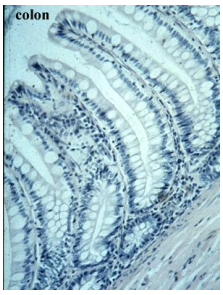
Slide 1	# Targeted Cancer Therapies Mark McKeage Medical Oncology Specialist Professor in Clinical Pharmacology	
Slide 2	## Learning goals • Define cancer at different levels of biological organisation • Distinguish between cytotoxic chemotherapy and targeted therapy • Know the mechanisms of action, molecular targets and clinical indications of imatinib, gefitinib, trastuzumab and sunitinib • From that information, be able to predict their major side-effects	
Slide 3	## Cancer • Definition- • A disease of populations of cells that live, divide, invade and spread without regard to normal limits • Normally, cell growth, death and location are tightly regulated in the body	

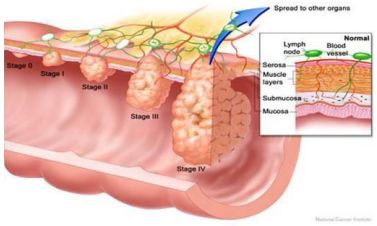
Slide 4

Colonic Epithelium

Normal



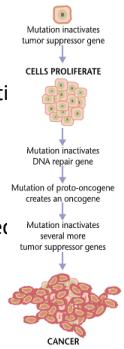
Cancer



Slide 5

Molecular basis of cancer

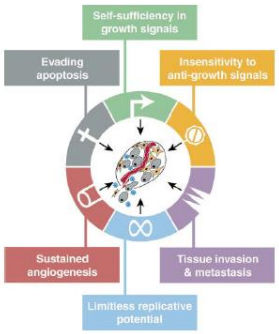
- Cancer is a disease caused by abnormalities in DNA
  - Exogenous carcinogens, DNA replicati errors, inherited
- Cancer genes
  - Oncogenes (activated)
  - Tumour suppressor genes (inactivate
- Cancer biomolecules maybe good targets for therapy



Slide 6

Cellular basis of cancer

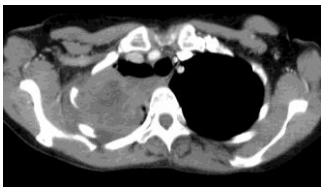
- Cancer is a disease of populations of cells that live, grow, invade and spread without respect to normal limits
- Cells acquire a series of common key phenotypic characteristics

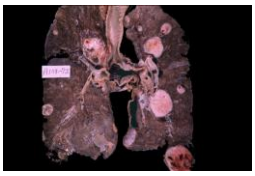


Hanahan D and Weinberg RA Cell 2000; 100: 57-70

Slide 7

Pathophysiological basis of cancer





- Growth and invasion of primary tumours
- Metastasis and distant effects of wide-spread disease
- Systemic effects of paraneoplastic syndromes

Slide 8

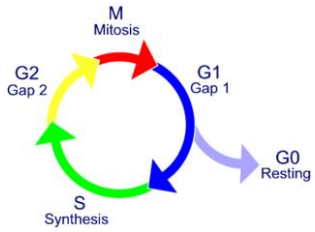
Cancer Chemotherapy: Targets

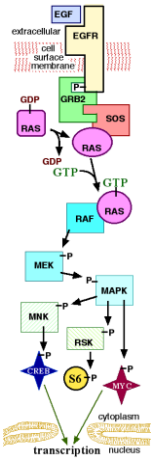
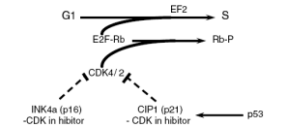
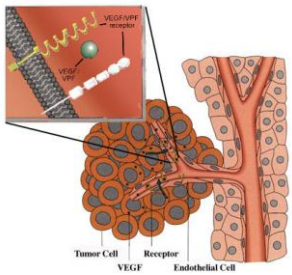
- Cancer chemotherapy targets cycling cells without discriminating between normal and diseased cells
- Selective toxicity of cancer chemotherapy is based on higher numbers of cycling cells present in tumours relative to normal tissues
- Many adverse effect of cancer chemotherapy are due to the cycling of normal cells
  - eg. alopecia, blood cytopaenias

Slide 9

Cancer chemotherapy targets cycling cells

- Antimetabolites
  - eg. methotrexate
  - Inhibit DNA synthesis
  - S-phase specific
- Antimicrotubule drugs
  - eg. paclitaxel
  - Inhibit mitotic spindle
  - M-phase specific



Slide 10	# Oncogenes • Modified genes encoding abnormal proteins that increase probability of tumour formation • Formed from proto-oncogenes by chromosomal translocation, mutation or amplification • Often genes and proteins in mitogenic signal transduction pathways, – eg. MAPK/ERK pathway 	
Slide 11	# Tumour suppressor genes • Genes that, if deleted or mutated, increase the probability of tumor formation • Normally, often promote apoptosis or repress cell cycle • Examples of – TP53 (encodes p53) – RB1 encodes retinoblastoma protein – Cyclin dependent kinase inhibitor 4/2 (CDK4/2, p16, INK4a)  Fig. 2. The G1/S phase transition and the role of the p53, Rb and p16 tumour suppressor genes.	
Slide 12	# Tumour angiogenesis • To grow >2mm^2, tumours need a blood supply for O_2, nutrients, metastasis and waste product removal • Tumours induce blood vessel growth by secreting angiogenic factors – VEGF – BFGF 	

Slide 13

Targeted Cancer Therapy

- Drug treatments that interfere with specific molecules needed for tumour development and/or progression.
  - Most recent form of cancer therapy
  - May be more effective and safer than chemo
  - May allow individualization of therapy

Slide 14

Targeted Cancer Therapies

- Small Molecular drug
  - Block specific enzymes or growth factor receptors
  - eg, imatinib, gefitinib, sunitinib
- Monoclonal antibodies
  - Bind to growth factors or their receptors
  - eg, trastuzumab, bevacizumab

Slide 15

Examples of targeted therapies

Malignant disease	Molecular Target	Targeted therapy
Chronic myeloid leukaemia	Bcr-abl	Imatinib
Non-small cell lung cancer	Mutant EGFR	Gefitinib
Breast Cancer	Her-2	Trastuzumab
Renal cell cancer	VEGF	sunitinib

Slide 16

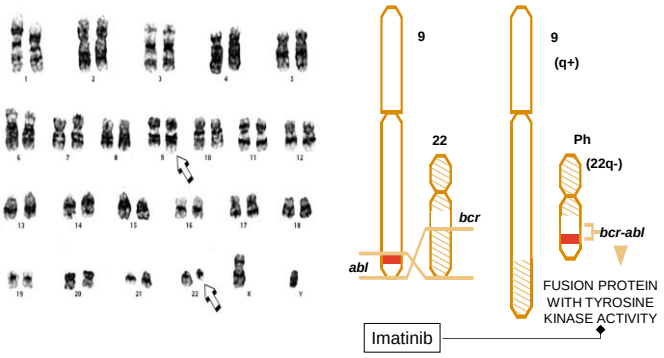
Chronic Myeloid Leukaemia

- A form of leukaemia, about 200 new cases/yr in NZ
- Characteristic chromosomal translocation, the Philadephia chromosome
- Accumulation of myeloid leukaemia cells in blod and bone marrow
- Treatment
  - Previously chemotherapy and immunotherapy
  - Now targeted therapy

Slide 17

Chronic Myelogenous Leukaemia (CML)

Acquisition of the Philadelphia Chromosome [t(9;22) translocation], abnormal fusion protein (*bcr-abl*) and self-sufficiency of growth signals.



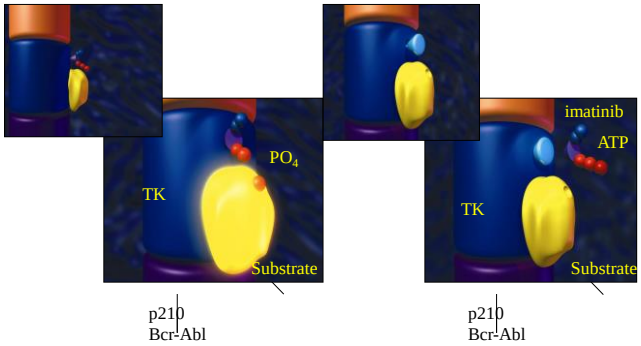
Slide 18

Clinical pharmacology of imatinib (gleveec)

- Clinical Indications:
  - Chronic Myelogenous Leukaemia (CML)
  - Gastrointestinal Stromal tumours (GIST)
- Tyrosine Kinase activation
  - CML: chromosomal translocation/unique fusion protein (bcr-abl)
  - GIST: point mutation activating c-kit
- Imatinib:
  - Small MW inhibitor of bcr-abl and c-kit tyrosine kinases, that binds ATP-binding site thereby inhibiting tyrosine kinase activity
- Adverse effect profile: generally well tolerated

Slide 19

Mechanism of Action of imatinib (Gleevec)



p210 Bcr-Abl

p210 Bcr-Abl

Imatinib is not entirely selective for Bcr-Abl; it also inhibits c-Kit and PDGF-R.

Mechanism of Action of Gleevec™

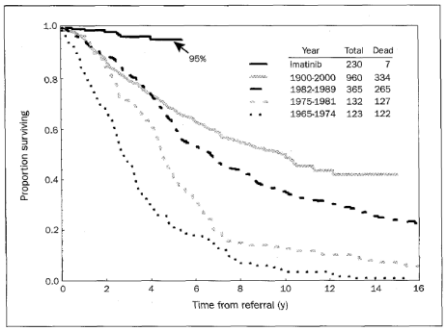
- Gleevec is an inhibitor of Bcr-Abl fusion tyrosine kinase.
- Gleevec acts by inhibiting the binding site for ATP to the Abl kinase, thus blocking the phosphorylation of tyrosine residues on substrate protein.[1]
- Blocking the binding of ATP inactivates the Abl kinase because it cannot transfer phosphate to its substrate.
- By inhibiting phosphorylation, Gleevec prevents the activation of signal transduction pathways that induce the leukemic transformation processes that cause CML.
- Gleevec is not entirely selective for the Bcr-Abl tyrosine kinase; it also inhibits the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor c-Kit.

Reference

1. Goldman JM, Melo JV. Targeting the BCR-ABL tyrosine-kinase in chronic myeloid leukemia. *N Engl J Med*. 2001;344:1084-1086.

Slide 20

Survival of patients with CML treated in different eras compared to those treated with imatinib

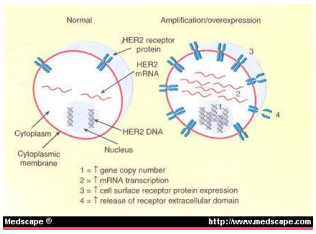


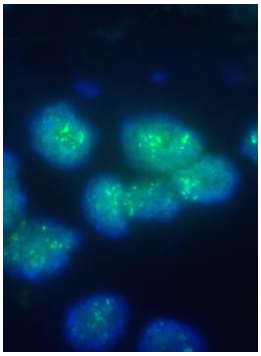
Quintas-Cadama A and Cortes A Mayo Cinic Proceedings 2006 81:973-88

Slide 21

Breast cancer

Acquisition of self-sufficiency in growth signals by genetic amplification of HER-2 (human epidermal growth factor receptor-2)





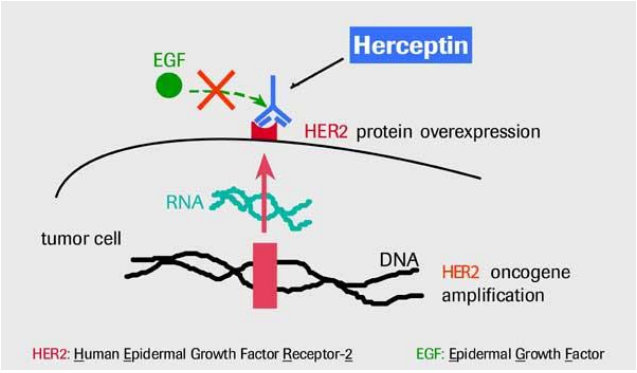
Slide 22

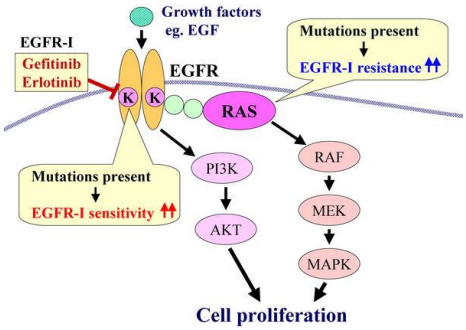
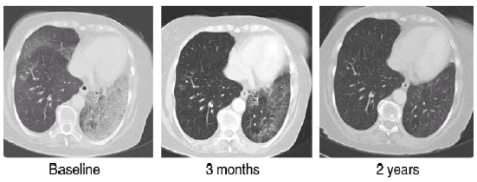
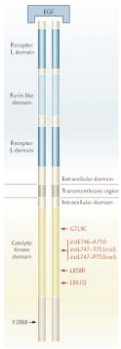
Clinical pharmacology of trastuzumab

- recombinant humanised monoclonal antibody
- selectively targets extra-cellular domain of human epidermal growth factor receptor 2 protein (HER2)
- HER2 activation: gene amplification
- Indication: breast cancer
- Adverse effect profile: infusion reactions

Slide 23

Mode of Action: trastuzumab



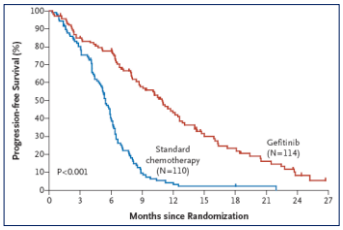
Slide 24	**Non-small cell lung cancer (NSCLC)** Acquisition of self-sufficiency in growth signals by somatic mutation of ras or EGFR (human epidermal growth factor receptor-1)  	
Slide 25	**Activating Mutations in EGFR Underlie NSCLC Responsiveness to Gefitinib**  • 32 of 37 pts (87%) with major responses to gefitinib or erlotinib have mutations in the TK domain of EGFR • EGFR mutations in responding tumours cluster with in the ATP binding pocket • Mutated EGFR were hyper-sensitive to EGF stimulation and gefitinib inhibition 	In the future, use will be made more selective drugs like gefitinib or Iressa in postoperative adjuvant chemotherapy for NSCLC.
Slide 26	**Clinical Pharmacology of Gefitinib** • Small MW selective inhibitor of human epidermal growth factor receptor 1 (EGFR) • Bind ATP-binding site, inhibiting EGFR tyrosine kinase activity • EGFR activation: point mutations, deletions and gene amplification • Indication: non-small cell lung cancer • Adverse effect profile: mechanism-based skin and GI toxicities	

Slide 27

Gefitinib or chemotherapy for non-small cell lung cancer with mutated EGFR

- 230 pts
- EGFR mutant
  - (95% - 19del or L858R)
- Median PFS
  - 10.8 vs 5.4
- HR
  - 0.3 (P<0.0001)
- Different toxicity

Gefitinib versus chemotherapy



Maemondo N Engl J Med 2010;362:2380-8

Slide 28

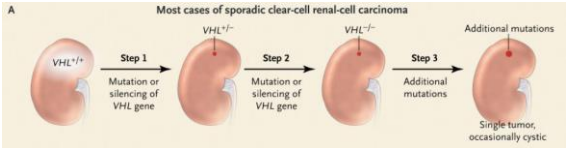
Renal cell cancer

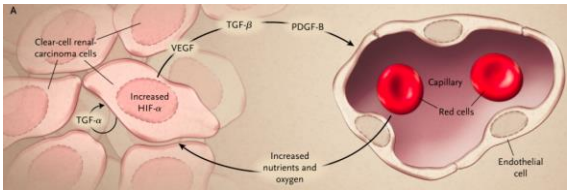
- The most common form of kidney cancer
  - 367 cases per year in NZ
- Associated with loss of von Hippel Lindau tumour suppressor gene
- Treatment
  - Surgery for localised disease
  - Advanced disease
    - Previously immunotherapy, now targeted therapies

Slide 29

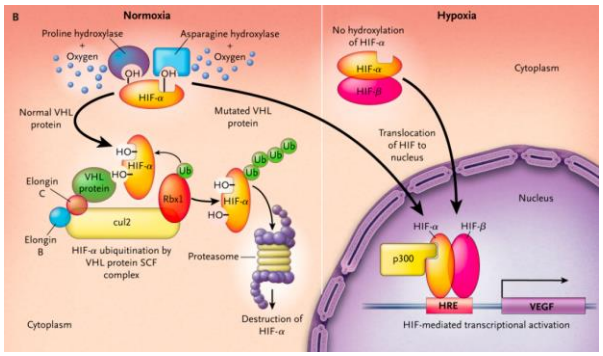
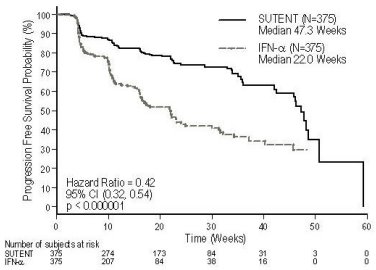
Renal-cell carcinoma

Acquisition of sustained angiogenesis through mutation of von Hippel-Lindau gene (VHL)





NEJM 535; 23; 2005; TGF, transforming growth factor; HIF, hypoxia inducible factor; VEGF, vascular endothelial growth factor, PDGF, platelet-derived growth factor

Slide 30	Transcriptional regulation of angiogenic factors -Central role of Von Hippel-Lindau protein (VHL)  NEJM 535; 23; 2005	
Slide 31	Impact of sunitinib on progression free survival in metastatic renal cell cancer  	
Slide 32	Clinical Pharmacology of Sunitinib • Small MW selective inhibitor of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors • Bind ATP-binding site, inhibiting receptor tyrosine kinase activity • RTK activation: VHL mutation • Indication: renal cell carcinoma • Adverse effect profile: hypertension,haemorrhage, cardiac failure	

Slide 33

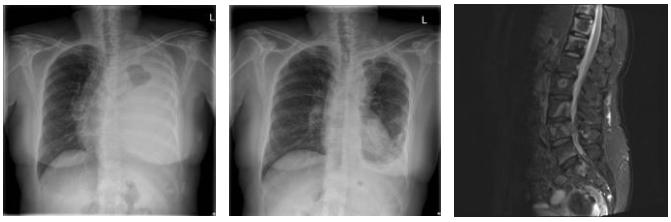
Summary

- Targeted therapies inhibit specific molecules required for oncogenic transformation of growth signal transduction pathways
- Vascular-targeting therapies interfere with tumour blood vessels
- Mechanism-related adverse effects relating to normal tissue expression of targets
- Individualisation of therapy by detecting target in tumour biopsies

Slide 34

Case Presentation

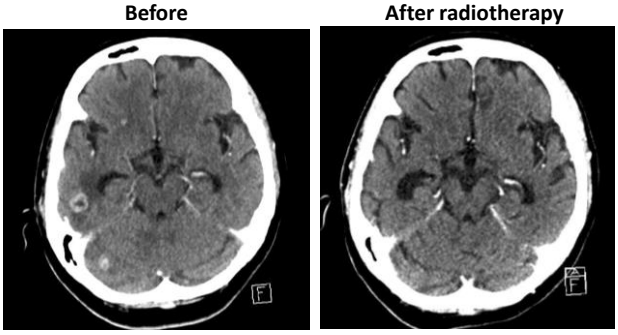
- 55 yr old Asian female never smoker
- Hx: Two months worsening breathlessness and low back pain
- O/E: Left pleural effusion
- Investigations: CXR, pleural aspiration, staging CT scan, lymph node biopsy
- Diagnosis: Primary lung adenocarcinoma, EGFR exon 19 deletion mutation detected, stage IV pleural, lymph node and bone metastasis

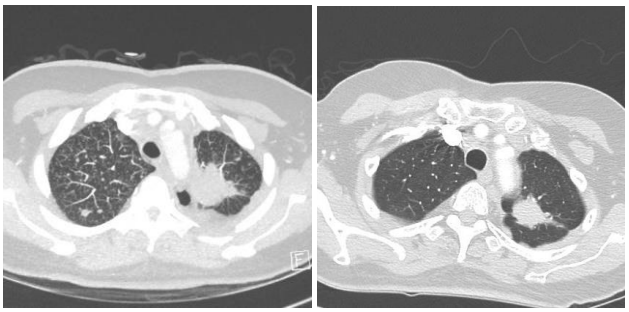
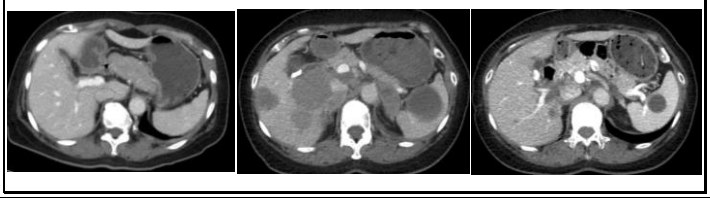


Slide 35

Pharmacological mechanisms of resistance - brain metastases

Before **After radiotherapy**



Slide 36	## Gefitinib – EGFR tyrosine kinase inhibitor drug treatment **Before** **After 3 months** 	
Slide 37	## Genetically mediated acquired resistance – secondary EGFR mutation • Progressive disease 1 yr after starting gefitinib • EGFR T790M mutation detected in plasma and liver samples • Commenced 3rd generation EGFR TKI Presentation ➔ Gefitinib ➔ Progression after one year ➔3rd generation TKI ➔ response 	
Slide 38	## Short answer question: example For this patient, an oncologist recommended treatment with the targeted therapy drug gefitinib. 1. What is the mechanism of action of gefitinib? 2. How is selective toxicity achieved in cancer targeted therapy with gefitinib? 3. List two common Type A (augmented pharmacological effect) adverse drug reactions expected from gefitinib?	