# Metabolic disorders

Prof. Dr. Viktor Grünwald

Clinic for Hematology, Hemostasis, Oncology, and Stem Cell Transplantation

Medizinische Hochschule Hannover

# Disclosures

**Consultancy**

- BMS, GSK, Mologen, MerckSerono, Novartis, Pfizer

**Honoraria**

- Bayer, BMS, Boehringer Ingelheim, GSK, MerckSerono, Novartis, Pfizer, Astellas, Johnson & Johnson

**Research funding**

- GSK, Pfizer

# Fatigue – a common symptom in cancer patients

- Incidence varies in overall cancer population (40-100%)
- Fatigue is stage and disease related
- Chronic fatigue may occur after curative therapy
- Lack of standardized and systemic evaluation

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

# Provision and Discussion of Survivorship Care Plans Among Cancer Survivors: Results of a Nationally Representative Survey of Oncologists and Primary Care Physicians

*Danielle Blanch-Hartigan, Laura P. Forsythe, Catherine M. Alfano, Tenbroeck Smith, Larissa Nekhlyudov, Patricia A. Ganz, and Julia H. Rowland*

Listen to the podcast by Dr Cheung at www.jco.org/podcasts

Danielle Blanch-Hartigan, Catherine M. Alfano, and Julia H. Rowland, National Cancer Institute, Bethesda, MD; Laura P. Forsythe, Patient-Centered Outcomes Research Institute, Washington, DC; Tenbroeck Smith, American Cancer Society, Atlanta, GA; Larissa Nekhlyudov, Harvard Medical School and Harvard Vanguard Medical Associates, Boston, MA; and Patricia A. Ganz, University of California Los Angeles Schools of Medicine and Public Health, Los Angeles, CA.

Published online ahead of print at www.jco.org on April 21, 2014.

Supported by Contract No. HHSN261200700068C from the National Cancer Institute and by intramural research funds from the American Cancer Society Behavioral Research Center.

The views expressed in this report do not necessarily represent the views of the US Government or the American Cancer Society.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Danielle Blanch-Hartigan, PhD, MPH, Office of Cancer Survivorship, National Cancer Institute, 9609 Medical Center Dr, MSC 9764, Rockville, MD 20850; e-mail: danielle.hartigan@nih.gov.



0732-183X/14/3299-1/$20.00

DOI: 10.1200/JCO.2013.51.7540

## ABSTRACT

**Purpose**
Survivorship care planning should involve discussions between providers and cancer survivors to address survivors' needs and optimize adherence. We examined the frequency and factors associated with oncologists' and primary care physicians' (PCPs) reports of provision of written survivorship care plans (SCPs) and discussion of survivorship care recommendations with survivors.

**Methods**
A nationally representative sample of 1,130 oncologists and 1,020 PCPs was surveyed about survivorship care practices with survivors. Logistic regression models predicted multilevel factors associated with providing SCPs or discussing recommendations with survivors.

**Results**
Although a majority of oncologists (64%) reported always/almost always discussing survivorship care recommendations with survivors, fewer also discussed who survivors should see for cancer-related and other follow-up care (32%); fewer still also provided a written SCP to the survivor (< 5%). Survivorship care recommendations and provider responsibility were not regularly discussed by PCPs and survivors (12%). Oncologists who reported detailed training about late and long-term effects of cancer were more likely to provide written SCPs (odds ratio [OR], 1.73; 95% CI, 1.22 to 2.44) and discuss survivorship care planning with survivors (OR, 2.02; 95% CI, 1.51 to 2.70). PCPs who received SCPs from oncologists were 9× more likely (95% CI, 5.74 to 14.82) to report survivorship discussions with survivors.

**Conclusion**
A minority of both PCPs and oncologists reported consistently discussing and providing SCPs to cancer survivors. Training and knowledge specific to survivorship care and coordinated care between PCPs and oncologists were associated with increased survivorship discussions with survivors. These nationally representative data provide a useful benchmark to assess implementation of new efforts to improve the follow-up care of survivors.

*J Clin Oncol 32. © 2014 by American Society of Clinical Oncology*

## INTRODUCTION

There are approximately 14 million cancer survivors in the United States, and this number is projected to increase substantially with the aging of the population and improvement of survival rates.[1,2] Survivors, most of whom will live years after cancer treatment, have unique health care needs,[3,4] including prevention or management of chronic and late physical and psychosocial effects of treatment and comorbid conditions. Survivorship care planning has been proposed as a way to meet these needs.[4]

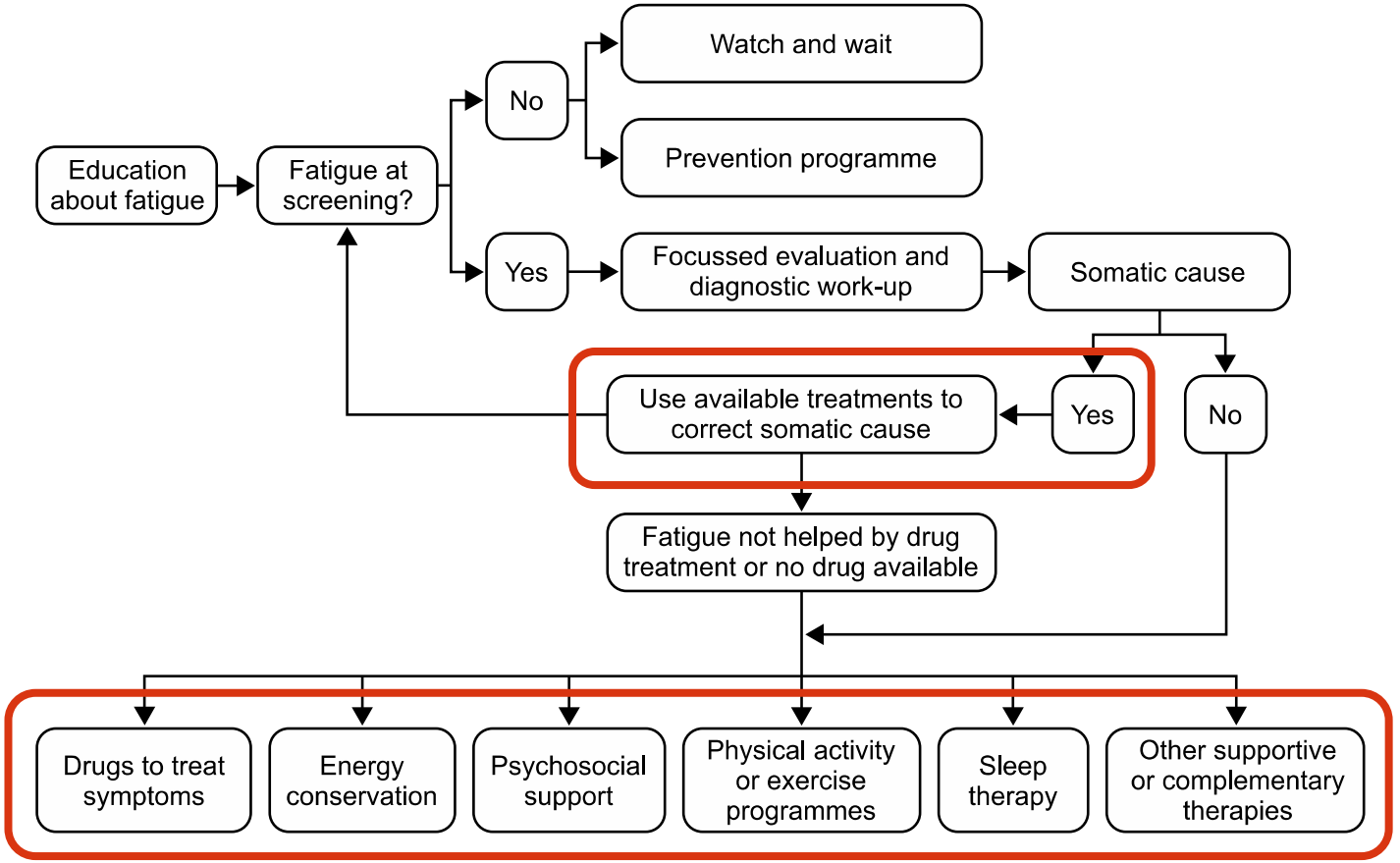
The Institute of Medicine report "From Cancer Patient to Cancer Survivor: Lost in Transition" recommends that all survivors completing primary treatment receive a survivorship care plan (SCP), including a written treatment summary and an individualized follow-up plan, from their oncology provider.[4] Recommendations suggest that survivorship care planning should also include discussions with survivors about care recommendations and delineation of which provider (eg, oncologist, primary care physician [PCP], or other specialist) is responsible for overseeing cancer-related and other medical

# Cancer Survivors

- Long-term effect after the end of therapy
- survivorship programs are beneficical

# Fatigue in metastatic disease

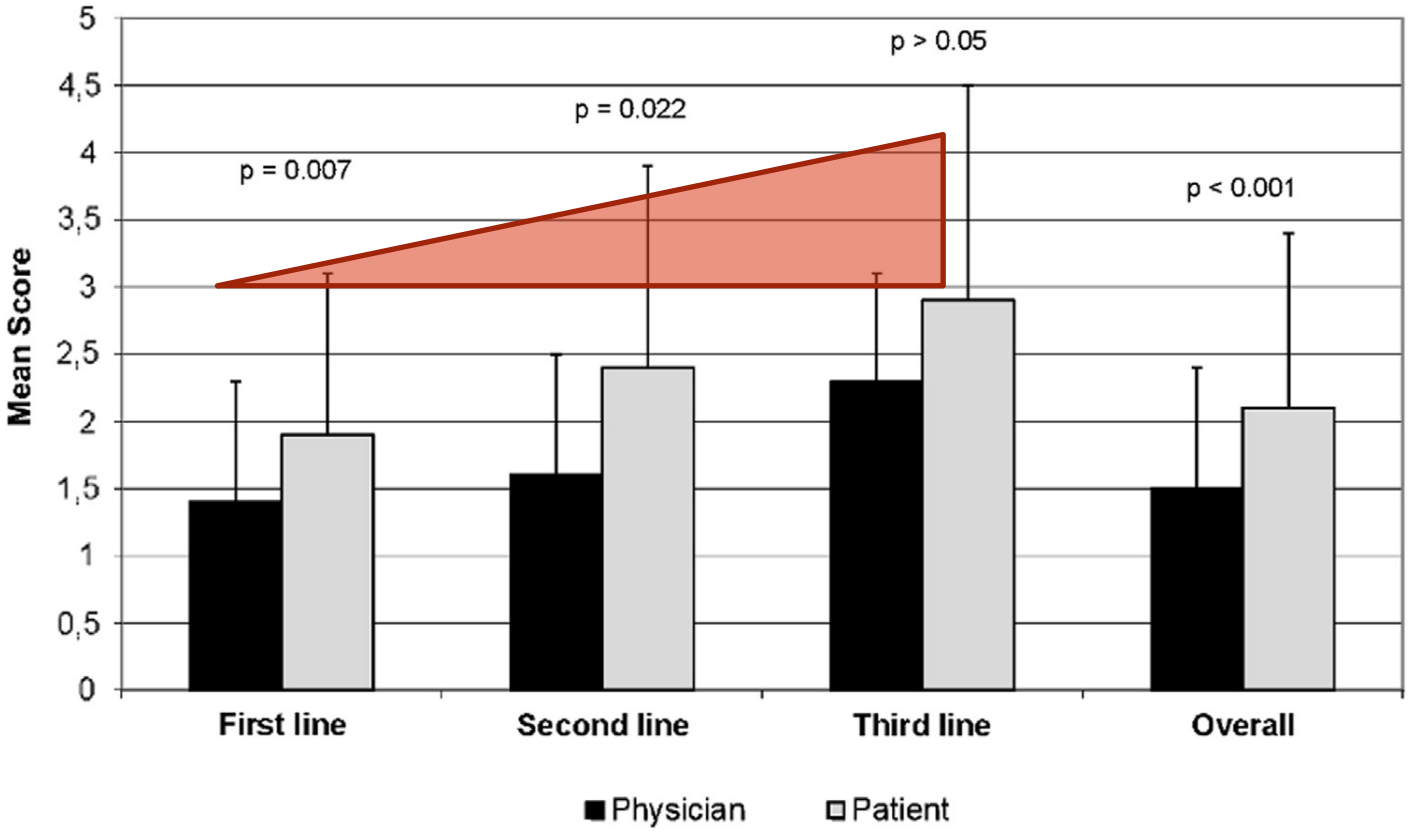
# Pre-existing fatigue should trigger preventive measures




Koornstra et al. (2014). Cancer Treatment Reviews, 40(6), 791–799. doi:10.1016/j.ctrv.2014.01.004

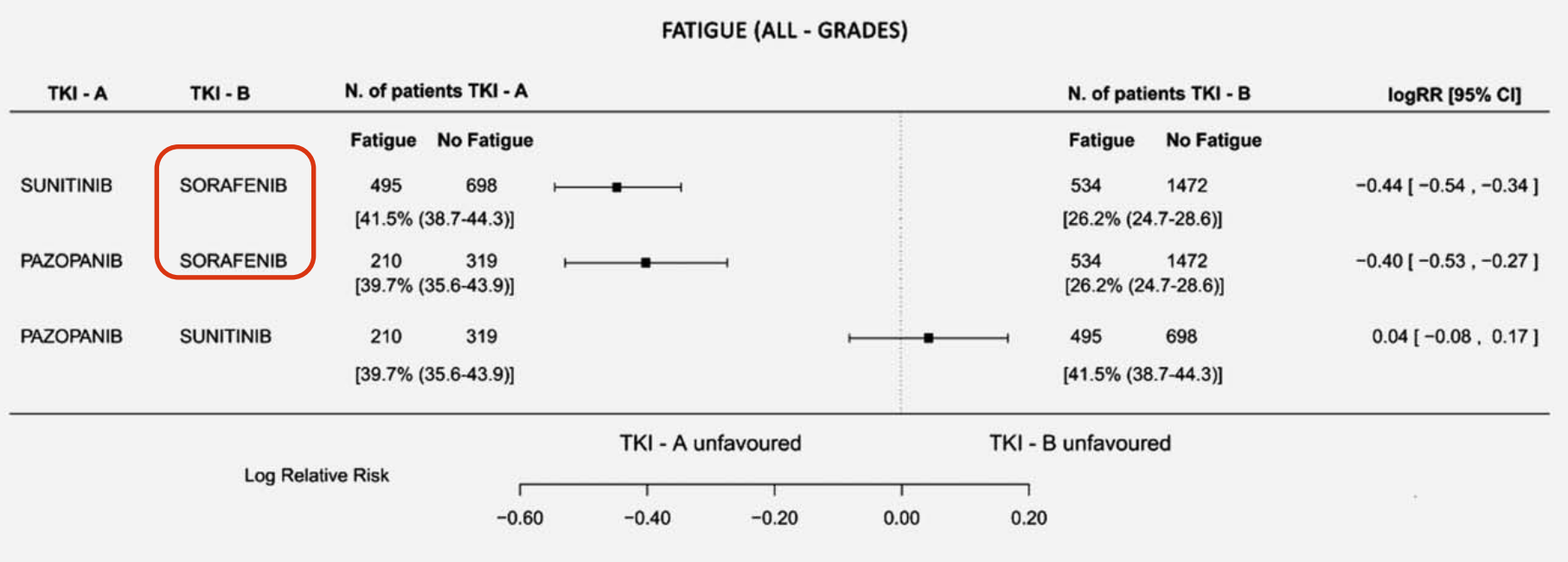
# Fatigue is a composite endpoint of toxicity and cancer

(RCC patient population)




Goebell et al. Urologic Oncology 2013: 1-9

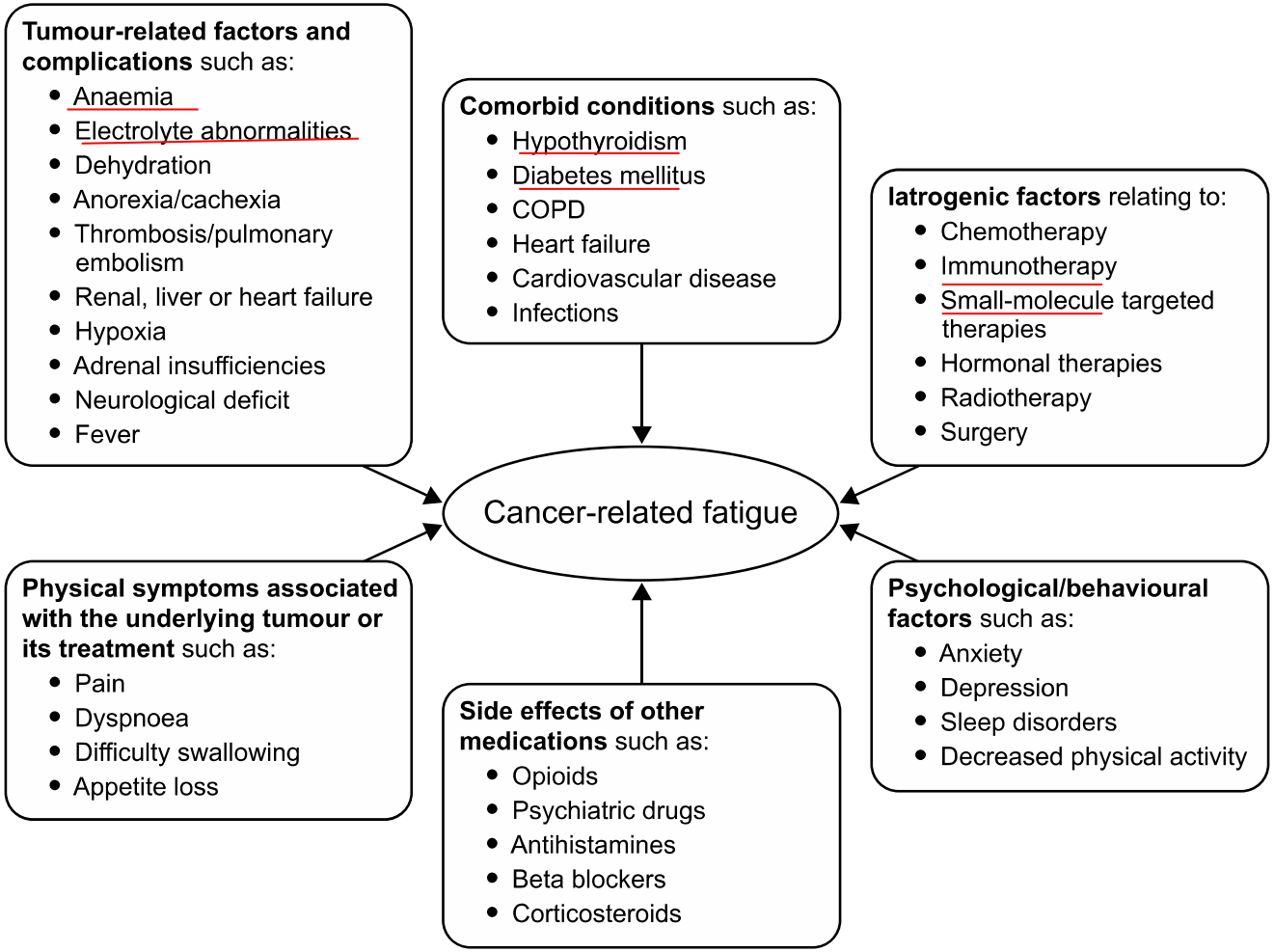
# Fatigue varies among different TKIs




Santon et al. 2014 Int J Cancer, in press

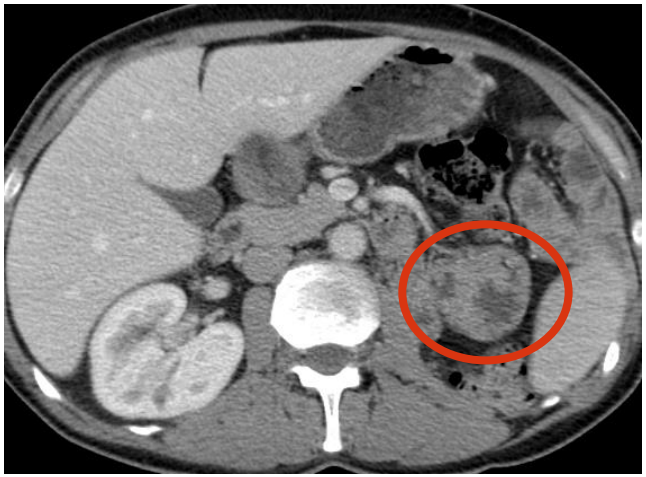
# How to untangle toxicity, comorbidity, and cancer related fatigue?

# Fatigue – a multilayer problem



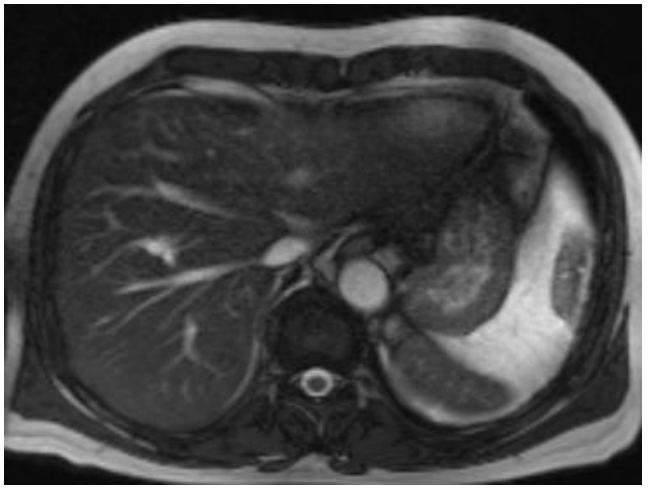

Koornstra et al. (2014). Cancer Treatment Reviews, 40(6), 791–799. doi:10.1016/j.ctrv.2014.01.004

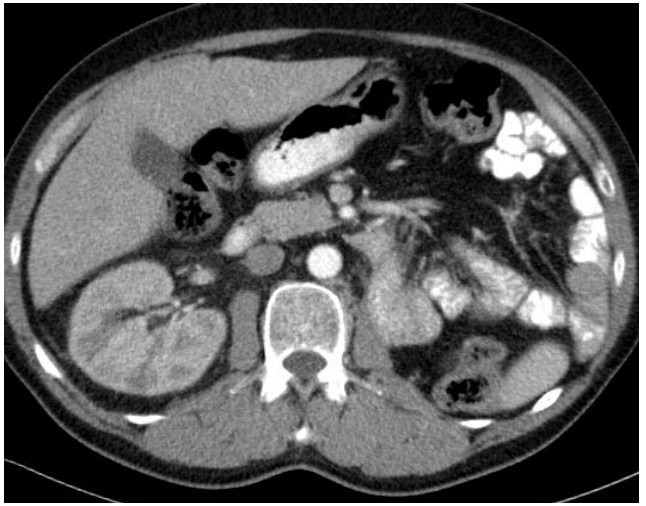
# Synchronous mRCC with fatigue, nightsweats & weight loss



**PFS 40+ mo.**

***Sunitinib:***
symptomatic relieve, response





# Approach to treatment-related fatigue

- Exclude disease progression first
- Evaluate metabolic causes:

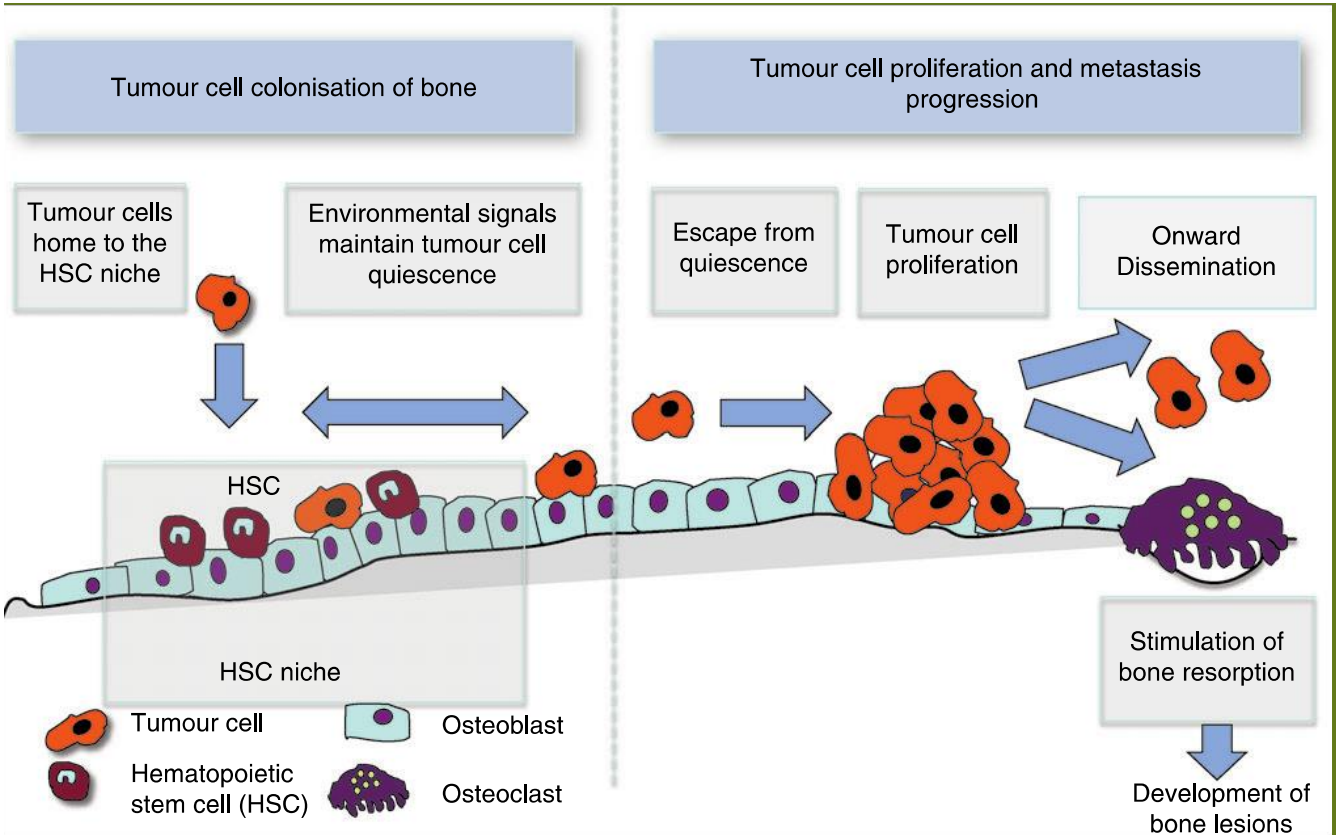
**Hyper-calcemia**

**Anemia**

**Diabetes**

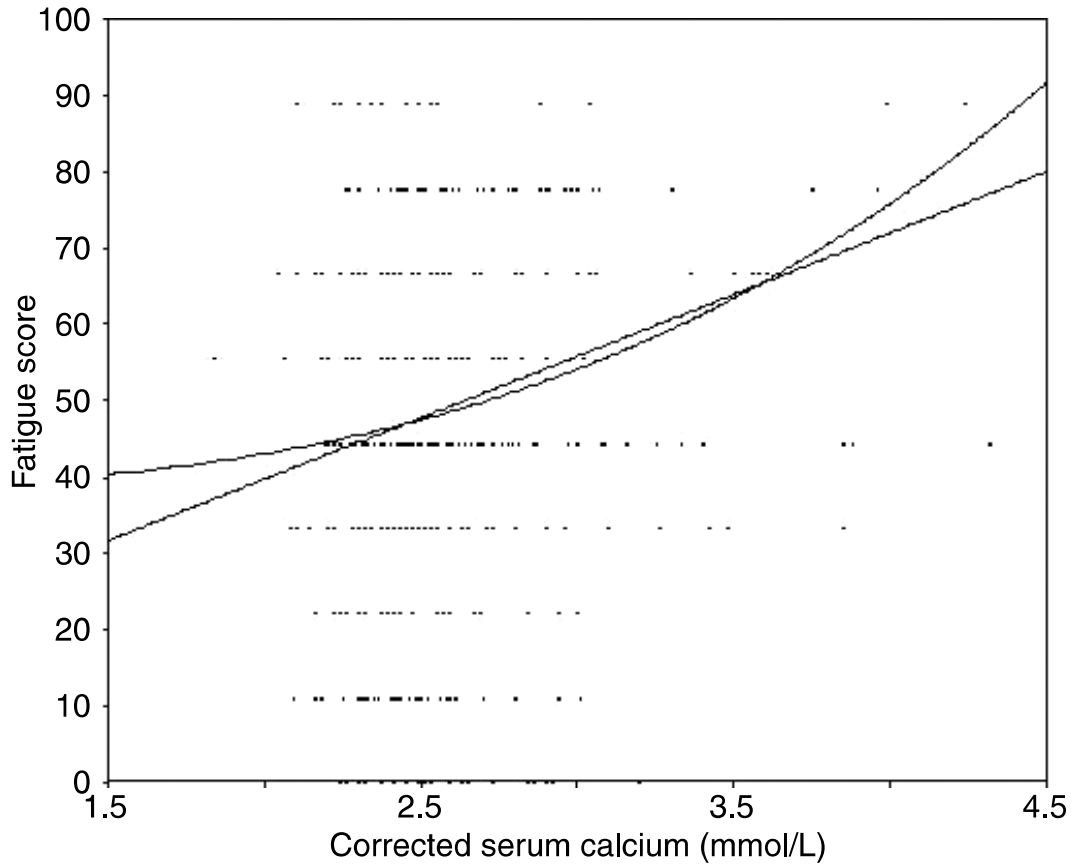
**Endocrino-pathy**

# Hypercalcemia in cancer patients



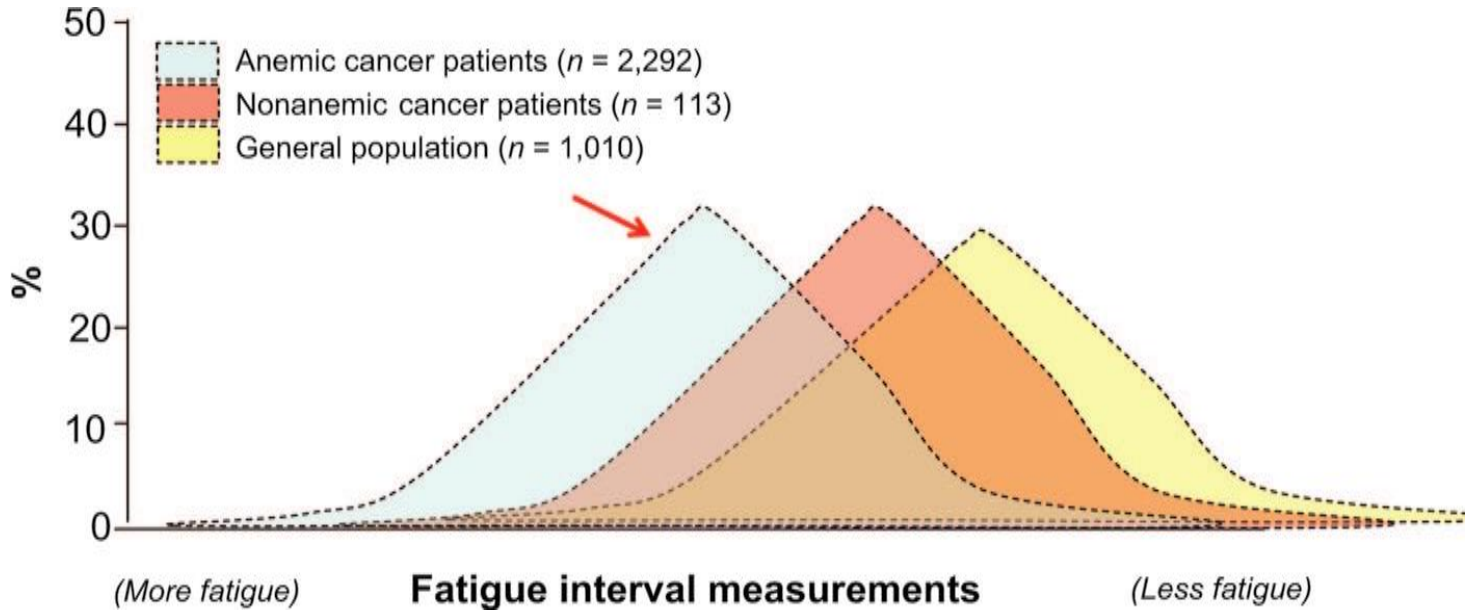

Coleman et al. *Annals of Oncology* 25 (Supplement 3): iii124–iii137, 2014
doi:10.1093/annonc/mdu103
Published online 29 April 2014

# Hypercalcemia is associated with fatigue



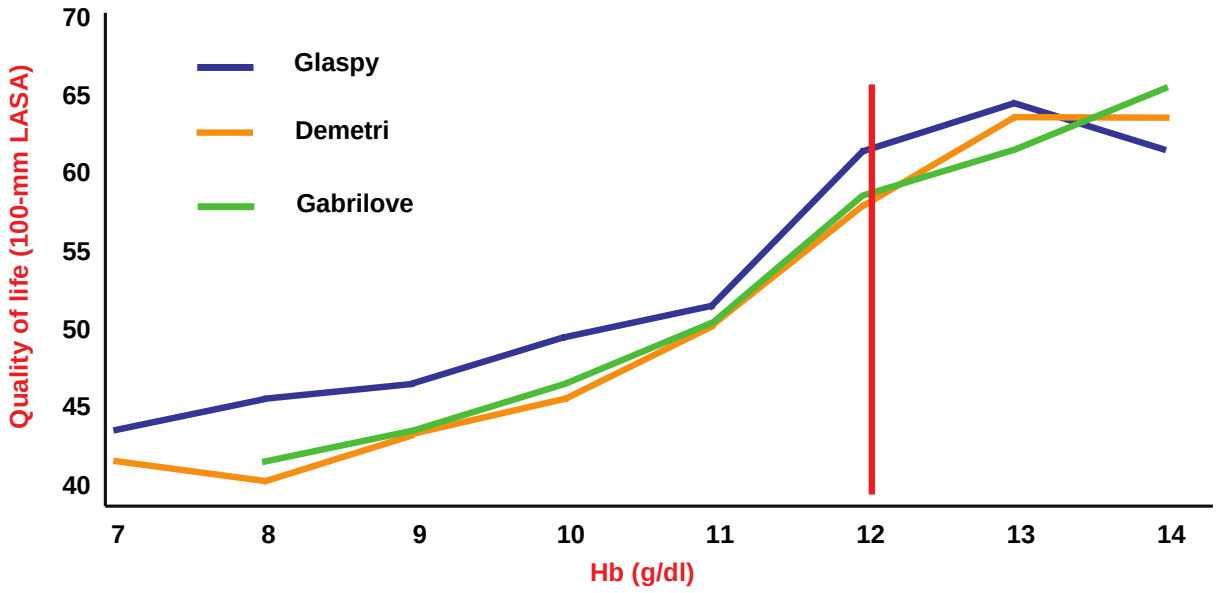

Wisloff et al. Eur J Hem 2006

# Anemia is associated with fatigue in cancer patients




Spivak et al. Oncologist 2009, 14: 43-56

# Correction of anemia may improve QoL in cancer patients

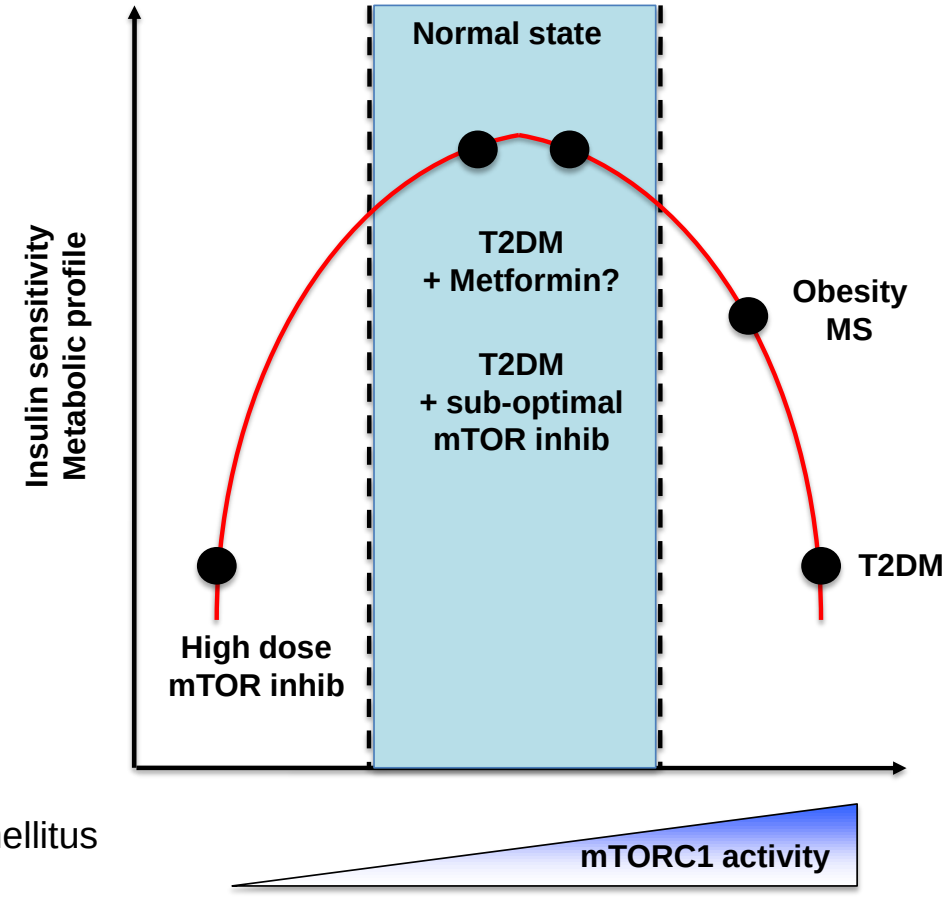



| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Glaspy | – | 267 | 740 | 918 | 833 | 308 | 287 | 223 |
| Demetri | 59 | 352 | 770 | 753 | 547 | 391 | 313 | 160 |
| Gabrilove | 156 | 466 | 1134 | 1426 | 844 | 544 | 410 | 168 |

Erythropoetin studies in tumor-associated anemia

Spivak et al. Oncologist 2009, 14: 43-56

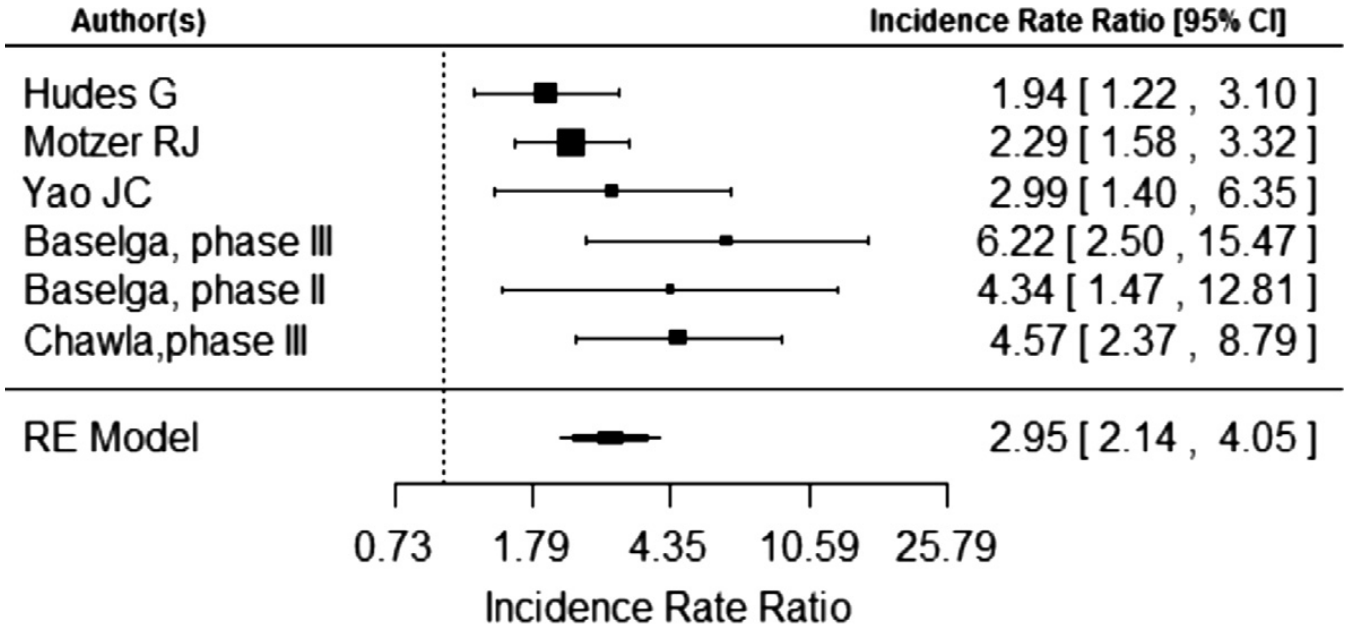
# mTORC1 activity – key player for metabolic homeostasis




T2DM: type 2 diabetes mellitus
MS: metabolic syndrome

Vergès, B., Walter, T., & Cariou, B. (2013). *European Journal of Endocrinology / European Federation of Endocrine Societies*. doi:10.1530/EJE-13-0586

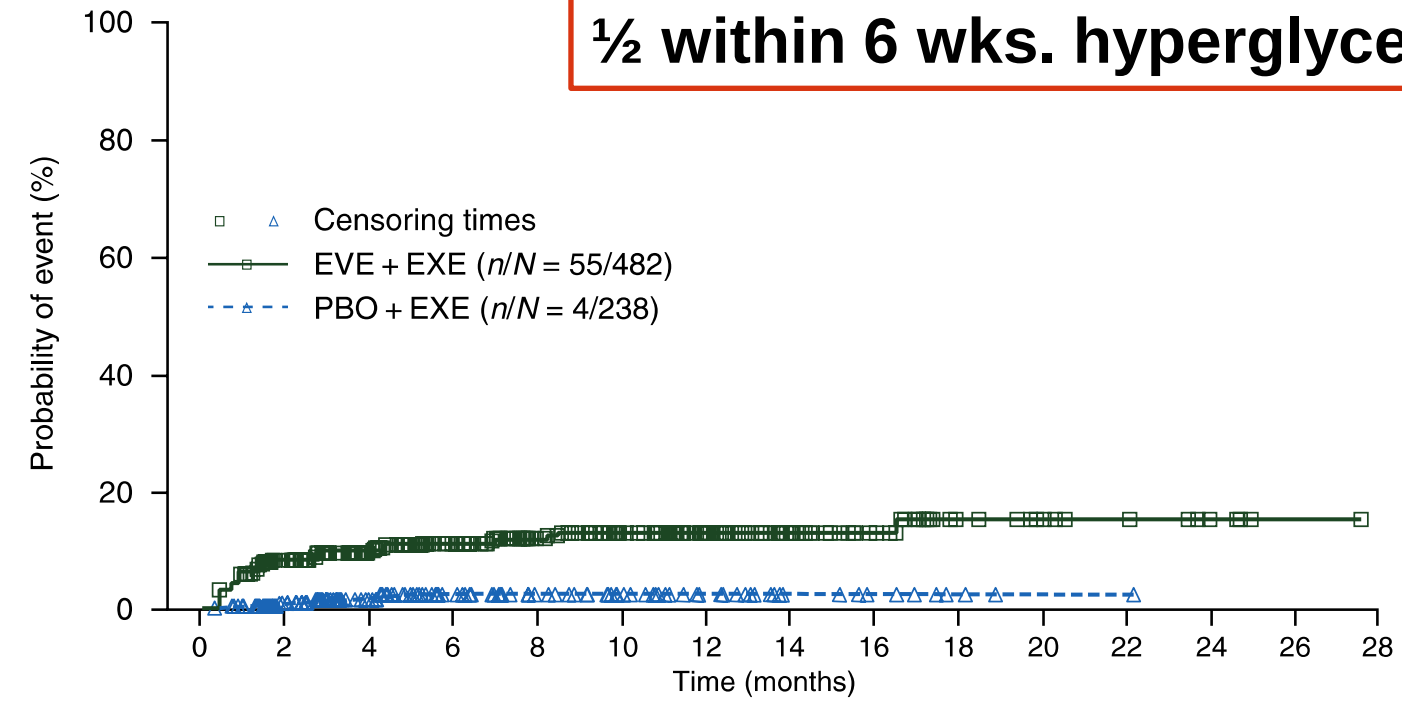
# Current mTOR inhibitors (mTORi) induce hyperglycemia




Sivendran et al. (2014). Cancer Treatment Reviews, 40(1), 190–196. doi:10.1016/j.ctrv.2013.04.005

# BOLERO-2: hyperglycemia is an early event (≥ grade 2)

**9, respectively 10% have DM at start**
**½ within 6 wks. hyperglycemic**




Number of patients still at risk

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EVE + EXE | 482 | 394 | 306 | 242 | 189 | 145 | 96 | 64 | 43 | 22 | 15 | 10 | 4 | 1 | 0 |
| PBO + EXE | 238 | 171 | 117 | 72 | 48 | 34 | 21 | 11 | 7 | 3 | 1 | 1 | 0 | 0 | 0 |

Rugo, et al. (2014). Annals of Oncology, 25(4), 808–815. doi:10.1093/annonc/mdu009

# Novel dual kinase inhibitors achieve the highest diabetes rate

| Drug | Hypertriglyceridemia (%) | | Hypercholesterolemia (%) | | Hyperglycemia (%) | |
|---|---|---|---|---|---|---|
| | All Grades | Grades 3 to 4* | All Grades | Grades 3 to 4† | All Grades | Grades 3 to 4‡ |
| Approved | | | | | | |
| Everolimus | 71 | < 1 | 76 | 3 | 50 | 12 |
| Placebo (n = 416)[9] | 30 | 0 | 32 | 0 | 23 | 1 |
| Temsirolimus | 27 | 3 | 24 | 1 | 26 | 11 |
| IFN-α (n = 408)[10] | 14 | 1 | 4 | 0 | 11 | 2 |
| Investigational§ | | | | | | |
| PI3K inhibitors[14-17] | | | | | | |
| GDC-0941 | None described | | None described | | 48 | 2 |
| BKM120 | None described | | None described | | 30 | 5 |
| PI3K/mTOR inhibitors[18-21] | | | | | | |
| XL765 | None described | | None described | | 10 | 0 |
| GSK2126458 | None described | | None described | | 7 | 2 |
| GDC-0980 | None described | | None described | | 83 | 14 |
| Akt inhibitors[22-24] | | | | | | |
| GDC-0068 | None described | | None described | | 41 | 0 |
| MK-2206 | None described | | None described | | 13 | 3 |
| GSK2141795 | None described | | None described | | 19-21 | 4 |
| mTOR (TORC1 or TORC1/2) inhibitors[25-27] | | | | | | |
| Ridaforolimus | 41 | 0 | 28 | 0 | 22-28 | 6-13 |

Abbreviations: IFN-α, interferon alfa; mTOR, mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; TC, total cholesterol; TG, triglycerides.
*TG > 500 mg/dL.
†TC > 400 mg/dL.
‡Glucose > 250 mg/dL.
§Data from phase I trials.

Busaidy et al. (2012). Journal of Clinical Oncology.
doi:10.1200/JCO.2011.39.7356

# Individualized monitoring approach

| | euglycemic | Pre-diabetic | diabetic |
|---|---|---|---|
| **Fastening glucose (mmol/L)** | **<6.0** | **6.0-7.0** | **>7.0** |
| **HbA1c (%)** | **<6.0** | **6.0-6.4** | **≥6.5** |
| **Monitoring 1. month** | **2 weeks** | **1-2x weekly** | **daily** |

- Individual glucose monitoring during further treatment

Adapted from Vergès, B., Walter, T., & Cariou, B. (2013). *European Journal of Endocrinology / European Federation of Endocrine Societies*. doi:10.1530/EJE-13-0586

# Treatment of mTORi-induced hyperglycemia

***Start treatment if:***

- Fastening glucose: >7.0 mmol/L (>125 mg/dl)
- or random Glucose >200 mg/dl
- or HbA1c >6.5%

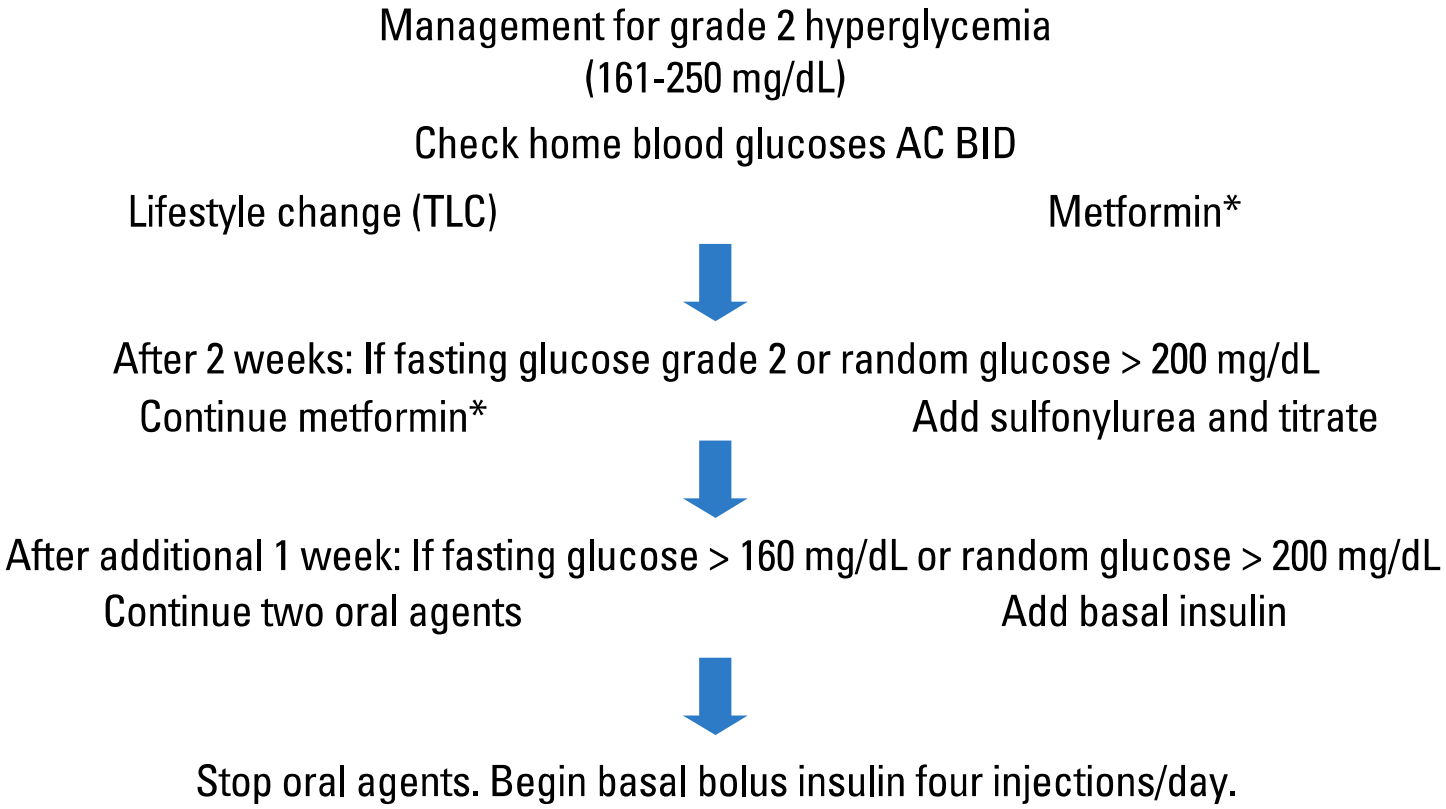
***Choice of treatment:***

- 1st choice: metformin
- sulfonyl urea, or glitazone
- Insulin

- Target HbA1c: 7.0-8.0%

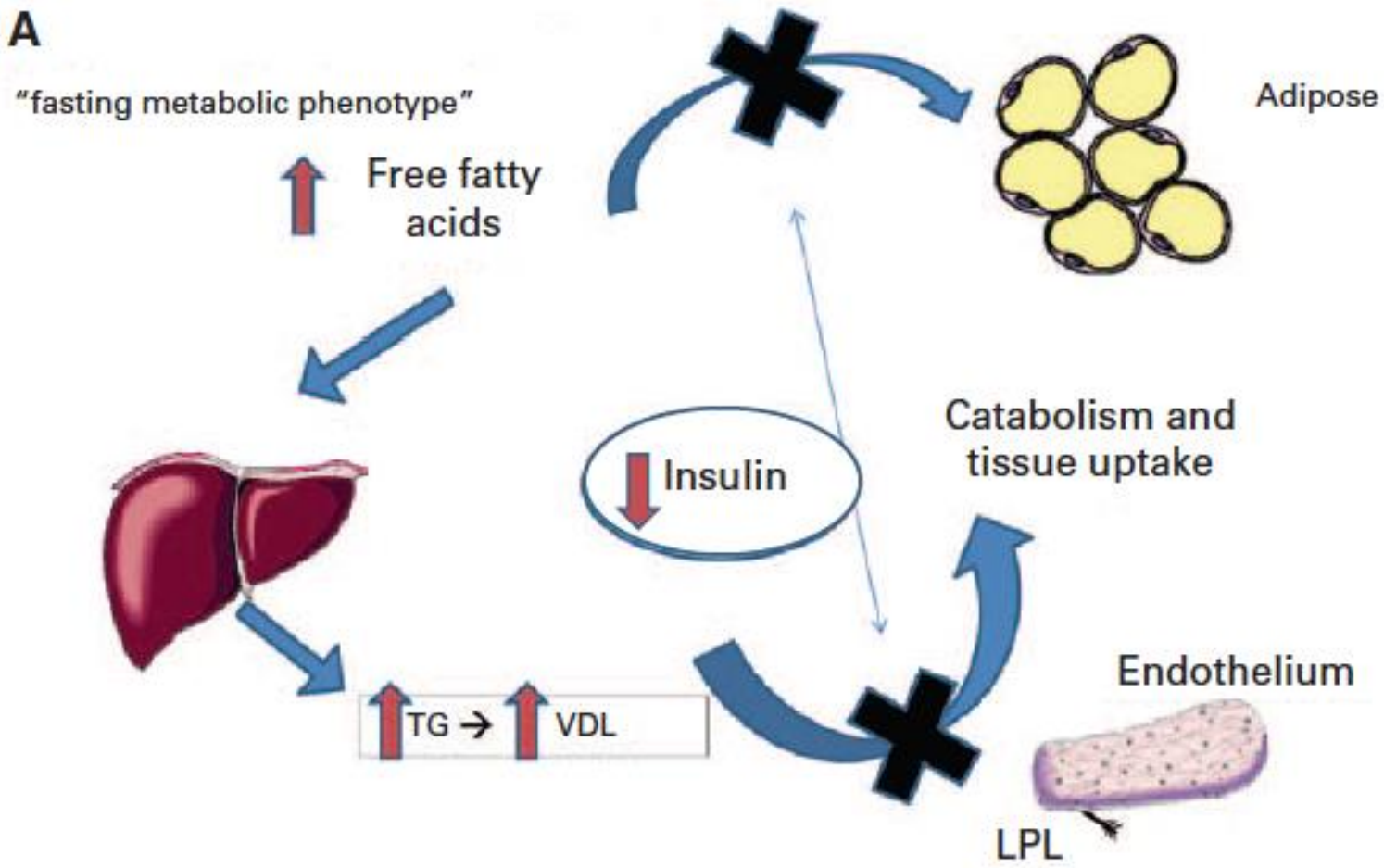
Vergès, B., Walter, T., & Cariou, B. (2013). *European Journal of Endocrinology / European Federation of Endocrine Societies*. doi:10.1530/EJE-13-0586

# Treatment algorithm for therapy-associated hyperglycemia




Busaidy et al. (2012). Journal of Clinical Oncology.
doi:10.1200/JCO.2011.39.7356
*do not use if creatinine >1.3 mg/dl

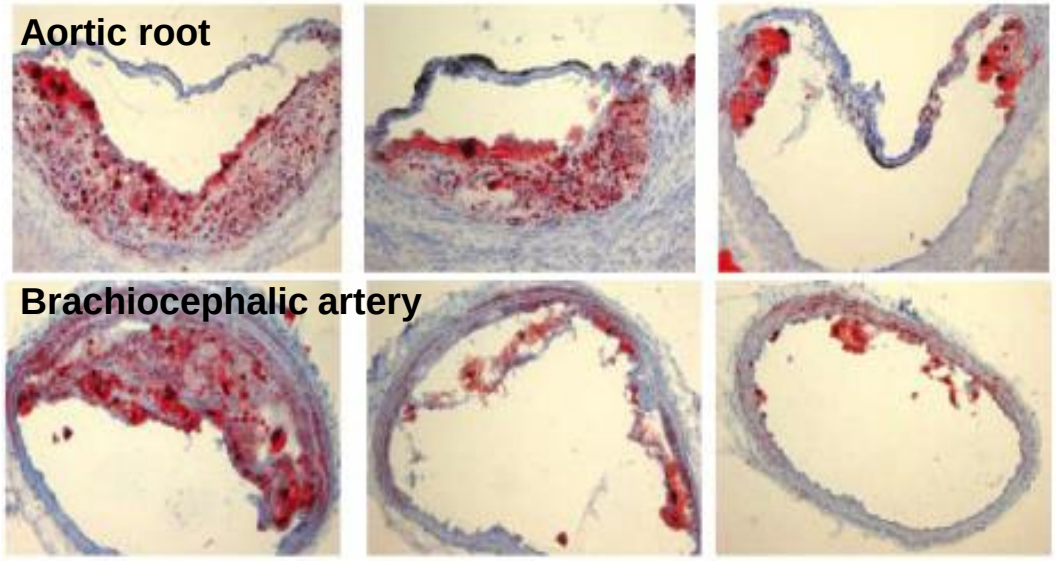
# mTORi-induced hyperlipidemia



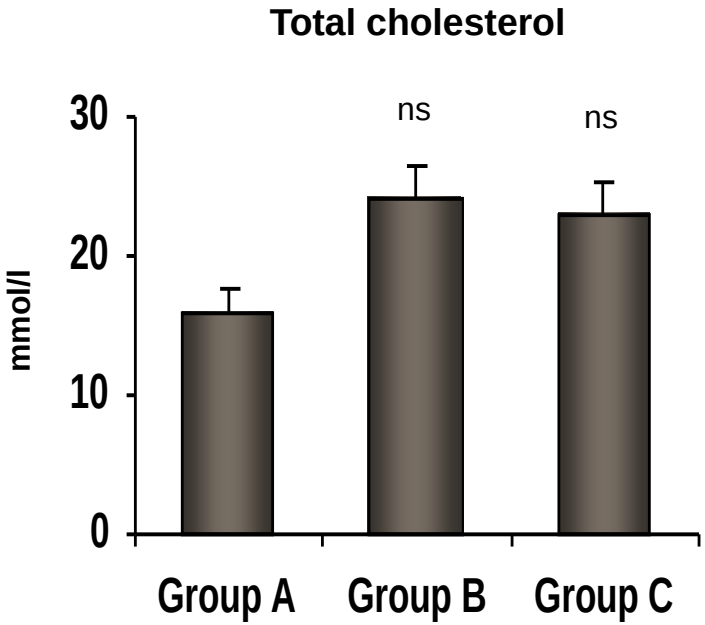

Busaidy et al. (2012). Journal of Clinical Oncology. doi:10.1200/JCO.2011.39.7356

# mTOR, hyperlipidaemia, and atherosclerosis in LDLR$^{-/-}$ mice

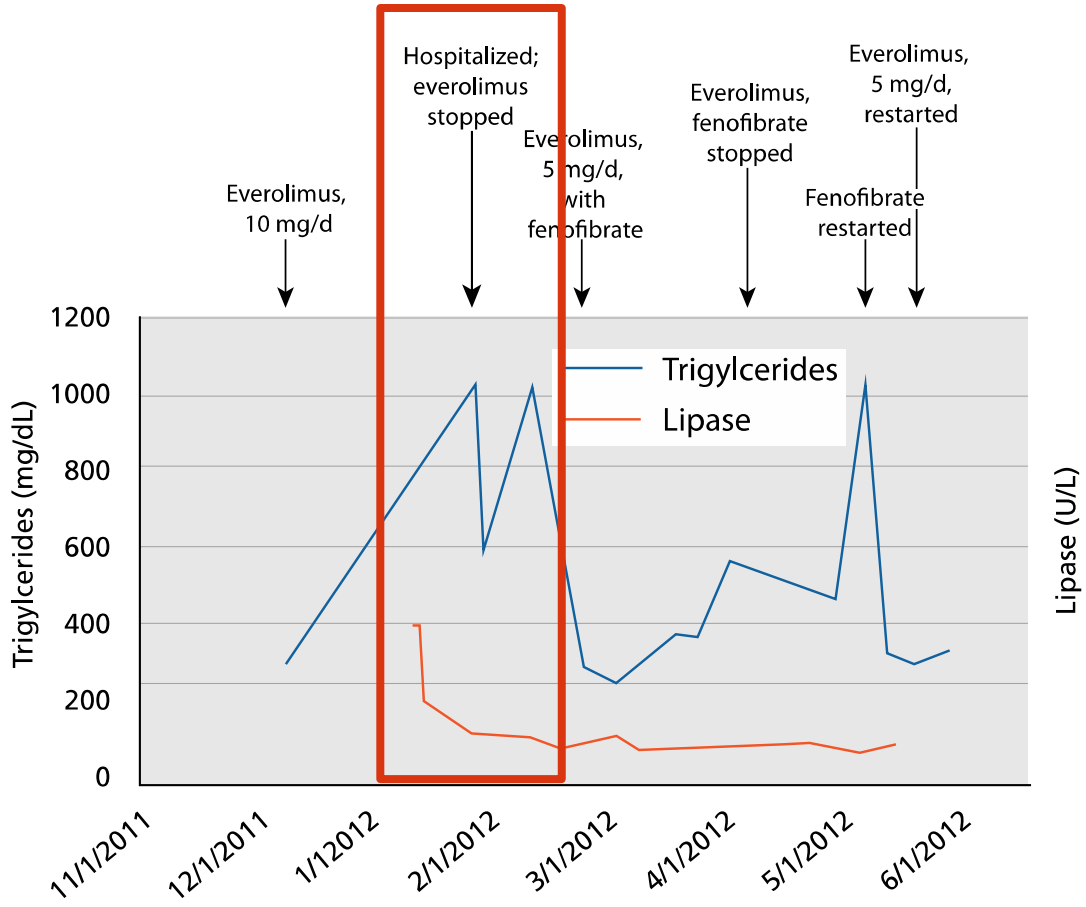
**mTOR inhibition decouples plasma lipid from cellular deposition of lipid**




Control | RAD001 0.05 mg/kg/day | RAD001 1.5 mg/kg/day



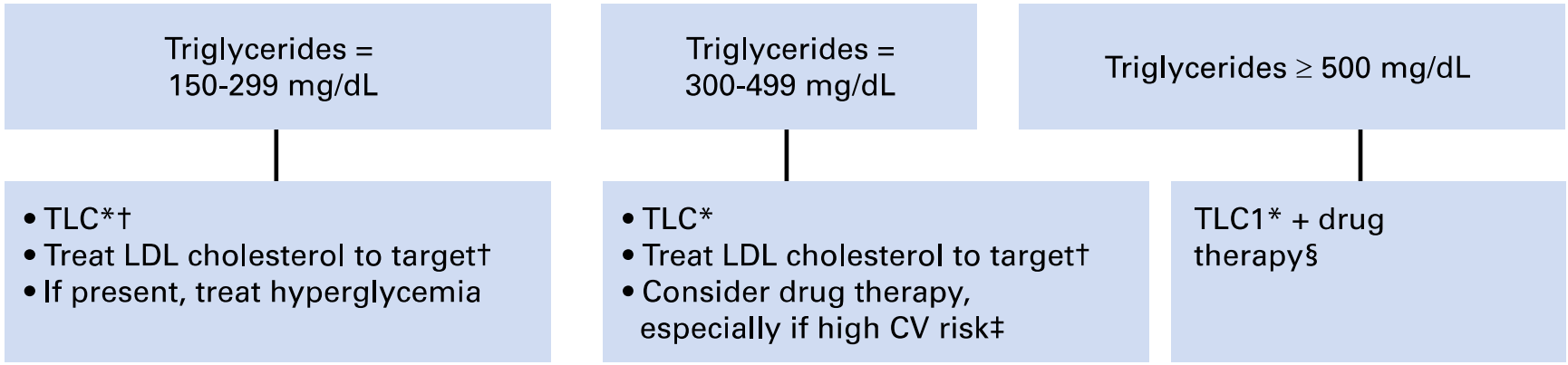
# Everolimus associated hypertriglyceridemia and pancreatitis




**Hypertriglyceridemia**
71% with Everolimus
27% with Temsirolimus

Subramaniamet al. (2013). Journal of the National Comprehensive Cancer Network : JNCCN, 11(1), 5–9.

# When to treat hypertriglyceridemia




TLC: therapeutic lifestyle changes

***Medical treatment:***

- fibrate, fish oil, nicotinic acid

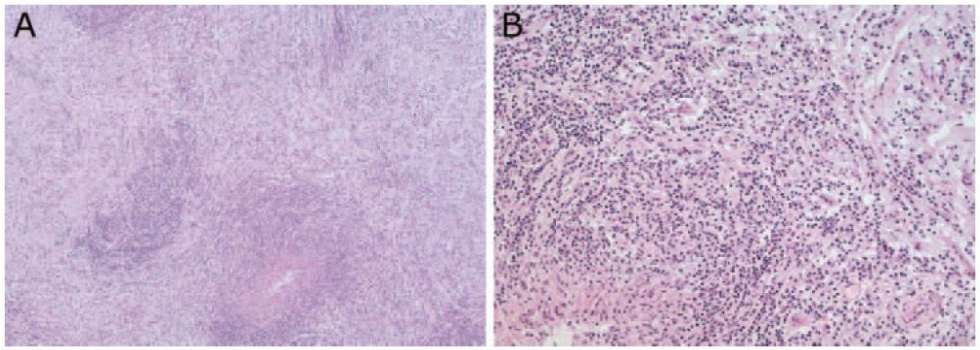
Busaidy et al. (2012). Journal of Clinical Oncology.
doi:10.1200/JCO.2011.39.7356

# Endocrinopathies – a common AE of cancer treatment

| Agent | Incidence | Occurrence |
|---|---|---|
| CTLA4 mAb | 0-19% | NR |
| PD-1 mAb | 2-3% | NR |
| Tositumumab | 9-64% | 6-24 mo. |
| TKI | 32-85% | 4-94 wks |
| Alemtuzumab | 7-30% | 9-31 mo. |
| IMiD | 6-20% | 1-6 mo. |

Torino et al. (2013). Thyroid; 23(11), 1345–1366.
doi:10.1089/thy.2013.0241

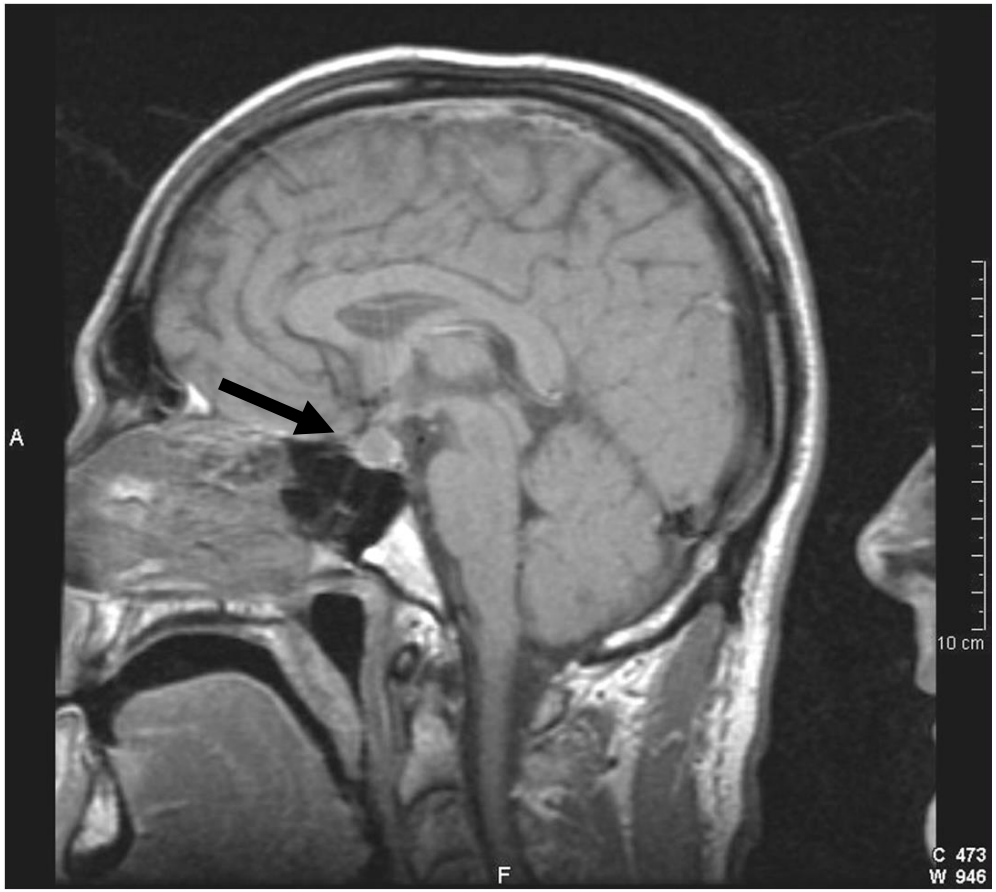
# Autoimmune-Hypophysitis




Inflammation and cellular (lymphocytic) infiltration of the pituitary gland

- Initially described in 1962
- Estimated incidence 1:9.000.000
- Rare disease, which is often associated with other autoimmune endocrinopathy or through compression
- May occur postpartal, M. addison, Thyreoiditis, LCH, sarcoidosis
- Today often recognized as immune-related event

# Hypophysitis: clinic



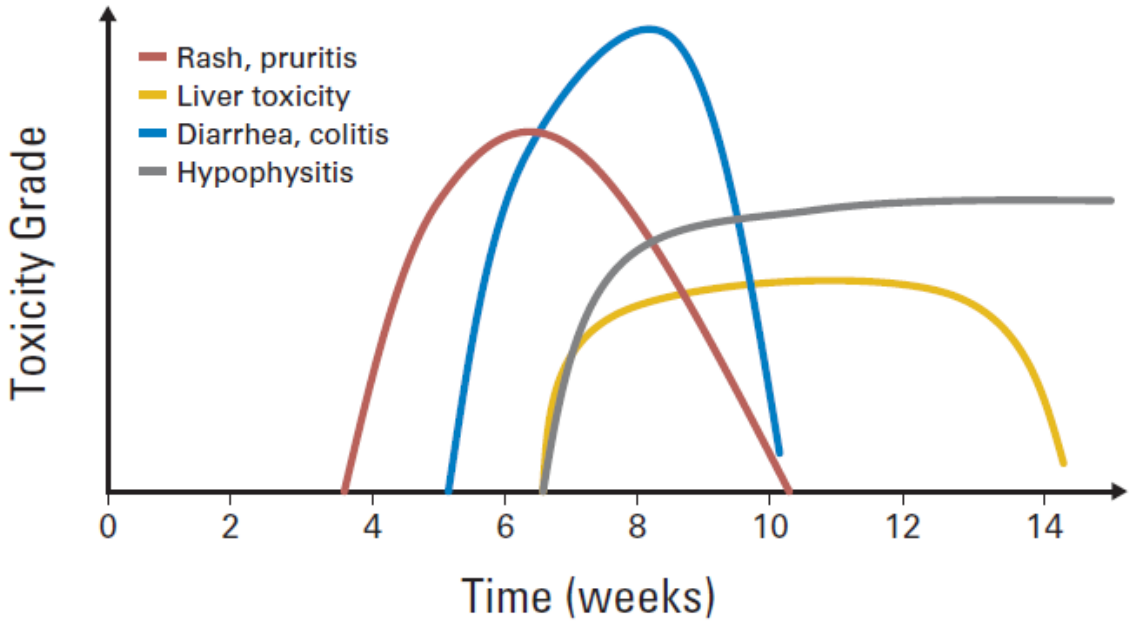

- Confusion
- Apathy
- Anopsy
- Cephalgia
- Hypotension
- Abdominal pain
- Polyuria

Blansfield, J.A. et al. (2005). J. Immunother. 28, 593–598.

# Immune related (ir)AEs

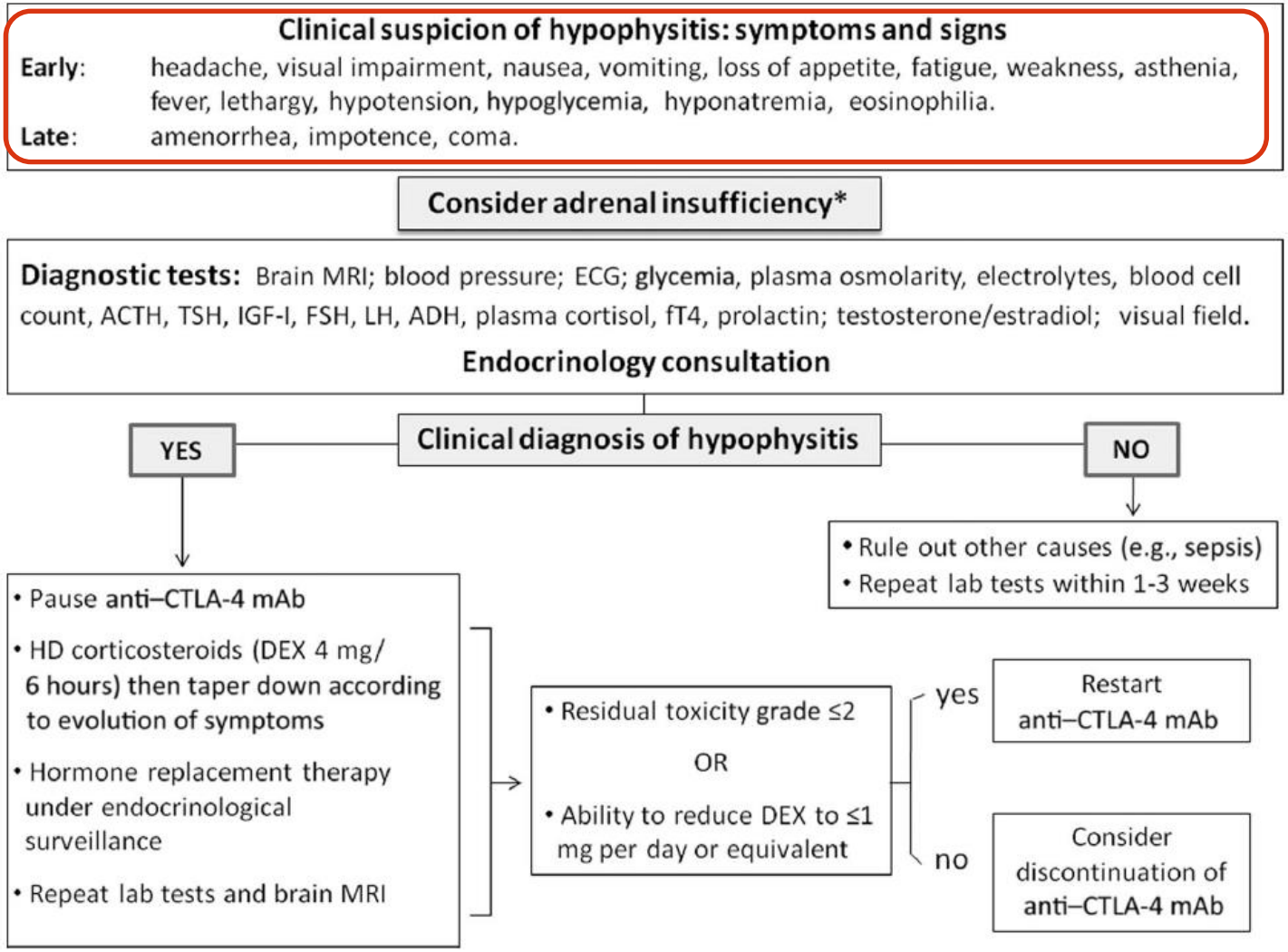
**Table 2.** Occurrence of Adverse Events With Ipilimumab (10 mg/kg)

| Adverse Event | Any Grade (%) | Grade 3 or 4 (%) |
|---|---|---|
| Skin (rash, pruritus) | 47-68 | 0-4 |
| GI (diarrhea, colitis) | 31-46 | 8-23 |
| Hepatitis | 3-9 | 3-7 |
| Hypophysitis | 4-6 | 1-5 |




Weber et al. J CLIN ONCOL 2012

# Hypophysitis: monitoring & treatment




Torino et al. THE ONCOLOGIST 2012

# Future field of research

- Physicians and nurses underestimate symptoms onset, frequency, and severity in comparison to patients‘ rating
- Studies should include patient reported outcome (PRO) measures
- Structured assessment of cancer related symptoms should be incorporated into clinical practice
- AE-nurse may improve management

# Conclusion

- Fatigue is among the most common symptoms in cancer patients
- Lack of specifity of fatigue requires a broad spectrum to monitor during cancer therapy
- Metabolic changes are frequent during the course of treatment, and incidence vary between classes of agents
- Routine monitoring should include the assessment of glucose, calcium, Hb, lipids, and hormones in cancer patients