TARGETED/PERSONALISED THERAPY -CLINICAL IMPLICATIONS OF GENETIC/MOLECULAR PROFILING OF TUMOURS

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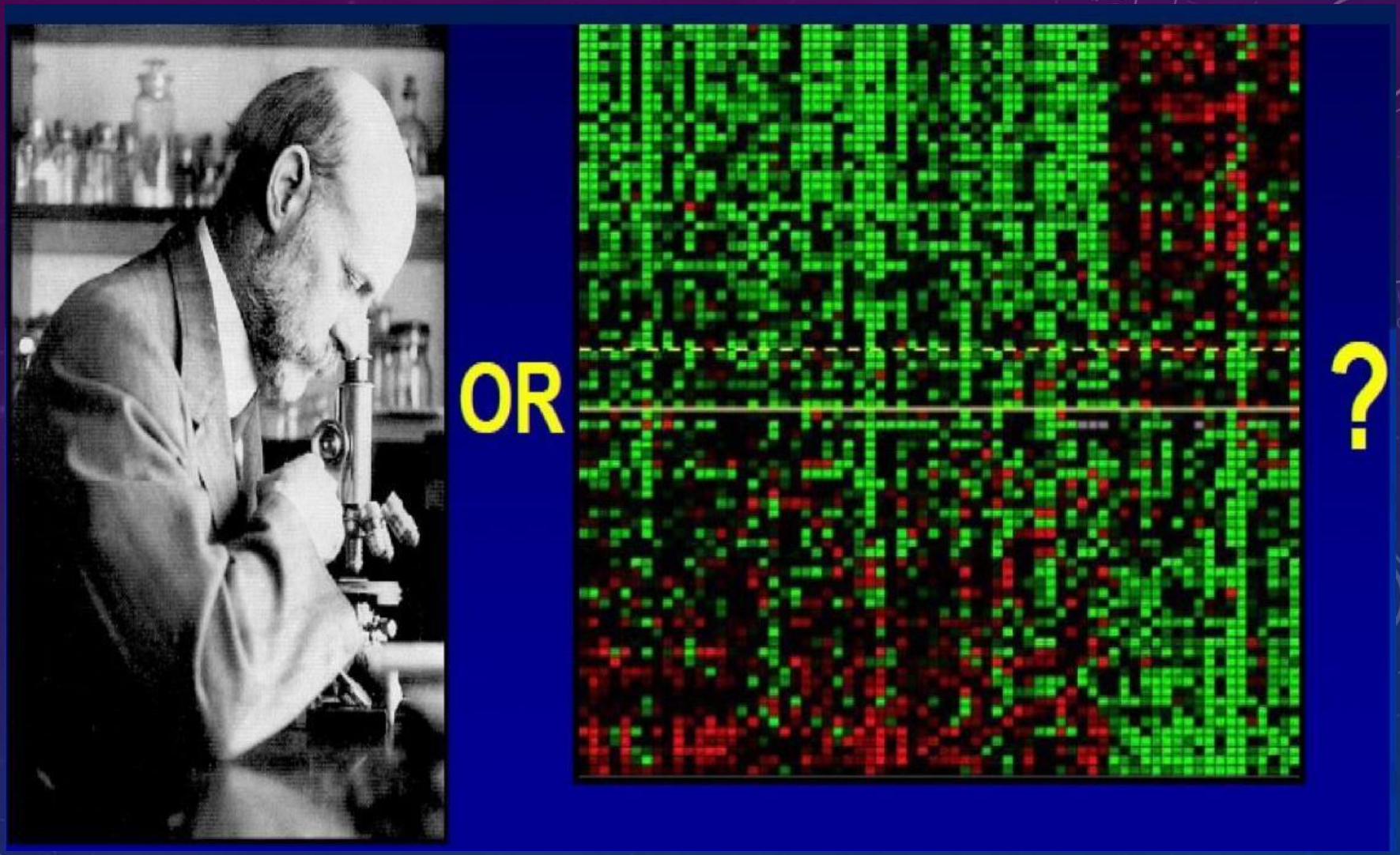

OR
?

- Personalized medicine
- Customized medicine
- Targeted therapy

Use of one's genetic information for diagnostic, prognostic, predictive & therapeutic purposes in healthcare especially oncology

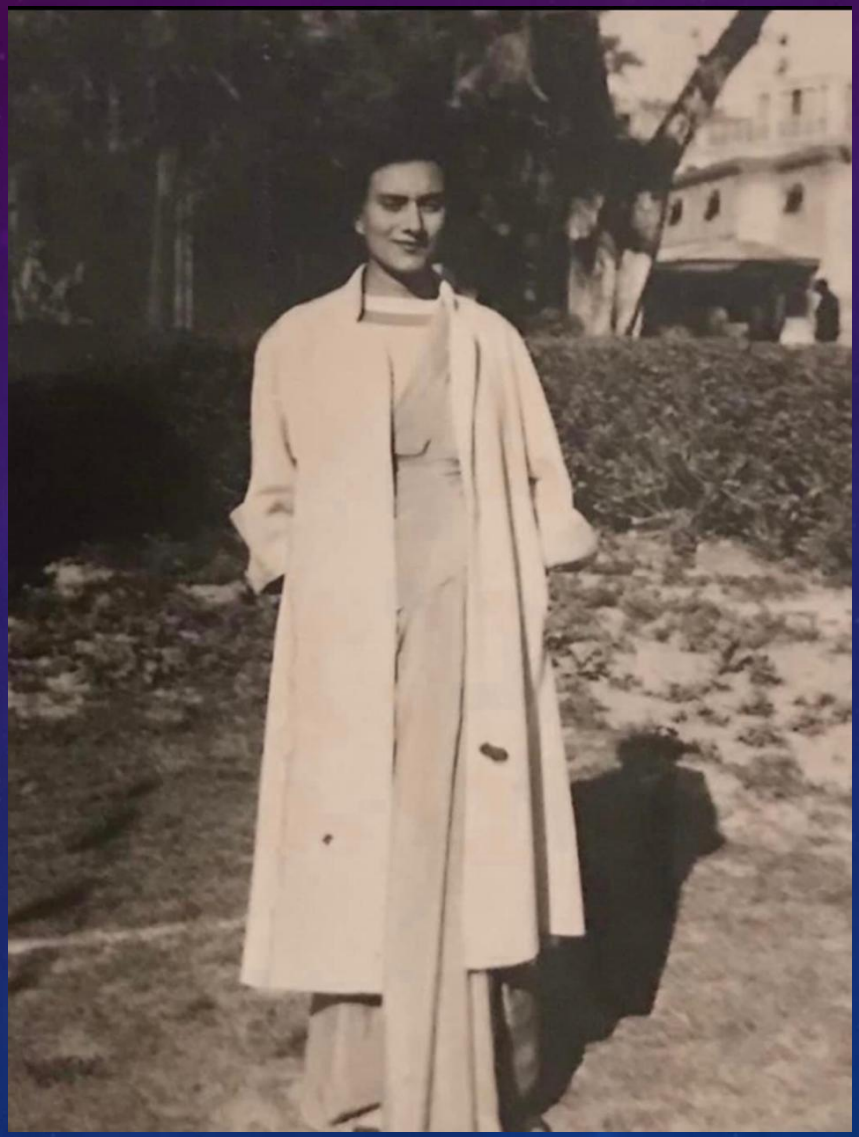
'Right drug for Right person'

- Since targeted drugs act on specific targets on cancer cells only and not on healthy cells, therefore less side effects

- **PFS** (progression free survival) & **OS** (overall survival) are much improved with targeted therapy as compared to conventional chemotherapy

- Both chemo & targeted therapies can be combined to have better results in selected cases

Late Dr. Shamim Qureshi



The Eagle, Famous Pub in Cambridge

Historic table where Crick & Watson announced Human DNA structure


Newsweek
THE INTERNATIONAL NEWSMAGAZINE
April 10, 2000
THE RACE TO DECODE THE HUMAN BODY
CURING DISEA
DESIGNING BABIES
PLAYING GO
GENOM

Human Genome Project (HGP)

To find out 3 billion base pairs and mapping & sequencing of 20000 genes

- **1990 to 2003**
- **3 billion dollars**
- **6 countries UK, France, Germany, China, USA, Japan**

NGS - Next Gene Sequencing

GENETIC INFORMATION IS OBTAINED BY

❑ GENE PROFILING

Whole Gene Profiling

NGS (next generation sequencing)

Targeted Gene Profiling

NGS

Gene Microarray

RT – PCR

FISH

❑ PROTEIN PROFILING

IHC

Protein microarray

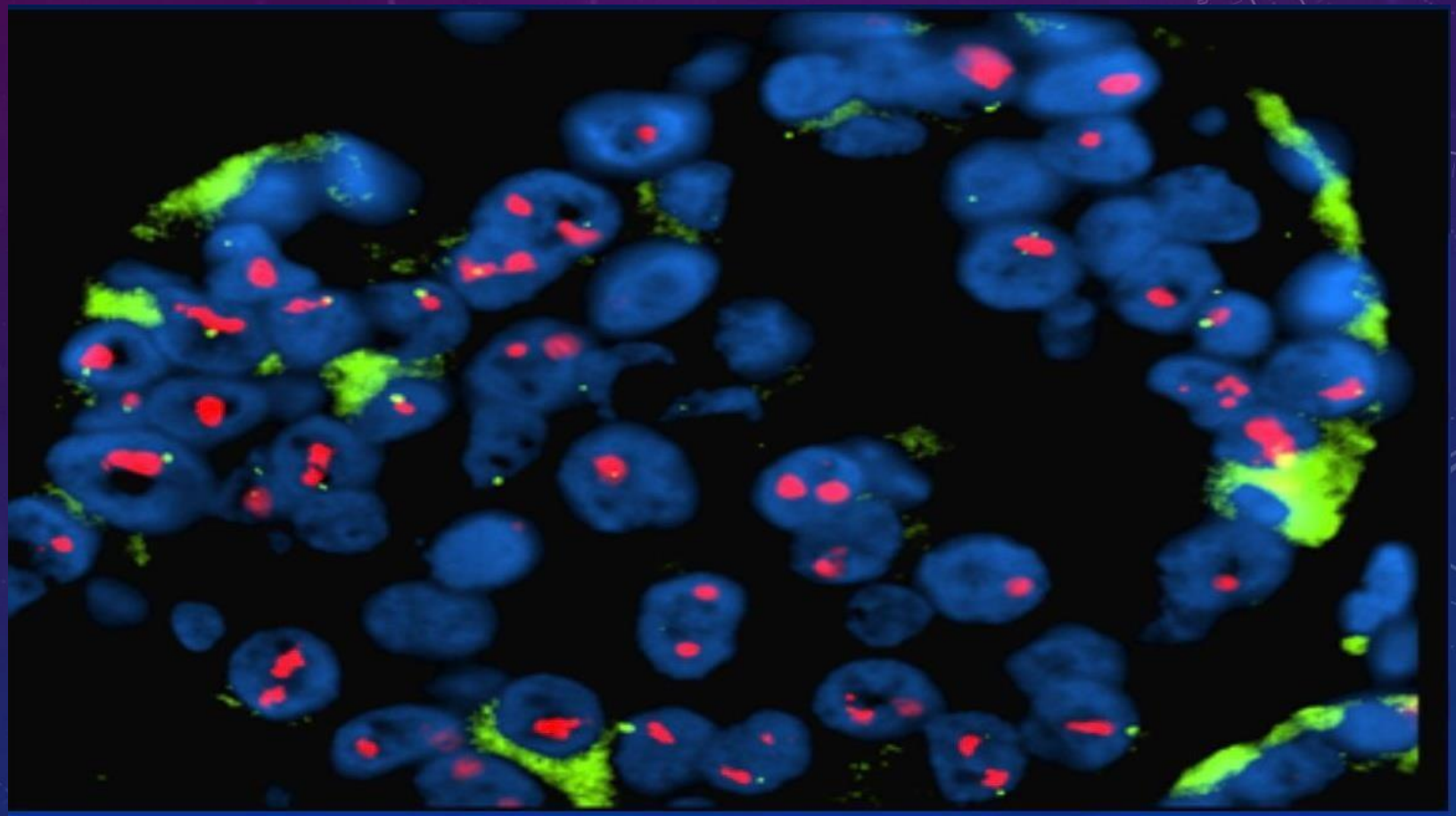
IHC (immunohistochemistry)

Her2	Breast, Gastric, Esophagus
ER & PR	Breast
MMR/MSI	Colorectal, Endometrium, Esophagus, Gastric
PDL-1	NSCLC
ALK, ROS1	NSCLC
BRAF V600E	Melanoma
P16	Pan cancer

FISH (Fluorescent In-situ Hybridization)

• **Her2** (equivocal/1+ on IHC)	Breast, gastric, esophagus
• **ALK, ROS1, MET, RET**	NSLC
• **MYC Amp**	Breast
• **TFE3**	Renal
• **NTRK1, 2, 3, FGFR1, 2 Amp**	Pan Cancer
• **EWSR1, MSM2, CKD4**	Sarcoma
• **BCL2, BCL6, MYC, MALT1, IGH**	Lymphoma
• **NTRK3**	Head & Neck

FISH



RT – PCR

- **HPV Genotype Profiling (FFPE)**

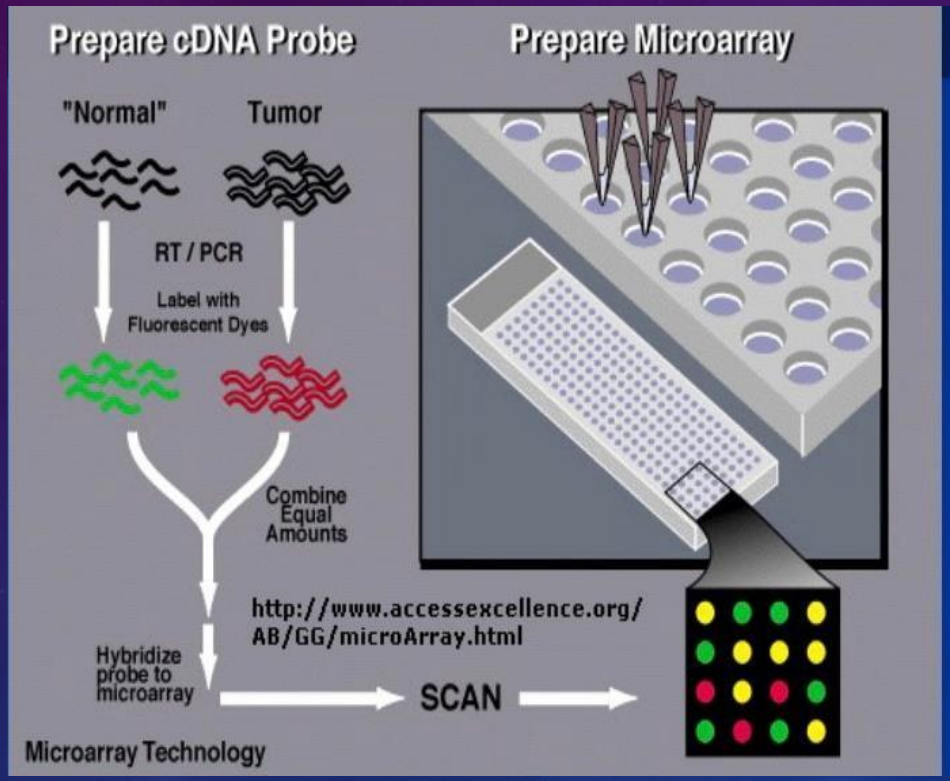
  low and high risk genotypes

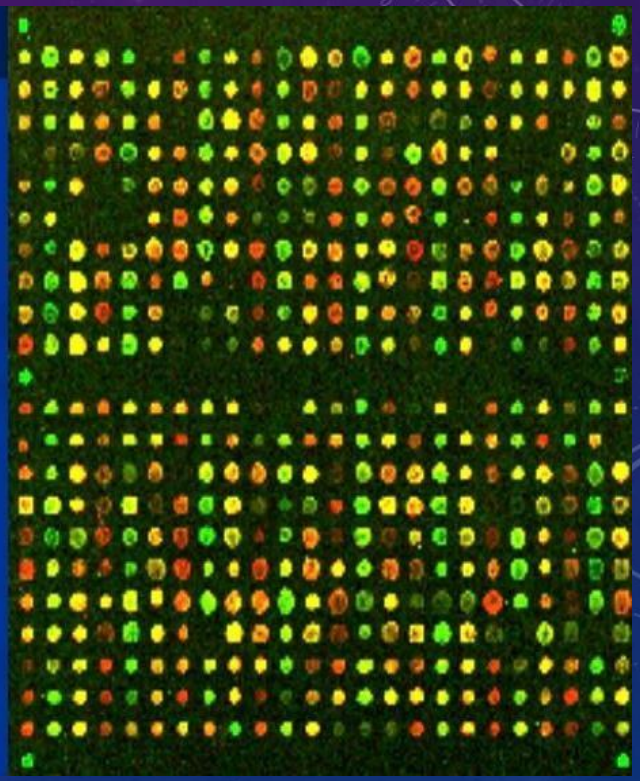
- **Breast Prosigna**

  Prognostic Gene Signature assay

  (only on ER + Her2 & LN negative patients)

GENE MICROARRAY





NGS

- **Colorectal Panel**

  KRAS, BRAF, NRAS, MMR/MS (MLH1, MSH2, MSH6, PMS2, POLE

- **Lung Cancer Panel (NSCLC)**

  ALK, EGFR, ROS1, MET, BRAF, KRAS, NYRK 1, 2, 3

- **Melanoma Panel**

  BRAF, KIT, NRAS, NTRK1/2/3

- **Thyroid Cancer Panel**

  BRAF, KRAS, NRAS, HRAS, RET
- **Pancreas Cancer Panel**

  BRCA1, BRCA2, NTRK1/2/3
- **Biliary Panel**

  NTRK1/2/3, FG
- **Glioma Panel**

  BRAF, IDH1/2, EGFR, MYC, TP53, CDKN2A

Specimen Requirements

- **NGS/MMR/Methylation**

  8 4uM sections plus 2 H&E slides

- **FISH**

  2 uM section for each probe plus 1 H&E slide

RELEVANT GENES

❑ ONCOGENES

Normal proto-oncogenes promote cell growth: encoding GF, GFR, signal transducing proteins, nuclear transcription factors & cyclins.

Genetic damage (mutation, translocation, amplification) to proto-oncogenes leads to their activation called **Oncogenes,** causing abnormal unregulated growth.

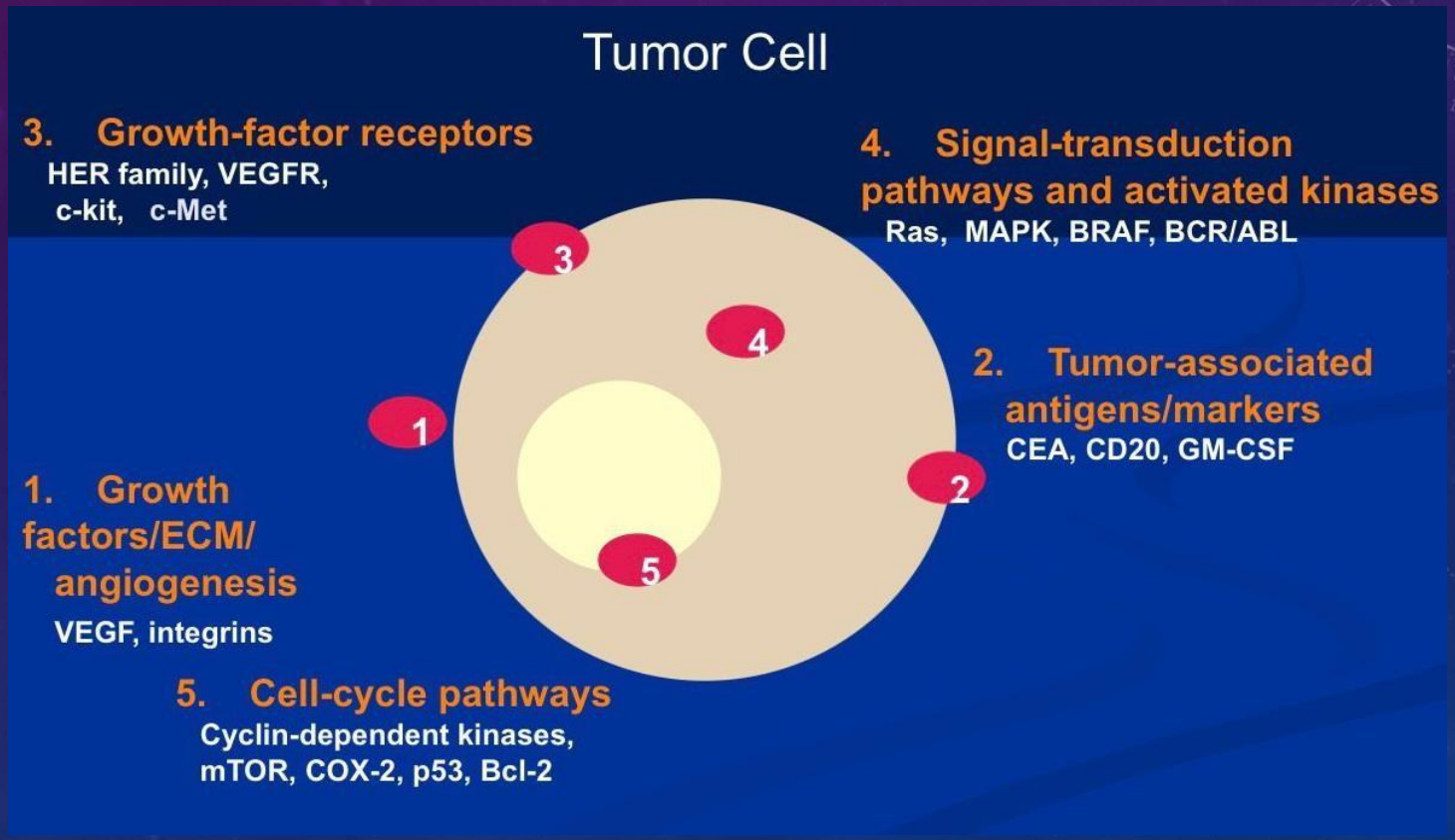
❑ MMR (mismatch repair genes)

Repair genetic damage

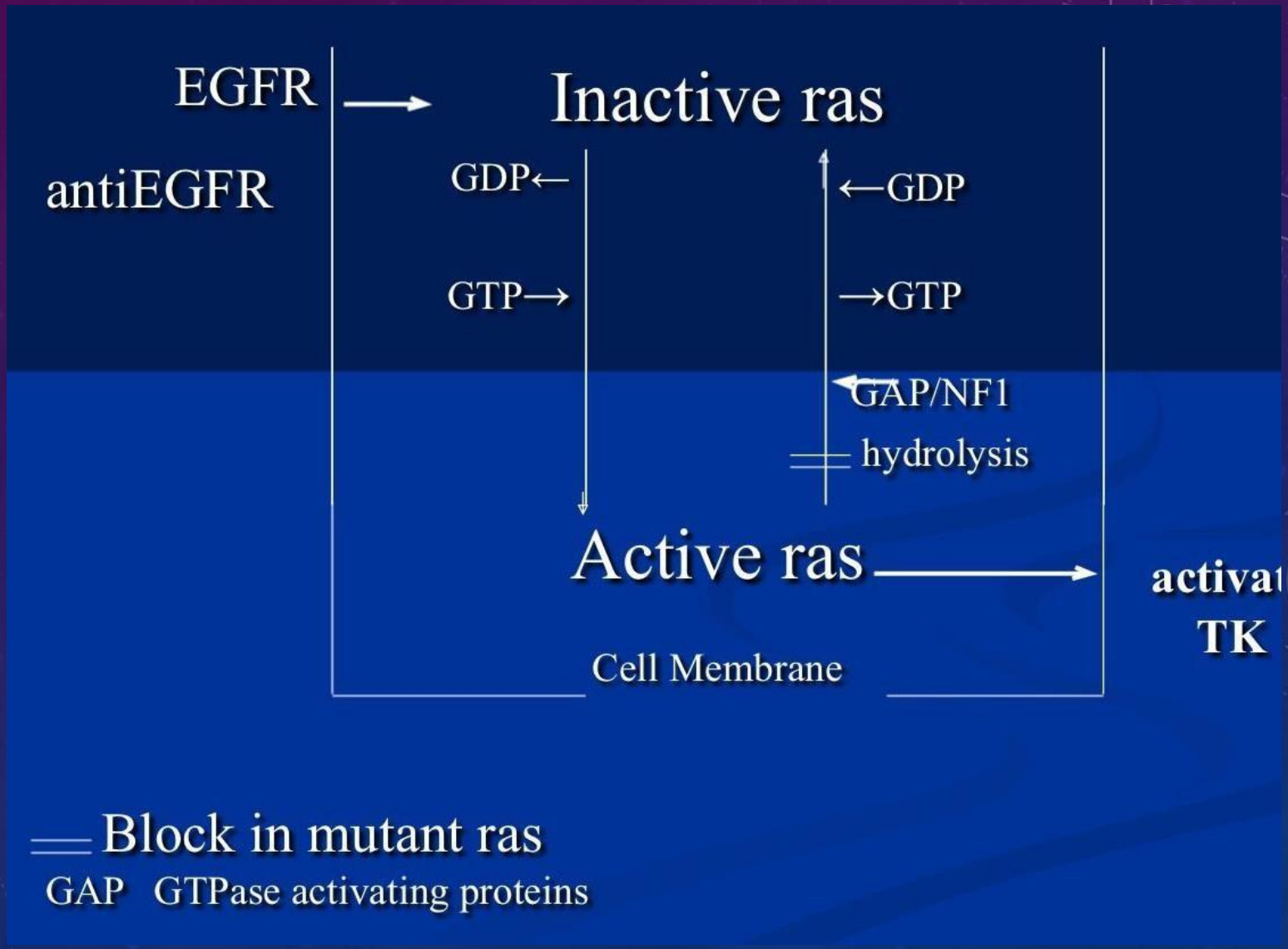
Loss of expression causes damaged genes to pass on to next generation

❑ Immune checkpoint inhibitors

BIOLOGICAL TARGETS FOR CANCER THERAPY



EGFR & TK (tyrosine kinase) INHIBITORS



IMMUNE CHECKPOINT INHIBITORS ACT ON

PDL – 1 (programmed death ligand) receptors

- Receptors on the cancer cells & APC (antigen presenting cell)
- Normally keep cytotoxic T lymphocytes away from cancer cells
- If these receptors are occupied by monoclonal antibodies/immune checkpoint inhibitor drugs then cancer cells will be destroyed by cytotoxic T lymphocytes which is patient's own immune system

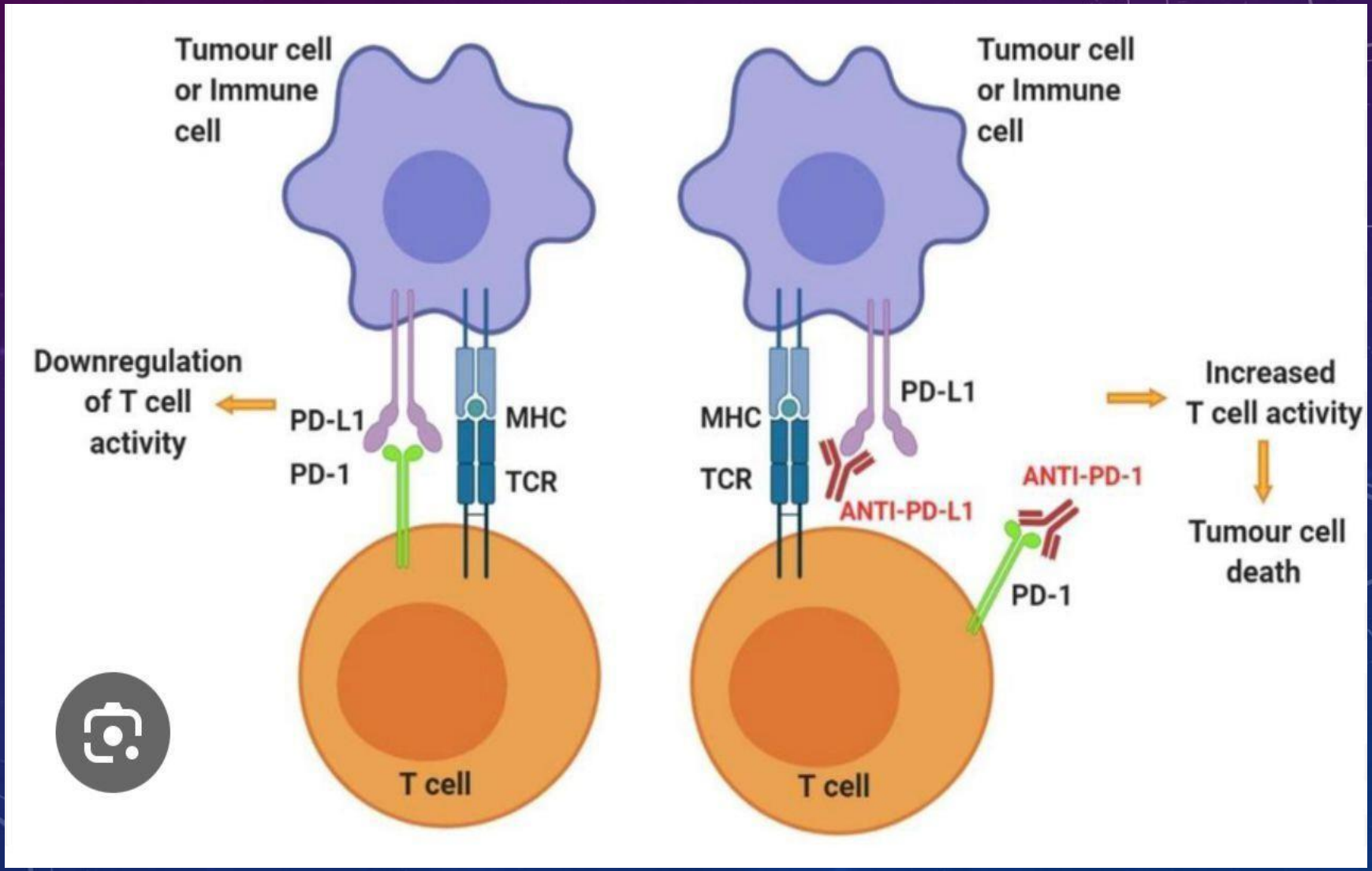
PD – 1 receptors

- are receptors expressed on APC only

CTLA – 4 receptors

- another immune checkpoint inhibitor used metastatic melanoma

Mechanism of PDL-1 Inhibitor



Types of Immunotherapy

- Cytokines
  - IL2
  - Interferon
- Immune Modulators
  - Lenalidomide
- Cancer vaccines
  - BCG for NMIBC
- Monoclonal antibodies
  - Rituximab – anti-CD20
  - Trastuzumab – anti-HER2
- Virus therapy
  - T-VEC for melanoma
- CAR-T therapy

When is immunotherapy used?

- Neoadjuvant (with chemo)
  TNBC (triple negative breast cancer)

- Adjuvant (post-op)
  Bladder cancer

- Palliative (incurable)
  Monotherapy, e.g. first-line treatment
  Monotherapy as maintenance
  Combination with chemotherapy

THERAPEUTIC APPLICATIONS

TWO TYPES OF DRUGS:

- MONOCLONAL ANTIBODIES

  GROWTH FACTOR RECEPTOR ANTAGONISTS (EGFR)
  IMMUNE CHECK POINT INHIBITORS (PDL-1, PD-1, CTLA-4)

  ANTI ANGIOGENIC

- SMALL MOLECULE INHIBITORS

  TYROSINE KINASE INHIBITORS (TKI OF EGFR, CMET & ALK, CKIT)

More effective in combination with platinum based chemotherapy

MONOCLONAL ANTIBODY

- Bind & block extra-cellular domain of growth factor receptor.
- Large molecule, cannot enter cell
- I/V only, hospital supervised

EGFR Receptor Antagonist

Cetuximab

- EGFR overexpressed in many cancers CRC, H & N, Breast, NSCLC
- FDA approved use in recurrent & metastatic CRC

Trastuzumab (Herceptin)

- Her2 receptors antagonists (Epidermal growth factor receptor 2)
- Mutation causes unregulated cell proliferation
- 25 % of breast cancers are Her2 positive, more aggressive but response to Her2 antibodies.
- 10 years OS is 84 % if Herceptin combine with surgery & Chemo from 70 % without Herceptin
- ER & PR with Her2 + respond better than triple negative
- Also used for Her2 + gastric & esophageal adenocarcinoma

Immune checkpoint inhibitors

- **Pembrolizumab (PD-1 inhibitor)**

  NSCLC, H & N SCC, Melanoma, Breast

- **Nivolumab** (PD-1 inhibitor)

  CRC, Esophagus, HCC, NSCLC, melanoma, Gastric, Cervical, Hodgkins

- **Ipilmumab** (CTLA-4 inhibitor)

  NSCLC, melanoma, RCC

- **Atezolizumab (Tecentriq)** PDL-1 inhibitor

  NSCLC, urothelial, melanoma, H & N SCC, lymphoma

- **Durvalumab (imtinzib)** PDL-1 inhibitor

  NSCLC, SCLC, unresectable HCC, bile duct & GB CA

- **Avelumab (Bavencio)**

  locally advanced & metastatic urothelial carcinoma, Merkel cell carcinoma.

Anti CD20 antibodies

- **Retuximab**

  B cell NHL, Autoimmune diseases

Bevacizumab

Anti VEGF (Vascular endothelial growth factor)

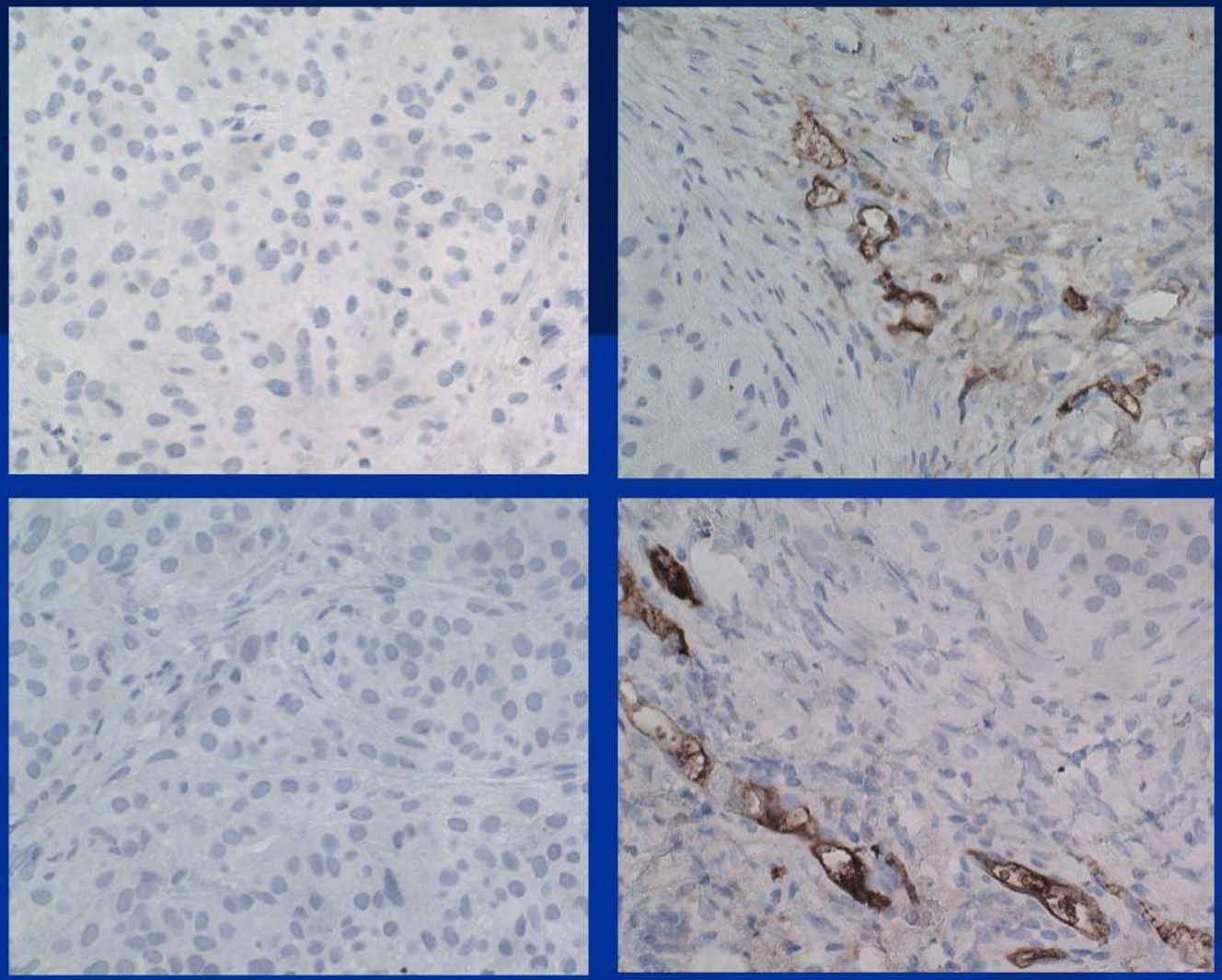
- VEGF overexpressed in many tumours CRC (including metastatic), breast, RCC, HCC , and gliomas
- Drug decreases angiogenesis causing tumour necrosis

Treatment with PHA-665752 reduces tumor size in H69 tumors in nude mice

Treated

Control

PHA-665752 reduces angiogenesis in A549 cells



Treated with PHA-665752

Treated with vehicle

SMALL MOLECULE INHIBITORS

- Can be absorbed through oral route
- Can enter intracellular environment

- **EGFR tyrosine kinase inhibitor**

  Osimertenib

  3rd generation NSCLC

  Erlotinib

  NSCLC, breast

- **ALK inhibitor**

  Alectinib

  NSCLC

- cMet tyrosine kinase inhibitor

  Crizotinib

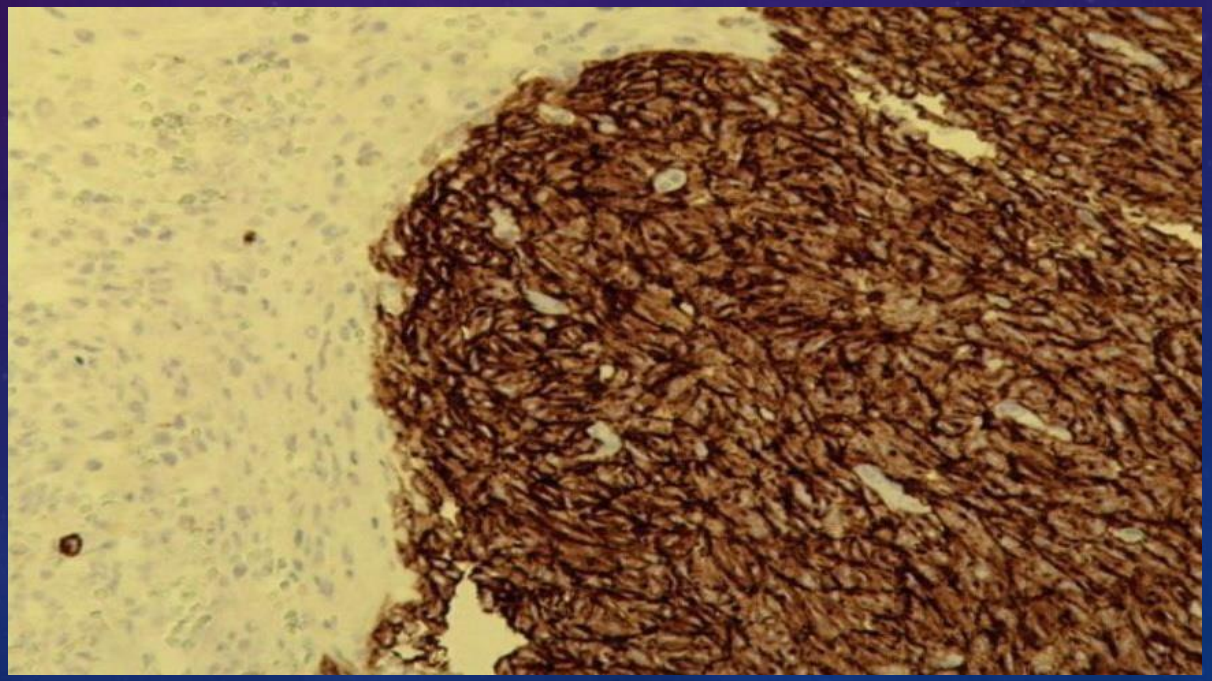
  NSCLC

- Inhibitor of c-Kit

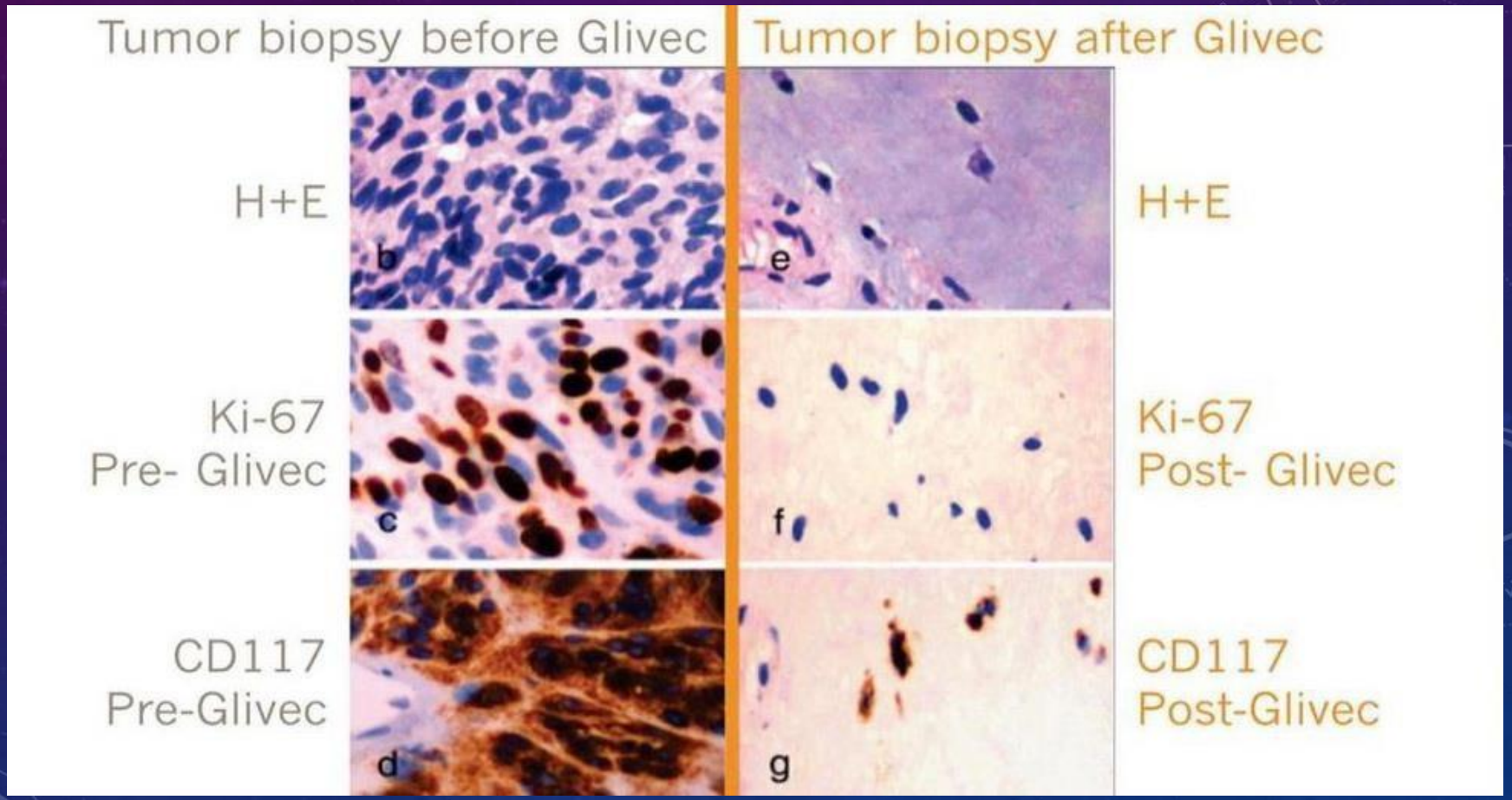
  Imatinib Mesylate (Glivec)

GIST IHC (CD 117)

- 90 % of GIST express mutant c-kit expression
- In most studies more than 50% patients with metastatic GISTs have stable disease
- Once daily tablet of 400 or 600 mg with fewer side effects



TREATMENT OF UN-RESECTABLE AND/OR METASTATIC GIST WITH GLIVEC



LATEST CLINICAL TRIALS OF TARGETED THERAPY

LUNG CANCER

- EGFR mutation exon 19 and 21

Flaura Trial:

Median OS (overall survival) of 38.6 months for patients on Osimertinib, compared to 31.8 months for those on Gefitinib or Erlotinib

- ALK mutation

Alex Trial:

5-year OS for patients receiving Alectinib was approximately 62.5% vs 45.5 for Crizotinib arm

❑ Immunotherapy in NSCLC

Keynote 024 Trial (Pembrolizumab):

Patients with PD-L1 expression of ≥50% Pembrolizumab significantly improved OS as a first-line treatment compared to chemotherapy. Median OS was 30.0 months with Perbrolizumab, compared to 14.2 months with chemotherapy alone

CheckMate-227 trial (Nivolumab + Ipilimumub)

Combination of immunotherapy agents, showed median OS of 17.1 months for patients receiving Nivolumab and Ipilimumab compared to 14.9 months with chemotherapy alone.

MELANOMA

- Approximately 50 % of melanoma patients harbour BRAF mutation and eligible for targeted therapy with BRAF / MEK inhibitors with response rate of nearly 70%
- BRAF mutant melanomas are more aggressive than BRAF wild with often brain metastasis
- On Feb 2024 FDA granted accelerated approval of Lifileucil for patients with un-resectable metastatic melanoma after prior treatment with PDL-1 & BRAF inhibitors
- With these new treatments people with stage 4 melanoma are living for longer

HER2-NEGATIVE METASTATIC / UNRESECTABLE GASTRIC & ESOPHAGEAL ADENOCARCINOMA

Phase III Trial (CheckMate 649)

- Nivolumab plus fluorouracil and oxaliplatin
- Median F/U of 36 months showed improved OS to 21 vs 10 %
- PFS 11 vs 7%

METASTATIC COLORECTAL CARCINOMA

PHASE III TRIAL (KEYNOTE-177)

- Treatment-naïve dMMR/MSI-H mCRC treated with pembrolizumab with or w/o bevacizumab or cetuximab until disease progression or unacceptable toxicity
- Median f/u of 32 months improved PFS 16.5 VS 8.2 months
- Two-year PFS 48 vs 19 %

CHALLENGES OF USING GENETIC INFORMATION IN HEALTHCARE

REGULATORY POLICIES

- To integrate genetic information for clinical use & drug development

- Genomic reference library to uphold reliability

INTELLECTUAL PROPERTY RIGHTS

- Important for investment & interest
- DPA (data protection act) regarding patient protection for genetic information
- 2013 supreme court ruled that natural occurring genes cannot be patented while synthetic DNA can

REIMBURSEMENT POLICES

- Cost effectiveness Vs benefits
- Efficacy of various genetic tests in general population
- Insurance Polices – new concept of individual genetic risk in contrast to common shared risk

? IGNORANCE IS A BLISS, KNOWING TOO MUCH OF ONE'S OWN GENOME COULD LEAD TO

- Necessary Vs Unnecessary apprehension
- True Vs False sense of reassurance
- Significant Vs Insignificant genetic alteration
- Intervention Vs No intervention

KEY POINTS

- Genetic testing (gene or protein profiling) is necessary prior to select therapy in individual patients

“Personalized Medicine”

- Regulatory polices & intellectual property rights needs to be redefined

- These new drugs are more like tumorstatic than tumorcidal therefore we are stabilizing cancers and making them like a chronic disease such as HTN, DM, RA etc. So that people live with cancer rather than dying from it.

- Small jumps in oncology are equivalent to long leaps

OMG I did not have this mutation when last time I checked my 3 billion base pairs

Thank You