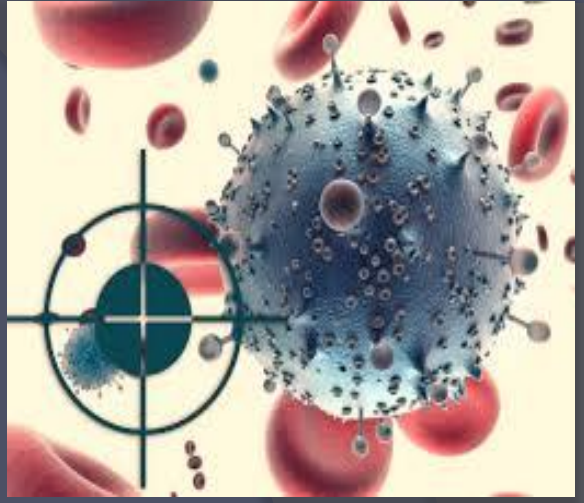
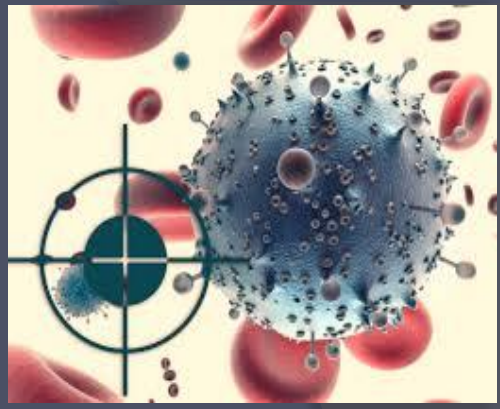
**ΘΕΡΑΠΕΥΤΙΚΕΣ ΠΡΟΣΕΓΓΙΣΕΙΣ ΣΤΟΝ ΚΑΡΚΙΝΟ ΤΟΥ ΠΝΕΥΜΟΝΑ**
Τρίκαλα 28/05/2016



# ΣΤΟΧΕΥΜΕΝΕΣ ΘΕΡΑΠΕΙΕΣ ΣΤΟΝ ΚΑΡΚΙΝΟ ΤΟΥ ΠΝΕΥΜΟΝΑ

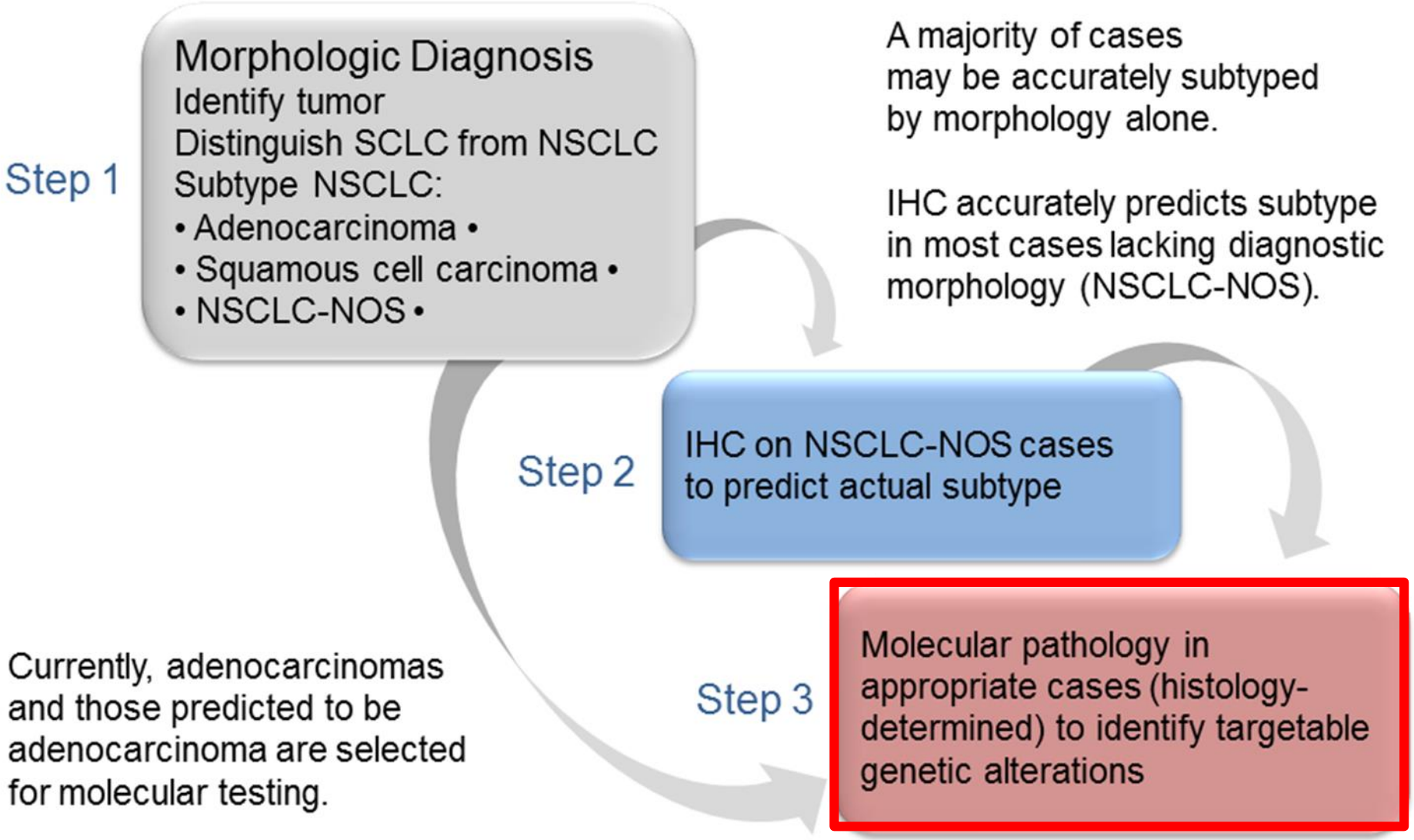
**ΚΕΡΕΝΙΔΗ ΝΟΡΑ**
**Επ. Καθηγήτρια Πνευμονολογίας**
ΠΝΕΥΜΟΝΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

# Στοχευμένες θεραπείες



- Μοριακή ανάλυση
- Αναστολείς του EGFR
  - TKI's: 1ης, 2ης και 3ης γενιάς
  - Μονοκλωνικά αντισώματα
- Αναστολείς του ALK: 1ης και 2ης γενιάς
- Αναστολείς του VEGF
- Προοπτικές
- Συμπεράσματα

# Διάγνωση του ΚΠ



# Υλικό για μοριακή ανάλυση

- Συνεργασία πνευμονολόγου, κυτταρολόγου/ παθολογοανατόμου, μοριακού βιολόγου.

- Μη πλακώδες ΚΠ

- Όλα τα υλικά formalin ή alcohol-fixed

(κυτταρολογικό ή ιστολογικό δείγμα)

  - Κατάλληλο δείγμα για μοριακή ανάλυση

    PCR- EGFR: >500 καρκινικά κύτταρα, 20% κυτταροβρίθεια

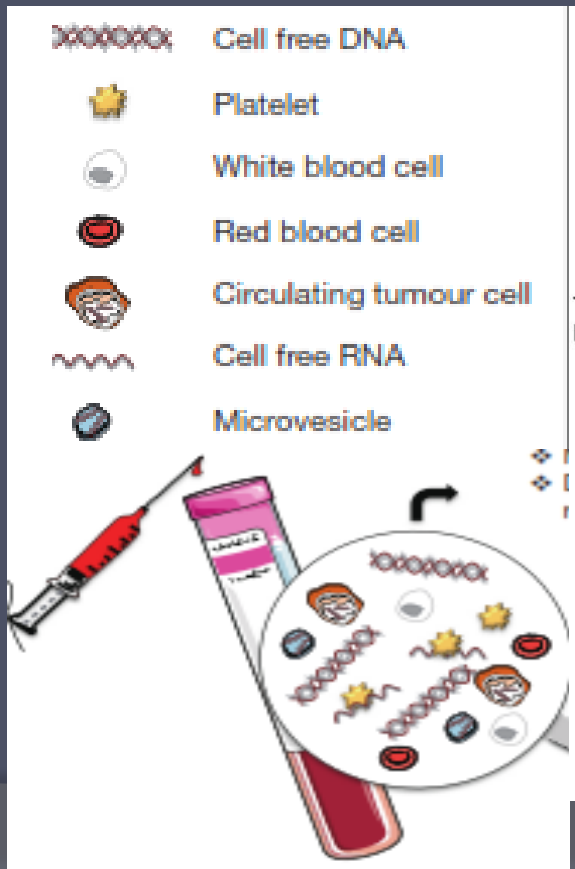
    IHC, FISH- ALK: >50 καρκινικά κύτταρα

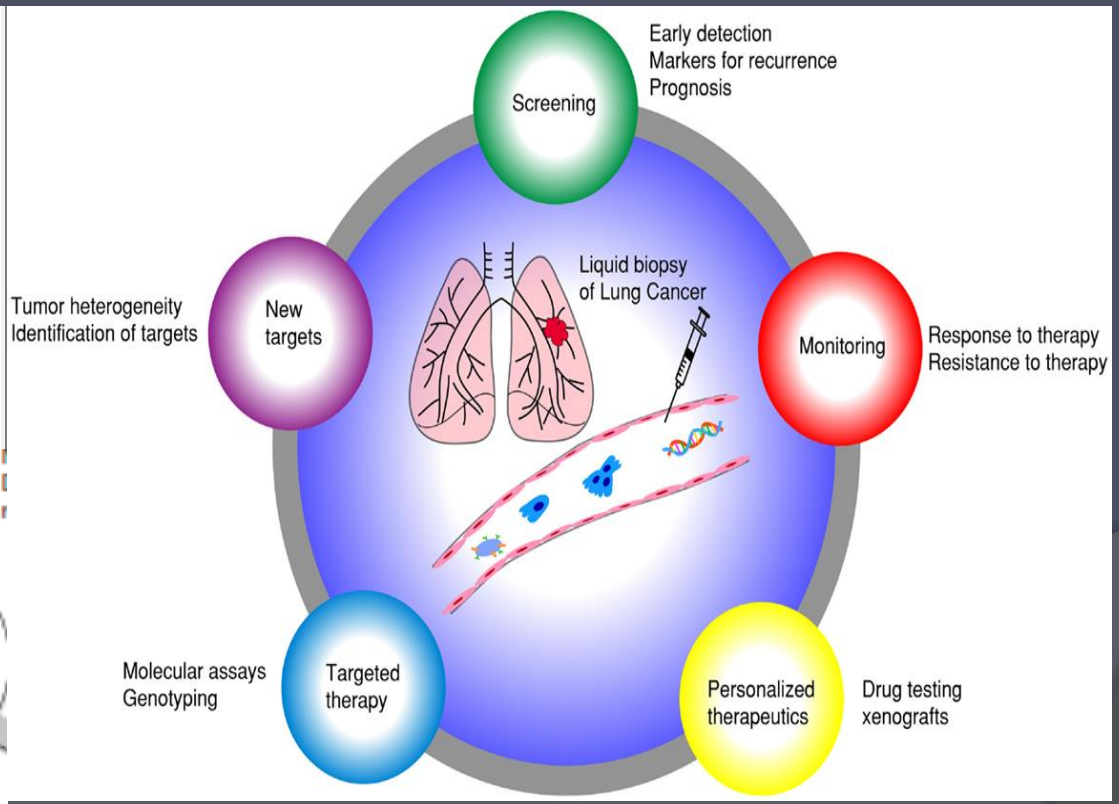
- Περιφερικό αίμα (liquid biopsy)

# Liquid biopsy...

- Circulating tumor cells (CTCs)
- or Circulating tumor DNA(ctDNA)

- Blood: serum, plasma,
- Urine

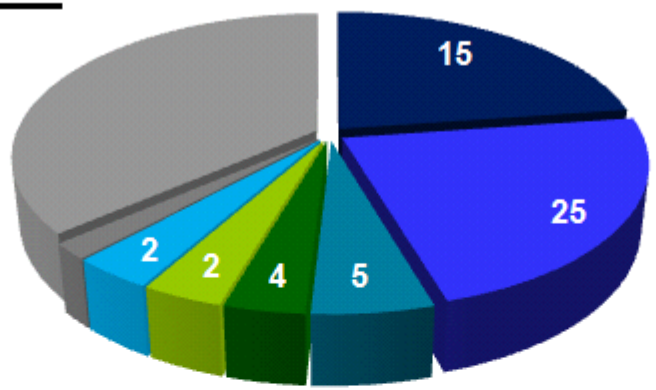



N. Karachaliou et al. Ann Transl Med 2015

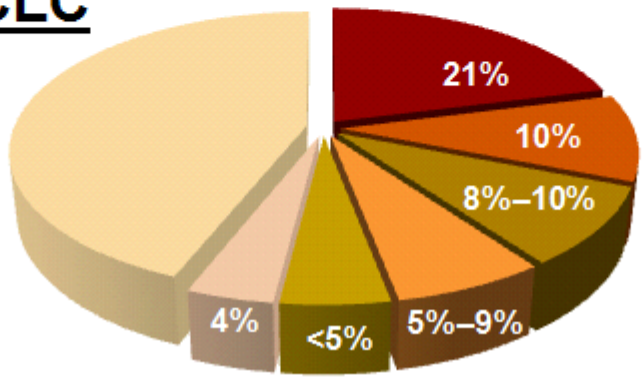
# NSCLC: Μοριακό Προφίλ

## Adenocarcinoma




- ***EGFR* mutation[1]**
- ***KRAS* mutation[2]**
- ***ALK* rearrangement[3]**
- *MET* amplification[4]
- *PIK3CA* mutation[4]
- *HER2* mutation[4]
- *ROS1* rearrangement
- Others or unknown

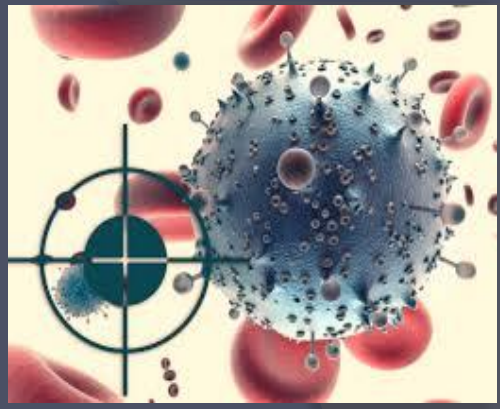
## Squamous NSCLC




- ***FGFR1* amplification[5]**
- ***PTEN* mutation[6]**
- ***PDGFRA* amplification[7]**
- *PIK3CA* mutation[4,8]
- *MET* amplification[4]
- *DDR2* mutation[9]
- Others or unknown

*1. Heist RS, Engelman JA. Cancer Cell 2012;21;448.e2; 2. Herbst RS, et al. N Engl J Med 2008;359:1367–1380; 3. Scholl LM, et al. J Thorac Oncol 2013;8:322–328; 4. Pao W, Girard N. Lancet Oncol 2011;12:175–180; 5. Dutt A, et al. PLoS One 2011;6:e20351; 6. Jin G, et al. Lung Cancer 2010;69:279–283; 7. Heist RS, et al. J Thorac Oncol 2012;7:924–933; 8. Spoerke JM, et al. Clin Cancer Res 2012;18:6771–6783; 9. Hammerman PS, et al. Cancer Discov 2011;1:78–89*

# Στοχευμένες θεραπείες

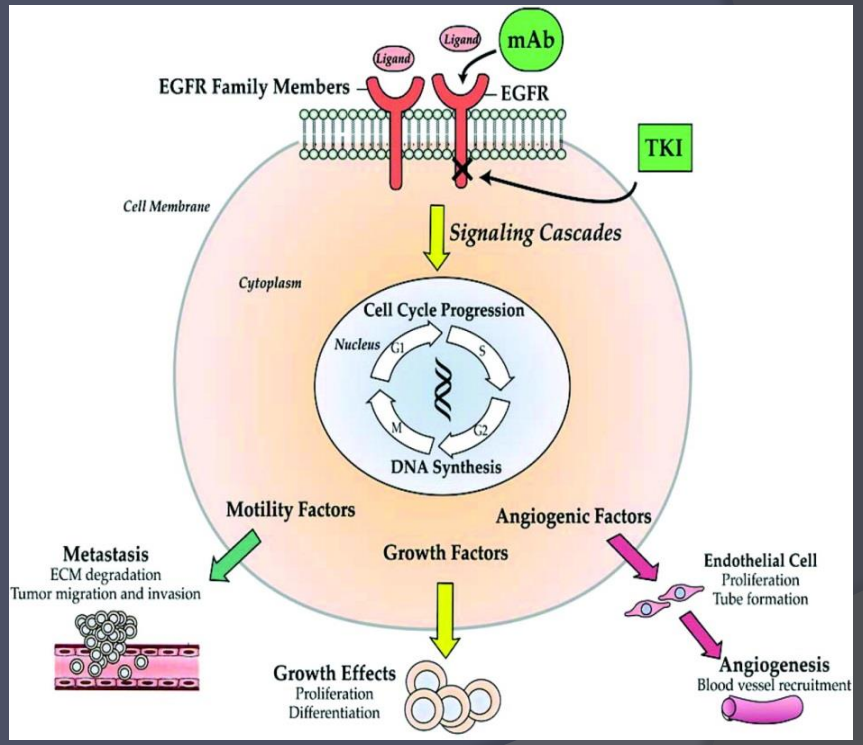


- Μοριακή ανάλυση
- Αναστολείς του EGFR
  - TKI's: 1ης, 2ης και 3ης γενιάς
  - Μονοκλωνικά αντισώματα
- Αναστολείς του ALK: 1ης και 2ης γενιάς
- Αναστολείς του VEGF
- Προοπτικές
- Συμπεράσματα

# Αναστολείς του EGFR

- Αναστολείς τυροσινικής κινάσης (TKI's)
  - **Erlotinib,**
  - **Gefitinib,**
  - **Afatinib**
  - **Osimertinib**

- Μονοκλωνικό αντίσωμα που ενώνεται με το εξωκυττάριο τμήμα του EGFR
  - **Cetuximab**
  - **Necitumumab**



# EGFR TKI's

- **First Generation EGFR TKI's**
  - **Gefitinib (Iressa, AstraZeneca's)**
  - **Erlotinib (Tarceva, Roche)**
- **Second Generation EGFR TKI's**
  - **Afatinib (Gilotrif, Boehringer)**
  - *Dacomitinib (Pfizer)*
- **Third Generation EGFR TKI's**
  - **Osimertinib (Tagrisso, AstraZeneca's)**
  - *Rociletinib (*Clovis Oncology)

# Randomized, First-Line Studies in NSCLC Patients With *EGFR* Mutation

| Trial | EGFR TKI | n | *EGFR* Mutation | Response Rate (%) | PFS (months) | OS (months) |
|---|---|---|---|---|---|---|
| IPASS | Gefitinib | 1217 | 261 | | | 21.6 vs 21.9<br>HR=1.0 (0.76–1.33) |
| First-SIGNAL | Gefitinib | 309 | 42 | | | 27.2 vs 25.6<br>HR=1.04 (0.50–2.18) |
| NEJ002 | Gefitinib | 224 | 224 | | | 30.5 vs 23.6 |
| WJTOG-3405 | Gefitinib | 172 | 172 | | | 35.5 vs 38.8<br>HR=1.185 (0.76–1.83) |
| OPTIMAL | Erlotinib | 154 | 154 | | | 22.7 vs 28.9<br>HR=1.04 (0.69–1.58) |
| EURTAC | Erlotinib | 173 | 173 | | | 19.3 vs 19.5<br>HR=1.04 (0.65–1.68) |
| LUX-Lung 3 | Afatinib | 345 | 345 | | | 28.2 vs 28.2 |
| LUX-Lung 6 | Afatinib | 364 | 364 | | | 23.1 vs 23.5 |

**ORR 70%**

**(56-85%)**

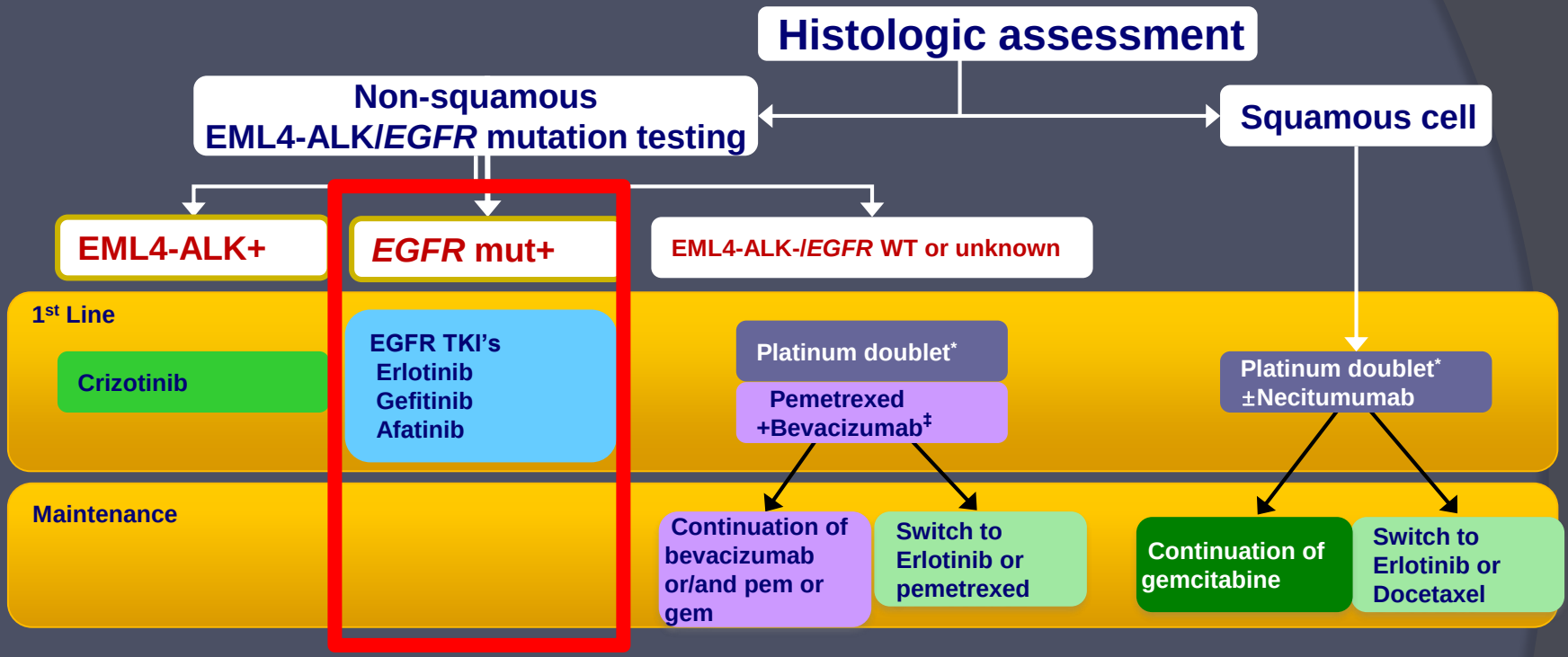
**PFS 10m**

**(8-13.7m)**

22-35m


Mok TS, et al. *N Engl J Med.* 2009;361:947-957; Fukuoka M, et al. *J Clin Oncol* .2011;29:2866-2874.
Han J-Y, et al. *J Clin Oncol.* 2012;10:1122-128; Maemondo M, et al. *N Engl J Med.* 2010;362:2380-2398.
Mitsudomi T, et al. *Lancet Oncol.* 2010;11:121-128; Mitsudomi T, et al. *J Clin Oncol.* 2012;30(Suppl.): Abstract 7521.
Zhou C, et al. *Lancet Oncol.* 2011;12:735-742; Zhou C, et al. *J Clin Oncol.* 2012;30(Suppl.): Abstract 7520.
Rosell R, et al. *Lancet Oncol.* 2012;13:239-246; Yang JC, et al. *J Clin Oncol.* 2012;30:(suppl; abstr LBA7500).
Wu Y-L, et al. *J Clin Oncol.* 2013;31(Suppl.): Abstract 8016.

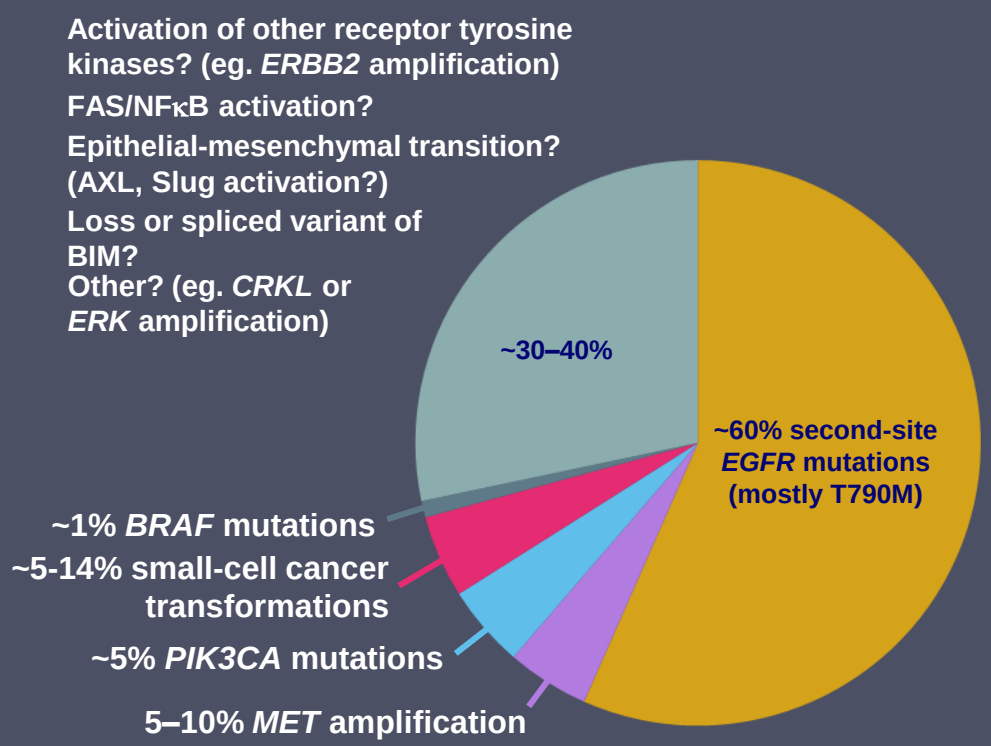
# NCCN guidelines in NSCLC (version 3.2016)




Adapted from NSCLC
NCCN Guidelines (version 3.2016)

*For PS 3–4, best supportive care only; ‡If eligible for bevacizumab
¶Bevacizumab is not licensed for second-line use in NSCLC
Cis = cisplatin; Gem = gemcitabine; Pem = pemetrexed;

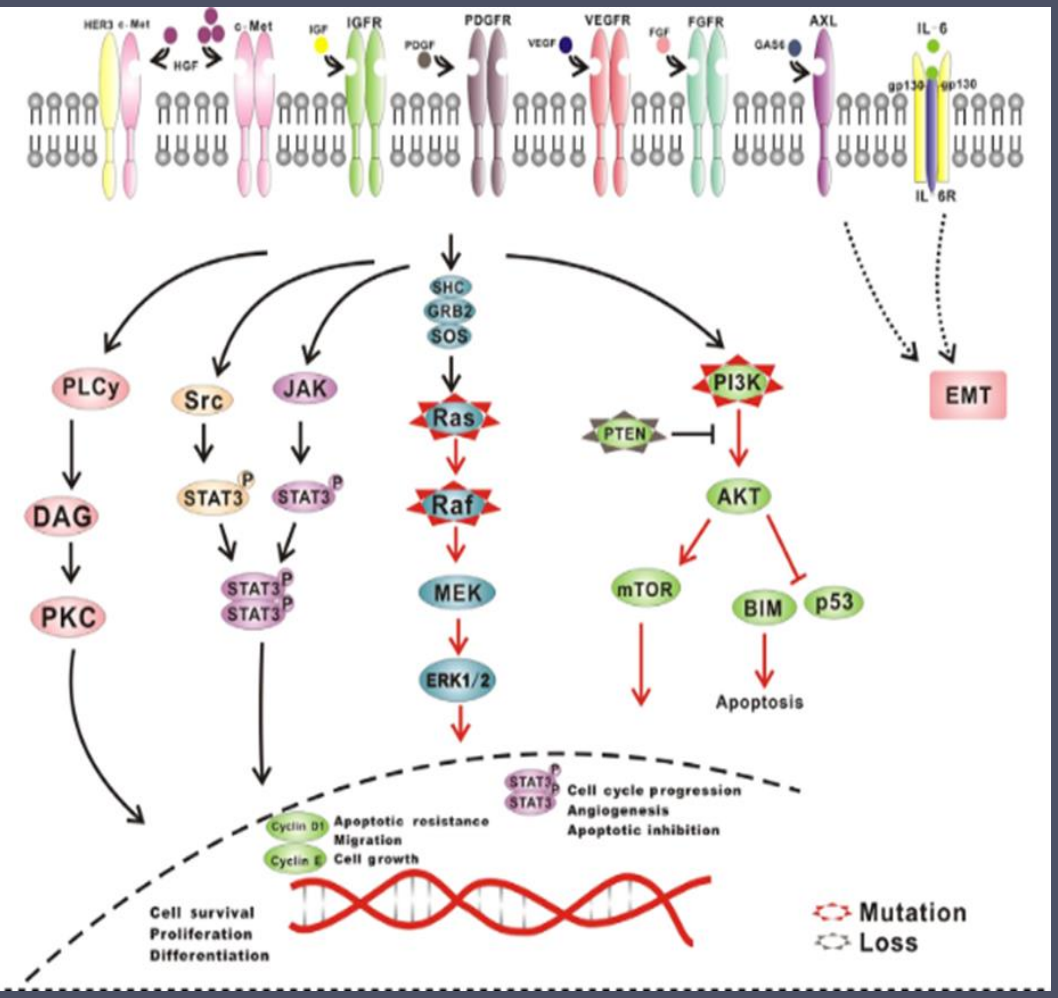
# Μηχανισμοί επίκτητης αντίστασης σε EGFR TKIs




- Νέες μεταλλάξεις αντίστασης (T790M, D761Y, L747S, T854A etc.)
- Ενεργοποίηση εναλλακτικών οδών μεταγωγής σήματος ( Her Family, MET, HGF, IGFR, VEGF, PDGF, FGR, AXL, IL6 etc.
- Ανωμαλίες σε γονίδια των καθοδικών σηματοδοτικών μονοπατιών (Kras, BRAF, PTEN, PIK3CA, BIM …) ,
- Παράλληλη σηματοδότηση (IGF+EGFR)
- Εξαλλαγή σε SCLC
- Επιθηλιακή σε μεσεγχυματική εξαλλαγή
- Συλλογή ATP-δεσμευτικής κασέτας (ABC)
- Άγνωστοι μηχανισμοί

Ohashi et al, J Clin Oncol 2013

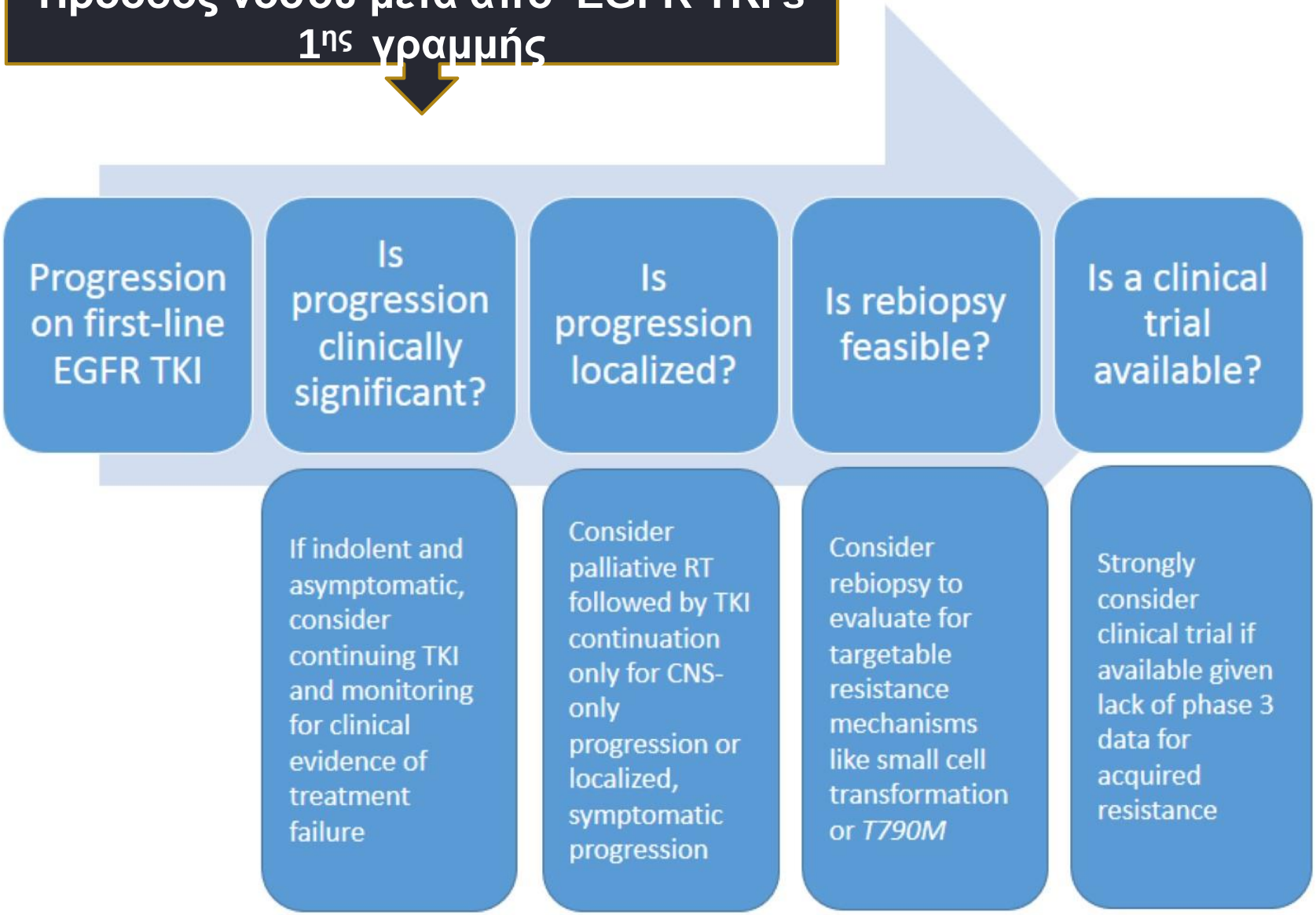
# Μηχανισμοί επίκτητης αντίστασης σε EGFR TKIs



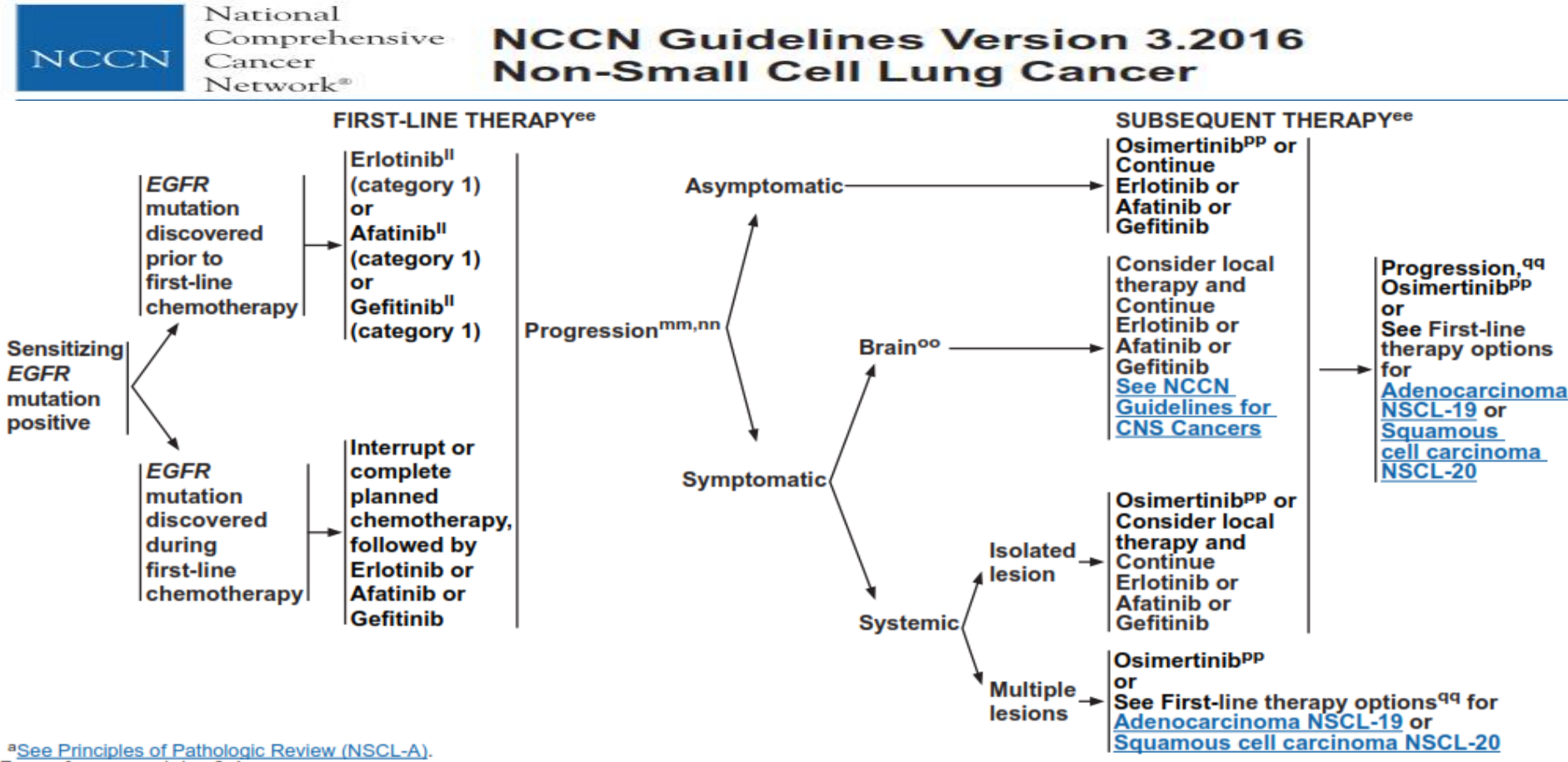

- Νέες μεταλλάξεις αντίστασης (T790M, D761Y, L747S, T854A etc.)
- Ενεργοποίηση εναλλακτικών οδών μεταγωγής σήματος ( Her Family, MET, HGF, IGFR, VEGF, PDGF, FGR, AXL, IL6 etc.
- Ανωμαλίες σε γονίδια των καθοδικών σηματοδοτικών μονοπατιών (Kras, BRAF, PTEN, PIK3CA, BIM …)
- Παράλληλη σηματοδότηση (IGF+EGFR)
- Εξαλλαγή σε SCLC
- Επιθηλιακή σε μεσεγχυματική εξαλλαγή

Ohashi et al, J Clin Oncol 2013

# Πρόοδος νόσου μετά από EGFR TKI's 1ης γραμμής



# Πρόοδος νόσου μετά από EGFR TKI's 1ης γραμμής




[a] See Principles of Pathologic Review (NSCL-A).

[ll] For performance status 0-4.

[mm] Prior to changing therapy, a biopsy is reasonable to determine mechanism of acquired resistance.

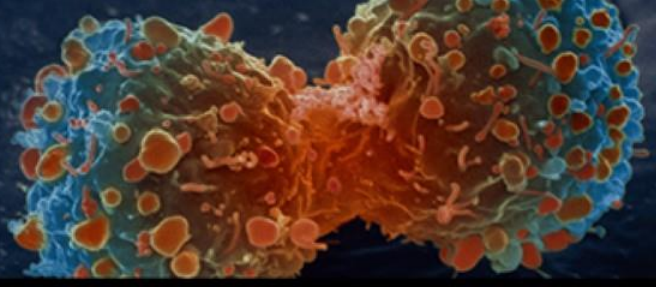
[nn] Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.

[oo] Consider pulse erlotinib for carcinomatosis meningitis.

[pp] Osimertinib is approved for patients with metastatic EGFR T790M mutation-positive tumors, as determined by an FDA-approved test or other validated laboratory developed test performed in a CLIA-approved laboratory.

[qq] Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.

# Feasibility of Rebiopsy



## Rebiopsy during disease progression in patients treated by TKI for oncogene-addicted NSCLC

Cecile Bosc · Gilbert R. Ferretti · Jacques Cadranel · Clarisse Audigier-Valette · Benjamin Besse · Fabrice Barlesi · Chantal Decroisette · Sylvie Lantuejoul · François Arbib · Denis Moro-Sibilot

Received: 23 April 2014 / Accepted: 28 July 2014


**Abstract** All lung cancer patients with mutant epidermal growth factor receptor (EGFR) or rearranged EML4-ALK eventually develop acquired resistance to treatment. Rebiopsy may give insight into the resistance mechanisms and direct further lines of treatment. Here, we evaluate the potential interest and limitations of rebiopsy. Patients with mutant EGFR or rearranged EML4-ALK non-small cell lung cancer (NSCLC) and acquired resistance to tyrosine kinase inhibitors were included in a retrospective study to determine the percentage of patients who underwent rebiopsy and whether rebiopsy would have been possible, or not, in the remaining patients. In a cohort of 84 patients from 6 institutions, a biopsy had been performed in 39 cases. Biopsy samples were sufficient for histopathological or cytological examination in 35 cases (89.7 %). Complete or partial response had been observed in 84.5 % of patients whose cancer further progressed and who underwent rebiopsy. A biopsy could have been considered in 30 of the 45 remaining patients. Those with brain ($N$=9) and bone ($N$=2) metastases and/or with contraindications ($N$=6) were excluded (two patients had both brain metastases and a contraindication). The rebiopsy target was thoracic in 62 % of cases and on distant metastases in 38 % of cases. Patients with NSCLC and an activating mutation could undergo a rebiopsy in 72 % of cases. A response to treatment does not preclude the possibility of rebiopsy at the time of progression.

**Keywords** EGFR mutant lung cancer · ALK rearrangement · Targeted therapy · Acquired resistance · Molecular diagnosis

## Feasibility and clinical impact of re-biopsy in advanced non small-cell lung cancer: A prospective multicenter study in a real-world setting (GFPC study 12-01)

Christos Chouaid[a], Cecile Dujon[b], Pascal Do[c], Isabelle Monnet[d], Anne Madroszyk[e], Herve Le Caer[f], Jean Bernard Auliac[g], Henri Berard[h], Pascal Thomas[i], Herve Lena[j], Gilles Robinet[k], Nathalie Baize[l], Acya Bizieux-Thaminy[m], Gislaine Fraboulet[n], Chrystele Locher[o], Jacques Le Treut[p], Stephane Hominal[q], Alain Vergnenegre[r,*]

[a] Service de pneumologie AP/HP, Saint Antoine, Paris, France
[b] CH Le Chesnay, France
[c] CAC, Caen, France
[d] CHI Creteil, France
[e] CAC Marseille, France
[f] CH Draguignan, France
[g] CH Mantes la Jolie, France
[h] HIA Toulon, France
[i] CH Gap, France
[j] CHU Rennes, France
[k] CHU Brest, France
[l] CHU Angers, France
[m] CH La Roche sur Yon, France
[n] CH Cercy Pontoise, France
[o] CH Meaux, France
[p] CH Aix en Provence, France
[q] CH Annecy-Genevois, Pringy, France
[r] CHU Limoges, France

ARTICLE INFO

*Article history:*
Received 16 June 2014
Received in revised form 20 August 2014
Accepted 22 August 2014

*Keywords:*
Non small cell lung cancer
Re-biopsy
Clinical management
Guidelines
Biomarkers

ABSTRACT

*Objectives:* When advanced non-small-cell lung cancer (NSCLC) progresses during first-line treatment, re-biopsy may be indicated to detect a possible new biological profile (comparison to initial status, emergence of resistance biomarkers, or assessment of new biomarkers). The aim of this pragmatic prospective multicenter study was to assess the feasibility and clinical utility of re-biopsy in advanced NSCLC in a real-world setting.
*Methods:* The main inclusion criteria were advanced NSCLC with an indication for repeat biopsy identified by the patient's clinician. The primary outcome was the percentage of successful procedures. Secondary outcomes were the type of procedure, new biological status, tolerability of the procedure, and clinical utility (treatment modification).
*Results:* From May 2012 to May 2013, 18 centers enrolled 100 patients (males: 44%; median age: 64.8 years; PS 0/1: 88%; adenocarcinoma: 89%; EGFR mutated: 50%; no initial biological profile: 16.4%). Re-biopsy was not possible in 19.5% of cases and provided no or too few tumor cells in 25.6% of cases. Repeat biopsy was useful for guiding treatment in 30.4% (25/82) of cases. Complications were infrequent (2 cases of moderate bleeding and 1 case of pneumothorax).
*Conclusion:* Re-biopsy of advanced NSCLC is feasible in the real-world setting, with acceptable adverse events. Guidelines are needed on the indications of re-biopsy, the choice of procedure, the sampling site, and laboratory analysis.

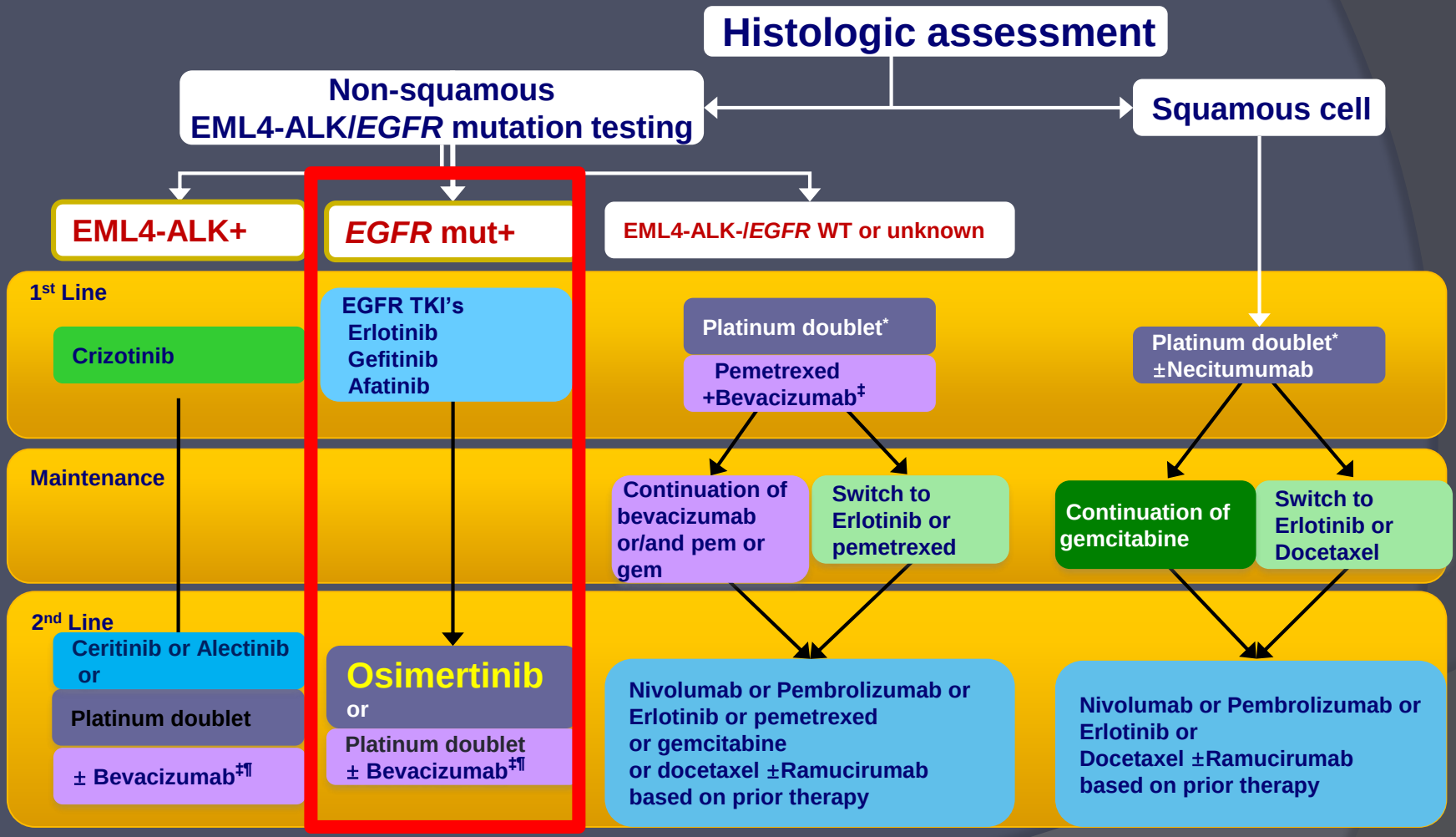


**Feasible in 70-80% of cases**

Bosc C, et al. *Target Oncol.* 2015;10:247-253. Chouaid C, et al. *Lung Cancer.* 2014;86:170-173.

Medscape EDUCATION

# NCCN guidelines in NSCLC (version 3.2016)




*For PS 3–4, best supportive care only; ‡If eligible for bevacizumab
¶Bevacizumab is not licensed for second-line use in NSCLC
Cis = cisplatin; Gem = gemcitabine; Pem = pemetrexed;

Adapted from NSCLC
NCCN Guidelines (version 3.2016)

# Third Generation EGFR TKI's

- **Osimertinib (Tagrisso AZD9291 [AstraZeneca's]**
- **Rociletinib (CO-1686 [Clovis']**

- HM61713 [Hanmi's]
- ASP8273 [Astellas]
- EGF816 [Novartis]

# Third Generation EGFR TKI's

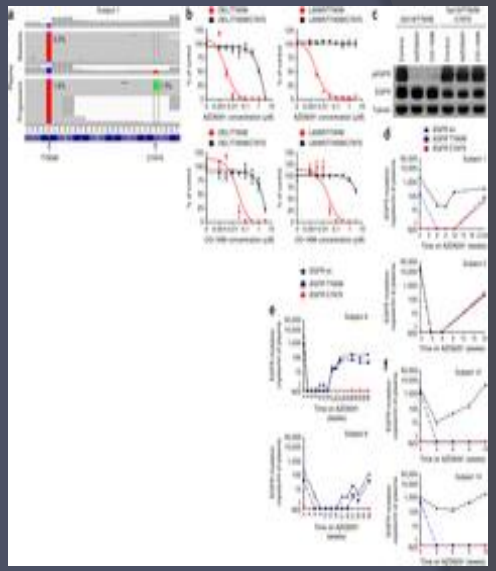
- **Osimertinib  Tablet 80mgx1**
- $12,750/month

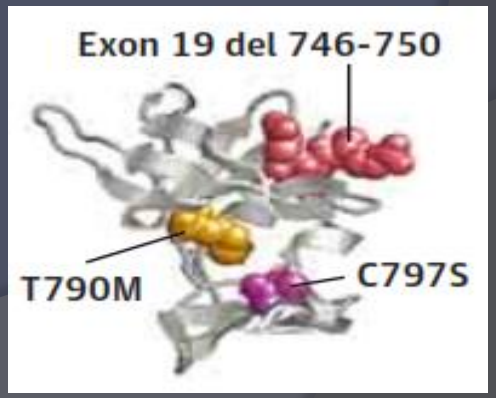
- US Food and Drug Administration (FDA) 11/2015
- The European  Medicines Agency (EMA) 02/2016

| | | |
|---|---|---|
| RR 62%, PFS 11m | AURA (NCT01802632) | • Phase 1 extension<br>• Further assessment of efficacy/tolerability of osimertinib 80 mg qd in patients with *T790M*-positive NSCLC |
| RR 66%, PFS 9.7m | AURA2 (NCT02094261) | • Confirmatory global phase 2<br>• Assessment of efficacy/tolerability of osimertinib 80 mg qd in patients with *T790M*-positive NSCLC |
| | AURA3 (NCT02151981; recruiting) | • Phase 3<br>• Osimertinib vs platinum-based doublet chemotherapy as second-line therapy in patients with *T790M*-positive advanced/metastatic NSCLC that has progressed following EGFR TKI therapy |

# Resistance to T790M mutation

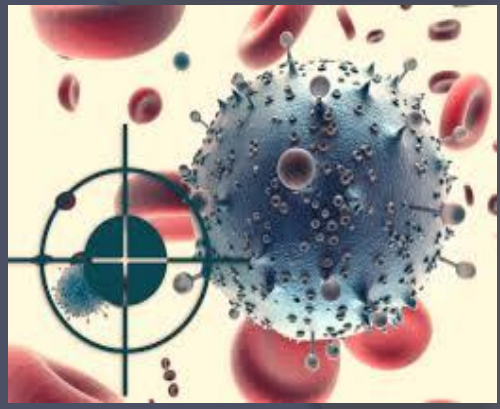
- 15 patients positive for the T790M mutation before treatment developed **Osimertinib** resistance (cfDNA, droplet digital PCR ):
- 6 cases C797S mutation
- 5 cases maintained the T790M mutation but did not acquire the C797S mutation
- and 4 cases lost the T790M mutation despite the presence of the underlying *EGFR* activating mutation.





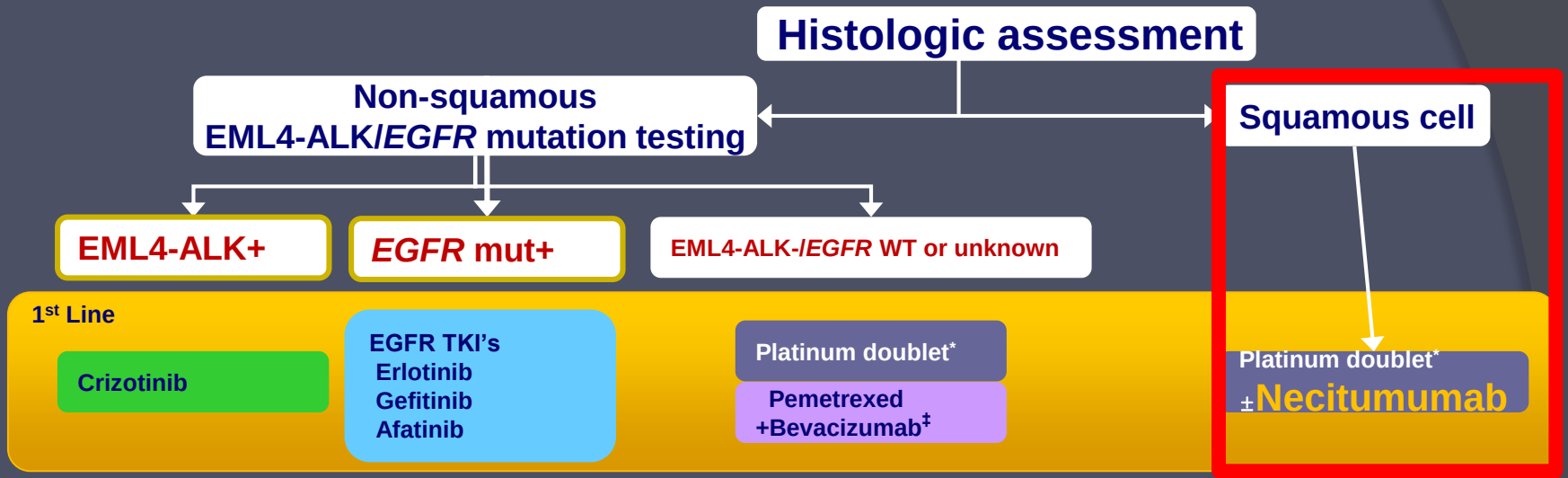

Thress K et al. Nature Medicine 2015

# Στοχευμένες θεραπείες



- Μοριακή ανάλυση
- **Αναστολείς του EGFR**
  - TKI's: 1ης, 2ης και 3ης γενιάς
  - **Μονοκλωνικά αντισώματα**
- Αναστολείς του ALK: 1ης και 2ης γενιάς
- Αναστολείς του VEGF
- Προοπτικές
- Συμπεράσματα

# NCCN guidelines in NSCLC (version 3.2016)




Adapted from NSCLC
NCCN Guidelines (version 3.2016)

*For PS 3–4, best supportive care only; ‡If eligible for bevacizumab
¶Bevacizumab is not licensed for second-line use in NSCLC
Cis = cisplatin; Gem = gemcitabine; Pem = pemetrexed;

# Necitumumab (Portrazza)

- Monoclonal antibody that targets EGFR

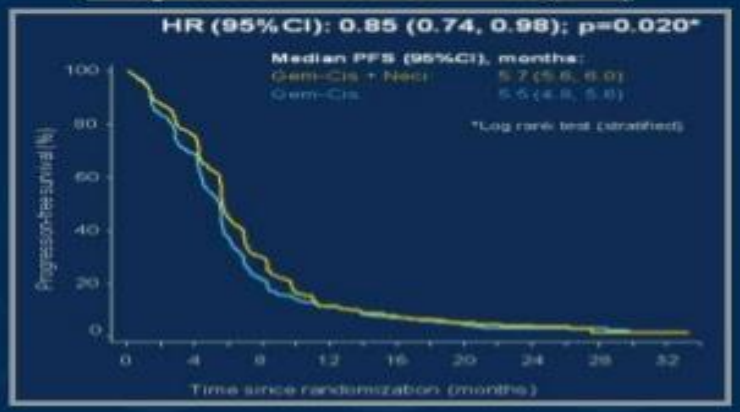
FDA 11/2015

## SQUIRE: Efficacy of Necitumumab

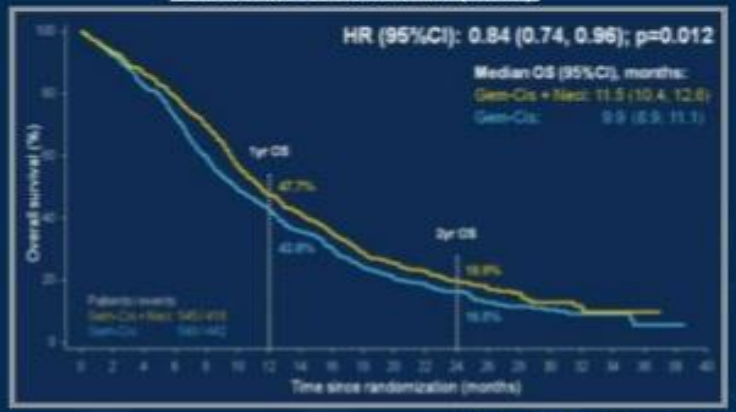
| | Chemo/Neci (N = 545) | Chemo alone (N = 548) | P |
|---|---|---|---|
| ORR (CR + PR) | 31.2% | 28.8% | 0.400 |
| DCR (CR + PR +SD) | 81.8% | 77.0% | 0.043* |

*Cochran-Mantel-Haenszel test (stratified)

Progression-Free Survival (ITT)



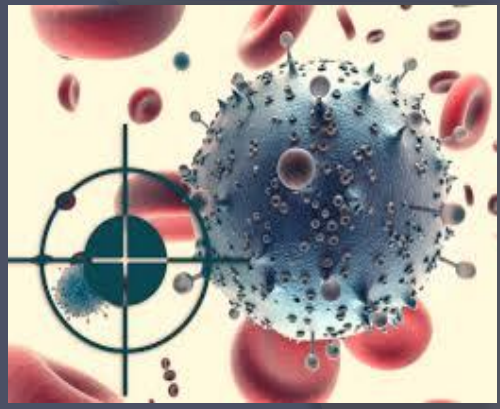

Overall Survival (ITT)




Thatcher, A#8008

BEST OF ASCO
2014 ANNUAL MEETING

# Στοχευμένες θεραπείες



- Μοριακή ανάλυση
- Αναστολείς του EGFR
  - TKI's: 1ης, 2ης και 3ης γενιάς
  - Μονοκλωνικά αντισώματα
- **Αναστολείς του ALK: 1ης και 2ης γενιάς**
- Αναστολείς του VEGF
- Προοπτικές
- Συμπεράσματα

# ALK αναστολείς

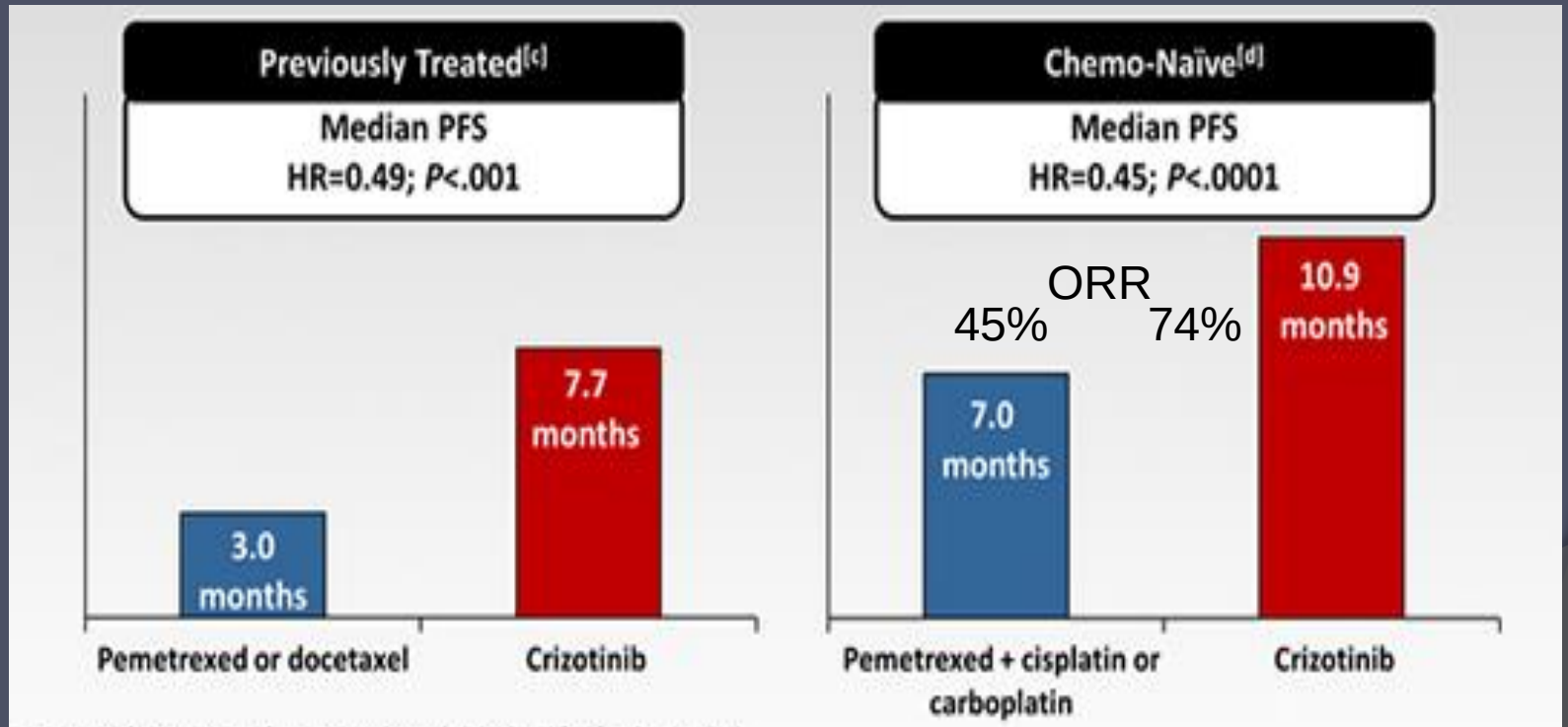
- 1ης γενιάς
  - Crizotinib (Xalkori, Pfizer)
- 2ης γενιάς ALK αναστολείς
  - Ceritinib (Zykadia, Novartis)
  - Alectinib  (Alecensa, Roche's)
- AP26113
- X-396




1.Shaw, et al. N Engl J Med 2014; 2.Ou SL., et al. *J Clin Oncol* 2015
3. Ou, et al. ECC 2013; 4. Ou, et al. WCLC 2013

# Crizotinib in ALK+ NSCLC

- Phase I και II PFS 9.7 και 8.1μ αντίστοιχα [a,b]
- Phase III [c,d]

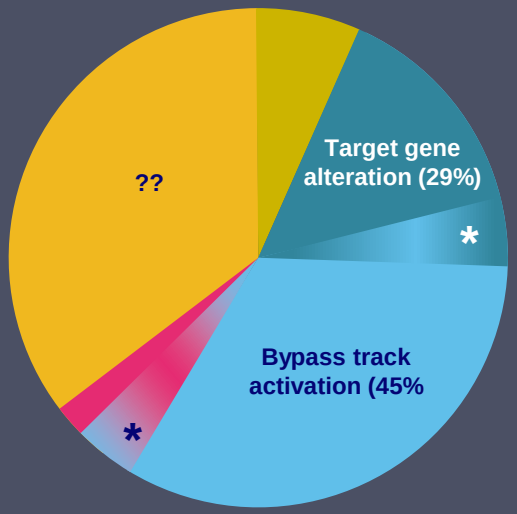



a. Camidge DR, et al. *Lancet Oncol*. 2012;13(10):1011-1019.
b. Kim D-W, et al. ASCO 2012. Abstract 7533.
c. Shaw AT, et al. *N Engl J Med*. 2013;368(25):2385-2394.
d. Mok TS, et al. ASCO 2014. Abstract 8002.

Medscape EDUCATION

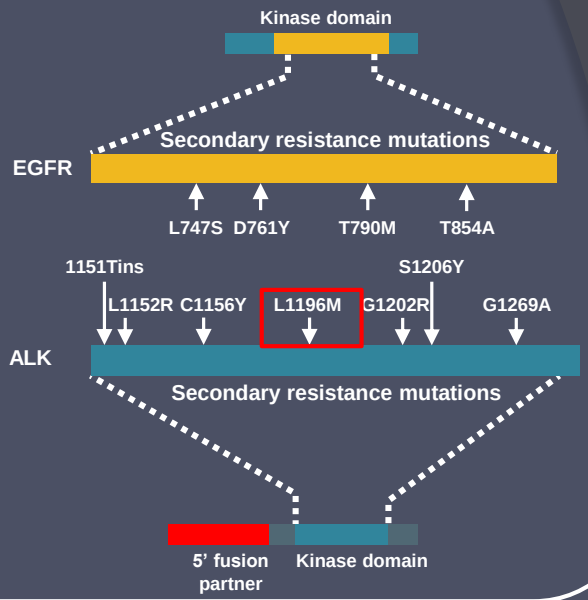
# Crizotinib: επίκτητη αντίσταση

## Acquired resistance[1–2]

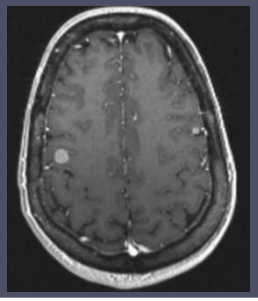



- *ALK* amplification
- *ALK* mutation
- *EGFR* activation
- *CKIT* amplification
- Unknown

30%




## Brain metastases[3–5]



- CNS was the first site of progression in 46% of *ALK*+ crizotinib treated patients

1. Shaw & Engelman. J Clin Oncol 2013; 2. Gainor & Shaw. J Clin Oncol 2013
3. Chun, et al. Cancer Biol Ther 2012; 4. Weickhardt, et al. ASCO 2012; 5. Otterson, et al. ASCO 2012

# Ceritinib in ALK-positive NSCLC ASCEND-1, 2 and 3: Objective Response Rates

| | ASCEND-1[1] | | ASCEND-1[1] | ASCEND-2[2] | | ASCEND-1[1] | ASCEND-3[3] |
|---|---|---|---|---|---|---|---|
| | **All** | | **ALKi pre-treated** | | | **ALKi Naive** | |
| | **n=246** | | **n=163** | **n = 102*** | | **n=83** | **n=106*** |
| Complete Response,% | 2 | | 2 | - | | 1 | - |
| Partial Response, % | 60 | | 55 | 49 | | 71 | 68 |
| Stable Disease,% | 17 | | 18 | 36 | | 17 | 20 |
| Progressive Disease,% | 7 | | 10 | 12 | | 0 | 8 |
| Unknown, % | 14 | | 16 | 3 | | 11 | 4 |
| **Overall Response Rate, %** | **62** | | **57** | 49 | | **72** | 68 |
| **Clinical Benefit Rate, %** | **79** | | **75** | 85 | | **89** | 88 |

**BIRC: Blinded Independent Central Review Committee*


[1] *Kim DW, et al. Lancet Oncol. 2016 Mar 10. pii: S1470-2045(15)00614-2*
[2] Mok T. et al. JCO, 2015 ASCO Annual Meeting (May 29 - June 2, 2015). Vol 33, No 15_suppl (May 20 Supplement), 2015: 8059
[3] Felip E. et al. JCO, 2015 ASCO Annual Meeting (May 29 - June 2, 2015). Vol 33, No 15_suppl (May 20 Supplement), 2015: 8060

# Ceritinib in ALK-positive NSCLC
## ASCEND-1, 2 and 3: PFS and Duration of Response

| | ASCEND-1[1] | | ASCEND-1[1] | ASCEND-2[2] | | ASCEND-1[1] | ASCEND-3[3] |
|---|---|---|---|---|---|---|---|
| | **All** | | **ALKi pre-treated** | | | **ALKi Naive** | |
| | n=246 | | n=163 | n=140 | | n=83 | n=124 |
| PFS, median (mo) | **9.0** (6.9-11.0) | | **6.9** (5.6-8.7) | 7.2 (5.4-9.0) | | **18.4** (11.1-NE) | 11.1* (9.3-NE) |
| DOR, median (mo) | 9.7 | | 8.3 (6.8-9.7) | 9.7 (5.6-12.9) | | 17.0 (11.3-NE) | 9.3 (9.1-NE) |
| 12-month PFS | | | 27% | | | 62% | |
| 12-month OS | | | 67% | | | 83% | |

*Data from ASCEND-3 are not mature.

Median duration of follow-up (months):
ASCEND-1 ALKi pre-treated: 10.2 (0.1-24.1); ASCEND -1 ALKi naive: 12.5 (0.4-22.2); ASCEND-2: 11.3 (0.1-18.9); ASCEND-3: 8.31 (0.6-16.3)

[1]*Kim DW, et al. Lancet Oncol. 2016 Mar 10. pii: S1470-2045(15)00614-2*
[2]Mok T. et al. JCO, 2015 ASCO Annual Meeting (May 29 - June 2, 2015). Vol 33, No 15_suppl (May 20 Supplement), 2015: 8059
[3]Felip E. et al. JCO, 2015 ASCO Annual Meeting (May 29 - June 2, 2015). Vol 33, No 15_suppl (May 20 Supplement), 2015: 8060

# ALK inhibitors

## Alectinib[1–2]

### 12/2015

**Phase I/II data (n=70)**

- Japanese patients
- ORR 94% in crizotinib-naïve patients following chemotherapy

**Phase II data (n=47)**

- ORR 55% in crizotinib-failed patients
- RR 52% in brain metastasis

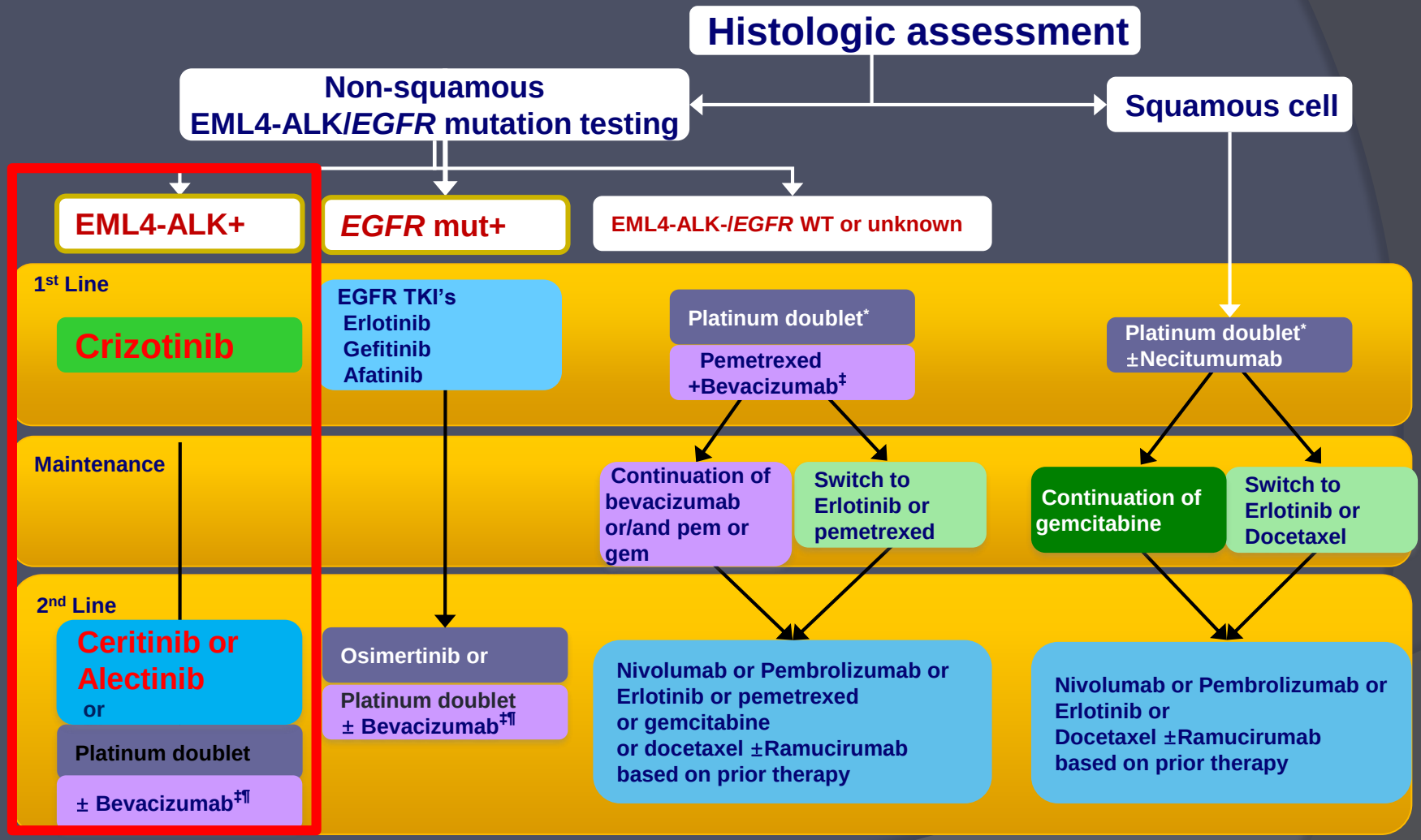
**Key ongoing studies**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1–4L | NCT01685138 | Ph II | Ceritinib (single-arm) | ≥2L‡ | NCT01801111 | Ph II | Alectinib |
| ≥3L‡ | NCT01685060 | Ph II | Ceritinib (single-arm) | | | | |

*6% of patients had cancers other than NSCLC
‡following crizotinib failure

1. Seto, et al. Lancet Oncol 2013
2. Ou SL., et al. J Clin Oncol 2015

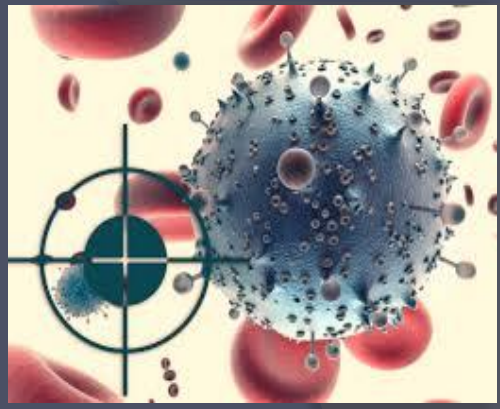
# NCCN guidelines in NSCLC (version 3.2016)




*For PS 3–4, best supportive care only; ‡If eligible for bevacizumab
¶Bevacizumab is not licensed for second-line use in NSCLC
Cis = cisplatin; Gem = gemcitabine; Pem = pemetrexed;

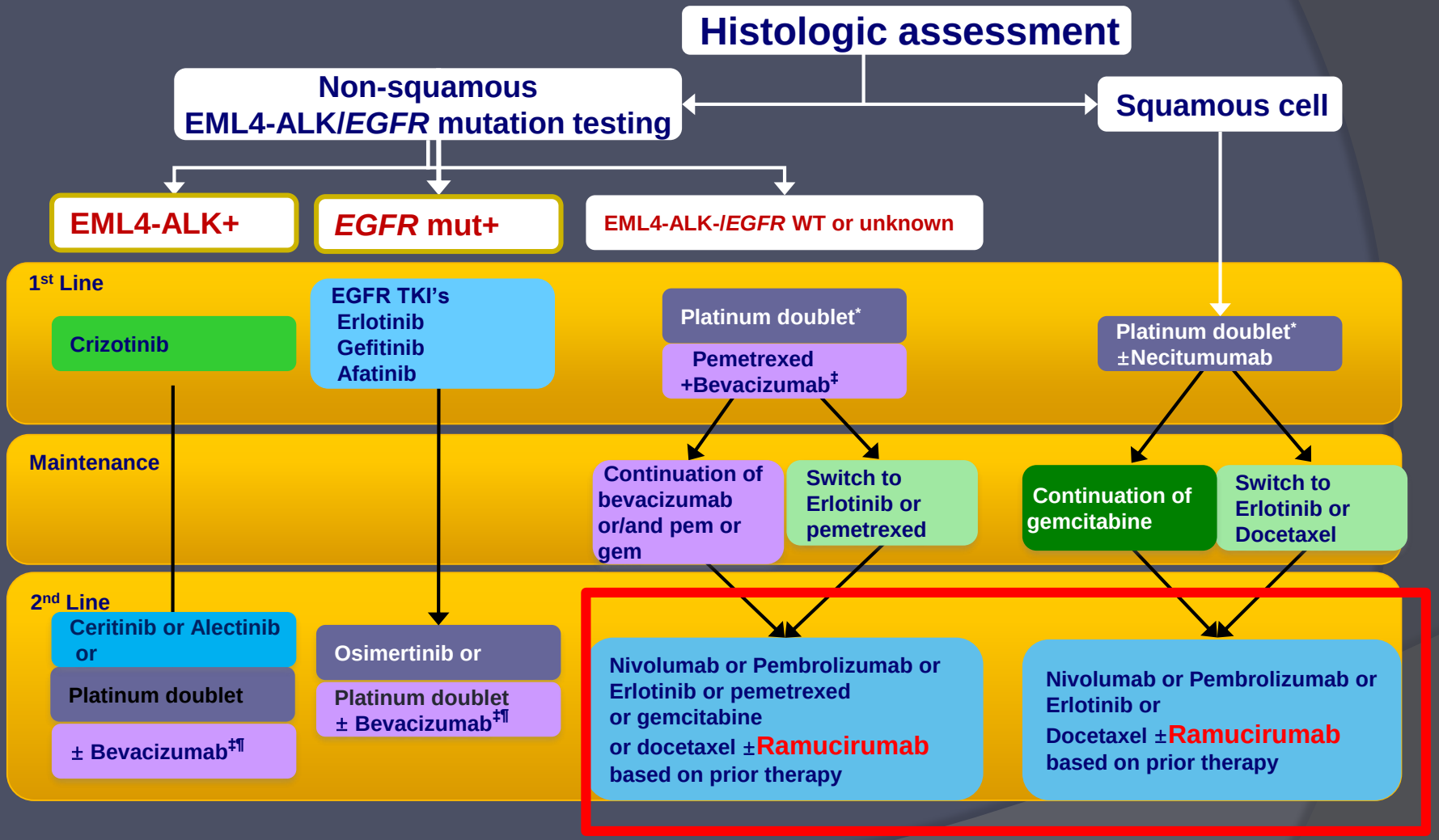
Adapted from NSCLC
NCCN Guidelines (version 3.2016)

# Στοχευμένες θεραπείες



- Μοριακή ανάλυση
- Αναστολείς του EGFR
  - TKI's: 1ης, 2ης και 3ης γενιάς
  - Μονοκλωνικά αντισώματα
- Αναστολείς του ALK: 1ης και 2ης γενιάς
- **Αναστολείς του VEGF**
- Προοπτικές
- Συμπεράσματα

# NCCN guidelines in NSCLC (version 3.2016)

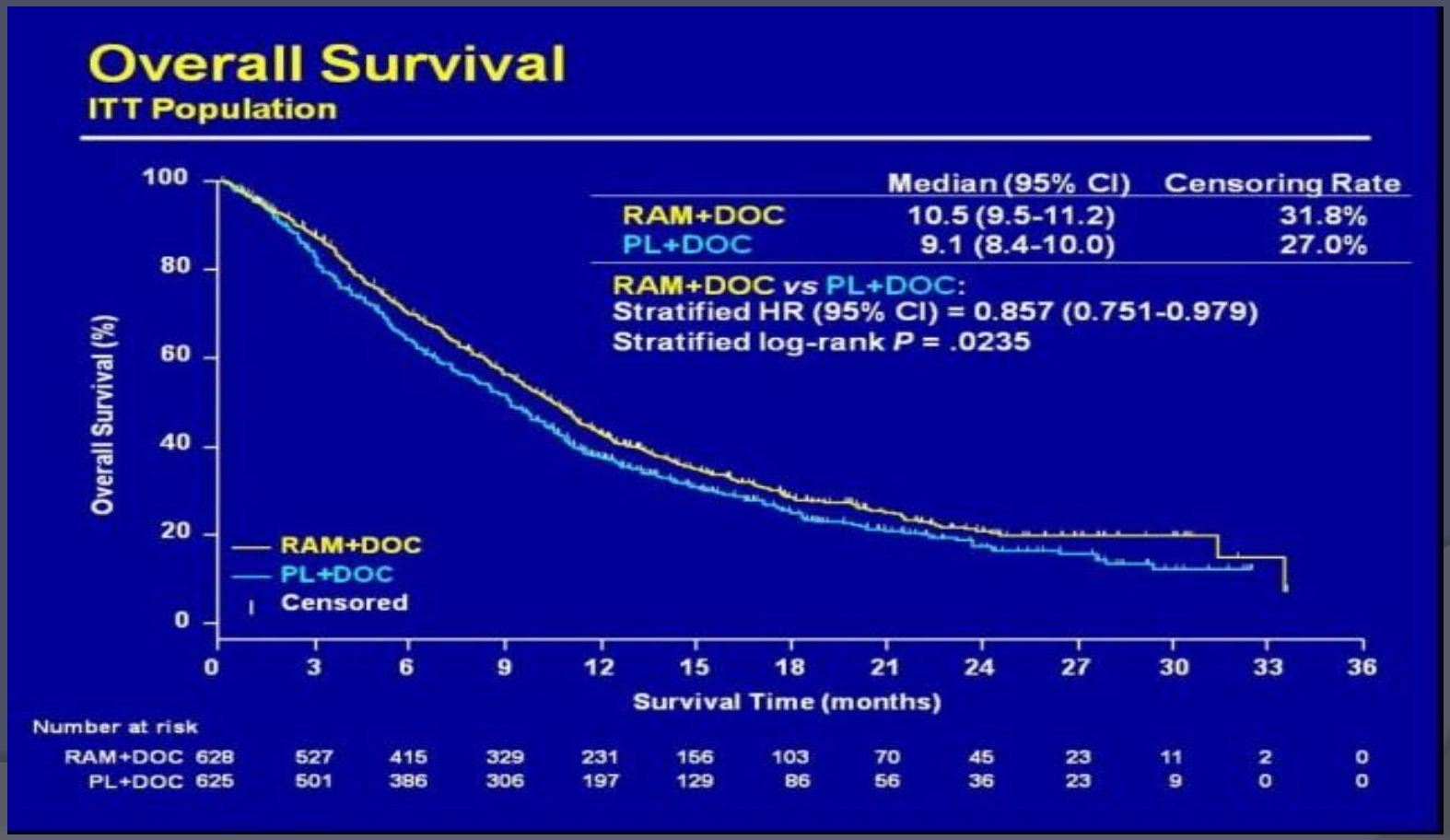



*For PS 3–4, best supportive care only; ‡If eligible for bevacizumab
¶Bevacizumab is not licensed for second-line use in NSCLC
Cis = cisplatin; Gem = gemcitabine; Pem = pemetrexed;

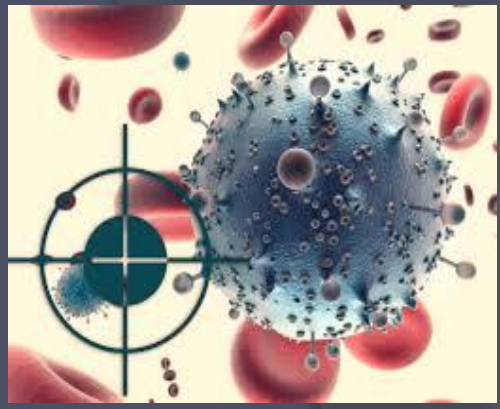
Adapted from NSCLC
NCCN Guidelines (version 3.2016)

# REVEL: Second-line Docetaxel + Ramucirumab (Cyramza) vs Docetaxel + Placebo, *Phase 3 Study*

- Antiangiogenesis agent: Monoclonal antibody that binds to VEGFR2

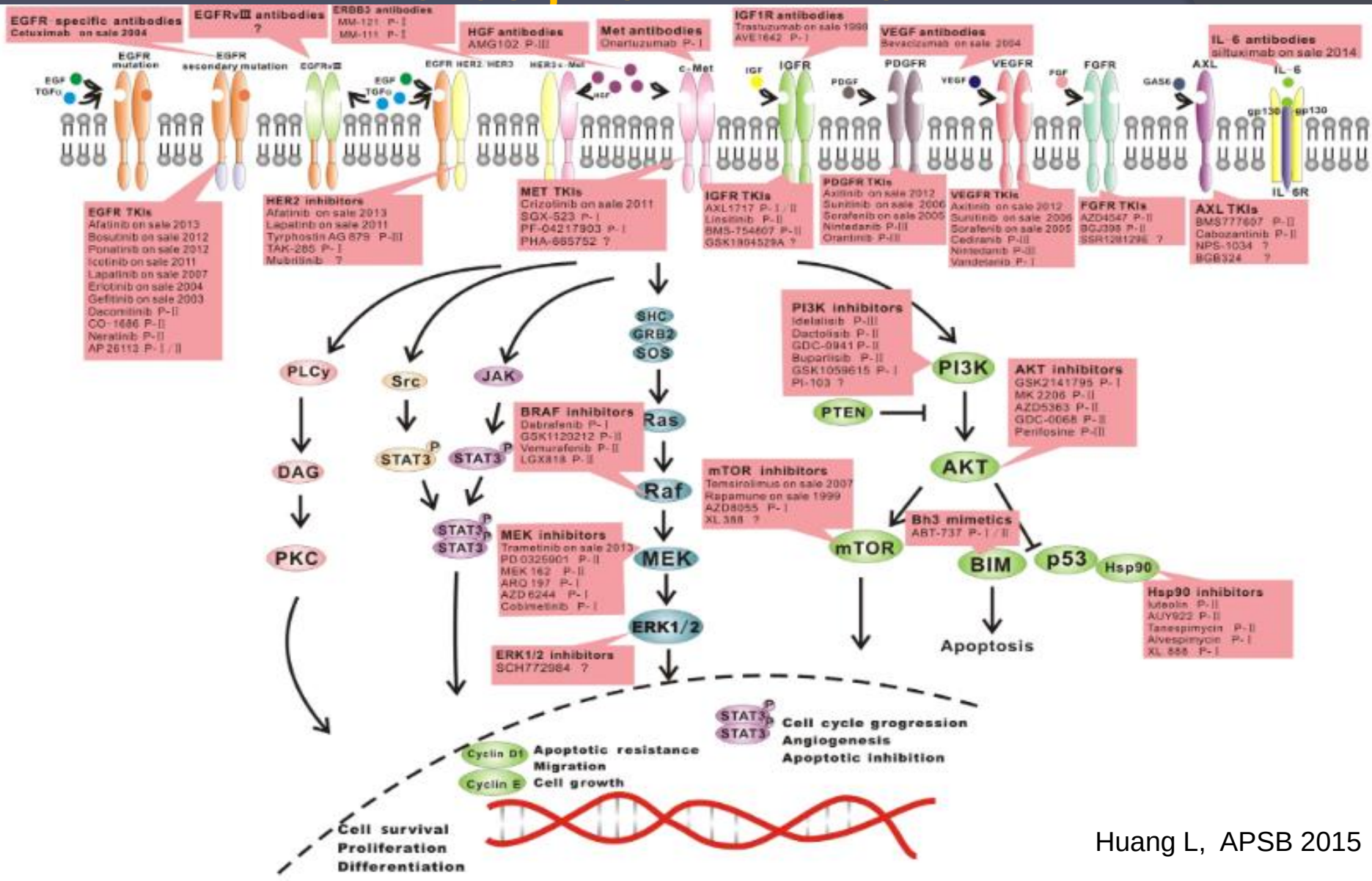


# Στοχευμένες θεραπείες



- Μοριακή ανάλυση
- Αναστολείς του EGFR
  - TKI's: 1ης, 2ης και 3ης γενιάς
  - Μονοκλωνικά αντισώματα
- Αναστολείς του ALK: 1ης και 2ης γενιάς
- Αναστολείς του VEGF
- **Προοπτικές**
- **Συμπεράσματα**

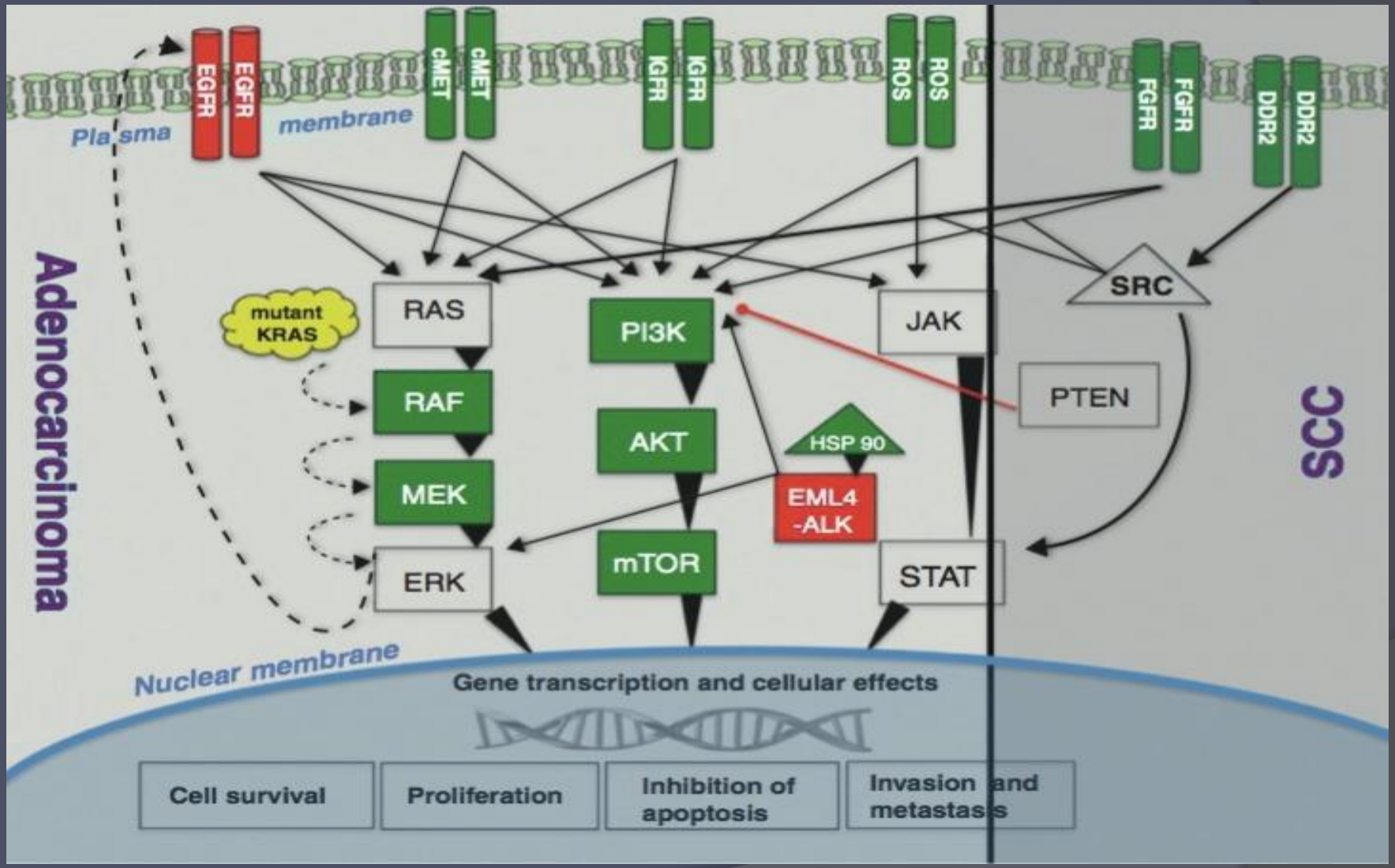
# Πιθανοί στόχοι υπερνίκησης της αντίστασης στους EGRF –TKI's




Huang L, APSB 2015

**Figure 5** The potential targets for the relative treatment to overcome the resistance to EGFR-TKIs.

# Άλλοι στόχοι




Chan B, *TLCR* 2015

# The NSCLC pipeline includes multiple options across therapy categories

## Key In-Market and Investigational Agents for NSCLC


Source: IMS Health R&D Focus ™, clinicaltrials.gov, company websites Dec. 2014

Chart notes:
The chart includes globally marketed and emerging therapies in NSCLC as of Dec. 2014. Opdivo approval for NSCLC Mar 2015 * denotes: ALK +ve NSCLC, ^ denotes: EGFR +ve NSCLC pts., ** Phase II/III, ^^ denotes trial ongoing only in Israel, S denotes Phase III planned

# Συμπεράσματα

- Από την εμπειρική θεραπεία περάσαμε στην εξατομικευμένη θεραπεία
- Ο ιστολογικός τύπος του ΜΜΚΠ και στη συνέχεια το μοριακό προφίλ του όγκου (EGFR, ALK, ROS1, RET….) καθορίζει τη θεραπευτική προσέγγιση στα μη πλακώδη
- Οι Υγρές βιοψίες και οι Επαναληπτικές  βιοψίες μπορούν να συνεισφέρουν στη θεραπεία
- Η συνεργασία όλων των ειδικοτήτων εξασφαλίζει τη βέλτιστη θεραπευτική αντιμετώπιση

# Ευχαριστώ...