Resistance to anticancer agents : a multifactorial problem

Charles Dumontet

- Cancer treatment options

  the cancer cell, the environment

- What is resistance to therapy ?

  clinical and preclinical definitions

- Why do treatments fail ?

- How can we improve the activity of cancer therapy ?

Cancer treatment options

A brief history of cancer therapy options

surgery +++

radiotherapy (Hodgkin's)

hormone therapy

cytotoxic agents

immunotherapy

Currently > 50% of cancer patients are treated with an exclusively local treatment

Only systemic therapy can cure disseminated or locally advanced disease

Curative ablation

Operable localized disease

Surgery and other localized therapies

early diagnosis +++

basal cell carcinoma, majority of breast, cervix, surveillance of colorectal polyps, …

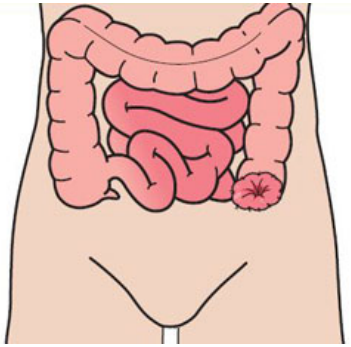
Operable disease with high risk of dissemination

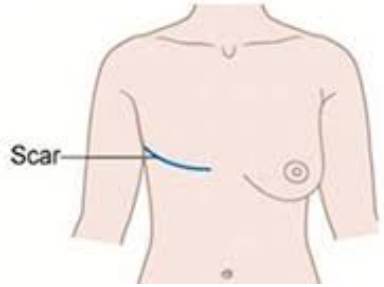
Adjuvant therapy: destroy residual tumor cells

Locally invasive colorectal cancer, breast cancer with involved lymph node, deep melanoma, …

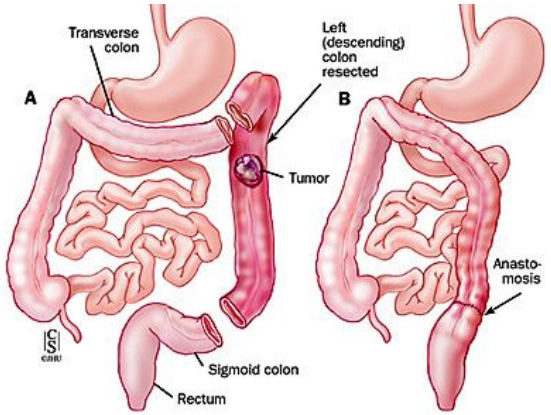
Surgery

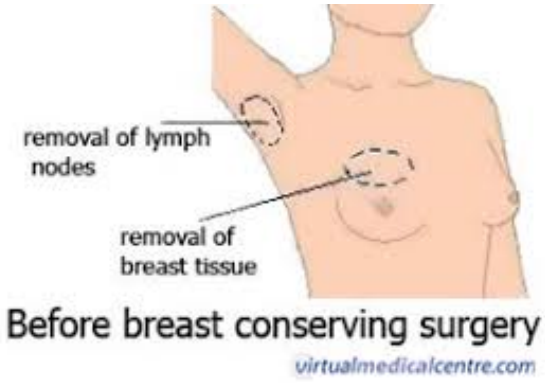
« radical »





« conservative »

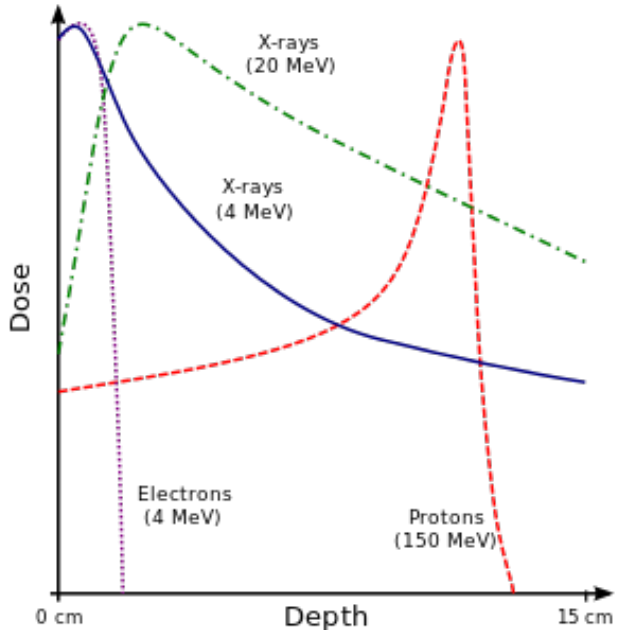




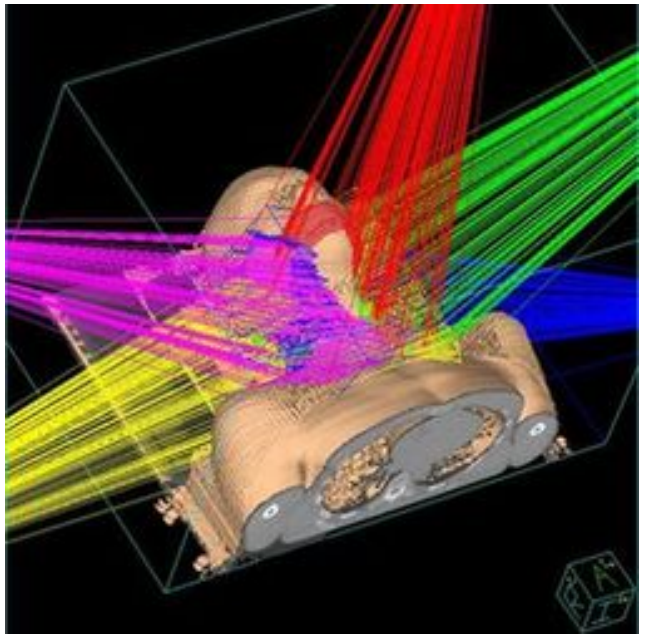
Radiotherapy

electrons, X rays, protontherapy + metabolic, brachytherapy

Penetration Depth



Conformational administration



Deliver maximal dose to tumor
minimal dose to healthy tissues

Other physical approaches

Thermodestruction or « thermoablation »

microwave, radiofrequency, US, thermocoagulation

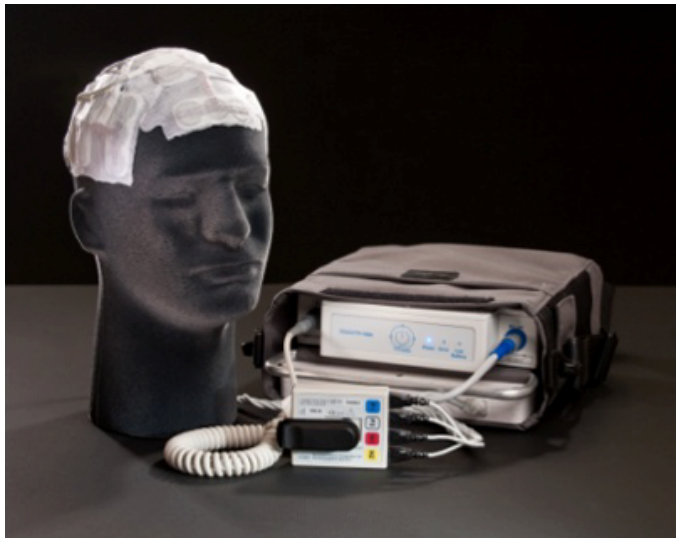
HIPEC = hyperthermic intraperitoneal chemotherapy

Cryotherapy or « cryoablation »

cervical cancer, skin cancer

Electrotherapy

glioblastoma



Local therapies ablate the tumor as a whole: tumor cells and the microenvironment, irrespectively of tumor cell properties and/or role of microenvironment

Unoperable disease

Locally advanced disease (unoperable)

physical treatment, « debulking », neoadjuvant

Majority of pancreatic, lung, ovary, glioblastoma, colorectal with local invasion, …

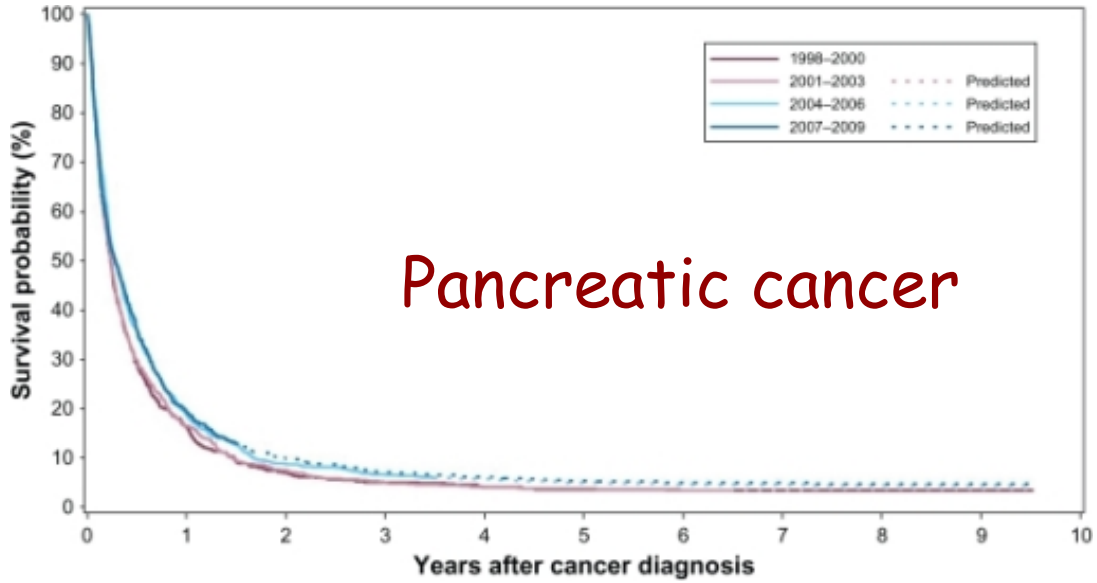
Disseminated disease

systemic therapies

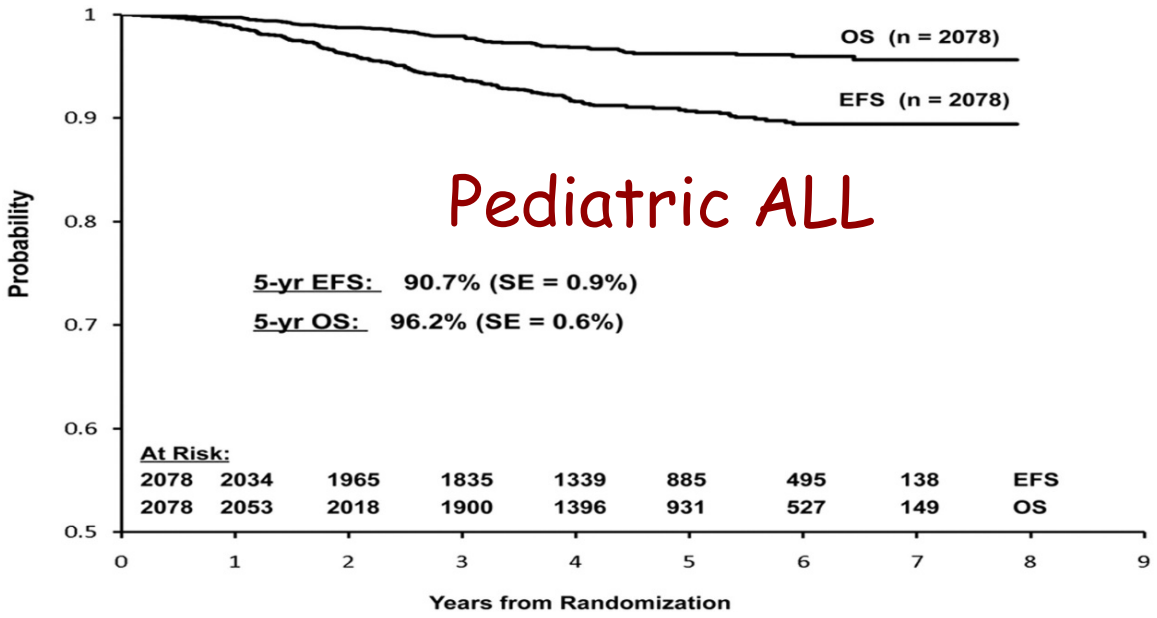
Metastases

Hematological malignancies

Very heterogeneous situations



Pancreatic cancer



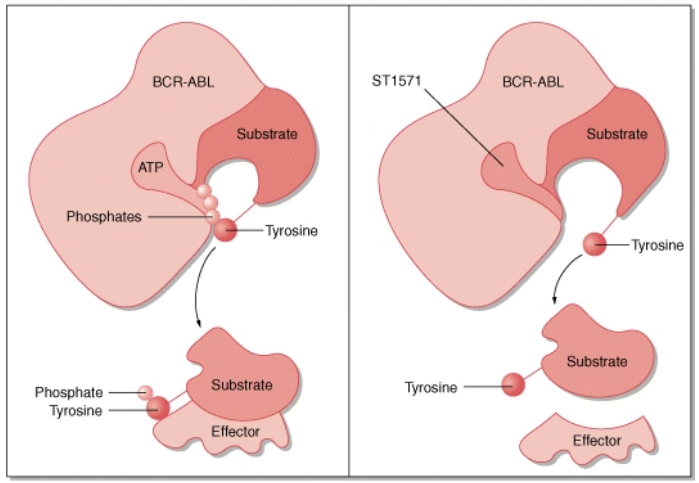
Pediatric ALL

Systemic therapies take into account specific characteristics of the tumor cell and/or the microenvironment

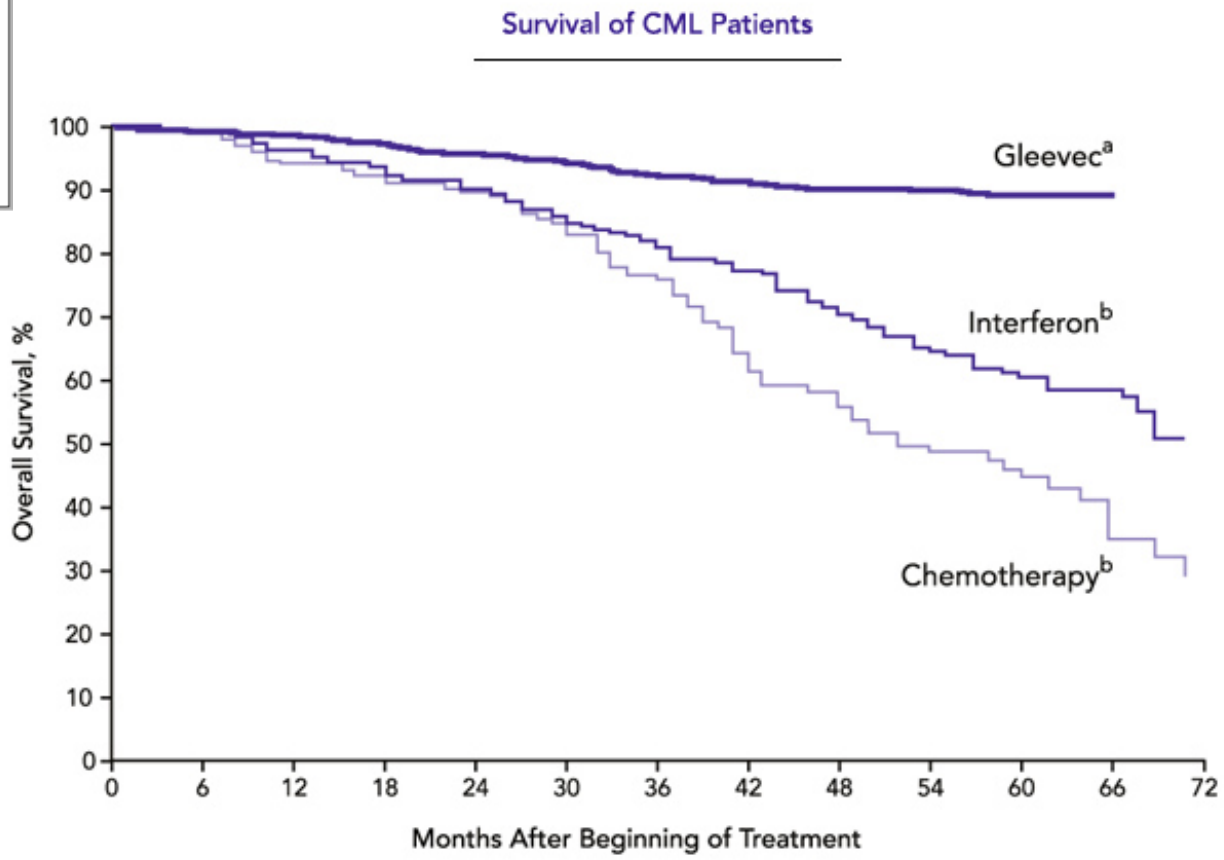
Cancer cells are characterized by:

- Uncontrolled proliferation — Cytotoxic agents
- Dependence on hormones — Hormone therapy
- Dedifferentiation — Differenciating agents
- Expression of a specific target
  membrane antigen
  molecular abnormality — Targeted therapies
- Inability to initiate or complete apoptosis — Apoptosis inducers

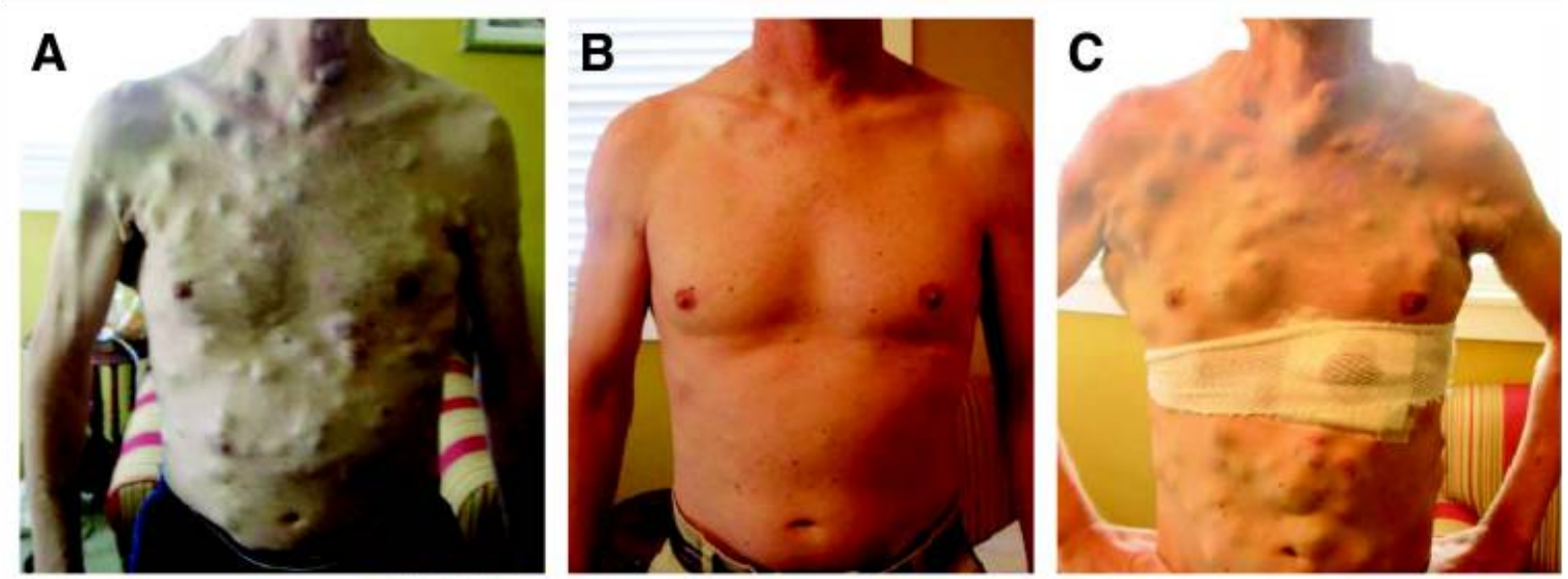
Targeted therapies: *kinase inhibitors*



2002 : approval of imatinib in chronic myelogenous leukemia (CML)

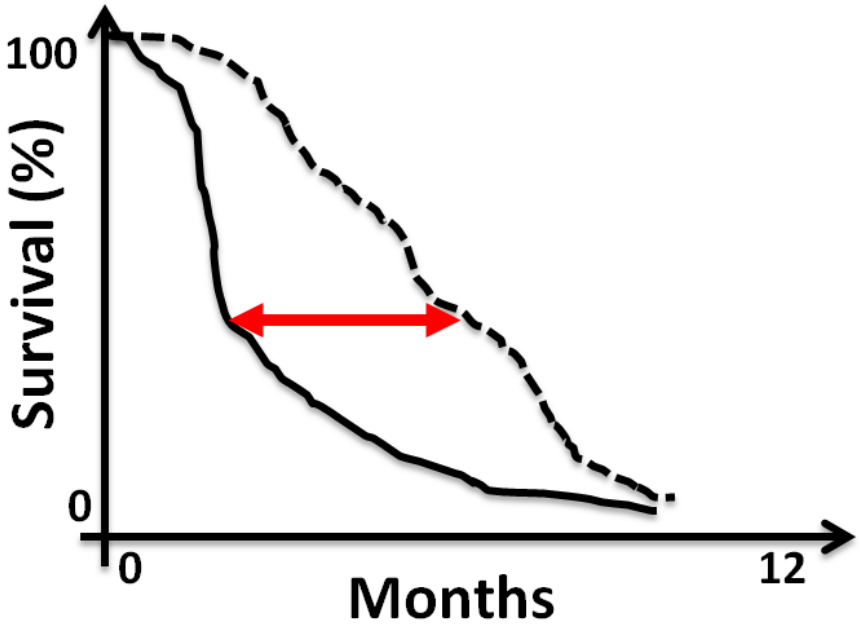


Vemurafenib and melanoma



Before BRAFi 15 weeks 23 weeks

Wagle N, et al. JCO. 2011 Aug 1;29(22):3085-96



Adapted from Chapman PB, et al. N Engl J Med. 2011 Jun 30;364(26):2507-16.

Targeted therapies:
tumor antigen specific immunotherapy

Therapeutic monoclonal antibodies targeting a tumor antigen (CD20 in lymphoma, Her2 in breast cancer)

T cell engagers: recruitment of a cytotoxic T lymphocyte to a CD19+ leukemic cell by a CD3xCD19 bispecific antibody

CAR-T cells: chimeric engineered T cells designed to amplify in the host, directed against tumor antigen

The tumor microenvironment:

- Provides nutrients through tumor vasculature

Anti angiogenic therapy

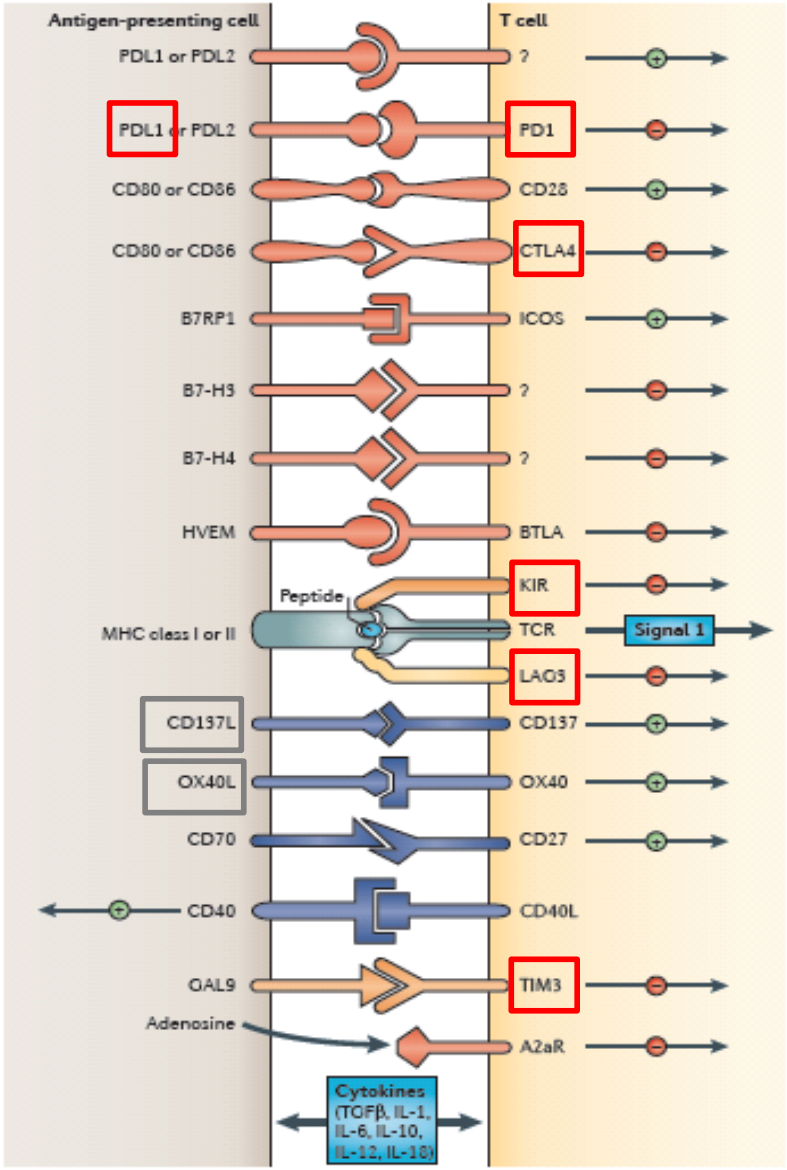
- Contains immune cells, including antitumor cells and immunosuppressive cells

Immune checkpoint inhibitors

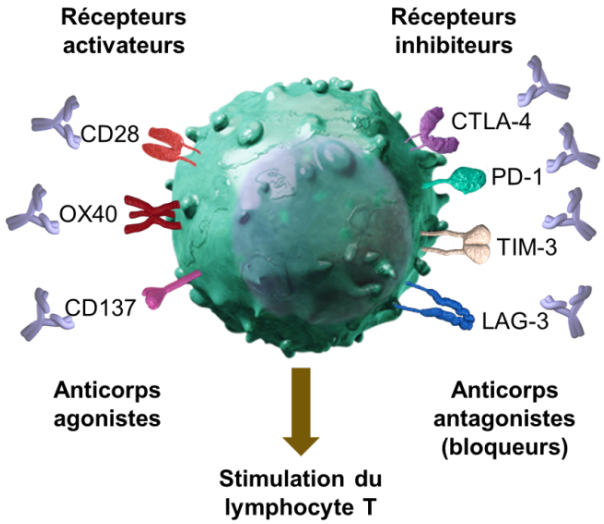
-Is perverted by the tumor cells to become protumorigenic:
Cancer Associated Fibroblasts (CAF)
Cancer Associated Adipocytes (CAA), …

Cell polarization therapies

The immune system is regulated by activators and inhibitors

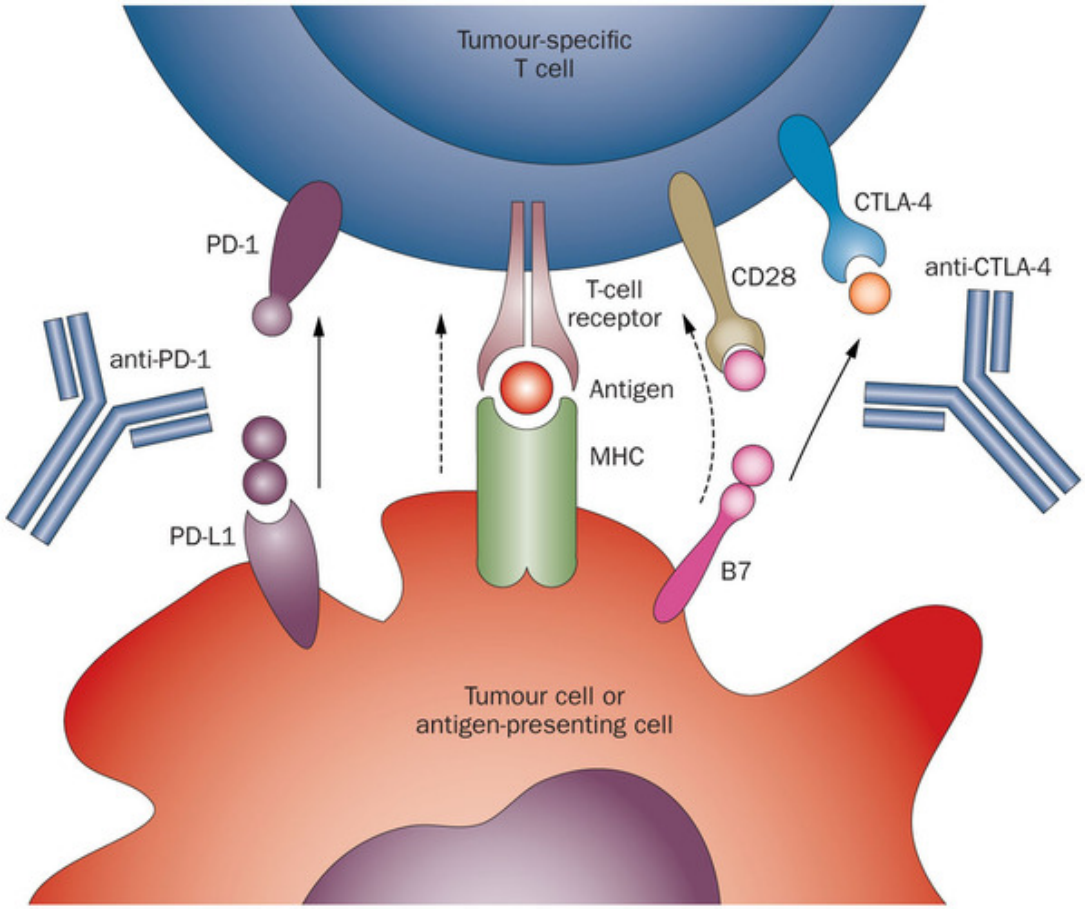


- Inhibitory signals = antagonist agents
- Co stimulatory signals = agonist agents



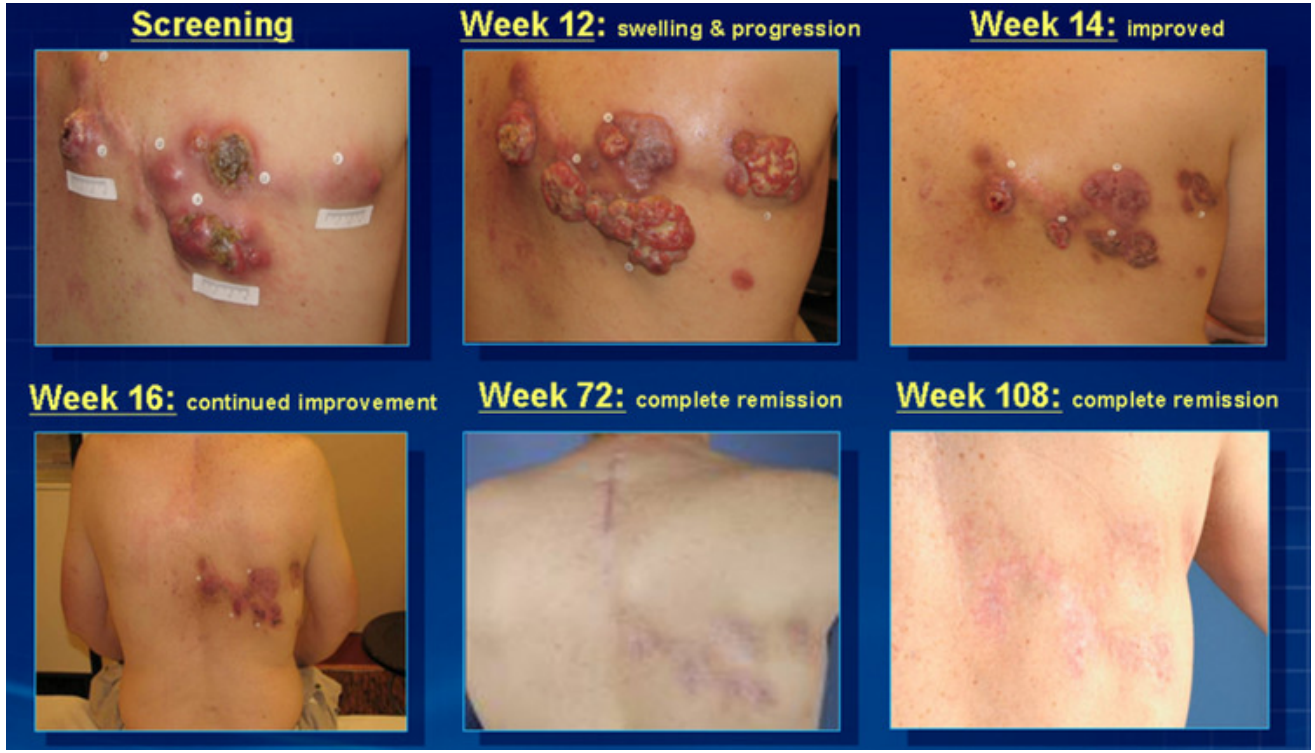
Pardoll, Nat Rev Cancer 2012

Immune checkpoint inhibitors

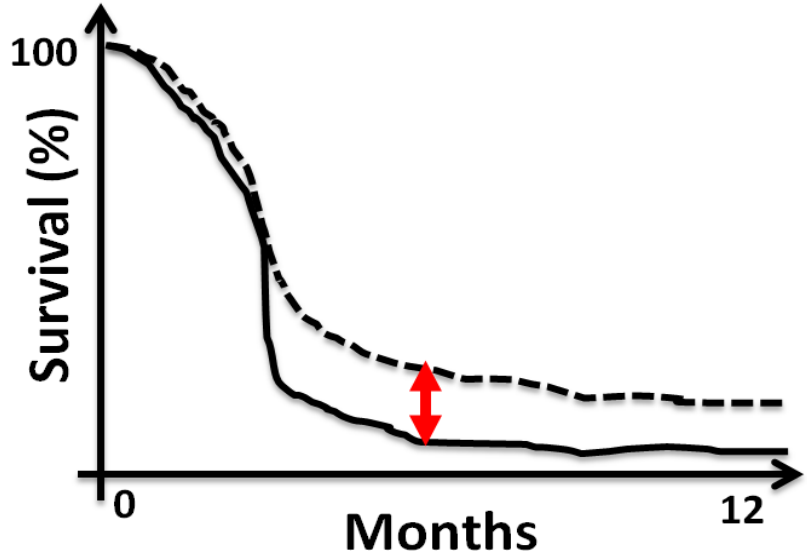


Mutliple indications
Prolonged effect

Ipilimumab and melanoma

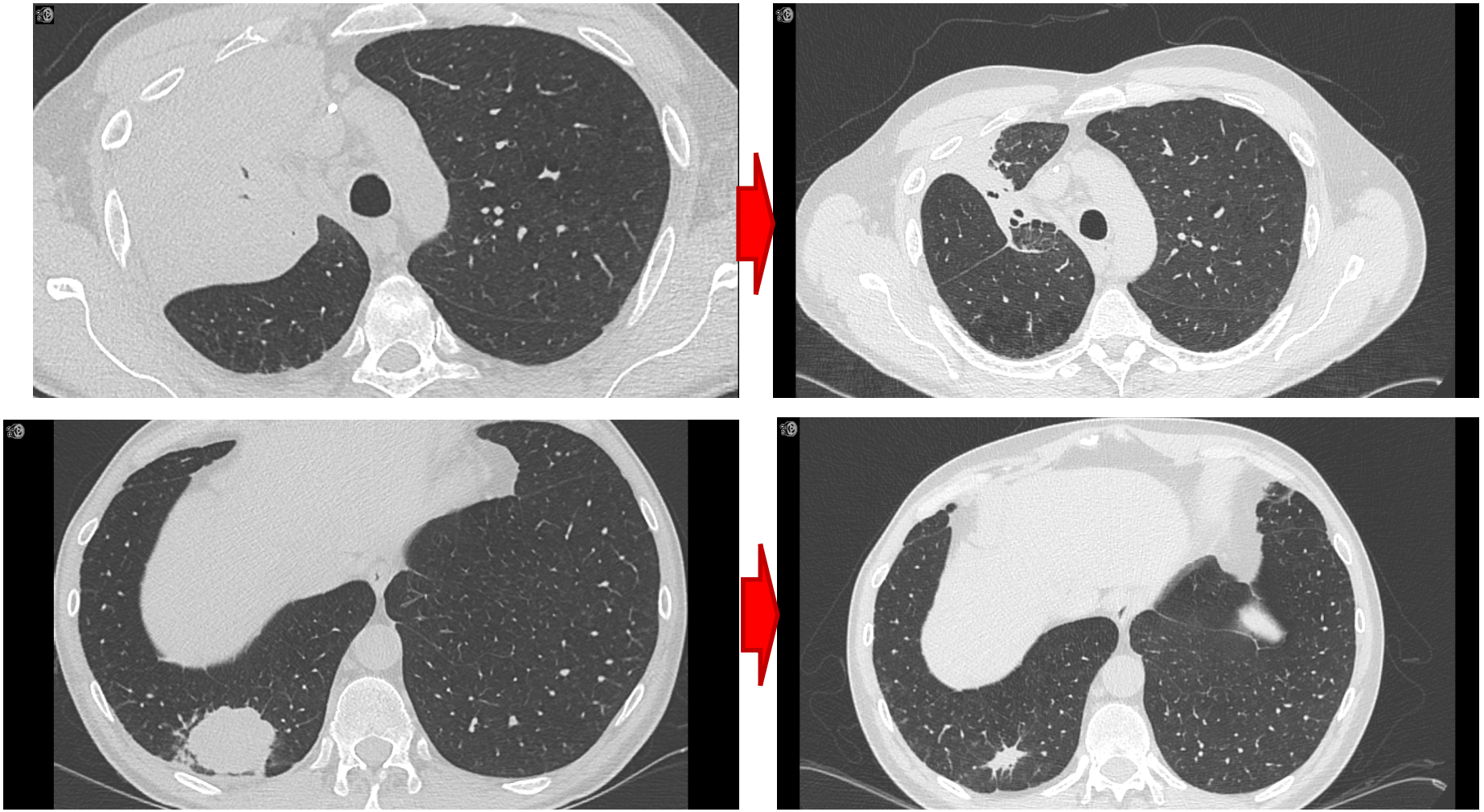


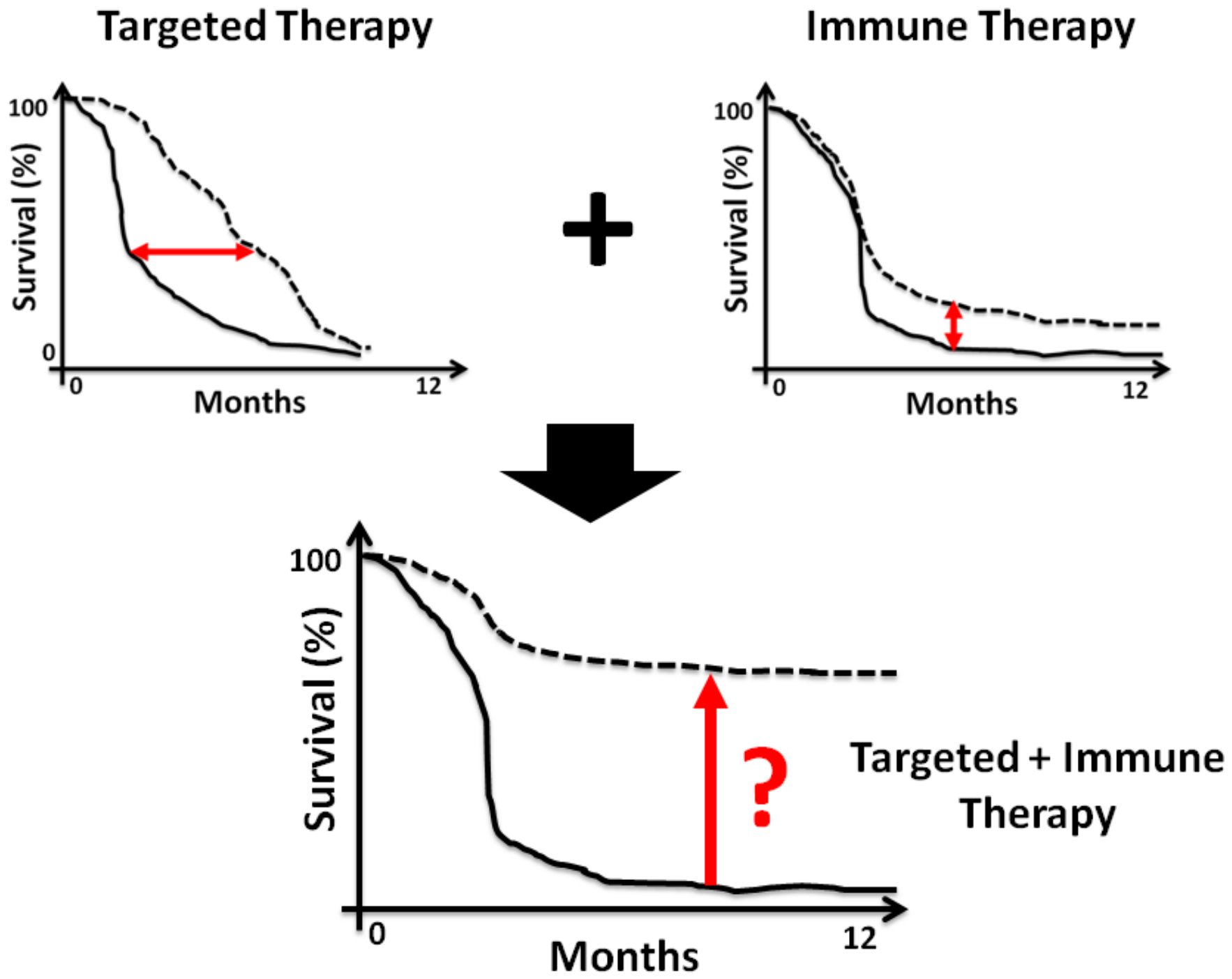
Hodi et al.
Abstract #3008
ASCO 2008



Adapted from Hodi FS, et al.
N Engl J Med. 2010
Aug 19;363(8):711-23.

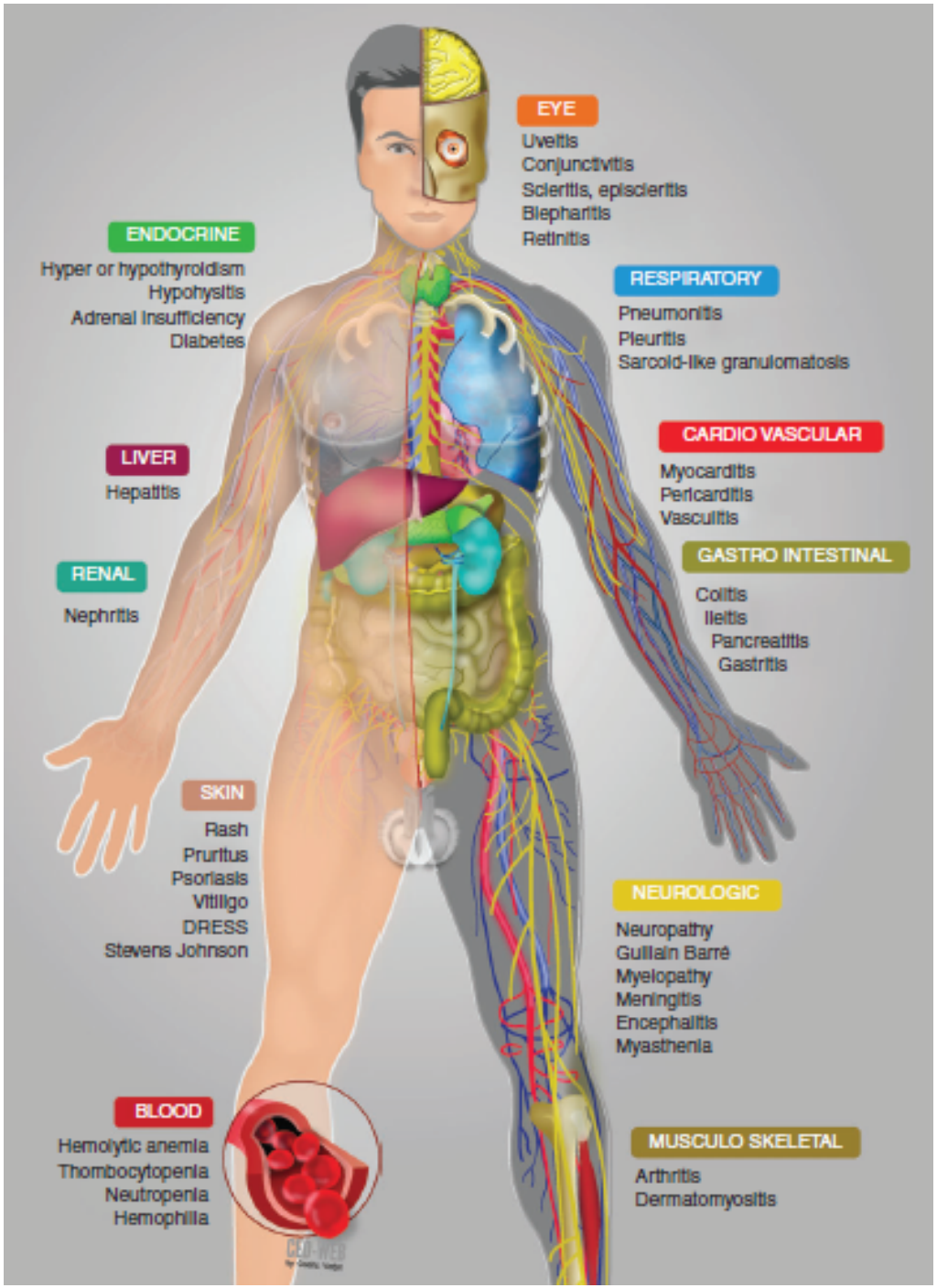
Lung tumor after 6 weeks of anti PDL1 therapy




Targeted Therapy
Immune Therapy
100
Survival (%)
0
0
Months
12
100
Survival (%)
0
Months
12
100
Survival (%)
?
Targeted + Immune Therapy
0
Months
12

Side effects

Autoimmune diseases

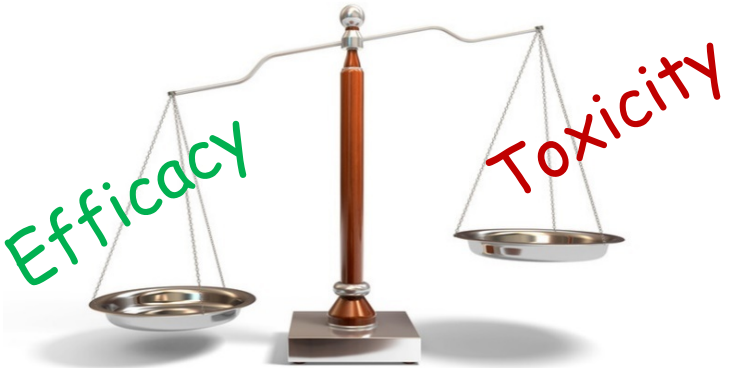


Champiat, Ann Oncol 2016

Therapeutic index

Most cytotoxic agents are more active at higher dose.

In the curative setting the aim is to use the highest « tolerable » dose, which is highly context-dependent

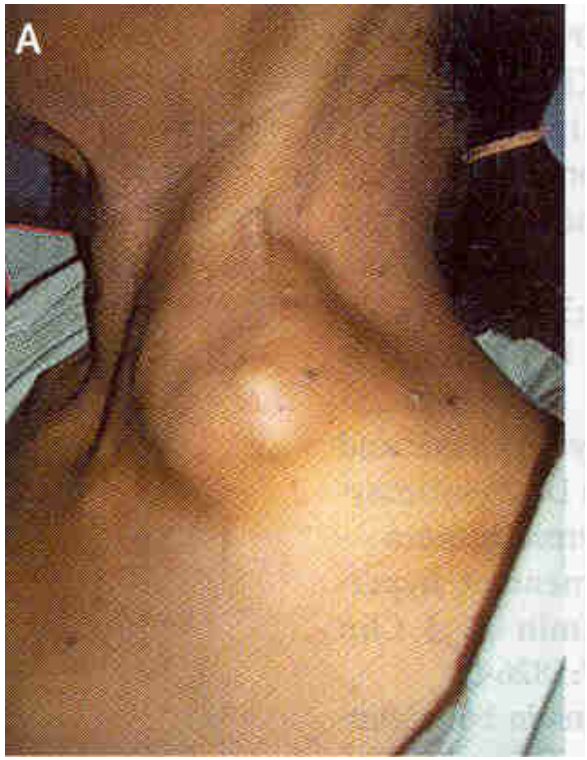


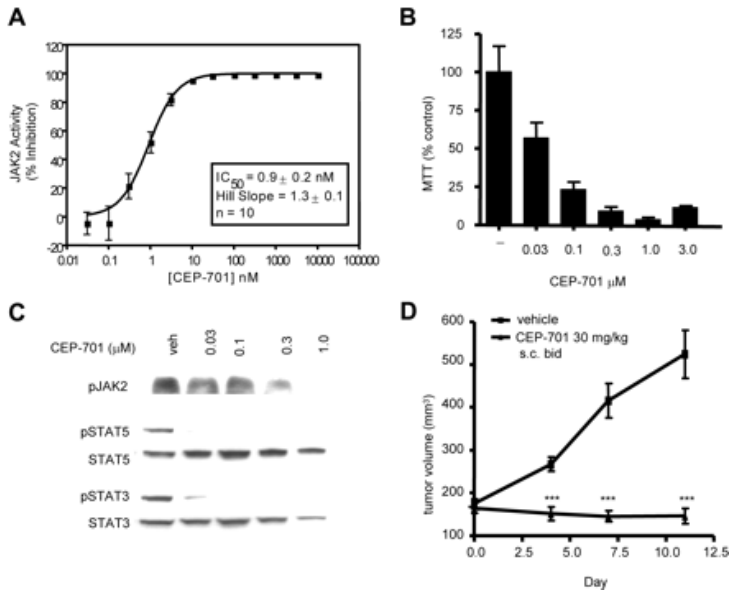
Targetted agents provide, to some degree, a better toxicity profile.

Aim is to combine agents with non-overlapping toxicities.

What is resistance to therapy ?

Clinical and Experimental Definition(s) of chemoresistance





Clinical definition of resistance

for solid tumors

Is defined by the lack of « clinical response »

- complete response (CR): no trace of disease

-Partial response (PR): > 50% reduction of all measurable tumor sites

- Progressive disease: increase of at least 25% of one site or new tumor site

- Stable disease (SD): no PR, no PD

Disease is considered ***sensitive*** when tumor mass decreases by at least 50%.

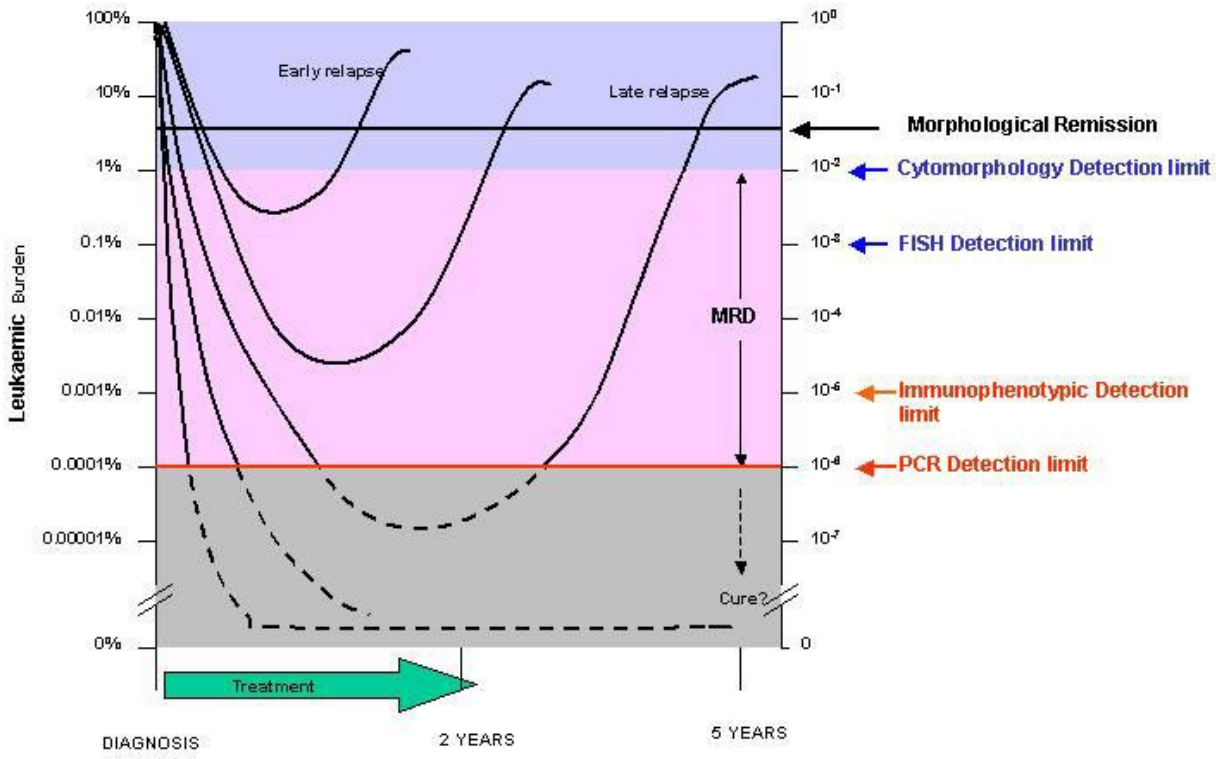
Includes a number of very different situations:

-"authentic" complete remission = cure

- Infraclinical disease: 10^6 to 10^9 cells

- Partial response: $10^{10...12}$ cells

Concept of Minimal Residual Disease (MRD)



Biological definition

In vitro, chemoresistance can only be ***relative***

A « resistant line » will be compared to, and often derived from, a « parental » sensitive line.

In vitro sensitivity can be determined by a variety of assays, which directly or indirectly cell proliferation in the presence or absence of cytotoxic agents.

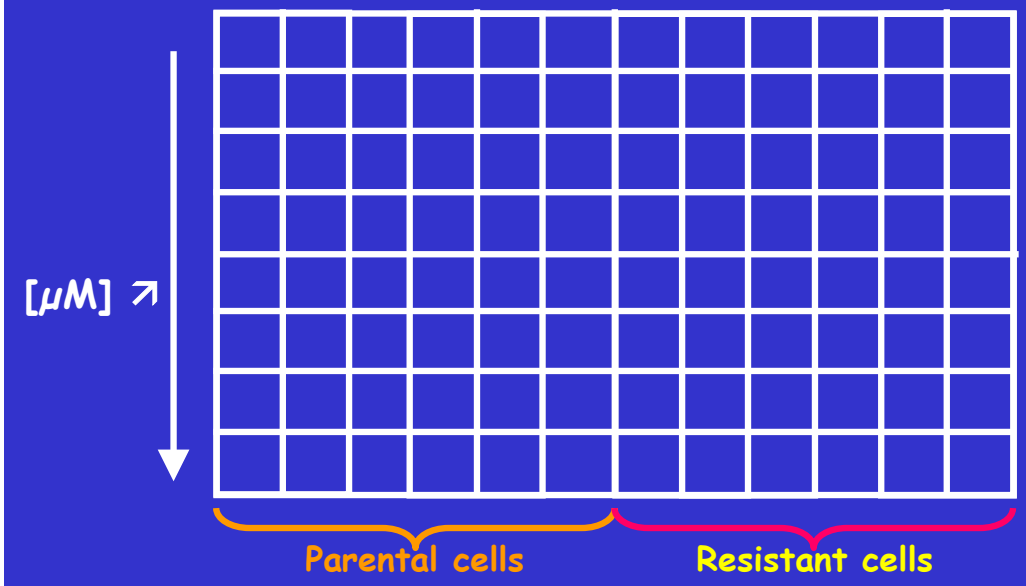
A « resistant » line can be obtained:

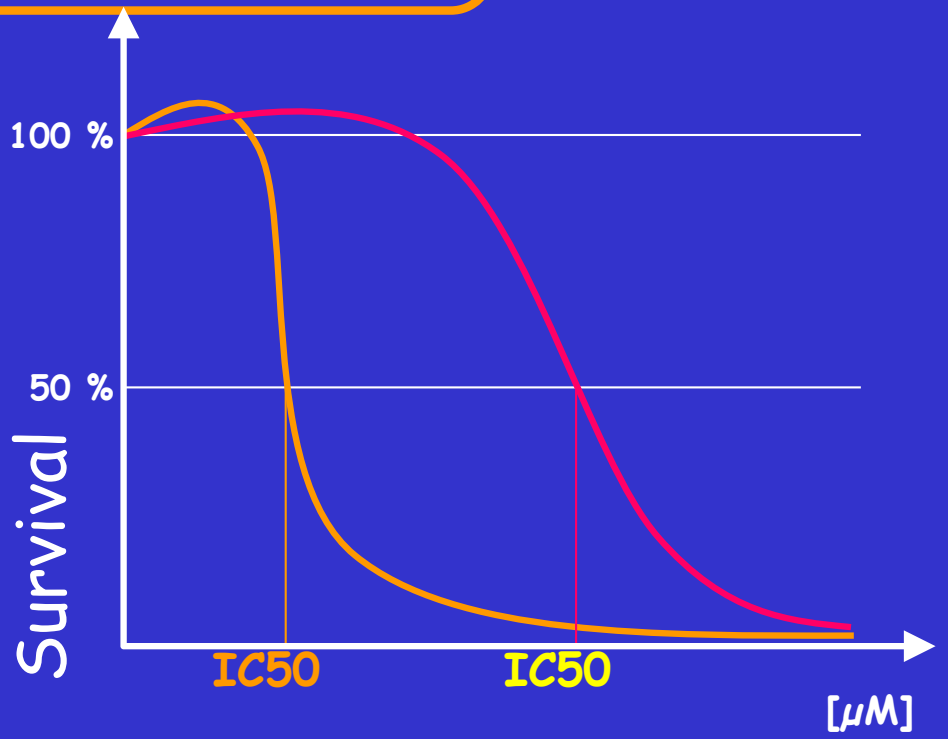
- by exposure to incrementally increased concentrations of a selecting agent, usually over a period of several months
- by a short and stringent exposure to a selecting agent
- by modification of a gene of interest (transfection, down regulation) reproducing a resistance mechanism

in vitro sensitivity to anticancer agents

MTT cytotoxicity assay

Determination of IC50 and resistance ratios





$$RR = \frac{IC50_{resistant}}{IC50_{parental}}$$

RR > 1 ➔ Resistance

RR = 1 ➔ No résistance

RR < 1 ➔ Sensitization

« resistant / parental » cell lines are very useful tools to identify resistance mechanisms or test new agents

However the resistance phenotype may only be valid under *in vitro* conditions. Results obtained in this model cannot be automatically transposed in vivo or to the clinic.

Limits of *in vitro* models

- clinical relevance is uncertain
- difficulty to transpose *in vitro* results to the clinic
- instability of models
- multiplicity of resistance mechanisms

Why do treatments fail ?

Patients are different

They will respond positively (tumor response) or negatively (toxicity) differently according to their genetic make-up and living habits

Tumors are different

Each tumor is different. In spite of recurrent abnormalities the number of potential diagnostic entities is huge.

Tumors are heterogeneous and unstable

Allowing massive opportunities for emergence of resistance disease

Resistance is a frequent and dynamic event

Intrinsic chemoresistance

Some tumors are refractory to therapy from the onset

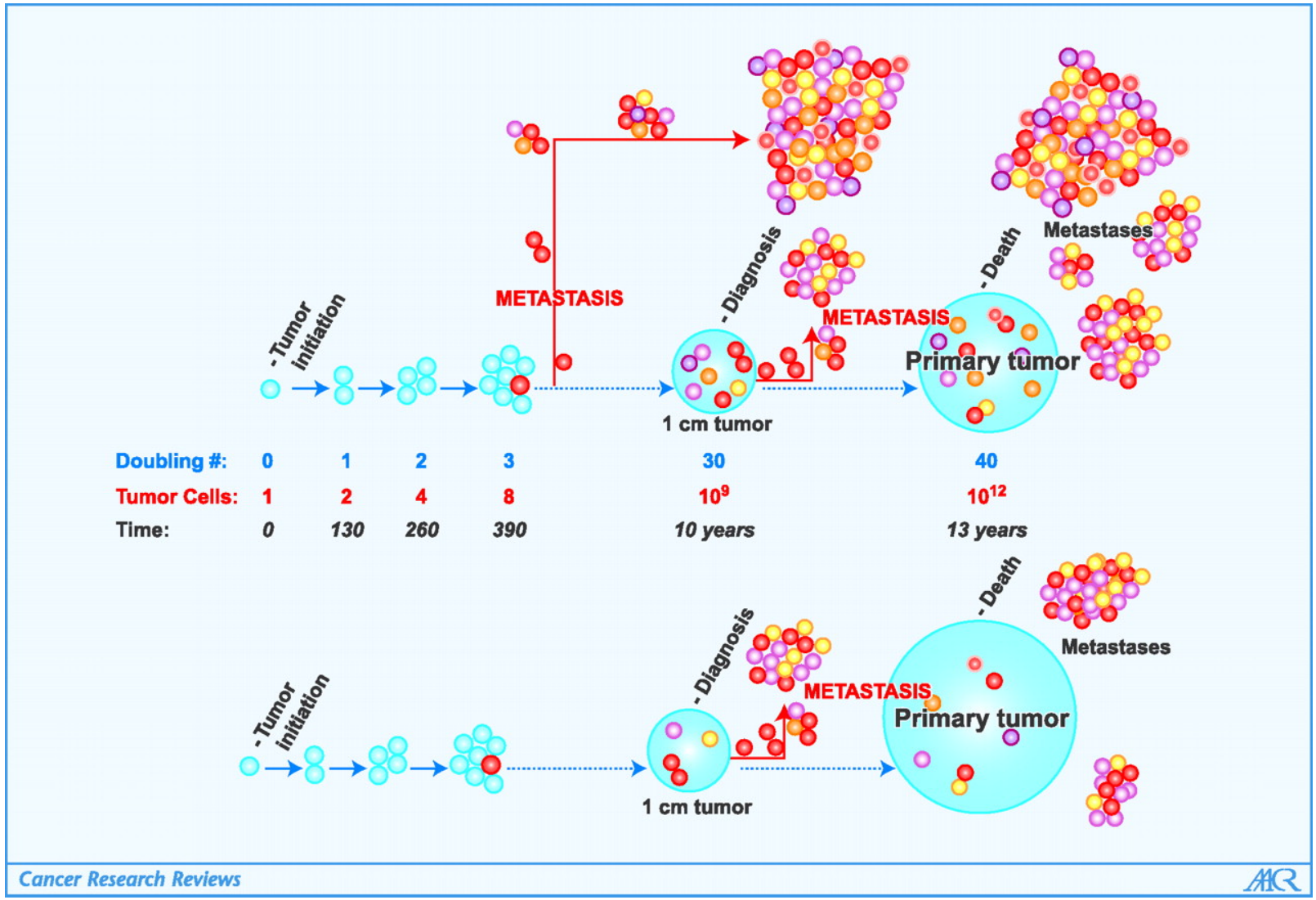
example : low reponse rates in pancreatic cancer

Acquired chemoresistance

Some cancer cells develop resistance

Example: acute myeloid leukemia patients are in remission in > 80% of cases, but only 30% will be cured of their disease

Clonal heterogeneity



Resistance must now take into account the environment

Immune environment

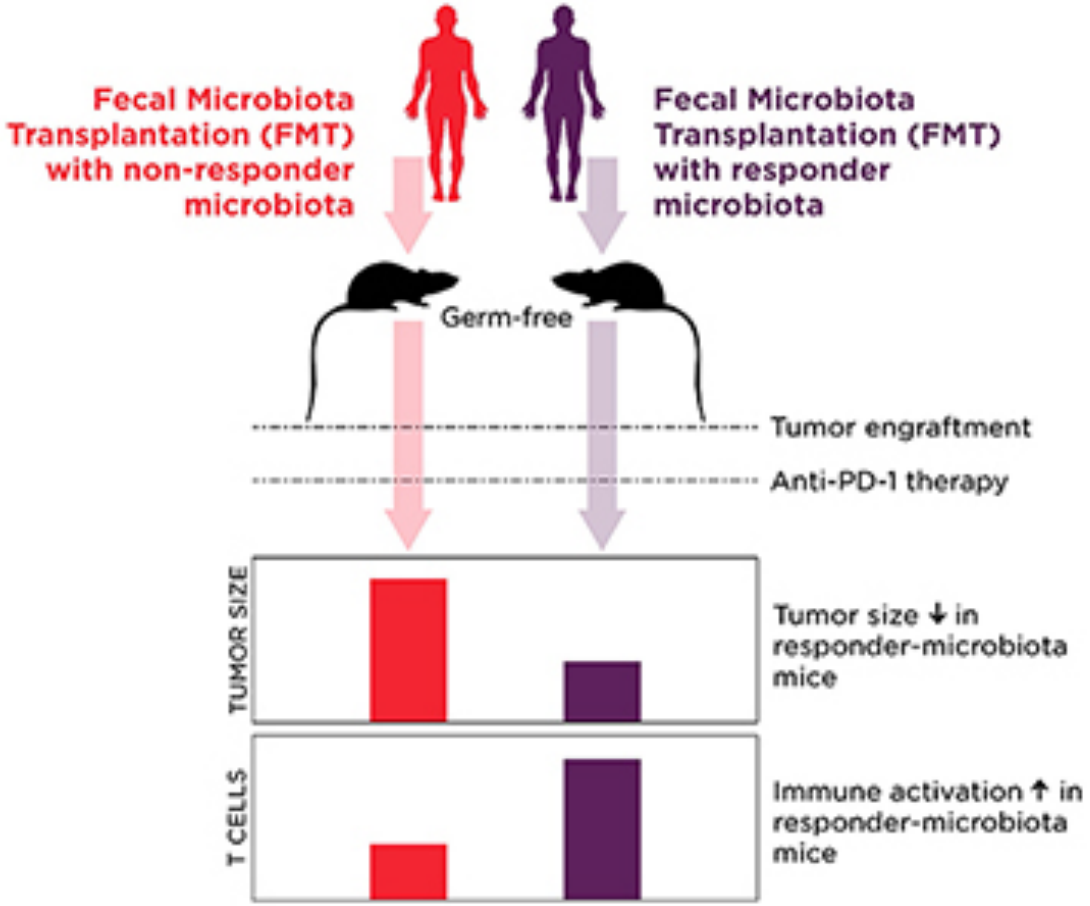
- Increasing number of immune suppressive cells
  - Tregs: T regulatory cells
  - TAM2 : tumor associated macrophages type 2
  - TAN2: tumor associated neutrophils type 2

Niche effect

- Protective effect of
  - Stromal cells
  - Adipocytes

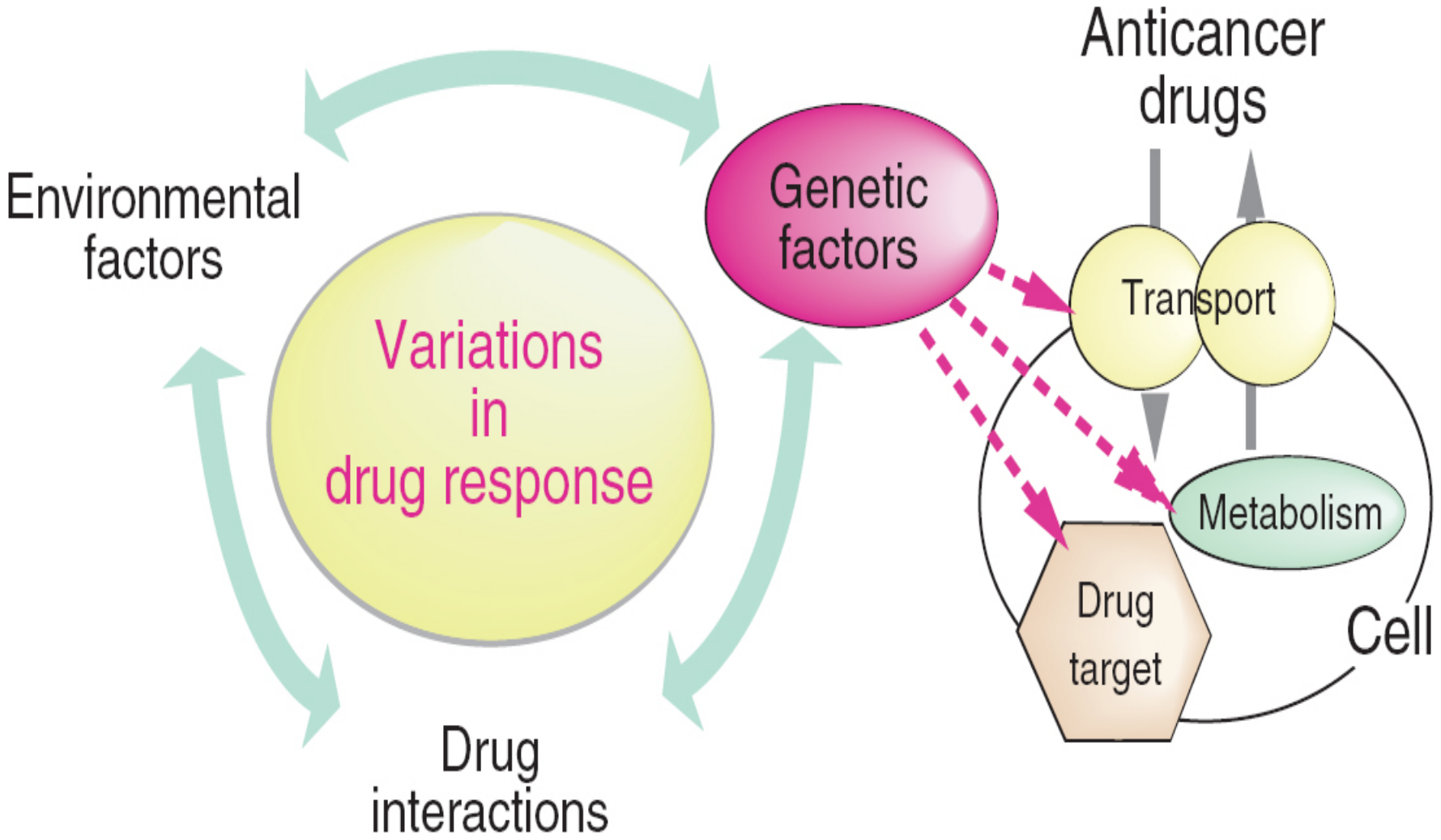
… even the distant environment

Distant immune stimulation has an impact on sensitivity to immune checkpoint inhibitors



Routy & Zitvogel
Science, 2018

How can we improve the activity of cancer therapy ?


Anticancer drugs
Environmental factors
Genetic factors
Variations in drug response
Transport
Metabolism
Drug target
Cell
Drug interactions

Personalized medicine: what are we really talking about ?

Also called « precision medicine »

Treatment taking into account:

The characteristics of the tumor

The characteristics of the patient

Does not mean a different treatment for each patient

Is closer to a « médecine à la carte »

MENU

RELISHES

Ripe Olives — Celery

Green Onions — Radishes

SOUP

Oyster Soup

ENTREES

Spiced Sugar Cured Ham

ROASTS

Roast Young Tom Turkeys

Cranberry Sauce — Giblet Gravy

Chestnut Dressing

VEGETABLES

Candied Sweet Potatoes — Potato Croquettes

SALAD

Fruit Salad

DESERT

Fruit Cake — Hard Sauce

Lemon Meringue Pie

Assorted Candies — Assorted Nuts

Cluster Raisins — Ice Cream

Candy Canes

Cigars — Cigarettes

Coffee

GEORGE H. UPTON,
CHIEF COMMISSARY STEWARD — UNITED STATES NAVY

Personalized medicine: not really a recent concept

« Adapted » therapy has been around for some time

Staging

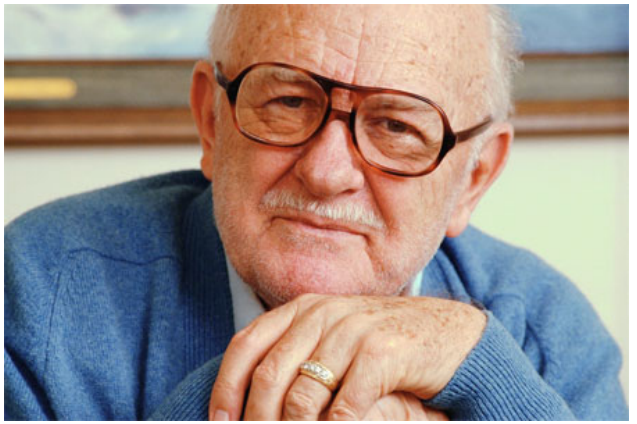
TNM: tumor, lymph node, metastasis

Pronostic factors and indices

clinical parameters
biological parameters

Impact de l'âge

Tolerance issues
When treated similarly eldely patients respond the same way



Personalized medicine: what does it change ?

Several parameters are likely to be adapted:

Type of therapy

RCP : reunion de concertation pluridisciplinaire

Dose and rythm of administration

continous vs. fractionated, low vs. high dose

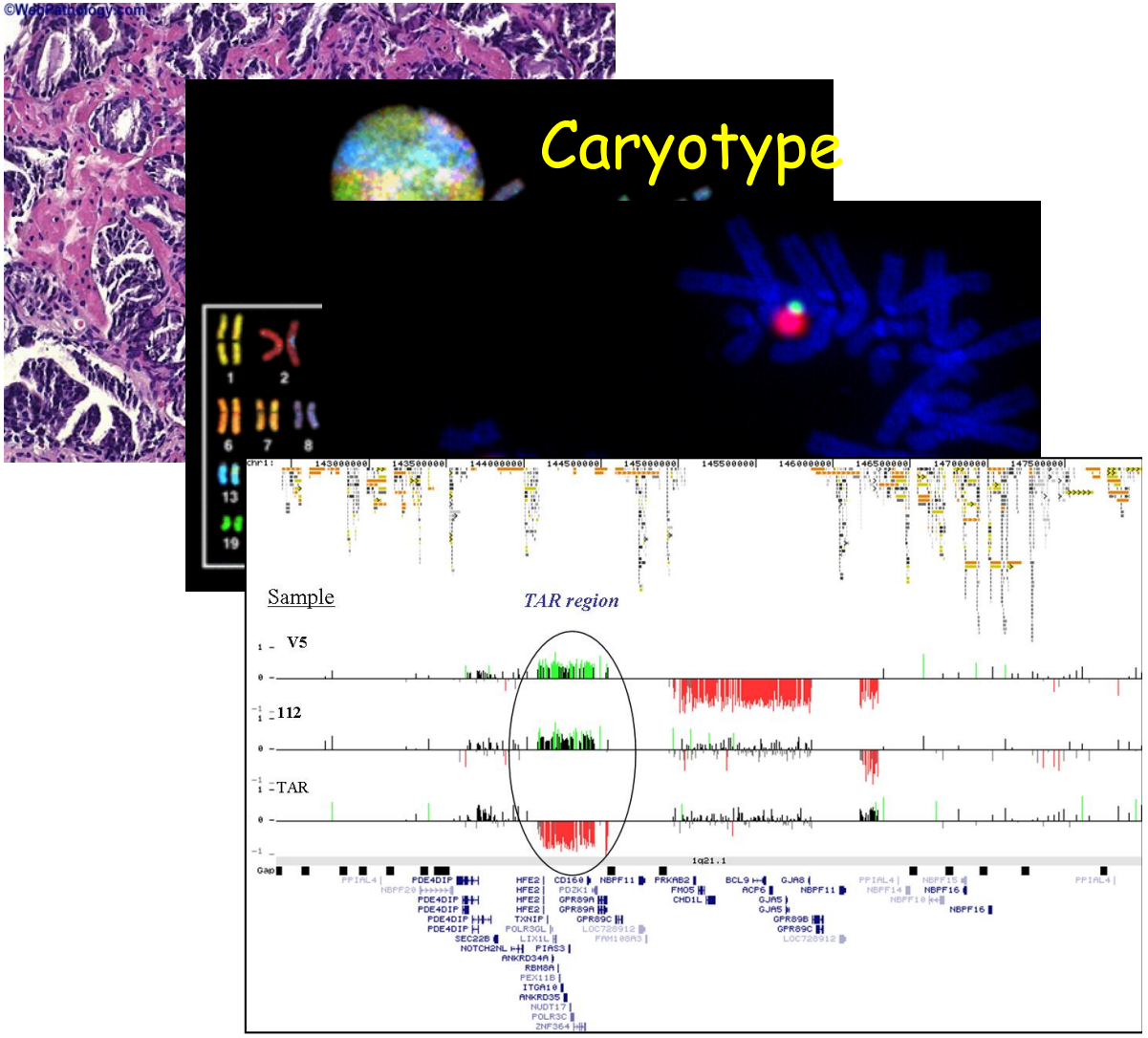
Depending on age and comorbidities

Organ failure

Ongoing or previous therapies

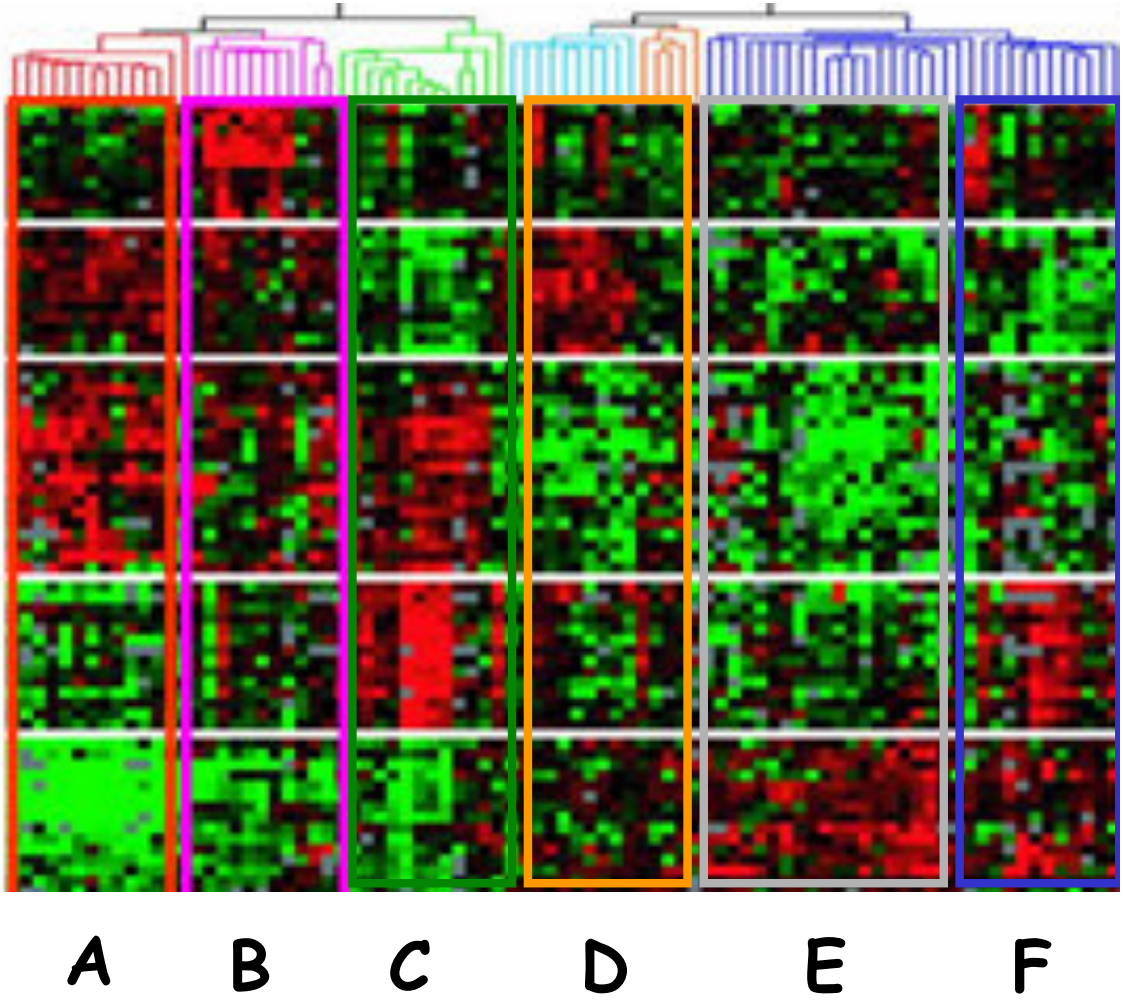
Refined diagnosis and classification

Microscopie
Anatomo-pathologiste

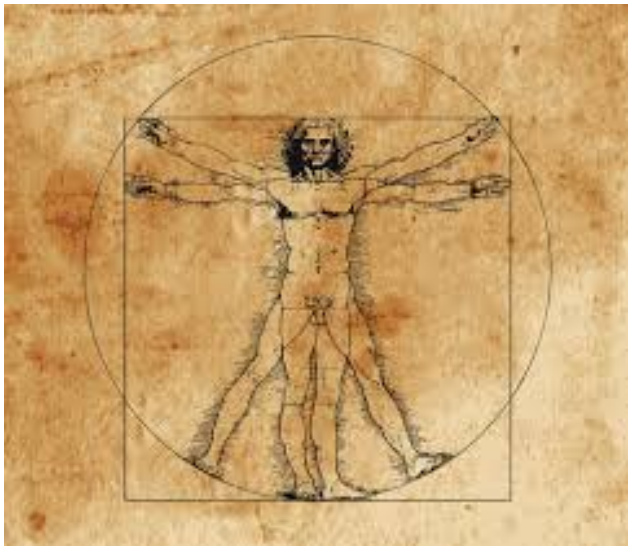


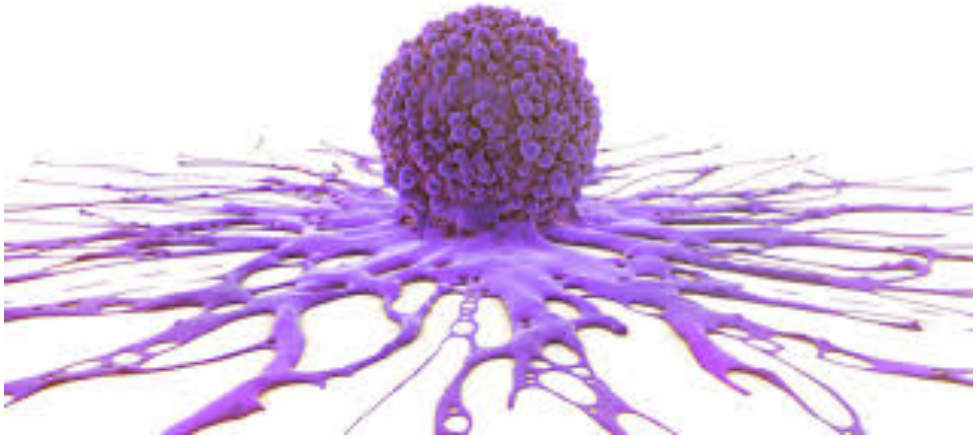
→ >10^8 information/ sample

Will a refined diagnosis lead to better adapted therapy ?



The new challenge: understanding the relationships between the tumor, the treatment and the patient

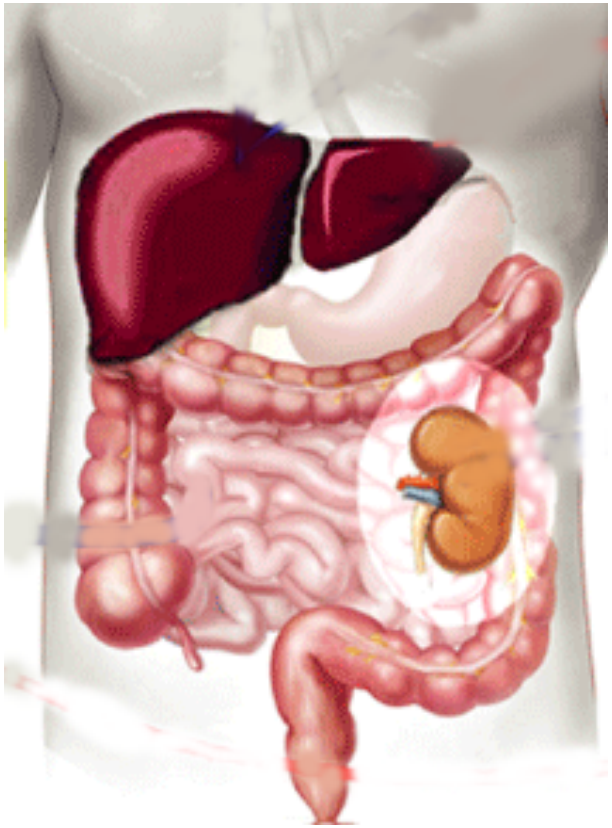




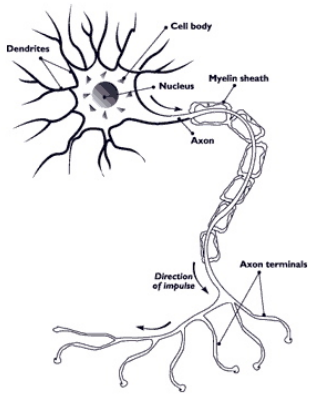
Differences in sensitivity to side effects are at least partly due to genetic make-up or «SNPs » (single nucleotide polymorphisms)

These SNPs have an impact on drug metabolism and/or sensitivity to toxicity

Elimination tissues



Fragile tissues

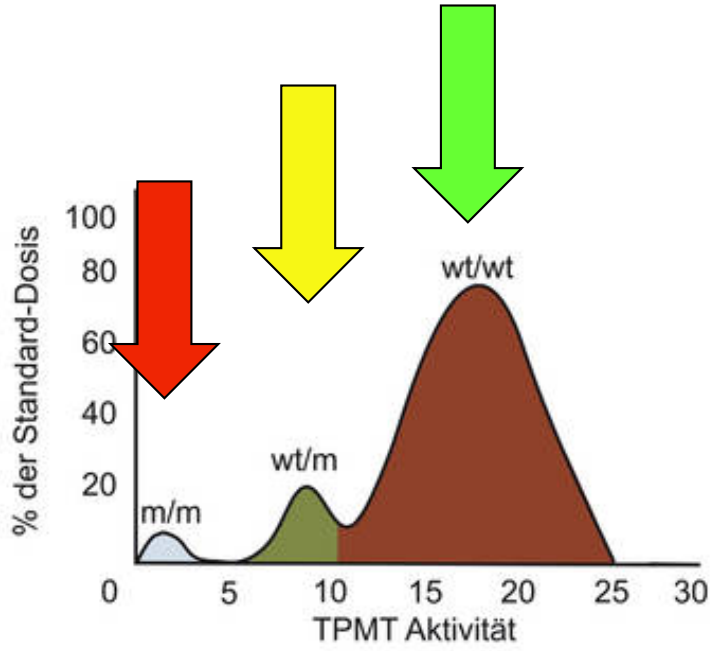


Emergence of pharmacogenetics

- Example of a child afflicted with Acute Lymphoblastic Leukemia (ALL) and treated with 6-mercaptopurine

- Metabolism by thiopurine méthyl transférase (TPMT)

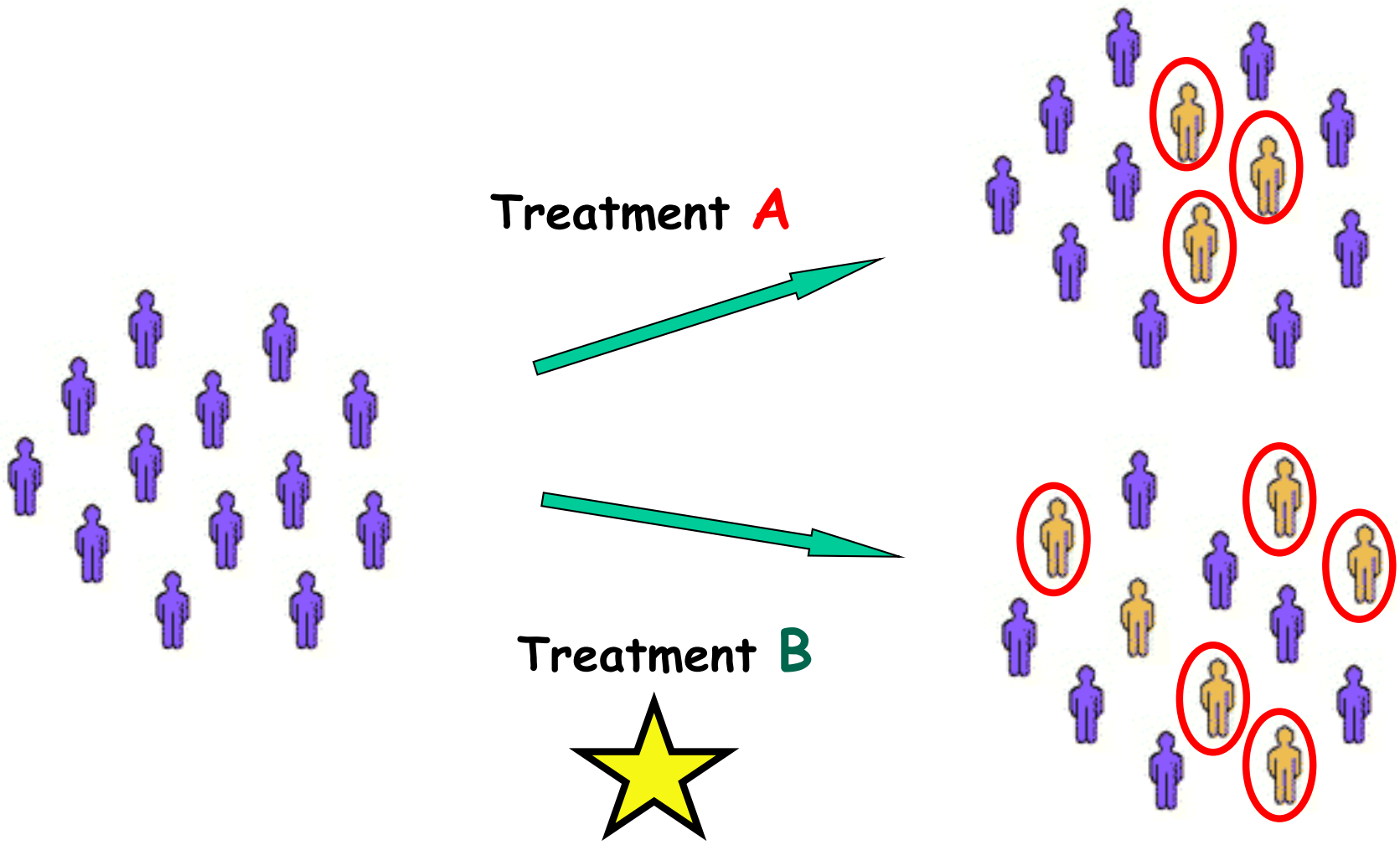
- Low enzyme activity: accumulation of agent and strong toxicity



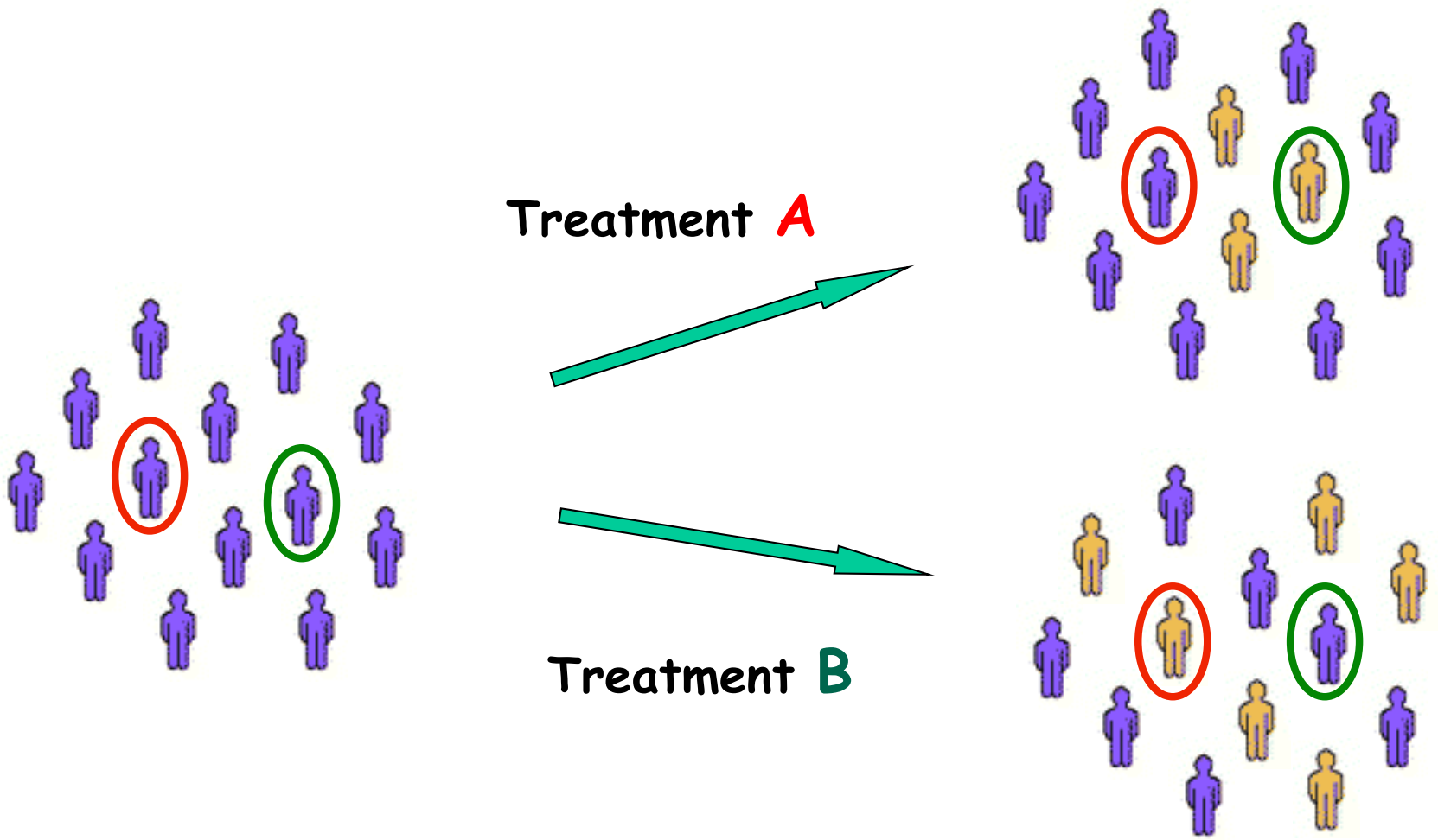
Traditionally:

choice of « best possible treatment »

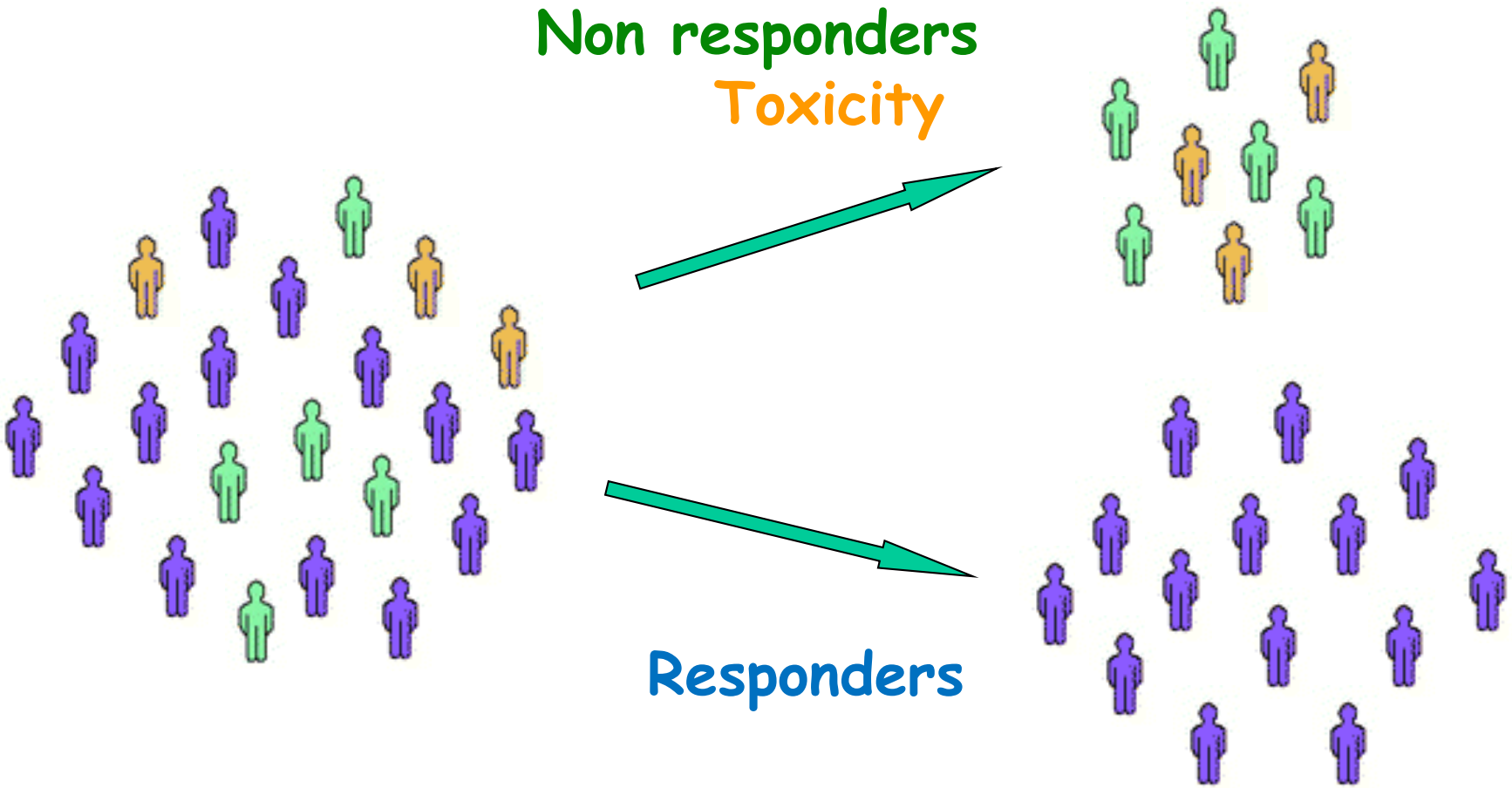
Statistical concept based on randomized trials



Is not always correlated with optimal therapy at the individual level



Define and apply predictive factors of response and toxicity

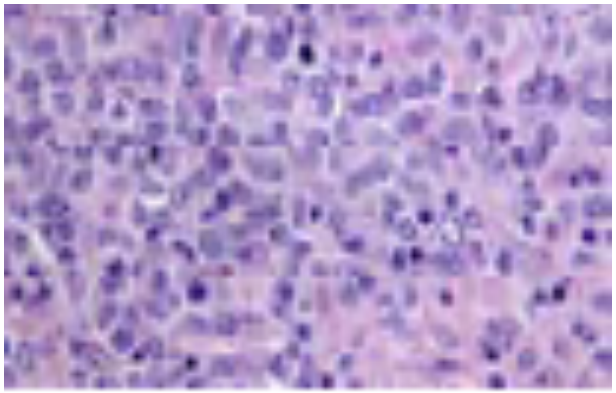


Avoid side effects
Use the right treatment before resistance emerges

Biomarkers for targeted therapies

- Is it logical to use the treatment?

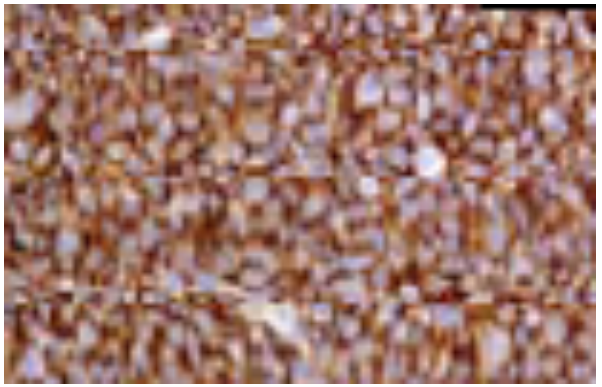
  = is the target present ?



negative

⇩

Use other therapy



positive

⇩

Try treament

How will treatments be selected in the future ?