Chemotherapy, Targeted therapy, Immunotherapy

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Definition of malignant tumor

Cell clones, which are

- independent
- immortal
- invasive
- capable to creat metastasis
- capable to induce immune tolerance

Mutations of oncogenes, tumor suppressor genes

DNA-repair mechanisms

Apoptosis

Diversity of malignant tumors

At molecular level: DNA,

almost all

Grouping according to

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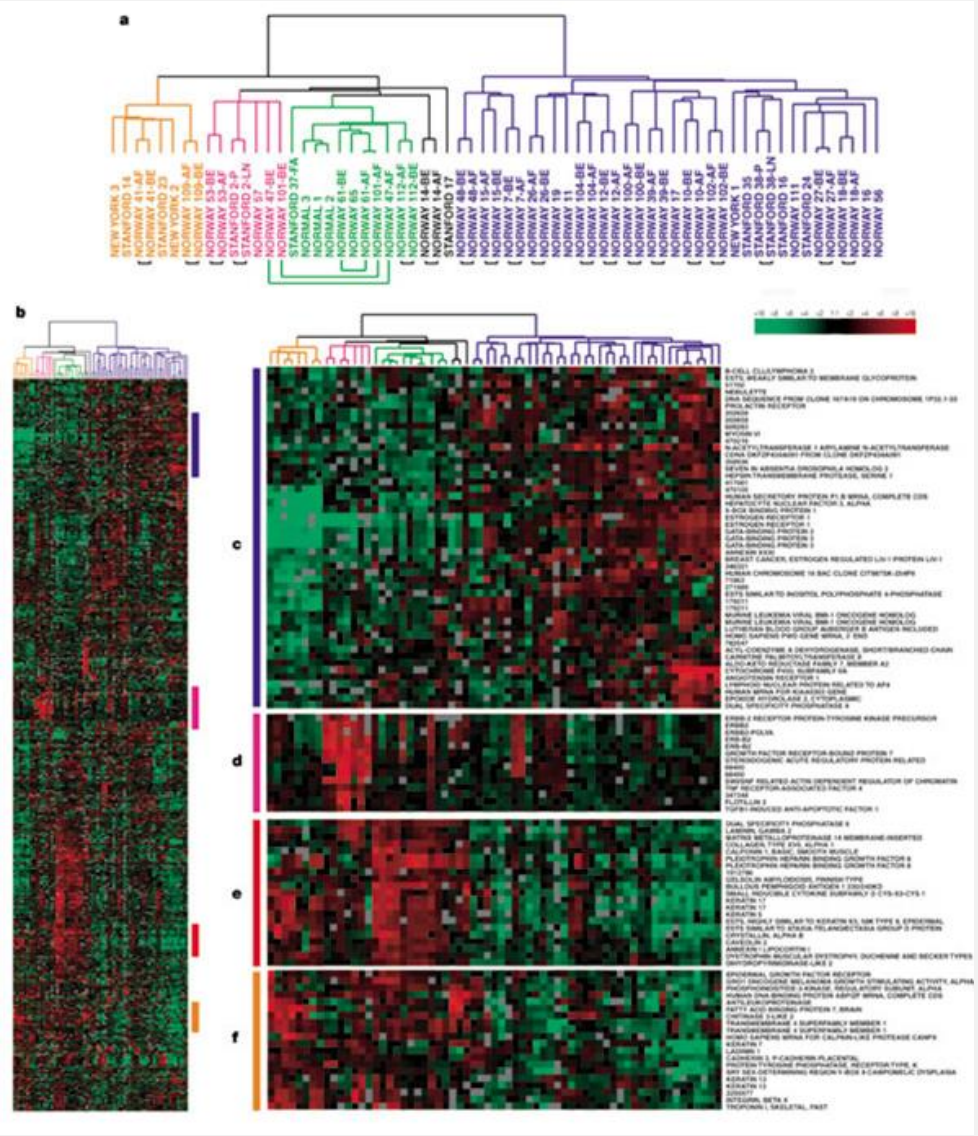


Types of medical treatment in cancer management

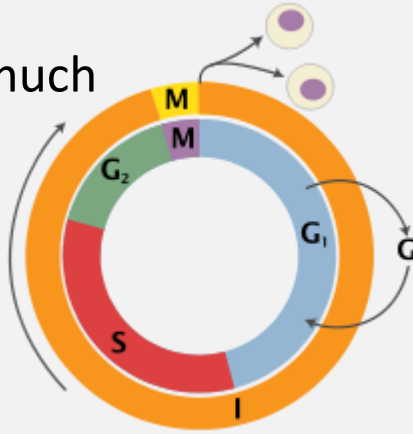
- Chemotherapy/cytotoxic agents
- Targeted therapies
  - Endocrine treatment
  - Enzyme inhibitors (mostly TKI)
  - Biologics (mostly antibody based)
- Supportive/palliative treatment

Mode of action of chemotherapy

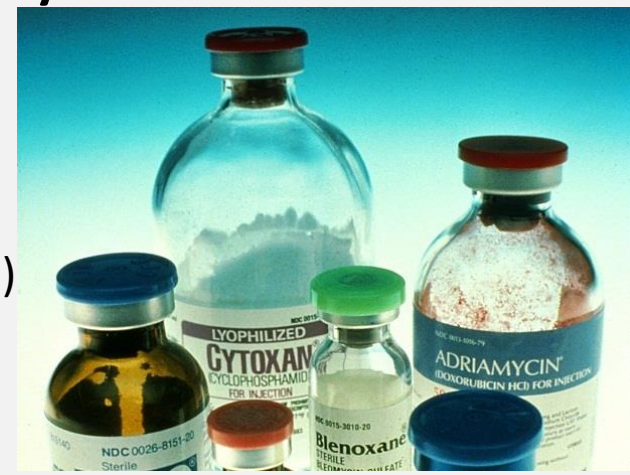
- The chemotherapy agents impair cell division (mitosis): direct DNA damage, antimetabolits, enzyme-inhibition (topoisomerase I. és II.), microtubule-inhibition.
- Apoptosis – programmed cell death
- Effectively targets fast-dividing cells – cancer cells divide much faster than normal cells.

  But:

  - there are malignancies with slower growth rates, such as indolent lymphomas, tend to respond to chemotherapy much more modestly
  - fast dividing normal cells also susceptible – side effects



Groups of chemotherapy compounds

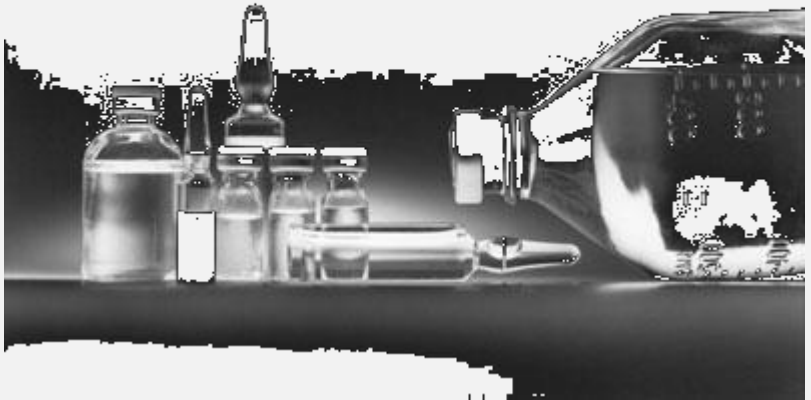


- Alkylating agents
  - nitrogen mustards (cyclophosphamid, ifosfamide,etc.)
  - nitrosoureas (carmustine, lomustine, etc.)
  - tetrazines (dacarbazine, temozolomide, etc.)
  - platinum salts (pl. cisplatin, carboplatin, oxaliplatin)
- Anti-metabolites
  - purines/pyrimidine-analoges
  - anti-folates
- Antibiotics
  - anthracyclines (pl. TOPO II-inhibitors - doxorubicin), mitoxantron, mitomycin
- Plant derived compounds
  - TOPO I-inhibitors: topotecan, irinotecan, etoposid
  - anti-microtubule agents (vinca-alkaloids, taxanes (docetaxel, paclitaxel)

Delivery

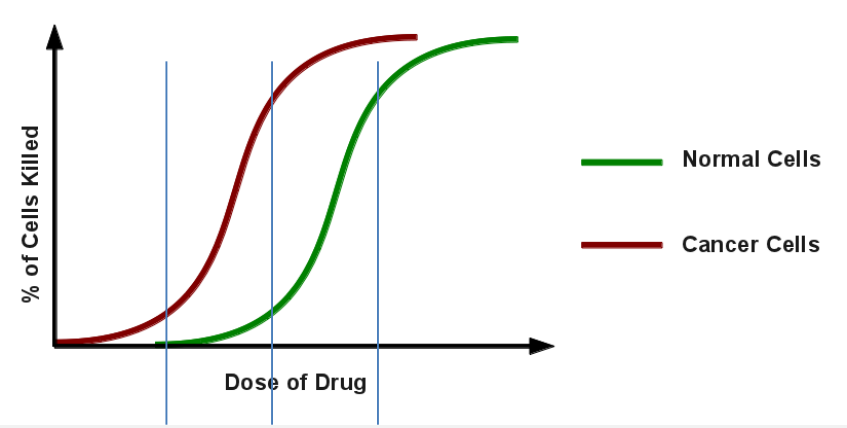
- Aim of therapy:
  - neoadjuvant – adjuvant – palliative
- Way of delivery:
  - intravenous – intramusculare – per os – locoregional/intraarterial
- Monotherapy – combination therapy
- Combination with other modality: radio-chemoterapy, chemo-biologocal
- Dosing: conventional dose – dose dense therapy – high dose therapy –

  metronomic low dose



Dosing

- Low dose – ineffective
- Hihg-dose – intolerable side effects
- Dose window



- weight (mg/kg), BSA (body surface area, mg/m^2), AUC (area under the curve)

Cure rate with chemotherapy alone in advenced (metastatic) malignant diseases

Malignancy	Cure rate (%)
In childhood:	
Acut lymphoid leukaemia	>50
Non-Hodgkin lymphoma	>50
Burkitt lymphoma	>50
Wilms tumor	>50
Ewing's sarcoma	>50
Embryonal rhabdomyosarcoma	>50
In adulthood:	
Gestational choriocarcinoma	90
Germinal cell testicular cancer	>75
Hodgkin lymphoma	>50
Agressive Non-Hodgkin lymphoma	>50
Akut myeloid leukaemia	25-50
Ovarial cancer	10-20

Side effects

Chemotherapy causes harm to fast dividing normal cells, too, such as haemopoetic stem cells, mucosa cells in gastrointestinal tract, dermal cells (hair bulb,nail) and germinal cells.

- **Side effects in GI tract**: stomatitis/mucositis, loss of apetite, nausea/vomiting, diarrhoea.
- **Affecting epithelium**: photosensitization, alopetia, nail-changes.
- **Blood cells**: citopenias (fatigue, spontaneous bleeding, infection).
- **Germ cells:** conceptional or procreativ impotency.

Supportive – nausea/vomiting

Cause: irritation of mucosa, chemo-receptor trigger zone. Role of serotonine.

Anticipatory vomiting.

Treatment, prevention:

- serotonine antagonists (ondansetron, granisetron, palonosetron, etc.)
- neurokinin-1 receptor antagonists (aprepitant, fosaprepitant)
- corticosteroids

Supportive – agranulocytosis, febrile neutropenia

Severe neutropenia – absolute neutrophyl count (ANC) <0,5 G/l

Agranulocytosis – ANC <0,1 G/l

Severe attenuation of immuno-system.

If fever presents: febrile neutropenia.

„Sterile circumstances”, antibiotics, antimycotics, antiviral drugs, colony stimulating factors (G-CSF, GM-CSF).

Side effects – organ damage

- Cardiotoxicity: anthracyclin (irreversible), trastuzumab (reversible), taxane (arrhytmia)
- Lung fibrosis: trastuzumab, taxane, ifosfamide
- Kidney: platinas, ifosfamide, cyclophosphamide
- Liver: many drugs (lapatinib)
- Peripheral nerves: platinum, vinca alkaloids, taxane
- Infertility, gonadal damage
- Second malignancy (<1%): in younger age mostly solid tumours, in the elderly mostly AML/MDS[1]

1.Brown LM, et al. Risk of second non-hematological malignancies among 376,825 breast cancer survivors. *Breast Cancer Res Treat*. 2007;106(3):439–451

Hystory of hormonal treatment

1896: George Beatson (surgeon in Glasgow) published 3 cases, oophorectomy infuenced favourably breast cancer

1937 – diethylstilboestrol, prostate tumour

1969 – tamoxifen, breast cancer

2000 and beyond aromatase inhibitors

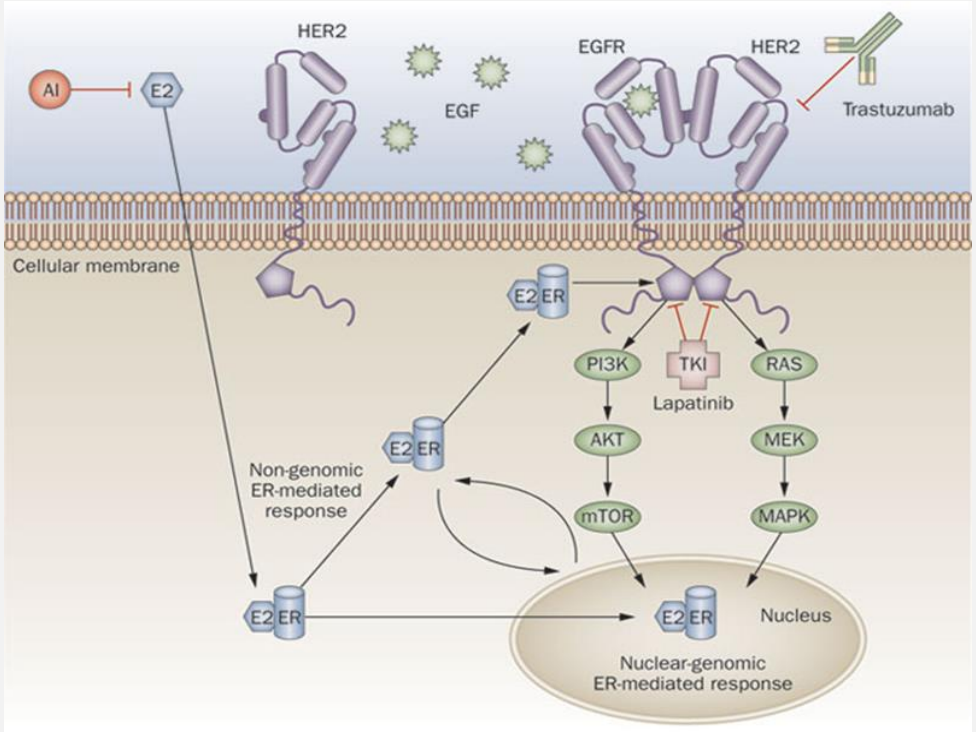
Hormonal therapy

There are tumours susceptible to hormonal environment (breast, prostate, endometrial).

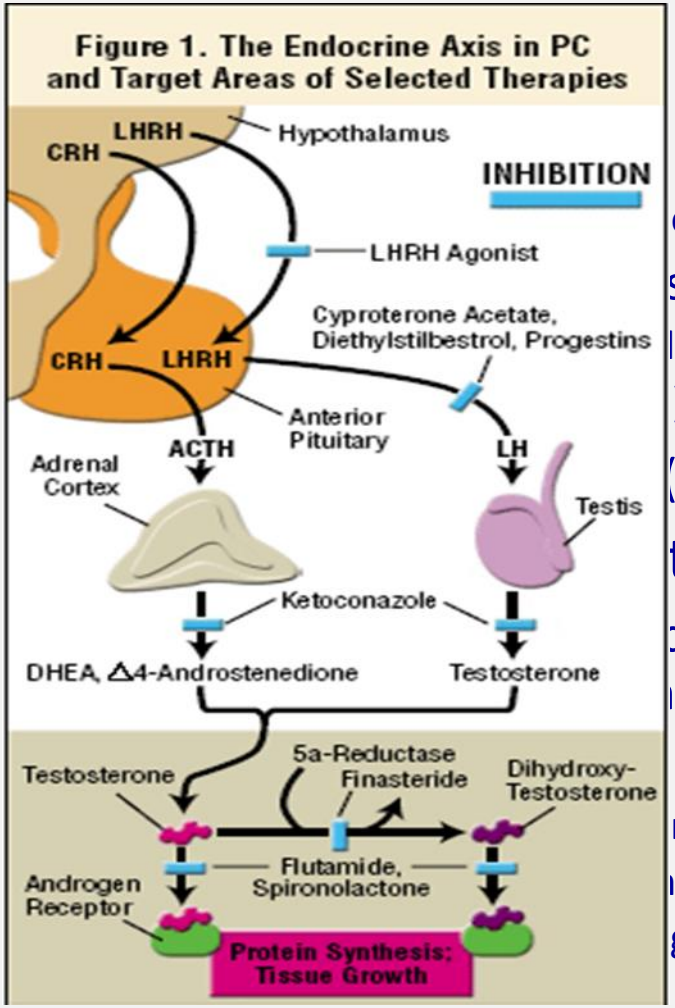
The presence of a hormone is essential for growth and spread of neoplasm – inhibiting hormonal effect is anti-neoplastic.

Targeted treatment.

Cytostatic therapy.



Hormonal compounds



evel

erelin, triptorelin, buserelin, leuprolelin, stb.)

s (AI)

le, anastrozole)

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(abiraterone)

ts

dokrine receptor modulator: tamoxifen,
obosarm)

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ide, bicalutamide, enzalutamide)

ges

Clinical use

- Breast cancer
  - Premenopausa:
    - tamoxifen (inhibition on cancer cells - peripheral)
    - tamoxifen + GnRH-analog (central effect) or oophorectomy
  - Postmenopausa
    - tamoxifen
    - aromatase inhibitors
    - fulvestrant

Clinical use

- Prostate cancer
  - Androgen deprivation
    - Surgical castration
    - Chemical castration (GnRH-analog): keep serum testosteron under castrational level
  - Anti-androgen
  - Peripheral enzyme inhibition

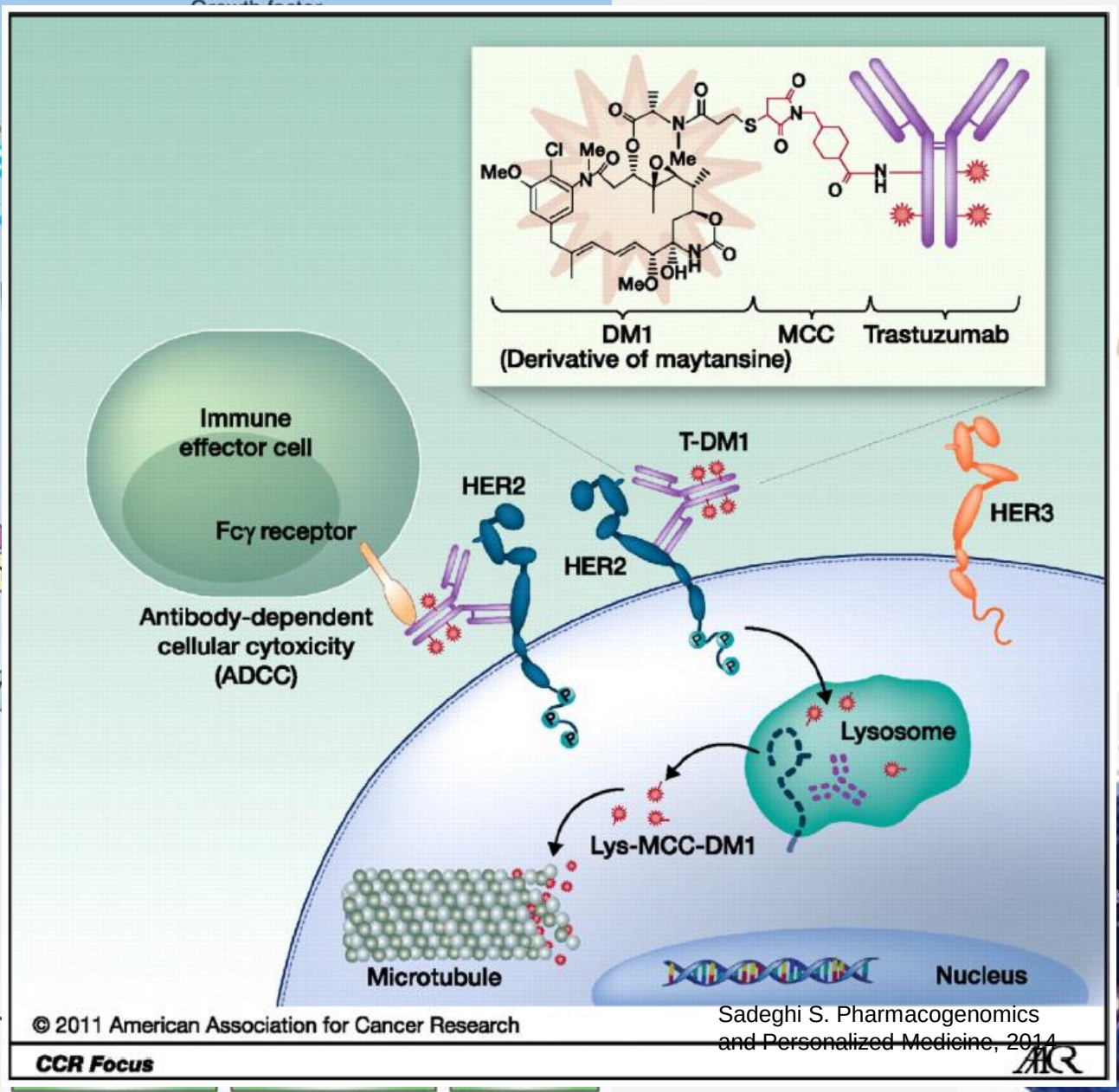
aim to

Total androgen blokade

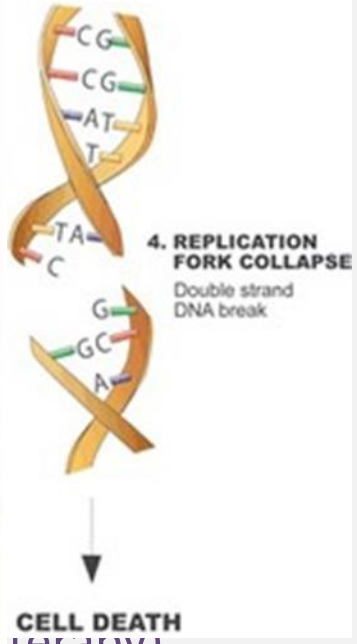
Side effects of endicrine treatment

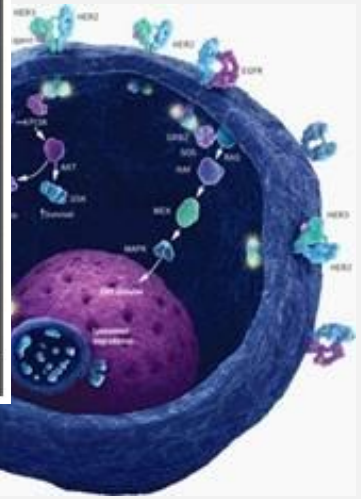
- common:
  - vasomotor symptoms (hot flashes, sweating)
  - musculosceletal (arthralgia)
  - metabolic disturbances (weight gain, cholesterin, heart and vascular complications, osteoporosis)
  - venous thromboembolia (VTE)
  - mood alteration (depression)
  - fatigue

- breast cancer:
  - vaginal dryness or discharge (infection, dyspareunia)
  - endometrium carcinoma (tamoxifen)
- prosztate cancer
  - erection problems, impotency
  - breast tenderness, gynecomasty



Sadeghi S. Pharmacogenomics and Personalized Medicine, 2014





Integrins

FKBP

Temsirolim

p7

Cancer cell growth

Medscape Source: Cancer Control © 2009 H. Lee Moffitt Cancer Center and Research Institute, Inc.

Classes

1. Low molecular weight drugs– generally enzyme inhibitors: tyrosine kinase inhibitors (TKI)
2. Antibody
    1. Epidermal growth factor family
        - HER1 (EGFR) – cetuximab, panitumumab
        - HER2 – trastuzumab, pertuzumab
    2. Vascular endothelial growth factor (VEGF)
        - bevacizumab, aflibercept
    3. Haematology: rituximab (CD20), alemtuzumab (CD52)

    Antibody-drug conjugates: trastuzumab emtansin (TDM1), brentuximab vedotin (CD30), tositumomab I^{131} (CD20)

Low molecular weigth drugs

- In general more than one target
- For efficacy target is needed– biomarker
- Intracellular
- Pe os
- Susceptible the activity of cytochrome P450 enzyme

Side effects:

  - Loss of apetite, loss of weight, diarrhea
  - Blodd counts, liver enzyme
  - rash
  - hypothyreosis

Mechanism of action

The beginning of revolution: Glivec (imatinib) 2001 (**C-KIT**)

EGFR: erlitinib, gefitinib, lapatinib.

B-RAF-inhibitor: vemurafenib, dabrafenib, encorafenib.

MEK-inhibitor: cobimetinib, trametinib, binimetinib

mTOR-inhibitor: temsirolimus, everolimus.

Mainly **angiogenesis** inhibitor multikinase inhibitors: sunitinib, sorafenib, pazopanib, vandetanib.

ALK-inhibitor: crizotinib, ceritinib, alectinib, brigatinib, lorlatinib.

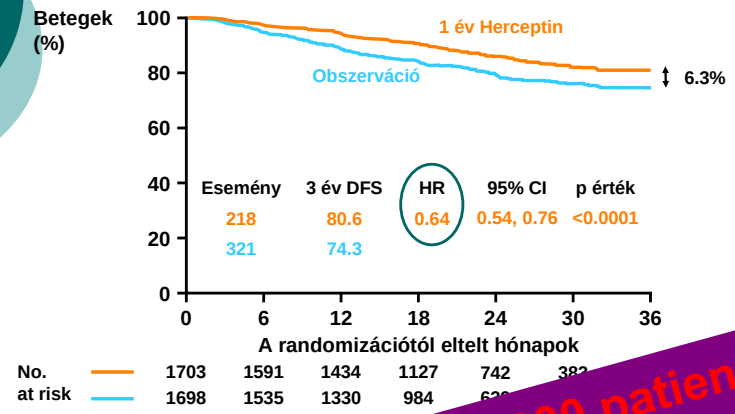
NTRK-gátlók: larotrectinib, entrectinib

The drugs are testet in different histologies and molecular abnormalities:

traditionally according to organ of origin ⟷ target oriented

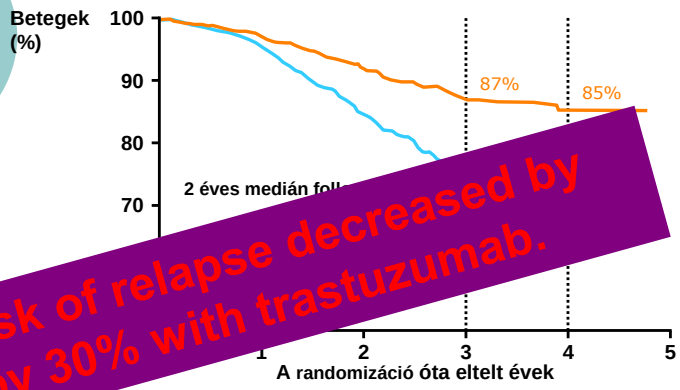
Adjuváns trastuzumab kezelés

HERA trial: DFS
(kezelni szándékozottak; FU median 2 év)



CI, confidence interval; HR, hazard ratio

B-31 és N9831 összevont analízis: DFS

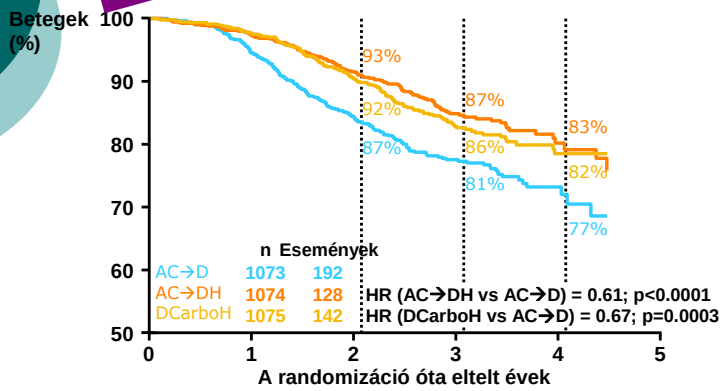


oxorubicin + cyclophosphamide; H, Herceptin; P, paclitaxel

Romond et al 2005

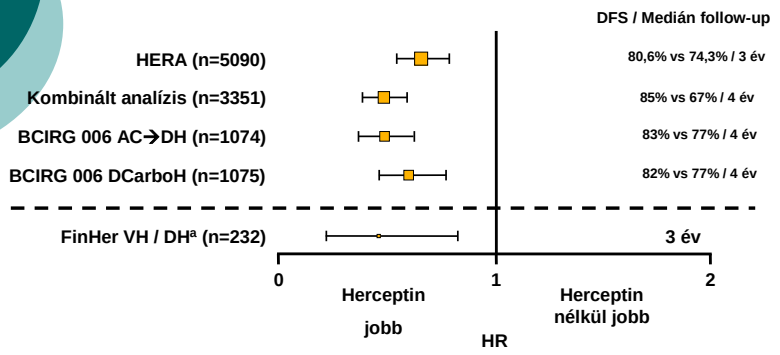
Approximately 14000 patients. Risk of relapse decreased by 50%, risk of death decreased by 30% with trastuzumab.

DFS 2. interim analysis



Slamon et al 2006

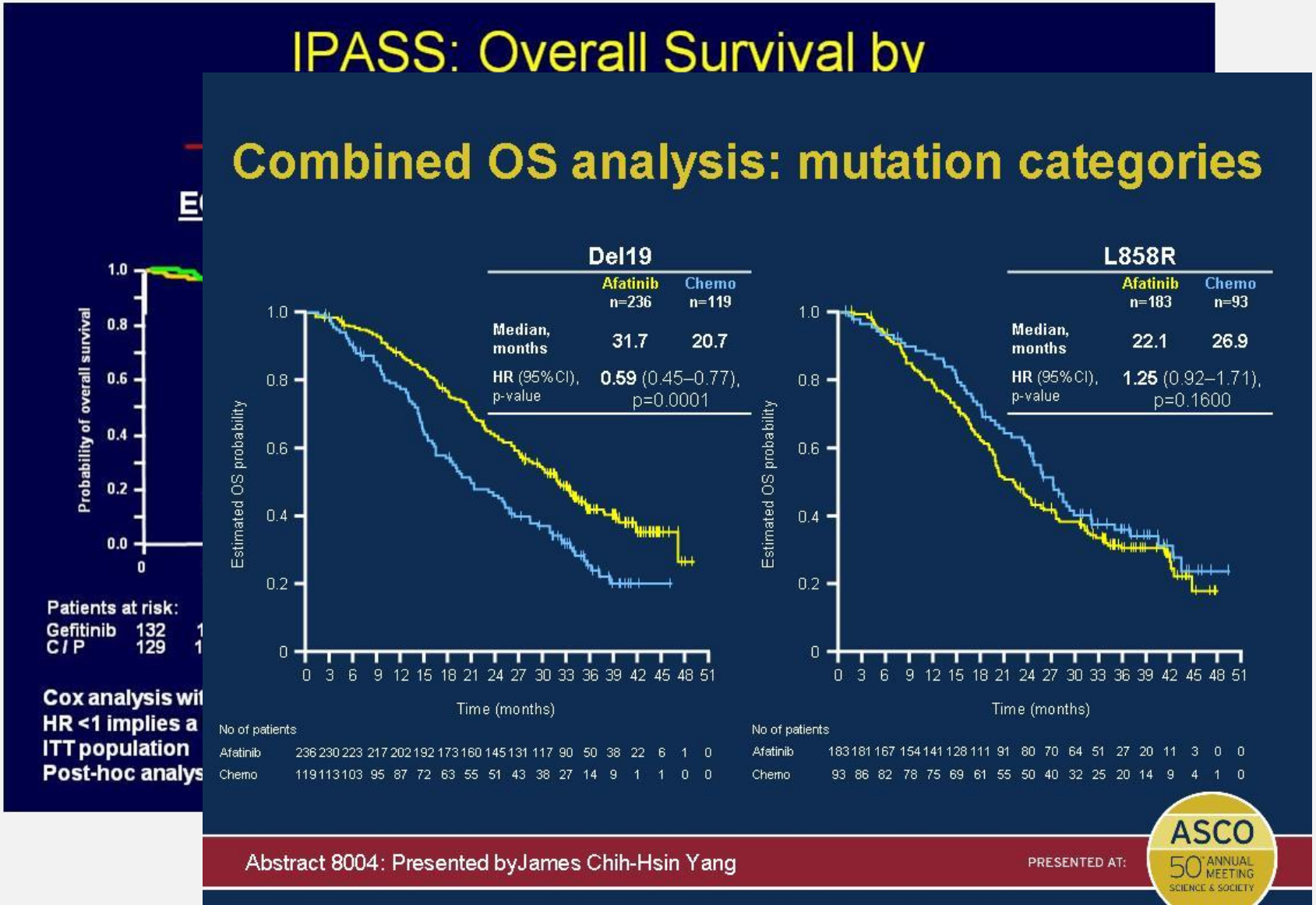
Adjuváns Herceptin vizsgálatok: DFS összehasonlítása



[a]Relapse-free survival; V, vinorelbine

Romond et al 2005; Joensuu et al 2006; Slamon et al 2006; Smith et al 2007

Biomarker needed!



„Cross-talks”

Different signal pathways are not independent from each other.

One can substitute the other – resistence.

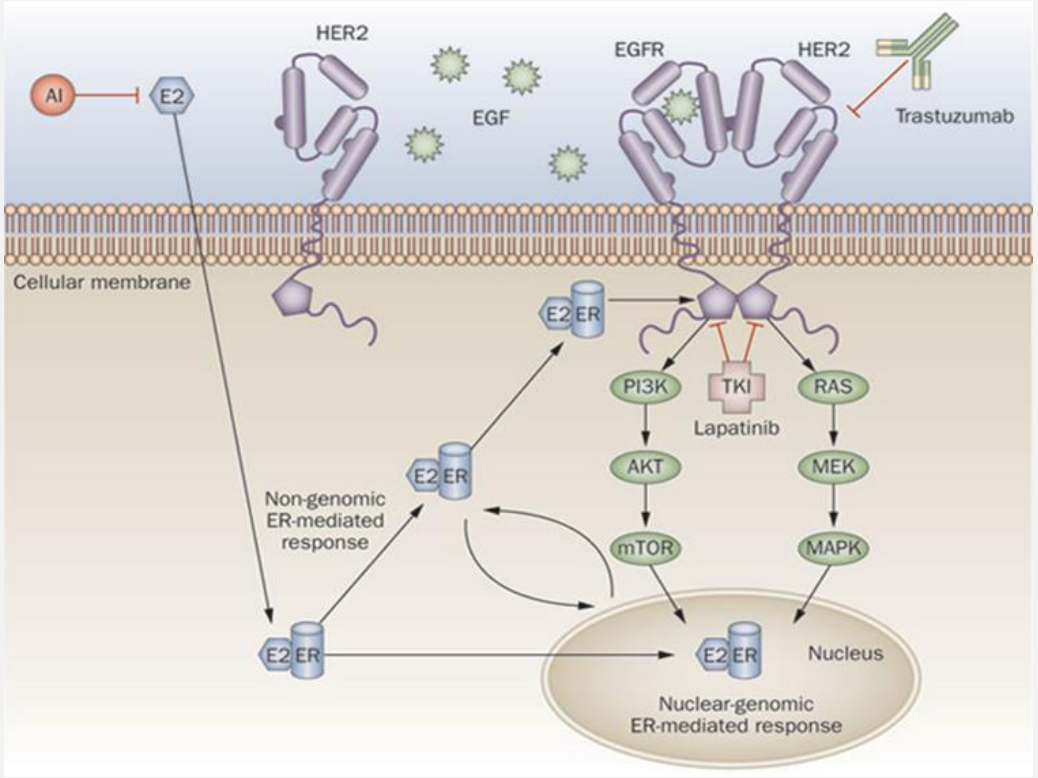
Targeting more enzymes can overcome resistence.

trastuzumab + lapatinib

trastuzumab + mTOR-inhibitor

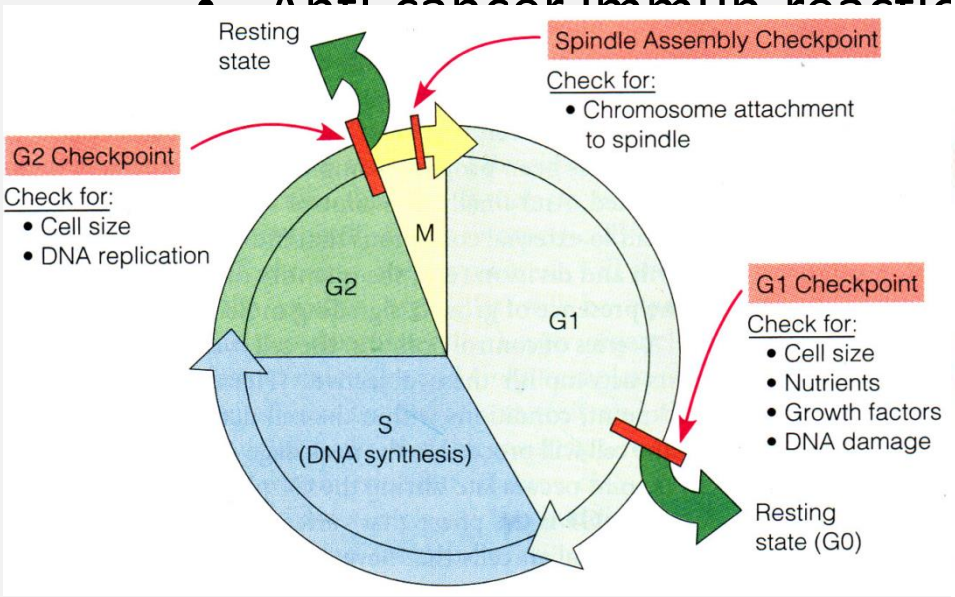
AI + mTOR-inhibitor

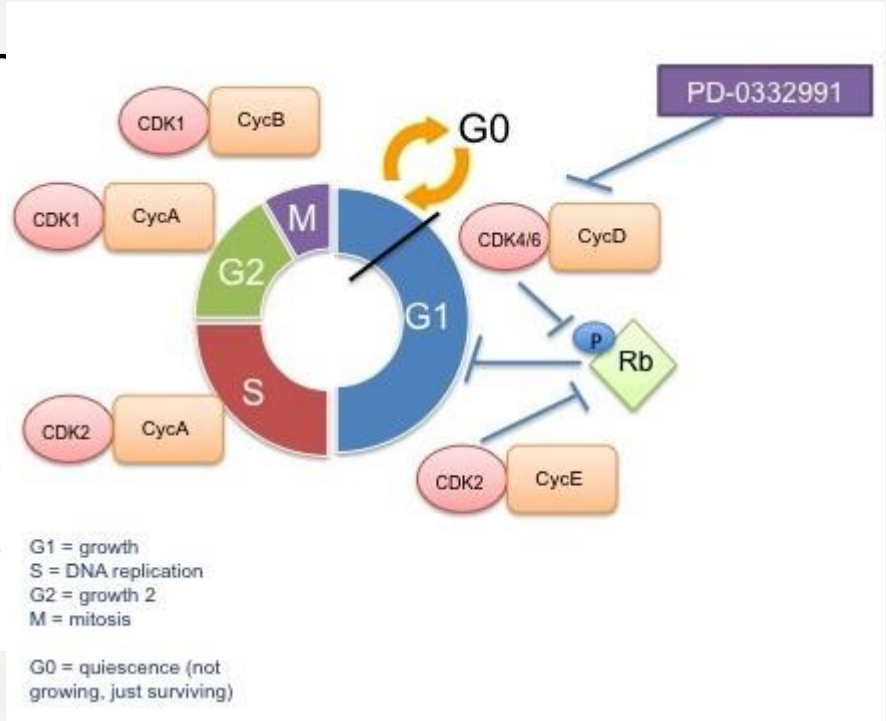
BRAF-i + MEK-i



„Checkpoint" inhibitors (⇔ agonists)

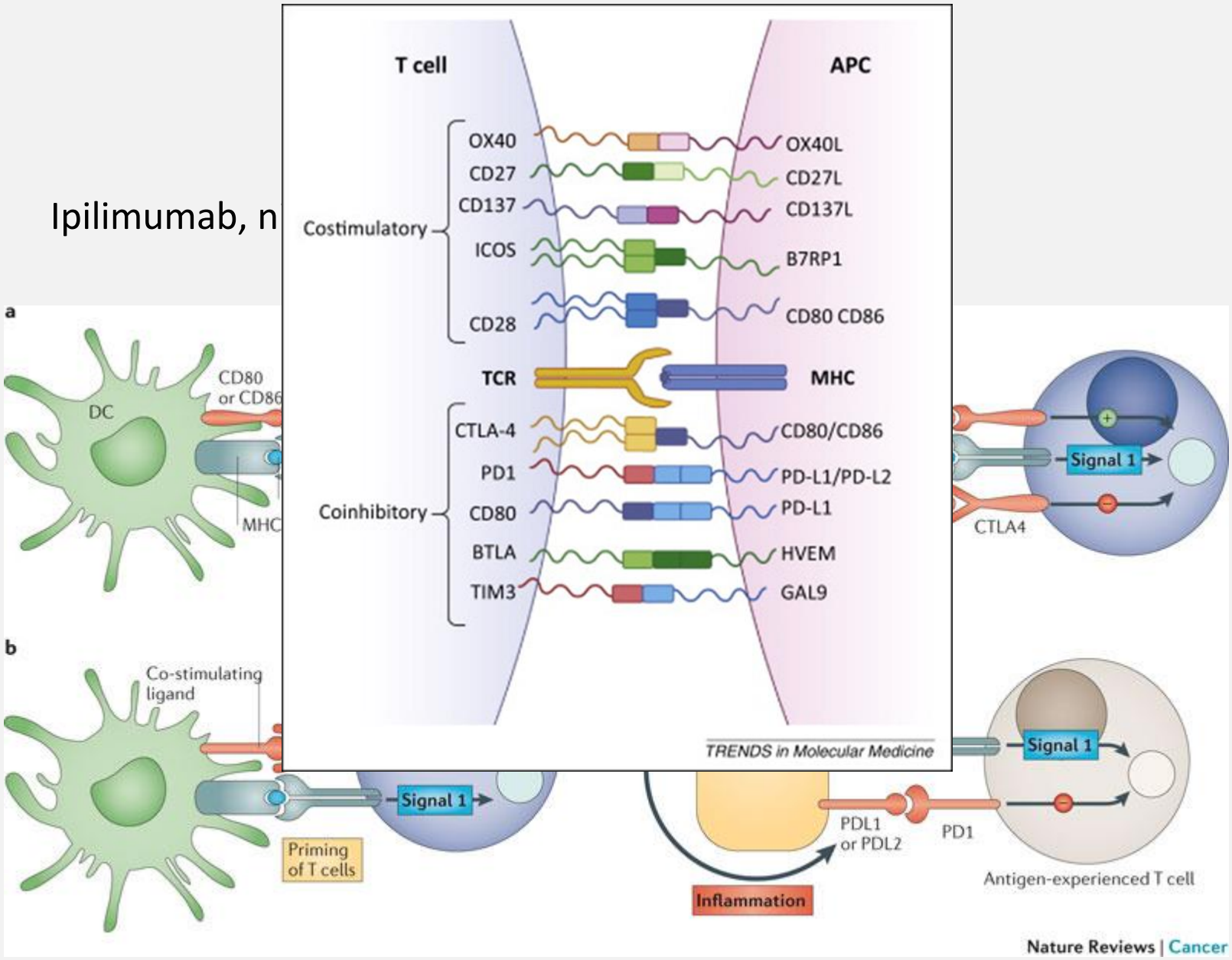
- Cell-cycle: cyclin-dependent kinase inhibitor





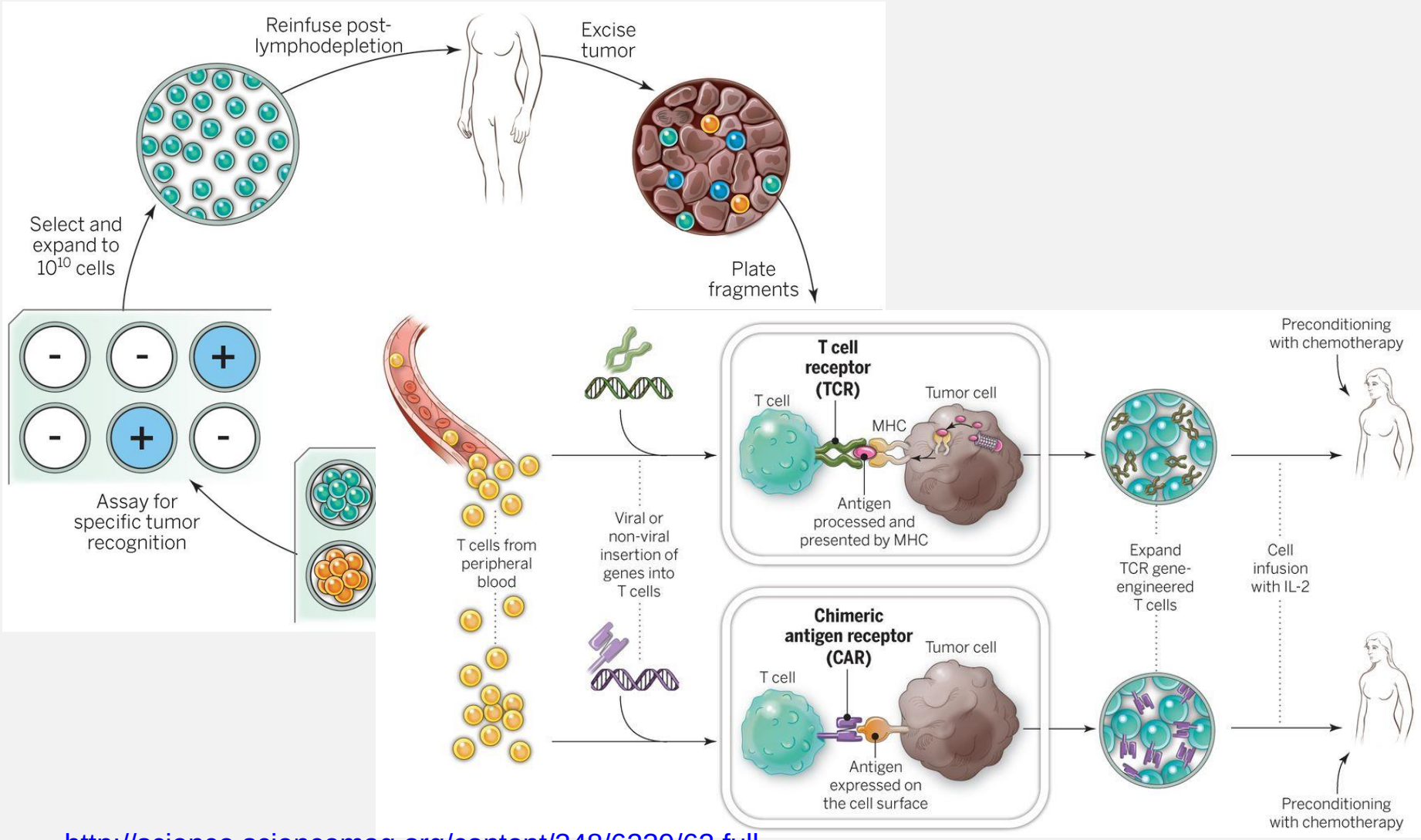
oncogenesandcancer.wordpress.com, thecancergeek.files.wordpress.com

Ipilimumab, n



Drew M. Pardoll. Nature Reviews Cancer 12, 252-264

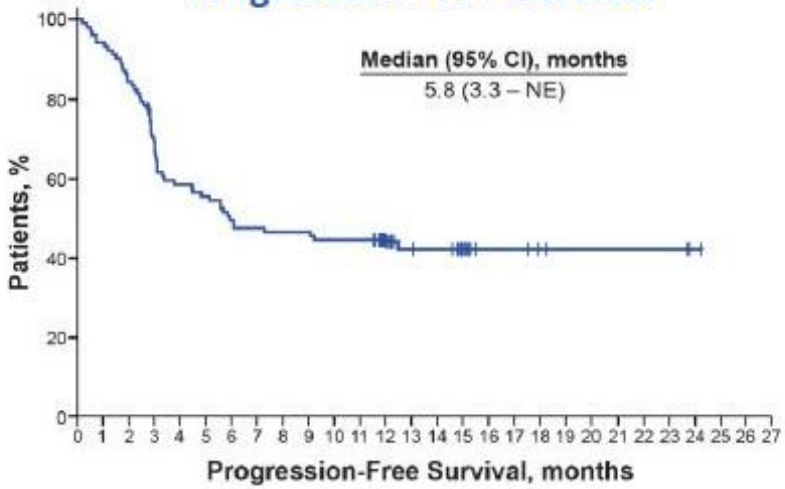
Adoptive T-cell transfer (ACT)



http://science.sciencemag.org/content/348/6230/62.full

Axicabtagene ciloleucel in refracter large B-cell non-Hodgkin lymphoma

Progression-Free Survival

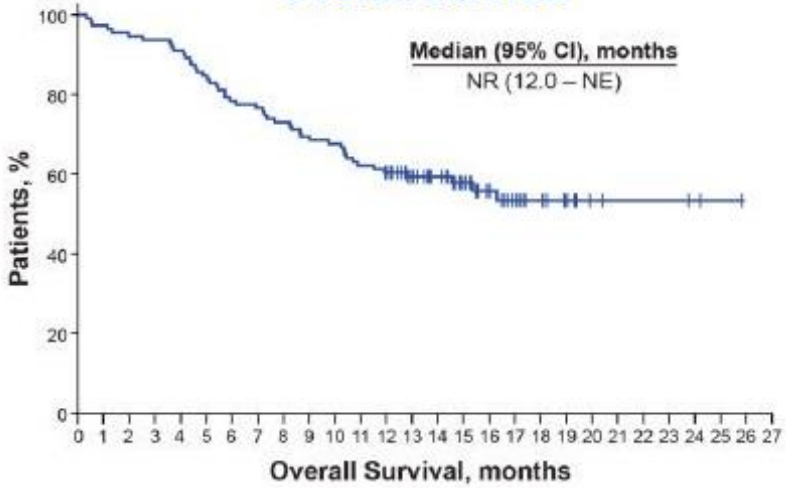


Patients at Risk

108 90 61 52 49 47 34 20 6 4 3 3 1

Landmark	PFS
6-month	49
12-month	44
18-month	41

Overall Survival



Patients at Risk

108 102 98 84 78 72 63 40 23 11 4 3 2 0

Landmark	OS
6-month	78
12-month	59
18-month	52

NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival.

Neelapu et al ASH 2017 578