Anticancer Drugs
Part 4

Dr. Heba Khader

Dr. Rawan Abudalo

Pharmacology 3

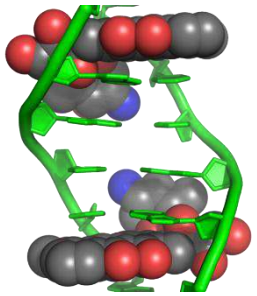
Antitumor antibiotics

- These include:
  1. Anthracyclines
  2. Bleomycin
  3. Dactinomycin (Actinomycin D)
  4. Mitomycin

  They are cell cycle nonspecific with bleomycin as an exception.

Anthracyclin antibiotics

- The anthracyclin antibiotics (**doxorubicin** and **daunorubicin**) are among the most widely used cytotoxic anti-cancer drugs.
- **Mechanism of action**



Four major mechanisms:

(1) inhibition of topoisomerase II

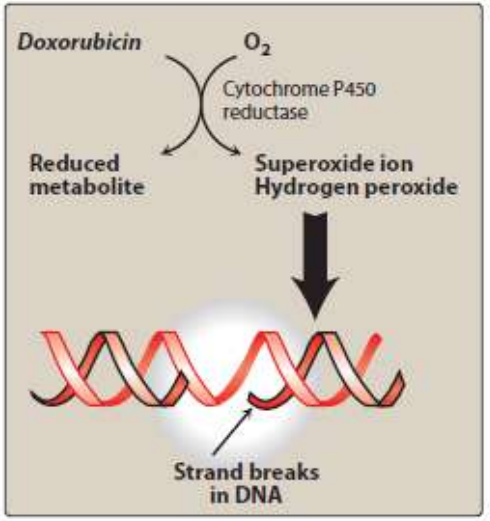
(2) high-affinity binding to DNA through intercalation, with consequent blockade of the synthesis of DNA and RNA, and DNA strand scission

(3) generation of free radicals through an

iron-dependent process

(4) binding to cellular membranes to alter fluidity

and ion transport.



Anthracyclin antibiotics

Pharmacokinetics: All these drugs must be administered IV, because they are inactivated in the GI tract.

- Extravasation is a serious problem that can lead to tissue necrosis.
- Undergo extensive hepatic metabolism. The bile is the major route of excretion, and the drug dose must be modified in patients with impaired hepatic function

- Because of the dark red color of the anthracycline drugs, the veins may become visible surrounding the site of infusion, and red discoloration of urine may occur.

Anthracyclin antibiotics

Specific Toxicity:

- **Cardiotoxicity :**Irreversible, dose-dependent cardiotoxicity
  - Results from the generation of free radical and lipid peroxidation
  - Reduced with:
    - Lower weekly doses .
    - Treatment with the iron-chelating agent dexrazoxane
    - **Liposomal-encapuslated formulations of doxorubicin**

Bleomycin

- Bleomycin is a small peptide that contains a DNA-binding region and an iron-binding domain at opposite ends of the molecule.
- Cell-cycle specific agent that causes cells to accumulate in the **G_2 phase**.

MOA:

- A DNA-bleomycin-Fe^{2+} complex undergoes oxidation to DNA-bleomycin-Fe^{3+}.
- The liberated electrons react with oxygen to form superoxide or hydroxyl radicals, which in turn attack and destroy the phosphodiester bonds of DNA

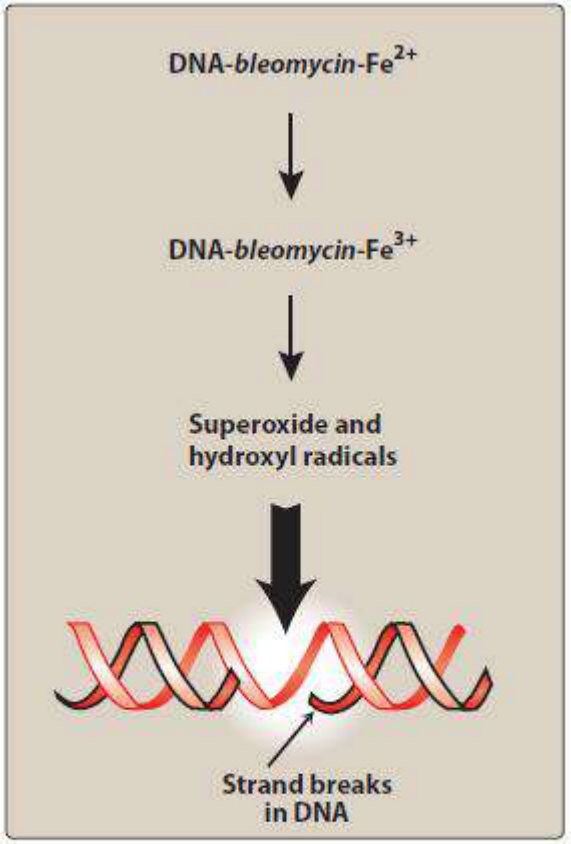


Figure 46.17
Bleomycin causes breaks in DNA by an oxidative process.

Bleomycin

- **Pharmacokinetics:**
  - Administered parenterally.
  - The bleomycin-inactivating enzyme (a hydrolase) is high in a number of tissues (for example, liver and spleen) but is low in lung and is absent in skin (accounting for the drug's toxicity in those tissues.

- Specific adverse effects:
  - **Pulmonary toxicity** is the most serious adverse effect.
  - **Hypertrophic skin changes** and **hyperpigmentation** of the hands are prevalent.

MICROTUBULE INHIBITORS-Plant alkaloids

- These classes differ in their structures and MOA but share the multidrug resistance mechanism.

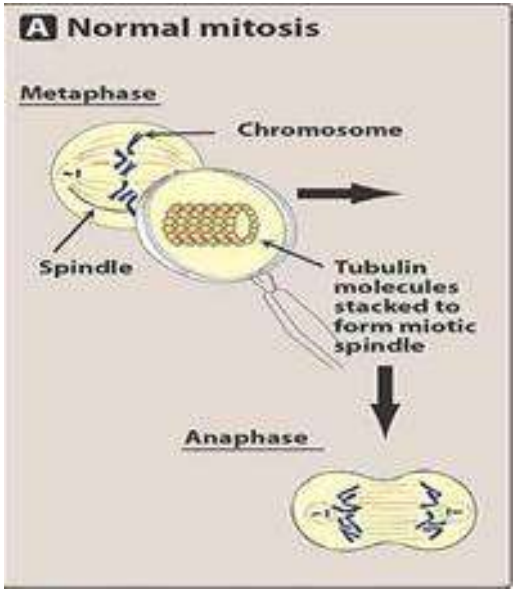
- **Cell cycle specific agents**
  - Vinca alkaloids (vinblastine, vincristine)
  - Taxanes (paclitaxel, docetaxel)

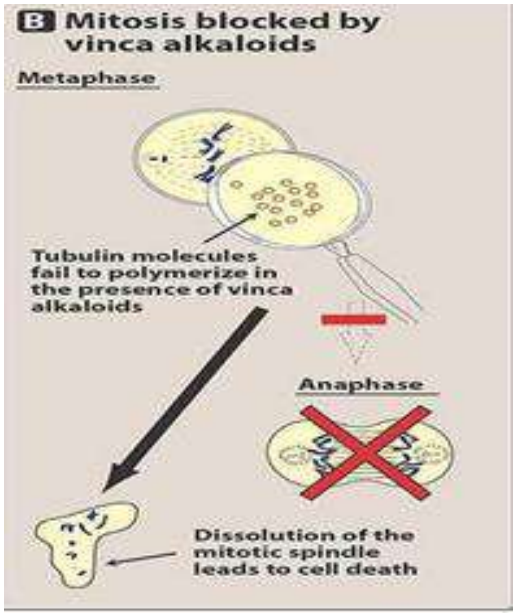
Vinca alkaloids: Vinblastine, Vincristrine

- Structurally related compounds derived from *Vinca rosea* (Vinblastine & vincristrine).

- Despite their structural similarity, there are significant differences between them in regard to clinical usefulness and toxicity.

- **MOA:** The vinca alkaloids bind avidly to tubulin <u>& inhibition tubulin polymerization</u>, which disrupts assembly of microtubules. This inhibitory effect results in mitotic arrest in metaphase (M) prevent, and cell division cannot be completed





Vinca alkaloids: Vinblastine, Vincristrine

- **Pharmacokinetics :**
- Intravenous injection leads to rapid cytotoxic effects and cell destruction.
- The vinca alkaloids are concentrated and metabolized in the liver by the cytochrome P450 pathway. They are excreted into bile and feces.

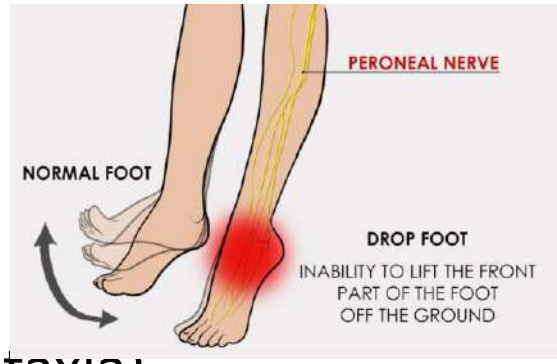
- **ADRs**

<u>Vinblastine</u>:

- NV, **bone marrow suppression**, alopecia.

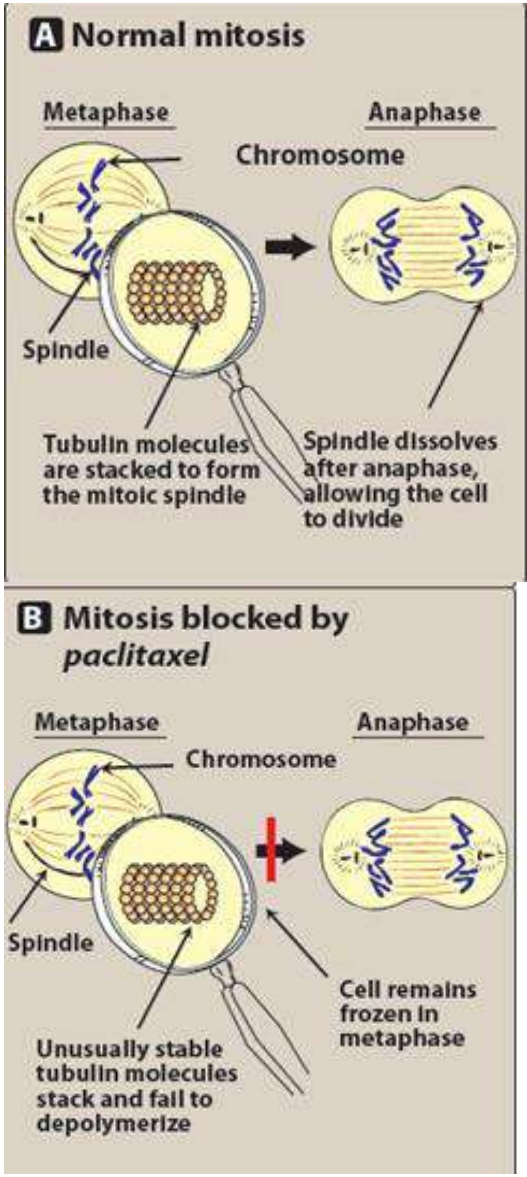
<u>Vincristine</u>:

- **Neurotoxicity**: peripheral sensory neuropathy (paresthesias, loss of reflexes, foot drop, and ataxia)
- Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)



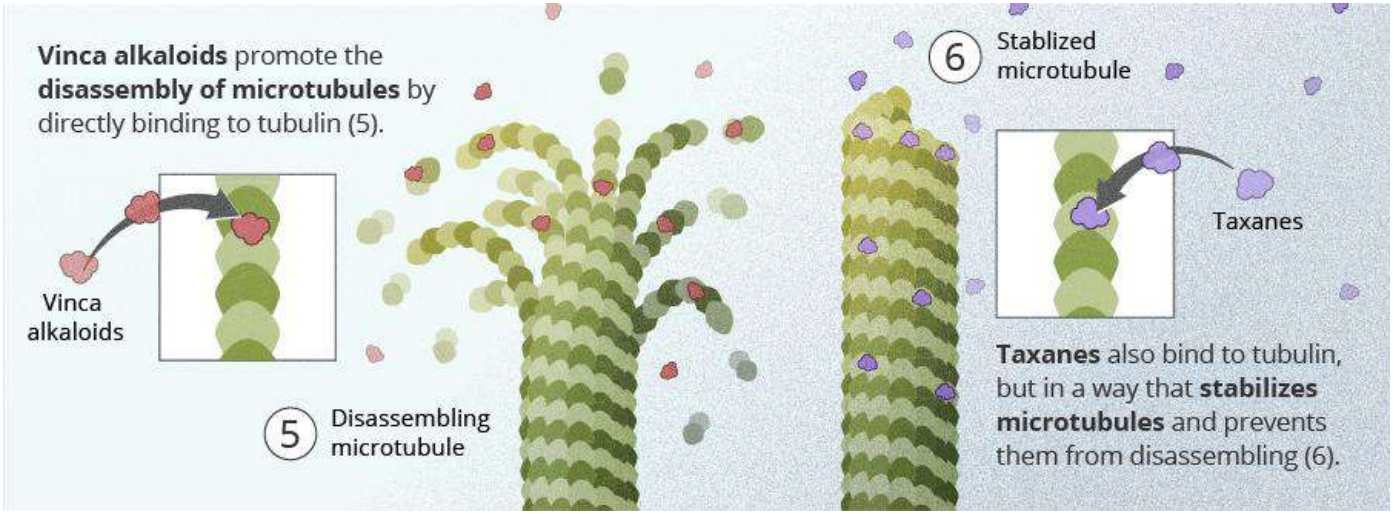
Taxanes: Paclitaxel, Docetaxel

- **Cell cycle specific (G2/M phase of the cell cycle)**
- **MOA**: They bind reversibly to the β-tubulin subunit promoting polymerization and stabilization of the polymer rather than disassembly. Thus, they shift the depolymerization-polymerization process to accumulation of microtubules. The overly stable microtubules formed are nonfunctional, and chromosome desegregation does not occur. This results in death of the cell

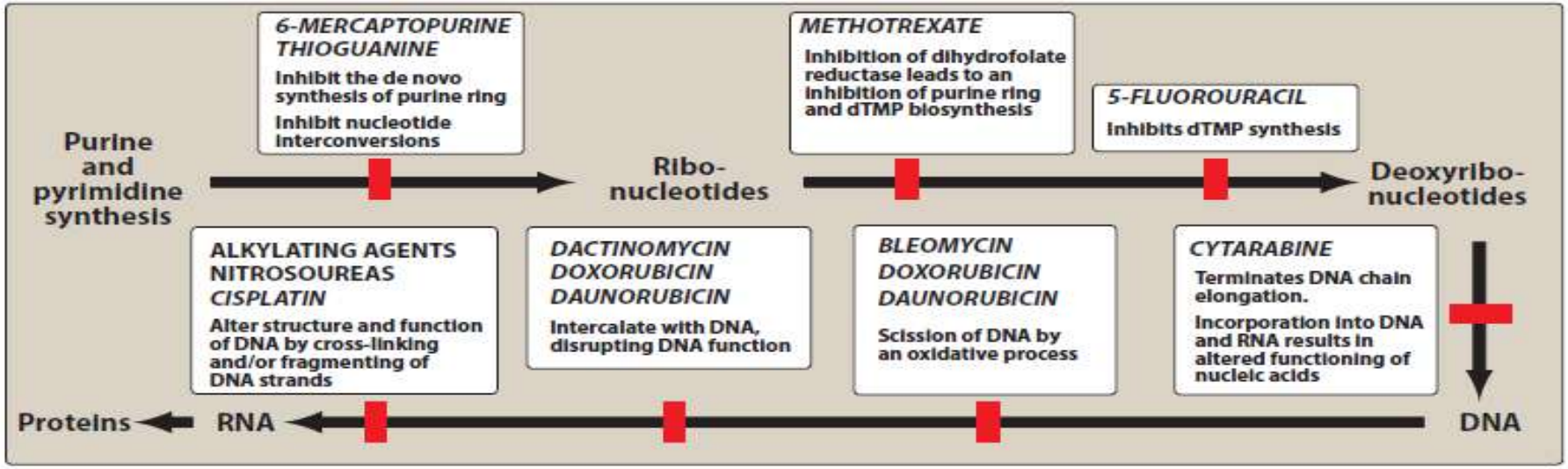


Taxanes: Paclitaxel, Docetaxel

- **ADRs:**
  - **Neutropenia:** treatment with colony stimulating factor (Filgrastim) can help
  - **Peripheral neuropathy**
  - **Transient, asymptomatic bradycardia:** Paclitaxel
  - **Fluid retention:** Docetaxel
  - **Serious hypersensitivty:** patients are pre-treated with dexamethazone, diphenylhydramine.


Vinca alkaloids promote the **disassembly of microtubules** by directly binding to tubulin (5).
Vinca alkaloids
5 Disassembling microtubule
6 Stablized microtubule
Taxanes
Taxanes also bind to tubulin, but in a way that **stabilizes microtubules** and prevents them from disassembling (6).

Mechanisms OF CANCER CHEMOTHERAPY



Hormonal anticancer

Steroid Hormones and Their Antagonists

- **Tumors that are steroid hormone–sensitive may be either**
  - **Hormone responsive**, in which the tumor regresses following treatment with a specific hormone.
    - As in the case of the cytotoxic effect of glucocorticoids at higher doses (ex. prednisone) on lymphomas
  - **Hormone dependent**, in which removal of a hormonal stimulus causes tumor regression and can be accomplished by
    - Surgery (ex. orchiectomy for patients with advanced prostate cancer) or by
    - Drugs (ex. in breast cancer, for which treatment with the antiestrogen tamoxifen is used to prevent estrogen stimulation of breast cancer cells).

- **For a steroid hormone to influence a cell, that cell must have intracellular receptors that are specific for that hormone.**

Prednisone

- A potent, synthetic, anti-inflammatory corticosteroid.

Mechanism of action:

- Prednisone itself is inactive and must first be reduced to prednisolone by 11-β- hydroxysteroid dehydrogenase in the liver.
- This steroid then binds to a receptor that triggers the production of specific proteins that induce apoptosis in certain cells.

Pharmacokinetics:

- Readily absorbed orally.
- Prednisolone is glucuronidated and excreted into the urine along with the parent compound.

Adverse effects:

- Predispose to infection (immunosuppressant action)
- Ulcers and pancreatitis.
- Hyperglycemia, osteoporosis, and change in mood (euphoria or psychosis).

Tamoxifen

- Classified as a selective estrogen receptor modulator **(SERM).**
- used for first-line therapy in the treatment of estrogen receptor–positive breast cancer.

- The action of tamoxifen is not related to any specific phase of the cell cycle.

Pharmacokinetics:

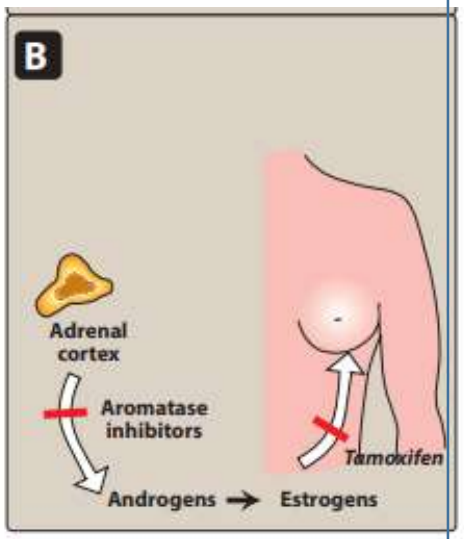
- Effective orally.
- Partially metabolized by the liver to active and non-active metabolites.
- Unchanged drug and its metabolites are excreted predominantly through the bile into the feces

Adverse effects:

- Hot flashes, nausea, vomiting, skin rash, vaginal bleeding, and discharge.
- Tamoxifen has the potential to cause endometrial cancer.

Aromatase inhibitors

- The aromatase reaction is responsible for the extra-adrenal synthesis of estrogen from androstenedione.
- Peripheral aromatization is an important source of estrogen in postmenopausal women.
- Example: **Anastrozole** and **letrozole**
- they have become first-line drugs for the treatment of breast cancer in postmenopausal women.



GnRH analogs.

They occupy the GnRH receptor in the pituitary, which leads to its desensitization and, consequently, inhibition of release of FSH and LH. ➡ both androgen and estrogen synthesis are reduced

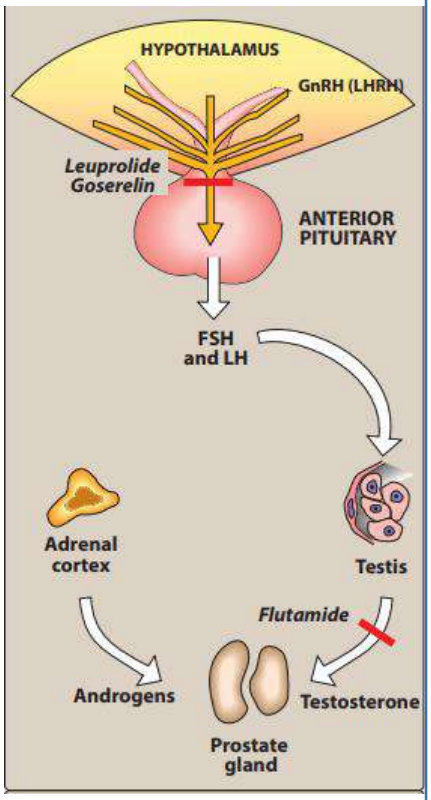
Example: **Leuprolide, goserelin**.

Used for prostatic cancer and breast cancer

Nonsteroidal antiandrogens.

They compete with the natural hormone for binding to the androgen receptor and prevent its translocation into the nucleus

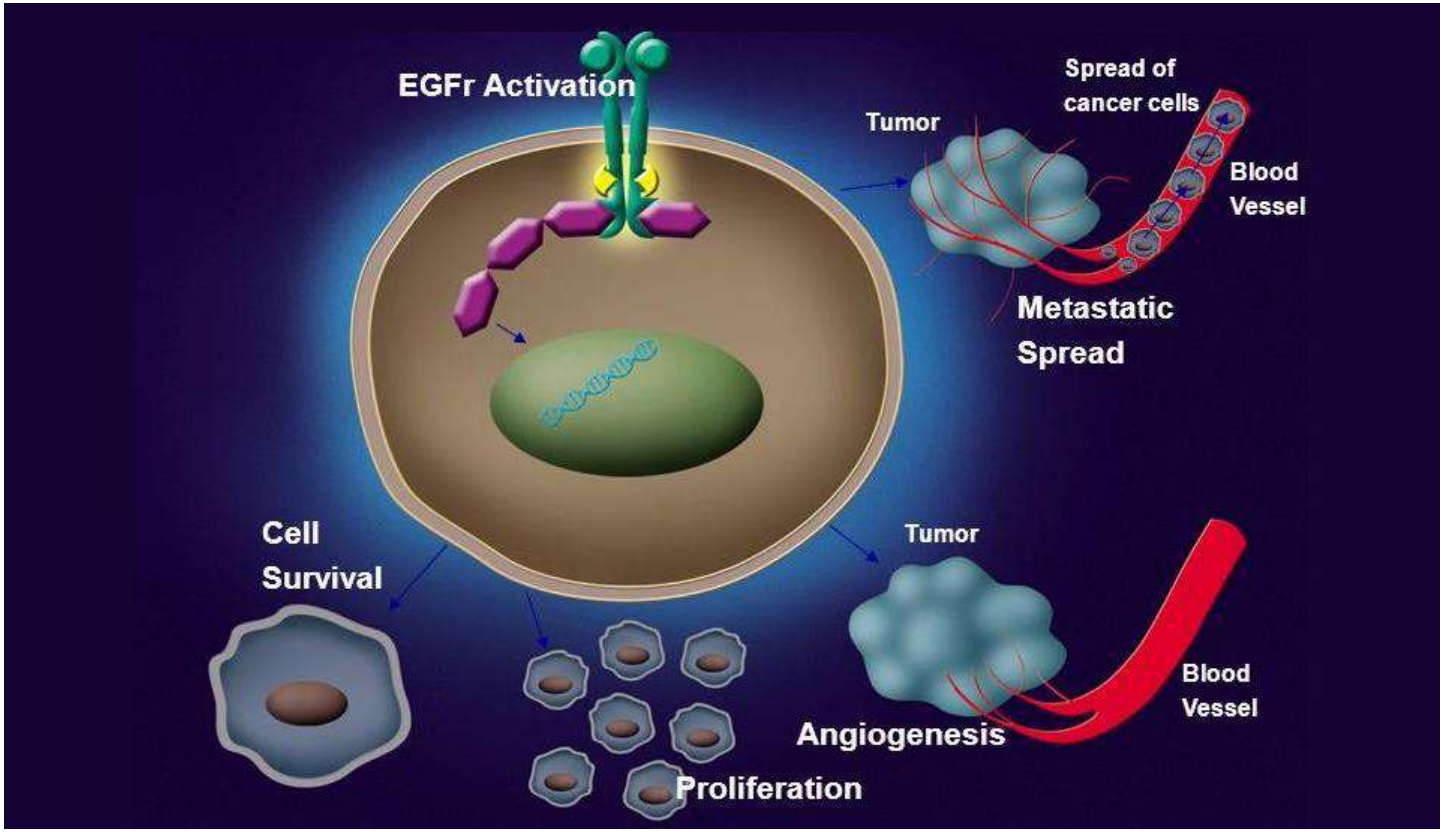
Example: **Flutamide,** oral antiandrogens used in the treatment of prostate cancer.



Monoclonal Antibodies

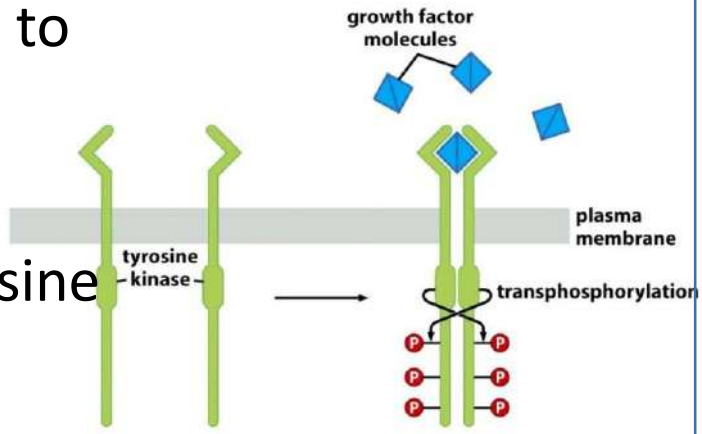
- Monoclonal antibodies are an active area of drug development for anticancer therapy and other nonneoplastic diseases (i.e, inflammatory bowel disease, rheumatoid arthritis)
- They are directed at specific targets (i.e, growth factor receptors).
- Often have different adverse effect profiles as compared to traditional chemotherapy agents.
- All of these agents are administered intravenously, and infusion-related reactions are common.

Epidermal Growth Factor Receptor (EGFR)



EGFR/ TK activity

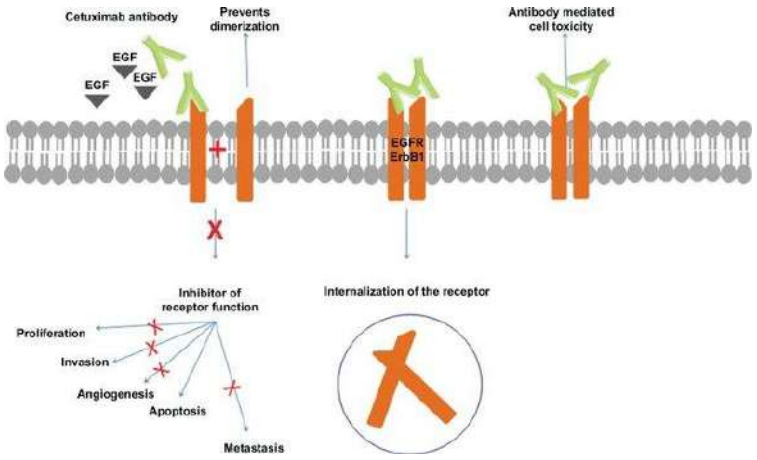
- No ligand – EGFR is a monomer
- EGF binds to one monomer which then moves through the membrane to find another monomer, a dimer is formed.
- Once dimerisation occurs, each tyrosine kinase (TK) domain phosphorylates tyrosine domains on the opposite monomer (transphosphorylation).
- Phosphorylation activates a series of downstream signalling pathways.



Growth factor receptor inhibitors

- **Activation of the EGFR** signaling pathway results in downstream activation of several key cellular events involved in **cellular growth and proliferation, invasion and metastasis, and angiogenesis**.

- The epidermal growth factor receptor (EGFR) is overexpressed in a number of solid tumors, including colorectal cancer, head and neck cancer, non-small cell lung cancer, and pancreatic cancer.



Growth factor receptor inhibitors

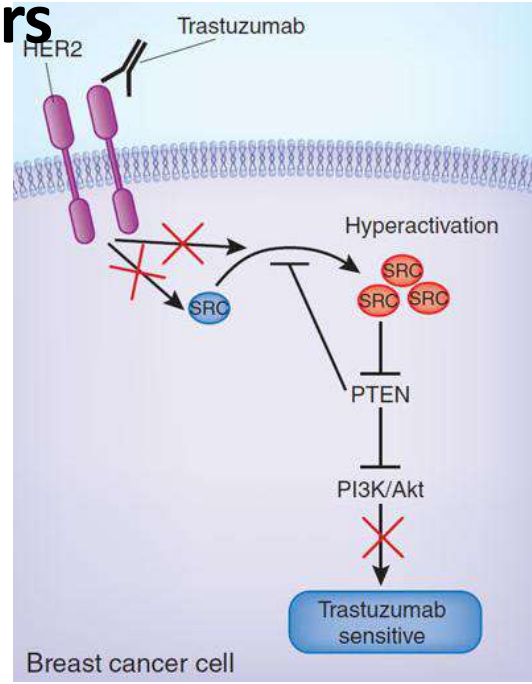
- **Cetuximab** is monoclonal antibody directed against the extracellular domain of the EGFR.
- It inhibits tumor cell growth and increases apoptosis.

- **Cetuximab** main adverse effects:

1. Acneiform skin rash (Rash has been correlated with increased response).
2. Hypersensitivity infusion reaction (Premedication with antihistamines is required)
3. Hypomagnesemia (electrolytes should be monitored).

Growth factor receptor inhibitors

Trastuzumab



- In patients with metastatic breast cancer, overexpression of human epidermal growth factor–receptor protein 2 (HER2) is seen in 25 to 30 % of patients.
- Trastuzumab specifically targets the extracellular domain of the HER2 growth receptor in breast cancer tissue and inhibits the proliferation of cells that overexpress the HER2 protein.

Adverse effects:

1. Cardiomyopathy (contractile dysfunction and reduced left ventricular systolic function)
2. infusion-related fever and chills (premedication with antihistamines and acetaminophen is required)

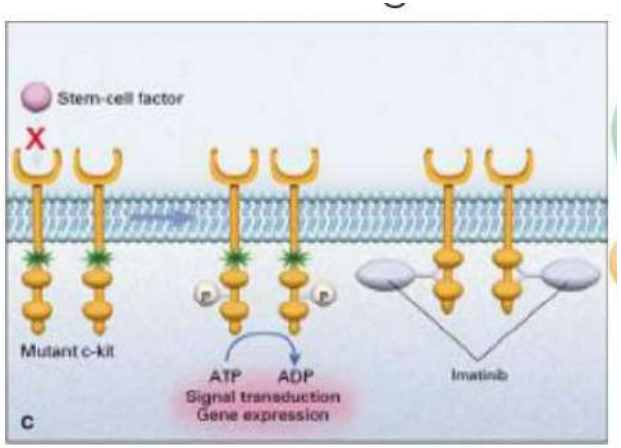
Tyrosine kinase inhibitors

- The tyrosine kinases are a family of enzymes that are involved in several important processes within a cell, including signal transduction and cell division.
  - At least 50 tyrosine kinases mediate cell growth or division by phosphorylation of signaling proteins. They have been implicated in the development of many neoplasms.
- The tyrosine kinase inhibitors are administered orally, and these agents have a wide variety of applications in the treatment of cancer.

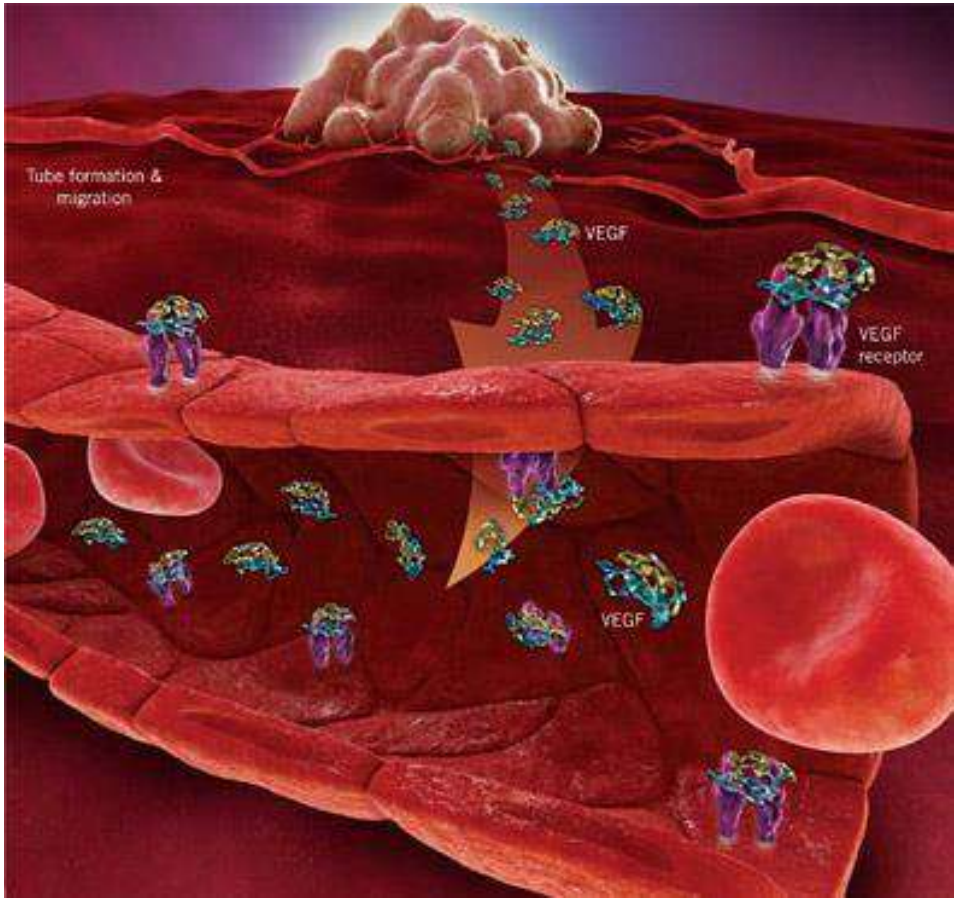
TYROSINE KINASE INHIBITORS (TKIs)

TKs are enzymes involved in transfer of a phosphate group from adenosine-3-phosphates (ATP) to tyrosine, serine or threonine residues.

- Protein phosphorylation is one of the most important events in regulating cell activities.
- Some oncoproteins need phosphorylation for regulation and activation.
- **Imatinib** inhibits the tyrosine kinase activity of the protein product of the bcr-abl oncogene that is commonly expressed in chronic myelogenous leukemia (CML)

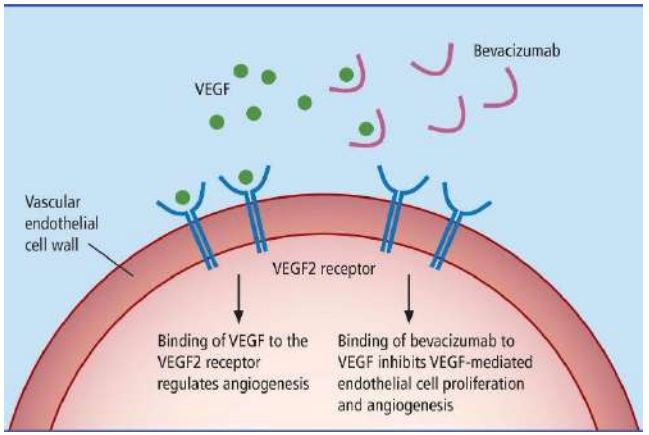


Targeting Tumour Angiogenesis



VEGF inhibitors

- The vascular endothelial growth factor (VEGF) is one of the most important angiogenic growth factors. The growth of both primary and metastatic tumors requires an intact vasculature. As a result, the VEGF-signaling pathway represents an attractive target for chemotherapy.



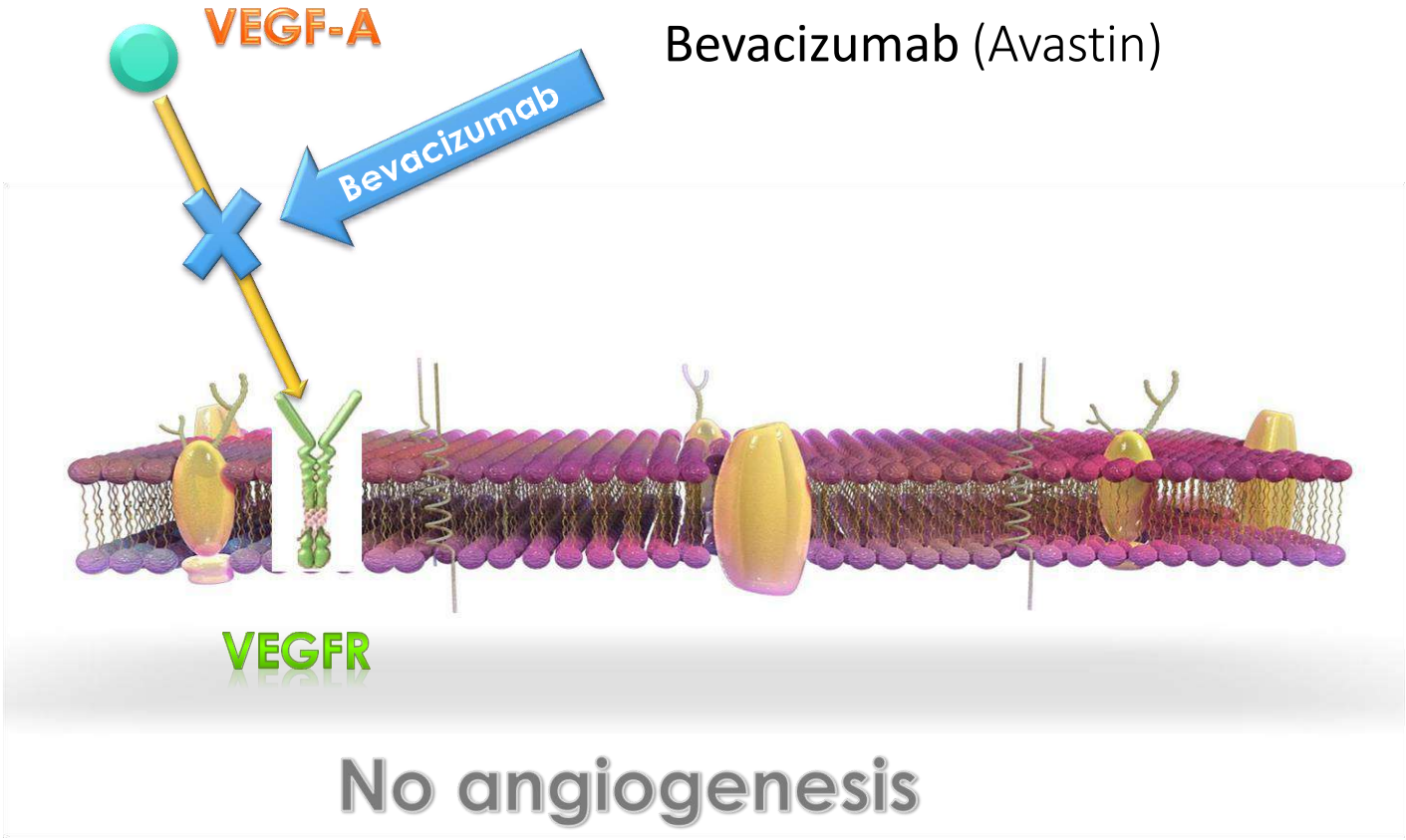
Bevacizumab binds VEGF and prevents binding of VEGF to its receptors on endothelial cells which inhibits vascularization of the tumor.

Adverse effects:

Hypertension

Wound healing problems (surgical procedures should be held)

Bevacizumab (Avastin)



No angiogenesis

Proteosome inhibitors

- Proteasomes are cellular complexes that break down proteins.
- Proteasome inhibition prevent degradation of pro-apoptotic factors such as the p53 protein, permitting activation of programmed cell death in neoplastic cells.

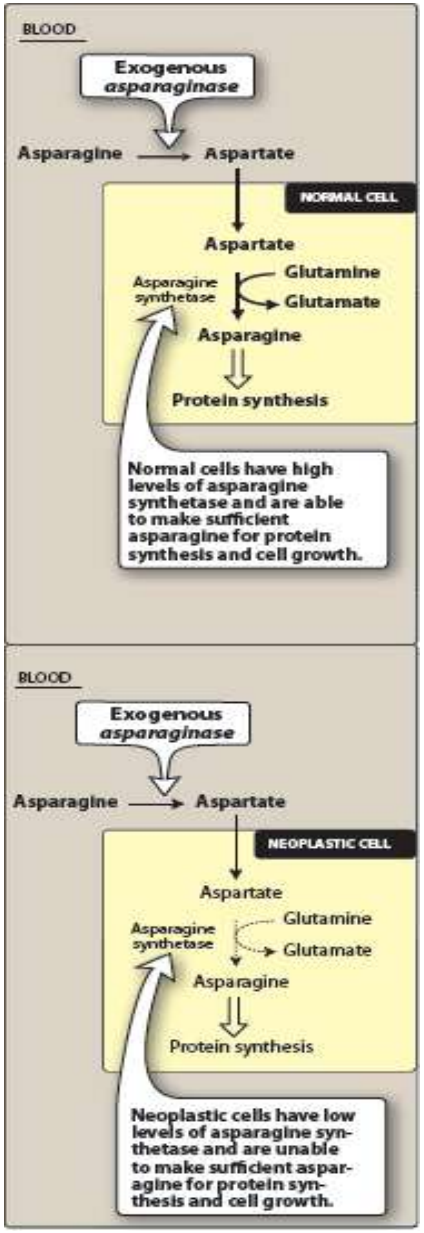
- The first proteasome inhibitor was **bortezomib.**
- Bortezomib is known to cause herpes zoster reactivation. Patients should receive antiviral prophylaxis while on bortezomib therapy.
- Other ADR: neuropathy, myelosuppression.

Asparaginase

- **Asparaginase** (L-asparagine amidohydrolase) is an enzyme occasionally used to treat childhood acute lymphoblastic leukemia (ALL).

- It hydrolyzes circulating L-asparagine to aspartic acid and ammonia. Because tumor cells in ALL lack asparagine synthetase, they require an exogenous source of L-asparagine for protein synthesis. Thus, depletion of L-asparagine results in effective inhibition of protein synthesis. In contrast, normal cells can synthesize L-asparagine and thus are less susceptible to the cytotoxic action of asparaginase.

- must be administered either IV or IM, because it is destroyed by gastric enzymes.



Immunotherapy

- Immunotherapy with **immune checkpoint inhibitors** is a rapidly evolving option for cancer treatment.
- The goal of immune checkpoint inhibitors is to block the checkpoint molecules, such as the **programmed death (PD - 1) receptor**, that normally help to keep the immune system in check.
- By blocking these molecules, the immune system is better able to attack the tumor and cause destruction.
- The two most commonly used checkpoint inhibitors are **pembrolizumab** and **nivolumab**.

Targeting the PD-1 Pathway Involved in Tumour Immunosuppression Is a Promising Therapeutic Approach

- PD-1 receptors are normally expressed on various immune cells, including T cells
- Tumor cells can express the PD-1 ligands, PD-L1 and PD-L2[1]
- PD-L1 and PD-L2 bind to the PD-1 receptors to inhibit the activated T cells and allow tumor cells to evade the immune response[1]

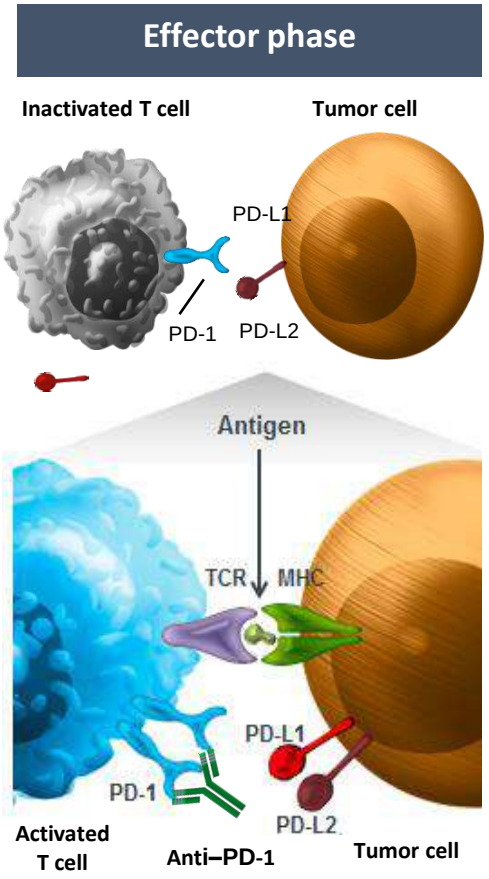


Image adapted from Pardoll DM. *Nat Rev Cancer.* 2012;12(4):252–264.
PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2; MHC = major histocompatibility complex; TCR = T-cell receptor.

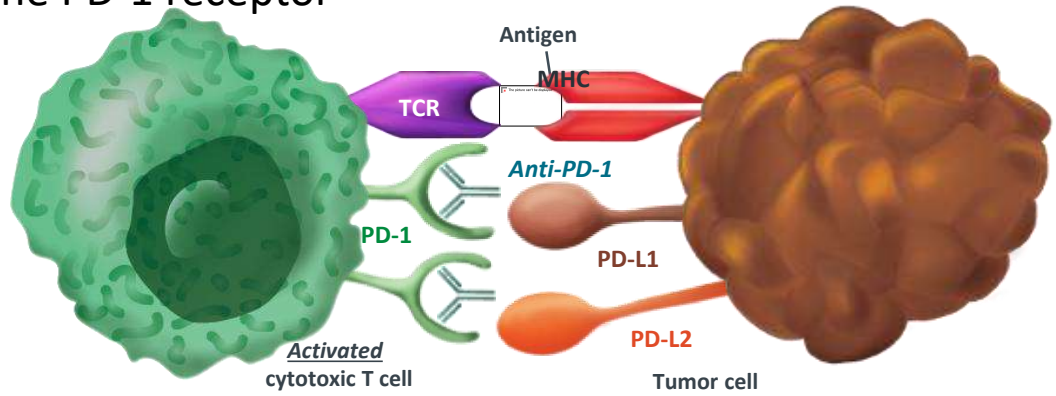
PD-1 Receptor Inhibition May Provide More Complete Pathway Blockade Than Targeting a Single Ligand

- Anti–PD-1 antibodies block PD-L1 and PD-L2 from binding to PD-1 in the tumor microenvironment.

PD-L1 Ligand Inhibition

PD-L1 and PD-L2 are ligands located on tumor cells

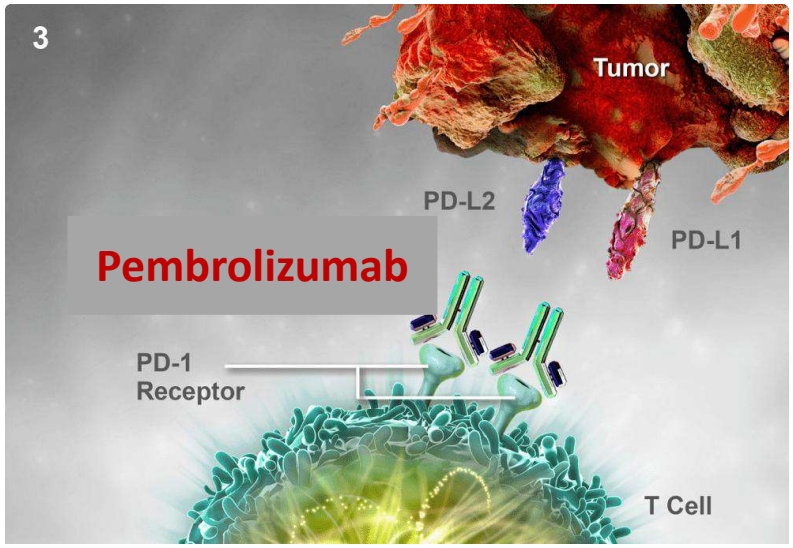
- Antibodies targeting the PD-L1 ligand on tumor cells only block the binding of PD-L1 to the PD-1 receptor



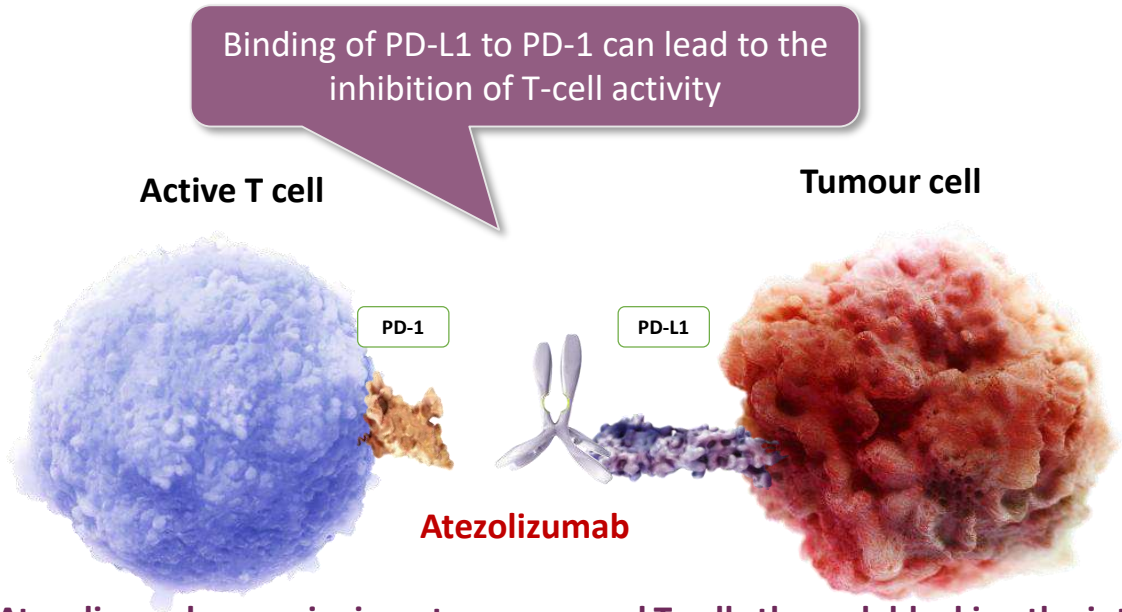
PD-1 = programmed death receptor-1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2.

PD-1 Receptor Blockers (**Pembrolizumab**)

By inhibiting the PD-1 receptor from binding to its ligands, **Pembrolizumab** reactivates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and reactivates antitumor immunity.



Atezolizumab can reactivate suppressed T cells in the tumour microenvironment

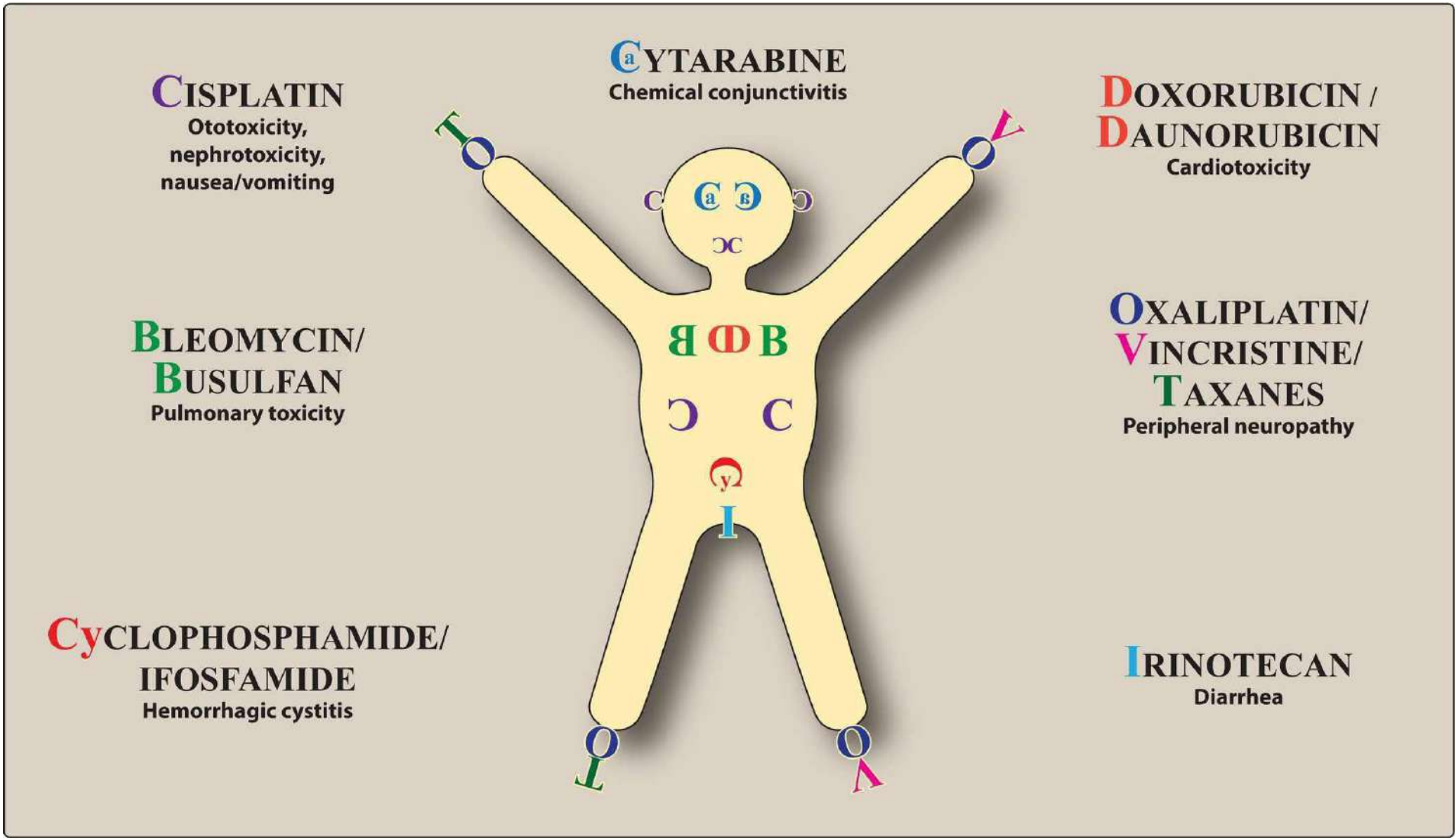


Atezolizumab can reinvigorate suppressed T cells through blocking the interactions of PD-L1 (on tumour cells with PD-1 (on T cells) in the tumour microenvironment

Immunotherapy

- The adverse reactions consist of potentially severe and even fatal immune-mediated adverse events.
- Adverse events include diarrhea, colitis, pneumonitis, hepatitis, nephritis, neurotoxicity, dermatologic toxicity in the form of severe skin rashes, and endocrinopathies such as hypo- or hyperthyroidism.
- Patients should be closely monitored for the potential development of signs and symptoms of toxicity and promptly treated with corticosteroids if necessary.

Summary Of Toxicity Of Chemotherapeutic Agents.



The End