TOXICITY IN AN ERA OF NOVEL ANTICANCER THERAPY

A Primer for the Non-Oncology Pharmacist

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MSHP Annual Seminar
January 27, 2018

Pharmacist Learning Objectives

- Describe the various indications and mechanisms of action of novel anticancer therapies, with particular focus on cancer immunotherapy and molecularly targeted agents
- Explain the common toxicity profiles that are unique to each class of novel anticancer therapy, with particular focus on cancer immunotherapy and molecularly targeted agents
- Discuss appropriate management strategies for the toxicities commonly seen with cancer immunotherapy and molecularly targeted agents

General Anticancer Drug Classes

- Cytotoxic Chemotherapy
  - Direct killing of cancer cells
- Molecularly Targeted Therapy
  - Blocking specific molecules involved in the growth and spread of cancer cells
  - Monoclonal antibodies (“-mabs”)
  - Small molecule inhibitors (“-ibs”)
- Cancer Immunotherapy
  - Stimulating or suppressing the immune system to aid in controlling cancer cells

https://www.cancer.gov/publications/dictionaries/cancer-terms. Accessed January 15, 2018.

What's The Big Deal?

- Meta-analyses of newer anticancer drugs have demonstrated increased odds of adverse events (AEs)
  - Toxic death
  - Treatment discontinuation
  - Severe AEs
- Increased Healthcare Costs
  - Reported costs of managing one Grade 3-4 AE range from $300 to $30,000 (2013 cost)
- Lack of data on anticancer agents approved by the FDA since 2011

Niraula S, et al. *J Clin Oncol*. 2012;30(24):3012-3019.
Niraula S, et al. *J Clin Oncol*. 2014;32(32):3634-3642.

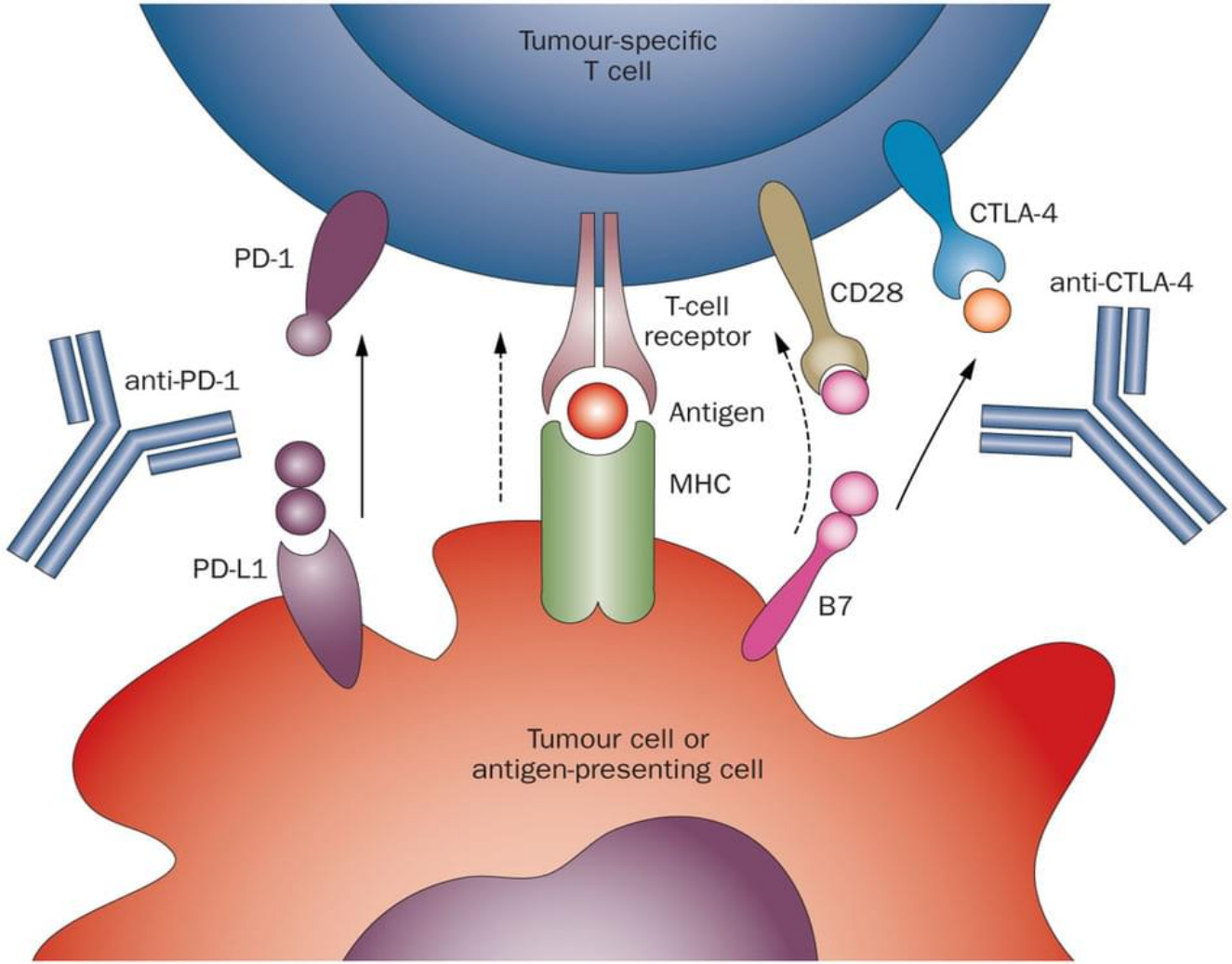
“Traditional” Chemotherapy Side Effects

Fatigue	Pain	Cytopenias
Nausea & Vomiting	Diarrhea	Mucositis
Infertility	Alopecia	Appetite Loss

https://www.cancer.net/navigating-cancer-care/how-cancer-treated/chemotherapy/side-effects-chemotherapy. Accessed January 15, 2018.

CANCER IMMUNOTHERAPY: PD-1/PD-L1 INHIBITORS

Mechanism of Action



Drake CG, et al. *Nat Rev Clin Oncol*. 2014;11(1):24-37.

Indications: PD-1 Inhibitors

- Nivolumab
  - Melanoma
  - Non-Small Cell Lung Cancer
  - Renal Cell Carcinoma
  - Classical Hodgkin Lymphoma
  - Head & Neck Cancer
  - Bladder Cancer
  - MSI-H or dMMR Colorectal Cancer
  - Hepatocellular Carcinoma

  Administered IV every 2 weeks

- Pembrolizumab
  - Melanoma
  - Non-Small Cell Lung Cancer
  - Head & Neck Cancer
  - Classical Hodgkin Lymphoma
  - Bladder Cancer
  - Gastric Cancer
  - MSI-H or dMMR solid tumors
    - Adult AND pediatric patients

  Administered IV every 3 weeks

Opdivo [package insert]. Princeton, NJ: Bristol-Myers Squibb Co; 2018.
Keytruda [package insert]. Whitehouse Station, NJ: Merck & Co, Inc; 2017.

Indications: PD-L1 Inhibitors

- Atezolizumab
  - Non-Small Cell Lung Cancer
  - Bladder Cancer

  Administered IV every 3 weeks
- Avelumab
  - Merkel Cell Carcinoma
    - Adult AND pediatric patients
  - Bladder Cancer

  Administered IV every 2 weeks
- Durvalumab
  - Bladder Cancer

  Administered IV every 2 weeks

Tecentriq [package insert]. South San Francisco, CA: Genentech, Inc; 2017.
Bavencio [package insert]. Rockland, MA: EMD Serono, Inc; 2017.
Imfinzi [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.

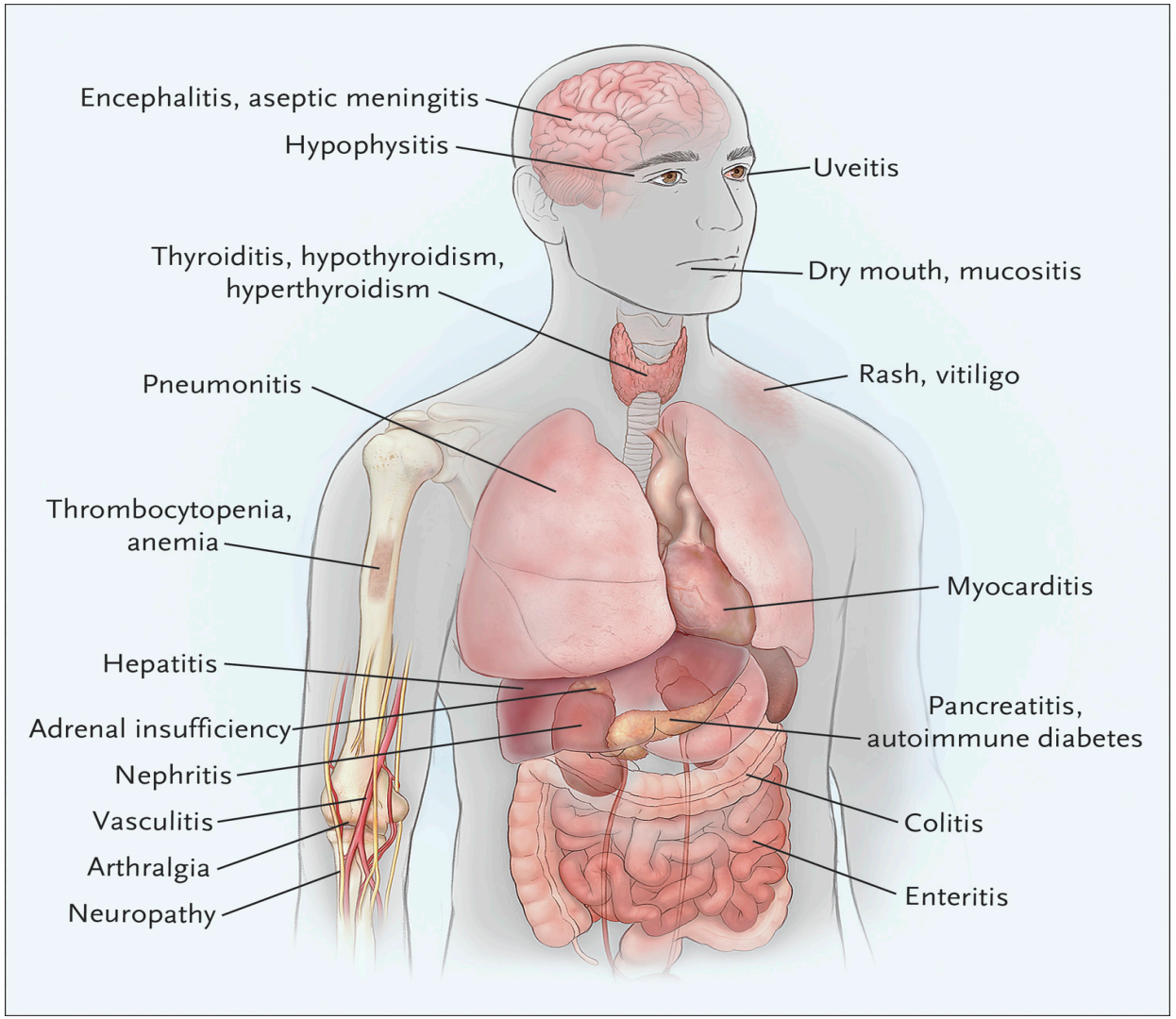
Immune-Related Adverse Events (irAEs)

- Excessive immunity against normal organs
  - ↑ T-cell activity
  - ↑ Autoantibodies
  - ↑ Inflammatory cytokines

- Overall incidence of severe irAEs appears similar among patients with different tumor types
  - Grade 3-4 AE rate <20%
  - Treatment-related death rate <10%

Postow MA, et al. *N Engl J Med*. 2018;378(2):158-168.
Friedman CF, et al. *JAMA Oncol*. 2016;2(10):1346-1353.

Distribution of irAEs



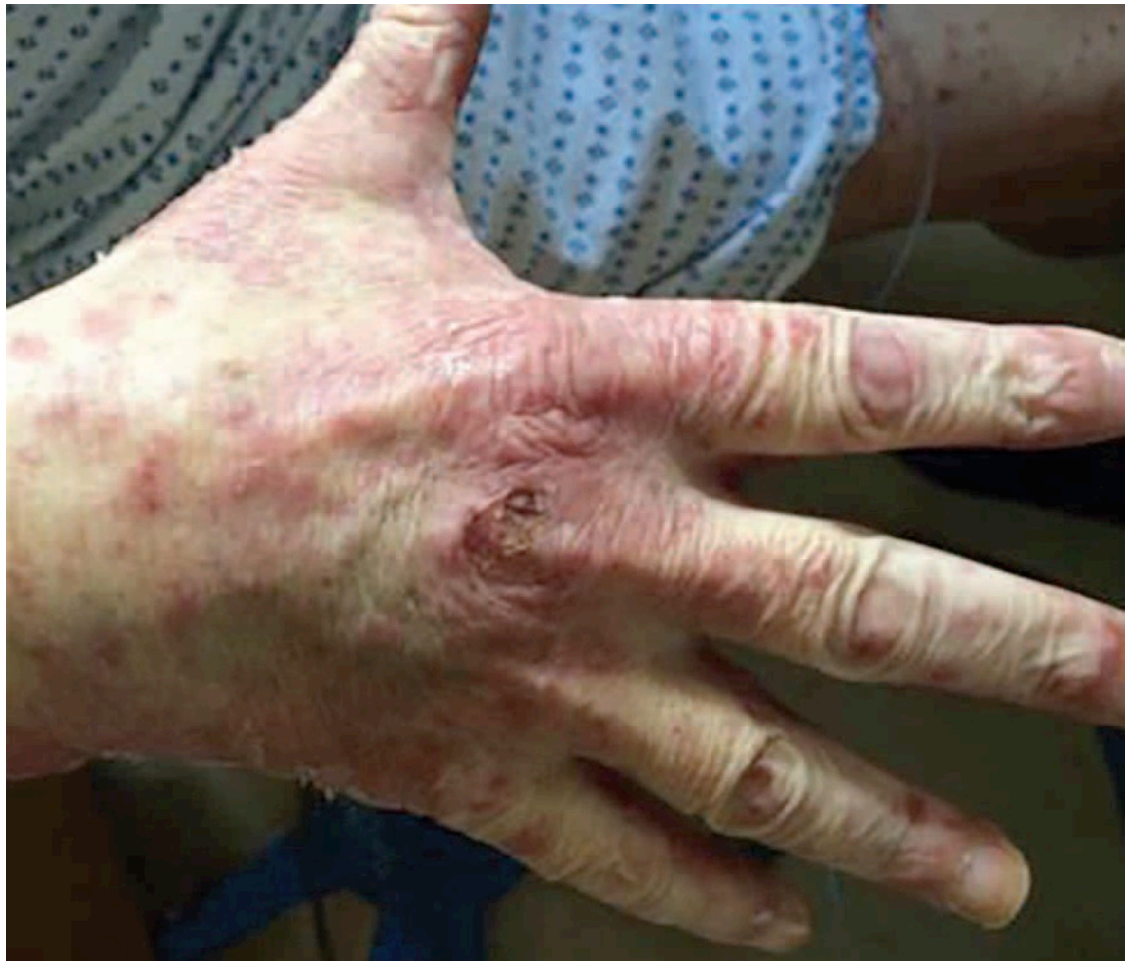
Postow MA, et al. *N Engl J Med*. 2018;378(2):158-168.

Treatment of irAEs

- Hold Immunotherapy
- Systemic Corticosteroids
- Additional Immunosuppression

Skin Reactions

- Rash, Pruritus most common irAEs
- ~40% incidence
- Typical onset within 2 weeks of starting therapy
- Presentation:
  - Erythematous maculopapular rash across limbs, trunk
- Rare occurrences:
  - SJS/TEN
  - Vitiligo



Friedman CF, et al. *JAMA Oncol*. 2016;2(10):1346-1353.

Skin Reactions: Management

Grade 1 (<10% BSA)

- Continue treatment
- Topical steroids, antihistamines

Grade 2 (10-30% BSA)

- Hold treatment
- Prednisone 0.5-1 mg/kg PO daily with 2-week taper

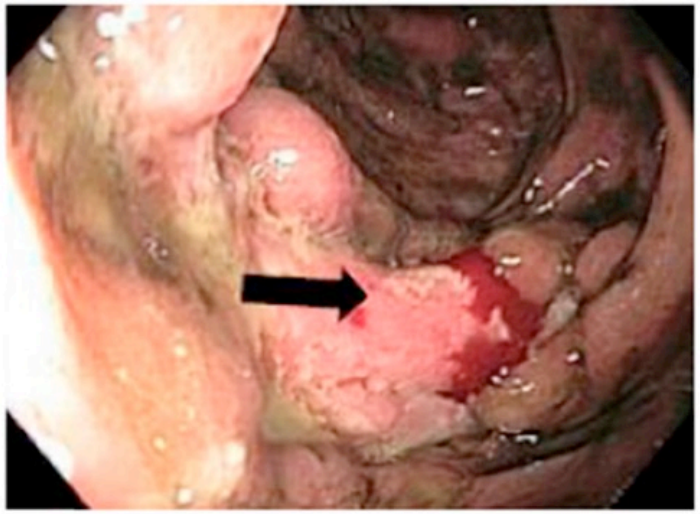
Grades 3-4 (>30% BSA)

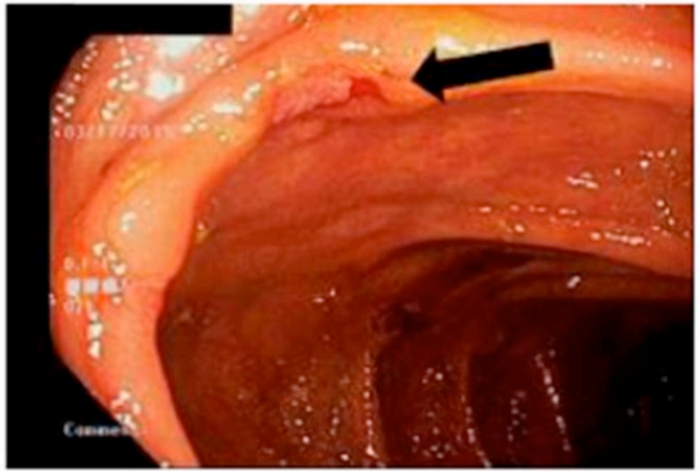
- Hold treatment (permanently stop if grade 4); obtain skin biopsy
- Prednisone 1-2 mg/kg daily or IV equivalent with 4-week taper

Spain L, et al. *Cancer Treat Rev*. 2016;44:51-60.

Diarrhea / Colitis

- ~20% incidence
- Median onset varies from 7 weeks to 6 months after starting treatment
- Colitis presentation:
  - Abdominal pain
  - Blood, mucus in stool
  - Large bowel inflammation on imaging





Spain L, et al. *Cancer Treat Rev*. 2016;44:51-60.
Weber JS, et al. *Oncologist*. 2016;21(10):1230-1240.

Diarrhea / Colitis: Management

Severity	Management Strategies
Grade 1 (<4 stools/day over baseline)	• Continue treatment • Symptom management (PO fluids, anti-motility agents)
Grade 2 (4-6 stools/day over baseline)	• Hold treatment • If persists >5 days, start 0.5-1 mg/kg/day prednisone or IV equivalent until improvement, then taper over 2-4 weeks
Grade 3-4 (≥7 stools/day over baseline)	• Hold treatment (permanently discontinue for grade 4 event) • Admit for IV hydration and observation • Start 1-2 mg/kg/day prednisone or IV equivalent until improvement, then taper over 1-3 months • If no improvement in 2-3 days, add infliximab 5 mg/kg (AVOID in sepsis or perforation) • Sigmoidoscopy / biopsy recommended to exclude other causes

*Always rule out noninflammatory causes of diarrhea!

Spain L, et al. *Cancer Treat Rev*. 2016;44:51-60.
Weber JS, et al. *Oncologist*. 2016;21(10):1230-1240.

Hepatitis

- ↑ ALT/AST (± ↑ bilirubin)
- Onset usually 8-12 weeks after start of therapy
- 1-6% incidence
- Presentation typically asymptomatic
- Rule out noninflammatory causes
- Monitor labs every 2-3 days

Management	
Grade 2 (LFTs 3-5x ULN, T.bili ≤3x ULN)	• Hold treatment • If persists >5-7 days, start 0.5-1 mg/kg/day prednisone or IV equivalent until improvement, then taper over 1 month
Grade 3-4 (LFTs >5x ULN, T.bili >3x ULN)	• Hold treatment • Start 1-2 mg/kg/day prednisone or IV equivalent (taper as above) • If no improvement in 3-5 days, add mycophenolate mofetil • AVOID infliximab!

Weber JS, et al. *Oncologist*. 2016;21(10):1230-1240.

Pneumonitis

- Generally uncommon (<10%)
- Onset typically several months after start of treatment
- Possible symptoms: URI, dyspnea, hypoxia
- CT imaging: bilateral consolidative and ground glass opacities
- Mild-moderate cases:
  - Oral steroids (prednisone 1-2 mg/kg/day)
- Moderate-severe cases:
  - Admission ➔ High-dose steroids (methylprednisolone 2-4 mg/kg/day IV)
  - Prophylactic antibiotics for opportunistic infections
  - Additional immunosuppression if no improvement after 48 hours

Friedman CF, et al. *JAMA Oncol*. 2016;2(10):1346-1353.

Endocrinopathies

- 4-10% incidence
- Median onset ~10 weeks after start of treatment
- Usually requires permanent hormone replacement

Hypophysitis

- Clinical symptoms: fatigue, HA, hypogonadism
- Brain MRI: pituitary enlargement
- Low ACTH, cortisol
- Endocrinology consult

Thyroid Dysfunction

- Hypothyroidism:
  - Levothyroxine
- Hyperthyroidism:
  - Symptomatic treatment with β-blockers and steroids
  - Endocrinology consult

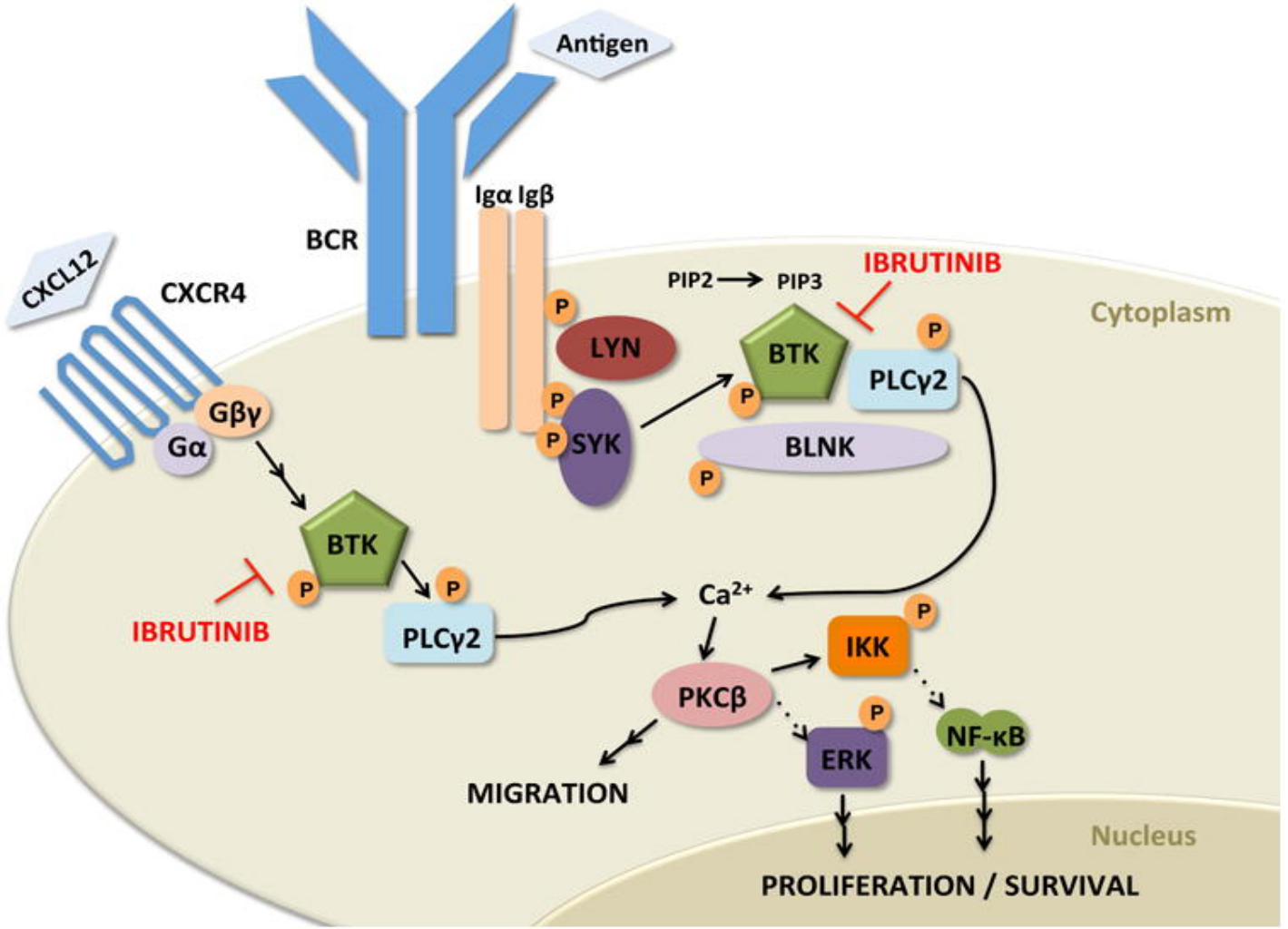
Adrenal Crisis

- Clinical symptoms: severe dehydration, hypotension, hyperkalemia, hyponatremia
- Stress dose steroids

Friedman CF, et al. *JAMA Oncol*. 2016;2(10):1346-1353.

TARGETED THERAPY: BTK INHIBITORS

Mechanism of Action



Sivina M, et al. *Br J Haematol*. 2014;166(2):177-188.

Indications

- Ibrutinib
  - Chronic Lymphocytic Leukemia
  - Waldenström's Macroglobulinemia
  - Chronic Graft Versus Host Disease

  Dose: 420 mg PO daily
  - Mantle Cell Lymphoma
  - Marginal Zone Lymphoma

  Dose: 560 mg PO daily

- Acalabrutinib
  - Mantle Cell Lymphoma

  Dose: 100 mg PO BID

Imbruvica [package insert]. Sunnyvale, CA: Pharmacyclics LLC; 2017.
Calquence [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.

Bleeding / Bruising

- A systematic review of 4 RCTs of ibrutinib showed a 2.93-fold increased incidence of any grade bleeding (p=0.03)

- Incidence of major bleeding with ibrutinib:
  - Concomitant antiplatelet therapy: 2.5%
  - Concomitant anticoagulant therapy: 3.2%
  - Concomitant antiplatelet + anticoagulant therapy: 21%

- Concomitant Vitamin K antagonists were excluded from most ibrutinib trials

- Similar major bleeding rates seen with acalabrutinib

de Weerdt I, et al. *Haematologica*. 2017;102(10):1629-1639.

Bleeding / Bruising

- Hold BTK inhibitor 3-7 days before and after invasive procedures
- Avoid concomitant warfarin; switch to either LMWH or a DOAC
- Avoid combined AC and AP treatment with BTK inhibitor due to increased bleeding risk

de Weerdt I, et al. *Haematologica*. 2017;102(10):1629-1639.

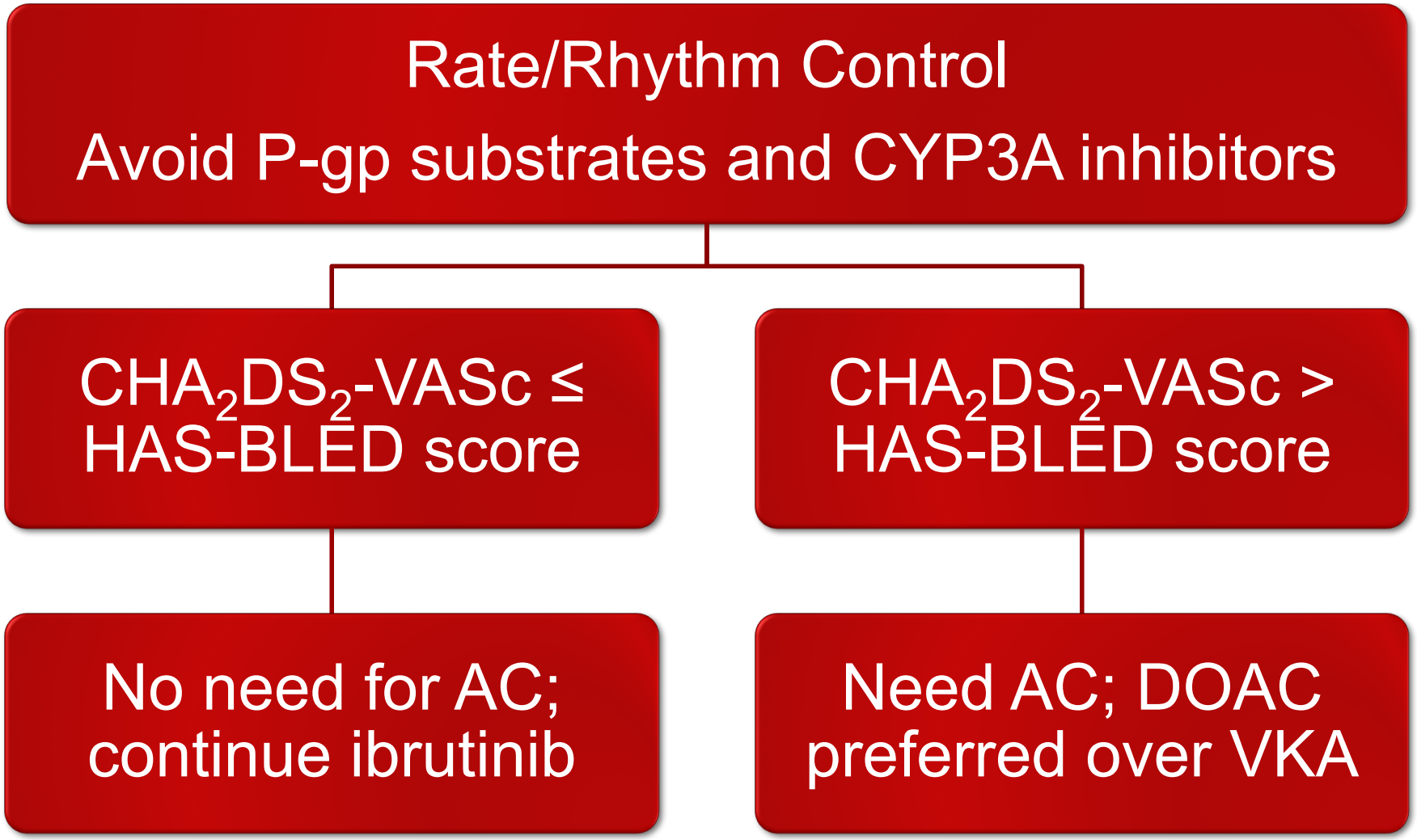
Cardiovascular Effects

- Hypertension
  - 26% incidence with 46 months of ibrutinib
  - Monitor BP regularly and treat per usual guidelines
  - No need for dose reduction or discontinuation of ibrutinib

- Atrial Fibrillation
  - 9% incidence with 46 months of ibrutinib; 3% incidence with acalabrutinib
  - Neither dose reduction nor discontinuation of therapy seems to alter resolution rate of AF
  - Treat AF per usual guidelines, being mindful of drug interactions

de Weerdt I, et al. *Haematologica*. 2017;102(10):1629-1639.

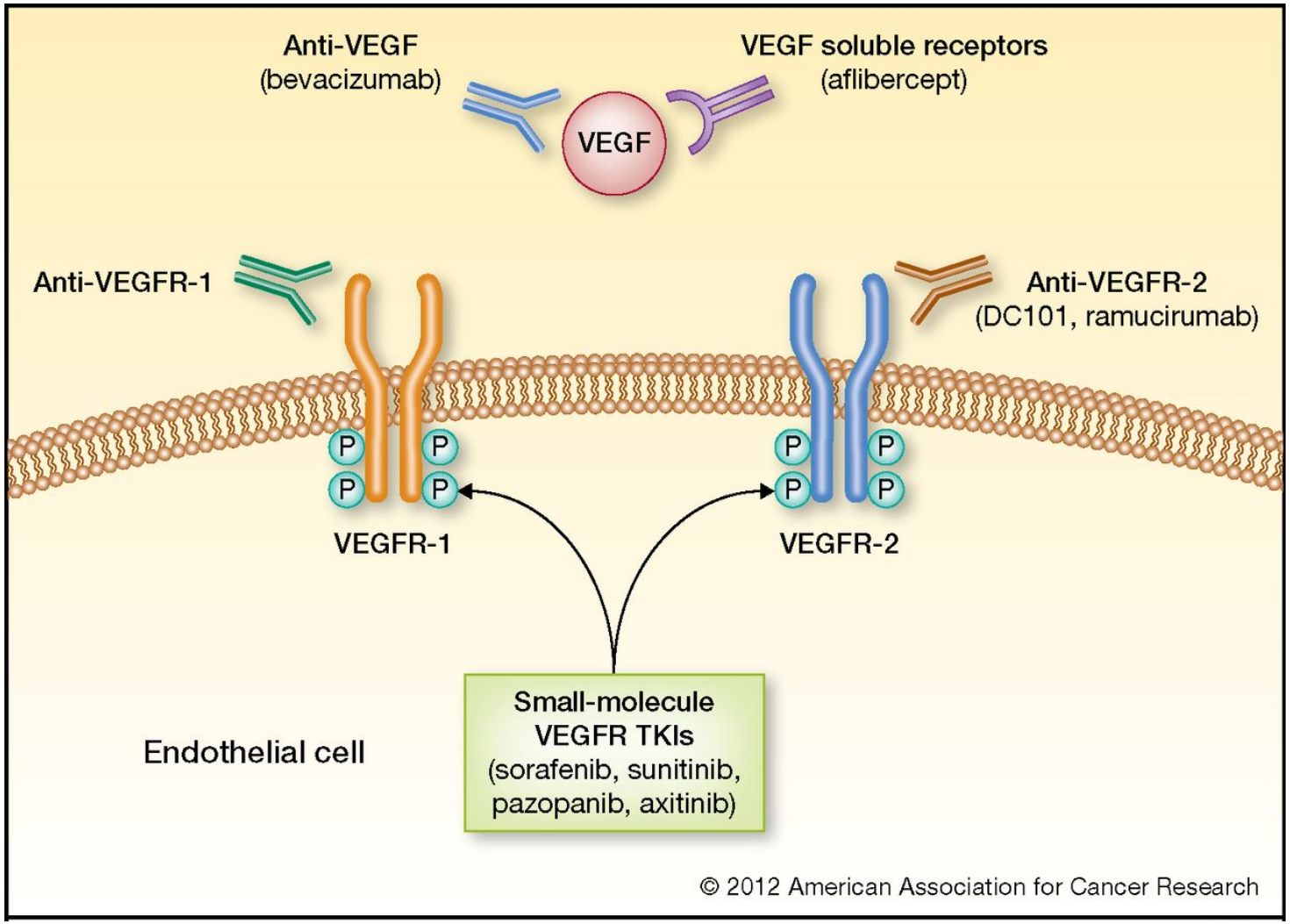
Atrial Fibrillation



de Weerdt I, et al. *Haematologica*. 2017;102(10):1629-1639.

TARGETED THERAPY: VEGF INHIBITORS

Mechanism of Action



Chau CH, et al. *Clin Cancer Res*. 2012;18(18):4868-4871.

Indications: IV Agents

- Bevacizumab
  - Colorectal Cancer
  - Non-Small Cell Lung Cancer
  - Glioblastoma
  - Renal Cell Carcinoma
  - Cervical Cancer
  - Ovarian/Fallopian tube/Peritoneal Cancer

  Administered every 2 or 3 weeks

- Ramucirumab
  - Gastric Cancer
  - Non-Small Cell Lung Cancer
  - Colorectal Cancer

  Administered every 2 or 3 weeks

Avastin [package insert]. South San Francisco, CA: Genentech, Inc; 2017.
Cyramza [package insert]. Indianapolis, IN: Eli Lilly & Co; 2017.

Indications: Oral Agents

- Sunitinib
  - Renal Cell Carcinoma
  - GI Stromal Tumor (GIST)
  - Pancreatic Neuroendocrine Tumor

  Dose: 37.5 – 50 mg PO daily
- Pazopanib
  - Renal Cell Carcinoma
  - Soft Tissue Sarcoma

  Dose: 800 mg PO daily
- Sorafenib
  - Hepatocellular Carcinoma
  - Renal Cell Carcinoma
  - Thyroid Cancer (Differentiated)

  Dose: 400 mg PO BID
- Regorafenib
  - Colorectal Cancer
  - GIST
  - Hepatocellular Carcinoma

  Dose: 160 mg PO daily

Sutent [package insert]. New York, NY: Pfizer Inc; 2017.
Votrient [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.
Nexavar, Stivarga [package inserts]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2017.

Indications: Oral Agents

- Axitinib
  - Renal Cell Carcinoma

  Dose: 5-10 mg PO BID
- Cabozantinib
  - Renal Cell Carcinoma

  Dose: 60 mg PO daily
  - Thyroid Cancer (Medullary)

  Dose: 140 mg PO daily
- Lenvatinib
  - Thyroid Cancer (Differentiated)

  Dose: 24 mg PO daily
  - Renal Cell Carcinoma

  Dose: 18 mg PO daily
- Vandetanib
  - Thyroid Cancer (Medullary)

  Dose: 300 mg PO daily

Inlyta [package insert]. New York, NY: Pfizer Inc; 2014.
Cabometyx, Cometriq [package inserts]. South San Francisco, CA: Exelixis, Inc; 2017.
Lenvima [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2017.
Caprelsa [package insert]. Cambridge, MA: Genzyme Corp; 2016.

Hypertension

- Class effect of VEGF inhibition
- Incidence ranges from 11% - 43% in trials
- Significant risk factors:
  - Pre-existing HTN
  - Renal Cell Carcinoma
- Multiple theorized mechanisms
- Management
  - Regular BP monitoring (every 2-3 weeks once stable)
  - Treat HTN as per usual guidelines
  - No specific data to indicate a preferred anti-HTN agent
    - ACEI/ARB for effect on proteinuria?
  - Discontinue VEGF inhibitor if hypertensive crisis occurs

Abbas A, et al. *Target Oncol*. 2015;10(4):487-499.

Proteinuria

- Class effect of VEGF inhibition
- Incidence:
  - All grades: 7% - 49%
  - Grade 3-4 (≥3.5 g/L): 0.8% - 15%
- Directly related to dose and development of HTN
- Multiple theorized mechanisms

- Management
  - Regular UA screening
  - If 1+ proteinuria present on UA, obtain urine protein/creatinine ratio
  - Hold VEGF inhibitor for proteinuria ≥2-3 g/24 h until resolution to baseline
  - Discontinue VEGF inhibitor for nephrotic syndrome

Abbas A, et al. *Target Oncol*. 2015;10(4):487-499.

Hand Foot Skin Reaction (HFSR)

- More common with small molecule VEGF inhibitors
- Symptoms:
  - Callus formation
  - Superficial blistering
  - Localized to pressure zones
  - Pain / heat intolerance possible
- Appears within 4-6 weeks of starting treatment; mostly grade 1-2

Management	
Throughout treatment	• Daily skin care: urea 10% cream TID to hands & feet • Thick socks, comfortable shoes • Cotton gloves on hands • Avoid hot water
Grade 1 HFSR	• Use urea 20%-40% cream (instead of 10%)
Grade 2 HFSR	• All of the above PLUS • Topical lidocaine or PO anti-inflammatory (ex: ibuprofen) for symptomatic relief
Grade 3 HFSR	• All of the above PLUS • Modify dose/hold treatment

Walko CM, et al. *Semin Oncol*. 2014;41:S17-S28.

Diarrhea

- More common in small molecule VEGF inhibitors
- Management:

Non-pharmacologic Interventions

- Maintain hydration with electrolyte-containing fluids
- Eat frequent, small meals
- Avoid dairy, high-fiber, high-fat, greasy, spicy foods

Pharmacologic Interventions

- Loperamide 4 mg initial dose, followed by 2 mg q2-4h until diarrhea-free for 12 hours
- Diphenoxylate/atropine 5 mg loading dose, then 2.5-5mg four times daily
- Opium tincture 0.3-1 mL every 2-6 hours until controlled

Walko CM, et al. *Semin Oncol*. 2014;41:S17-S28.

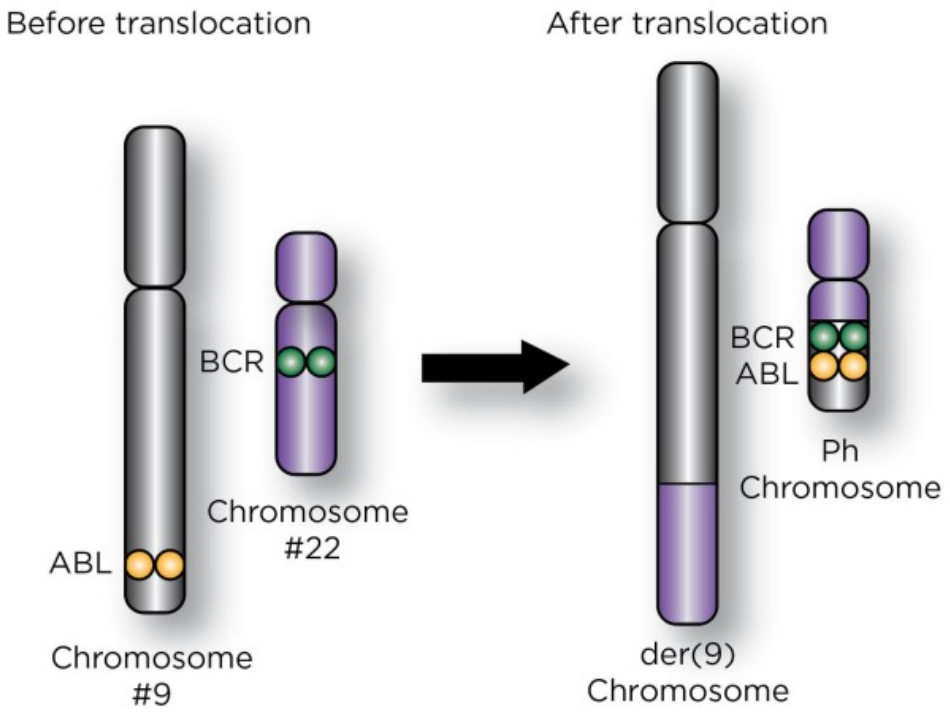
Other Selected Toxicities of VEGF Inhibitors

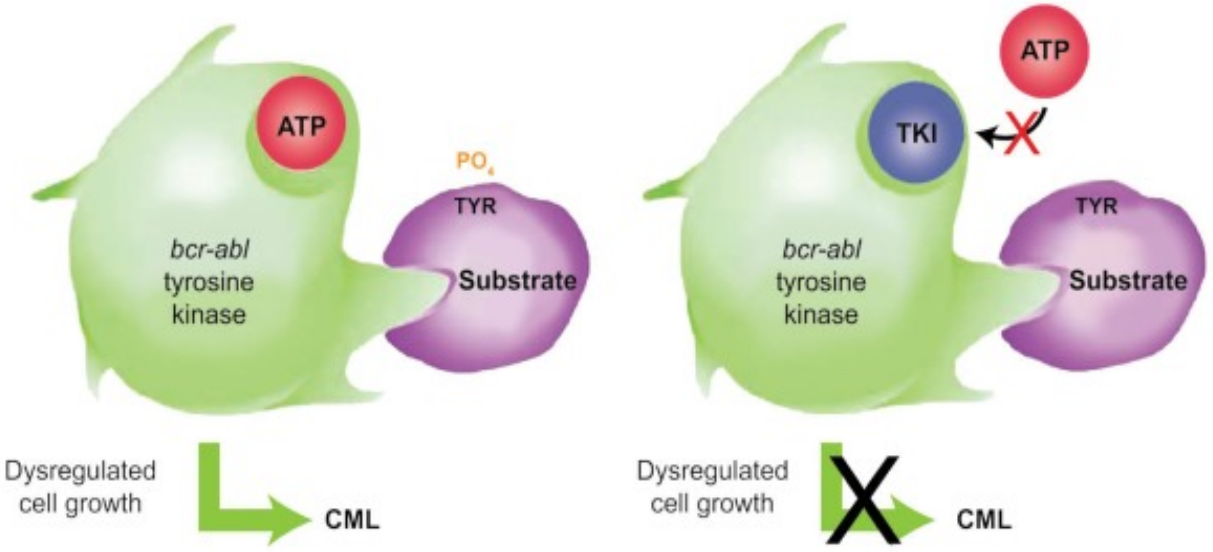
- Impaired Wound Healing
- Gastrointestinal Perforation
- Hemorrhage
- Arterial Thrombosis

Chen HX, et al. *Nat Rev Clin Oncol*. 2009;6(8):465-477.

TARGETED THERAPY: BCR-ABL TYROSINE KINASE INHIBITORS

Mechanism of Action





Bauer S, et al. *J Adv Pract Oncol*. 2012;3(3):151-160.

Indications

- CML, newly diagnosed
  - Imatinib 400-800 mg daily
- CML, newly diagnosed or resistant
  - Dasatinib 100-140 mg daily
  - Nilotinib 300-400 mg BID
  - Bosutinib 400-500 mg daily
- CML, T315I-positive or resistant/intolerant to all other TKIs
  - Ponatinib 45 mg daily

Rea D. *Ann Hematol*. 2015;94:S149-S158.

Imatinib: Selected Toxicities

Fluid Retention

- Weight gain, periorbital and lower limb edema
- >50% incidence in trials
- Manage with diuretics
- Consider ECHO to check LVEF

Muscle Cramps

- Mostly nocturnal, in lower limbs
- ~40% incidence in trials
- Check CK for rhabdomyolysis
- Manage with Ca/Mg supplements and tonic water

Rea D. *Ann Hematol*. 2015;94:S149-S158.

Dasatinib: Selected Toxicities

- Pleural Effusions
  - Reported incidence: 10% at 1 year, 14% at 2 years, 19% at 3 years
  - Interrupt dasatinib until resolution, then reintroduce at lower dose
  - Consider short course of prednisone to accelerate recovery
  - Thoracentesis in severe cases

- Pulmonary Arterial Hypertension (PAH)
  - At 3 year follow-up, 3% incidence compared to 0% with imatinib
  - Check ECHO at baseline for high-risk patients and if symptomatic
  - If confirmed, discontinue dasatinib and refer to cardiologist

Rea D. *Ann Hematol*. 2015;94:S149-S158.

Nilotinib: Selected Toxicities

- QT interval prolongation **(BLACK BOX WARNING)**
  - Reports of sudden deaths
  - Monitor for hypokalemia and hypomagnesemia and correct deficiencies
  - Check ECG at baseline, 7 days after initiation or any dose adjustment, then periodically

QTc >480 ms: Hold nilotinib, check/correct K/Mg, review other drugs

QTc <450 ms and within 20 ms of baseline after 2 weeks: resume at prior dose

QTc 450 – 480 ms after 2 weeks: resume at reduced dose

QTc returns to >480 ms: discontinue nilotinib

Tasigna [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.

Nilotinib: Selected Toxicities

- Vascular and Metabolic Toxicity
  - Risk of CV events (IHD, PAD, cerebrovascular disease) at 6-year follow-up:
    - Imatinib 400 mg daily → 2.5%
    - Nilotinib 300 mg BID → 10%
    - Nilotinib 400 mg BID → 16%
- Nilotinib may aggravate pre-existing arteriosclerosis
- Monitoring Recommendations:
  - Fasting Lipid Panel: baseline, then every 3-6 months
  - Fasting Blood Glucose: baseline, then every 3-6 months
  - Ankle-Brachial Index: baseline, then every 3-6 months

Moslehi JJ, et al. *J Clin Oncol*. 2015;33(35):4210-4218.

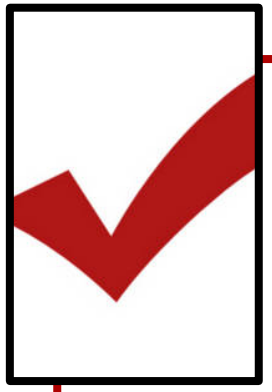
Selected Toxicities of Other TKIs

Bosutinib
- Diarrhea

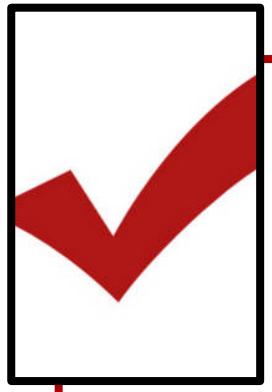
Ponatinib
- Vascular Occlusion
- Heart Failure
- Hepatotoxicity
- VTE
- Pancreatitis

Rea D. *Ann Hematol*. 2015;94:S149-S158.

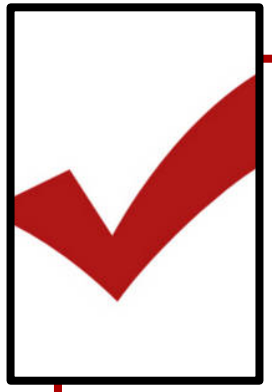
Key Points to Remember!



By activating the immune system, PD-1/PD-L1 inhibitors can cause numerous immune-related adverse events; mainstay of treatment is corticosteroids



Molecularly targeted therapies have a wide variety of class-specific adverse effects; long-term data suggest CV and pulmonary risks with BCR-ABL TKIs



Through prompt identification of these toxicities, health-system pharmacists can help develop an effective management strategy that will mitigate both patient harm and healthcare costs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QUESTIONS
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