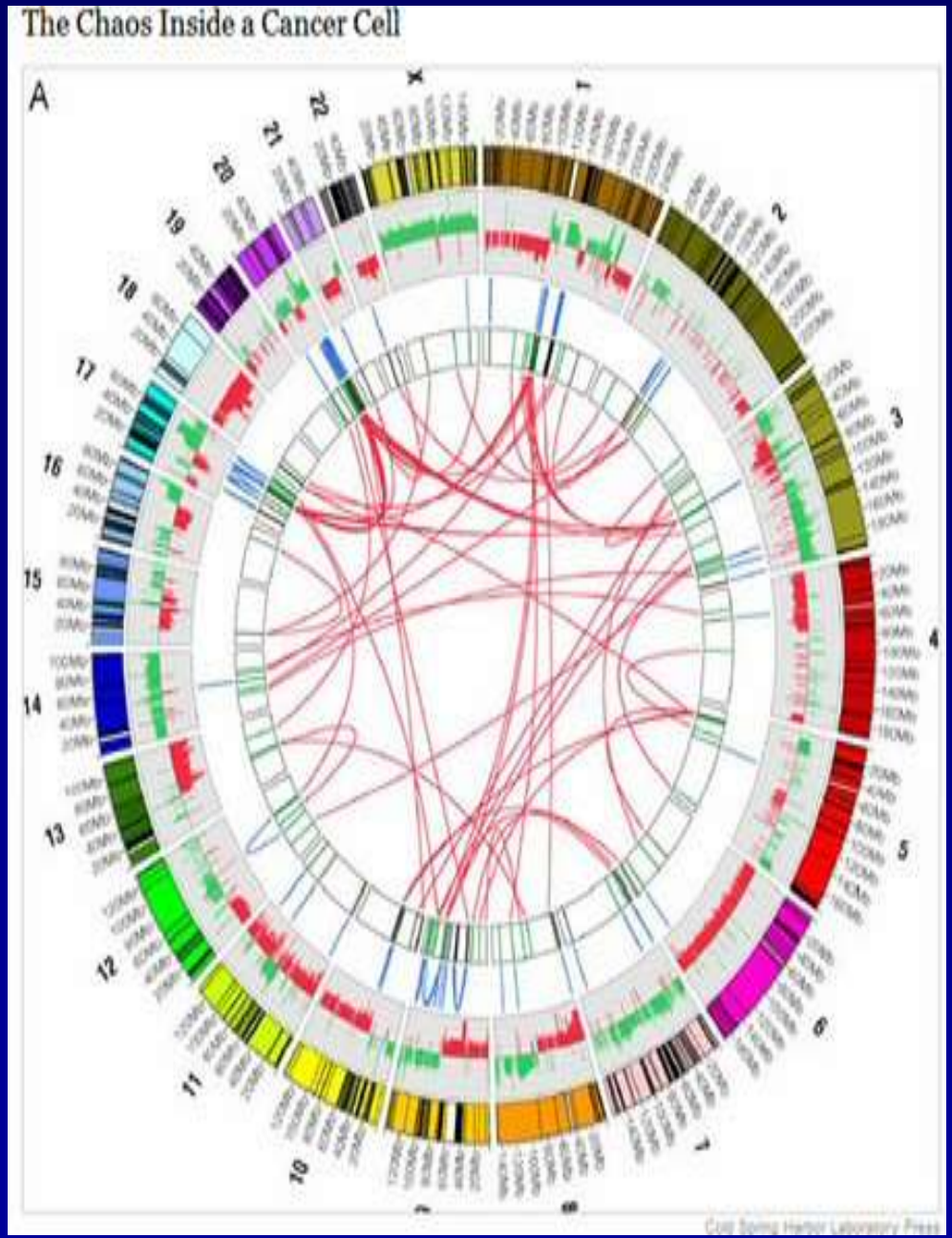


21^{0} Πανελλήνιο Πνευμονολογικό Συνέδριο
18-21 Οκτωβρίου 2012

"Ο ρόλος του μονοπατιού EGFR στη θεραπεία του ΜΜΚΠ"

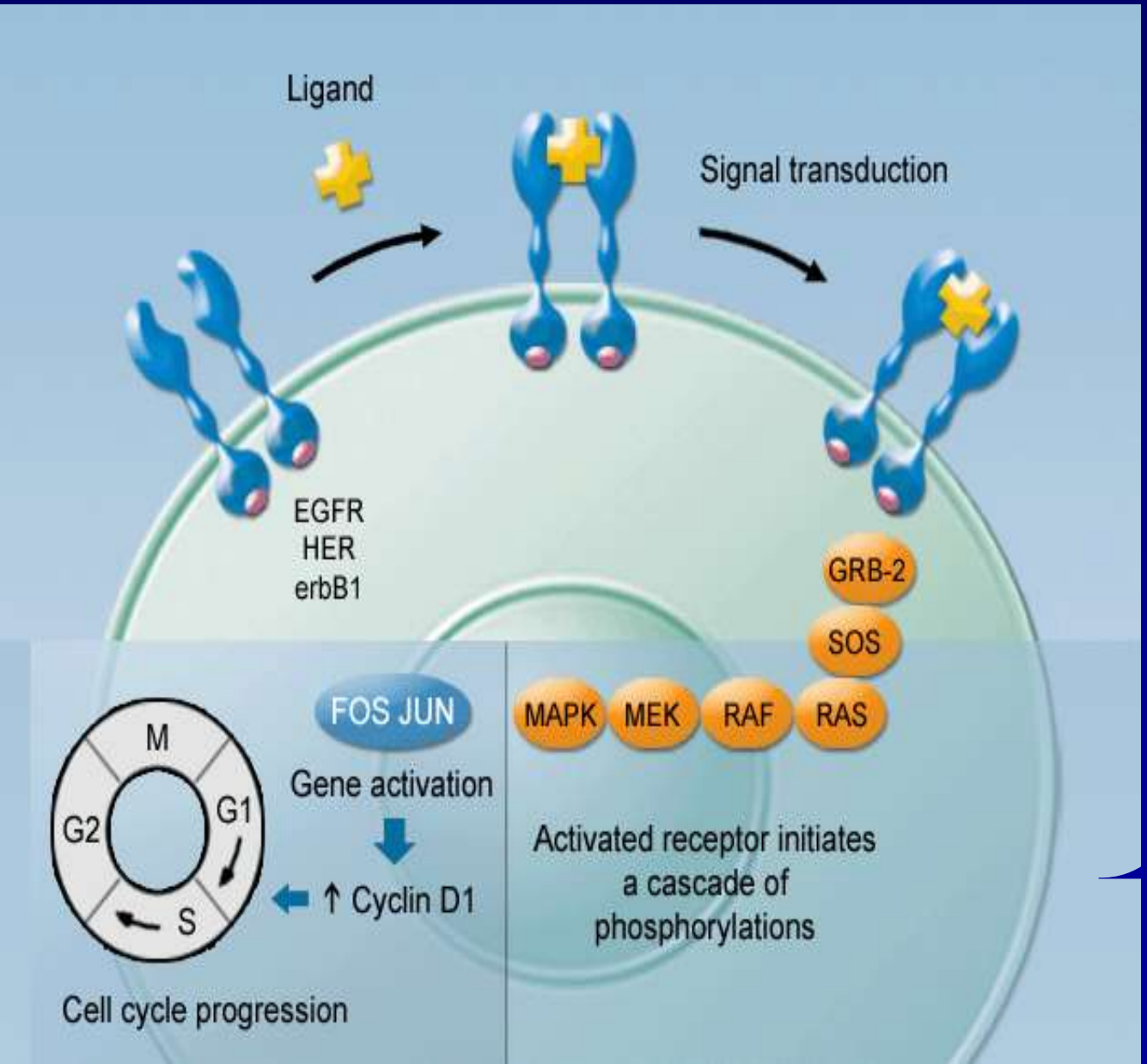
Ιωάννης Χ. Γκιόζος

Πνευμονολόγος MD, FCCP

Επιστημονικός Συνεργάτης
Ιατρικής Σχολής Αθηνών
Ογκολογική Μονάδα Γ'ΠΠ
ΓΝΝΘΑ "Η Σωτηρία"

Δεν προκύπτει σύγκρουση συμφερόντων

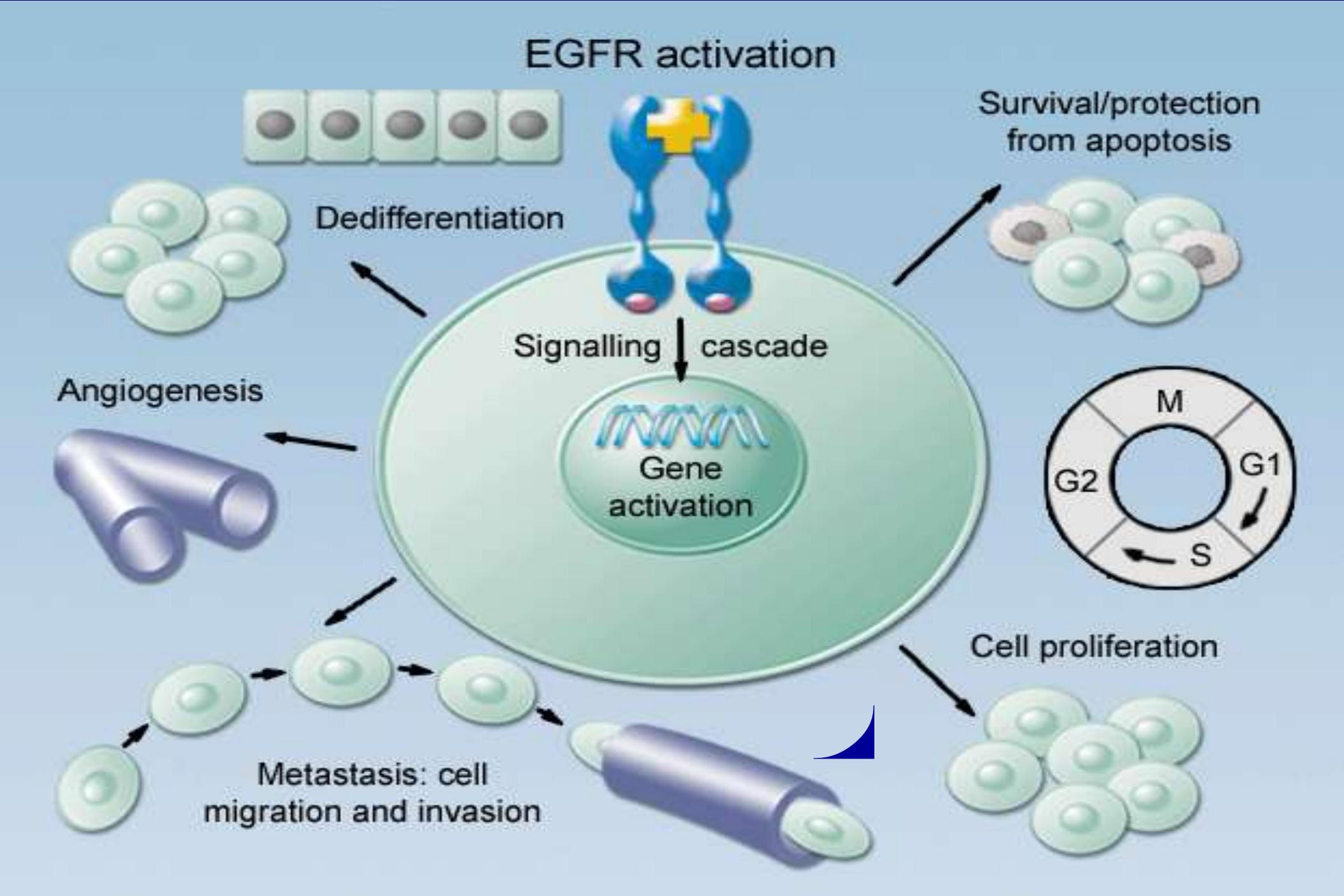
EGFR signaling



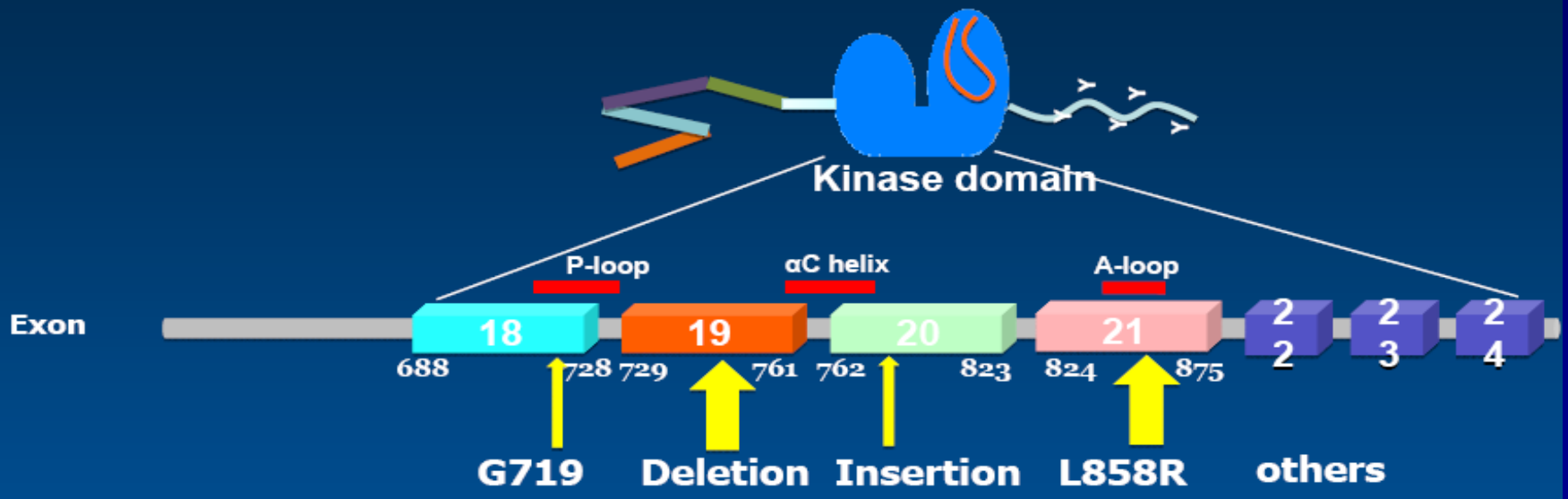
- EGFR is activated by growth factors.

- EGFR-activation leads to the building of homo- or hetero-dimers receptors.

- Receptor dimerization initiates an intracellular signaling cascade, gene activation and the stimulation of cell cycle progression.

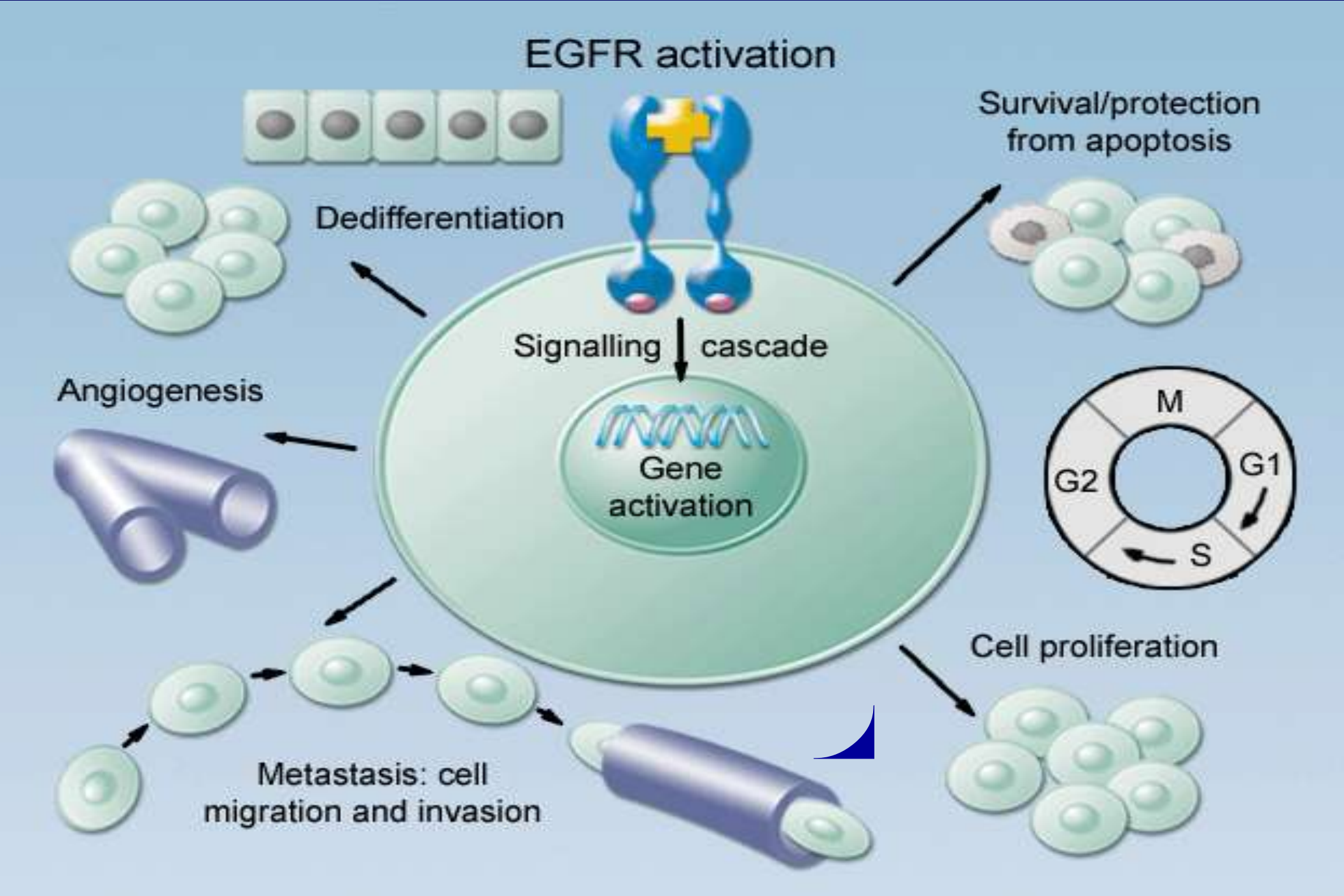

EGFR activation
Survival/protection from apoptosis
Dedifferentiation
Signalling cascade
Angiogenesis
Gene activation
M
G1
S
G2
Cell proliferation
Metastasis: cell migration and invasion

EGFR Mutation: Distribution and Incidence

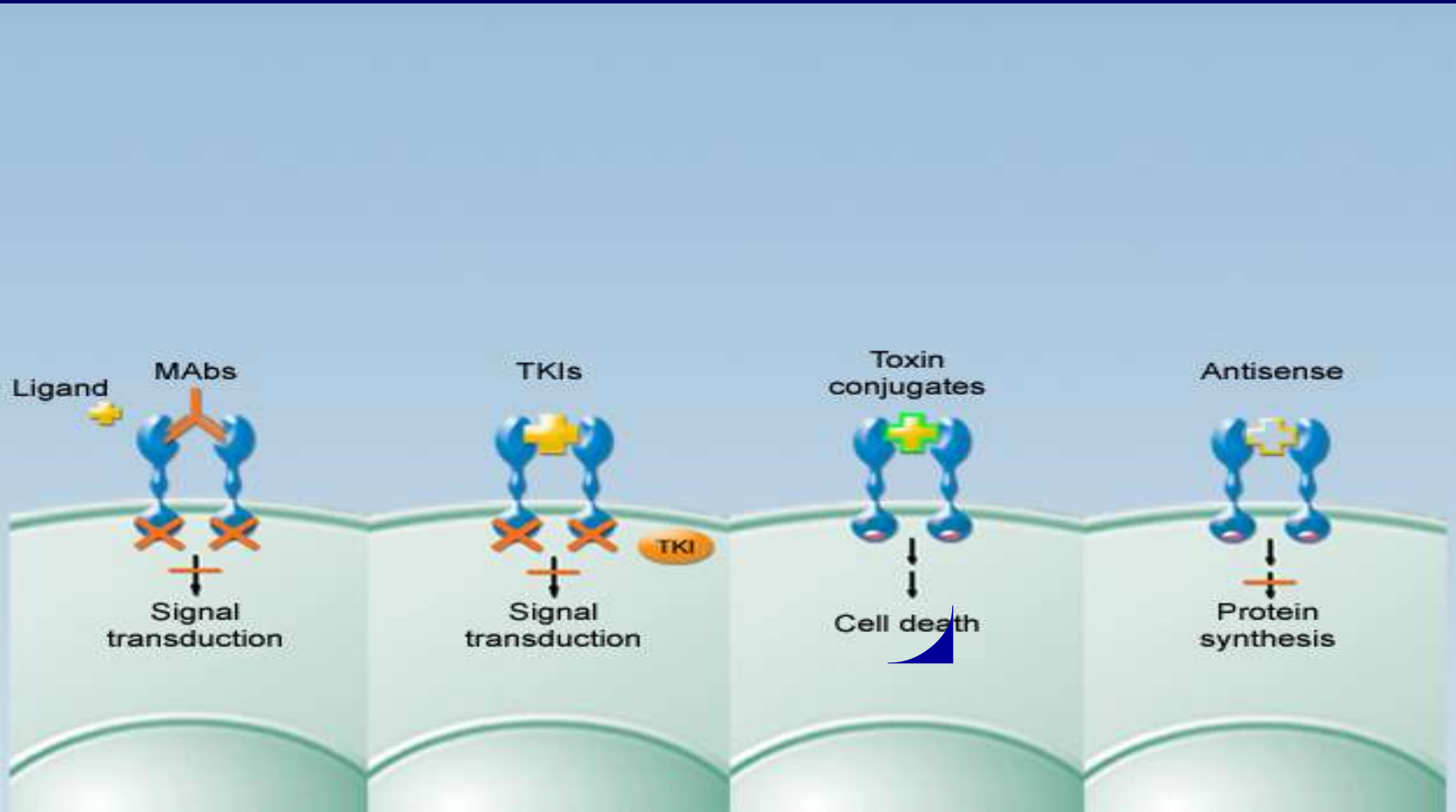


Incidence (N=569)	**3.2%**	**48.2%***	**3.7%****	**42.7%***	**2.2%**

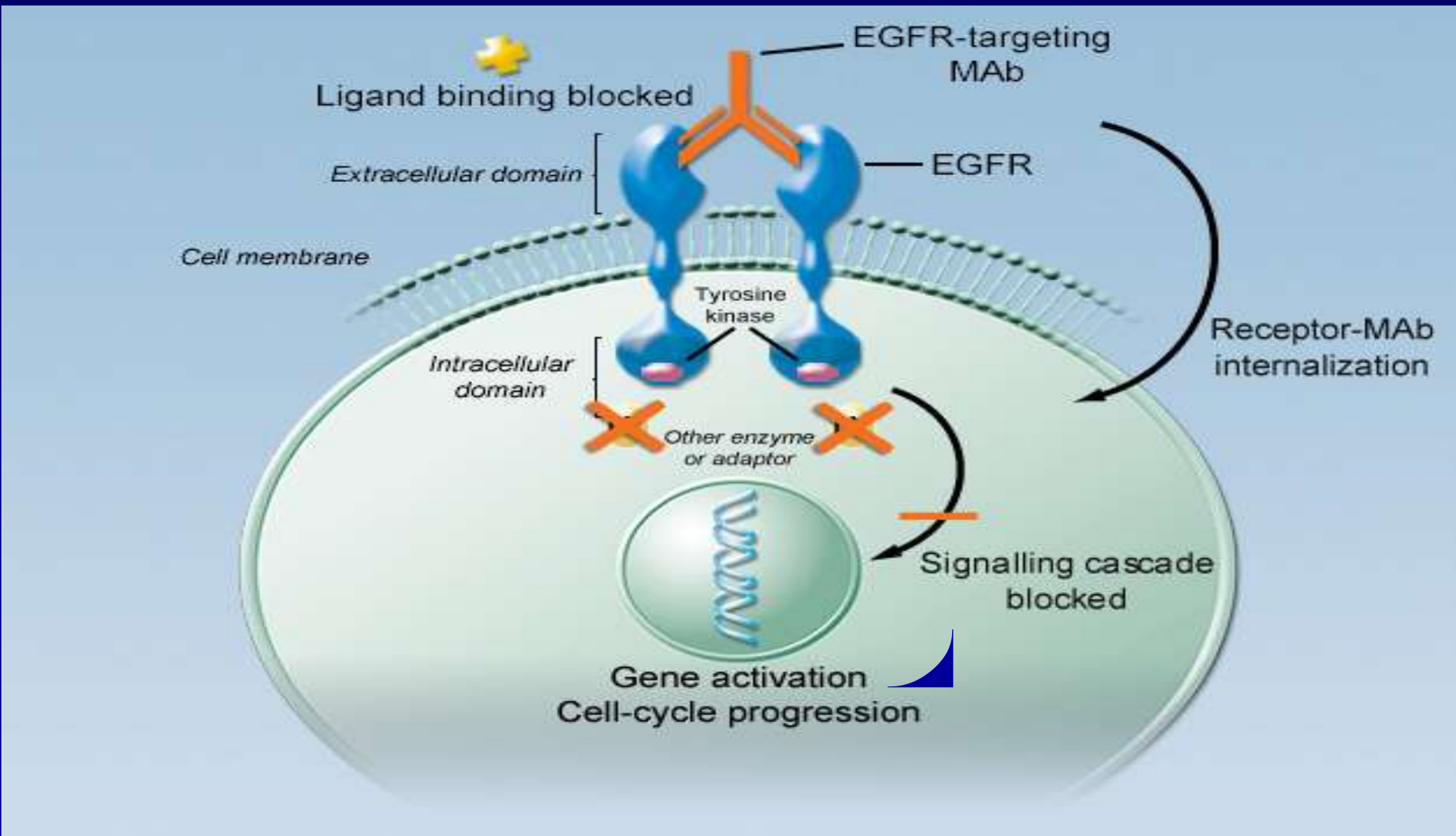
*Activating mutations with increased EGFR-TKI sensitivity
**Resistance mutations
Reviewed by Mitsudomi et al. *Cancer Science* 2007.


EGFR activation
Survival/protection from apoptosis
Dedifferentiation
Signalling cascade
Angiogenesis
Gene activation
M
G1
S
G2
Cell proliferation
Metastasis: cell migration and invasion

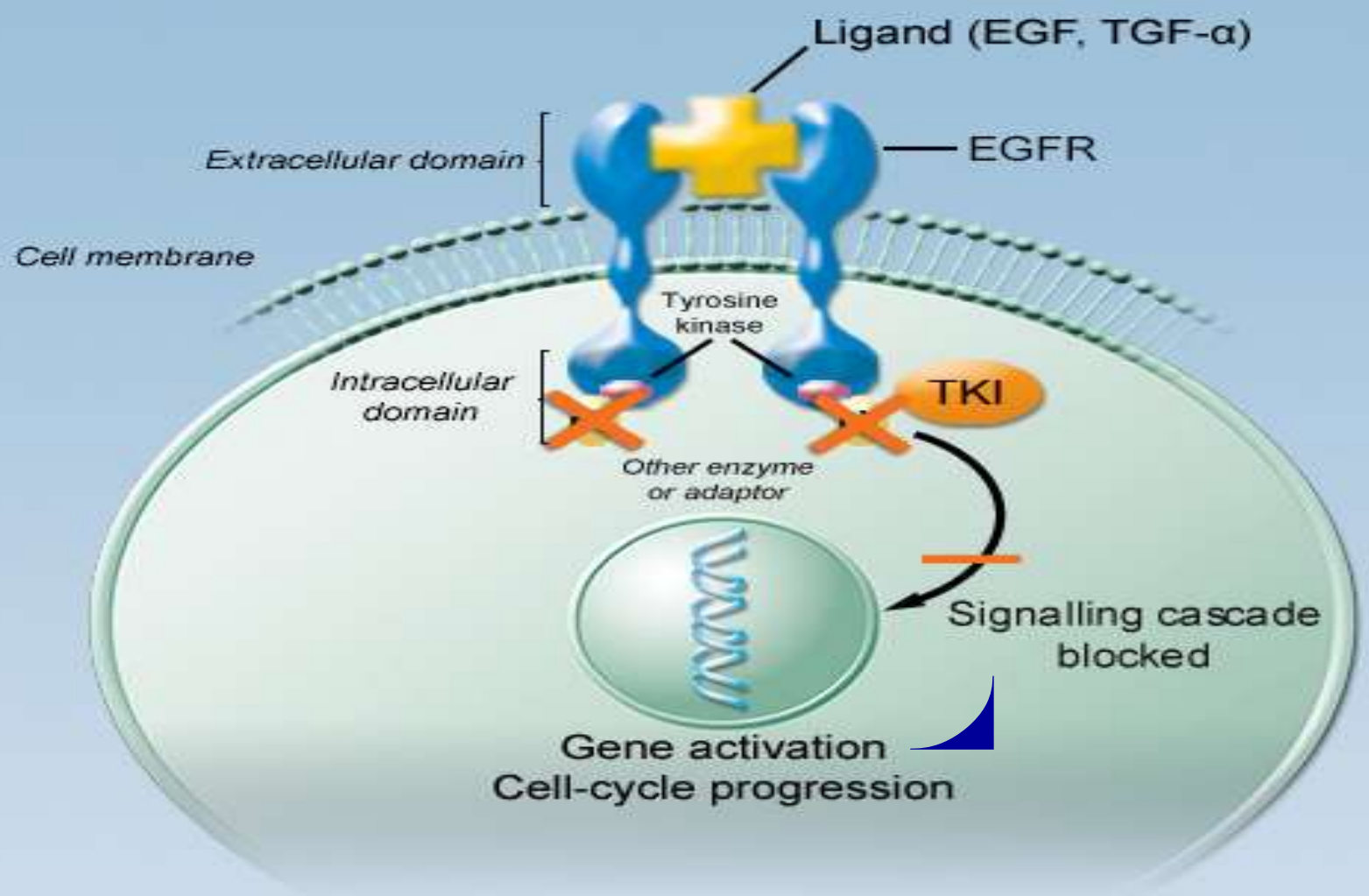
EGFR-targeting approaches



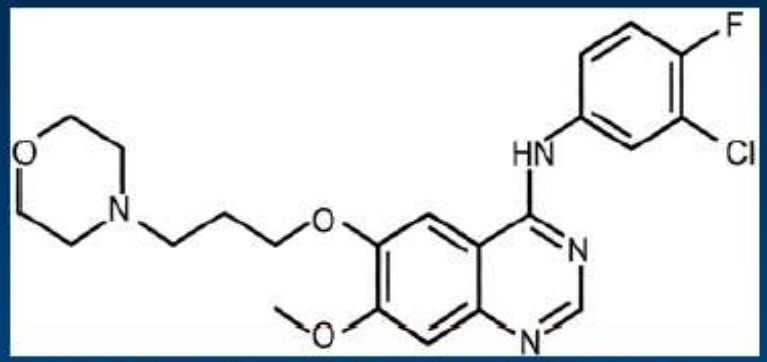
EGFR inhibition via mAbs



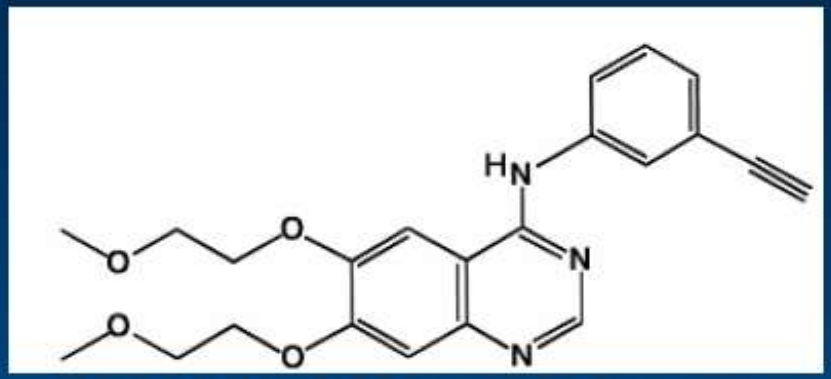
EGFR inhibition via tyrosine kinase inhibitors



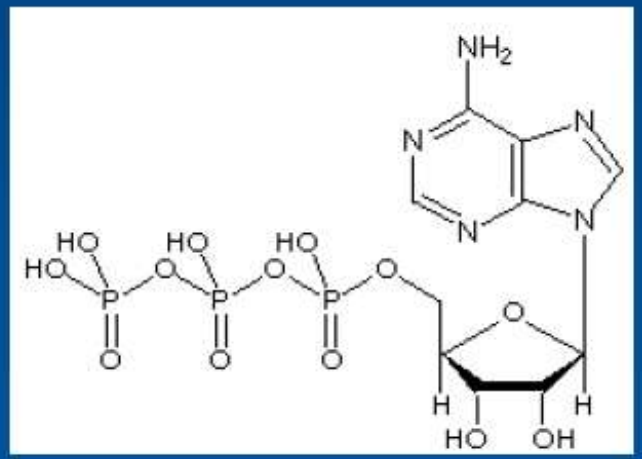
Gefitinib and Erlotinib – Related Quinazoline EGFR-TKIs



ZD1839, Gefitinib, Iressa

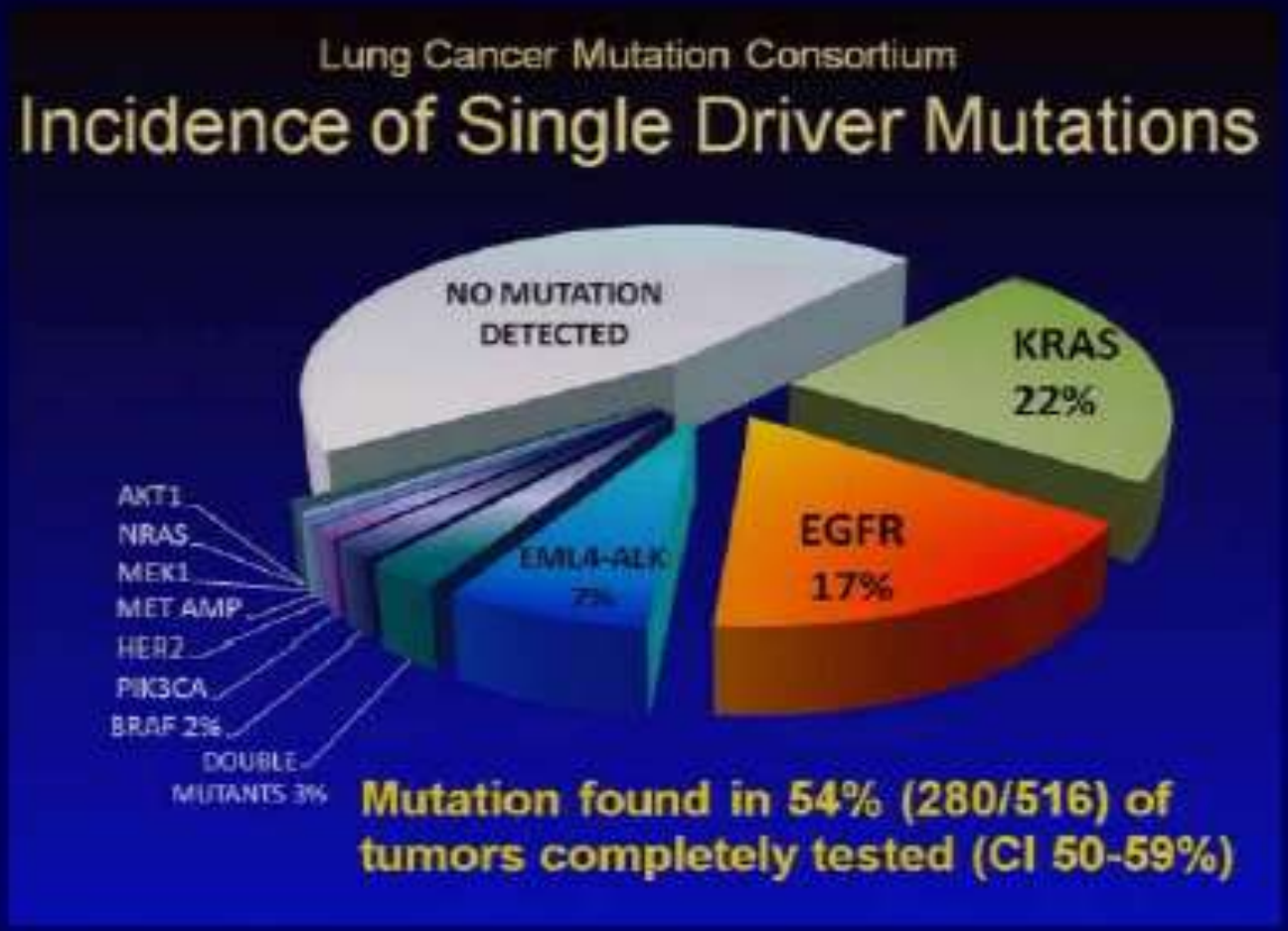


OSI-774, Erlotinib, Tarceva



ATP

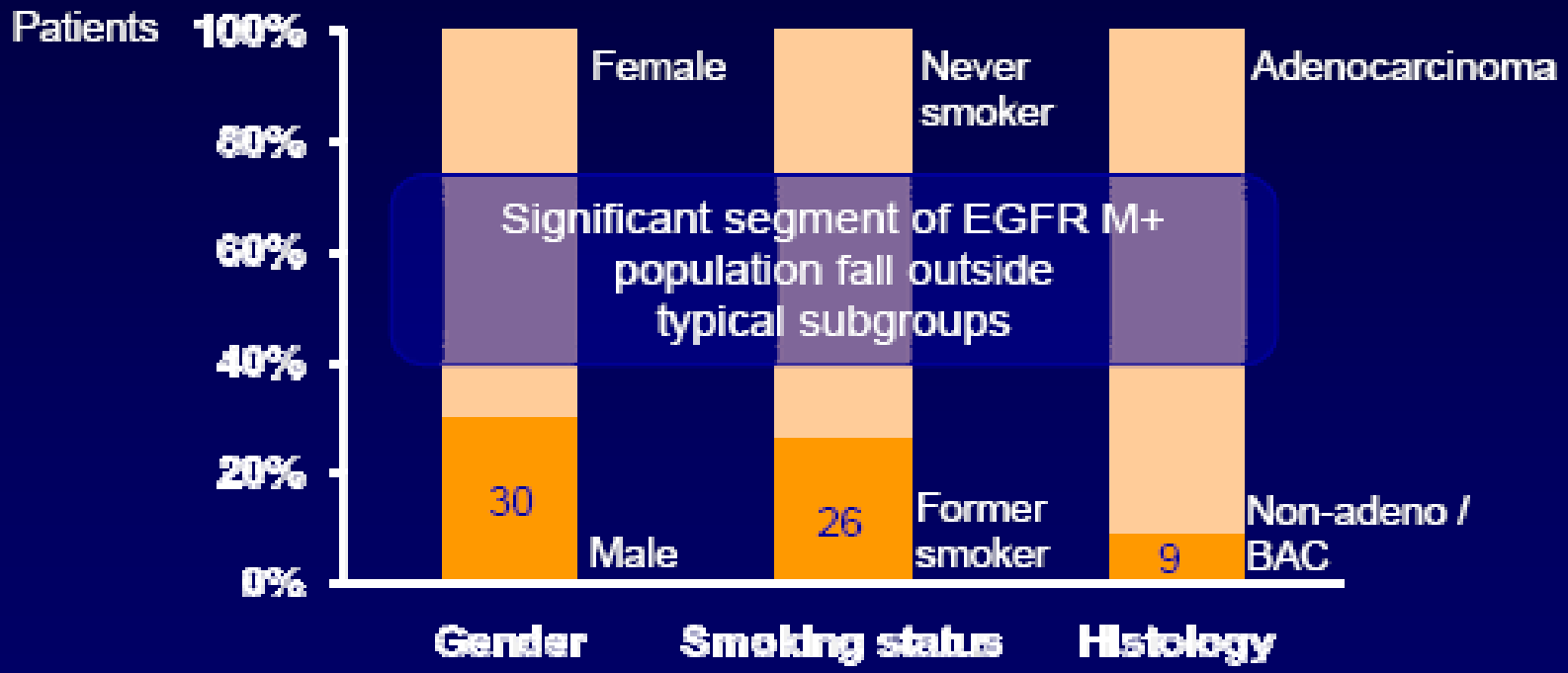
Identification of driver mutation in tumor specimens from 1000 patients with lung adenocarcinoma: The Lung Cancer Mutation Consortium (LCMC)



Kris MG et al., ASCO 2011, #CRA7506

Clinical characteristics do not completely predict EGFR mutation status

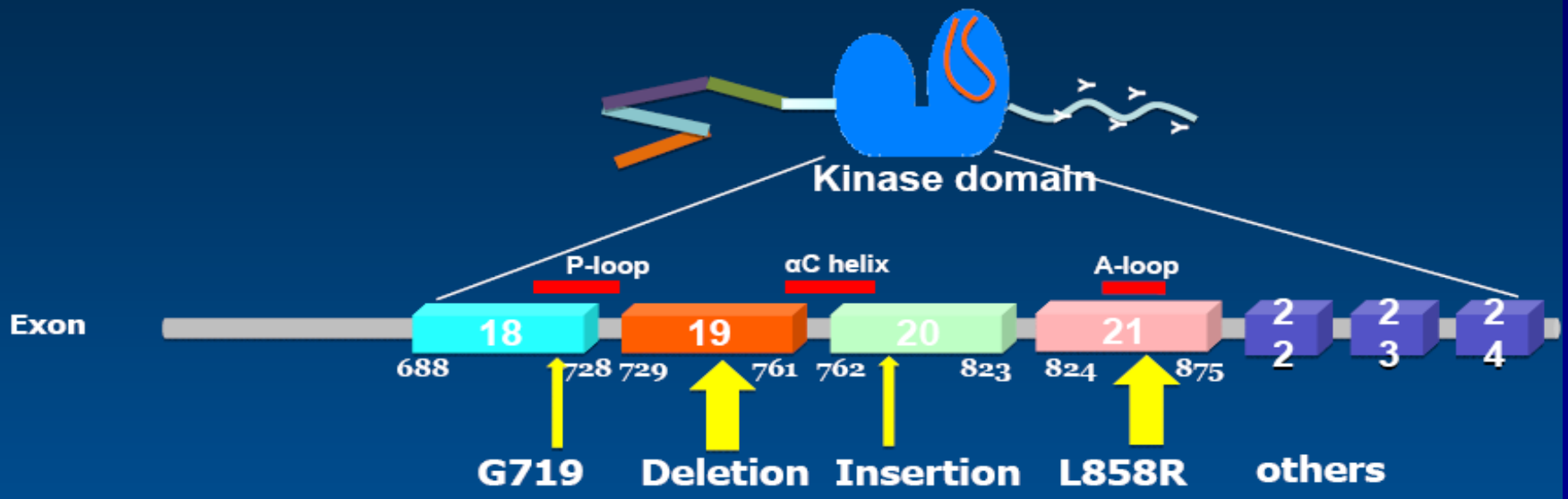
Spanish Lung Cancer Group trial in advanced NSCLC patients with EGFR mutations (n=350)[1]



BAC, bronchioloalveolar carcinoma

[1]Rosell et al 2009

EGFR Mutation: Distribution and Incidence



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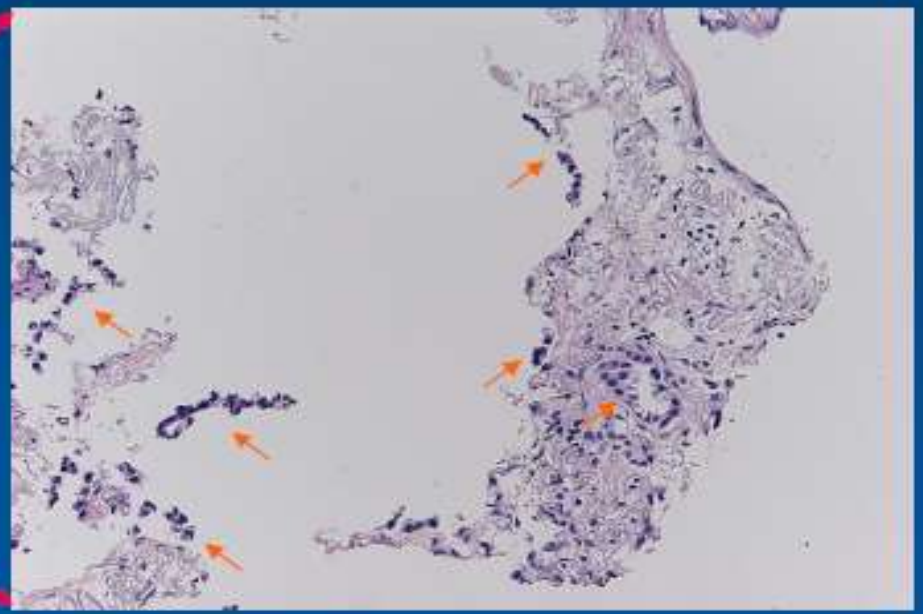
*Activating mutations with increased EGFR-TKI sensitivity
**Resistance mutations
Reviewed by Mitsudomi et al. *Cancer Science* 2007.

Biopsy specimen of lung cancer should contain at least 5% tumor cells determined by pathologist.

Transbronchial lung biopsy

CT guided biopsy



Tumor cells < 5% of normal cells

Randomized Trials of EGFR TKI vs Chemotherapy as First Line Treatment

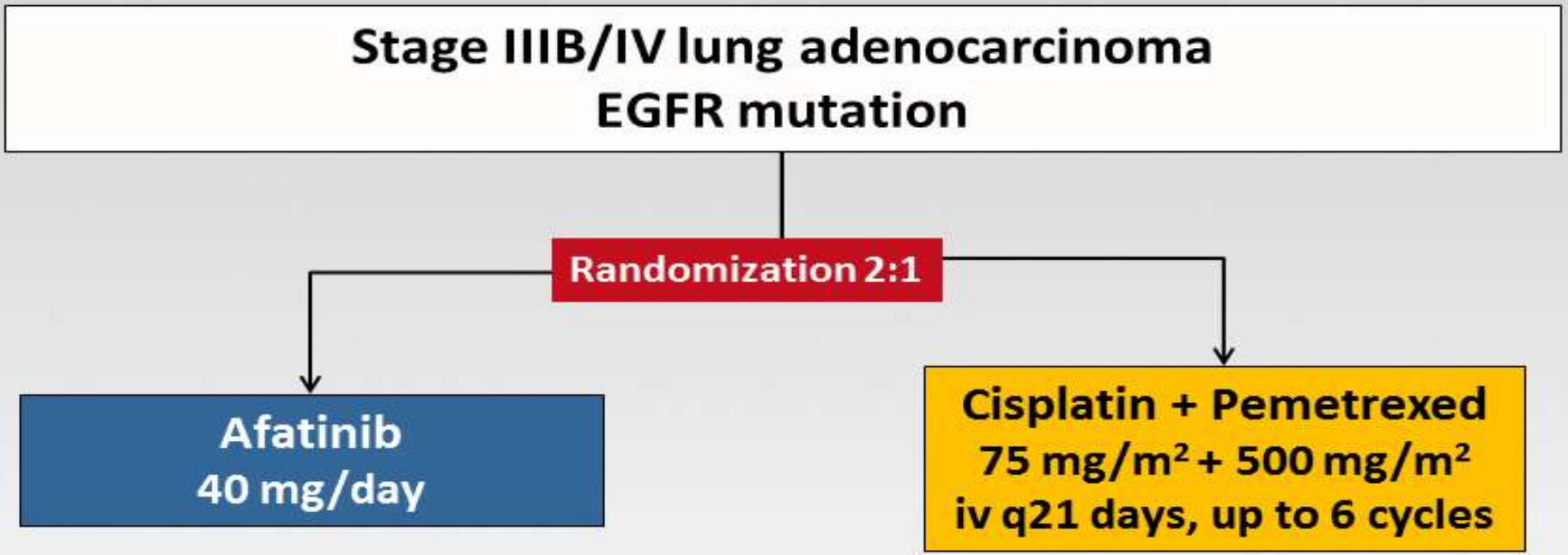
Study	Response Rate	PFS
EURTAC	58% vs 15%	10 vs 5 mo (HR 0.37)
OPTIMAL	83% vs 36%	13 vs 5 mo (HR 0.16)
NEJ 002	74% vs 31%	11 vs 5 mo (HR 0.30)
WJTOG 3405	62% vs 31%	9 vs 6 mo (HR 0.49)
IPASS	71% vs 47%	10 vs 6 mo (HR 0.19)
LUX LUNG 3	56% vs 23%	11 vs 7 mo (HR 0.58)

In patients with stage IV *EGFR* mutant lung cancer, EGFR TKIs are standard first-line treatment, but median PFS <12 months

Mitsudomi T. Lancet Oncol 2010;11:121-128. Maemondo M. N Engl J Med 2010;362:2380-2388. Zhou C. Lancet Oncol 2011;12:735-742. Rosell R. Lancet Oncol. 2012; 13:239-46. Mok T. N Engl J Med 2009;361: 947-57. Yang JCH. J Clin Oncol 2012 (Proc ASCO Annual Meeting). 30:LBA7500

IASLC

LUX-Lung 3 Trial



Primary endpoint: PFS
Secondary endpoints: ORR, DCR, DoR, tumor shrinkage, OS, PRO, safety, PK

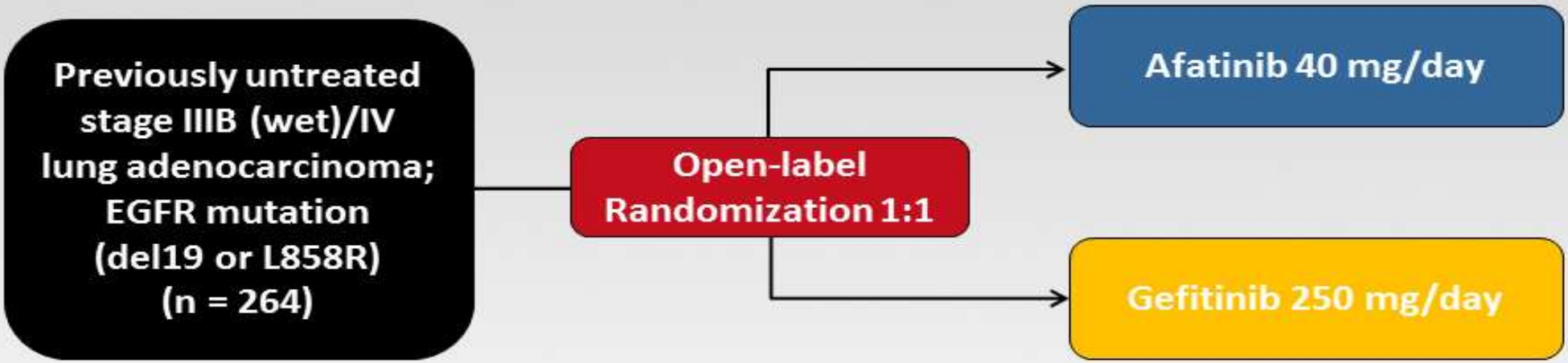
DCR = disease control rate; DoR = duration of response; EGFR = epidermal growth factor receptor; ORR = objective response rate; OS = overall survival; PFS = progression-free survival ; PK = pharmacokinetics; PRO = patient-reported outcomes

Yang JC, et al. ASCO 2012. Abstract LBA7500.

Three Classes of *EGFR* Mutations According to EGFR-TKI Sensitivity

- High sensitivity
  - Exon 19 deletion≥L858R, L861Q>G719S
- Intermediate sensitivity (erlotinib≥gefitinib)
  - D761Y, L747S
- Resistant (Response rate=0%)
  - T790M
  - Exon 20 insertion mutation

LUX-Lung 7: First-line Afatinib vs Gefitinib in EGFR-Mutant NSCLC



Primary endpoints:

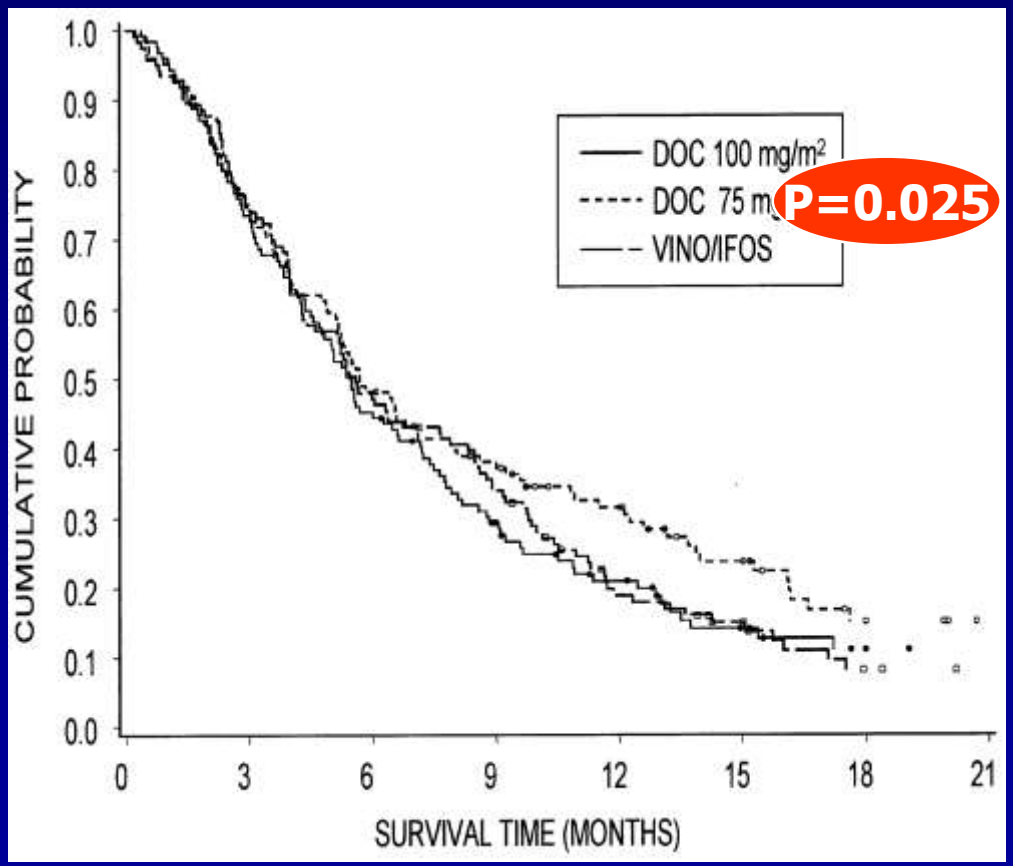
- PFS
- Disease control rate at 12 months

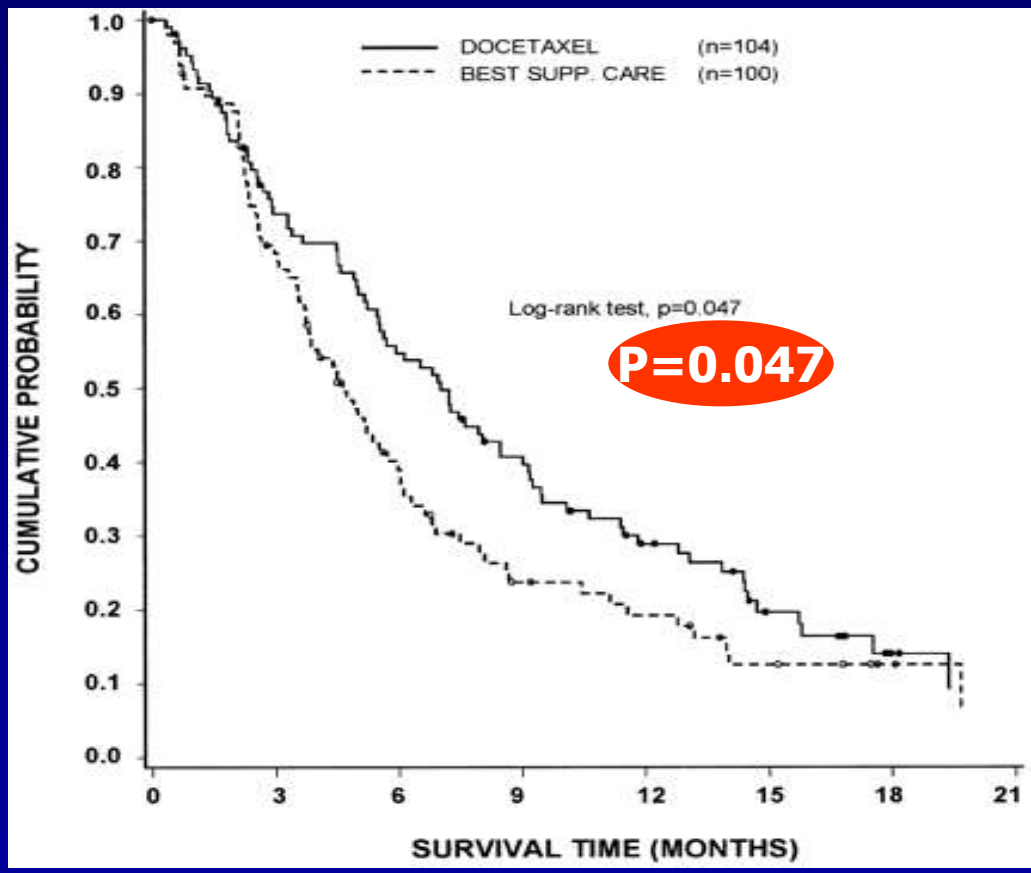
http://www.clinicaltrials.gov/ct2/show/NCT01466660

Medscape EDUCATION

ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ 2η ΓΡΑΜΜΗΣ

Docetaxel (Taxotere®)





Fossella, F. V. et al. J Clin Oncol; 2000;18

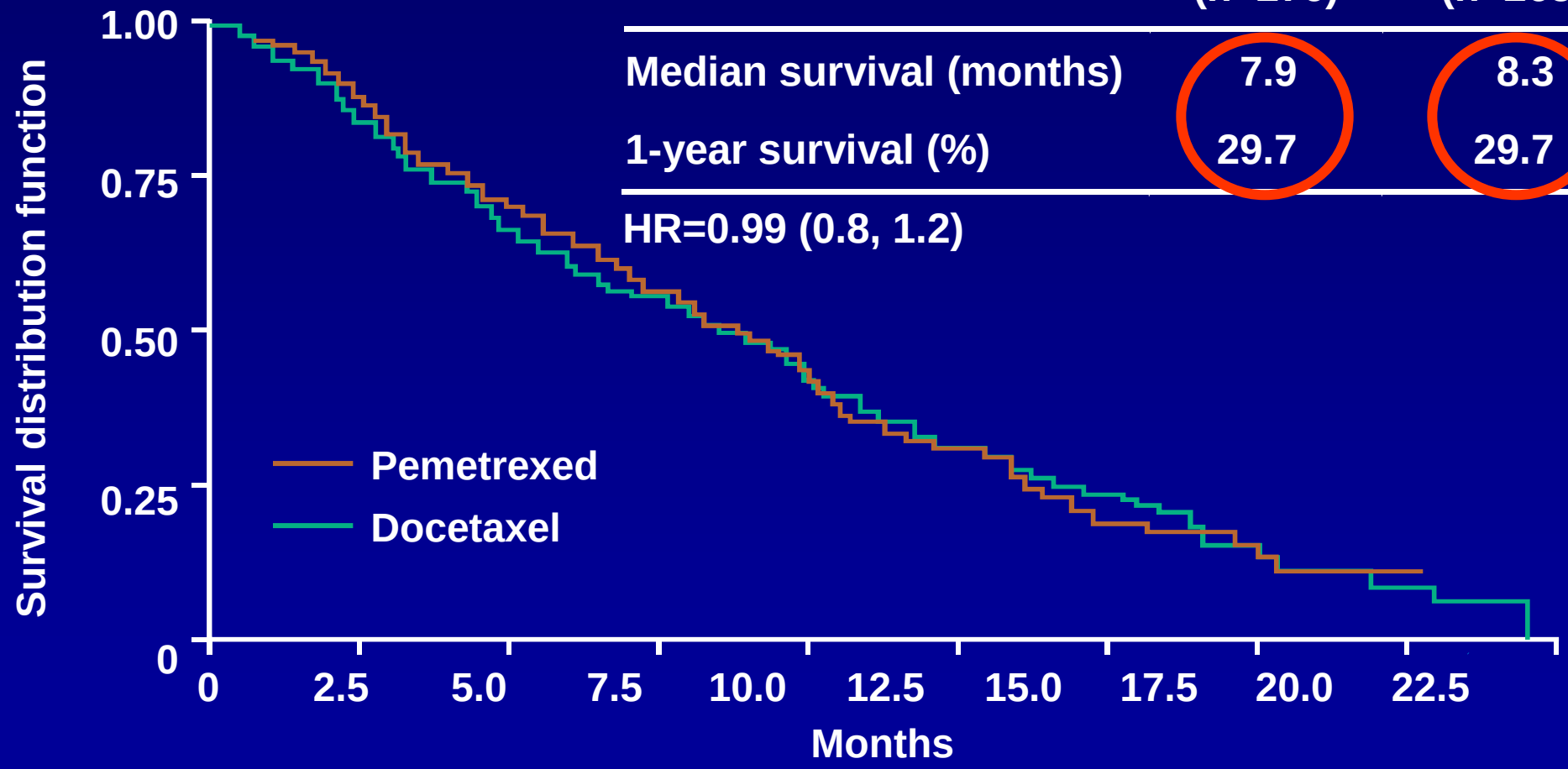
Shepherd FA, et al. J Clin Oncol; 2000,18

ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ 2η ΓΡΑΜΜΗΣ

Pemetrexed

	Docetaxel (n=276)	Pemetrexed (n=265)
Median survival (months)	7.9	8.3
1-year survival (%)	29.7	29.7

HR=0.99 (0.8, 1.2)



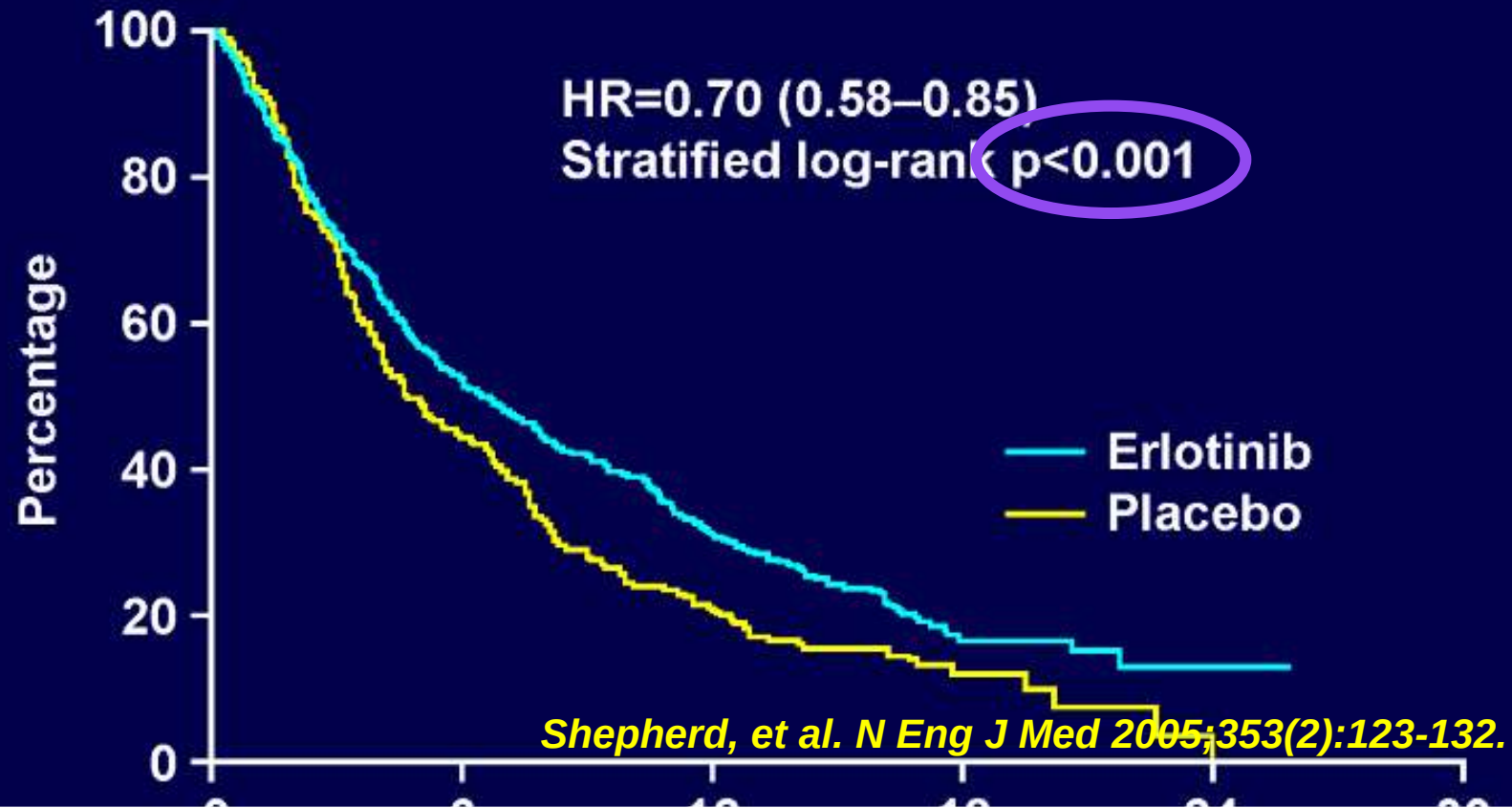
Hanna N, et al. J Clin Oncol 2004;22

ERLOTINIB: OVERALL SURVIVAL

42.5% improvement in median survival

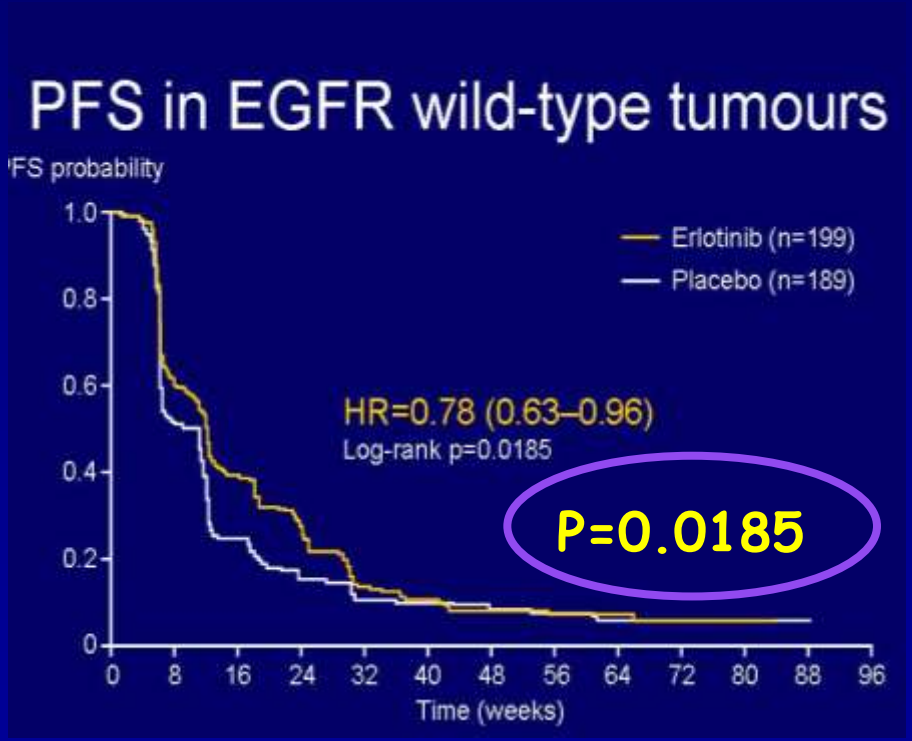
National Cancer Institute Of Canada
Institut national du cancer du Canada
Clinical Trials Group
Groupe Des Essais Cliniques

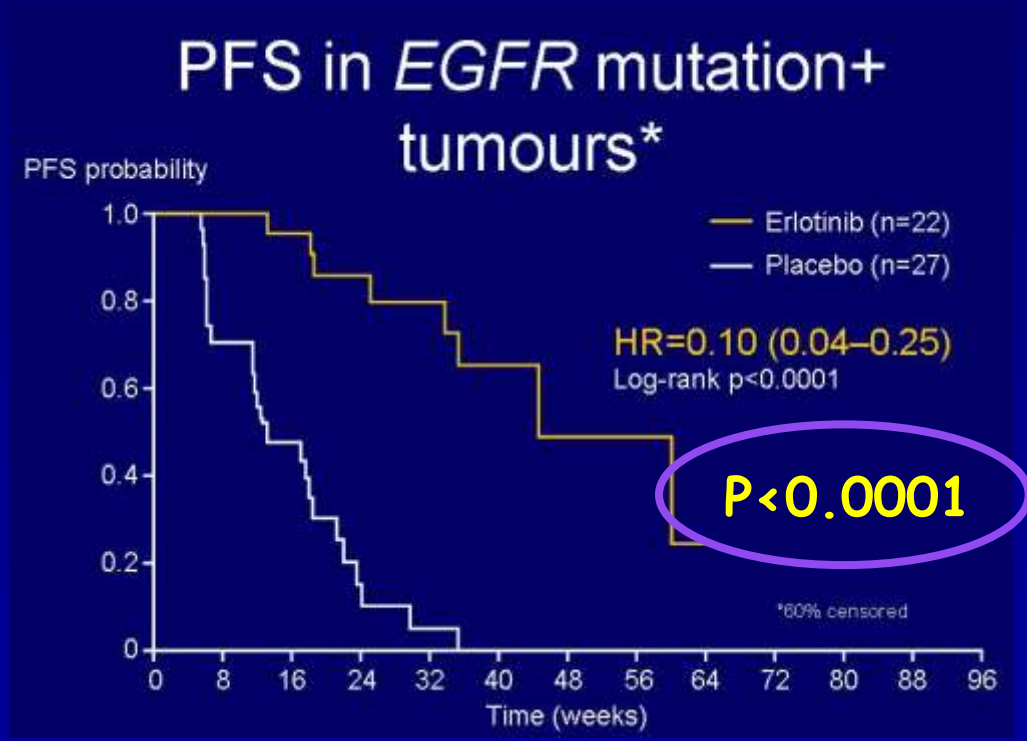
BR.21: overall survival



Shepherd, et al. N Eng J Med 2005;353(2):123-132.

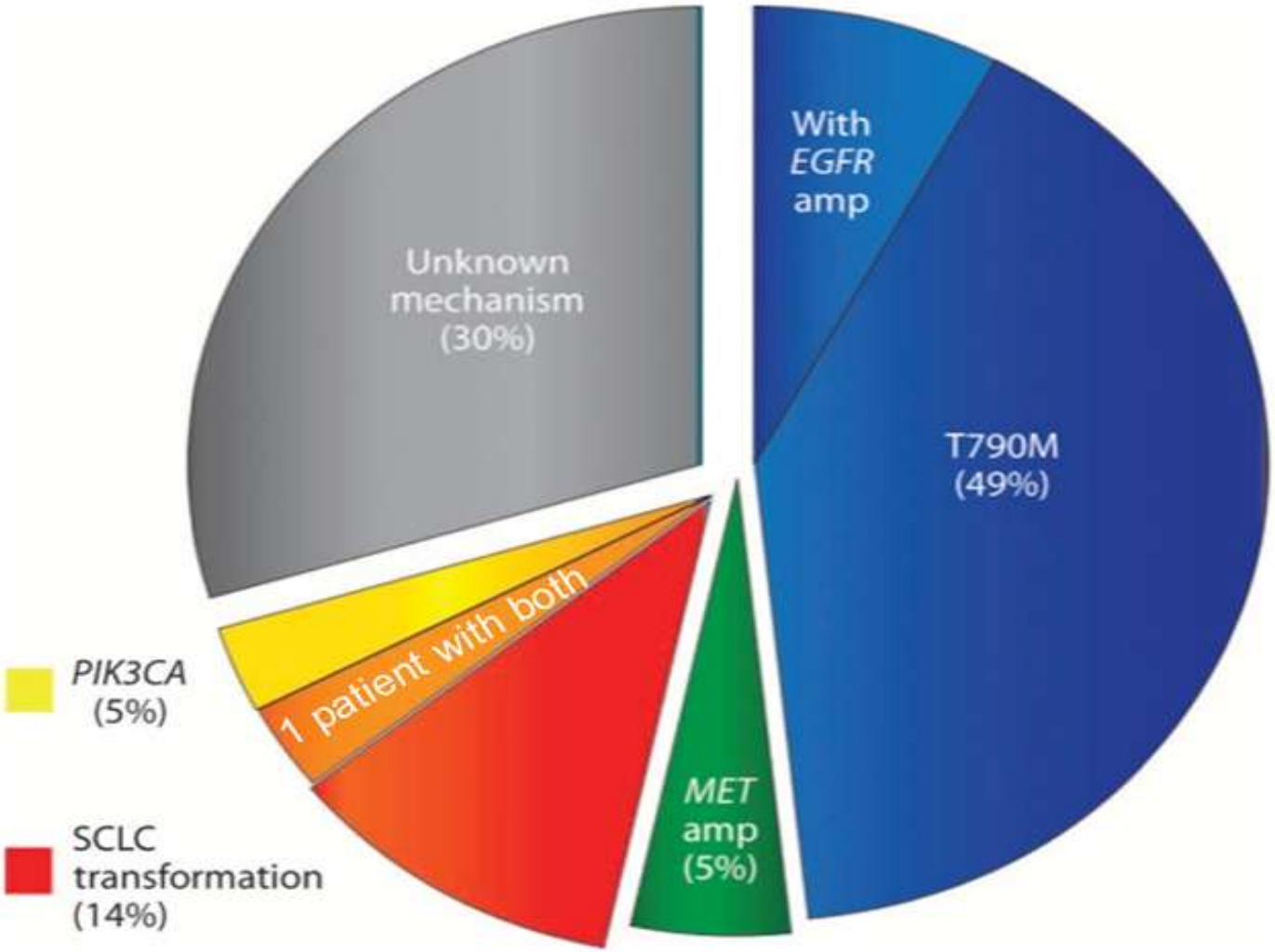
SATURN Trial : Erlotinib as maintenance therapy after successful 1st line treatment





Capuzzo et al [abstract 8001], ASCO 2009

Defined Mechanisms of Acquired Resistance to EGFR TKIs



From Sequist LV, et al. *Sci Transl Med*. 2011;3:75ra26. Republished with permission from AAAS.

Treatment Selection Is Moving From Histology-Based to Targeting Oncogenic Drivers

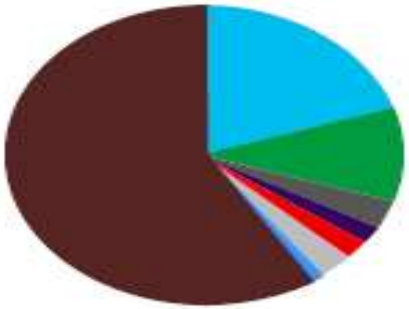
1999 Histology-driven selection

Adenocarcinoma

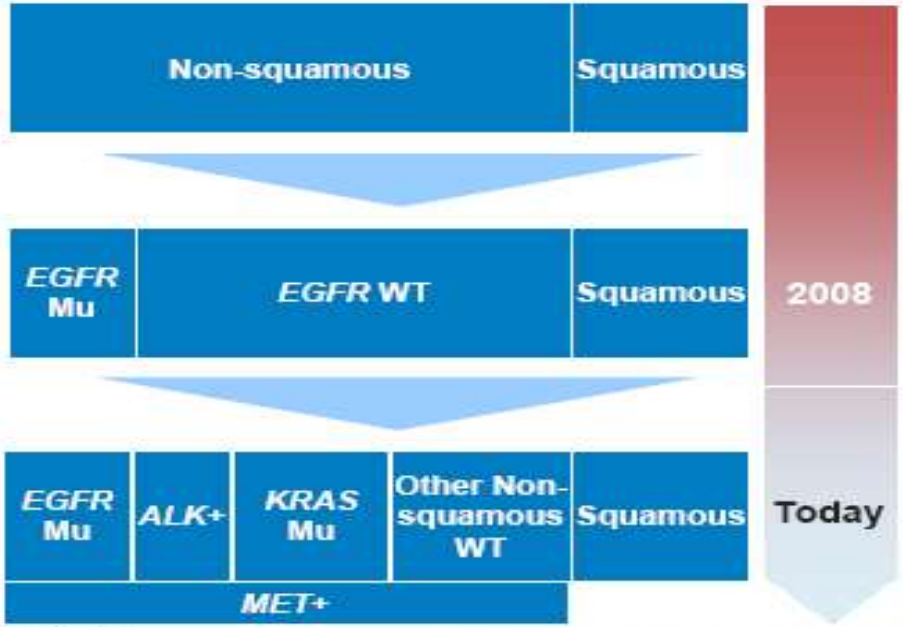
Squamous-cell carcinoma

Large cell carcinoma

2010 Targeting oncogenic drivers*



Evolution of NSCLC treatment

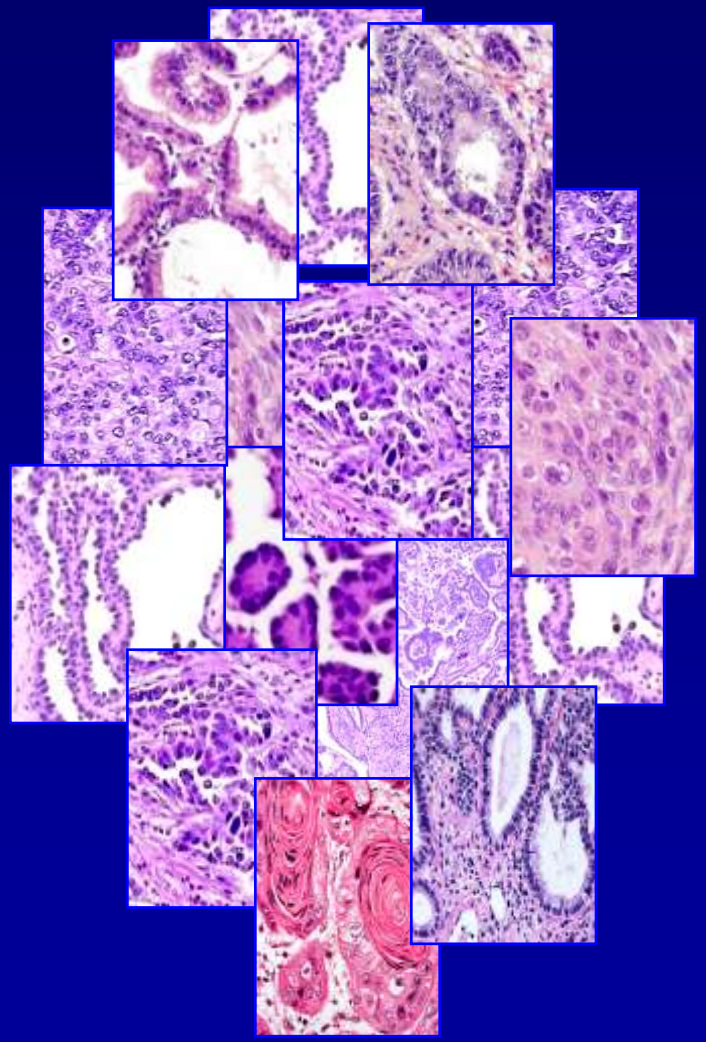


*Incidence of mutations in adenocarcinoma provided as an example

Current Standard of NSCLC Care

Figure: Massachusetts General Hospital, data on file. Horn L, Pao W. *J Clin Oncol.* 2009;26:4232–4235.

ΕΞΑΤΟΜΙΚΕΥΣΗ ΤΗΣ ΘΕΡΑΠΕΙΑΣ




ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗ
ΠΡΟΣΟΧΗ ΣΑΣ