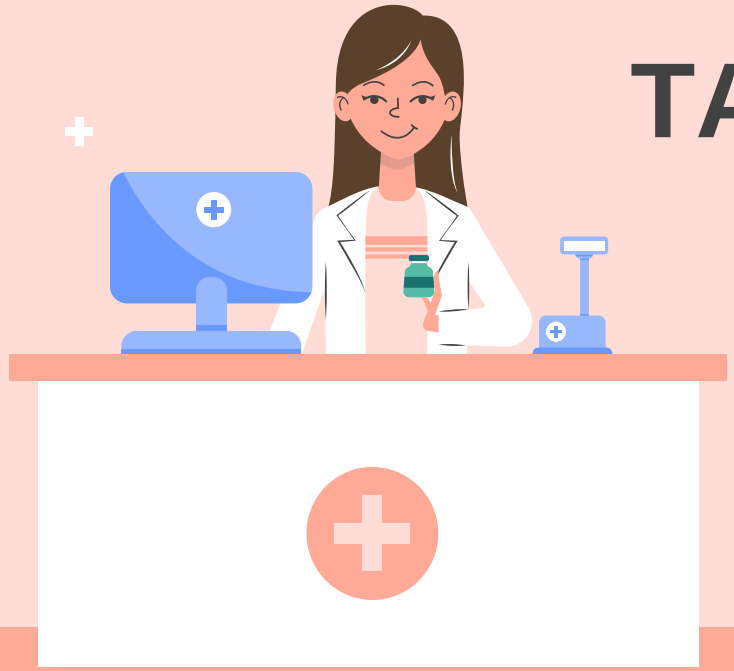


TARGETED CANCER THERAPY

Emma Gray – Pharmacist (Wellington Hospital)

CNO SIG Foundation Day 2025

LEARNING OBJECTIVES

01 Describe the principles of a targeted approach to cancer treatment using monoclonal antibodies

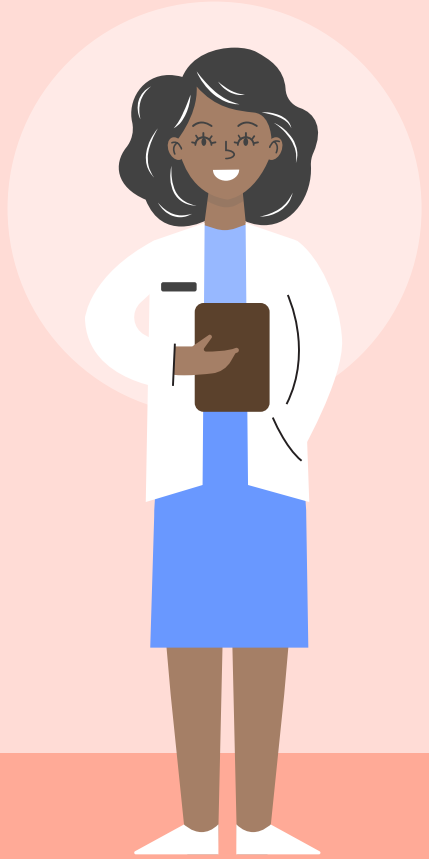
02 Describe the principles of a targeted approach to cancer treatment using small molecule inhibitors

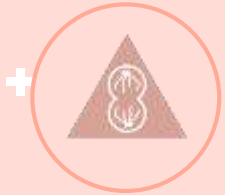
03 Describe the principles of targeting angiogenesis as part of cancer treatment

04 Explain basic mechanisms of:

- Anti CD-20 antibodies
- PARP inhibitors
- EGFR inhibitors
- HER-2 targeted treatment

What is the difference between traditional and targeted therapy?



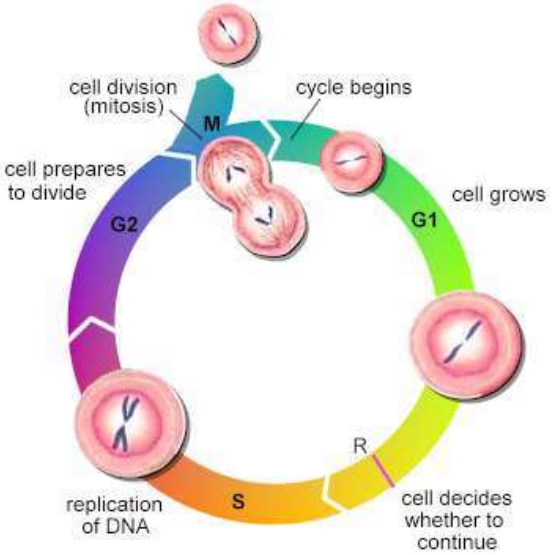


Traditional

- Kill all fast dividing cells
- Discovered by chance
- Inexpensive
- Side effects
- Small molecules
- Excretion via liver and kidneys
- Cytotoxic handling procedures

Targeted

- Target specific molecular targets or signalling pathways
- Reverse engineered (rational drug design)
- Expensive
- Restricted use (funding criteria)
- Less toxicities
  - Large proteins
  - Removal via the immune system



TRADITIONAL CHEMOTHERAPY

MOA = interruption of DNA replication

Examples:

- Alkylating agents (*ifosfamide)*
- Anthracyclines (*doxorubicin*)
- Vinca alkaloids (*vincristine*)
- Topoisomerase inhibitors (*irinotecan*)
- Anti-metabolites (*methotrexate*)
- Platinums (*cisplatin*)
- Taxanes (*paclitaxel*)

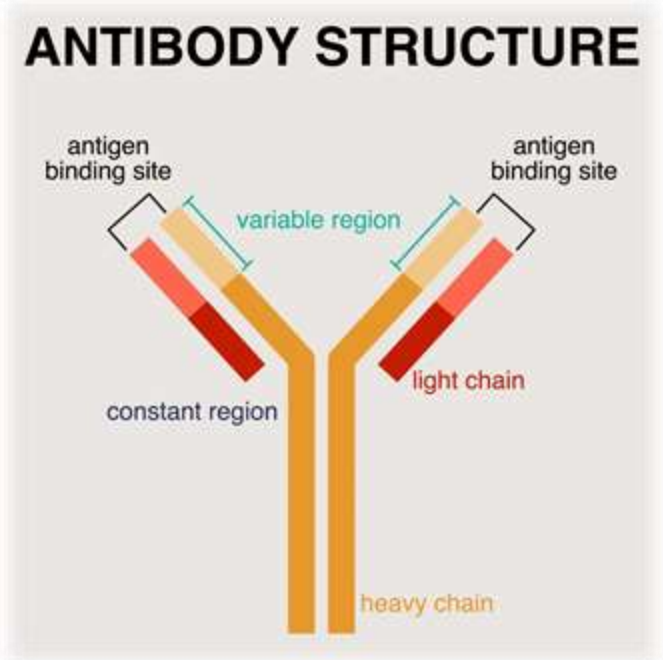
01 MONOCLONAL ANTIBODIES

“An antibody is a protein made by plasma cells in response to an antigen (a substance that causes the body to make a specific immune response). Each antibody can bind to only one specific antigen.”

— National Cancer Institute

WHAT IS AN ANTIBODY?

- Also known as IMMUNOGLOBULIN
- Made by plasma cells in the immune system
- Y-shaped proteins that bind to a specific antigen
- Binds to an antigen to FIGHT and ELIMINATE pathogens
- Examples of antibodies include:
  - IgM
  - IgG
  - IgE
  - IgA
  - IgD



MONOCLONAL ANTIBODIES

- Copies of antibodies mass-produced in a laboratory
- Act like natural antibodies in the body
- Target specific antigens or molecules
- End in the suffix -mab

Examples:

- Rituximab
- Trastuzumab
- Pertuzumab
- Pembrolizumab
- Cetuximab
- Bevacizumab
- Daratumumab

DIFFERENT TYPES OF MABS

MABs can be produced using different methods, resulting in four main types based on their origin:

Murine

Fully derived from mice. Named used the prefix “o-” or suffix “-omab”

Chimeric

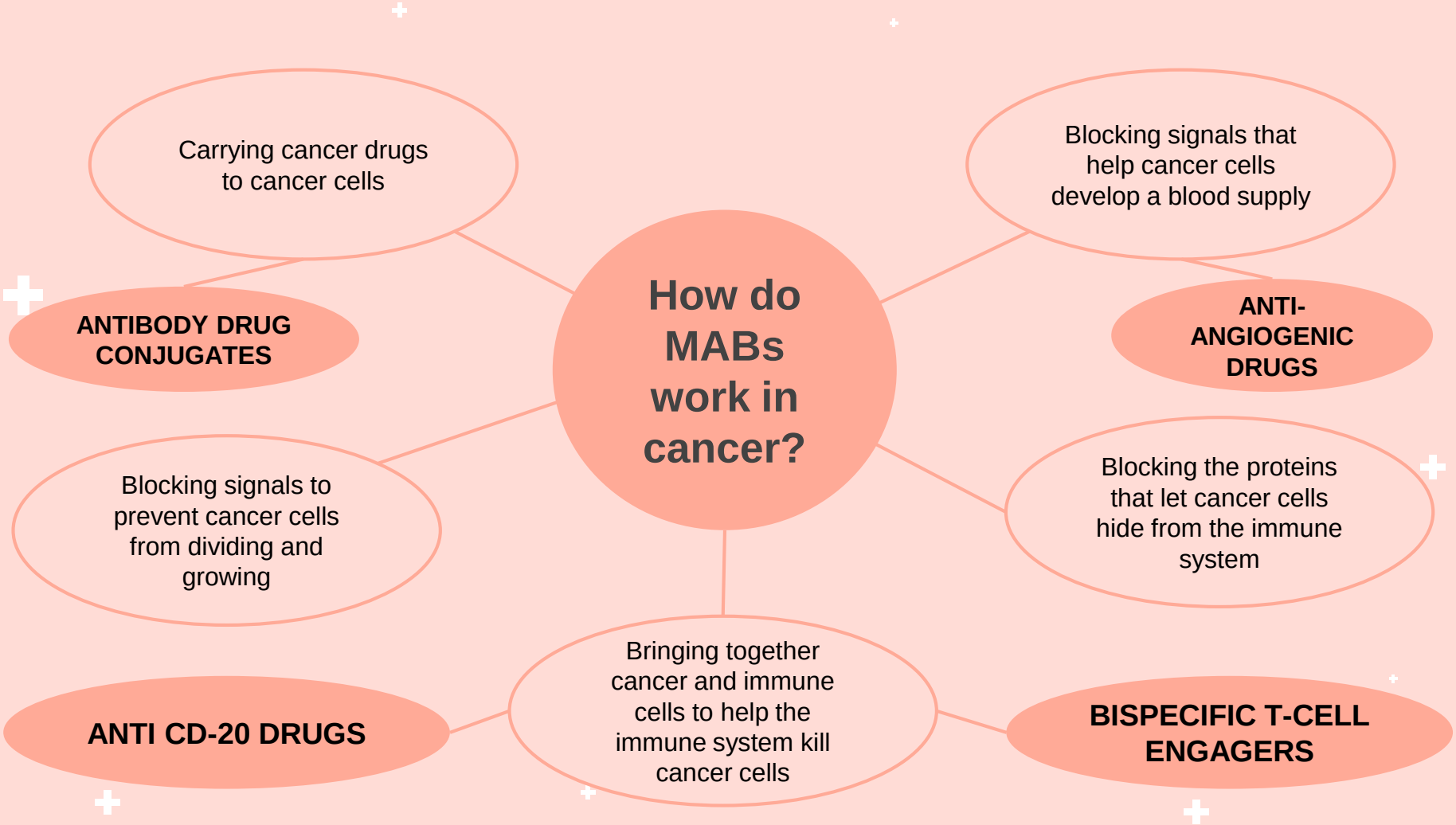
Composed of human constant regions and mouse variable regions. Named using the suffic “-ximab”

Humanized

Majority of human sequence, with only a small portion of mouse sequence. Named using the suffix “-zumab”

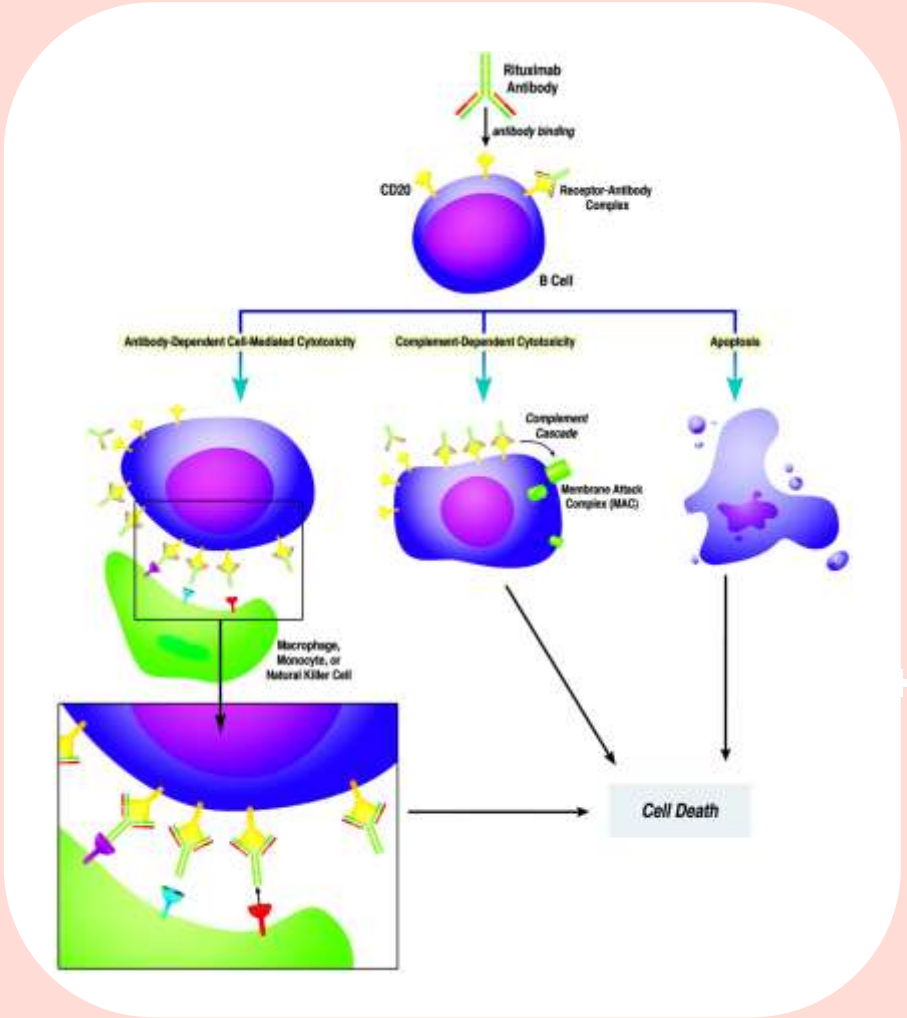
Fully human

Fully derived from human sequences. Named using “-umab”


How do MABs work in cancer?
Carrying cancer drugs to cancer cells
ANTIBODY DRUG CONJUGATES
Blocking signals that help cancer cells develop a blood supply
ANTI-ANGIOGENIC DRUGS
Blocking signals to prevent cancer cells from dividing and growing
Blocking the proteins that let cancer cells hide from the immune system
Bringing together cancer and immune cells to help the immune system kill cancer cells
ANTI CD-20 DRUGS
BISPECIFIC T-CELL ENGAGERS

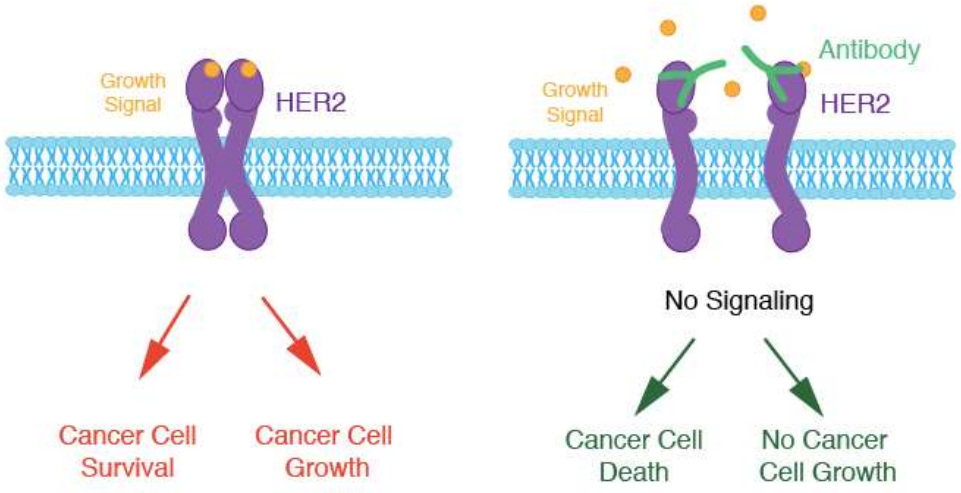
RITUXIMAB – ANTI CD-20 DRUG

- Used in Non Hodgkins Lymphoma
- CD-20 = receptor on 90% of NHL cells
- Rituximab works in three ways:
  - ADCC
  - CDC
  - Apoptosis induction
- Can also be used in autoimmune conditions:
  - SLE
  - ITP

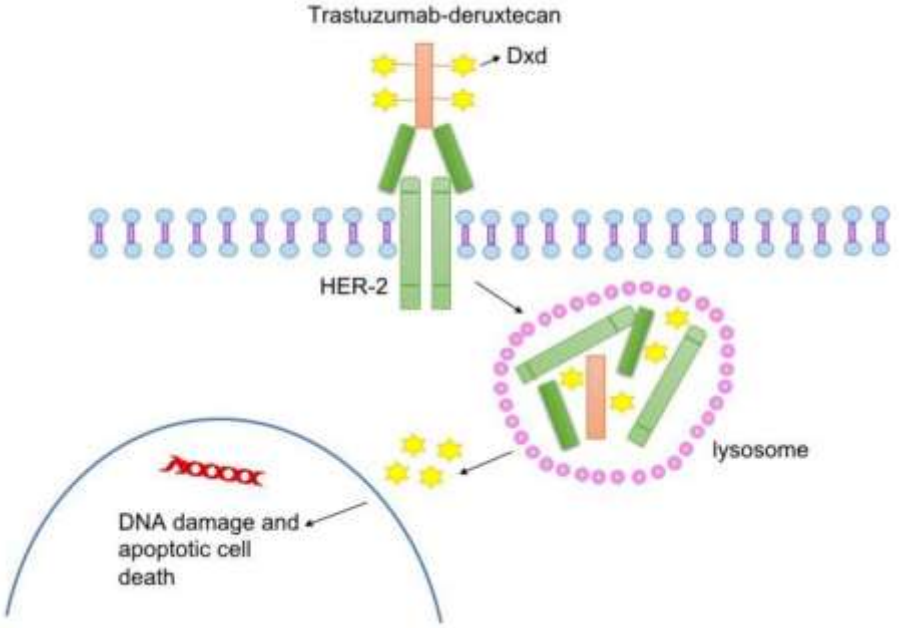


HER2+ BREAST CANCER

- **HER2 = human epidermal growth factor receptor 2**
- 25-30% of breast cancers overexpress HER2
  - Gastric cancers can also be treated with HER2 agents in NZ
- HER2 receptor activation causes cell proliferation and growth
- Use of agents like trastuzumab can inhibit this activation and signal from occurring



ENHERTU - ANTIBODY DRUG CONJUGATE



- Enhertu = **trastuzumab deruxtecan**
- Combination of monoclonal antibody + cytotoxic
- For treatment of HER2+ breast cancer
  - In NZ – only funded for metastatic HER2+ cancer
- Targeted treatment as cytotoxic delivered to the cells carrying the appropriate receptor
- More side effects due to the cytotoxic component when compared with trastuzumab
- NOT EQUIVALENT TO TRASTUZUMAB

PROBLEMS WITH MABS

- Large proteins
  - Slow distribution kinetics
  - Limited tissue penetration
  - IV formulations only
- Cost
  - Expensive products
  - Biosimilars can improve this but have to wait for patent to end
- Infusion related reactions
  - Caution needed when administering these drugs

BIOSIMILAR VS. GENERIC

What is the difference between these terms?

GENERIC

Generic drugs are pharmaceuticals that contains the same chemical substance as a proprietary drug that was originally protected by chemical patents. Will undergo bioequivalence studies.

BIOSIMILAR

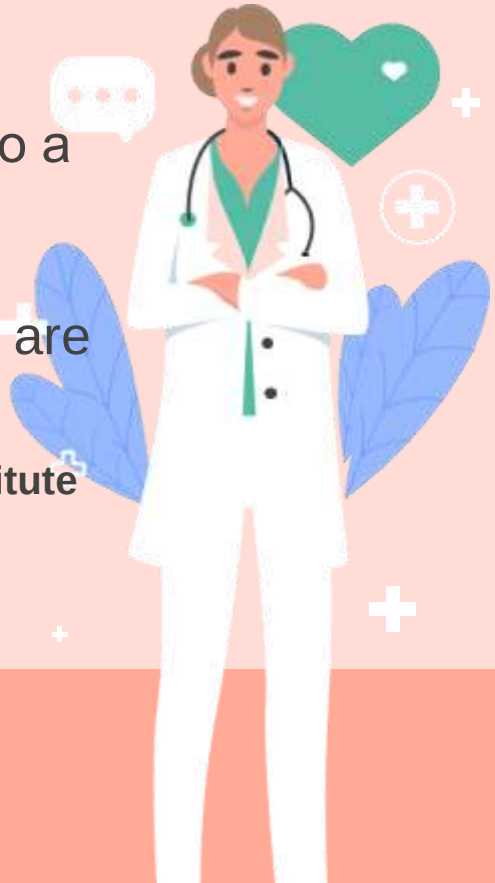
Biosimilar monoclonal antibodies are highly similar versions of already authorised medicines, aiming to provide a comparable therapeutic option with potential cost savings. A traditional bioequivalence study can not be applied due to the complexity of the drug.

SMALL MOLECULE INHIBITORS

02

“A small molecule drug can enter cells easily due to a low molecular weight. Once inside the cells, it can affect other molecules, such as proteins, and may cause cancer cells to die. Many targeted therapies are small molecule drugs.”

— National Cancer Institute

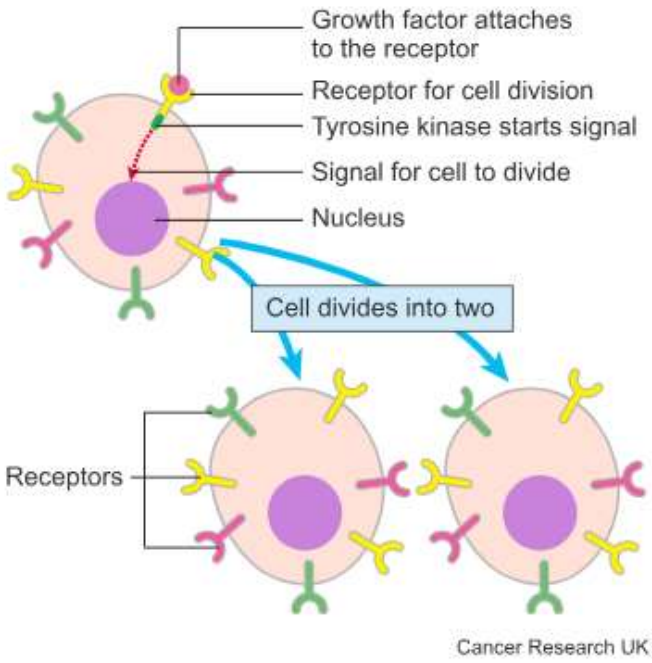


WHAT ARE SMALL MOLECULE DRUGS?

- Usually denoted by the suffix “-nib”
- Target specific molecules within cancer cells (e.g. proteins)
- Administered orally
- Shorter half-life
- Include **tyrosine-kinase inhibitors**
    - Examples:
        - Dabrafenib
        - Trametinib
        - Ibrutinib
        - Imatinib
        - Pazopanib
        - Ruxolitinib
        - Sunitinib

Growth factor examples:

- Epidermal growth factor (EGF)
- Vascular endothelial growth factor (VEGF)
- Human epidermal growth factor receptor 2 (HER2)

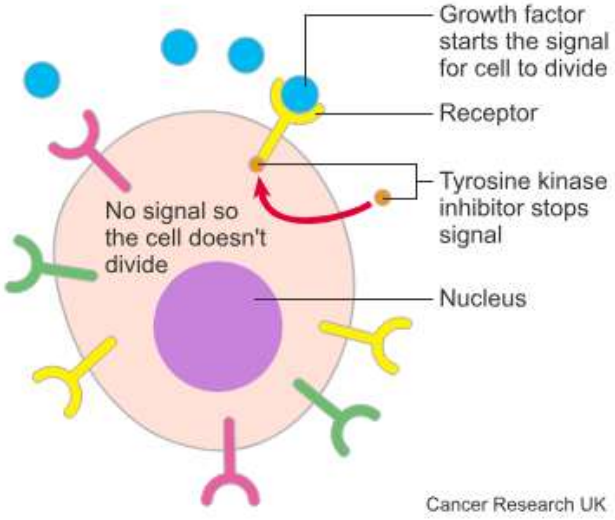


Tyrosine kinase (enzyme) acts as a ‘on-off’ switch to signal the cell to divide.

TYROSINE KINASE INHIBITORS (TKIs)

What is TYROSINE KINASE?

- Enzyme that transfers a phosphate group from ATP to a tyrosine residue in a protein
- Important for signal transduction
- Tyrosine kinase-linked receptors stimulation division of cells
- Mutated tyrosine kinase enzymes cause unregulated cell division – no off switch!



How do TKIs work?

- Bind to the receptor and block the signal from being sent
- If the signal isn't sent, the cell will not divide
- Can block a single type or multi type of tyrosine kinase enzymes

TKI EXAMPLE – IMATINIB

- Used in Chronic Myeloid Leukaemia – Philadelphia+ chromosome
  - Philadelphia chromosome = translocation between chromosomes 9 and 22 creating the BCR-ABL fusion gene
- Works by binding to the BCR-ABL fusion protein ATP site, locking it and therefore inhibiting enzyme activity
- Ultimately results in the “switching-off” of the signaling pathway for cell division

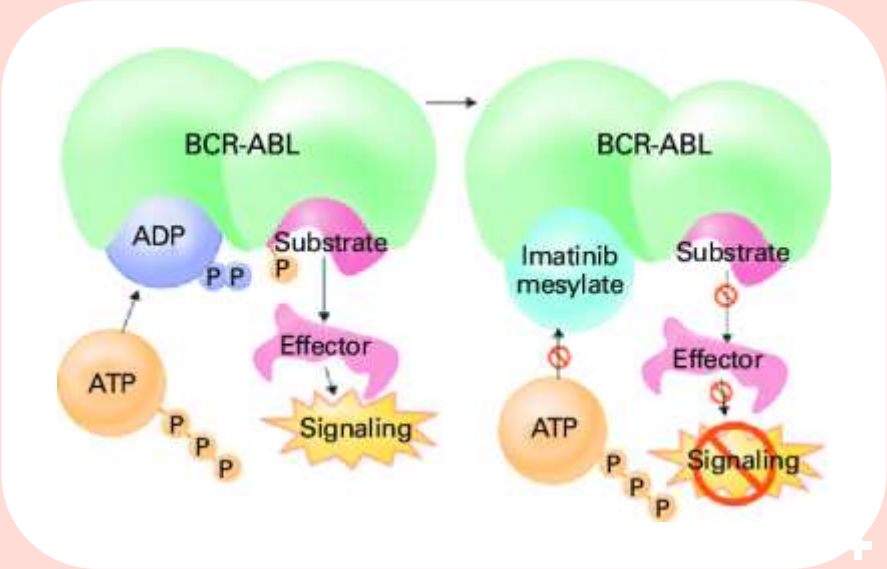
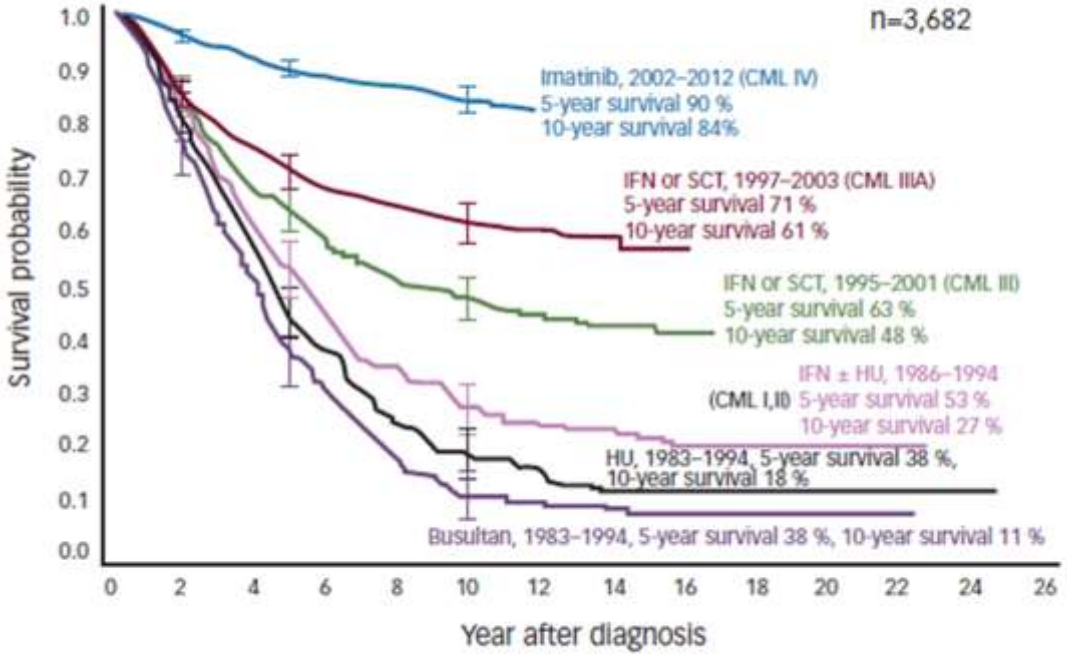


Figure 1: Survival with CML over Time – The German CML-Study Group Experience 9/2014

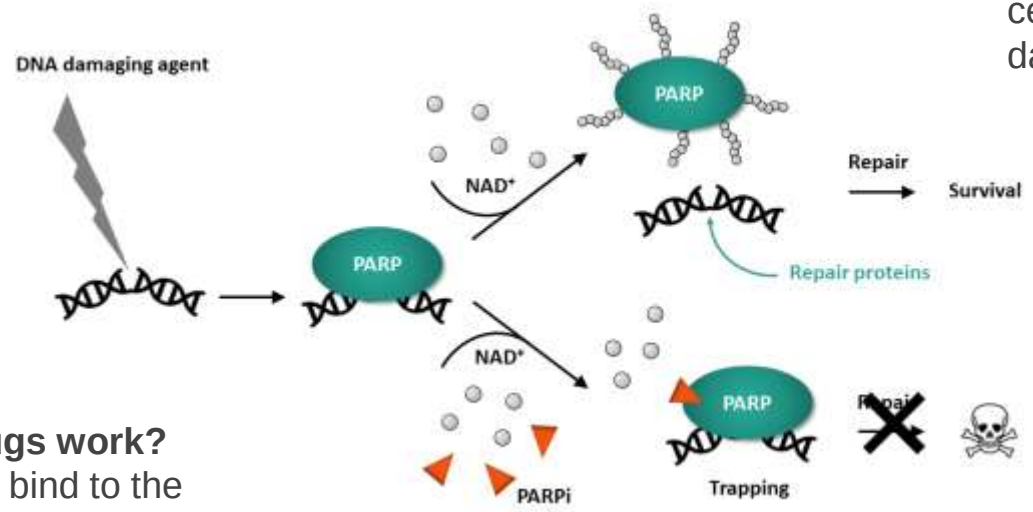


HU = hydroxyurea; IFN = interferon; SCT = stem cell transplantation. Survival with chronic myeloid leukaemia (CML) as observed in five consecutive randomised treatment options studies of the German CML Study Group 1983–2014. Kindly authorised by R Hehlmann.

PARP INHIBITORS

What is PARP?

- Enzyme found in our cells that helps repair damaged cells



How do PARPi drugs work?

- PARP inhibitors bind to the enzyme to inactivate it
- Damaged cells will die from apoptosis

PARPi EXAMPLE - OLAPARIB

- Used in **ovarian epithelial cancer** in NZ
- Maintenance treatment after platinum chemotherapy
- Funding needs BRCA1 or BRCA2 gene mutation
  - Approx. 15% of ovarian epithelial cancer have BRCA mutations
- Currently listed as $3700 for 56 tablets on community schedule
  - Usual dose = 300mg bd = 4 tabs daily
- Brand = Lynparza

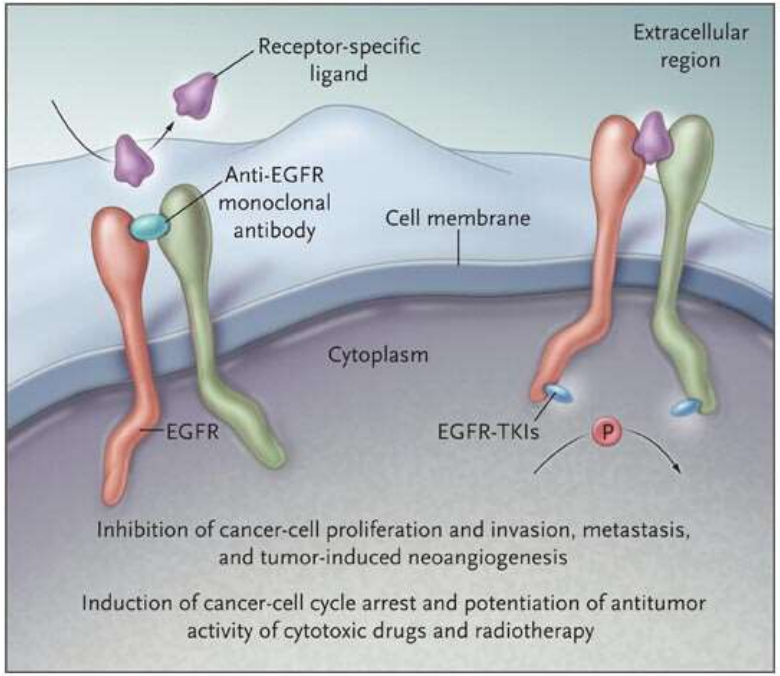
Initial application — Ovarian cancer
Applications only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months.
Prerequisites(tick boxes where appropriate)

- ☐ Patient has a high-grade serous* epithelial ovarian, fallopian tube, or primary peritoneal cancer
- and ☐ There is documentation confirming pathogenic germline BRCA1 or BRCA2 gene mutation
- and
  - ☐ Patient has newly diagnosed, advanced disease
  - and ☐ Patient has received one line** of previous treatment with platinum-based chemotherapy
  - and ☐ Patient's disease must have experienced a partial or complete response to the first-line platinum-based regimen
  - or
  - ☐ Patient has received at least two lines** of previous treatment with platinum-based chemotherapy
  - and ☐ Patient has platinum sensitive disease defined as disease progression occurring at least 6 months after the last dose … the penultimate line** of platinum-based chemotherapy
  - and ☐ Patient's disease must have experienced a partial or complete response to treatment with the immediately preceding platinum-based regimen
  - and ☐ Patient has not previously received funded olaparib treatment
- and ☐ Treatment will be commenced within 12 weeks of the patient's last dose of the immediately preceding platinum-based reg…
- and ☐ Treatment to be administered as maintenance treatment
- and ☐ Treatment not to be administered in combination with other chemotherapy

EGFR INHIBITORS

What is EGFR?

- **EGFR = epidermal growth factor receptor**
- Epidermal growth factor assists in helping cells grow and divide
- EGFR mutations can be found in lung cancer
- Around 32% of NSCLC cases worldwide involve an EGFR mutation



Can we use EGFR as a target?

- EGFR TKIs
  - Osimertinib
  - Gefitinib
  - Erlotinib
- Anti-EGFR MABs
  - Cetuximab

EGFR-TKIs EXAMPLE - OSIMERTINIB

- Funded in NZ for Non Small Cell Lung Cancer (NSCLC)
- Irreversible inhibitor of EGFR tyrosine kinase with selectively for several mutant forms including T790M
- Cells must exhibit:
  - EGFR mutations for **first line tx**
  - T790M mutations for **second line tx**
- Side effect = acneiform rash. Direct result of EGFR inhibition
  - Reported to occur in approx. 80% of patients
  - Can be treated with doxycycline, moisturiser and HC 1% cream

Initial application — NSCLC – first line
Applications from any relevant practitioner. Approvals valid for 4 months.
Prerequisites(tick boxes where appropriate)

- ☐ Patient is currently on treatment with osimertinib and met all remaining criteria prior to commencing treatment

or

- ☐ Patient has locally advanced or metastatic, incurable, non-squamous non-small cell lung cancer (NSCLC)

and

- ☐ Patient is treatment naïve

or

- ☐ Patient has received prior chemotherapy in the adjuvant setting and/or while awaiting EGFR results

or

- ☐ The patient has discontinued gefitinib or erlotinib due to intolerance

and

- ☐ The cancer did not progress while on gefitinib or erlotinib

and

- ☐ There is documentation confirming that the cancer expresses activating mutations of EGFR

and

- ☐ Patient has an ECOG performance status 0-3

and

- ☐ Baseline measurement of overall tumour burden is documented clinically and radiologically

Initial application — NSCLC – second line
Applications from any relevant practitioner. Approvals valid for 4 months.
Prerequisites(tick boxes where appropriate)

- ☐ Patient is currently on treatment with osimertinib and met all remaining criteria prior to commencing treatment

or

- ☐ Patient has locally advanced or metastatic, incurable, non-squamous non-small cell lung cancer (NSCLC)

and

- ☐ Patient has an ECOG performance status 0-3

and

- ☐ The patient must have received previous treatment with erlotinib or gefitinib

and

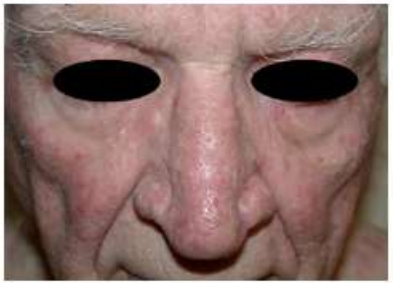
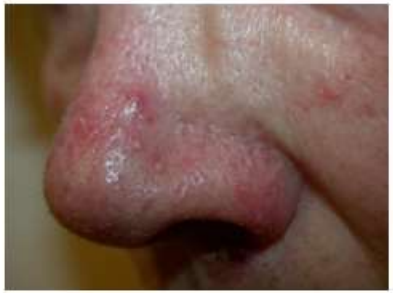
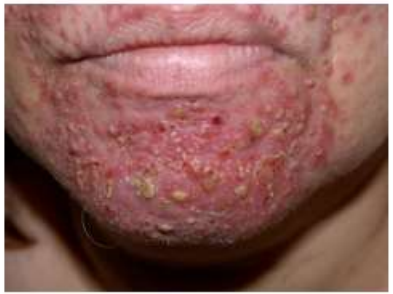
- ☐ There is documentation confirming that the cancer expresses T790M mutation of EGFR following progression on or after erlotinib or gefitinib

and

- ☐ The treatment must be given as monotherapy

and

- ☐ Baseline measurement of overall tumour burden is documented clinically and radiologically

	Mild	Moderate	Severe	
CTCAE grading* acneiform rash (papulopustular rash)	Grade 1	Grade 2	Grade 3	Grade 4
	Papules and/or pustules covering less than 10% body surface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 to 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL**; papules and/or pustules covering >30% BSA with or without mild symptoms	Papules and/or pustules covering more than 30% BSA, with moderate or severe symptoms; limiting self care ADL***; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated
				

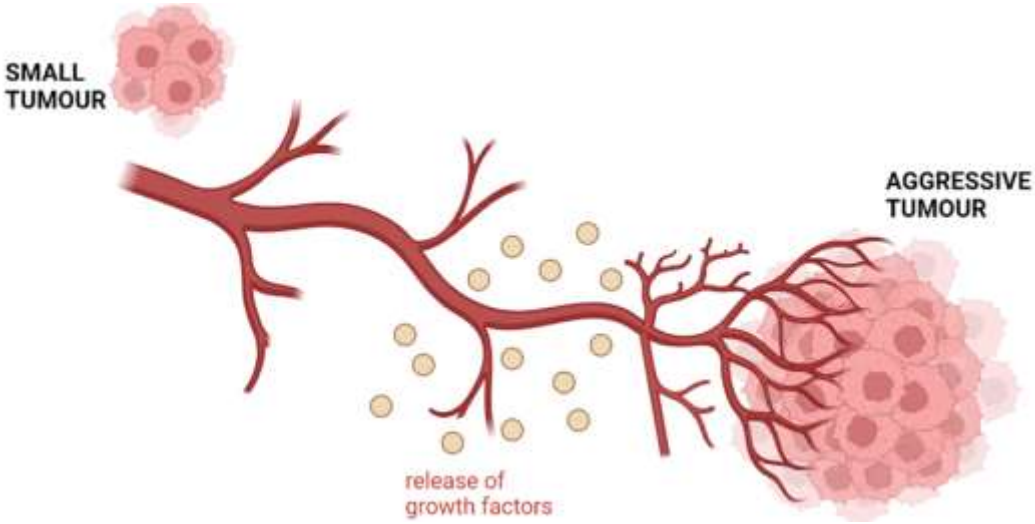
03

ANGIOGENESIS & BEVACIZUMAB

*“Tumour **angiogenesis** is the growth of new blood vessels that tumours need to grow. This process is caused by the release of chemicals by the tumour and by host cells near the tumour.”*

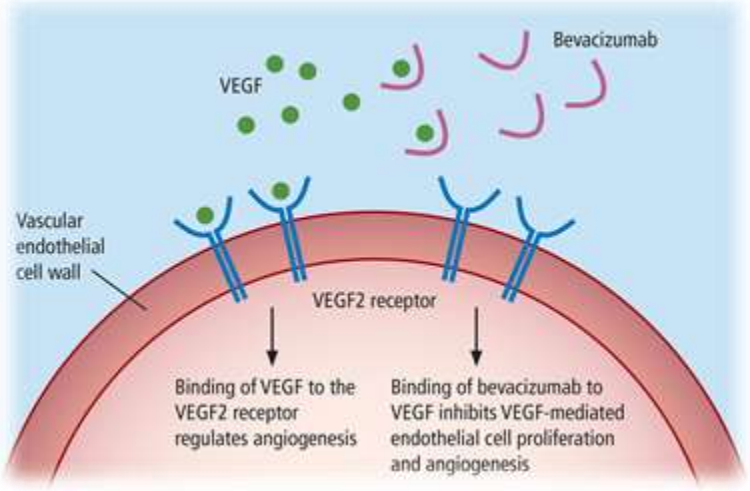
— National Cancer Institute

- Solid tumours need a blood supply to grow
- Cancer cells make vascular endothelial growth factor (VEGF)
- VEGF attaches to receptors on cells that line the walls of blood vessels and stimulate growth
- VEGF can be a target for drugs to prevent angiogenesis



What is BEVACIZUMAB?

- Monoclonal antibody
- Targeted therapy for VEGF
- IV formulation
- Limited funding in NZ



How does it work?

- Inhibits the binding of VEGF to its receptors
- Prevents angiogenesis
- Tumour does not get nutrients or oxygen

BEVACIZUMAB IN NZ

Initial application — advanced or metastatic ovarian cancer
Applications from any relevant practitioner. Approvals valid for 4 months.
Prerequisites(tick boxes where appropriate)

- ☐ The patient has FIGO Stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer

or

- ☐ The patient has previously untreated advanced (FIGO Stage IIIB or IIIC) epithelial ovarian, fallopian tube, or primary peritoneal cancer

and

- ☐ Debulking surgery is inappropriate

or

- ☐ The cancer is sub-optimally debulked (maximum diameter of any gross residual disease greater than 1cm)

and

- ☐ Bevacizumab to be administered at a maximum dose of 15 mg/kg every three weeks

and

- ☐ 18 weeks concurrent treatment with chemotherapy is planned

- Currently only funded in hepatocellular carcinoma and ovarian cancer
- Biosimilar just released – Vegzelma
- Vegzelma is approx. a tenth of the cost of Avastin
- ??More indications to be funded in future

Initial application — unresectable hepatocellular carcinoma
Applications from any relevant practitioner. Approvals valid for 6 months.
Prerequisites(tick boxes where appropriate)

- ☐ Patient is currently on treatment with bevacizumab, and met all remaining criteria prior to commencing treatment

or

- ☐ Patient has locally advanced or metastatic, unresectable hepatocellular carcinoma

and

- ☐ Patient has preserved liver function (Child-Pugh A)

and

- ☐ Transarterial chemoembolisation (TACE) is unsuitable

and

- ☐ Patient has not received prior systemic therapy for the treatment of hepatocellular carcinoma

or

- ☐ Patient received funded lenvatinib before 1 March 2025

or

- ☐ Patient has experienced treatment-limiting toxicity from treatment with lenvatinib

and

- ☐ No disease progression since initiation of lenvatinib

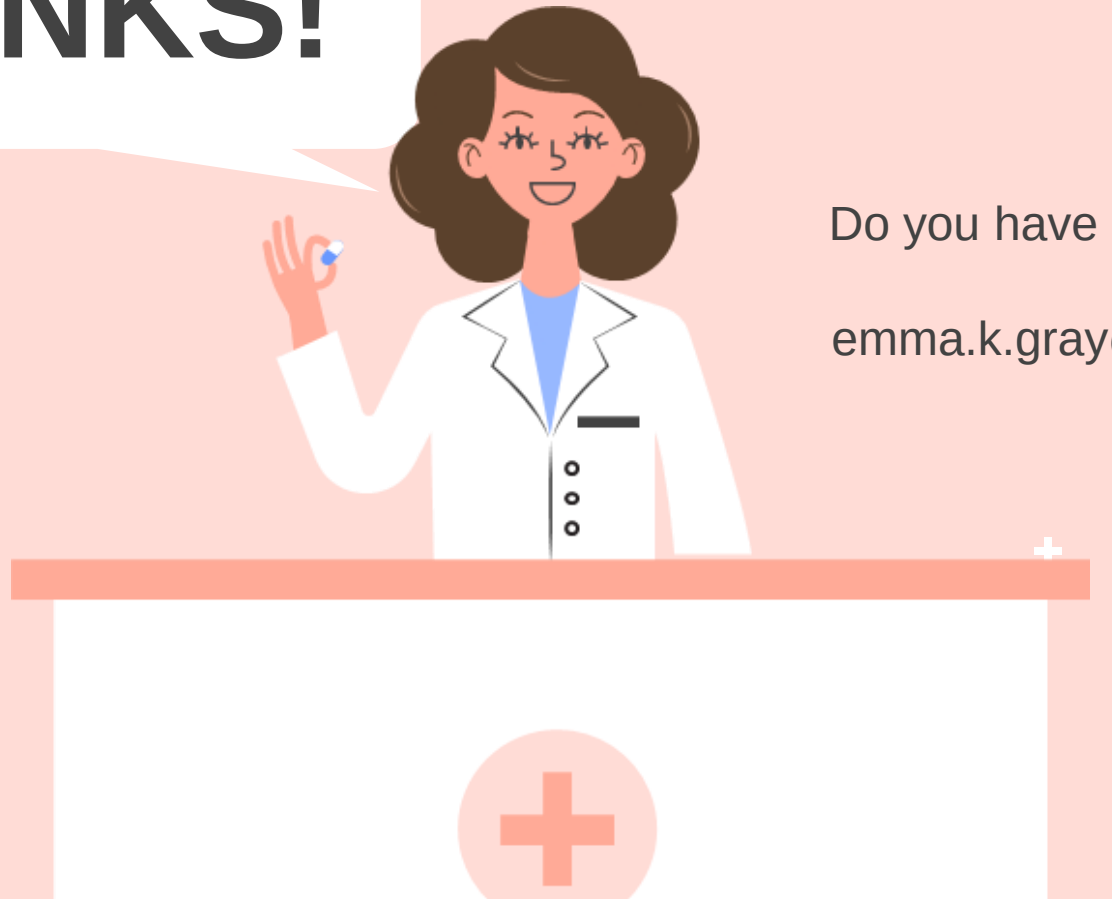
and

- ☐ Patient has an ECOG performance status of 0-2

and

- ☐ To be given in combination with atezolizumab

THANKS!



Do you have any questions?

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