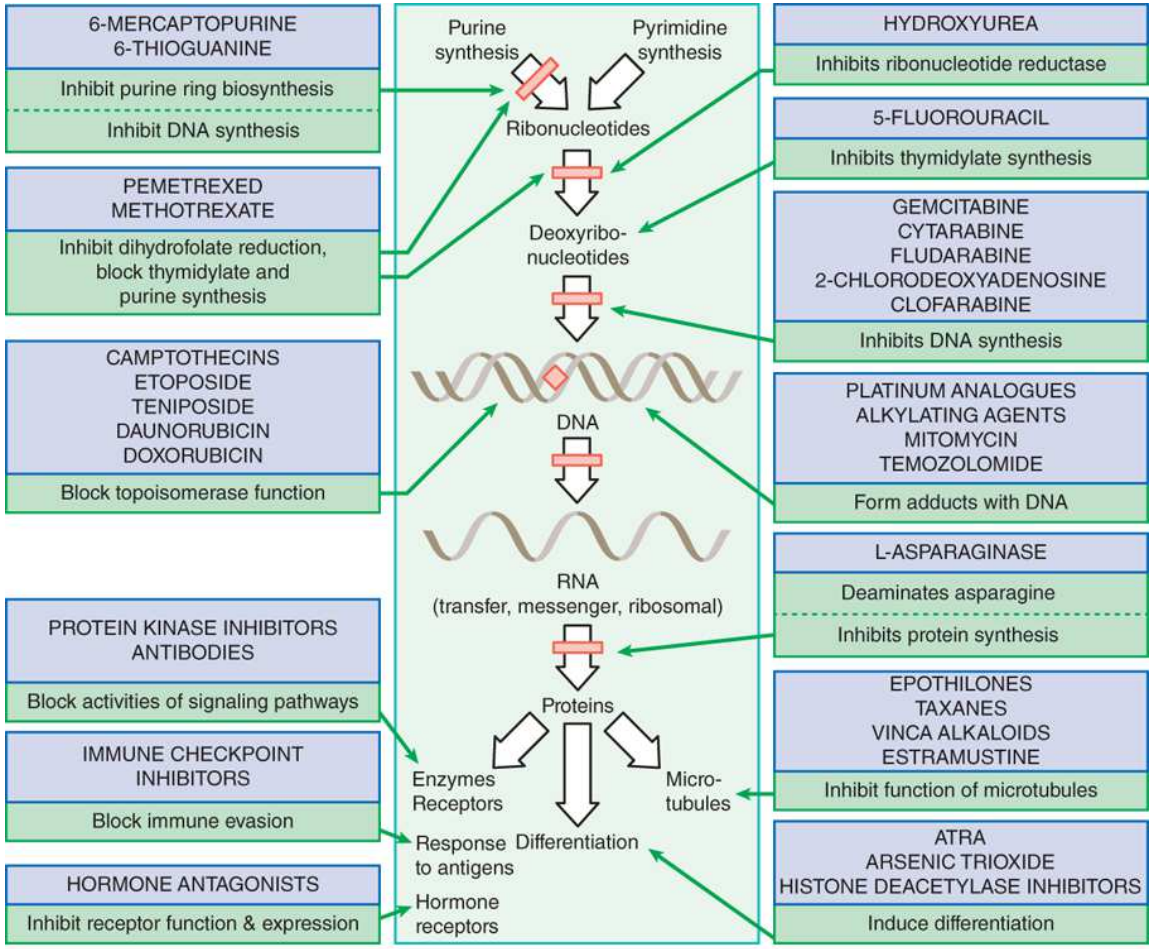
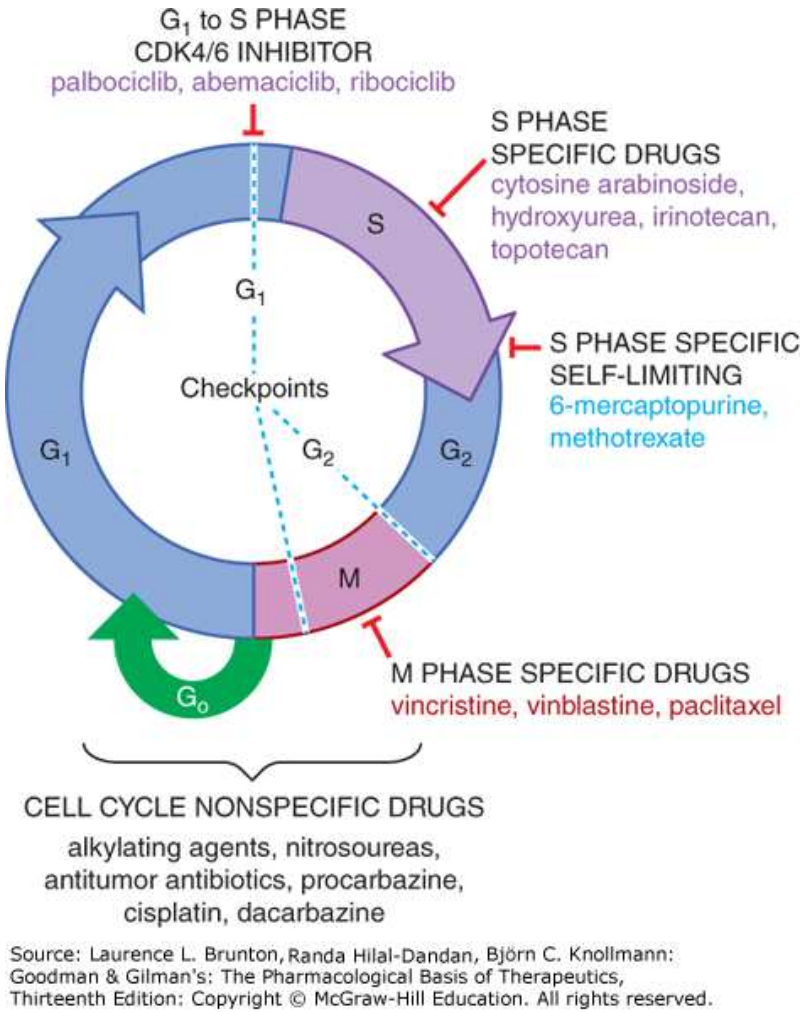
PHARMACOLOGY

ANTI-CANCER AGENTS

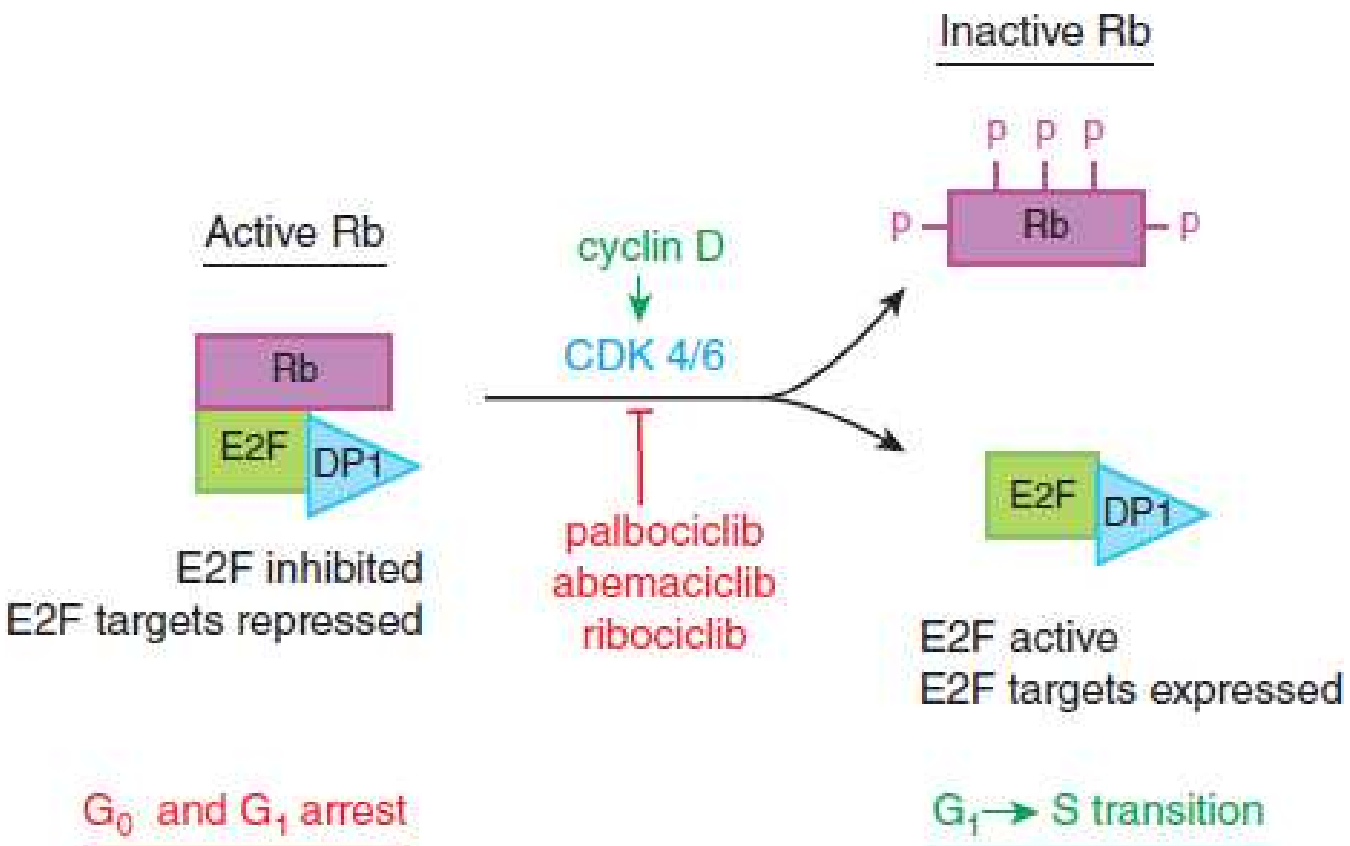
Kenneth Alonso, MD, FACP



Mechanisms and sites of action of some of the drugs used in the treatment of cancer.



Cell cycle specificity of drugs used in the treatment of cancer.



CDK4 inhibitors: retinoblastoma protein, cyclin-dependent protein kinases, and the regulation of cell cycle progression. In quiescent and differentiated cells (in G_0 or in cells arrested in G_1), the Rb protein is active and interacts with a heterodimer of the transcription factor E2F and its dimerization partner DP1, repressing transcription of promoters regulated by E2F. As a cell begins a cycle of division, cyclins activate CDKs that phosphorylate Rb, disrupting the Rb-E2F/DP complexes and permitting accumulation of active E2F complexes that drive transcription. This cell cycle checkpoint is frequently compromised in cancers due to cyclin D amplification, loss of Rb function, or loss of negative regulators of CDK4/6. Hyperphosphorylation of Rb can occur via mutations in Rb or expression of viral oncoproteins targeting Rb, placing the cell in a state of extensive proliferation, with reduced capacity to exit the cell cycle. Inhibition of CDK4/6 can cause G_1 arrest in susceptible cells (Dyson, 2016). CDK inhibitors (in red lettering) are identified by the disyllabic suffix "ciclib."

Alkylating agents

- Metabolism produces unstable alkyl groups that attack nucleophilic centers of proteins and nucleic acids
- Intrastrand cross-links of guanidine-guanidine
- Pulmonary fibrosis a complication as Type I pneumocytes damaged

Alkylating agents

- Methylates guanine at O_6 position
- DNA adduct induces futile recycling of mismatch repair process.
- Chlorambucil (nitrogen mustard)
- CCNU
- Streptozocin
- Dacarbazine
- Procarbazine is a hydrazine derivative
- Temozolomide is an imidazotetrazine derivative (oral; penetrates CNS)

Alkylating agents

- Methylates guanine at N_2 position
- Trabectedin is a tetrahydroisoquinolone
- Covalently bound to minor groove of DNA. Widens minor groove as DNA bends towards major groove. Activated (not constitutive) transcription is inhibited.
- DNA sequence specific; GC triplets bound more frequently.

Alkylating agents

- Adducts are recognised by the nucleotide excision repair (NER) machinery, then the recruited Rad13 (XPG) protein binds to DNA.
- XPG endounclease interacts with the minor groove-bound drug by means of an arginine residue located in the COOH terminus.
- Other proteins of the NER machinery trying to repair the damage are then hijacked, forming larger, more toxic complexes.
- Lastly, during the S phase, the aforementioned complexes give rise to double stand DNA breaks.

Alkylating agents
Nitrosoureas

- Lipophilic
- Break down in water to produce 2 reactive intermediates
- Chloroethyl carbonium ion (create adducts and cross-link DNA strands)
- Isocyanate (decreases glutathione levels, inhibiting DNA repair and RNA maturation)
- BCNU (carmustine)
- CCNU (lomustine)
- Streptozocin

Alkylating agents
Alkyl Sulfonate

- Busulfan
- Hydrolysis leads to production of highly reactive carbonium ion
- Binds to cysteine of histone proteins (DNA protein bound)
- Reacts with sulfhydryl groups of glutathione, disrupting cellular redox mechanism, increasing oxidative stress. Predominant metabolism.
- Phenytoin reduces AUC by 15%

Alkylating agents
Triazine

- Hexamethylamine
- Dacarbazine, procarbazine, temozolamide
- p450 activation

  Hepatic vascular toxicity differs from vascular occlusive disease
- Potentiates barbiturates, opiates, antihistamines, phenothiazines
- Hypertensive reaction with sympathomimetics or high tyramine foods
- Disulfiram reaction with alcohol
- Rash and pulmonary infiltrates as Type III allergic ity reaction

Alkylating agents
Nitrogen mustards

- Cyclophosphamide
- Prodrug
- Multistep p450 activation to 4-OHC and its tautomer, aldophosphamide, which is then oxidized to cyclophosphoramide, by aldehyde dehydrogenase (ALDH)
- This metabolite is only formed in cells that have low levels of ALDH.
- Forms DNA crosslinks both between and within DNA strands
- Cytotoxic
- Modulates dendritic cells, upregulates IFN, suppresses T_{reg} and myeloid derived suppressor cells, and promotes T_{H1}.
- Reduces plasma cholinesterase

Alkylating agents
Nitrogen mustards

- Ifosfamide
- MESNA (sodium 2-mercapto ethane sulfonate) administered concurrently to reduce bleeding in bladder as acrolein metabolite of phosphoramide accumulates
- Inactivated in bloodstream to dimesna when filtered by the kidney, reactivates to mesna
- Through Michael addition (acts as sulfhydryl donor), detoxifies acrolein
- Mesna's sulfhydryl group binds to Lactoperoxidase within the thiocyanate binding site
- Mechlorethamine
- Melphalan
- Bendamustine
- Ethylenimine
- Thiotepa

Alkylating agents
Platinum compounds

- Cisplatin and carboplatin
- Cisplatin is a squared planar platinum(II) complex composed by a central metal atom coordinated with two chlorides and two ammonia molecules in a cis configuration (trans form active as well)
- Chlorides are labile and interchange with hydroxyl ions
- In the cell, where chloride levels are low, cationic form is promoted and is much more reactive than the molecule in the blood
- Molecule has high affinity for Nitrogen and Sulfur donors
- Binds to N_7 guanine and adenine
- Form intrastrand DNA adducts that produce single-strand breaks when removed by DNA mismatch repair processes.
- Not a radiosensitizer.

Alkylating agents
Platinum compounds

- Oxaliplatin
- Adducts are not repaired by the same DNA mismatch repair processes as those with cisplatin.
- Decreases phosphorylation of BCL2, ABD, BAX, promoting apoptosis.
- Radiosensitizes.
- Augments superoxide function (NOX3 activation).

Alkylating agents
Mitomycin

- Requires activation to produce alkylating effect
- Promotes intra-stand cross-links between guanidine-guanidine.
- MDR 170 resistance
- Radiosensitizer
- DT-diaphorase inactivates in microsomal fraction of liver
- Vascular occlusive disease, pneumonitis, and hemolytic uremic syndrome as complications of use

Antimetabolites

- Azacitidine
- As with decitabine is a pyrimidine nucleoside analog of cytidine that inhibits DNA methyltransferase
- Cytarabine, gemcitabine (fluorine substituted deoxycytidine that requires enzyme activation) inhibits DNA polymerase
- Leads to hypomethylation of DNA and is directly toxic to abnormal hematopoietic cells in the marrow.

Antimetabolites

- Cladribine, clofaribine, nelarabine are purine analogs
- Active triphosphate metabolite inhibits ribonucleotide reductase, DNA chain extension (incorporation into DNA), and DNA polymerase a
- Fludaribine converts to Adenine arabinoside and enters cell via membrane carrier and is then rephosphorylated
- Inhibits riboncleotide reductase, DNA polymerase a, DNA primase and RNA primer formation, ligase I as well as induces apoptosis and is incorporated into RNA and DNA

Antimetabolites

- Cytosine Arabinoside enters cell by membrane carrier and activated intracellularly to nucleotide metabolite
- Inhibit DNA polymerase a, b (synthesis, repair)
- Inhibit ribonucleotide reductase
- Inhibit membrane glycoprotein and glycolipid synthesis
- Incorporate metabolites into DNA
- High levels of cytidine deaminase in GI, liver

Antimetabolites

- Azathioprine
- Prodrug
- Reductive cleavage of thioether by HPRT produces 6-mercaptopurine (6MP)
- Mediated by glutathione
- Convert to mono or triphosphate purine metabolite
- Within tissue, some 6MP converted to 6-thioguanine by TPMT with the addition of an amino group
- Both attach to ribose, are phosphorylated, and form the nucleotides that mimic inosinic acid (starting point for purine synthesis) and guanylic acid (mimic guanidine)
- Incorporated into DNA and RNA (non-functional)

Antimetabolites

- Product inhibition of GAPT, blocking purine synthesis (negative feedback)
- Triphosphate form blocks synthesis of BCL-XL by binding GPT binding protein RAC1, promoting apoptosis
- HGPRT decrease as source of resistance
- Increased risk of bone marrow aplasia in poor metabolizers (thiopurine S-methyltransferase (TPMT) *3A/*3A homozogytes)
- Wild-type homozygotes may experience decreased drug action at usual dosages
- 6 MP is a xanthine oxidase inhibitor (as is allopurinol)

Antimetabolites

- Pentostatin is a purine analog; irreversibly inhibits adenosine deaminase.
- 5-FU is a Pyrimidine analog of uracil.
- Functions as an anti-metabolite.
- Active metabolite (FdUMP) forms stable covalent complex with thymidilate synthetase in the presence of low folate
- FUTP incorported into RNA processing, FdUTP into DNA synthesis
- Radiosensitizes
- Dihydropyrimidine dehydrogenase metabolism in extrahepatic tissues

Antimetabolites

- Capecitabine is an oral pro-drug of 5-FU converted by thymidine phosphorylase.
- Preferentially converted in the liver and in tumor.
- Dihydropyrimidine dehydrogenase metabolism in extrahepatic tissues
- Floxuridine is catabolized to 5FU.
- Methotrexate enhances 5FU activity if given before 5FU (increase 5FU nucleotides)
- 5FU and leucovorin (provides reduced folates)

Antimetabolites

- Gemcitabine requires intracellular phosphorylation in a rate-limiting step by deoxycytidine kinase to form its active metabolites.
- One, difluorodeoxycytidine diphosphate directly inhbits ribonucleontide reductase; the other, diflurodeoxycytidine triphosphate is incorporated into DNA.
- ATP depletion underlies its action as a radiosensitizer.

Antimetabolites

- Methotrexate is a dihydrofolic acid reductase inhibitor.
- Deplete reduced folates
- Inhibits de novo purine and thymidylate synthesis (MTX and polyglutamates)
- Form DNA strand breaks (nucleotide depletion and incorporation of dUTP)
- Synergistic with 5FU as well as with zoledronic acid (biphosphonate).
- Increased thymidine synthetase activity leads to resistance.
- Precipitates in acid urine
- May cause Type III allergic pneumonitis

Anti-microtubular agents
Topoisomerase II inhibitors

- Topoisomerase II creates temporary double stranded DNA breaks and reseals them after managing torsion of DNA supercoils
- Anthracyclines
- Doxorubicin, daunorubicin, idarubicin, mitoxantrone
- Require free radical intermediate (presence of iron)
- Intercalates into DNA through hydrogen bonding, causing crosslinks and strand breaks.
- Quinone moiety generates reactive oxygen species
- Forms adducts linking to guanine

Anti-microtubular agents
Topoisomerase II inhibitors

- MDR-1 (P-glycoprotein) and MRP resistance
- Increased glutathione levels associated with resistance,
- Mitoxantrone also interferes with RNA and is a potent inhibitor of topoisomerase II
- Doxorubicin upregaulates Antigen Presenting Cells
- Cardiotoxic
- Radiosensitizer

Anti-microtubular agents
Topoisomerase II inhibitors

- Epipodophyllotoxins
- Etoposide and Teniposide
- With DNA and topoisomerase II, forms a ternary complex
- Single strand DNA break
- Enhance methotrexate toxicity if delivered beforehand
- MDR 170 resistant

...

Anti-microtubular agents
Topoisomerase I inhibitors

- Topoisomerase I relaxes torsionally strained DNA (constitutively expressed throughout all phases of cell cycle)
- Topoisomerase I inhibitors block the release of Topoisomerase I from the cleavable complex and forming a ternary complex
- Irinotecan, topotecan
- Prevents religation as binds both to the enzyme and DNA with Hydrogen bonds.
- SN-38 lactone is active form

Anti-microtubular agents
Topoisomerase I inhibitors

- Poor metabolizers are homozogytes for uridine diphosphate glucuronosyltransferase (UGT1A1) *28/*28.
- This is associated with increased risk of adverse effects (diarrhea, bone marrow aplasia).May cause Type III allergic pneumonitis
- MDR (P-glycoprotein) resistance
- Glucoronidated SN-38 is major excretion product

Anti-microtubular agents
Taxanes

- Taxol
- C13 ester on 15 membered taxane ring with free 2-OH group for maximal activity
- Stabilizes GTP-bound tubulin in the microtubule, thereby inhibiting the process of cell division as depolymerization is prevented.
- Binds to N-terminal amino acid in β-tubulin and stabilize tubulin polymers, promoting microtubular assembly, inhibiting disaggregation.
- Primarily blocks cells in mitosis but also may prevent transition from G_0 to S phase

Anti-microtubular agents
Taxanes

- Paclitaxel, docetaxel, cabazitaxel
- Paclitaxel interacts with toll-like receptors, to enhance dendritic cell activation, maturation, and cytokine secretion.
- MDR 170 resistant
- Cross-react with vinca alkaloids, doxorubicin, etoposide
- p450 metabolism

Anti-microtubular agents
Taxanes

- Radiosensitizer as active in G2/M cellular arrest. May also induce reoxygenation in tumor, induce apoptosis.
- PI3K deregulation associated with resistance.
- CHFR lack associated with taxane sensitivity.
- BRCA1 over-expression associated with resistance.

Antti-microtubular agents
Epithelone

- Bind to N-terminal amino acid in β-tubulin and stabilize tubulin polymers, promoting microtubular assembly, inhibiting disaggregation.
- Unlike taxanes, do not induce MDR (multiple drug resistance, p-glycoprotein) gene.
- Water soluble

Anti-microtubular agents
Vinca alkaloids

- Vinblastine, vincristine, vinorelbine
- Bind to the β-III isotype of β-tubulin and inhibit microtubule formation arrests cell in metaphase.
- M-phase specific.
- MDR 170 resistance

mTOR inhibition

- mTOR is a serine-threonine kinase that recognizes stress signals via the PI3K/Akt pathwy.
- Inhibition results in G1 growth arrest, retardation of tumor angiogenesis, induction of apoptosis, and reduce expression of HIF-α.
- Evorolimus is an mTOR inhibitor.
- Temisrolimus is an mTOR inhibitor.
- Radiosensitizer.
- Penetrates blood-brain barrier.
- Oral ulcerations and myelosuppression common.

Intercalating agents

- Irinotecan, topotecan inhibit topoisomerase-1.
- Poor metabolizers are homozogytes for uridine diphosphate glucuronosyltransferase (UGT1A1) *28/*28.
- This is associated with increased risk of adverse effects (diarrhea, bone marrow aplasia).
- Etoposide, teniposide inhibit topoisomerase-II.
- If methylated, resistant.

Antibiotics
Bleomycin

- Bleomycin is a glycopeptide antibiotic
- Contains DNA binding region (A2 peptide) and iron binding region at opposite end of peptide
- Chelates metals, producing superoxide or hydroxyl radical

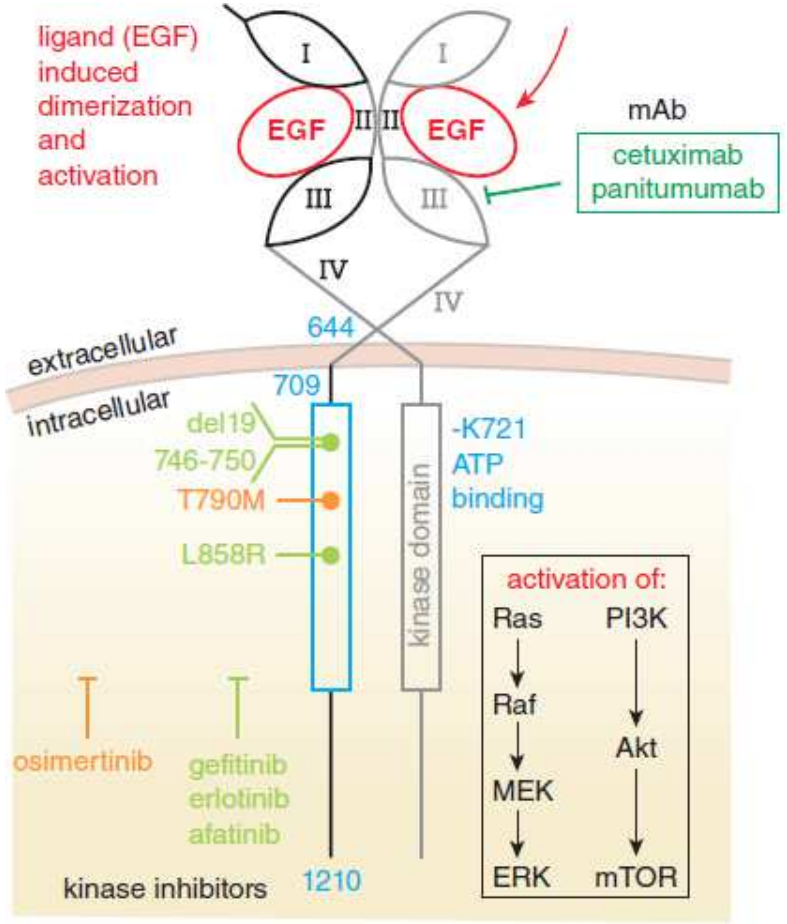
  Single and double strand DNA breaks
- Induce scission by abstracting the hydrogen atom from the base
- G2 phase most active
- Oxygen, heat increase pulmonary toxicity
- Dactinomycin is an actinomycin antibiotic.

Others

- Arsenic trioxide induces apoptosis of promyelocytic leukemia cells and damages or degrades the fusion protein PML/RARα.
- Prolongs QTc
- Bexarotene selectively binds and activates retinoid X receptor (RXR).
- Regulates cell proliferation.
- Tretinoin is a retinoid.
- Regulates cell proliferation by targeting RARα.
- All-trans retinoic acid promotes myotubule formation.

Others

- Porfimer is a photosensitizer.
- Activated by light.
- Asparaginase depletes the amino acid, asparagine, required by some leukemia cells.
- Mitotane is cytotoxic to adrenal cells.



Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

Monoclonal antibodies

- Cetuximab is mouse derived anti-EGFR antibody.
- Blocks EGF-induced auto-phosphorylation as well as induces its internalization and degradation. Inhibits nuclear translation of EGFR.
- Radiosensitizes as EGFR effective inducer of DNA protein kinase activity; blocking nuclear translation limits DNA repair.
- K-RAS mutations render cetuximab ineffective.

Monoclonal antibodies

- Bevacizumab is a recombinant humanized monoclonal antibody that binds to and inhibits the VEGF receptor on the extracellular surface.
- Normalize tumor vasculature.
- Gemtuzumab is a humanized monoclonal antibody against cell surface protein CD33 conjugated with a cytotoxic antitumor antibiotic, calichemaicin.
- Binding leads to internalization of the antibiotic with resulting DNA double strand breakage and death.

Monoclonal antibodies

- Rituximab is a chimeric monoclonal antibody directed at the CD20 antigen on lymphocytes. Rituximab modulates SRC , decreasing IL-10 (and STAT3 and BCL).
- Alemtuzumab is a humanized monoclonal antibody against cell surface protein CD52.
- Expressed on lymphocytes.
- Induces cell-lysis.

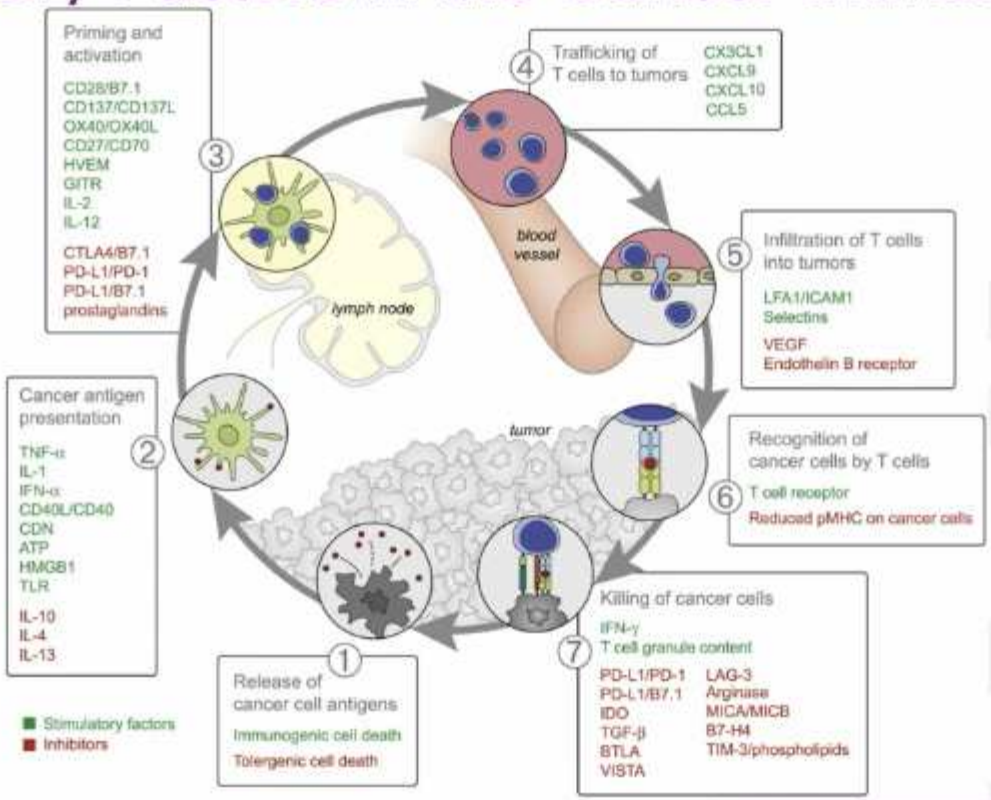
Monoclonal antibodies

- Ofatumumab is a chimeric anti-CD20 antibody whose Fab domain binds specifically to both the small and large extracellular loops of the CD20 molecule.
- The Fc domain mediates immune effector functions to result in B-cell lysis in vitro (may be complement mediated or ADCC mediated).
- Tisotumab vedotin-tftv (anti-Tissue Factor antibody conjugated with microtubule disruptor, MMAE) in PD-L1 negative cervical cancer. Blocks angiogenesis as well.
- Ocular toxicity

Monoclonal antibodies

- Trastuzumab is a humanized monoclonal antibody directed at EGFR-2 (HER2).
- mTOR pathway disruption associated with resistance.
- Trastuzumab emtansine and trastuzumab deruxtecan are EGFR-2 antibody directed conjugates; emtansine (DM1, a microtubule disruptor); deruxtecan, topoisomerase-1 inhibitor
- Panitumumab is a mouse based monoclonal antibody directed at the epidermal growth factor receptor.
- Denosumab is a “human” monoclonal antibody against RANK ligands.

Inhibitory Factors in the Cancer-Immunity Cycle



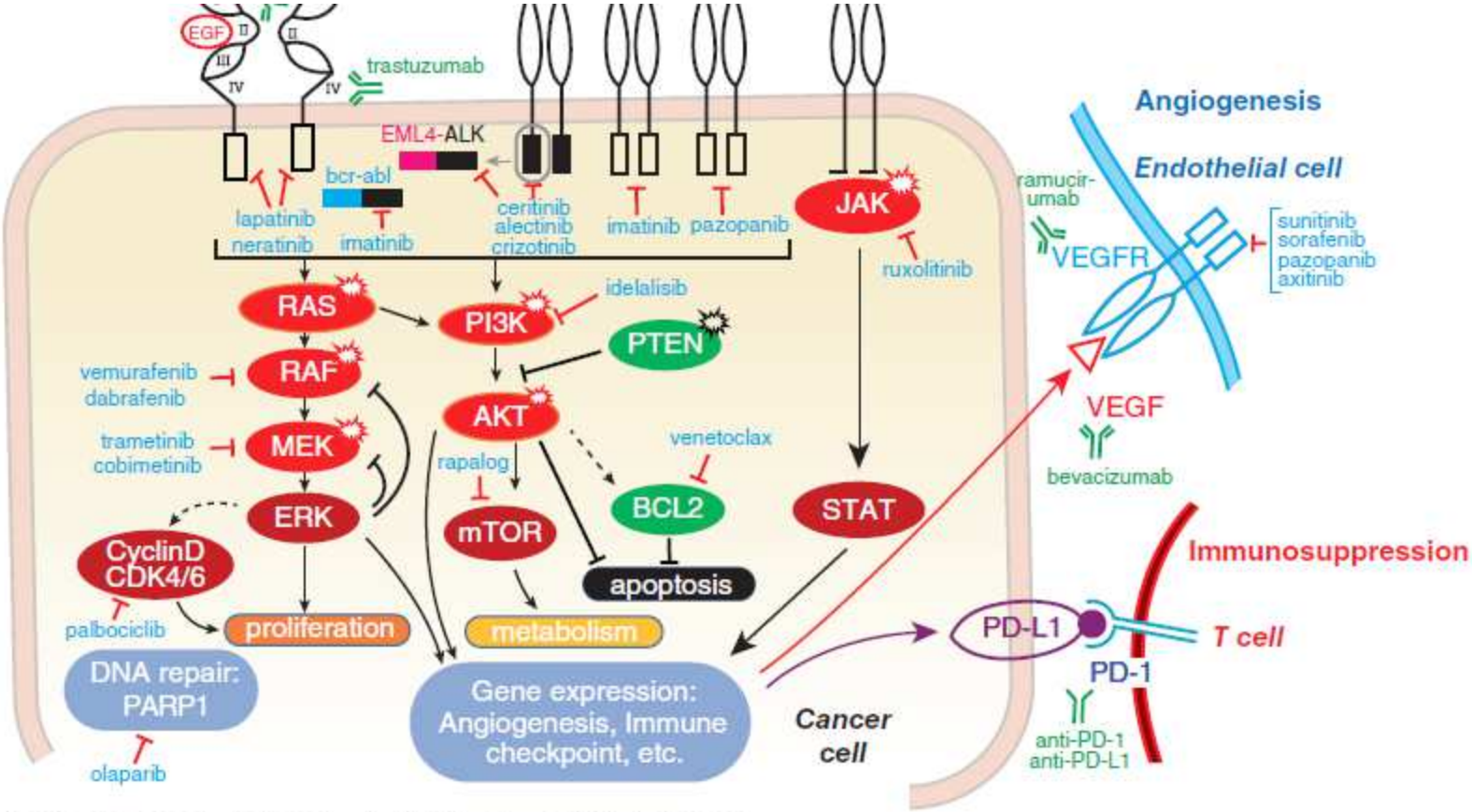
Chen, DS, Mellman I. Immunity. 2013 Jul 25;39(1):1-10

Immune blockade

- Nivolumab is a “fully human” monoclonal IgG4 antibody that blocks the interaction between PD-1 and its ligands.
- Activation of the PD-1 checkpoint pathway in T cells by PD-L1 or PD-L2 evokes a negative regulatory immune response and inactivates T cells
- Ilpilmumab is a “fully human” IgG1 monoclonal antibody that binds to CTLA-4
- CTLA-4 is upregulated during the antigen priming of T cells and binds B7 on APCs to attenuate the T-cell response

Immune blockade

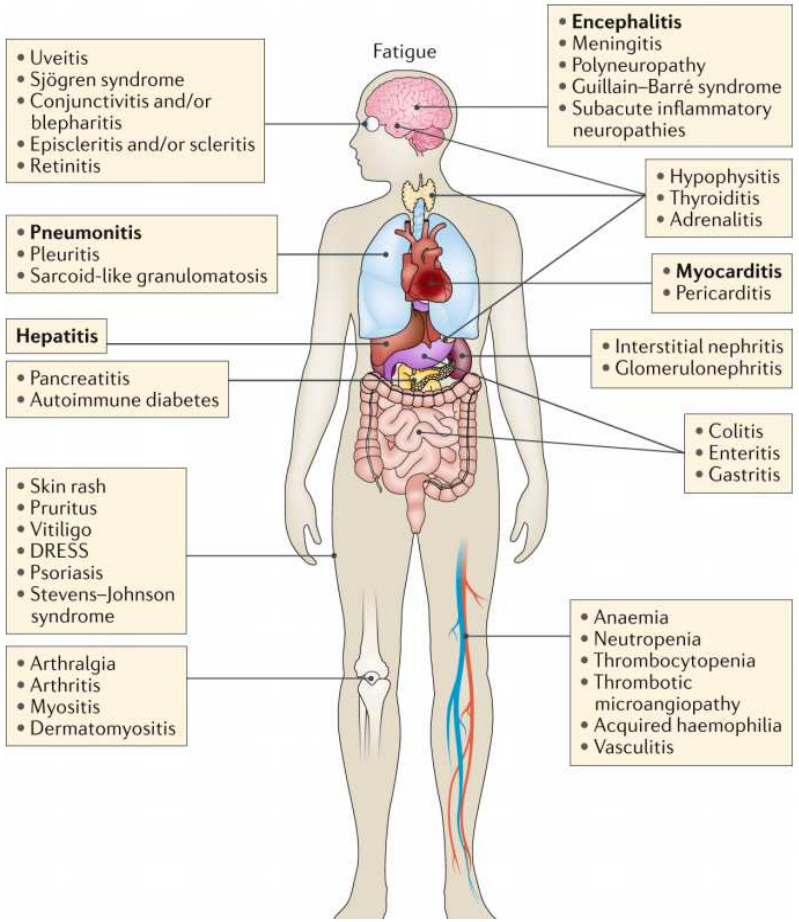
- Pembrolizumab is a “humanized” monoclonal IgG4-κ isotype antibody that blocks interaction between PD-1 and its ligands.
- Atezolizumab is a “fully human” IgG1 monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and B7-H1.
- PD-L1 is expressed in many cancers and thus can suppress the activation of cytotoxic T cells that enter the tumor
- Palbociclib is a checkpoint inhibitor (CDK 4/6)
- Blocks transition from G to S phase



Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

The Spectrum of Immune-Related AEs

Numerous organs/tissues may be affected



Martins, et al. *Nature Reviews Clin Oncol*. 2019:16:563–580.

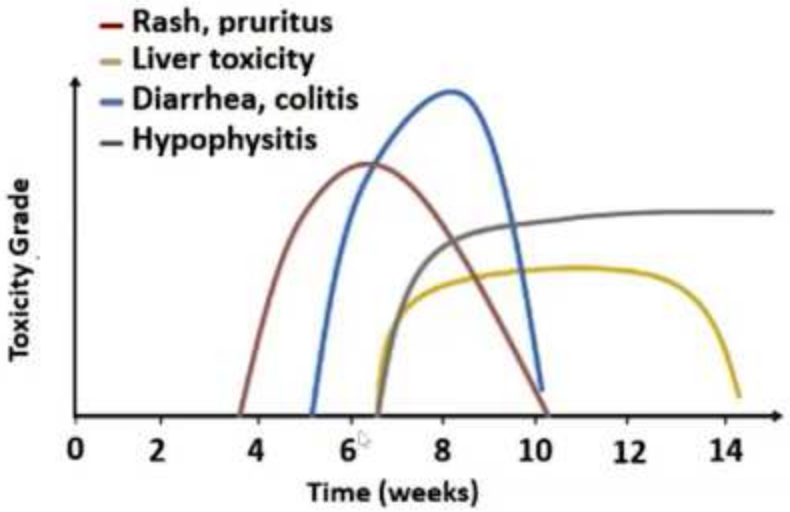
Adverse effects of tyrosine kinase inhibitors

- Most common side effects are hand-foot syndrome, diarrhea, hypertension, fatigue
- Bleeding and hepatotoxicity are serious side effects
- Mucositis is uncommon

Adverse effects of PD-LI and CTLA-4 blockade

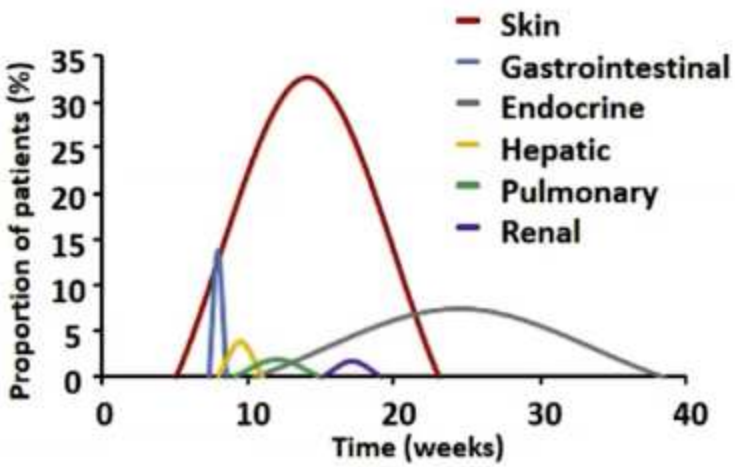
- Transaminitis, colitis, endocrinopathy (especially, thyroid) common adverse effects
- Stop drug if grade 2 reaction; begin high dose steroids; restart with caution
- If grade 3, the anti-TNF antibody, infliximab, may be used; do not restart medication
- If uveitis or colitis, use infliximab
- If neuropathy, myocarditis, interstitial lung disease, or hepatitis, administer intravenous immunoglobulin
- High risk patients include post-transplant, those with autoimmune disease or HBV/HCV/HIV

CTLA-4 Blockade[a]

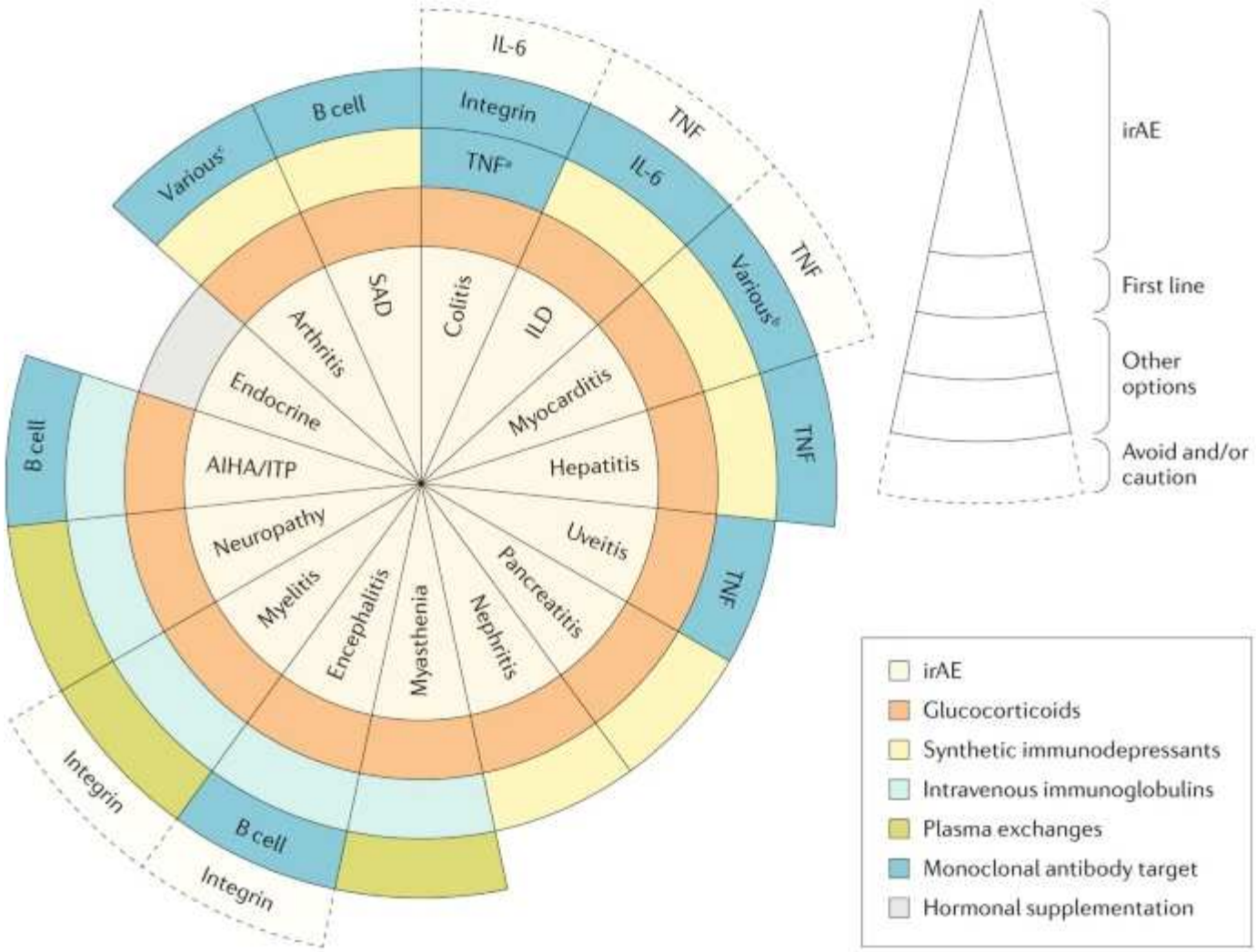


J Clin Oncol 2012;30:2691-2697

PD-1 Blockade[b]



J Clin Oncol 33(15 suppl), 2015;9018-9018


IL-6
TNF
TNF
TNF
TNF
TNF
Integrin
Integrin
B cell
B cell
B cell
Various*
Various*
TNF*
IL-6
SAD
Colitis
ILD
Arthritis
Myocarditis
Endocrine
Hepatitis
AIHA/ITP
Uveitis
Neuropathy
Pancreatitis
Myelitis
Encephalitis
Myasthenia
Nephritis
irAE
First line
Other options
Avoid and/or caution
irAE
Glucocorticoids
Synthetic immunodepressants
Intravenous immunoglobulins
Plasma exchanges
Monoclonal antibody target
Hormonal supplementation

Molecular targeted therapies
Proteasome inhibitor

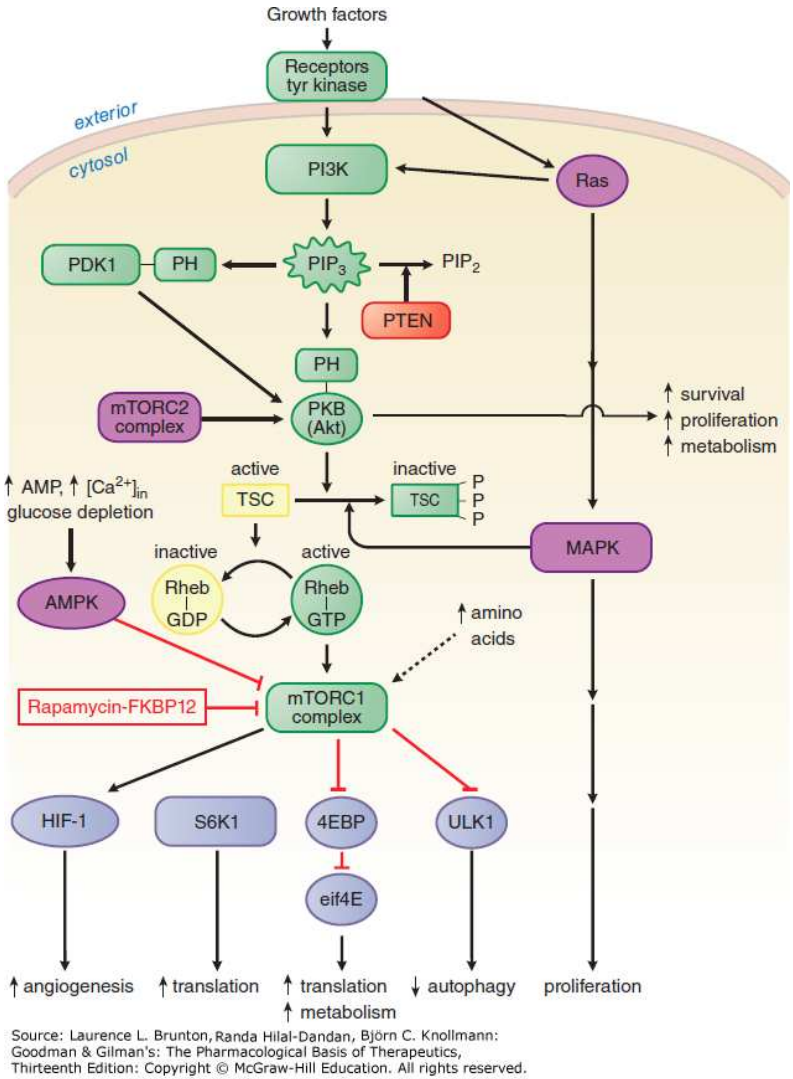
- Bortezomib reversibly binds the chymotrypsin-like subunit of the 26S proteasome, interrupting the NF-κB pathway, preventing targeted proteolysis.
- Accumulations activate the programmed cell death via caspase-mediated pathways
- Also Inhibits the EGFR receptor, blocks degradation.
- Not effective with radiation.
- Synergistic with anthracyclines.

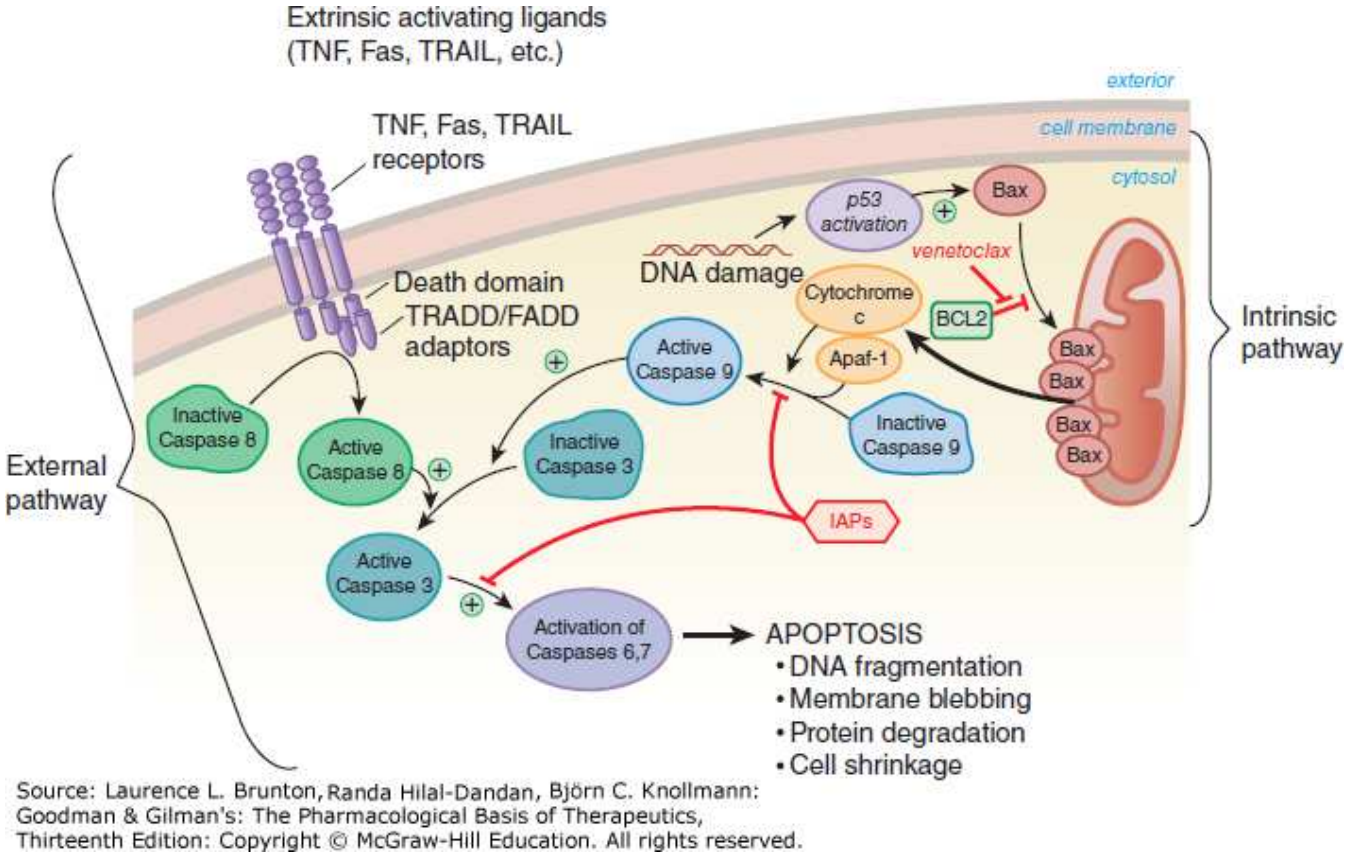
Molecular targeted therapies
Tyrosine kinase inhibitors

- Imatinib inhibits receptor tyrosine kinases BCR-ABL, PDGF, stem cell factor (C-KIT).
- Sorafenib is a multi-kinase inhibitor. It inhibits dendritic cells, NK cells, and induction of primary antigen-specific T cell responses
- Gefitinib and erlotinib are small molecule tyrosine kinase inhibitors that inhibit unregulated EGFR signaling by binding to the intracellular ATP binding site, preventing tyrosine kinase activity.
- Long-term use arrests cells in G_1 phase.
- Radiosensitizer.

Molecular targeted therapies
Tyrosine kinase inhibitors

- Dasatinib is a tyrosine kinase inhibitor.
- Sunitinib is a multikinase inhibitor. It preserves dendritic cell, NK, and T effector cell function while depleting myeloid derived suppressor cells and T_{reg} activity (promoting T_{H1}) and reducing CTLA4 and PD1 negative stimulatory molecules.
- Nilotinib is a kinase inhibitor.
- Lapatinib is a kinase inhibitor.
- Sorafenib is a kinase inhibitor.





Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

BH3 mimetics enhance apoptosis. Permeability of the outer mitochondrial membrane to cytochrome c is regulated by proteins required for forming pores, including proapoptotic BAX and BAK. BAK and BAX are rendered inactive by binding to the BH3 domains of antiapoptotic proteins such as BCL2. BH3 mimetic drugs (venetoclax) target BCL2 and its interaction with BAX/BAK, reducing the inhibitory effect of BCL2 on apoptosis progression, enhancing cytochrome c release, and sensitizing the cell to apoptosis. Cancer cells may be resistant to apoptosis by overexpression of BCL2; BH3 mimetics such as venetoclax release the resultant blockade and promote apoptosis.

Hormones

- Goserlin, leuprolide, triptorelin are LHRH agonists.
- Sustained administration leads to suppression of pituitary gonadotropins.
- Bicalutamide is antiandrogenic.
- Estramustine is a nitrogen mustard alkylating agent in combination with estradiol, and induces microtubule instability.
- Flutamide is a nonsteroidal antiandrogen.
- Nilutamide is an antiandrogen.
- Testolactone is a steroid aromatase inhibitor.
- Medroxyprogesterone.

Hormones

- Tamoxifen is an anti-estrogen.
- Selective estrogen receptor modulators (SERM) also promote T_{H2}, inhibit dendritic cell activation and maturation, block B cell maturation.
- Raloxifene is a selective estrogen modulator (limit bone loss)
- Toremifine is a nonsteroidal anti-estrogen.

Hormones

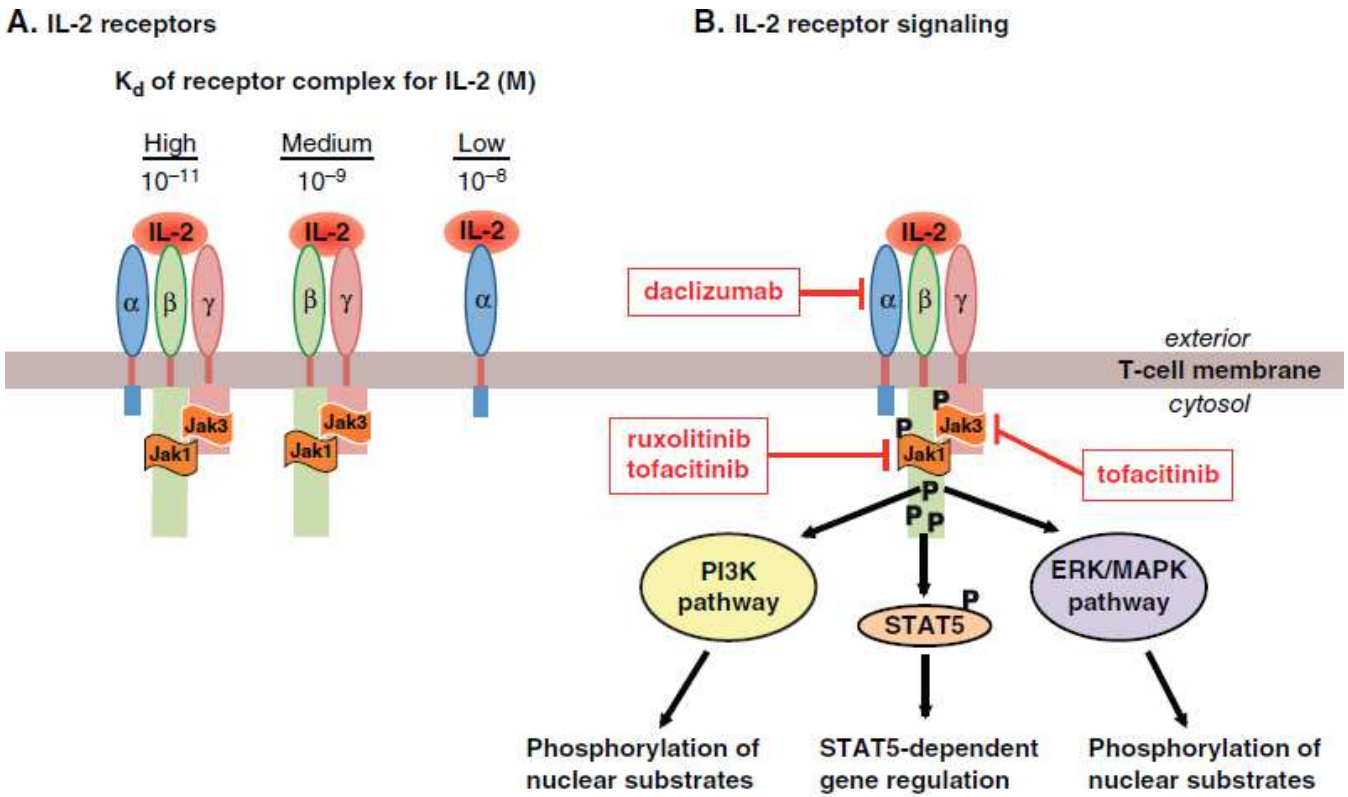
- Fulvestrant is a selective estrogen receptor degrader
- Fulvestrant binding configuration prevents ER dimer formation.
- ERα is not degraded.
- Cross-talk is not a problem.
- Useful in tamoxifen and aromatose inhibitor failures as well as first-line therapy.

Hormones

- Anastrazole and letrozle are non-steroidal estrogen antagonists that bind to the heme groups of CYP19, blocking aromatase activity.
- Both diminish CD24+CD25+ T_{reg} cells, and sensitize cells to ADCC.
- Neither affects plasma lipids.

Hormones

- Exemestane is a steroidal estrogen antagonist that irreversibly inactivates aromatase, blocking estrogen peripheral action.
- No effect on cognition.
- No cross-talk.
- Greater risk of osteoporosis than with tamoxifen.
- Better clinical outcomes, however.



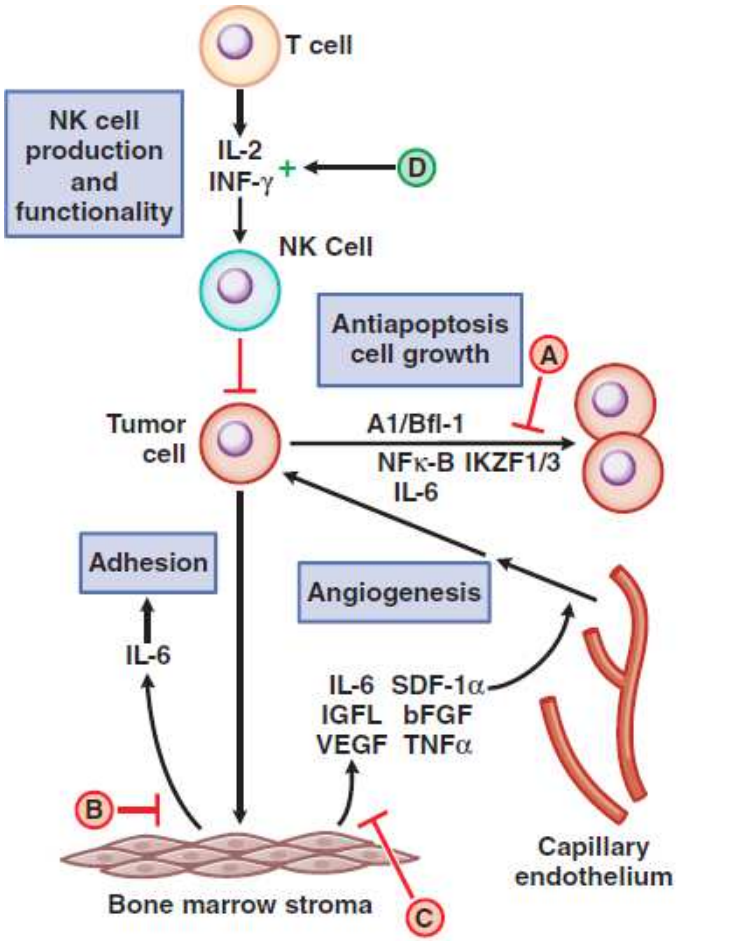
Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

Biologics

- IL-2
- Denileukin difitox is a fusion protein of diphtheria toxin fragments linked to IL-2 sequences; interacts with IL2-receptors, inhibiting cellular protein synthesis.
- May lead to capillary leak
- Interferon-α and interferon-β suppress cell proliferation and enhance lymphocyte cytotoxicity and macrophage phagocytic activity.
- 15 subtypes of IFN-α
- 2a immunogenic (25% of patients)

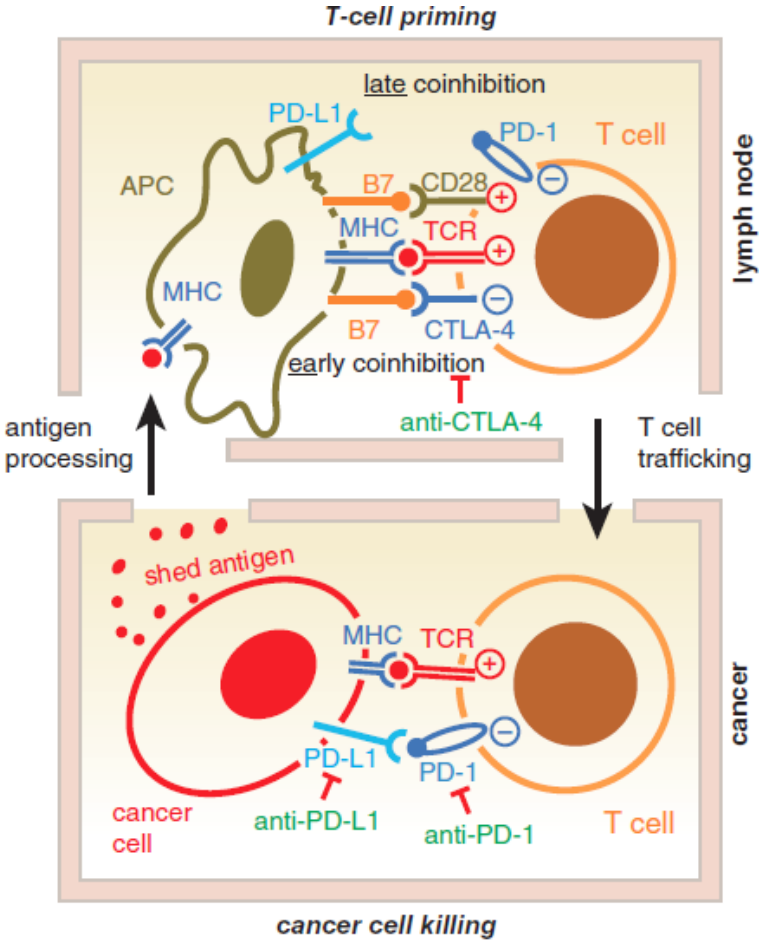
Others

- VEGF inhibits thymic T cell development and suppresses dendritic cell activation and maturation.
- PARP inhibitors block single strand break repair (allowing conversion to double strand break and repair by homologous recombination during mitosis).
- Lenalomide is a thalidomide analogue.
- Affects micro-vessel density.
- Induces tumor cell apoptosis directly through its effect on stromal support cells.
- Suberoylanilide hydroxamic acid, romidepsin are histone deacetylase inhibitors.
- Enzastaurin is a PKCβ inhibitor



Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

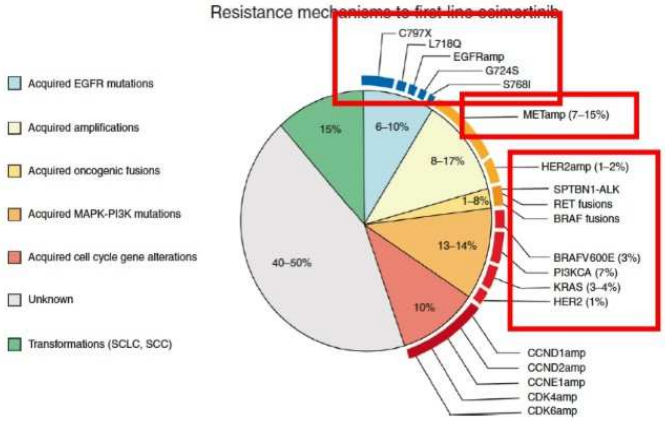
Overview of proposed mechanisms of anti-myeloma activity of thalidomide and its derivatives



Source: Laurence L. Brunton, Randa Hilal-Dandan, Björn C. Knollmann: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, Thirteenth Edition: Copyright © McGraw-Hill Education. All rights reserved.

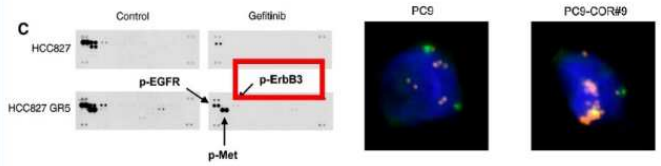
EGFR TKI RESISTANCE: BIOLOGY

MOLECULAR MECHANISMS of ACQUIRED RESISTANCE



Leonetti, et al. B J Cancer 2019;121:725

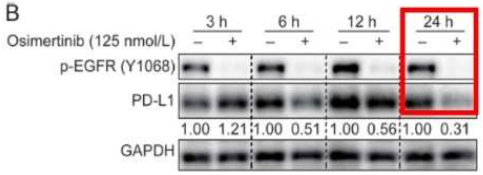
HER3 activation, EGFR amplification



Not *per se* a mechanism of resistance, but evidence of co-activation with MET

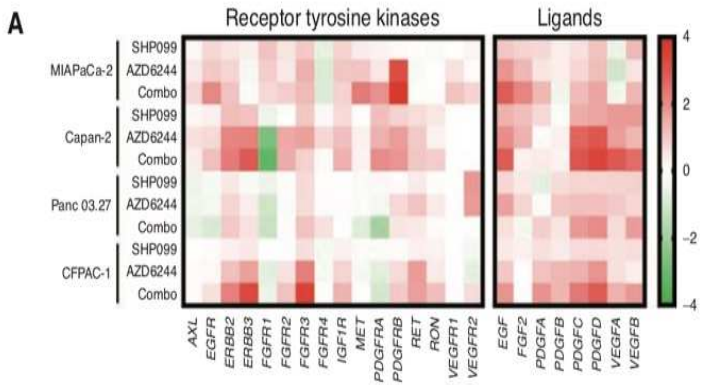
Nakaga, et al Cancer Res 2017; 77: 2078
Engelman, et al. Science 2007;76:1039

IMMUNE ESCAPE?



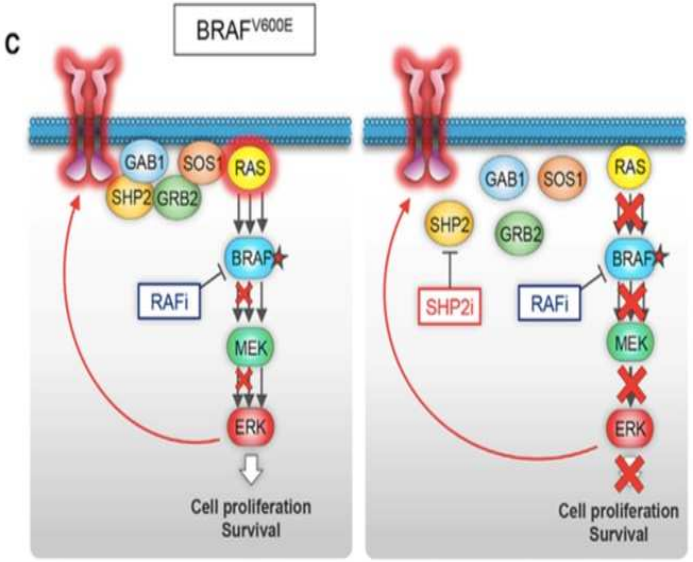
Jiang, et al. Acta Pharmacol 2017;38:1512

Adaptive resistance: pathway redundancy



Broad repertoire of RTK and ligands activated in response to MEK inhibition

RTK = receptor tyrosine kinase



Adaptive resistance to RAFi in BRAF V600E CRC

SHP2 dependent (pY542SHP2): ERBB, MET RTK

Fedele et al. Can Disc 2018

BRAFi + MEKi + SHP2i in BRAF V600E

Ahmed et al. Cell Report 2019

Presented By: Ignacio Garrido-Laguna, MD, PhD
Ignacio.garrido-laguna@hci.utah.edu

Chimeric antigen receptor T cells

- CART cells contain the antigen-binding domain of a monoclonal antibody to confer recognition of the targeted tumor antigen coupled to intracellular domains capable of activating T cells
- When expressed in T cells, these CARs recognize cell surface antigens and activate T cells independent of antigen presentation by a MHC molecule as required for physiologic antigen presentation
- Immunoeffector cell-associated neurotoxicity syndrome (oncolysis) and cytokine storm as complications

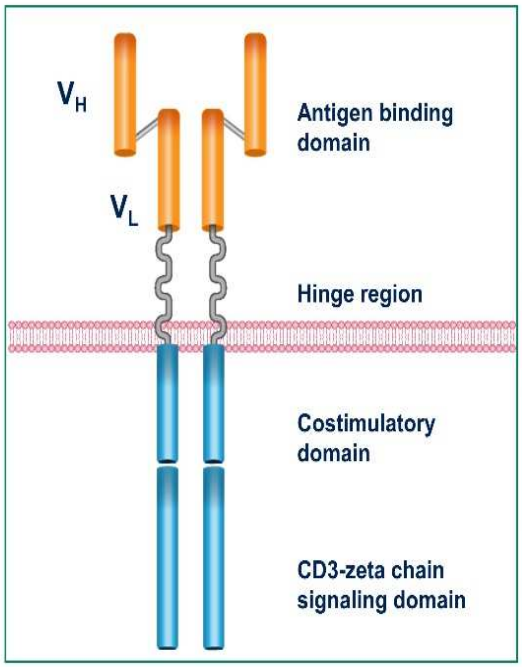
CAR = Chimeric Antigen Receptor

Antigen Binding Domain

Antigen specificity

Activation Domains

Signal Transduction



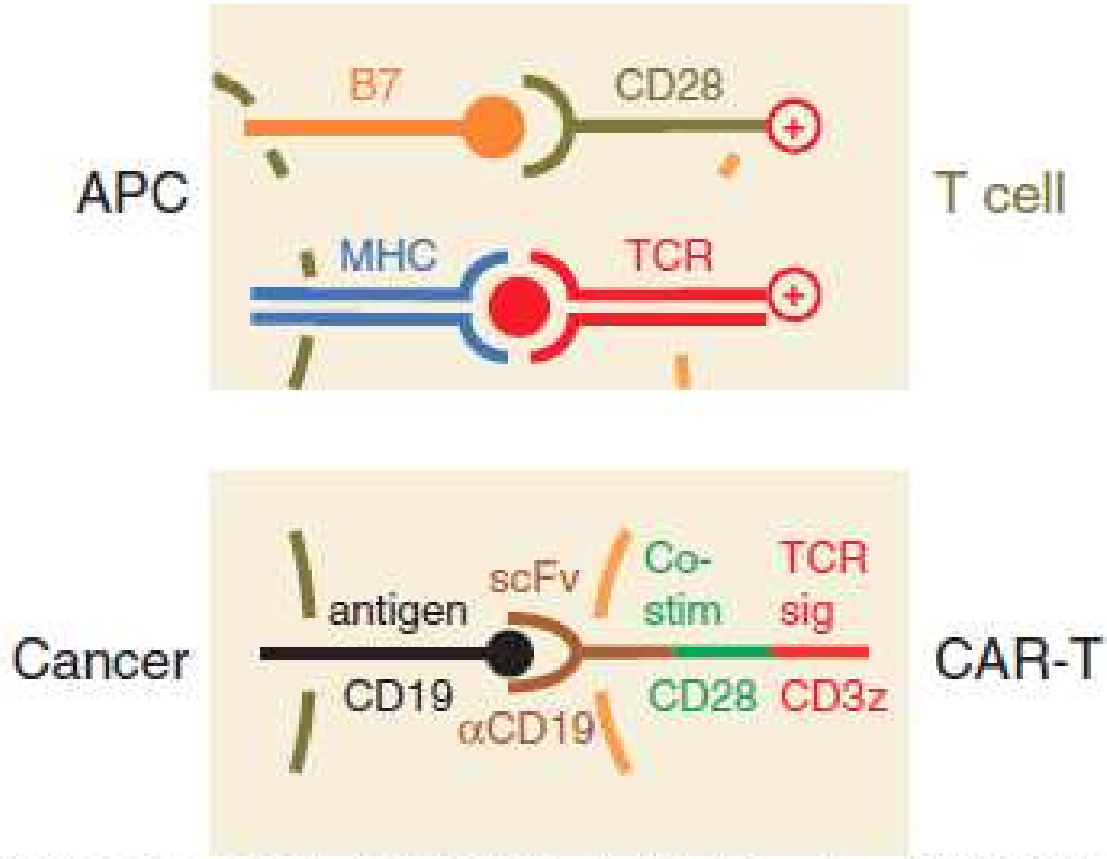
scFv
Single-chain variable fragment (scFv) bypasses MHC antigen presentation, allowing direct activation of T cell by cancer cell antigens

Hinge region
Essential for optimal antigen binding

Costimulatory Domain: CD28 or 4-1BB
Enhances proliferation, cytotoxicity and persistence of CAR T cells

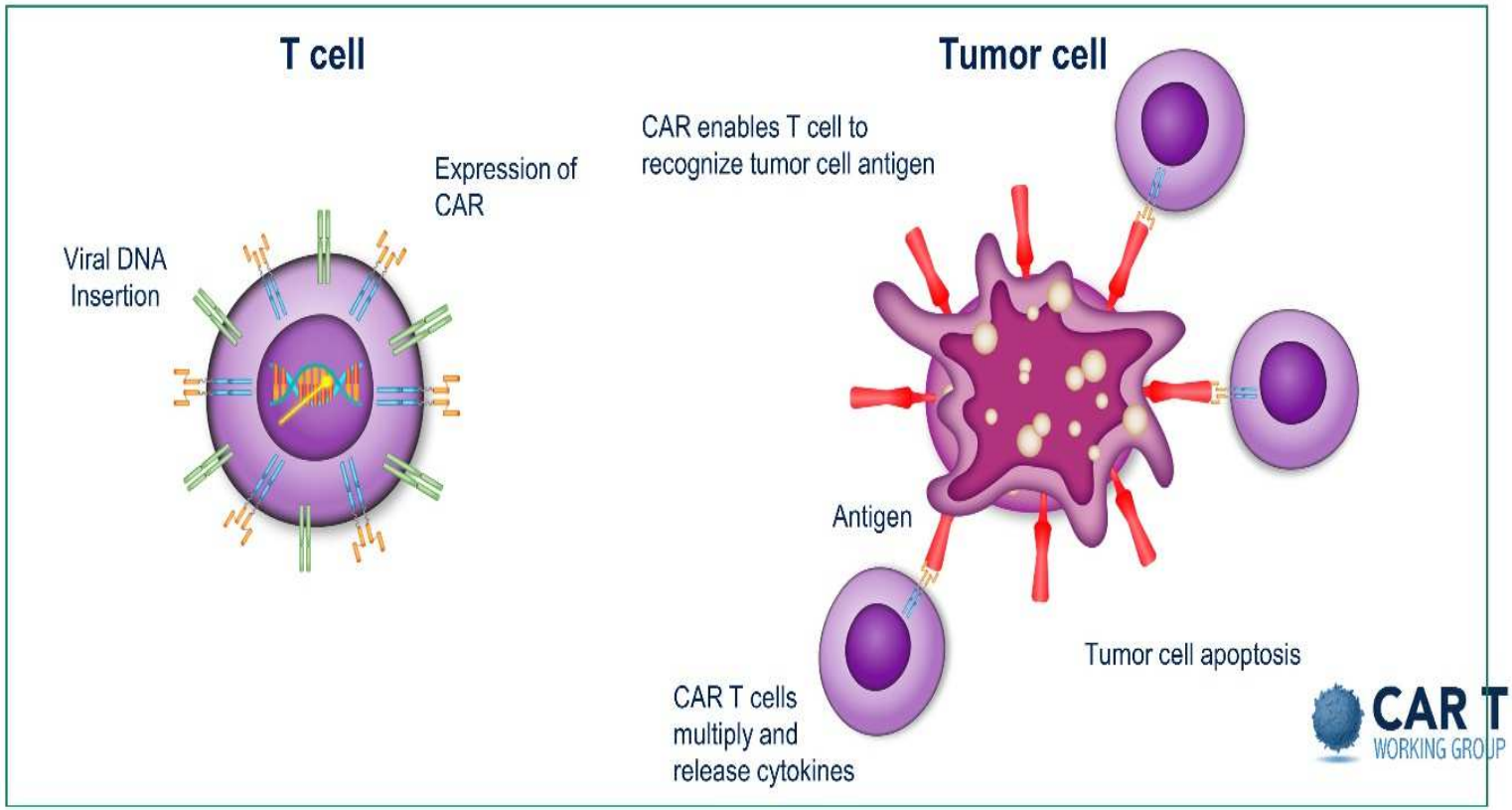
Signaling Domain: CD3ζ chain
Proliferation and activation of CAR T cells
CAR T-cell-mediated killing of tumor cells

CAR T WORKING GROUP

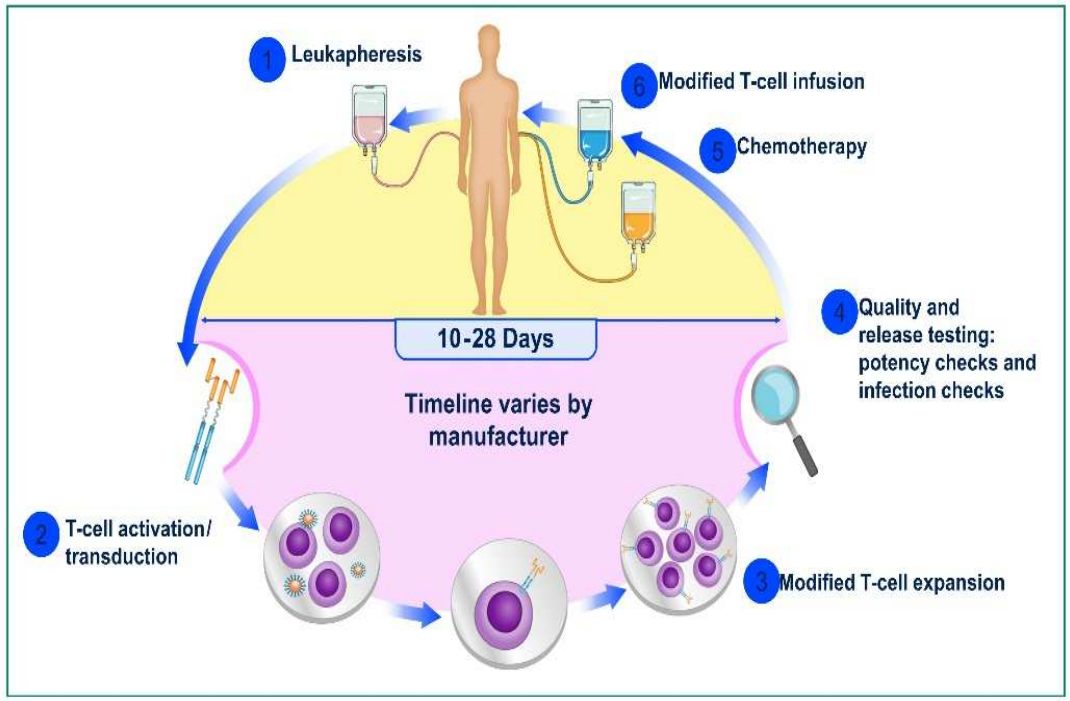


Chimeric antigen receptor (CAR) T cell activation by a target antigen on cancer cells. T cells are harvested from a cancer patient and transduced with a CAR expression vector. Elements in a CAR: extracellular, single-chain antibody fragment of the variable domain (scFv) that recognizes the targeted antigen; intracellular co-stimulatory domain (e.g. from CD28); intracellular signaling domain of the TCR. CD19 is shown as an antigen example. APC-mediated stimulation of T cells is depicted for comparison (see figure 67-5).

CAR T Cells: Mechanism of Action

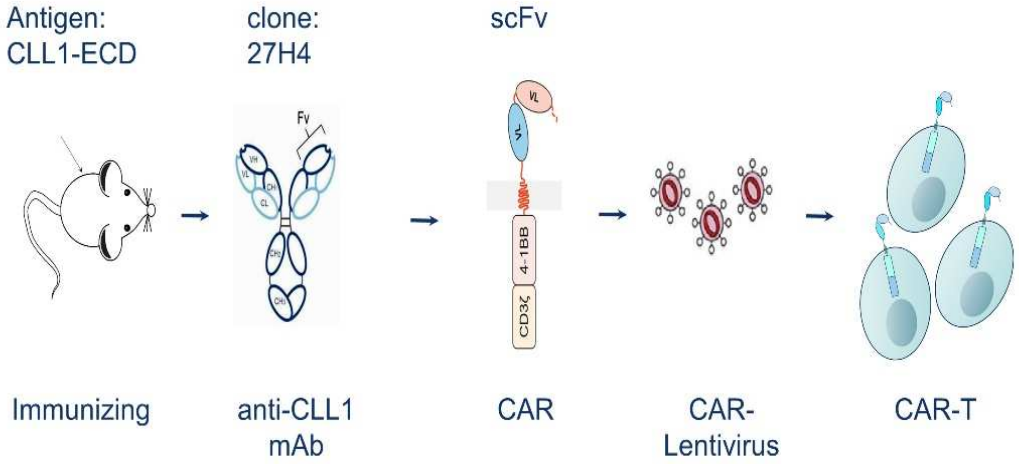


Schema of CAR T Apheresis to Therapy



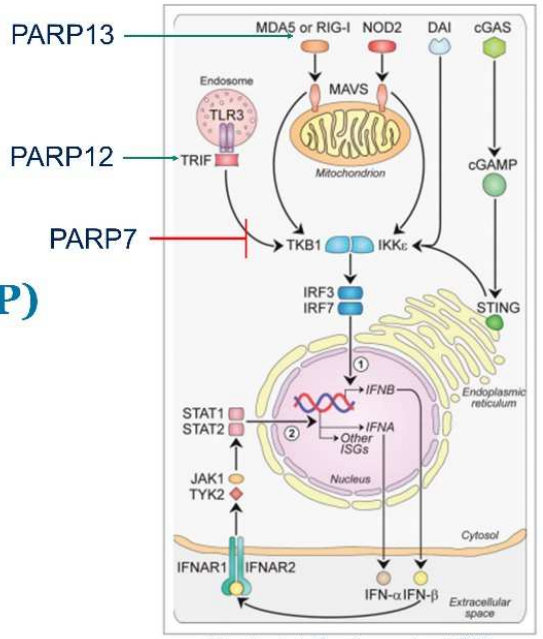
CAR T
WORKING GROUP

Result 1: anti-CLL1 CAR-T cells generation



Type I Interferons and PARP

- **Type I IFN found in all vertebrates**
- **Mediated by JAK-STAT**
  - IFN-alpha 2a approved for hairy cell leukemia in 1986
- **Poly (ADP-ribose) polymerase (PARP) enzymes recognized role in DNA repair**
- **PARPs regulate the innate immune response at many different points**



Musella et al, Oncoimmunology 2017

Musella et al, Oncoimmunology 2017
Fehr et al, Genes and Development 2020

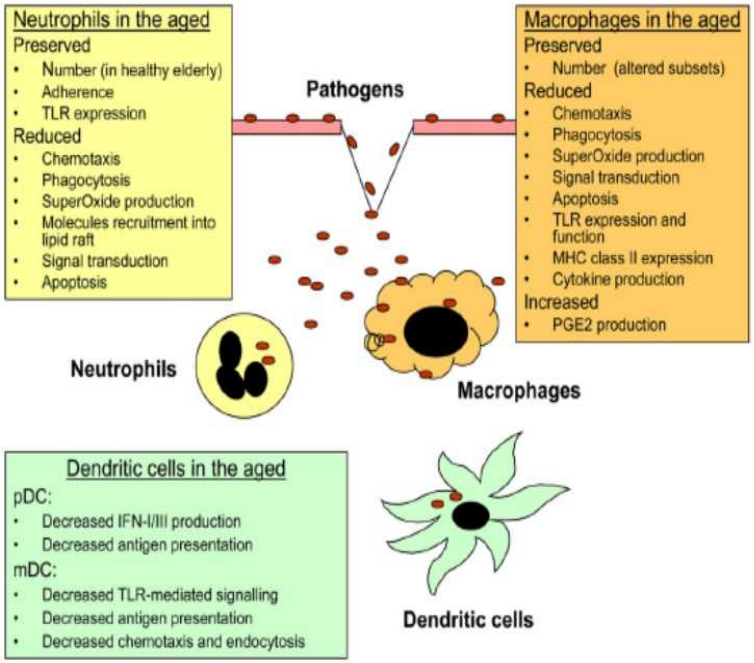
Vaccines

- Sipuleucel-T
- Patient peripheral blood cells are exposed to a human recombinant protein, Prostatic acid phosphatase (PAP)-GM-CSF.
- APCs present among the blood cells are thought to take up and process PAP and direct the immune response toward the antigen.

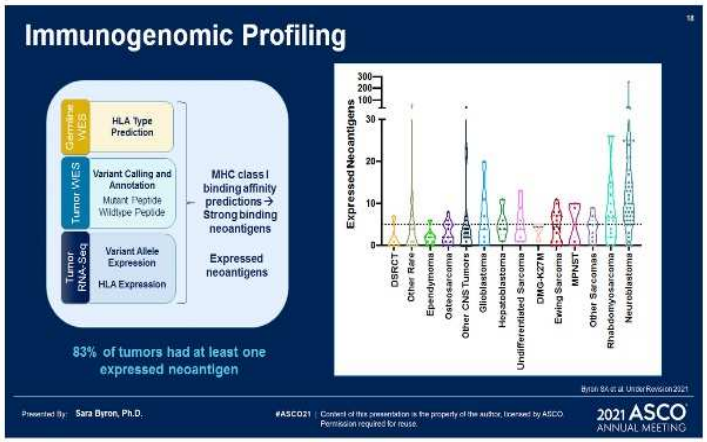
Vaccines

- Infusion
- T-VEC is an oncolytic herpesvirus that replicates within tumors and expresses GM-CSF.
- Tumor antigens are released after virally induced cell death, and the presence of GM-CSF can promote an antitumor immune response.
- Direct injection.

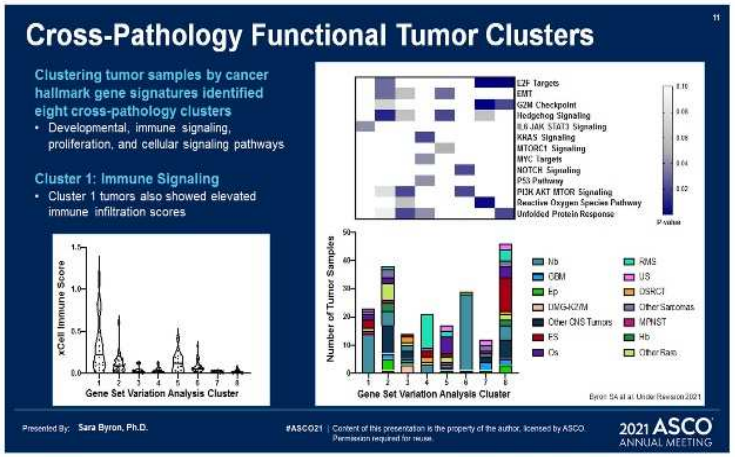
Immunotherapy in the elderly: immunosenescence and efficacy concerns

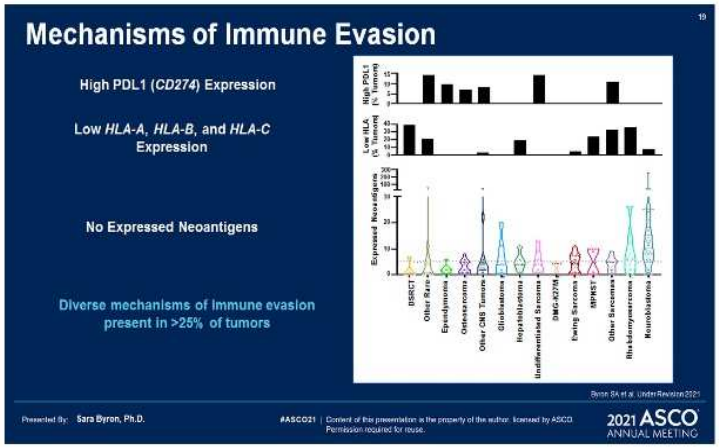


Solana R, *et al.,* Innate immunosenescence:; Sem Immunol 24:331–41, 2012,



New immune targets to be explored?





➢ To be validated in post-genomic studies