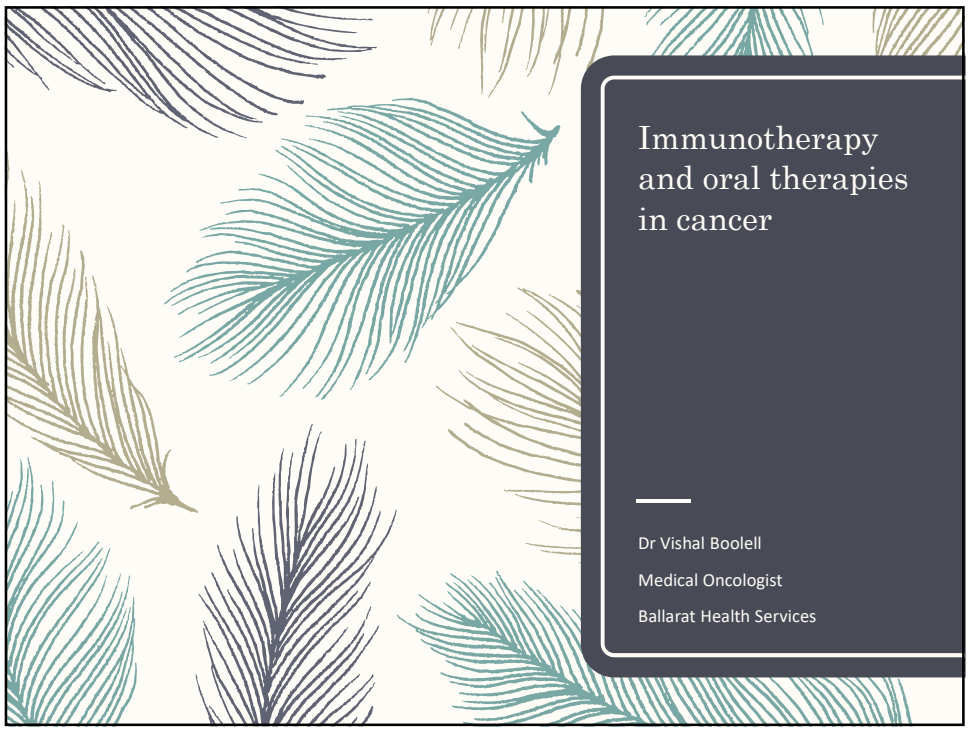
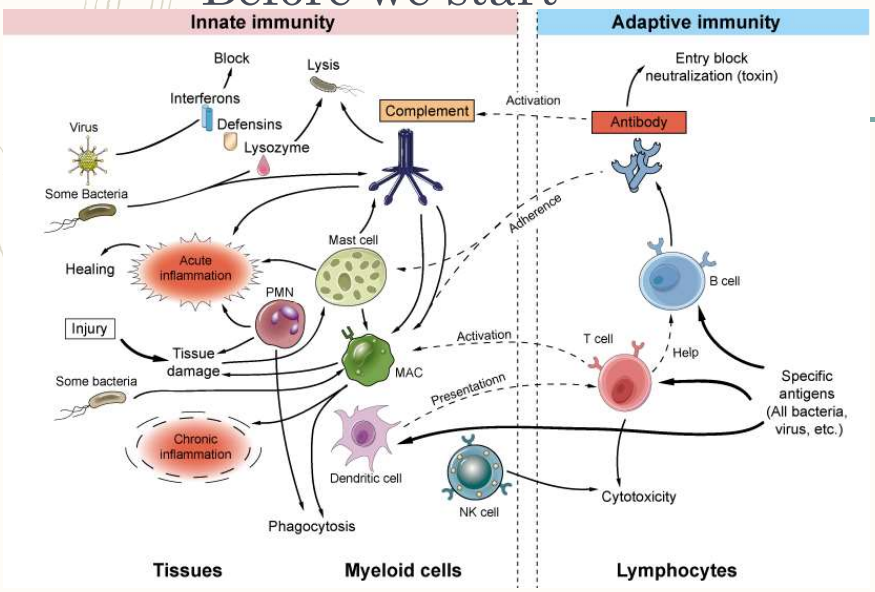


Outline

- Immunotherapy
  - Concepts
  - Treatments
  - Side effects
  - Important interactions
- Oral therapies
  - Break down into cancers
  - Focus on method of action
  - Relevant drug interactions

Before we start



Immunotherapy

Immunotherapy

- Involves harnessing the body's own immune system to fight cancer
- First person to describe this was William Coley, an orthopaedic surgeon in 1890
  - Injected streptococcus into patients' cancers with variable results
- Shunned by modern medicine in favour of radiotherapy
- Eventually researched up to now...

Immunotherapy

- essing the body's own immune system to fight
- o describe this was William Coley, an surgeon in 1890
  - ptococcus into patients' cancers with variable
- modern medicine in favour of radiotherapy
- Eventually researched up to now...

Immunotherapy

essing th fight

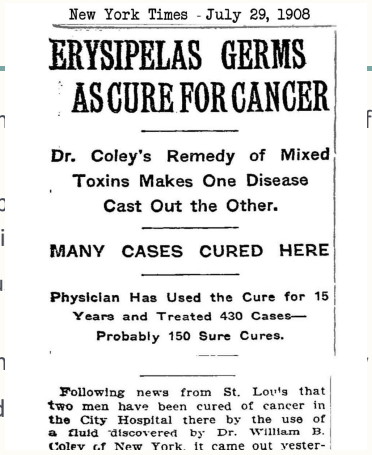
o describ

surgeon i

ptococcu

nodern n

– Eventually researched



New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

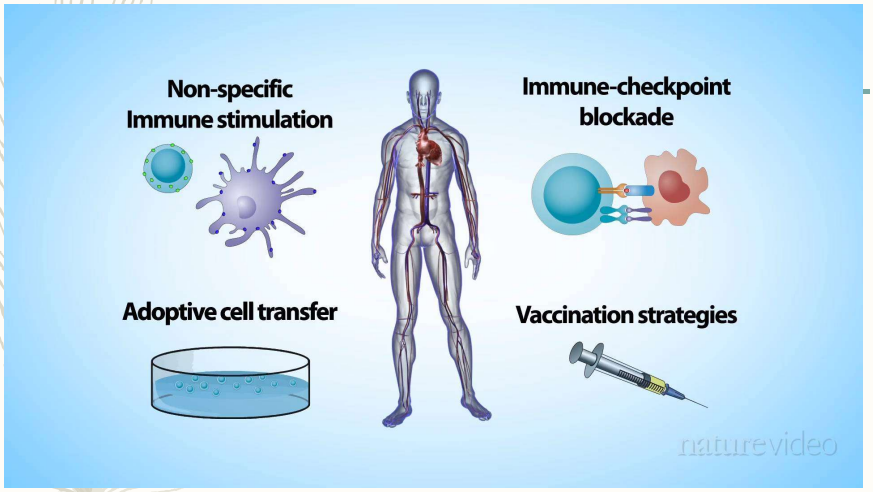
Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases—Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yester-

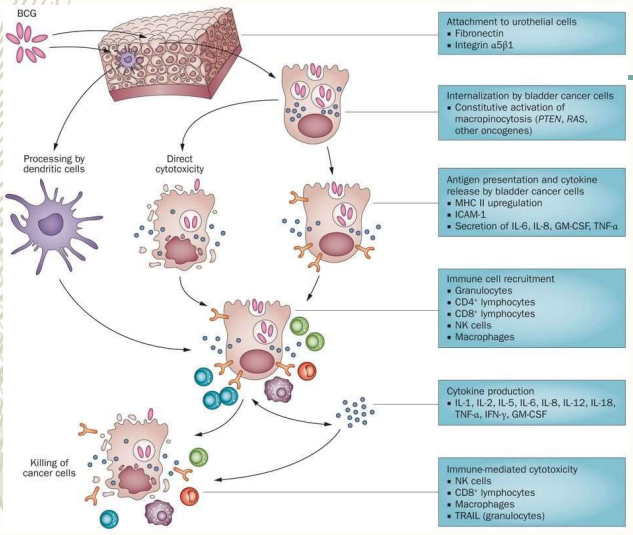
Modern immunotherapy



Non specific immune stimulation

- Oldest version, some success
- IL 2, IFN in melanoma and renal cell
- Most successful and still in use is BCG for superficial bladder TCC

BCG



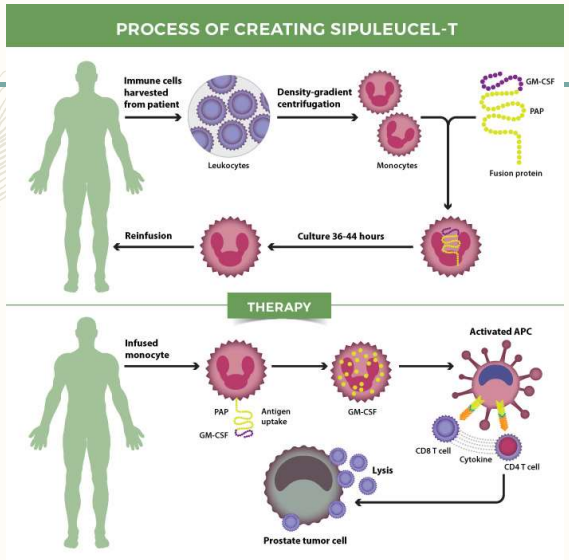
Vaccines

- Can be to treat different conditions
- Vaccines against cancer causing viruses have been very successful
  - HPV and cervical cancer
  - Hepatitis B and hepatoma
- Sipuleucel-T in prostate cancer

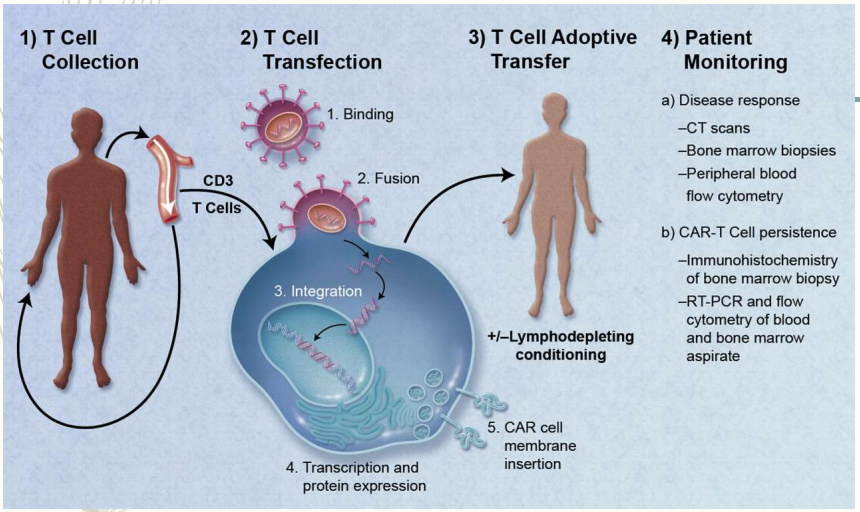
Sipuleucel-T

- Leukapheresis done to harvest dendritic cells
- Incubated with PAP (prostatic acid phosphatase) – present in 95% prostate Ca
- Reinfused into patient and given in 3 cycles every 2 weeks
- Improved survival by 4 months in largest trial
- Approved in US but not used much, company went bankrupt as well

Sipuleucel-T



Adoptive cell transfer

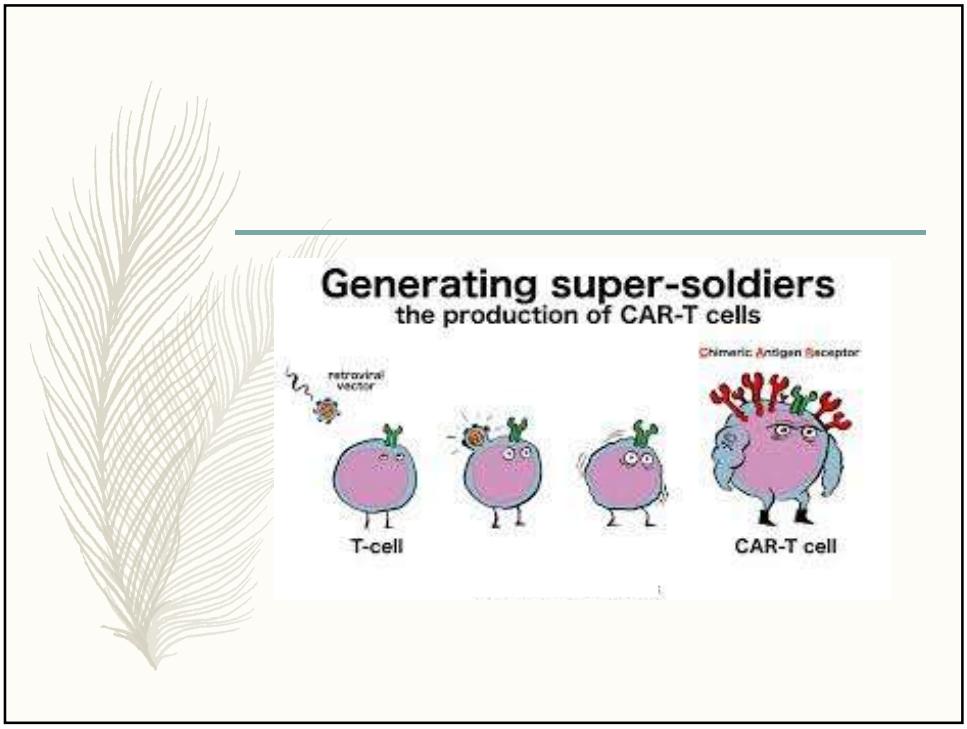


CAR T cell therapy

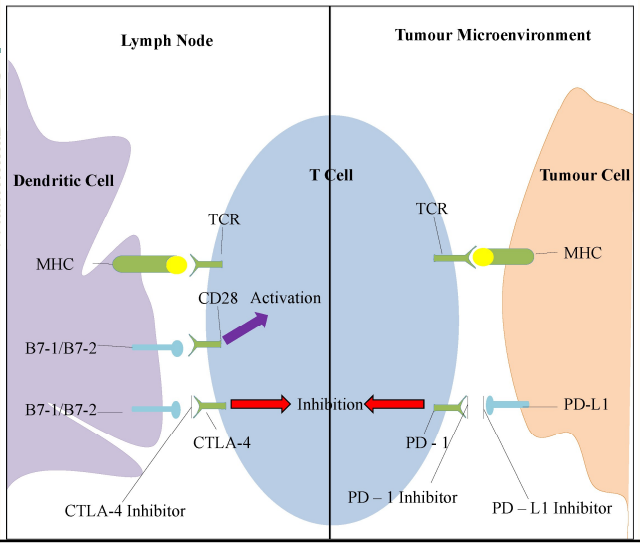
- Chimeric antigen receptor t cells
- Harvest T cells
- Genetically engineer to express a specific CAR (specific to cancer)
- Patient has lymphodepletion chemotherapy followed by infusion of CAR T cells
- Cells kill cancer through entire spectrum of immune system

CAR T cell therapy

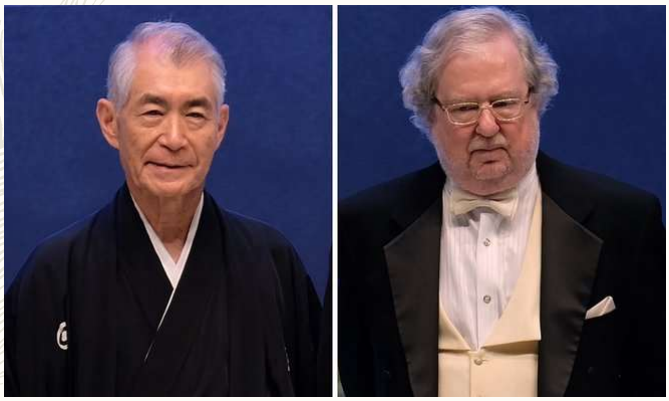
- Still new but has shown great results with B cell haematological malignancies (B cell ALL and relapsed DLBCL)
- Toxicity significant
  - Cytokine release syndrome (causes fever, fatigue, myalgia, nausea, capillary leak, multiorgan failure)
  - Neurological syndromes (delirium, seizures, aphasia, cerebral oedema)
  - Anaphylaxis



Checkpoint inhibitors



Tasuku Honjo and James P Allison

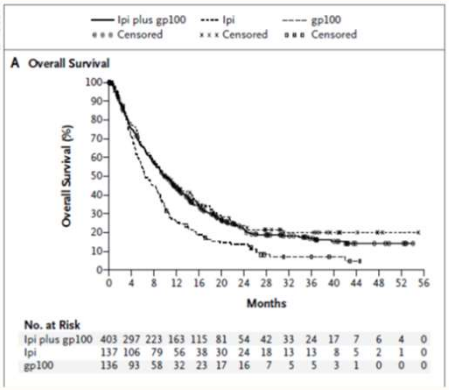


CTLA 4 inhibitors

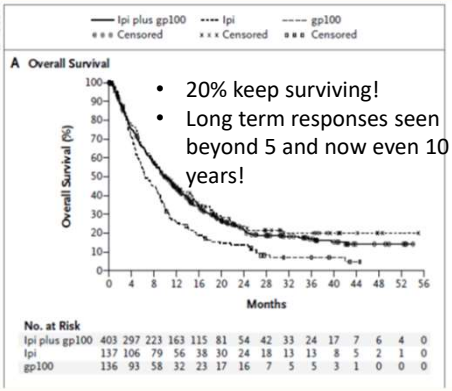
CTLA 4 inhibitors

- Most well known is Ipilimumab or Yervoy
- Monoclonal antibody to CTLA 4
- 1st tested in metastatic melanoma
- Average survival of this group was 9-12 months
- 1st tested in 2nd line

Ipilimumab



Ipilimumab



- 20% keep surviving!
- Long term responses seen beyond 5 and now even 10 years!

Ipilimumab- adverse events

- Adverse events reported in 95-98% of patients, serious adverse events in 45%
- New toxicities, immune related
  - Diarrhoea, specially colitis (can be fatal)
  - Pneumonitis
  - Hepatitis
  - Hypothyroidism
  - Hypophysitis
  - Rarer neurological issues
- Financial toxicity.....

Ipilimumab- adverse events

IPILIMUMAB

Source: Chemotherapy Items for Private Hospital use - Explanatory Notes

Body System: ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS > ANTINEOPLASTIC AGENTS > OTHER ANTINEOPLASTIC AGENTS

▸ Note

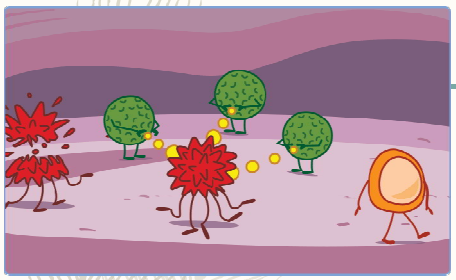
▸ ⚠ Authority Required (STREAMLINED)

Code & Prescriber	Name, manner of administration	Max amount	No. of repeats	DPMA	Max Safety Net	Max price to consumer
2638W	IPILIMUMAB Injection (PI, CMI) Available brands: Yervoy (ipilimumab 200 mg/40 mL injection, 40 mL vial) Yervoy (ipilimumab 50 mg/10 mL injection, 10 mL vial)	360 mg	3	$48160.74	$38.30	$38.30

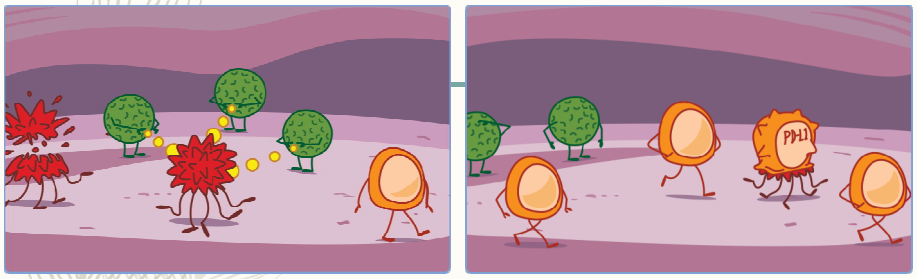
- Hypophysitis
- Rarer neurological issues
- Financial toxicity.....

PD 1 and PD L1 inhibition

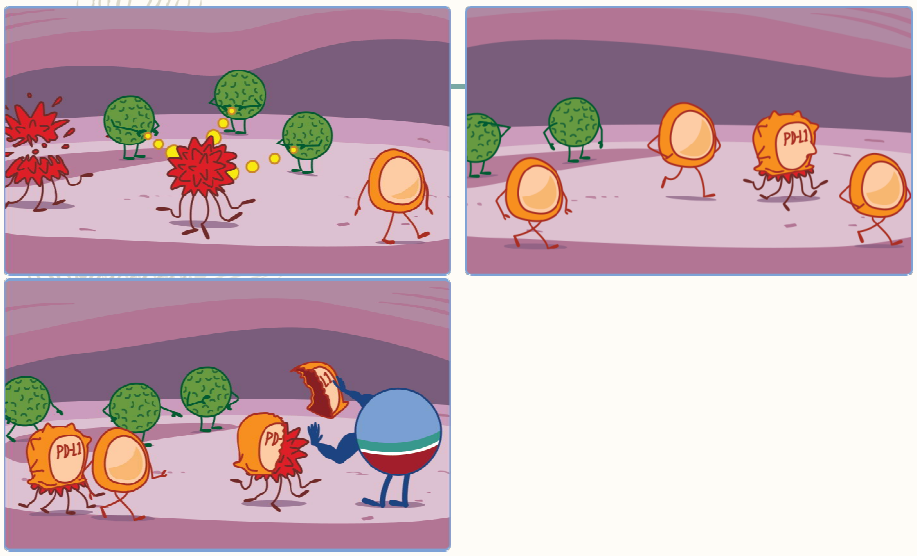
PD 1 and PD L1 inhibition



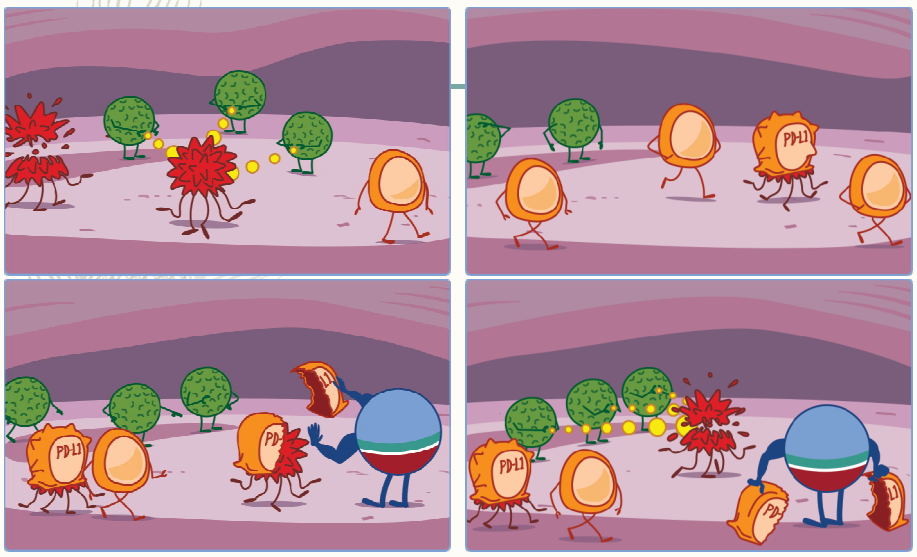
PD 1 and PD L1 inhibition



PD 1 and PD L1 inhibition



PD 1 and PD L1 inhibition



PD1/PD L1 inhibitors

- Exerts effect in tumour microenvironment, therefore less toxic
- Risk of a serious adverse event 1-2% but probably underestimated due to length of follow up on trials
- Most well known:
  - Pembrolizumab (Keytruda)
  - Nivolumab (Opdivo)
  - Atezolizumab (Tecentriq)
  - Durvalumab, Cemiplimab, Avelumab

PD1/PD L1 inhibitors

NIVOLUMAB

Source: Chemotherapy Items for Public Hospital use - Explanatory Notes

Body System: ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS > ANTINEOPLASTIC AGENTS > OTHER ANTINEOPLASTIC AGENTS

Note

Authority Required (STREAMLINED)

Code & Prescriber	Name, manner of administration	Max amount	No. of repeats	DPMA	Max Safety Net	General Patient Price
10745M	NIVOLUMAB Injection (PI, CMI)	360 mg	11	$7560.13	$39.50	$39.50
	Available brands					
	Opdivo (nivolumab 40 mg/4 mL injection, 4 mL vial)					
	Opdivo (nivolumab 100 mg/10 mL injection, 10 mL vial)					

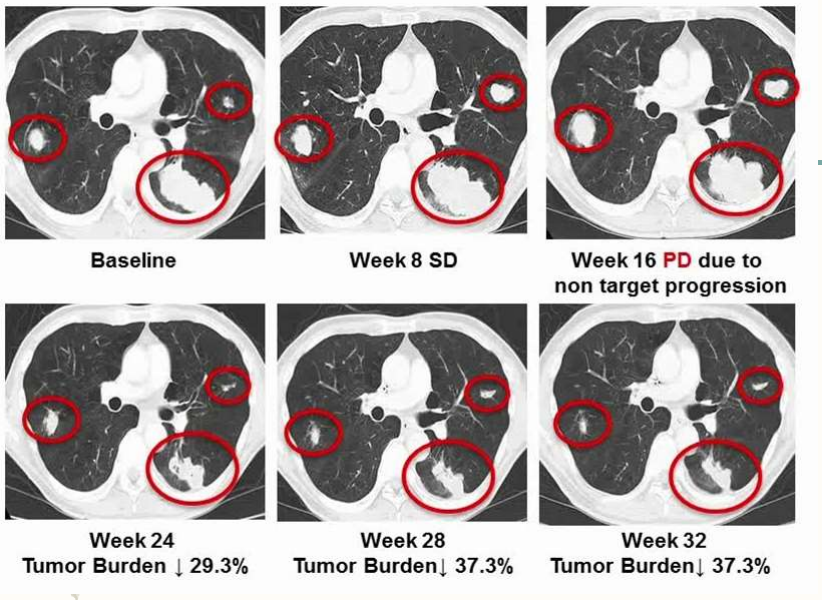
- Nivolumab (Opdivo)
- Atezolizumab (Tecentriq)
- Durvalumab, Cemiplimab, Avelumab

Combination

- If each one is good, then both must be better!!
- More and more trials exploring this
- Higher risk of adverse events but possibly higher chance of long term survival
- Also combining with chemotherapy, targeted agents

Response to checkpoint inhibition

- May get worse before it gets better – due to immune infiltration
- Usually however, patients are asymptomatic if this happens
- Responses may take a while to appear
- Rule is if there is progression but patient is clinically well, continue treatment and re-evaluate at next scan- pseudoprogression



Abscopal effect

- Describes a phenomenon in metastatic cancer where localised treatment of a tumour leads to response in tumours outside the scope of the localised treatment
- Seen in melanoma and checkpoint inhibition; palliative RT to a site of disease leads to response elsewhere
- Effect is thought to be due to the stimulation of the immune system by RT

Adverse events

- Can affect a wide variety of systems
  - Skin (with either)
  - Colitis (more common with CTLA 4)
  - Hepatitis (more common with CTLA but changing)
  - Pneumonitis (more common in PD 1/PD L1)
  - Endocrine
  - Musculoskeletal
  - Renal
  - Neurological
  - Ocular
  - Haematologic
  - Cardiac

Rare

Adverse events

- Can affect a wide variety of systems
  - **Skin (with either)**
  - **Colitis (more common with CTLA 4)**
  - **Hepatitis (more common with CTLA but changing)**
  - **Pneumonitis (more common in PD 1/PD L1)**
  - **Endocrine**
  - Musculoskeletal
  - Renal
  - Neurological
  - Ocular
  - Haematologic
  - Cardiac

Rare

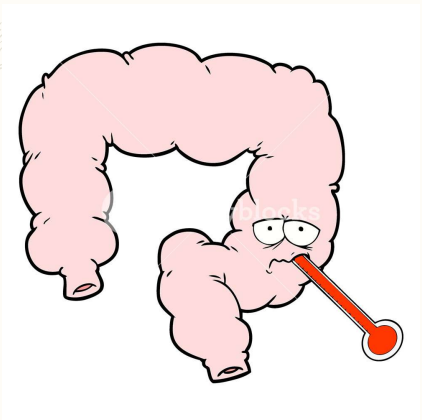
Grading severity

- Trial based grading often done from Grade 1 to 5
- Easier to think
  - Grade 1 – mild
  - Grade 2 – moderate
  - Grade 3 – Severe
  - Grade 4 – Life threatening
  - Grade 5 – Death

Skin toxicities

- Most common is rash or pruritus
- Rarely can get bullous dermatoses or SJS/TENS
- Mild reaction: Continue immunotherapy, skin emolients and topical steroids
- Moderate: May need to hold treatment, consider Prednisolone 1mg/Kg tapering over 4-6 weeks
- More severe: Derm input, methylprednisolone

Colitis



Colitis

- Almost always with CTLA 4 blocking only
- If present, still needs a standard workup
  - FBE, EUC, LFT, cortisol, TFT, ESR, CRP
  - Stool culture (rule out infection), also faecal calprotectin (can help with monitoring for inflammation)
  - CT scan to assess risk of perforation, colonoscopy to assess risk of ulceration (predictor of poor response to steroid therapy)

Colitis - management

- Grade 1 (< 4 stools/day over baseline)
  - Can continue treatment, monitor only unless prolonged
- Grade 2 (4-6 stools/day over baseline)
  - Pause treatment
  - Treat with pred 1mg/kg with tapering over 4-6 weeks

Colitis - management

- Grade 3 (7 or more stools over baseline)
  - Discontinue treatment
  - May need admission
  - Prednisolone as before or IV methylpred if not settling
  - Infliximab if does not improve
- Grade 4 (life threatening)
  - Same as above, hospitalisation indicated
  - Early use of infliximab

Hepatitis

Hepatitis

- Main tests of relevance are:
  - AST
  - ALT
  - Bilirubin
- If elevated, urgent review and stop therapy
- Steroids as previously outlined
- Can sometimes also be due to liver metastases

Pneumonitis

Pneumonitis

- Mild: monitor but can continue Rx
- Moderate (symptomatic, limiting dADLS): steroid therapy with pred, stop Rx but can restart if resolves
- Severe: Discontinue permanently, IV methylprednisolone, may need infliximab, mycophenolate

Endocrine

Endocrine

- Thyroid disorders
  - Hyperthyroid
  - Hypothyroid
- Primary adrenal insufficiency
- Hypophysitis
- Diabetes
- Management of these more dependent on endocinology support for replacement

Beware

- Immune related toxicities can progress and can escalate
  - Other toxicities present
- No real time point that is more common, can occur with 1st dose
- Adverse events can turn up much later, long after immunotherapy has been ceased

Important interactions

- Concomitant steroids
- Interactions with other cancer drugs
- Flu vaccine

Steroids and immunotherapy

- Recent retrospective analysis suggest patients on steroids at the time of starting immunotherapy less likely to benefit from it
- Those who started steroids after starting (for side effects) had preserved response rates
- Unclear if this is due to steroids interfering with T cell function and efficacy v/s poor prognostic cases

Interaction with cancer drugs

- Higher rates of specific toxicity depending on combination
  - Increased rate of hepatitis with nivolumab and sunitinib
  - Same with ALK inhibitors, also higher rate of pneumonitis
  - More will be discovered with new combination trials
  - Also affects what treatment you give next post immunotherapy

Flu vaccine

- Initial reports suggested increased risk of adverse events post flu vaccine
- Subsequent analysis and retrospective studies have not shown correlation
- Still case by case discussion of risk v/s benefits
- Risk zone identified as flu vaccine given up to 2 months prior to starting or anytime whilst on treatment

Indications

- Now used in a wide variety of cancer
  - Melanoma
  - Renal
  - Lung
  - Bladder
  - Head and neck cancers
  - Merkel cell cancers
  - Metastatic cutaneous SCC
  - Hodgkin's lymphoma
  - Also being trialled in multiple other cancers: alone, in combination with other IO agents or chemotherapy

Who can't have it?

- Poor performance status
- Patients with significant autoimmune conditions
- HIV and Hep C – excluded from all trials but safe to have if on treatment with undetectable viral load
- Active infection
- Unreliable

Immunotherapy- future pathways

- Right now, both pathways look at removing inhibitory signals
- Extensive research underway to find targets that could turn on immune system and turn off in other ways
- May lead to different combinations for different cancers
- Immunotherapy is now an integral part of cancer treatments

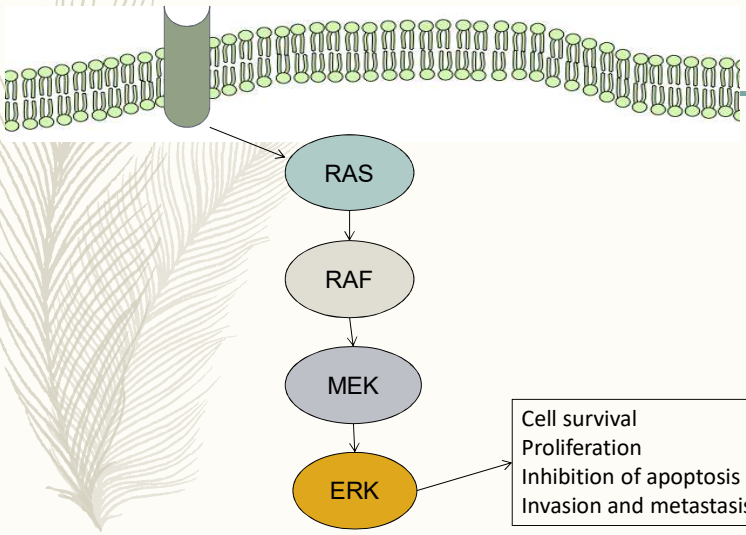
Questions?

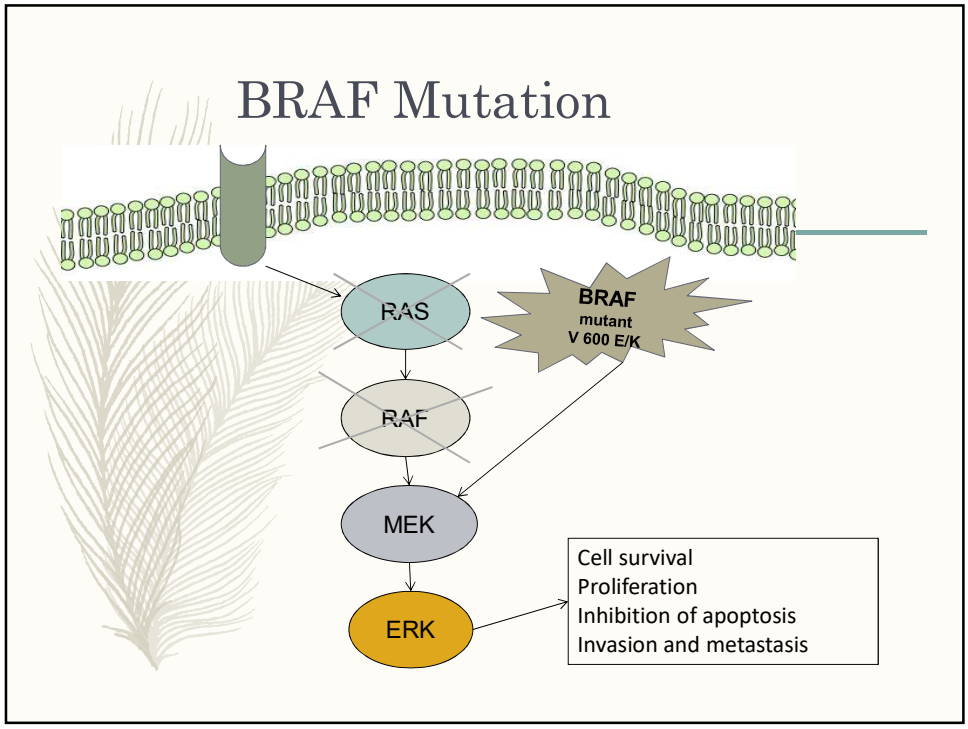
Oral therapies in cancer

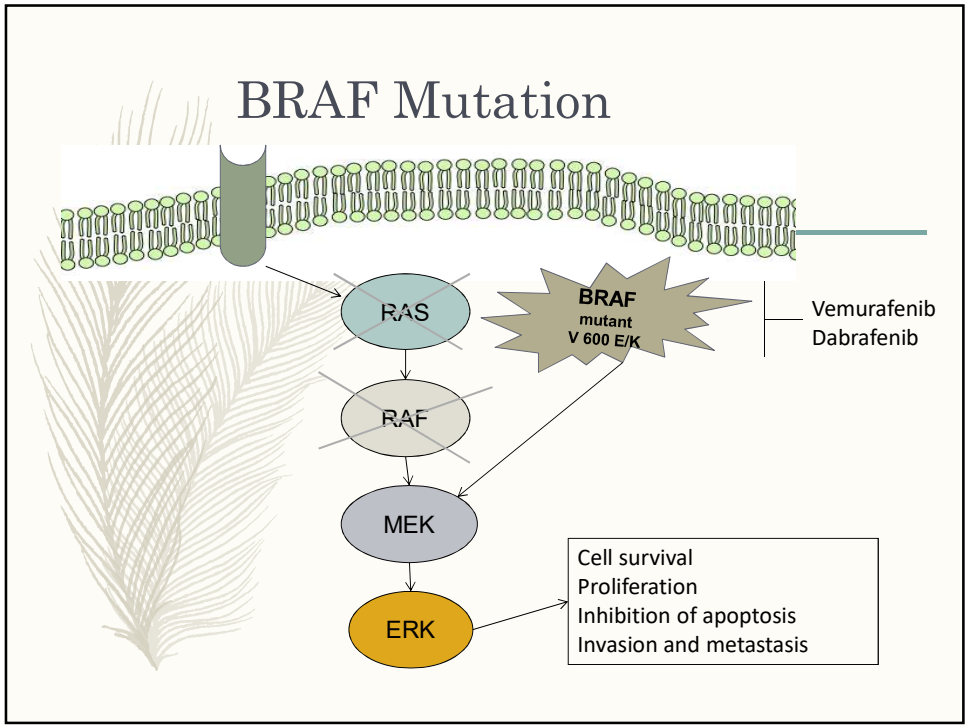
Melanoma

- Up to 60% of melanoma express BRAF mutations
- Available oral therapies are BRAF and MEK inhibitors
- Exert effect through MAP Kinase pathway

MAP kinase pathway



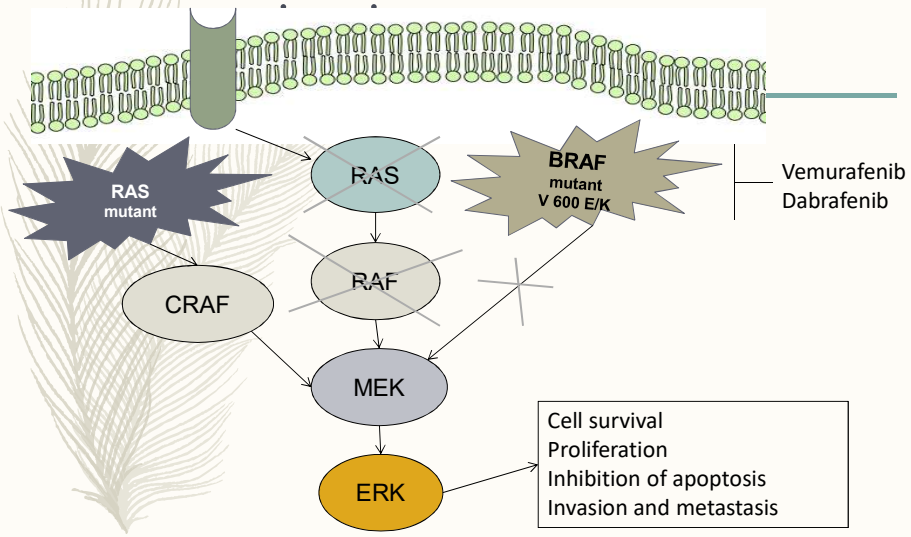

BRAF Mutation
RAS
BRAF
mutant
V 600 E/K
RAF
MEK
ERK
Cell survival
Proliferation
Inhibition of apoptosis
Invasion and metastasis


BRAF Mutation
RAS
BRAF
mutant
V 600 E/K
Vemurafenib
Dabrafenib
RAF
MEK
ERK
Cell survival
Proliferation
Inhibition of apoptosis
Invasion and metastasis

BRAF inhibitors

- Well tolerated
- Odd side effect of keratoacanthoma or even cutaneous SCC
  - Happened in up to 26% of patients

Paradoxical MAP K



Combination BRAF/MEK inhibition

- Cutaneous SCC in only 7% of patients in combination arm
- Main side effects: fever, fatigue, nausea, diarrhoea
- Fever can be quite prominent and hard to manage
- Combinations available:
  - Dabrafenib and Trametinib
  - Vemurafenib and Cobimetinib

Drug interactions

- Vemurafenib and Dabrafenib both can prolong QTc, need to be careful other drugs that can do this e.g. haloperidol, TCA, citalopram, escitalopram, ondansetron, methadone
- Vem, Dab and Cobi all go through CYP3A4
  - Inhibitors such as aprepitant, fluconazole, grapefruit juice can increase toxicity (Reduced clearance)
  - Inducers such as phenytoin, phenobarb, dexa, St John's Wort can reduce efficacy due to increased clearance
  - Other drugs metabolised by CYP3A4 such as benzos can have their efficacy reduced due to induction

Things to think about

- Dabrafenib solubility decreases with rise in pH
  - Antacids therefore can reduce plasma concentration
- Vemurafenib is an inhibitor of P gp
  - Can reduce clearance of other drugs metabolised by P gp such as apixaban, dabigratan, loperamide
  - Can lead to increased toxicity from those drugs

Oral therapies in Breast Cancer

- Endocrine therapies
  - Tamoxifen
  - Letrozole, anastrozole
  - Exemestane
- Everolimus
- Ribociclib, CDK 4/6 inhibitors
- Lapatinib, neratinib

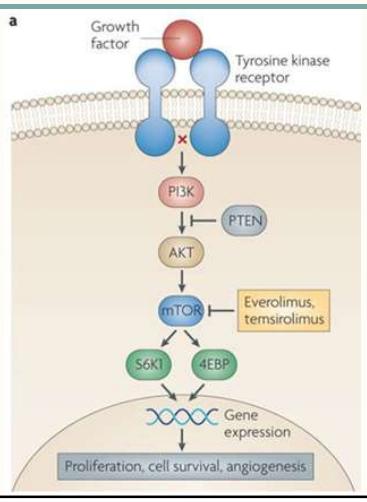
Tamoxifen

- Selective oestrogen receptor modulator (SERM)
- Prodrug – needs CYP2D6 to convert to active metabolite
- Side effects
  - Hot flashes
  - Arthralgias/myalgias
  - Thromboembolism
  - Rarely can cause endometrial cancers

Interactions

- CYP2D6 inhibitors reduce conversion to active drug (reduces efficacy)
  - SSRIs such as fluoxetine, paroxetine, citalopram, escitalopram, sertraline
  - Buproprion
  - Typical antipsychotics (quetiapine, risperidone, clozapine)

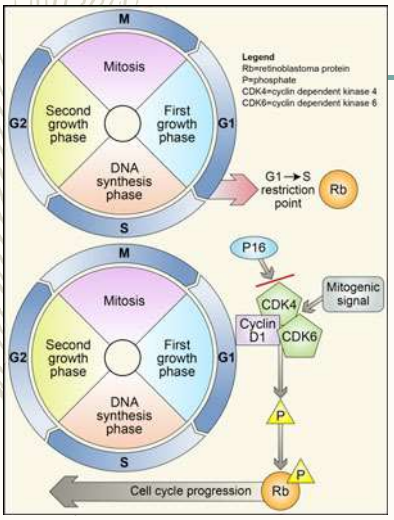
Everolimus



Toxicities and interactions

- Unpleasant drug!
- Mucositis
- Diarrhoea, fatigue, anorexia, rash, fluid retention
- Pneumonitis, hepatitis
- Hyperglycemia, hypercholesterolemia
- Eliminated through CYP3A4 and P gp, so inhibitors

CDK 4/6 inhibition



- ER +ve breast cancer dependent on CDK 4 for proliferation
- Combination of endocrine therapy and CDK 4/6 inhibitors has best evidence
- Drugs include Palbociclib, Abemaciclib, Ribociclib
- Ribociclib available on PBS for metastatic breast cancer
- Main adverse events are neutropenia, significant issues with drug interactions

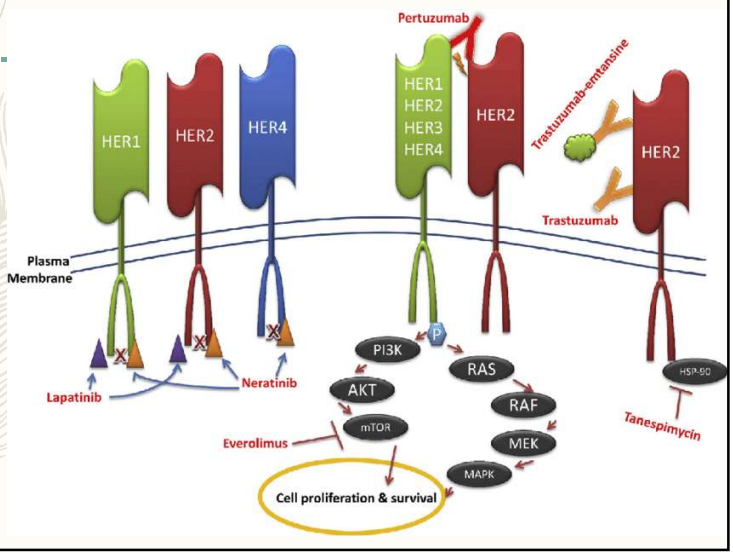
Ribociclib toxicities

- Prolonged QTc- need baseline assessment and follow up ECG
- Oral mucositis, fatigue, diarrhoea
- Deranged LFTs
- Low Ca and/or PO4
- Low counts- neutropenia, thrombocytopenia, anaemia

Ribociclib interactions

- Need to avoid drugs that prolong QTc (haloperidol, TCA, citalopram, escitalopram, ondansetron, methadone)
- Strongly metabolised by CYP3A4
  - Need close monitoring with inhibitors (need DR of ribociclib)
  - Also need to be aware of inducers

Lapatinib/Neratinib



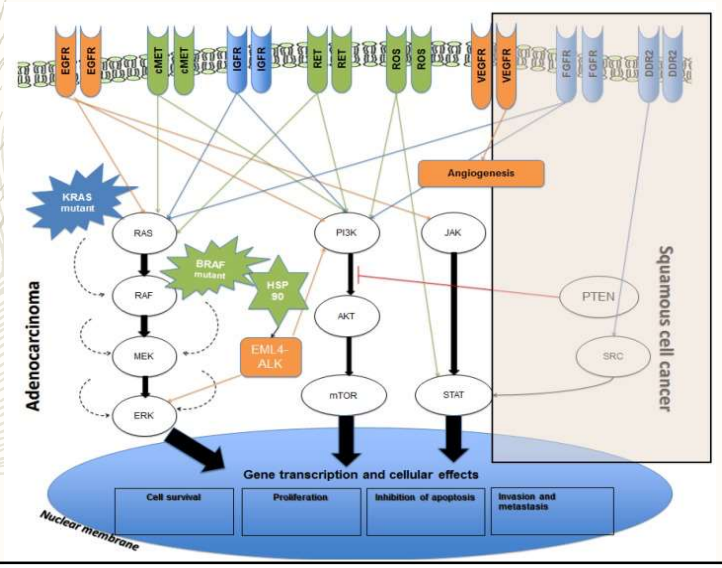
Toxicities

- Diarrhoea
- Nausea
- Abdo pain
- Mucositis
- Fatigue
- Rash
- Eliminated through CYP3A4 and P gp
- Antacids also interfere with absorption

Lung Cancer

- EGFR inhibitors
  - Gefitinib
  - Erlotinib
  - Afatinib
  - Osimertinib
- ALK inhibitors
  - Crizotinib
  - Alectinib
  - Ceritinib
  - Lorlatinib

Lung cancer mutations



EGFR inhibitors

- Depending on drug, toxicities vary
- Rash, fatigue
- Mucositis
- Paronychia
- Cardiotoxicty and pulmonary toxicity (class effect)

Interactions

- Same as most TKIs
  - CYP3A4
  - P gp
- Antacids interfere with absorption
- Smoking interferes with efficacy

ALK Inhibitors

- Fatigue, diarrhoea
- Hepatotoxicty
- Pulmonary toxicity
- Bradycardia
- Prolonged QTc

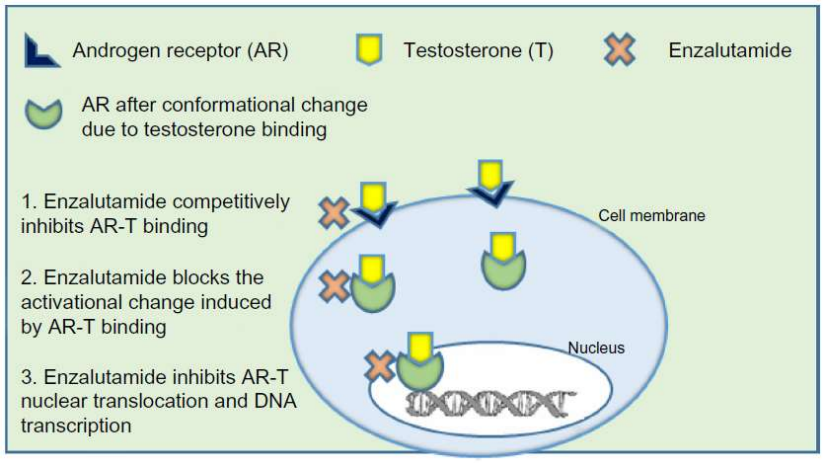
Interactions

- Same as EGFR inhibitors
- Also need to avoid any drug that can prolong QTc
- Similarly drugs that can worsen bradycardia (anti arrythmics) should be used with caution

Prostate

- Many new drugs have been used for a while now
- Most relevant
  - Enzalutamide
  - Abiraterone

Enzalutamide



Enzalutamide

- Blocks androgen binding to androgen receptor
- Also blocks nuclear translocation of the androgen receptor as well as the association of the androgen receptor with nuclear DNA
- Efficacy shown in both pre and post chemo setting
- Can be used in either setting
- No need for steroids concurrently

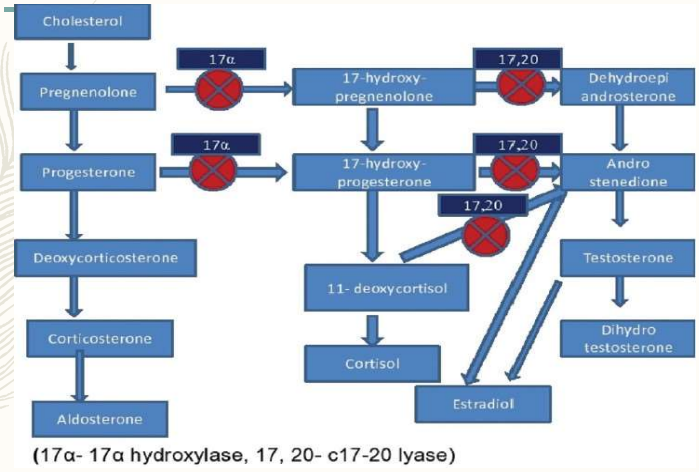
Toxicities

- Fatigue
- Anorexia, arthralgias, hot flashes
- Dizziness
- HTN
- Hepatotoxicity
- Seizures (reported in 0.5%)

Interactions

- Strong inducer of CYP3A4 and CYP2C19
- Can reduce levels of oxycodone, fentanyl, methadone
- Can also reduce levels of dexamethasone, PPIs
- Difficult to gauge impact of interactions but important given the patient population and drugs involved

Abiraterone



Abiraterone

- Small molecule that inhibits CYP 17 gene (including both 17,20-lyase and 17-α-hydroxylase)
- This blocks androgen synthesis in tumour, testes and adrenals
- Needs steroid replacement, also risk of LFT derangement
- Efficacy shown in pre and post chemo setting as well as castration sensitive disease

Toxicity

- Fatigue
- Hot flashes
- HTN
- Hypokalaemia
- Steroid side effects

Interactions

- Spironolactone reduces efficacy and leads to resistance
- Potassium lowering drugs such as frusemide or thiazide (additive effect)
- Inhibits CYP2D6 and leads to reduced transformation of tramadol, codeine to active drug
- Similarly can increase toxicity of antipsychotics and antidepressants due to same inhibition

Which is better?

- No head to head trial so no one knows
- Can use either or
- Can change from one to other if intolerant
- Emerging issue with resistance
  - Androgen receptor isoform splice variant 7 (AR-V7)
  - Lacks binding site for androgen whilst retaining site that promotes tumour growth

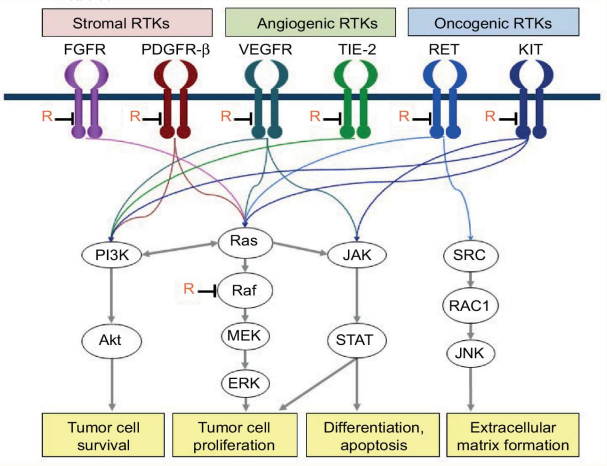
Colon cancer

- Regorafenib
- Lonsurf (Trifluridine/Tipiracil)

Regorafenib

– An exaggeration of targeted therapy!!!

Regorafenib



Toxicities

- Very toxic!
- Rash, hand and foot
- Diarrhoea, nausea
- Hepatotoxicity
- Fatigue
- Voice changes
- Similar interactions as most TKIs

Lonsurf (Trifluridine/Tipiracil)

- New oral chemotherapy option
- Only improved survival by 1.8 months!
- Toxicities significant
  - Diarrhoea
  - Mucositis
- No interactions but very toxic for small benefit

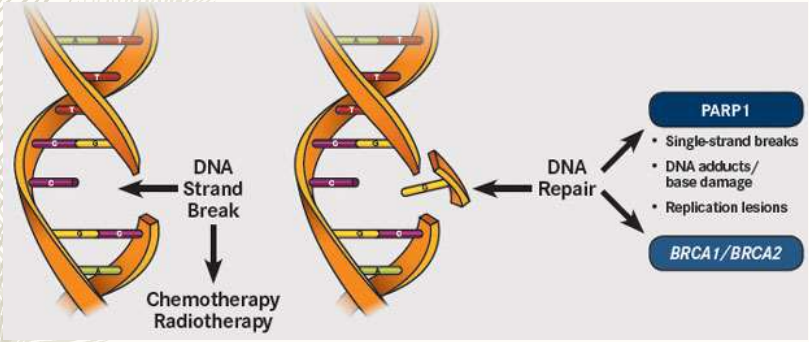
Ovarian Cancer

- Not many new drugs since platinum compounds
- Recently, PARP inhibitors have come on the scene

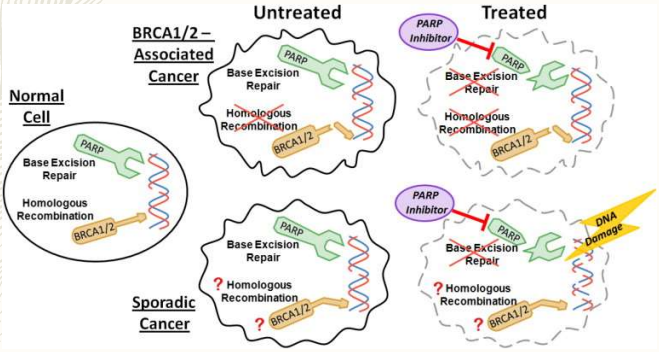
PARP inhibitors

- Poly (ADP-ribose) polymerase
- Nuclear enzymes involved in key cellular processes
  - Repairing DNA damage
  - Chromosome stability
  - Regulate apoptosis and cell division
  - Transcriptional regulation and differentiation
- PARP 1 expression is upregulated in some cancers implying a role for this enzyme in cancer cell survival and proliferation

PARP



PARP inhibition in BRCA mutated tumours



Toxicities

- Cough
- Constipation
- Dysgeusia
- Peripheral oedema
- Headaches
- Strongly metabolised by CYP3A4
- Same interactions as with most TKIs

Conclusion

- Impossible to remember all interactions
- We are all still learning
- New therapies coming in every few months
- Combination makes predicting issues more difficult
- Always ask for help


Questions?