Precision Oncology How, why and when?

Dr Tony Dhillon, Consultant Medical Oncologist, Royal Surrey Hospital, Guildford, Surrey, UK.

Alternative title from Stefan Shuster

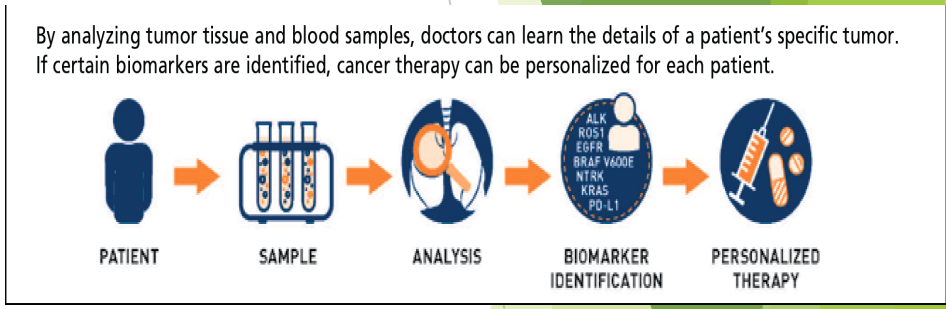
- Indiana Dhillon - Raiders of the lost NTRK...

Disclosures

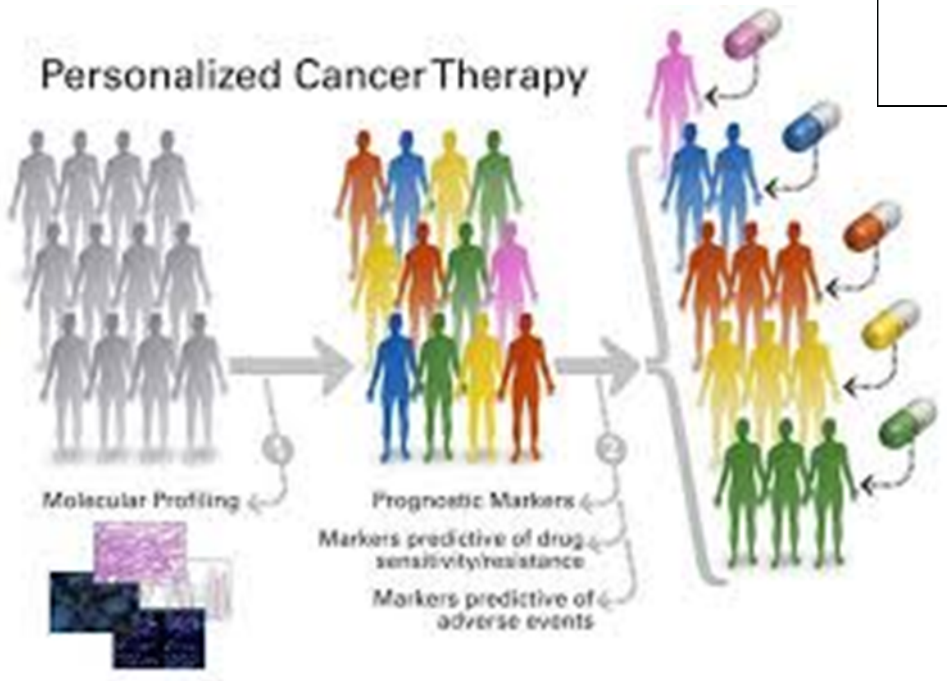
- I have had research funding from BMS, Merck Serono and Novartis
- I had had honorarium from Everything Genetic, Servier, Guardant, Caris, Eli Lilly, Sanofi-Aventis, Amgen and MSD

Precision oncology

- Molecular profiling of tumours to identify targetable alterations



DATAR CANCER GENETICS

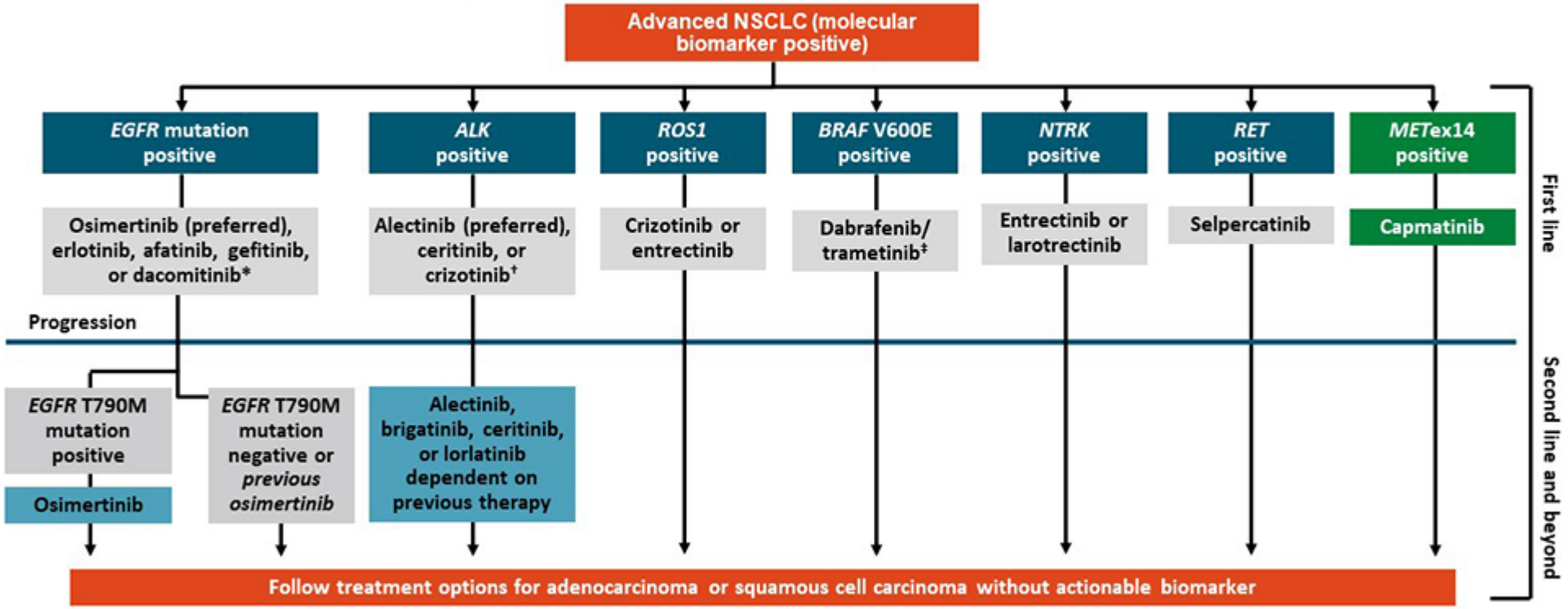


What is precision oncology?

- The right drug for the right patient at the right time

- Genomic characteristics- mutations, fusions, deletions..
- Somatic and germline
- Protein characteristics – over (expression)
- Based on the belief that histology is insufficient to guide treatment and that molecular alterations result in many different kinds of cancer

Current Treatment Paradigm for Molecular Biomarker–Positive Advanced NSCLC



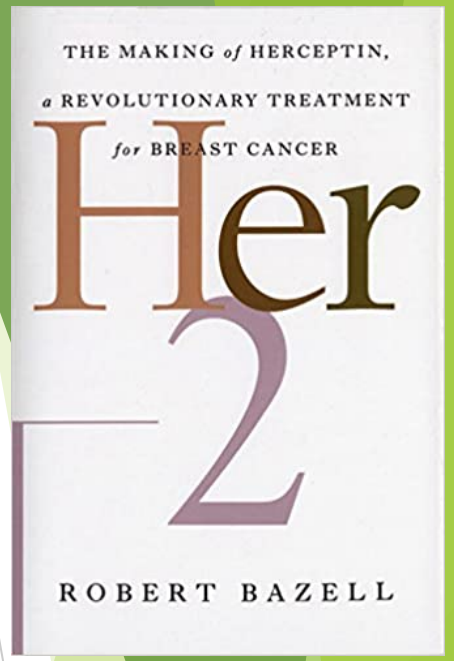
*Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib approved for *EGFR* exon19del, exon 21 L858R; afatinib for *EGFR* G719X, S768I, L861Q.
†Brigatinib under priority review by the FDA for first-line *ALK* positive NSCLC. ‡Or as second-line after CT.

A bit of history… HER2 and the development of herceptin

- Late 1980s: Dennis Slamon et al; discover that up to one quarter of breast cancer have overexpression of HER2 and that patients with these tumours appear to have a poor prognosis.
- 1987, 1992: Other researchers show that HER2 overexpression induces tumour growth
- 1992 Genentech engineers a humanized HER2 antibody and begin clinical trials
- How to choose which patients should be treated?

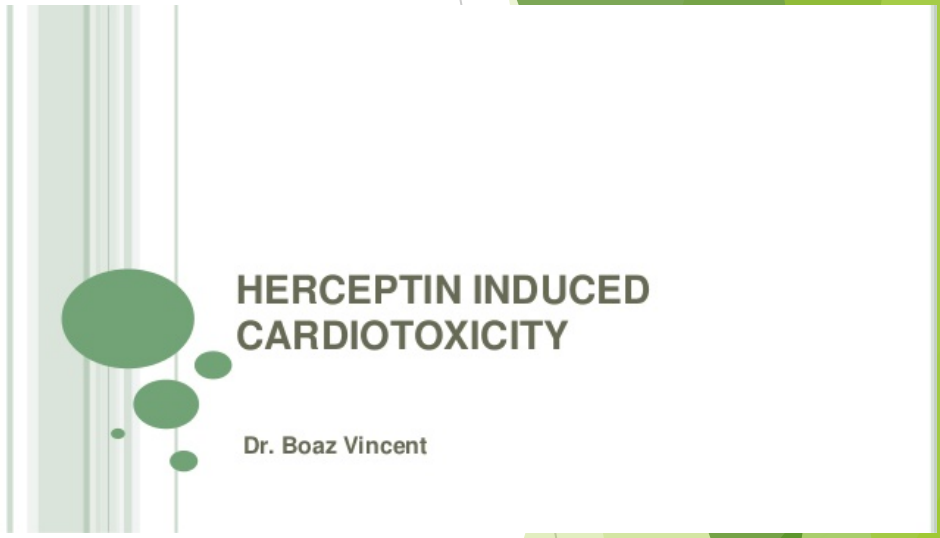
A bit of history… HER2 and the development of herceptin

- FDA approval based on 2 pivotal studies; patients had HER2 2+ or 3+ tumours t
- Phase II single agent: response rate of 12%, median response lasted 9.1 months, median survival 13 months
- Phase III RCT of 1st line chemo ±Herceptin- higher response rate (50% vs 32%), improved median survival (25.1 vs 20.3 months)

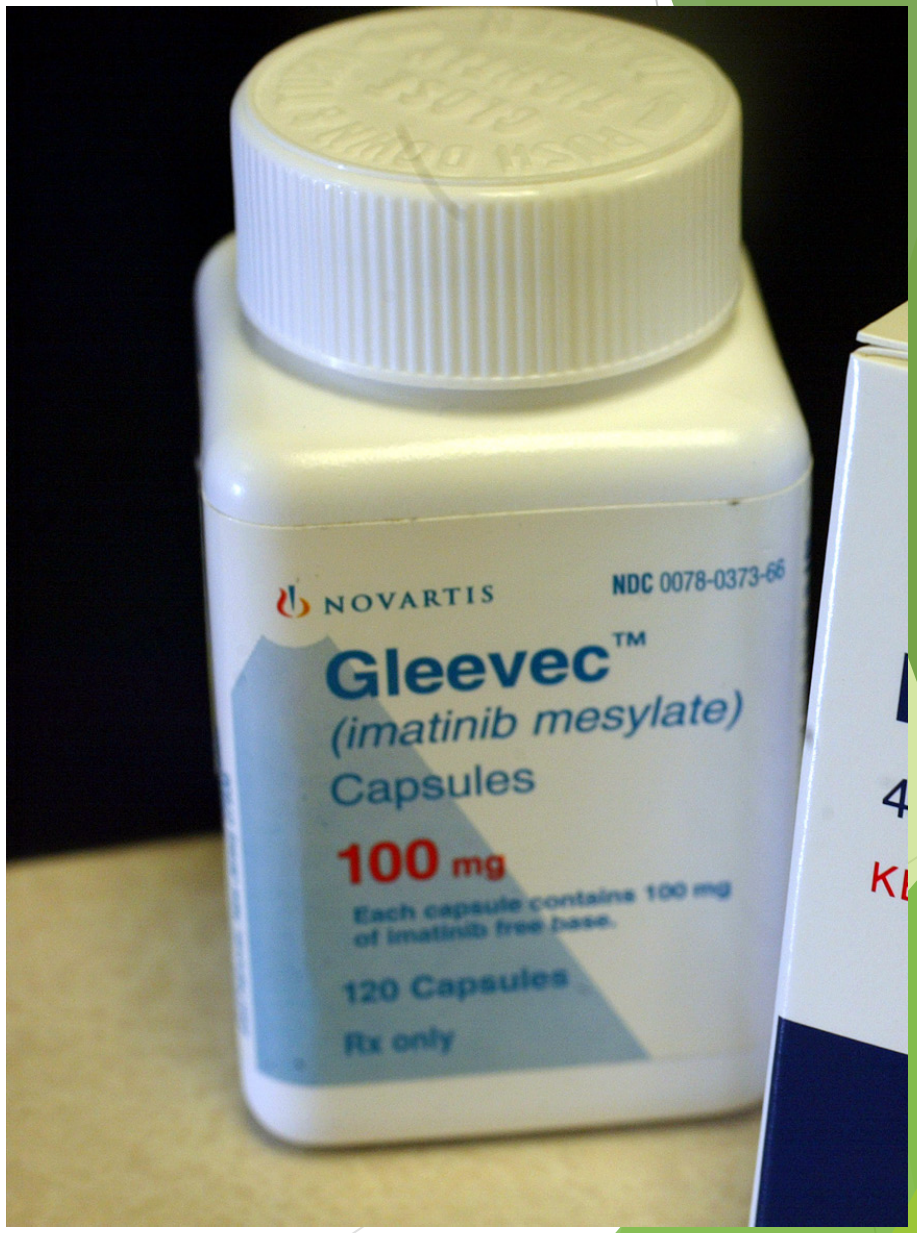


HER2 and the development of Herceptin

- But..emerging cardiac toxicity- 5% cardiac dysfunction



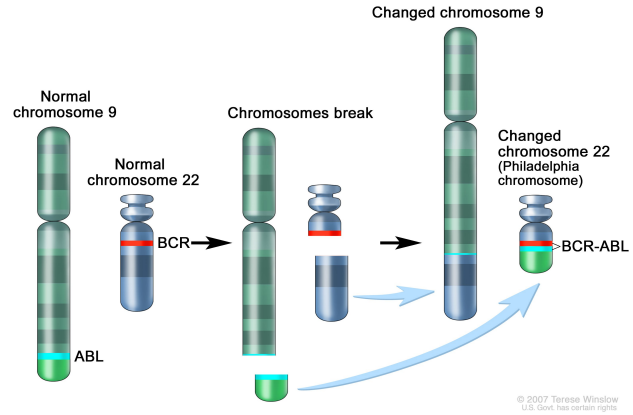
Another magic bullet..



The long road to Gleevec

- 1845: CML described
- 1960: Novell and Hungerford describe the minute chromosome present in the blood of 7 patients
- Early 1970s: Caspersson and O' Riordan and colleagues identified the minute chromosome as #22, Rowley identified its balance translocation with #9.
- 1970s/1980s Retrovirus work performed work to identify oncogenes- including c-abl, translocation from 9q to the breakpoint cluster region of 22q in patients with CML.

The long road to Gleevec



- Mid-1980s: Davis and Ben-Neriah and colleagues find that the resulting mRNA transcript is a tyrosine kinase
- 1990: Heisterkamp and colleagues identify BCR-ABL translocation as both necessary and sufficient to induce CML
- Early 1990s: High throughput screens of chemical libraries the 2-phenylaminopyrimidnines as promising inhibitors of BCR-ABL.
- 1996: Druker and colleagues publish in vitro and in vivo data on imatinib

The promises and limitations of technology

- IHC evaluation of protein expression, FISH for translocations

- Mutational hotspot testing

- Next generational sequencing

  - ctDNA analyses; whole exome or whole genome sequencing; proteomic analyses, DNA methylation patterns

  - Information that is not actionable
  - Intratumoral heterogeneity
  - Driver vs passenger mutations
  - Temporal Heterogeneity

Clinical examples of benefits of whole genome sequencing..

- 40 year old female presenting with weight loss and fatigue
- Mother has Lynch Syndrome (dMMR)- manifested as MSI-High
- Found to have metastatic colon cancer (peritoneal mets) (adenocarcinoma)

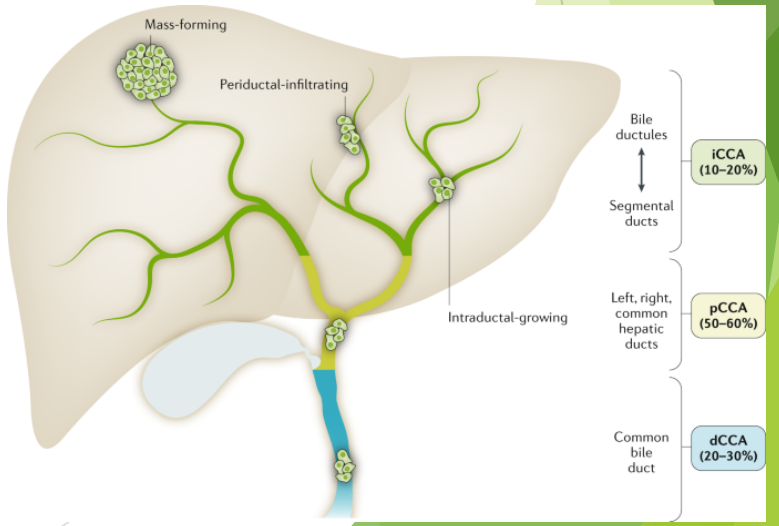
- IHC performed pMMR!
- We know that we miss 10% of MSI-High patients by using simple IHC for MMR
- Used Next-Generation Sequencing (NGS): rapidly examines and more broadly detects DNA mutations, copy number variations and gene fusions across the genome
- Results shows MSI-High

Clinical examples of benefits of whole genome sequencing..

- Patient is now eligible for IO which gives this young patient of a long durable response or even cure- not the case with standard cytotoxic chemotherapy
- Sequencing revealed the MSI-High!!

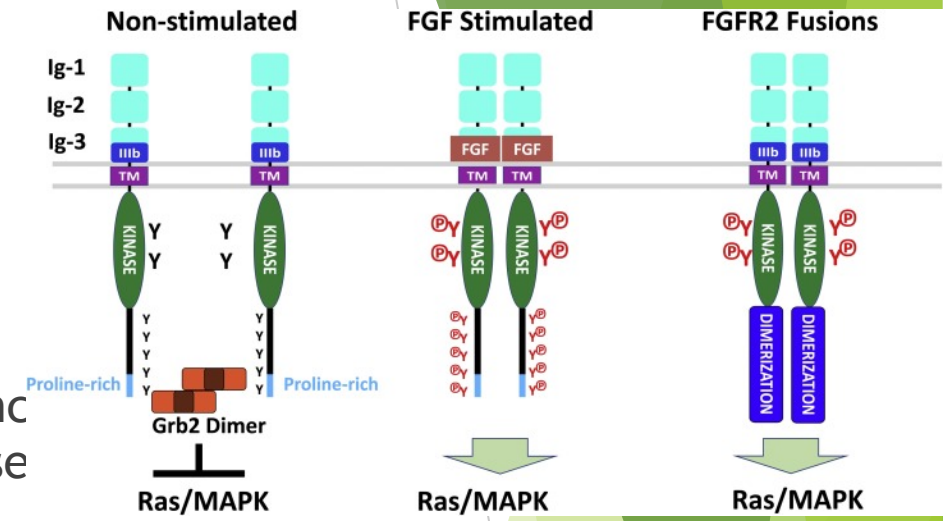
Clinical examples of benefits of whole genome sequencing..

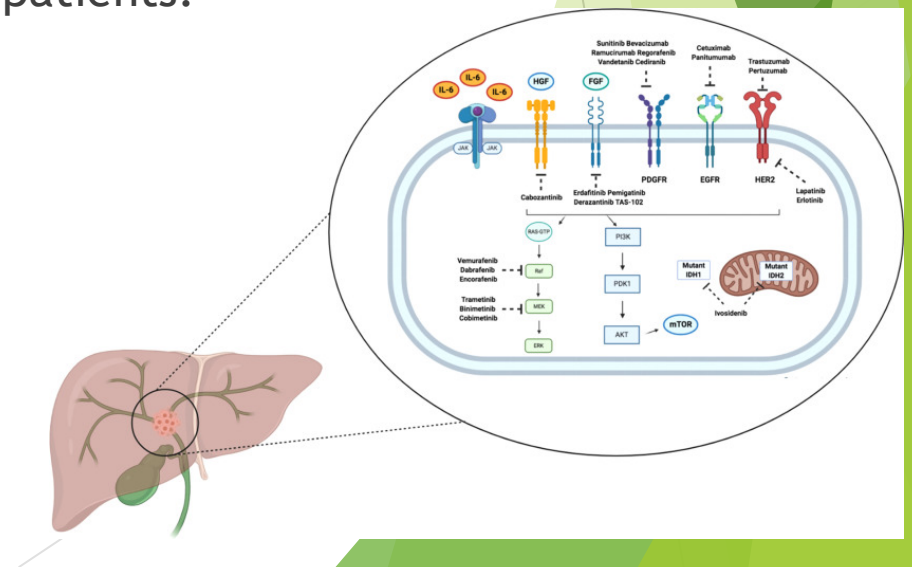
- 63 male metastatic intrahepatic cholangiocarcinoma
- Standard chemotherapy Gemcitabine and Cisplatin-one size fits all
- Data shows 50% of cholangiocarcinoma's have actionable mutations!
- Only MMR done on NHS! But drugs for actionable mutation are out there!!
- Patient asked me- any personalise my treatment?
- He paid for sequencing



Clinical examples of benefits of whole genome sequencing..

- Found to have FGFR fusion protein
- Pemigatinib- selective, potent, oral inhibitor of FGFR1, 2, and 3
- FIGHT-202 trial Pemigatinib for previously treated, locally advanc metastatic cholangiocarcinoma: a multicentre, open-label, phase
- The median DOR was 9.1 months with responses lasting ≥ 6 months in 24 of the 38 (63%) responding patients and ≥ 12 months in 7 (18%) patients.





Summary

- Precision oncology has a long and fascinating history
- Right drug- right time- right patient!!
- Limitations!!
- Maximise information about the patient's cancer to make the best decisions for the management of patients cancer.
- Future includes using ctDNA temporally, RNA and protein profiles and microbiome signals to make treatment decisions.