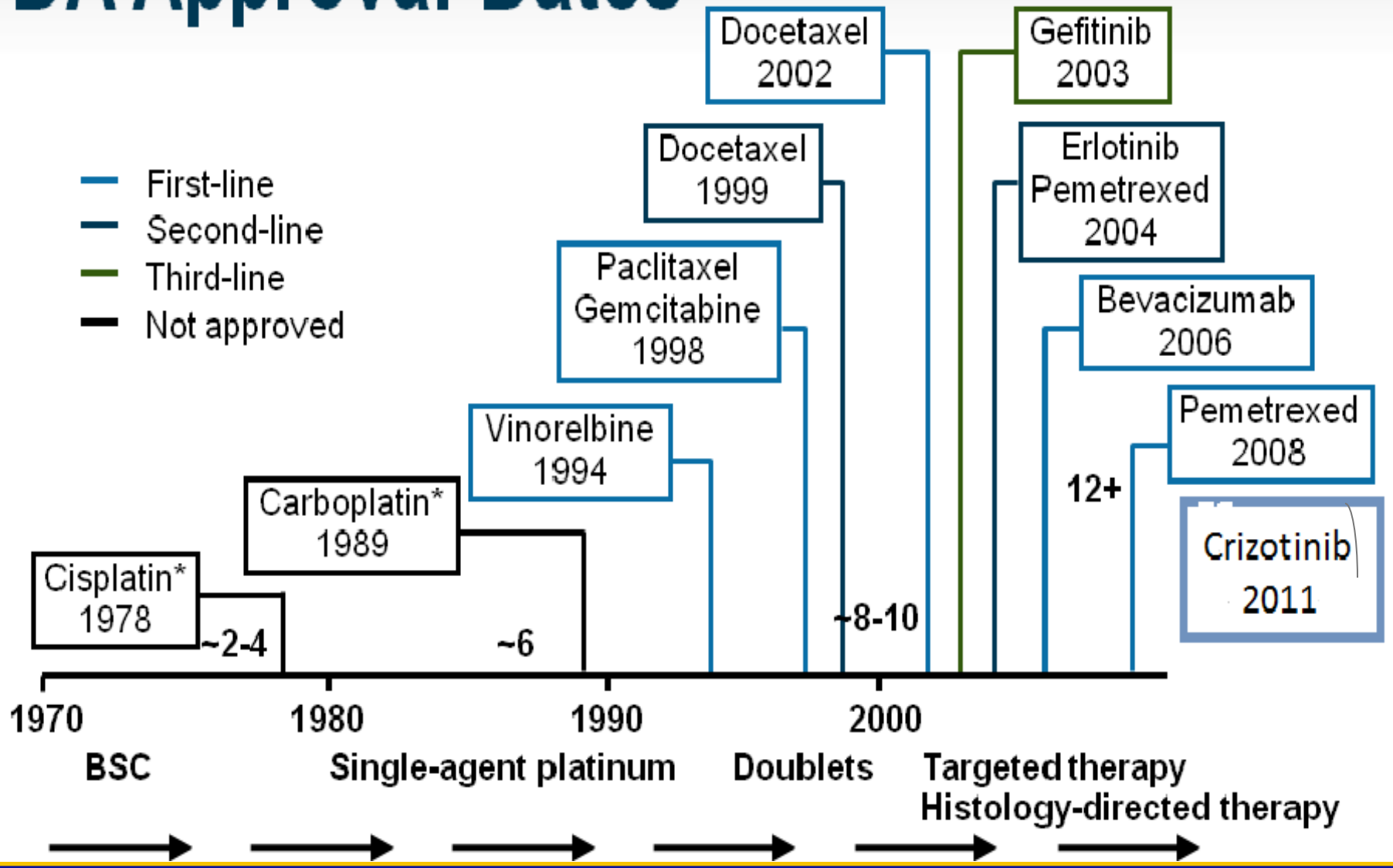
Optimizing Outcome In NSCLG EGFR Mutations

Nabeel Rajeh, MD

History of Therapy in Advanced NSCLC: FDA Approval Dates



Case Presentation

- 52 years old female
- 40 years history of smoking
- Productive cough and 10% weight loss
- Cxray unremarkable
- Basic hematology and oncology profile -ve
- Lung mass hilar lymphadenopathy
- CT scan and PET CCT scan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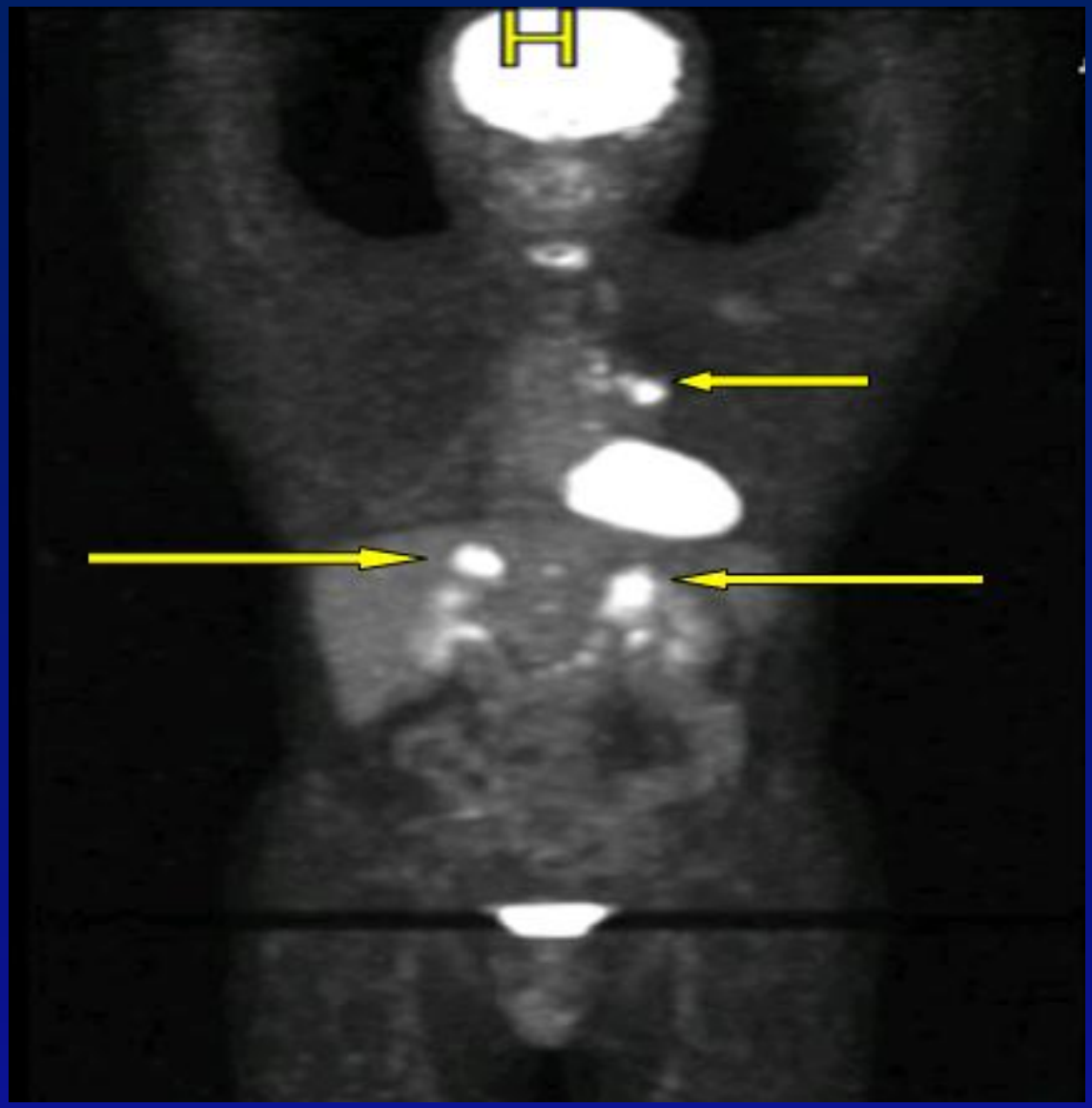
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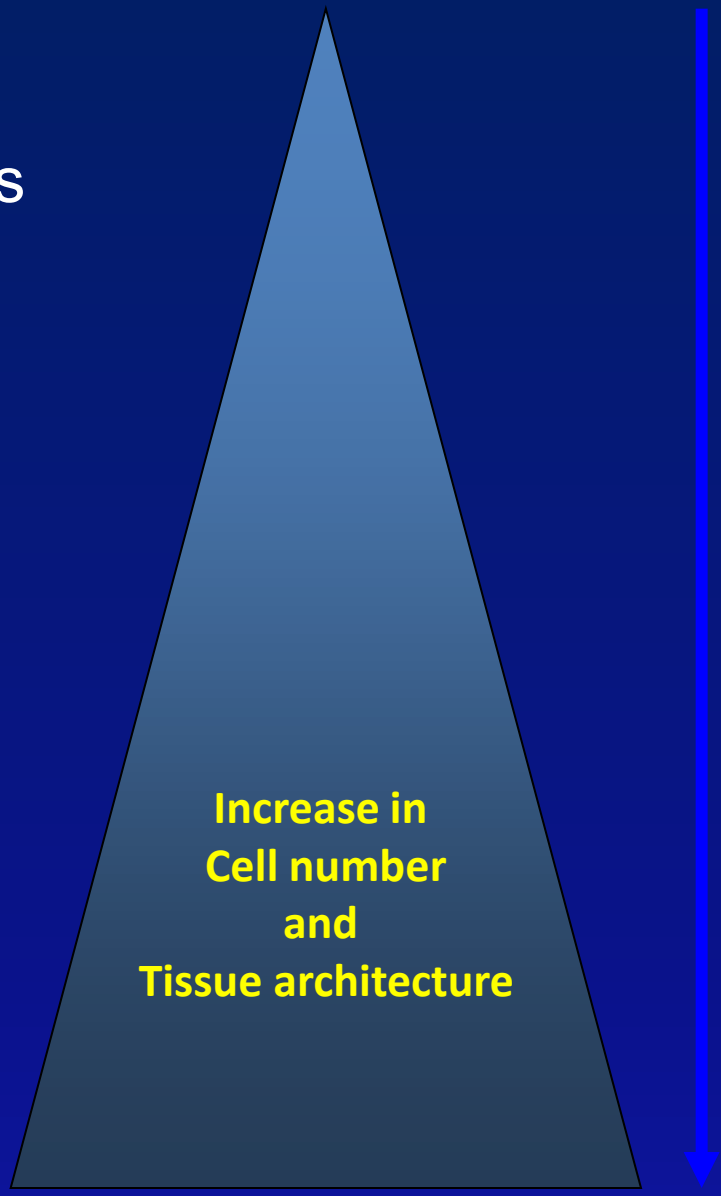
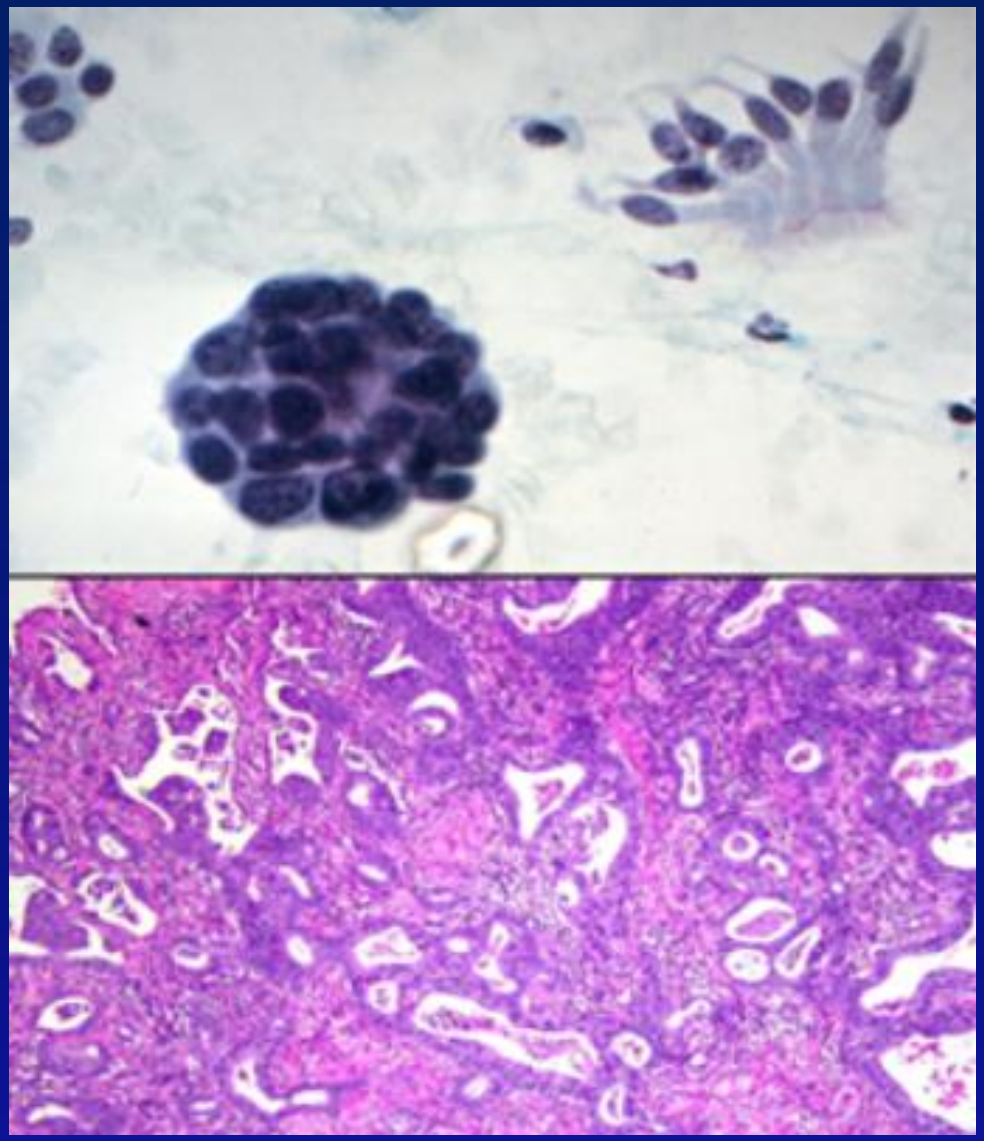
‘Biopsy’ techniques in lung cancer diagnosis

- Sputum cytology
- Bronchial brushings and washings
- Fluids
- FNA cytology – primary or mets
- **Transbronchial biopsy**
- **Bronchial biopsy**
- **Core biopsy – primary or mets**
- **Liver biopsy**
- **Mediastinoscopy**
- **Lymph node excision**
- **VATS biopsy / resection**
- **Thoracotomy tumour excision**

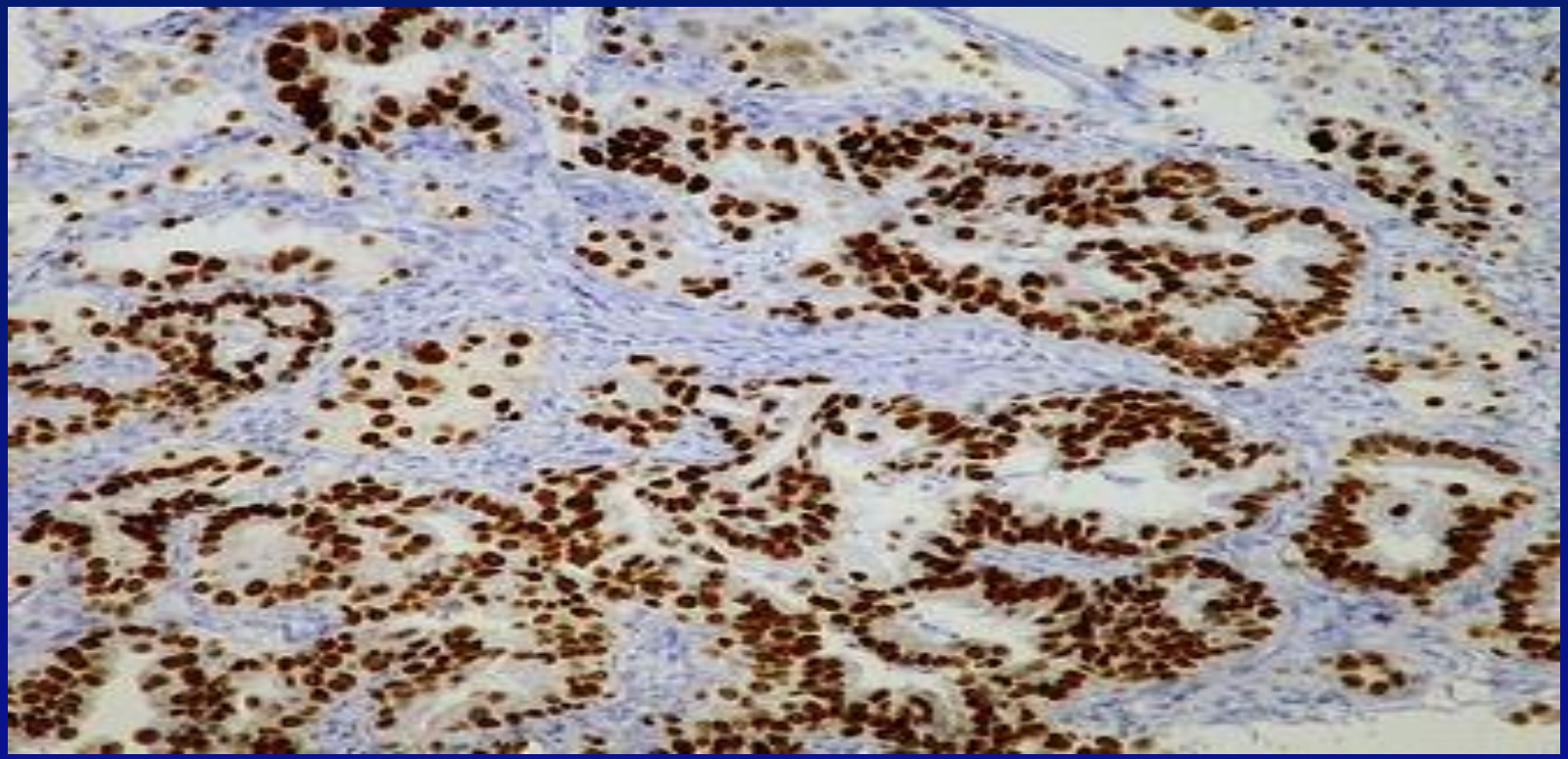




Pathology & Immunhistochimistry

- Cryopreserved rather than paraffin-embedded
- Detailed pathology not NSCLC
- BAC is discouraged
- Minimally invasive non-invasive adenocarcinoma
- TTF-1 for adenocarcinoma cells
- P53 for squamous cells
- CK 5, 6 , Napsin A, chromogranin, others

TTF1 in adenocarcinoma



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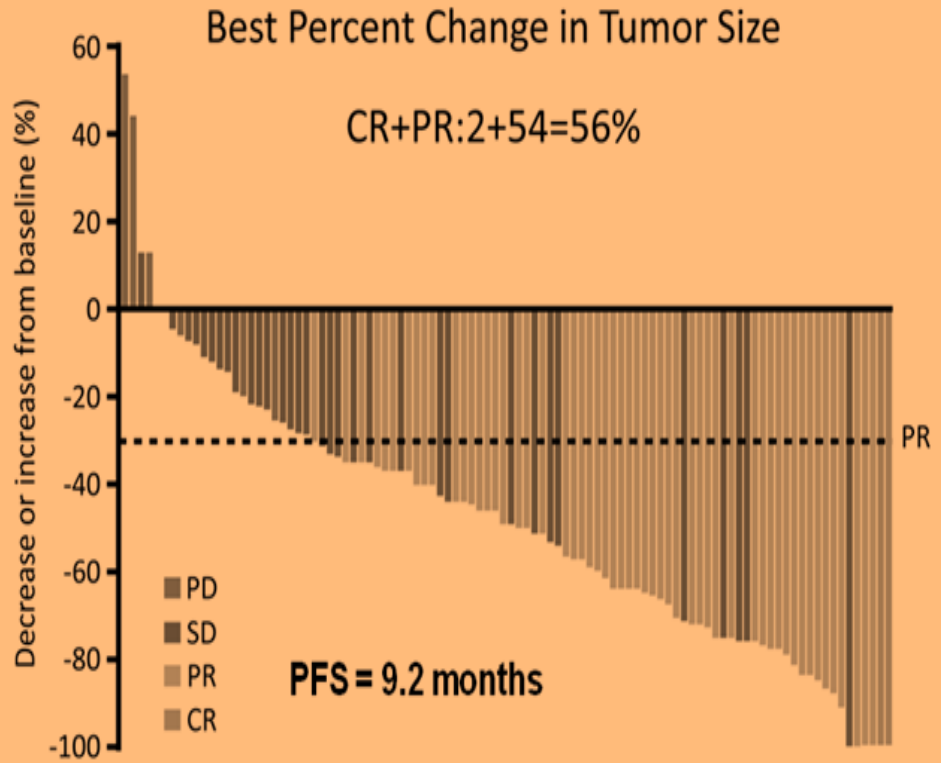
- Basic hematology and oncology profile -ve
- Lung mass hilar lymphadenopathy
- CT scan and PET CCT scan
- Adenocarcinoma is confirmed

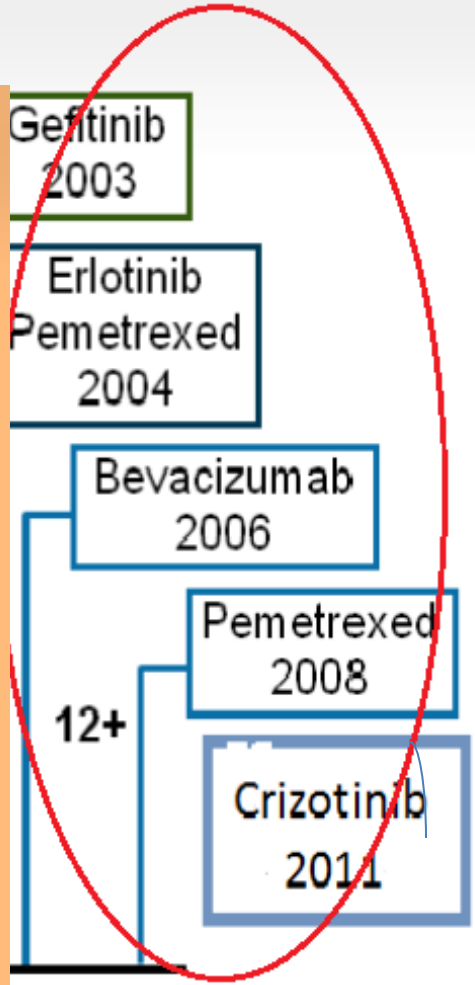
Molecular Profiling for this patient

- His tumor should undergo molecular testing for ALK, EGFR, KRAS, Her2 at time of diagnosis
- His tumor should undergo molecular testing for the above at time of progression
- EGFR is only required at diagnosis
- Molecular testing should not be done routinely

History of Therapy in Advanced NSCLC: FDA Approval Dates

Crizotinib in NSCLC: Clinical Response



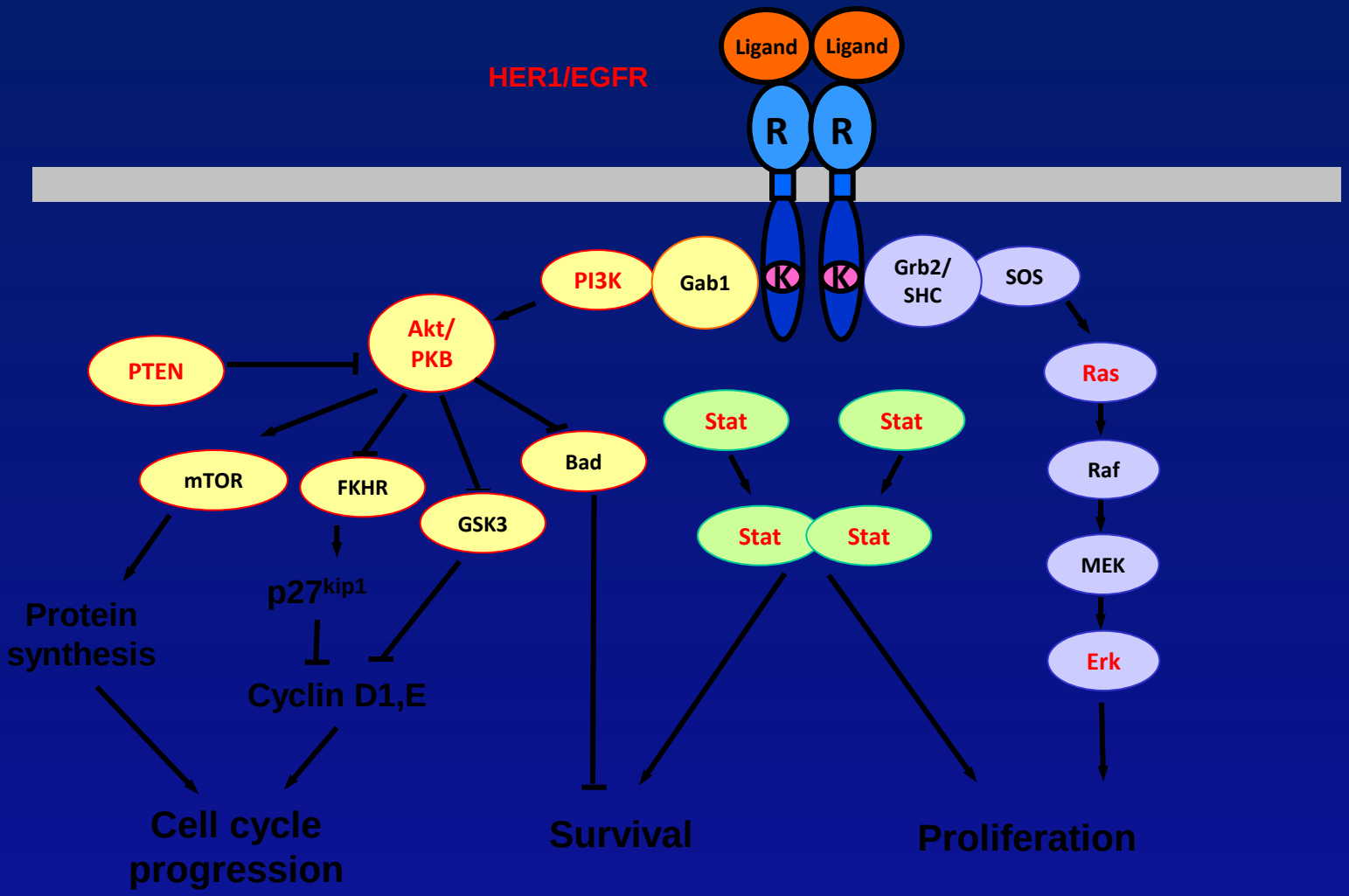


ed therapy
Histology-directed therapy

EGFR Rationale

- EGF had been identified in 1963, and its receptor
- EGF-R is then purified.
- Autocrine hypothesis: TGF-α produced by tumor cells can auto-stimulate activation of the cell's EGF Receptors.
- EGF-R are overexpressed in a variety of human tumor cells which correlated with prognosis
- EGF-R subsequently is identified as a cellular oncogene, with homology to the viral oncogene, erbB
- Gene transfer and transgenic experiments subsequently prove that overexpression of activated EGFR can be a transforming event

The EGFR target pathways



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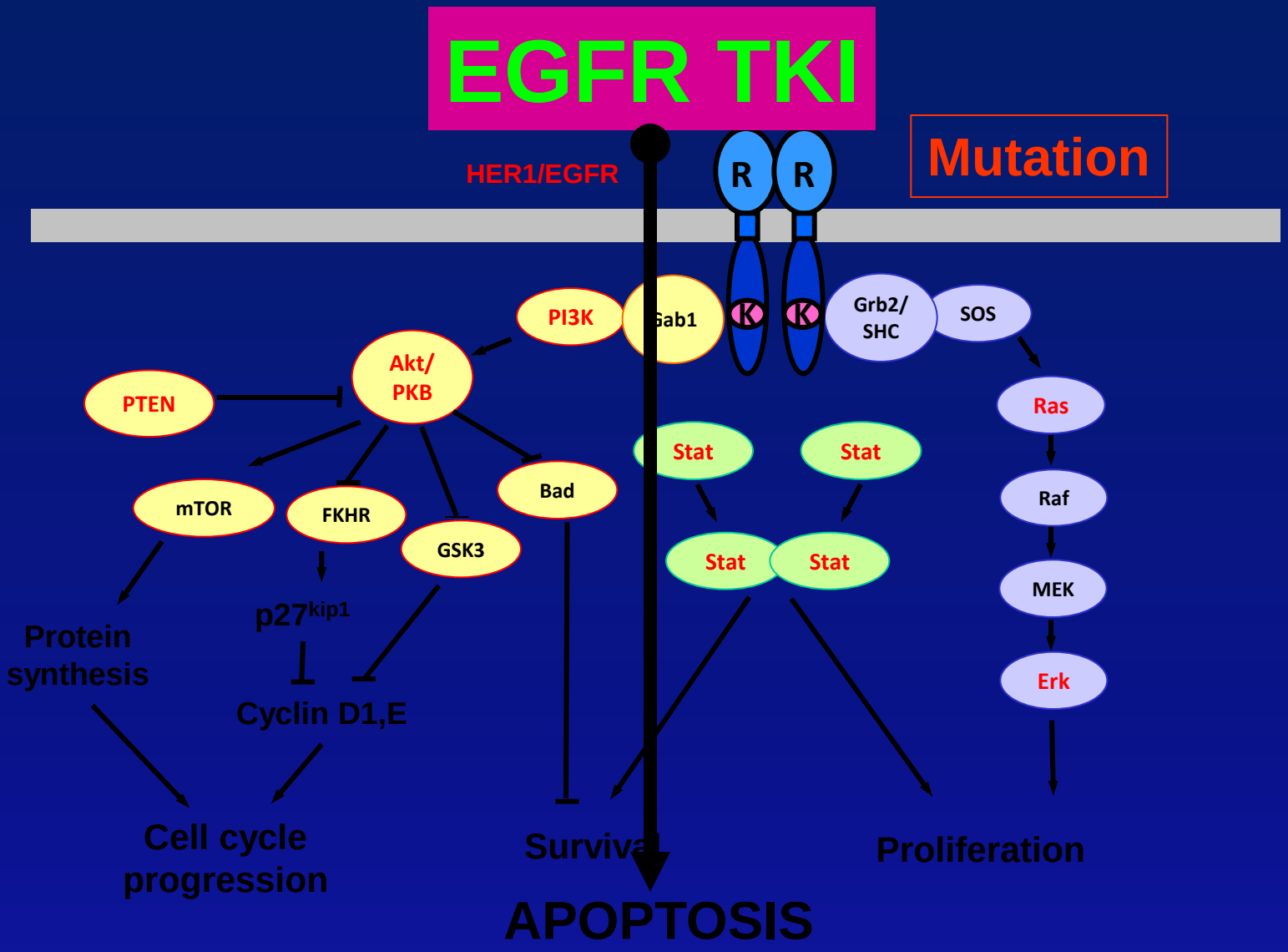


Hypothesis of EGFR targeted therapy

- Monoclonal antibodies which bind to EGF receptors and block access to EGF or TGF-α may prevent cell proliferation
- EGFR tyrosine kinase inhibitors may Inhibit signal transduction pathways that depend on activation of the Tyrosine kinase

Selective Therapy in NSCLC: Targeted therapy

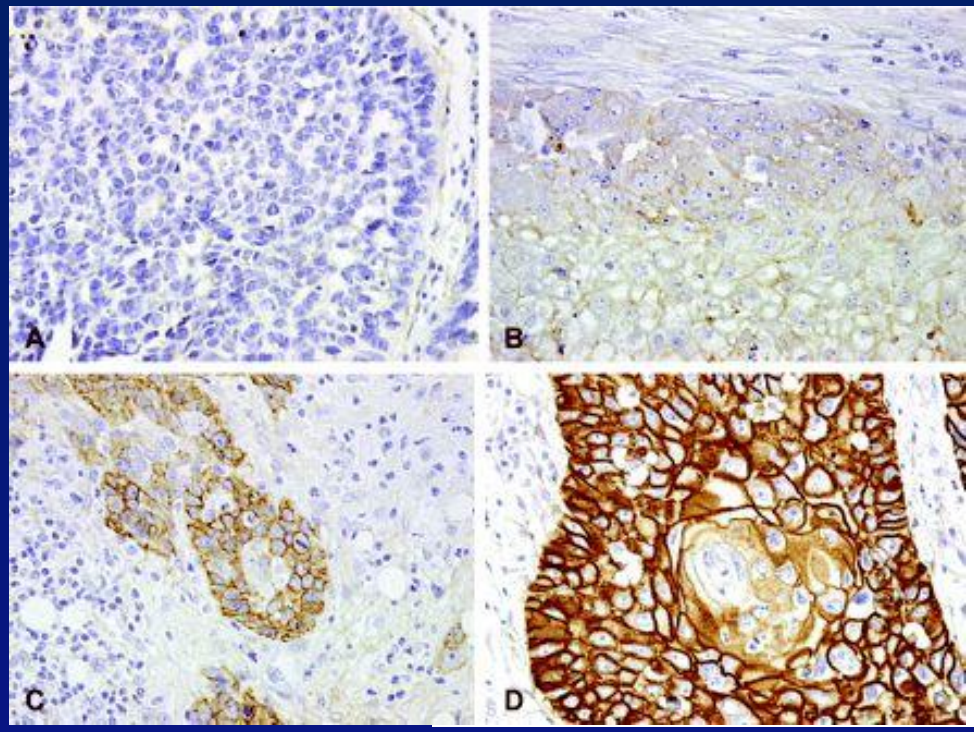
Specific molecules

- EGFR
  - gefitinib,
  - erlotinib,
  - cetuximab etc
- VEGF
  - bevacizumab
- IGFR1
  - MAb CP 751,871

Molecular Pathways driving Malignant Progression

Cell cycle progression
Cell proliferation
Anti-apoptosis
Cell survival
Angiogenesis

Standardized EGFR IHC test ?



- EGFR pharmDx™ is an IHC test that was originally developed to fulfill the need to establish eligibility for Erbitux™ (cetuximab) clinical trials
- The need for a standard, reproducible test method was crucial
- A complete set of reagents, control cell lines, and scoring guidelines to ensure reproducible IHC results

EGFR pharmDx™

Standardised staining conditions?
Standardised scoring systems ?
Is there tissue available for testing ?

Predictive of response but not OS in pivotal BR21 trial
(Shepherd et al, NEJM 2005; 353, 123-32, Tsao MS et al, NEJM 2005; 133-44)

Results

- *EGFR overexpression is frequent in bronchial adenocarcinomas but no association was found between immunohistochemistry scoring and response to TKI anti-EGFR*

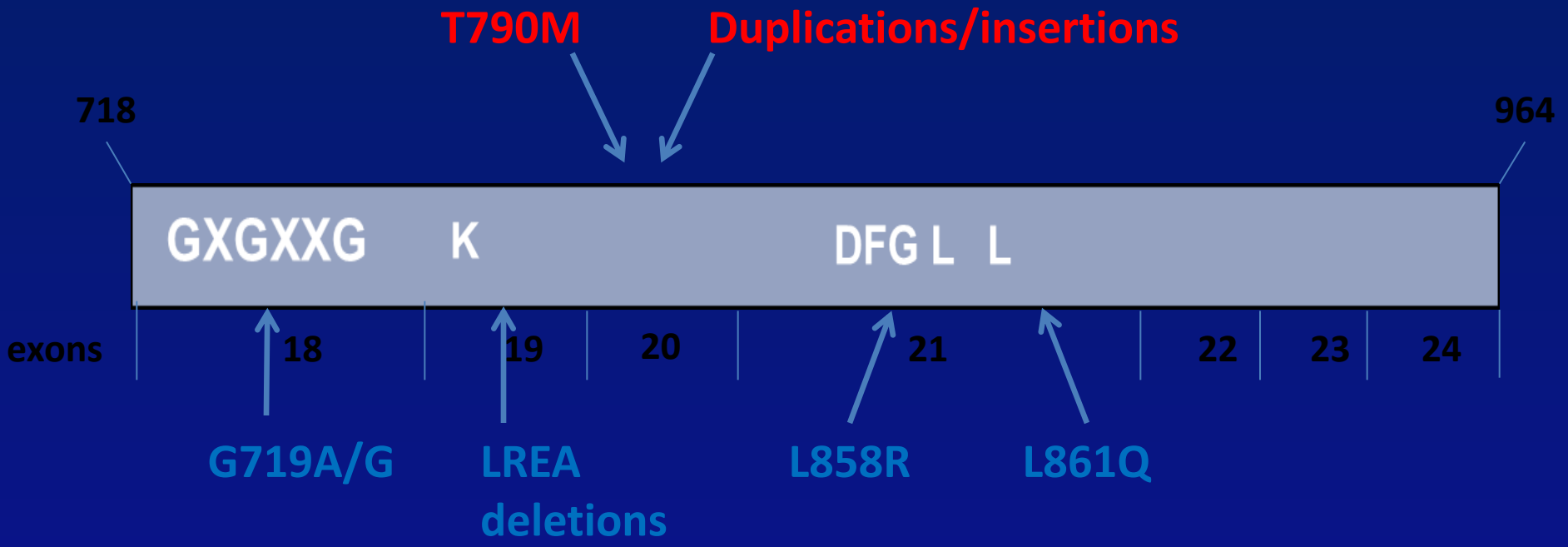
Is EGFR overexpression needed?

A Study by Saltz/ ASCO 2001 shows the correlation between IHC scoring and response rate:

- EGFR level — Response Rate
  - 1+ — 24%
  - 2+ — 21%
  - 3+ — 23%

Mutations in EGFR TKD

Mutations, associated with drug resistance



Mutations, associated with drug sensitivity

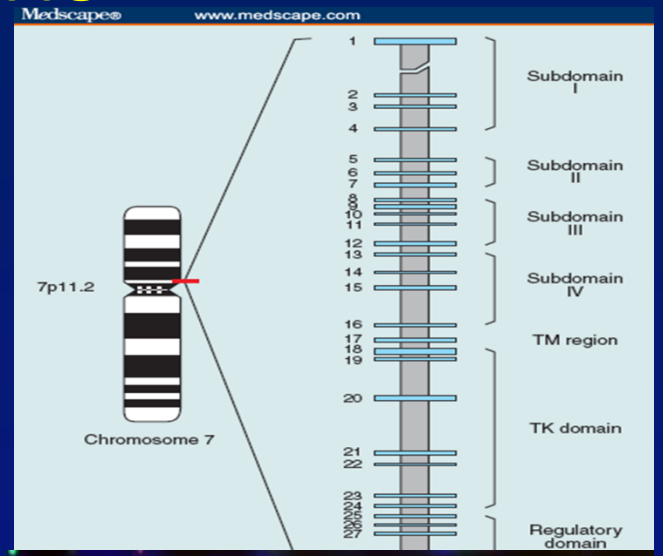
Adopted from Pao et al. AAAS-FDLI Colloquium on Personalized Medicine, October 27, 2009

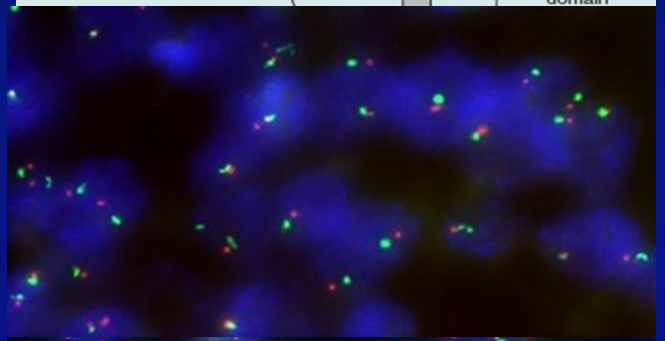
Prevalence of EGFR mutations

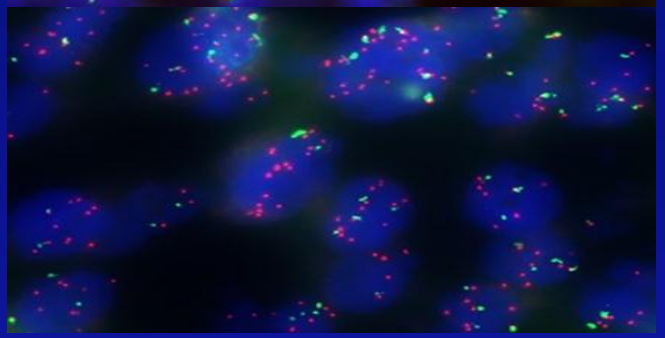
- EGFR mutations 10% of western
- EGFR mutations 50% of asian
- EML4-ALK1 translocation 5%
- HER2 mutations 1%-3%

EGFR mutations

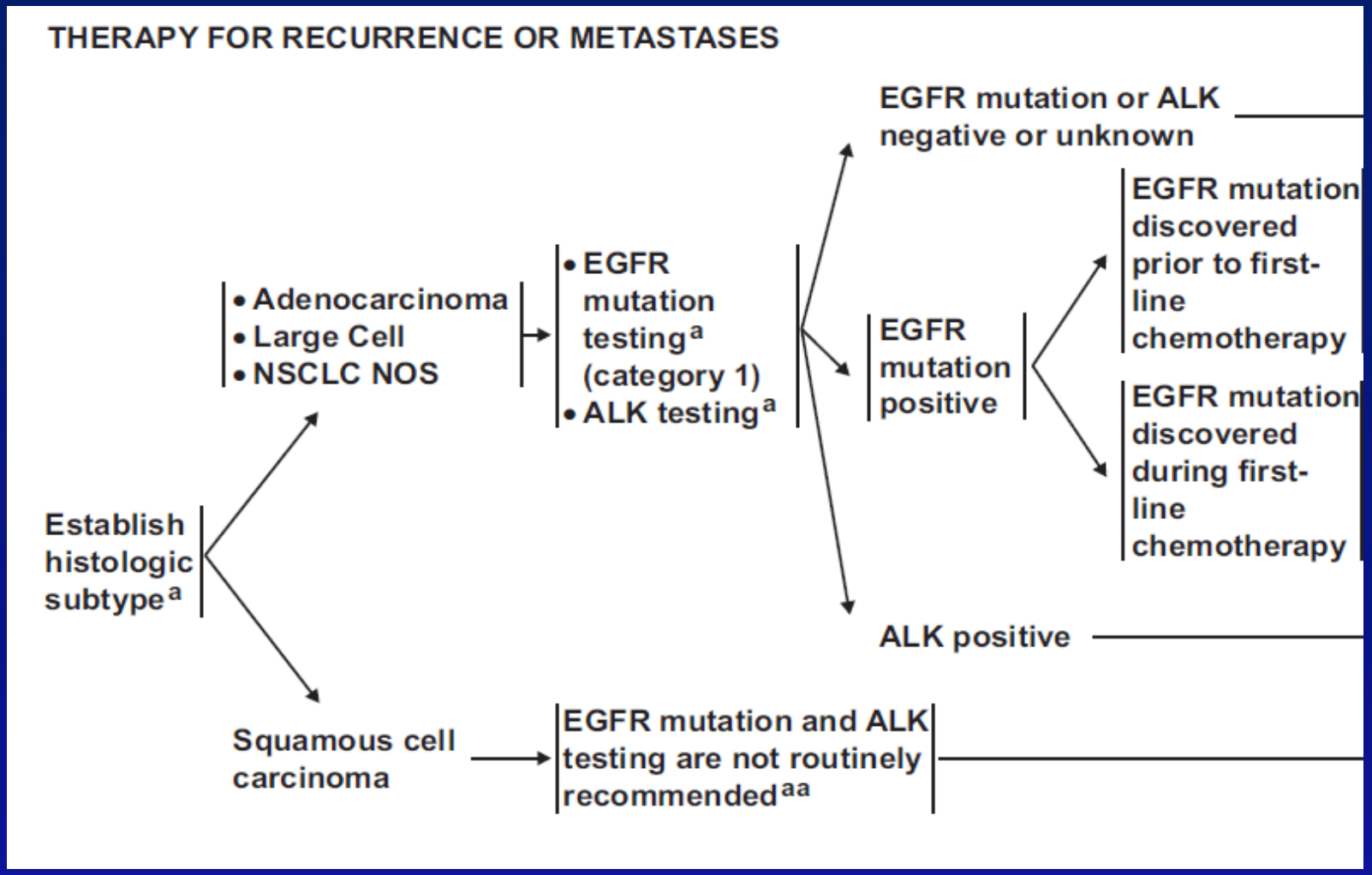
- EGFR is localised on chromosome 7p12
- This part of chromosome is usually increased in non small cell lung carcinoma
- The *presence of more than 2 copies for genes coding for EGFR is frequently associated with mutation*
- *Can be done by PCR, Pyro-sequencing, Snapshot, FISH*







NCCN 2012 Guidline



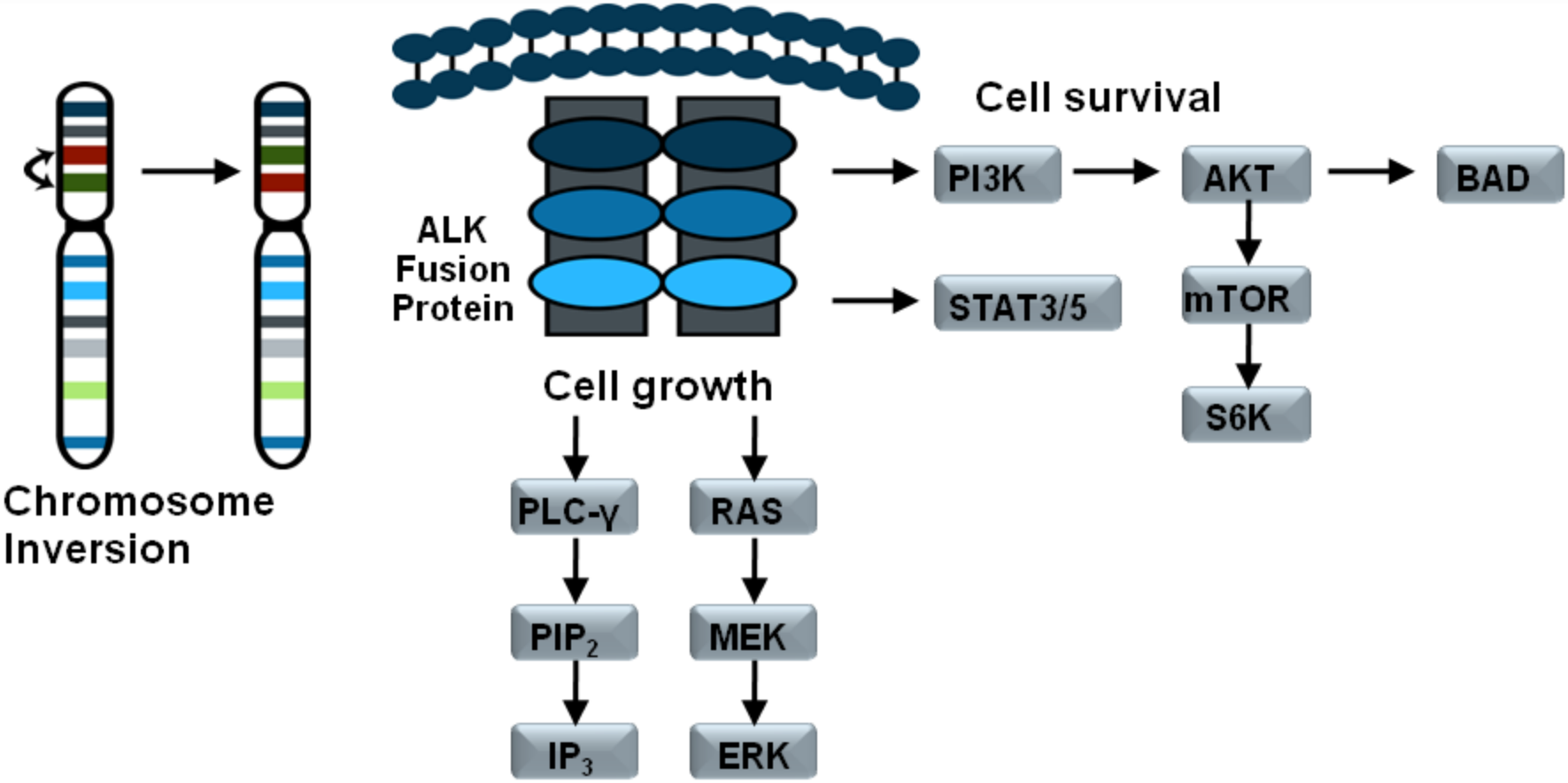
Detection of EGFR mutations

- The study of EGFR mutation should be obtained from ***tumor cells***
- Identification of alteration in exons 18, 19, 20 and 21 (short arm of chr 7).
- Study of mutation is performed after extraction of tumor DNA from either biopsies, sputum, bronchial washing or surgical specimens

Response to EGFR TKIs

- Patient characteristics
  - Ethnic origin: East asian
  - Gender: Female
  - Smoking status: Never smokers
- Tumour Histology
  - Adenocarcinoma
  - Bronchioloalveolar carcinoima (BAC)
  - Papillary carcinoma
- **Presence of "target"**
  - EGFR

ALK Fusion Oncogenes and Downstream Pathways



ERK = extracellular-signal regulated kinase; IP_3 = inositol triphosphate; MEK = MAP/ERK kinase; mTOR = mammalian target of rapamycin; PIP_2 = phosphoinositide (4,5) bisphosphate

Adapted from Shaw AT, et al. *Clin Cancer Res.* 2011;17:2081-2086.

Crizotinib in NSCLC: Study Design

Eligibility:

- Advanced NSCLC
- Refractory to standard therapy
- ALK rearrangement

N = 82

Crizotinib
50 mg daily
300 mg twice a day
Dose-escalation study
Final regimen: 250 mg twice a day

Other requirements:

- Adequate bone marrow and organ function
- Resolution of previous treatment-related toxic effects
- PS = 0-2

Kwak EL, et al. *N Engl J Med.* 2010;363;1693-1703.

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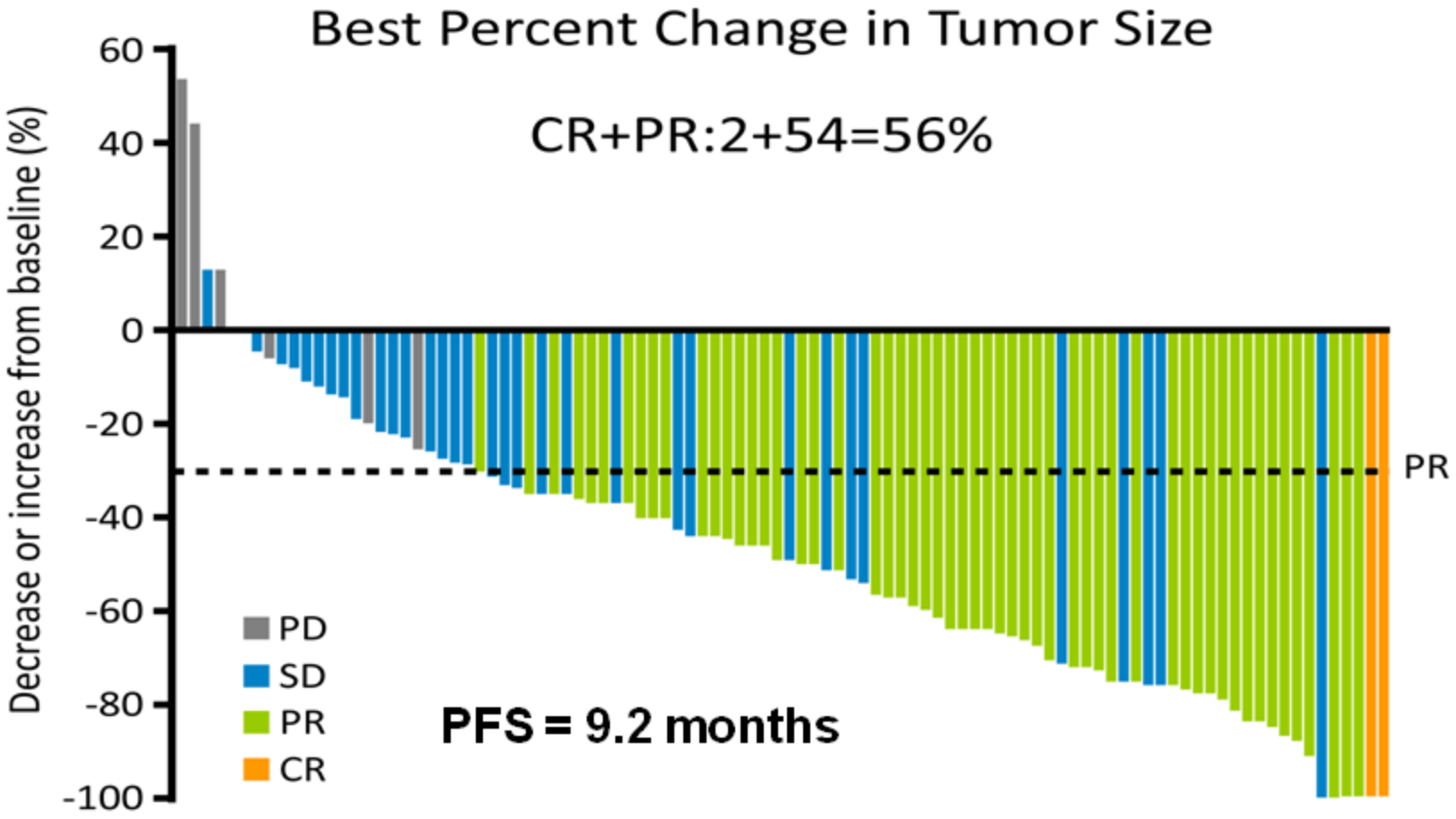

Camidge DR, et al. ESMO 2010. Abstract 366PD.

Case Presentation

- 52 years old female, smoker,
- Metastatic adenocarcinoma of the lung
- Declined EGFR mutation testing
- Carboplatin Docitaxel chemotherapy 4 cycles
- CT scan showed progressive disease
- EGFR testing is mandatory
- KRAS mutaations is needed
- Alk rearrangement testing is an option

Conclusion

- Improved technology in diagnostic imaging.
- Improved technology in diagnostic molecular pathology.
- New chemotherapy drugs
- Improvements in radiation treatment planning and delivery
- New target treatment for certain patient is the standard of care first line therapy
- *A good oncologist is the one who give the right drugs to the right patient at the right time when he has the right radiologist and the right pulmonologist and the correct pathologist*

THANK YOU
FOR YOUR ATTENTION

Nabeel Rajeh, MD