Cancer Pharmacology II

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Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

Objectives

- Describe the mechanism of action and pharmacology of chemotherapy agents and targeted therapies used for the treatment of hematologic and solid tumor malignancies
- Identify the need for dose adjustments of cancer therapies based on organ dysfunction
- Recognize common and unique adverse drug reactions of cancer therapies and associated prevention and management strategies

Monoclonal Antibodies

Will not be discussed
New drugs

Alemtuzumab
Amivantimab
Avelumab
Atezolizumab
Bevacizumab
Blinatumomab
Caplacizumab-yhdp
Cemiplimab
Cetuximab
Daratumumab
Dostarlimab
Dinutuximab
Durvalumab
Eculizumab
Elotuzumab
Emapalumab
Emicizumab-kxwh
Ipilimumab
Isatuximab
Margetuximab
Mogamulizumab
Necitumumab
Nivolumab
Obinutuzumab
~~Olaratumab~~
Ofatumumab
Olaratumab
Panitumumab
Pembrolizumab
Pertuzumab
Ramucirumab
Ravulizumab-cwvz
Rituximab
Rituximab hyaluronidase
Siltuximab
Tagraxofusp-erzs
Trastuzumab
Trastuzumab hyaluronidase
Trastuzumab, pertuzumab hyaluronidase
Ziv-aflibercept

Antibody Drug Conjugates

Will not be discussed
New drugs

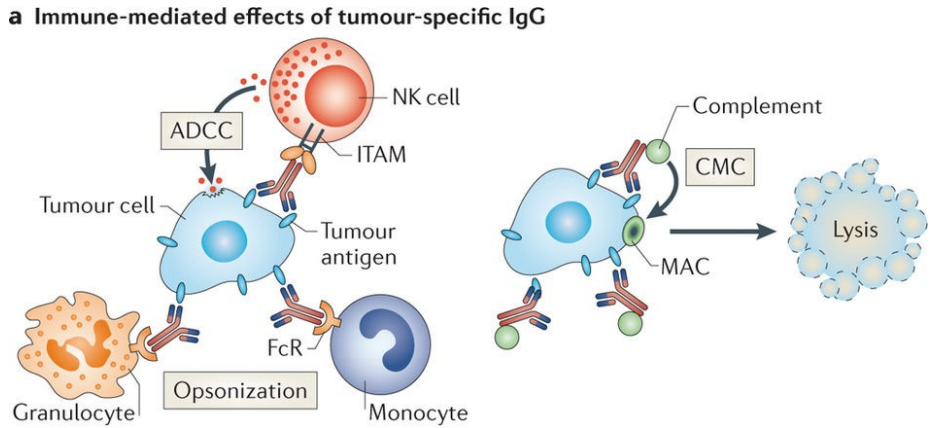
ADO-trastuzumab emtansine
Belantamab mafodotin
Brentuximab vedotin
Enfortumab vedotin
Gemtuzumab ozogamicin
Ibritumomab tiuxetan
Inotuzumab ozogamicin
Loncastuximab tesirine
Moxetumomab-pasudotox
Polatuzumab vedotin
Sacituzumab govitecan
Trastuzumab deruxtecan

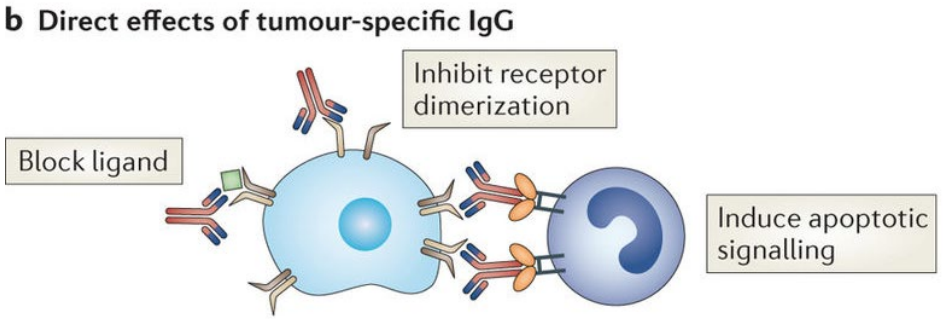
Will not be discussed
New drugs

Abemaciclib
Acalabrutinib
Afatinib
Alectinib
Alpelisib
Avapritinib
Axitinib
Binimetinib
Bosutinib
Brigatinib
Cabozantinib
Capmatinib
Ceritinib
Cobimetinib
Copanlisiba
Crizotinib
Dabrafenib
Dacomitinib
Dasatinib
Duvelisib
Enasidenib
Encorafenib
Entrectinib
Erdafitinib
Erlotinib
Everolimus
Fedratinib
Gefitinib
Gilteritinib
Glasdegib
Ibrutinib
Idelalisib
Imatinib
Infigratinib
Ivosidenib
Lapatinib
Larotrectinib
Lenvatinib
Lorlatinib
Midostaurin
Neratinib
Niraparib
Nilotinib
Olaparib
Osimertinib
Palbociclib
Pazopanib
Pemigatinib
Pexidartinib
Ponatinib
Pralsetinib
Regorafenib
Relugolix
Ribociclib
Ripretinib
Rucaparib
Ruxolitinib
Selpercatinib
Selumetinib
Sonidegib
Sorafenib
Sotorasib
Sunitinib
Talazoparib
Tazametostat
Tepotinib
Tivozanib
Trametinib
Tucatinib
Umbralasib
Vandetanib
Vemurafenib
Vismodegib
Zanubrutinib

Monoclonal Antibody (mAb) Overview

- Mechanism of action
  - Engineered antibody binds target transmembrane protein
  - Direct effects on malignant/target cells to disrupt cell signaling and growth
    - Blocks binding of a ligand or inhibits dimerization of a receptor
  - Mediate antibody-dependent cellular cytotoxicity (ADCC)
  - Mediate complement mediated cytotoxicity (CMC)
  - Enhance responsiveness to chemotherapy or radiation





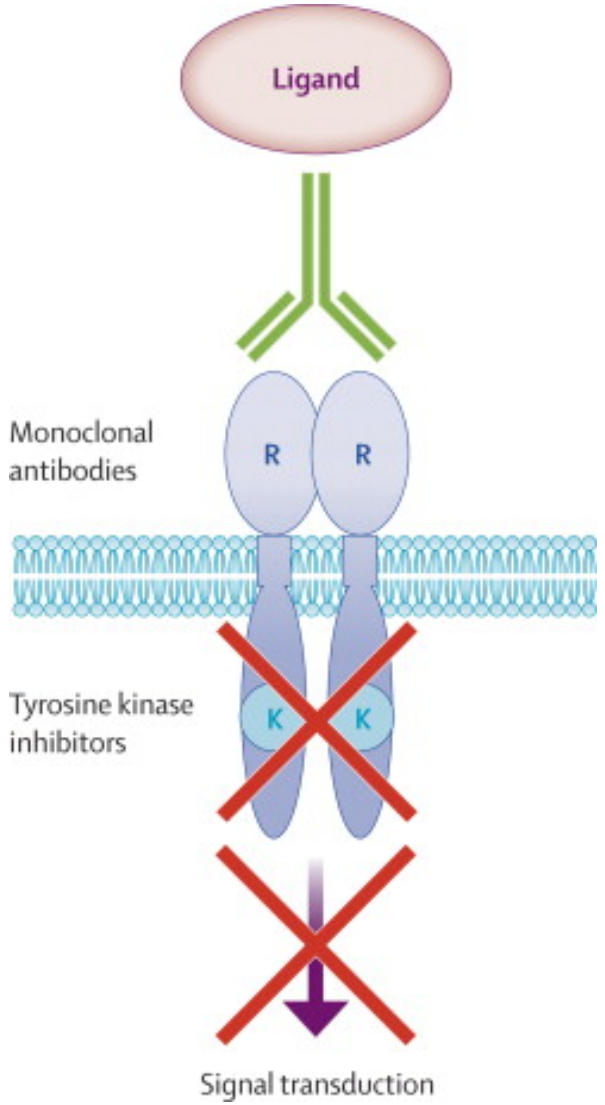
Nature Reviews Cancer. 2015. 15;361-370.

Monoclonal Antibody (mAb) Overview

- Most do not require dose adjustments (or not studied) for renal or hepatic impairment
- Most mAbs carry a **Black Box Warning** for infusion reactions
- Premedications: H1 blocker, H2 blocker, corticosteroid, acetaminophen
  - Varies by agent
  - 1st infusion vs. all infusions
- Monitoring period post-infusion suggested for some agents
- Management of infusion reactions:
  - Stop infusion
  - Medication management includes agents above if not given initially, additional steroid (hydrocortisone), meperidine for rigors, oxygen, epinephrine, etc.
  - Grade 1-2: resume at 50% of previous rate after symptom resolution

Tyrosine Kinase Inhibitors (TKI) Overview

- Mechanism:
  - Inhibition of tyrosine kinase enzyme results in blockade of multiple cell signal transduction pathways
  - Affects cell proliferation, survival, and invasion
- Must consider timing of administration in relation to food
- Must consider patient compliance
  - Multiple tablets per doses
  - Multiple doses per day
  - Ability to take tablets
- Must consider drug-drug interactions (DDIs) that require specific dose adjustment



Lancet Oncol. 2007. 8(8):738-743.

TKIs and QTc prolongation

- FDA considers any drug that prolongs the QTc by 5msec to be a QTc prolonging agent
  - QTc varies by up to 60 msec in the same patient throughout the day
- Some TKIs have specific dose adjustments/parameters for QTc: Nilotinib
  - Dose dependent effect
  - Obtain baseline EKG, 7 days after any dose change, and periodically
  - Contraindicated in hypokalemia, hypomagnesemia, or long QT syndrome
  - Correct electrolyte imbalances prior to initiation

Yap YG, et al. Heart. 2003. 89:1363-1372.

TKIs as CYP P450 substrates

- Food to avoid: grapefruit juice, pomegranate juice, starfruit, Seville oranges
- Smoking is a CYP1A2 inducer
- Most common interaction is through CYP3A4

Strong 3A4 inhibitors	Strong 3A4 inducers
Voriconazole, ritonavir, posaconazole, ketoconazole, itraconazole, clarithromycin, diltiazem, idelalisib	Rifampin, carbamazepine, enzalutamide, phenytoin, St. John's wort




Monoclonal Antibodies and Tyrosine Kinase Inhibitors

CD20 Targeting mAbs

	Rituximab (Rituxan)	Rituximab hyaluronidase (Rituxan Hycela)
Target	Chimeric	
Uses	NHL, CLL, ALL, Waldenstrom's	
Dosing	375 mg/m^2 500 mg/m^2	1400mg (23,400 units) in 11.7ml over 5 min 1600mg (26,800 units) in 13.4ml over 7 min
ADRs	TLS, neutropenia	
BBW	Infusion reactions, mucocutaneous reactions, PML, HBV reactivation	
Premed	APAP, H1 blocker	
Note (s)	HBV core antibody and surface antigen testing for all patients If surface antigen positive, prophylactic therapy with entecavir recommended	
		Must have 1 full dose of IV rituximab prior to SubQ administration Hyaluronidase reversibly opens up interstitial space in SubQ tissue to deliver >2.3ml

NHL: non Hodgkins lymphoma; CLL: chronic lymphocytic leukemia; ALL: acute lymphocytic leukemia; TLS: tumor lysis syndrome; APAP: acetaminophen; PML: progression multifocal leukencephalopathy; HBV: hepatitis B virus
ADR: adverse drug reaction; BBW: black box warning; premed: premedications

CD20 Targeting mAbs

	Ofatumumab (Arzerra)	Obinutuzumab (Gazyva)
Target	Fully human	Humanized
Uses	CLL, Waldenstrom's	CLL, FL
Dosing	• Initial: 300mg D1, 1000mg D8 • Then: 1000-2000mg Qweek, or Q28days • Then: 1000-2000mg Q4-8weeks	• C1D1: 100mg • C1D2: 900mg • C1D8 & D15: 1000mg • Then: 1000mg Q28d • Then: 1000mg Q2monthsx2yr
ADRs	Infusion reactions, TLS	Infusion reactions, TLS, neutropenia, thrombocytopenia
BBW	HBV reactivation, PML	HBV reactivation, PML
Premed	APAP, H1 blocker, corticosteroid	
Note	HBV core antibody and surface antigen testing for all patients If surface antigen positive, prophylactic therapy with entecavir recommended	

CLL: chronic lymphocytic leukemia; FL: follicular lymphoma; TLS: tumor lysis syndrome; APAP: acetaminophen; PML: progression multifocal leukencephalopathy; HBV: hepatitis B virus; ADR: adverse drug reaction; BBW: black box warning; premed: premedications

Key Points: CD20 Targeting mAbs

- Infusion reactions and premedication
- HBV reactivation
- No SubQ Rituximab until patient tolerates IV rituximab infusion

HER2 Targeting mAbs

	Trastuzumab (Herceptin)	Pertuzumab (Perjeta)	Margetuximab (Margenza)
Target	HER2		
Uses	Neo/adjuvant, met HER2+ breast cancer; HER2+ gastric cancer	Neoadj, adjuvant, met HER2+ breast cancer **with trastuzumab**	Metastatic HER2+ breast after 2 lines of therapy
Dosing	4mg/kg then 2mg/kg Qweek 8mg/kg then 6mg/kg Q3week	840mg, then 420mg Q3week	15mg/kg Q3 weeks
Re-load	Re-load for dose delay >1 week	Re-load for dose delay ≥6 weeks	n/a
Cardiotox BBW	• LVEF at baseline and periodically during treatment • Monitoring, hold/discontinuation parameters **DIFFERENT** for each agent		
Other BBW	Infusion reactions, pulmonary toxicity, embryo-fetal toxicity	Embryo-fetal toxicity	Embryo-fetal toxicity
Other ADR		Rash, diarrhea	

LoRusso PM. Clin Cancer Res. 2011. 17 (20): 6437-47.
HER2: human epidermal growth factor receptor 2; ADR: adverse drug reaction; BBW: black box warning

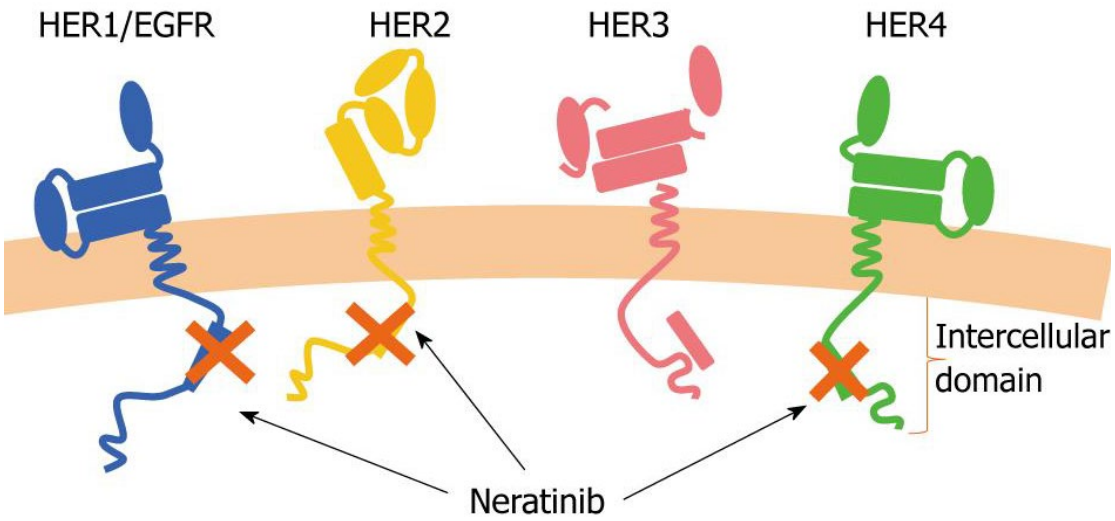
HER2 Targeting TKIs

	Lapatinib (Tykerb)	Neratinib (Nerlynx)	Tucatinib
Target	ErbB-1 (HER1, EGFR) and ErB-2 (HER2); reversible	Pan-HER inhibitor: HER1, HER2, HER4; irreversible	HER2 and 4, minimal inhibition of HER1
Uses	HER2+ mBC with letrozole or capecitabine	Extended adjuvant therapy for HER2+ BC; with capecitabine for mBC	With capecitabine and trastuzumab for HER2+ mBC
Dosing	Different dose with capecitabine vs letrozole • Child-Pugh C: dose adjust • Empty stomach	240mg daily with food • Child-Pugh C: 80mg daily • Avoid PPIs and H2 blockers • Admin 3h after antacids	300mg twice a day
DDI	Dose reduce with CYP3A4 inhibitors	Substrate of 3A4	**Inhibits CYP3A4 and Pgp**
BBW	• Hepatotoxicity – fatal deaths • AST/AST >3xULN and Tbili>2xULN • Do not rechallenge		
ADR	• **DIARRHEA** • Cardiotoxicity – hold if LVEF≥grade 2, resume if recovered (LVEF baseline and periodic) • Rash, QTc prolongation, pneumonitis	• **DIARRHEA**: Antidiarrheal prophylaxis for C1 - C2 • D1-14: loperamide 4mg TID • D15-56: loperamide 4mg BID • D57-365: loperamide 4mg PRN • Hepatotoxicity	• Diarrhea • Hepatotoxicity

HER2: human epidermal growth factor receptor 2; ADR: adverse drug reaction; BBW: black box warning; DDI: drug drug interactions; mBC: metastatic breast cancer

Key Points: HER2 Targeted Therapy

- Cardiotoxicity
- Diarrhea
- Hepatotoxicity with the TKIs



Park Y. World J Clin Oncol. 2011. 2(2):125-134.

EGFR Targeting mAbs

	Cetuximab (Erbitux)	Panitumumab (Vectibix)	Necitumumab (Portrazza)
Target	Binds ligand binding site of EGFR (HER1, c-ErbB-1)		
Uses	CRC, SCCHN	Metastatic CRC monotherapy; mCRC first-line with FOLFOX	Metastatic NSCLC with gemcitabine + cisplatin
Dosing	400mg/m^2 loading dose then 250 mg/m^2 weekly	6mg/kg every 14 days	800mg D1,8 Q3 weeks
ADR	Infusion reactions, acneiform rash, diarrhea, hypoMg, fatigue	Infusion reactions, acneiform rash, diarrhea, hypoMg, hypoCa, keratitis	Infusion reactions, rash, thromboembolism
BBW	Infusion reactions Cardiopulmonary arrest	Dermatologic toxicity	Cardiopulmonary arrest Hypomagnesemia
Premeds	H1 blocker		• If previous grade 1-2 inf rxn: H1 blocker with next infusion • If recurrent grade 1-2 inf rxn: H1 blocker, APAP, dex
Notes	Patients with NRAS or KRAS mutation are unlikely to benefit. Panitumumab ineffective in BRAF V600E mutation.		

EGFR: epidermal growth factor receptor; CRC: colorectal cancer; SCCHN: squamous cell carcinoma of the head and neck; NSCLC: non small cell lung cancer; Rxn: reactionADR: adverse drug reaction; BBW: black box warning; premeds: premedication; Mg: magnesium; Ca: calcium

EGFR Targeting TKIs

	Erlotinib (Tarceva)	Gefitinib (Iressa)	Afatinib (Gilotrif)
Targets	EGFR (reversible)		EGFR (irreversible) HER2, HER4
Uses	mNSCLC* with EGFR exon 19 or exon 21 (L858R) mutation Metastatic pancreatic cancer with gemcitabine	mNSCLC* with EGFR exon 19 or exon 21 (L858R) mutations	mNSCLC with EGFR exon 19 or exon 21 (L858R) mutations Squamous mNSCLC
Dosing	100-150mg daily Empty stomach • Caution with Tbili>3xULN	250 mg daily	40mg daily, empty stomach • Dose reduced for renal function
ADR	Rash, diarrhea, hemorrhage, hepatotoxicity, corneal ulcerations	Rash, diarrhea, hepatotoxicity, ocular toxicity	Cardiovascular toxicity, diarrhea, stomatitis, hepatotoxicity, ocular toxicity, paronychia
DDI	• CYP3A4, CYP1A2 inh/ind • Smoking • Acid-reducing agents	• CYP3A4 inducer • Acid-reducing agents	• Pgp inh/ind: reduce/increase by 10mg
Notes	*Higher binding affinity for EGFR exon 19 deletion or exon 21 (L858R) mutations		Consider LVEF at baseline and periodically

EGFR: epidermal growth factor receptor; CRC: colorectal cancer; mNSCLC: metastatic non small cell lung cancer; ADR: adverse drug reaction; DDI: drug drug interactions; LVEF: left ventricular ejection fraction

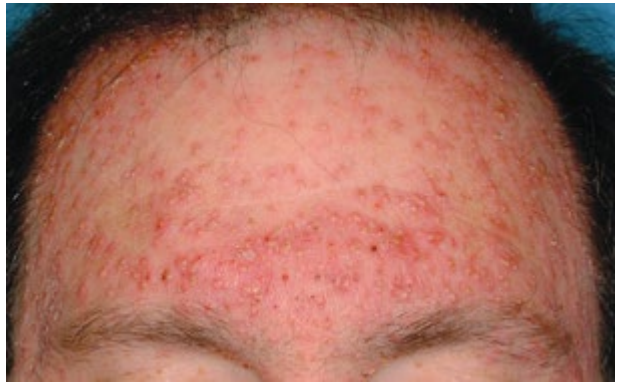
EGFR Targeting TKIs

	Osimertinib (Tagrisso)	Dacomitinib (Vizimpro)
Target	Mutated EGFR (irreversible) (T790M, L858R, exon 19 del)	EGFR (irreversible), including exon 19del and exon 21 L858R sub HER2, HER4
Uses	**Adjuvant therapy for EGFR mutated NSCLC** 1st line NSCLC, EGFR mutated mNSCLC EGFR T790M mutated mNSCLC	First line mNSCLC, EGFR mut+ exon 19 del or exon 21 L858R sub
Dosing	80mg daily W/3A4 inducer: 160mg daily	45mg daily
DDI	Rash, diarrhea, nail toxicity, ocular toxicity, nausea, QTc prolongation, bone marrow suppression (rare), cardiotox	Avoid PPI Strong CYP2D6 inhibitor
ADR		Rash, diarrhea, pneumonitis/ILD
Notes	Consider LVEF at baseline and periodically	Take H2 blocker 10h before or 6h after dacomitinib

EGFR: epidermal growth factor receptor; mNSCLC: metastatic non small cell lung cancer; ADR: adverse drug reaction; DDI: drug drug interactions; LVEF: left ventricular ejection fraction

EGFR Dermatologic Toxicity Management

- Rash correlated with drug response
  - Dose reductions only for severe reactions
- Develops within first 2 weeks of treatment
- Limit sun exposure, use sunscreen
- Moisturize
- Topical or systemic antibiotics
- May use topical corticosteroids, sparingly



Am Fam Physician 2008;77:311-19

Key Points: EGFR Targeted Therapy

- Dermatologic toxicity – acne-like rash
- Diarrhea
- Smoking induces erlotinib clearance – need to dose adjust

VEGF Targeting mAbs

	Bevacizumab (Avastin)	Ramucirumab (Cyramza)	Ziv-aflibercept (Zaltrap)
Target	VEGF (ligand)	VEGFR2 (receptor)	VEGF-A, VEGF-B, P_LGF (ligand)
Uses	Cervical, mCRC, mRCC glioblastoma, NSCLC (non-squamous), ovarian	Adv gastric/GEJ w/paclitaxel mNSCLC with docetaxel mCRC with FOLRIRI	mCRC in combination with FOLFIRI (2^{nd} line following oxaliplatin-based regimen)
Dosing	5-15 mg/kg IV every 2-3 weeks	8 mg/kg IV Q2 wks 10 mg/kg IV Q3 wks (lung)	4 mg/kg IV Q2 weeks
ADR	HTN, diarrhea, stomatitis, hand-foot syndrome, proteinuria, VTE/ATE, asthenia Ramucirumab and ziv-aflibercept: dose reductions for HTN or proteinuria		
	Myalgia, ovarian failure	Infusion reaction, thyroid dysfunction	Voice disorder
BBW	Black box warnings removed		Hemorrhage, GI perf, wound healing
Premed		IV H1 blocker Prev rxn: + APAP + steroid	
Notes	Hold for 28 days before and after surgeries	Hold prior to surgery	Hold for 28 days before and after surgeries

VEGF/R: vascular endothelial growth factor/ receptor; NSCLC: non small cell lung cancer; CRC: colorectal cancer; RCC: renal cell carcinoma; GEJ: gastroesophageal junction; HTN: hypertension, VTE/ATE: venous/arterial thromboembolism
BBW: black box warning; premed: premedication; Rxn: reactionADR: adverse drug reaction; DDI: drug drug interactions;

Antiangiogenic TKIs

	Sorafenib (Nexavar)	Sunitinib (Sutent)	Pazopanib (Votrient)	Axitinib (Inlyta)
Target	VEGFR, PDGFR, cKIT			VEGFR
	FLT3, BRAF, RET	CSFR1, RET, FLT3	FBFR1/3, Lck, etc	
Uses	RCC, HCC, DTC	RCC, GIST, PNET	RCC, STS	RCC
Dose	400 mg BID Empty stomach	50mg QD x 4wk Q6wk PNET:37.5 mg daily	800 mg QD, empty stomach, avoid acid suppression	5 mg→7mg→10mg Q12H Uptitrated Q2weeks without Grade 2 ADRs
	Lack clear dose adjustment guidelines			
DDI	Warfarin Avoid 3A4 inh/ind	3A4 inhibitor/inducer: dec/inc dose incrementally	3A4 inhibitor: 400mg 3A4 inducer: avoid	3A4 inh or Child-Pugh Class B: decrease by 50%
ADR	HTN, HFS, diarrhea, N/V, fatigue, myelosuppression, hair/skin pigment changes			
Rare ADR	Proteinuria/nephrotic syndrome, wound dehiscence, GI perforation, hypothyroidism, arterial thrombosis, hemorrhagic events, QTc prolongation			
Notes			Discontinue 7d prior to surgery	Discontinue 24h prior to surgery

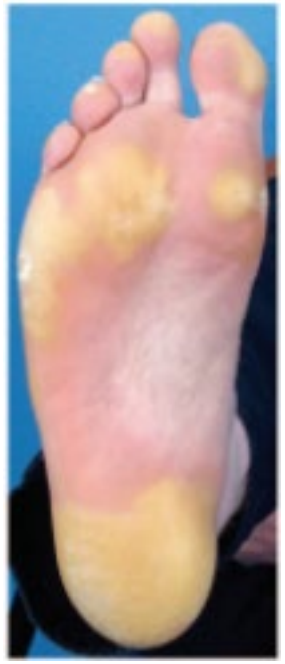
VEGF/R: vascular endothelial growth factor/ receptor; RCC: renal cell carcinoma; HCC: hepatocelluclar carcinoma; DTC: differentiated thyroid cancer; GIST: gastrointestinal stromal tumor; STS: soft tissue sarcoma; PNET: primitive neuroectodermal tumor; HTN: hypertension, HFS: hand foot syndrome; N/V: nausea/vomiting ADR: adverse drug reaction; DDI: drug drug interactions

Antiangiogenic TKIs

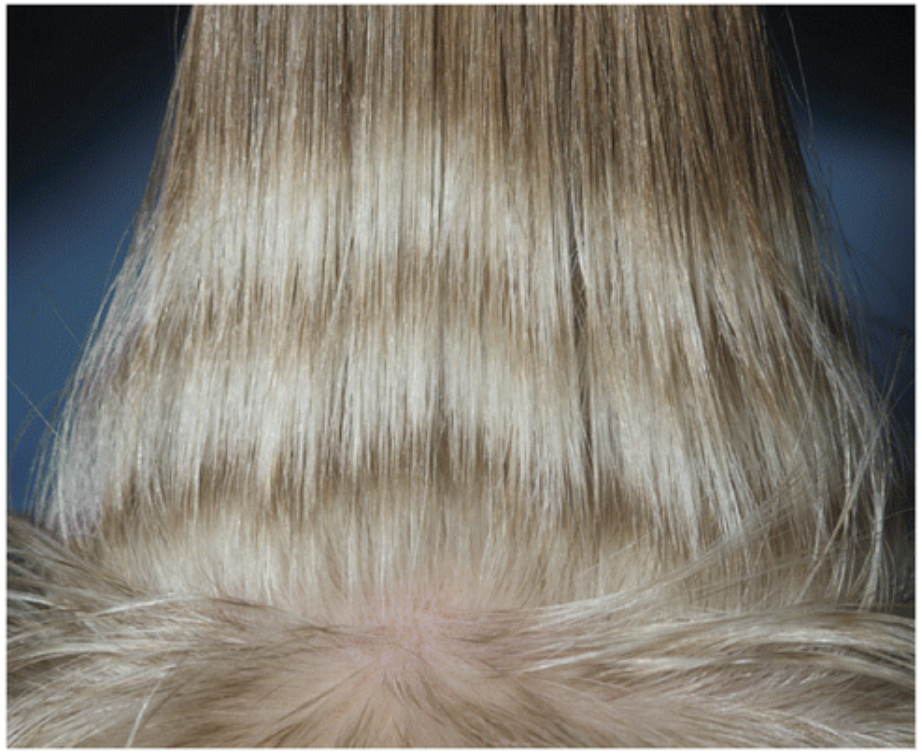
	Tivozanib (Fotivda)
Target	VEGFR-1, 2, 3
Uses	Advanced renal cell carcinoma after 2 prior lines of treatment
Dose	1.34mg QD D1-21 Q28days
DDI	Avoid strong CYP3A4 inhibitors/inducers
ADR	HTN, diarrhea, proteinuria, thyroid dysfunction, dysphonia, nausea
Rare ADR	Venous and arterial thromboembolism, RPLS, cardiac failure
Notes	Hold for 24h prior to elective surgery Hold for at least 2 weeks after major surgery

VEGF/R: vascular endothelial growth factor/ receptor; HTN: hypertension; RPLS: reverse posterior leukencephalopathy syndrome; ADR: adverse drug reaction; DDI: drug drug interactions

VEGF Dermatologic Toxicity



Hand-foot skin reaction



Hair discoloration

Brzezniak C, et al. N Engl J Med. 2014. 370:e277.
Gomez P, et al. The Oncologist. 2011. 16:1508-1519.

Multikinase TKIs

	Regorafenib (Stivarga)	Lenvatinib (Lenvima)
Target	Antiangiogenic: VEGFR1, 2, 3; TIE-2 Anti-proliferation: PDGFR, FGFR, MAPK Anti-oncogenic: c-Kit, RAF-1 Other: BRAF, Ret, etc	Antiangiogenic: VEGFR Anti-proliferation: FGFR, PDGFR Anti-oncogenic: KIT Other: RET
Uses	HCC 2nd line treatment of mCRC, GIST	Differentiated thyroid cancer (DTC) RCC with everolimus
Dose	160mg QD x21d (28 day cycle) • Low fat breakfast (specified) • Dose reduce by 40mg increments	24mg QD for DTC 18mg QD for RCC Adjust: CrCl<30ml/min or Child-Pugh C
ADR	Dysphonia, HFS, HTN, GI perforation, hemorrhage, wound healing, proteinuria, SCC of the skin	Moderate emetogenicity, diarrhea, ATE/MI, GI perforation, hemorrhage, proteinuria, HFS, QTc prolongation, hepatotoxicity
BBW	Hepatotoxicity	
DDI	CYP3A4 inh/ind: no recommendations Warfarin	

VEGF/R: vascular endothelial growth factor/ receptor; RCC: renal cell carcinoma; HCC: hepatocelluclar carcinoma; DTC: differentiated thyroid cancer; HTN: hypertension, HFS: hand foot syndrome; GI: gastrointestinal
SCC: squamous cell carcinoma; ATE: arterial thromboembolism; MI: myocardial infarction; HFS: hand foot syndrome; ADR: adverse drug reaction; DDI: drug drug interactions; BBW: black box warning

Multikinase TKIs

	Vandetanib (Caprelsa)	Cabozantinib (Cometriq, Cabometyx)
Target	Antiangiogenic: VEGFR1, 2, 3; TIE-2 Anti-proliferation: PDGFR, FGFR, MAPK Anti-oncogenic: c-Kit, RAF-1 Other: BRAF, Ret, etc	Antiangiogenic: VEGFR Anti-proliferation: FGFR, PDGFR Anti-oncogenic: KIT Other: RET
Uses	Medullary thyroid cancer (MTC)	RCC, MTC
Dose	300mg daily • QTc<450msec to initiate; K^+>4mEq/L • CrCl<50ml/min: 200mg daily • Not recommended for Child-Pugh B/C • Avoid CYP3A4 inducers	Cabometyx, RCC: 60mg QD Cometriq (MTC): 140mg -180mg QD • Empty stomach • Dose adjust for 3A4 inh/ind • Dose adjust for C-P Class A/B
ADR	**Rash,** diarrhea, heart failure, HTN, CVA, hemorrhage, hypothyroidism	HFS, diarrhea, hemorrhage, HTN, proteinuria, VTE/ATE, wound healing, stomatitis, hair color change
BBW	**QTc prolongation (requires FDA REMS program)**, torsades de pointes, sudden death	Cometriq: Perforations, fistulas, hemorrhage
Notes	**Cometriq and Cabometyx not interchangeable**	
	Avoid QTc prolonging agents	Hold 28d prior to surgery

VEGF/R: vascular endothelial growth factor/ receptor; RCC: renal cell carcinoma; K: potassium; CrCL: creatinine clearance; HTN: hypertension, HFS: hand foot syndrome; VTE/ATE: venous/arterial thromboembolism; CVA: cerebrovascular accident; ADR: adverse drug reaction; DDI: drug drug interactions; BBW: black box warning

Key Points: VEGF Targeted Therapy

- Hypertension
- Proteinuria/nephrotic syndrome
- Considerations for holding therapy around the time of procedures
- Update: BBW removed for bevacizumab and ramucirumab

CCR4 Targeting mAb

	Mogamulizumab (Poteligeo)
Target	CCR4
Uses	Relapsed, refractory mycosis fungoides or Sezary syndrome after ≥1 prior therapy
Dose	1mg/kg IV D1, 8, 15, 22 C1, then 1mg/kg D1, 15 Q28 days • Premed with diphenhydramine and APAP for first infusion, then PRN
ADR	Autoimmune toxicity, lymphocytopenia, dermatologic toxicity/drug eruption (24%), infections (20%), infusion reactions (34%), diarrhea (24%)
Monitoring	Monitor closely for early evidence of transplant related complications in patients who have previously received hematopoietic transplant
Notes	Median onset of rash 15-31 weeks

APAP: acetaminophen; PRN: as needed; ; ADR: adverse drug reaction

EGFR/MET Targeting mAb

	Amivantamb (Rybrevant)
Target	EGFR and MET receptor
Uses	Locally advanced, mNSCLC with EGFR exon 20 insertion after platinum-based chemo
Dose	1050mg if <80kg; 1400mg if ≥ 80kg Split infusion of first dose into Day 1 and Day 2 Followed by weekly infusion for 4 weeks then Q2 weeks Peripheral line for the first two weeks
Premed	Diphenhydramine and acetaminophen with every infusion Dexamethasone with initial dose (Days 1 and 2), then as needed
ADR	Infusion reactions Acneiform rash, paronychia Ocular toxicity
Serious ADR	ILD/pneumonitis

mNSCLC: metastatic non small cell lung cancer; ILD: interstitial lung disease; premed: premedication; ADR: adverse drug reaction;

Tyrosine Kinase Inhibitors

CDK Targeting TKIs

	Palbociclib (Ibrance)	Ribociclib (Kisqali)	Abemaciclib (Verzenio)
Target	Cyclin dependent kinase 4 and 6		
Uses	Breast cancer, advanced or metastatic; HR+, HER2-		
Dose	125mg QD x21 days every 28 days with aromatase inh or ovarian suppression • Take with food • CYP3A4 inh: 75mg QD	600mg QD x 21days every 28 days with letrozole in the morning • CYP3A4 inh: 400mg QD • Child-Pugh B/C: 400mg QD	150mg BID with aromatase inh or fulvestrant • CYP3A4 inh: 100mg BID • Child-Pugh C: 150mg QD 200mg BID as a single agent • CYP3A4 inh: 150mg BID
ADR	Neutropenia, nausea, stomatitis, diarrhea	Hepatotoxicity, neutropenia, QTc prolongation, nausea, diarrhea	**Diarrhea,** neutropenia, hepatotoxicity, VTE, inc SCr
Monitoring	CBC Q2weeks x2months, then PRN	CBC, LFTs Q2weeks x2 months, then monthly Electrolytes monthly x6 months EKG Q2 weeks x3, then PRN	CBC, LFTs Q2 weeks x2 months, then monthly x2 months, then PRN
Notes	Avoid grapefruit	Avoid grapefruit	More CDK4 activity/less CDK6 = less neutropenia Avoid grapefruit

HR: hormone receptor; HER2: human epidermal growth factor receptor 2; inh: inhibitor; VTE: venous thromboembolism; SCr: serum creatinine; CBC: complete blood count; PRN: as needed; ADR: adverse drug reaction

CDK Targeting TKIs

	Trilaciclib (Cosela)
Target	Cyclin dependent kinase 4 and 6
Uses	Chemotherapy induced myelosuppression
Dose	240mg/m2 prior to platinum-etoposide or topotecan base chemo for ES-SCLC • Administer on day of chemo
DDI	Inhibits OCT2
ADR	Infusion site reactions, hypersensitivity reactions, ILD
Notes	Interval between trilaciclib doses on sequential days <28 hours Allow 96 hours to elapse after last trilaciclib dose before resuming chemo

ES-SCLC: extensive stage- small cell lung cancer; ILD: interstitial lung disease; ADR: adverse drug reaction; DDI: drug drug interactions

Key Points: CDK 4/6 Inhibitors

- Palbociclib = neutropenia
  - Low percentage of febrile neutropenia
- Ribociclib = neutropenia + QTc prolongation + hepatotoxicity
- Abemaciclib = diarrhea
  - Asymptomatic increase in SCr – consider using cystatin C if necessary
- All are CYP3A4 substrates and require dose reduction with a CYP3A4 inhibitor
  - Avoid grapefruit juice

PARP Inhibitors

	Olaparib (Lynparza)	Rucaparib (Rubraca)	Niraparib (Zejula)	Talazoparib (Talzenna)
Target	Poly-ADP ribose (PARP)			
	Ovarian cancer BRCA mut, HER2- mBC Prostate, Pancreatic	Ovarian cancer Prostate cancer	Ovarian cancer	BRCA mut, HER2- mBC
Dose	300mg BID • CYP3A4 inh: 200mg BID • Dose reduce for renal fx	600mg BID	300mg QD • Consider 200mg QD if<77kg and/or b/l platelet <150K	1mg daily • 0.75mg with Pgp inh • Dose reduce for renal fx
ADR	Nausea, fatigue, diarrhea, anemia, neutropenia, secondary malignancy	Nausea, constipation/diarrhea, dysgeusia, anemia, neutropenia, asymptomatic inc SCr, secondary malignancy	**Thrombocytopenia**, neutropenia, anemia, nausea, insomnia, HTN and hypertensive crisis, secondary malignancy	Neutropenia, anemia, thrombocytopenia, nausea, transaminitis, diarrhea, secondary malignancy
Notes	Tablets and capsules are not interchangeable		Begin no later than 8 weeks after platinum regimen	

mBC: metastatic breast cancer; fx: function; b/l: baseline; SCr: serum creatinine; HTN: hypertension; ADR: adverse drug reaction

Key Points: PARP Inhibitors

- Dose reduce for renal dysfunction: olaparib, talazoparib
- More hematologic toxicity: niraparib, talazoparib
- Olaparib FDA approved in first-line maintenance setting for BRCA mutated patients with ovarian cancer
- Olaparib and talazoparib approved for breast cancer

BRAF/MEK Targeted TKIs

	Vemurafenib | cobimetinib (Zelboraf | Cotellic)		Dabrafenib | trametinib (Tafinlar | Mekinist)		Encorafenib | binimetinib (Braftovi |Mektovi)	
Target	BRAF/MEK					
Uses	BRAF V600E or V600K mutated, unresectable or metastatic melanoma					
	Erdheim-Chester, V600E mutated		• Adjuvant melanoma • BRAF V600E mutated mNSCLC • Adv/met anaplastic thyroid ca			
Dose	• DDI: warfarin, digoxin	• Reduce dose for short term use (<14 d) of 3A4 inhibitor	• Empty stomach • Avoid acid reducers if possible	• Empty stomach	• Reduce dose for use with CYP3A4 inhibitors	• Dose adjust for increased Tbili
Class ADR	GI toxicity (Nausea, vomiting, diarrhea) Risk for cutaneous SCC if BRAF inhibitor used alone					
Unique ADR	CK elevation, **retinal events,** photosensitivity, rash, diarrhea		**Pyrexia**, hypertension, lymphedema, hand-foot syndrome		CK elevation, **blurred vision/ocular toxicity**	
Notes	Dabrafenib - Hemolytic anemia if G6PD deficient					

mNSCLC: metastatic non small cell lung cancer; ca: cancer; DDI: drug drug interaction; GI gastrointestinal; SCC: squamous cell carcinoma; CK: creatine kinase; ADR: adverse drug reaction

ALK Targeting Inhibitors

	Crizotinib (Xalkori)	Ceritinib (Zykadia)	Alectinib (Alecensa)	Brigatinib (Alunbrig)
Target	ALK, c-MET, ROS1, RON	ALK, IGF-1R, ROS1	ALK, RET	ALK, ROS1, FLT3, EGFR
		Activity if crizotinib resistant		
Uses	mNSCLC, ALK+, ROS1+	mNSCLC, ALK+		
Dose	250mg PO BID • Dose reduce for renal fx • Avoid high fat meals	750mg PO daily • 3A4 inh: reduce by 1/3 • Empty stomach	600 mg PO BID • Take with food	• 90mg QDx7 days, then 180mg daily • Restart at initial dose if interrupted by >14d • 3A4 inh: reduce by 50%
ADR	Bradycardia, hepatotoxicity, pulmonary toxicity, QTc prolongation			**Pulmonary toxicity**, pancreatitis, hyperglycemia, visual disturbance
	Moderate emetogenicity, ocular toxicities	**Moderate emetogenicity**, neuropathy, hyperglycemia, pancreatitis	Myalgia, photosensitivity	
Notes	Avoid grapefruit juice			

mNSCLC: metastatic non small cell lung cancer; ALK: anaplastic lymphoma kinase; fx: function; ADR: adverse drug reaction

ALK Targeting Inhibitors

	Lorlatinib (Lorbrena)
Target	ALK, ROS1
Uses	ALK+ metastatic NSCLC • Active in patient with resistance to crizotinib • Activity against multiple mutant forms of ALK
Dose	100mg daily • Dose reduce to 0.75mg with Pgp inhibitors (amiodarone, verapamil, carvedilol) • Dose reduce for renal function
DDI	Dose reduce if given with strong CYP3A4 inhibitor
ADR	Hypercholesterolemia, peripheral edema, peripheral neuropathy, hepatotoxicity, tinnitus, cognitive effects (Slowed speech, word finding ability), AV block (rare)
Monitoring	Serum cholesterol/triglycerides (baseline, monthly x2 months) ECG at baseline, then intermittently
Notes	Penetrates BBB

mNSCLC: metastatic non small cell lung cancer; ALK: anaplastic lymphoma kinase; DDI: drug drug interaction; ADR: adverse drug reaction; BBB: blood brain barrier

Key Points: ALK Inhibitors

- Lorlatinib hypercholesterolemia management: statins, +/- fibrates, +/- fish oil, +/- nicotinic acid

Severity	Guidance
Mild: Cholesterol ULN–300 mg/dL OR Triglycerides 150–300 mg/dL Moderate: Cholesterol >300–400 mg/dL OR Triglycerides >300–500 mg/dL	• Introduce or modify lipid-lowering therapy • Continue at the same lorlatinib dose
Severe: Cholesterol >400–500 mg/dL OR Triglycerides >500–1,000 mg/dL	• Introduce lipid-lowering agent or increase dosage of ongoing lipid-lowering therapy, or change to a new lipid-lowering therapy • Continue at the same lorlatinib dose without interruption
Life threatening: Cholesterol >500 mg/dL OR Triglycerides >1000 mg/dL	• Introduce lipid-lowering agent or increase dosage of ongoing lipid-lowering therapy, or change to a new lipid-lowering therapy • Withhold lorlatinib dose until hyperlipidemia is moderate or mild before rechallenging at same dose while maximizing lipid-lowering therapy • If severe hyperlipidemia recurs despite maximal lipid-lowering therapy, reduce lorlatinib dose by one dose level (by 25 mg)

- Ceritinib has more GI toxicity (diarrhea, nausea, vomiting)
- Pulmonary toxicity with brigatinib requires up-titration

Costa RB. Oncotarget. 2018. 9;22137-46. Bauer TM. The Oncologist. 2019; 24:1103-10

NTRK Targeting Inhibitor

	Larotrectinib (Vitrakvi)	Entrectinib (Rozlytrek)
Target	Tropomyocin receptor kinase protein	
Uses	Advanced or metastatic solid tumors with *NTRK* gene fusion	*ROS1*+ metastatic NSCLC Adv or met solid tumors with *NTRK* gene fusion
Dose	100mg BID • Dose reduce for hepatic impairment • Mg/m2 dosing for peds or if BSA <1m^2	600mg daily
DDI	Avoid (or dose reduce by 50%) with strong CYP3A4 inhibitors and avoid (or double the dose) with strong CYP3A4 inducers	Avoid with grapefruit juice Dose reduce to 100mg daily with strong CYP3A4 inh and 200mg daily with moderate CYP3A4 inh
ADR	Transaminitis Neurotoxicity (dizziness, gait disturbance, delirium, tremor, paresthesia)	Heart failure, neurotoxicity, skeletal fractures, hepatotoxicity, hyperuricemia, QTc prolongation
Monitoring	LFTs Q2 weeks during the first month, then monthly	
Notes	Oral solution available for pediatrics	

NSCLC: non small cell lung cancer; DDI: drug drug interaction; ADR: adverse drug reaction;

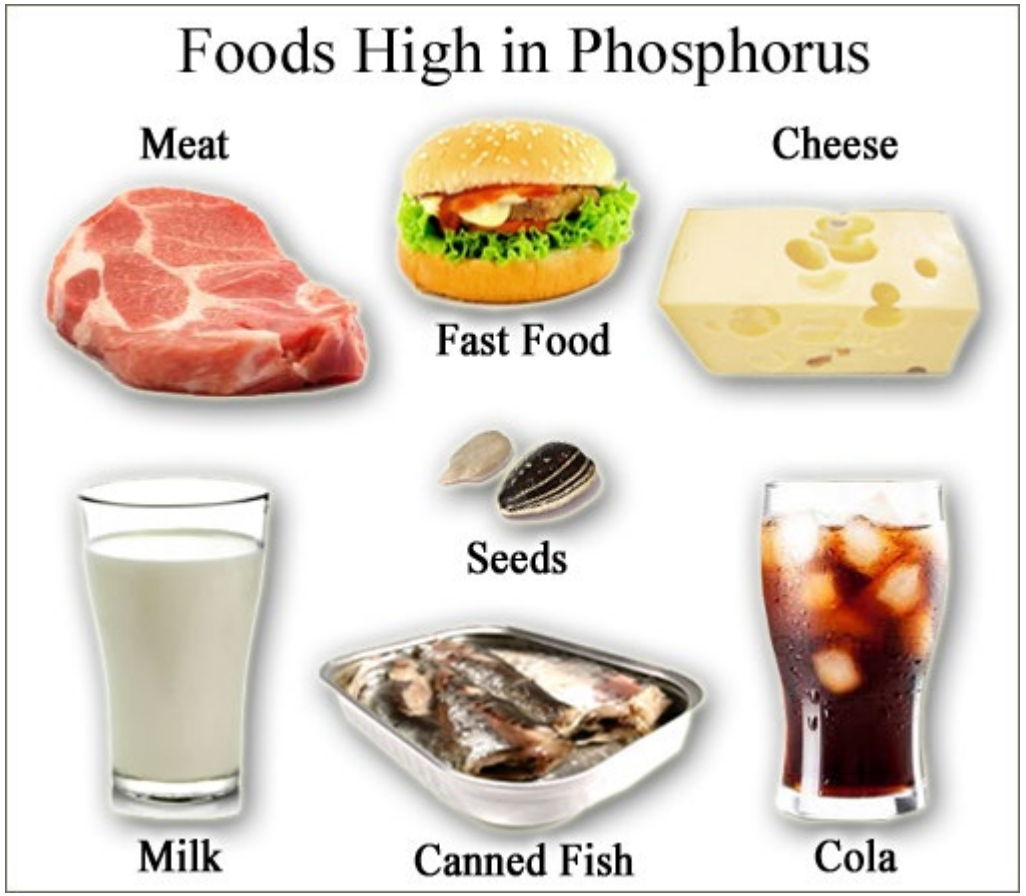
FGFR Targeting Inhibitor

	Erdafitinib (Balversa)	Pemigatinib (Pemazyre)	Infigratinib (Truseltiq)
Target	Fibroblast growth factor receptor kinase (FGFR1/2/3/4); RET, PDGFR, KIT, FLT4, VEGFR2	FGFR1, 2, and 3	FGFR2 fusion
Uses	FGFR mutated urothelial carcinoma, advanced or metastatic	Metastatic cholangiocarcinoma with FGFR2 fusion	Metastatic cholangiocarcinoma with FGFR2 fusion or rearrangement
Dose	8mg daily for 14-21 days If phosphate <5.5mg/dl and well-tolerated, increase to 9mg daily	13.5mg daily on Days 1-14, every 21 days	125mg Days 1-21, every 28 days Take on an empty stomach Dose reduce for renal/hepatic dysfunction
DDI	Substrate of CYP2C9 and CYP3A4	CYP3A4 inhibitors: avoid if possible or reduce pemigatinib dose	CYP3A4 inhibitors/inducers Acid reducing agents: avoid/separate
ADR	Hyperphosphatemia, Ocular toxicity		
Monitoring	Serum phosphate level at baseline and D14-D21 Ophthalmologic exams at baseline, monthly x4 months, then Q3 months	Eye exam monthly Q2 months x6 months, then Q3 months	Eye exam at 1 month, 3 months, then Q3 months

DDI: drug drug interaction; ADR: adverse drug reaction;

Hyperphosphatemia Management

- Hydration
- Low phosphate diet
  - 600-800mg daily
- Discontinue calcium supplements
- Sevelamer
  - Hold during week off (infigratinib)



http://www.nutrientsreview.com/minerals/phosphorus-phosphate.html

Hyperphosphatemia Management

30% patients required phosphate lower therapy with erdafitinib and pemigatinib

Lab	Erdafitinib	Lab	Pemigatinib	Lab	Infigratinib
7-9mg/dl	Hold erdafitinib Weekly phos until <5.5 DR if phos >5.5 for >1 wk Add phosphate lowering therapy	>7mg/dl - ≤10mg/dl	Initiate phosphate lowering therapy Monitor phosphate weekly Hold if >7mg/dl w/in 2 weeks of starting phosphate lowering therapy	>5.5mg/dl - ≤7.5mg/dl	Initiate or dose adjust phosphate binder Monitor phosphate weekly (hold during week off tx)
9-10mg/dl	Hold erdafitinib Weekly phos until <5.5 Restart at reduced dose			>7.5mg/dl	Hold until phos ≤5.5 Resume if phos >7.5 for <7d DR if phos >7.5 for >7 or if phos >9
>10mg/dl	Hold erdafitinib Weekly phos until <5.5 Restart at 2 dose levels lower	>10mg/dl	Initiate phosphate lowering therapy Hold if >10mg/dl w/in 1 week of starting phosphate lowering therapy		

Phos: phosphate; DR: dose reduce; tx: treatment

BCR-ABL Targeting TKIs

	Imatinib (Gleevec)	Dasatinib (Sprycel)	Nilotinib (Tasigna)
Target	BCR-ABL, PDGF, SCF, c-Kit	BCR-ABL, SRC family, c-Kit, EPHA2, PDGFR For imatinib resistance except T315I & F317V mut	BCR-ABL, c-Kit, PDGFR For imatinib resistance
Uses	Ph+ CML, Ph+ ALL, GIST, aggressive systemic mastocyctosis, MDS w/PDGF rearrangements	Ph+ CML, newly dx or resistant/intolerant, Ph+ ALL	Ph+ CML, newly dx or resistant/intolerant
Dose	400mg QD with food Range: 100-800mg QD • 3A4 inducer: inc 50% • CrCl<40: dec 50% • Severe hep dz: dec 25% • DDI: warfarin	100-180mg PO daily • 3A4 inh: reduce dose • 3A4 ind: increase dose • Empty stomach • Antacids 2h before/after • Avoid PPI/H2 blockers	300-400mg PO Q12 hours • 3A4 inh: reduce by 100mg • Child-Pugh A/B/C: reduce initial dose, then titrate up • Empty stomach • Antacids 2h before/after
ADR	Bone marrow suppression, cardiovascular dysfunction, edema, hypothyroidism		
	Rash, hepatotoxicity, AKI, TLS, moderate emetogenicity	Rash, PAH, hemorrhage, TLS, QTc prolongation	Electrolyte abnormalities, hepatotoxicity, inc lipase
Notes	Use 400mg tabs to reduce iron exposure		BBW: QTc prolongation

CML: chronic myelogenous leukemia; ALL: acute lymphocytic leukemia; GIST; gastrointestinal stromal tumor; MDS: myelodysplastic syndrome; dz: disease; AKI: acute kidney injury; TLS: tumor lysis syndrome; PAH: pulmonary arterial hypertension; inc: increased; BBW: black box warning; DDI: drug drug interactions; ADR: adverse drug reaction;

BCR-ABL Targeting TKIs

	Bosutinib (Bosulif)	Ponatinib (Iclusig)
Target	BCR-ABL, SRC family, c-Kit, PDGFR Activity in imatinib resistance except T315I and V299L	BCR-ABL, VEGFR, FGFR, PDGFR, FGFR, EPH, and SRC kinases, as well as KIT, RET, TIE2, and FLT3
Use	Ph+ CML in patients with resistance or intolerance to prior therapy	
		Resistant Ph+ ALL or with T315I mut
Dose	500-600mg PO daily with food • CrCl<50: 400mg daily • CrCl<30: 300mg daily • Child-Pugh A/B/C: 200mg daily	45mg PO daily • 3A4 inh: reduce to 30mg daily • Child-Pugh A/B/C: 30mg daily
ADR	Bone marrow suppression, edema	
	Moderate emetogenicity, nausea, diarrhea, pancreatitis, QTc prolongation	Arrhythmias, GI perf, HTN, ocular toxicity, hemorrhage, neuropathy, pancreatitis, TLS, wound healing
BBW		**Arterial occlusion (35%), heart failure, hepatotoxicity, VTE**
Notes	Antacids/H2 blockers 2h before/after	Optimal dose not identified

CML: chronic myelogenous leukemia; TLS: tumor lysis syndrome; HTN: hypertension; GI perf: gastrointestinal perforation; VTE: venous thromboembolism
BBW: black box warning; ADR: adverse drug reaction

Key Points: BCR-ABL Targeting TKIs

- Avoid or time acid-suppressing agents with dasatinib, nilotinib, and bosutinib
- All are substrates of CYP3A4
  - Dose reduction and monitoring w/concurrent CYP3A4 inh with dasatinib, nilotinib, and ponatinib
- More fluid retention with dasatinib and imatinib
- Ponatinib has the most distinct toxicity profile

JAK Targeting TKIs

	Ruxolitinib (Jakafi)	Fedratinib (Inrebic)
Target	JAK 1 and JAK 2	JAK2 (selective) and FLT3
Use	GVHD, steroid refractory; myelofibrosis; polycythemia vera	Myelofibrosis
Dose	GVHD: 5-10mg BID MF: 5-20mg BID based on plt count • Dose reduce per CrCl <60ml/min & Tbili	400mg QD if plt >50 • Dose reduce for CrCl 15-29ml/min
DDI	Dose reduce for use w/strong CYP3A4 inhibitor	
ADR	Bone marrow suppression, edema	
	Anemia, infection, lipid abnormalities, non-melanoma skin cancer	Anemia, GI tox (N/V/diarrhea) Less common:hepatotox, amylase/lipase elevations
BBW		Encephalopathy (Wernicke's)
Notes	Taper at discontinuation d/t withdrawal syndrome	Baseline B1 (thiamine) prior to initiation

GVHD: graft versus host disease; MF: myelofibrosis; CrCl: creatinine clearance; plt: platelets; GI: gastrointestinal; N/V: nausea/vomiting; DDI: drug drug interaction; BBW: black box warning; ADR: adverse drug reaction

Bruton's Tyrosine Kinase Inhibitors

	Ibrutinib (Imbruvica)	Acalabrutinib (Calquence)	Zanubrutinib (Brukinsa)
Target	Bruton's tyrosine kinase		
Uses	CLL/SLL, MCL, MZL, Waldenstrom's, cGVHD	MCL after 1 prior therapy	MCL, relapsed/refractory
Dose	CLL/WM: 420mg daily MCL: 560mg daily	100 mg Q12 hours • Avoid PPIs; separate 2h from H2 blockers	160mg BID or 320mg daily with food • Dose reduce with CYP3A4 inh
Common ADR	**Diarrhea**, nausea, fatigue, rash myalgias/arthralgias, myelosuppression		Myelosuppression, hemorrhage, infection
Serious/ Rare ADR	**Grade 3/4 bleeding**, **AFib,** infection	Afib/flutter, bleeding, infection, secondary malignancies	Afib/flutter
Note	Avoid strong 3A4 inhibitors & inducers - dosing recommendations available		Consider holding for 3-7 days around procedures
	Infection prophylaxis for HSV, PJP		

CLL: chronic lymphocytic leukemia; SLL: small lymphocytic leukemia; MCL: mantle cell lymphoma; MZL: marginal zone lymphoma; cGVHD: chronic graft versus host disease; WM: Waldenstroms macroglobulinemia; PPI: proton pump inhibitor; Afib: atrial fibrillation; ADR: adverse drug reaction

BCL-2 Targeting TKI

	Venetoclax (Venclexta)
Target	BCL-2, an anti-apoptotic protein
Uses	• Relapsed/refractory CLL, 17p deletion • AML, newly diagnosed, with azacitidine, decitabine, or cytarabine
Dose	Dose titrated up • Adjusted for TLS and heme toxicity • Premeds: hydration and antihyperuricemic therapy
DDI	Dose reduce by 75% for concurrent strong CYP3A4 inhibitor Dose reduce by 50% for concurrent moderate CYP 3A4 inhibitor
ADR	**TLS;** neutropenia > anemia, thrombocytopenia, diarrhea, nausea

TLS Risk Assessment & Monitoring

- Start allopurinol 2-3 days prior to therapy initiation
- Outpatient hydration with 1.5 to 2L orally (or IV) for low and medium risk
  - Low risk: all lymph nodes <5 cm and ALC <25,000/mm^3
  - Medium risk: all lymph nodes <5 cm and ALC <25,000/mm^3
- INPATIENT: PO hydration as above with additional 150-200 ml/hour
  - High risk: any LN ≥10 cm OR ALC ≥25,000/mm^3 and any LN ≥5 cm
  - Consider rasburicase if baseline uric acid is high

CLL: chronic lymphocytic leukemia; AML: acute myelogenous leukemia; TLS: tumor lysis syndrome; LN: lymph nodes; ALC: absolute lymphocyte count; DDI: drug drug interaction; ADR: adverse drug reaction

PI3Kδ Targeting TKIs

	Idelalisib (Zydelig)	Copanlisib (Aliqopa)	Duvelisib (Copiktra)	Umbralasib (Ukoniq)
Target	Phosphatidylinositol 3-Kinase delta			
		PI3K-alpha	PI3K-gamma	Casein kinase -1ε
Uses	CLL/SLL, relapsed FL, relapsed	FL, relapsed	CLL/SLL relapsed, refractory FL relapsed, refractory	Relapsed, refractory FL/MZL
Dose	150mg BID • Dose reduce for strong CYP3A4 inhibitor	60mg IV D1, 8, 15 Q28 days • Dose reduce to 45mg if given with strong CYP3A4 inhibitor	25mg BID • Dose reduce for 15mg BID if given with strong CYP3A4 inhibitor	800mg QD
ADR	Neutropenia, rash, diarrhea			
	Colitis, GI perf, hepatotoxicity	Hyperglycemia, hypertension	Colitis, hepatotoxicity	Colitis, hepatotoxicity, rash
BBW	Hepatotoxicity, diarrhea/colitis, infection (PCP/CMV), pneumonitis, intestinal perforation		Infection (PCP/CMV), diarrhea/colitis, cutaneous reactions, pneumonitis	
Notes	PCP prophylaxis during treatment and continue until CD4+>200			

CLL: chronic lymphocytic leukemia; SLL: small lymphocytic leukemia; FL: follicular lymphoma; MZL: marginal zone lymphoma; GI perf: gastrointestinal perforation; ADR: adverse drug reaction; BBW: black box warning

PIK3α Targeting TKIs

	Alpelisib (Piqray)
Target	Phosphatidylinositol 3-Kinase alpha
Uses	Metastatic or advanced PIK3CA mutated, HR+, HER2- breast cancer
Dose	300mg PO daily with fulvestrant
DDI	Substrate of CYP2C9 and CYP3A4
ADR	• Hyperglycemia – start treatment with metformin +/- other diabetes medications • Rash – H1 blocker (loratadine/cetirizine) daily may decrease incidence of rash by 50% • Diarrhea
Monitoring	Fasting plasma glucose baseline, weekly x2 weeks, then monthly HbA1c Q3 months

DDI: drug drug interaction; ADR: adverse drug reaction;

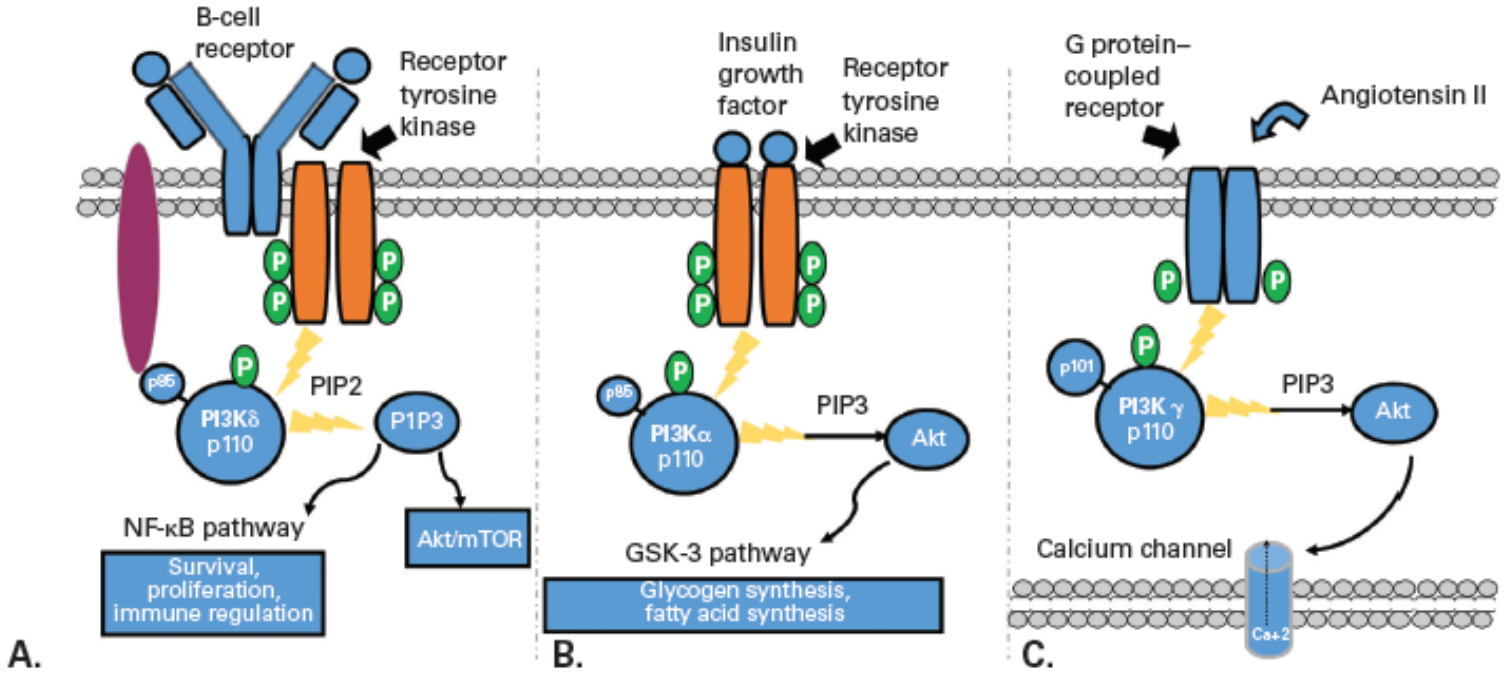
Key Points: PI3K Targeting Agents

Subunit matters!

Alpha = hyperglycemia

Delta = autoimmune-like toxicities (hepatotoxicity, colitis, pneumonitis)

Gamma = hypertension



Greenwell IB. Oncology (Williston Park). 2017. 31(11):821-8

MET Targeting TKIs

	Capmatinib (Tabrecta)	Tepotinib (Tepmetko)
Target	MET	
Uses	mNSCLC, MET exon 14 skipping alteration	
Dose	400mg BID • Avoid CYP3A4 inducers	450mg QD with food • Avoid dual CYP3A and Pgp inhibitors
ADR	Hepatotoxicity (G3-4: 6% Photosensitivity Nausea (All grade 44%, G3-4 2.7%) Peripheral edema (All grade: 52%, G3-4 9%) Diarrhea (All grade 18%, G3-4 0.3%)	Hepatotoxicity (G3-4: 4.2%) Nausea (All grade: 27%, G3-4 0.8%) Peripheral edema (All grade: 70%, G3-4 9%) Diarrhea (All grade: 26%, G3-4 0.4%)
Rare ADR	ILD(4.5% capmatinib vs 2.2% tepotinib)	
Notes	LFTs Q2 weeks x3 months, then monthly or as clinically indicated Patient should wear sun protective clothing and sunscreen, limit sun exposure	
	16% discontinuation rate 54% dose interruption 23% dose reduction	20% discontinuation rate 44% dose interruption 30% dose reduction

mNSCLC: metastatic non small cell lung cancer; ILD: interstitial lung disease; ADR: adverse drug reaction;

RET Targeting TKIs

	Selpercatinib (Retevmo)	Pralsetinib (Gavreto)
Target	RET, as well as VEGF and FGFR	
Uses	mNSCLC, RET fusion positive RET-mutant MTC; RET-fusion positive thyroid cancer	
Dose	>50kg: 120mg BID <50kg: 160mg BID Dose reduce for hepatic impairment Avoid PPI, or separate H2 blockers/antacids	400mg QD on an empty stomach
DDI	Avoid CYP3A4 inhibitors	
ADR	HTN, hepatotoxicity, QTc prolongation	HTN, hepatotoxicity
Rare ADR	Hemorrhagic events, HSR (may require steroids 1mg/kg)	ILD, hemorrhagic events
Monitoring	Basekube blood pressure, at 1 week, then Q month LFTs at baseline, Q2 weeks x3 months, then monthly	
Notes	Impaired wound healing (hold 7 days before and 2 weeks after surgery)	Do not administer for at least 2 weeks after major surgery

mNSCLC: metastatic non small cell lung cancer; ILD: interstitial lung disease; MTC: medullary thyroid cancer; PPI: proton pump inhibitors; HTN: hypertension; HSR: hypersensitivity reactions; ADR: adverse drug reaction; DDI: drug drug interactions

KRAS Targeting TKIs

	Sotorasib (Lumakras)
Target	RAS GTPase
Uses	KRAS G12C-mutated, locally advanced or metastatic NSCLC after one prior line of therapy
Dose	960mg PO daily
DDI	Avoid PPIs. Separate from antacids or H2 blockers Avoid CYP3A4 inhibitors or inducers Caution with Pgp substrates
ADR	• Hepatotoxicity • Diarrhea and nausea in 1/3 of patients • Musculoskeletal pain
Serious ADR	• ILD/pneumonitis
Monitoring	LFTs Q3 weeks x3 months, then monthly if indicated

NSCLC: non small cell lung cancer; PPI: proton pump inhibits; ILD: interstitial lung disease; DDI: drug drug interaction; ADR: adverse drug reaction;

Immune Checkpoint Inhibitors

CTLA-4 Checkpoint Inhibitor

	Ipilimumab (Yervoy)
Target	CTLA-4 (cytotoxic T-lymphocyte associated antigen 4)
Uses	Melanoma, metastatic/unresectable, adjuvant Renal cell cancer, advanced (with nivolumab) mCRC, MSI-H or dMMR (with nivolumab) With nivolumab for HCC after sorafenib and NSCLC first line PDL1>1% or recurrent, metastatic after 2 lines of chemo
Dose	Metastatic: 3mg/kg Q3 weeks Adjuvant: 10mg/kg Q3 weeks x4, then 10mg/kg Q12 weeks x3 years 1mg/kg Q3 weeks x4 doses with nivolumab
ADR	Immune related adverse events particularly colitis

mCRC: metastatic colorectal cancer; MSI-H: microsatellite instability-high; dMMR: mismatch repair deficient; HCC: hepatocellular carcinoma; ADR: adverse drug reaction

PD-1 Checkpoint Inhibitors

	Pembrolizumab (Keytruda)	Nivolumab (Opdivo)	Cemiplimab (Libtayo)	Dostarlimab (Jemperli)
Target	Binds PD-1 receptor			
Use	• Many disease state approvals Tumor agnostic approvals: • MSI-H, dMMR solid tumor • TMB-H solid tumor	• Many disease state approvals	• Cutaneous squamous cell carcinoma	• dMMR recurrent endometrial cancer
Dose	200mg Q3 weeks 400mg Q6 weeks	240mg Q2 weeks 480mg Q4 weeks 3mg/kg Q2 weeks	350mg Q3 weeks	500mg Q3 weeks x4, then 1000mg Q6 weeks

MSI-H: microsatellite instability-high; dMMR: mismatch repair deficient; TMB-H: tumor mutational burden high

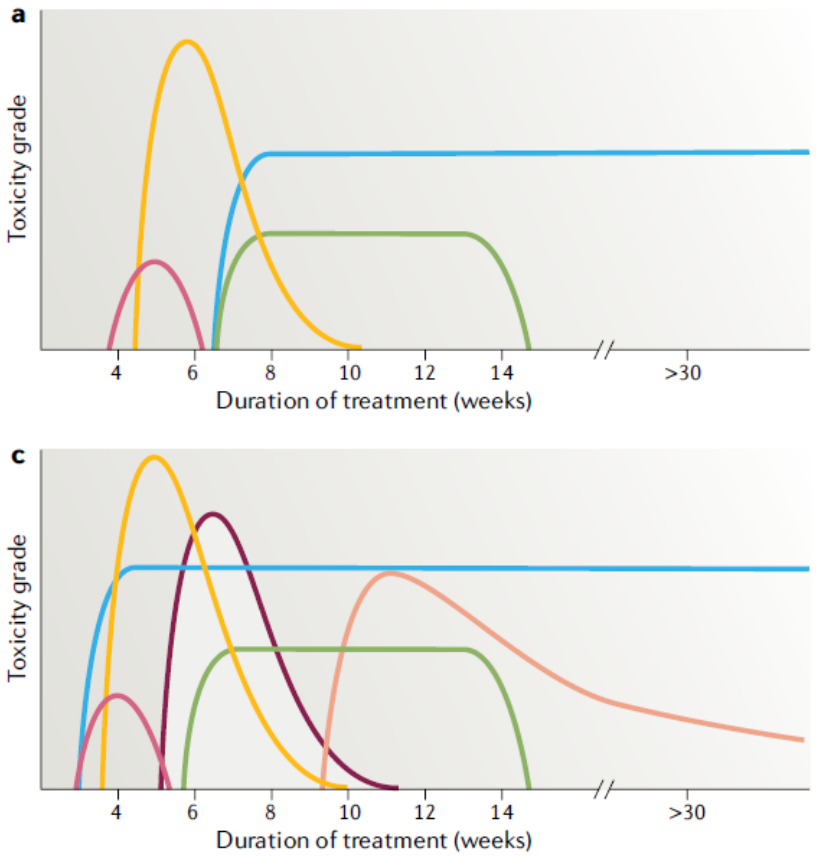
PD-L1 Checkpoint Inhibitors

	Atezolizumab (Tecentriq)	Avelumab (Bavencio)	Durvalumab (Imfinzi)
Target	Binds PD-L1 receptor		
Use	• NSCLC, met • Urothelial carcinoma, advanced/metastatic	• Merkel cell, met • Urothelial carcinoma, advanced/metastatic	• Urothelial carcinoma, advanced/metastatic
Dose	1200mg Q3 weeks	10mg/kg Q2 weeks	10mg/kg Q2 weeks
Premed		H1 blocker, APAP for first 4 infusions	

NSCLC: non small cell lung cancer; Premed: premedication; APAP: acetaminophen

Immune Related Adverse Events

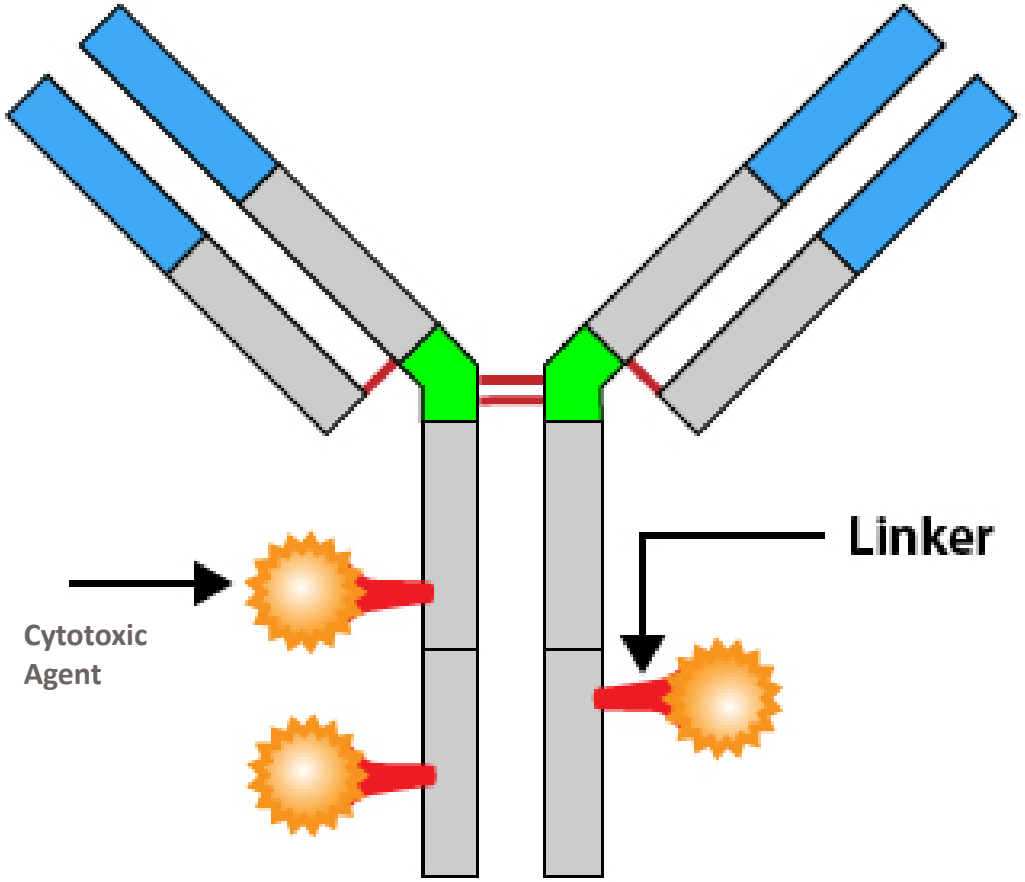
- Dermatologic toxicities
  - Rash, pruritus
- GI toxicity
  - Colitis
  - Hepatitis
  - Pancreatitis
- Endocrine toxicity
  - Diabetes mellitus
  - Thyroid, adrenal, hypophysitis
- Pulmonary toxicity
- Renal Toxicity
- Ocular toxicity
- Nervous system toxicity
- Musculoskeletal toxicity



Panel A: ipilimumab; Panel B: anti-PD-1 or anti-PD-L1 therapy; Panel C: Ipilimumab + anti-PD-1 therapy: Martins F. Nature Reviews; 2019; 16: 563-78.

Antibody-Drug Conjugates

Antibody-Drug Conjugates



Cytotoxic Agent	Side effect profile
Vedotin, mafodotin – auristatin	Neuropathy
Ozogamicin – calicheamicin	Hepatotoxicity
Emtansine – maytansinoid	Neuropathy
Immunotoxin – Pseudomonas exotoxin, diphtheria toxin	Capillary leak syndrome
Deruxtecan, govitecan	Neutropenia, diarrhea

Antibody-Drug Conjugates

	Brentuximab vedotin (Adcetris)	Inotuzumab ozogamicin (Besponsa)	Gemtuzumab ozogamicin (Mylotarg)
Target	CD30	CD22	CD33
Uses	HL, relapsed/refractory HL, after HSCT anaplastic large cell lymphoma	Relapsed/refractory B-cell ALL	Newly diagnosed and relapsed/refractory AML
Dose	1.8mg/kg Q3 weeks (max 180mg) Avoid if CrCl<30ml/min Child-Pugh A: 1.2mg/kg	0.8mg/m2 D1, 0.5mg/m2 D8&15 Q21d • CR/Cri: 0.5mg/m2 Q28d	3mg/m^2 D1, 4, 7 (max 4.5mg) with 7+3 6mg/m^2 D1, 3mg/mg^2 D8
ADR	Infusion reactions, rash, **peripheral neuropathy**, bone marrow suppression, diarrhea, hepatotoxicity	Bone marrow suppression, hepatotoxicity, QTc prolongation, embryo-fetal toxicity	Infusion rxn (anaphylaxis), hemorrhage, LFT elevations, bone marrow suppression, resp distress
BBW	PML	Hepatotoxicity (VOD); Increased risk of post-SCT non-relapse mortality	Hepatotoxicity (VOD)
Premed		APAP, H1 blocker, steroid	
Notes	MMAE – microtubule inh	Calicheamicin – causes dsDNA breaks	

HL: Hodgkin lymphoma; ALL: acute lymphocytic leukemia; AML: acute myelogenous leukemia; HSCT; hematopoietic stem cell transplant; CrCl: creatinine clearance; CR: complete response
Premed: premedication; ADR: adverse drug reaction; PML: progressive multifocal leukencephalopathy; VOD: veno-occlusive disease; ds: double strand

Antibody-Drug Conjugates

	Polatuzumab vedotin (Polivy)	Moxetumomab pasudotox (Lumoxiti)	Enfortumab vedotin (Padcev)
Target	CD79B	CD22	Nectin-4
Uses	DLBCL, relapsed/refractory	Hairy cell leukemia, relapsed/refractory	Urothelial cancer after PD1/PDL1 inhibitor + platinum based chemo
Dose	1.8mg/kg Q21d x6 cycles w/BR	0.04mg/kg D1, 3, 5 Q28 days • Requires pre/post hydration • Consider ASA 81 daily for thromboprophylaxis	1.25mg/kg D1, 8, 15 Q28days (max 125mg)
ADR	Infusion reactions, **peripheral neuropathy**, bone marrow suppression, hepatotoxicity	Hypocalcemia, infusion rxn, AKI, diarrhea	Moderate emetic risk, peripheral neuropathy, hyperglycemia, ocular disorder, skin reactions
BBW		Capillary leak syndrome, HUS	
Premed	H1 blocker, APAP	APAP, H1 blocker, H2 blocker Post-med: dex 4mg; H1 blocker + APAP for 24h after PRN	
Notes	Need PJP and HSV prophylaxis	Made in polysorbate 80	

DLBCL: diffuse large B-cell lymphoma; BR: bendamustine, rituximab; ASA: aspirin; AKI: acute kidney injury; HUS: hemolytic uremic syndrome
Premed: premedication; ADR: adverse drug reaction; APAP: acetaminophen; BBW: black box warning

Antibody-Drug Conjugates

	ADO-trastuzumab emtansine (Kadcyla)	Trastuzumab deruxtecan (Enhertu)	Sacituzumab govitecan (Trodelvy)
Target	HER2	HER2	Trop2
Uses	Adjuvant HER2+ breast cancer for residual disease HER2+ metastatic breast cancer	Metastatic HER2+ breast cancer	Triple negative breast cancer
Dose	3.6mg/kg Q3week • Dose adjust for liver and heme toxicities • Substrate of CYP3A4	5.4mg/kg Q3 week	10mg/kg D1, 8 Q21 days
ADR	Hepatotoxicity, embryo-fetal toxicity, stomatitis	Neutropenia, Diarrhea, Alopecia Moderate emetogenicity	Alopecia Moderate to high emetogenicity
BBW		Interstitial lung disease (9%, fatal in 2.6%)	Neutropenia Diarrhea
Premed			H1 blocker, H2 blocker, APAP
Notes			Patients with UGT1A1*28 allele at increased risk for neutropenia

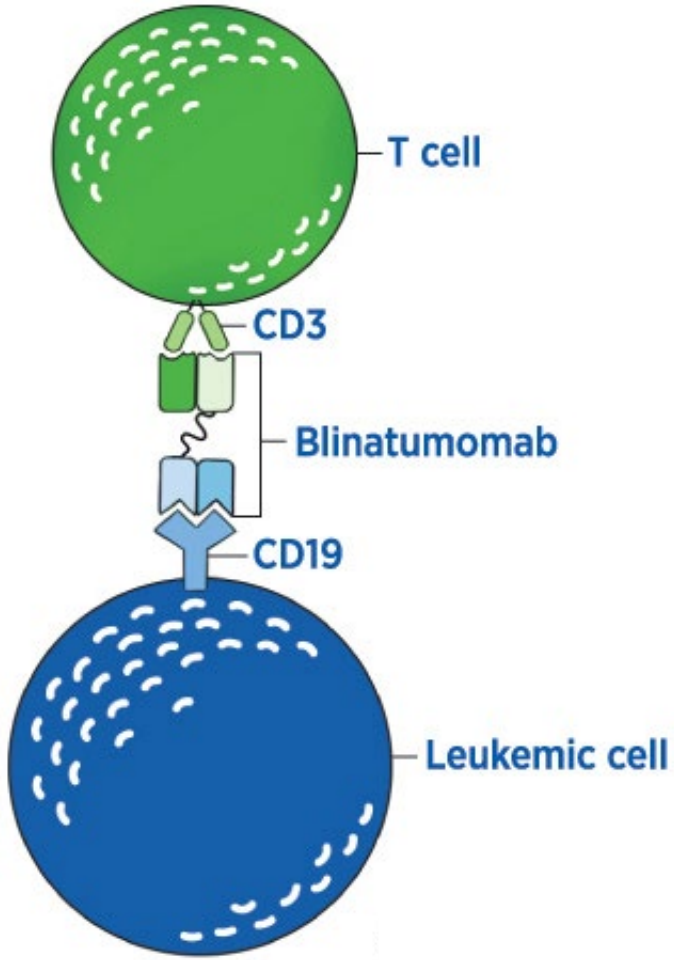
HER2: human epidermal growth factor receptor 2; Premed: premedication; ADR: adverse drug reaction; APAP: acetaminophen; BBW: black box warning

Key Points: Antibody-drug conjugates

- No dose loading with antibody-drug conjugates
- Most require premedication regimens
  - Except brentuximab vedotin and trastuzumab emtansine
- Knowing the cytotoxic agent can predict side effect profile

Bi-specific T-cell engager:
Blinatumomab (Blincyto)

	Blinatumomab
Target	CD19 B cells, CD3 T cells
Uses	Relapsed/refractory ALL, ALL MRD+
Dose	**NEW dosing for MRD+: fixed dose starts at 28mcg daily CIVI** For relapsed/refractory: hospitalization for C1D1-9, C2D1-2
ADR	Hepatotoxicity
BBW	Cytokine Release Syndrome, neurotoxicity



Honey K. AACR. 2014.
ALL: acute lymphocytic leukemia; MRD: minimal residual disease; ADR: adverse drug reaction; BBW: black box warning

Biosimilars

Biosimilar Pearls

- Per FDA, the biosimilar product is:
  - Expected to produce the same clinical result as the reference product
  - Switching between products does not increase safety risks or decrease effectiveness

- Interchangeability depends on your health system

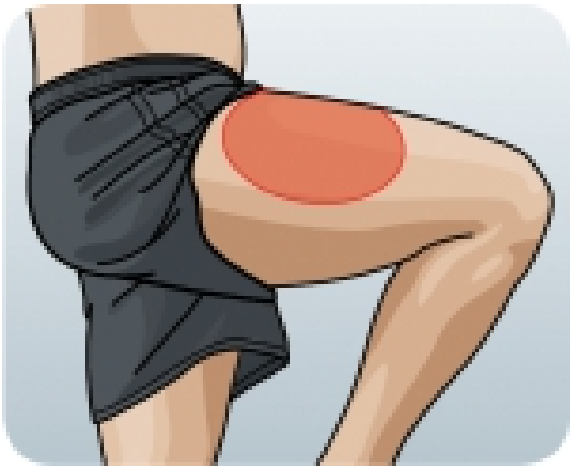
- Insurance coverage of the drug varies by insurance company

New Formulations

- Drug with different formulations must undergo FDA approval for the specific formulation

- Hyaluronidase reversibly opens up interstitial space in SubQ tissue to deliver volumes >2.3ml

- Currently approved drugs with new formulations:
  - Rituximab hyaluronidase (Rituxan Hycela)
  - Trastuzumab hyaluronidase (Herceptin Hylecta)
  - Daratumumab hyaluronidase (Darzalex Faspro)
  - Pertuzumab, trastuzumab, hyaluronidase (Phesgo)



Current Oncology Biosimilars

Originator product	Biosimilar
Filgrastim (Neupogen)	Filgrastim-sndz (Zarxio) Filgrastim-aafi (Nivestym) Tbo-filgrastim (Granix) is *not* a biosimilar
Pegfilgrastim (Neulasta)	Pegfilgrastim-jmdb (Fulphila) Pegfilgrastim-cbqv (Udenyca) Pegfilgrastim-bmez (Ziextenzo) Pegfilgrastim-apgf (Nyvepria)
Trastuzumab (Herceptin)	Trastuzumab-dkst (Ogivri) Trastuzumab-pkrb (Herzuma) Trastuzumab-dttb (Ontruzant) Trastuzumab-qyyp (Trazimera) Trastuzumab-anns (Kanjinti)
Ritxuimab (Rituxan)	Rituximab-abbs (Truxima) Rituximab-pvvr (Ruxience) Rituximab-arrx (Riabni)
Bevacizumab (Avastin)	Bevacizumab-awwb (Mvasi) Bevacizumab-bvzr (Zirabev)

Cancer Pharmacology II

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