

# LATEST ADVANCES IN MEDICAL ONCOLOGY

- A normal cell differentiates, grows, matures, divides and dies. The number of newly created cells is equal to the number of cells that die
- Loss of regulatory mechanisms leads to hyperplasia, metaplasia, dysplasia and neoplasia
- Neoplasias (tumors) can be benign or malignant
- Benign ("benign") tumors grow locally and expansively, have preserved intercellular cohesion and clear boundaries

## **CHARACTERISTICS OF MALIGNANT CELLS**

1. AVOIDANCE OF IMMUNOLOGY SURVEILLANCE
2. AVOIDANCE OF APOPTOSIS
3. AUTOSTIMULATION OF GROWTH
4. INSENSITIVE TO SIGNALS TO STOP GROWTH
5. INFINITE DIVISION/GROWTH
6. ABILITY TO INDUCE NEO-ANGIOGENESIS
7. CAPACITY OF INVASION AND METASTASIS

# ETIOLOGY

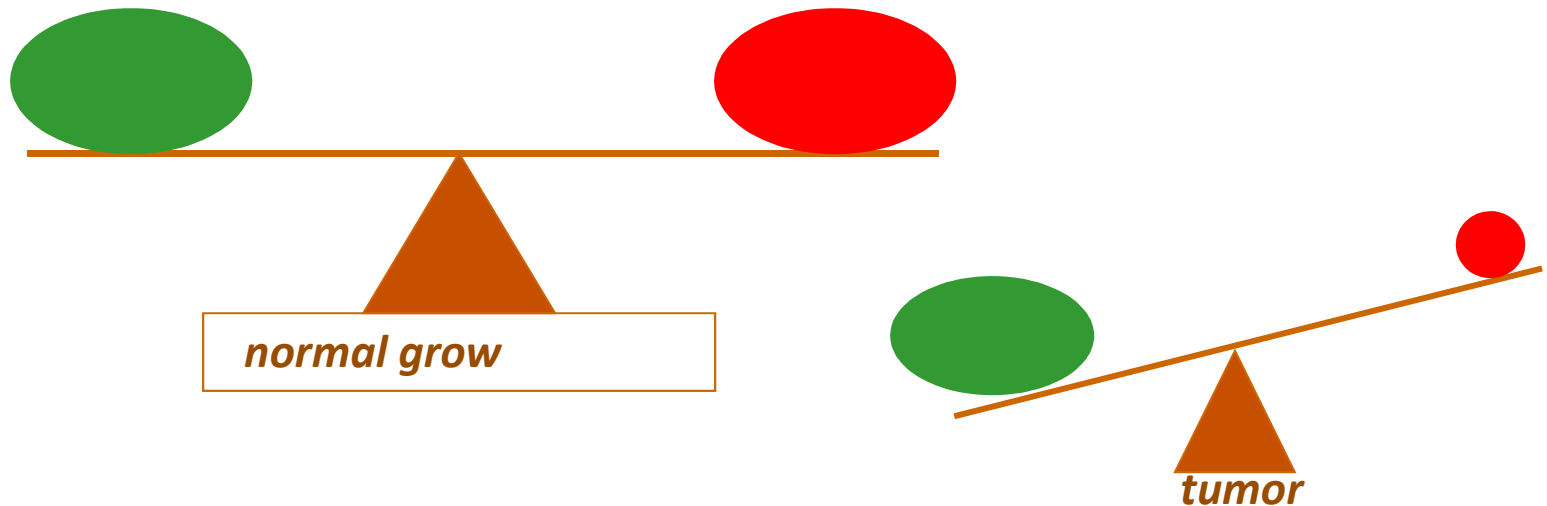
- The process of the formation of a malignant tumor is called oncogenesis
- Oncogenes
- Tumor suppressor genes
- Reparation mechanisms

**oncogen**

*proliferation*

**tumor- supresor gen**

*inhibition*



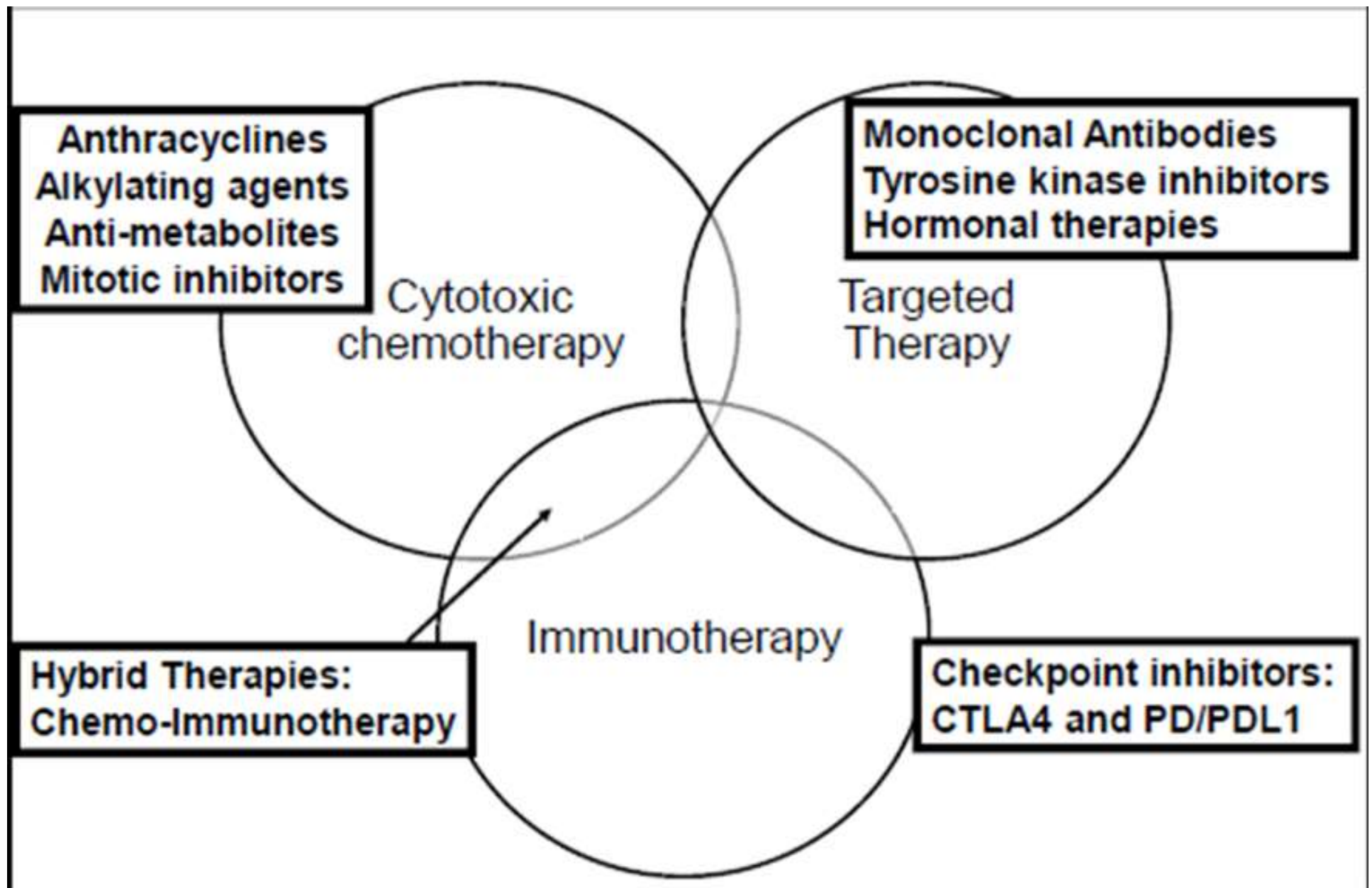
Personalized medicine

- give the right medicine
- to the appropriate patient
- at the right time

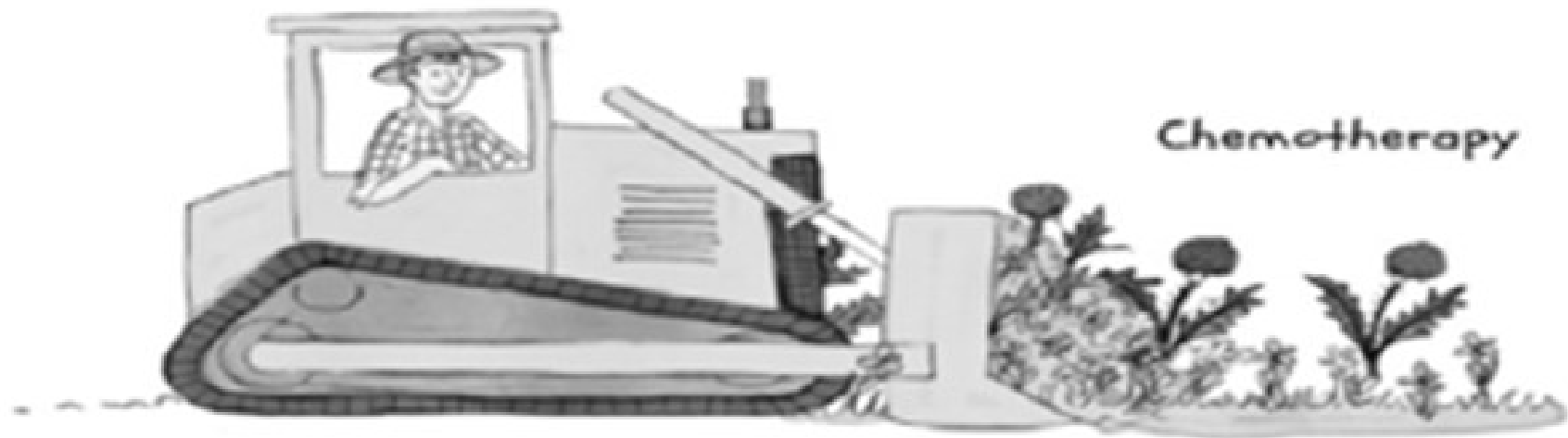
MODERN THERAPIES:

IMMUNOTHERAPY

TARGET THERAPY

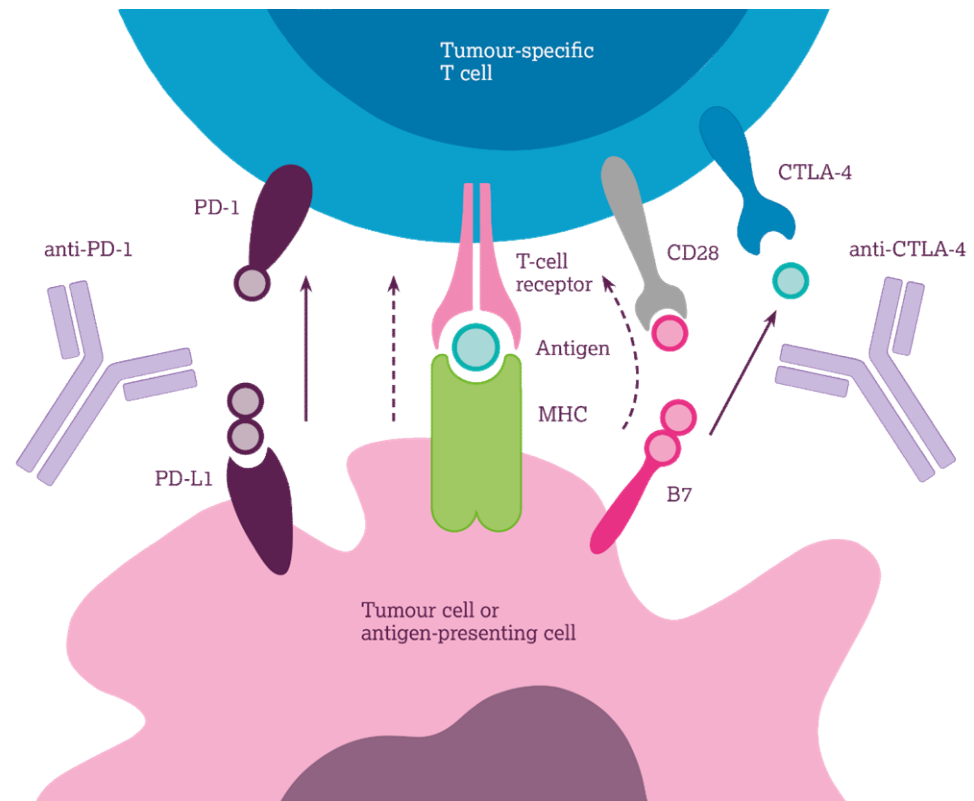


## Targeted Therapies Pick Out Cancer Cells



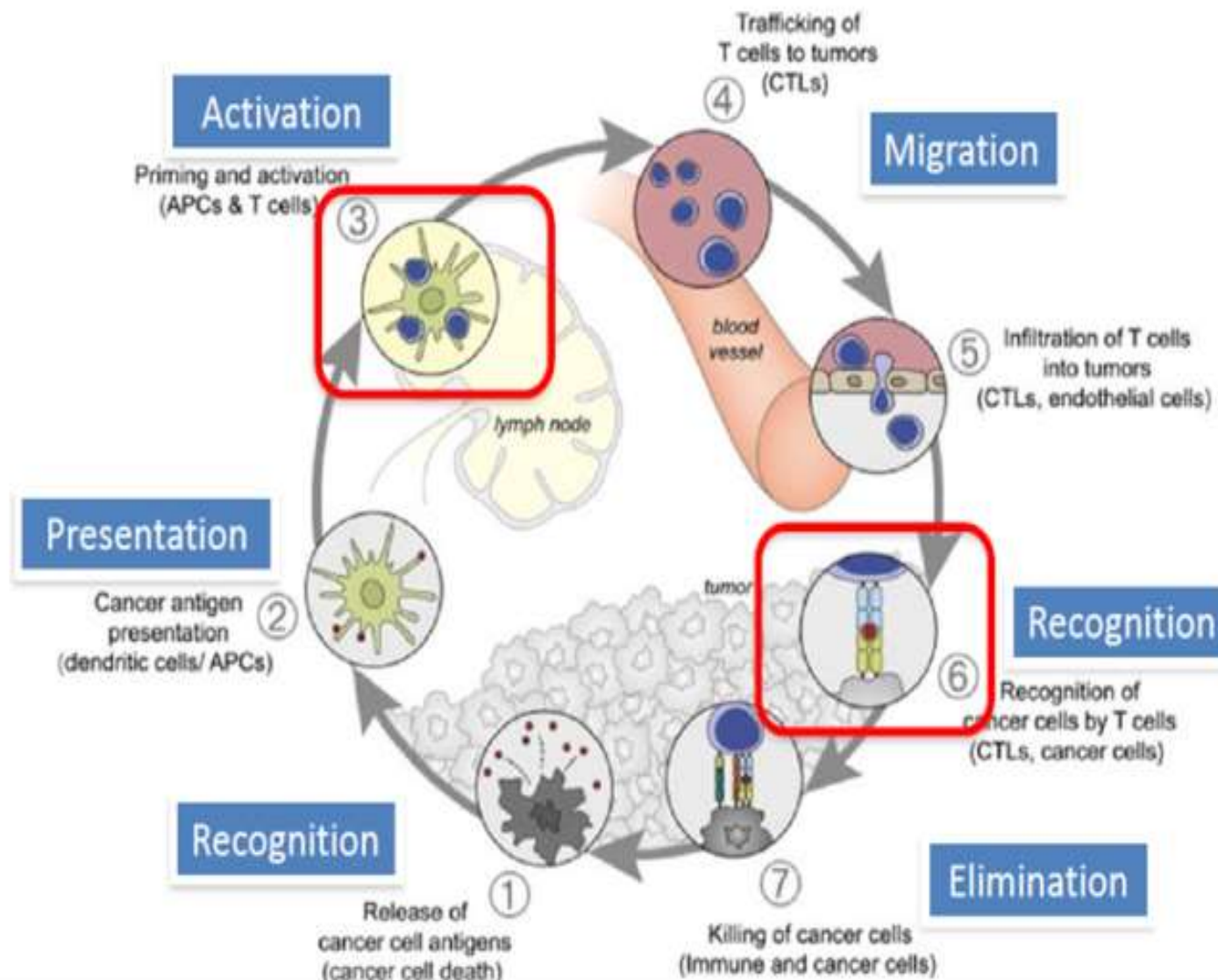
# Immunotherapy

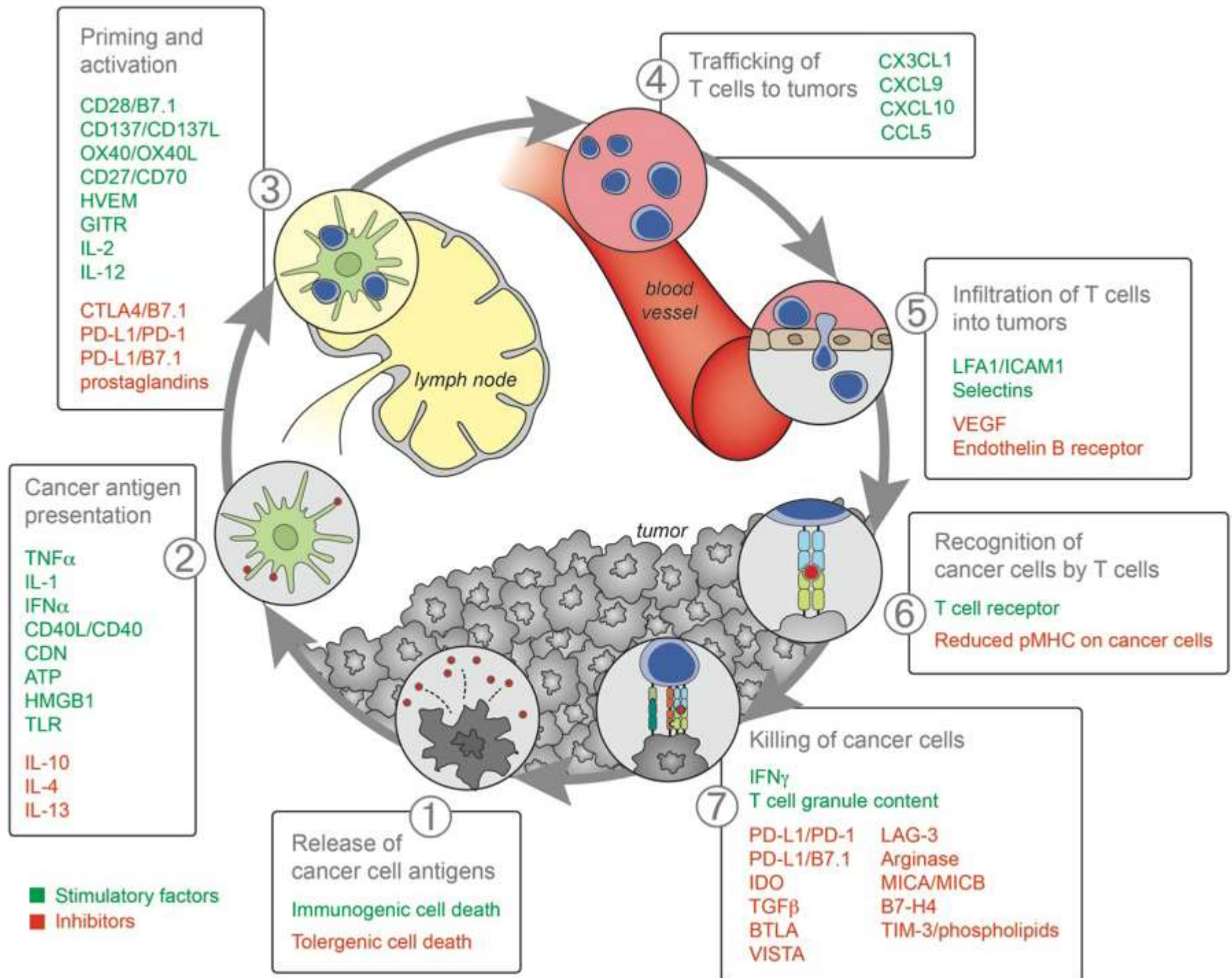
- A rapidly growing field in the treatment of malignant tumors
- They target PD-1, PDL-1, CTLA-4
- They work by stimulating our immune response
- pembrolizumab, nivolumab, ipilimumab, atezolizumab ...
- The toxicity profile is different from classical chemotherapy



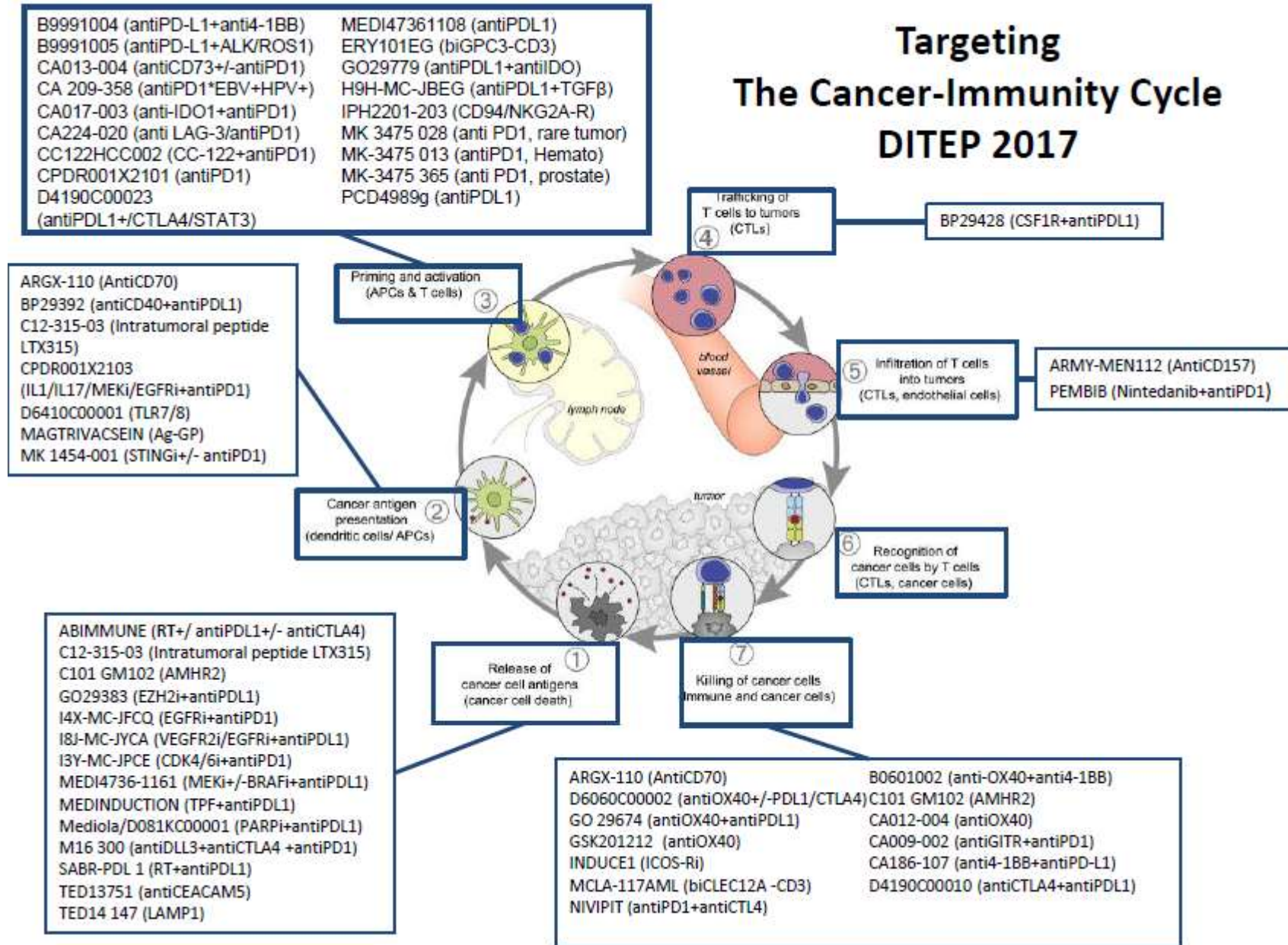
Based on a diagram from García-Tejido, P., Cabal, M. L., Fernández, I. P., & Pérez, Y. F. (2016). Tumor-infiltrating lymphocytes in triple negative breast cancer: the future of immune targeting., 10(Suppl 1), 31-39, which was licenced under CC-BY-NC 3.0. *Clinical Medicine Insights: Oncology*







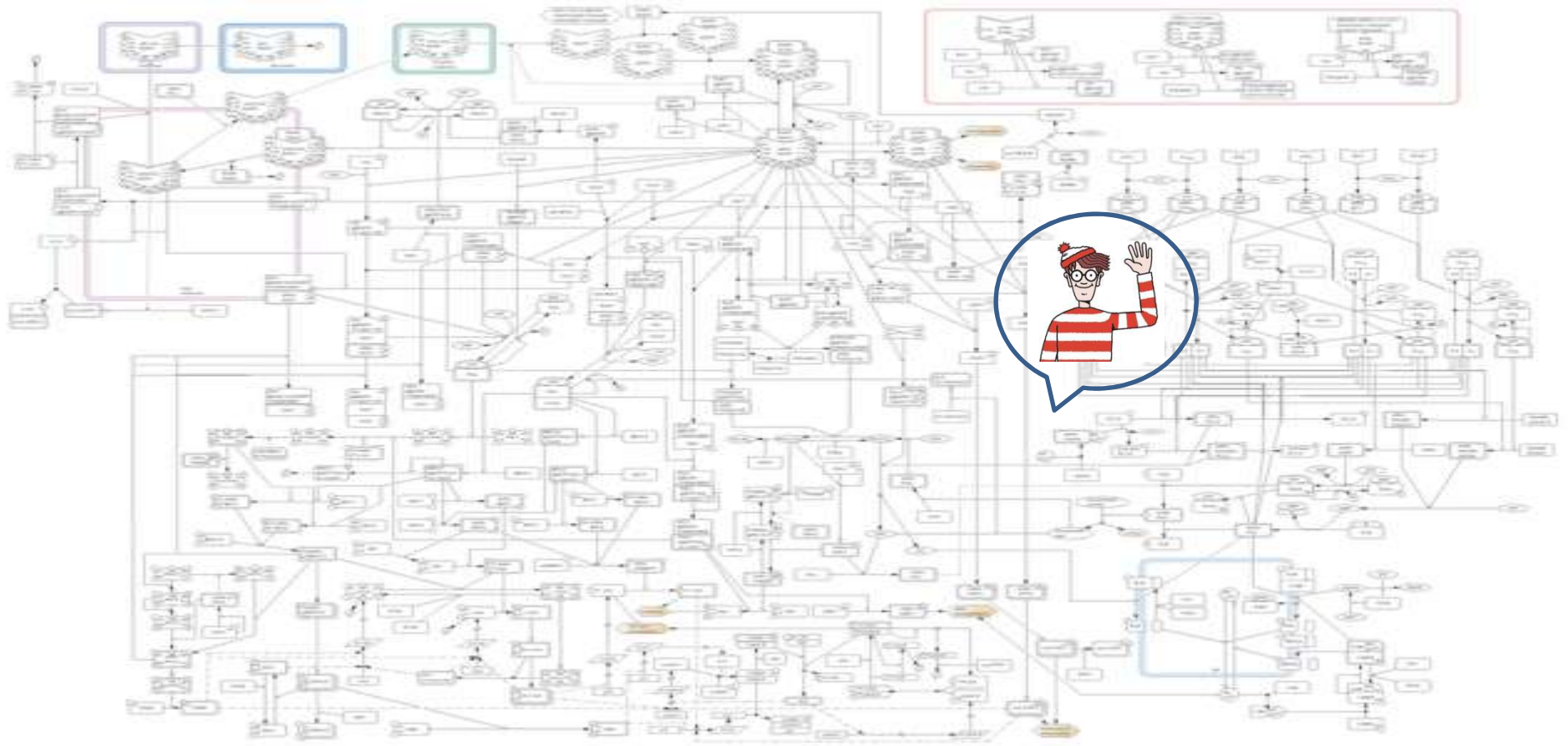
# Targeting The Cancer-Immunity Cycle DITEP 2017

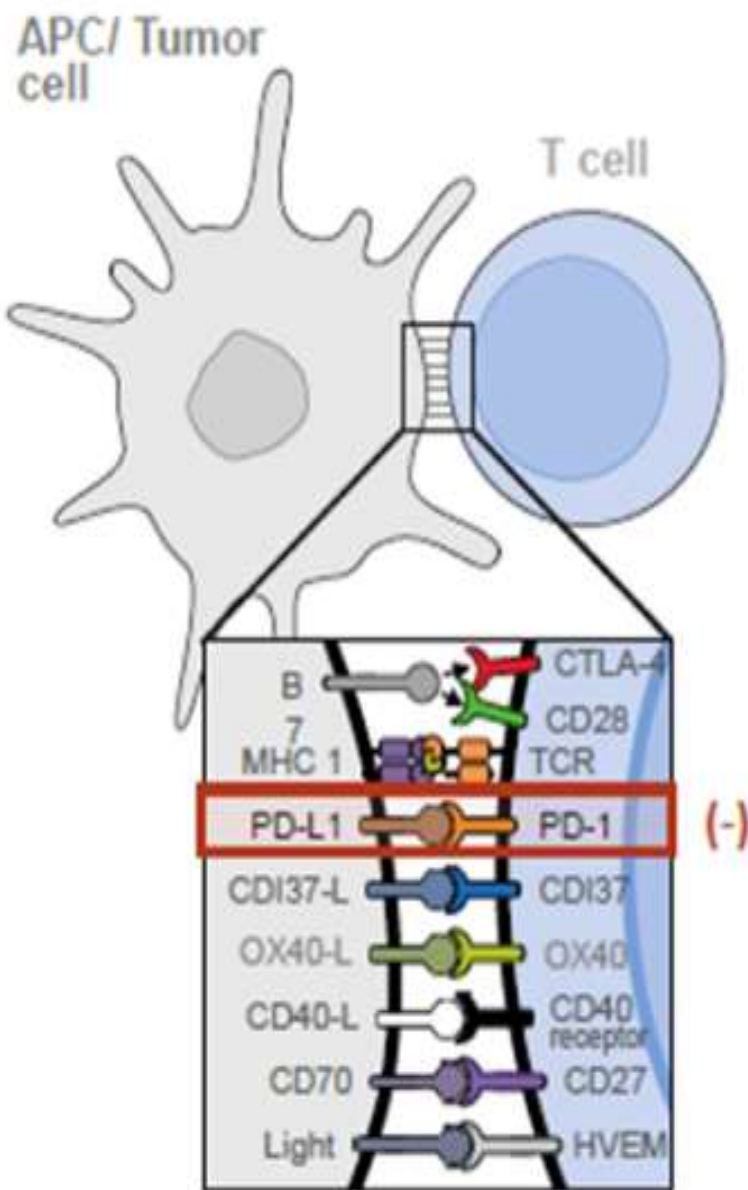




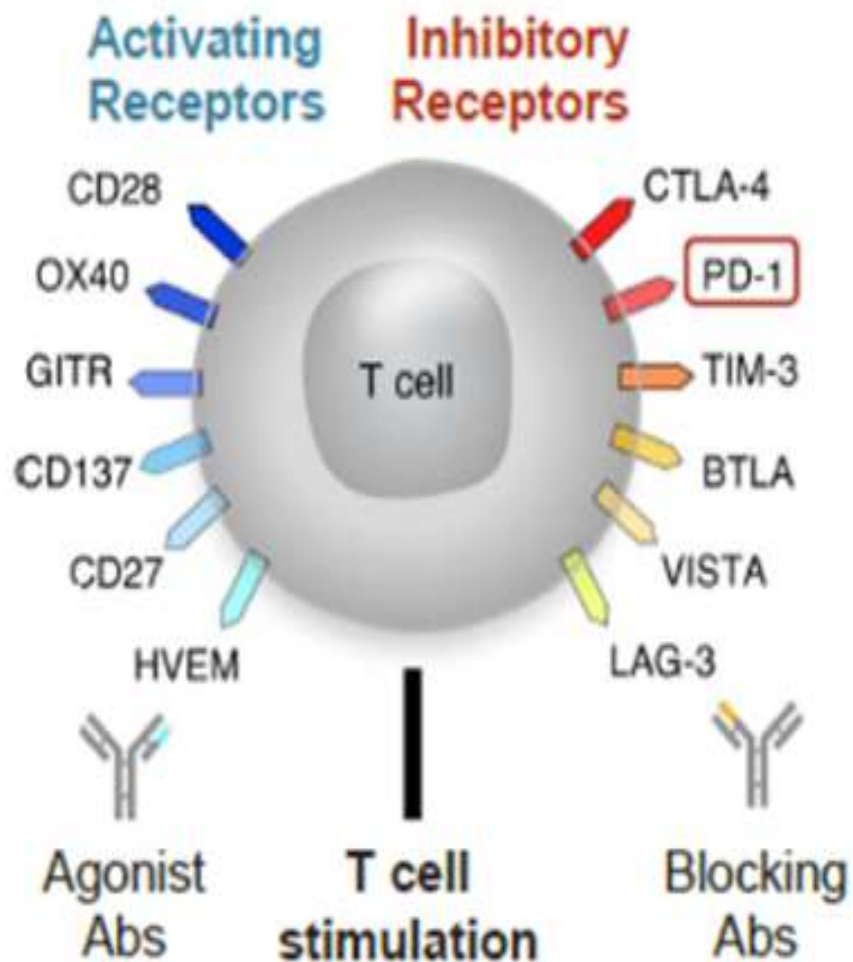
# Complexity of Immunotherapy

## EGFR Pathway Map

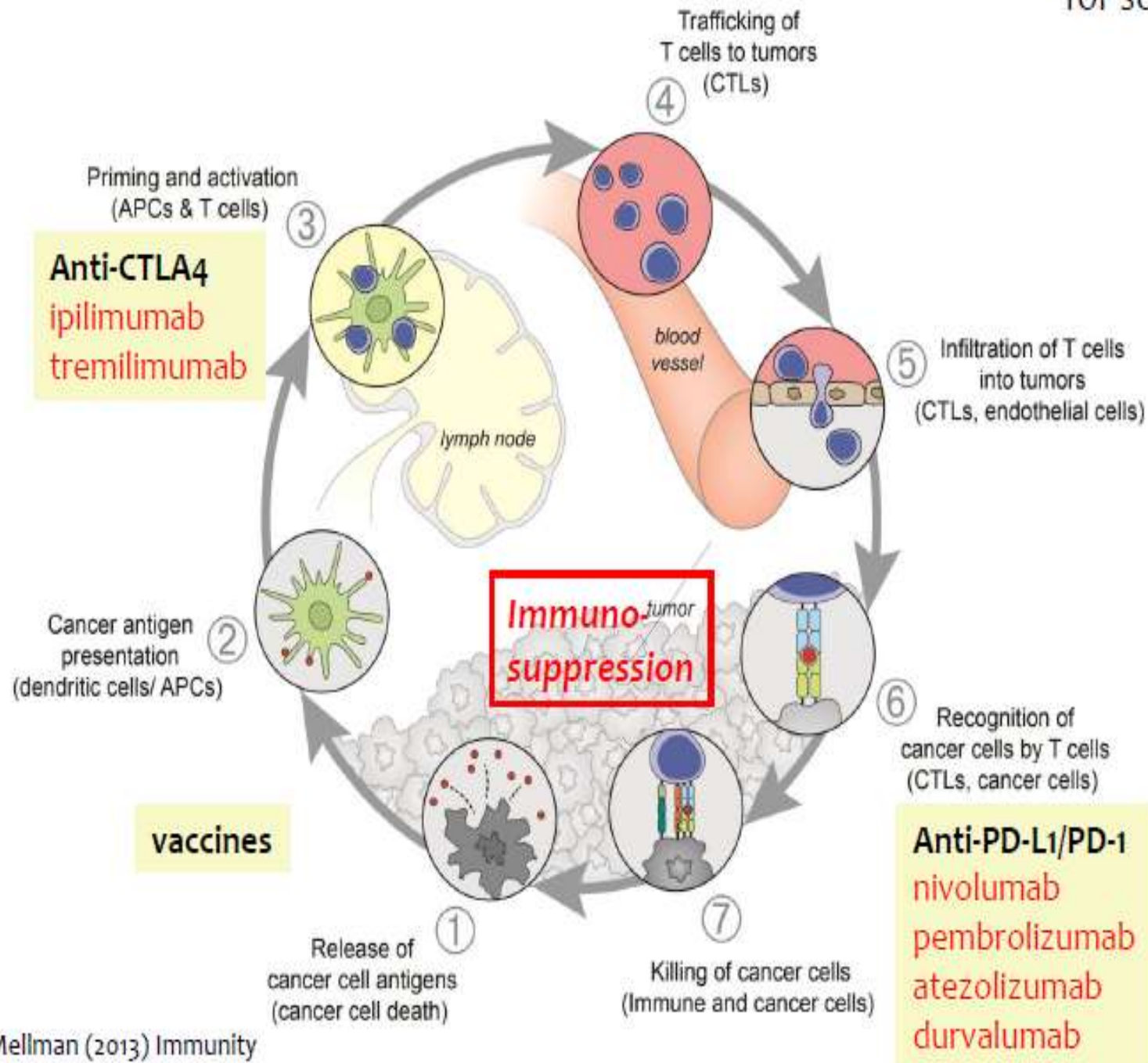




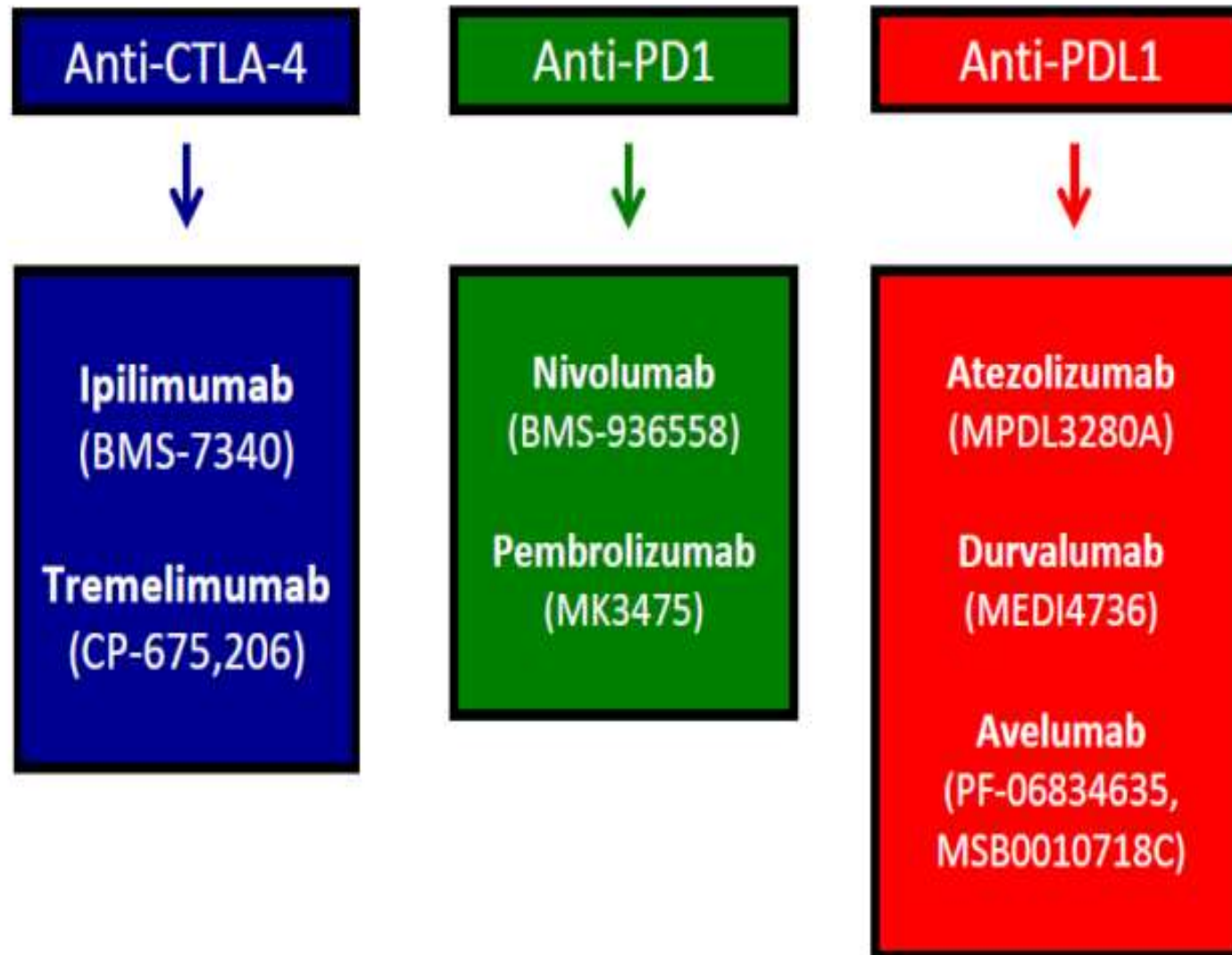
## T CELL TARGETS FOR MODULATING ACTIVITY



\*for some patients



# Immune checkpoint inhibitors



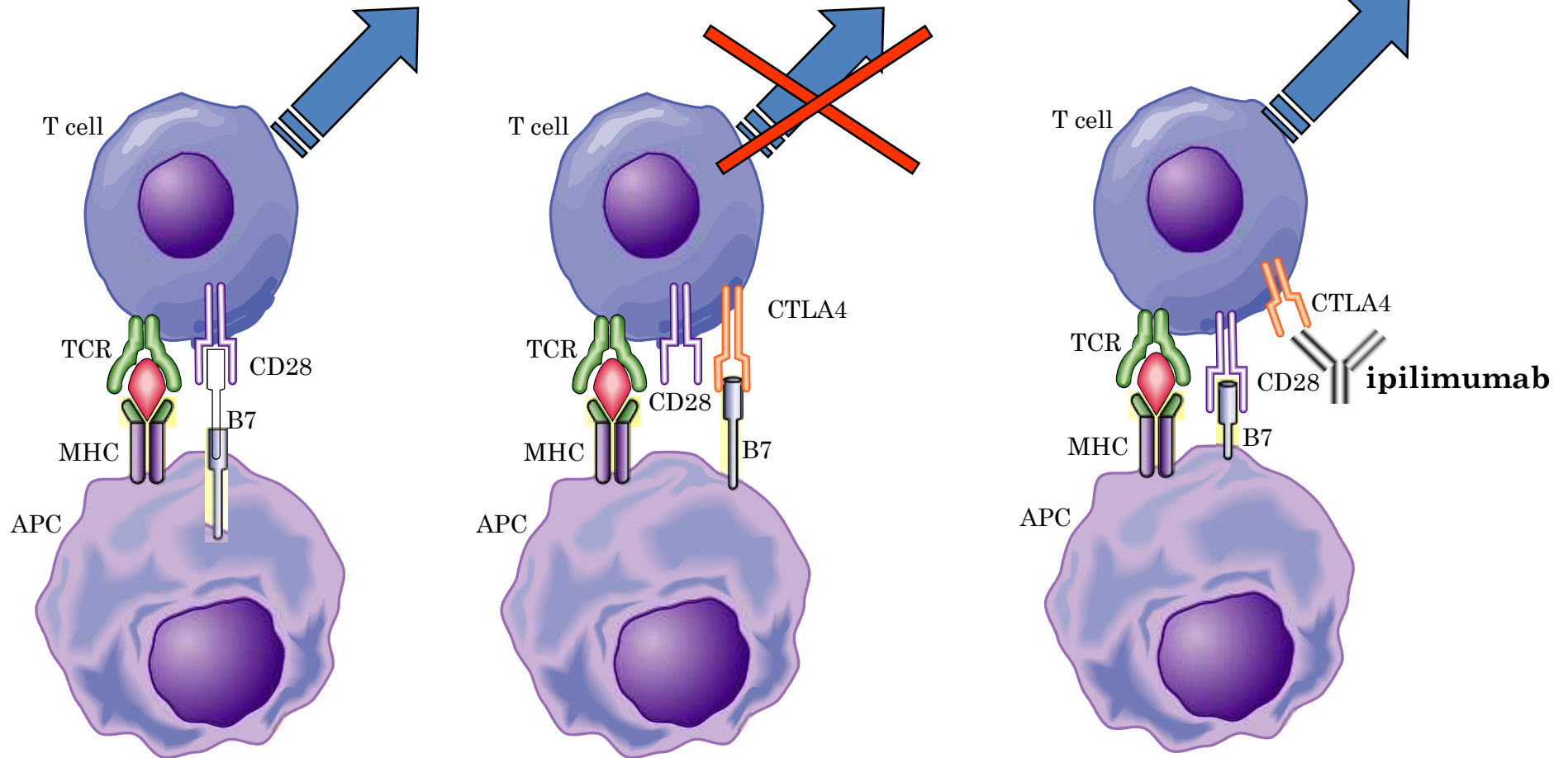
# Cytotoxic T-lymphocyte-associated Protein 4 - CTLA4

- The interaction of B7 and CD28 leads to the activation of T cells
- CTLA4 is not normally expressed on the surface of T lymphocytes.
- 48 to 72 hours after B7/CD28 interaction, CTLA4 begins to be upregulated on the surface of T lymphocytes
- CTLA4, which has a higher affinity for B7 than CD28, competes with CD28 for binding to B7
- Binding of B7 to CTLA4 results in reduced activation of T lymphocytes



# IPIILIMUMAB

**Co-stimulation via CD28: T-cell activation**      **CTLA-4 blocks co-stimulation: No T-cell activation**      **Ipilimumab blocks CTLA-4: T-cell activation**



Adapted from Lebbé et al. ESMO 2008

APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; TCR, T-cell receptor.

Programmed death-ligand 1 (PD-L1)  
Programmed cell death protein 1 (PD-1)

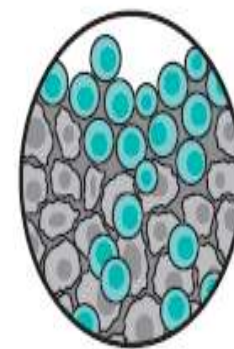
- PD-1 receptor is overexpressed on infiltrating T lymphocytes, and these are functionally exhausted cells
- Ligand: PDL-1 and PDL-2 (tumor cell /APC)
- Increased expression of PDL-1 is correlated with reduced length of survival
- By blocking PD-1 or PDL-1, the functionality of infiltrating T lymphocytes is restored and the level of immunosuppression caused by the tumor is reduced.

**Fig. 3. Mechanism of action of PD-1–blockade therapy.**

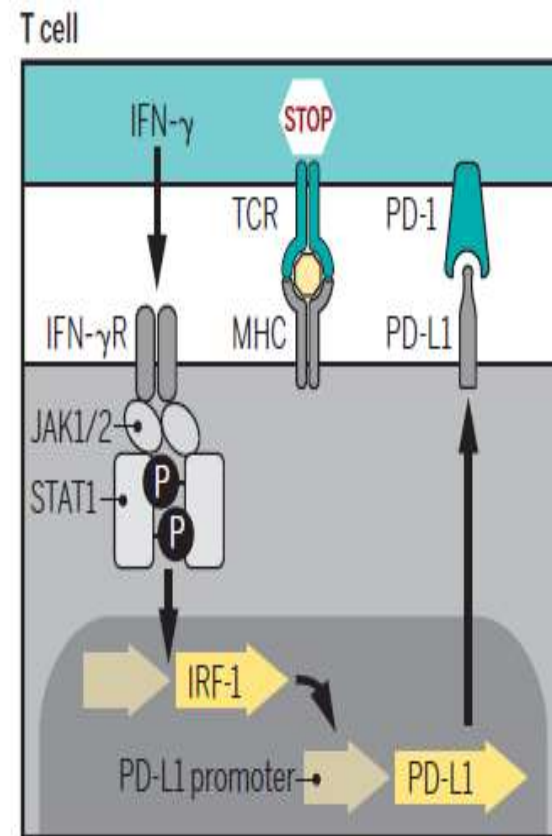
**(Left)** TCR recognition of the cognate antigen presented by MHC molecules on the surface of cancer cells results in T cell activation. T cells then produce IFN- $\gamma$  and other cytokines. Cancer cells and other cells in the tumor microenvironment have IFN- $\gamma$  receptors (IFN- $\gamma$ R) that signal through JAK1/2, which phosphorylate (P) and activate signal transducers and activators of transcription (STAT) proteins that dimerize and turn on a series of interferon-response genes, including interferon regulatory factor 1 (IRF-1), which binds to the promoter of PD-L1, leading to its surface expression. The reactive expression of PD-L1 turns off the T cells that are trying to attack the tumor, and these T cells remain in the margin of the cancer. **(Right)** Blockade of the PD-1–PD-L1 interaction with therapeutic antibodies results in T cell proliferation and infiltration into the tumor, inducing a cytotoxic T cell response that leads to an objective tumor response.



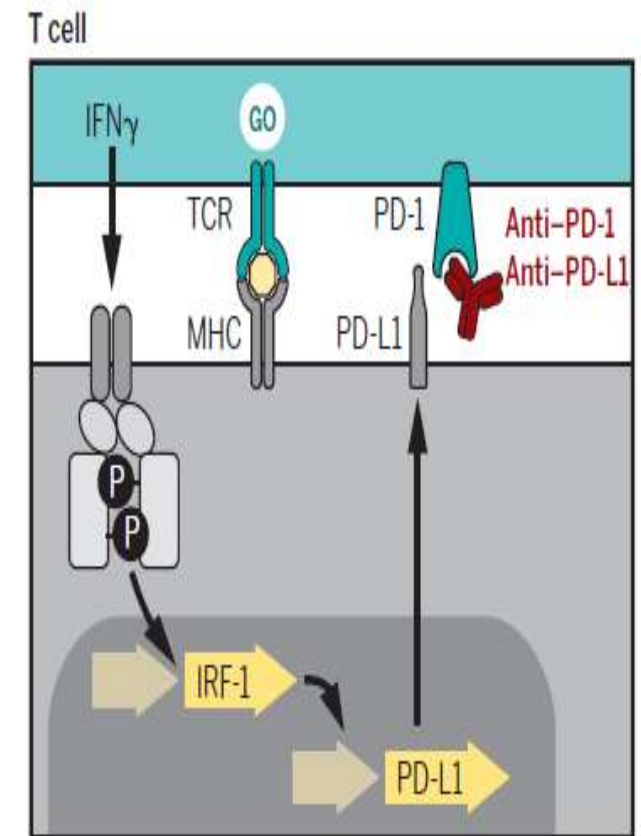
Cancer cells sense they are under attack from T cells by recognizing IFN- $\gamma$ , which leads to the reactive expression of PD-L1.



Blocking the PD-1–PD-L1 interaction takes away the signal that prevented T cells from attaching to cancer cells and leads to tumor infiltration.

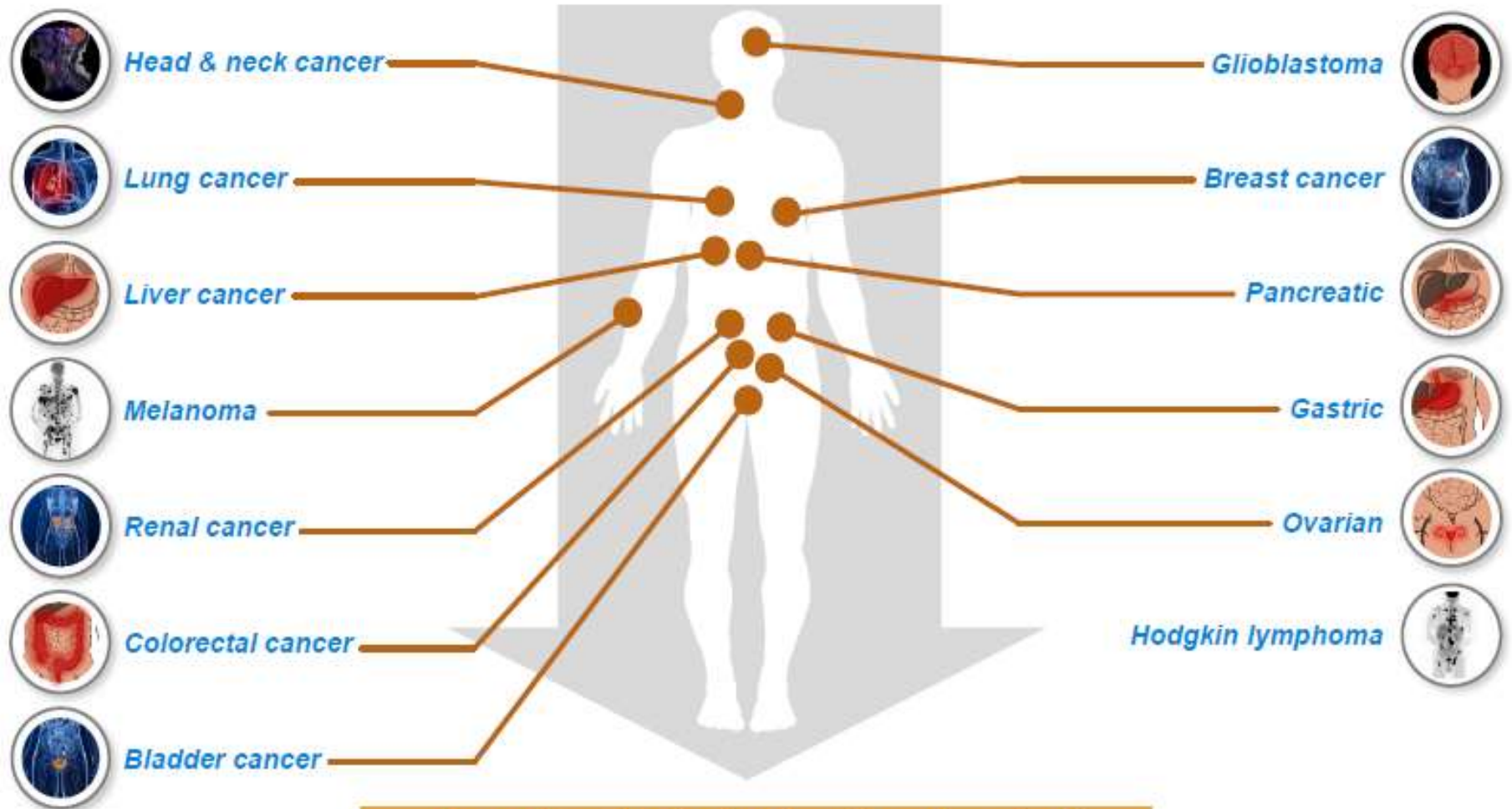


Cancer cell (or tumor macrophage)



Cancer cell (or tumor macrophage)

# Broad activity for anti-PD-L1/PD-1 in human cancer



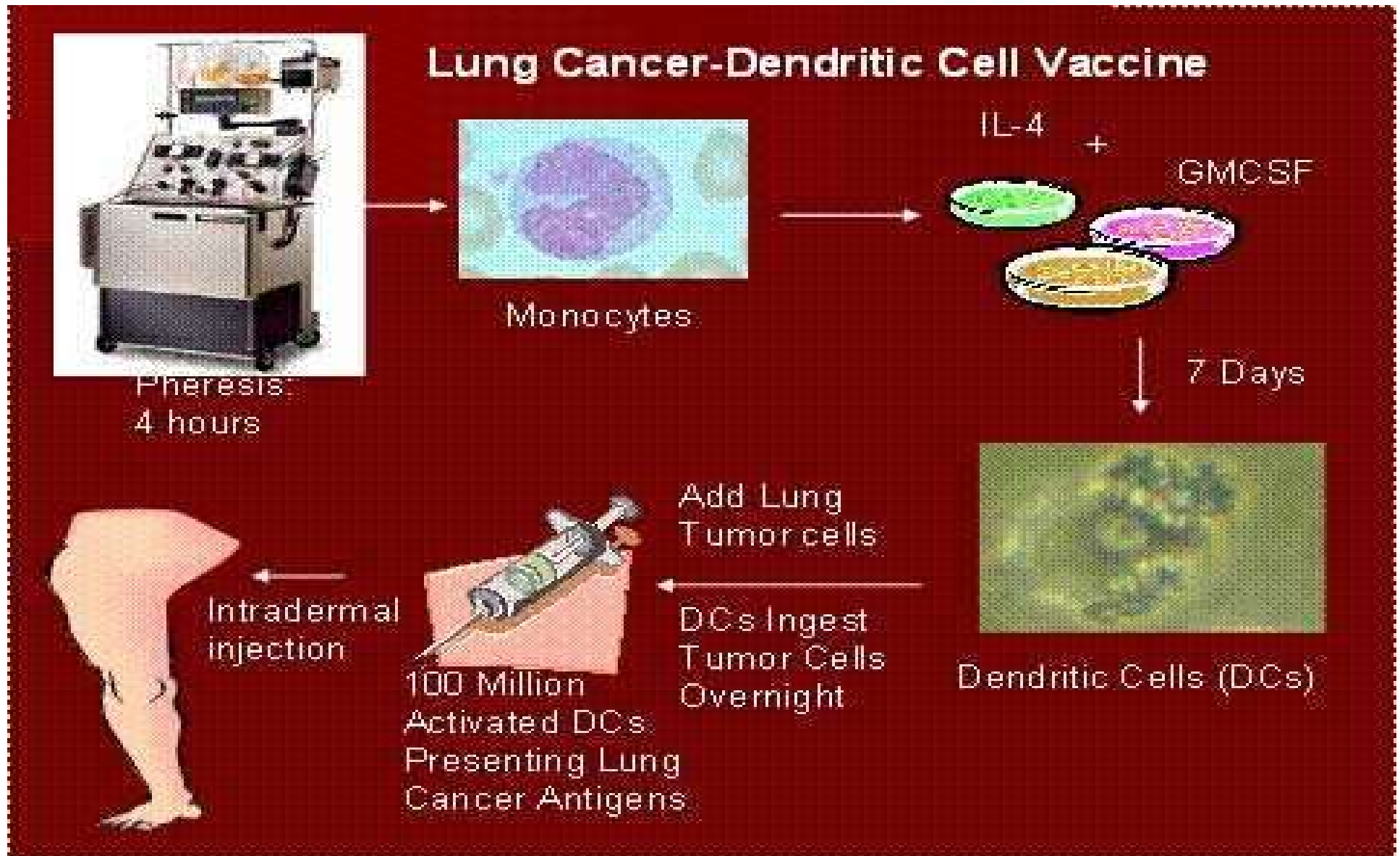
Broad activity, but only subset of patients benefit: ~10-30%

# VACCINES

- Antitumor vaccines are intended for treatment, not prophylaxis.
- The planned goal is to provide an immune system response to the presence of a tumor.
- They differ from the HPV vaccine, which causes cervical cancer
- The HPV vaccine is a traditional prophylactic vaccine that targets a single disease.
- At the moment, vaccines for the treatment of cancer are used mainly in clinical studies.



# VACCINATION WITH DENDRITIC CELLS



# ANTIGEN VACCINES

- The possibility of production of tumor antigens in laboratory conditions.
- Antigens can be specific for a certain type of tumor, or they can stimulate an immune response in multiple types of cancer.
- They are injected into the patient's body, causing an immune response

# Anti-Idiotip VACCINES

- Based on the idea that antibodies can also act as antigens and trigger an immune response.
- The idea is to inject antibodies that are antigenically similar to tumor cells into the patient and thus trigger an immune response
- Tests are performed in lymphoma



# DNA VACCINES

- The idea is to use tumor genes instead of antigens.
- Cells in the body take up the injected genes, which leads to continuous production of antigens
- In this way, the continuous presence of the antigen that produces the immune response is ensured

# OncoVAX

- Autologous vaccine for CRC ST II.
- Approved by the FDA in 2006.
- It is used in adjuvant treatment.
- 254 patients received OncoVAX or placebo.
- 57.1% reduction in relative risk.

# Sipuleucel-T (Provenge)

- Dendritic cell vaccine intended for asymptomatic patients with androgen-independent prostate cancer (AIPC).
- Approved by the FDA in 2005.
- It targets prostatic acid phosphatase (PAP), which is found in 95% of prostate cancers
- 98 patients treated with vaccine or placebo.
- ~3.3 months, i.e. 21% prolongation of median survival
- After three years, 32% of patients in the vaccinated group compared to 21% in the placebo group.

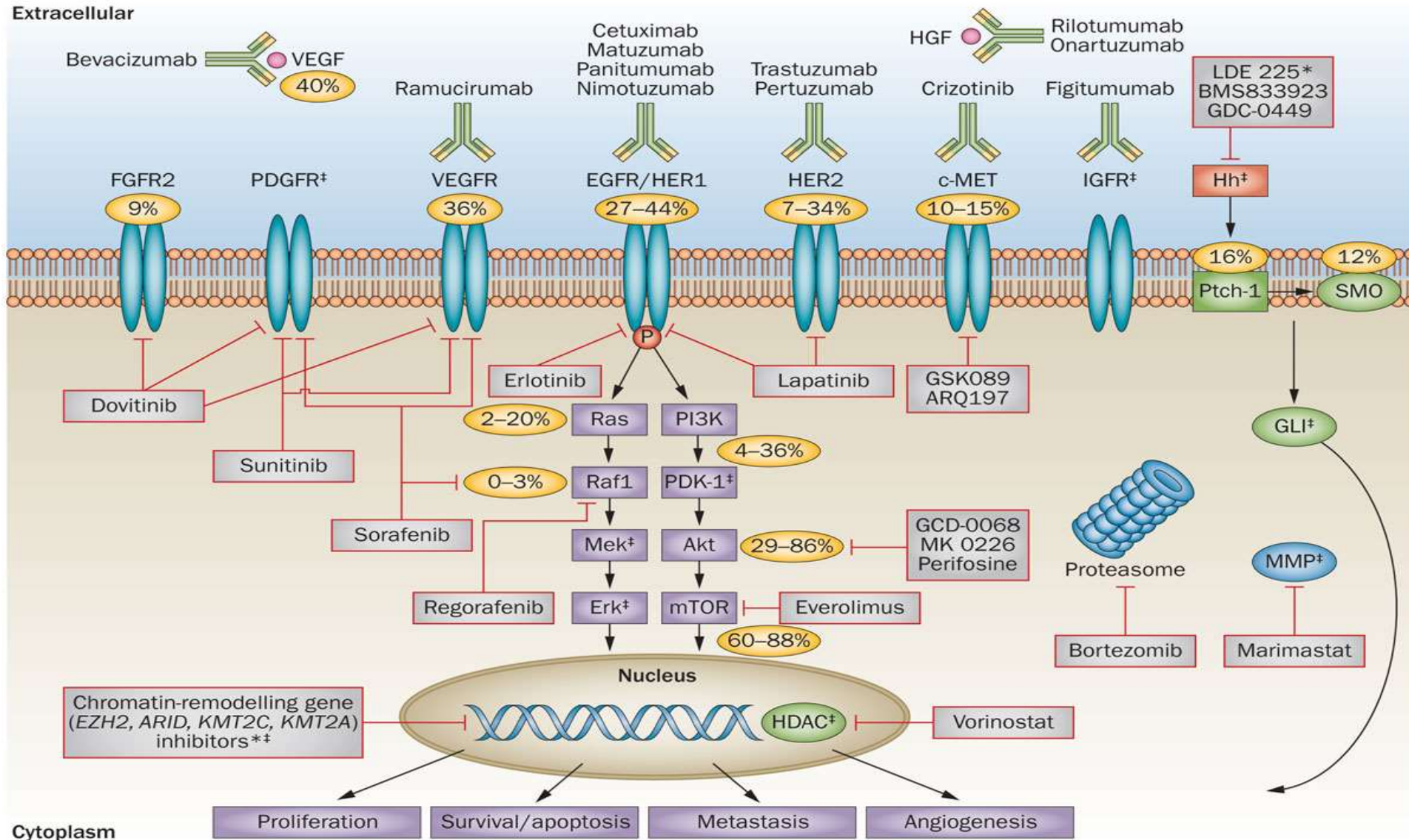
# RESPONSE EVALUATION FOR IMMUNOTHERAPY

- Permissive not restrictive
- RECIST/mWHO modified by immunological criteria
- First radiological examination the most critical (pseudo-progressions)
- irResponders with new lesions also but decrease in baseline lesions
- PD should be confirmed after 4 w

**TABLE 2. Immune-Related Response Criteria Defined<sup>28</sup>**

Immune-related complete response (irCR)	Complete disappearance of all lesions (whether measurable or not, and no new lesions)
	Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented
Immune-related partial response (irPR)	Decrease in tumor burden $\geq 50\%$ relative to baseline
	Confirmed by a consecutive assessment at least 4 weeks after first documentation
Immune-related stable disease (irSD)	Not meeting criteria for irCR or irPR, in the absence of irPD
Immune-related progressive disease (irPD)	Increase in tumor burden $\geq 25\%$ relative to nadir (minimum recorded tumor burden)
	Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented

Extracellular



# TARGET THERAPY

- It is aimed at a precisely defined molecular target that is either extracellular or intracellular
- Target correlates with tumor biology
- The target is correlated with the therapeutic effect
- The goal is to kill tumor cells selectively and specifically
- The ideal situation would be if the target is necessary for the survival of the malignant cell
- That the target is not expressed on healthy cells
- Thus to cause the death of malignant cells without or with minimal consequences for healthy cells
- That the target can be identified with existing tests

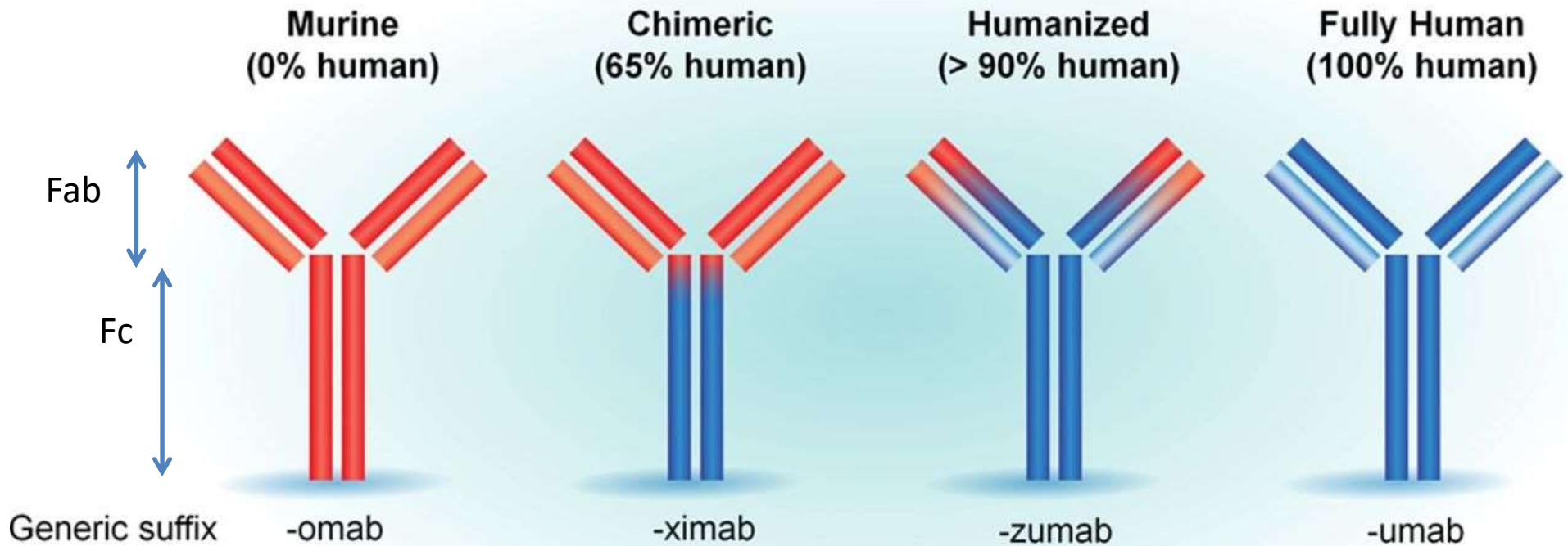
# “TARGETS”

- Steroid receptors: for ER+ breast, prostate and lymphoma cancers
- HER2: for breast and stomach cancer
- ALK: for NSCLC
- CD20: for lymphoma
- bcr/Abl: for CML
- c-Kit: for GIST
- Hedgehog: for basal cell carcinoma and medulloblastoma
- RET: for medullary thyroid carcinoma
- b-RAF: for melanoma

- Receptors that are acted upon by chemical agents are also targets
- EGFR, Erlotinib in NSCLC and Pancreas
- ALK, Crizotinib in lung cancer
- TK, several different drugs, sunitinib in kidney cancer, imatinib in CML and GISTa
- CDK4/6, Palbociclib in breast cancer
- BRAF, MEK1/2, Dabrafenib and trametinib in melanoma



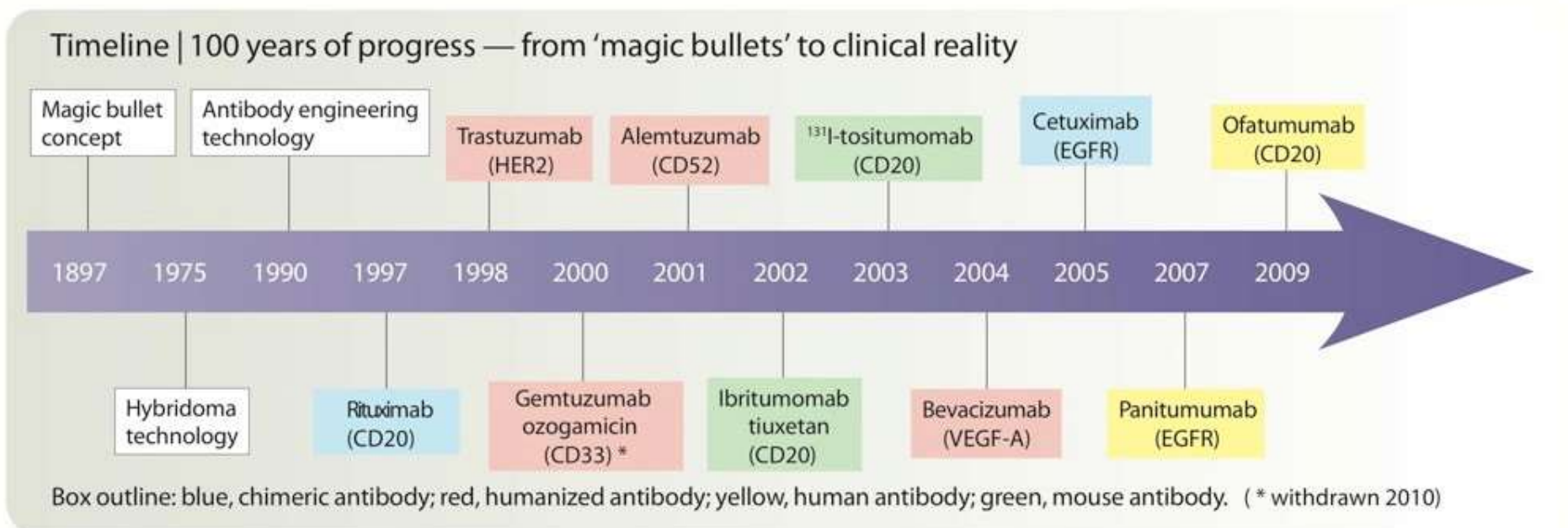
# Types of mAbs



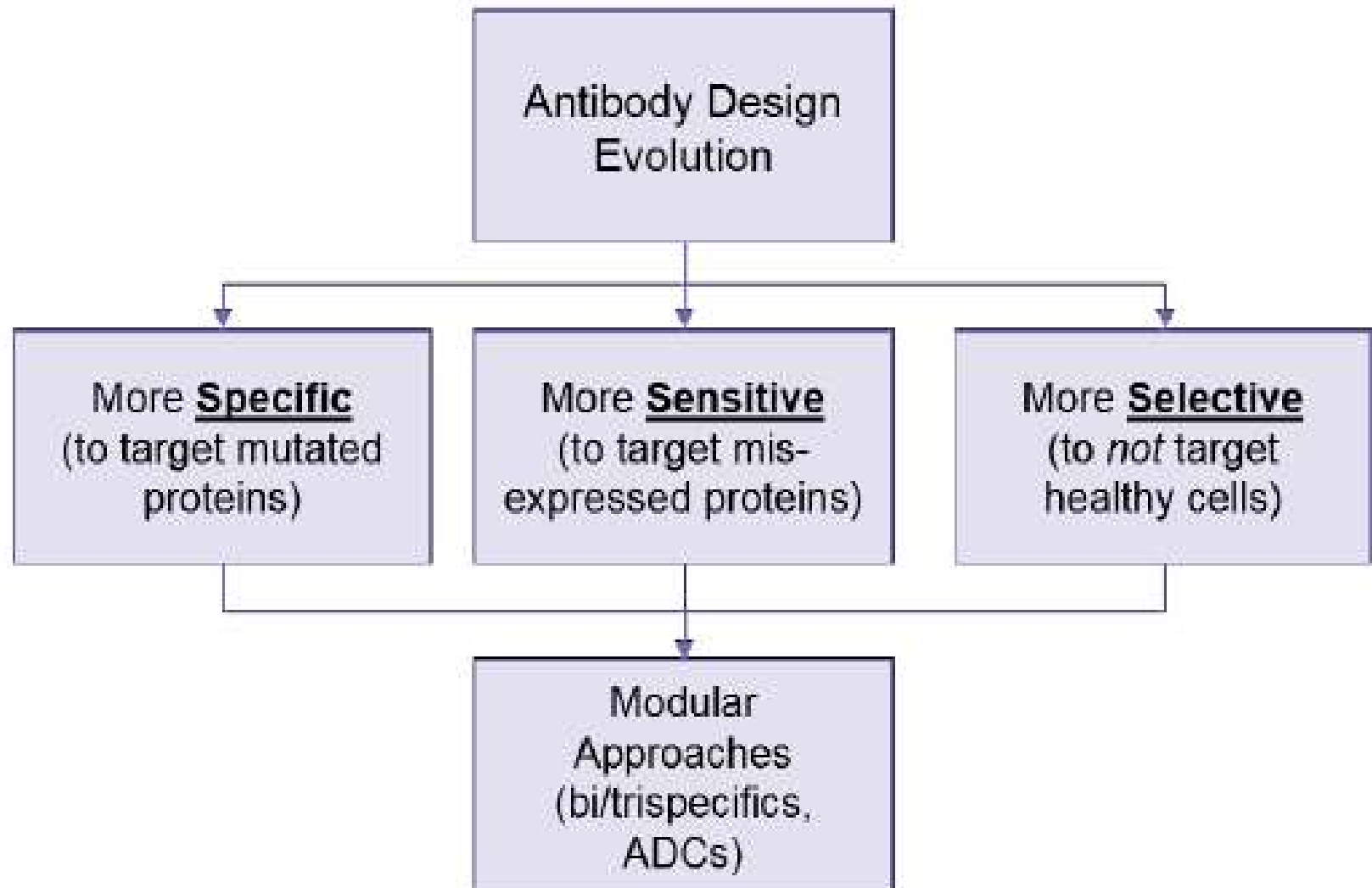
Blue denotes human component

Orange denotes murine component

# Monoclonal antibodies in therapy. I. Cancer.

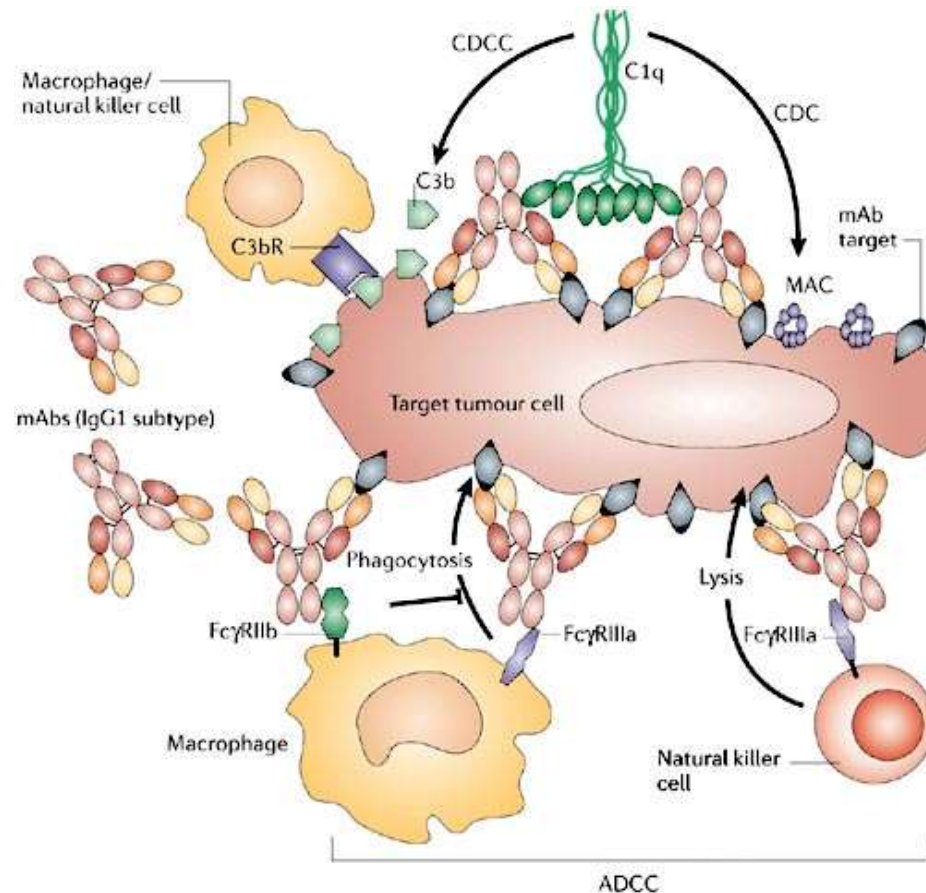


Weiner LM et al. *Nat Rev Immunol* 10:317 (2010), modified

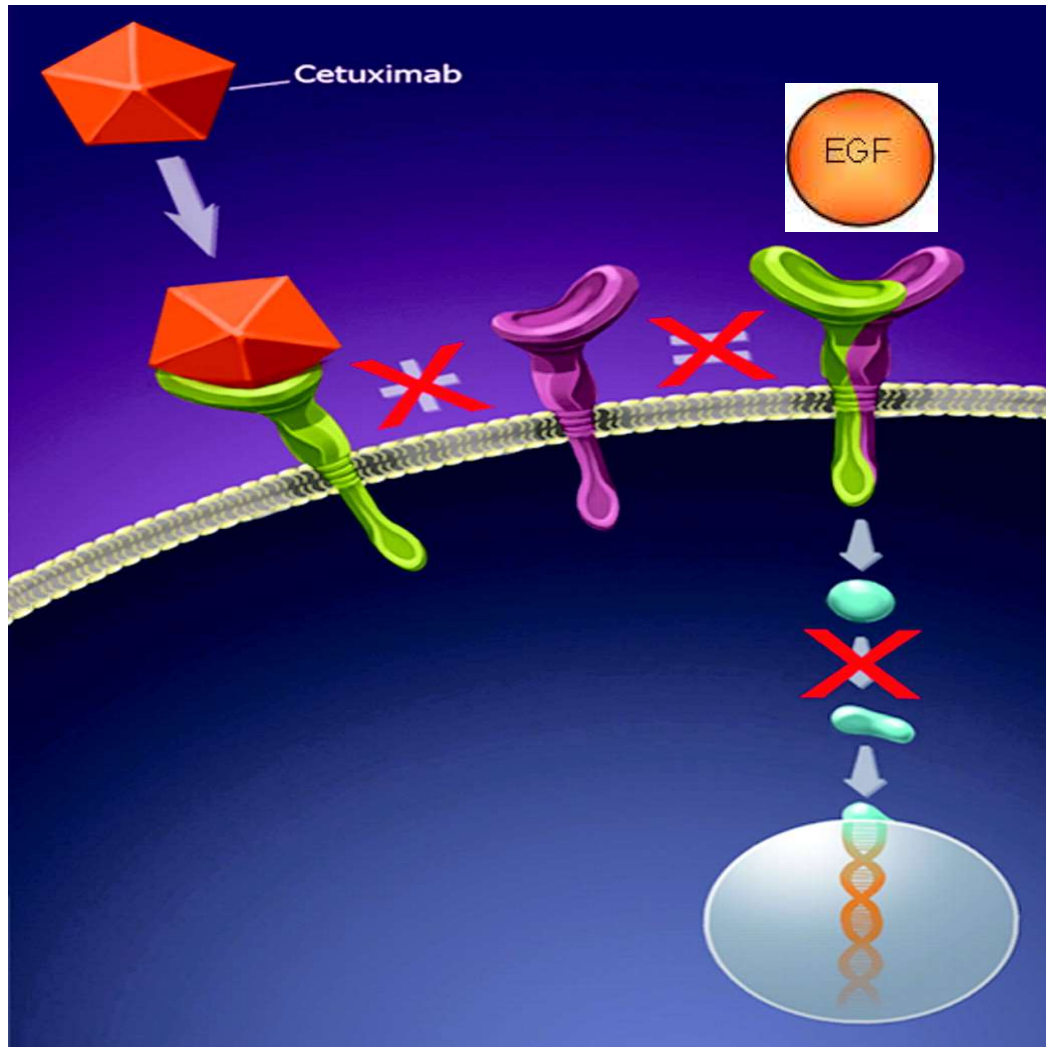


# mAbs

1. They make tumor cells more visible to our immune system by binding to specific sites on them

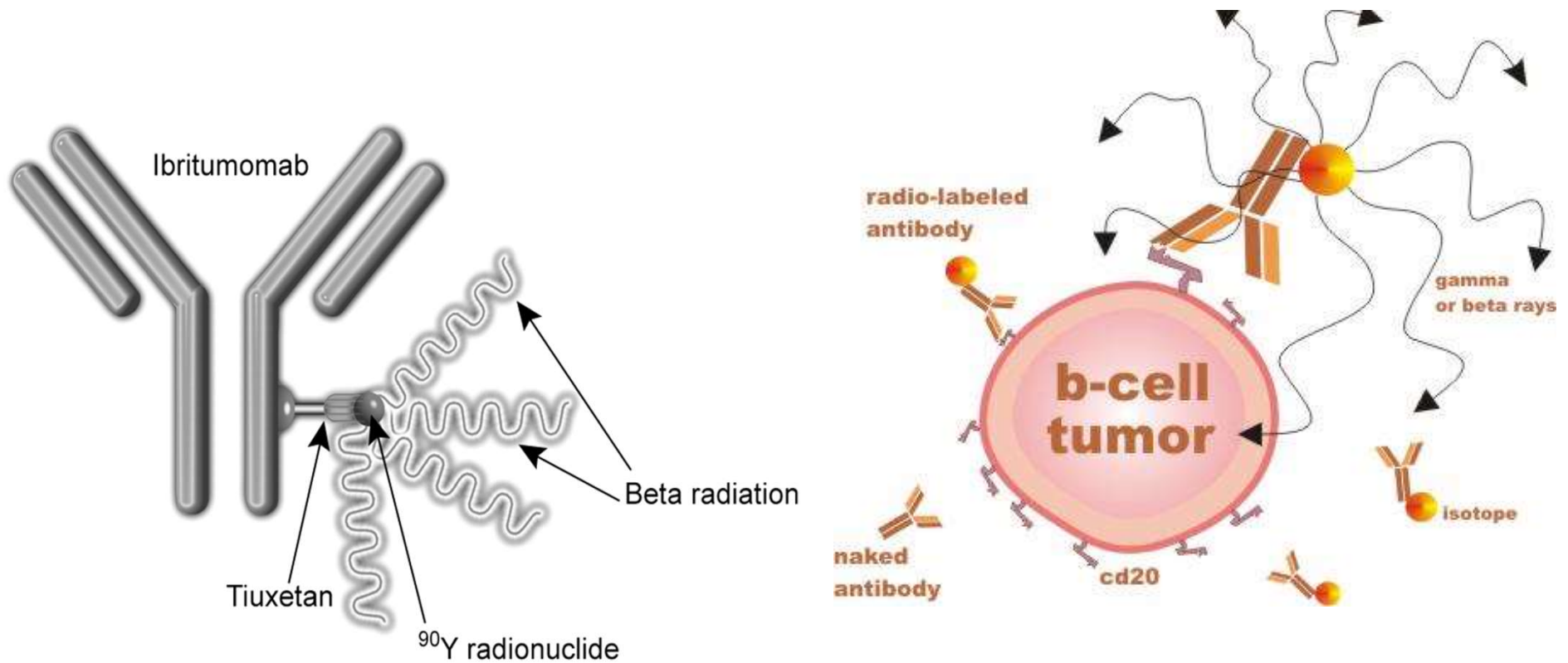


They block the signals for the growth of tumor cells



growth signal  
(epidermal growth factor).

### 3. They can be used as carriers of radiation sources or cytotoxic drugs (ADCs).

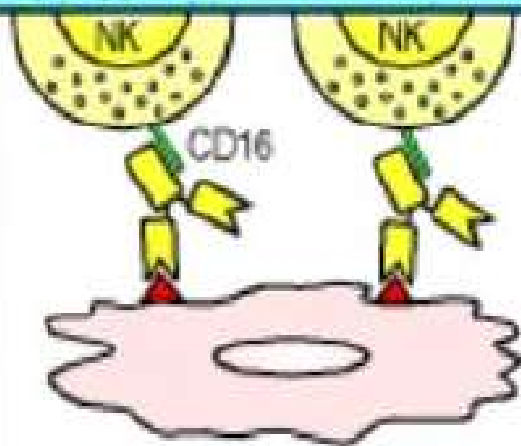




**Tumor-specific antibody**



**Antibodies bind to the tumor cell**

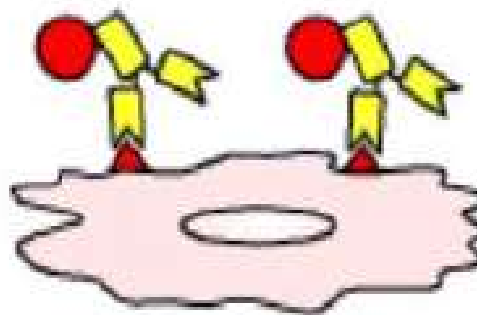


NK cells with Fc receptors (CD16) are activated to kill the tumor cells

**Tumor-specific antibody conjugated to toxin**



**Antibody-toxin conjugates bind to the tumor cell**

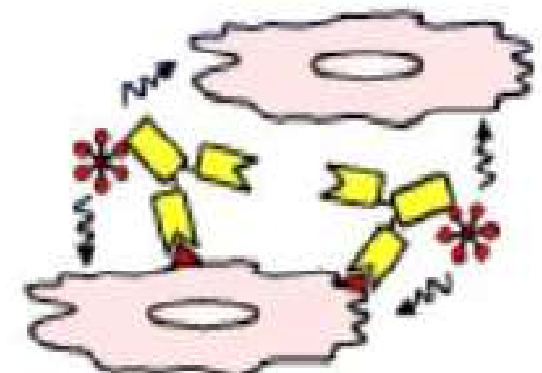


Conjugates are internalized, killing the cell

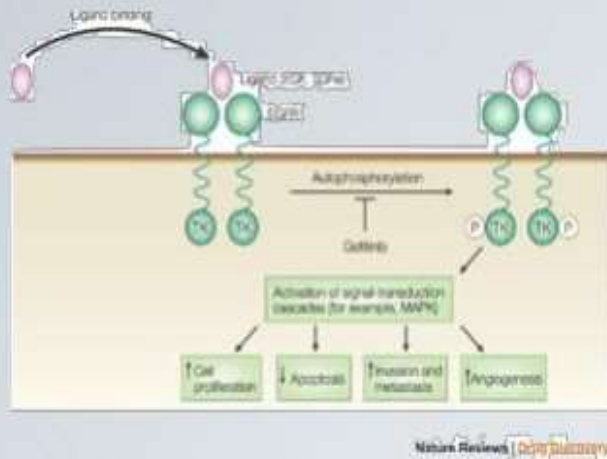
**Tumor-specific antibody conjugated to radionuclide**



**Radioactive antibody binds to the tumor cell**



Radiation kills the tumor cell and neighboring tumor cells

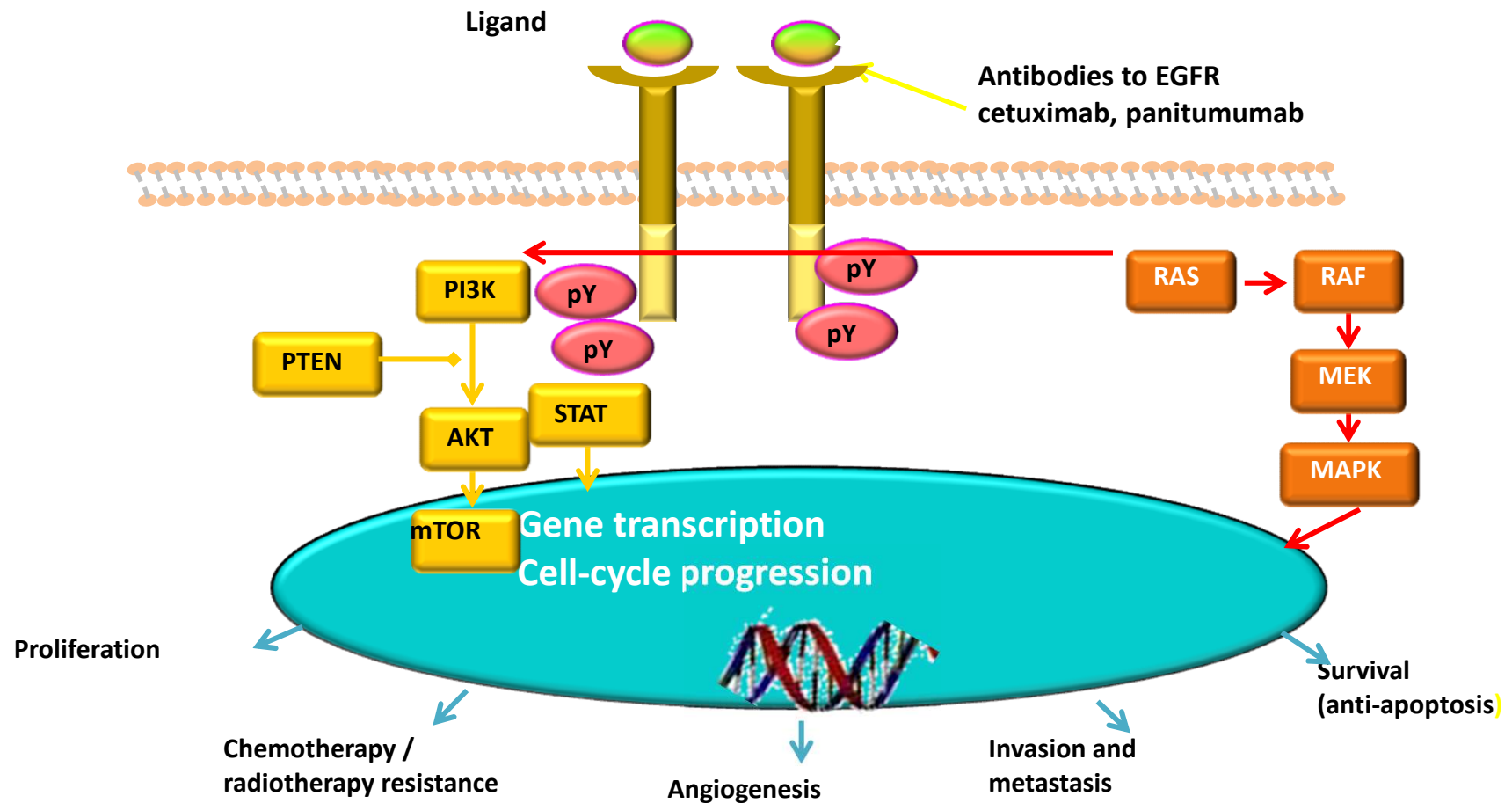


# EGFR

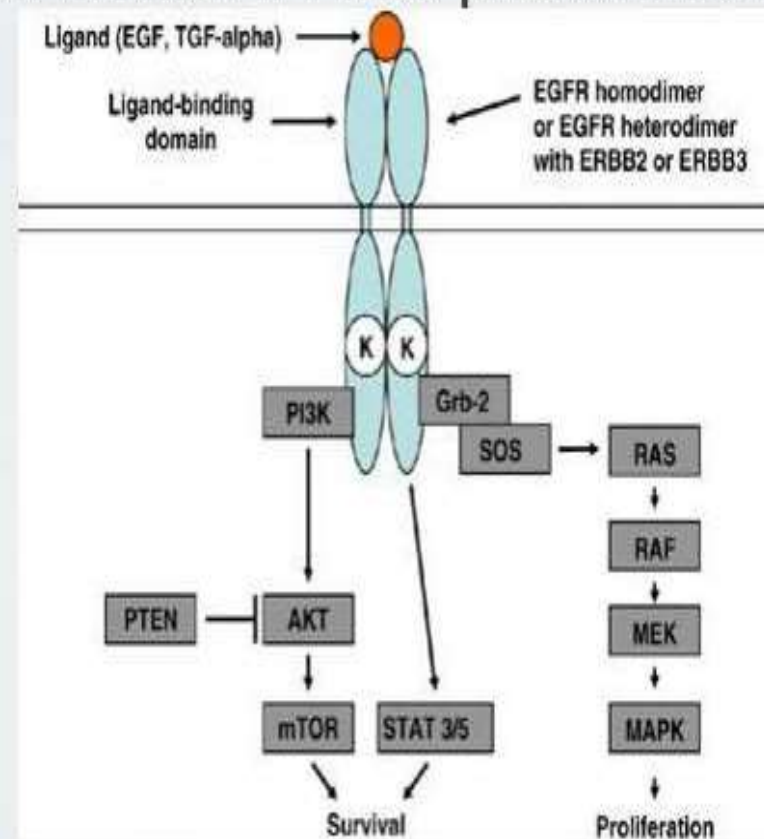
- One of the ErbB family of tyrosine kinase receptors involved in growth and differentiation.
- Known to be present on the surface of healthy cells and is abnormally expressed and activated in many tumor types including colorectal tumors.
- Activation of EGFR by its ligands-EGF and transforming growth factor  $\alpha$ , initiate downstream signaling mechanisms which in turn result in cellular **growth, differentiation, and proliferation**.

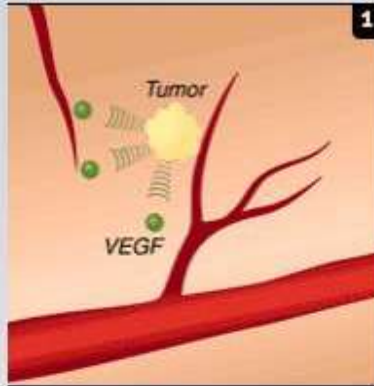


# EGF Receptor: Role in CRC Therapy

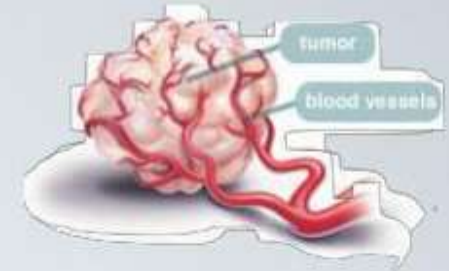


- Benefit of cetuximab treatment was confined to patients who had a tumor with no K-ras mutation.
- It had little or no effect in the presence of a K-ras mutation.

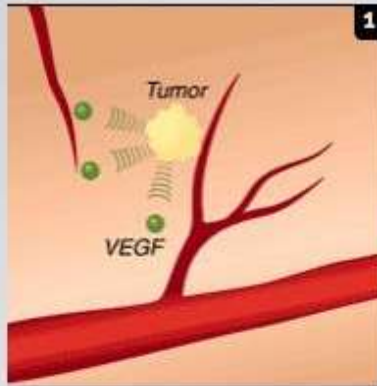




# VEGF



- Central to the entire angiogenic process.
- VEGF molecule interacts with cell surface VEGF receptors
  - growth and differentiation of vascular endothelial cells.
  - formation of new blood vessels.

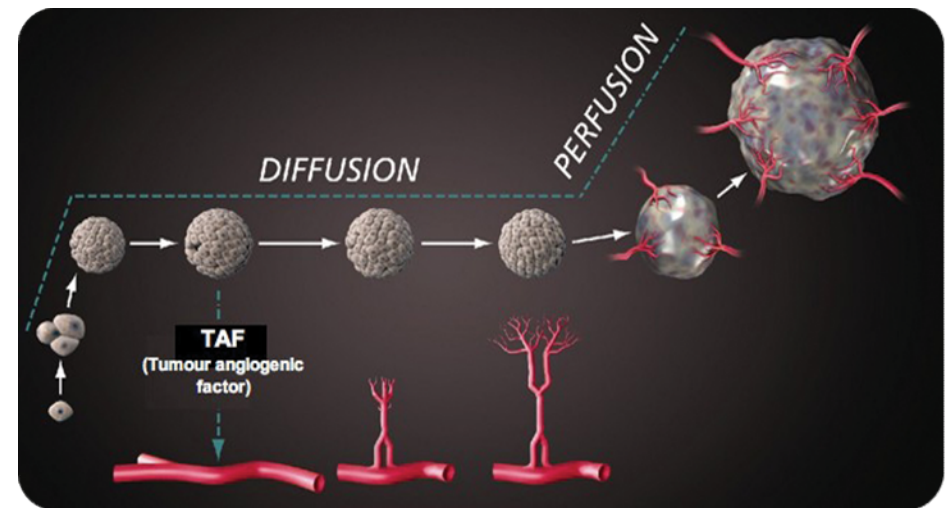
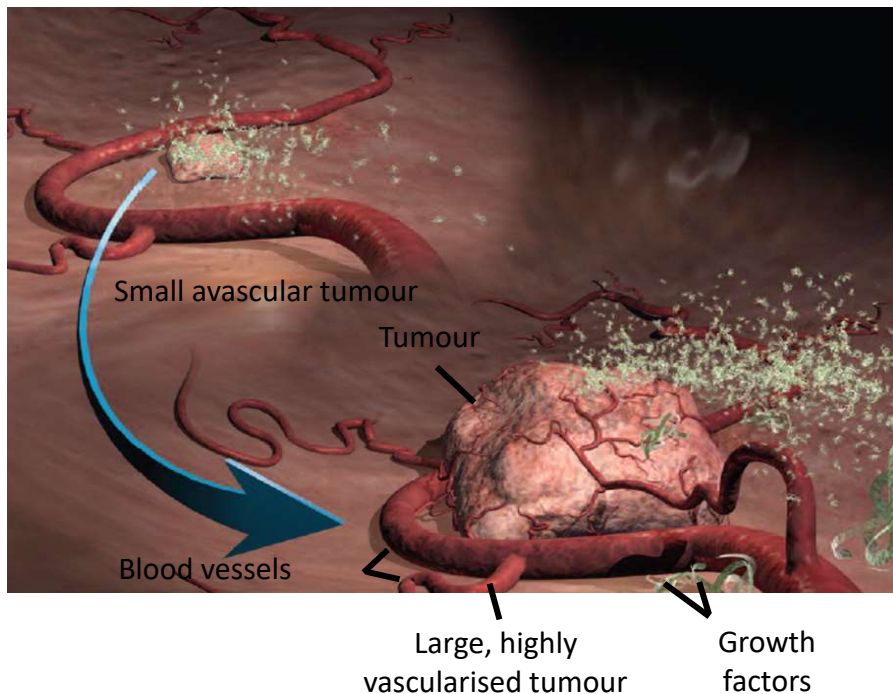


# VEGF

- Expressed by 40-60% of colorectal cancers
  - correlates with disease **recurrence** and **survival**
- VEGF is involved in the angiogenic switch to vascular malignant growth of **micrometastases**, which can cause tumor **relapse**.

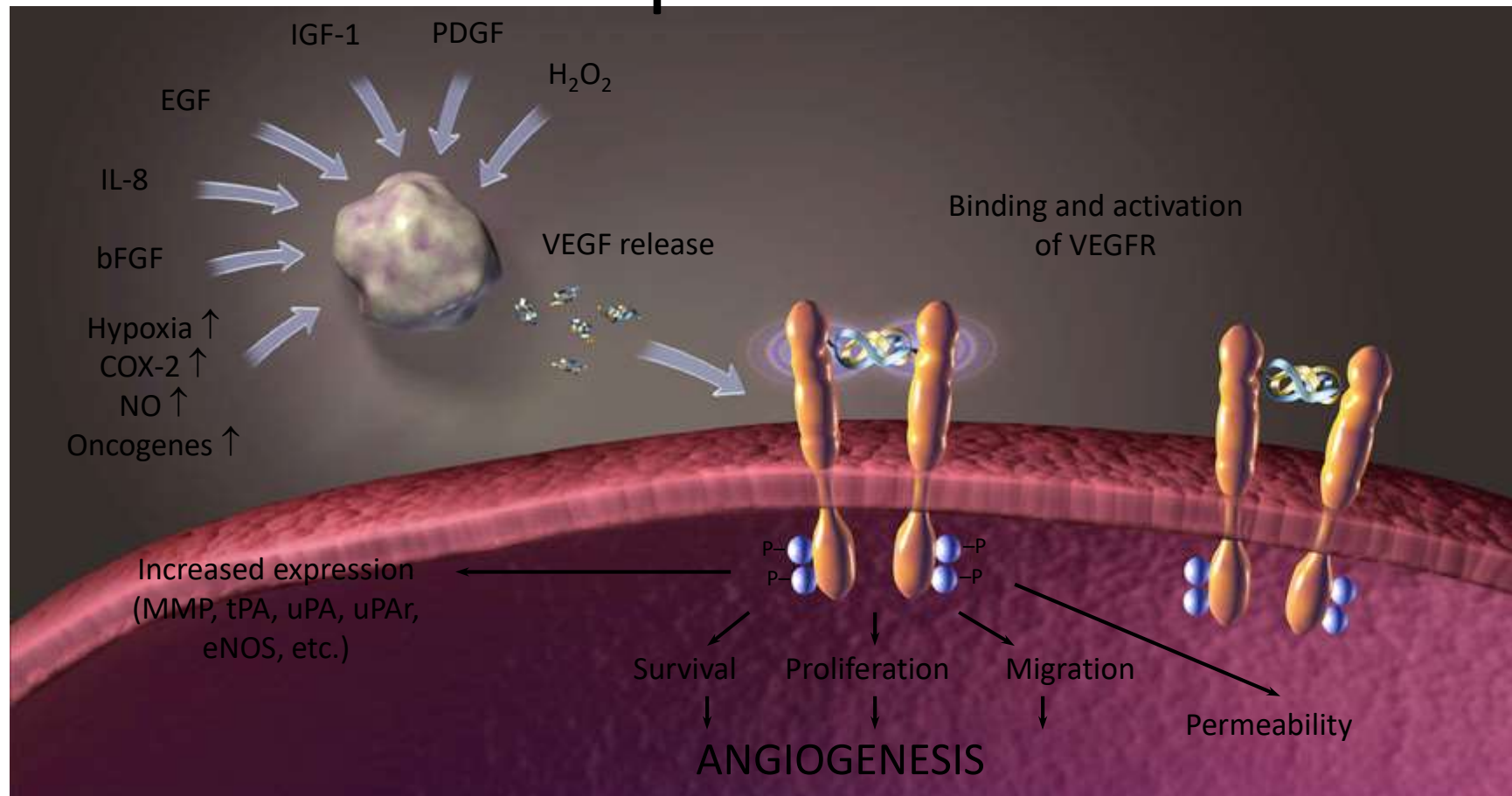
# Angiogenesis is essential to tumour development

- An independent blood supply is required for a tumour to grow beyond 2mm in diameter
- Larger tumours rely on their vasculature for survival and further growth

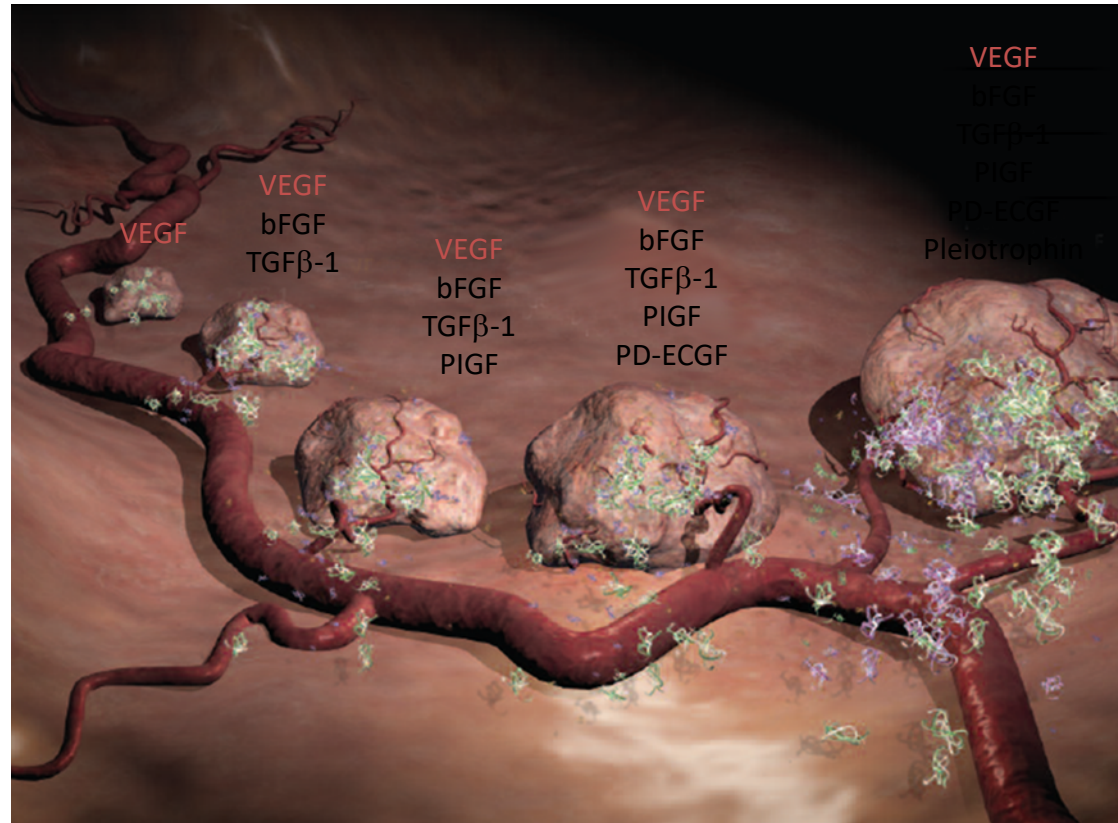




# Tumour characteristics and environment promote VEGF expression



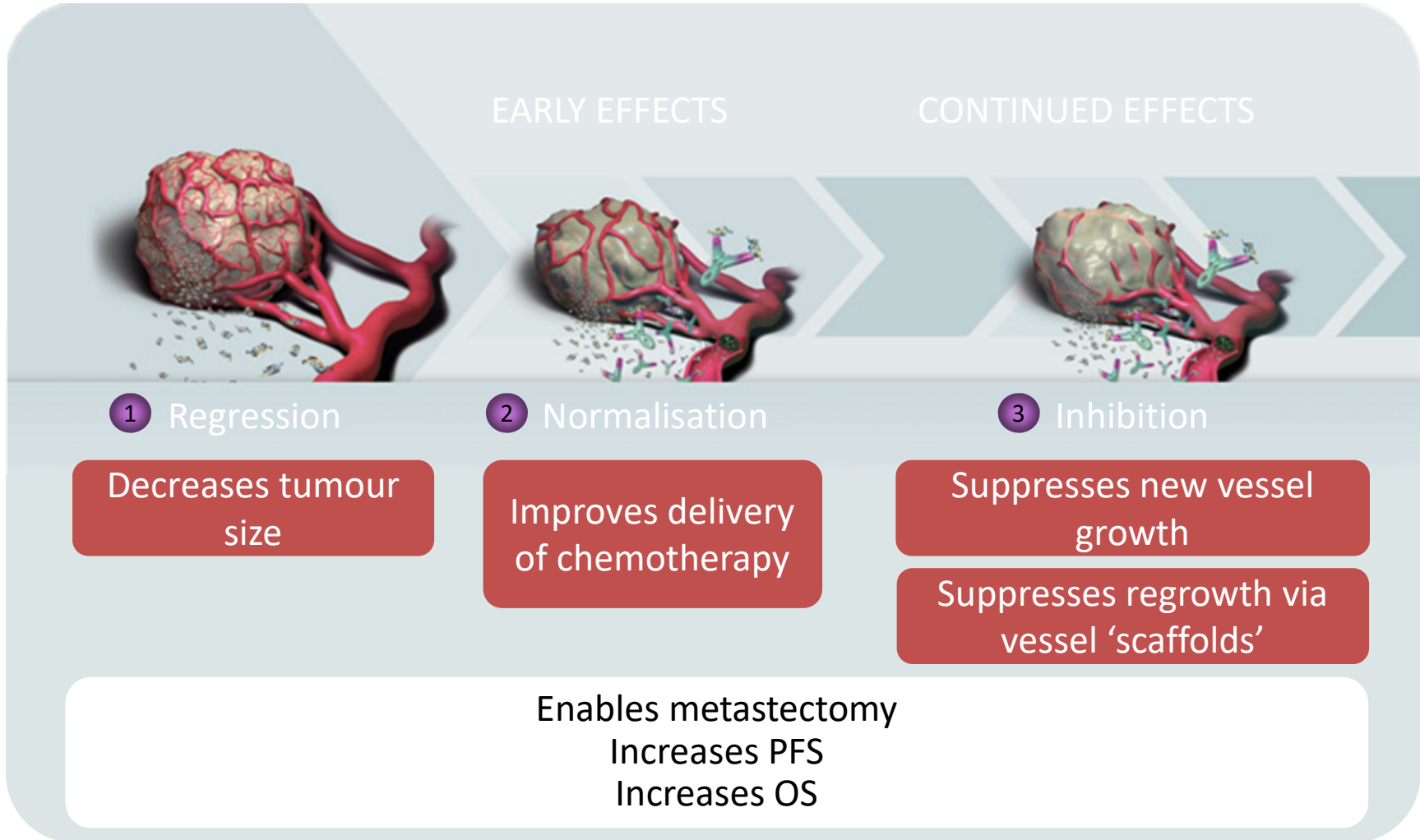
# VEGF, the 'key' of angiogenesis, is expressed throughout tumour development



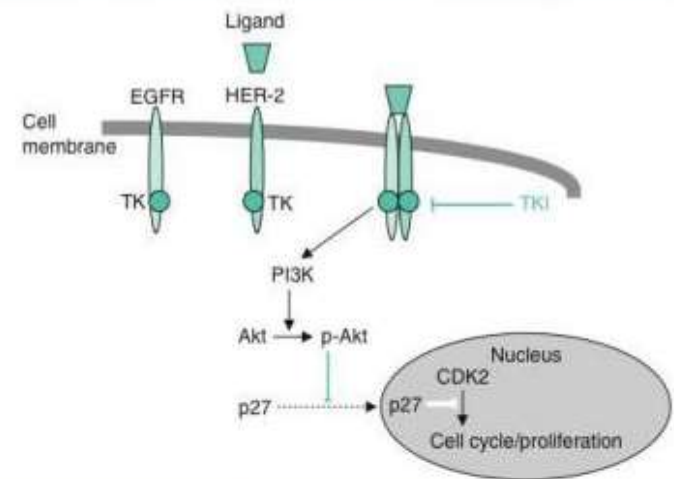
- VEGF is present throughout the tumour life cycle
- As secondary pathways emerge, VEGF continues to be overexpressed



# Bevacizumab MoA: early and continued benefits



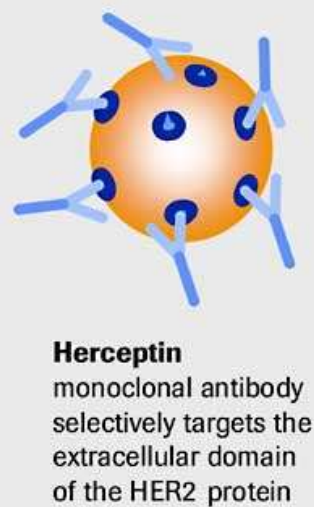
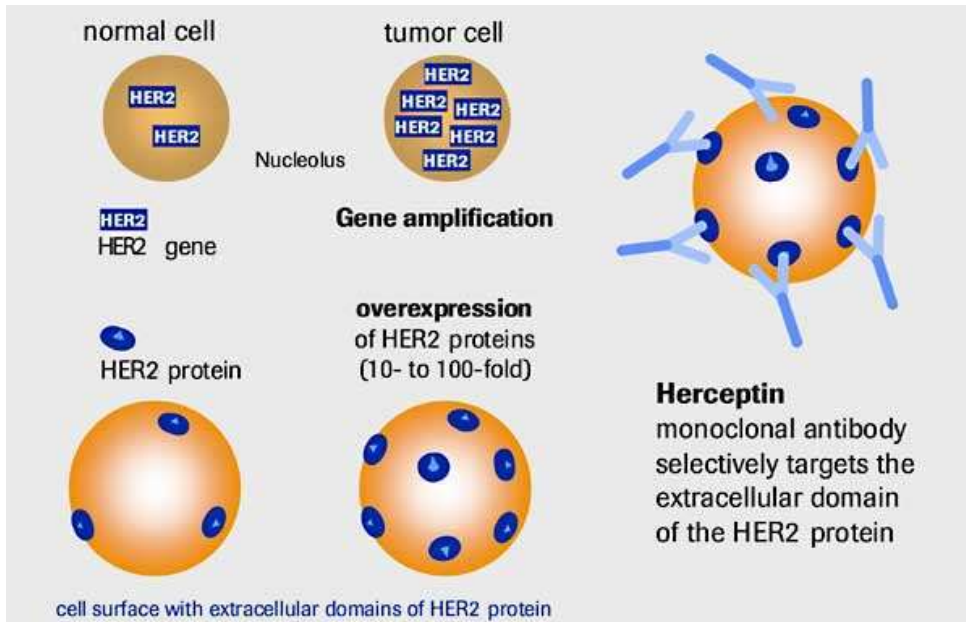
# HER2



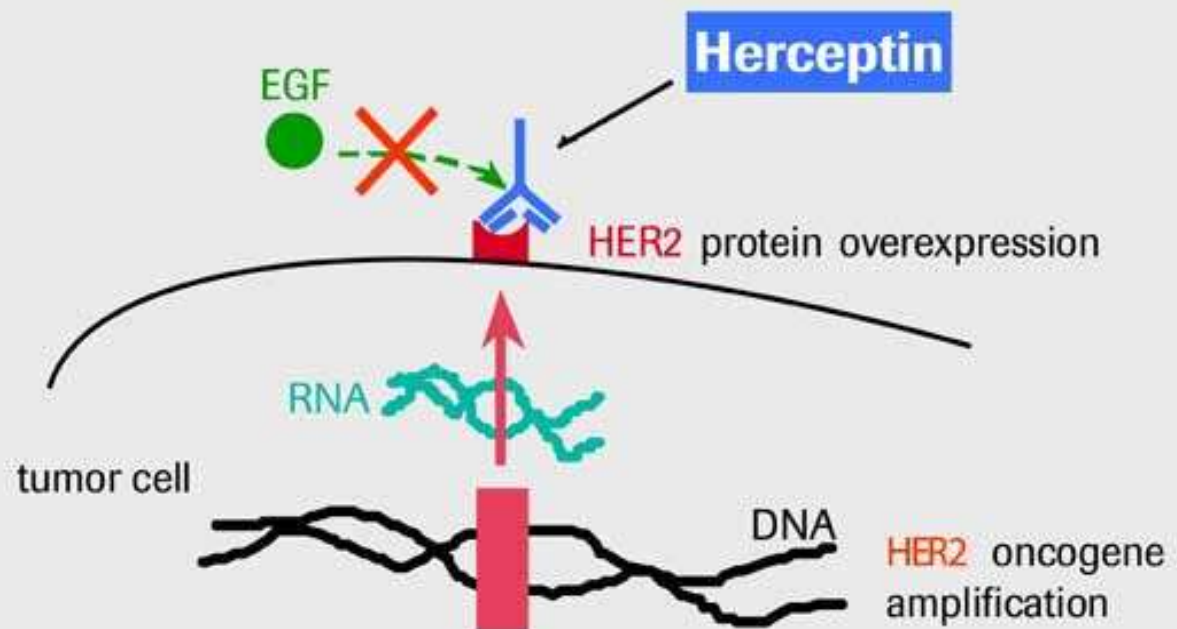
- ~ 25-30% of breast tumors overexpress human epidermal growth factor receptor 2
- HER2 is part of the tyrosine kinase family, and overexpression is associated with aggressive disease and a poor prognosis.

# HER2-positive clinical impact

- Associated with poor outcomes:
  - ↑ Distant metastases
  - ↑ Nodes + disease
  - ↑ Highest risk of recurrence
  - ↓ Overall Survival
  - High grade tumors
  - Endocrine therapy resistance



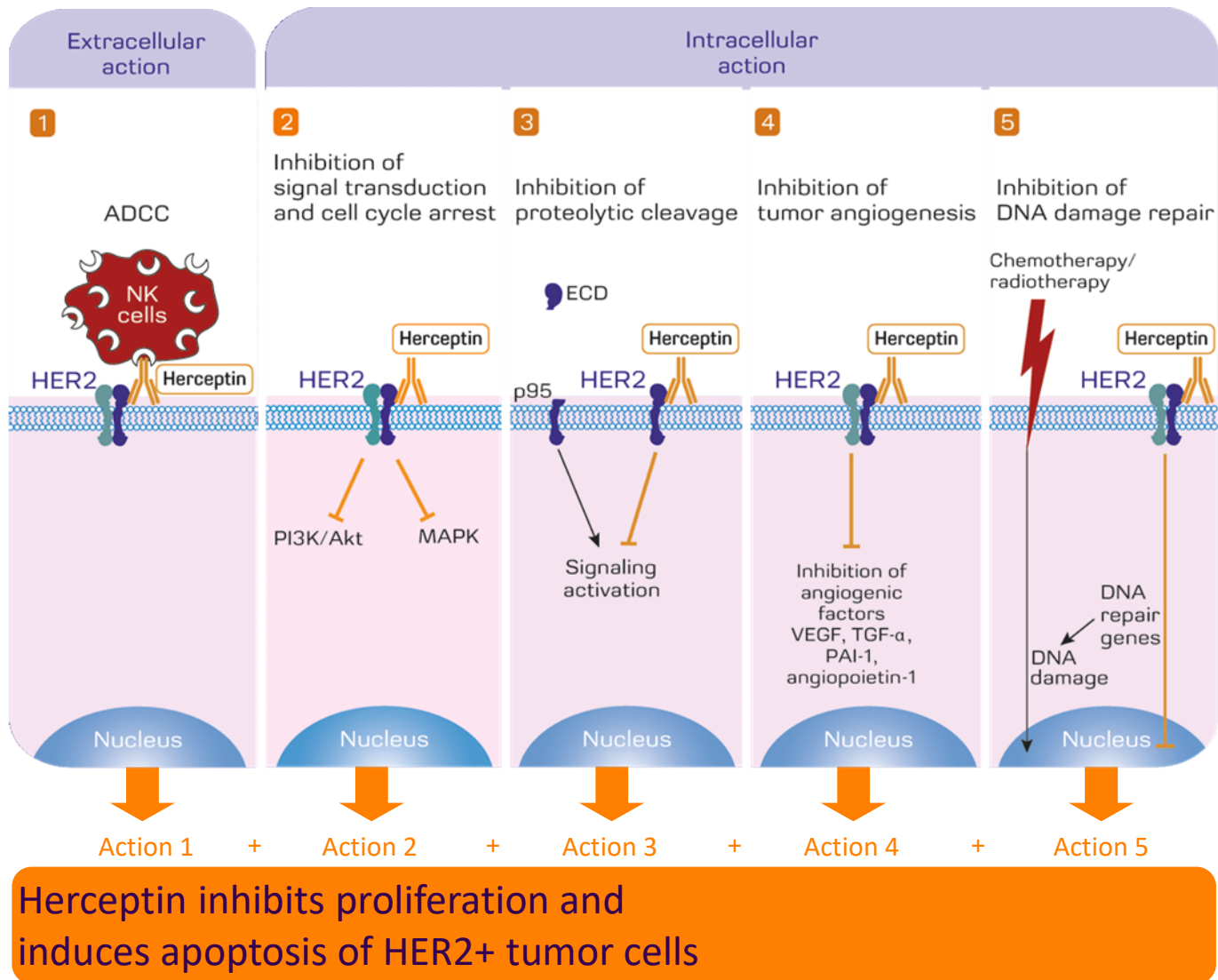
**Trastuzumab (Herceptin)**  
is a monoclonal antibody that interferes with the HER2. Its main use is to treat certain breast cancers.



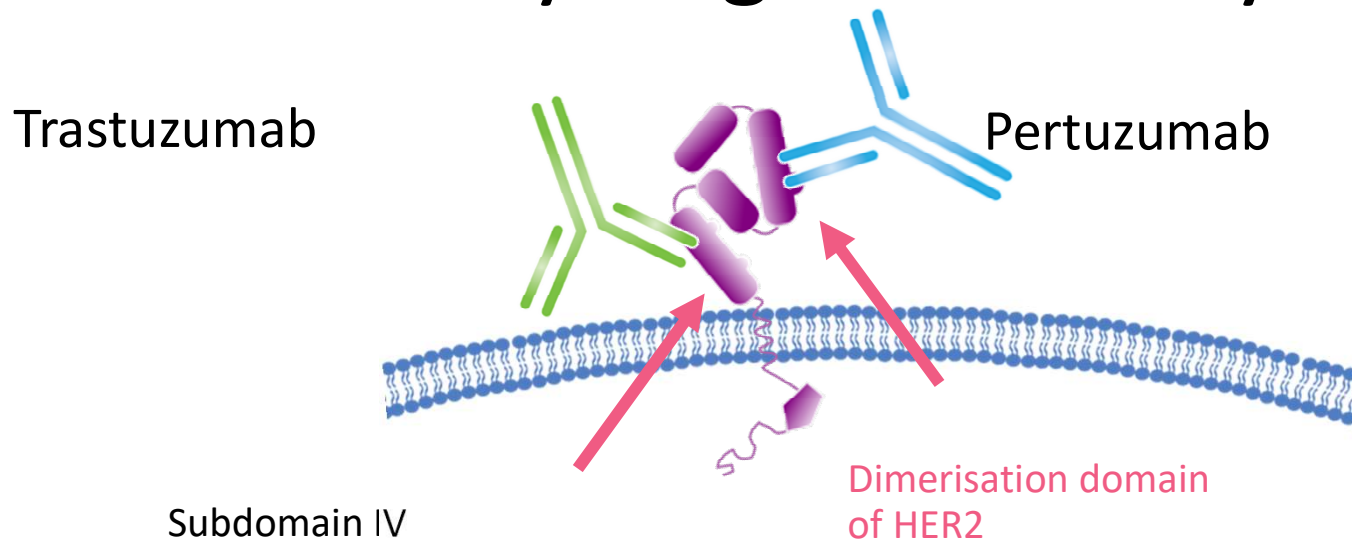
**HER2:** Human Epidermal Growth Factor Receptor-2

**EGF:** Epidermal Growth Factor

# 5 mechanisms of action



# Pertuzumab and trastuzumab bind to different regions on HER2 and have synergistic activity



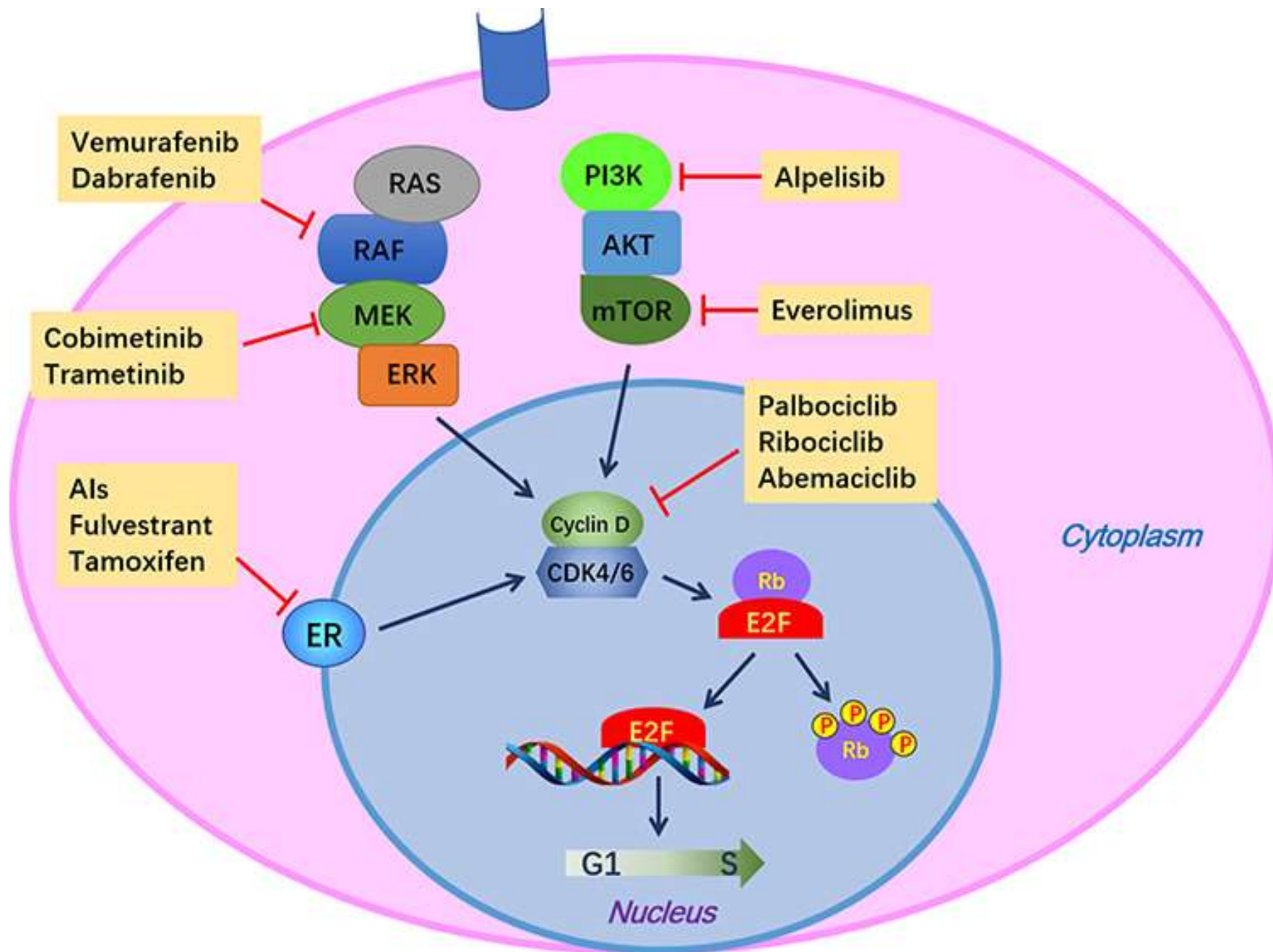
- Preferentially inhibits ligand-independent HER2 signalling
- Prevents shedding of HER2 ECD
- Flags cells for destruction by the immune system

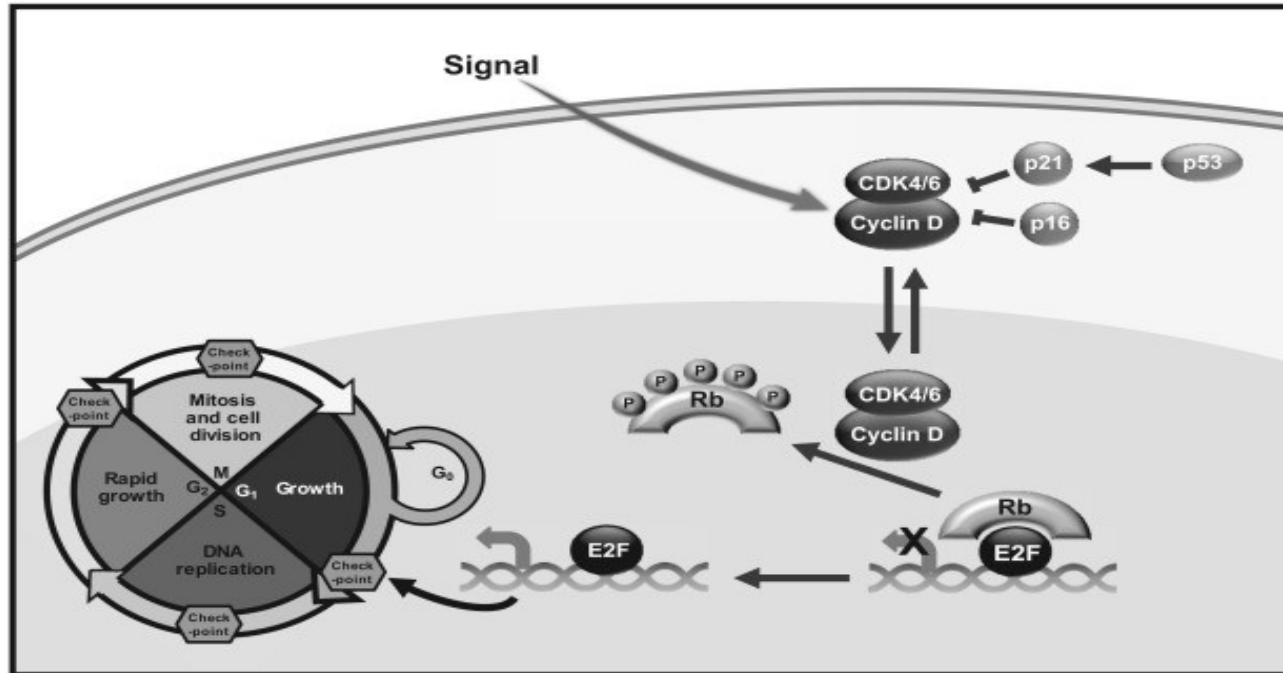
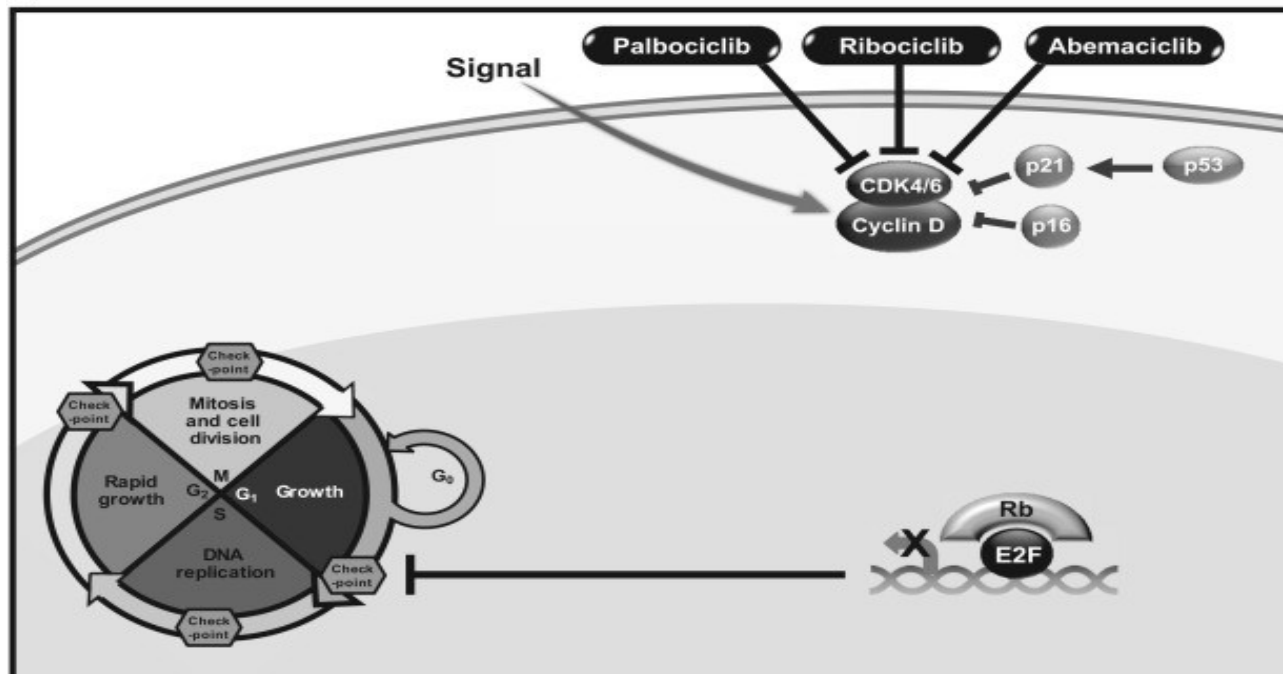
- Inhibits HER2 forming dimer pairs
- Suppresses multiple HER signalling pathways, leading to a more comprehensive blockade of HER signalling
- Flags cells for destruction by the immune system

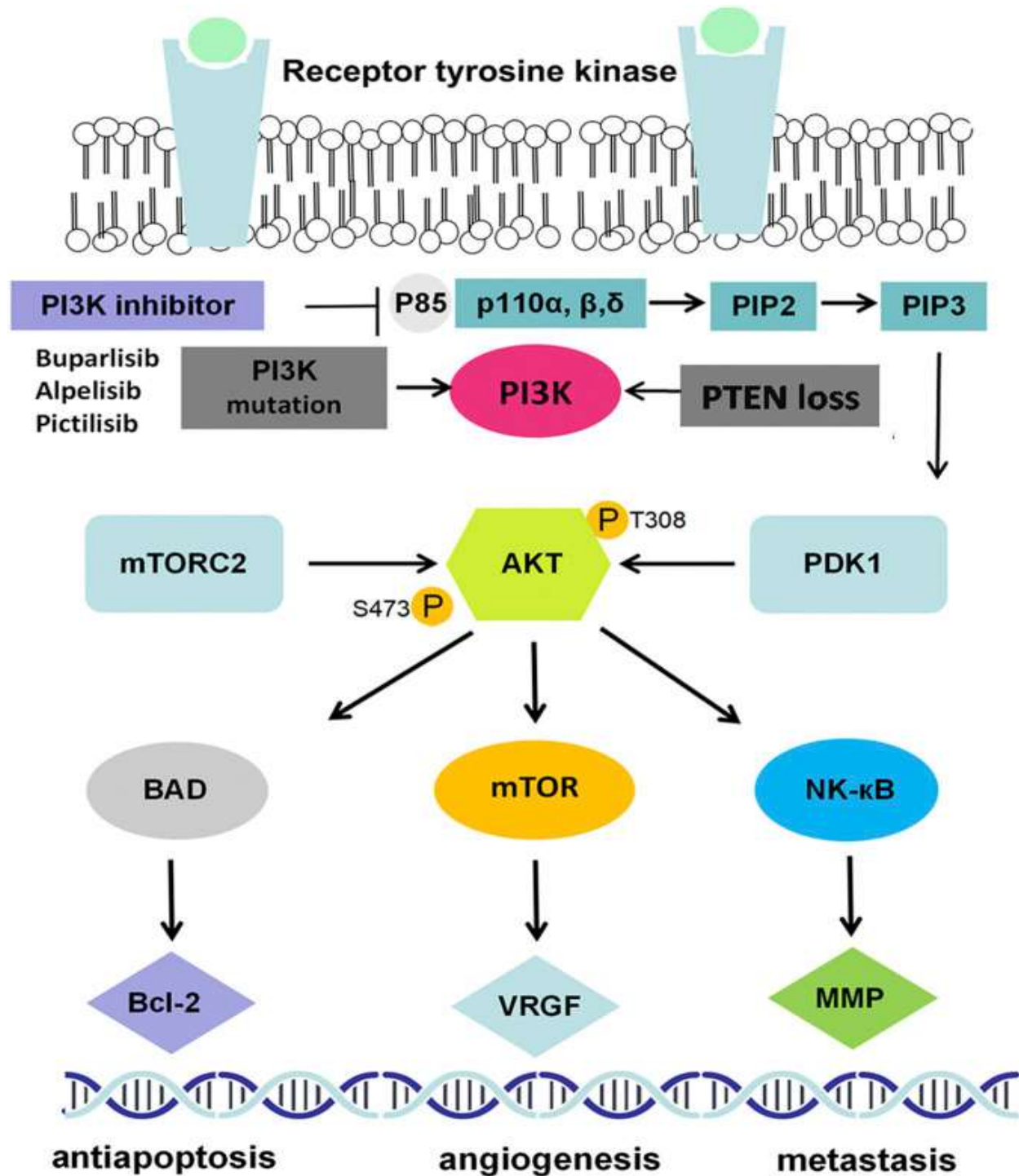
- Pertuzumab is a monoclonal antibody that binds to different epitopes on HER2 compared with trastuzumab.
- The combination of pertuzumab and trastuzumab is more active than a single anti HER2 drug because of a more comprehensive signaling Blockade. Moreover, several studies have demonstrated that dual block of HER2 combined with chemotherapy is superior in both the metastatic, neoadjuvant and adjuvant settings compared with a single HER2 blockade



- Consequently, the dual block combination with pertuzumab and trastuzumab significantly improved PFS compared with trastuzumab plus an AI.
- The combination of trastuzumab and lapatinib is based on the different mechanisms of action of these drugs that simultaneously target the intracellular and extracellular HER2 domains.



**A****B**

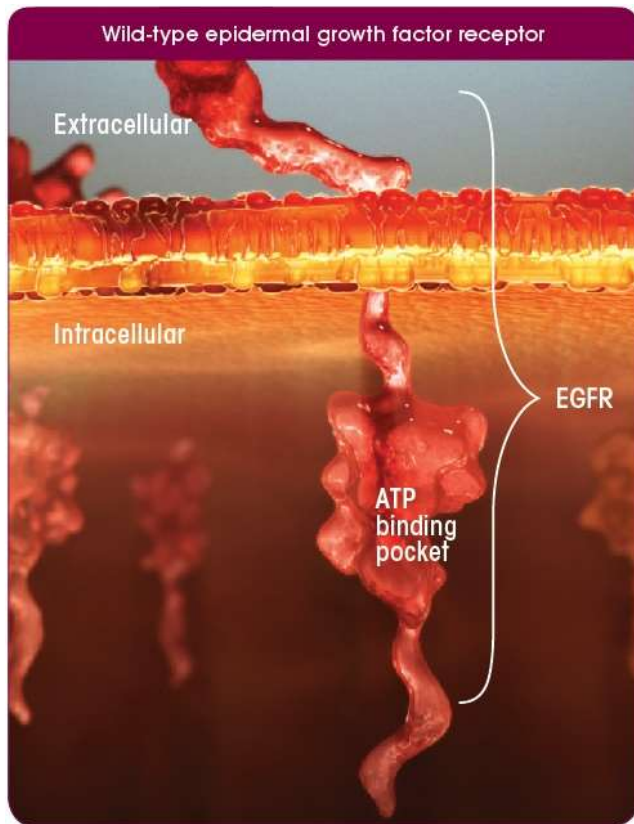


- **Alpelisib – PIQRAY (Pivikto)**, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen
- **Buparlisib**
- **Pictilisib**
- **Idelalisib – Zydelig**
- **Copanlisib - Aliqopa**

## MALI MOLEKULI

- Unlike MAbs, small molecule agents can permeate through plasma membranes and interact with the cytoplasmic domains of cell surface receptors and various intracellular signalling molecules that regulate cell proliferation, differentiation and apoptosis.
- Protein tyrosine kinases are crucial mediators in such signalling pathways and many are deregulated in malignant cells, making them targets for therapeutic agents.

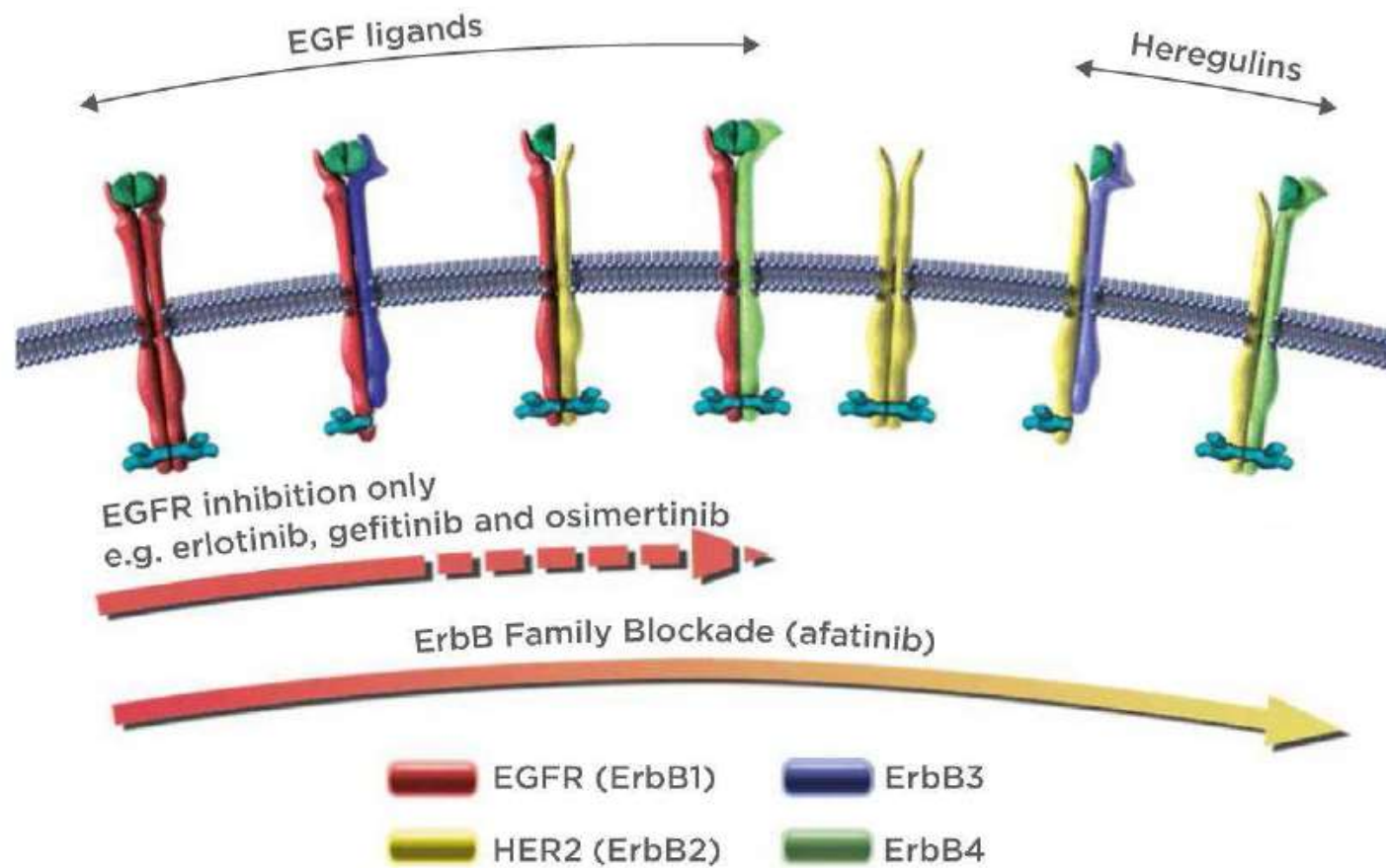
# EGFR



- Receptor epidermalnog faktora rasta (EGFR) aktivira dva signalna puta koja kontrolišu normalnu ćelijsku proliferaciju i anti-apoptotsku aktivnost
- EGFR je prekomerno aktivan kod oko 80% NSCLC, uzrokujući abnormalnu aktivaciju signalnih puteva
- Prekomerna ekspresija EGFR-a je povezana sa agresivnom bolešću i lošim preživljavanjem

- EGFR mutacije se uvek pojavljuju u TK domenu
- receptorima nije potrebno prisustvo liganda za aktivaciju TK domena, što dovodi do trajne hiperaktivacije PI3K signalnog puta dovodi do povećanog preživljavanja tumorskih ćelija



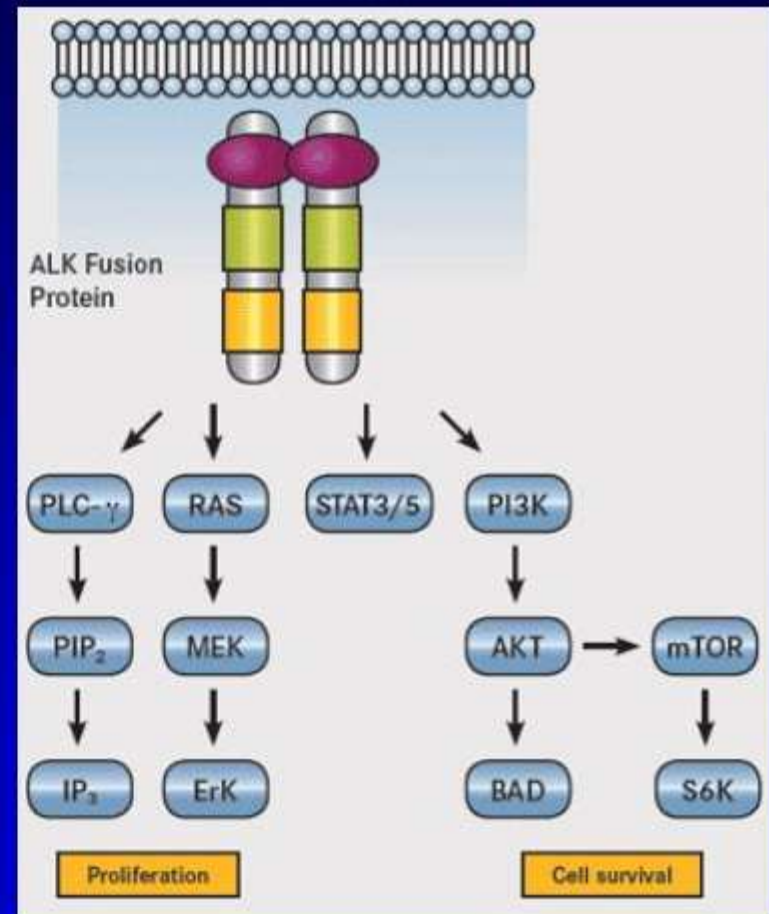


- Heregulin (HRG) is a soluble secreted growth factor, which, upon binding and activation of ErbB3 and ErbB4 transmembrane receptor tyrosine kinases, is involved in cell proliferation, invasion, survival and differentiation of normal and malignant tissues. The HRG gene family consists of four members: HRG-1, HRG-2, HRG-3 and HRG-4, of which a multitude of different isoforms are synthesized by alternative exon splicing, showing various tissue distribution and biological activities. Disruption of the physiological balance between HRG ligands and their ErbB receptors is implicated in the formation of a variety of human cancers. The general mechanisms involved in HRG-induced tumorigenesis is discussed.

- The *NRG1* gene is located in chromosome 8 in region 8p12. This gene encodes the growth factor neuregulin 1 (*NRG1*). *NRG1* contains an epidermal growth factor (EGF)-like domain, which binds to human tyrosine kinases of the ErbB/HER receptor group, specifically ERBB3 and ERBB4, leading to the activation of ErbB-mediated downstream signaling pathways that translate into cell growth. This has led to the development of targeted therapies to *NRG1* that are currently underway

# ALK Inhibitors

- ALK normally functions in the brain
- First rearrangement in lung cancer discovered 2007 in Japan
- Upstream of multiple cancer pathways
- 2010 starting clinical trials on ALK inhibitor
- 2011 FDA approved crizotinib



anaplastic lymphoma kinase (ALK)

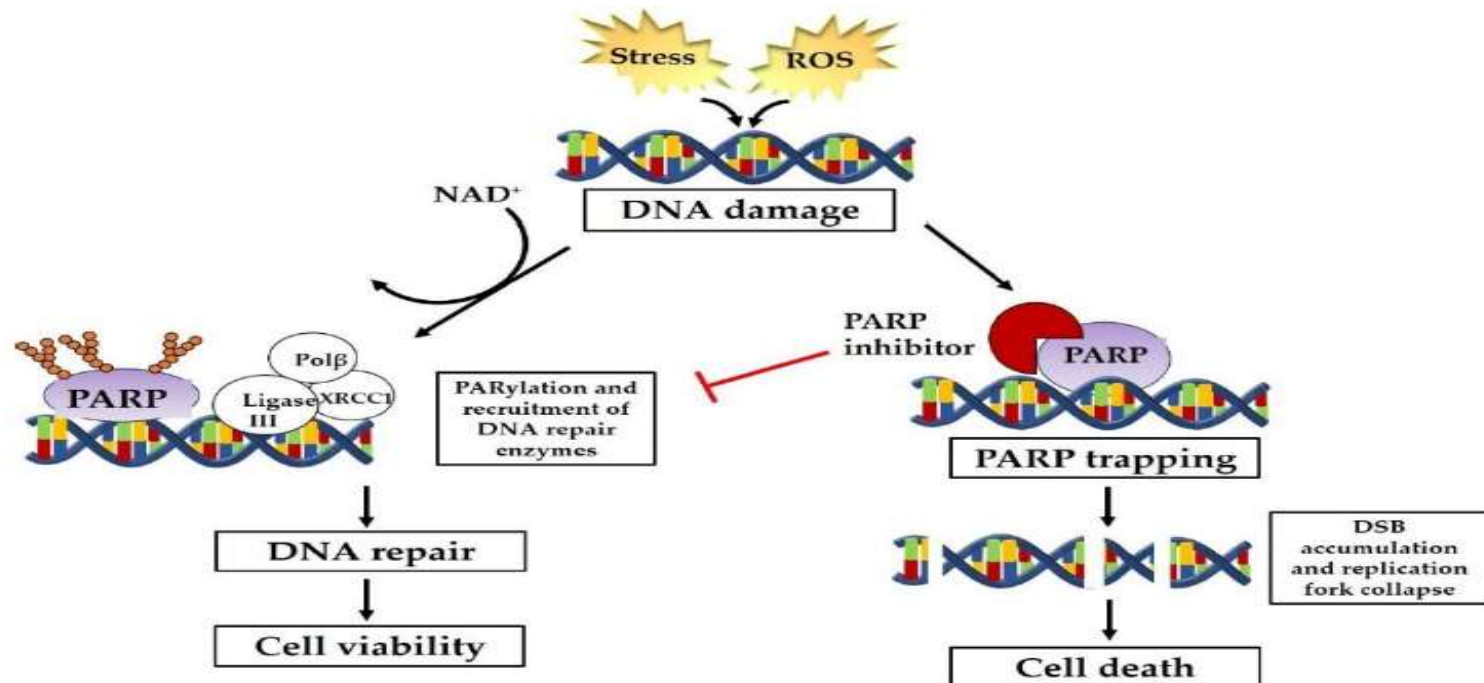
U NSCLC, ALK mutacija dovodi do fuzionisanja sa echinoderm microtubule-associated protein- like 4 (EML4) .

EML4–ALK onkogen dovodi do ćelijskog umnožavanja i pojačanog preživljavanja tumorskih ćelija

- Acquired resistance to crizotinib has been observed to occur through a variety of mechanisms **including ALK dependent mechanisms** (ALK amplification, secondary *ALK mutations*), and ***“bypass tracks”*** such as increased EGFR phosphorylation and KRAS mutations. Progression within the CNS may occur because of inadequate penetration of crizotinib in the CSF, although recent data with alectinib suggest that CSF concentrations are not predictive of efficacy .
- Resistance to crizotinib has led to the development of next-generation ALK-inhibitors, including ceritinib and alectinib. In a dose-finding phase I study, alectinib demonstrated impressive activity with 55% of patients experiencing a response, and 52% of patients with brain metastases experienced a response in the CNS

**Poly (ADP-ribose) polymerases (PARPs)** igraju važnu ulogu u mnogim ćelijskim procesima ( replikaciji, rekombinovanju i naročito reparaciji DNA)

Neki tumori, naročito oni sa prisutnom BRCA1/2 mutacijom, zavise od PARP posredovane reparacije da bi preživeli.



**Figure 1.** PARP pathway overview. Cellular stress such as oxidative stress from reactive oxygen species causes DNA damage in the form of single- and double-strand breaks. Under normal conditions, the PARP pathway is activated. ADP-ribose units are recruited to sites of DNA strand breaks in a process known as PARylation. With the assistance of PARP and other DNA repair enzymes, repair of DNA strand breaks occurs, and the cell remains viable. This figure provides an overview of what happens in the presence of a PARP inhibitor in BRCA-mutated cells which have defects in the homologous recombination repair pathway. The PARP inhibitor mediates inhibition of PARylation, thereby preventing repair of DNA strand breaks via the PARP pathway or the homologous recombination repair pathway. This synthetic lethality in which both repair pathways are nonfunctional contributes to unrepaired single-strand breaks and double-strand breaks; accumulation of double-strand breaks ultimately leads to apoptosis and cell death. (DSB = double-strand break; PARP = poly (ADP-ribose) polymerase; ROS = reactive oxygen species)



## mTOR inhibitori

In 1964 a Canadian researchers expedition from the Ayerst-Wyeth Pharmaceuticals traveled to Easter island to gather soil samples and plants.

In 1972 the expedition team and a microbiology team identified and isolated RAPAMYCIN from the mycobacterium *Streptomyces Hygroscopicus*



Several years later Rapamycin demonstrated antifungal activity blocking the G1 to S phase of the cell cycle.

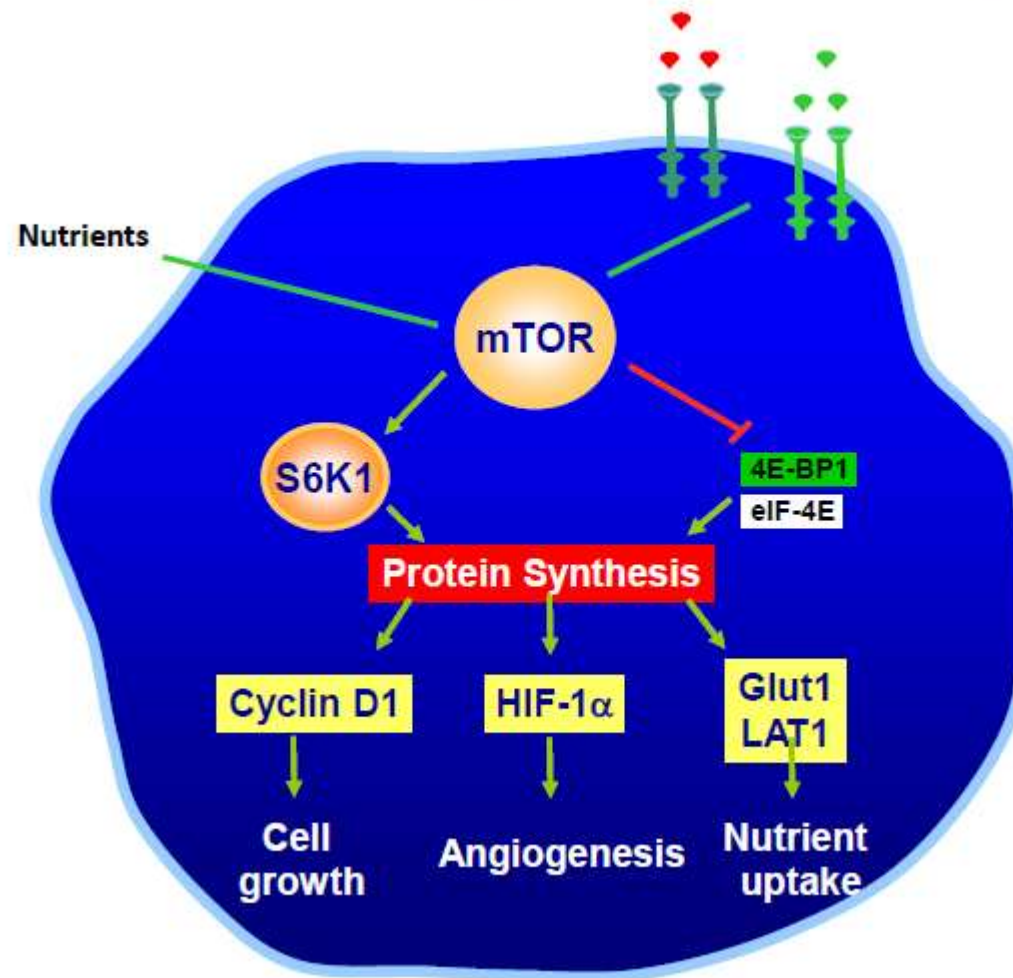
The block of G1 to S phase of the cell cycle in T-lymphocytes revealed a potent immunosuppressant activity of Rapamycin in mammals.



Two classes of resistant yeast had mutations in genes named TOR1 and TOR2 in honor of the Spalentor, a gate of the city of Basel, where TOR was first discovered.



## mTOR activation supports cancer cell growth



# BRAF inhibitori

- The BRAF gene is a proto-oncogene found on chromosome 7, and becomes an oncogene when mutated. The gene codes for a protein (a serine-threonine kinase) that sends signals from outside of the cell to the nucleus that in turn drives the growth of a cell. Discovered in 2002, the oncogene is now known to be an important driver in more than one type of cancer.

- There are more than 30 different types of mutations that may occur in the BRAF gene, and the most common types of mutations can vary with the type of cancer.
- **BRAF V600E and BRAF V600K**
- With melanoma, BRAF V600 E and BRAF V600K account for roughly 90% of BRAF mutations (with BRAF V600E by far the most common).
- **Non-V600 BRAF Mutations**
- With lung adenocarcinoma, around 50% to 80% of BRAF mutations are non-V600 variants. In colorectal cancer, 22% to 30% are non-V600 variants.<sup>1</sup>
- **Classes of BRAF Mutations**
- The science is in its infancy with regard to evaluating the different types of BRAF mutations with respect to treatment and prognosis. A 2019 study looked at BRAF mutations in non-small cell lung cancer; separating these into three classes with different clinical characteristics. It could be that in the future, specific therapies will be designed to treat subsets of BRAF mutations rather than BRAF mutations in general.<sup>2</sup>



- **BRAF Inhibitors**

- BRAF inhibitors are medications that target the pathways cancer cells use to grow in tumors that harbor BRAF mutations. Unlike chemotherapy drugs, these medications do not "kill" cancer cells, but rather control the growth of a tumor by interrupting the signaling pathway that leads to cell growth and division. As such, they do not (usually) "cure" a cancer, but can sometimes control the growth of a cancer for a significant period of time.

- **Combined Therapy**

- BRAF inhibitors are most often used along with medications that inhibit the growth of a tumor at other points in the signaling pathway (such as MEK inhibitors). Interestingly, adding a MEK inhibitor to a BRAF inhibitor is actually associated with *fewer* side effects than using a BRAF inhibitor alone. The combination also appears to work for a longer period of time.

- **Triple Therapy**

- With both melanoma and colon cancer, combining a BRAF inhibitor and a MEK inhibitor with another medication has shown promise in clinical trials.

- **BRAF Inhibitors**

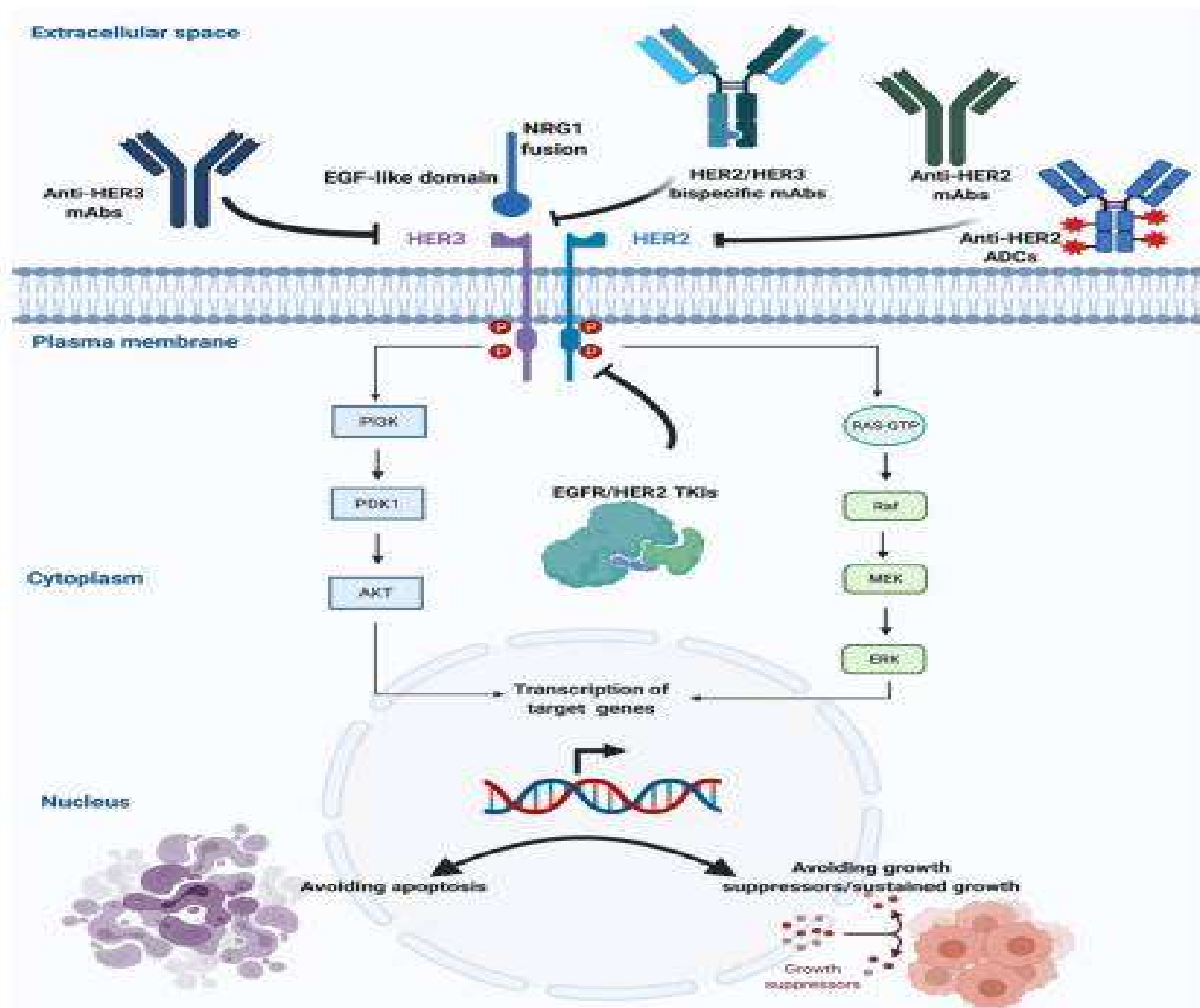
- There are now three BRAF inhibitors that have been approved. These drugs directly attack the protein coded for by the mutated BRAF gene.
- Zelboraf (vemurafenib): This was the first drug approved in 2011 for BRAF V600E mutations
- Taflinar (dabrafenib): Taflinar was approved (in combination with Mekinist) in 2013 for both V600 E and V600K mutations
- Braftovi (encorafenib)

- **MEK Inhibitors**

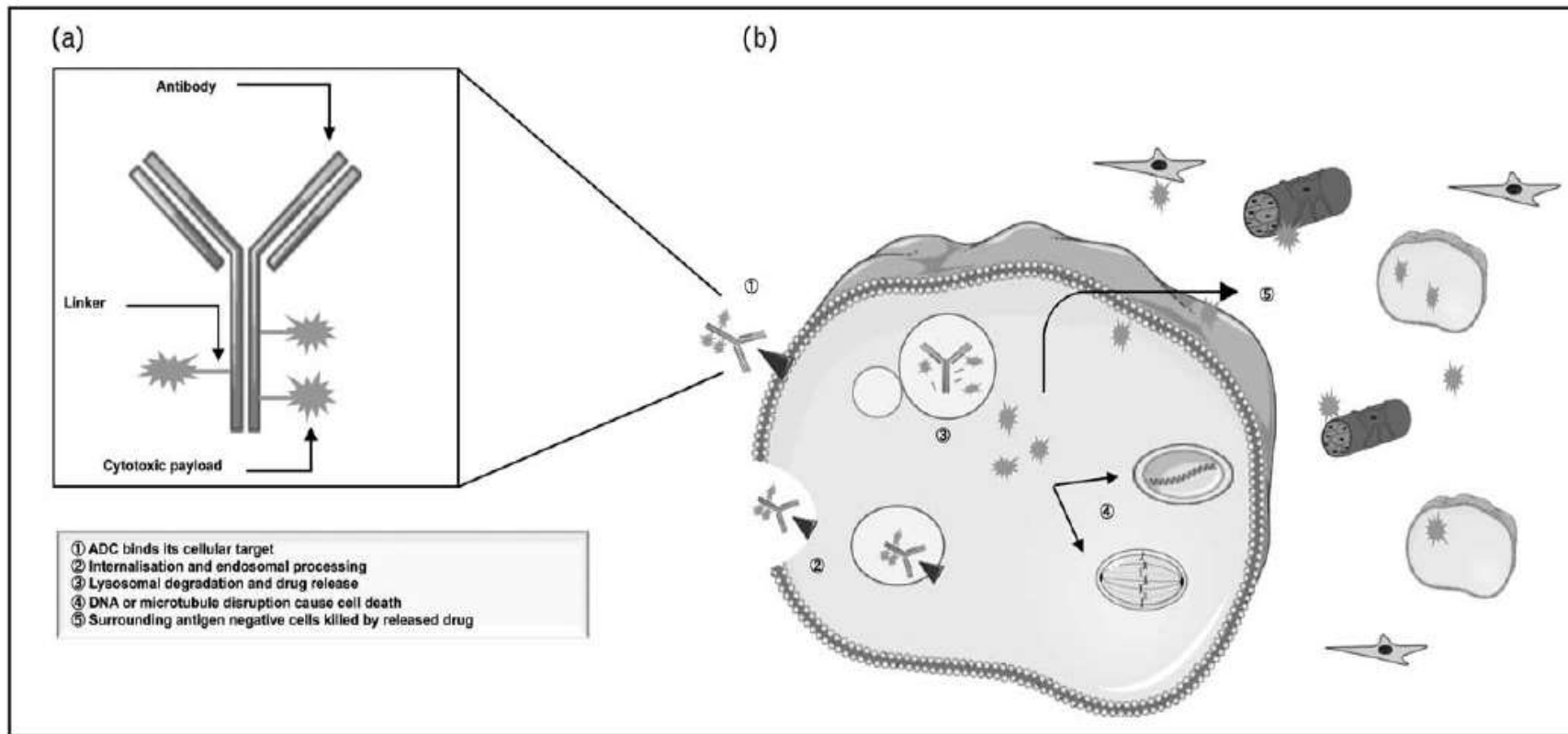
- Mekinist (trametinib)
- Cotellic (cobimetinib)
- Mektovi (binimetinib)

- **Triple Therapy**

- Clinical trials are in progress evaluating the combination of targeted therapy (BRAF and MEK inhibitors) with immunotherapy drugs known as checkpoint inhibitors (PD-1 and PD-L1 inhibitors). These include a few promising studies published in June of 2019 that suggest that, for at least some people, the combination may result in a longer response:
- A combination of Tafinlar and Mekinist plus Keytruda (pembrolizumab)
- A combination of Zelboraf and Cotellic plus Tecentriq (atezolizumab)



First in class, ado-trastuzumab emtansine (T-DM1) has been the first FDA-approved anti-HER2 ADC, recently joined by trastuzumab deruxtecan



**FIGURE 1.** Structure and mechanisms of action of ADCs. (a) The antibody, the linker, and the cytotoxic agent are the critical elements in ADCs. (b) Mechanism of action of ADCs in target cell and bystander killing of antigen-negative tumor cells and damage to tissue that support the tumor growth such as endothelial cells and pericytes of tumor neovasculature or stromal cells, resulting in enhanced antitumor activity of ADCs.

Antibody–drug conjugates (ADCs) are a new class of drugs composed of a conjugate of monoclonal antibodies (mAbs) and a cytotoxic drug. The basic principle is to deliver the cytotoxic drug only to the tumor cells, which would significantly reduce the systemic negative effects of the treatment. Cytotoxic drugs (maytansins and auristatins) that are used in conjugates are significantly more cytotoxic than conventional chemotherapeutics, and therefore are not used independently but only as part of ADC. They mainly act through tubulin, preventing the formation of microtubules, or damaging DNA.

**Trastuzumab emtansine (Kadcyla)**

trastuzumab deruxtecan ( Enhertu)

**Indatuximab ravtansine**

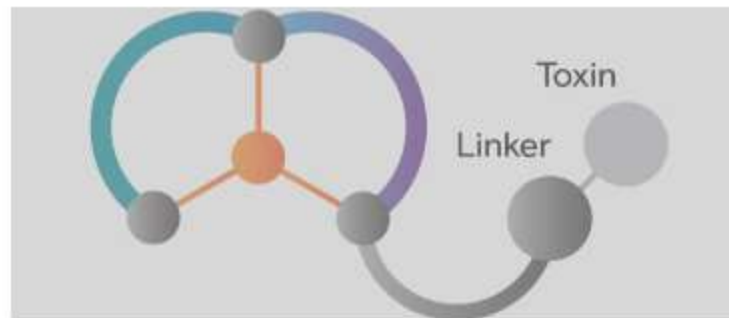
**anetumab ravtansine**

**brentuximab vedotin (Adcetris)**

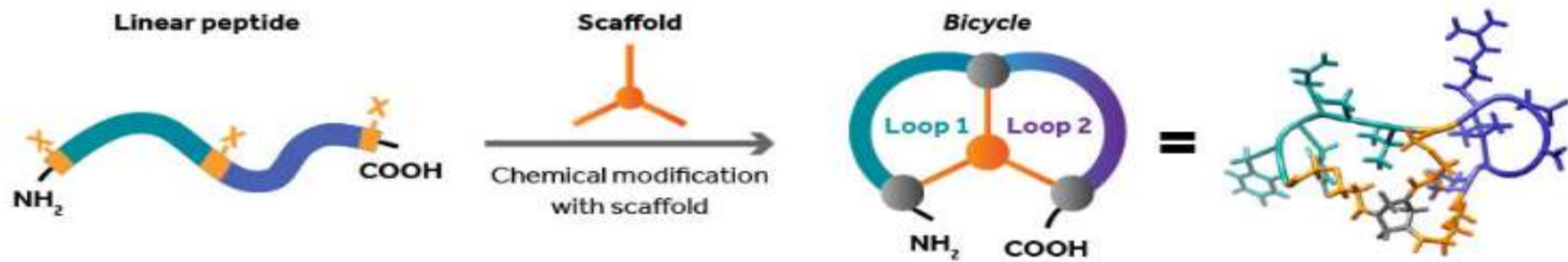
**polatuzumab vedotin (Polivy)**



- ADCs also damage healthy cells, although they are designed to do so minimally.
- ADCs can bind to any cell that expresses the target site.
- ADCs can damage surrounding cells by diffusion
- Once metabolized, ADCs can release toxins and damage the liver.
- By combining linear peptides, Bicycle Therapeutics obtained the bicyclic structure "Bicycles" with high affinity and selectivity

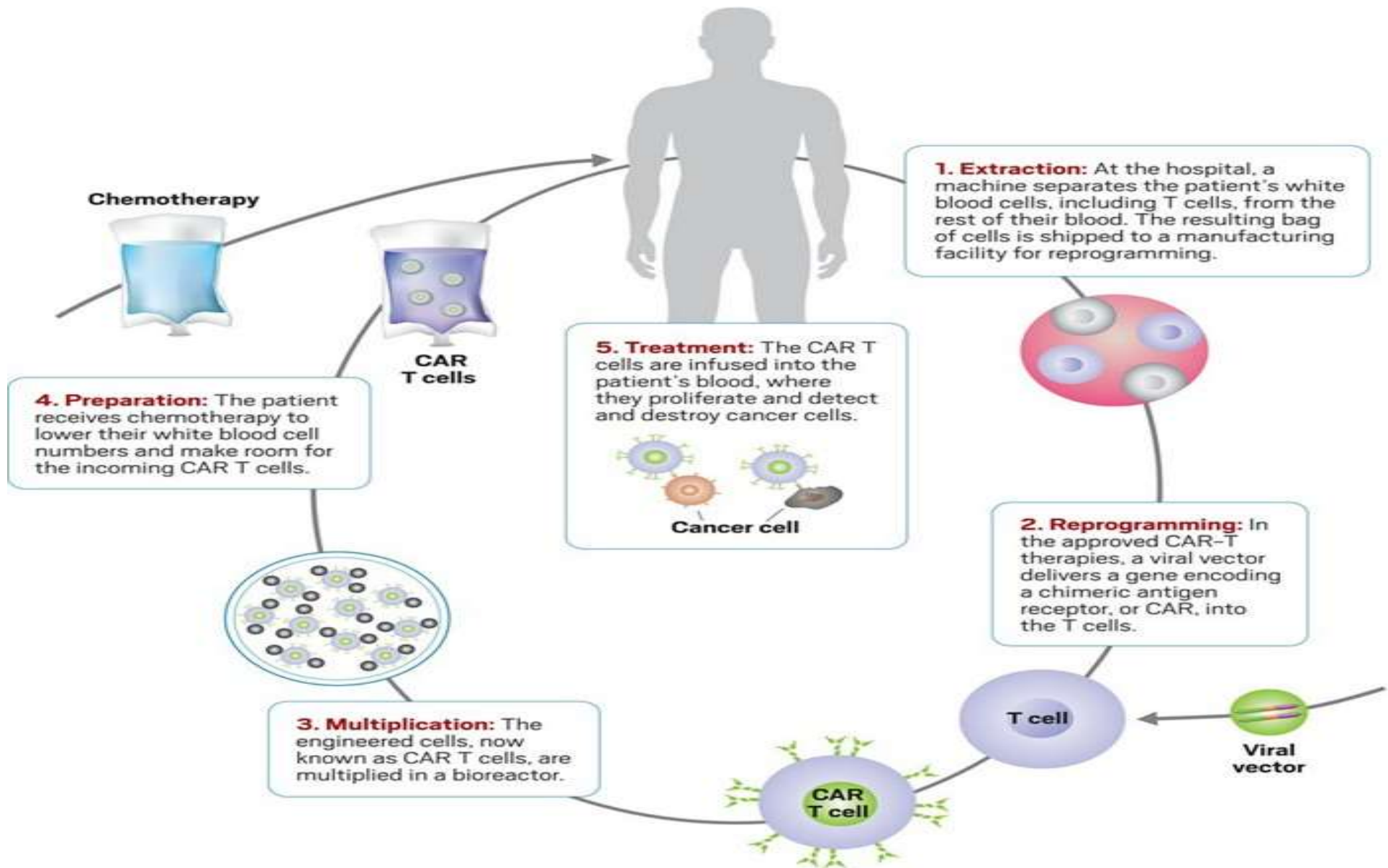


The structure of Bicycle's 'Bicycle Toxin Conjugate'.



*Bicycle Therapeutics combines linear peptides with scaffolds to create bicyclic molecules, or Bicycles, that have high affinity and selectivity. Bicycle-toxin conjugates can be built from simple Bicycles or from complex Bicycles, such as tandems, trimers, and tetramers. Multimeric Bicycles can deliver combinatorial pharmacology.*

- Bicycles are about 100 times smaller than monoclonal antibodies, and are therefore able to penetrate the tumor cell very easily and efficiently.
- They have a half-life of only a few hours, and are metabolized by renal excretion, which minimizes systemic toxicities
- Each bicyclic therapeutic targets a specific tumor antigen delivering a bound and cytotoxic drug.
- BT8009, targets the Nectin-4 molecule that is overexpressed on tumor cells of several types of tumors - bladder, breast, lung and pancreas.
- In preclinical trials, it showed higher efficacy and lower toxicity compared to classic ADCs.



three chimeric antigen receptor (CAR)-T cell products -axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel have been approved by the U.S. Food and Drug Administration for the treatment of large B cell lymphoma,

# TOOKAD VTP\*: Photosensitizing Drug and Light Delivery System

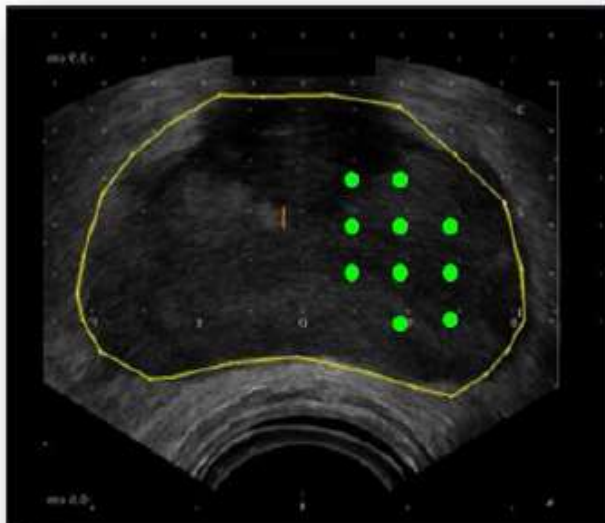
- Administered intravenously
- TOOKAD is activated locally when illuminated by low energy, non-thermal laser light
- Rapidly constricts blood supply, resulting in tumor necrosis



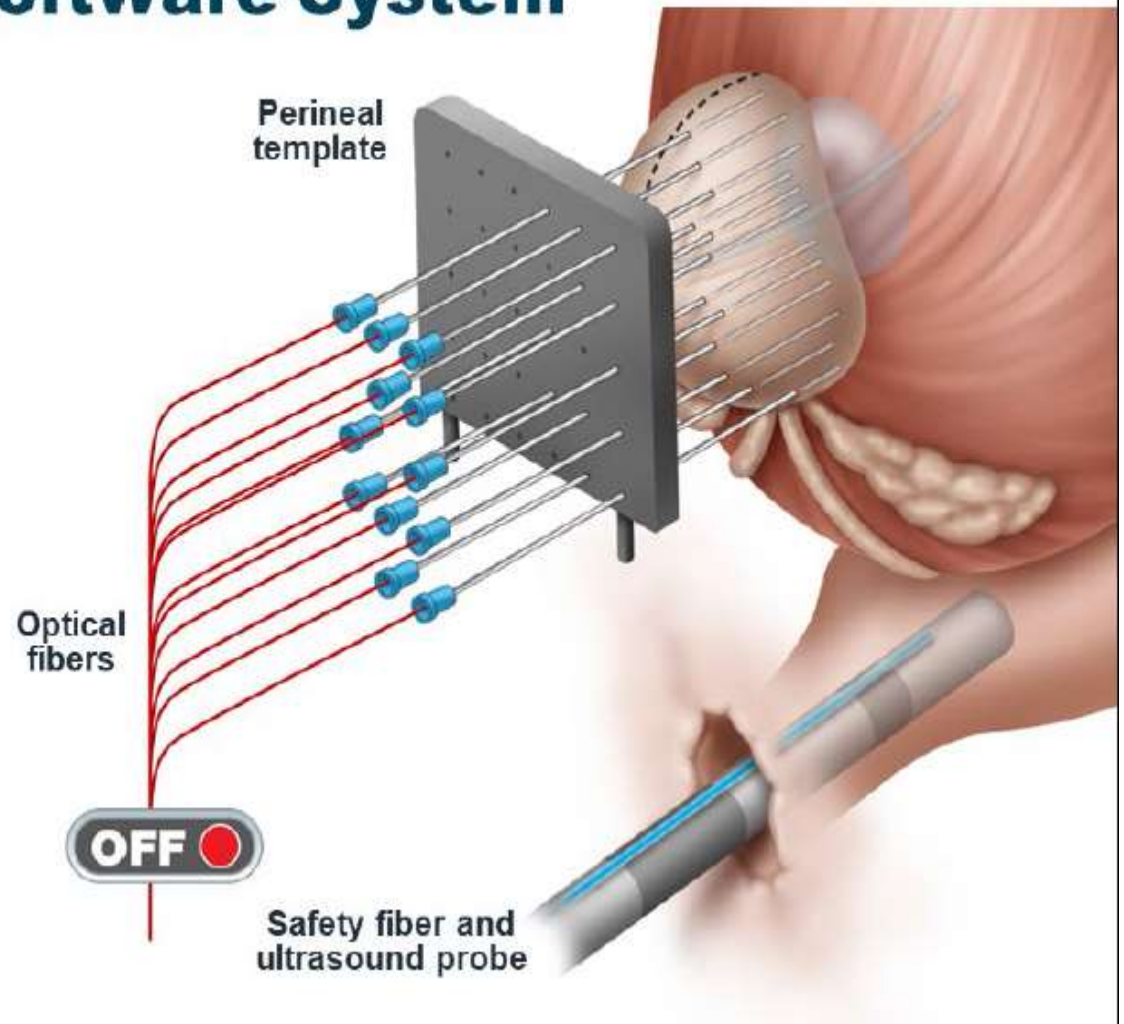
\*Vascular Targeted Photodynamic



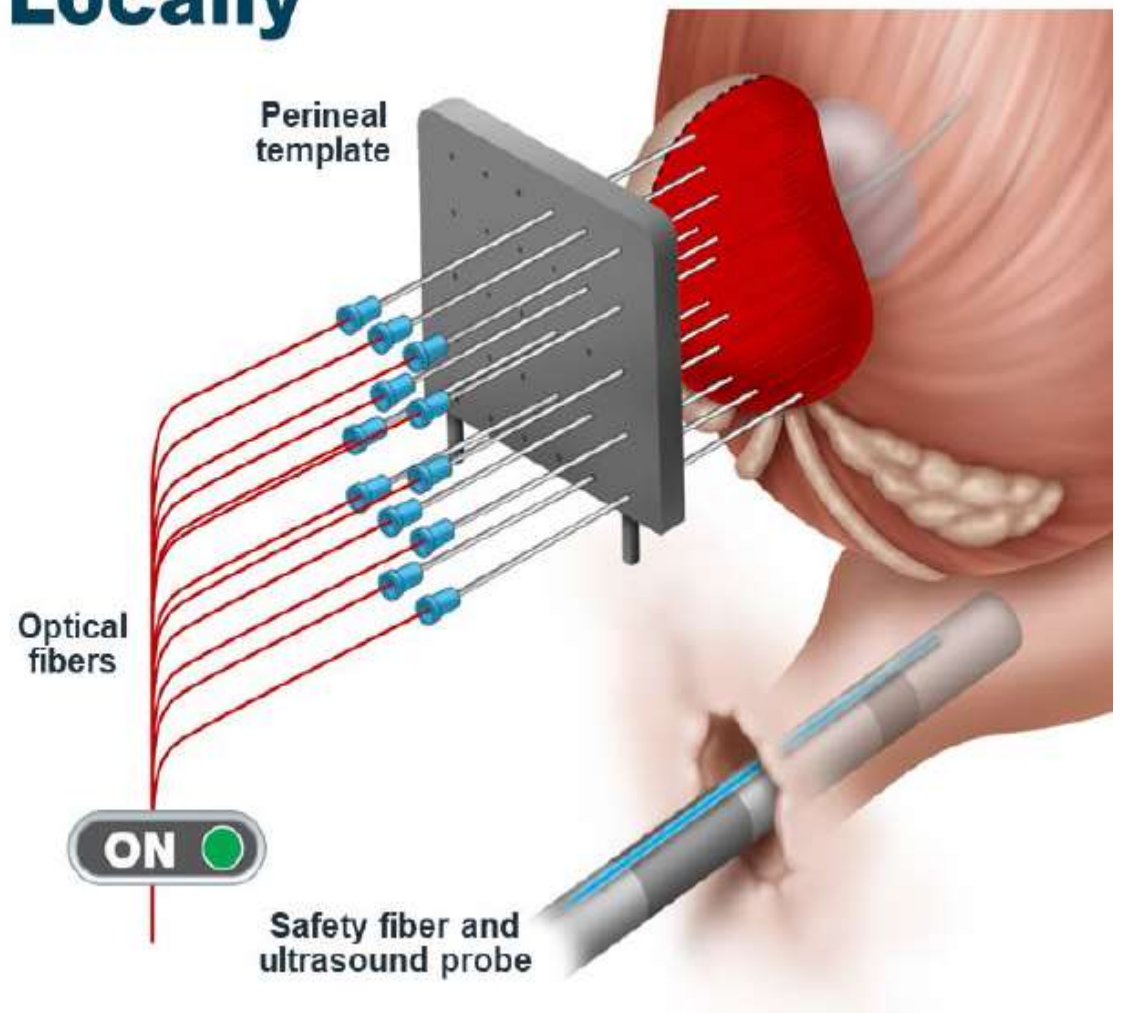
# Optical Fiber Placement is Ultrasound-Guided Utilizing TOOGUIDE Software System



4 mg/kg  
intravenously  
over 10 min



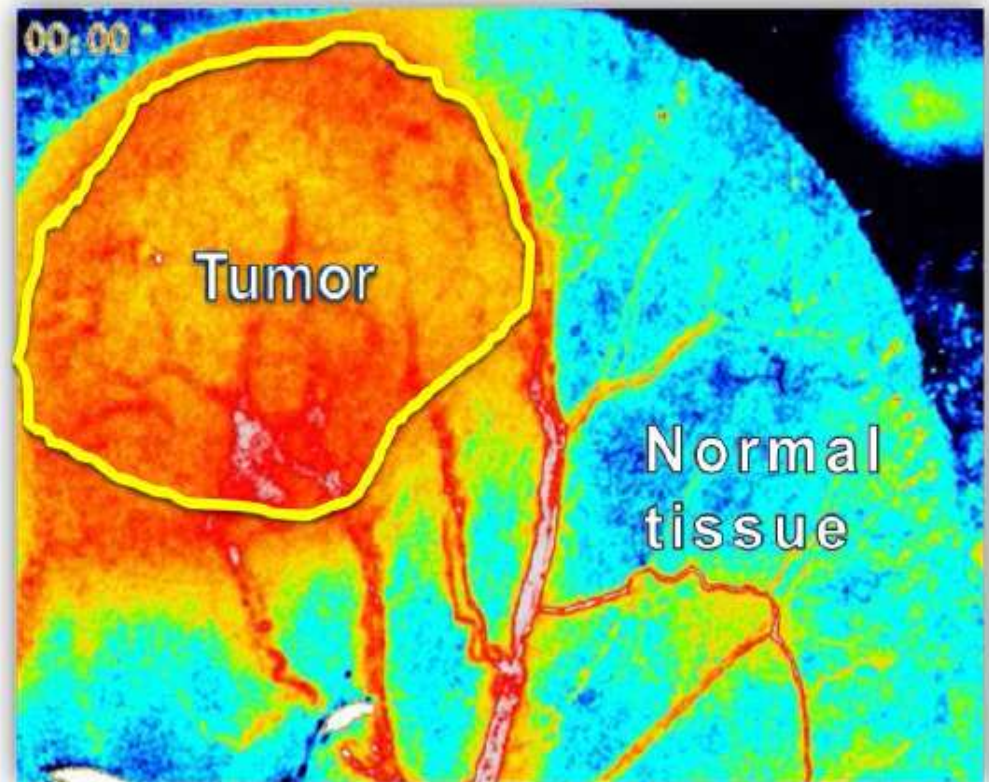
# Optical Fiber Near-Infrared Illumination Activates TOOKAD Locally





# TOOKAD VTP Leads to Selective Vascular Occlusion

- Light-activated drug reacts with oxygen in circulating red blood cells triggering
  - Vasodilation
  - Vasoconstriction
  - Vascular occlusion



# NANO PARTICLES

- ABCD nanoparticle structural paradigm
- A: active pharmaceutical ingredient,
- B: lipids,
- C: a stealth/biocompatibility polymer layer (like PEG),
- D: targeting layer-receptor specific ligand)

Navigating/targeting moiety  
(i.e., receptor specific ligand)

Transporting  
vehicle (i.e., lipid)



Stealth/biocompatibility polymer  
(i.e., PEG)

Cytotoxic agent

# TYPES OF NANO PARTICLES

- The high **surface area-to-volume ratio** of **Magnetic Iron Oxide Nano-particles (MIONs)** results in a tendency to aggregate and absorb plasma proteins upon intravenous injection, leading to rapid clearance by the reticuloendothelial system.
- Additionally, they are limited in their capacity for drug loading and rapid drug clearance after intravenous administration.
- Thus, **MIONs** are commonly protected with a polymer coating to improve their dispersity and stability.

- ***Liposomes*** have been intensively investigated for the sustained and controlled delivery of imaging and therapeutic agents for cancer diagnosis and cancer treatment, which can result in high diagnostic and therapeutic efficiency and low side effects.
- Coating **MIONs** with **liposomes** can prevent them from aggregation and opsonization, while evading nanoparticle uptake by the reticuloendothelial system, increasing colloidal stability in physiological solutions, and increasing its blood circulation time.

- Moreover, *liposomes* can be easily conjugated with ligands that target disease-specific receptors or other molecules.
- Improved stability in plasma benefits accumulation of MNP in tumor lesions via magnetic targeting and the enhanced permeability and retention effect.



- **Polyethylene glycol (PEG)**, with the advantage of low recognition by the reticuloendothelial system, has been deemed to be the answer for delivery of drugs with a poor plasma pharmacokinetic profile.
- The **stability** of MNP in plasma can be **greatly increased** when modified with PEG.

➤ **However,**

**it has been reported that PEG fails to completely avoid uptake by macrophages and still partially activates complement systems, which leads to shorter circulation time.**