Personalized Medicine – Oncology as a model

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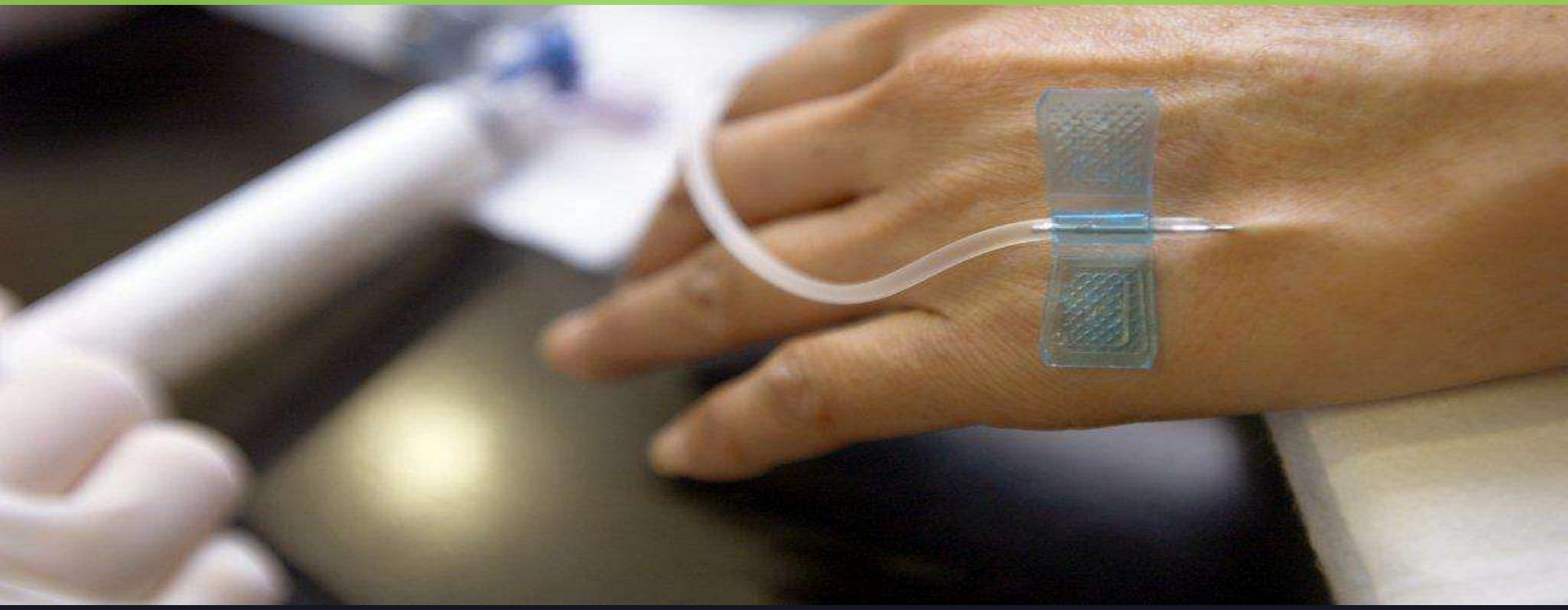

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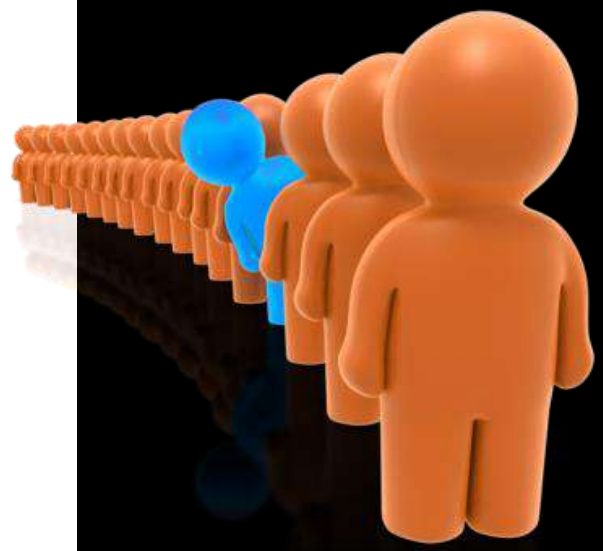
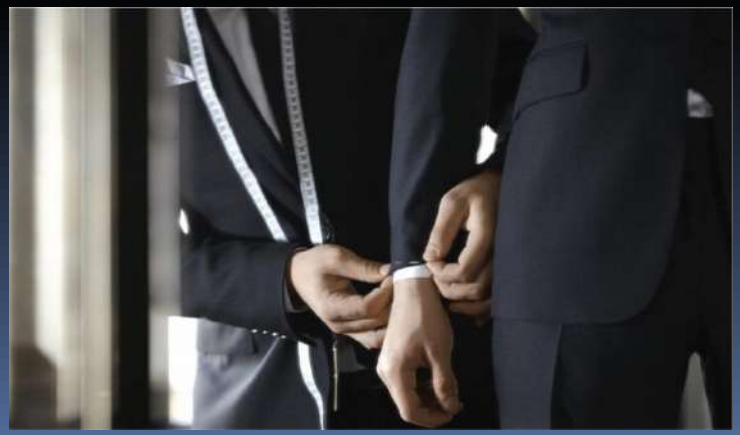
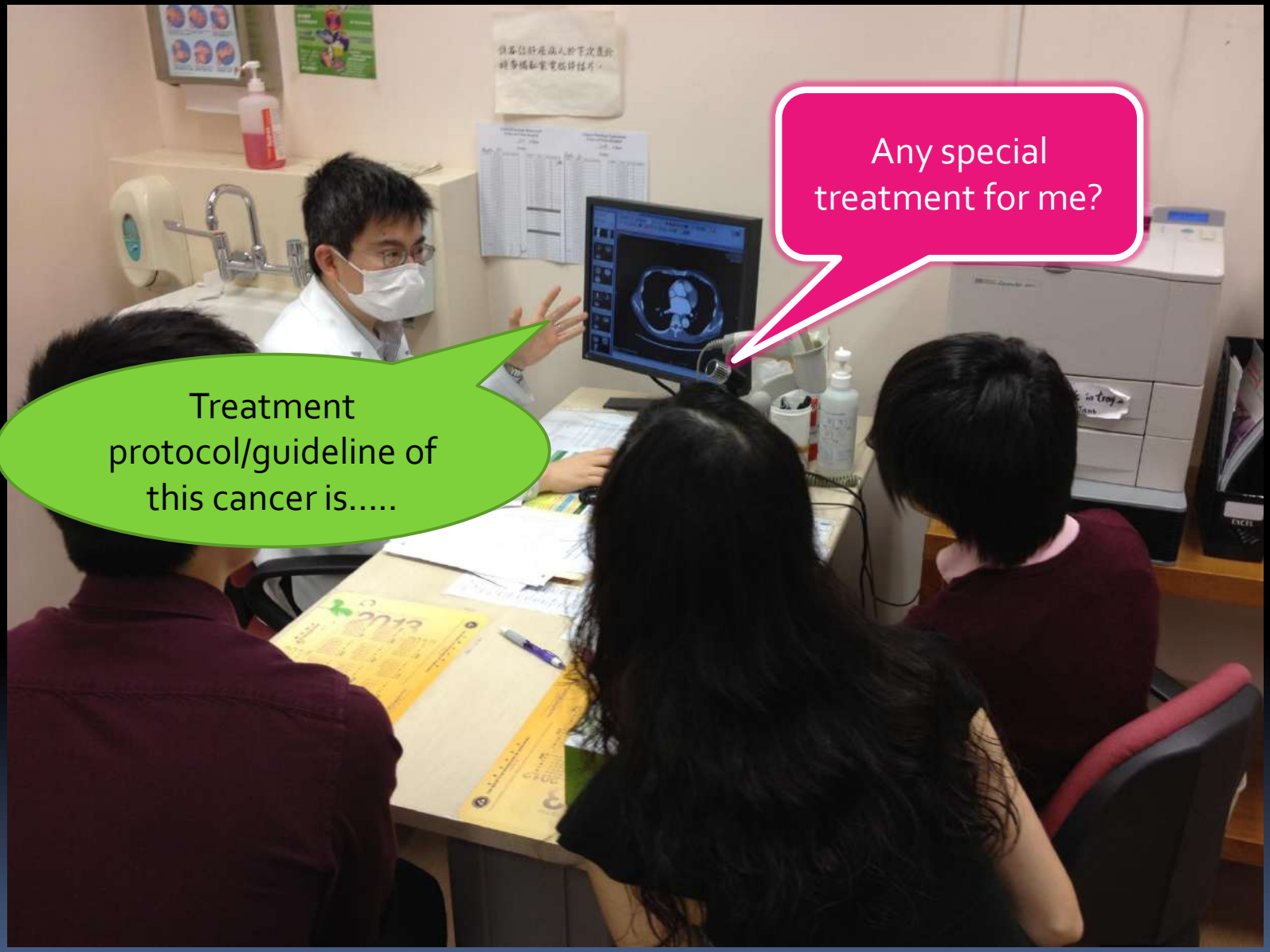
Personalization is everywhere






Any special treatment for me?
Treatment protocol/guideline of this cancer is.....

Definition of Personalized Medicine

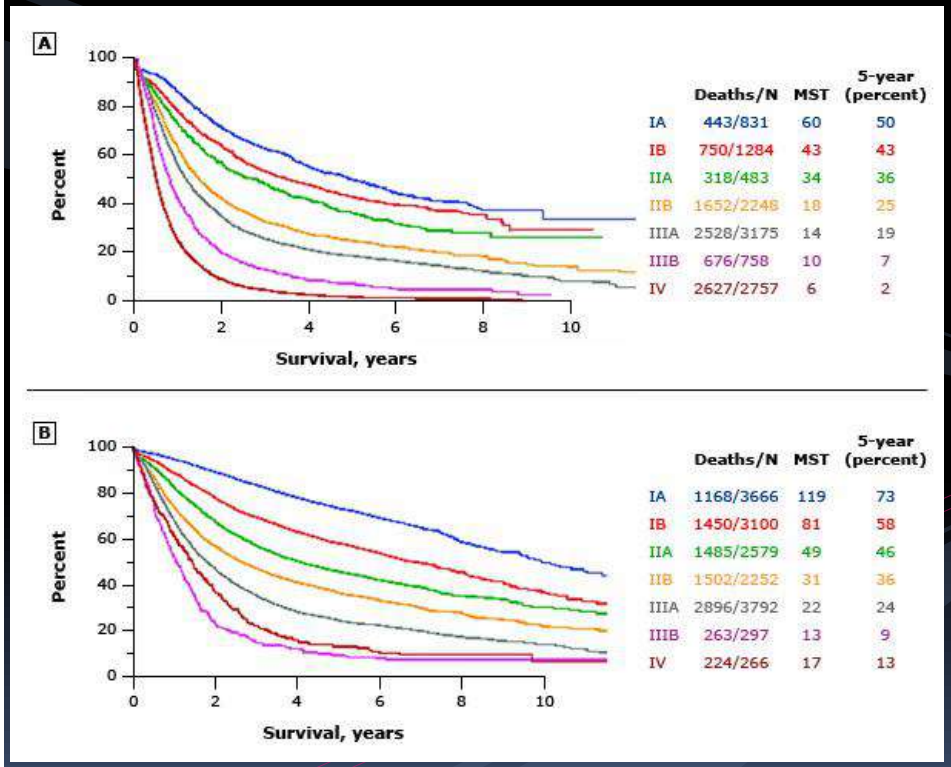
- Personalized Medicine (NCI)
  - A form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease.
  - In cancer, personalized medicine uses specific information about a person's tumor to help diagnose, plan treatment, find out how well treatment is working, or make a prognosis.

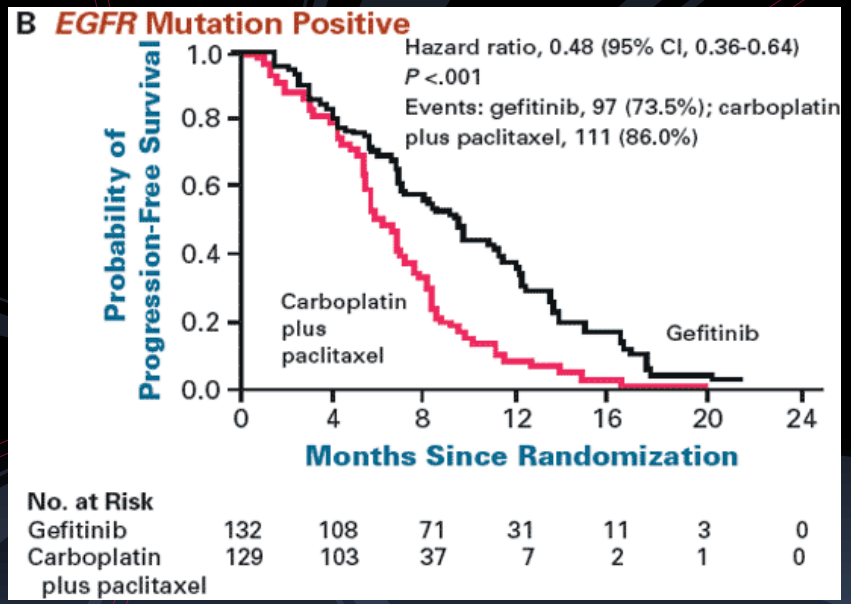
Outline

- Why personalized medicine for cancer?
- Current approach of personalized treatment for cancer
- Future direction of personalized treatment for cancer

WHY PERSONALIZED MEDICINE FOR CANCER?

Clinical: Every patient is different





Different survival outcome even with the same stage or treatment

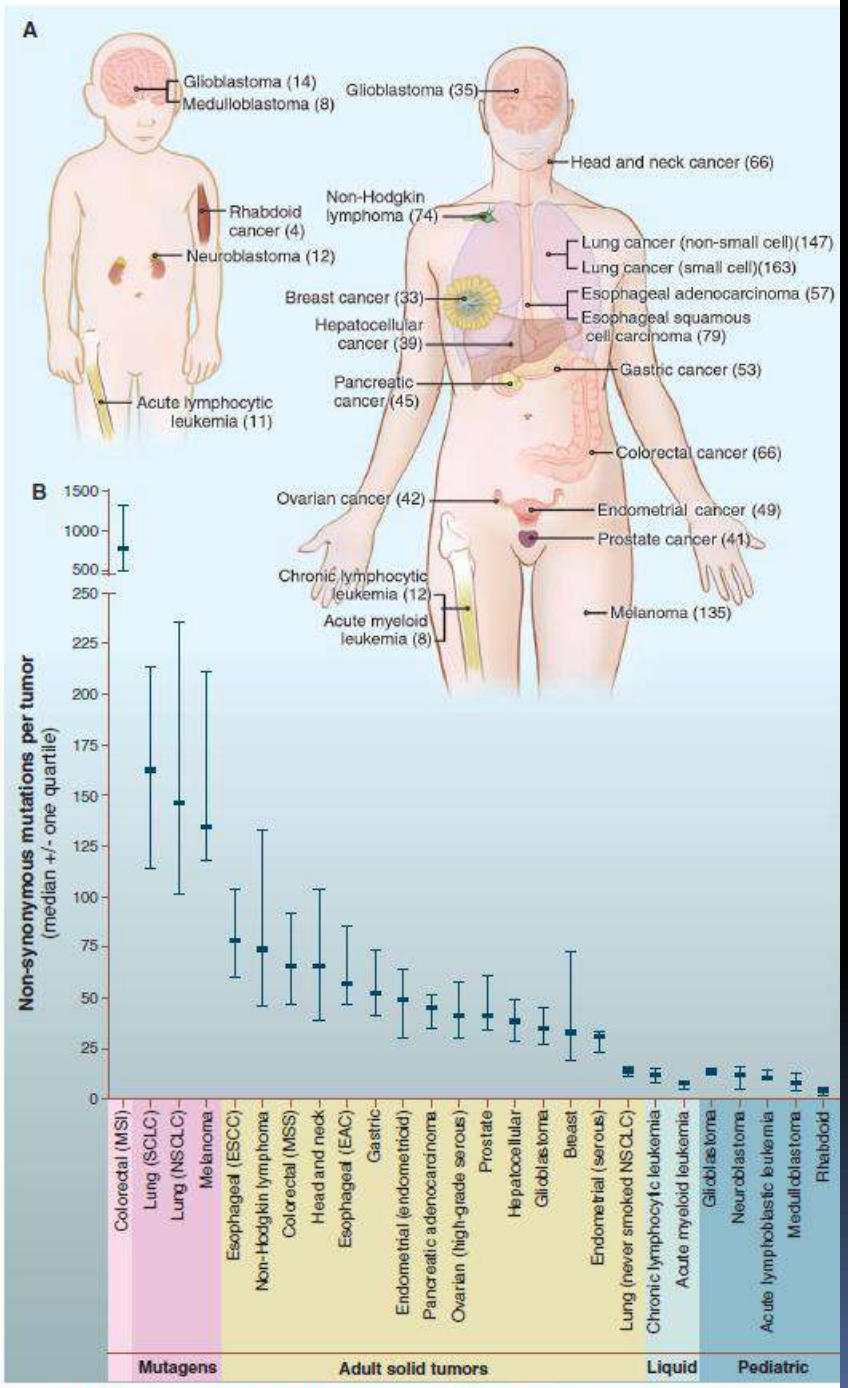


Fig. 1. Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies. (A) The genomes of a diverse group of adult (right) and pediatric (left)

Cancer is characterized by an accumulation of a number of genetic mutations

Vogelstein B et al. Science 2013; 339; 1546-1558

High inter-patient heterogeneity

Breast cancer as an example

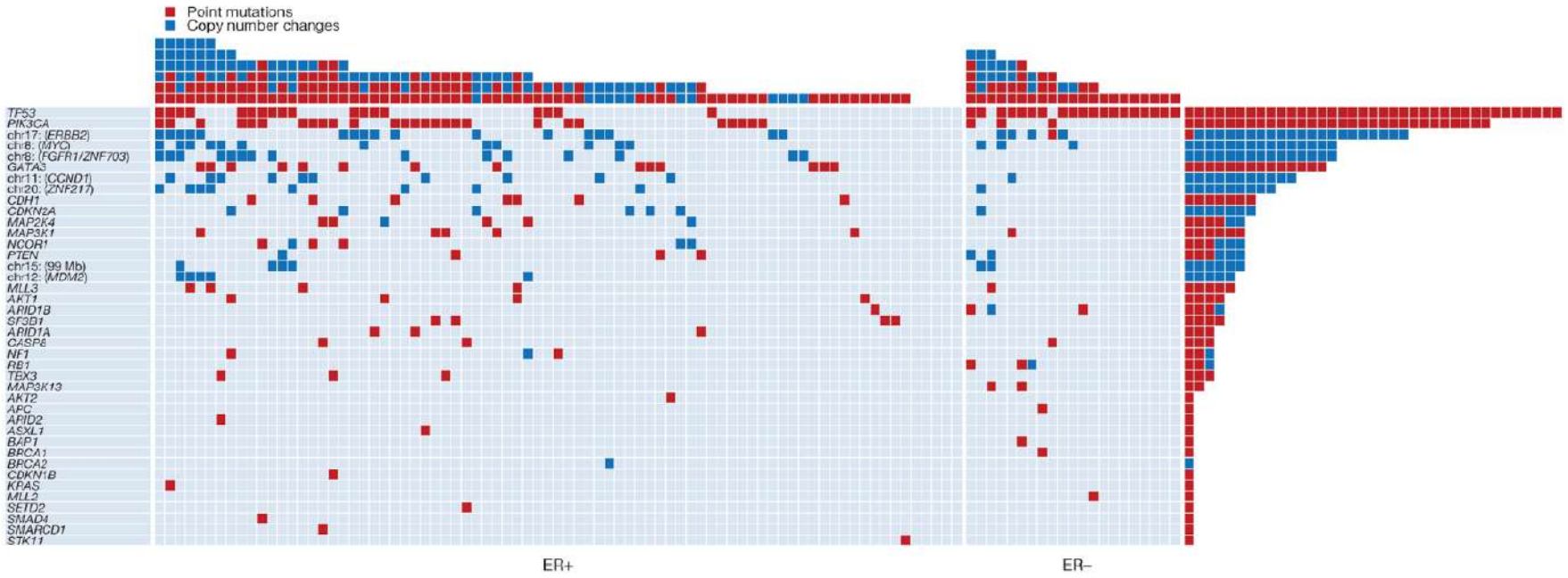
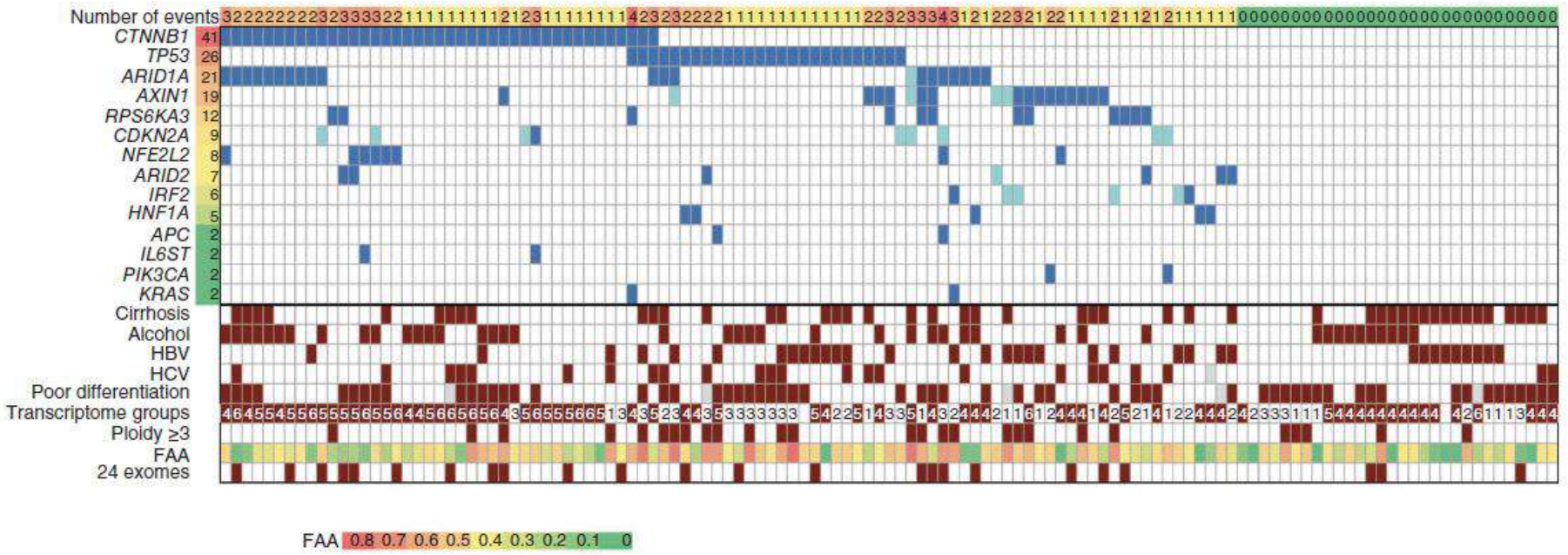


Figure 2. The landscape of driver mutations in breast cancer

Stephens PJ et al. Nature 2012; 486: 400-404

High inter-patient heterogeneity

Liver cancer as an example



Guichard et al. Nature genetics 2012; 44: 694-698

Conventional chemotherapy

Cytotoxic chemotherapy

- Mechanism: non-specific cell killing via DNA damage

→ Side effects (e.g. hair loss, vomitting, mucositis, fever)

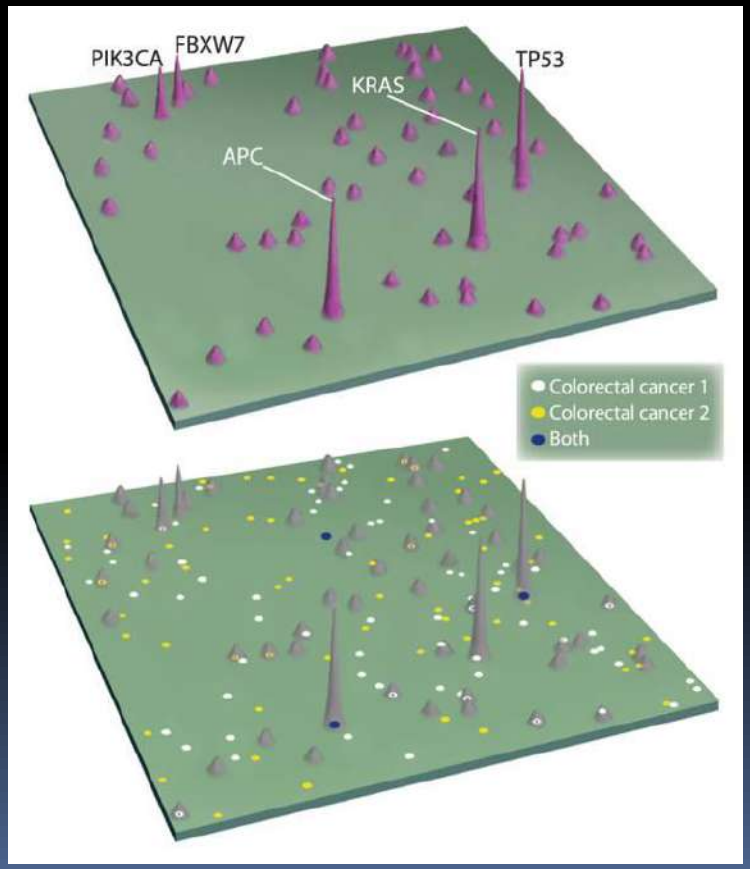
When we give chemotherapy

Chemo: We don't know who is going to respond…..

CURRENT APPROACH OF PERSONALIZED MEDICINE FOR CANCER

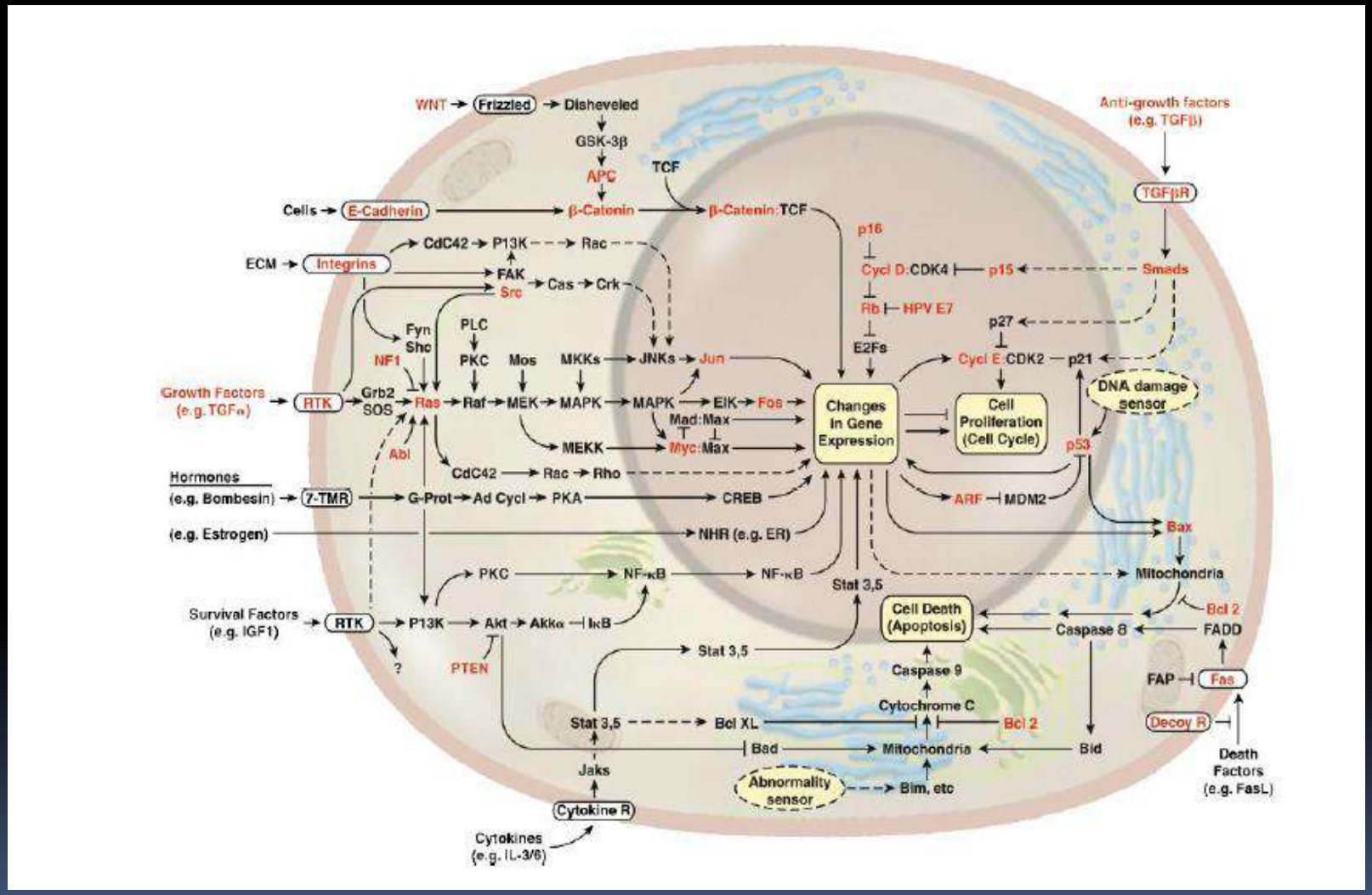
Concept 1: driver mutation

- Driver mutations vs. passenger mutations



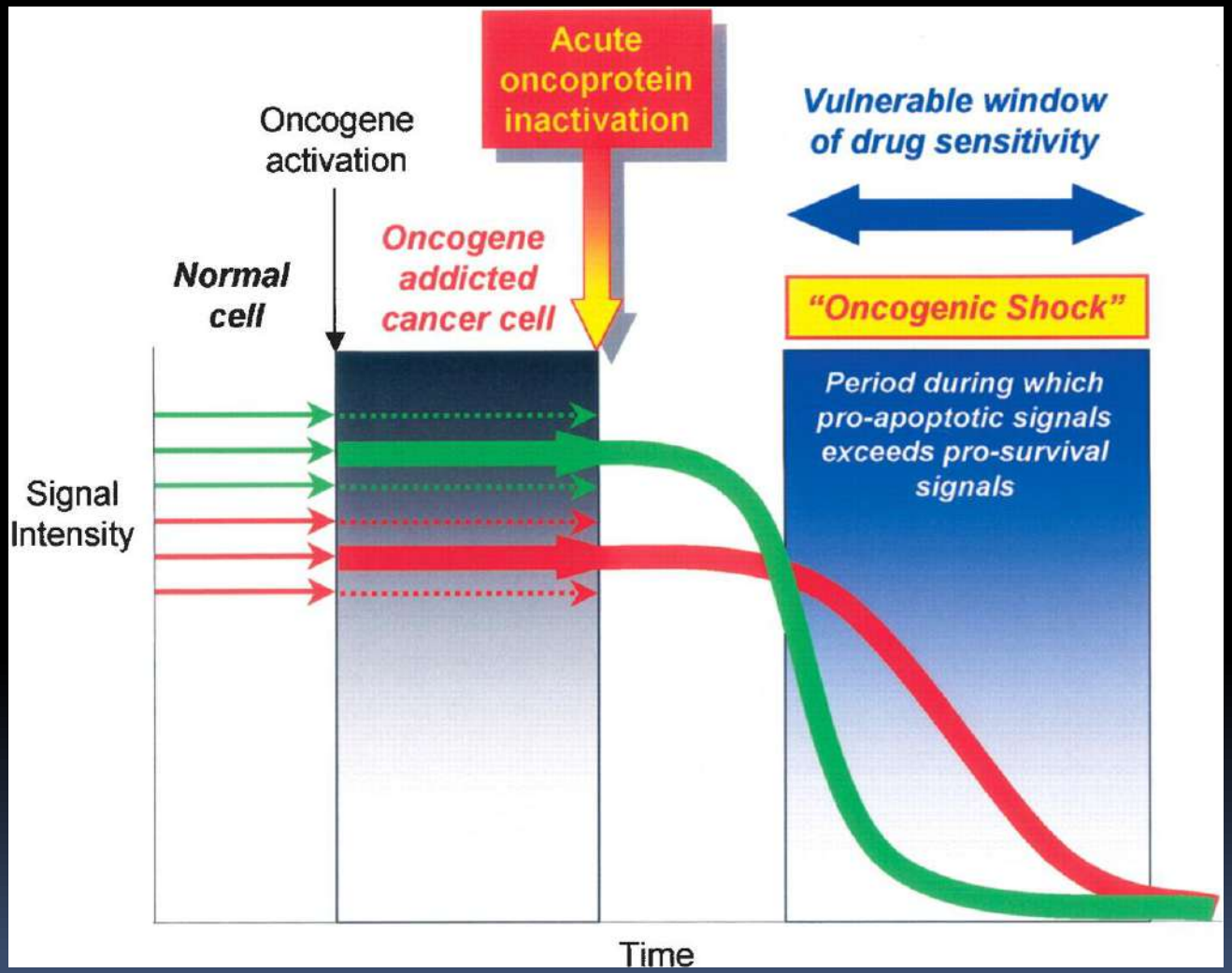
- Driver mutations (Mountains)
  - confers a selective growth advantage
- Passenger mutations (Hills)
  - background mutations
  - not associated with growth advantage
  - related to age

Genetic mutations linked to signaling pathways



Hanahan et al Cell 2000

Cancer cells addicted to a particular oncogene/pathway



Sharma S V , Settleman J Genes Dev. 2007;21:3214-3231

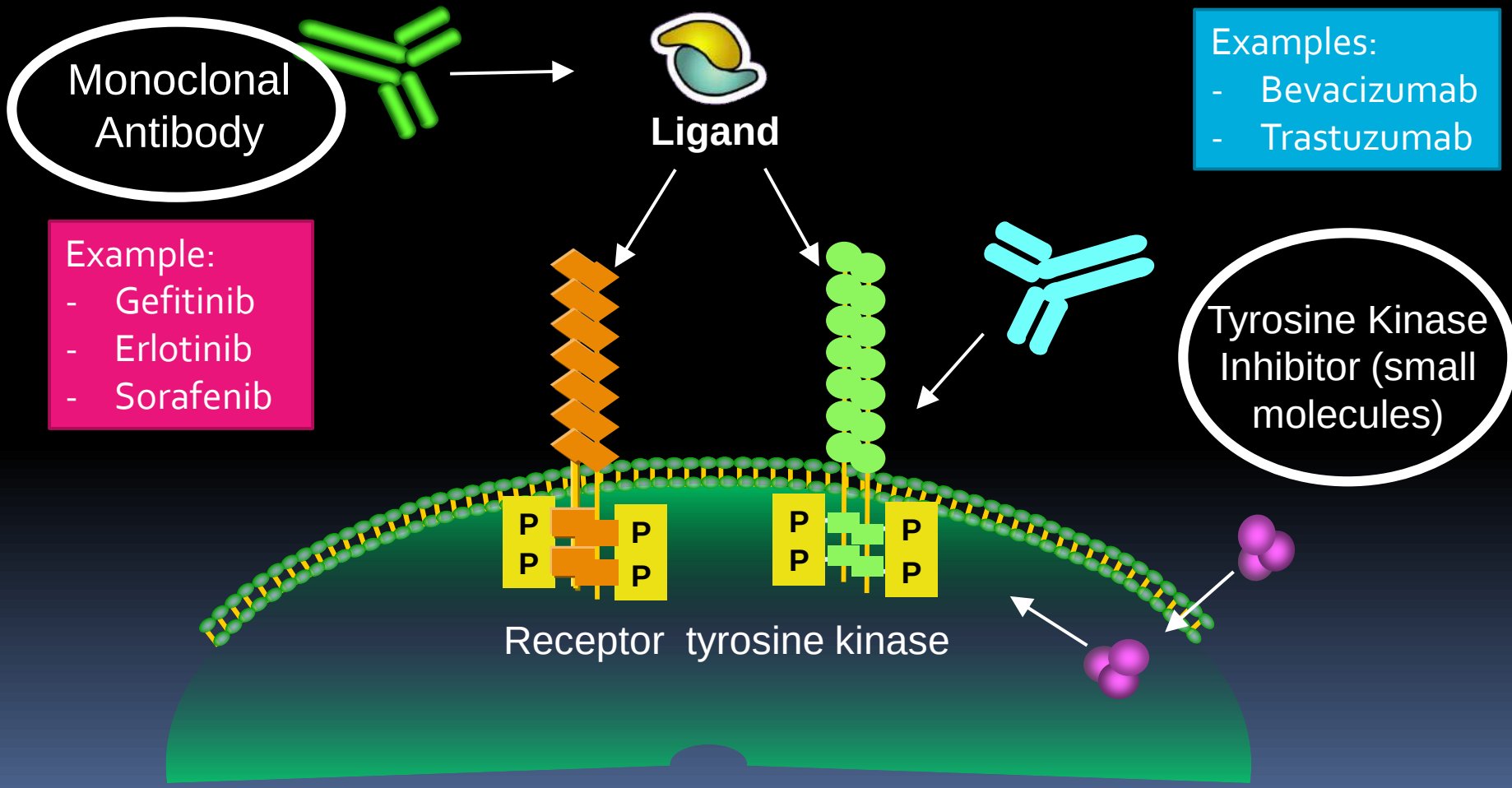
AIM

- If we can identify the 'driver' mutation
- AND if we can specifically target the 'driver' mutation

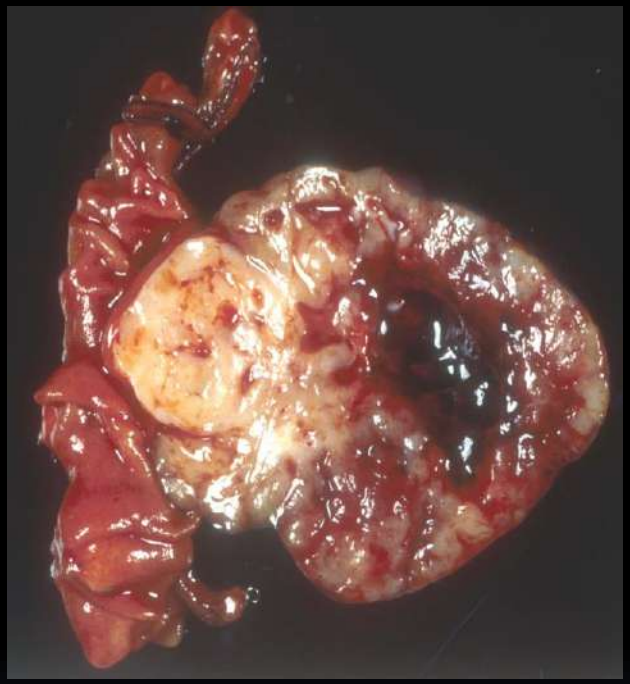
→We can induce significant treatment response

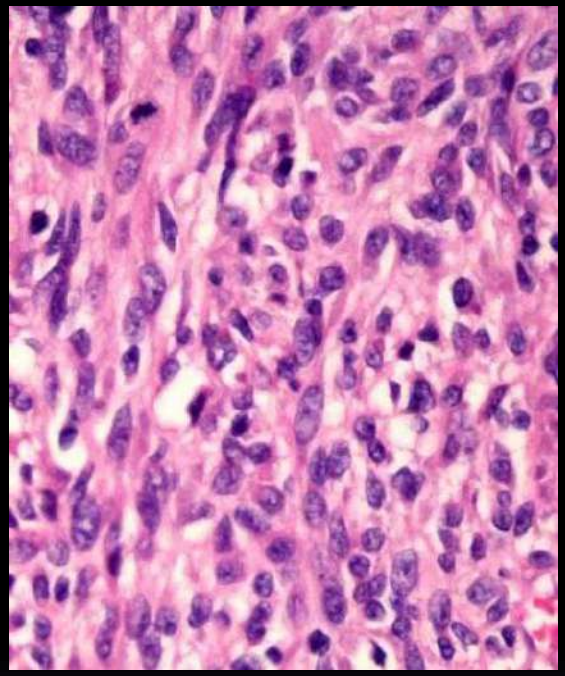
→ We can predict the response and select patient for the right treatment

Mechanism of targeted agents: Two Classes

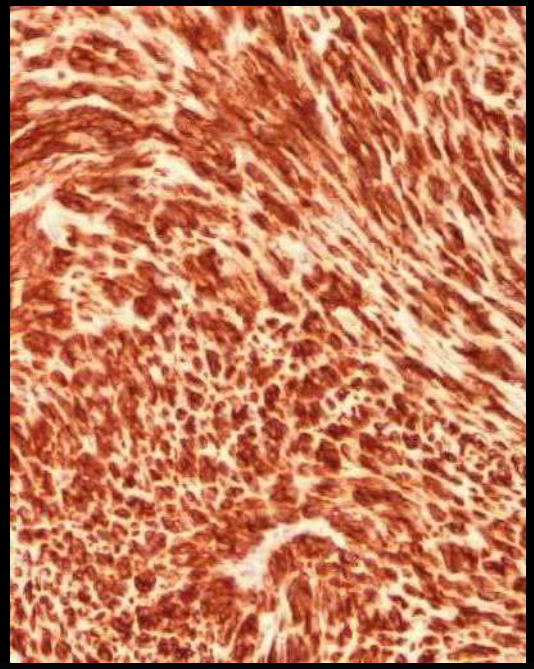


Gastrointestinal Stromal Tumor (GIST)





c-kit



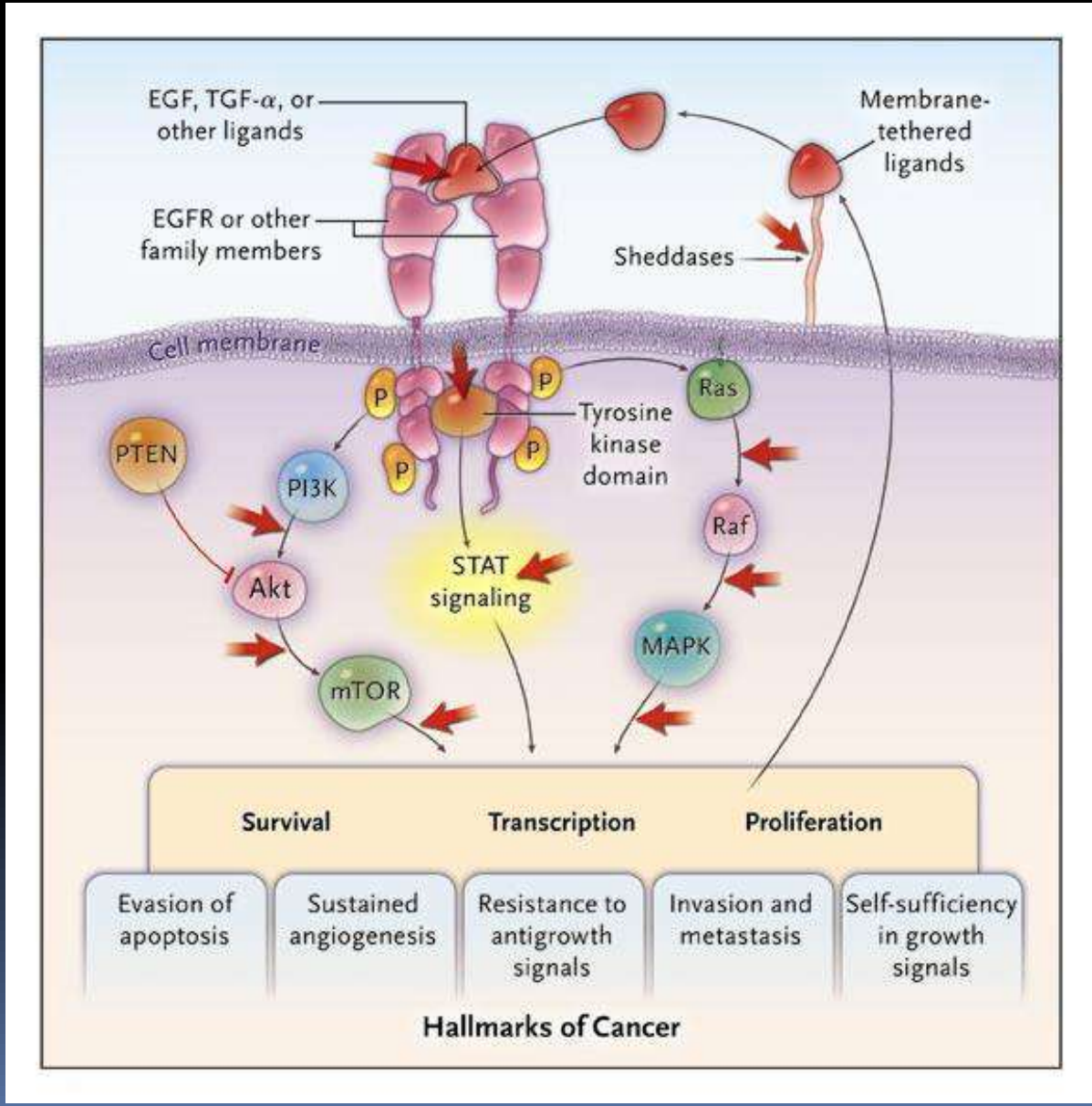
- Before the era of targeted treatment, inoperable GIST has an extremely poor prognosis
- Imatinib targeting the c-kit significantly prolongs the overall survival > 5 years.

Lung Cancer as an example

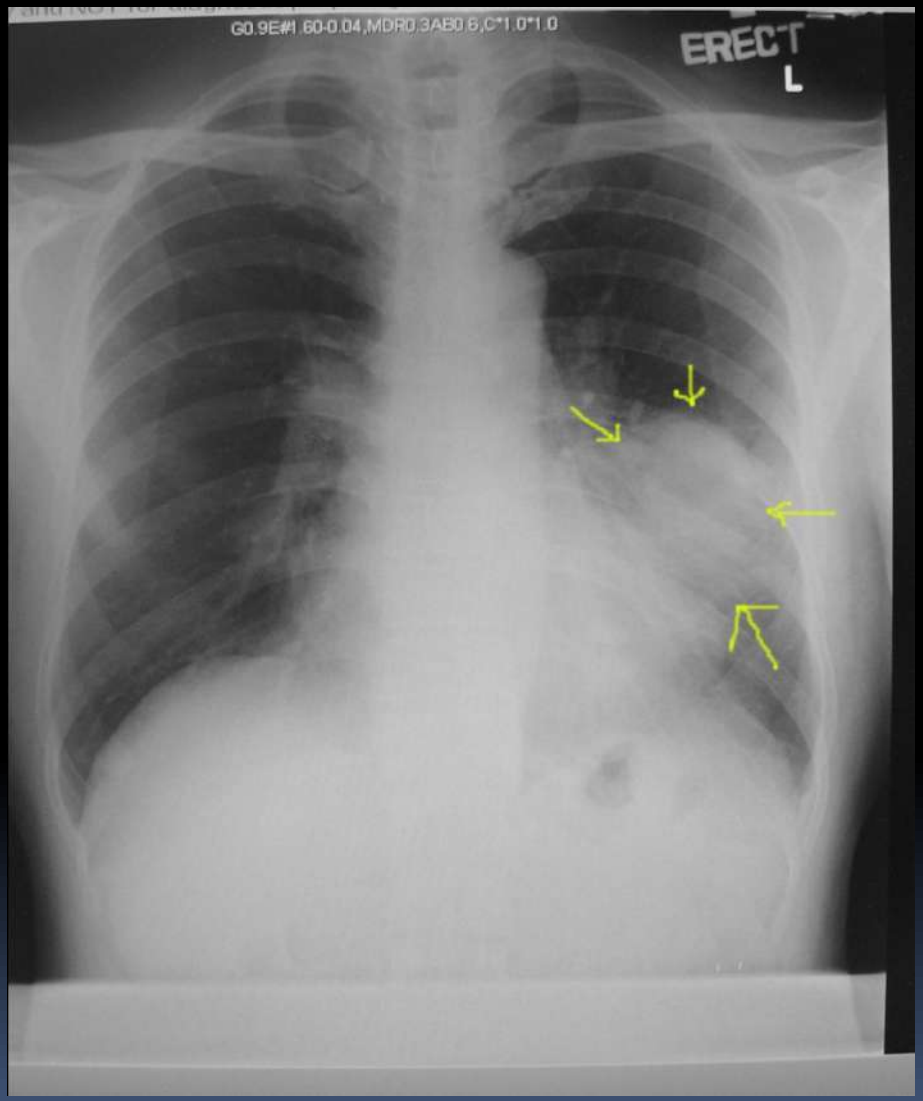
- Stage IIIb or IV disease Non-small cell lung cancer
  - Regardless of histology subtype (Squamous cell carcinoma, Adenocarcinoma, Large cell, BAL..)
  - 1st-line treatment: Doublet chemotherapy (platinum as the backbone)
  - Plateau of efficacy: median survival ~10 months, RR ~30%

Epidermal Growth Factor Receptor (EGFR) in Lung cancer

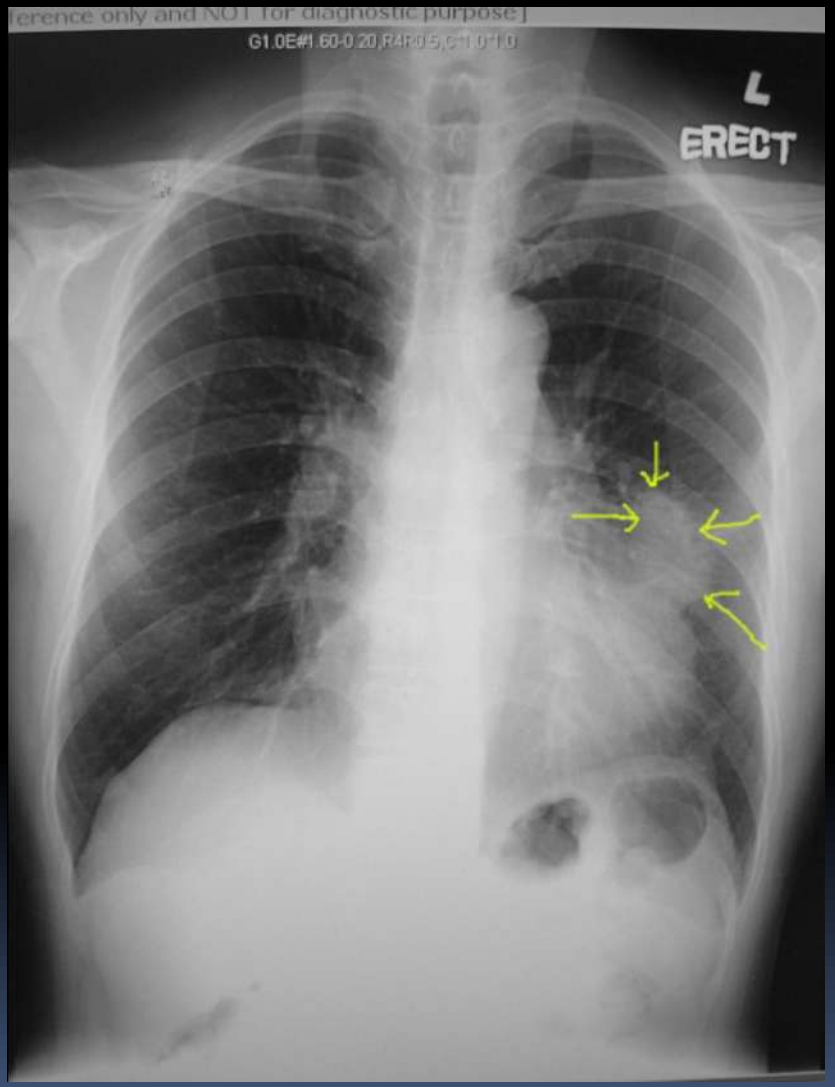
TKI



Case 1

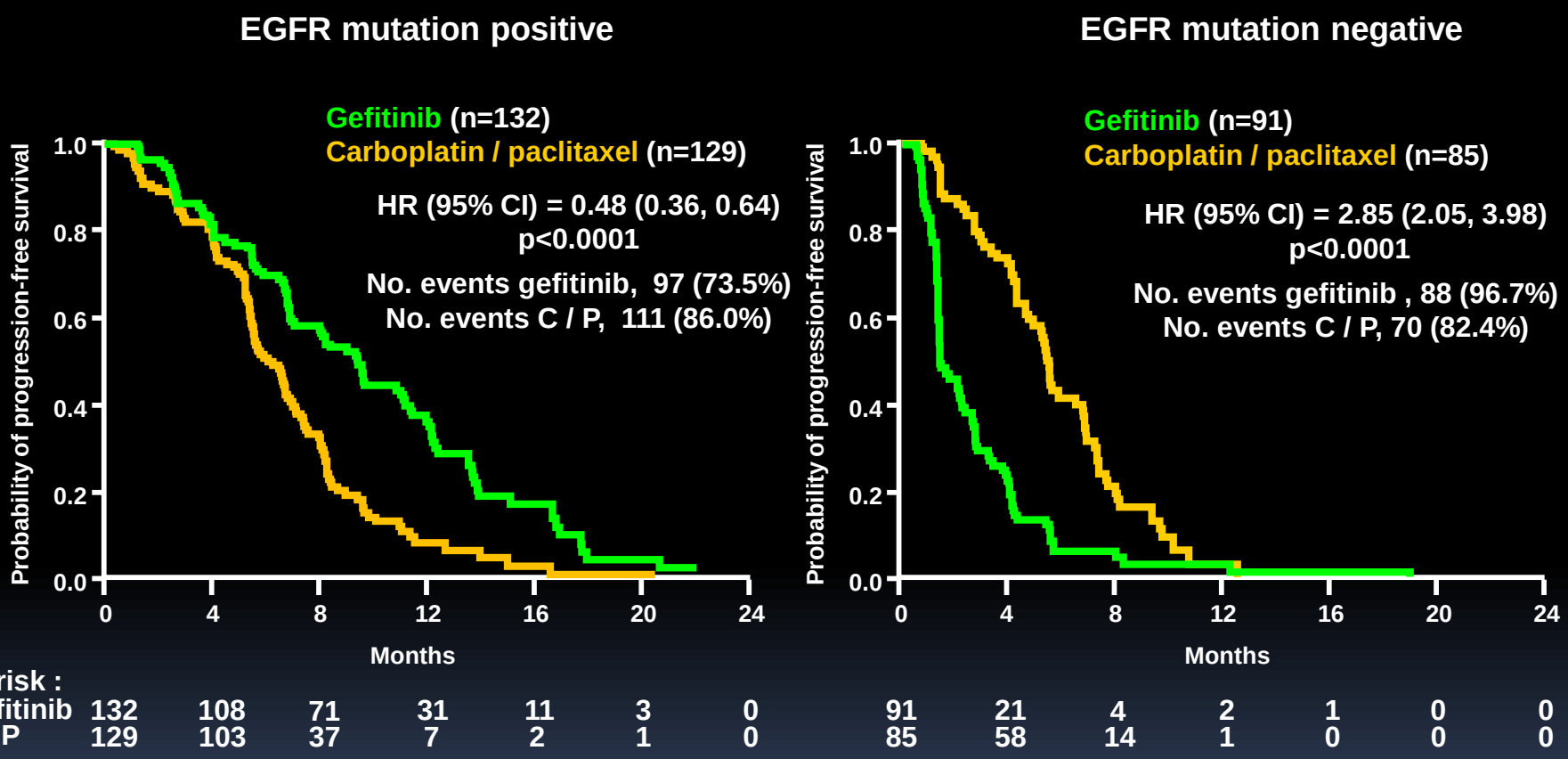


Before Gefitinib



After Gefitinib

Progression-free survival in EGFR mutation positive and negative patients

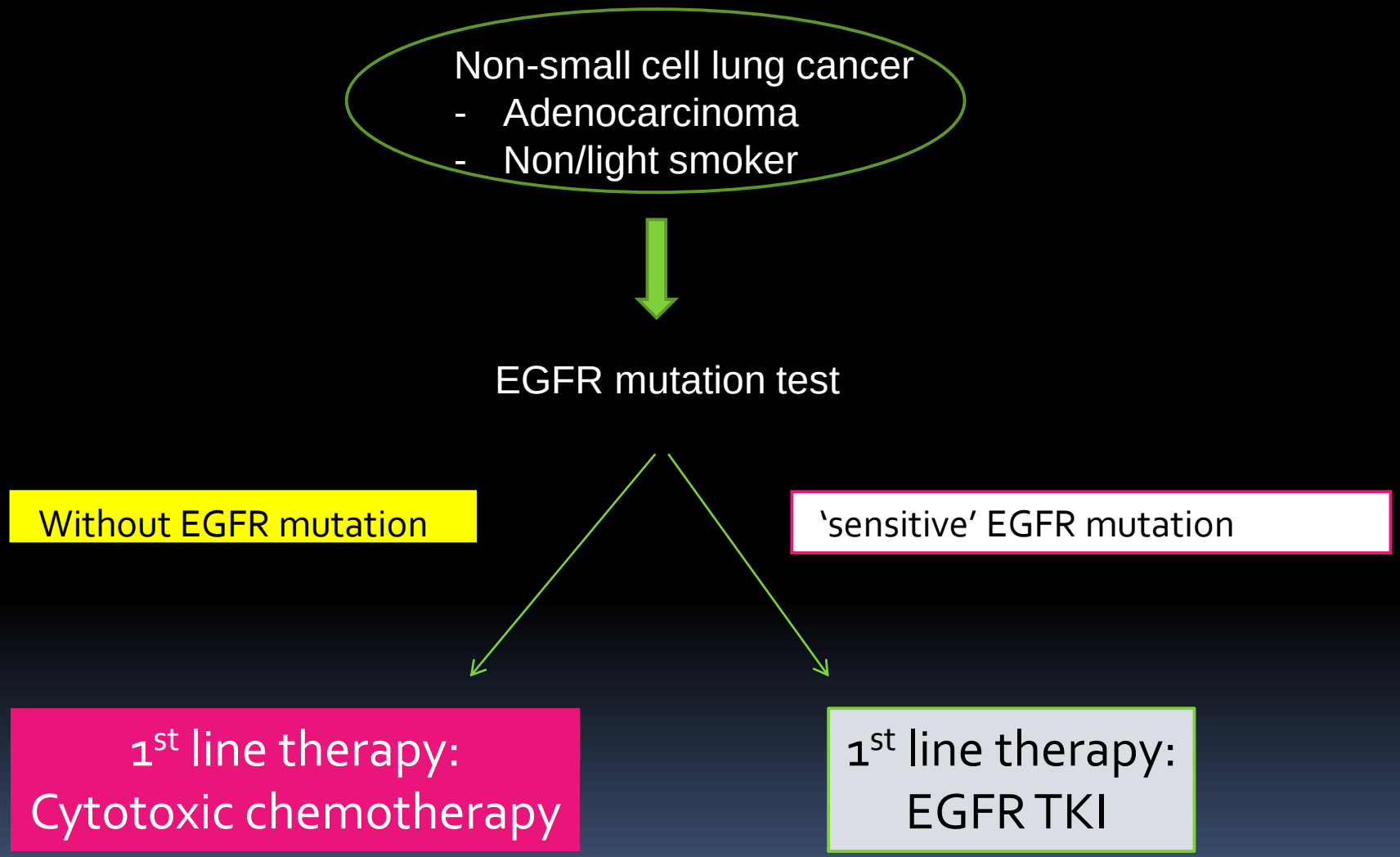


Treatment by subgroup interaction test, p<0.0001

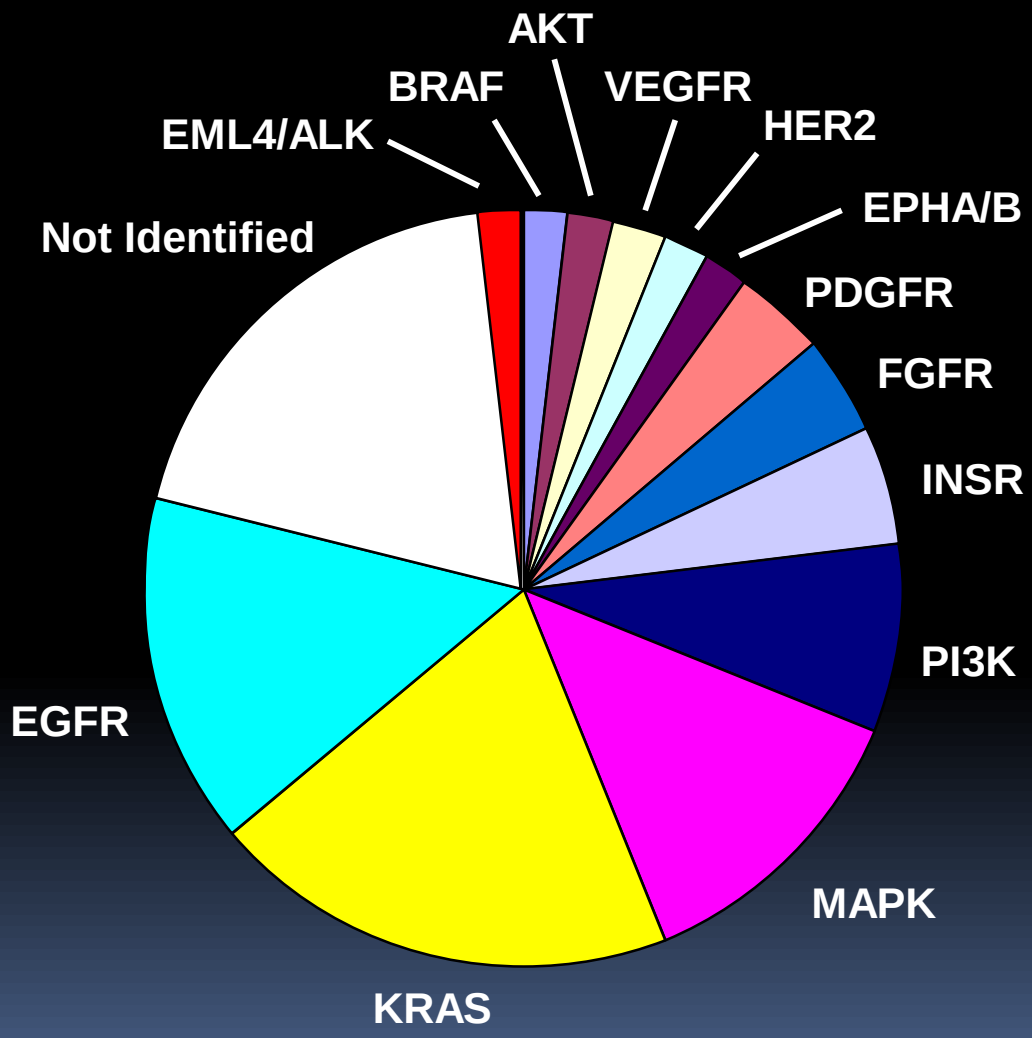
ITT population
Cox analysis with covariates

Mok et al NEJM 361:947 2009

Non-small cell lung cancer



Lung cancer driven by multiple somatic mutations
N=188 Tumors and 623 Genes in adenocarcinoma

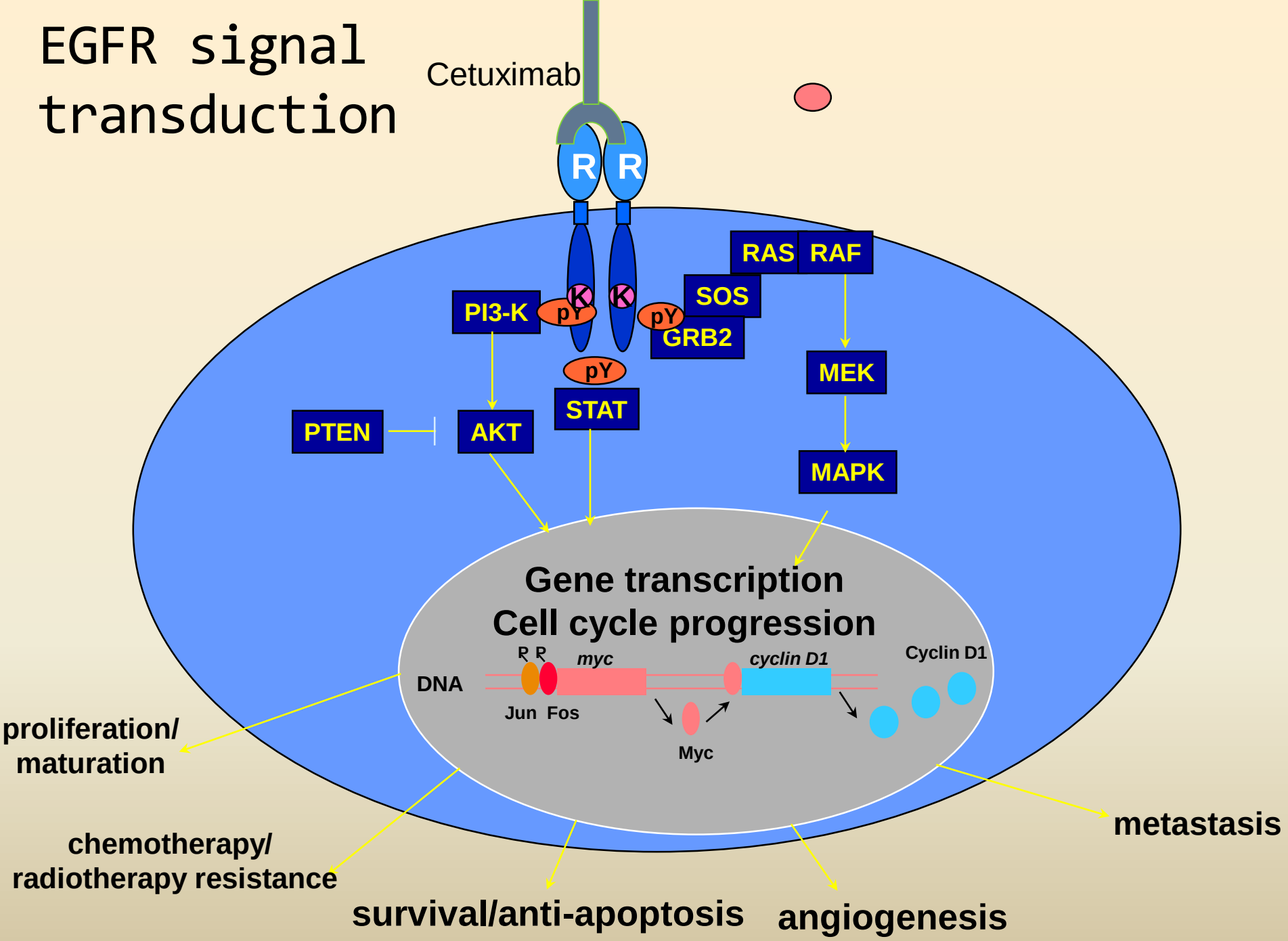


Modified from L Ding *et al. Nature* 455, 1069-1075 (2008)

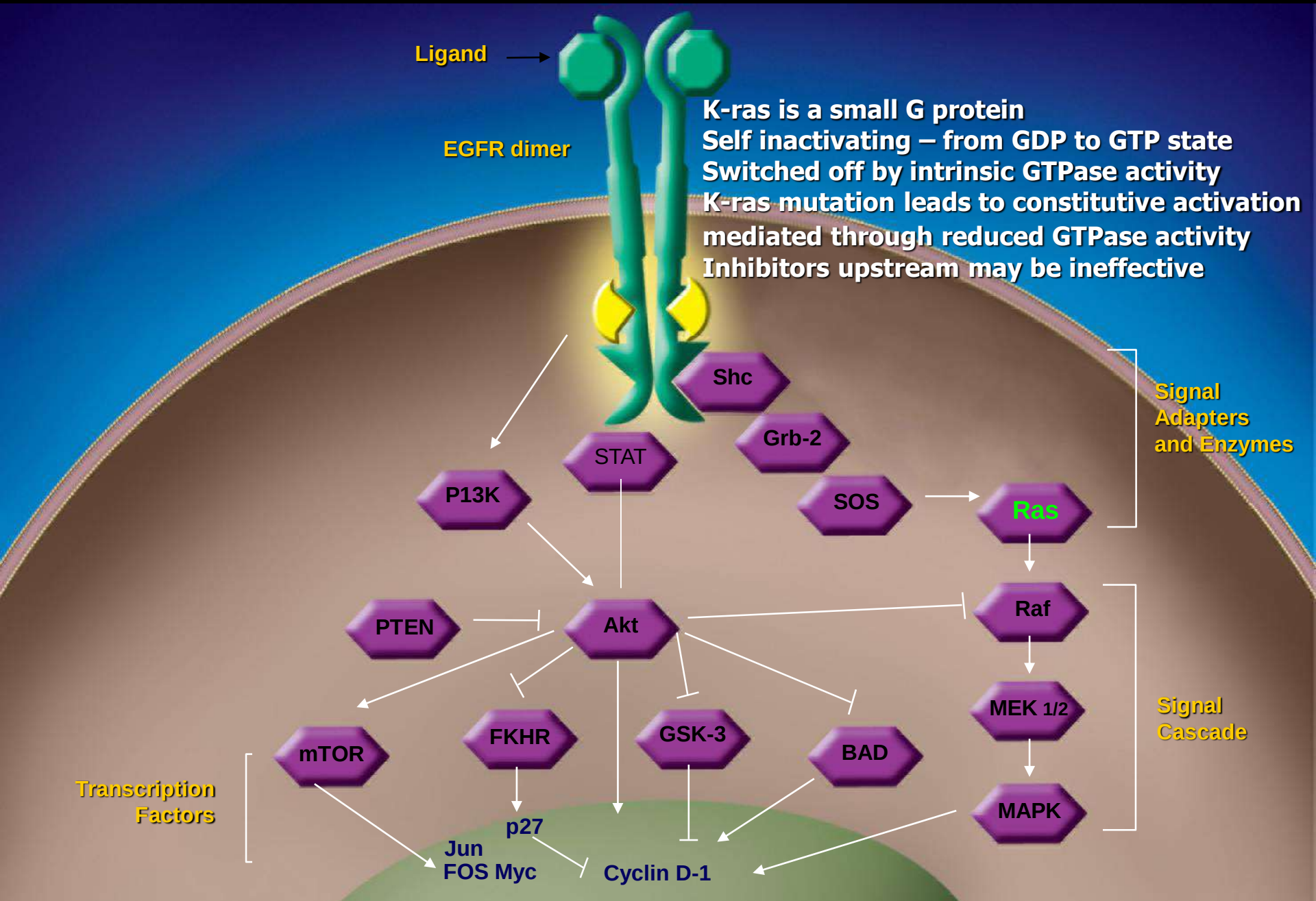
Concept 2: Resistant Mechanism

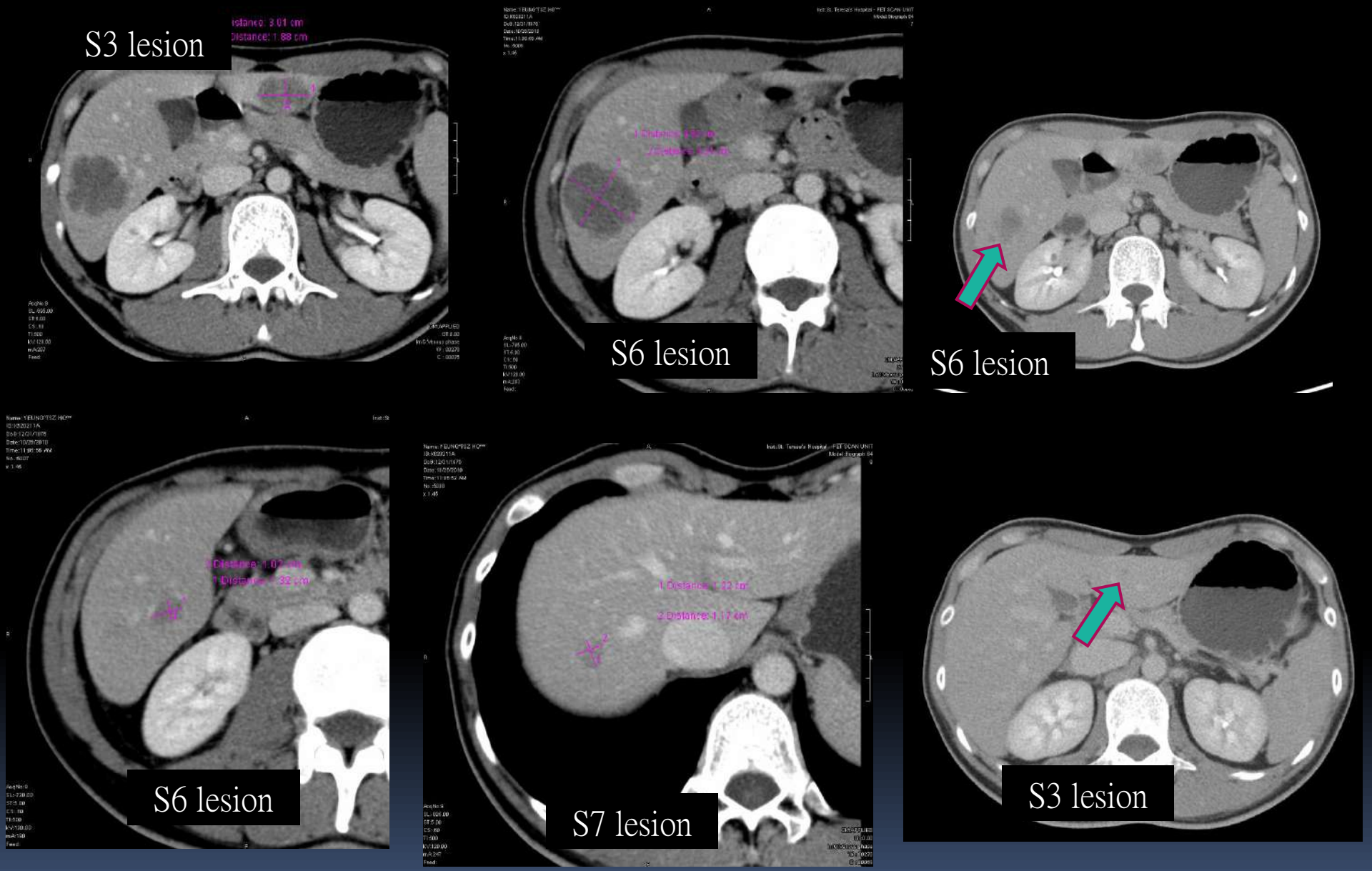
- Downstream activation of molecules can predict resistance to targeted treatment acting on upstream molecules

EGFR signal transduction



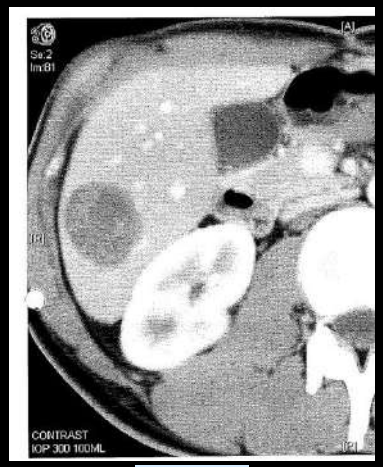
EGFR Signaling Cascade and *K-ras*





KRAS: wild type; no mutant; treatment with anti-EGFR monoclonal antibody and chemotherapy

Reassessment CT after Chemotherapy and targeted treatment



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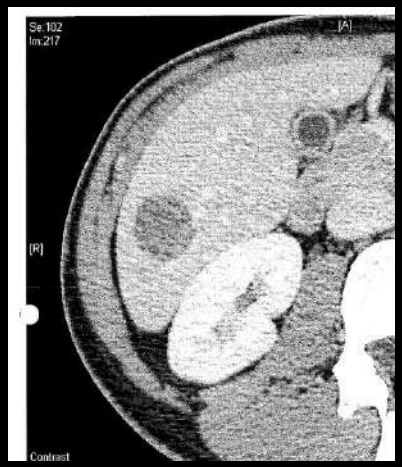

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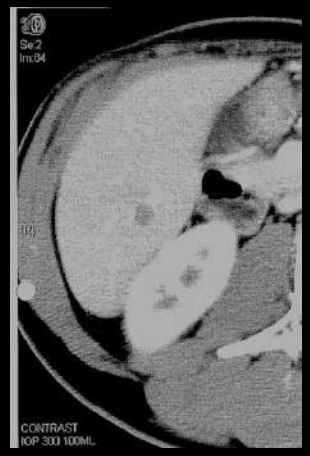

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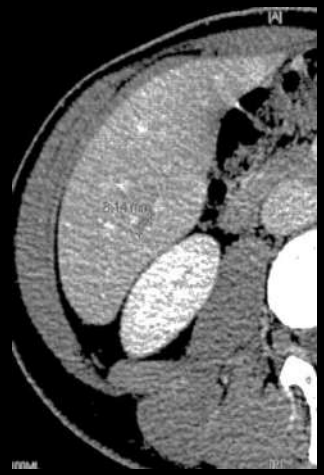

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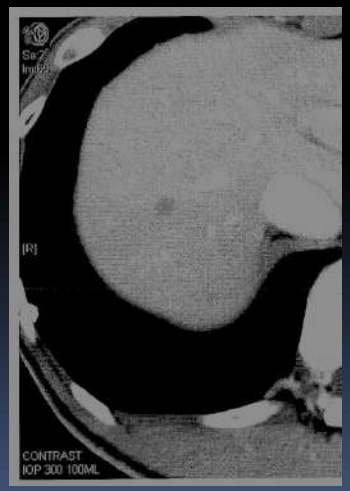

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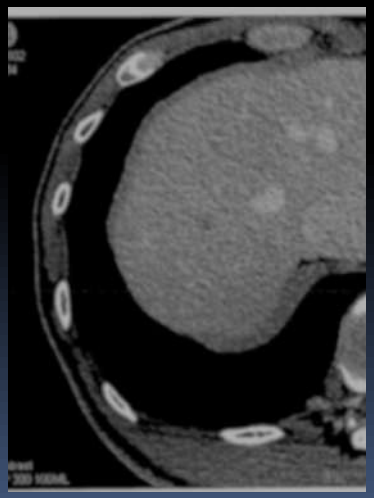

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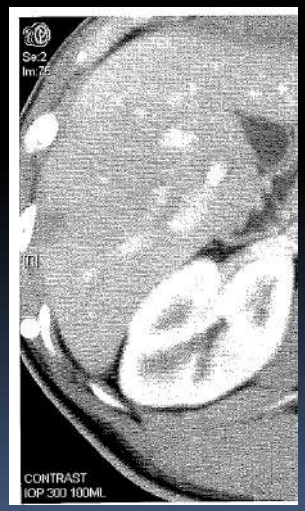

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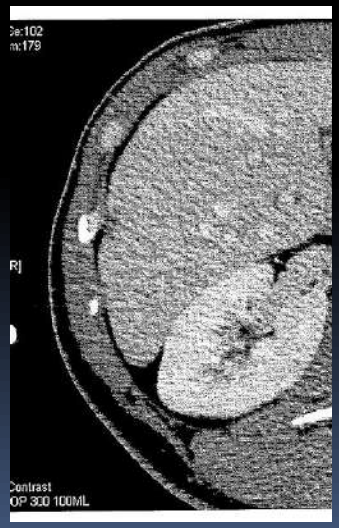
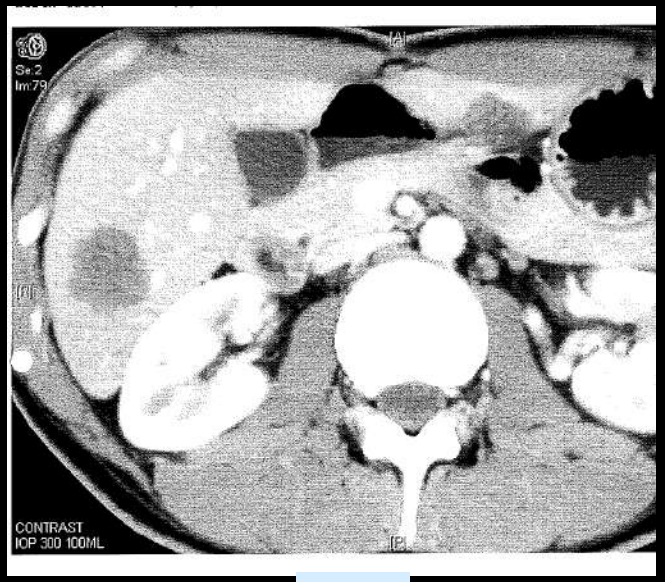


Post

Reassessment CT



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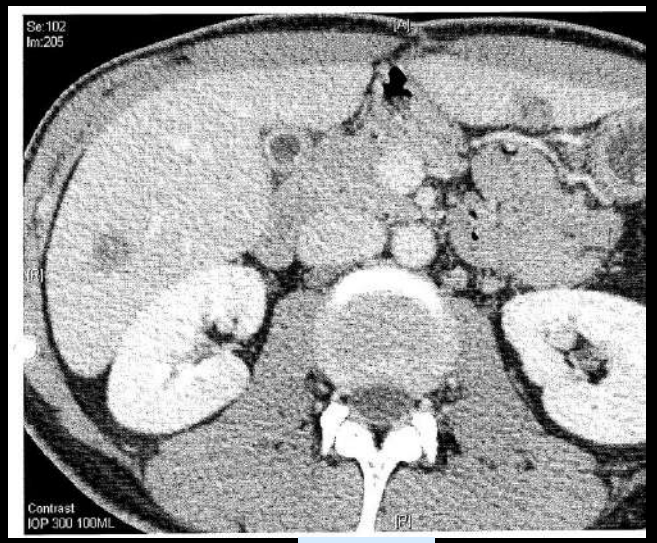
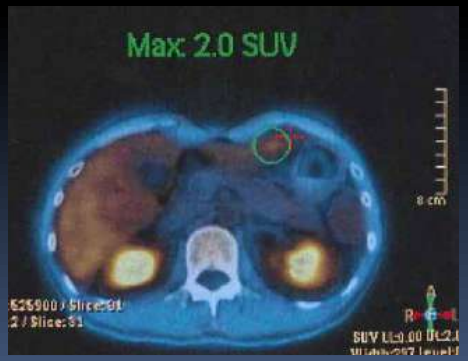
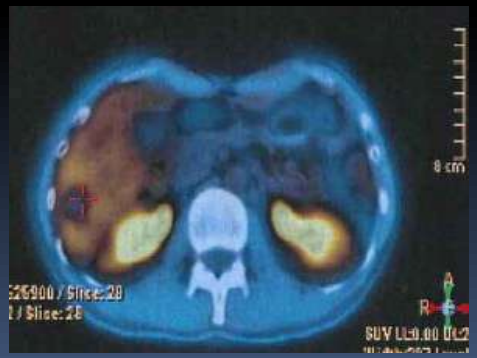
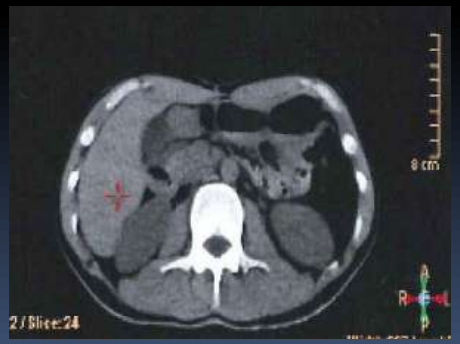


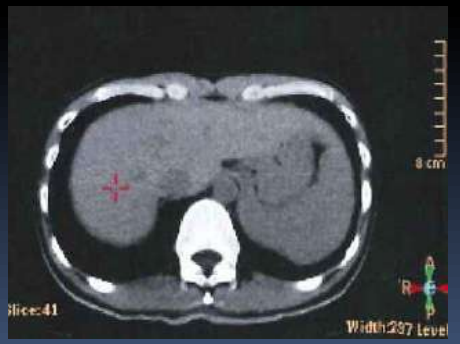
Post

PET CT showed only hypermetabolic lesion in S3









Progress

- Right hepatectomy and segment III wedge resection done (+ cholecystectomy)
- Patient remains disease-free for 5 years now

DIAGNOSIS
I. Liver, right lobe, excision:
- Metastatic adenocarcinoma x4, in keeping with colorectal primary.
- Maximal dimension of 0.5 cm, 0.7 cm, 0.7 cm and 2.5 cm.
- Prominent necrosis with foreign body reaction, in keeping with chemotherapy effect.
- Resection margin clear.

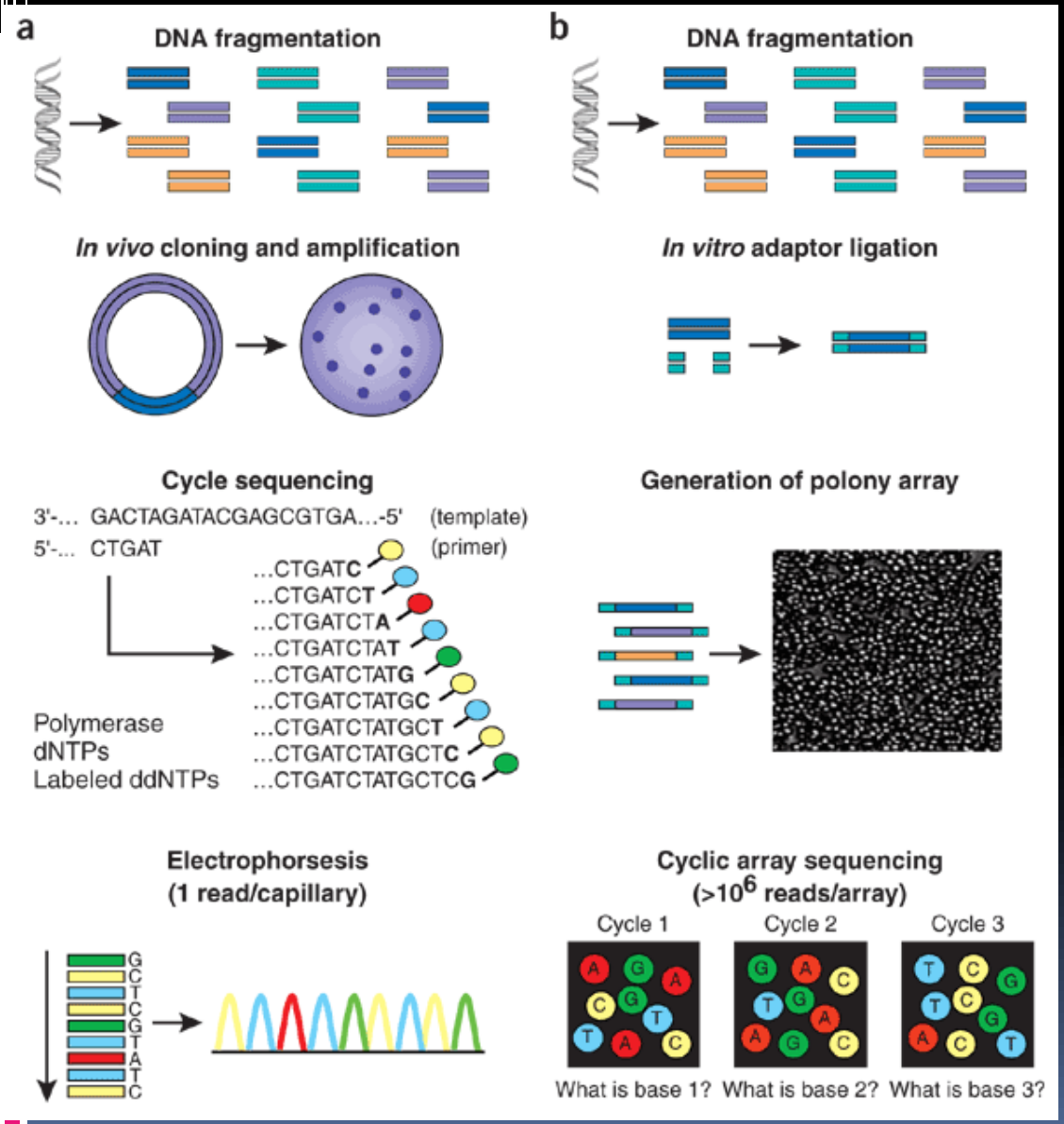
II. Liver, segment 3 lesion, excision:
- Metastatic adenocarcinoma, in keeping with colorectal primary.
- Maximal dimension of 1.5 cm.
- Prominent necrosis with foreign body reaction, in keeping with chemotherapy effect.
- Resection margin clear.

FUTURE DIRECTION OF PERSONALIZED TREATMENT FOR CANCER

Research Gap

- Most of the time, more than one gene are involved
- Not all cancer (e.g. liver cancer, pancreatic cancer, bone/soft tissue sarcoma) have identifiable ‘driver’ mutations.

Next Generation sequencing



Conventional sequencing

- Only large fragments of DNA 500-900bp are analyzed
- Preferred in the setting of known DNA mutations

NGS

- High-throughput
- Larger volume at faster speed
- Unknown mutations can be detected

Shendure J et al. Nature biotechnology 2008; 26: 1135-1145

Sequencing the tumor before treatment

Patient Results

3 genomic alterations	pp1-2
2 therapies associated with clinical benefit	pp3-4
2 therapies with lack of response	pp3-4
50+ clinical trials	pp5-6

Tumor Type: Colorectal Cancer

Genomic alterations identified
PTEN Loss
KRAS G12D
APC E941*, E1552

Additional disease-relevant genes with no reportable alterations detected
BRAF

Therapeutic Implications

Genomic Alterations Detected	FDA Approved Therapies (In patient's tumor type)	FDA Approved Therapies (In another tumor type)	Potential Clinical Trials
PTEN Loss	None	Temsirolimus Everolimus	Yes. See Clinical Trials section.
KRAS G12D	(-) Panitumumab‡ (-) Cetuximab‡	None	Yes. See Clinical Trials section.
APC E941*, E1552*	None	None	Yes. See Clinical Trials section.
BRAF No alteration detected			

‡ (-) Patient may be resistant to therapy

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type.

Electronically Signed by Jeffrey S. Ross | May 29, 2012 | CLIA Number: 22D2027531
Foundation Medicine, Inc., One Kendall Square Ste B3051, Cambridge MA | 617.481.2200

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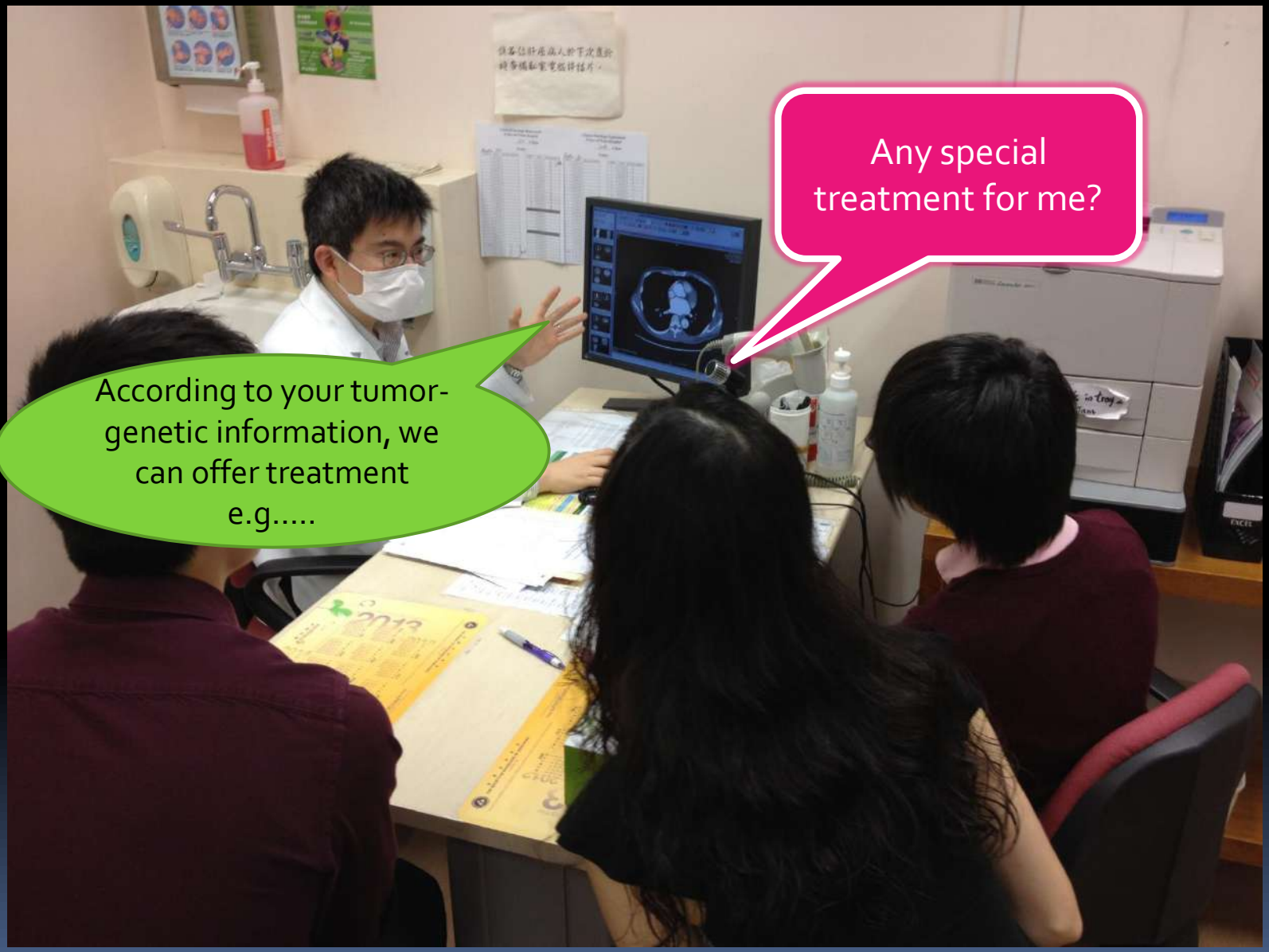
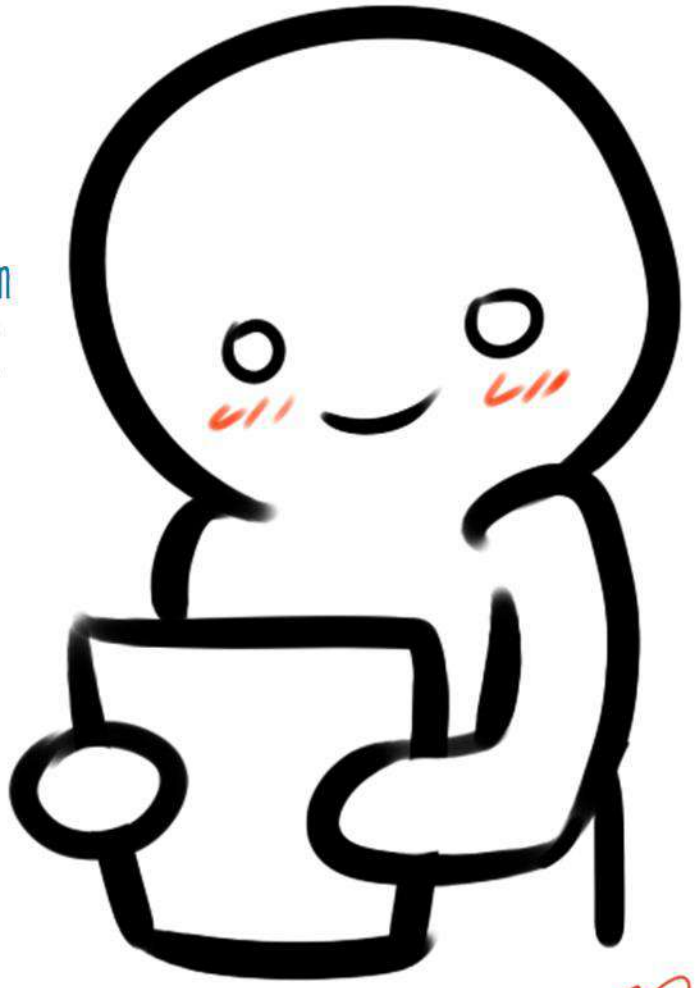
Challenges

- The same mutation may not have the same meaning in different cancer.
- A lot of mutations (genetic lesions) are not druggable.
- Mechanism other than genetic mutations
  - Epigenetic
  - Transcriptome changes

A lot of translational and clinical works to do!


Any special treatment for me?
According to your tumor-genetic information, we can offer treatment e.g.....

danke 謝謝 ngiyabonga teşekkür ederim спасибо dank je thank you gracias tapadh leat bedankt hvala mauruuru mochchakkeram dziękuję go raibh maith agat obrigado salun sukriya kop khun krap arigatō takk dakujem grazie мерси terima kasih 감사합니다 ευχαριστώ merci



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