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IL DIGIUNO IN MEDICINA: È UTILE?

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3. Metformin as a repurposed therapy in advanced non-small cell lung **cancer** (NSCLC): results of a phase II trial.
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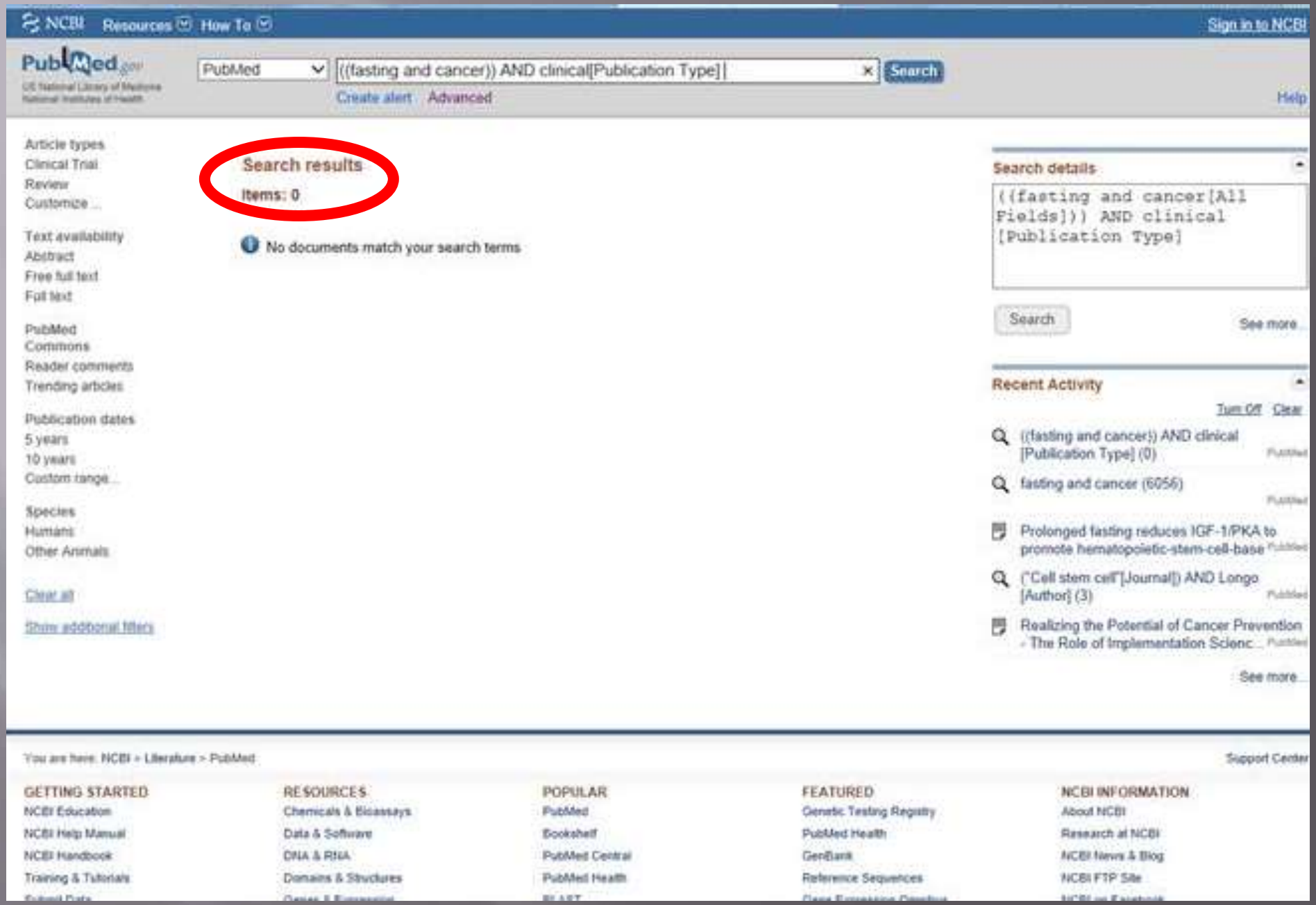
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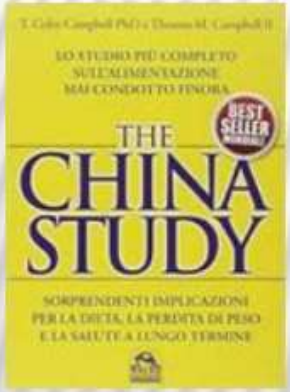
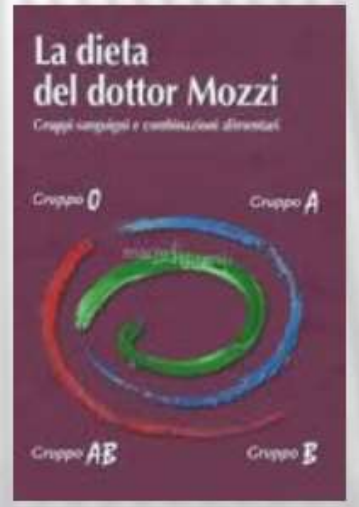
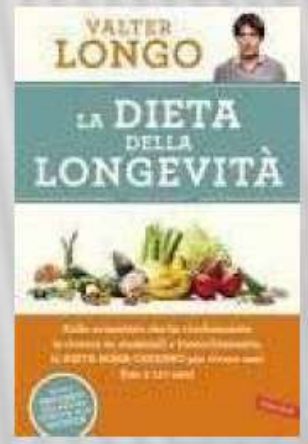
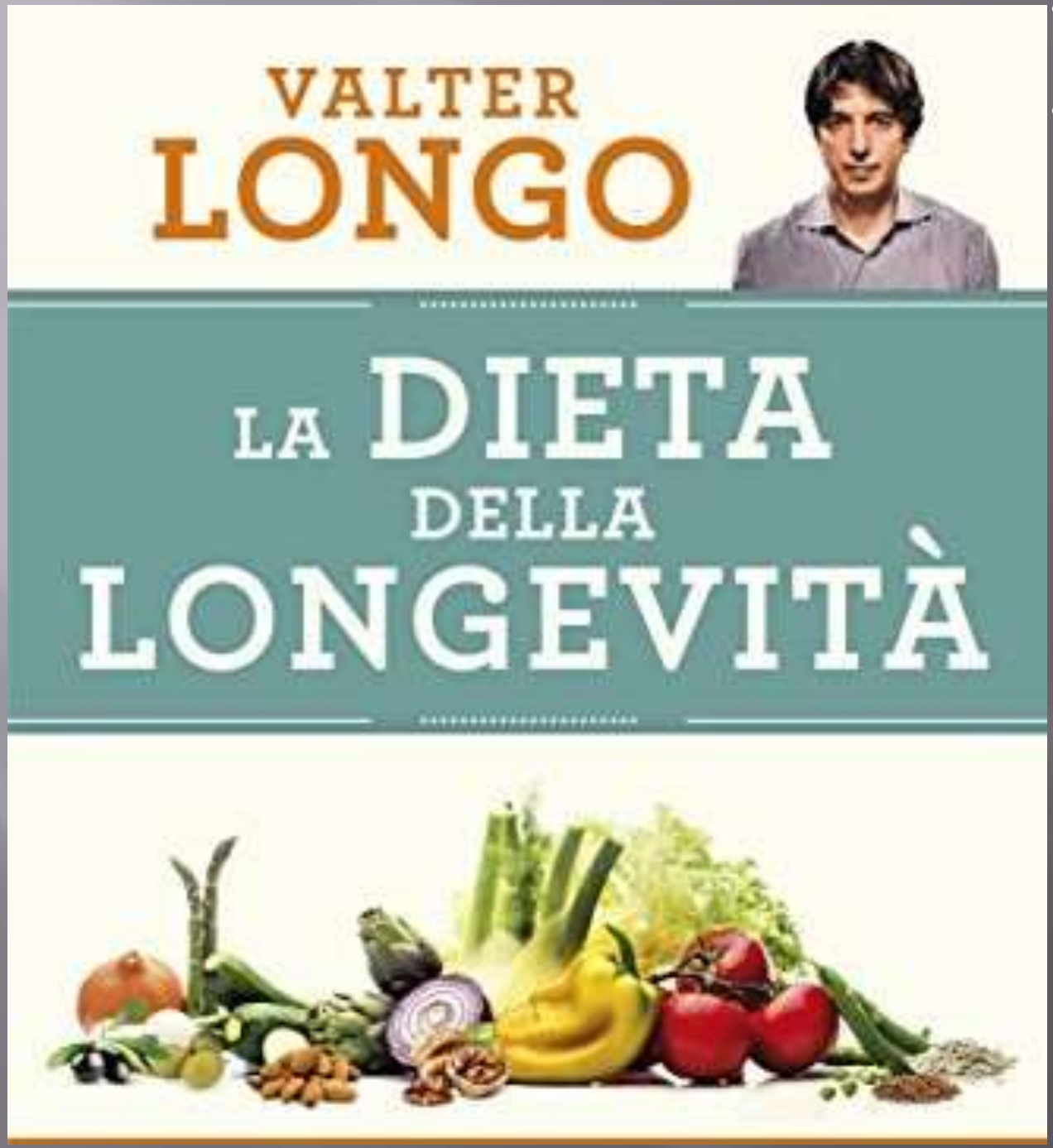






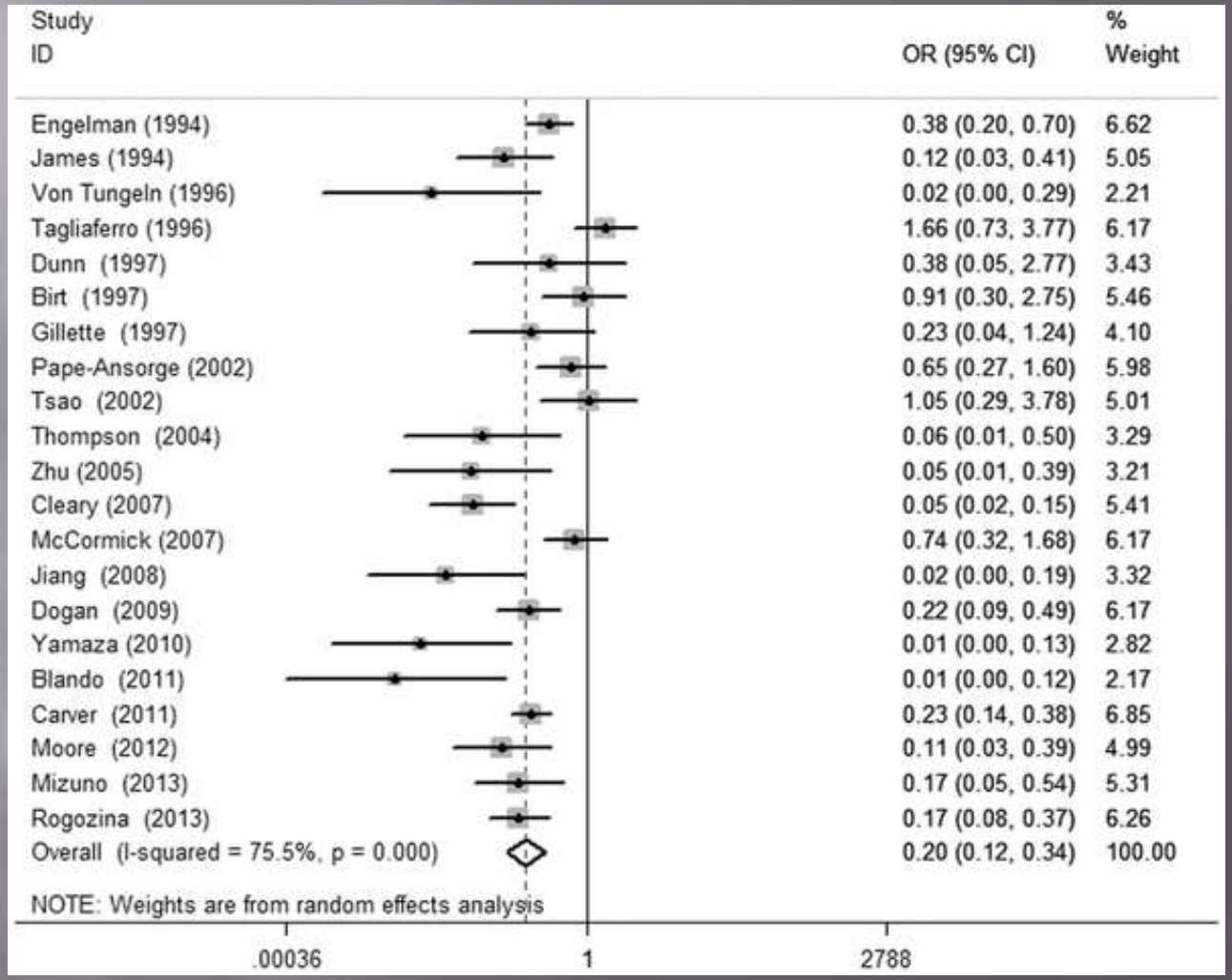


- **Dalle «Iene»**

- Ma in che cosa consiste dunque questa dieta mima-digiuno? Ce lo spiega la simpatica Toffa delle iene che si presta all'esperimento: un giorno a 1000 kcal seguito da quattro giorni a 750 kcal. Una dieta da fame, che può generare attacchi bulimici, depressione, infertilità, demuscolazione, rallentamento tiroideo. Toffa apre con curiosità il pacchettino del primo giorno (naturalmente commercializzato da una società apposita afferente al Longo), che contiene: una bustina di tè, dei liofilizzati e una barretta. Che devono bastare per tutto il giorno. Nei quattro giorni successivi si diminuisce ancora.

- L'utilizzo della dieta chetogenica per trattare i tumori parte dalle osservazioni del fisiologo Otto Warburg, premio Nobel per la Medicina nel 1931, il quale scoprì che le cellule tumorali hanno un utilizzo predominante della "glicolisi anaerobia" (effetto Warburg) e cioè sono in grado di utilizzare lo zucchero (glucosio) presente nel sangue, senza passare attraverso l'ossidazione, sia in presenza sia in assenza di ossigeno. Questa caratteristica ha chiarito che le cellule cancerogene hanno una grande necessità di zucchero per duplicarsi rapidamente, quindi, se si riesce a ridurre la quantità di zucchero disponibile, in un certo senso le si "affama" rendendo più complessa e lenta la loro duplicazione. La dieta chetogenica, riducendo drasticamente l'apporto di carboidrati assunti dal paziente, inibisce l'utilizzo del glucosio nelle cellule tumorali e diventa quindi uno strumento terapeutico: la dieta come una vera e propria "metabolic cancer therapy".
- Nella dieta chetogenica l'apporto calorico dei carboidrati viene sostituito aumentando i grassi che, degradati nel nostro organismo, si trasformano in corpi chetonici che non possono essere utilizzati dalla cellula tumorale. Questa modificazione dell'alimentazione mette quindi "a dieta" il tumore. A questo si aggiunge il fatto che la situazione di chetosi obbliga la cellula tumorale a una sorta di stress metabolico molto più elevato rispetto al tessuto sano, con la riduzione dell'ossidazione delle cellule sane e l'attivazione di una particolare serie di geni che hanno dimostrato di ridurre la duplicazione della cellula colpita dal
- La dieta chetogenica, generalmente, è applicata da sola o in coppia con una riduzione delle calorie introdotte dal paziente, questo allo scopo di ridurre i livelli di insulina presenti nel sangue, in quanto essa è un fattore di crescita e di duplicazione di tutte le cellule, e quindi anche delle cellule tumorali.

Figure 2. Forest plot for the association between caloric restriction diet and tumor incidence.



Lv M, Zhu X, Wang H, Wang F, Guan W (2014) Roles of Caloric Restriction, Ketogenic Diet and Intermittent Fasting during Initiation, Progression and Metastasis of Cancer in Animal Models: A Systematic Review and Meta-Analysis. PLOS ONE 9(12): e115147. https://doi.org/10.1371/journal.pone.0115147
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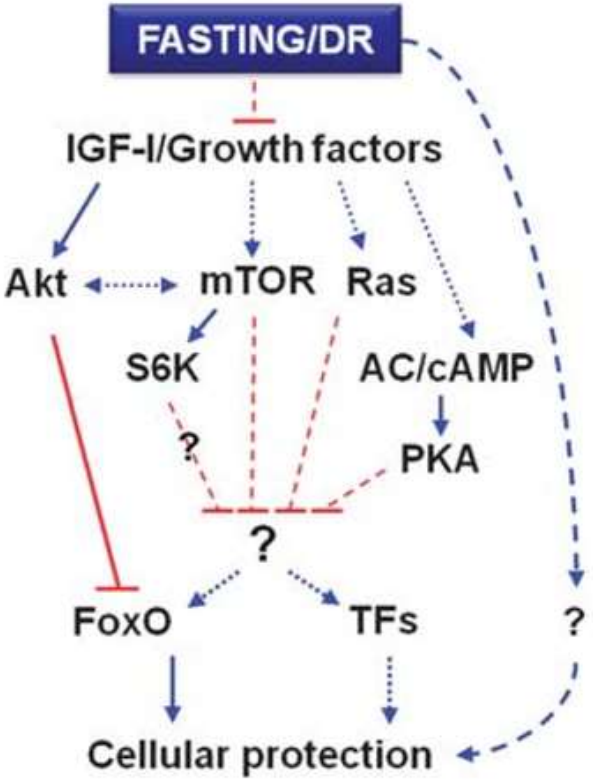
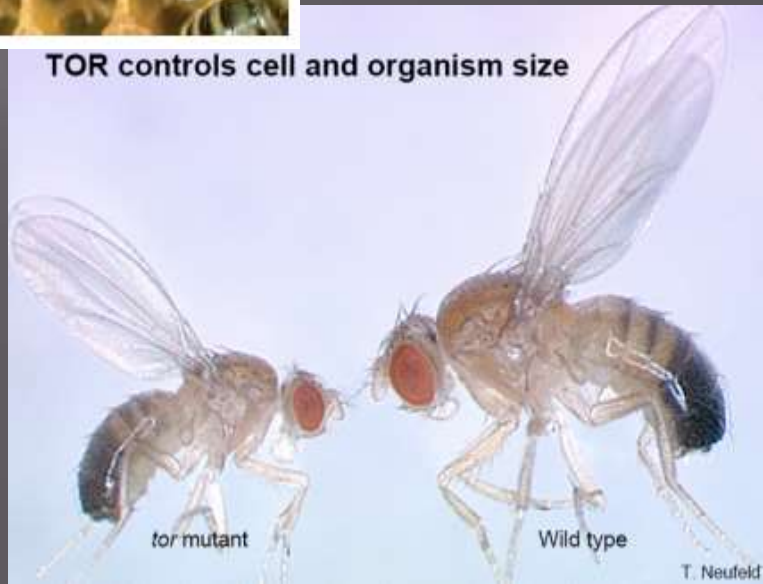


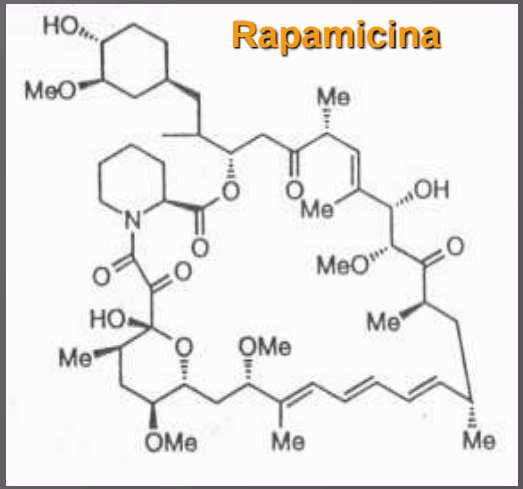
Figure 2 Fasting leads to a significant reduction in circulating IGF-I levels. The partially conserved IGF-I signaling pathways negatively regulate the FoxO family of transcription factors through Akt. Ras and Tor also function downstream of IGF-I, although their roles in the regulation of stress resistance and aging are poorly understood. Mice deficient in type 5 adenylyl cyclase (AC) are stress resistant (Yan *et al.*, 2007). Notably, oncogenic mutations that cause the hyperactivation of IGF-I, Akt, Ras, mTOR and PKA are among the most common in human cancers (Hanahan and Weinberg, 2000).

mTOR: controllo delle dimensioni della cellula

Apis mellifera

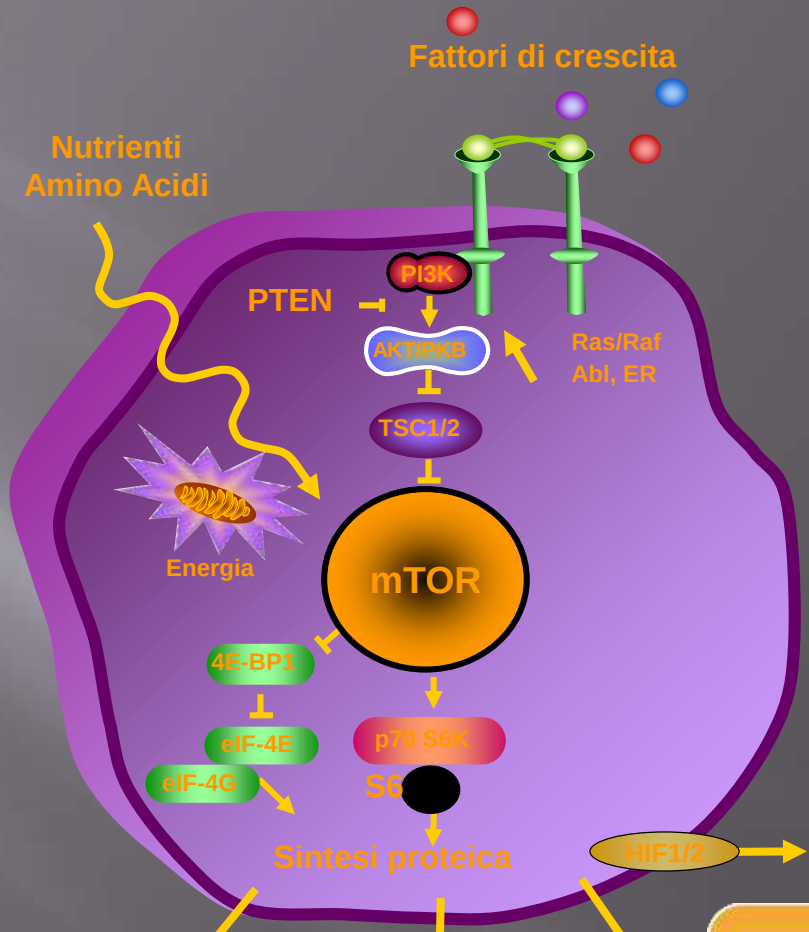


RAPAMICINA:
il caso di un bersaglio, mTOR (*mammalian Target Of Rapamycin*), definito da un farmaco

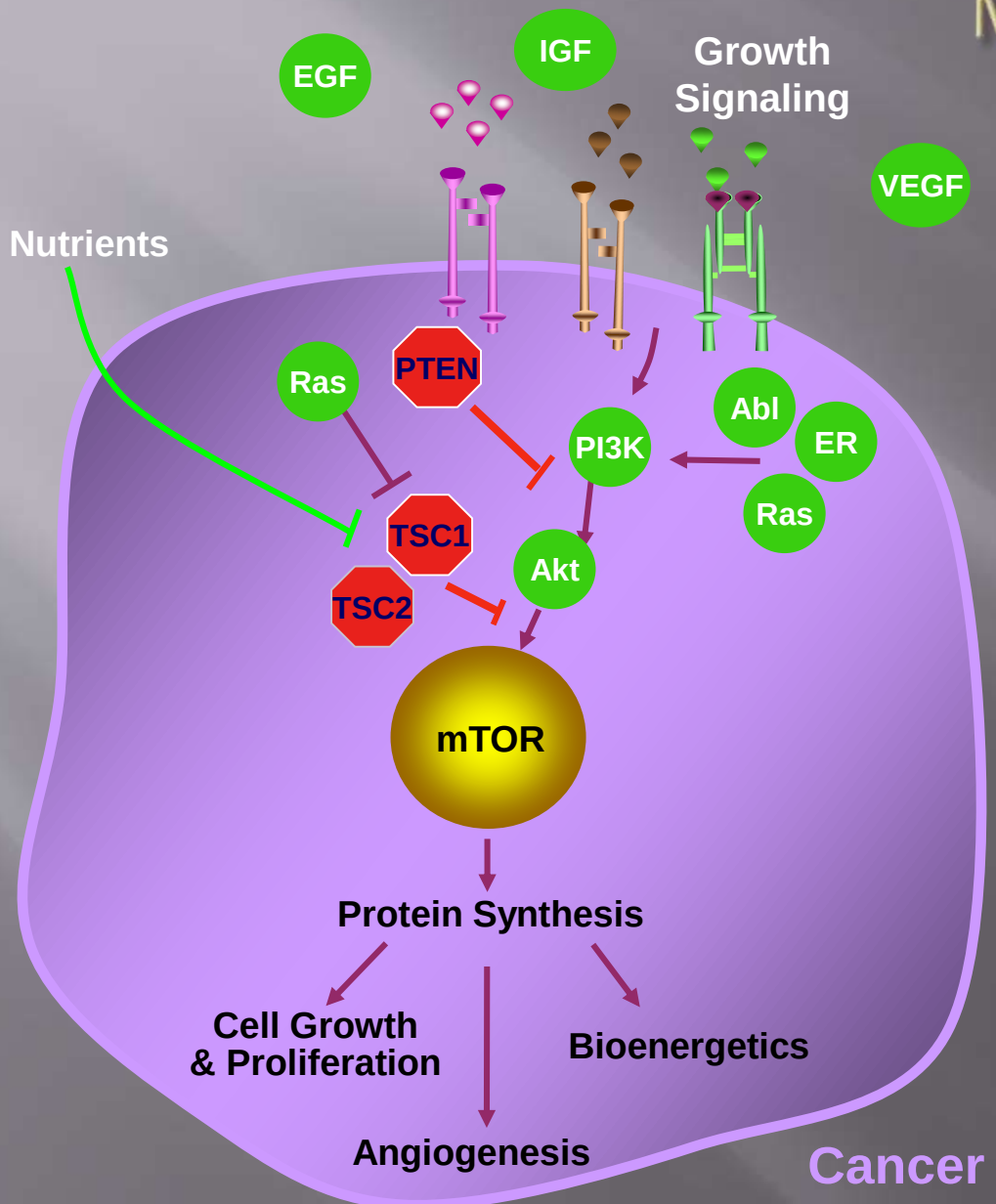


Rapa Nui (Isola di Pasqua)

mTOR è un regolatore centrale della crescita tumorale: integra piu' segnali che traduce in *output* destinati a regolare tre pilastri della vita cellulare



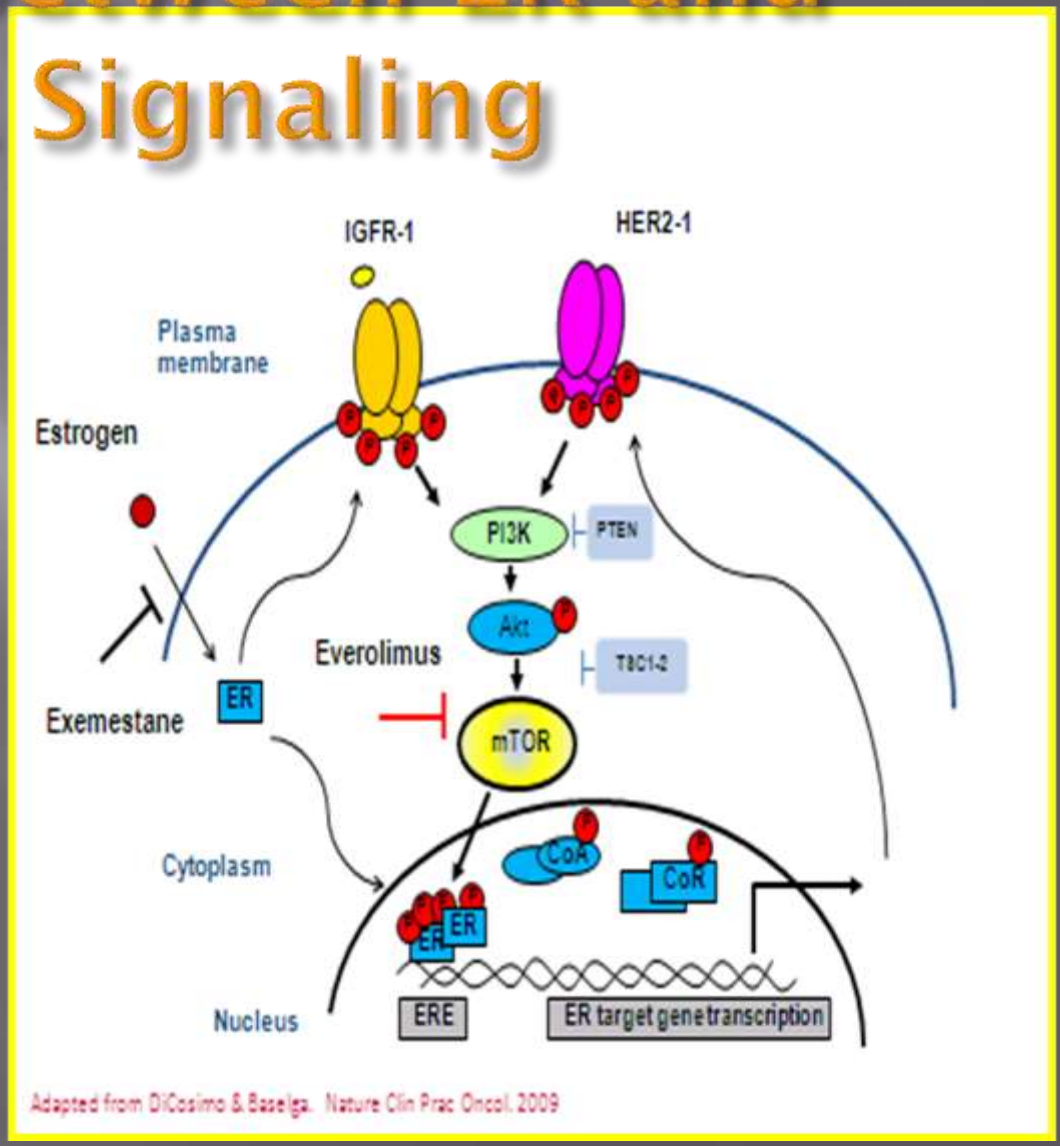
mTOR Pathway is Deregulated by Mutations in Cancer



- Normal cell growth, proliferation, and metabolism are maintained by a number of mTOR regulators[1,2]
- Regulators of mTOR activity
  - mTOR activating
  - mTOR deactivating
- Deregulation of mTOR can result in loss of growth control and metabolism[1,3]
- Mutations in the mTOR pathway have been linked to specific cancers[4]

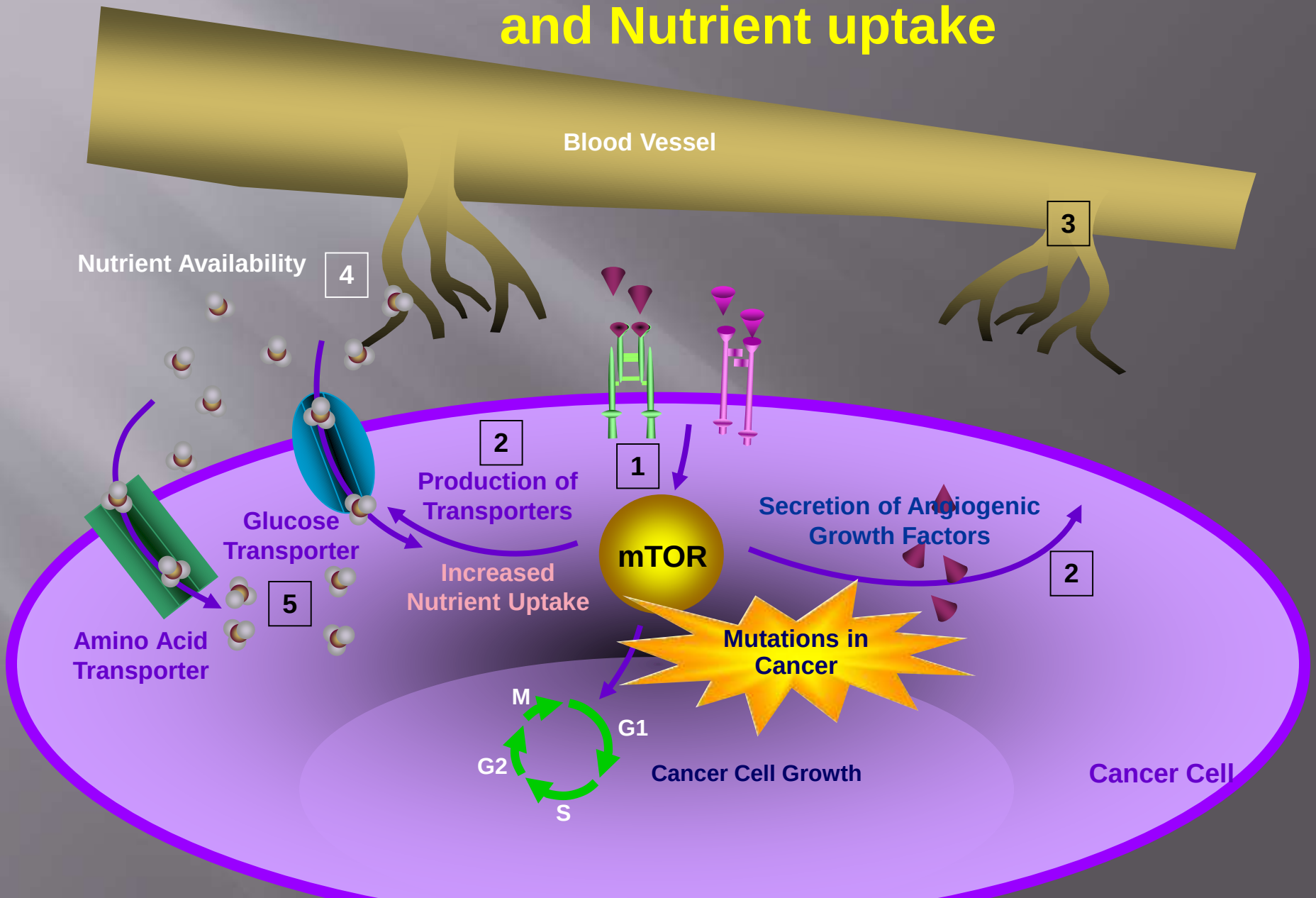
Crosstalk between ER and mTOR Signaling

- mTORC1 activates ER in a ligand-independent fashion[1]
- Estradiol suppresses apoptosis induced by PI3K/mTOR blockade[2]
- Hyperactivation of the PI3K/mTOR pathway is observed in endocrine-resistant breast cancer cells[3]
- **mTOR is a rational target to enhance the efficacy of hormonal therapy**

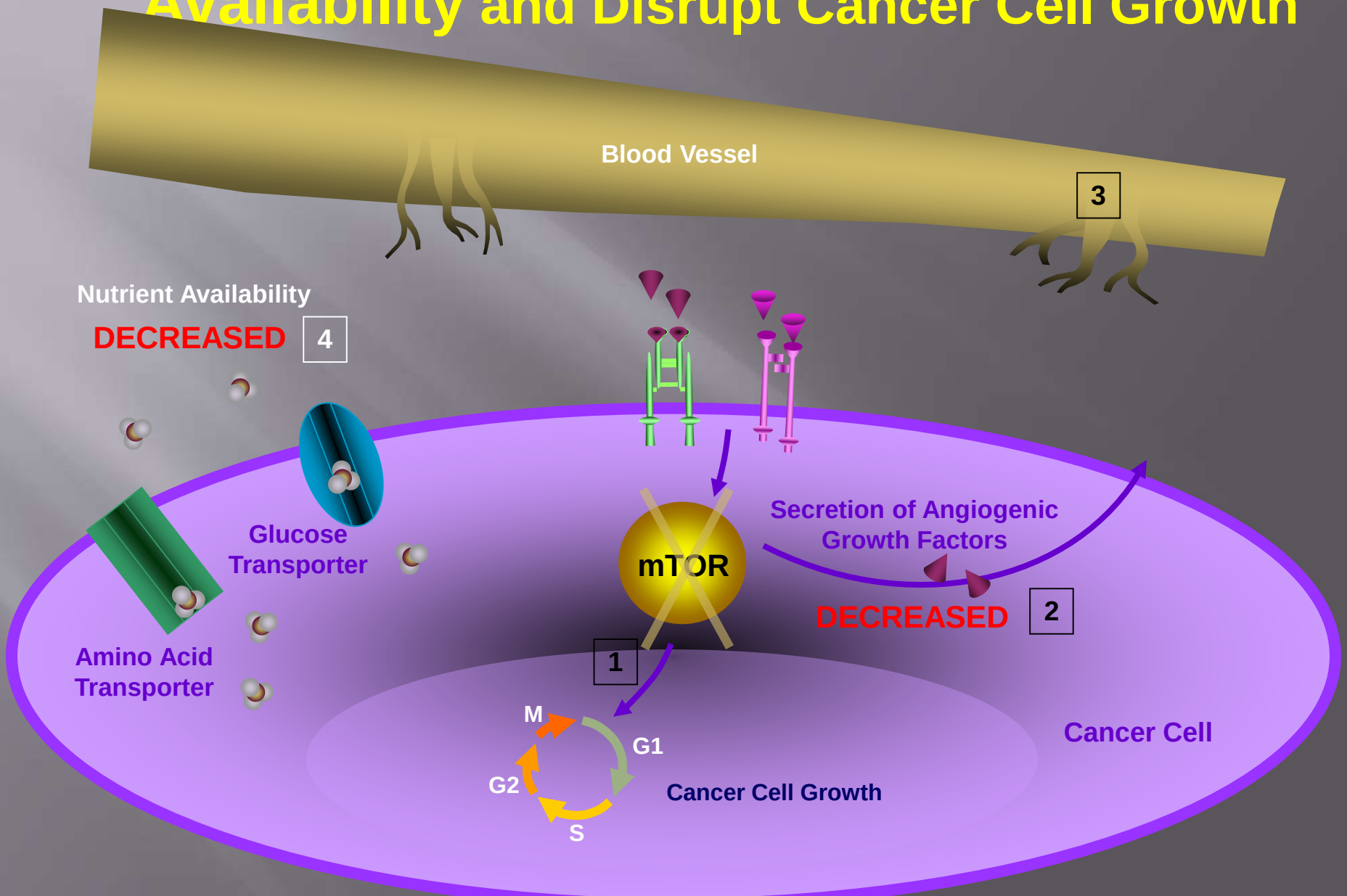


1. Yamnik, RL. J Biol Chem 2009; 284(10):6361-6369.
2. Crowder, RJ. Cancer Res 2009;69:3955-62.
3. Miller, TW. J Clin Invest 2010; 120(7):2406-2413.

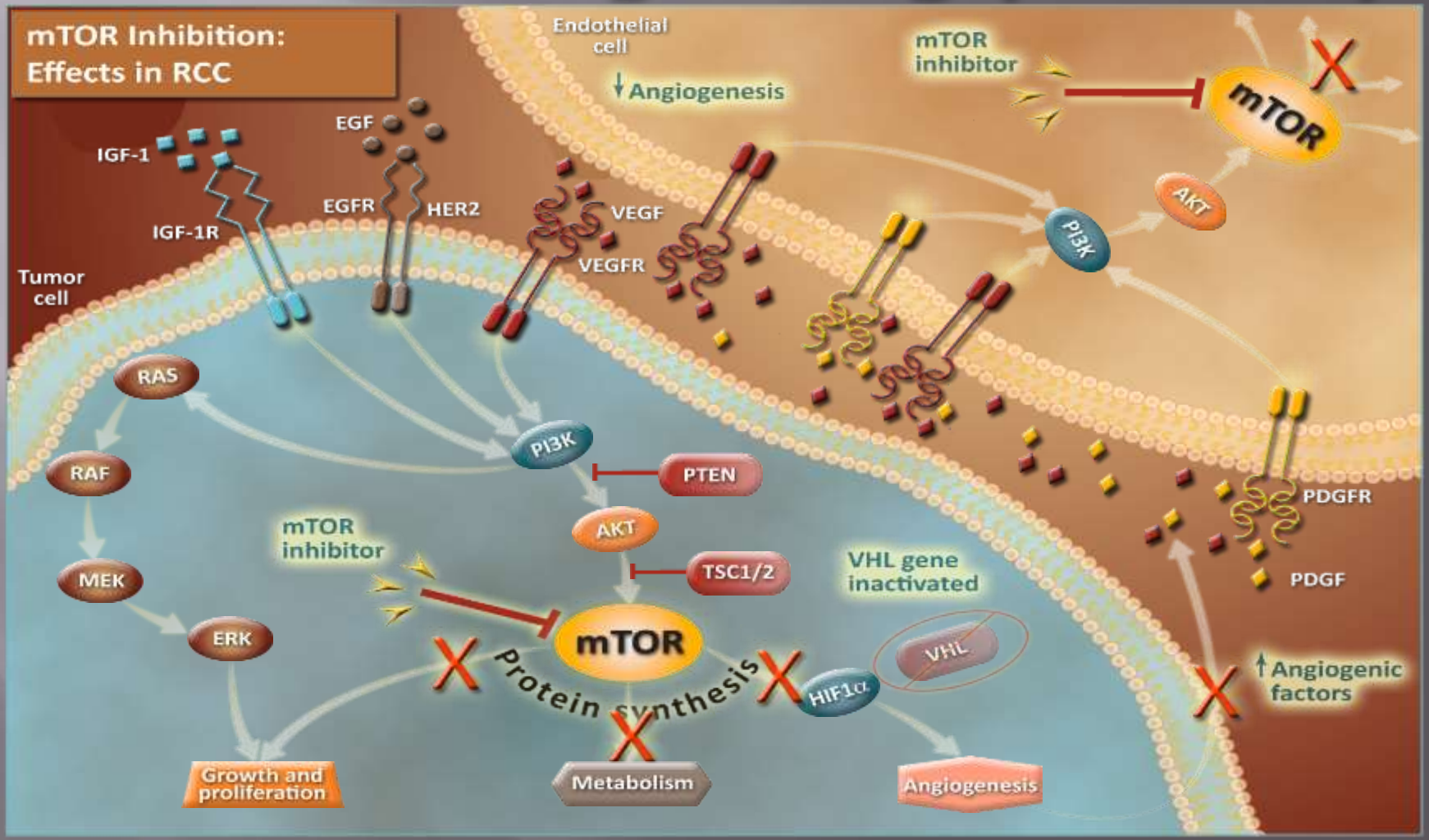
mTOR Coordinates Cancer Cell Growth and Nutrient uptake



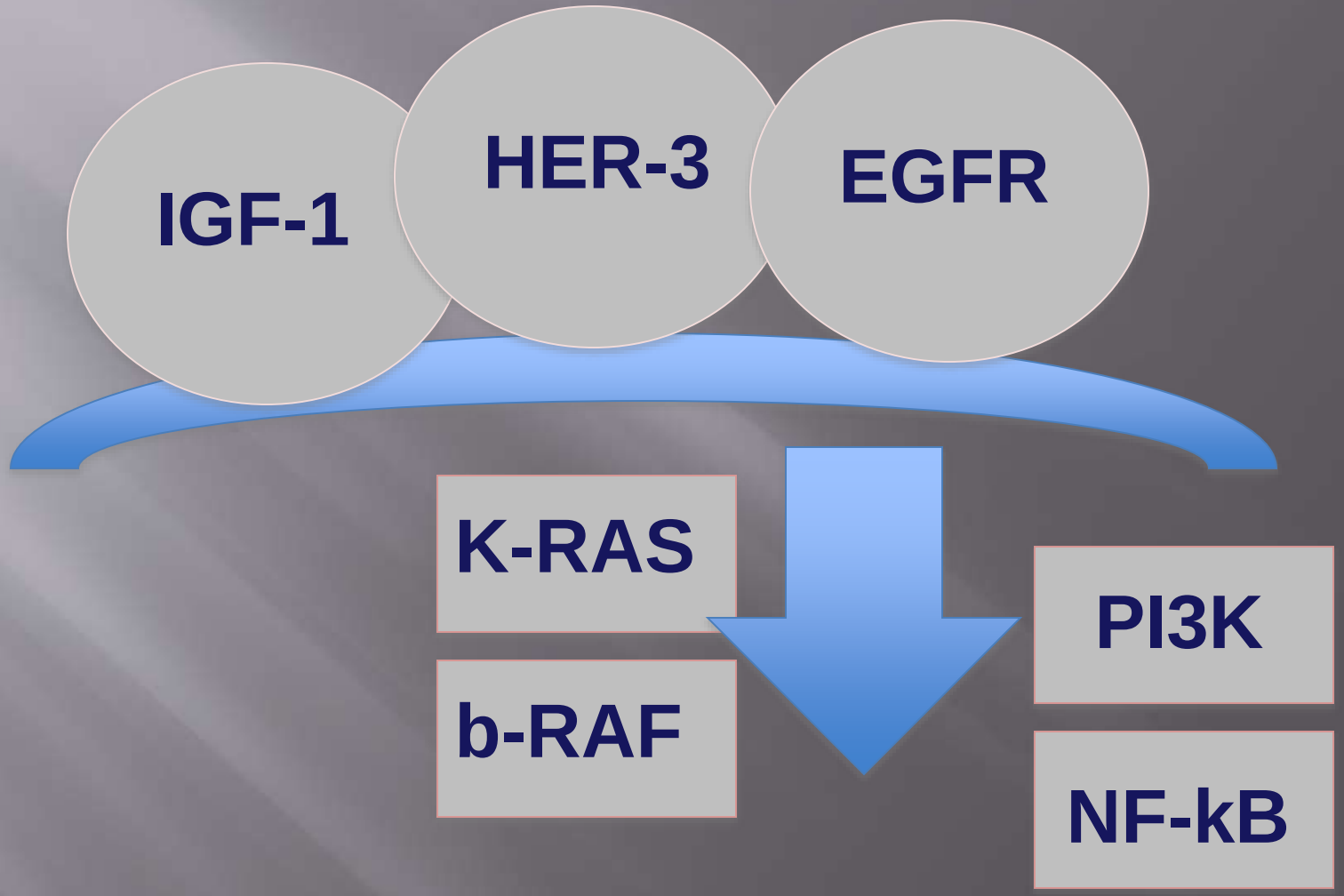
mTOR Inhibition Suppress Nutrient Availability and Disrupt Cancer Cell Growth



Everolimus inhibits the mTOR signaling pathway

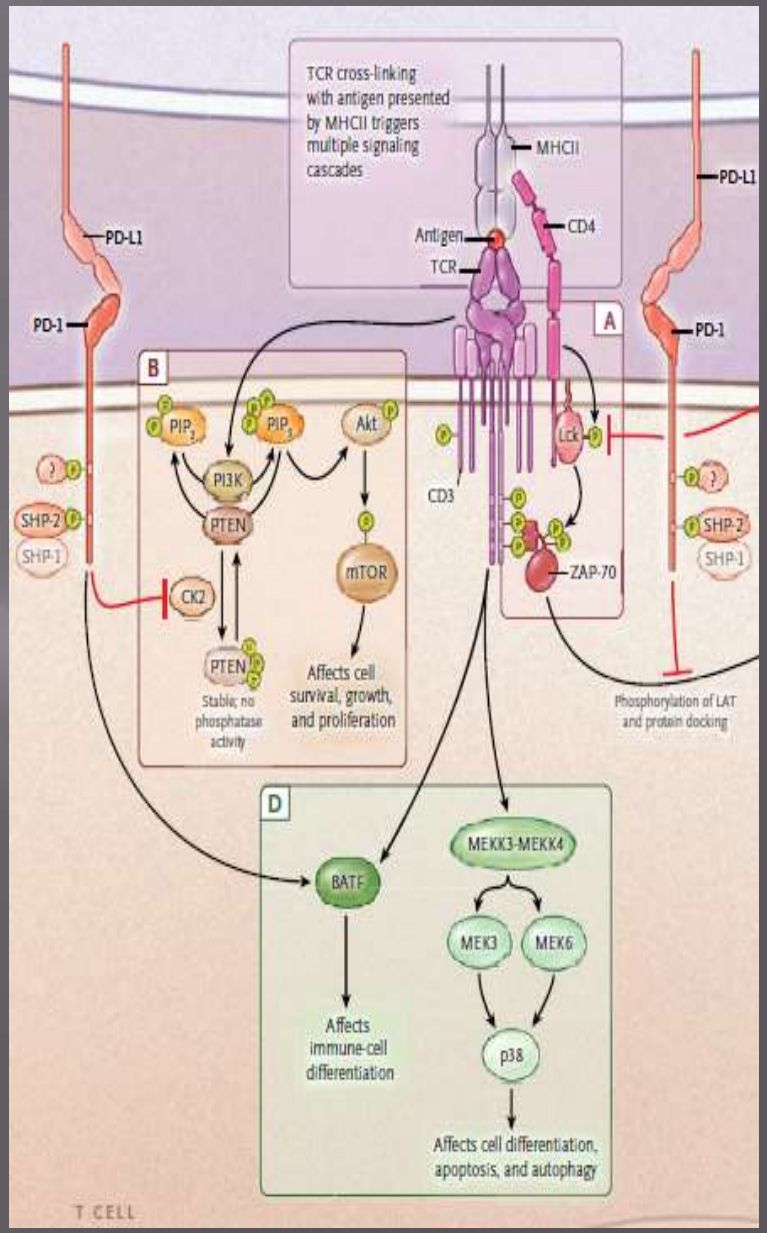


Receptors cross-talk…Downstream translation



mTOR pathway & PD-1/PD-L1

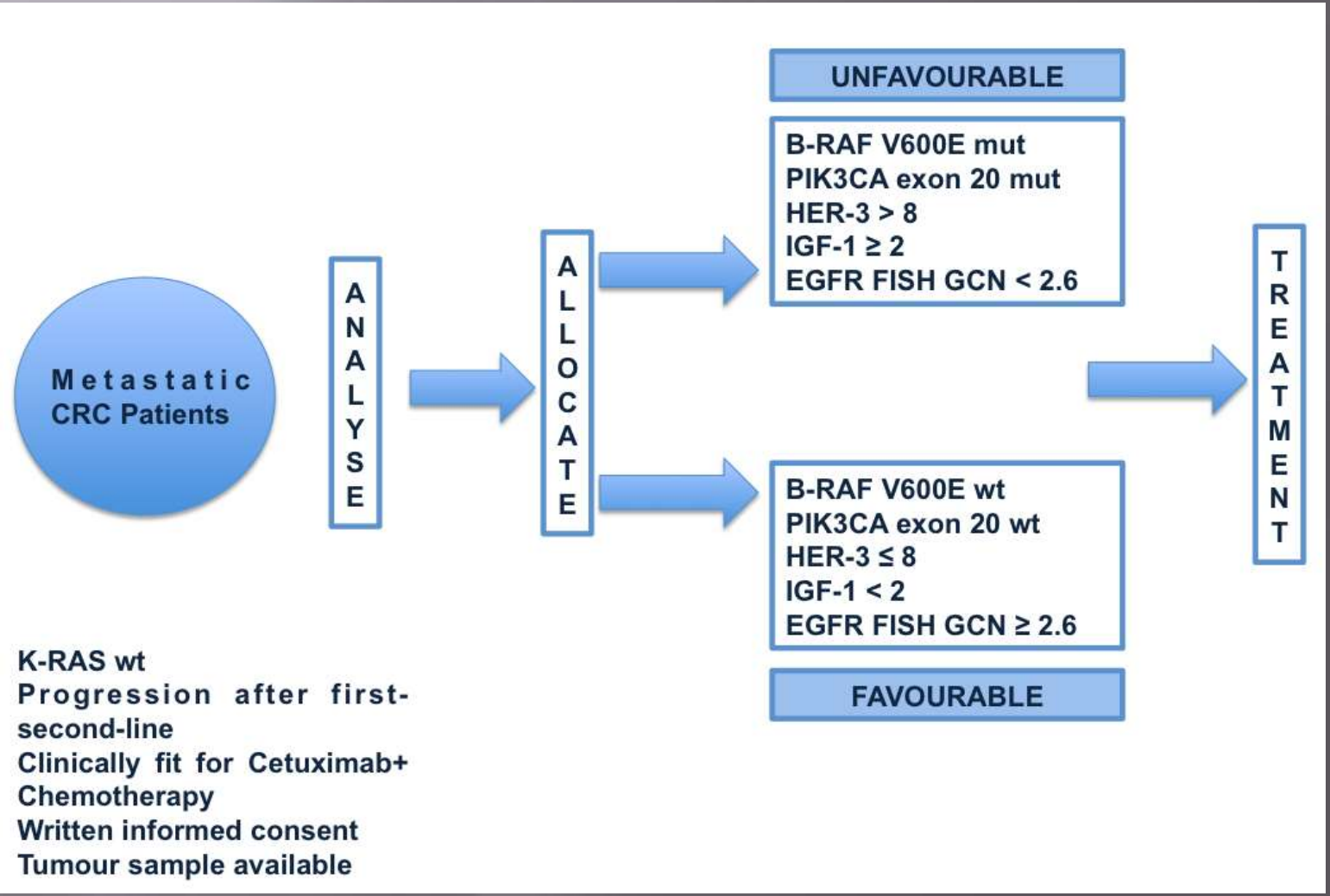
- Activation of PI3K-Akt-mTOR pathway is inhibited by PD-1/PD-L1



Ligation of PD-1 that is expressed in activated T cells by PD-L1 expressed on antigen-presenting cells, nonhematopoietic parenchymal cells, or tumors alters T-cell metabolic reprogramming by inhibiting glycolysis, amino acid metabolism, and mitochondrial metabolism and promoting the accumulation of polyunsaturated fatty acids (PUFA) and activation of fatty acid oxidation (Panel A). By restraining T cells from remodeling their metabolism properly, PD-1 may alter T-cell differentiation, leading to impaired differentiation of T effector cells (T_{EFF}) and T memory cells (T_M) and enhanced differentiation of T regulatory cells (Treg) and T exhausted cells (T_{EX}). PD-L1 functions as an inhibitory receptor to transmit antiapoptotic signals to cancer cells (Panel B). Because cancer cells are highly glycolytic and have enhanced activation of the PI3K–Akt pathway, expression of PD-L1 might result in increased levels of PI3K–Akt–mTOR activation and an elevated rate of tumor-intrinsic glycolysis as a consequence of improved survival.

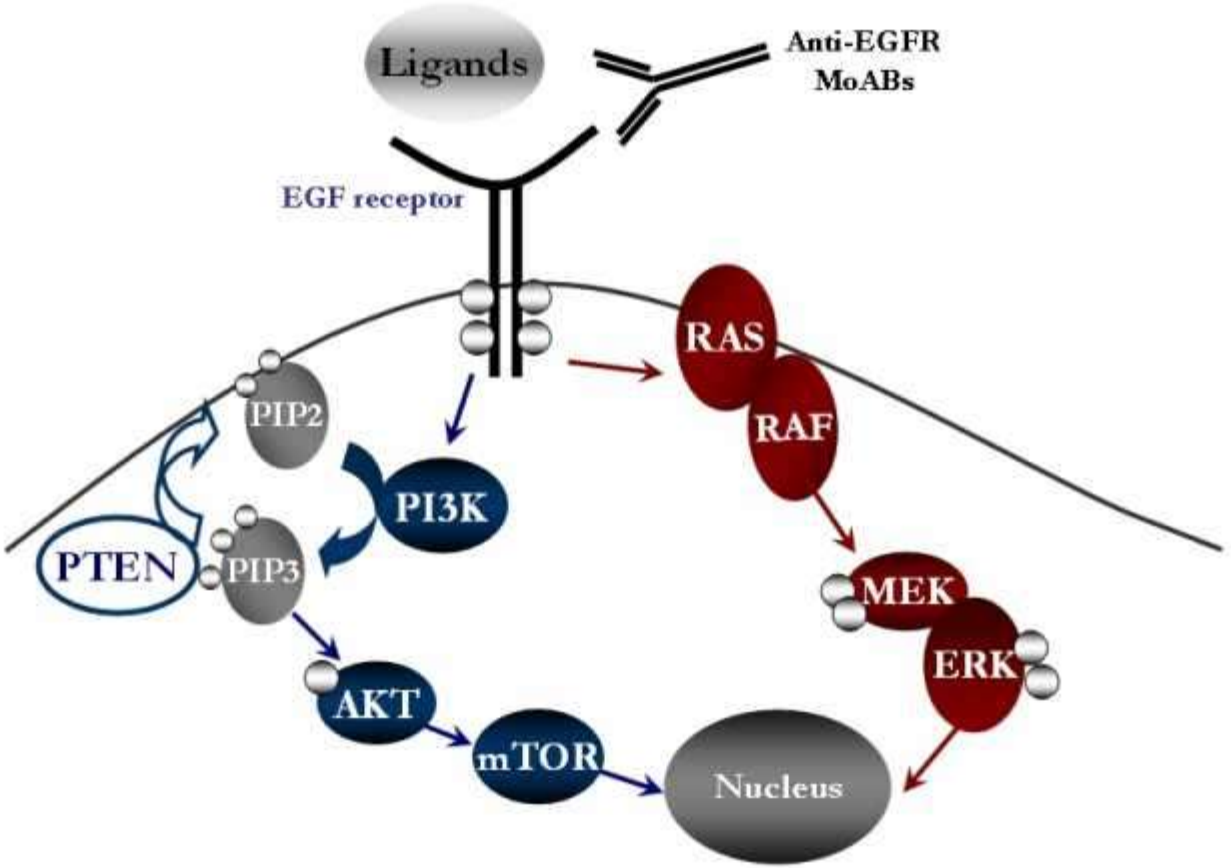
Vassiliki A et al, *NEJM* 201

Prospective validation? Not yet…but

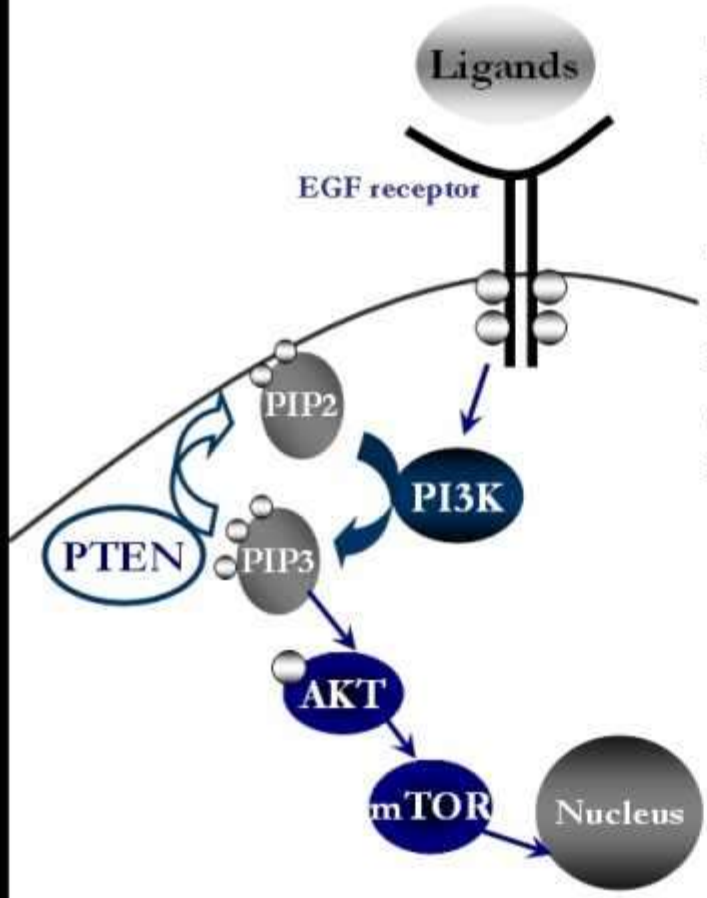


Scartozzi et al. ASCO 2013

Main EGFR signalling pathways



PTEN

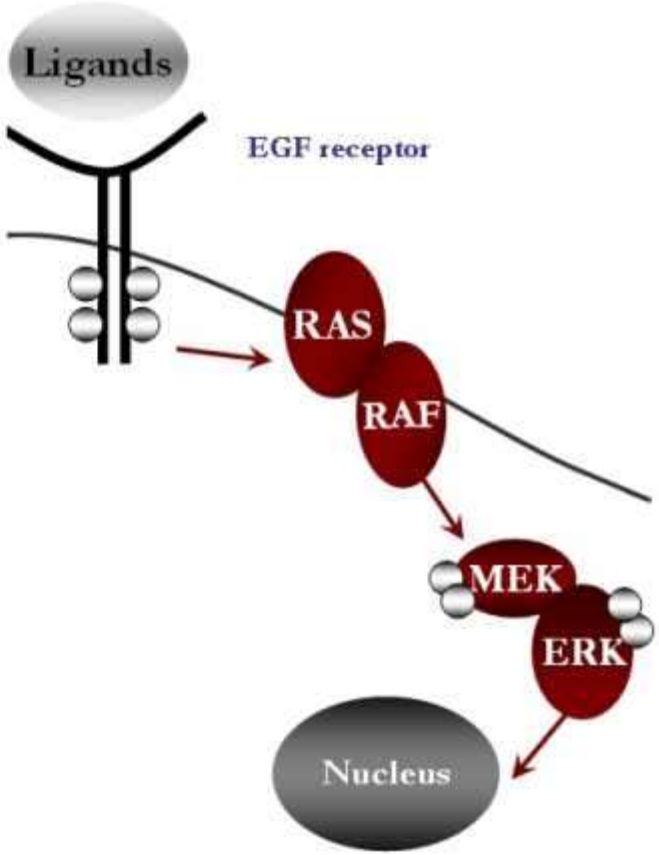


- *PTEN* (phoshatase and tensin homologue deleted on chromosome 10) gene encodes a phosphatase, whose major substrate is PIP-3
- Loss of PTEN (mono or bi-allelic inactivation, but also epigenetic silencing) results in increased PIP-3 concentration
- Increase of PIP-3 leads to AKT hyperactivation

PROTECTION FROM APOPTOSIS

KRAS

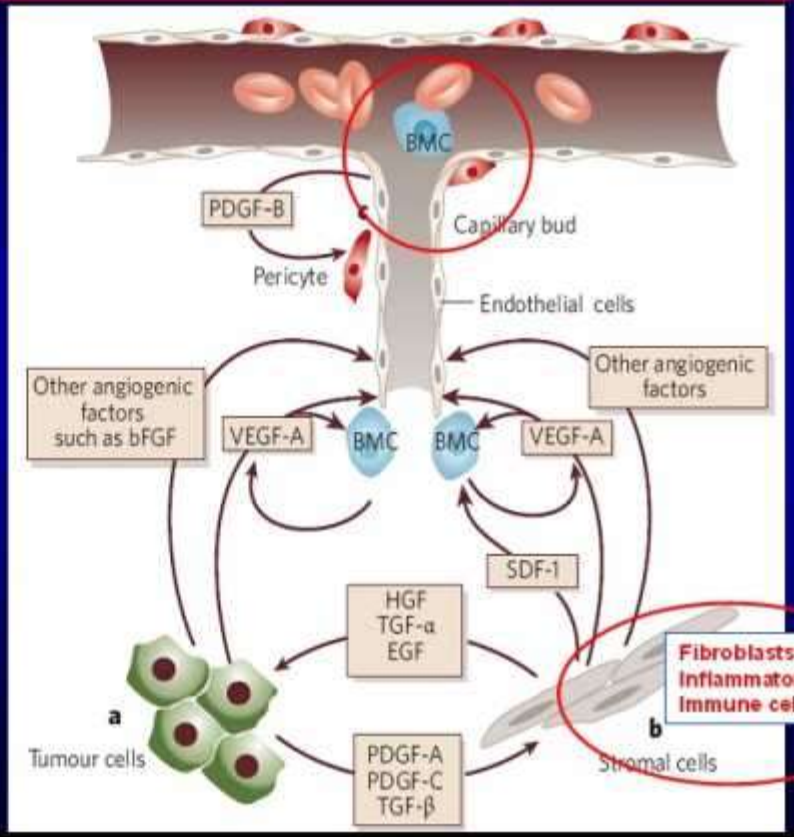
- ***KRAS*** (human homolog of the Kirsten rat sarcoma-2 virus oncogene) encodes a small self-inactivating signal-transducing GTP-binding protein
- ***KRAS*** can harbor oncogenic mutations that yield a constitutively active protein
- Activated Ras stimulates Raf-1, which leads to MAPK phosphorylation



CELL PROLIFERATION

Il microambiente tumorale è costituito da cellule tumorali stromali, immunitarie e infiammatorie

Il microambiente condiziona le risposte al trattamento

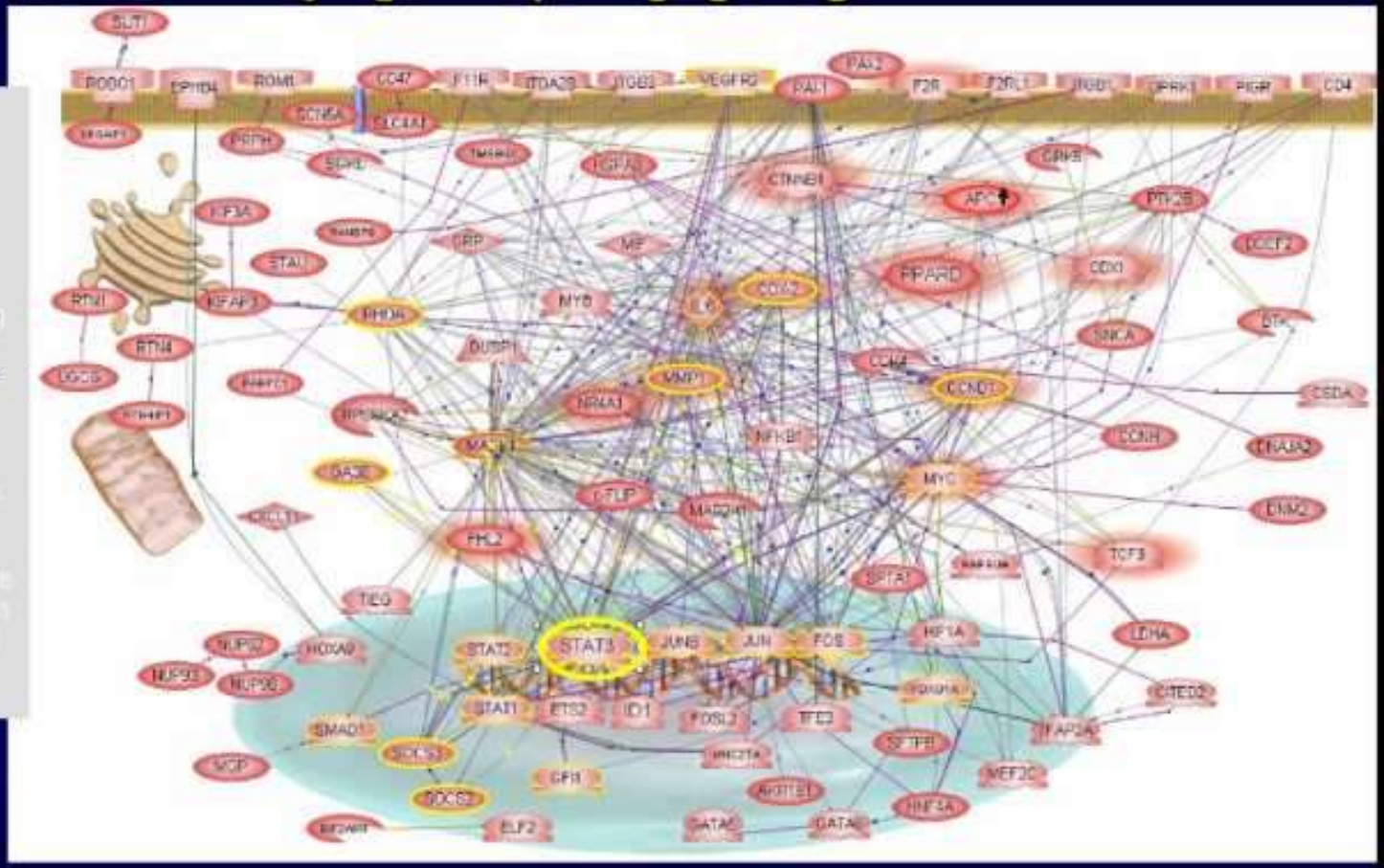


Ferrara & Kerbel *Nature* 438: 967–974, 2005

Angiogenic signaling network: A gene regulatory network constructed from inversely regulated proangiogenic genes.

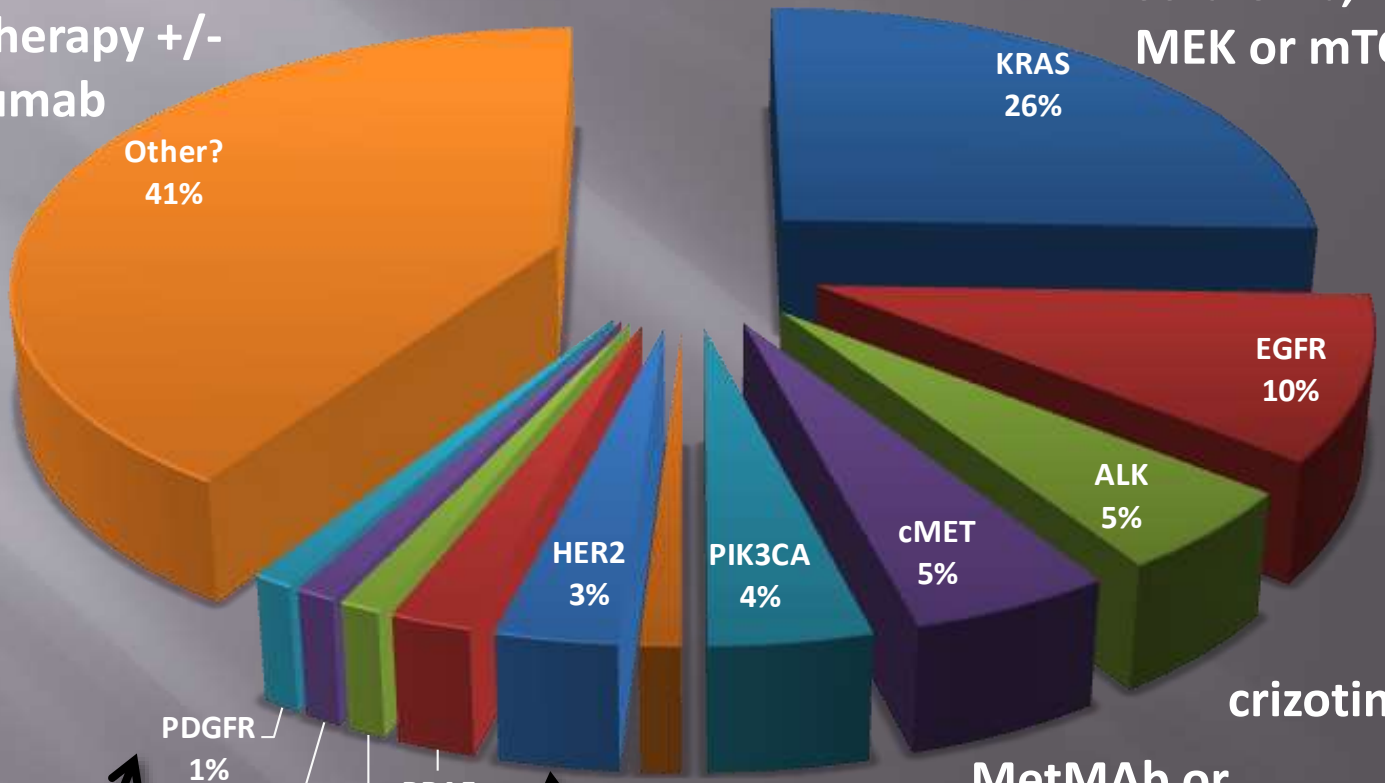
highlighted are:
- gene interactions based on promoter binding site (green lines),
- protein modification (yellow lines),
- protein–protein binding (violet lines),
- gene expression (blue lines),
- and gene regulation (black lines).

The signaling pathways are shown with PPAR/-catenin (red shadows), demonstrate the interconnectedness of the pathways within the angiogenic network.



Abdollahi A, Transcriptional network governing the angiogenic switch in human pancreatic cancer. *PNAS* 104: 12890-12895, 2007

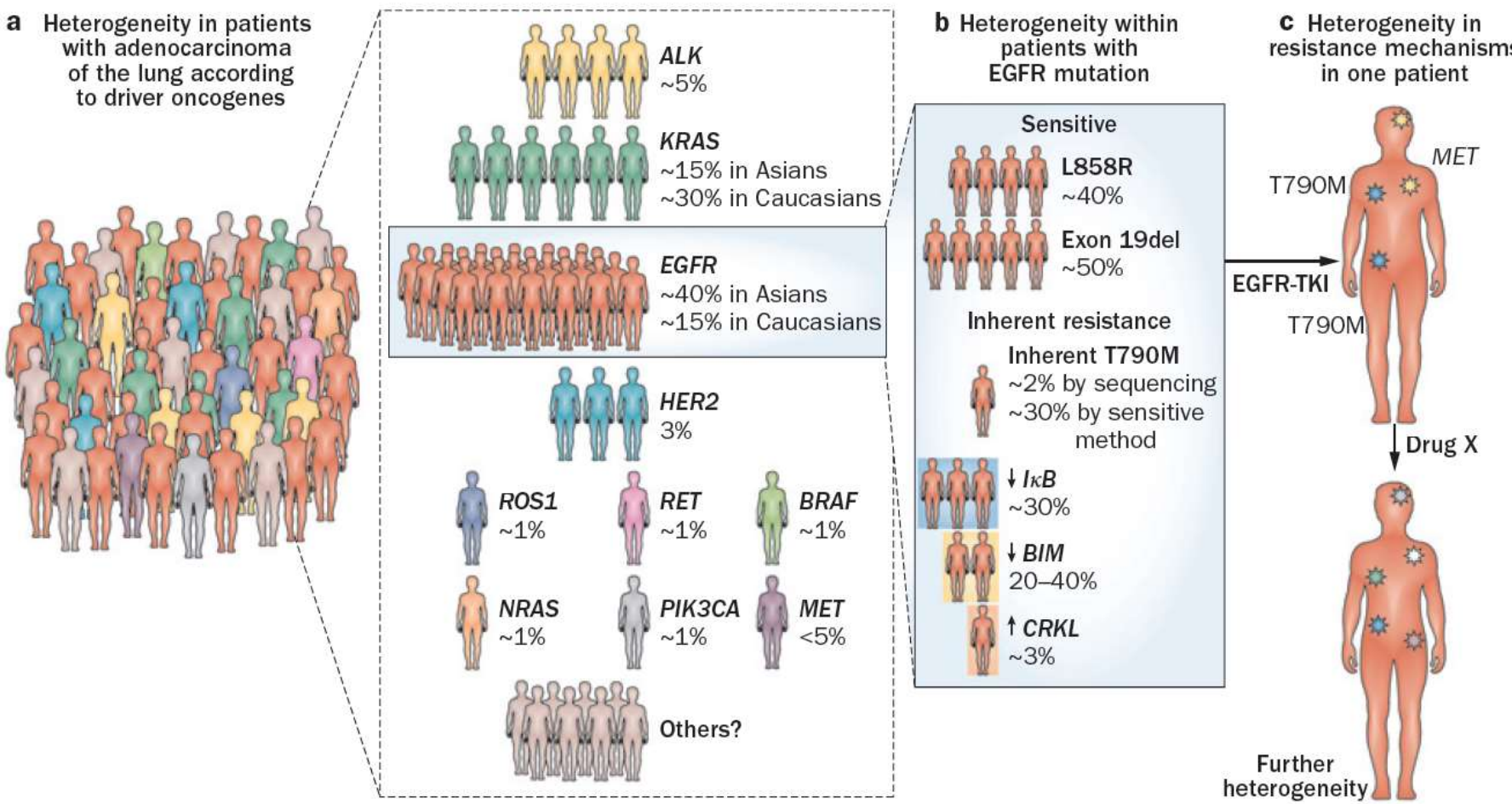
The Future of Molecularly Defined Lung Cancer



Modified from L Ding *et al. Nature* 2008

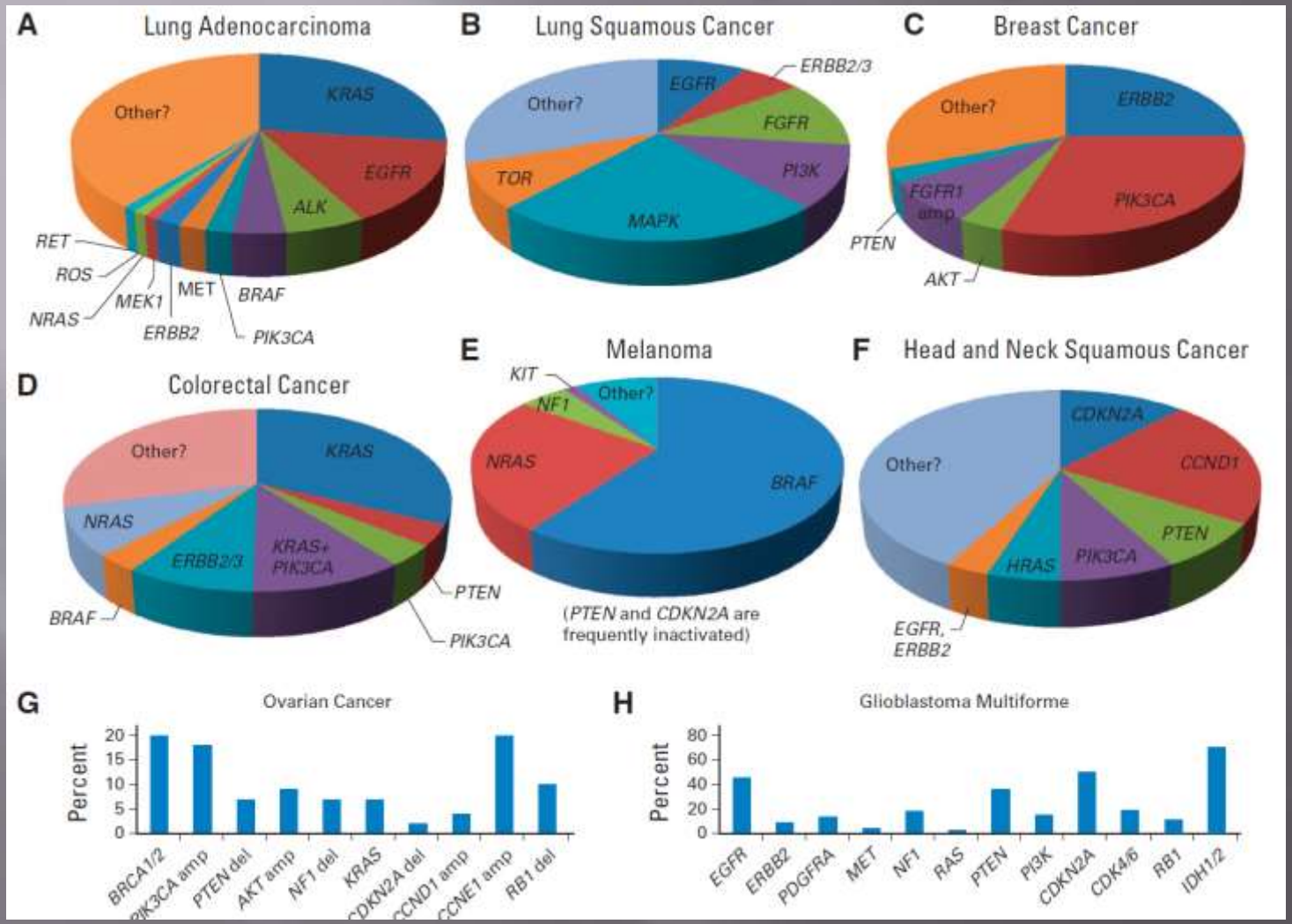
The efficacy of targeted therapy is affected by

TUMOR HETEROGENEITY

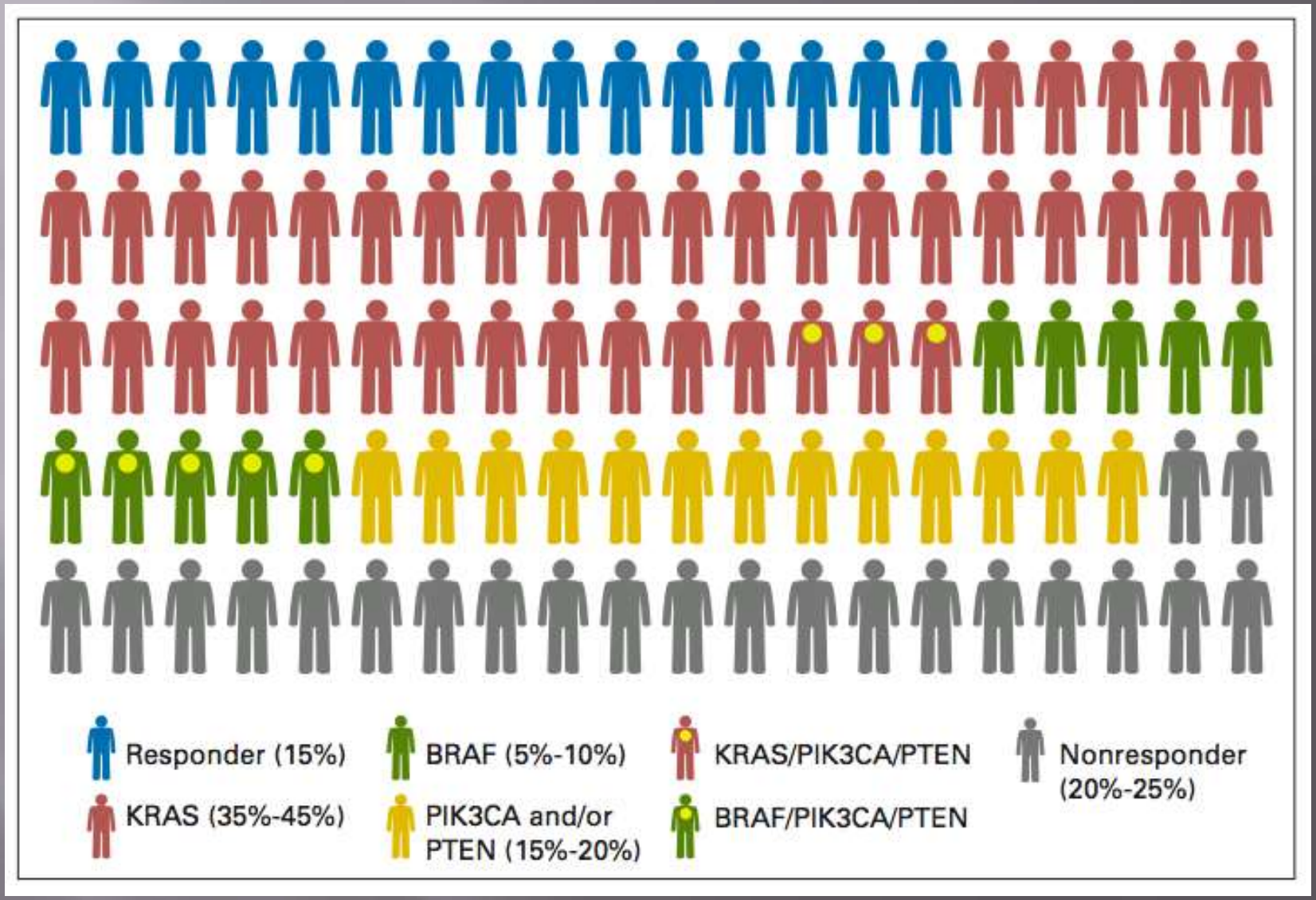


Mitsudomi Nat Rev Clin Oncol 2013

Genomic alterations affecting actionable signaling pathways

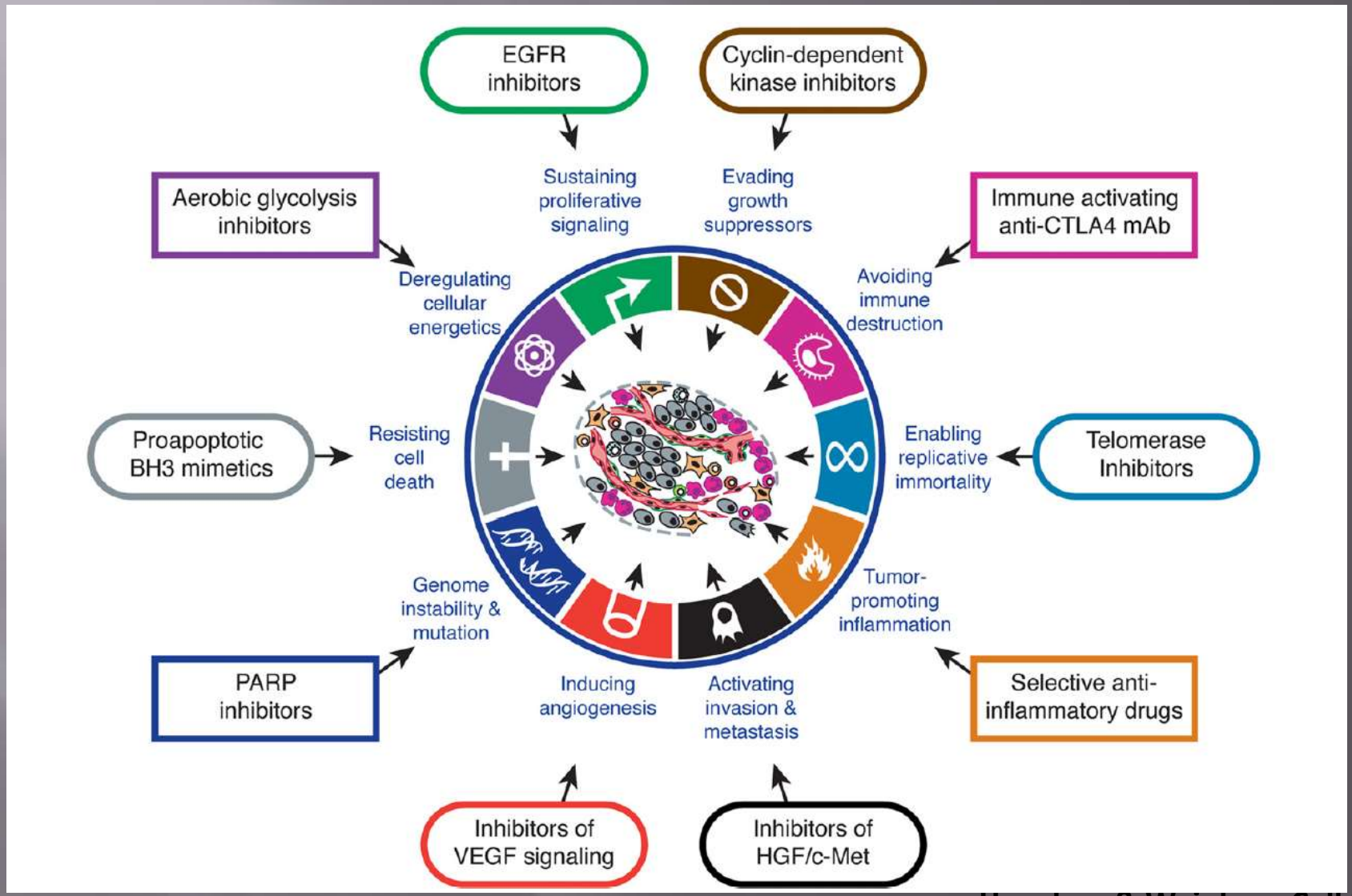


Garraway JCO 2013



Bardelli et Al JCO 2010

Signal transduction pathways involved in the proliferation and survival of cancer cells

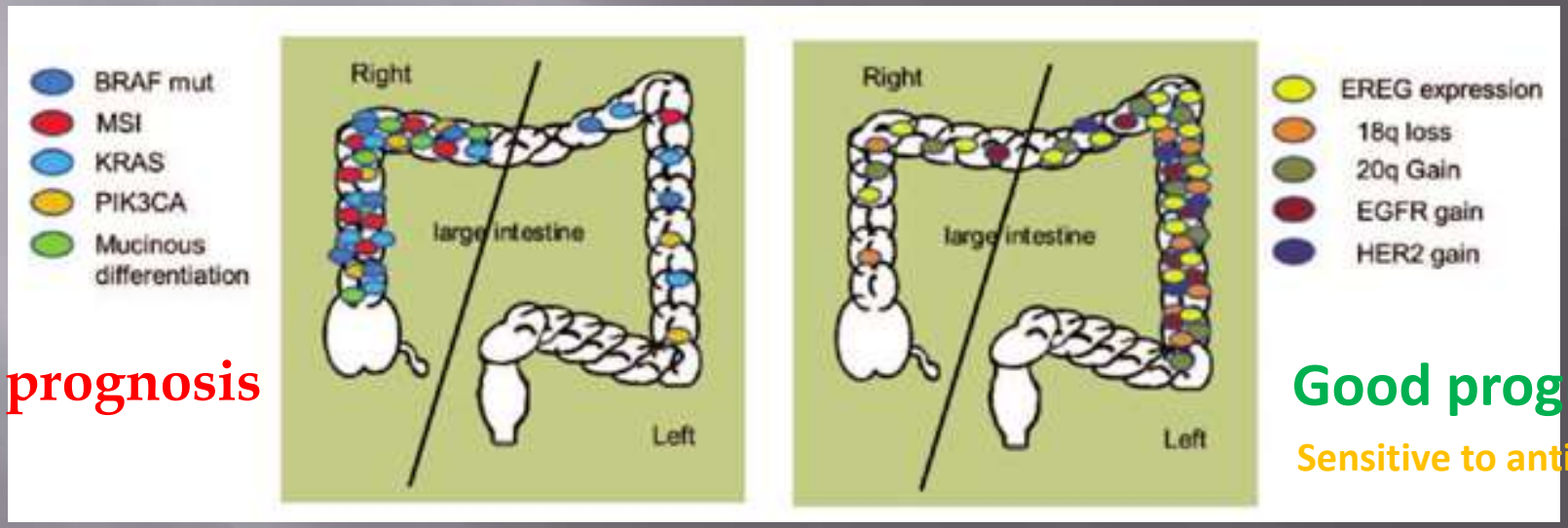


Hanahan & Weinberg Cell 2011

Left vs Right side

KRAS/NRAS analysis: The randomized phase 2 PEAK trial

- Clinical and molecular analysis of proximal vs distal colon cancers from PETACC 3 study (n=2849, + 219 metastatic pts)



Poor prognosis

Good prognosis

Sensitive to anti-EGFRs

Missiaglia E et al, ASCO 2013, #3526

Table 2 Fasting protects against chemotherapy toxicity, in part by reducing IGF-I levels

Drug	*Mode of action*	*Effect of fasting and/or reduced IGF-I*
Doxorubicin	DNA intercalation	Protection by fasting and reduced IGF-I (mice)
Cyclophosphamide	DNA alkylation	Protection by reduced IGF-I (mice)
5-Fluorouracil	Anti-metabolite	Protection by reduced IGF-I (mice)
Etoposide	Topoisomerase II inhibition	Protection by fasting, but sensitized by reduced IGF-I (mice)
Docetaxel	Microtubule stabilization	
Carboplatin	DNA alkylation	Reduced side-effects by fasting (human)
Paclitaxel	Microtubule stabilization	
Gemcitabine	Anti-metabolite	

Abbreviation: IGF-I, insulin-like growth factor 1.

As tested in mice, fasting and the reduction of circulating IGF-I protect against doxorubicin, cyclophosphamide and 5-fluorouracil (5-FU) (Lee *et al.*, 2010; Raffaghello *et al.*, 2008). Notably, fasting protected against etoposide, but the reduction of IGF-I alone showed opposite results, suggesting a more complex role of fasting beyond IGF-I in the protection against certain drug categories. In a recent case series, patients that voluntarily fasted during chemotherapy reported significantly reduced side-effects (Safdie *et al.*, 2009). In several cases, chemotherapy was limited by toxic side-effects, but upon fasting, patients were able to resume normal treatment schedule. The chemotherapeutics administered to these patients include a combination of docetaxel, carboplatin, paclitaxel and gemcitabine.

Oncogene (2011) 30, 3305–3316

www.nature.com/onc

REVIEW

Fasting vs dietary restriction in cellular protection and cancer treatment: from model organisms to patients

C Lee and VD Longo

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Fasting in clinical applications

Historically, fasting was performed for both medical and religious purposes (Kerndt *et al.*, 1982; Michalsen *et al.*, 2005; Johnstone, 2007). Much has also been learned about the effects of fasting from data on the victims of famine and war (Scrimshaw, 1987; Kalm and Semba, 2005), and also data from subjects fasting voluntarily for 40 days or longer (Kerndt *et al.*, 1982). Beyond its traditional practice, fasting has been demonstrated to have clinical benefits. Notably, clinical studies have shown that water-only fasting for 10–14 days significantly improved hypertension by reducing systolic blood pressure points more than two-fold compared with that of a combined vegan, low-fat, low-salt diet and exercise (Goldhamer *et al.*, 2001; Goldhamer, 2002). Moreover, the safety of fasting in patients with chronic disease has been studied in a large cohort study with over 2000 participants (Michalsen *et al.*, 2005). In this study, the authors determined that fasting (350kcal/day) was safe and considered by many of the participating subjects to be beneficial to their chronic disease (Michalsen *et al.*, 2005).

In a recent report, 10 patients with a variety of malignancies voluntarily fasted for up to 180 h in combination with chemotherapy, and reported a reduction in common chemotherapy-associated side-effects such as vomiting, diarrhea, fatigue and weakness (Safdie *et al.*, 2009) (Table 2). Notably, in the cases where cancer progression could be followed, there was no evidence that fasting protected tumors or interfered with chemotherapy efficacy. A controlled randomized clinical trial testing the effect of fasting on cancer treatment underway at the University of Southern California Norris Cancer Center is expected to provide more conclusive clinical data on the effect of fasting on chemotherapy toxicity and efficacy.

- Basta qualche giorno di digiuno per risvegliare il sistema immunitario, rinforzarlo e ringiovanirlo, sia in età avanzata sia in caso di tumore, rendendo l'organismo più reattivo e combattivo contro le malattie. Resa nota sulla rivista Cell Stem Cell, la scoperta è del genovese Valter Longo, Direttore dell'Istituto di Longevità della University of Southern California.

  Gli esperti hanno anche iniziato sperimentazioni su pazienti con tumore e sugli anziani per vedere gli effetti del digiuno e di una dieta 'mima-digiuno' sul sistema immunitario. Già in un precedente studio, Longo e i colleghi genovesi dell'Ospedale Gaslini avevano dimostrato che la 'terapia del digiuno' potenzia di molto l'effetto della chemio (anche di 20 volte nel caso di cancro su animali). A seguire, i ricercatori hanno ideato la dieta 'mima-digiuno' ora in sperimentazione clinica.

  La dieta è più sicura del digiuno perché evita carenze nutritive. Con gli anni anche il sistema immunitario invecchia e diviene meno funzionante, quindi l'anziano è più esposto a rischio infezioni e altre malattie. Lo stesso avviene nel cancro. Gli esperti hanno visto che esponendo topolini per qualche giorno al digiuno, prima della chemio, i globuli bianchi si riducono ma poi subito dopo aumentano e risultano rinvigoriti grazie a staminali che vengono riversate nel sangue.

  "Abbiamo scoperto che questo effetto è in grado di accendere le cellule staminali rendendole in grado non solo di rigenerare cellule immunitarie e fermare l'immunosoppressione causata dalla chemioterapia, ma anche di ringiovanire il sistema immunitario di topi", conclude Longo.

Toward a cancer-specific diet.
Bozzetti F, Zupec-Kania B.
Clin Nutr. 2016 Oct;35(5):1188-95.

- **CONCLUSION:** There is a large consensus in literature that maintaining a normal body weight and preserving the lean body mass through an adequate nutrition is beneficial in cancer patients. ***The nutritional approach through a ketogenic diet which may be toxic for the cancer cells while is well utilized and tolerated by the patient seems promising in a next future.***

Low carbohydrate diet and ketogenic diet. Different forms of this diet exist, some with a moderate reduction of carbohydrates some with a reduction to about 10% of total energy intake with the aim of inducing ketosis. Schmidt *et al.* (23) published a pilot study on 16 patients with advanced cancer, on a diet with a maximum of 70 g carbohydrates per day, for an intended eight weeks. Two patients died, three did not accept the diet and three had progressive disease. Quality of life was assessed in five patients who finished the study. Emotional function and sleep quality was better while other parameters remained stable or deteriorated. The authors argue that this was due to the advanced stage of their cancer. Side-effects of the diet were fatigue and constipation.

- In an older study, a ketogenic diet with high amounts of omega-3-fatty acids was fed enterally to patients with cachexia from cancer. The authors did not describe a positive effect on cachexia or on the course of disease (26).
- Pre-clinical data are ambiguous. Some show a reduction of tumor. Yet some in vitro as in vivo experiments, gave warnings as to the safety of this diet. In vitro data showed that cancer cells not only adapt to the situation but develop mutations and characteristics of stem cells. One hypothesis is that the diet puts the tumor under stress and thus selects for resistance and malignancy. In an experiment on mice, the tumors in the diet-treated group initially grew less but later tumor growth accelerated and exceeded that of the control group (28, 29, 30, 31).

A Nutritional Perspective of Ketogenic Diet in Cancer: A Narrative Review

Camila L.P. Oliveira, Stephanie Mattingly, Ralf Schirrmacher, Michael B. Sawyer, Eugene J. Fine, Carla M. Prado,

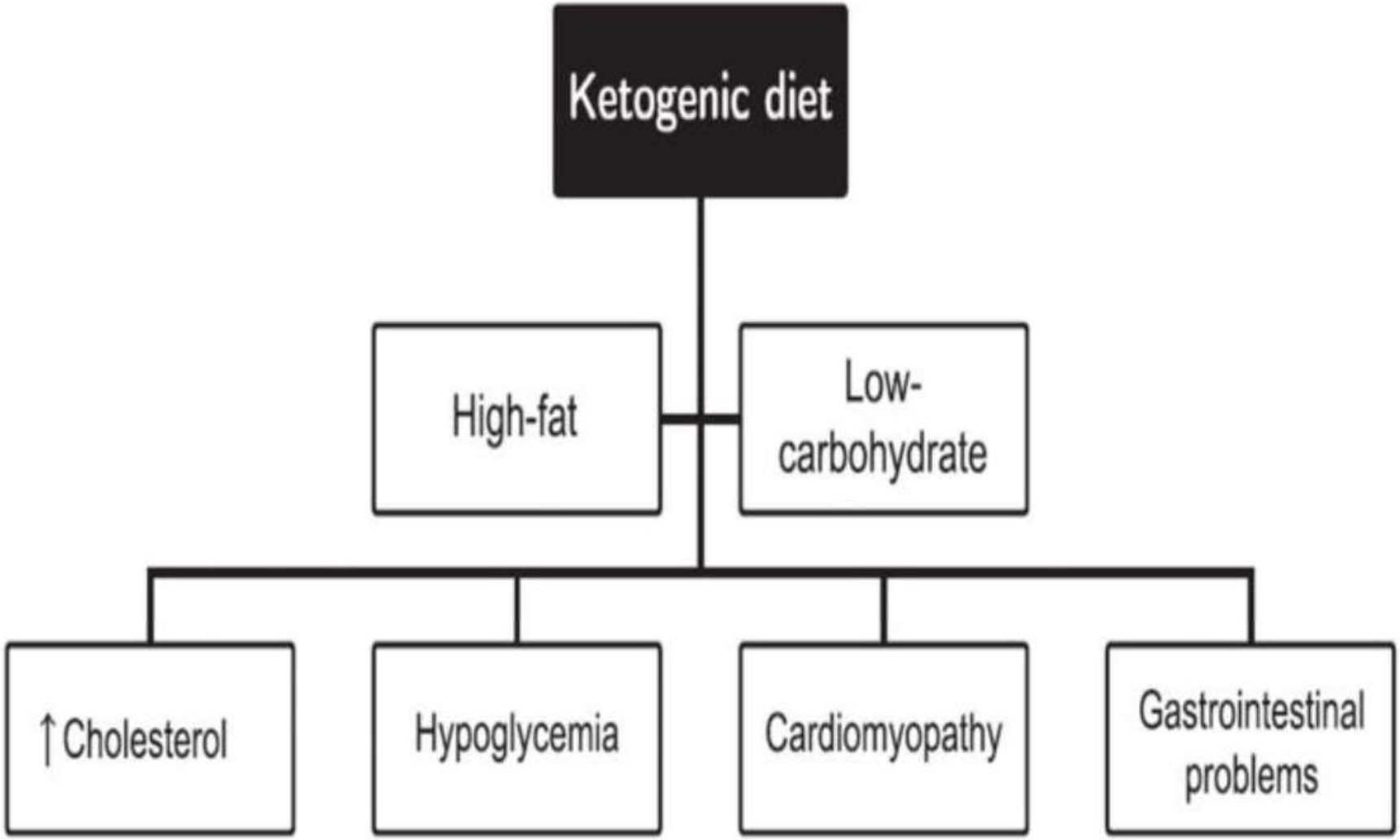
Journal of the Academy of Nutrition and Dietetics 2017

- The use of KD in cancer shows potentially promising, but inconsistent, results. **The limited number of studies and differences in study design and characteristics contribute to overall poor quality evidence, limiting the ability to draw evidence-based conclusions.**

Systematic review: isocaloric ketogenic dietary regimes for cancer patients
Erickson, N., Boscheri, A., Linke, B. et al.
Med Oncol (2017) 34: 72

- This systematic review therefore presents and evaluates the clinical evidence on isocaloric KD dietary regimes and reveals that evidence supporting the effects of isocaloric ketogenic dietary regimes on tumor development and progression as well as reduction in side effects of cancer therapy is missing. Furthermore, an array of potential side effects should be carefully considered before applying KD to cancer patients. In regard to counseling cancer patients considering a KD, more robust and consistent clinical evidence is necessary before the KD can be recommended for any single cancer diagnosis or as an adjunct therapy.

DIETA CHETOGENICA: EFFETTI COLLATERALI



ANTICANCER RESEARCH
International Journal of Cancer Research and Treatment

Counseling Patients on Cancer Diets: A Review of the Literature and Recommendations for Clinical Practice

JUTTA HUEBNER[1] ⇑, SABINE MARIENFELD[2], CLARE ABBENHARDT[3], CORNELIA ULRICH[3], KARSTEN MUENSTEDT[4], OLIVER MICKE[5], RALPH MUECKE[6] and CHRISTIAN LOESER[7]

Discussion

In summary, we did not identify clinical evidence on level 1 or 2 for any of the described diets. One randomized study, including a vegan diet, has been published (40). Due to the complexity of the intervention (including supplements and major lifestyle changes) no conclusion on the effects of the mentioned diets is possible to date.

Table II. *Overview on cancer diets.*

Diet	Term	Number of articles found in Medline	Number of articles found after restriction	Number of articles on clinical to cancer and [a]	Features of the diet trials	Concept of the diet	Clinical data published	Benefits for cancer patients	Risks for cancer patients
Alkaline diet	Alkaline diet	2,993	13	0	Diet with vegetables and low-sugar fruits, avoidance of sugar, grains, dairy and meat	Acidosis is the reason for diseases such as cancer	None	-	-
Bircher-Benner diet	Bircher-Benner diet	0	0	0	Diet with fruit, vegetables and nuts; spartan physical discipline; gardening work	Sun as source of all energy; This energy is provided by nutrients and work in sunlight	None	No benefit proven for cancer patients, as vegetarian diet possibly beneficial	-
Breuss cure	Breuss diet OR Breuss cure	1	0	0	Living on vegetable tea juice and only for at least 42 days (38)	Aim is to starve the tumor	None	-	Malnutrition and weight loss; patients are advised to refute any conventional therapy during the Breuss cure
Budwig diet	Budwig diet OR protein-oil diet	3	0	0	Omega-3-fatty acids and proteins with high content of sulphur from curd cheese and linseed oil (39)	Cancer arises from an abundance of trans-fatty acids and a deficit in omega-3 and -6 fatty acids	None	As additional serving Budwig's curd cheese consisting of curd cheese and linseed oil offers additional caloric intake to patients loosing weight	Following the strict diet: deficiency in vitamins and other micronutrients
Fasting	Fasting	3803	14	0	Abstenence from nutrients for a period of time	Cancer can be starved	None	-	Malnutrition and weight loss
Gerson regimen	Gerson diet OR Gerson regimen OR coffee enema	91	24	0	To increase potassium, patients should consume juice of at least 10 kg of fruits and vegetable per day. Fat should be avoided. Proteins from animals are only allowed n small quantities. Three	Cancer arises from a misbalance between potassium and sodium	Hildenbrandt (16) Lechner and Kronberger (17) Molassiotis and Peat (18) (see text)	-	Case reports: Death or sepsis and coma from hyponatremia as well as hyperkalemia (11, 12)

Table II. *Continued*

Diet	Term	Number of articles found in Medline	Number of articles found after restriction	Number of articles on clinical to cancer and [a]	Features of the diet trials	Concept of the diet	Clinical data published	Benefits for cancer patients	Risks for cancer patients
Kelley/ Gonzalez Regimen	Gonzalez regimen OR Kelley regimen OR pancreatic enzymes	0	322	2	Combination of freeze-dried pancreatic enzymes, vitamins, minerals coffee enemas	Cancer is caused by toxins from the environment	Gonzalez (21) Chabot (22)	-	Meteorism flu-like symptoms low-grade fever muscle aches skin rashes misbalance of electrolytes
Ketogenic Diet	"Diet, Carbo-hydrate-Restricted" [MeSH] OR "Ketogenic Diet"[MeSH]	419	13	0	No refined carbohydrates, reduction of carbohydrates, caloric intake mainly by fat (omega-3 and 6 fatty acids) and proteins; aim: rising ketone level	Diet is based on the Warburg effect which describes that cancer cells gain energy preferably by anaerobe glycolysis; reducing carbohydrates shall stop growth of cancer cells	Schmidt (23) Chu-Shore (24) Nebeling (25)	-	Deficiency in micronutrients loss of appetite nausea constipation loss of weight hypoglycemia hyperlipidemia dehydration metabolic acidosis fatigue sedation (27)
Livingston-Wheeler Regimen	"Livingston-Wheeler regimen" OR "Livingston regimen" OR "Progenitor Cryptocides"	0	0	0	Autogenous vaccine from bacteria derived from body fluids gamma globulin, BCG antibiotics diet with low sodium fruits and vegetables	Cancer is caused by a bacterium (*Progenitor cryptocides*) which Ms Livingston thought to have discovered in patients.	None	-	Injections may lead to immunological reactions
Macro-biotic diet	Macrobiotic diet [MeSH]	46	9	0	Cereals are the most important part of nutrition; modern versions of the macrobiotic diet comprise of 50 to 60% cereals and 20 to 30% vegetables, small amounts of fish and eggs; meat, milk products, sugar, potatoes and tomatoes are discouraged (33).	Cancer arises from a misbalance between yin and yang	Carter (34) US Congress (35) Sherlock (36) Bowman (37) Lindner (38) Dwyer (39)	-	Under strict diet several deaths have been reported; loss of weight deficiencies in proteins, vitamin B12, C, D, zinc, calcium and iron; anemia and scorbat (35, 36, 37, 38)
Moermann diet	Moermann diet	0	0	0	Lactovegetarian diet; vitamins A, B, C,D, E, iodine, sulfur, iron, selenium;citric acid no meat, fish, white flour,	Chronic deficiency of eight essential substances leads to metabolic	None	-	Misbalance of micronutrients

Table II. *Continued*

Table II. *Continued*

Diet	Term	Number of articles found in Medline	Number of articles found after restriction	Number of articles on clinical to cancer and [a]	Features of the diet trials	Concept of the diet	Clinical data published	Benefits for cancer patients	Risks for cancer patients
					Animal fats, beans, peas, lentils, mushrooms, potatoes, sugar, salt, margerine and other hydrogenated oils, coffee, caffeine, egg whites, alcohol, tobacco	Disturbances and alkalosis; microorganisms (symbionts) transform healthy cells into cancer cells; diet will rob the symbionts of their growth medium			
Raw food	Raw food	10,883	45	0[b]	Consumption of uncooked (mostly also unprocessed) food	Cooked food leads to diseases as cancer	None	Avoidance of preservation of food by salting or toxins created by cooking (*e.g.* hetero-cyclic amins)	Less tolerance of raw food in case of mucositis during cancer therapy or in patients with stoma; higher risk of (gastrointestinal) infections[c]
Vegan diet	Vegan diet	650	124	1[d]	Complete avoidance of animal products	Strict vegetarian diet, often ethical considerations	Ornish (42)	High delivery of dietary fibre, vitamin C, vitamin E, folic acid, magnesium; low amount of saturated fat	Weight loss deficiency in vitamin B12, D, calcium, zinc

[a]filter: AND "neoplasm [MeSH]" Filter:Humans, Clinical Trial, Review, Case Reports, Comparative Study; [b]Several clinical studies on primary cancer prevention were excluded; [c]In patients with stable immune system, risk of infection is low if meals are selected and prepared carefully; [d]Several publications on primary prevention or only reporting laboratory data (*e.g.* level of phytoestrogenes or carotenoids) without clinical data were excluded.

Table IV. *Recommendations for counseling patients on cancer diets.*

1	All cancer patients should be offered advice on healthy nutrition and cancer diets. If needed, specialists should help the patient to ensure sufficient intake of macro- and micronutrients. (Adaptation from the ethical discussion of Gilmour et al. (42)).
2	Counseling on cancer diets should be available at a low threshold. That means, it should be part of the communication between oncologist and patient or the oncologist should transfer the patient to a specialist who is working in close contact with the tumor center.
3	Qualification: Caregivers giving advice on cancer diets should have knowledge on and experience in nutrition and oncology. Furthermore, they should know details of cancer diets and the strategies with which they are propagated. They must be trained in communication skills. These qualifications should be acquired and regularly updated.
4	Before starting a consultation, the consultant should know about the patient's disease and former and planned therapy. A history of nutrition before disease became apparent should be taken. The patient's (and family's) attitude towards eating is also important.
5	Eating is a social process. Family members often feel responsible for preparing meals and ensuring nutrition. Therefore, members of the family and close friends should be welcomed to the consultation.
6	The individual's history of weight and nutrition since cancer diagnosis should be considered. Furthermore, it is crucial to understand patient's actual attitude, his needs and his objections concering the process of eating. Eating has highly emotional aspects and the consultant should try to understand the point of view of the patient. Attitudes of family members and friends are also of interest. It is important to know patient's beliefs concerning diets and their influence on cancer. If they are interested in or adhere to a cancer diet, their expectations and his experiences should be asked for.
7	Lack of knowledge or misconceptions should be pointed out and the scientific evidence explained. If the patient has a misunderstanding of the situation of their disease, it may be helpful to explain this first and then advance to talking about nutrition and diets. If it is not the oncologist, who is doing the consultation, it may be useful to refer the patient to them, if misconceptions on the disease persist. Communication with respect means that individual beliefs of the patient should be acknowledged but divergent concepts between the patient's point of view and the medical point of view should be named.
8	A list of items and questions to discuss should be agreed. All cancer diets the patient wants to discuss should be described from a scientific point of view but using lay vocabulary. Besides pointing out lack of evidence, fallacies in the underlying cancer theories must be addressed and adverse effects such as malnutrition must be discussed. In order not to leave the patient discouraged, an individual concept of healthy nutrition should be provided.
9	Counseling should be adapted to the patient's needs and resources. It may be helpful to refer to cultural specifics.
10	Counseling on cancer diets should always has to be done in the context of the cancer treatment and should consider treatment aims and aspects of psycho-oncology and palliative care if appropriate.
11	If a more complex problem with eating (*e.g.* loss of weight, malnutrition) exists, the patient must be offered further support.
12	In any consultation it should be regarded whether the patient and/or his family need psychological support. In this case the patient/family should be referred to a psycho-oncologist.
13	The most important points discussed should be put down in a letter to the patient. If appropriate a list of recommendations on nutrition should be included. This letter must be written in a language which lay persons can understand.
14	Follow-up of the patient should be offered.
15	If the patient adheres to a cancer diet despite counseling against it, follow-up is of great importance in order to detect adverse events early and to be able to discuss the diet again. Besides measuring weight, malnutrition can be detected by taking blood levels of micronutrients, or measuring muscle mass or albumin in order to assess protein deficiency. If deficits become obvious, the patient should be informed of the consequences and strongly advised against continuing the diet. In the case of their further adhering to the diet prescription of supplements must be discussed even if they are no adequate substitute.

Counseling patients on cancer diets: a review of the literature and recommendations for clinical practice. Anticancer Res. 2014 Jan;34(1):39-
Huebner J[1], Marienfeld S, Abbenhardt C, Ulrich C, Muenstedt K, Micke O, Muecke R, Loeser C.

We listed 13 cancer diets simulating an internet search for which we systematically reviewed clinical data. In the next step we derived recommendations on counseling patients using a Delphi process.

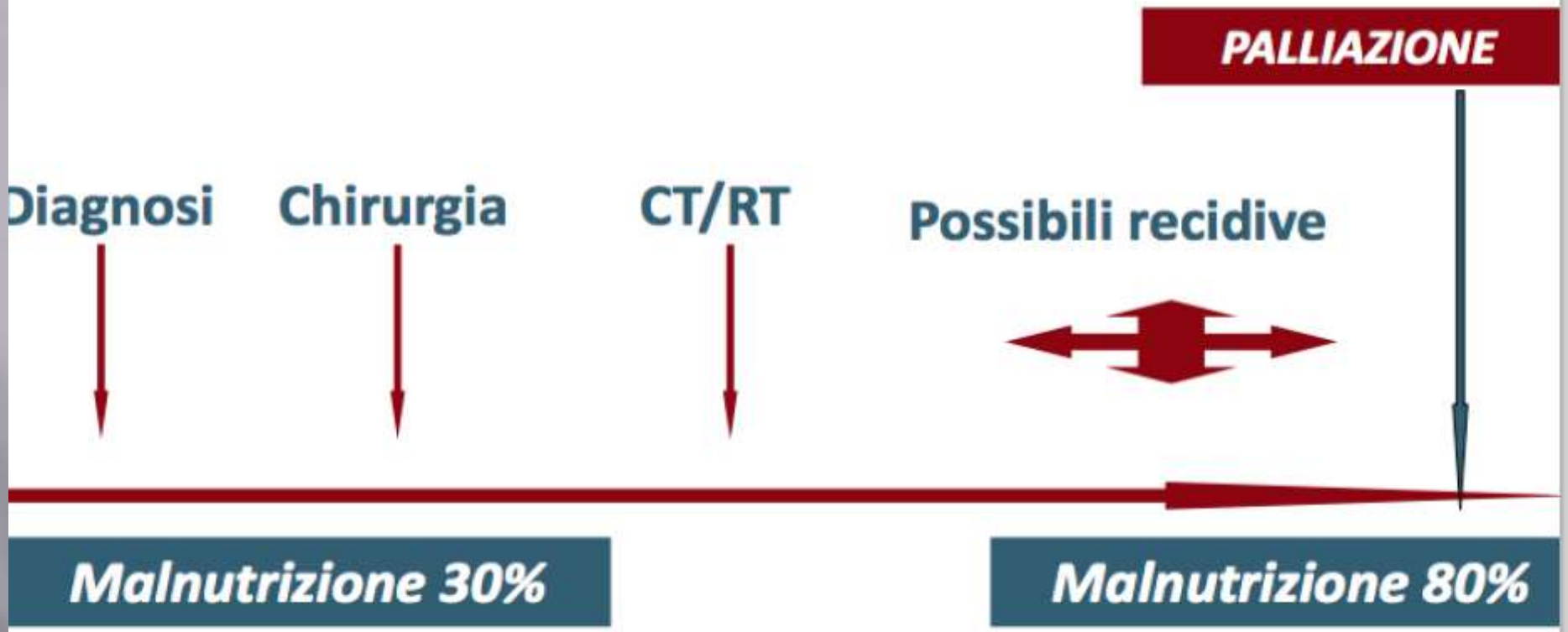
RESULTS:

We evaluated the following diets: raw vegetables and fruits, alkaline diet, macrobiotics, Gerson's regime, Budwig's and low carbohydrate or ketogenic diet. We did not find clinical evidence supporting any of the diets. Furthermore, case reports and pre-clinical data point to the potential harm of some of these diets. From published recommendations on counseling on complementary and alternative medicine, we were able to derive 14 recommendations for counseling on cancer diets.

CONCLUSION:

Considering the lack of evidence of benefits from cancer diets and potential harm by malnutrition, oncologists should engage more in counseling cancer patients on such diets. Our recommendations could be helpful in this process.

Iter terapeutico nel paziente oncologico e prevalenza di malnutrizione*



Malnutrizione: depauperamento delle riserve energetiche, proteiche e di altri nutrienti, tale da determinare alterazioni della composizione corporea, o delle funz biologiche, aumentando il rischio di morbidità e mortalità

Stratton et al 2003 – Kaikani W, Bachmann P. Bull Cancer 2009

Eziopatogenesi della malnutrizione nel paziente oncologico

Malnutrizione

Ridotta assunzione di alimenti

- stenosi gastroenterico
- disfagia/afagia
- anoressia

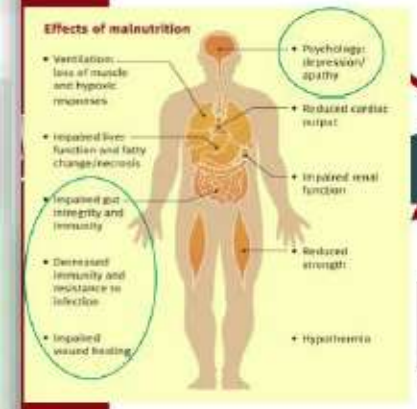
Malassorbimento

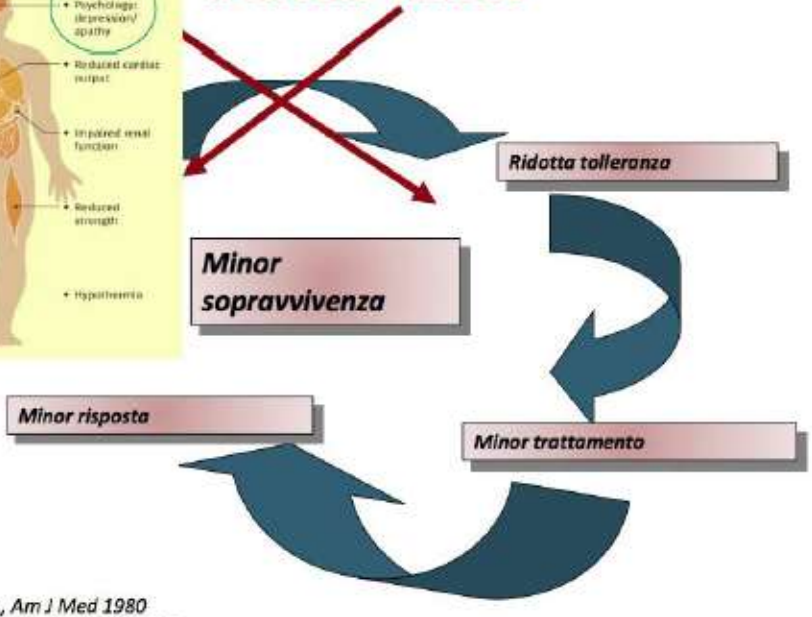
- effetti collaterali CT/RT
- esiti chirurgia
- esiti radioterapia

Alterato Metabolismo

- Aumento citokine proinfiammatorie
- metab.energetico
- metab.glucidico
- metab.lipidico
- metab.proteico

Malnutrizione e sopravvivenza: il circolo vizioso





Dewys et al., Am J Med 1980
Klein S et al, Am J Clin Nutr 1997
Barret M et al, Oncology 2012

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Diagnostic Criteria for the Classification of Cancer-Associated Weight Loss

Lisa Martin, Pierre Senesse, Ioannis Gioulbasanis, Sami Antoun, Federico Bozzetti, Chris Deans, Florian Strasser, Lene Thoresen, R. Thomas Jagoe, Martin Chasen, Kent Lundholm, Ingvar Bosaeus, Kenneth H. Fearon, and Vickie E. Baracos

8160 Pazienti in Canada ed Europa Registrati con peso, calo ponderale e BMI e seguiti nel tempo.
BMI e calo ponderale sono fattori predittivi indipendenti della sopravvivenza

Raccomandazioni pratiche AIOM-SINPE per il supporto nutrizionale nel paziente oncologico

- Lo screening nutrizionale deve essere eseguito con strumenti validati a partire dalla diagnosi e ripetuto sistematicamente ad intervalli regolari nei pazienti affetti da neoplasie, che, per tipologia, stadio o trattamento, possono influenzare negativamente lo stato di nutrizione.

- I pazienti a rischio nutrizionale devono essere prontamente inviati per una valutazione completa e la prescrizione del supporto nutrizionale ai servizi di nutrizione clinica o a personale medico con documentate competenze di nutrizione clinica in ambito oncologico.

- Il supporto nutrizionale deve essere gestito tempestivamente e in modo mirato per ogni paziente, in base alle condizioni nutrizionali, allo stato clinico, ai trattamenti previsti e ai risultati attesi. Esso deve comprendere il counseling nutrizionale personalizzato e la nutrizione artificiale (enterale, parenterale, con supplementi orali), in base all'assunzione spontanea e tollerata degli alimenti e alla sua efficacia.

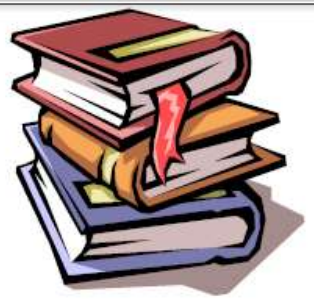
- Il supporto nutrizionale e le modifiche dietetiche devono mirare al mantenimento o al recupero dello stato nutrizionale, favorendo l'incremento degli introiti proteici e calorici o preservandoli. Diete "alternative" ipocaloriche per la cura del cancro (es. macrobiotiche o vegane) non sono raccomandate poiché potenzialmente dannose.

- Il supporto nutrizionale può essere integrato nei programmi di cure palliative, in base a valutazioni individuali caso per caso, alle implicazioni sulla qualità di vita, alle aspettative di sopravvivenza ed alla volontà consapevole dei pazienti.

- La nutrizione artificiale domiciliare deve essere prescritta e regolarmente monitorata utilizzando protocolli definiti e condivisi tra oncologi e nutrizionisti clinici.

- I parametri di valutazione dello stato nutrizionale devono essere considerati come obiettivi rilevanti o potenziali fattori di confondimento nell'interpretazione dei risultati della ricerca clinica oncologica.

- Studi clinici d'intervento adeguatamente disegnati sono necessari per migliorare le evidenze a favore del supporto nutrizionale nei differenti ambiti di cura per i pazienti oncologici.



The effects of short-term fasting on tolerance to (neo) adjuvant chemotherapy in HER2-negative breast cancer patients: a randomized pilot study

de Groot *et al. BMC Cancer* (2015) 15:652
DOI 10.1186/s12885-015-1663-5

13 cases

Safety and feasibility of fasting in combination with platinum-based chemotherapy

Dorff *et al. BMC Cancer* (2016) 16:360
DOI 10.1186/s12885-016-2370-6

20 cases (breast, urothelial, ovarian, NSCLC

Fasting and Cancer Treatment in Humans: A Case series report

AGING, December 2009, Vol.1 No.12

10 cases (breast, prostate, ovarian, uterine, NSCLC, esophageal adenocarcinoma)

Table 1 List of ongoing clinical trials using ketogenic diets in cancer treatment

Condition	Intervention	Identifier
Pancreatic Neoplasms	Ketogenic diet with concurrent chemoradiation	NCT01419483
Head and Neck Neoplasms	Ketogenic diet with concurrent chemoradiation	NCT01975766
Carcinoma, NonSmall-Cell Lung	Ketogenic diet with concurrent chemoradiation	NCT01419587
Glioblastoma	Energy-restricted ketogenic Diet	NCT01535911
Breast Cancer	Ketogenic diet, low glycaemic and insulinaemic diet	NCT02092753
Glioblastoma Multiforme	Ketogenic diet	NCT01865162
Cancer	Ketogenic diet	NCT01716468
Recurrent Glioblastoma	Calorie-restricted ketogenic diet and transient fasting with concurrent radiation	NCT01754350
Glioblastoma	Ketogenic diet with concurrent chemoradiation	NCT02046187

Branco A.F. et Al; European Journal of Clinical Investigation Vol 46, 2016

I FATTORI DI RISCHIO : OMS

Cause delle malattie croniche

Fonte: Oms

FATTORE DI RISCHIO : SPECIFICA CONDIZIONE CHE RISULTA STATISTICAMENTE ASSOCIATA ALLO SVILUPPO DI UNA MALATTIA