Pharmacologic Review of Cancer Therapy Essentials:

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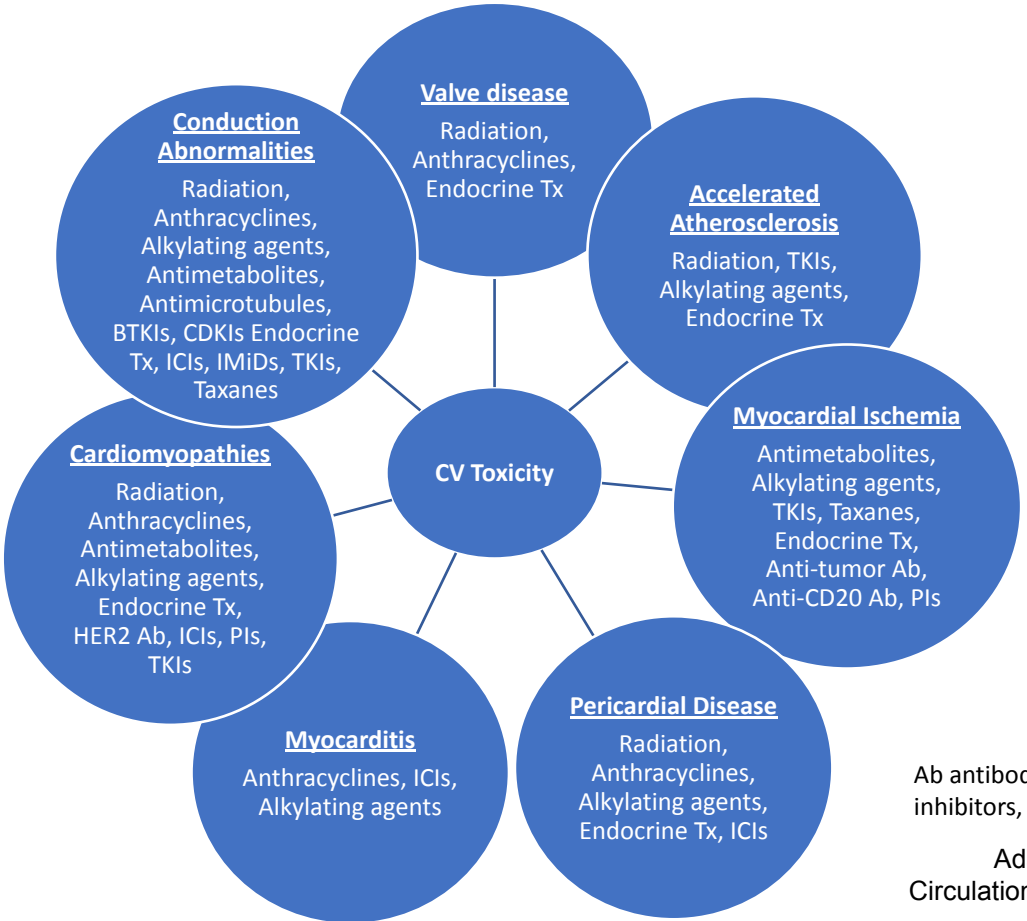
Objectives and Disclosures

- Identify the mechanisms of action as it relates to both oncologic efficacy and cardiotoxicity of common cancer treatment therapies and the resultant impact on cardiovascular disease for the following therapies

- I have nothing to disclose related to this presentation

Cardiovascular Toxicity of Cancer Therapies



Additional CV Toxicities

Systemic Hypertension
Alkylating Agents, Antimicrotubules, TKIs, PIs

Pulmonary Hypertension
Alkylating agents, Antimicrotubules, PIs

Vasospasm
Antimetabolites, Antimicrotubules, Alkylating agents

Thrombosis
Alkylating agents, Antimicrotubules, Endocrine Tx, IMiDs, PIs, TKIs

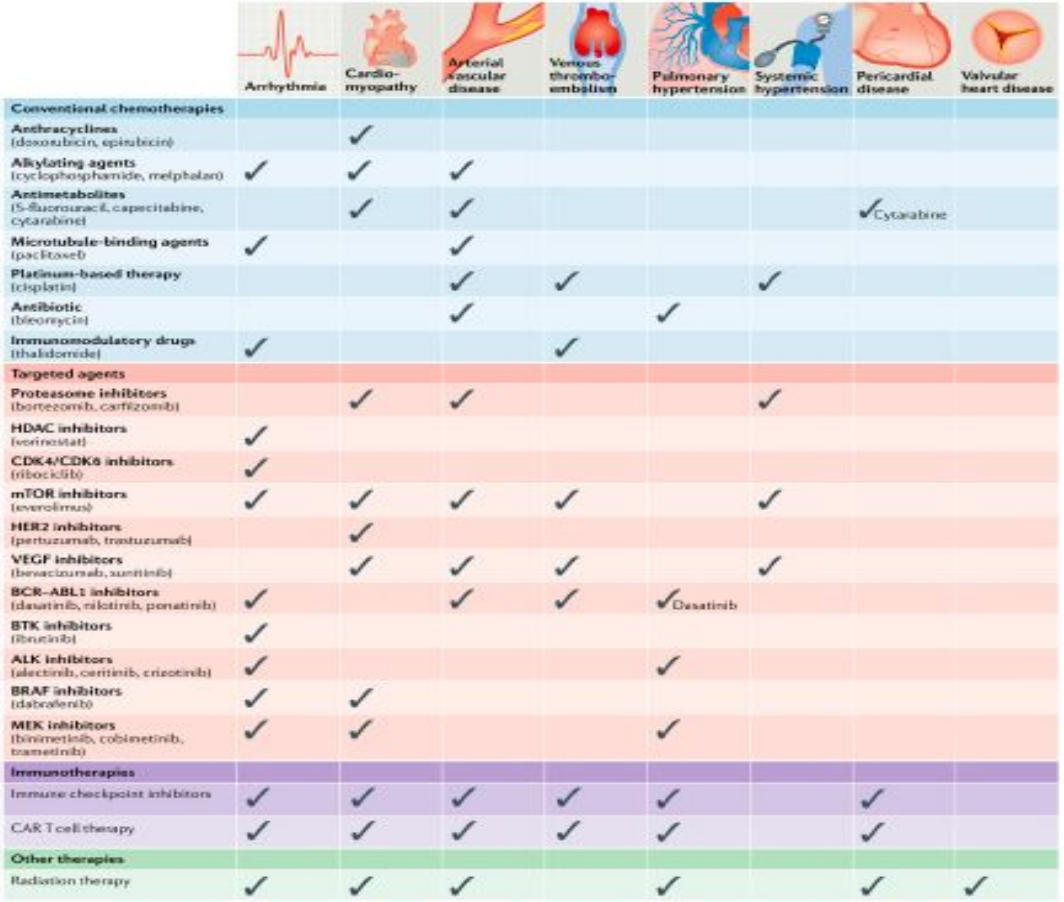
Stenosis
Endocrine Tx, TKIs

Vasculitis
ICIs

Ab antibody, BTK Bruton tyrosine kinase inhibitors, ICIs immune checkpoint inhibitors, IMiDs immunomodulators, PIs proteosome inhibitors, Tx therapies

Adapted from Front Cardiovasc Med 2020; 6:187, Circulation 2019; 139:e579-e602, Circ Res 2016;118:1008-1020

Cardio-toxicities of Anticancer Therapy



	Arrhythmia	Cardio-myopathy	Arterial vascular disease	Venous thrombo-embolism	Pulmonary hypertension	Systemic hypertension	Pericardial disease	Valvular heart disease
Conventional chemotherapies								
Anthracyclines (doxorubicin, epirubicin)		✓						
Alkylating agents (cyclophosphamide, melphalan)	✓	✓	✓					
Antimetabolites (5-fluorouracil, capecitabine, cytarabine)		✓	✓				✓Cytarabine	
Microtubule-binding agents (paclitaxel)	✓		✓					
Platinum-based therapy (cisplatin)			✓	✓		✓		
Antibiotic (bleomycin)			✓		✓			
Immunomodulatory drugs (thalidomide)	✓			✓				
Targeted agents								
Proteasome inhibitors (bortezomib, carfilzomib)		✓	✓			✓		
HDAC inhibitors (vorinostat)	✓							
CDK4/CDK6 inhibitors (ribociclib)	✓							
mTOR inhibitors (everolimus)	✓	✓	✓	✓		✓		
HER2 inhibitors (pertuzumab, trastuzumab)		✓						
VEGF inhibitors (bevacizumab, sunitinib)		✓	✓	✓		✓		
BCR–ABL1 inhibitors (dasatinib, nilotinib, ponatinib)	✓		✓	✓	✓Dasatinib			
BTK inhibitors (ibrutinib)	✓							
ALK inhibitors (alectinib, ceritinib, crizotinib)	✓				✓			
BRAF inhibitors (dabrafenib)	✓	✓						
MEK inhibitors (binimetinib, cobimetinib, trametinib)	✓	✓			✓			
Immunotherapies								
Immune checkpoint inhibitors	✓	✓	✓	✓	✓		✓	
CAR T cell therapy	✓	✓	✓	✓	✓		✓	
Other therapies								
Radiation therapy	✓	✓	✓		✓		✓	✓

Nat Rev Cardiol. 2020; 17(8): 474–502

Classes of Cancer-Directed Therapies

Cytotoxic Chemo

- [ ] Alkylating Agents
- [ ] Antimetabolites
- [ ] Antimicrotubular Agents
- [ ] Topoisomerase Inhibitors
- [ ] Cytotoxic Antibiotics

Hormone Therapy

- [ ] Anti-estrogens
- [ ] Anti-androgens
- [ ] Peptide Hormones

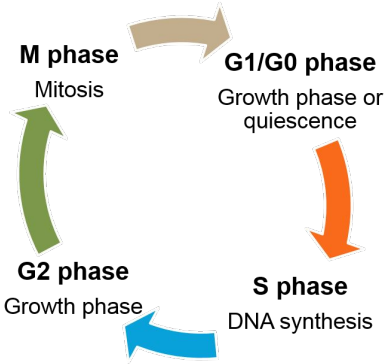
Targeted Therapy

- [ ] Biologic Agents (mAbs)
- [ ] Small Molecules (TKIs)
- [ ] Antibody-Drug Conjugates

Immunotherapy

- [ ] Checkpoint Inhibitors
- [ ] Cellular Therapies
- [ ] Bi-specific T-cell Engagers
- [ ] Cytokine Therapy
- [ ] Oncolytic Viruses

Toxicity of Cytotoxic Cancer Therapies

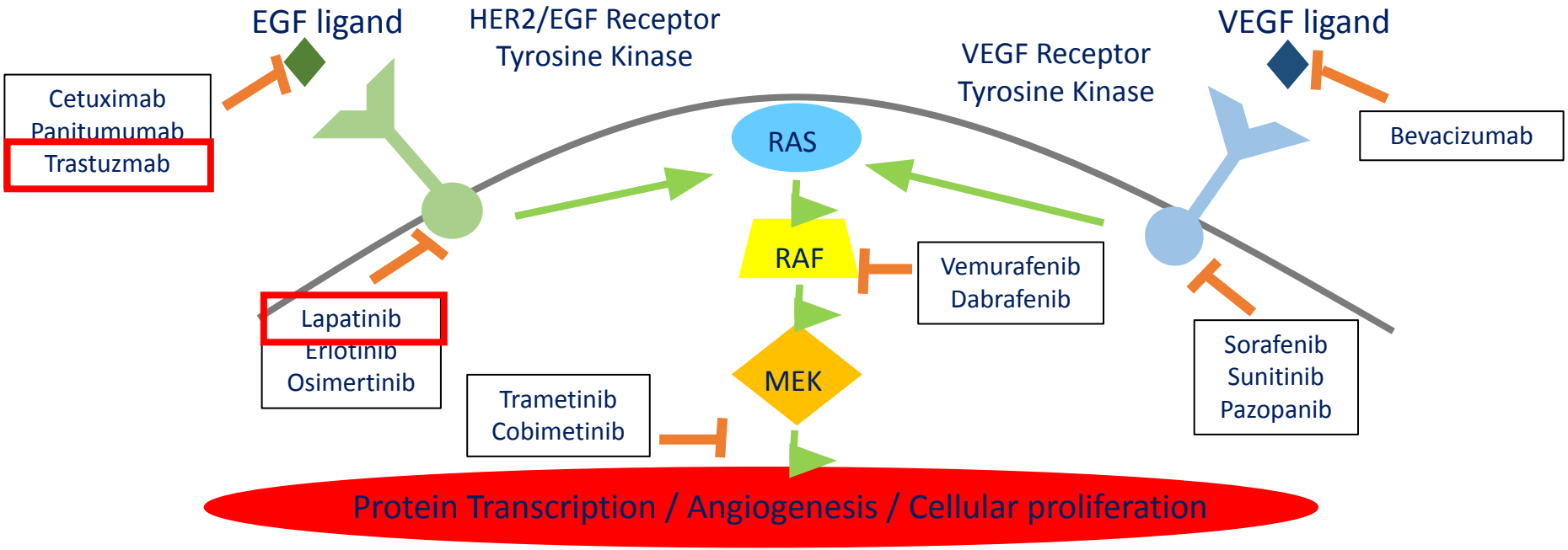


Class	Mechanism of Cytotoxicity
Cell Cycle Non-specific: Effects exerted at any phase of the cell cycle	
Alkylating Agents (e.g., cisplatin, cyclophosphamide)	Form cross links in DNA to inhibit replication
Anthracyclines (e.g., doxorubicin, daunorubicin)	Inhibit topoisomerase to prevent proper replication and form free radicals that damage DNA
Cell Cycle Specific: Effect exerted on actively dividing cells only	
Antimetabolites (e.g., 5-fluorouracil, methotrexate)	Structurally similar to bases/enzymatic substrates and lead to stalling of replication
Antimicrotubules (e.g., paclitaxel, vincristine)	Prevent proper assembly or breakdown of microtubules and shut down mitosis

Cytotoxic chemotherapies work by inhibiting steps in the cell cycle to prevent cells from dividing. The major toxicity is myelosuppression, with additional toxicities related to drug class (nausea/vomiting, diarrhea, kidney injury, hemorrhagic cystitis, etc).

Goodman & Gilman's: 2019; 13e: McGraw-Hill

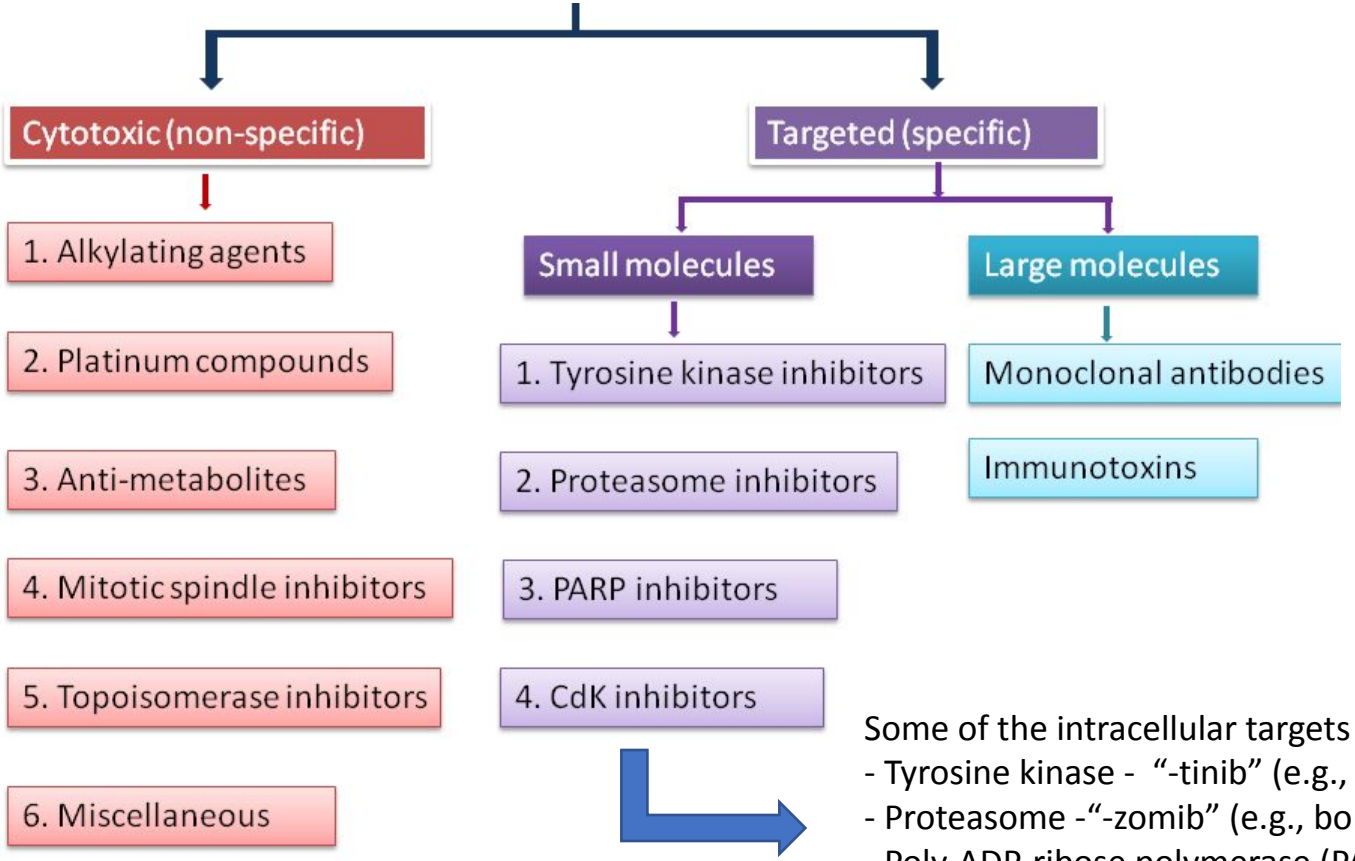
Toxicity of Targeted Cancer Therapies



Targeted therapies can be either monoclonal antibodies (which bind extracellularly – "-mabs"), or small molecule inhibitors (which bind intracellularly – "ibs") to a specific protein to exert their effect on tumor cells. The toxicity profile of these medications tends to be related to the protein which they target.

Goodman & Gilman's: 2019; 13e: McGraw-Hill

Cytotoxic and Targeted Chemotherapy



Some of the intracellular targets for the "-ibs" include:
- Tyrosine kinase - "-tinib" (e.g., imatinib)
- Proteasome -"-zomib" (e.g., bortezomib)
- Poly-ADP-ribose polymerase (PARP) - "-parib" (e.g., olparib)
- Cyclin-dependent kinase -"-ciclib" (e.g., seliciclib)

J Med Chem 2021; 64:4410–4429

Small Molecule Inhibitors

(Approved as of September 1, 2022)

EGFR
- Erlotinib
- Gefitinib
- Afatinib
- Dacomitinib
- Osimertinib
- Mobocertinib

JAK
- Fedratinib
- Pancritinib
- Ruxolitinib

BCL-2
- Venetoclax

ALK
- Crizotinib
- Ceritinib
- Brigatinib
- Alectinib
- Lorlatinib

FLT3
- Gilteritinib
- Midostaurin

SMO
- Glasdegib
- Sonidegib
- Vismodegib

BRAF
- Vemurafenib
- Dabrafenib
- Encorafenib

MEK
- Cobimetinib
- Trametinib
- Binimetinib
- Selumetinib

PI3K
- Alpelisib
- Duvelisib
- Idelalisib
- Umbralisib

NTRK
- Larotrectinib
- Encorafenib

MET
- Capmatinib
- Tepotinib

RET
- Selpercaptinib
- Pralsetinib
- Vandetanib

HDAC
- Panobinostat
- Vorinostat

HER2
- Lapatinib
- Neratinib
- Tucatinib

BCR/ABL
- Imatinib
- Dasatinib
- Nilotinib
- Ponatinib
- Asciminib

FGFR
- Erdafitinib
- Infigratinib
- Pemigatinib

VEGF
- Sunitinib
- Sorafenib
- Lenvatinib
- Cabozantinib
- Lenvatinib
- Pazopanib
- Axitinib
- Regorafenib
- Tivozanib

EZH2
- Tazemetostat

HIF-2α
- Belzutifan

CDK
- Ribociclib
- Palbociclib
- Abemaciclib

BTK
- Acalabrutinib
- Ibrutinib
- Zanubrutinib

IDH
- Enasidenib
- Ivosidenib

Nuclear Export
- Selinexor

PARP
- Niraparib
- Olaparib
- Rucaparib
- Talazoparib

PDGFR
- Avapritinib
- Ripretinib

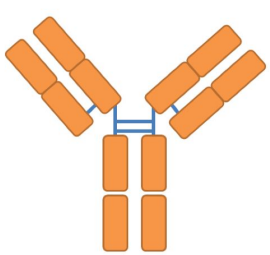
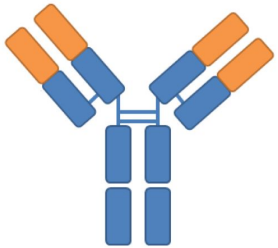
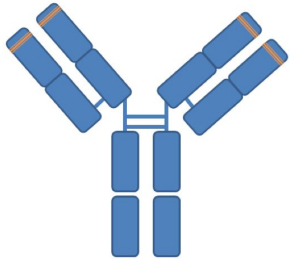
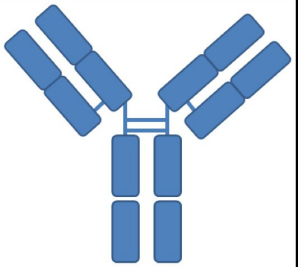
mTOR
- Everolimus
- Sirolimus

CSF1R
- Pexidartinib

Name	Target	Use
Rituximab	CD20	Lymphoma
Trastuzumab	HER-2	Breast, GI
Alemtuzumab	CD52	CLL
Ibritumomab	CD20	Lymphoma
Cetuximab	EGFR	H&N, Lung, colorectal
Panitumumab	EGFR	Colorectal cancer
Ofatumumab	CD20	Lymphoma, CLL
Ipilimumab	CTLA-4	Melanoma
Pertuzumab	HER-2	Breast
Brentuximab-vedotin	CD30	Lymphoma
Bevacizumab	VEGF	Colon, lung, renal, brain
Pembrolizumab	PD-1	Melanoma
Obinutuzumab	CD20	CLL
Trastuzumab-DM1	HER-2	Breast
Ramucirumab	VEGFR2	Gastric, Lung
Nivolumab	PD-1	Melanoma, Lung, NHL
Blinatumomab	BiTE	ALL
Necitumumab	EGFR	Lung

Monoclonal Antibodies

(Agents listed limited to those approved in 1997-2015)

Murine mAb	Chimeric mAb	Humanized mAb	Human mAb
			
0% human	~65% human	~95% human	100% human
Highly immunogenic	Reduced immunogenicity	Further reduced immunogenicity	Further reduced immunogenicity
Short half-life	Extended half-life	Extended half-life	Extended half-life
Induces anti-drug antibodies (HAMA)	Induces anti-drug antibodies (HACA)	Reduced induction of anti-drug antibodies	Reduced induction of anti-drug antibodies
Blinatumomab	**Rituximab**	**Bevacizumab**	**Ipilimumab**

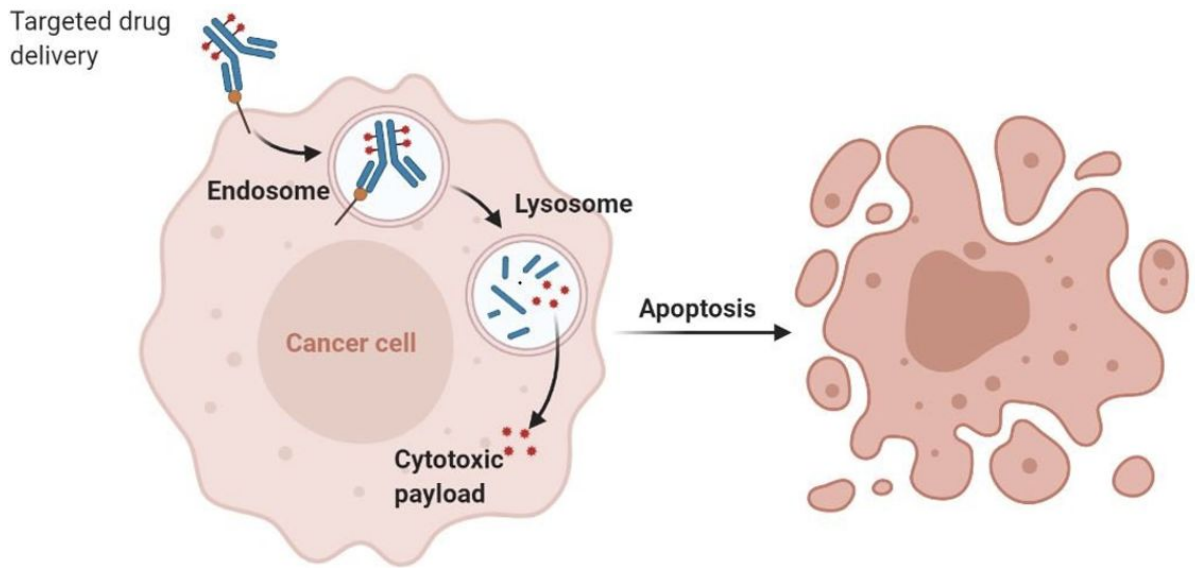
- "-ximab" - chimeric human-mouse (e.g., rituximab)
- "-zumab" - humanized mouse (e.g., bevacizumab)
- "-mumab" - fully human (e.g., ipilimumab)

- "tu" - target is the cancer or tumor (e.g., rituximab)
- "ci" - designates the circulatory system (e.g., bevacizumab)
- "li" - identifies the immune system target (e.g., ipilimumab)

https://www.oncologynurseadvisor.com/home/hot-topics/chemotherapy/understanding-drug-naming-nomenclature/

Antibody-Drug Conjugates (ADCs)

Target	Drug
HER2	T-DM1 & T-Dxd
CD30	Brentuximab Vedotin
Nectin-4	Enfortumab Vedotin
BCMA	Belantamab Mafodotin
TF	Tisotumab Vedotin
CD33	Gemtuzumab Ozogamicin
CD-19	Loncastuximab Tesirine
Trop-2	Sacituzumab Govitecan



A monoclonal antibody (mAbs) is covalently attached to a cytotoxic drug via a chemical linker - combines both the advantages of **highly specific** targeting ability and **highly potent** killing effect, both accurate and efficient.

Signal Transduction and Targeted Therapy 2022; 7:1-25

Molecular Mechanisms of Cardiotoxicity

Anticancer Therapy	Molecular Mechanisms of Cardiotoxicity	
Anthracyclines (e.g., doxorubicin)	Activate Nucleus TopIIβ Generate ROS Activate TOPImt	Fe^{2+} overload Damage transcription Prevent DNA repair
Alkylating Agents (e.g. cyclophosphamide)	Cause endothelial dysfunction Cause thrombosis	Direct DNA damage
Antimetabolites (e.g., 5-FU, capecitabine)	Inhibit angiogenesis Cause endothelial dysfunction	Generate ROS
Antimicrotubules (e.g., paclitaxel)	Inhibit microtubule formation	Activate NCS-1 causing Ca^{2+} overload
HER2/ERB2 Antibodies (e.g., trastuzumab)	Inhibit Pro-survival NRG-1/ErbB Pathway	Generate ROS
TKIs/VEGFR Antibodies (e.g., sunitinib)	Inhibit angiogenesis Cause endothelial dysfunction	Cause energy depletion
Radiation Therapy	Inhibit angiogenesis Cause endothelial dysfunction	Cause energy depletion Generate ROS

TKIs tyrosine kinase inhibitors, VEGFR vascular endothelial growth factor receptor, NRG-1 neuregulin-1, HER2/ErbB2 human epidermal growth factor receptor 2, TopImt mitochrondrial topoisomerase I, TOPIIβ topoisomerase IIβ, ROS reactive oxygen species, NCS-1 neuronal calcium sensor 1

Adapted from NPJ Precision Oncology 2017; 1:31

Chemotherapy Frequency and Route

- **Frequency**
- - Cycles (usually 14-28 days)
- e.g. Carboplatin d1, etoposide d1-3 q2
- - Extended infusion
- e.g. 5FU over 96 hrs
- - Continuous dosing
- e.g. oral targeted agents

- **Route**
- - Intravenous Bolus
- e.g. Vinorelbine 30 mg/m^2 over 6-10 mins qwk
- - Intravenous Infusion
- e.g. Paclitaxel 175 mg/m^2 over 3 hrs q3wks
- e.g. Fluorouracil 2400 mg/m^2 over 46 hrs

Other Routes

- Intrathecal (leukemia/lymphoma w/ CNS)
- Intravesicular (bladder cancer)
- Intraperitoneal (ovarian cancer)
- Surgical implants (Giladel wafer for brain tumor)
- Hepatic artery chemoembolization (liver cancer)
- Intra-tumoral (melanoma)

How to Evaluate Cardiotoxicity of Drugs

- **Get to know your drug (package insert, drug information database)**
  - Mechanism of action
  - Pharmacokinetics/pharmacodynamics
  - Targets (and it's down stream effects)
  - Known cardiac warnings/ADEs
  - Major non-cardiac ADE and black box warning
  - Any recommended cardiac monitoring

- **Understand how and who it was studied in**
  - Population of patients in pivotal trial, inclusion and exclusion criteria, how long were they followed, any cardiac ADE observed
- **Understand how it was approved**
  - Standard versus accelerated approval
- **Continue to monitor ADE notifications**
  - FDA Medwatch (https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program#subscribe)
- **Consider YOUR patient**
  - Age, pertinent comorbidities, underlying cardiac history, previous/concurrent therapy exposure (how many "hits" has their heart taken), drug interaction risk

Example work up: Zanubrutinib (Brukinsa™)

Get to know your drug	*Mechanism of action*	Small-molecule, covalently bound, inhibitor of BTK at cysteine 481
	Target & Downstream effects	BTK inhibitor covalently bound at cysteine 481
	Pertinent PK/PD	• Half life: ~2.4 hours • Hepatic metabolism: Primarily through CYP3A • Excretion: 87% (38% unchanged drug) in feces and 8% (<1% unchanged drug) in urine • Interactions with Strong CYP3A4 inducers/inhibitors
	Known cardiac warnings/ADE	• Atrial fibrillation and atrial flutter have occurred in a small percentage of patients (2%) • Grade ≥3 were reported in 0.6% of patients
	Non-cardiac ADE (>20%)	• Hematologic toxicity (ANC, hemoglobin, and platelets), infection risk (upper respiratory tract infection, pneumonia), rash, diarrhea, and cough
	Black Box	• None
	Cardiac monitoring	• Signs and symptoms of atrial fibrillation and atrial flutter

Brukinsa (zanubrutinib) [prescribing information]: San Mateo, CA: ©BeiGene, Ltd;

Pivotal Trial BGB-3111-AU-003 and BGB-3111-206	*Population*	69%/78% male, average age 70 (range 42-86)/60.5 (range: 34-75)
	Inclusion/ Exclusion	• Previously treated MCL patients with at least one prior line of therapy • Excluded: QTcF >450 msecs or other significant ECG abnormalities
	Length of follow up	• 35.9 weeks (~9 months)
	Cardiac ADE	• None reported • Contingent on FDA approval: "The FDA also noted in its approval that patients treated with zanubrutinib should be monitored for hemorrhage, signs and symptoms of infection, cytopenias, and cardiac arrhythmias."
FDA related	*Approval type*	Accelerated based on overall response rate
	Medwatch	None, as of January 09, 2021
Apply	*Consider your patient*	Age, pertinent comorbidities, underlying cardiac history, previous/concurrent therapy exposure (how many "hits" has their heart taken), drug interaction risk • Most are > 65 male with a very high potential to have some underlying cardiac history (HTN, high cholesterol), extra concern if any toxicity with previous platinum, immunotherapy or antrhacycline
Analyze	*Verdict*	Consider baseline monitoring for baseline EKG before starting zanubrutinib to assess baseline status Consider cardio-oncology referral based on baseline work up or any symptoms

BGB-3111-206 (NCT03206970). clinicaltrials.gov and BGB-3111-AU-003 (NCT02343120).

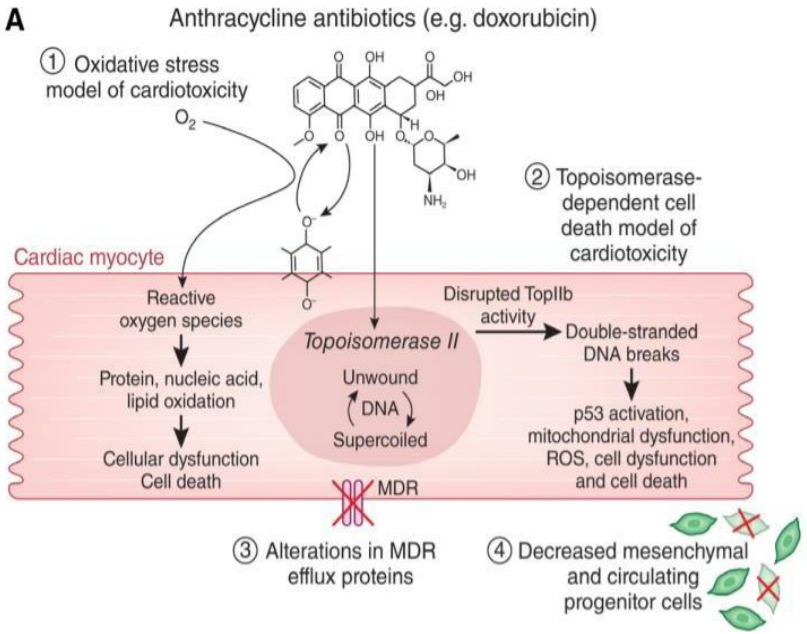
General Pharmacology: Anthracyclines

Drugs in Class: Daunorubicin, Doxorubicin (Adriamycin), Liposomal Doxorubicin (Doxil, Lipodox), Epirubicin (Ellence), Idarubicin (Idamycin PFS)

Pharmacologic Category: Topoisomerase II inhibitor

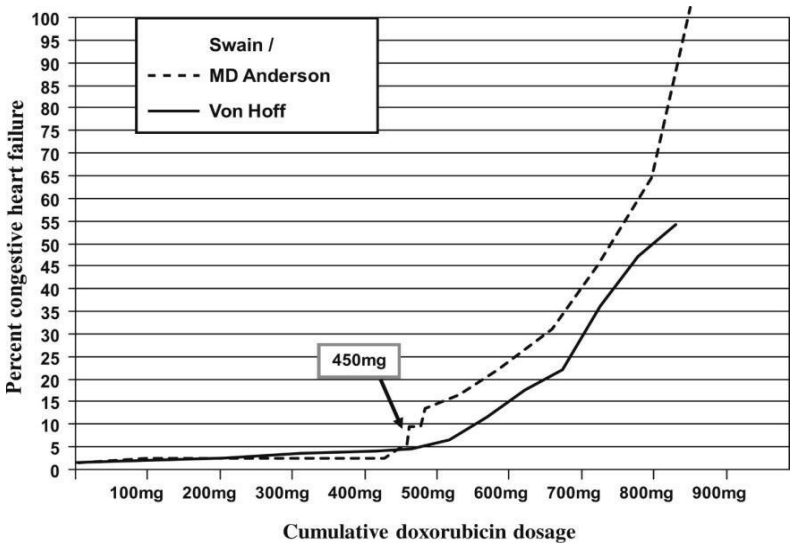
Mechanism of Action for Therapeutic Benefit:
Multi-faceted through:

- **DNA intercalation:** Topoisomerase II inhibition preventing DNA from being re-ligated and anthracyclines insert themselves between neighboring base pairs of DNA **inhibiting DNA/RNA synthesis**
- **Reactive Oxygen Species (ROS):** Redox reactions cause excess ROS which cause **oxidative stress**, DNA damage and lipid peroxidation triggering **cell apoptosis**
- **DNA adduct formulation:** Adduct formulation blocks specific transcription factors causing **cell death**



Circ Res 2016; 118:1008-20

Cardiotoxicity: Anthracyclines



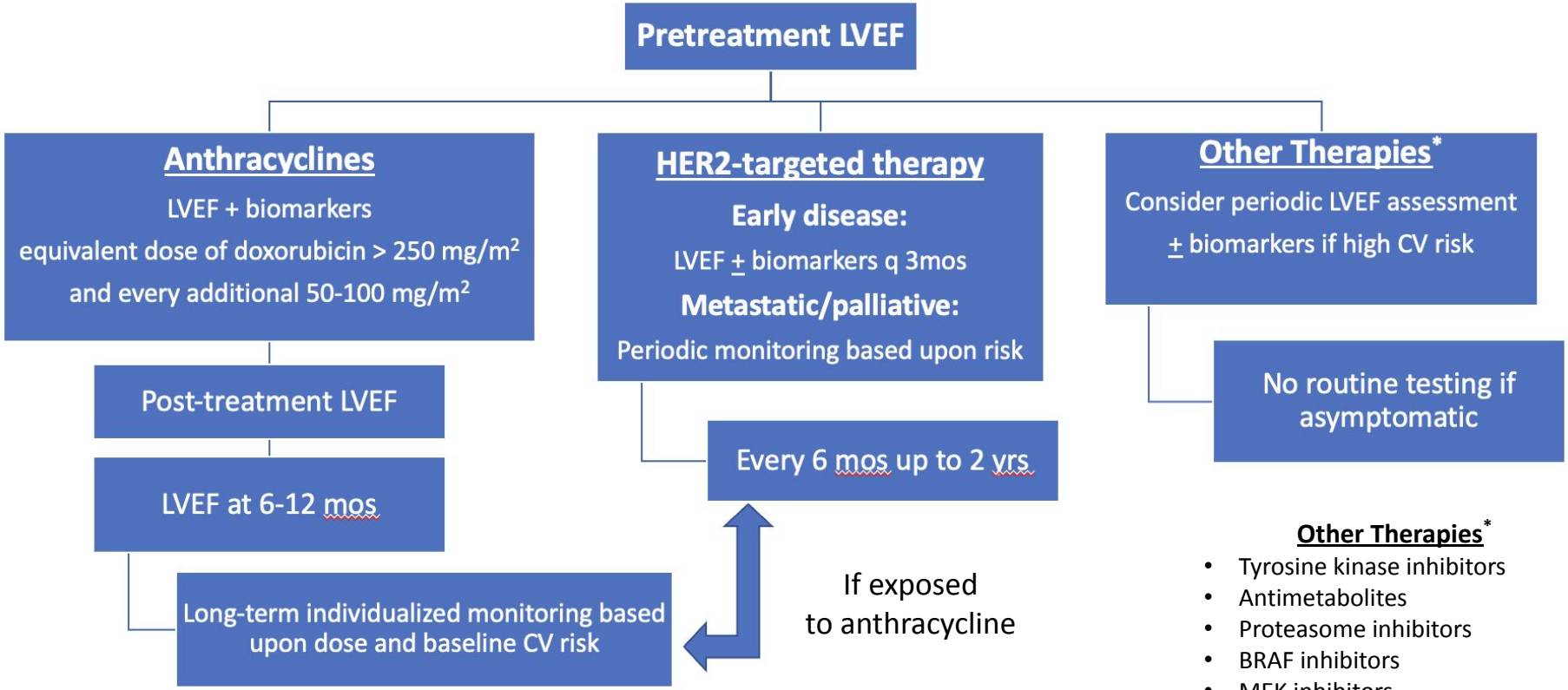
Risk Factors for Anthracycline Cardiotoxicity
Age (extremes of age, < 4 and >/= 65)
Female gender
Underlying cardiovascular disease
History of prior irradiation involving the heart/mediastinum
Previous anthracycline exposure or cardiotoxic treatment
Cumulative Dose
Type of anthracycline and administration type
Genetics (ABCB1, ABCC1, CAT, CBR3, NCF4, NQ01, NR1/2, RARG, SLC22A16, TOP2A, HAS3, CELF4, TTN)

Recommended maximum amount of doxorubicin is **between 450 – 550 mg/m^2**

Anthracycline	Doxorubicin Equivalency	Recommended Max Cumulative Dose
Doxorubicin, Daunorubicin	1 mg	550 mg/m^2
Idarubicin	5 mg	150 mg/m^2
Epirubicin	0.5 – 0.67 mg	900 mg/m^2

Armenian S ASCO 2017, Curgliano Ann Oncol 2012, Mele D Heart Fail Rev 2016, Seidman Circulation 2019, Armenian S ASCO 2017, Curgliano Ann Oncol. 2012, Feijen EAM J Clin Oncol 2015, Swain Cancer 2003, Von Hoff Ann Int Med 1979.

Monitoring Strategies for Cardiotoxicity



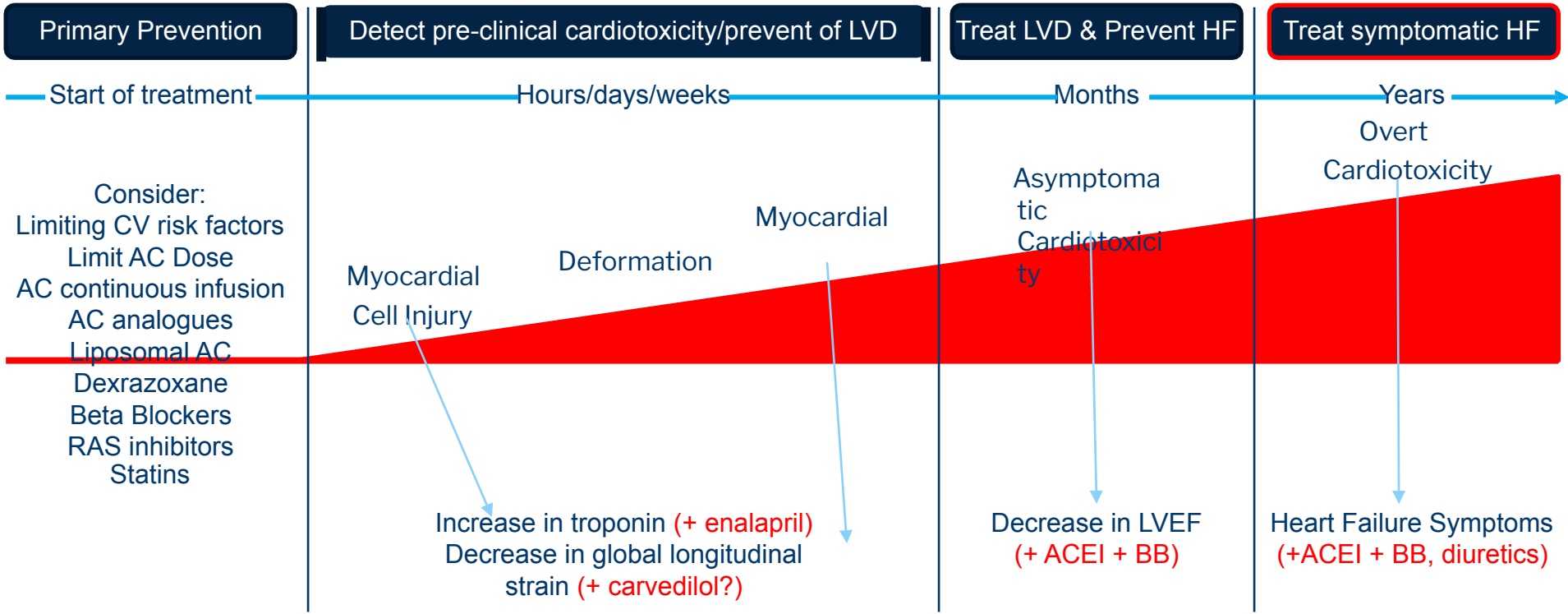
Other Therapies*

- Tyrosine kinase inhibitors
- Antimetabolites
- Proteasome inhibitors
- BRAF inhibitors
- MEK inhibitors
- Immune checkpoint inhibitors

Adapted from JCO Oncol Pract 2021; 17:228-236

Cardiotoxicity: Anthracyclines

Strategies for Cardiotoxicity Management



What about ARNIs and SGLT2Is???

Front Cardiovasc Med 2020; 7: 26

Summary: Anthracyclines

Pharmacology

- Topoisomerase II inhibitor that introduces therapeutic effect by causing apoptosis due to DNA intercalation, enzyme interaction, reactive oxygen species (ROS) generation and DNA adduct formulation
- Used in many malignancies at varying dosages

Cardiotoxicity

- Risk is related to **cumulative dose** exposure
- Considered **not reversible** initially, emerging literature suggests **reversible**
- Manifests as LV dysfunction and heart failure, often **symptomatic**
- Monitor risk via echocardiogram
- Role for dexrazoxane in select populations, GDMT for LVEF preservation

General Pharmacology: HER-2 Targeted Therapy

Drugs in Class: Ado-Trastzumab Emtansine (Kadcyla)*, Fam-Trastuzumab Deruxtecan (Enhertu)*, Lapatinib (Tykerb)**, Margetuximab (Margenza), Neratinib (Nerlynx)**, Pertuzumab (Perjeta), Trastuzumab (Herceptin), Tucatinib (Tuskya)**

Pharmacologic Category:

All listed are anti-HER-2

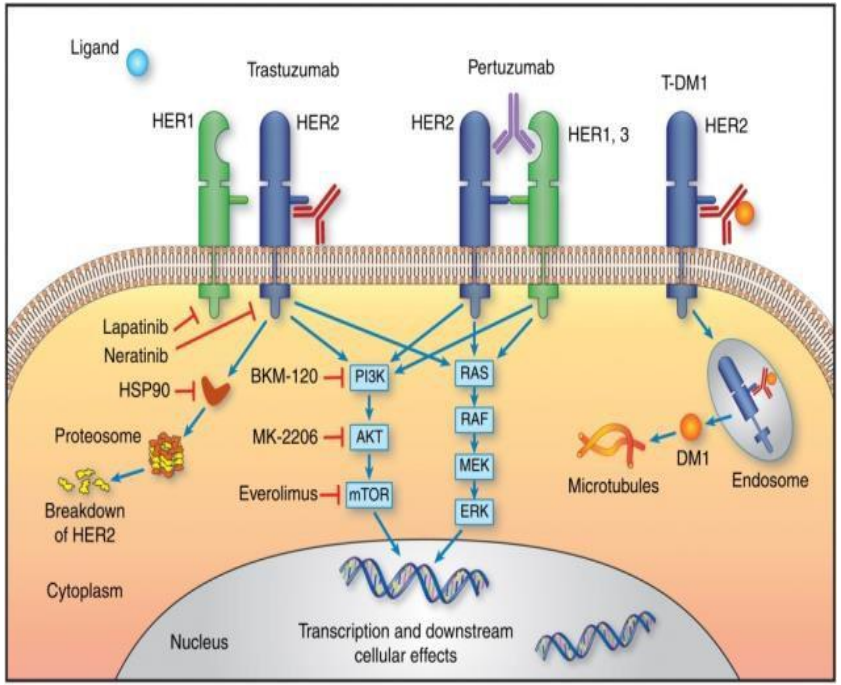
*Antibody-drug conjugate

**EGFR Tyrosine Kinase Inhibitor

Mechanism of Action for Therapeutic Benefit:

HER2-targeted therapies are humanized monoclonal antibody that **blocks the activation of specific epidermal growth factors with the HER2/neu receptor**

- Disrupts the phosphorylation of intracellular tyrosine kinases that are critical regulators of cell growth and survival



Singh. Br J Cancer 2014

Cardiotoxicity: HER-2 Targeted Therapy

- Mechanism of toxicity incompletely understood
- Inhibition of ErbB2 and neuregulin signaling can disrupt cardio-protective signaling, diminishing the ability of the heart to recover
- **Not cumulative dose related**
- Usually **reversible**
- Further impacted by patient **specific risk factors**

Risk Factors for HER-2 Cardiotoxicity
Past use of ACs (especially at > 250 mg/m^2 of doxorubicin)
Concomitant use of anthracyclines
Short interval between anthracycline & trastuzumab
Pre-existing Cardiac Conditions (Hypertension, Dyslipidemia, LVEF ≤ 50%, HF, CAD, Atrial fibrillation/flutter)
Diabetes
Obesity (BMI ≥ 30 kg/m2)
Renal Failure
Age ≥ 60
Black Race

Florido. J Am Heart Assoc. 2017. Litvak. Cancer 2018. Nemeth. Br J Pharmcol. 2017.

Cardiotoxicity: HER-2 Targeted Therapy

Do all HER-2 therapies carry the same cardiac risk? **NO**

Initial trastuzumab use associated with varying CTRCD based upon therapy combinations

3 – 15 % for monotherapy and up to 27% with concurrent anthracycline

Ado-trastuzumab emtansine

- Allows intracellular drug delivery specifically to HER-2 overexpressing cells, **carrying lower rates of cardiac risk**
- Asymptomatic LVEF decrease: 1.2 - 1.7%
- Grade 3 – 4 HF: 0 – 0.6%

Fam-Trastuzumab Deruxtecan

- Allows intracellular drug delivery specifically to HER-2 overexpressing cells, **carrying lower rates of cardiac risk**
- Asymptomatic LVEF decrease: 0.9%
- Grade 3 – 4 HF: 0%

Pertuzumab (+ trastuzumab)

- Binds to a different HER2 epitope, allowing for clinical synergism without increased toxicity
- Asymptomatic LVEF decrease: 1 – 7.4%
- Grade 3 – 4 HF: < 3.3%

Margetuximab (+ cytotoxic chemotherapy)

- Allows intracellular drug delivery specifically to HER-2 overexpressing cells, **carrying lower rates of cardiac risk**
- Asymptomatic LVEF decrease: 1.9%
- Grade 3 – 4 HF: < 2%

Baselga. NEJM. 2012.
Gianni. Lancet. 2012
Seidman. Clin. Oncol. 2002
Von Minckwitz. NEJM. 2018.

Chan Lancet Onc 2016
Modi. NEJM 2019.
Verma NEJM 2012

Choi Breast Cancer Res Treat 2017
Schneeweiss. Ann Onc. 2013.
von Minckwitz. NEJM. 2017

Cardiotoxicity: HER-2 Targeted Therapy

Do all HER-2 therapies carry the same cardiac risk? **NO**

Tucatinib	Lapatanib (+/- capecitabine)	Neratinib
•Reversible dual tyrosine kinase inhibitor against HER 2 and HER 3	•Reversible dual tyrosine kinase inhibitor against HER 1 and HER 2	•Irreversible dual tyrosine kinase inhibitor against HER 1 and HER 2
•Asymptomatic LVEF decrease: NR	•Asymptomatic LVEF decrease: 0.7 - 2%	•Asymptomatic LVEF decrease:< 1%
•Grade 3 – 4 HF: NR	•Grade 3 – 4 HF: 0%	•Grade 3 – 4 HF: 0%

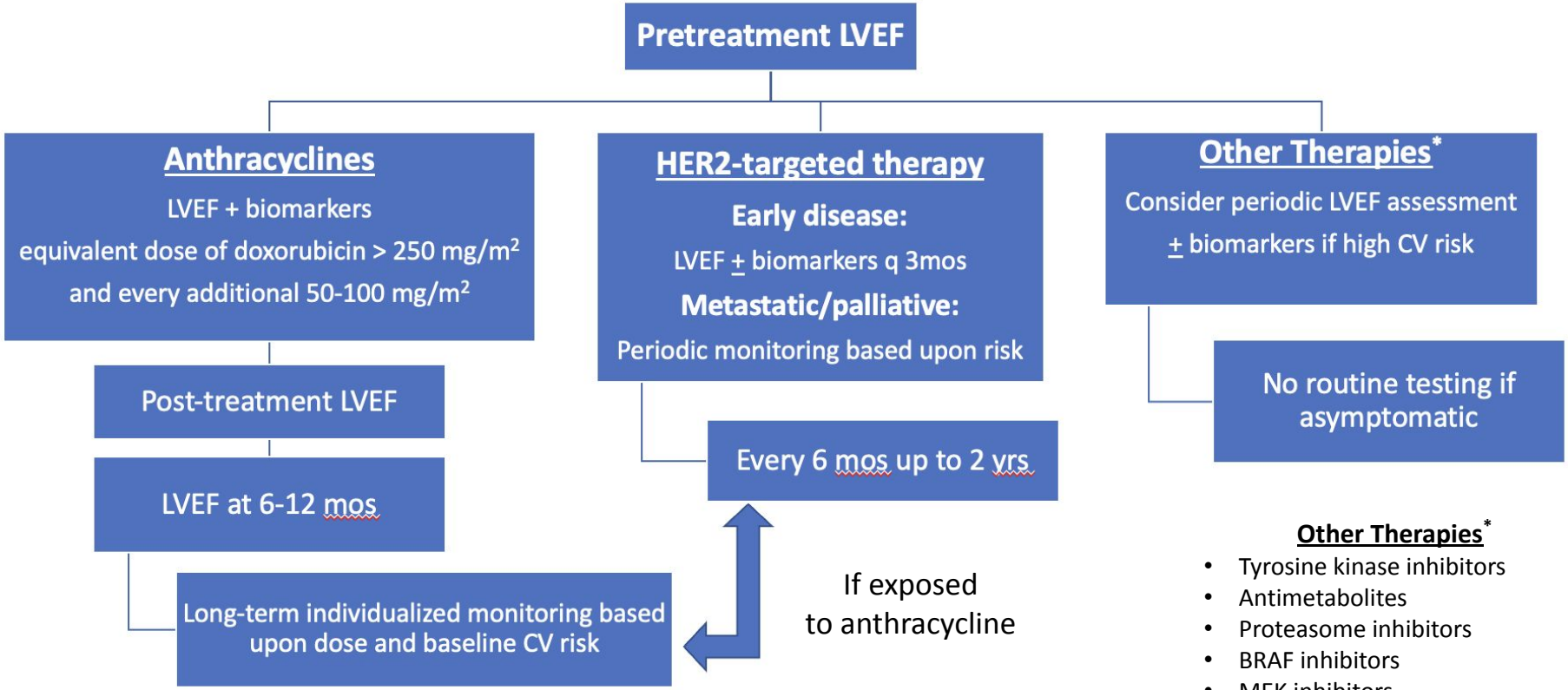
NR = not reported

Baselga. NEJM. 2012.
Gianni. Lancet. 2012
Seidman. Clin. Oncol. 2002
Von Minckwitz. NEJM. 2018.

Chan Lancet Onc 2016
Modi. NEJM 2019.
Verma NEJM 2012

Choi Breast Cancer Res Treat 2017
Schneeweiss. Ann Onc. 2013.
von Minckwitz. NEJM. 2017

Monitoring Strategies for Cardiotoxicity



Other Therapies*

- Tyrosine kinase inhibitors
- Antimetabolites
- Proteasome inhibitors
- BRAF inhibitors
- MEK inhibitors
- Immune checkpoint inhibitors

Adapted from JCO Oncol Pract 2021; 17:228-236

Cardiotoxicity: HER-2 Targeted Therapy

Strategies for Cardiotoxicity Management Per Package Insert Labeling

	Ado-Trastuzumab Emtansine	Fam-Trastuzumab Deruxtecan	Margetuximab	Lapatinib	Pertuzumab	Trastuzumab
HOLD	Hold for 3 weeks if LVEF is < 40% or 40 – 45% with a fall of >/= 10% from baseline	Hold for 3 weeks if LVEF is 40 – 45% with a fall of 10 – 20% from baseline	Hold for 4 weeks if >/= 16% decrease in LVEF from pre-treatment values or below instituinal normal limits + >/= 10 decrease from pre-treatment	Hold for at least 2 weeks in patients who are symptomatic from the LVEF drop	Hold for 3 weeks if LVEF 40% or 40 – 45% with a fall of > 10% from baseline	Hold for 4 weeks if LVEF falls ≥ 16% from baseline or if LVEF below institutional limits of normal and ≥ 10% fall from baseline
RESUME	LVEF > 45% and <10% from baseline	LVEF > 45% and < 10% from baseline	Resume if LVEF returns WNL within 8 weeks and decrease is </=15% from baseline	Resume at reduced dose if LVEF recovers after 2 weeks and patient is asymptomatic	LVEF > 45% or 40 – 45% and <10% from baseline	LVEF WNL ≤ 15% from baseline within 4 – 8 weeks
D/C	Symptomatic HF, LVEF remains < 40%, LVEF remains greater than 10% from baseline after holding	Symptomatic HF, LVEF remains < 40%, LVEF remains greater than 10% - 20% from baseline after holding	Permanently discontinue if decline persists > 8 weeks or dosing is interrupted on greater than 3 times for LVEF decline	Symptomatic HF	If not better with 3 week hold	Persistent (> 8 weeks) LVEF decline or for suspension of dosing on more than 3 occasions for cardiomyopathy

Cardiotoxicity: HER-2 Targeted Therapy

Evidence for continuing HER-2 therapy during mild cardiotoxicity

Reference	Type of Study	Population	Intervention	Results
SCHOLAR ONE ***Leong DP. JACC: Cardio Onc. 2019***	Phase I, prospective, single- arm	Patients on trastuzumab with LVEF 40% to lower limit of normal or ≥ 15% decline from baseline (n=20)	Patients were treated ACEIs and/or BBs in a cardio-oncology clinic, followed clinically and with serial echocardiograms for 1 year	Primary outcome was cardiac dose-limiting toxicity, defined as cardiovascular death, LVEF <35% • 18 patients (90%) received all planned trastuzumab doses • 2 patients (10%) developed heart failure (LVEF < 40%) • No deaths **Feasible to continue trastuzumab despite mild cardiotoxicity if given appropriate supportive therapies**
SAFE-HEaRt ***Lynce F. JCO. 2018***	Phase I, prospective, single arm	Patients with stage I-IV HER2+ breast cancer, candidates for non-lapatinib therapy, LVEF ≥40% & < 50% without HF symptoms (n=31) 17 with prior AC 15 on trastuzumab alone, 14 on trastuzumab and pertuzumab, 2 on ado- trastuzumab emtansine	All patients had cardiology visits and ECHOs at baseline, during treatment and 6 mos after treatment, and received ACEIs and BBs unless contraindicated	Primary endpoint was completion of planned oncologic HER2 therapy without development of a cardiac event (CE), • 22 patients completed HER2 therapy without development of a CE with 5 continuing on study • 3 patients met CE criteria: 2 developed symptomatic HF (at 24 and 36 wks) and 1 had protocol defined LVEF decline to 35% at 12 wks, all were taken off study. • Demographics, previous anthracyclines and baseline LVEF did not predict development of CEs. • Elevation of troponin preceded 2 of 3 CEs which was significant (p = 0.003) **Patients with breast cancer and mildly reduced LVEF can safely receive HER2 therapies in the setting of regular cardiac monitoring and treatment with BB and ACEi.**

Summary: HER-2 Targeted Therapy

Pharmacology

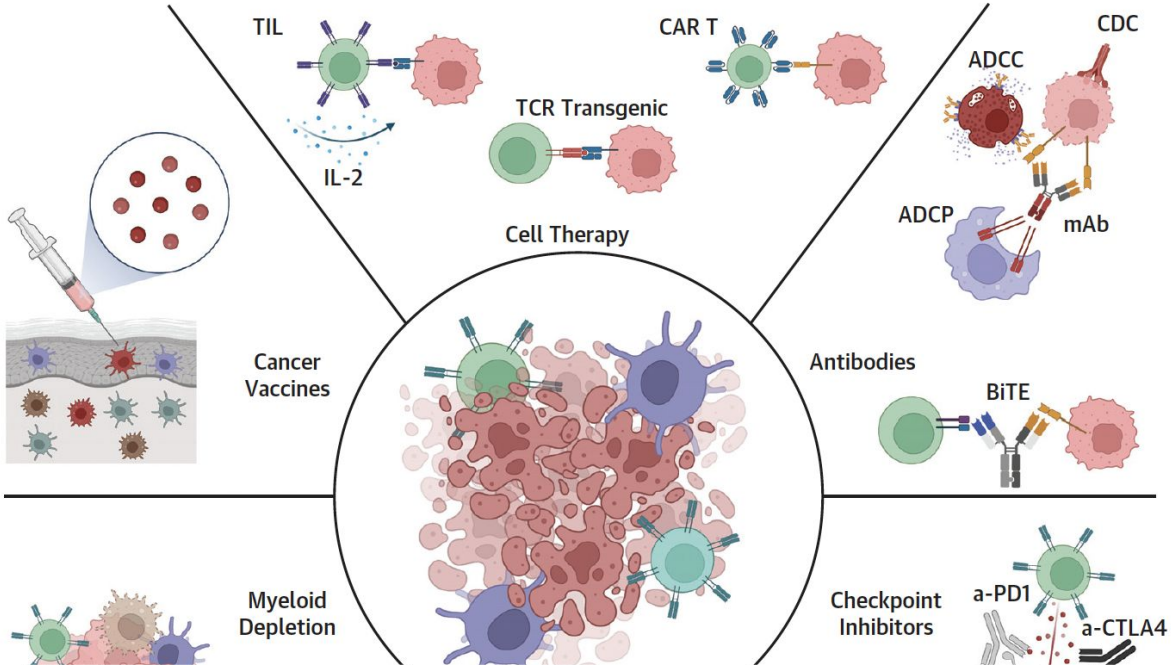
- Humanized monoclonal antibody that blocks the activation of HER2/neu receptor to cause downstream signaling effects to impair cell growth and survival
- Used in HER2 positive malignancies, mostly breast cancers

Cardiotoxicity

- Risk is **NOT related to cumulative dose** exposure
- Is **reversible** (in most cases), patients can be re-challenged
- Manifests as **asymptomatic** LVEF (most often)
- Monitor risk via echocardiogram
- Less robust data for RAS inhibitors and beta blockers for LVEF preservation

Landscape of Cancer Immunotherapy

JACC: CardioOncology 2022; 4:563-78



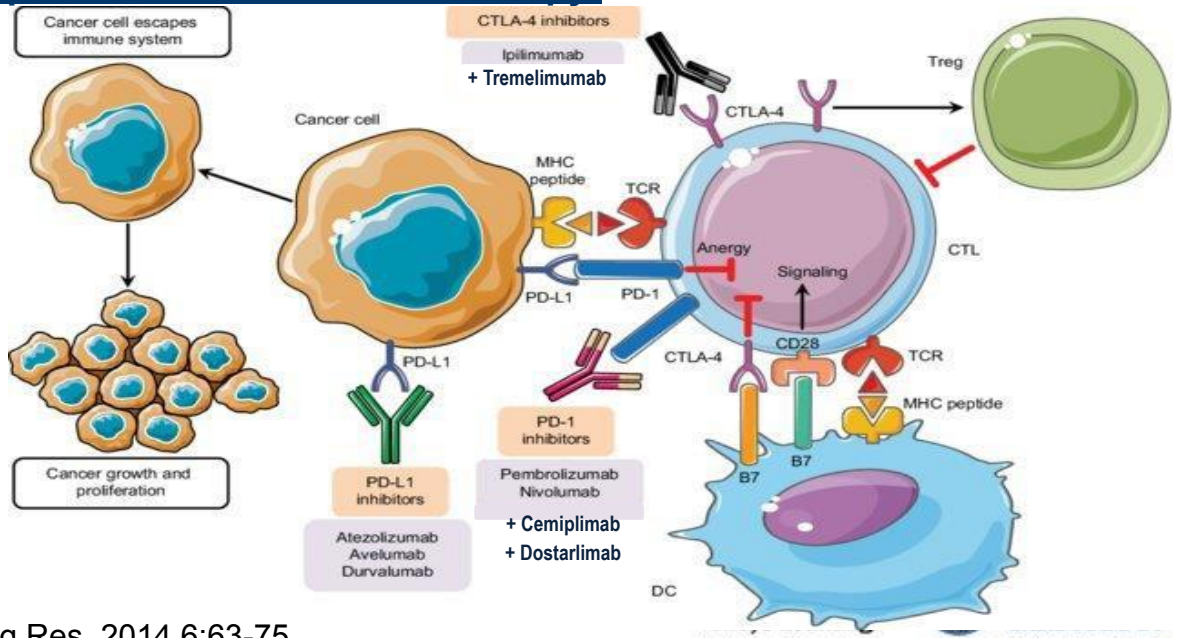
Agents	Disease	Toxicity (Frequency)
PD-1 inhibitor ± CTLA-4 inhibitor (various products)	Various	Myocarditis (0.06%-0.15% for PD-1 vs 0.26%-0.27% for combination)
CAR-T (various products)	NHL (88%), myeloma (8%)	CRS (59%), elevated troponin (54%), decreased LVEF (28%), decompensated HF (3%-10%), arrhythmia (3%-4%), CV death (4%)
Tebentafusp Blinatumomab	Uveal melanoma B-ALL	CRS (89%), hypotension (38%), hypertension (6%) CRS (14.2%), hypotension (12%), cardiac disorders (2.2% vs 2.8% with chemotherapy)

General Pharmacology: Immune Checkpoint Inhibitors

- **Drugs in Class:** Atezolizumab (Tecentriq), Avelumab (Bavencio), Cemiplimab (Libtayo), Durvalumab (Imfinzi), Ipilimumab (Yervoy), Nivolvumab (Opdivo), Pembrolizumab (Keytruda), Nivolumab and Relatlimab (Opdulag), Tremelimumab (Imjudo), Dostarlimab (Jemperli)
- **Pharmacologic Category:** Immune Checkpoint Inhibitors (ICI)
- **Mechanism of Action for Therapeutic Benefit of Immunotherapy:**

Cancer cells can evade the immune system through various mechanisms including T-cell inactivation by checkpoint dysregulation.

ICIs **remove the breaks placed on T-cell mediated responses** and reactivates the immune system's defense against foreign cells.



Breast Cancer. 2019; 11: 321–328., Cancer Manag Res. 2014 6:63-75

General Pharmacology: Immunotherapy

Select Examples of Malignancies Used In and Dosing Schema

Atezolizumab

UCC, NSCLC, TNBC, SCLC

Dose: 840 mg IV q2 weeks or 1200 mg IV q3 weeks or 1680 mg IV q4 weeks, given with chemotherapy in all but UCC

Avelumab

Merkel Cell, UCC, RCC

Dose: 800 mg IV every 2 weeks, add axitinib 5 mg twice daily in RCC

Cemiplimab

Metastatic/surgery ineligible locally advanced cutaneous squamous cell carcinoma

Dose: 350 mg IV every 3 weeks

Durvalumab

UCC, NSCLC Stage III

Dose: 10 mg/kg IV every 2 weeks

Ipilimumab

Metastatic/adjuvant melanoma, RCC, MSI-H/dMMR mCRC

Dose: 3 mg/kg every 3 weeks x 4 doses (metastatic melanoma), 10 mg/kg IV every 3 weeks x 4 doses then every 12 weeks x 3 years (adjuvant melanoma) or in combination with Nivolumab at 1 mg/kg every 3 weeks x4 doses

Nivolumab

Melanoma, NSCLC, RCC, cHL, HNSCC, UCC, MSI-H/dMMR mCRC, HCC

Dose: 240 mg IV every 2 weeks or 480 mg IV every 4 weeks can also be given with Ipilimumab in 1 mg/kg or 3 mg/kg doses/intervals pending indication

Pembrolizumab

Melanoma, NSCLC, SCLC, HNSCC,cHL, PMBCL, UCC, MSI-H cancers, Gastric Cancer, Esophageal Cancer, Cervical Cancer, HCC, Merkel Cell, RCC, Endometrial Cancer

Dose: 200 mg IV every 3 weeks, in some malignancies is combined with chemotherapy/targeted therapy

UCC Urothelial Cell Carcinoma, NSCLC Non-Small Cell Lung Cancer, TNBC Triple Negative Breast Cancer, SCLC Small Cell Lung Cancer, RCC Renal Cell Carcinoma, MSI-H Microsatellite Instability-High, dMMR Mismatch Repair Deficient, mCRC Metastatic Colorectal Cancer, cHL Classical Hodgkin's Lymphoma, HNSCC Head and neck squamous cell cancer, HCC Hepatocellular Carcinoma, PMBCL Primary Mediastinal Large B-Cell Lymphoma

General Pharmacology: Immunotherapy

Malignancies Used In and Dosing Schema

Dostarlimab

dMMR (endometrial cancer or other solid tumors[a])

Dose:
Dose 1 - 4: 500 mg q3wks,
Dose 5 and beyond: 1 gm q6wks

Tremelimumab

uHCC

Dose:
> 30 kg: 300 mg IV[b]
< 30 kg: 4 mg/kg IV[b]

Nivolumab and Relatlimab

Unresectable or metastatic melanoma
(pediatric or adult)

Dose: 480 mg nivolumab and 160 mg relatlimab IV q4wks[c]

[a]**Endometrial cance**r, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation or **Solid tumors**, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options
[b]As single dose with first dose of durvalumab, followed by durvalumab as a single agent every 4 weeks
[c]Adult patients and pediatric patients 12 years of age or older who weigh at least 40 kg

dMMR mismatch repair deficient, unresectable hepatocellular carcinoma (uHCC)

Cardiotoxicity: Immune Checkpoint Inhibitors

Not observed in high amounts (0.09% - 0.27%) in initial ICI studies, true incidence **likely underestimated**

Post-marketing surge of cardiac complications suggesting incidence **as high as 1.14% with a 27-46% fatality rate**

ICI-induced cardiotoxicity can develop **as soon as after 1 dose (average of 3 cycles)**

Risk Factors for ICI Cardiotoxicity
Combination ICI
Underlying autoimmune disease
Pre-existing cardiovascular disease
Diabetes
Concurrent immune related AE's like myositis, myasthenia gravis, and hepatitis

At this time, there does not appear to be any known association with tumor response, tumor type, or additional specific clinical features that predispose these patients to these serious cardiac adverse event.

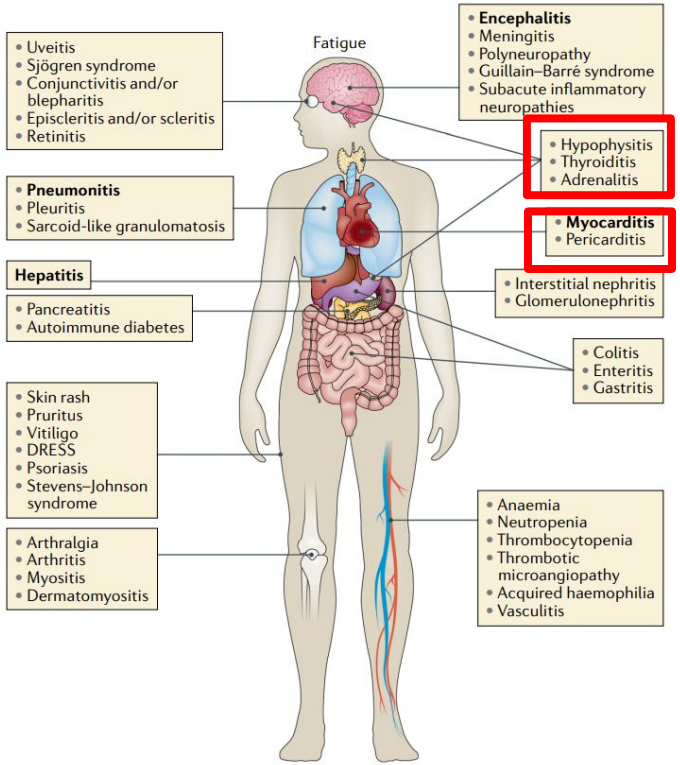
Asnani A. Curr Oncol Rep. 2018.
Varricchi G. ESMO Open. 2017
Zhou YW. Front Pharmacol. 2019.
Michel L. Int J Cardiol Heart Vasc. 2019.
Wang DY. Curr Cardiol Rep. 2017.
Lyon AR. Lancet Oncol. 2018

Additional Checkpoint Inhibitor Toxicities

Pre-clinical data suggest that both CTLA-4 and PD-1 play critical roles regulating immune homeostasis in the myocardium.

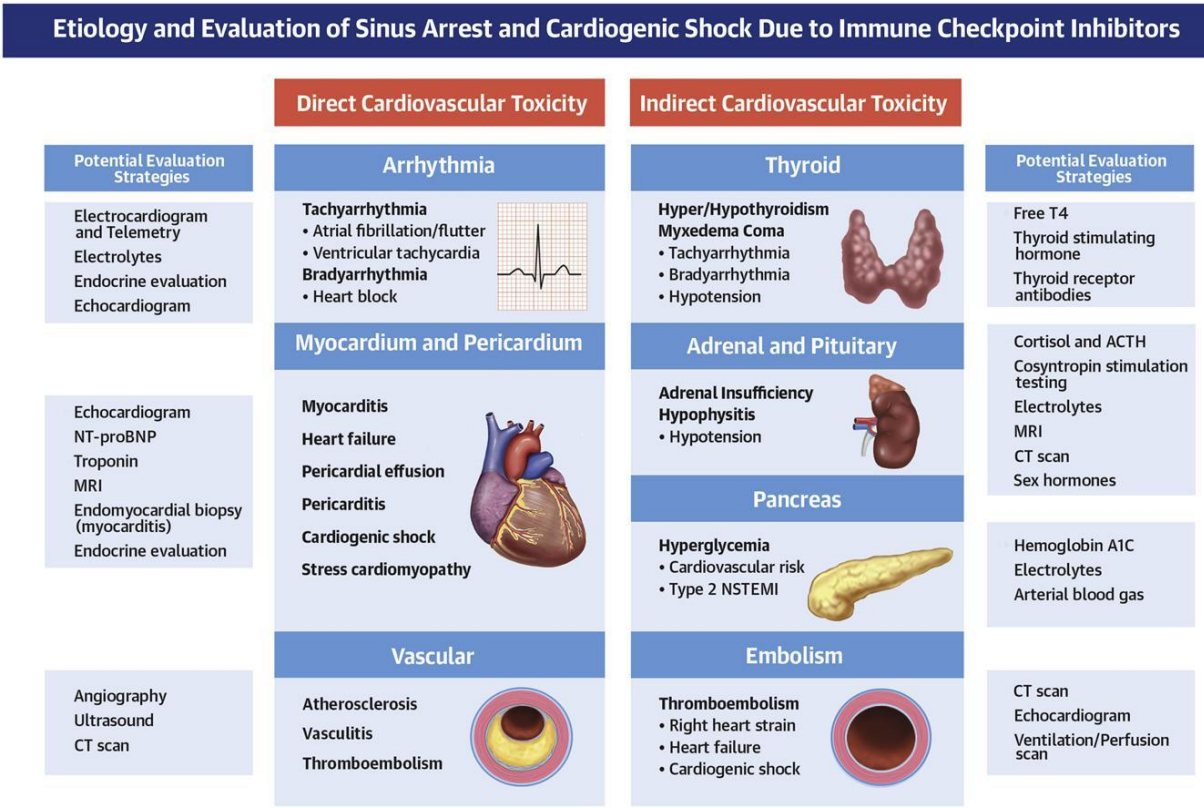
Myocarditis / Pericarditis / Myopericarditis
LV dysfunction without myocarditis
Asymptomatic noninflammatory LV dysfunction
Heart block
Takotsubo-like syndrome
Myocardial infarction
Coronary vasospasm
Arrhythmias

Also, indirect cardiovascular effects via endocrinopathies.



Nat Rev Clin Oncol 2019;16:563-580

ICIs: Sinus Arrest & Cardiogenic Shock



No primary prophylaxis therapies

Recommend **baseline monitoring prior to treatment**

- Risk factor assessment
- Cardiac troponin, BNP/NT-proBNP
- ECG. ECHO

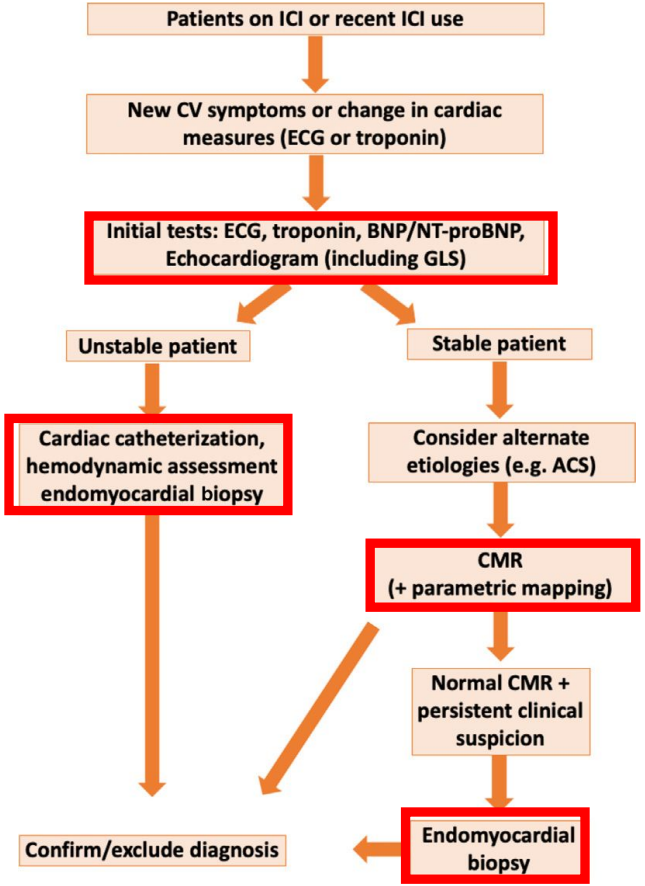
No Guideline Consensus!

Symptoms should lead to **prompt** cardiac evaluation

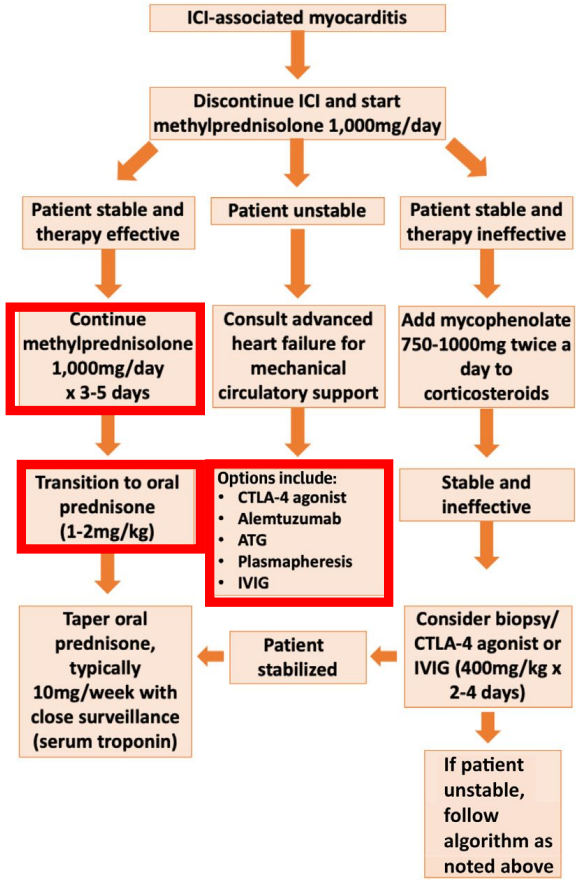
- chest pain, dyspnea, orthopnea, myalgia, lightheadedness, syncope, palpitation, fatigue peripheral edema

Kris Kumar. J Am Coll Cardiol CardioOnc. 2020

Proposed Diagnostics



Proposed Treatments



Prednisone Considerations

- Consider supportive care if long duration of steroids
  - GI protection with a PPI
  - Antimicrobial prophylaxis

Other Dosing

- IVIG 400 mg/kg x2-4 days
- ATG 30 mg/kg every other day x6 doses or 15 mg/kg twice daily x10 doses
- Infliximab 5 mg/kg can repeat at 2 weeks as needed (caution if heart failure)

JACC: CardioOnc 2021; 3:35–47, J Am Heart Assoc 2020; 9:e013757.
DOI: 10.1161/JAHA.119.013757, Oncologist 2018; 23:879-886

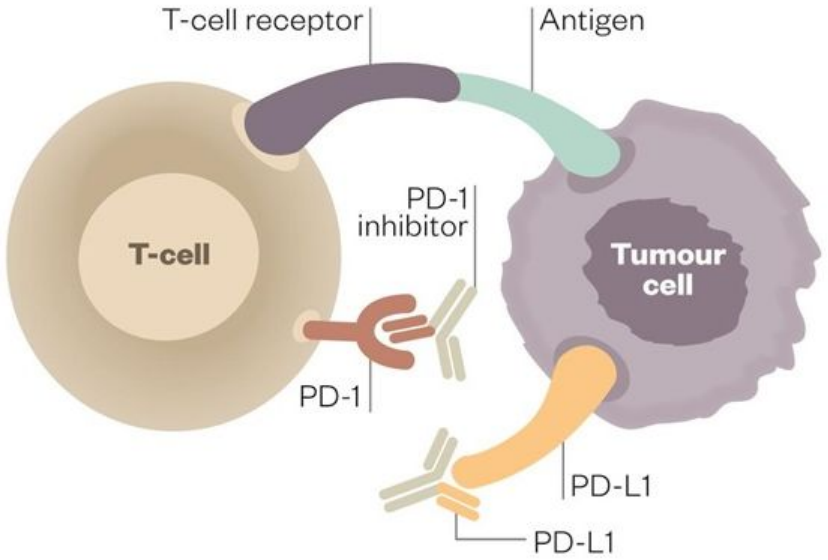
Challenges with Combination Therapy

Potential challenges:
- Indistinguishable clinical presentation
- Additive or synergistic effects on frequency
- Distinct management strategies

Differential Diagnosis:
- Timing of symptoms onset
- Relative incidence of contributory agent
- Timing of symptom improvement

Dual-Checkpoint Blockade
Checkmate 067
Ipilimumab + Nivolumab

Chemoimmunotherapy
Keynote 189
Carboplatin + Pemetrexed + Pembrolizumab



Immunotherapy + VEGFI
Keynote 426
Pembrolizumab + Axitinib

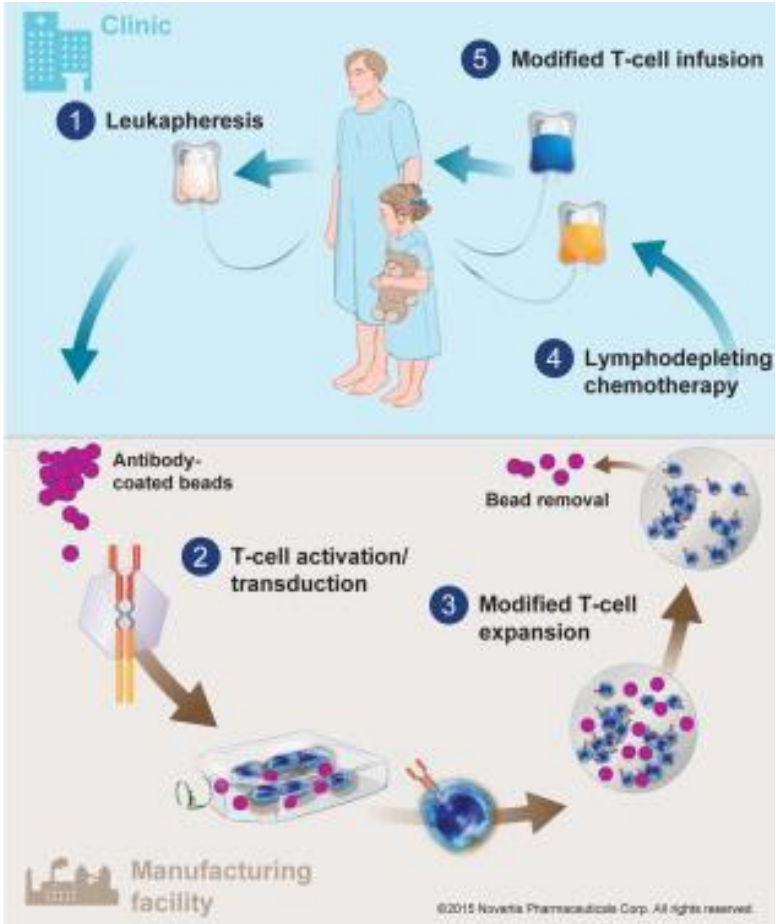
PD-L1 + BRAF/MEKI
IMspire150
Cobimetinib + Vemurafenib + Atezolizumab

Chimeric Antigen Receptor T (CAR-T) Cells

Genetically modified **autologous** T-cells directed towards target antigen on tumor cells; FDA approved in 2017

One–time infusion, 2-14 days after lymphodepleting chemotherapy

BRAND NAME	GENERIC NAME	TARGETED DISEASE
Kymriah™	tisagenlecleucel	Follicular Lymphoma, Diffuse Large B-cell Lymphoma, or Lymphoblastic Leukemia
Yescarta™	axicabtagene ciloleucel	Follicular Lymphoma or Diffuse Large B-cell Lymphoma
Tecartus™	brexucabtagene autoleucel	Mantle Cell Lymphoma or Acute Lymphoblastic Leukemia
Breyanzi®	lisocabtagene maraleucel	Large B-cell Lymphoma
Abecma®	idecabtagene vicleucel	Relapsed or Refractory Multiple Myeloma
Carvykti™	ciltacabtagene autoleucel	Relapsed or Refractory Multiple Myeloma



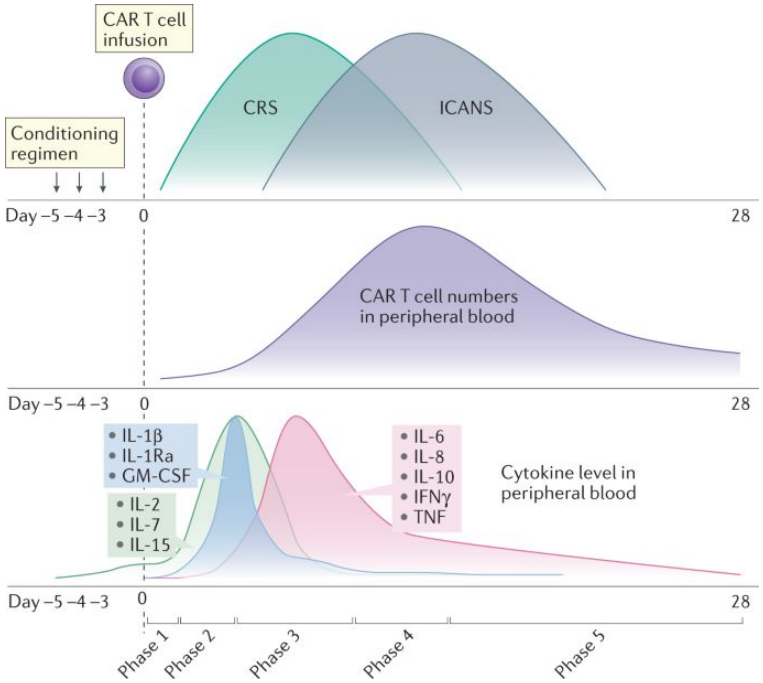
JACC: CardioOncology 2022; 4:563-78, J Immunotherapy Cancer 2018; 137:1-12, Mol Ther Method Clin Dev 2019; 16:136-44

CAR-T Toxicity

- Conditioning Regimen
  - Myelosuppression
  - Close monitoring & antimicrobial prophylaxis

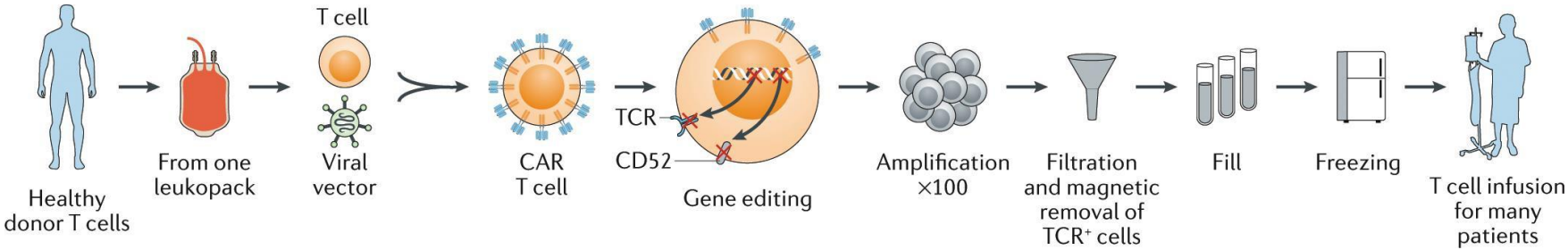
- Cytokine Release Syndrome (CRS)
  - Fever, hypotension, hypoxia
  - Supportive care (IV fluids, antipyretics, antibiotics, oxygen, vasopressors)
  - Anti-IL-6 therapies & steroids

- Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)
  - Graded using ICE scores
  - Anti-IL-6 therapies & steroids



Nat Rev Immunol 2022; 22:85-96, J Clin Oncol 2021; 39:3978-92

“Off-the-shelf” **Allogeneic** CAR-T Cells



Advantages:

- Cryopreserved product for immediate use
- Product standardization based on donor selection and processing
- Allows for multiple cell modifications in a single product
- Re-dosing or combination of CAR-T cells directed against multiple targets
- Potentially reduced cost

Risks:

- Graft-versus-Host Disease (GVHD)
- Rapid elimination (“rejection”)

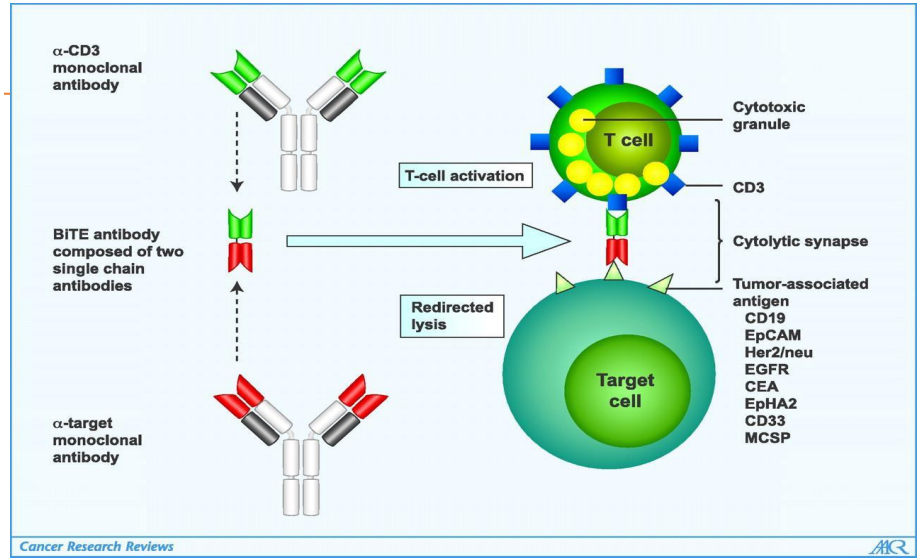
Nat Rev Drug Discov 2020; 19:185-199

Bi-specific T-cell Engager (BiTE)

- Relies upon patient's **endogenous** T cells, not ex-vivo activated and expanded T cells (CAR-T)

- Two linked Fab fragments :
  - One arm recognizes tumor
  - One arm binds T-cells (CD3) or other target
  - Activates MHC-independent cytotoxic activity

- Toxicities:
  - CRS (pre-medication), ICANS



Drug Name	Target	Indication
Blinatumomab (Blincyto)	CD3/CD19	B-cell Acute lymphoblastic leukemia(B-ALL)
Amivantamab-vmjw (Rybrevant)	EGFR/cMet	NSCLC
Tebentafusp-tebn (Kimmtrak)	GP100/CD3	Unresectable or metastatic uveal melanoma
Teclistamab-cquv (Tecavayli)	CD3	Relapsed or refractory multiple myeloma
Mosunetuzumab-axgb (Lunsumio)	CD3	Relapsed or refractory follicular lymphoma

Nat Rev Clin Oncol 2020; 17:418-434, Cancer Res 2009; 69:4941-4

Summary: Immunotherapy

•Pharmacology

- ICIs remove the breaks placed on T-cell mediated responses
- CAR-T and BiTE therapies utilize genetically modified autologous (or allogenic) and endogenous T-cells, respectively
- ICIs as well as CAR-T and BiTE therapies used in a wide-range of and rapidly growing number of cancer types

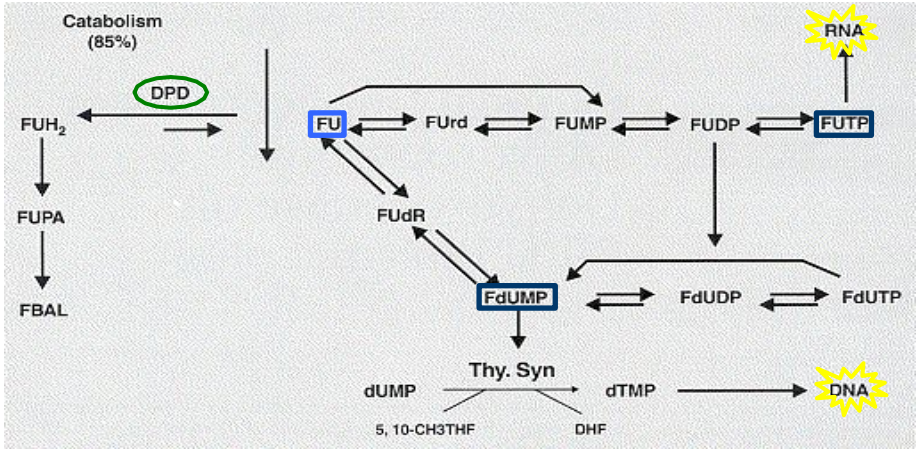
•Cardiotoxicity

- ICI-myocarditis and other cardiac complications is **NOT related to cumulative dose** exposure, risk is **rare**, but associated with a **high fatality rate**
- ICI-myocarditis managed by **holding the ICI** and administering **corticosteroids** and possible immunosuppression, data on the value of screening and surveillance approaches are lacking
- CAR-T and BiTE therapies are primarily associated with **cytokine release syndrome (CRS)** and **neurotoxicity syndrome (ICANS)** among other potential cardiotoxicities

General Pharmacology: Fluoropyrimidines

- **Drugs in Class:** Fluorouracil (5-FU) and Capecitabine (Xeloda)

- **Mechanism of Action:**
  - **F-UMP** (an active metabolite) **replaces uracil in RNA and inhibit cell growth;** the active metabolite **F-dUMP, inhibits thymidylate synthetase, depleting thymidine triphosphate** (a necessary component of DNA synthesis) leading to cell death.
  - Capecitabine is a pro-drug of 5FU

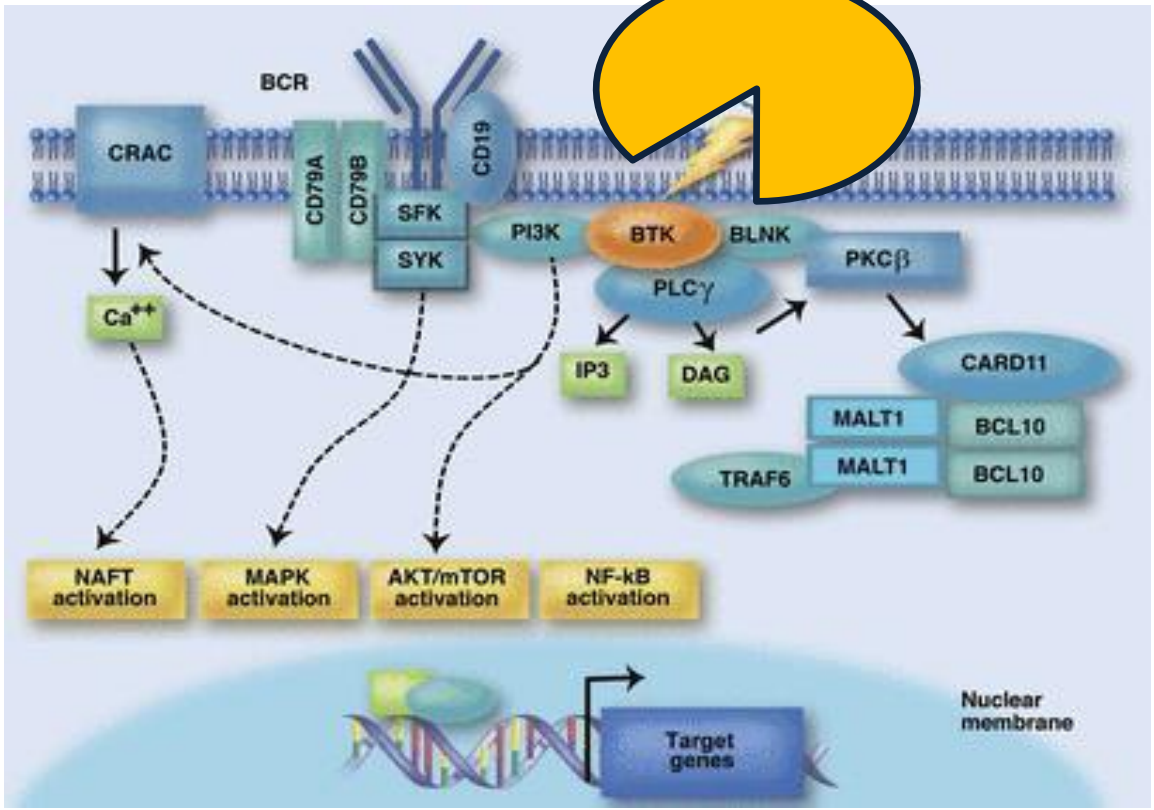


Cardiotoxicity: Fluoropyrimidine Therapy

- Proposed mechanism of cardio-toxicity
  - The underlying mechanism of toxicity is not well established, proposed to be related to **metabolite of 5FU(fluoroacetate) since the half life of the parent molecule is so short**
    - **Myocardial toxicity** from antimetabolite
      - Exacerbated by DPD enzyme deficiency, administration type (infusional versus bolus)
    - **Coronary vasospasm** due to drug induced vasoconstriction of smooth muscle
    - **Thrombogenic effect** due to endothelial injury
- Clinical Incidence: Bolus dosing 1.6 – 3%, infusion dosing 2 – 18%
- Clinical Presentation
  - Chest pain be atypical or typical, or consistent with an acute coronary syndrome. Asymptomatic ECG changes have also been reported

Mosseri M. Cancer Res. 1993;53(13):3028. Muneoka K. Int J Clin Oncol. 2005
Padegimas A. J Am Coll Cardiol CardioOnc.

Bruton's Tyrosine Kinase Inhibitors (BTKi's)



BTKi‘s

- Oral targeted agent: **Covalently** bound to **cysteine 481** on Bruton’s tyrosine kinase
- Chronic therapy
- FDA approved agents:
  - **acalabrutinib (Calquence)**
  - **ibrutinib (Imbruvica)**
  - **zanubrutinib (Brukinsa)**

Cardiotoxicity: BTKi's

- Atrial fibrillation, hypertension, sudden cardiac death, and ventricular arrhythmias have been reported
- Proposed mechanism of cardiotoxicity
  - May be a class wide effect, however, varies by target affinity of each BTK and second generation BTKi's have yet to reach the same exposure as ibrutinib to confirm labeling claims of less cardiac toxicity
  - BTK appears to be expressed in human cardiac tissue
  - Left atrial abnormality identified by ECG may be a moderately specific and sensitive finding that may independently identify an increased risk for ibrutinib related atrial fibrillation
- Major presenting symptoms
  - Highest incidence of atrial fibrillation has been observed in ibrutinib treated populations during the first 6 months of treatment
  - Majority of cases of atrial fibrillation are grade 1 or 2
  - Once toxicity resumes to grade 1 or baseline, BTKi may be reinitiated
  - Dose reduction or permanent discontinuation may be warranted in severe or refractory arrhythmias

More et al. ACC. Available at: https://www.acc.org/latest-in-cardiology/articles/2020/01/21/08/46/ibrutinib-associated-cardiotoxicity

Mato et al. Cancer Biol Ther. 2018;19

BTKi's Toxicity Comparison

	AFib	Bleeding/ Bruising	Myalgia/ Arthralgia	Diarrhea	Rash	Headache
Acalabrutinib	≤3%	≤8%	21%	31%	18%	39%
Ibrutinib	≤9%	≤44%	14-40%/ 11-24%	36-59%	12-29%	12-18%
Zanubrutinib	2%	10-11%	14-19%	20-23%	25-36%	-

Calquence [package insert]. Wilmington, DE; AstraZeneca Pharmaceuticals LP, 2017 Imbruvica [package insert]. Sunnyvale, CA: Pharmacyclics LLC, 2020 Brukinza (zanubrutinib) [prescribing information]: San Mateo, CA: ©BeiGene, Ltd; 2019

Non-Covalent BTKi's

- ***Pirtobrutinib***
  - Reversible BTK inhibitor
  - Approved Jan 2023
  - Majority of AEs across trials were grade 1 or 2:

  > 10%: fatigues, edema, fever, musculoskeletal pain, arthritis, diarrhea, constipation, abdominal pain, nausea, dyspnea, cough, busing, hemorrhage, pneumonia, peripheral neuropathy, dizziness, rash

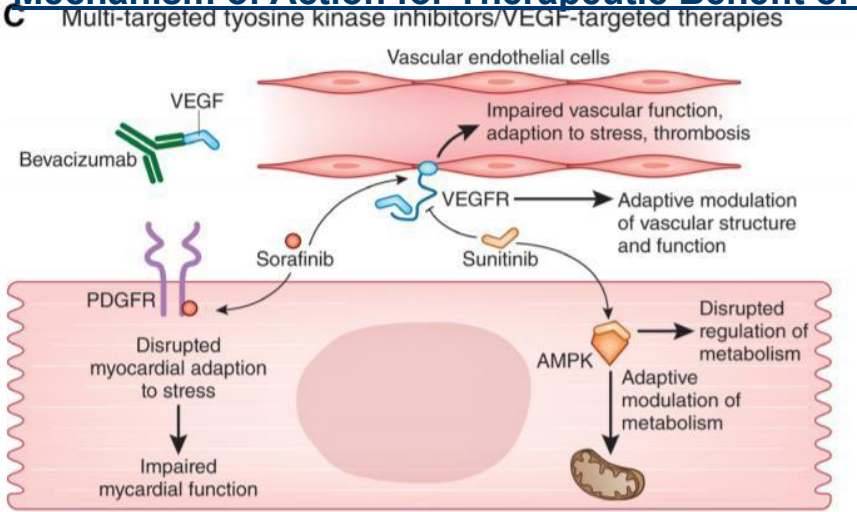
Adverse Event	All Grades	Grade 3 or 4
Peripheral edema	9%	-
Vision changes	7%	0.8%
Memory changes	7%	-
Headache	6%	0.8%
Urinary tract infection	6%	-
Atrial fibrillation or atrial flutter*	3.9%	1.6%
Herpesvirus infection	2.3%	0.8%
Hypertension	2.3%	-
Tumor lysis syndrome	0.8%	0.8%

Loxo Oncology at Lilly announces updated data from the phase 1/2 BRUIN clinical trial for LOXO-305 in chronic lymphocytic leukemia and small lymphocytic lymphoma at the American Society of Hematology annual meeting. News release. Eli Lilly and Company. December 7, 2020. Accessed December 7, 2020. https://prn.to/3mWBhMr

Vascular Endothelial Growth Factor Tyrosine Kinase Inhibitors (TKIs)

- **Drugs in Class:** Axitinib (Inlyta), Cabozantinib (Cabometyx/Cometriq), Lenvatinib (Lenvima), Pazopanib (Votrient),Regorafenib (Stivarga), Sorafenib (Nexavar), Sunitinib (Sutent), Vandetanib (Capresla)

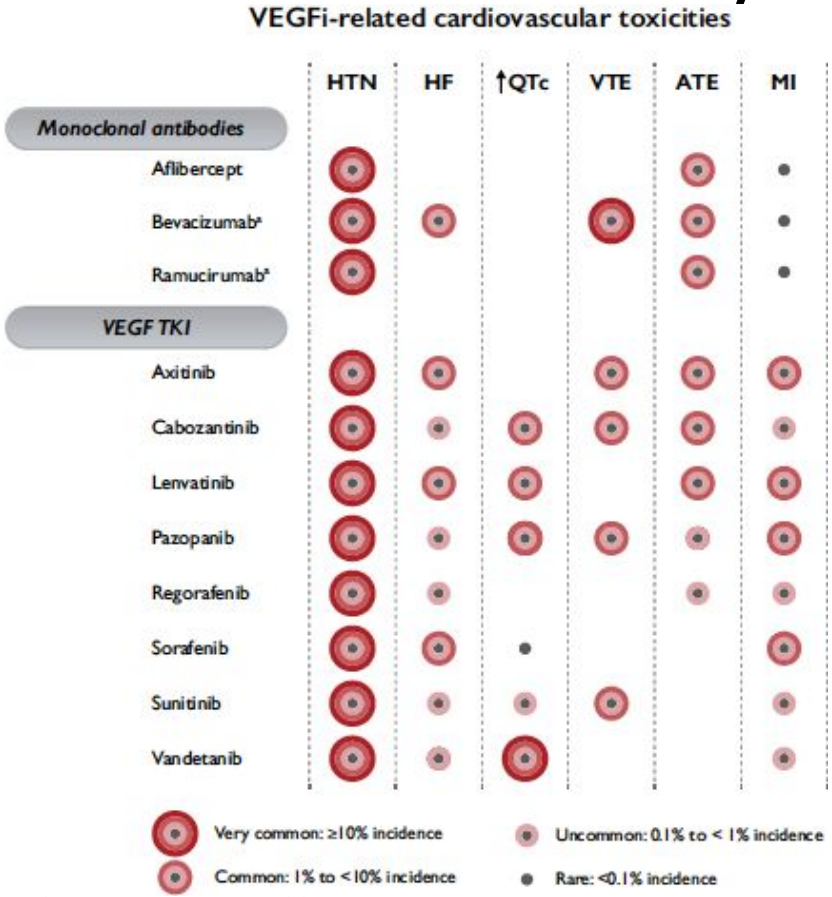
- **Mechanism of Action for Therapeutic Benefit of VEGF therapy:**

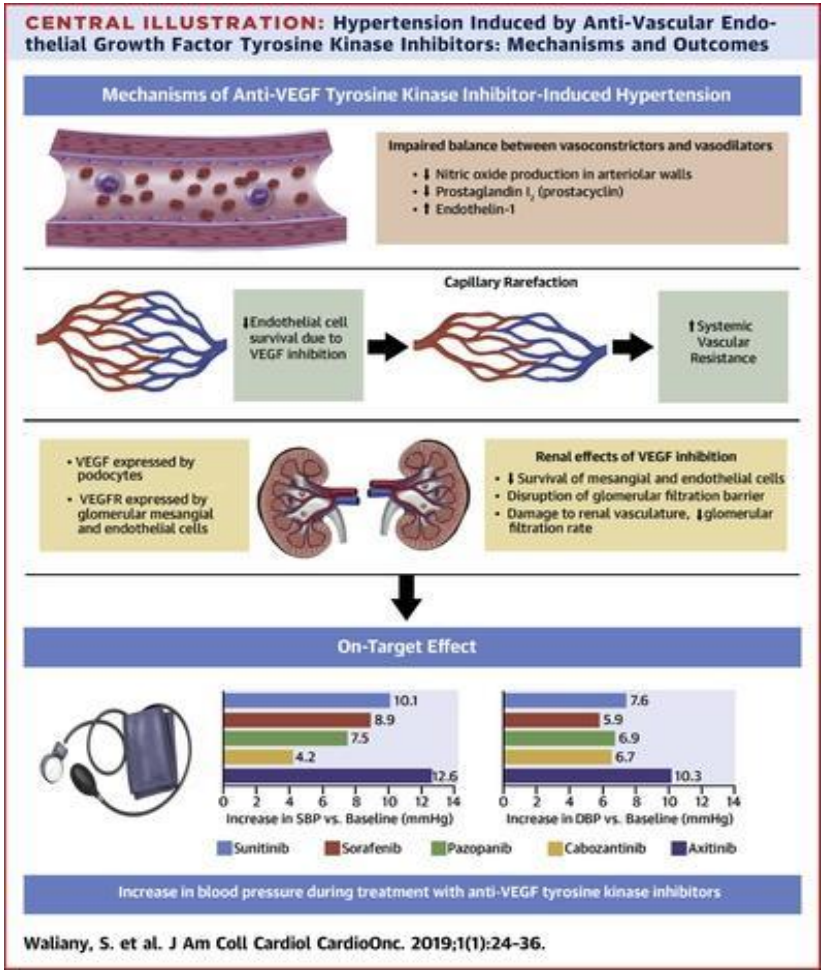


VEGF inhibitors block the transduction of intracellular signals through a variety of mediators impairing angiogenesis, lymphangiogenesis, vascular permeability, and vascular homeostasis in effect shutting off the growth mediators for cancer cells

Lenneman CG. Circ Res. 2016.

Cardiotoxicity: anti-VEGF TKIs



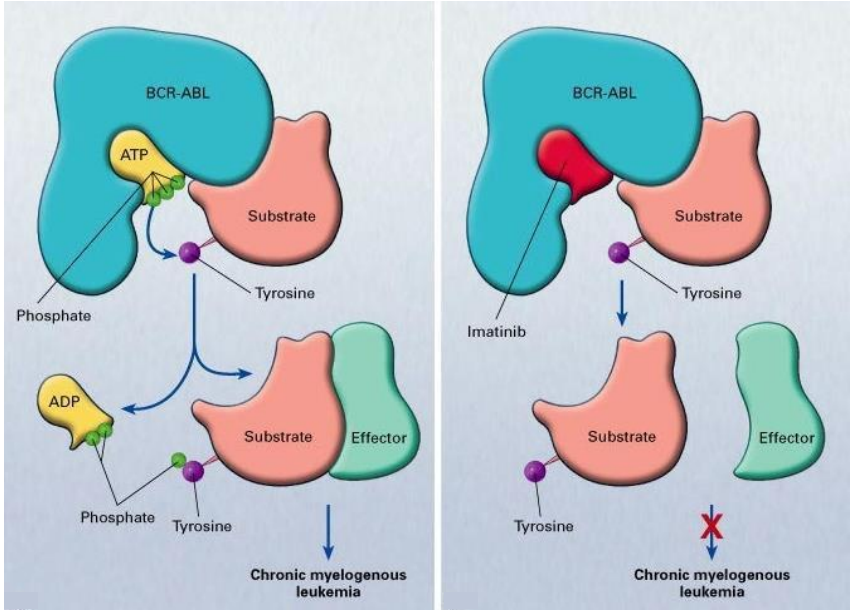


Versmissen J. Cardiovasc Research. 2019.
Waliany S. JACC: Cardioonc. 2019
Lyons AR,. Euro Heart J. 2022; 41(41): 4229-4361)

General Pharmacology: BCR-ABL TKIs

- **Drugs in Class:** Bosutinib (Bosulif), Dasatinib (Sprycel), Imatinib (Gleevec), Nilotinib (Tasigna), Ponatinib (Iclusig)

- **Mechanism of Action for Therapeutic Benefit of BCR-ABL therapy:**



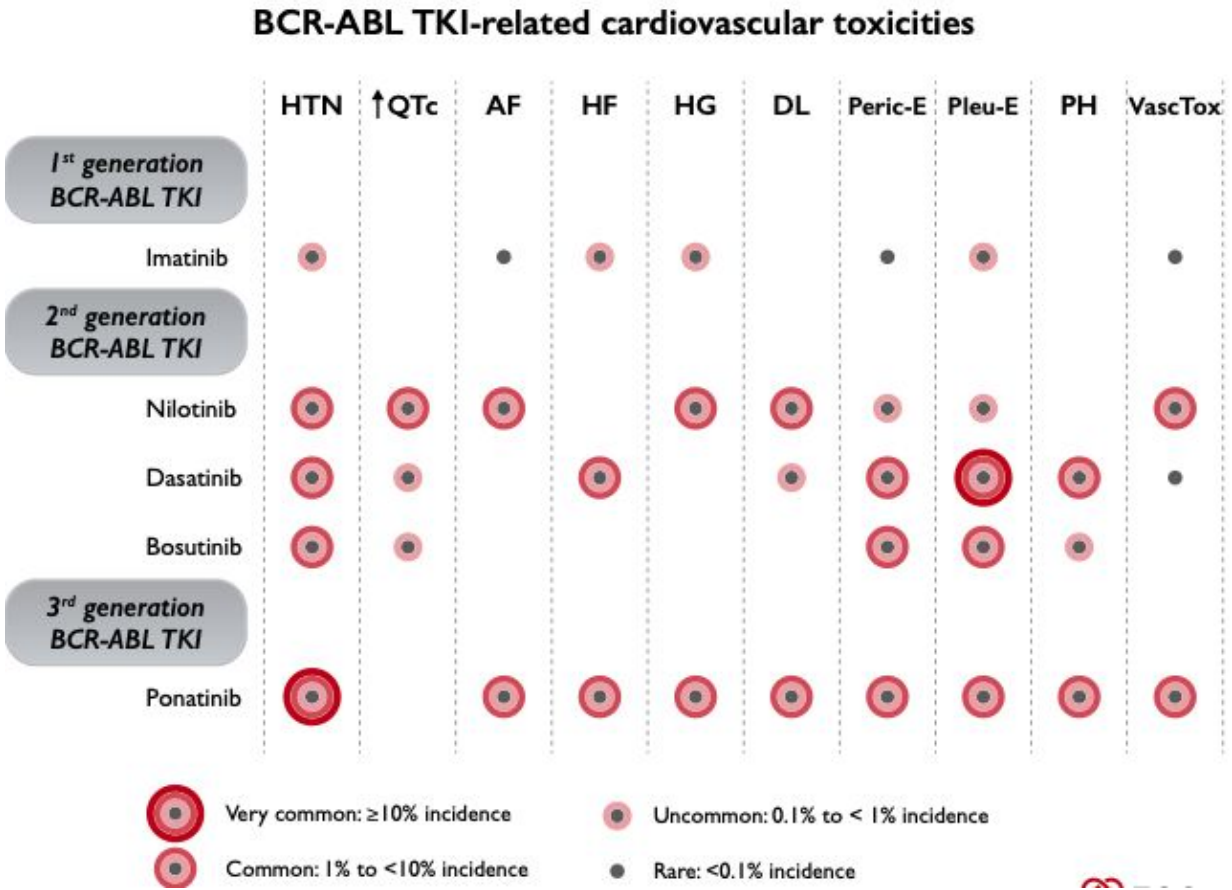
Savage and Antman. N Engl J Med.

Primarily binds to the amino acids of the BCR/ABL tyrosine kinase ATP binding site to stabilize and inactivate it, thereby preventing tyrosine kinase autophosphorylation and down stream effects which leads to apoptosis in Bcr-Abl positive cell lines as wellas in fresh leukemic cells in Philadelphia chromosome positive CML.

Most are multi-kinase inhibitors with more than one target, thus allowing for additional downstream effects, ability to overcome resistance

Cardiotoxicity: BCR-ABL TKIs

- Proposed mechanism of cardiotoxicity
  - Not a class wide effect, imatinib as been postulated to have positive vascular effect
  - Balance of understanding on target and off target effects coupled with patients underlying cardiac co-morbidities



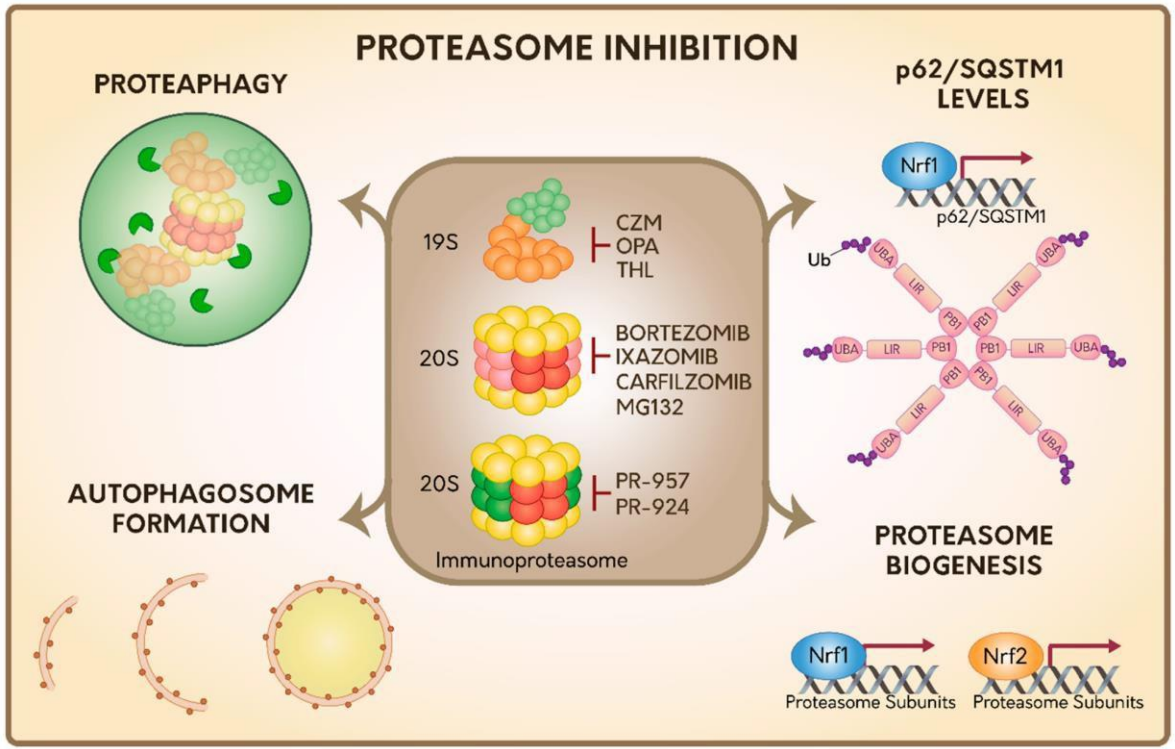
Aghel N. Vasc Health Rsk Manag. 2017.
Moslehi JJ. JCO. 2015.
Pasvolsky O. Cardio-Oncology. 2015.

Proteasome Inhibitors (PI)

- **Drugs in Class:**
  Bortezomib (Velcade), Carfilzomib (Kyprolis), Ixazomib (Ninlaro)

- **Mechanism of Action:**

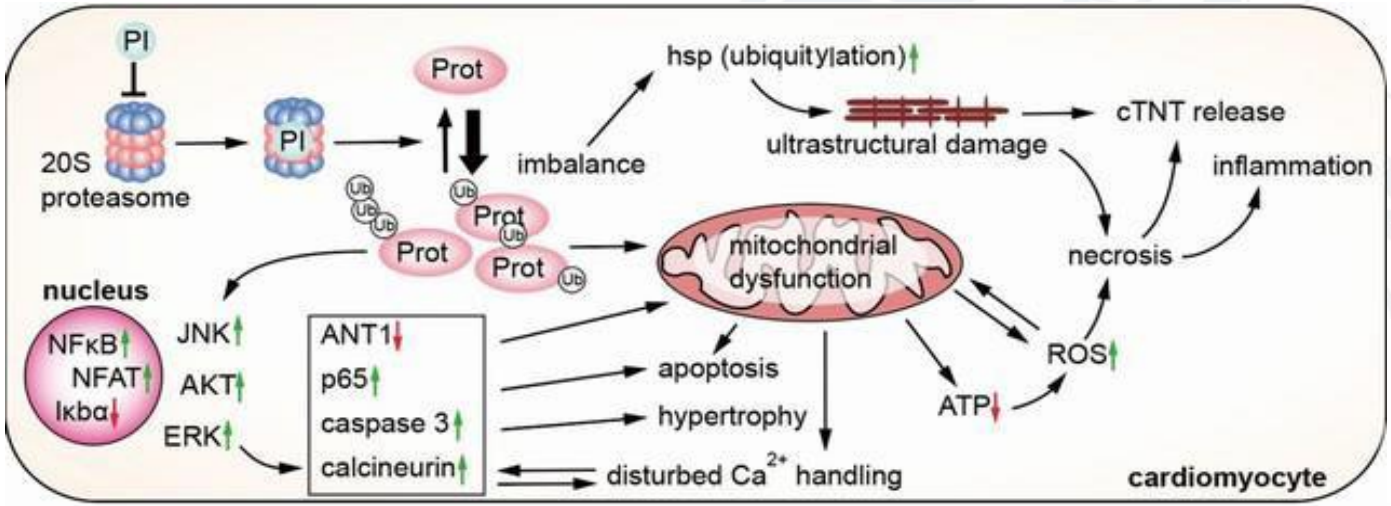
  Block peptide degradation inside the cell by ubiquitin-proteasome system by blocking proteasomes leading to activation of signaling cascades, cell-cycle arrest, and apoptosis



Albornoz et al. Int. J. Sci. 2019;20
Muz B. Drug Des Devel Ther. 2016

Cardiotoxicity: Proteasome Inhibitors

- Proposed mechanisms of cardiotoxicity
  - Cardiac myocytes are also known to have high rates of proteasome activity and protein turnover
    - **PI's impact on nitric oxide production and homeostasis by inducing mitochondrial dysfunction leading to increased ATP synthesis which can myocardial contractility and have adverse effects on vascular smooth muscle and plaque stability**
    - Irreversible binding leads to long-term downregulation of the UPS resulting in accumulation of misfolded proteins within cardiomyocytes causing adverse cardiac remodeling
- **Cardiac ADE are reversible and re-challenge is possible after cardiac toxicity**
  - Damage done to myocardial function appears reversible if identified and managed promptly
  - Once appropriate supportive therapy is initiated, PI may be resumed



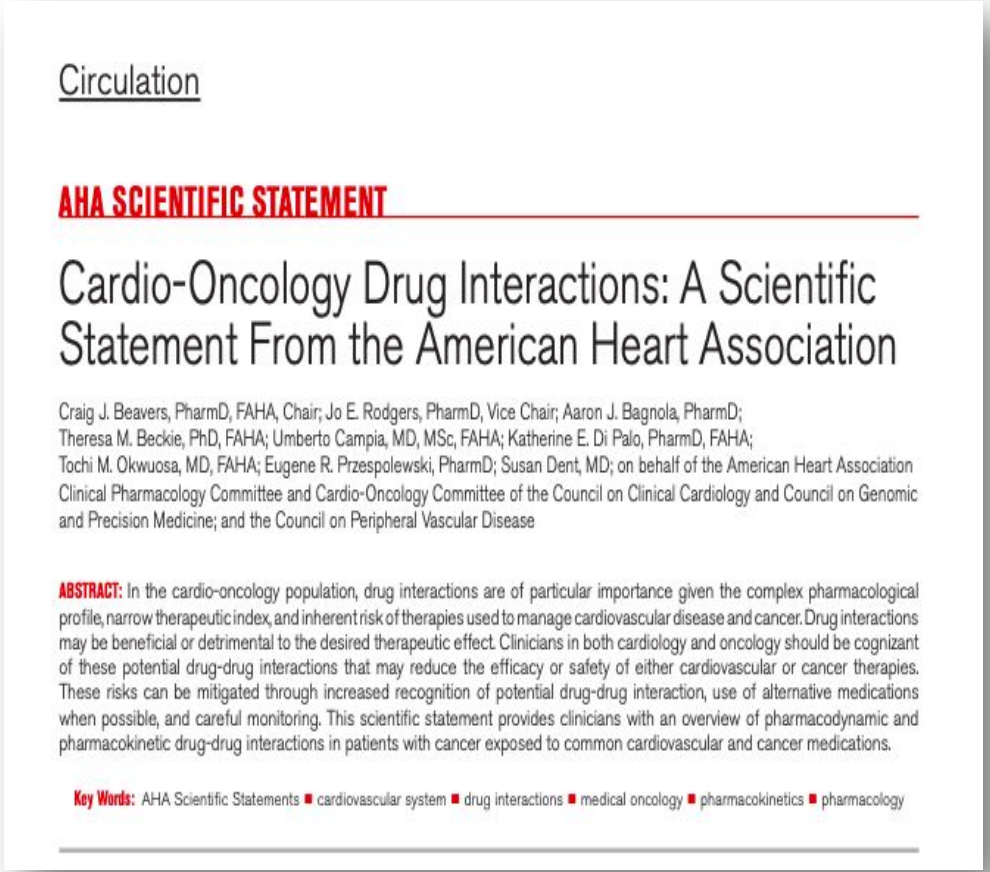
Bringhen S. Clin Lymphoma Myeloma Leuk. 2017
Guha A. Trends Cardiovasc Med. 2019
Jouni H. Am J. Hematol. 2017.
Rhea IB. Curr Treat in Cardio Medicine. 2018
Li W. JAMA Oncol. 2017
Waxman AJ. JAMA Oncol 2018
Heckmann JTD. 2018

Cardiotoxicity: Proteasome Inhibitors

- Rates observed with bortezomib and ixazomib are < 5%
- Cardiac ADE incidence of 22% with use of single agent carfilzomib
  - Most frequent AE: hypertension, arrhythmias, heart failure, VTE, dyspnea
  - Suspected reason is due to the **irreversible** binding of carfilzomib
  - Most cardiac AEs occurred relatively early in the course of treatment: 2–3 months from treatment initiation

Bringhen S. Clin Lymphoma Myeloma Leuk. 2017.
Koulaouzidis G Heart Fail Clin. 2017.
Patel VG. Curr Oncol Rep. 2019.
Lee DH. Curr Treat Option Cardio Med. 2018. Cornell RF.
JCO 2019

The Alphabet Soup of Drug-Drug Interactions in Cardio-Oncology



Circulation

AHA SCIENTIFIC STATEMENT

Cardio-Oncology Drug Interactions: A Scientific Statement From the American Heart Association

Craig J. Beavers, PharmD, FAHA, Chair; Jo E. Rodgers, PharmD, Vice Chair; Aaron J. Bagnola, PharmD; Theresa M. Beckie, PhD, FAHA; Umberto Campia, MD, MSc, FAHA; Katherine E. Di Palo, PharmD, FAHA; Tochi M. Okwuosa, MD, FAHA; Eugene R. Przespolewski, PharmD; Susan Dent, MD; on behalf of the American Heart Association Clinical Pharmacology Committee and Cardio-Oncology Committee of the Council on Clinical Cardiology and Council on Genomic and Precision Medicine; and the Council on Peripheral Vascular Disease

ABSTRACT: In the cardio-oncology population, drug interactions are of particular importance given the complex pharmacological profile, narrow therapeutic index, and inherent risk of therapies used to manage cardiovascular disease and cancer. Drug interactions may be beneficial or detrimental to the desired therapeutic effect. Clinicians in both cardiology and oncology should be cognizant of these potential drug-drug interactions that may reduce the efficacy or safety of either cardiovascular or cancer therapies. These risks can be mitigated through increased recognition of potential drug-drug interaction, use of alternative medications when possible, and careful monitoring. This scientific statement provides clinicians with an overview of pharmacodynamic and pharmacokinetic drug-drug interactions in patients with cancer exposed to common cardiovascular and cancer medications.

Key Words: AHA Scientific Statements ■ cardiovascular system ■ drug interactions ■ medical oncology ■ pharmacokinetics ■ pharmacology

Cancer risk increases with age…
Cardiovascular risk increases with age…
Polypharmacy increases with age!

Nightingale, *et al* (JCO 2015):

- Average number of medications taken by senior oncology patients (Rx, OTC, herbal): **9**
- Most common concomitant Rx medications target the cardiovascular system or high cholesterol

Sharma, *et al* (Cancer 2019):

- One in four patients on a BCR-ABl TKI for CML are on a PPI, which increases mortality

Balducci L, Goetz-Parten D, Steinman MA. Polypharmacy and the management of the older cancer patient. Ann Oncol. 2013 Oct;24 Suppl 7(Suppl 7):vii36-40.
Older Adult Oncology. National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2021. Accessed 11/25/2021.
Nightingale G, Hajjar E, Swartz K, Andrel-Sendecki J, Chapman A. Evaluation of a pharmacist-led medication assessment used to identify prevalence of and associations with polypharmacy and potentially inappropriate medication use among ambulatory senior adults with cancer. J Clin Oncol. 2015 May 1;33(13):1453-9.
Sharma M, Holmes HM, Mehta HB, Chen H, Aparasu RR, Shih YT, Giordano SH, Johnson ML. The concomitant use of tyrosine kinase inhibitors and proton pump inhibitors: Prevalence, predictors, and impact on survival and discontinuation of therapy in older adults with cancer. Cancer. 2019 Apr 1;125(7):1155-1162.

Cardio-oncology Drug Interactions

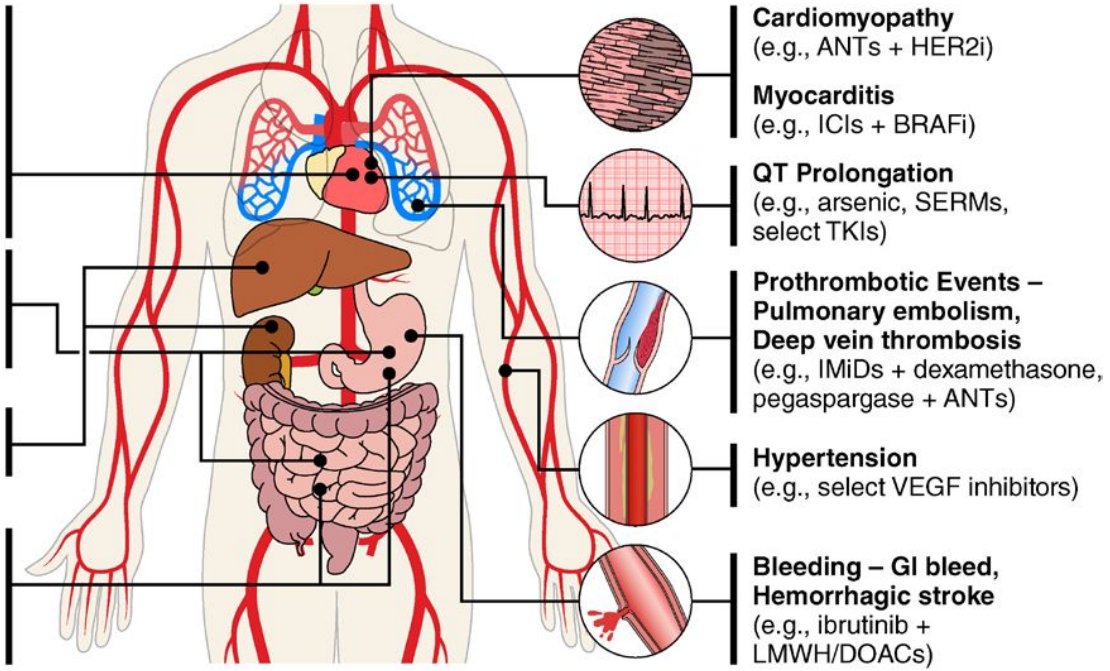
Pharmacokinetic Drug Interactions

Metabolism
- CYP1A2 (e.g., vemurafenib + carvedilol, verapamil + erlotinib)
- CYP2C9 (e.g., ibrutinib + warfarin, select ARBs + imatinib)
- CYP2C19 (e.g., clopidogrel + enzalutamide)
- CYP2D6 (e.g., tamoxifen + dronedarone)
- UGT (e.g. dapagliflozin + sorafenib)

- CYP3A4 (e.g. select TKIs + DOACs, atorvastatin + idelalisib, diltiazem + bosutinib)
- P-gp (e.g,. ANT + digoxin, select TKIs + DOACs, select beta-blockers + imatinib)

Elimination
(e.g., vinblastine + amiodarone)

Absorption
- CYP3A4 (e.g. select TKIs + DOACs, atorvastatin + idelalisib, diltiazem + bosutinib)
- P-gp (e.g,. ANT + digoxin, select TKIs + DOACs, select beta-blockers + imatinib)



Pharmacodynamic Drug Interactions

Cardiomyopathy
(e.g., ANTs + HER2i)

Myocarditis
(e.g., ICIs + BRAFi)

QT Prolongation
(e.g., arsenic, SERMs, select TKIs)

Prothrombotic Events – Pulmonary embolism, Deep vein thrombosis
(e.g., IMiDs + dexamethasone, pegaspargase + ANTs)

Hypertension
(e.g., select VEGF inhibitors)

Bleeding – GI bleed, Hemorrhagic stroke
(e.g., ibrutinib + LMWH/DOACs)

Beavers CJ, Rodgers JE, et al. Cardio-Oncology Drug Interactions:

A Scientific Statement From the American Heart Association. *Circulation*. 2022; 145(15): e811-e838.

Cardio-Oncology Related Pharmacodynamic Interactions

Interacting Medications	Monitoring	Management
Hypertension (HTN)		
Anti-VEGF TKIs VEGF trap Anti-VEGF monoclonal antibodies Bruton TKI Abiraternone + steroids mTOR inhibitors + endocrine NSAIDs/steroids + cancer cause HTN	Blood pressure monitoring	Manage per HTN guidelines VEGF- 1st ACEI, ARB; 2nd CCB; consider potassium sparing diuretic Abiraterone, prednisone to avoid renal insufficiency Avoid NSAIDs
Cardiomyopathy		
Anthracyclines, anti-HER2, taxanes, cyclophosphamide Immune checkpoint inhibitors Other HF inducing drugs	ECG, troponin, symptoms, BNP	Beta-blockers (HF approved, carvedilol) ACE Inhibitors/ARBs Anthracycline-dexrazoxane, administration changes

Beavers C, Rodgers JE, et al. Cardio-oncology Drug Interactions: A Scientific Statement of the American Heart Association. *Circulation*. In Press.

Cardio-Oncology Related Pharmacodynamic Interactions

Interacting Medications	Monitoring	Management
Thrombosis		
Immunodulatory agents + dexamethasone + doxorubin Pegaspargase + oral contraceptives Pegaspargase /Pronatinib+ prednisone/dexamethasone + doxorubicin	Complete blood count, doppler with asymptomatic, CT with symptomatic In some cases, fibrinogrin, INR, APTT, AT (pegaspargase + prednisone + doxorubicin)	Prevention: low molecular weight heparin (LMWH) for high risk Low-dose aspirin lower risk Treatment: direct acting oral anticoagulant (DOAC) and LMWH
Bleeding		
Select VEGF inhibitors/ BTKI + therapies that cause bleeding DOAC/warfarin + above Warfarin + 5-fluorouracil/capecitabine	Complete blood count, PT/INR, signs/symptoms of bleeding	Avoid or monitor

Beavers C, Rodgers JE, et al. Cardio-oncology Drug Interactions: A Scientific Statement of the American Heart Association. *Circulation*. In Press.

Pharmacodynamics: **Arrhythmia**

Cancer Therapies Associated with QT Prolongation
Ceritinib ++, Crizotinib ++, Dasatinib ++, Bosutinib ++, Nilotinib ++, Ponatinib +, Vemurafenib ++, Dabrafenib ++, Encorafenib +, Lapatinib +, Osimertinib +, Gilteritinib ++, Midostaurin ++, Panobinostat ++, Vorinostat ++, Toremifene ++, Lenvatinib ++, Pazopanib ++, Vandetanib ++, Sorafenib +, Sunitinib +, Arsenic +++, Doxorubicin +++, Glasdegib ++, Ivosidenib ++, Ribociclib ++, Selpercatinib ++, Entrectinib +
Other Therapies Associated with QT Prolongation
Antiemetic and prokinetic agents (e.g., droperidol, ondansetron) Antibacterial and antifungal agents (e.g., -mycins, -floxacins, -azoles) Psychotropic agents (e.g., citalopram, escitalopram, haloperidol, methadone)

Atrial Fibrillation: Ponatinib ++, Ibrutinib +++ Acalabrutinib ++, Zanubrutinib ++
Bradycardia: Crizotinib +++, Alectinib, Brigatinib, Ceritinib ++, Ponatinib +, Thalidomide +
AV Block: Lorlatinib ++; **Tachycardia:** Niraparib ++, Ponatinib +; **Ventricular arrhythmia:** Ibrutinib +

+ = rare or < 1 %; ++ = uncommon or 1% to 10%; +++ = frequent or >10%

Adapted from J Am Coll Cardiol 2021;77:2693–716 and Circ 2022; 145:e811-83

Pharmacokinetic Properties of Medications

ADME

Absorption

Change in GI pH
Adsorption, chelation, or complexing
Changes in GI motility
Modulation of drug transporter proteins

Distribution

Protein binding
Modulation of drug transporter proteins

Metabolism

Changes in first pass metabolism
Enzyme induction
Enzyme inhibition

Excretion

Changes in urinary pH
Changes in active renal tubular excretion
Enterohepatic shunt

Preston CL. Stockley's Drug Interactions, 12th ed. London: Pharmaceutical Press, 2019

Cardio-Onc PK DDIs: **DOACs**

DOACs: substrates of P-gp alone or dual CYP3A4 and P-gp (varying dependance)

	P-gp InHIBITORs	P-gp InDUCERs
Dabigatran (Pradaxa®)	**Varies by indication (NVAF vs DVT/PE)**	**AVOID** (e.g., rifampin)
Edoxaban (Savaysa®)	**No dose adjustment**	
	Dual strong P-gp & CYP3A4 InHIBITORs	**Dual strong P-gp & CYP3A4 InDUCERs**
Rivaroxaban (Xarelto®)	**AVOID** (e.g. ketoconazole, ritonavir, etc)	**AVOID** (e.g., rifampin, carbamazepine, phenytoin, St. John's Wort)
Apixaban (Eliquis®)	**Reduce dose to 2.5 mg BID** **AVOID** in patients already taking 2.5 mg BID	

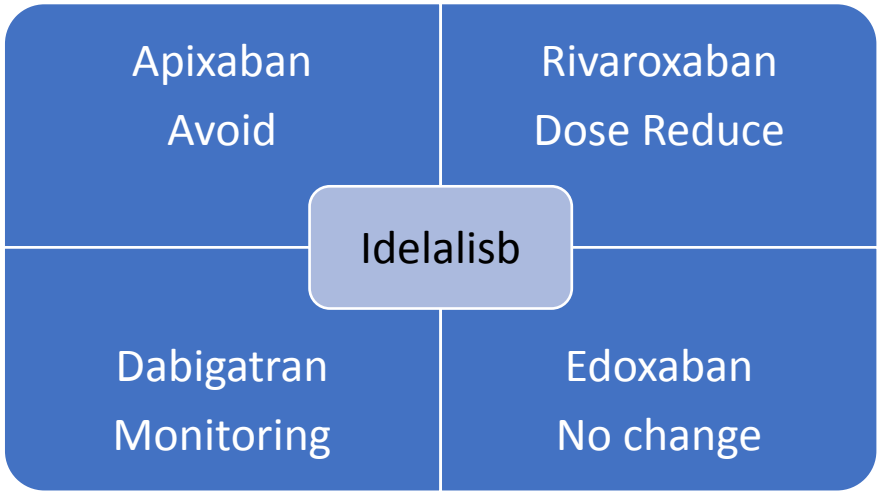
- **CYP3A4 inhibitors:** abiraterone, bicalutamide, capmatinib, ceritinib, dasatinib, erlotinib, encorafenib, entrectinib, gefitinib, idelalisib +++, imatinib ++, larotrectinib, lapatinib, nilotinib, palbociclib, panobinostat, ribociclib, rucaparib, ruxolitinib, tucatinib
  CYP3A4 inducers: apalutamide +++, brigatinib, dabrafenib +++, encorafenib, enzalutamide +++, lorlatinib, mitotane +++, tucatinib, vemurafenib +++
- **P-gp inhibitors:** abemaciclib, afatinib, alectinib, capmatinib, erlotinib, gefitinib, lapatinib, palbociclib, pemigatinib, sorafenib, sunitinib, tucatinib, venetoclax; **P-gp Inducers:** doxorubicin

DOAC dose reduction or avoidance may be required with various TKIs/other.

Circulation. 2022; 145(15): e811-e838, Pradaxa® Boehringer Ingelheim, Ridgefield, CT; 2014; Eliquis® Bristol-Myers Squibb, Princeton, NJ; 2014; Xarelto® Janssen, Titusville, NJ; 2014; Savaysa® Daiichi Sankyo, Parsippany, NJ; 2015

Unique Examples in Cardio-Oncology: Anticoagulants and Antiplatelets

- Direct acting oral anticoagulants (DOACs) either have dual CYP3A4 and P-glycoprotein (P-gp) or P-gp alone metabolism in variety dependance.
- Recommendations for avoidance or dose reduction vary with ***VEGF inhibitors and epidermal growth factor receptor inhibitors.***



Absorption

Several TKIs depend on acid environments for absorption.
Clinicians should evaluate the need for continued acid suppression therapy.

TKI	Acid-Suppressive Agent	Area Under the Curve Change
Axitnib	Rabeprazole 20mg daily	↓ 15%
Erlotinib	Omperazole 40mg daily	↓ 46%
Lapatinib	Esomepraozle 40mg daily	↓ 27%
Nilotinib	Esomeprazole 40mg daily	↓ 34%
Dasatinib	Omeprazole 40mg daily	↓ 43%
Imatinib	Omeprazole 40mg daily	No change

Campen C, et al. J Adv Pract Oncol 2017;8:609–620

Drug Interaction Information

- Oncology agents are approved at an increasing rate (numerically more).

- Use resources to help review interactions.

- Must reference multiple sources:
  - Primary literature
  - Case reports
  - Drug reference databases
  - Food and Drug Administration/National Institutes of Health website

Drug Information Software

Database	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
LexiComp	88.6%	96.9%	99.0%	70.5%	355
MicroMedex	69.0%	71.9%	89.8%	39.3%	270
Epocrates	85.6%	95.4%	98.5%	64.9%	344
Drugs.com	90.8%	90.6%	97.2%	73.4%	352
Medscape	81.2%	62.5%	88.6%	38.2%	280

Bossaer JBJ Oncol Pharm Pract. 2022;28:82–86

How to Check If Reaction Relevant

Check Drug Reference for the most up-to-date information.

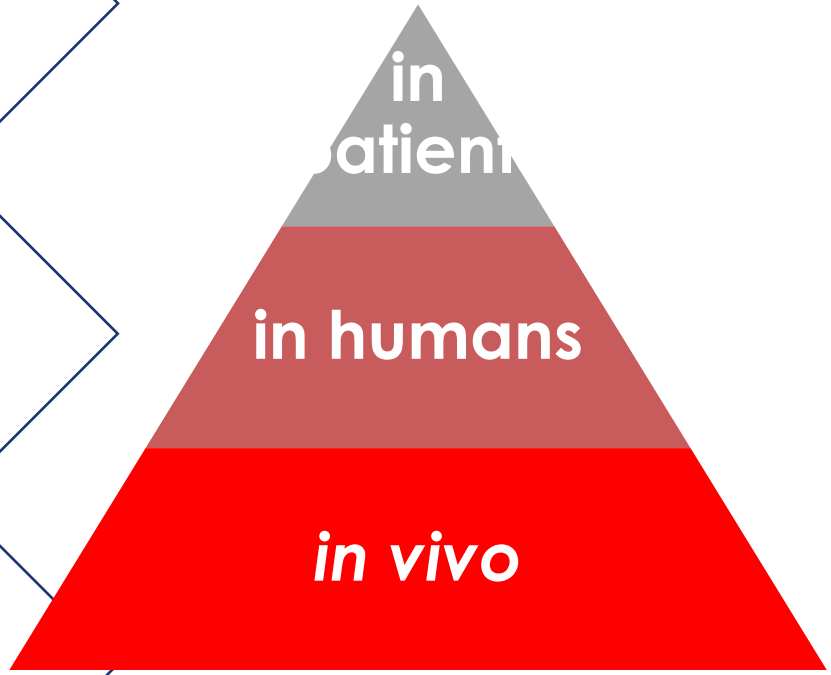
- **Click on the Interactions section.**
- **It will list whether the drug is a substrate or modifier of p-gp or CYP3A4**

Check the literature.

- **The most relevant and valuable reports are going to come from actual patients taking the drug for the disease state in question.**

Use the FDA criteria to interpret your findings.

- **See next slide or FDA website**



Conclusion

- Many oncologic therapies can cause acute and chronic cardiovascular adverse effects with varying presentations, time course, prevention, management, and reversibility

- Primary prevention of cardiotoxicity by optimizing cardiac risk factors should be recommended in all patients regardless of treatment

- It is important to consider pharmacology when evaluating cardiotoxic risk of new oncologic therapies

Pharmacologic Review of Cancer Therapy Essentials:

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University of Kentucky College of Pharmacy

/Baptist Health Paducah