Advanced Oncology Certified Nurse Practitioner

REVIEW COURSE 2024

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Targeted Therapies

Key Concepts

- Advances in nanotechnology enabled further understanding of cancer biology, resulting in development of targeted therapies that are changing the way we treat our oncology patients.
- Emergence of biotherapy and targeted therapy require same amount of vigilance to prevent reactions or to intervene rapidly when hypersensitivity reactions occur
- Anti angiogenesis agents: BLEEDING and HYPERTENSION
- EGFR inhibitors: RASH, DIARRHEA, hypoMg, INTERSTITIAL LUNG DISEASE
- Highlighting importance of patient education in preventing and managing side effects

Hallmarks of Cancer Cells

a. Sustained signaling for cell proliferation

b. Evasion of growth suppressors

c. Avoidance of cell death

d. Activation of tissue invasion and metastasis

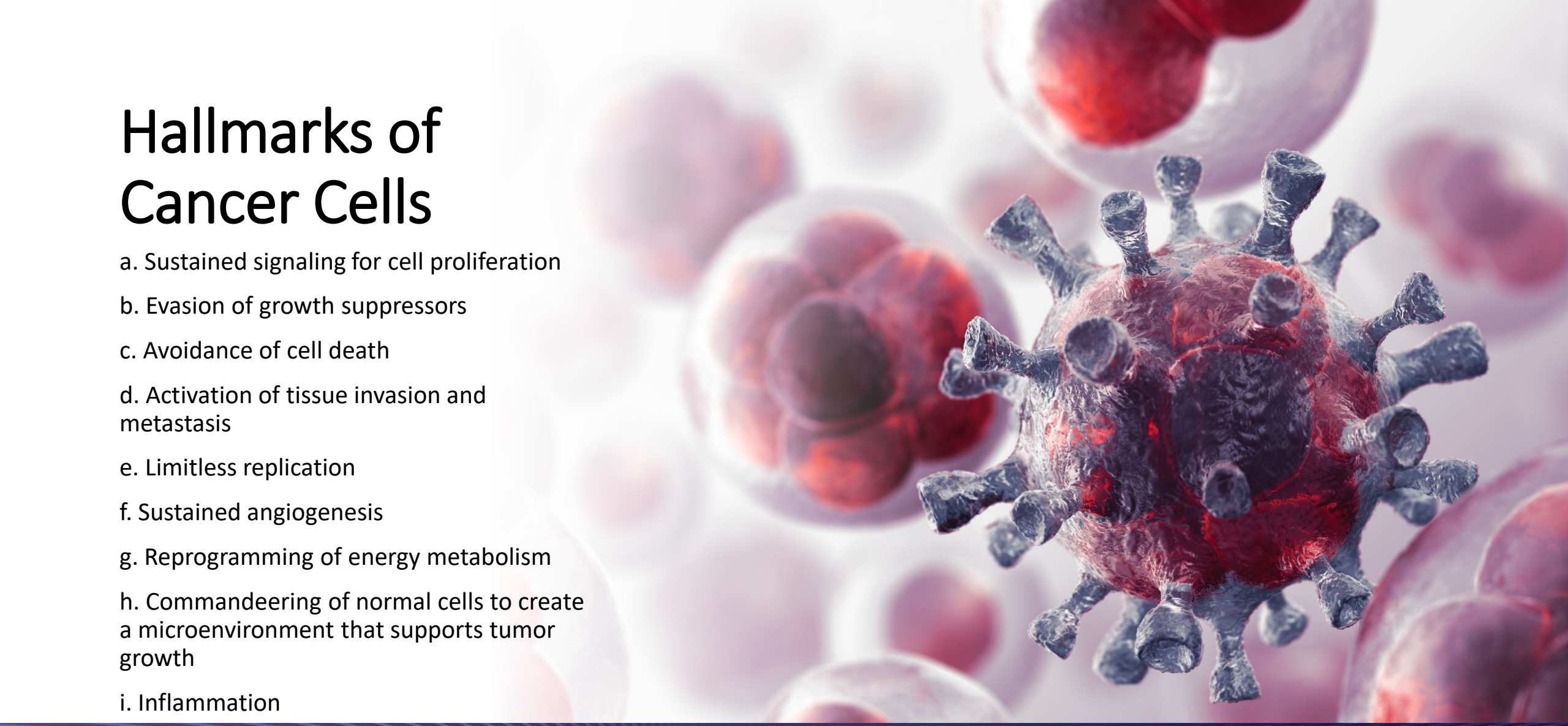
e. Limitless replication

f. Sustained angiogenesis

g. Reprogramming of energy metabolism

h. Commandeering of normal cells to create a microenvironment that supports tumor growth

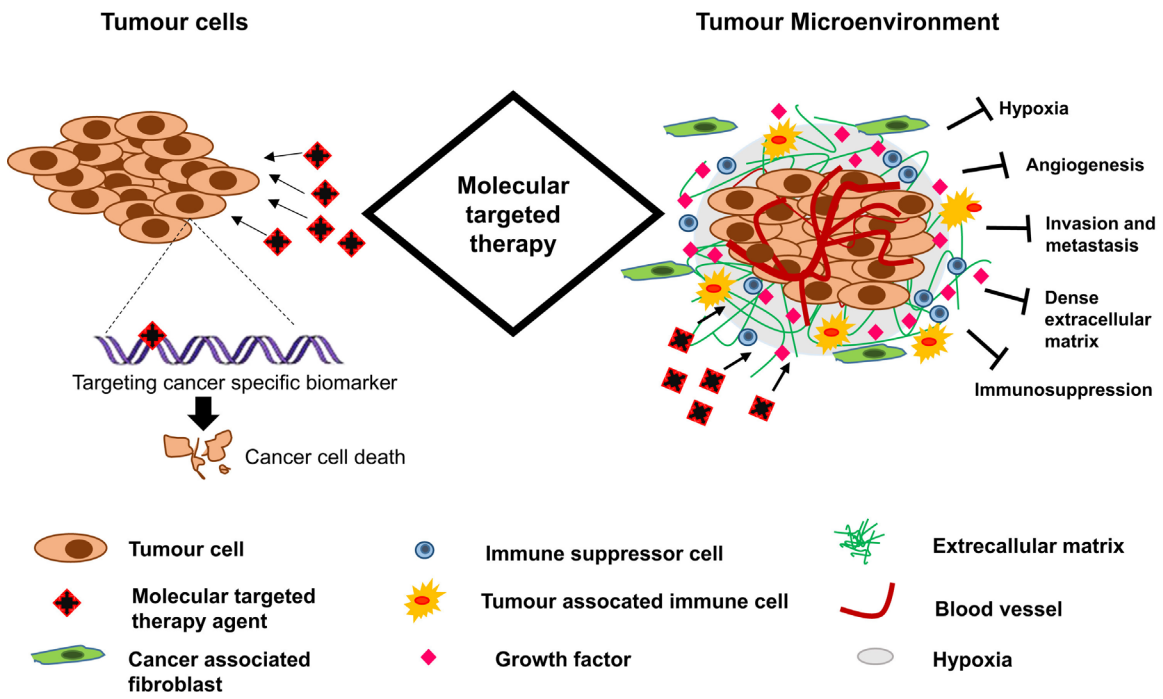
i. Inflammation



What is precision medicine?

- It is an emerging term to describe targeted agents (either biologic or molecular) that contribute to induce a specific response resulting in cancer cell death
- Offer a “targeted approach” in treating different types of cancer due to better understanding of molecular changes involved in cancer transformation and growth p. 154

Biologic Targeted Therapy



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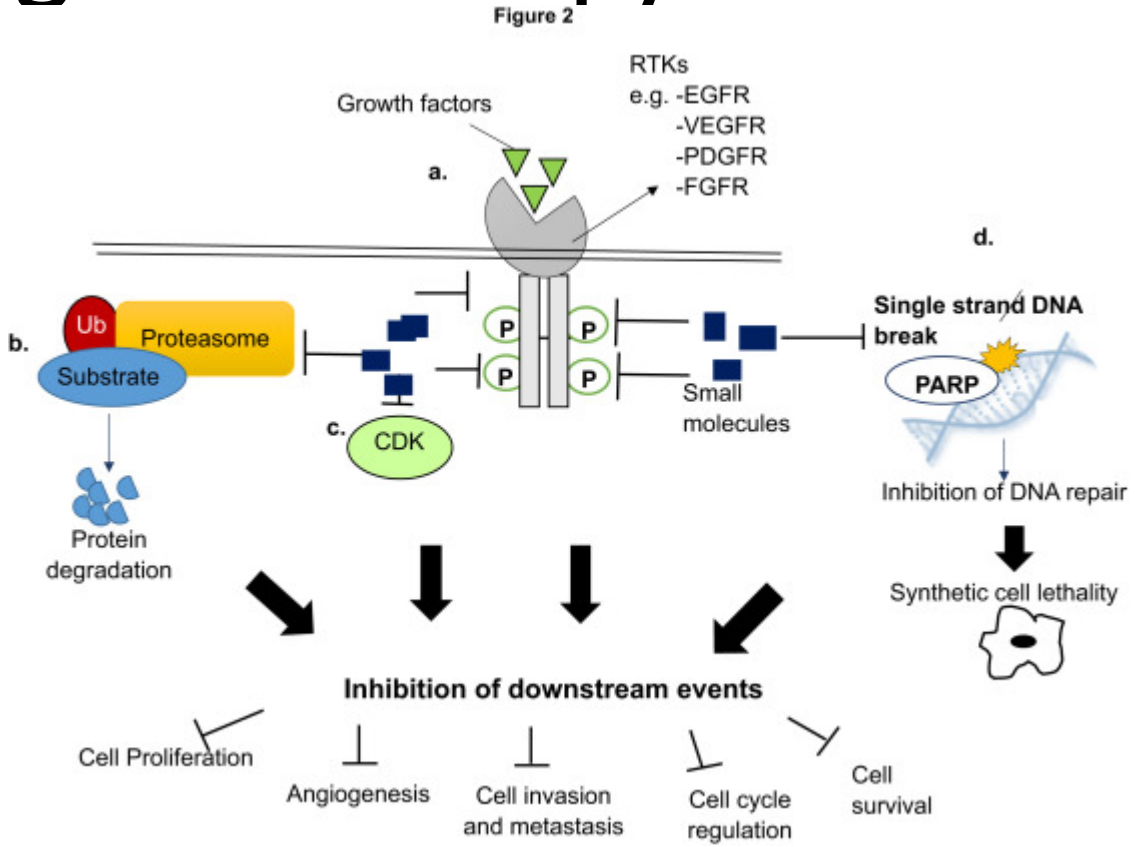
Biologic Targeted Therapy



Adapted from: https://www.sciencedirect.com/science/article/pii/S0014299918304011#f0010

Biologic Targeted Therapy

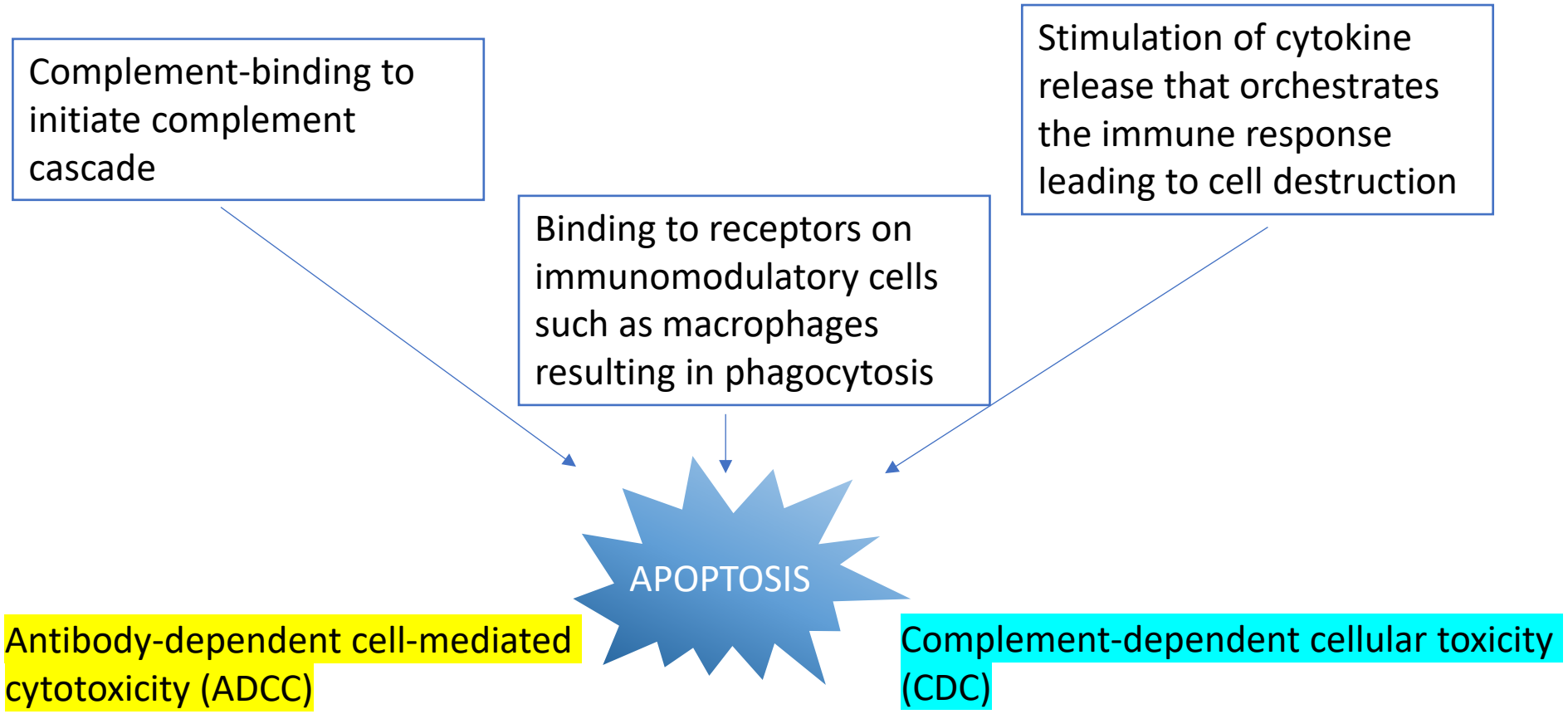
- May be given alone or in combination with chemotherapy or radiation therapy
- Targeted therapies direct response toward an identifiable target in a malignant cell while avoiding collateral damage to normal cells

- Almost all of them cause fetal harm
- Mandatory monitoring required for some therapies to ensure prevention of pregnancy
- No BREASTFEEDING or PREGNANCY!!!

Monoclonal Antibodies

- Also called (mAbs)
- Hybrid of a myeloma cell (that had lost its ability to make an antibody) + healthy B cell (that had been exposed to the antigen against which the antibody was to be developed)
- Modern mAbs are now manufactured using DNA recombinant technology

Fc (Constant)


Complement-binding to initiate complement cascade
Binding to receptors on immunomodulatory cells such as macrophages resulting in phagocytosis
Stimulation of cytokine release that orchestrates the immune response leading to cell destruction
APOPTOSIS
Antibody-dependent cell-mediated cytotoxicity (ADCC)
Complement-dependent cellular toxicity (CDC)

Fab (Variable)

- Binds to the antigen, can only bind to one antigen at a time

Monoclonal antibodies

IgG1 mAbs

- Ado Trastuzumab emtansine (Kadcyla)
- Bevacizumab (Avastin)
- Brentuximab vedotin (Adcetris)
- Cetuximab (Erbitux)
- Ofatumumab (Arzerra)
- Pertuzumab (Perjeta)
- Rituximab (Rituxan)
- Trastuzumab (Herceptin)
- Yttrium-90 Ibritumomab tiuxetan (Zevalin)

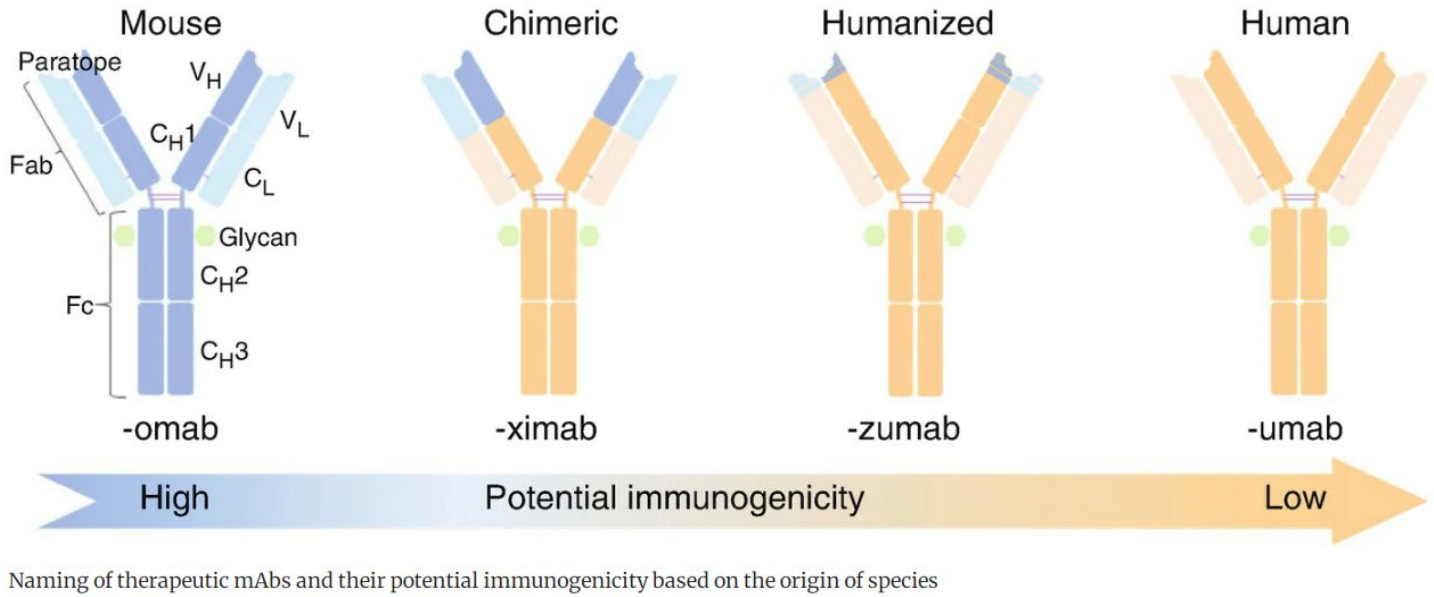
IgG2 mab

- Panitumumab (Vectibix)

Types of Monoclonal Antibodies

Fig. 3.7

From: Monoclonal Antibody Biology



Naming of therapeutic mAbs and their potential immunogenicity based on the origin of species

Adapted from: https://link.springer.com/chapter/10.1007/978-3-030-69032-8_3/figures/7

Unconjugated monoclonal antibodies

- Biologic activity involves attachment of mAb molecules to the antigen such as CD20 lymphocyte
  - Direct interference with the cell signaling of the target cell (cytostastic)
  - ADCC in which cytokines recruit phagocytes, T cells, natural killer cells which destroy the target cell
  - CDC, which the complement system is activated to destroy the target cell
  - Direct induction of apoptosis in antibody-bound cell
  - Release of inhibitory checkpoints so that target cell is attacked by immune system (anti CTLA-4 and T regulatory cells)

Unconjugated monoclonal antibodies and Immune Checkpoint Inhibitors

- **Rituximab**
  - Target: CD20 antigen
  - Indication: CD20 antigen-positive Non Hodgkin's Lymphoma, low grade or Follicular Lymphoma, Diffuse Large Cell Lymphoma (in combination with CHOP), CD20 positive Chronic Lymphocytic Leukemia, Rheumatoid Arthritis, Wegener granulomatosis, Microscopic Polyangiitis
  - Half life: 22 days
  - Side/Adverse Effects: Infusion reaction (chills, rigors, hypersensitivity, angioedema, bronchospasm, anaphylaxis
  - Caution: Tumor Lysis Syndrome, especially in pts with high tumor burden and during the first treatment

Unconjugated monoclonal antibodies and Immune Checkpoint Inhibitors

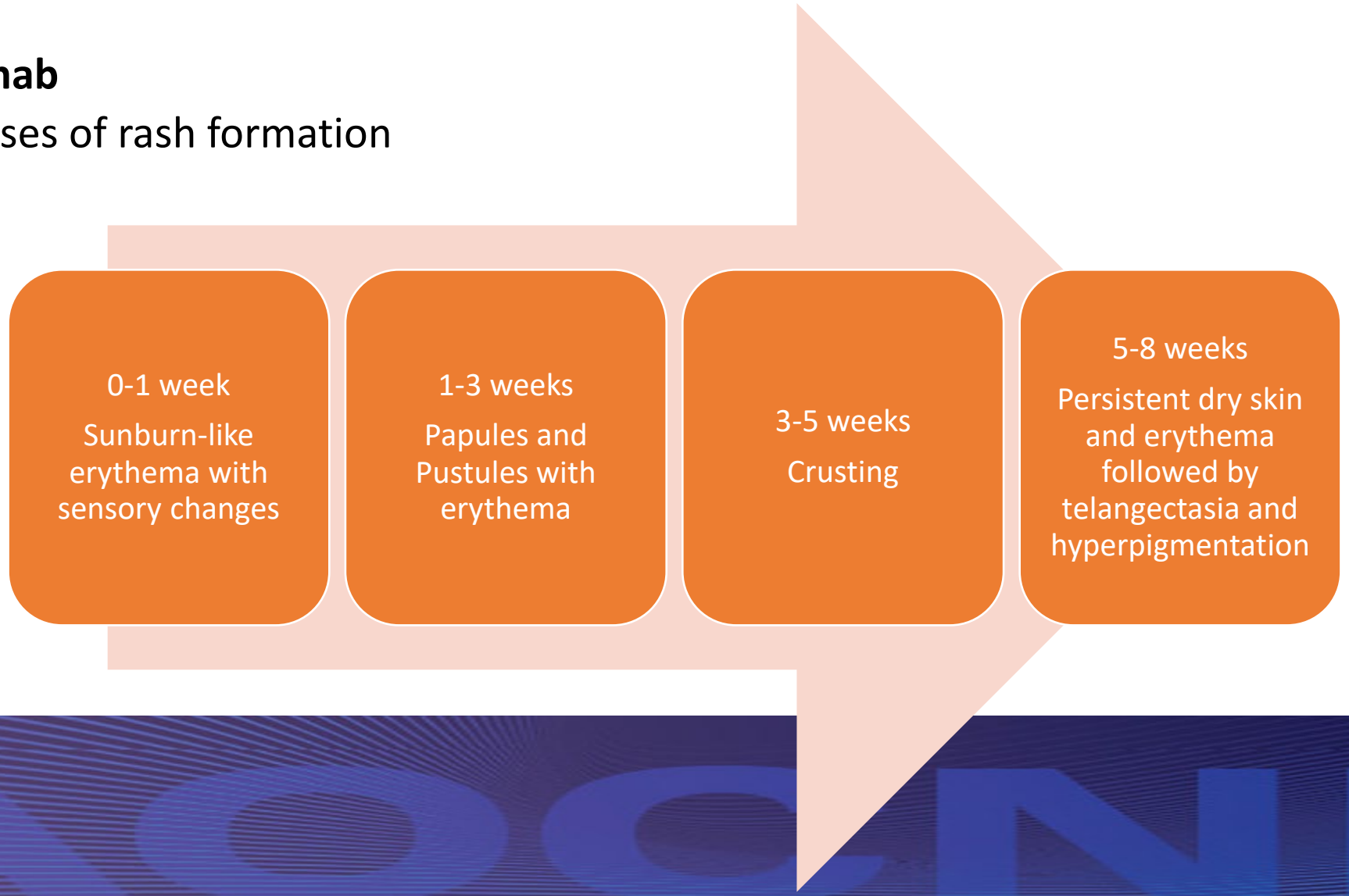
- **Trastuzumab**
  - Target: HER2 receptor/EGFR2
  - Indication: HER2+ or amplified breast cancers, gastric and gastroesophageal junction cancers with HER2 amplification
  - Dosing: Given every 21 days
  - Side Effects: Infusion reaction (fever, chills which respond to Acetaminophen or Diphenhydramine and Meperidine), N/V, headache, dizziness, hypotension, rash or asthenia, pain related to tumor). Serious reaction: Bronchospasm and Hypoxia.
  - Caution: Anaphylaxis, Angioedema, Pneumonitis or ARDS

- **Trastuzumab**
  - Risk of recurrence is reduced by 52% when Trastuzumab is added to chemotherapy
  - Monitoring: Baseline ECHO or MUGA prior to therapy then every 3 mos . Higher risk for cardiomyopathy if combined with Anthracycline therapy ***
  - Pulmonary toxicity: Watch out especially in pts with pre existing lung disease and extensive lung metastasis. Differentiate between acute reaction vs pulmonary toxicity
  - Infusion preparation: Must be prepared with NS only

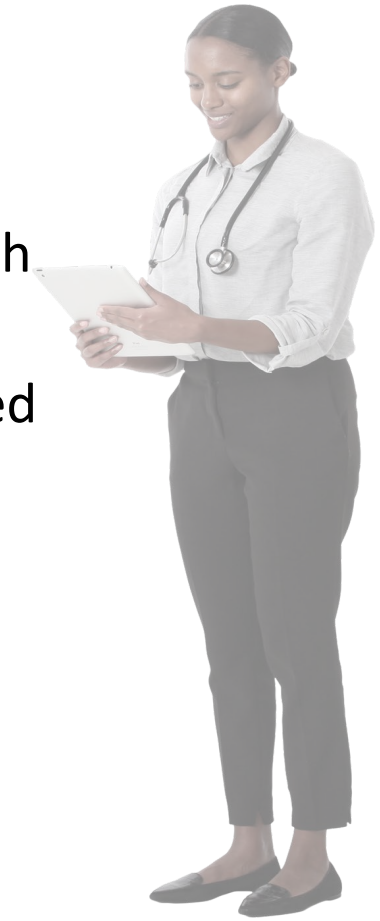
Unconjugated monoclonal antibodies and Immune Checkpoint Inhibitors

- **Cetuximab**
  - Target: EGFR1
  - Indication: Advanced colorectal cancer or head and neck cancer with KRAS- wild type expression (must do KRAS testing) or BRAF-wild type expression
  - Dosing: Loading dose then weekly maintenance dosing. Can be combined with radiation. Must be given 1 hr prior to platinum-based therapy
  - Side/Adverse effects: Severe reactions such as bronchospasm, hypotension, anaphylaxis. Requires INPATIENT administration. Other reactions include sterile inflammatory rash, alopecia, increased hair growth on face, eyebrows and eyelashes, paronychia, xerosis, pruritus, impaired absorption of Mg and Ca, interstitial lung disease

- **Cetuximab**
  - Phases of rash formation



- **Cetuximab**
  - Support symptomatic management of rash and to prevent infection until rash resolves.
  - Daily moisturizer, sunscreen, topical hydrocortisone, oral Doxycycline reduced incidence of grade 2 or higher rash
  - Maintain skin integrity
  - Cool baths
  - Dermatology referral if severe



- **Cetuximab**

Mild- Moderate	Severe
2% Clindamycin + 1% Hydrocortisone 2% Clindamycin + 1% Hydrocortisone + oral Minocycline 100mg BID x 4 weeks 1% Clindamycin + Doxycycline 100mg BID x 4 weeks	Treatment delay for 1-2 weeks vs drug discontinuation
	Clindamycin 2% + Hydrocortisone BID + oral Doxycycline or Minocycline 100mg BID
	Hydrocortisone 2.5% + Clindamycin 1% gel + Doxycycline 100mg BID + Methylprednisolone dose pack + Dose reduction of EFGR

Unconjugated monoclonal antibodies and Immune Checkpoint Inhibitors

- **Bevacizumab**
  - Target: ligand VEGF
  - Indication: Metastatic colorectal cancer, NONSQUAMOUS non small cell lung cancer, platinum-resistant ovarian cancer, fallopian tube cancer or primary peritoneal cancer
  - Dosing:
    A. Every 2 -3 weeks with Irinotecan or 5FU or Oxaliplatin for mCRC
    B. Every 3 weeks for nonsquamous NSCLC with Carboplatin/Paclitaxel
    C. Every 2 weeks for Glioblastoma or metastatic renal cell carcinoma
    D. Every 3 weeks for Persistent or metastatic cervical cancer with Carboplatin/Paclitaxel
    E. Every 2 weeks for Platinum-resistant ovarian cancer with peg-Doxorubicin or weekly Topotecan; every 3 weeks with Topotecan

- **Bevacizumab**
  - Common side effects
    - Hemorrhage
    - Gastrointestinal perforation
    - Arterial thrombotic events
    - Non GI fistula formation
    - Delayed wound healing complications
    - Necrotizing fasciitis (secondary to delayed wound healing and fistula formation)
  - Other serious adverse effects
    - Epistaxis
    - Asthenia
    - HTN
    - Constipation or Diarrhea
    - Headache
    - Less commonly: Posterior Leukoencephalopathy Syndrome, CHF in previously anthracycline-treated pts, ovarian failure, ovarian failure and Nephritic syndrome (MONITOR urine protein and do a 24-hr urine protein monitoring if 2+ or more)

- **Bevacizumab**
  - Half life: 28 days (do not give within 4 weeks of major surgery)

- **Bevacizumab**
  - Management of Side Effects
  - HTN- antihypertensive such as diuretics, ACE inhibitors or Ca Channel Blockers (ACE inhibitors preferred due to potential benefit on proteinuria)
  - Bleeding precaution
  - Neuro monitoring
  - Regular labs with each treatment
  - GI assessment for presence of fistula or perforation
  - Thorough patient education

Immune Checkpoint Inhibitors

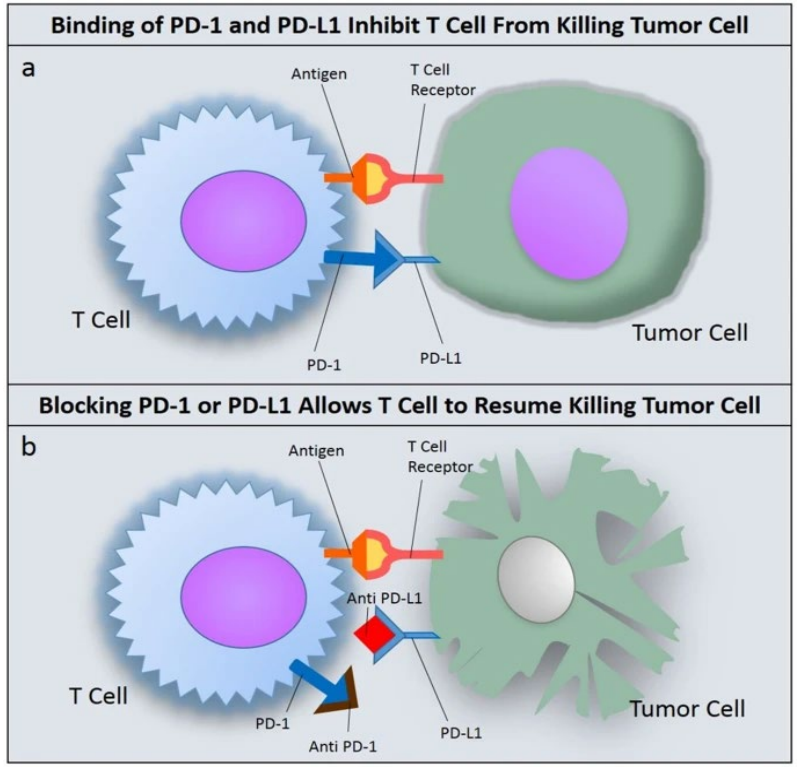
- Involves process of co-opting with normal cells to avoid immune surveillance either by surface molecule regulation or mediating co inhibitory signals
- Example is CTLA-4 (cytotoxic T-lymphocyte-associated antigen). Cancer cells are capable of activation of T-cells to they are not attacked

- **Ipilimumab**
  - Target: CTLA-4
  - Indication: Metastatic melanoma with risk evaluation and mitigation strategy (REMS) due to high risk for potentially fatal immune-related reactions due to T-cell activation and proliferation
  - Dosing: Every 3 weeks
  - Side effects: fatigue, nausea, vomiting, diarrhea, fever, headache, dizziness, rash and pruritus
  - Baseline labs: CBC with diff, TSH, free T4, LFT, amylase and lipase

- **Ipilimumab**
  - Management of side effects:
    - Premedication with antihistamine, antipyretics, IV or oral fluids, antipruritics

  - Immune-related serious adverse effects:
    - Hepatitis: monitor LFT's, pre chemo Hepatitis panel, GI referral
    - Enterocolitis: monitor bowel movements and abdominal symptoms for bowel perforation, rule out infection, supportive care and GI referral. Possible endoscopy, immunosuppressants, or steroids depending on severity. May need to hold treatment pending clearance.
    - Endocrinopathy: baseline hormone levels, thyroid and steroid levels. Neurologic monitoring to detect signs and symptoms of Hypophysitis
    - Dermatitis: supportive measures, Dermatology referral when severe

- **Pembrolizumab**
  - Target: PDL-1
  - Unresectable melanoma, disease progression after Ipilimumab +/- BRAF inhibitor if BRAF V600 mutation positive, PDL-1 positive triple negative breast
  - Dosing: Every 3 weeks
  - Side effects: similar to Ipilimumab
  - Needs confirmation of PDL-1 status for breast cancers
  - Immune-related serious adverse effects:
    - Hepatitis: monitor LFT's, pre chemo Hepatitis panel, GI referral
    - Enterocolitis: monitor bowel movements and abdominal symptoms for bowel perforation, rule out infection, supportive care and GI referral. Possible endoscopy, immunosuppressants, or steroids depending on severity. May need to hold treatment pending clearance.
    - Endocrinopathy: baseline hormone levels, thyroid and steroid levels. Neurologic monitoring to detect signs and symptoms of Hypophysitis
    - Dermatitis: supportive measures, Dermatology referral when severe



Adapted from: https://www.nature.com/articles/s41598-017-10946-2

ASCO Grading of ICI-Associated Immune Thrombocytopenia

Table 3. ASCO Grading of ICI-Associated Immune Thrombocytopenia

Grade	Neutrophils	Hemoglobin	Platelet level
Grade 1	2,500–2,000/mm³	< LLN to 10.0 g/dL	< 100/μL
Grade 2	2,000–1,500/mm³	< 10.0 to 8.0 g/dL	< 75/μL
Grade 3	1,500–1,000/mm³	< 8.0	< 50/μL
Grade 4	1,000–500/mm³	Life-threatening consequences; urgent intervention indicated	< 25/μL

Note. Brahmer et al. (2018); National Cancer Institute (2006). LLN = lower limit of normal.

Adapted from: https://www.advancedpractitioner.com/issues/volume-12,-number-4-%28mayjun-2021%29/management-of-hematologic-adverse-events-associated-with-immune-checkpoint-inhibitors.aspx

Immunotherapy-Related Toxicities

While immunotherapies are becoming essential in treating advanced malignancies, they also cause side effects from destruction of healthy cells leading to systemic toxicities

https://mdandersonorg.sharepoint.com/sites/internal-medicine/SitePages/Immuno-Oncology-Toxicity-Initiative.aspx

Immunotherapy-Related Toxicities

Immune-Related Adverse Event	Sign and Symptoms	Assessment and Management
Diarrhea, entero-related colitis	Diarrhea, abdominal pain, blood or mucus in the stool, bowel perforation, peritoneal signs, ileus	1. Preventative antidiarrheal 2. Rule out infection 3. Grade 1: symptomatic treatment 4. Grade 2: Hold drug, oral steroids 5. Grade 3-4: Hold, see algorithm

Immunotherapy-Related Toxicities

Immune-Related Adverse Event	Sign and Symptoms	Assessment and Management
Dermatologic	Erythematous or maculopapular rash, dry skin, pruritus, blisters, ulceration Steven Johnson or Toxic Epidermal Necrolysis	1. Mostly mild and do not require dose interruption 2. Hold severe for rashes; consider hospitalization, Dermatology consult and systemic steroids

Immunotherapy-Related Toxicities

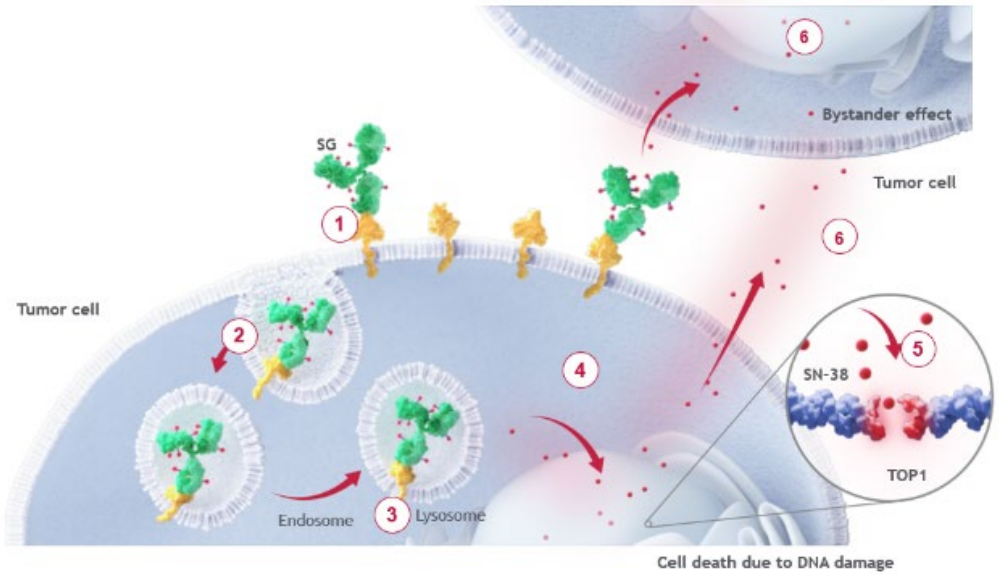
Immune-Related Adverse Event	Sign and Symptoms	Assessment and Management
Hepatitis	Elevated liver enzymes	1. Monitor liver function tests prior to initiation and each cycle 2. Baseline hepatitis labs 3. GI Hepatology consult 4. Hold for moderate elevations, permanently discontinue for severe elevations.

Immunotherapy-Related Toxicities

Immune-Related Adverse Event	Sign and Symptoms	Assessment and Management
Endocrine issues (hypophysitis, autoimmune thyroiditis)	Fatigue, headache, myalgias, anorexia, intractable nausea/vomiting, visual disturbances Hyponatremia due to SIADH or diabetes insipidus	1. Obtain brain MRI 2. Check baseline TFT's, cortisol, ACTH, LH, FSH and testosterone (males) 3. Recognize hypophysitis and adrenal crisis (symptoms mimic sepsis). THIS IS A MEDICAL EMERGENCY. 4. Initiate steroid, thyroid replacement immediately. 5. Monitor TSH, T4 every 3 weeks during Ipilimumab then 2-3 months after treatment

Antibody Drug Conjugates

- Conjugated monoclonal antibody with attached toxin or radio-isotope
- Radio-isotope example: yttrium-90 ibritumomab tiutxetan
- Toxins attached are usually chemotherapy attached by a linker molecule.
    - Examples: Ado Trastuzumab emtansine (Kadcyla), Brentuximab vedotin (Adcetris), Sacituzumab govitecan (Trodelvy)



Adapted from: https://www.askgileadmedical.com/docs/trodelvy/trodelvy-mechanism-of-action

- **Ado-trastuzumab emtansine**
  - Target: HER2 or EGFR2
  - Indication: HER2 positive or amplified breast cancer in the adjuvant or metastatic setting
  - Dosing: Every 3 weeks
  - Monitoring: pre treatment ECHO then every 3 mos while on active therapy, CBC and LFTS, respiratory symptoms such as cough, unexplained shortness of breath
  - Side effects: Infusion reaction (flushing, fever, chills, hypotension, wheezing, bronchospasm, tachycardia), peripheral neuropathy, fatigue, nausea headache, muscle aches, constipation/diarrhea, headache, elevated liver enzymes and thrombocytopenia
  - Adverse effects: Decreased ejection fraction, hepatotoxicity, drug-induced pneumonitis or interstitial lung disease (ILD)

- **Management of Side Effects:**
  - Decreased EF: if LVEF falls to less than 40% or 40-45% with 10% or greater absolute decrease compared to pre- treatment value, hold medication and repeat ECHO in 3 weeks. If no improvement after holding, permanently discontinue medication
  - Thrombocytopenia: Treatment parameters, hold treatment if Plt <50k, supportive transfusion
  - Infusion reaction: Pre medication, slowing infusion rates during initial treatment
  - Diarrhea: Anti diarrheal and patient education, replacement of electrolyte losses
  - Unexplained cough, persistent shortness of breath: Prompt imaging baseline chest Xray, CT chest to rule out infection, ILD and urgent referral to Pulmonary specialist
  - Elevated liver enzymes: Pre-chemotherapy labs and rule out infectious causes
  - Peripheral neuropathy: Usually mild, fall precautions, skin monitoring

- **Brentuximab vedotin**
  - Target: CD30
  - Indication: Hodgkin Lymphoma after failure of Stem Cell Transplant (SCT) or failure of at least 2 multi-agent chemotherapy agents in patients who are not SCT candidates. Anaplastic Large Cell Lymphoma after failure of at least one multi-agent chemo therapy regimen.
  - Dosing: Every 3 weeks for maximum of 16 cycles
  - Side effects: Infusion reaction (chills, nausea, dyspnea, pruritus, fever, cough), peripheral neuropathy, grade 3-4 neutropenia
  - Adverse effects: Decreased ejection fraction, hepatotoxicity, drug-induced pneumonitis or interstitial lung disease (ILD)

Single Targeted Tyrosine-Kinase Inhibitors

- Protein kinase inhibitors work within the cell and interrupt signaling pathways to stop uncontrolled cell signaling related to tumor mutations or epigenetic changes.
- These are often smaller molecules and can be given orally (in contrast with mAbs with bigger molecules and mostly given through IV infusion)
- Controls the intracellular domain to prevent DNA transcription
- Suffix: -inib
- Metabolized by the CYP3A4 microenzymes (POTENTIAL DRUG-DRUG INTERACTIONs)

Drugs Metabolized Through CYP3A4 Pathway

- Inducers
  - ❑Rifampin
  - ❑Phenytoin
  - ❑Phenobarbital
  - ❑St. John's Wort
  - ❑Carbamazepine
  - ❑Rifapentine
  - ❑Rifabutin

- Inhibitors
  - ❑Ketoconazole
  - ❑Itraconazole
  - ❑Grapefruit
  - ❑Clarithromycin
  - ❑Metronidazole
  - ❑Isoniazid
  - ❑Telithromycin
  - ❑Voriconazole

- **Afatinib (Gilotrif)**
  - Target: EGFR1, HER2 and HER4 inhibiting autophosphorylation
  - Indication: First line treatment for metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R mutations
  - Special consideration: Must be taken on an empty stomach, 1-2 hrs before or after a meal, avoid co administration with P-gp inhibitor or inducer if possible
  - Side effects: Diarrhea (most common), acneiform rash/dermatitis, stomatitis, paronychia, dry skin, decreased appetite or pruritis.
  - Adverse effects: ILD, hepatic toxicity, keratitis, bullous or exfoliative skin disorders and symptomatic left ventricular dysfunction
  - Monitoring: LFT's, diarrhea, cutaneous symptoms, lung symptoms

P-glycoprotein Inhibitors and Inducers

- Inducers
  - ❑ Rifampicin
  - ❑ Carbamazepine
  - ❑ Phenytoin
  - ❑ Phenobarbital
  - ❑ St. John's Wort

- Inhibitors
  - ❑ Ritonavir
  - ❑ Verapamil
  - ❑ Quinidine
  - ❑ Tacrolimus
  - ❑ Nelfinavir
  - ❑ Saquinavir
  - ❑ Amiodarone
  - ❑ Cyclosporine
  - ❑ Ketoconazole
  - ❑ Itraconazole
  - ❑ Erythromycin

Multitargeted Kinase Inhibitors

- Multitargeted kinase inhibitors has direct effects on many redundant cell signaling pathways
- This enables clinicians to provide a truly individualized therapeutic plan for specific cancer subtypes

First Generation Tyrosine Kinase Inhibitors Targeting Bcr-Abl

- **Imatinib Mesylate**
  - Target: Bcr-Abl TKI inhibitor, c-Kit, platelet-derived growth factor (PDGF) and stem cell factor
  - Indication: Newly diagnosed Chronic Myelogenous Leukemia (CML) in chronic phase, Philadelphia Chromosome+ CML, Gastrointestinal stromal tumor (GIST)
  - Dosing: ***
  - Special considerations: Metabolized by CYP3A4 pathway (DRUG INTERACTIONS) including warfarin. Use low molecular weight heparin or unfractionated heparin. Avoid activities that require mental alertness. Treatment is lifelong.
  - Side effects: Edema and fluid retention (most common), nausea, vomiting, anemia and thrombocytopenia

- **Imatinib Mesylate**
  - Adverse effects: CHF, hepatotoxicity, GI perforation, Steven Johnson Syndrome, hypothyroidism, dizziness, blurred vision or somnolence
  - Management: Monitoring of LFT's, urgent referral to Dermatology if suspected SJS, thorough pt education and activity restrictions + drug-drug interactions, baseline thyroid function labs, CBC with diff and CMP

Second Generation Tyrosine Kinase Inhibitors Targeting Bcr-Abl

- **Nilotinib (Tasigna)**
  - Target: Bcr-Abl TKI inhibitor, c-Kit, platelet-derived growth factor (PDGF) and stem cell factor
  - Indication: Newly diagnosed Chronic Myelogenous Leukemia (CML) in chronic phase, or patients resistant to other therapy such as Imatinib
  - Dosing: Given BID 12hrs apart on EMPTY STOMACH
  - Special considerations: Dose reduction in patients with hepatic impairment, neutropenia, gr. 3 thrombocytopenia or elevated QTc > 480ms.
  - Side effects: Hypomagnesemia and hypokalemia, myelosuppression, rash, headache, fatigue, nausea, vomiting, myalgias, diarrhea, constipation or asthenia
  - Adverse effects: Hepatotoxicity, pancreatitis

- **Nilotinib (Tasigna)**
  - Management of Side Effects: EKG monitoring, correction of electrolyte imbalances prior to therapy, avoid concomitant administration of QTc-prolonging drugs or strong CYP34A inhibitors

Second Generation Tyrosine Kinase Inhibitors Targeting Bcr-Abl

- **Dasatinib (Sprycel)**
  - Target: Bcr-Abl TKI inhibitor, c-Kit, platelet-derived growth factor (PDGF)-beta and stem cell factor
  - Indication: Newly diagnosed Ph+ Chronic Myelogenous Leukemia (CML) in chronic phase, chronic-phase, accelerated phase or blast crisis Ph+ CML resistant to prior therapy, Ph+ Acute lymphoblastic leukemia (ALL) resistant to prior therapy
  - Dosing: Given twice daily
  - Special considerations: Metabolized by the CYP34A pathway. Absorption is pH dependent, PPI should be replaced with antacids which must be taken 2 hrs prior or after dose. Do not take with St. John's Wort

- **Dasatinib (Sprycel)**
  - Side effects: Myelosuppression, fluid retention, diarrhea, headache, musculoskeletal pain, QTc prolongation and pulmonary hypertension

- **Bosutinib (Bosulif)**
  - Target: Bcr-Abl (fusion gene or Ph+ chromosome), SRC mutation
    - Spares normal hematopoietic cells
    - Overcomes resistance in patients who have been on TKI's for a long time
  - Indication: Ph+ CML
  - Dosing: PO once daily <u>WITH FOOD</u>
  - Special considerations: Metabolized by the CYP34A pathway. Do not administer with PPI's. Short-acting antacids should be used instead
  - Side effects: 80% of pts experience diarrhea. Neutropenia, thrombocytopenia, anemia, nausea and vomiting, abdominal pain, fatigue, rash, fever, less commonly hepatotoxicity and fluid retention

Third Generation Tyrosine Kinase Inhibitors Targeting Bcr-Abl

- **Ponatinib (Iclusig)**
  - Target: Bcr-Abl TKI inhibitor
  - Indication: T315I-positive CML or Ph+ ALL, CML or Ph+ ALL for whom TKI therapy is not indicated
  - Dosing: ***
  - Special considerations: Metabolized by the CYP34A pathway. Avoid pregnancy. REMS packet. Watch out for TLS and signs and symptoms of thromboembolism and vascular occlusion. Monthly pancreatic enzyme monitoring
  - Side effects: Hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea and pyrexia
  - Adverse effects: Thromboembolism and vascular occlusion, cardiac dysfunction, hepatic dysfunction, severe myelosuppression, pancreatitis, ocular toxicity, TLS

Miscellaneous Drug Targeting Bcr-Abl

- **Omacetaxine (Synribo)**
  - Target: Bcr-Abl TKI inhibitor
  - Indication: T315I-positive CML
  - Dosing: Subcutaneous administration
  - Special considerations: Patient medication teaching should include proper administration, PPE, safe handling of hazardous medication, disposal of chemicals
  - Side effects: Thrombocytopenia, anemia, neutropenia, fatigue, asthenia, injection site reaction, pyrexia, infection and lymphophenia

Angiogenesis Inhibitors

- Cancer make new blood vessels to deliver oxygen and nutrients to ensure continued growth once they reach 1-2mm in size. Blockage of VEGF or TKI prevent tumor growth.
- Chemotherapy combined with angiogenesis inhibitors normalize vasculature permitting entrance of chemotherapy into the tumor cells
- Tumor cells are dead-ends with multiple structure aberrations preventing effective delivery of toxins to the cancer cells
- Vasodilation is a process dependent on VEGF due to its effects on nitric oxide pathway
- CLASS EFFECT of ANGIOGENESIS inhibitors: HYPERTENSION and BLEEDING, intestinal perforation and proteinuria
- Fetotoxic!

- **Sunitinib (Sutent)**
  - Target: Multiple kinases affecting cell proliferation and angiogenesis
  - Indication: GIST after disease progression, advanced renal cell cancer, progressive and well-differentiated neuroendocrine tumor (pNET), that are unresectable, locally advanced or metastatic
  - Special considerations: Metabolized by CYP34A pathway (dose reduce if co-administering), monitor baseline EKG, LFT's and thyroid function
  - Adverse effects: Liver failure, cardiac toxicity, prolonged QTc with Torsades de Pointes, osteonecrosis of the jaw, thyroid dysfunction

- **Sorafenib (Nexavar)**
  - Target: Multitargeted TKI of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR (beta), FLT3 and c-Kit. Antiangiogenic and antiproliferative
  - Indication: Unresectable hepatocellular carcinoma or advanced renal cell cancer
  - Dosing: Twice daily 1-2 hours after eating
  - Special considerations: Drug interaction with CYP2C9 substrates : Warfarin. CYP3A4 inducers interaction and avoid co-administering with Doxorubicin or Irinotecan
  - Adverse effects: Cardiac ischemia or infarction, QTc prolongation, drug-induce hepatitis. Pts with risk factors require more frequent monitoring

- **Axitinib (Inlyta)**
  - Target: Multitargeted TKI of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR (beta), FLT3 and c-Kit. Antiangiogenic.
  - Indication: Used after failure of one prior systemic therapy
  - Dosing: Twice daily 12hrs apart
  - Special considerations: avoid CYP3A4 and CYP3A5 inhibitor, caution in patients with liver impairment. <u>STOP 24 hrs prior to surgery</u>
  - Adverse effects: Hypertensive crisis, venous or thromboembolic events, intestinal perforation, hemorrhage, fistula formation, increased LFT's, reversible Posterior Leukoencephalopathy syndrome (PLES)

- **Cabozatinib (Cometriq)**
  - Target: Multitargeted TKI of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR (beta), FLT3 and c-Kit. Antiangiogenic.
  - Indication: Progressive metastatic medullary thyroid cancer
  - Dosing: Once daily on EMPTY stomach
  - Special considerations: CYP3A4 substrate
  - Adverse effects: Thrombotic events,wound complications, hypertensive crisis, ONJ, palmar-plantar erythrodysesthesia syndrome, proteinuria, PLES

- **Pazopanib (Votrient)**
  - Target: Multitargeted TKI of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR (alpha and beta) and c-Kit.
  - Indication: Advanced renal cell carcinoma and soft tissue sarcoma after prior chemotherapy
  - Dosing: Once daily on EMPTY stomach
  - Special considerations: Caution in pts with hepatic dysfunction, avoid co administering with strong CYP3A4 inducers or inhibitors, hold if with urine protein 3+ and above
  - Adverse effects: Hepatotoxicity, prolonged QTc with Torsades de Pointes, decreased LVEF, hemorrhage, GI perforation, arterial and thrombotic events, PELS, hypertensive crisis, proteinuria and infections.

- **Regorafenib (Stivarga)**
  - Target: Multitargeted TKI of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR (alpha and beta) and c-Kit, BRAF, BRAF V600E
  - Indication: Metastatic colorectal cancer previously treated with chemotherapy, an anti-VEGF agent and if KRAS wild type, an anti EGFR therapy; locally advanced, unresectable or metastatic GIST previously treated with Imatinib and Sunitinib
  - Dosing: Once daily for 21 days then off for 7 days (28-day cycle) with low fat breakfast
  - Special considerations: Avoid co administering with strong CYP3A4 inducers or inhibitors
  - Adverse effects: Hemorrhage, dermatologic toxicity, HTN, cardiac ischemia/infarction, PELS, GI perforation and wound healing complications

- **Ziv-aflibercept (Zaltrap)**
  - Target: Multitargeted TKI
  - Indication: Metastatic colorectal cancer progressed on Oxaliplatin-containing regimen
  - Dosing: Administered IV every 2 weeks with 5-FU, Leucovorin and Irinotecan (FOLFIRI)
  - Special considerations: Avoid co administering with strong CYP3A4 inducers or inhibitors
  - Adverse effects: Fistula formation, HTN, hypertensive crisis, arterial thrombotic events, proteinuria, neutropenia, neutropenic complications, diarrhea and reversible PELS

Other Classes of Targeted Agents

- **Bruton Kinase inhibitor**
  - ❑**Ibrutinib (Imbruvica)**
    - Target: Intercepts processes that promote B-cell trafficking, chemotaxis and adhesion resulting in malignant B-cell survival, proliferation, migration and adhesion
    - Indication: Mantle cell lymphoma after 1 line of prior therapy, CLL after 1 line of therapy, Waldenstrom Macroglobulinemia with 17p deletion
    - Dosing: ***
    - Special considerations: Contraindicated in patients with baseline moderate to severe hepatic impairment, dose reduction in mild hepatic impairment
    - Adverse effects: Myelosuppression (neutropenia, thrombocytopenia, anemia), diarrhea, fatigue, myalgia, bruising, nausea, upper respiratory tract infection and rass

- **BRAF Kinase inhibitors**
  - ❑**Vemurafinib (Zelboraf), Dabrafenib (Tafinlar)**
    - Target: Interferes with Mitogen-activated protein kinase (MAPK) pathway to prevent cell proliferation and survival
    - Indication: Unresectable or metastatic melanoma and a BRAF V600E mutation
    - Dosing: Can combine Dabrafenib with Trametinib (Mekinist), reversible inhibitor of MEK1 and MEK2
    - Special considerations: Skin assessment
    - Adverse effects: <u>Can cause secondary cutaneous malignancies</u>

- **Mitogen-activated extracellular regulated kinase inhibitors (MEK)**
  - ❑**Trametinib**
    - Target: Interferes with MAPK signaling cascade that regulate cellular proliferation and apoptosis to prevent cell proliferation, differentiation and survival
    - Indication: Unresectable or metastatic melanoma and either a BRAF V600E and V600K mutation who has not received prior anti-BRAF therapy
    - Dosing: Can combine Dabrafenib with Trametinib (Mekinist), reversible inhibitor of MEK1 and MEK2
    - Special considerations: Skin assessment
    - Adverse effects: <u>Can cause secondary cutaneous malignancies</u>

- **PARP inhibitor**
  - ❑ **Olaparib (Lynparza)**
    - Target: Interruption in enzyme (PARP) that enables base-excision repair in malignant cells
    - Indication: Germline mutation of BRCA gene in advanced ovarian cancer with three or more lines of prior chemotherapy, breast cancer in the adjuvant setting or metastatic setting after 1 lines of prior chemotherapy
    - Dosing: PO daily
    - Special considerations: Watch out for secondary hematologic malignancies, elevation in creatinine
    - Side/Adverse effects: Anemia, nausea, fatigue, vomiting, diarrhea, dysgeusia, dyspepsia, headache, decreased appetite, arthralgia and dermatitis/rash

- **PIK3CA inhibitor**
  - ❑**Idelalisib (Zydelig)**
    - Target: PI3K-delta inhibitor that causes apoptosis and prevents B cell proliferation in malignant cells, BCR signaling blockade prevents chemotaxis and adhesion of malignant cells
    - Indication: Relapsed CLL in combination with Rituximab, relapsed follicular cell NHL with at least 2 lines of prior systemic therapy, relapsed small lymphocytic lymphoma after 2 prior lines of systemic therapies
    - Dosing: ***
    - Special considerations: Prevent diarrhea and neutropenic fevers
    - Side/Adverse effects: Fatigue, diarrhea, fever, chills, pneumonia (due to neutropenia), cough, rash, hyperglycemia, hypertriglyceridemia and increased AST/ALT

- **PIK3CA inhibitor**
  - ❑**Alpelisib (Piqray), Capivasertib (Trucap)**
    - Target: PI3K-delta inhibitor that causes apoptosis, BCR signaling blockade prevents chemotaxis and adhesion of malignant cells
    - Indication: Metastatic ER/PR + breast cancer with PIK3CA mutation
    - Dosing: PO daily
    - Special considerations: Baseline HbA1C
    - Side/Adverse effects: Fatigue, diarrhea, fever, chills, pneumonia (due to neutropenia), cough, rash, hyperglycemia and DKA, hypertriglyceridemia and increased AST/ALT

- **Cyclin-dependent kinase inhibitor**
  - ❑ **Palbociclib (Ibrance), Abemaciclib (Verzenio), Ribociclib (Kisqali)**
    - Target: CDK 4/6 pathway leading to cell proliferation
    - Indication: Metastatic ER/PR + HER2- breast cancer in combination with aromatase inhibitor or SERD
    - Dosing: Palbociclib and Ribociclib PO daily x 21 days then 7 days off , Abemaciclib PO BID
    - Special considerations: Baseline CBC, CMP, LFT's, EKG prior to Ribociclib, use Cystatin-C for monitoring renal function in patients taking Abemaciclib.
    - Side/Adverse effects: Fatigue, neutropenia, leukopenia, upper respiratory tract infections, nausea, stomatitis, alopecia, thrombocytopenia, decreased appetite, peripheral neuropathy and hepatotoxicity.

- **Hedgehog pathway inhibitor**
  - ❑**Vismodegib (Erivedge)**
    - Target: Hedghog pathway
    - Indication: Metastatic basal cell carcinoma, locally advanced basal cell carcinoma recurrence after surgery who are not candidates for surgery or radiation therapy
    - Dosing: ***
    - Special considerations: Excreted in the SPERM, no blood donation for 7 mos after stopping medication, must have effective birth control while on therapy
    - Side/Adverse effects: Muscle spasms, alopecia, dysgeusia, weight loss, fatigue, nausea, vomiting, diarrhea, anorexia, constipation, arthralgias, embryotoxic

Cytokines

- Interleukin 2
- Interferon alpha
- Interferon beta
- Interferon gamma

- **Side/Adverse effects: Flu-like symptoms, capillary leak syndrome, hepatotoxicity, cardiotoxicity, endocrinopathy, altered mental status, psychotic disorder, autoimmune disorders**

Colony-Stimulating Factors

- Erythropoietin
- Granulocyte CSF
- Neutrophil stem line stimulant
- Myeloid progenitor, granulocyte macrophage CSF

Side/Adverse effects: Increased tumor progression, venous and thrombotic effects, bone pains, flu-like symptoms, rare ARDS and splenic rupture.

NOT APPROVED FOR MYELOID MALIGNANCIES

Biologic Targeted Therapies

Drug Class	Target	Drugs and Indications	Side Effects
Unconjugated mAbs	CD19	Blinatumomab (Blincyto) for Philadelphia Chromosome negative relapsed or refractory B cell precursor ALL	• Fever, headache, peripheral edema, febrile neutropenia, nausea, hypoK, tremor, rash and constipation • CYTOKINE RELEASE SYNDROME • Neurotoxic-encephalopathy, AMS, seizures. Speech disorder, gait imbalance • Infection • Tumor lysis syndrome • Elevated liver enzymes

Biologic Targeted Therapies

Drug Class	Target	Drugs and Indications	Side Effects
Unconjugated mAbs	CD20	Rituximab (Rituxan) for relapsed or refractory low grade or follicular B-cell NHL -Previously untreated follicular B cell NHL chemotherapy and if response, maintenance -Nonprogressive low-grade NHL after CVP chemotherapy Previously untreated diffuse large B cell NHL with CHOP chemotherapy	• Fever, headache, peripheral edema, febrile neutropenia, nausea, hypoK, tremor, rash and constipation • CYTOKINE RELEASE SYNDROME • Neurotoxic-encephalopathy, AMS, seizures. Speech disorder, gait imbalance • Infection • Tumor lysis syndrome • Elevated liver enzymes

Practice Question No. 1

The patient is being considered for anti-HER2 therapy for her metastatic breast cancer. What is the most important deciding risk factor in deciding whether she can receive the monoclonal antibodies?

a. History of triple negative breast cancer
b. Right segmental pulmonary embolism
c. Cardiomyopathy
d. All of the above

Practice Question No. 2

Cetuximab targets:

a. CDK 4/6

b. CD 20

c. CDK 1/2

d. CD 55

Practice Question No. 3

GIST patient with KIT Exon 9 mutation. What is your treatment recommendation?

a. Imatinib

b. Lapatinib

c. Tucatinib

d. Ibrutinib

Practice Question No. 4

Patient is taking VEGFR inhibitor and experiences acneiform rash with pustules. What is the likely explanation?

a. EGFR receptor is in the subcutaneous tissue

b. Dosage was too high

c. Pt took medication with CYP34A inhibitor

d. Pt is having an allergic reaction

Practice Question No. 5

Patient with hormone receptor positive HER2 neu positive breast cancer treatment?

a. Abemaciclib with Letrozole

b. Paclitaxel or Docetaxel alone

c. Olaparib

d. Paclitaxel with monoclonal antibody

Practice Question No. 6

A patient develops HFMS from Sunitinib. What is the NP's next recommended step?

a. Switch to Sorafenib

b. Urea cream and oxycodone. Treatment with emollients and urea-based creams may soften the lesions.

c. Prednisone and phototherapy

d. All of the above

Practice Question No. 7

Indication for treatment of Cetuximab

a. Locally advanced, recurrent or metastatic squamous cell ca head and neck in combination with XRT.
b. KRAS mutation negative (wild type) EGFR expressing metastatic colorectal ca in combination with chemo as first line treatment.
c. Chronic myelogenous leukemia after failure of first line therapy
d. Non Hodgkins Lymphoma relapse after 2 lines of therapy

Practice Question No. 8

What is the indication for Ibrutinib?

a. Myelodysplastic syndrome

b. Mantel cell lymphoma

c. Pure erythroid leukemia

d. Metastatic melanoma

Practice Question No. 9

89/F with HR+ HER2+ breast cancer, post menopausal. Significant past medical history of HFrEF. What is your adjuvant therapy of choice?

a. Anastrozole
b. Trastuzumab
c. Doxorubicin
d. Bevacizumab

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Thank you!

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