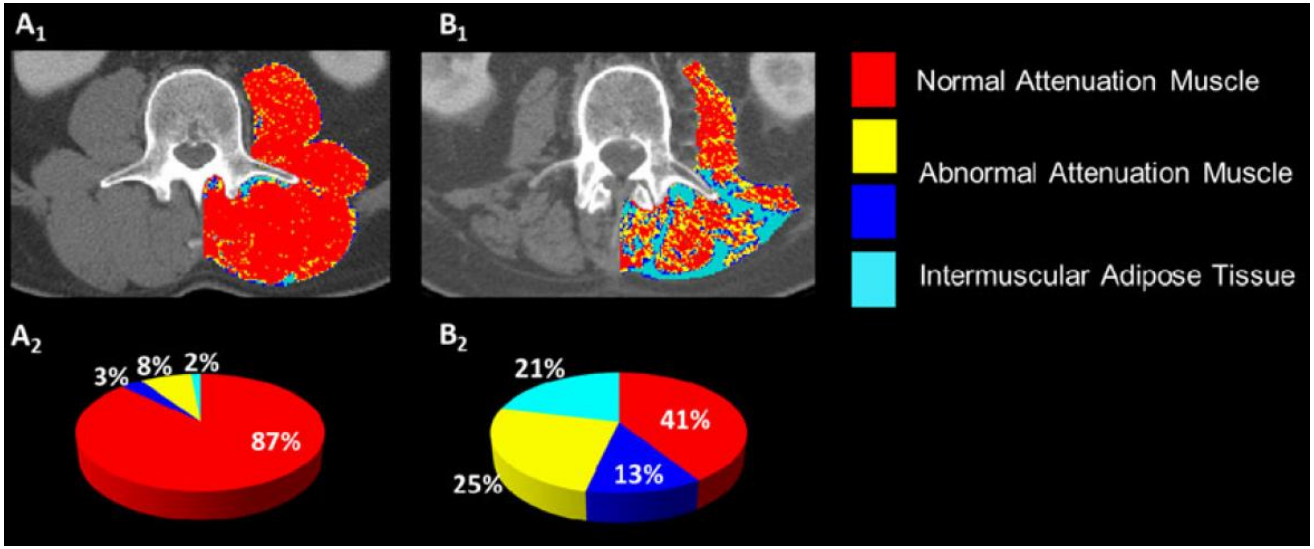
IGFBP-3: up-regulated in pancreatic tumor samples



Wasting effect of IGFBP-3 on C2C12 muscle cells

Huang et al. J Exp & Clin Cancer Res 2016;35:46

muscle myosteatosis, low (psoas) muscle radiodensity or low muscle attenuation: a feature of cachexia



Myosteatosis associated with

. Disease-free survival (P = 0.0002); Melanoma[1]

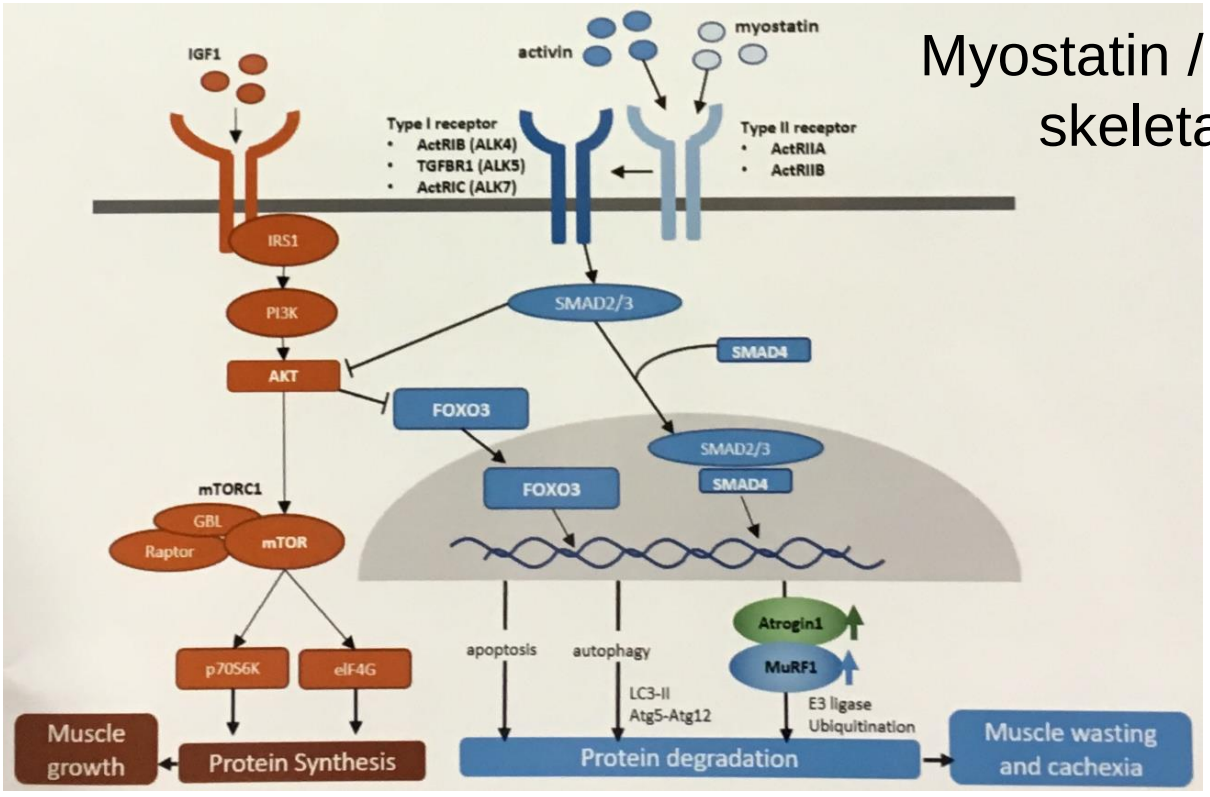
. Survival (HR 1·36, 95 % CI 1.2, 1.6); various tumors[2]

. Overall (HR 2.5, P<0.001), recurrence free (HR 1.6; P=0·004) survival; pancreatic[3]

. DFS (HR 1.53, P=0.041), OAS (HR 1.70, P<0.001), hospital stay (p= 0.034), 804 CRC pts, elective surgery[4]

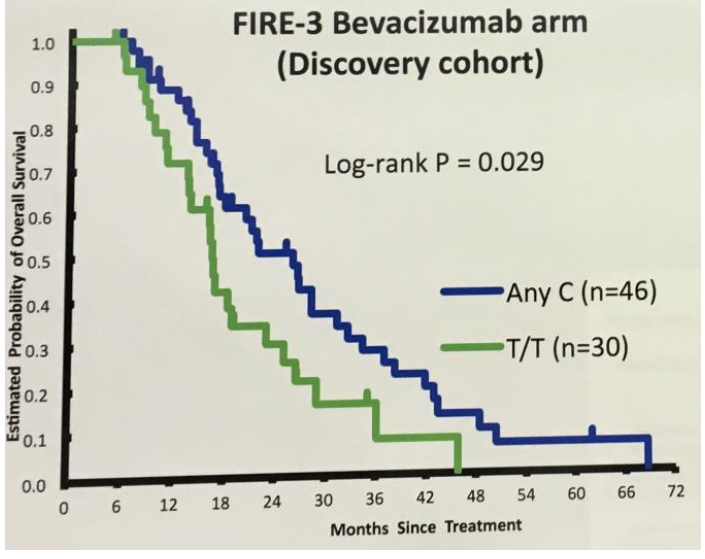
1: Sabel MS. Ann Surg Oncol 2011;18:3579–85 2: Martin L et al. J Clin Oncol 2013;31:1539–47
3: Okumura S et al. Surgery 2015; 157:1088–98 4: Malietzis G et al. Br J Surg 2016;103:572-80

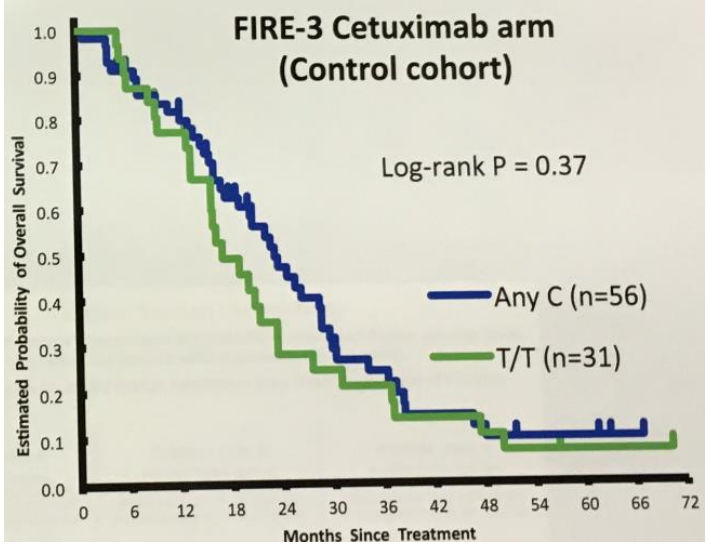
Myostatin / activin signaling pathway: skeletal muscle degradation



Variation in genes regulating cancer cachexia may affect prognosis of mCRC pts treated with Bevacizumab-based chemotherapy

ACVR2B rs2268755 in RAS mutant pts of FIRE-3 cohorts





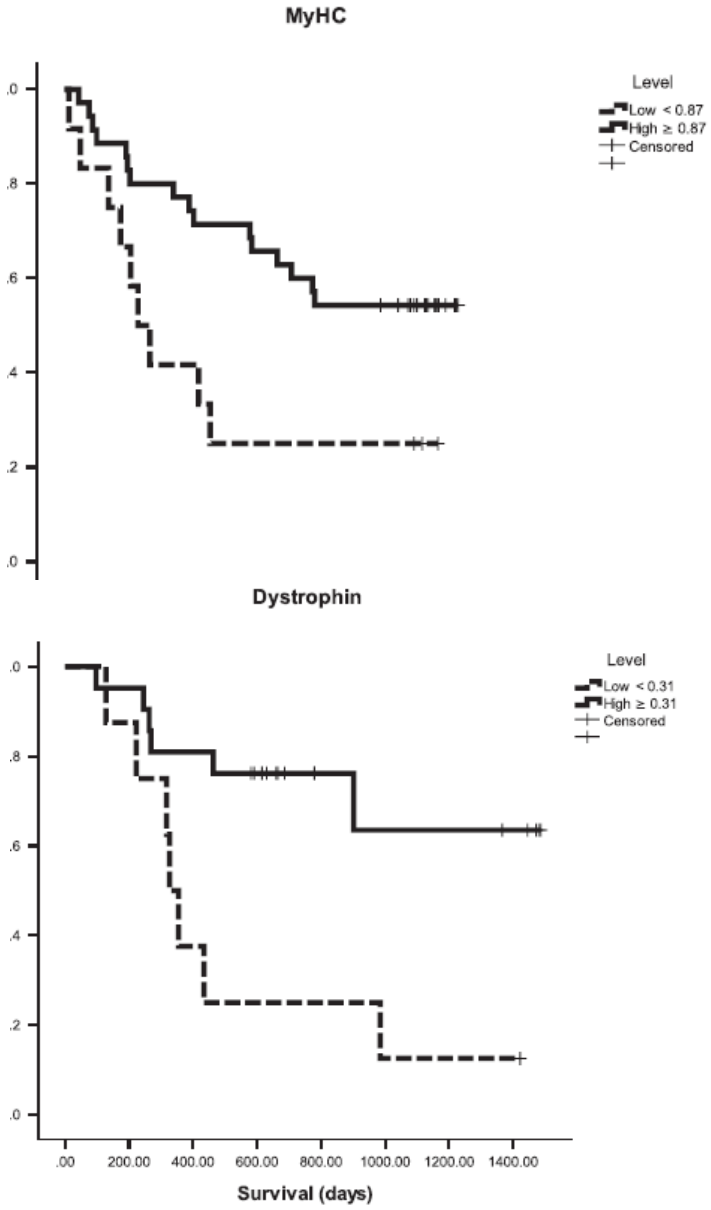
Miyamoto Y et al.
Poster ASCO 2016

Biomarkers of cancer cachexia

107 upper gastrointestinal cancer pts and 15 healthy controls, muscle biopsies

A. MyHC	Low (<0.87)	High (≥0.87)
n =	12	35
M/F	7/5	21/14
Age (year)	63 ± 7	64 ± 10
BMI (kg/m^2)	24.9 ± 4.4	25.4 ± 3.8
Weight-loss (%)	9.8 ± 7.4	9.6 ± 12.1
Cachexia (Y/N)	9/3	20/15
CRP (mg/L)	20.3 ± 41.6	12.1 ± 25.8
CRP ≥ 5 mg/L (Y/N)	7/5	14/21
KPS	88.2 ± 10.8	92.1 ± 12.1

B. Dystrophin	Low (<0.31)	High (≥0.31)
n =	8	21
M/F	5/3	10/11
Age (year)	62 ± 13	63 ± 9
BMI (kg/m^2)	26.8 ± 6.3	25.0 ± 4.3
Weight-loss (%)	9.5 ± 7.5	9.7 ± 11.3
Cachexia (Y/N)	7/5	14/21
CRP (mg/L)	45.8 ± 52.3	11.8 ± 22.4
CRP ≥ 5 mg/L (Y/N)	5/3	8/13
KPS	82.5 ± 8.9	84.3 ± 15.0



Survival low vs high MyHC levels (316 vs. 1326 days, P = 0.023), dystrophin levels (341 vs. 660 days, P = 0.008)

Changes in the structural elements of muscle (MyHC or dystrophin) appear to be survival biomarkers in cancer cachexia

Stephens NA et al. J Cachexia Sarcopenia Muscle. 2015;6:53-61.

How can I / we interfere to prevent or improve or ease cancer cachexia or sarcopenia in my patient?

First: identify the patients by routine screening!

Strength of recommendation STRONG *ESPEN Guidelines 7.2016*	*To detect nutritional disturbances at an early stage, we recommend to regularly evaluate nutritional intake, weight change and BMI, beginning with cancer diagnosis and repeated depending on the stability of the clinical situation.*
Level of evidence	Very low

Second: assess the patients

Strength of recommendation STRONG *ESPEN Guidelines 7.2016*	*In patients with abnormal screening, we recommend objective and quantitative assessment of nutritional intake, nutrition impact symptoms, muscle mass, physical performance and the degree of systemic inflammation.*
Level of evidence	Very low

Domains of cancer cachexia relevant for assessment

- Depletion of reserves: muscle mass *and* fat mass
- Nutritional intake *and* „gut-brain axis“ symptoms appetite
- Inflammation *and* tumor dynamics *and* hypoanabolism
- Neuro-muscular *and* emotional-cognitive function

1: Fearon K & Strasser F, et al. Lancet Oncol 2011 ;12:489-95
2: Argilés JM et al. J Am Med Dir Assoc 2010;11:229-30

Stage and classify the cachectic patient with in **routine cancer care**

Reserves (muscles)	**Weight loss history** (%; 1, 2, 6 mts), **BMI** **check edema!** *if fluid retention*: **CT L3** or DEXA
Intake (gut-brain)	**2 day diet diary**, % kcal/protein / needs **Appetite, hunger, satiety, taste/smell** **Rule out starvation** (S-NIS checklist, PG-SGA)
Catabolism	**Cancer dynamics** & **responsiveness** **CRP >10mg/l** (no clinical infection) **Albumin**
Function	**Physical function (KPS),** muscle strength Motivation/Participation

→ Decide on cachexia phase and goals of intervention

Assess & correct causes for malnutrition

- **Diet mistakes / misconceptions: too healthy, ..**
- **neglect for maintenance of nutritional intake**
  - “no eating” due to procedures, hospitalization[1]
  - helping patients to eat (edentulousness[1])
- **Secondary Nutrition-Impact symptoms**[2]
  - Pain, breathlessness, constipation, dysgeusia, …
  - Periods of nausea/vomiting, stomatitis, dysphagia, gastric acid
  - (partial) bowel obstruction, diarrhea, malabsorption, prolonged constipation, ..

(● Cachexia)

1: van der Pols-Vijlbrief R et al. Ageing Res Rev 2014;18:112-31
2: Omlin A et al. J Cach Sarcop Muscle 2013;55-61

Assess other causes for inflammation:

Infections
- If steep increase of C-Reactive Protein (x 2-5 /3-5 days)
- may consider empirical antibiotic therapy (after cultures)
- *may*[1] measure Pro-CalciTonin (neg & pos predictive value)[2]
- *may* use PCT/CRP ratio[3]

Corticosteroids

Chronic inflammatoric diseases

Pro-inflammatoric drugs & herbal therapies

(Cachexia)

1: Naito T et al. Intern Med 2015;54:1989-94; Chaftari AM et al. PLoS ONE 2015;10:e0130999
2: Sbrana A et al. New Microbiol 2016;39(3); Wu CW et al. Support Care Cancer 2015;23:2863-72
3: Hangai S et al. Leuk Lymphoma 2015;56:910-4; Markova M et al. Support Care Cancer 2014;21:2733-42

Cachexia requires multidimensional interventions delivered by multiprofessional teams

- Depletion of reserves: muscle mass *and* fat mass
- Nutritional intake *and* „gut-brain axis“ symptoms
- Inflammation *and* tumor dynamics
- Neuro-muscular *and* emotional-cognitive function

«Best Supportive Care[1]»

«Early Integrated Palliative Care[2]»

- ► needs-adjusted adequate **nutritional intake**
- ► adequate **physical function** (resistance training & activity)
- ► multidimensional **symptom control**, patient education
- ► **anticachexia** drugs
- ► tolerable **anticancer therapy** to control tumor activity
- ► Illness & **prognosis understanding**, disease coping
- ► **continuity of care** for patient & family members

1: Cherny JCO 2009; Zafar *Lancet Oncol 2012*
2: Smith T JCO 2012; Temel NEJM 2011; Jacobsen J J Pall Med 2011; Zimmermann C Lancet 2014; Bakitas M JAMA 2011 & JCO 2015; Temel ASCO 2016 (Lung & non-CRC GI)

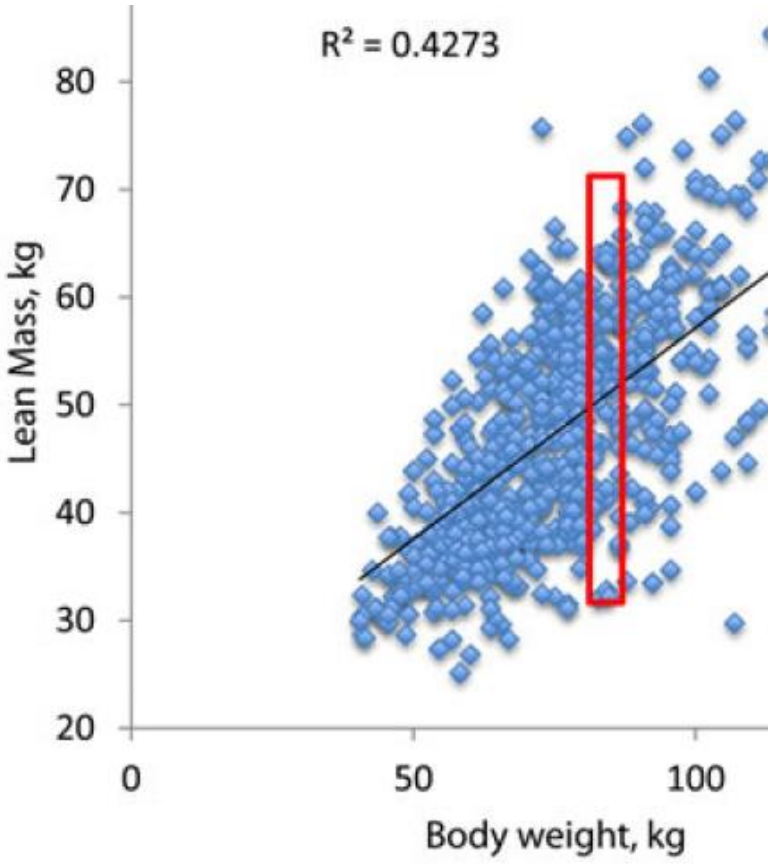
Nutritional counselling and patient & proxy education

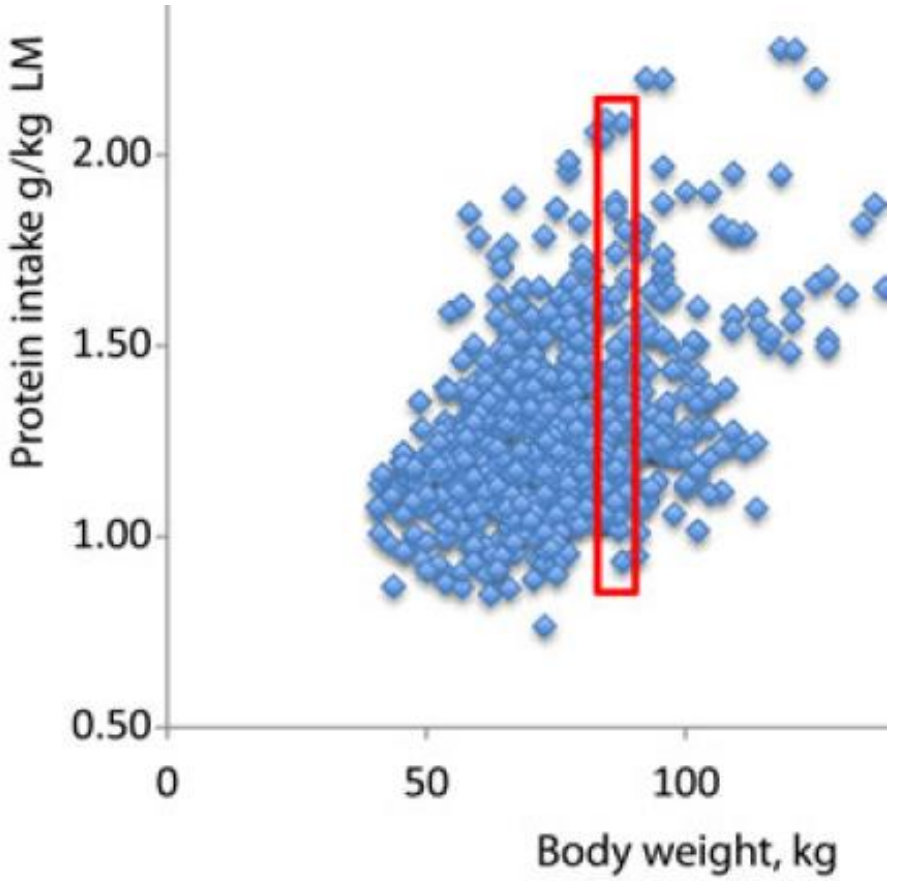
Strength of recommendation STRONG *ESPEN Guidelines 7.2016*	*We recommend nutritional intervention to increase oral intake in cancer patients who are able to eat but are malnourished or at risk of malnutrition. This includes dietary advice, the treatment of symptoms and derangements impairing food intake (nutrition impact symptoms), and offering oral nutritional supplements.*
Level of evidence	Moderate
Questions for research	effect of dietary advice and ONS on clinical outcome

Strength of recommendation STRONG	*We recommend that protein intake should be above 1 g/kg/day and, if possible up to 1.5 g/kg/day*
Level of evidence	Moderate
Questions for research	effect on clinical outcome of increased supply (1-2 g/kg/day) and composition of protein/amino acids

Many small meals, proteins & proteins & fat, cognitive control eating, change habits, oral supplements

How much shall my patient eat?





Data courtesy of Dr Vickie Baracos, University of Alberta

The calculations based on body weight may mislead the amount needed:
clinically monitoring including physical function is important

Evidence for Parenteral Nutrition (defined population, defined intervention, control, if patient-reported outcomes then mandatory placebo, defined time to endpoints, endpoints covering all important domains) **is poor**[1,2]

Bozzetti 2002	Prospective non-controlled trial
Chermesh 2011	Prospective non-controlled trial
Katzberg 2011	Cochrane systematic review - no RCTs, retrospective case control studies, and prospective cohort studies
Meier 2001	Prospective non-controlled trial
Orrevall 2005	Prospective non-controlled trial
Pironi 1997	Prospective non-controlled trial

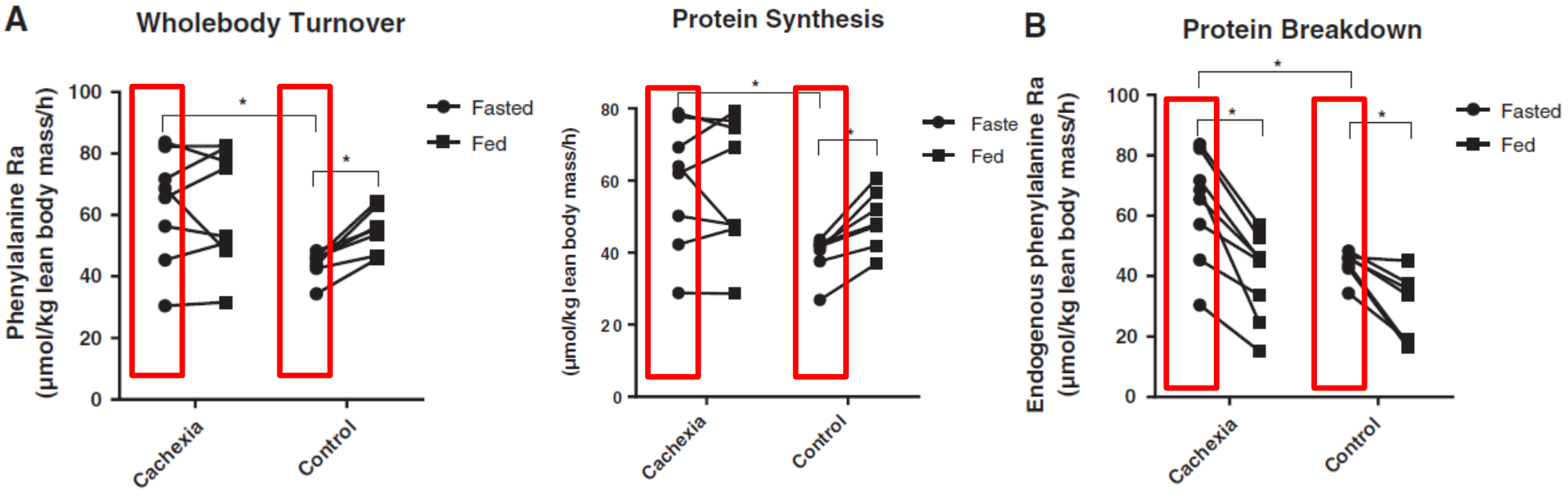
1: Good P et al. Medically assisted nutrition for adult palliative care patients. Cochrane 2014
2: Dev R et al. Curr Opin Support Palliat Care 2012:365-7

More prospective phase II studies or case series from 17-414 pts*

* Richter E Anticancer Res 2012;32:2111-8; Pelzer BMC Cancer 2010;10:86; 2: Orrevall Y Nutrients 2013; Bozzetti Ann Oncol 2014; Culine S Supp Care C 2014; Senesse P JPSM 2015; Chen Eur J Cancer Care 2013

Sip feeding in pancreatic cachectic cancer patients: influence of nutrition on protein kinetics

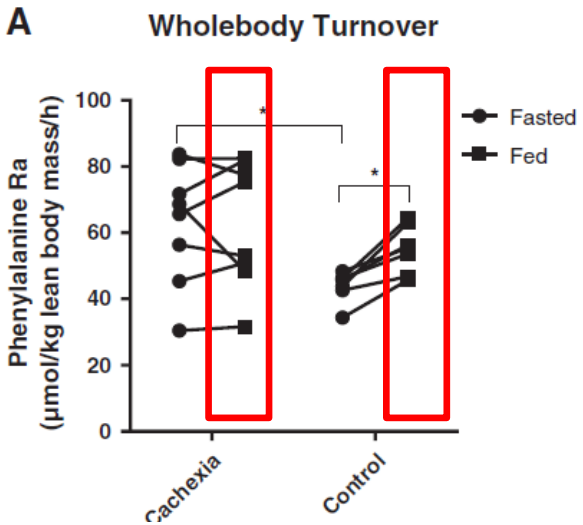
8 cachectic pancreatic cancer pts & 7 ctrls: cont iv Phenylalanin & Tyrosine over 8 h
Sipping oral Phenylalanin every 30 minutes, at 4h oral feeding

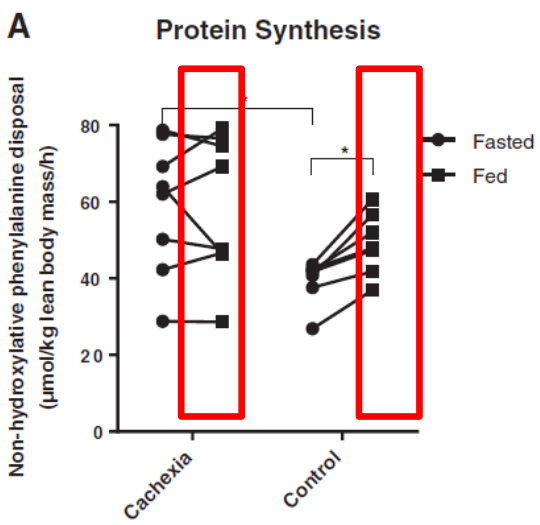


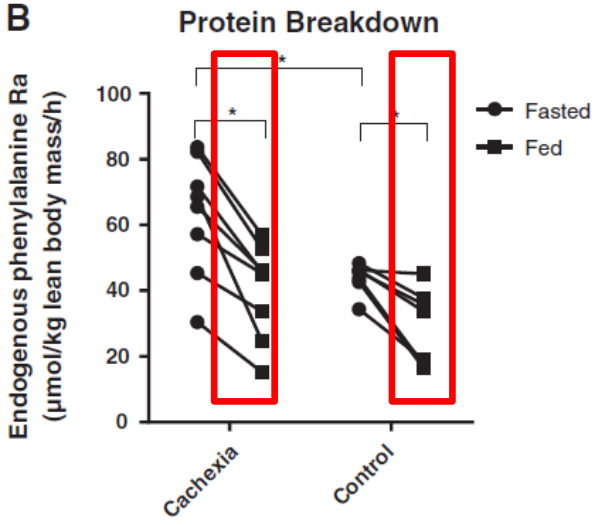
Baseline protein turnover, protein synthesis and protein breakdown is in cachectic pts **> higher** than controls
(63 vs 42, p=0.021; 67 vs 46, p=0.049)
These findings correlated wt CRP (rs=0.66, p=0.008)

van Dijk DP et al. J Cachexia Sarcopenia Muscle 2015;6:212-21

Sip feeding in pancreatic cachectic cancer patients: influence of nutrition on protein kinetics

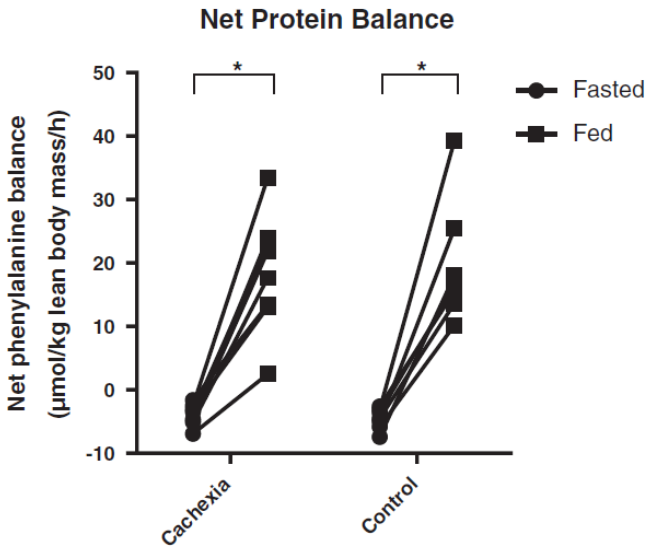






During feeding:

- Protein breakdown decreases both in cachexia (46, p=0.012) *&* ctrl (34, p=0.018)
- Protein synthesis unchanged in cachexia, *but* increase in ctrl (48, p=0.018)
- Positive net protein balance cachexia (-4 → 20) same as ctrl (-5 → 16), p=0.91



van Dijk DP et al. J Cachexia Sarcopenia Muscle 2015;6:212-21

Sip feeding in pancreatic cachectic cancer patients: influence of nutrition on protein kinetics

Cachexia and controls have a comparable anabolic response to feeding, butcachectic pts achieve it only by reducing protein breakdown (not increase synthesis)
Anabolic resistance may be less an issue in cachexia than sought: importance of antitumor and antiinflammation effects

- Protein breakdown decreases both in cachexia (46, p=0.012) *&* ctrl (34, p=0.018)
- Protein synthesis unchanged in cachexia, *but* increase in ctrl (48, p=0.018)
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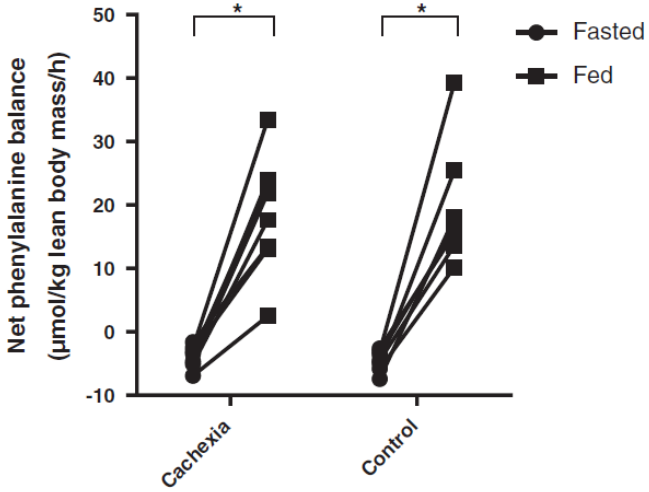


van Dijk DP et al. J Cachexia Sarcopenia Muscle 2015;6:212-21

Effective anticancer treatment improves cachexia

Retrospective 2301 patients with non-squamous NSCLC, platinum-based 1st line doublet, with/wt bevacizumab

421 pat > 5% weight gain; occuring in >50% by 3 weeks

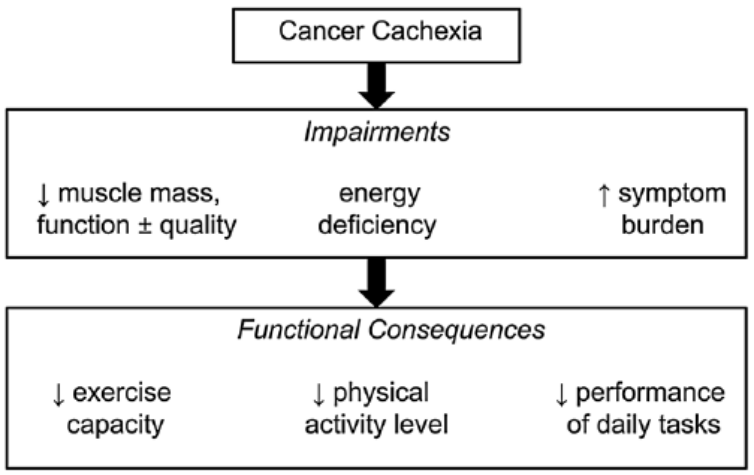
	weight gain > 5%	weight gain ≤ 5%
Survival	16.7 mts	10.7 mts
Response Rate	50.8%	25.4%
Dis Ctrl Rate	91.5%	63.6&

Logistic regression: weight gain associated wt age and BMI

→ **If anticancer treatment works, cachexia gets better**

Patel JD et al. Ann Oncol 2016 May 23

Exercise for cancer cachexia in adults: Cochrane review



RCTs, adults meet intl criteria for cancer cachexia, comparing a programme of exercise as sole or adjunct intervention to usual care or an active control.
10 databases, 3154 titles, 16 full text, up 6.2014

No RCT: data relevant for cachexia criteria

Pre-cachexia; weight loss ≤5% with anorexia and metabolic changes

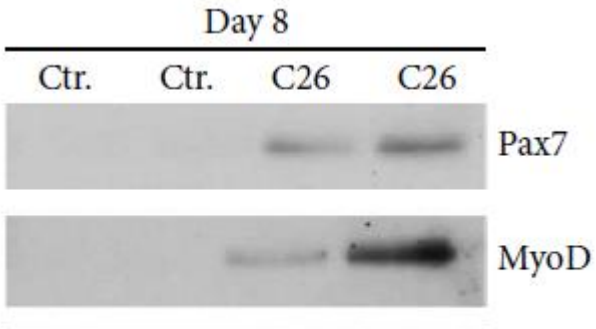
Cachexia; weight loss >5% in the past six months or body mass index (BMI) <20 kg/m^2 and ongoing weight loss >2% or sarcopenia, anorexia or systemic inflammation

BUT: potential for exercise to impact positively on muscle mass and strength, inflammatory markers, physical function

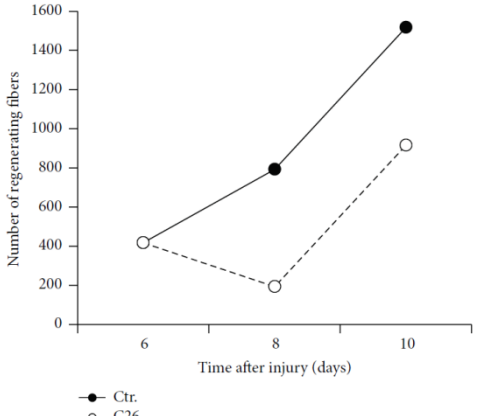
Strength of recommendation STRONG	*We recommend maintenance or an increased level of physical activity in cancer patients to support muscle mass, physical function and metabolic pattern.*
Level of evidence	High

Grande AJ, et al. *J Cachexia Sarcopenia Muscle* 2015; **6:** 208–11
Grande Aj et al. Cochrane Database Syst Rev 2014; 11 CD010804

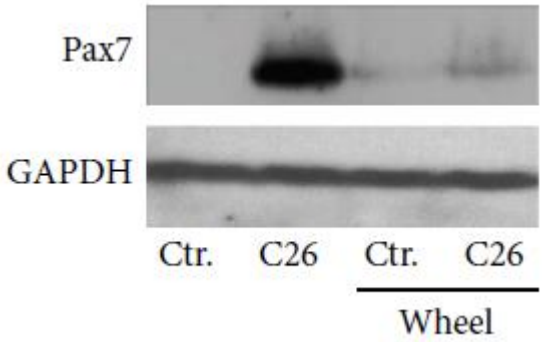
Moderate physical exercise downregulates Pax7 expression and rescues muscle mass and fiber size



Early regenerative marker expression in injured muscles

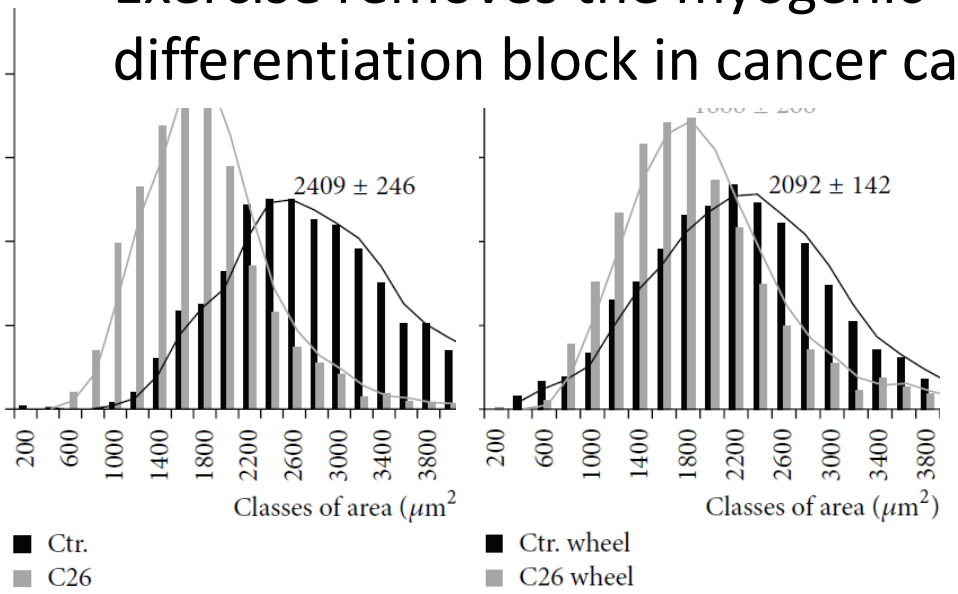


In cachectic mice (C26) less regenerative fibres (impaired myogenic potential) after muscle injury



Exercise (wheel) reduces Pax7 overexpression

Exercise removes the myogenic differentiation block in cancer cachexia.



Coletti D et al. Stem Cells International 2016, ID 6729268

Current drug *used for* cachectic patients

Cortico-steroids: effect *only* on appetite, *only* 1-2 weeks

placebo-ctrl RCTs: 4 mg Dexamethasone 2 wks or 16mg methylprednisolone bid 7 days improve fatigue, anorexia[1,2]

SE: proximal myopathy, candidiasis, depression, anxiety

→ *C-Steroids are only drugs to relieve short term distress*

Strength of recommendation WEAK *ESPEN Guidelines 7.2016*	*We suggest considering corticosteroids to increase the appetite of anorectic cancer patients with advanced disease for a restricted period of time (1-3 weeks) but to be aware of side effects (e.g. muscle wasting, insulin resistance, infections).*
Level of evidence	High

1: Yennu S et al. J Clin Oncol 2013;31:3076; 2: Paulsen O et al., J Clin Oncol 2014;32:3221

Current drug *often used for* cachectic patients

Procinetics: effect *only* on satiety, clinically important [1]
(Metoclopramide 4 x 10mg, Domperidon 4 x 10mg)

Strength of recommendation WEAK *ESPEN Guidelines 7.2016*	*In patients complaining about early satiety, after diagnosing and treating constipation, we suggest to consider prokinetic agents, but to be aware of potential adverse effects of metoclopramide on the central nervous system and of domperidone on cardiac rhythm*
Level of evidence	Moderate
Questions for research	Effect of prokinetics on oral nutritional intake in the context of optimal nutritional counselling

In clinical practice very few side effects, needs education

1: Del Fabbro E et al. J Palliat Med 2011;14:1004-8

Current drug *often used for* cachectic patients

Fish oil or eicosapentanoic acid

Fish oil contains EPA (omega-3-fatty acids)

Insufficient evidence (3 systematic literature reviews)[1]

Recent (small) RCTs: may improve muscle mass NSCLC[2,3]

Strength of recommendation WEAK *ESPEN Guidelines 7.2016*	*In patients with advanced cancer undergoing chemotherapy and at risk of weight loss or malnourished, we suggest to use supplementation with long-chain N-3 fatty acids or fish oil to stabilize or improve appetite, food intake, lean body mass and body weight.*
Level of evidence	Low

In clinical practice often poorly tolerated, tricks neeeded

1: Ries A Palliat Med 2012; 2: Murphy RA Cancer 2011;
3: van der Meij BS Eur J Clin Nutr 2012

Current drug rarely *used for* cachectic patients

Progestins: effect appetite (NNT 4), weight (NNT 12)
but *only* fluid or fat mass, *no* better QoL, anti-anabolic effect [1,2]

SE: Dyspnea, edema, impotence, thromboembolism, mortality

Strength of recommendation WEAK *ESPEN Guidelines 7.2016*	*We suggest considering progestins to increase the appetite of anorectic cancer patients with advanced disease but to be aware of potential serious side effects (e.g. thromboembolism).*
Level of evidence	High

In clinical practice almost never used, prefer education

1: Ruiz Garcia V et al. Cochrane Database Syst Rev 2013;3:CD004310
2: Dev R et al. Cancer 2007;110:1173

Drugs with *in*-sufficient evidence to improve cachexia

Cannabinoids to improve appetite
Non steroidal antiinflammatory drugs to increase body Weight
Amino acids to increase fat free mass
Androgens to increase muscle mass

→ No ESPEN recommendation

ESPEN Guidelines
7.2016

More clinical trials needed!
e.g. MENAC multinational study

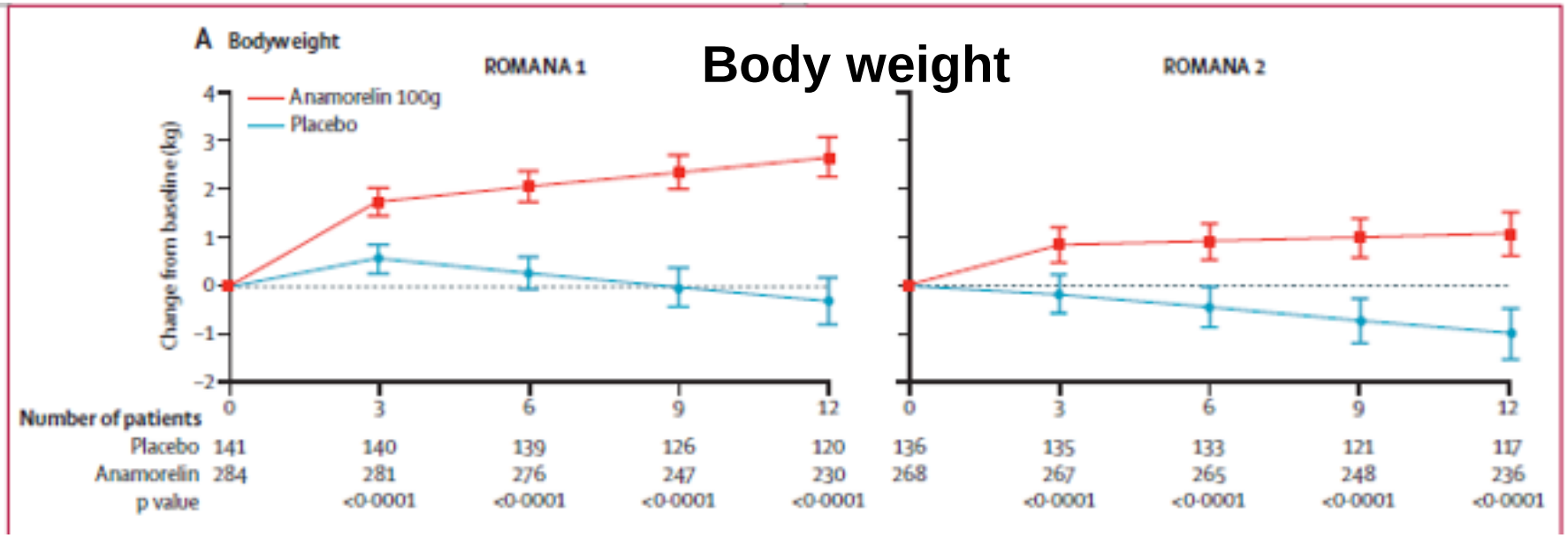
Anti-cachexia emerging drugs

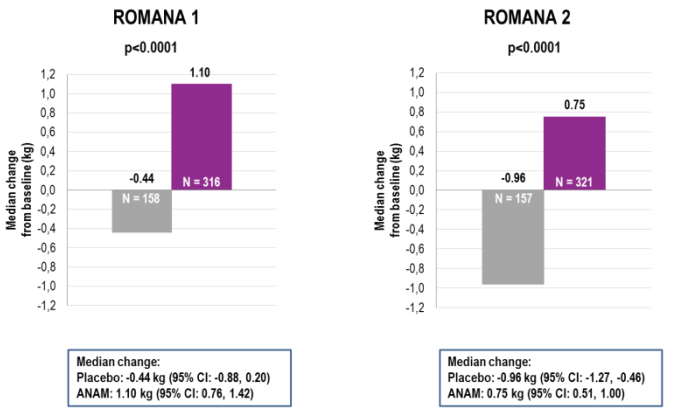
- Melanocortin Receptor 4-antagonists
- Ghrelin & its analogues (natural Ghrelin, *Anamorelin*, etc.)
  → ***Anamorelin*** *phase II (US, Japan) and III (global) trials*[1]
  Improve muscle & fat mass, symptoms, not (HG-) strenght
- Androgen (*SARMs*, ...), β2-mimetics,...
  → ***Enobosarm*** *two finished phase III trials (unpublished Power)*[2]
  Increase muscle mass, associated with stair climb power, fat ↓
- Muscle pathways (**anti-myostatin**, Act-RIIB,.)
- Anti-inflammatory (**anti-*IL-1***[3], anti-IL-6, anti-TNF, Lenalidomide, Thalidomide, EPA)
- many other promises

1: Temel J et al. Lancet Oncol 2016; 17: 519–31; Currow D et al. ASCO 2016, Poster; Garcia JM et al. Lancet Oncol 2015; 16: 108–16; Takayama K et al. Support Care Cancer 2016 Mar 23; 2: Dobs AS et al. Lancet Oncol 2013;14:335; Phase III: Crawford J et al oral presentation MASCC 2014;0546; 3: Hong DS Phase I Lancet Oncol 2014

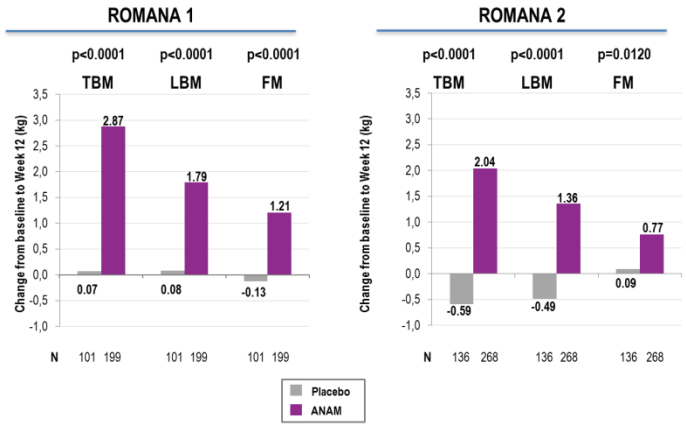
Anamorelin Romana 1&2

Body weight





Muscle mass



Fat mass

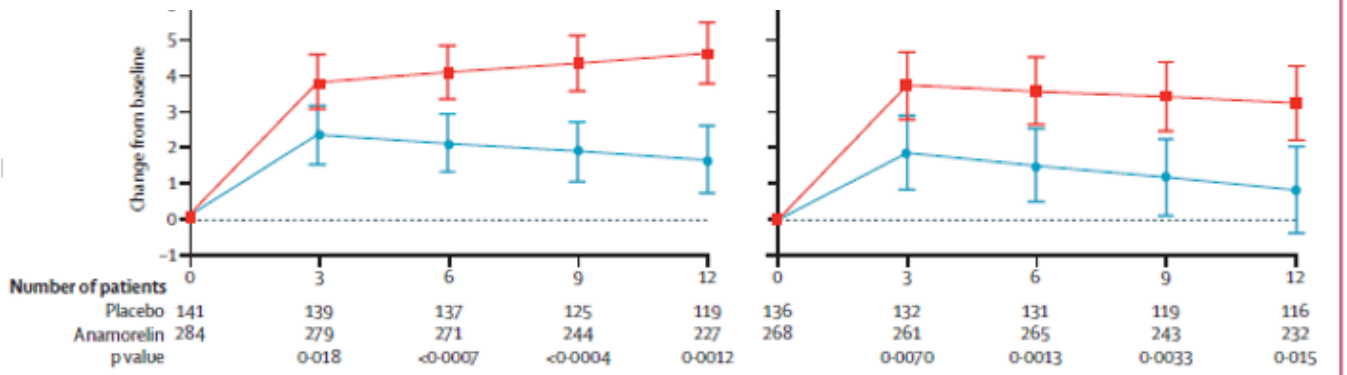
Survial:
no difference

Anticancer treatment toxicity:
not measured

Temel J et al. Lancet Oncol 2016; 17: 519–31

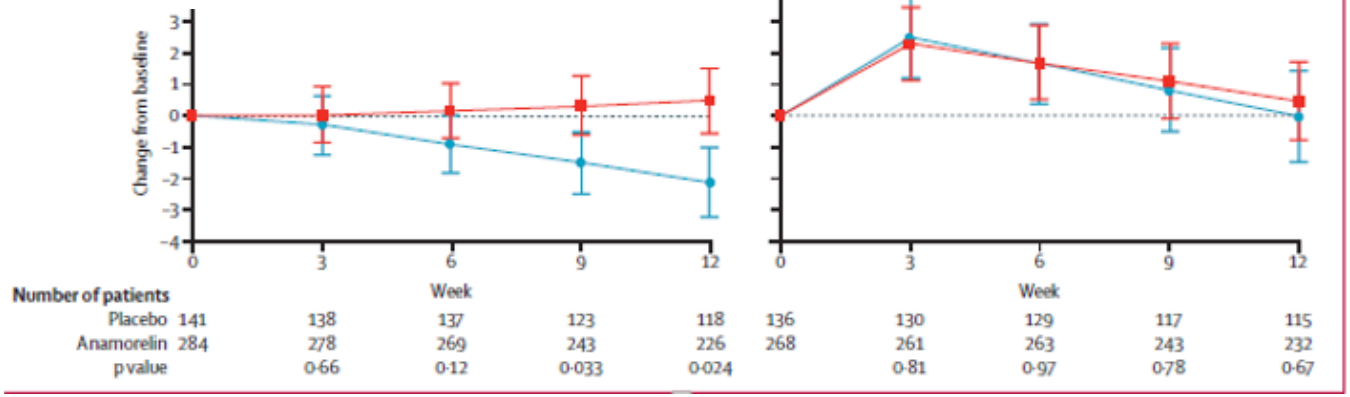
Anamorelin Romana 1&2

Anorexia-Cachexia Scale (FAACT)

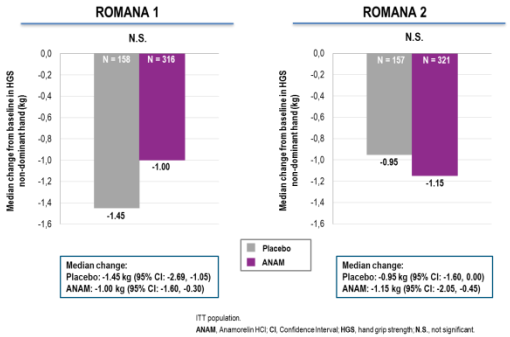


Number of patients										
Placebo	141	139	137	125	119	136	132	131	119	116
Anamorelin	284	279	271	244	227	268	261	265	243	232
p value		0·018	<0·0007	<0·0004	0·0012		0·0070	0·0013	0·0033	0·015

Fatigue Scale (Facit-F)



Number of patients										
Placebo	141	138	137	123	118	136	130	129	117	115
Anamorelin	284	278	269	243	226	268	261	263	243	232
p value		0·66	0·12	0·033	0·024		0·81	0·97	0·78	0·67



Muscle strenght:

Handgrip no change

Legs & physical activity not measured

Symptom improvement: only in patients with BMI ≤20*

Side effects: manageable hyperglycemia

Temel J et al. Lancet Oncol 2016; 17: 519–31;
Currow D et al. ASCO 2016, Poster

Kantonsspital St.Gallen

Conclusion

Cancer Cachexia and Sarcopenia are frequent in GI oncology and impact many relevant outcomes

A rational **therapeutic strategy** for cancer cachexia is based on the defined **phase** of cancer cachexia and its **target domains**: interventions and expected outcomes are different.

To optimize care for tis multidimensional problem, **mechanism-based interventions** with a clear focus on patients‘ quality of life, including both aspects of rehabilitation and alleviating suffering, involving multiprofessional teams are needed.

Cancer cachexia and sarcopenia relevant variables shall be included in (all) clinical GI-trials, as should also palliative care interventions (given latest evidence).

New drugs are needed, promising in pipeline, trials needed

Muchas gracias

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