Module 2 – Cancer Biology & Targeted Therapies

Learning objectives

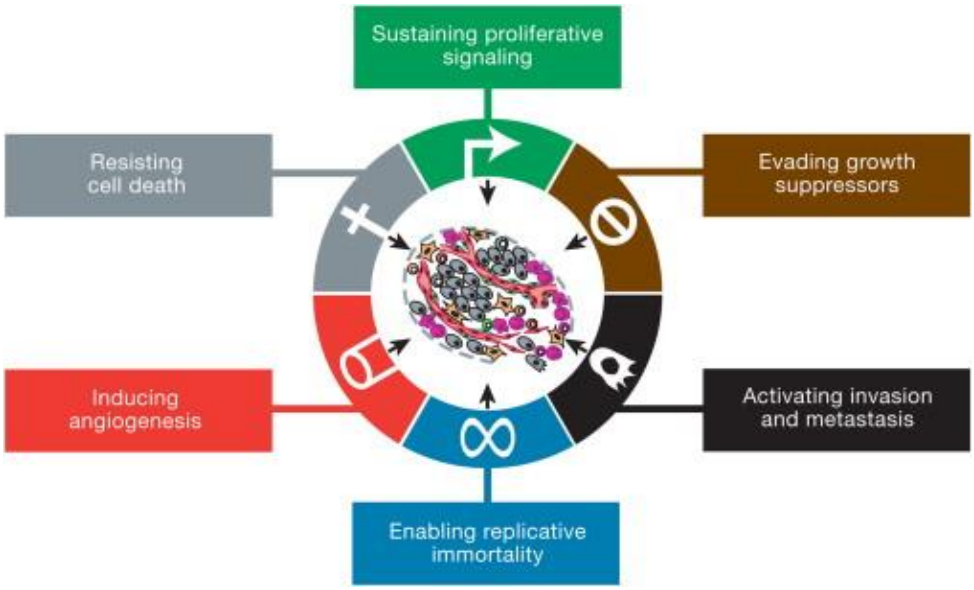
- Awareness of the hallmarks of cancer
- Following the principles of cytotoxics and combination chemotherapy
- Understanding biomarkers and druggable targets
- Targeted therapies in the clinic

Hallmarks of Cancer

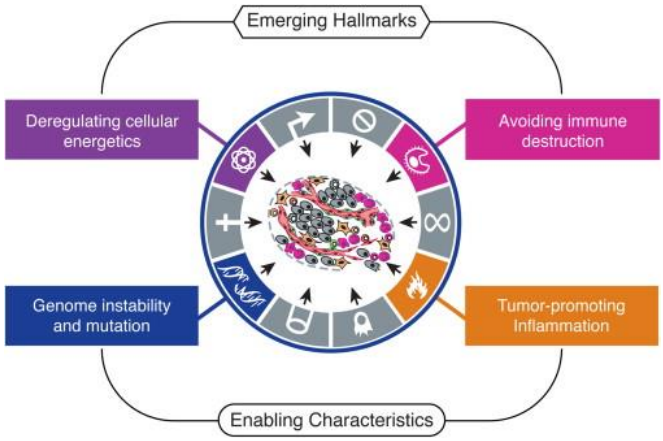
If there is one paper you should read to learn about Oncology, it would be Hanahan & Weinberg's Hallmarks of Cancer paper written at the beginning of the millennium. It has been updated in 2011 but the original paper has a certain purity and simplicity to it.

The authors explain that there is a set of mutations from a normal cell phenotype that are characteristic of cancer cells. The mutations (or hallmarks) may occur in different mutations may occur in different orders in different cells, but they are common characteristics of a range of over 100 distinct cancer types.

This is the original representation of the hallmarks from the 2000 paper. They did not include genomic instability in the original list, but argues that it was a prerequisite for the other hallmarks to occur.



The 2011 paper updated the hallmarks to include new areas of research, considering tumour metabolism, cancer immunology, and the role of inflammation as important hallmarks of cancer. They also upgraded Genomic instability to a hallmark in its own right.



If you are unfamiliar with these concepts in cancer biology, it would be worth brushing up your knowledge before proceeding with the module by reading the hallmarks paper. I also recommend the excellent CancerQuest website for a brief and current overview of cancer biology.

Cytotoxic chemotherapy

Paul Ehrlich first coined the term chemotherapy as the process of curing illness with chemical compounds. In his time, he was mainly referring to infection, but these days the term is used mostly for cancer therapy. Cytotoxic chemotherapy has a shady history, originating from mustard gas used in World War II. Accidental exposure of Italian soldiers revealed that they had depleted white cell counts, leading to its first clinical use in leukaemia.

Chemotherapy is big business, with leadings drugs still bringing in billions of dollars in sales to Pharma. Also chemotherapy is not going to be replaced by targeted therapies, in the same way that surgery has not been replaced by chemotherapy. A detailed review of cytotoxic chemotherapy is available in extension module E1. The key principles to understand are as follows:

Chemotherapy discovery. Cytotoxics are discovered through serendipity, screening programmes, or by copying and modifying existing drugs to enhance their bioavailability. Certain promising cytotoxics may be selected for clinical because they demonstrate efficacy in specific tumour types, but their action is not specific to a tumour type.

Chemotherapy mechanism**.** Most cytotoxics work by inhibiting cell division, either by interfering with DNA synthesis, or damaging DNA which results in replicative arrest, or interfering with mitosis.

Chemotherapy toxicity. Chemotherapy has the most dramatic effect on rapidly proliferating tissues. This is why it affects the bone marrow and the gut mucosa. Mucositis and neutropaenia are therefore common side effects. Nausea is caused by the effect of chemotherapy on the area postrema of the hypothalamus, and mediated through 5HT-3 and neurokinin receptors. We now have very effective anti-emetics that can block these pathways.

Chemotherapy scheduling. We give cytotoxics in cycles, typically every 3 weeks. The reason for this is to allow the bone marrow to recover from the effects of chemotherapy. High-dose chemotherapy is used in the treatment of haaematological malignancy to ablate the bone marrow, because this is the origin of the malignancy. The patient has to be ‘rescued’ by a bone marrow transplant.

Combination chemotherapy. We often use chemotherapy in combinations. There may be mechanistic synergy between the different agents (e.g. drugs targeting cells at different points in the cell cycle), and using drugs in combination means that the tumour is less likely to become resistant to therapy. It also means we can continue treatment if a patient develops a dose-limiting toxicity from one of the drugs.

If you can, try and observe the chemotherapy nurses as they discuss chemotherapy with a patient starting on treatment.

Druggable targets

Modern translational oncology follows a new type of path towards the development of blockbusting new drugs:

- Build a low-level model of your tumour, using cancer genetics and in-vitro / animal models.
- Identify key pathways that seem to be dysregulated in this tumour (canonical pathways)
- Identify the driver mutations in these pathways and work out what these do in the cell, usually at the protein level (a biomarker of this disease).
- Build a compound to target these mutations, usually by blocking a receptor.
- At the same time, build a test (biomarker assay) to tell whether a tumour has this mutation or not, and thereby predict whether or not the drug is likely to work for a given patient.
- Test your drug for efficacy and side effects (so-called off target effects) because no compound is 100% specific to your chosen cancer target, and many pathways may not be 100% specific to cancer cells.

What is exciting in oncology is that this process has been tremendously successful for some conditions where we previously did not have very good treatments. In this diagram, we map the new biological therapies onto the hallmarks of cancer, so you can see how much of our understanding of cancer biology has been turned into potential cancer therapy:

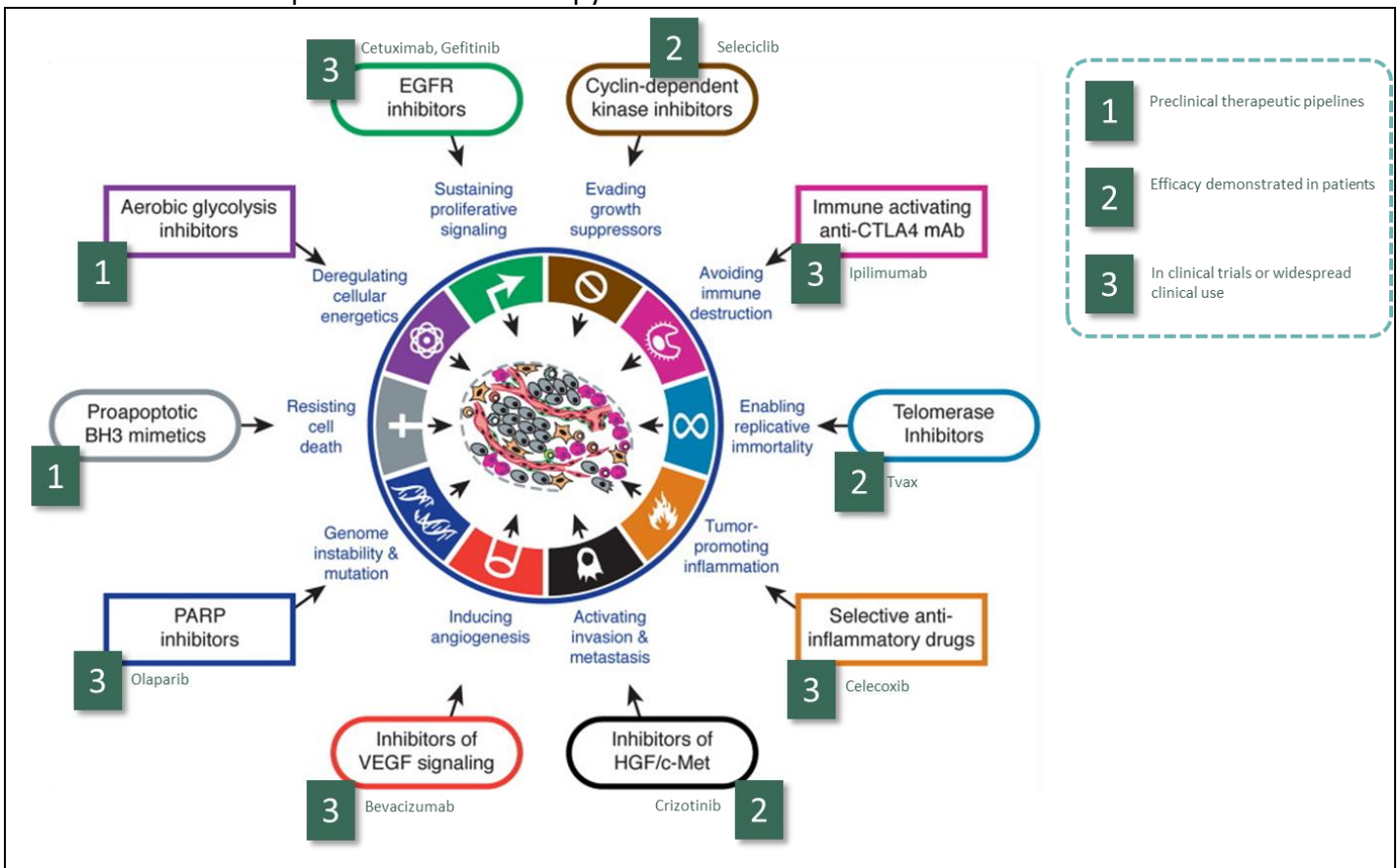


Figure 1: Druggable targets and their clinical status, overlaid onto the Hanahn & Weinberg hallmarks of cancer

Unlike chemotherapy agents, the biological therapies tend to have similar yet unpronounceable names. However there is a method to the madness – and if you know the code, it can make you sound very clever indeed. For me it's a bit like the day that someone explained to me that all bacteria ending in –ella are gram negative.

Name element	Meaning	Example
-mab	Monoclonal antibody	Trastuzumab
-ib	Small molecule inhibitor	Erlotinib
-ximab	Chimeric human-mouse antibody	Cetuximab
-zumab	Humanised mouse antibody	Pertuzumab
-ci-	Circulating system target	Bevacizumab
-tu-	Tumour target	Cetuximab
-tin-	Tyrosine kinase inhibitor	Afatinib
-zom-	Proteasome inhibitor	Bortezomib

So for example the generic name of Herceptin is Trastuzumab. We therefore know that the drug binds a tumour target and is a humanized mosu antibody therapy. In contrast Gleevec or Imatinib (the wonder drug for CML and gastrointestinal stromal tumours) is a small molecule inhibitor of tyrosine kinase. Go ahead and dazzle your friends with your newfound knowledge!

Targeted therapies in the clinic

As I mentioned above we have some real success stories for novel targeted therapies in the clinic, and you might meet patients on these therapies during your attachment. We will drill down into four different examples:

- B-RAF Kinase inhibitors in melanoma
- Targeted cancer immunotherapy
- EGFR and ALK inhibitors in non-small cell lung cancer
- Anti-angiogenic therapy in Neurofibormatosis Type 2

B-RAF kinase inhibitors in melanoma

The B-RAF gene is a classic example of a proto-oncogene. It encodes an intracellular signal transduction protein belonging to the RAF family, and falls in the MAP kinase pathway. Mutation of the B-RAF gene to become constitutively active is found in a range of common cancers. Approximately 40-60% of patients with melanoma will have a specific mutation in the B-RAF gene (V600E).

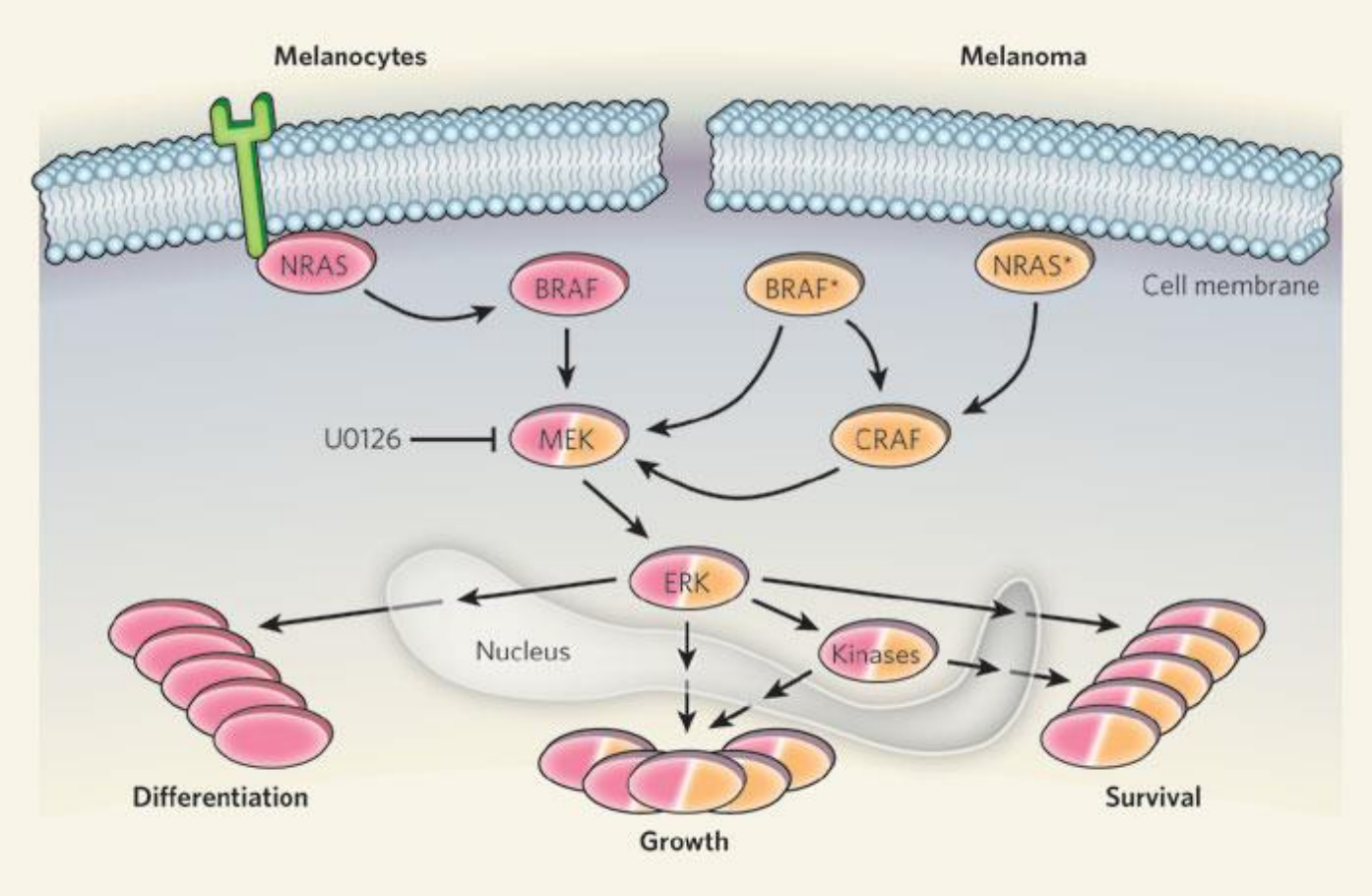


Figure 2: Diagram illustrating key regulator effects mediated by BRAF protein

Why is this important? Well up until about 5 years ago, we had very little in the way of effective therapies for melanoma. Dacarbazine, a very old alkylating agent, used to be used for fit patients. It is very toxic and has poor response rates (it works in about 5-8% of patients). Now we have novel targeted therapies which can inhibit the mutated gene product. As a result the drugs and high specificity and much fewer off-target effects, because the mutated protein is only found in tumour cells. Agents such as Sorafenib and Vemurafenib have a response rate of 50-60%, and are generally very well tolerated oral therapies. It is fair to say that the availability of these new drugs has transformed the outlook for patients with advanced melanoma.

Targeted cancer immunotherapy

Over the last decade the understanding of the role of the immune system in carcinogenesis, and specifically the mechanisms by which tumour cells evade detection and eradiation by the immune system has been studied, leading to the discovery of new therapies. The programmed cell death receptor is catchily abbreviated to PD-1 (I would have called in DEATH-1 if I discovered it) and is an important immune surveillance checkpoint involved in self-tolerance. PD-1 is overexpressed in a range of tumours, including melanoma, and many tumour cells will also overexpress PD-L1 which is the ligand to PD1. This is a good example of an autocrine loop where tumour cells will produce a signal that promotes its own proliferation or survival.

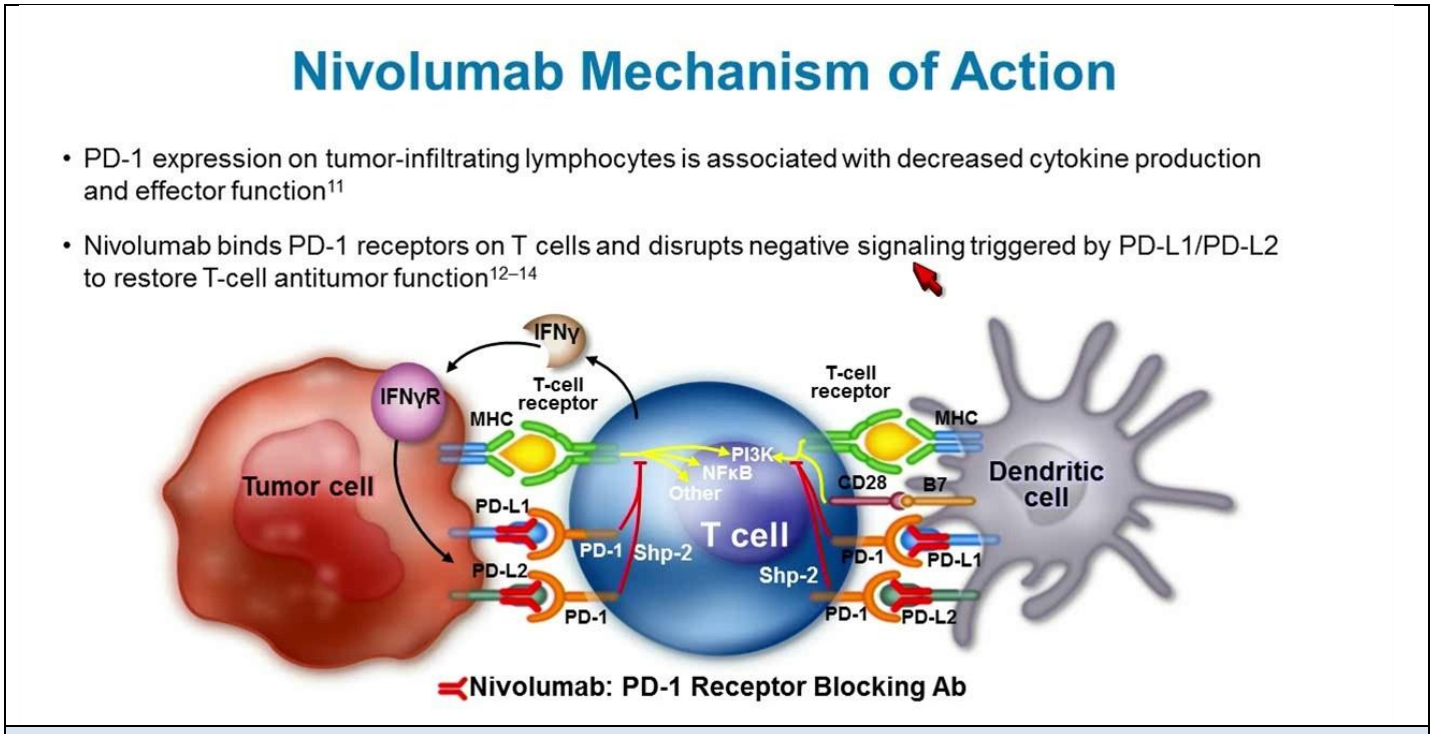


Figure 3 : Nivolumab is an antibody that disrupts the inhibitory signals that prevent T-cells from recognizing the tumour cells as being abnormal

Pembrolizumab and Nivolumab are monoclonal antibody therapies that inhibit the PD-1 receptor, which prevents the ability of tumour cells from evading the immune system. The treatment is quite toxic, with a significant risk of severe hepatitis, but can often induce long lasting remissions of tumours.

Ipilimumab is another antibody therapy directed at the CTLA4 receptor which is a similar fashion has an inhibitory effect on cytotoxic T-lymphocytes.

The magnitude of effect of nivolumab in combination with ipilimumab to activate the immune system is quite incredible. In 2015 the Checkmate study was published showing clinical outcomes for patients with advanced melanoma treated with this combination. Response rates were as high as 60% and further in those patients that responded, some had complete remission of their metastatic disease for over a year. It even caught the attention of the press (click here for BBC article). The downside – well these drugs are extremely expensive – ipilimumab costs $120,000 for 4 treatments and Nivolumab costs $25,000 for 4 treatments, and they can be extremely toxic too.

EGFR and ALK inhibitors in non-small cell lung cancer

The treatment landscape for metastatic non-small cell lung cancer (NSCLC) has also changed tremendously in the last few years. This group of patients often had significant cardiovascular and respiratory co-morbidities, and treatment with cisplatin containing chemotherapy was quite toxic.

Activating EGFR mutations occur in between 10 and 30% of NSCLC patients, depending on ethnicity and smoking status. Higher mutations rates are observed in non-smokers and patients with adenocarcinoma histology. Ethnicity is incredibly important. One of the EGFR inhibitors was initially developed and trialled in Japan, where the prevalence of EGFR mutations and adenocarcinoma histology is nearly 50%. The company then wanted to try the drug in the US, where EGFR mutation rates are much lower (5-10%). The problem is that in these first studies, they did not stratify patients to therapy according to EGFR status. Nowadays, EGFR testing is performed routinely on patients with NSCLC, particularly adenocarcinoma subtype and they are a predictive and prognostic assay. This means they both predict a response to therapy and act as an independent factor in patient survival. Drugs such as Erlotinib and Gefinitib are examples of oral EGFR tyrosine kinase inhibitors that have been used with great success in the clinic.

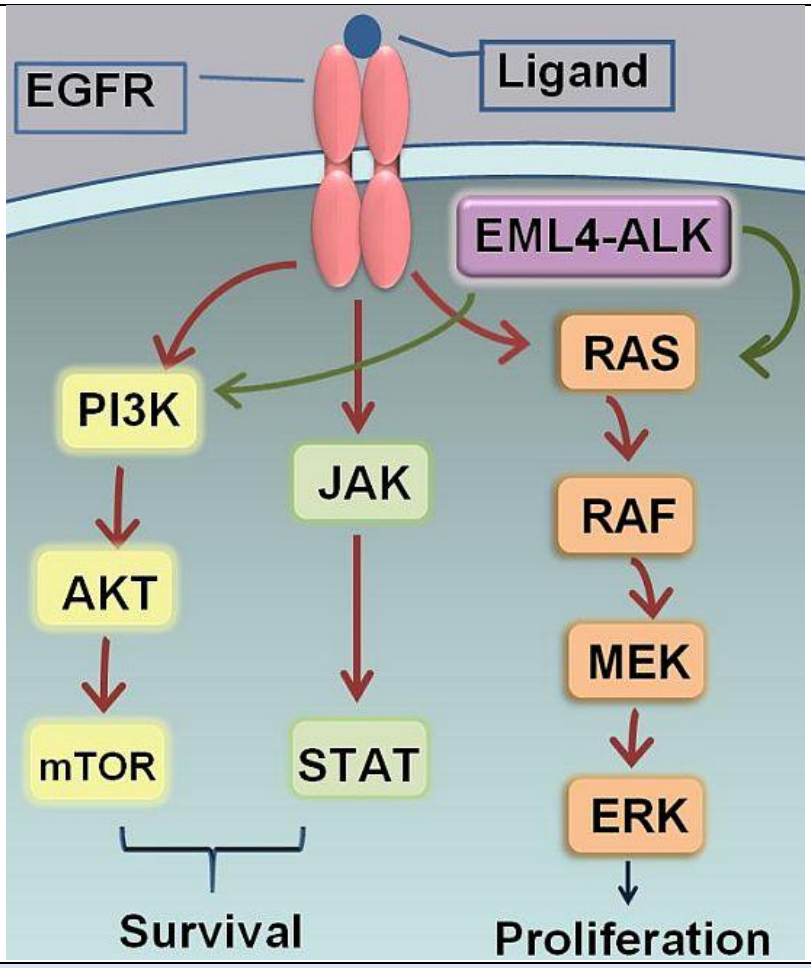


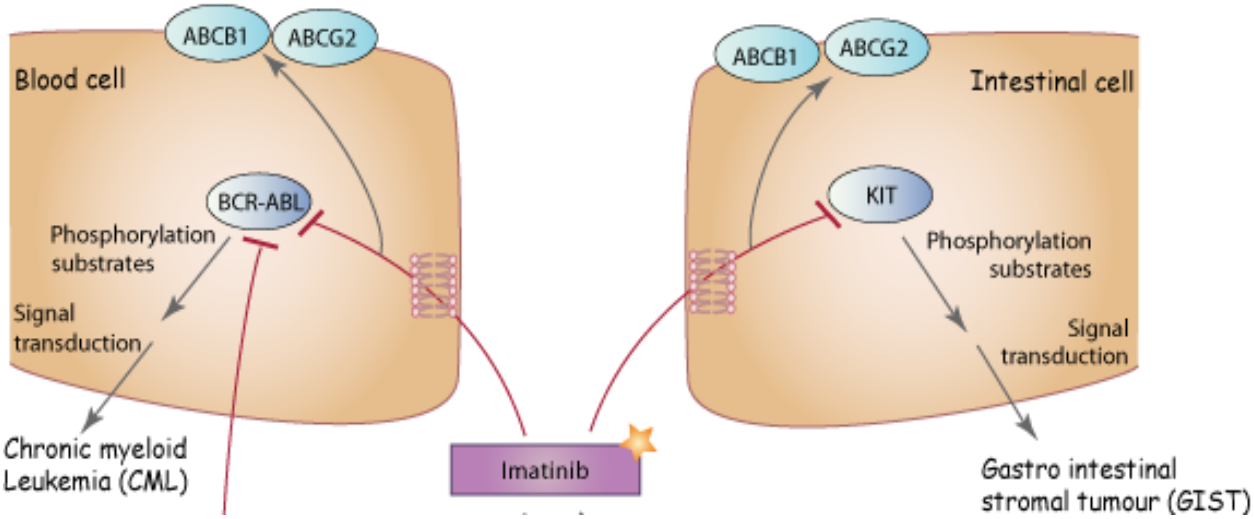
Figure 4 : Importance of EGFR and ALK pathways, important in non-small cell lung cancer

ALK is a similar fusion oncogene that has an activating effect on cell proliferation. It is important because some EGFR negative tumours will have an ALK mutation, and this represents a druggable target. New small molecule tyrosine kinase inhibitors such as crizotinib and ceritinib target this pathway and may provide a treatment strategy for patients who do not harbor EGFR and ALK mutations.

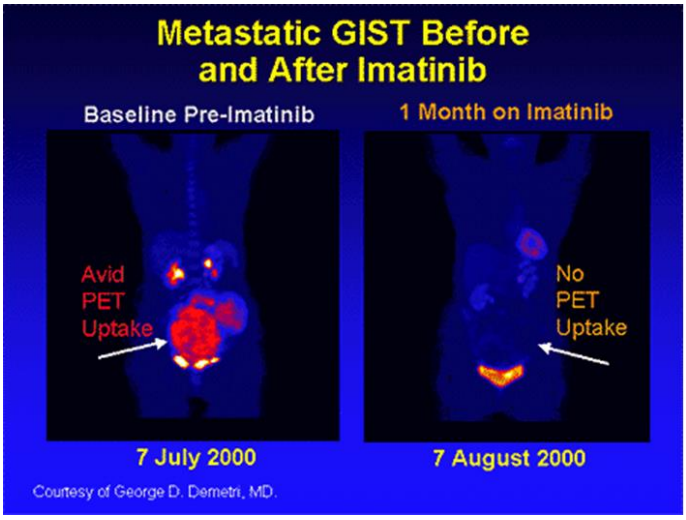
If you go to lung cancer clinic, it's worth asking about treatment for EGFR and ALK positive patients as this is a rapidly evolving field (that's a polite way of saying my crib notes might be out of date already!)

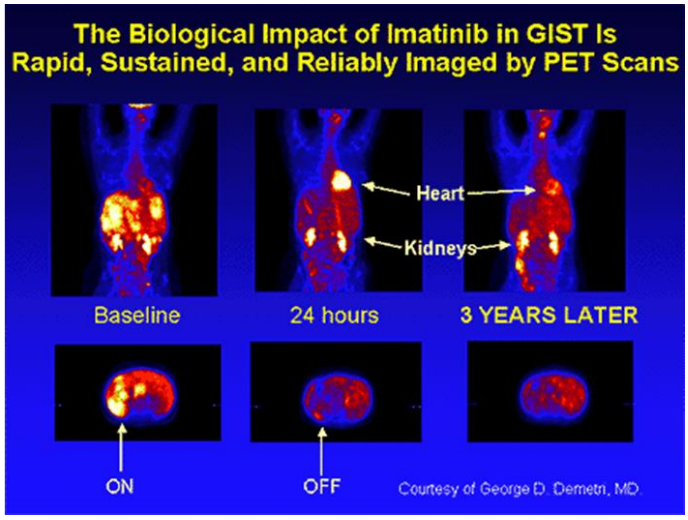
cKIT inhibition in myeloid leukaemia and GIST

Imatinib (Glivec) is a really good example of a targeted therapy 'success story' and was one of the first targeted therapies to come into common ptractice. It targets an oncogenic fusion protein called BCR-ABL, which forms a constitutively active tyrosine Kinase. The BCR-ABL translocation is also known as the Philadelphia chromosome, a mutation found in some chronic myeloid leukaemia which used to be resistant to therapy.



The same drug also targets cKIT which is overexpressed in a range of tumours, including melanoma, seminoma and a rare condition known as gastro-intestinal stromal tumour or GIST. Although GIST are rare, they are quite common in the Oncology Centre because they are an area of clinical interest for some of our oncologists! GISTS are hard to treat with conventional chemotherapy and radiotherapy, because the rich layer of stromal cells protects them from these treatments. Glivec can yield really dramatic responses in GIST, but you need to know how to look for the signs of a response, because responding tumours do not always shrink





FDG PET scanning reveals the reduction in metabolic activity, which can be seen very quickly after starting therapy.

Treatment assessment and RECIST criteria

This brings us to an interesting point – how do we assess disease response in solid tumours? In most cases radiologists use the RECIST criteria to report treatment response on cross sectional imaging. It's worth knowing a little about this. RECIST stands for Response Evaluation Criteria in Solid Tumors. They are a standardized method of assessing tumour response used in clinical trials. A radiologist identifies an index lesion that will be evaluated during treatment, and perform linear measurements of the lesion. Response criteria are evaluated as

- CR (complete response) = disappearance of all target lesions
- PR (partial response) = 30% decrease in the sum of the longest diameter of target lesions
- PD (progressive disease) = 20% increase in the sum of the longest diameter of target lesions

- SD (stable disease) = small changes that do not meet above criteria

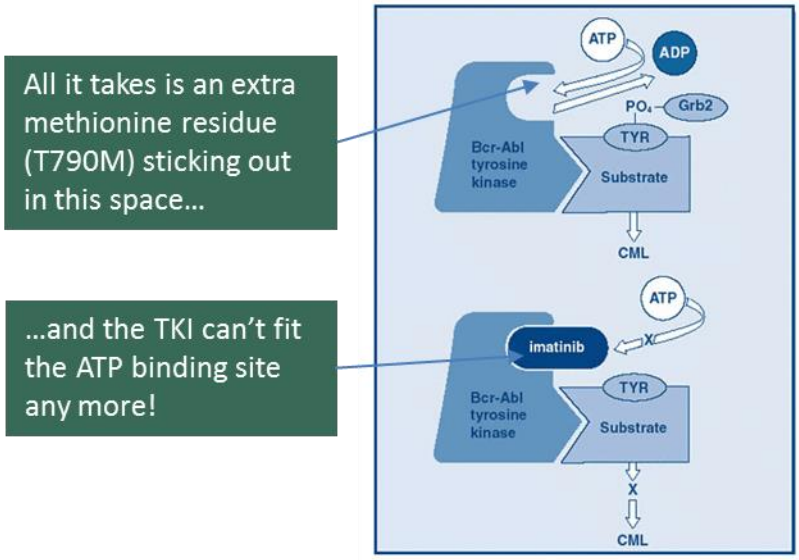
In other conditions such as germ cell tumours, advanced prostate cancer or ovarian cancer, we use a serum tumour marker (HCG & AFP, PSA and CA12.5 respectively)to assess treatment response. It's worth remembering that serum markers may drop before radiological changes are observed in a tumour.

It's also worth remembering that some tumours can apparently increase in size as a response to treatment (pseudoprogression), and sometimes in the case of metastatic disease, some leasions can shrink in response to therapy whilst others increase in size (differential response), reflecting differences in the underlying biology of different sites of metastatic disease.

There is a lot of interest in being able to use **circulating tumour DNA** as a marker of tumour load, and this is a strong research focus in the CRUK Cambridge Institute at present. CancerGRACE has a great video explaining the technique.

Resistance to therapy

Wonderful as these targeted therapies may sound, they do not work forever, and eventually resistance develops. The precise lock-and key nature of these agents makes them prone to 'steric hindrance', that is a small mutation in the proteins responsible for the shape of a receptor that prevent a TKI or antibody from binding to the target:



Most targeted therapies will work for a period of 10-12 months, and then it becomes necessary to switch to another agent. We are fortunate that is a range of tumours, there are several agents now available that target these pathways, allowing for rotation of treatment when resistance develops.

Conclusion

Systemic therapies in oncology is a huge area. I hope this module gives you some insight into the way that we have come from a background of using non-targeted cytotoxic drugs and are now moving towards a more mechanistic approach to cancer therapy. If you see a chemotherapy patient in clinic, take a look at their treatment history to try and understand the decision making behind their choice of treatment.

If you want to take a deeper dive into the world of chemotherapy, take a look at Module E1 on chemotherapy and Biological therapies.