CYP3A4 metabolism
Rolfamide
Vinca alkaloids
Taxanes
Etoposide
Bicalutamide
Crizotinib
Entinitib
osimertinib
Gefitnib
Pazopanib
Sorafenib
Sunitinib
Irametinib
Olaparib

CYP2C8
Cyclophosphamide
Enzalutamide

NOT METABOLISED BY CYP
Nintedanib

AUC with same doses in different races
Higher AUC for Japanese - paliocciclib
Lower AUC for Japanese - sorafenib
Higher AUC for asians - crizotinib

Affinity for Pgp
Afatanib
Pazopanib
Nintedanib

Higher levels/toxicity in asians
Afatinib
Crizotinib

Common Side effects of EGFRi/mTOR inhibitors - raised LFt, Qtc, arrhythmia, diarrhoea, skin and nail changes, ILD/pneumonitis
+mTOR - increased risk of pneumonitis

GnRH AGONIST
GnRH agonists: Leuprelin, goserlin. Suppress androgen levels in 21 days and oestrodiol in 28 days (initial flare)

GnRH antagonists: degarelix (first available GnRH agonists abarelix never reached clinical acceptance due to high rates of anaphylaxis, degarelix is the first oral than avoiding flare not advantage over agonists) Supresses levels in 3 days
Side effects include cardiac S/E (arrhythmia, blocks, MI, HTN)

ANTI ANDROGENS: inhibit Androgen Receptor. High/normal testosterone levels as no reduction in LH levels
Maintain some degree of potency and libido and do not have same side effects as GnRH acting agents
CAUSE more hepatotoxicity and gynaecomastia
BUT less bone loss, hot flushes
PSA responses when used alone in 50% of patients in 3-6 months
NOT USED ALONE as first line for advanced prostrate cancer
Either steroidal (cyproterone, megestrol) or non steroidal (bicalutamide, flutamide)
half life of bicalutamide - 5-6 days
If anantomor active. Metabolised by **CYP3A4** and hydroxylation followed by glucuronidation
Half life affected by liver disease.

ABIRATERONE
CYP 17alpha hydroxylase and CYP 17,20 lyase inhibitor in testes, prostate and adrenal
oral absorption increases with food
96% plasma protein bound
abiraterone acetate metabolised to abiraterone in liver
Inactive metabolites
Excreted in faeces
Continuous administration of abiraterone can increase ACTH levels and consequently cause increase in mineralocorticoid production. Hence Pred given alongside. e.g. hypokalemia as side effect
Can cause MI, HTN, LVF (<1 to 2%)
Severe hepatic disease
monitor LFTs
Cardiac toxicity, hot flushes

Avoid spironolactone as could risk activating AR

STRONG CYP450 INHIBITOR

ENZALUTAMIDE
renal excretion of hepatic metabolites
Androgen receptor antagonist (competitive), inhibits translocation of receptor to nucleus, DNA binding, coactivator recruitment.

HTN, neutropoxychatic effects, seizures GIT prolongation
fatigue (upto 50%, severe in 6%)
↑ tess cardio and hepatotoxic than abiraterone

Crosses blood brain barrier and can affect brain and GABA channels
enzalutamide is a Hepatic enzyme inducer:
Can decrease levels of midazolam, (CYP3a4 warfarin (2c9) and omeprazole (2C19)
IT IS ITSELF a substrate of 2C8 mainly (inhibited by gemfibrozil) and 3A4. 3A4 inducers drugs generally don't affect levels as much of enzalutamide. can also induce UGT1A1

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AFATINIB:

2nd gen TKI (also lapatinib)
HER2-HER4 EGFR inhibitor
Crosses BBB
active in cancer with del 19 and Exon 21 mutations
Irreversible binding with EGFR
Oral administration (NOT WITH FOOD)
CAUTION IN:
Decreased LVEF - 1-4 patients experience 10%-20% reduction in function
diarrhoea everyone, severe 15%
ILD (higher in asian patients)
Underlying renal impairment (higher exposure to doses) , age >65
fatigue
paronychia
hepatic dysfunction
nail changes

Afatinib is a substrate and inhibitor of Pgp. Given with rifampicin (which induces Pgp) results in lower afatinib levels. Given with ritonavir with inhibits Pgp - can increase afatinib levels if ritonavir is given before afatinib. With reduced renal function , reduced Pgp expression

Bevacizumab:
VEGF inhibitor
Clearance changed with changes in body wt

Contraindicated in untreated brain met

Caution: post op (delayed wound healing)
osteonecrosis of jaw
uncontrolled HTN
risk factors for thromboembolitic events:
Risks for CHF (anthracycline therapy or chest wall RT)
GI perforation
ovarian failure
fistula or GI perf
pulmonary haemorrhage
tumour associated haemorrhage (3-5%)
RPLS
proteinuria (renal thrombotic microangiopathy)

INTERACTIONS sal
with anthracycline: increased cardiotoxicity
with sunitinib - increased risk of MAHA
irinotecan - increased SN38 levels (???? how)

Cabozantinib
VEGFR2, c-Met, RET inhibitor ALK TKI
similar side effect profile to bevacizumab
also PPE as side effect

Cetuximab
EGFR inhibitor. Monoclonal Ab
Cell cycle specific - G1 phase
Metabolised when EGFR complex is internalised and degraded by liver and skin

Side effects: 2-5% severe infusion reactions
People can die of **sudden cardiorep arrest or develop ILD/pulmonary effects** (between 4th and 11th dose usually)
acneform rash, diarrhoea, nail changes
headache, abdominal pain
hypokal, hypomag - **urinary magnesium wasting**

CRIZOTINIB
ALK TKI/C-1 HGF-cMet . TKI
Metabolised in liver by CYP3A4. (also crizotinib is a moderate inhibitor of CYP3A4)
activated by a lactam and then metabolised by dealkylation and conjugation
Excreted mainly in faeces

Levels (AUC) 1.5 x higher in asians than non asians

SE vision disorders, bradycardia, QTc prolongation, phototoxic
neutropenia <10%
ALT/AST rises
diarrhoea
neuropathy (sensory)
pneumonitis in 2% patients (Rx threatening with start of treatment)

ERLOTINIB
EGFR TKI
Cell cycle specific
inhibits EGFR autophosphorylation and hence downstream signalling
metabolised by CYP 3A4
albumin and alpha 1 gp bound
Ph Affects solubility and absorption - so do not use with antacids
ILD risk in <1% - can be serious
<10 risk of raised transaminases, not significant

GEFTINIB
EFGR inhibitor TKI
inhibits autophosphorylation of receptors
Also affected by pH and **CYP3A4 metabolism**
Caution in **hepatic impairment, PT, Qtc**

NINTEDANIB
tki- vegfr, fgfr, pdgfr
ATP binding pocket of its three target receptor families
NOT METABOLISED BY CYP family
raised liver enzymes and GI disturbance
increased risk of strokes and MI
wt loss
Haemorrhage, HTN
Substrate of P Gp
(Pgp induced by rifampicin and carbamazepine/ inhibited by ketoconazole and erythromycin)

OSIMERTINIB
3rd generation TKI EGFR
T790M mutation effective
resistance develops in usually 10 months
Resistance usually due to Exon 20 C797S mutation
very common >10% patients - low neutrophils or low platelet counts
CAUTION IN **ILD or LONG QTc**
Metabolised by CYP3A4

OLAPARIB
Poly ADP Ribose polyermase inhibitor (PARP 1-3)
Giving with food increases AUC but delays time to peak)
Extensively metabolised by CYP3A4
Fatal pneumonitis can occur - vary with thoracic RT+ smoking, previous chemo

SE: anaemia, thrombocytopenia, febrile neutropenia, **neutropenic sepsis**, diarrhoea, nausea, fatigue, **secondary MDS, pneumonitis, stroke**
adjust dose in renal disease, CrCL <50

PALBOCICLIB

selective reversible inhibitor of Cdk 4/6
ALT/AST rise
Poorly crosses BBB due to efflux proteins
Metabolised by CYP3A and SULT (OA1)
AUC and Cmax reported as upto 35% higher for Japanese patients with same doses

anaemia, neutropenia, thrombocytopenia
fatigue, peri neuropathy, PE

PAZOPANIB
vegfr 1kl, pdgfr, c-kit, fgfr, IL-2 inhibitor
s
Highly protein bound to P-gp and BCRP
CYP3A4 metabolism

cardiac s/e
Severe hepatotoxic events
hepatotoxicity
wound healing issues
inhibits UGT1A1 - therefore if given to patients with Gilberts syndrome - hyperbilirubinemia

TRANSTUZUMAB
GD/G1 cell cycle toxicity
IgG humanised monoclonal Ab
Binds to HER2 extracellular domain and inhibits signalling. Destruction of cell by ADCC

Steady states tend to be lower in metastatic gastric cancer than breast cancer
Large molecular size

S/E
CCF 2% (severe 1%)
INFUSION RELATED REACTION 20-40% (severe 1%)

Cardiac dysfunction is NOT dose related and reversible - so good prognosis after adverse event. Baseline after 1.5 months. Assess with echo every 3 months on treatment, and 6 monthly post Rx for 2 years post, then yearly till 5 years complete.
Does not KILL myocytes but reduces contractility. Thus Can halt drug is drop in LVEF >10-15% from baseline, and restart in 3 weeks if needed.

Risk factors DO NOT INCLUDE RT
RT + trastuzumab causes leukopenia.

CCF risk factors include

Prior LVF <55%
Age >65
BMI >25
Prior anthracycline
Low LVF after paclitaxel
GIVEN With paclitaxel (SHOULD BE GIVEN AFTER)
Anthypertensives.

INFUSION REACTIONS: fever, NV, rash (etc to severe respiratory problems

INTERACTION
paclitaxel increases transtuzumab levels x 1.5 times. Higher risk of CCF

PERTUZUMAB

Binds dimerisation of HER2 with other EGFR members (EGFR2/HER2 no ligand, EGFR 3 - no kinase. Need to dimerise with either EGFR or EGFR2 different binding site than transtuzumab
Can also cause infusion reactions and CCF. RT seems to be risk factor for CCF with PERTUZUMAB IS LESS CARDIOTOXIC than transtuzumab
Asian patients more likely to have neutropenia when used with chemo(double risk 14 vs 26%)

S/E:
CCF, infusion reaction
fatigue
diarrhoea
rash

No interaction with drugs like taxanes, pem, erlotinib, cap - nil

TRANSTUZUMAB EMTANSINE
transtuzumab - MCC this either linker - DM1 (microtubule inhibitor)

binds to her2, internalised, degraded by lysosome, increased DM1 delivery to cells, G2/M arrest

DM1 CYP3A4 metabolism
Excreted through bile

CCF
ILD, pneumonitis
thrombocytopenia (severe 15%)
infusion reaction
fatigue
Hepatitis/Hepatotoxicity (PHTN, NRH)
peripheral neuropathy 22%
hypokalemia

SORAFENIB
VEGFR, PDGF, cKIT, RAF inhibitor
inhibits kinases in cells and vasculature
Active metabolite - **pyridine N oxide**
Japanese patients show a much lower AUC than caucasian patients.
CYP3A4 metabolism, UGT1A9

S/E
HTN 17%
MI 3%
fatigue
PPE
yellow skin discolouration
diarrhoea, GI perf
Cerebral haemorrhage
small risk of CNJ
TIA/PRES

LEVELS OF IRINOTECAN, DOCETAXEL and DOXO increase with sorafenib

SUNITINIB
VEGFR, PDGF, Ckit, RET, FLT3, CSF-1R
highly plasma protein bound
Active metabolite
ACTIVE Metabolite - SU12662
CYP3A4 metabolism

HTN UAT 14% patients, arrhythmia
CNJ
PPE
YELLOW discolouration of skin and urine common 30% patients - reversible
Hypothyroidism - screen every 2-3 months
DVT/PE
electrolyte imbalances
Severe cutaneous reactions including SJS,TEN
prolong QTc
Affected by CYP3A4 drugs
MAHA with bevacizumab

ITAMATINIB
faecal clearance
Active metabolite - desacetylated
Oral tablet

Decreased LVF
Increased PR interval
RVO,, retinal detachments, retinal pigmentation
colitis, perf
bleeding events
Caused degeneration of long bones and affects growth plate - don't use in TYA
ILD
Skin toxicity - almost all its
Rhabdomyolysis
Bleeding events, PE

Ddirofenib
CYP3A4 and 2C8
substrate and inducer
carboxy, desmethyl and hydroxy metabolites ACTIVE

QT c prolongations
renal failure
Secondary malignancies
Pyrexia

IMATINIB
BCR-ABL TKI
Long term use might lead to decrease in renal function over time
Reactivation of HBV
Bone marrow suppression (thrombocytopenia)
EDEMA

OCTREOTIDE
G1 specific
CAT s prolongation - be aware!
gall stones , do USS every 6-12 months