# Druggable Targets of Squamous Cell Carcinoma

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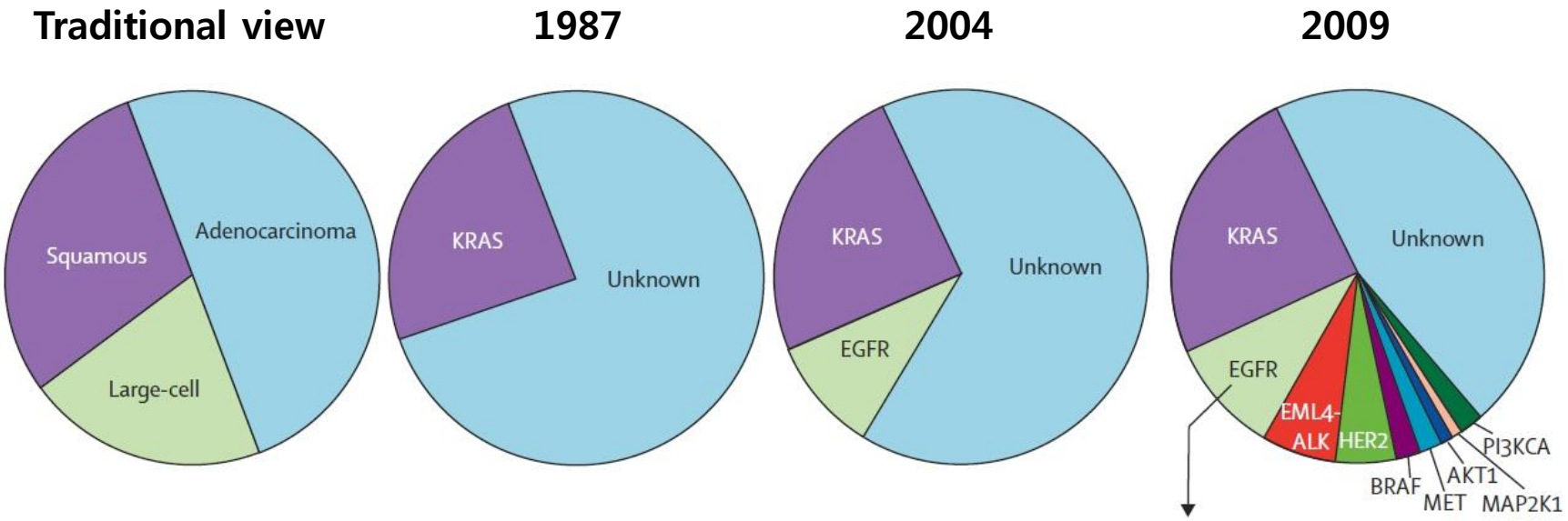
# Evolution of knowledge in NSCLC




Pao W & Girard N. Lancet Oncol 2011;12:175-80.

EP/PEV

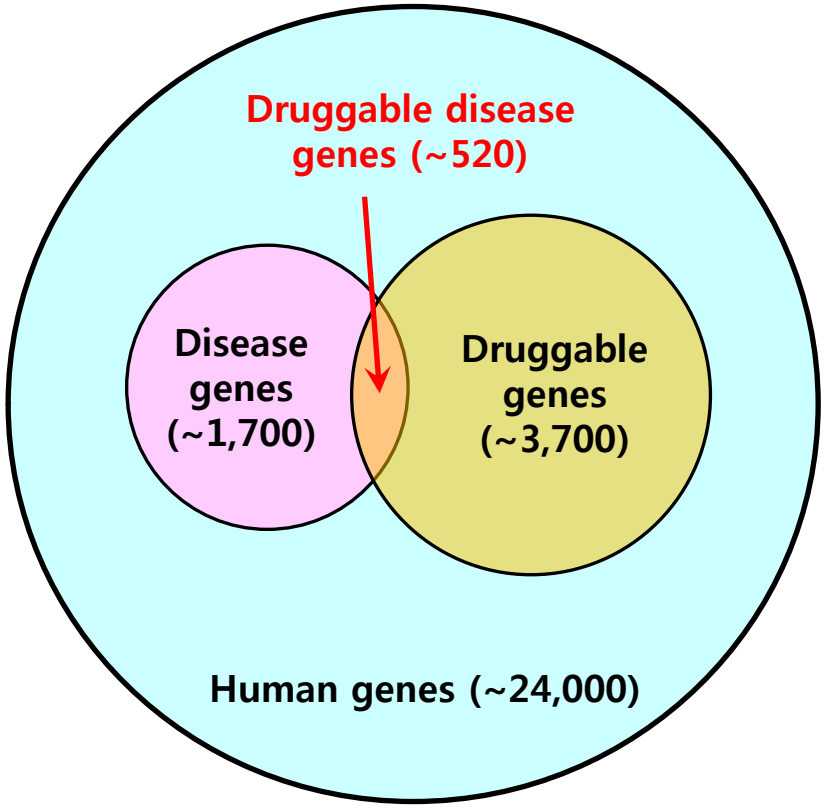
TP/GP

Gefitinib/Erlotinib

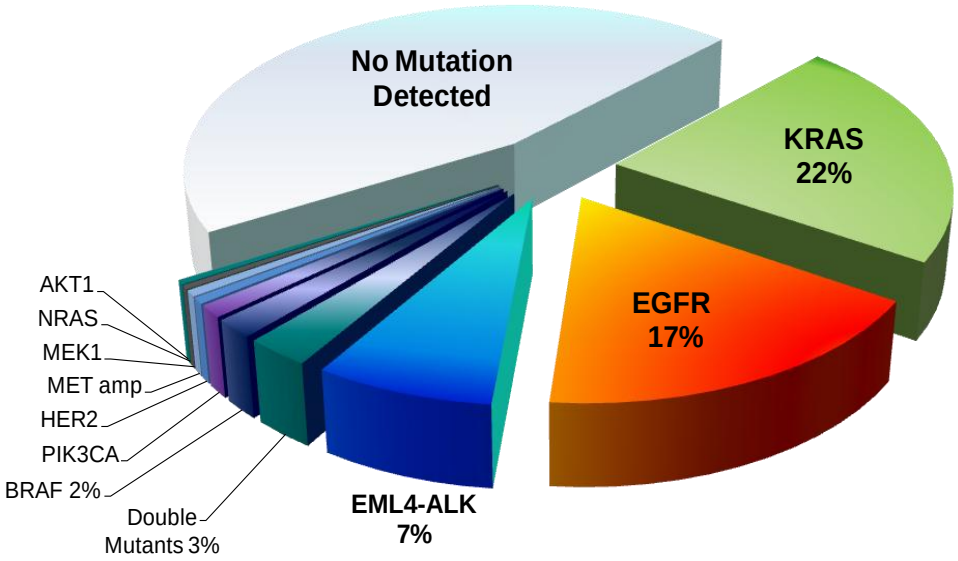
Pemetrexed, Bevacizumab

Crizotinib

# Potential "druggable" molecular targets?




## "Druggable" targets in lung adenocarcinomas




**Lung Cancer Molecular Consortium Lung Adenocarcinomas**

**Mutations found in 54% (280/516)**

Kris MG, et al. ASCO 2011 CRA7506
Johnson BE, et al. WCLC 2011 Abstract O16.01

Clinical features

Carcinogenesis

Targetable driver mutations

Clinical trials

**Clinical features**

Carcinogenesis

Targetable driver mutations

Clinical trials

# Squamouc cell lung cancer

- Associated most strongly with cigarette smoking
- Symptomatic with centrally located tumors
- Cavitation
- Tend to be locally aggressive
- Metastasis occurring less frequently than in adenoca.
- Consistantly express p63, negative for TTF1
- No effective targeted therapy
- Lack of efficacy or toxicity for: pemetrexed, bevacizumab
- Standard treatment of metastatic disease
  : platinum-based doublet

# Survival differences according to histology subtype within each diagnostic period

| Period | Histology | Hazard Ratio (95% CI) | *p* |
|---|---|---|---|
| 1990–1993 | Adenocarcinoma | Reference | |
| | Squamous | 0.990 (0.952–1.030) | 0.62 |
| | Large cell | 1.121 (1.068–1.177) | <0.0001 |
| | Other | 1.203 (1.159–1.250) | <0.0001 |
| 1994–1997 | Adenocarcinoma | Reference | |
| | Squamous | 1.007 (0.969–1.046) | 0.72 |
| | Large cell | 1.117 (1.063–1.173) | <0.0001 |
| | Other | 1.178 (1.140–1.217) | <0.0001 |
| 1998–2001 | Adenocarcinoma | Reference | |
| | Squamous | 0.997 (0.968–1.027) | 0.85 |
| | Large cell | 1.106 (1.060–1.153) | <0.0001 |
| | Other | 1.172 (1.144–1.200) | <0.0001 |
| 2002–2005 | Adenocarcinoma | Reference | |
| | Squamous | 1.033 (1.004–1.062) | 0.02 |
| | Large cell | 1.171 (1.117–1.240) | <0.0001 |
| | Other | 1.214 (1.189–1.240) | <0.0001 |

CI, confidence interval.

Morgensztern D, et al. J Thorac Oncol 2009;4:1524-9.

Clinical features

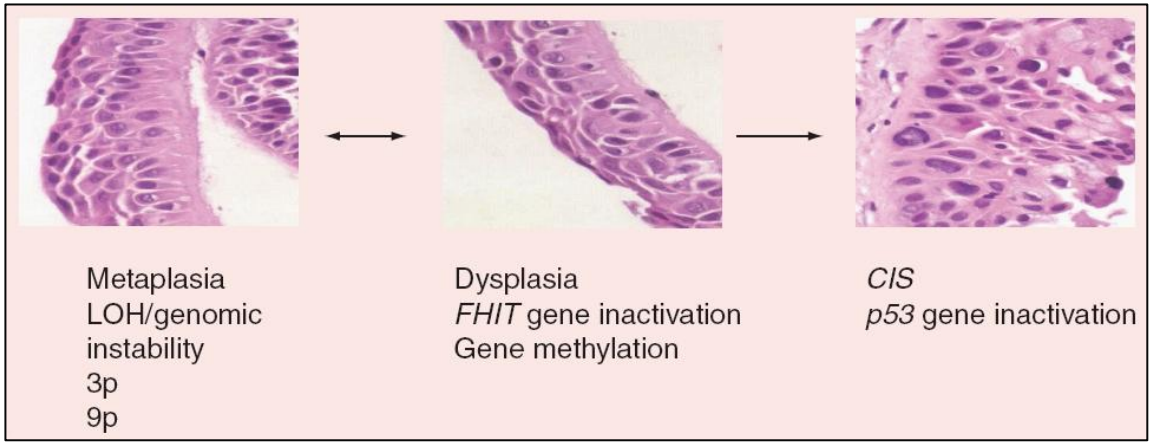
**Carcinogenesis**

Targetable driver mutations

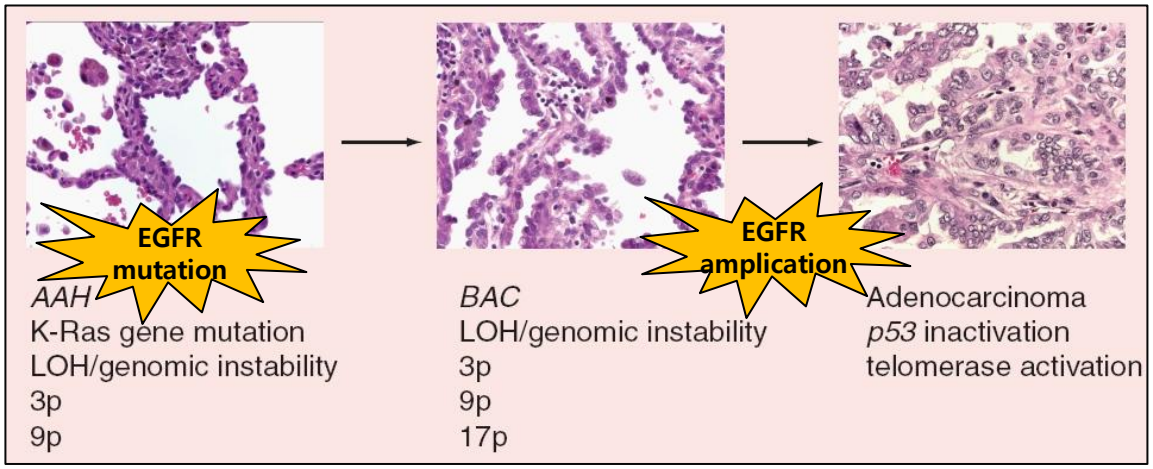
Clinical trials

# Sequential changes in multistep carcinogenesis of lung carcinoma

**Squamous cell carcinoma**

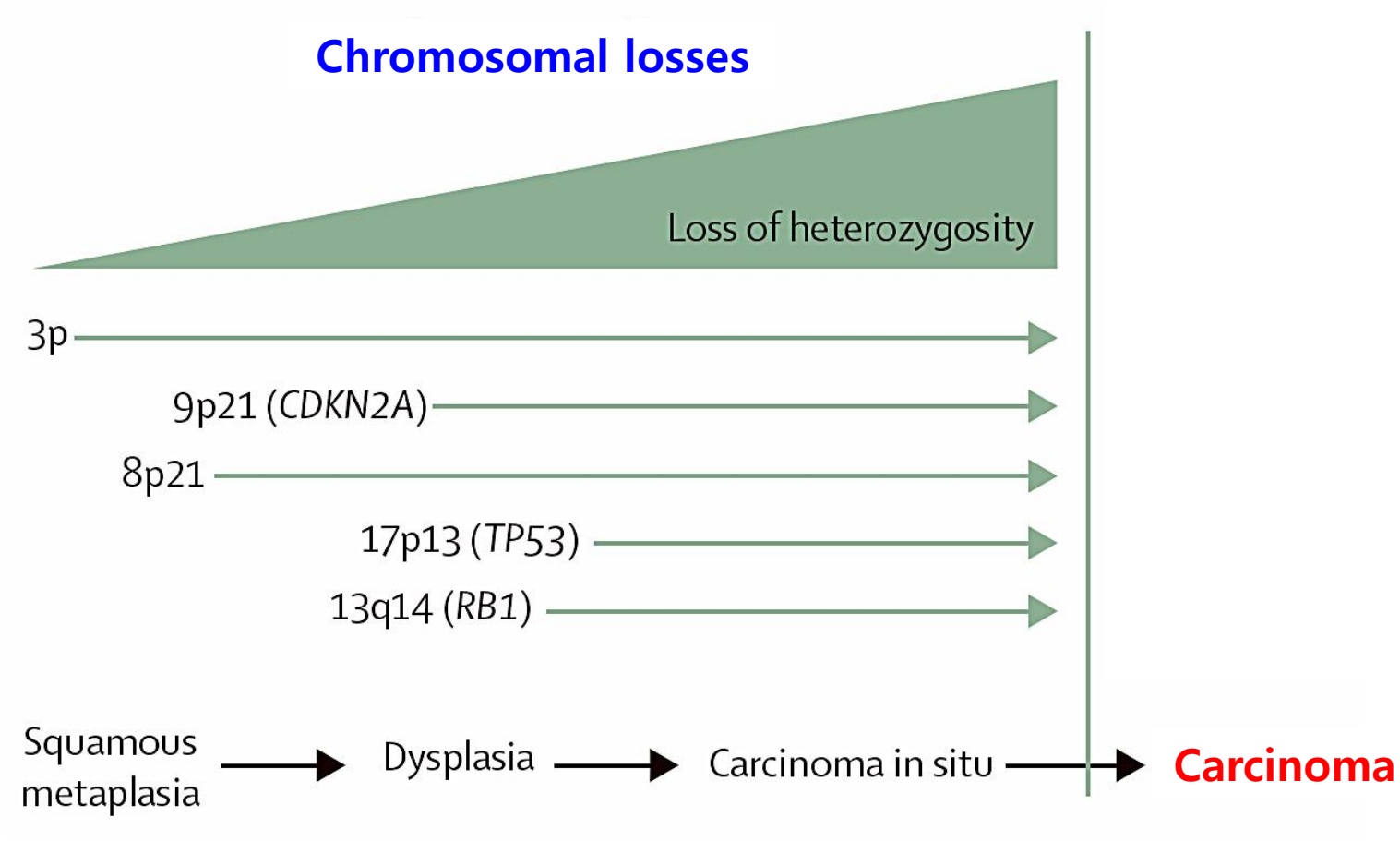



**Adenocarcinoma**




Dacic S. Expert Rev Mol Diagn 2007;7:77–86.

# Carcinogenic sequence of SQCLC




Drilon A, et al. Lancet Oncol 2012;13:e418–26.

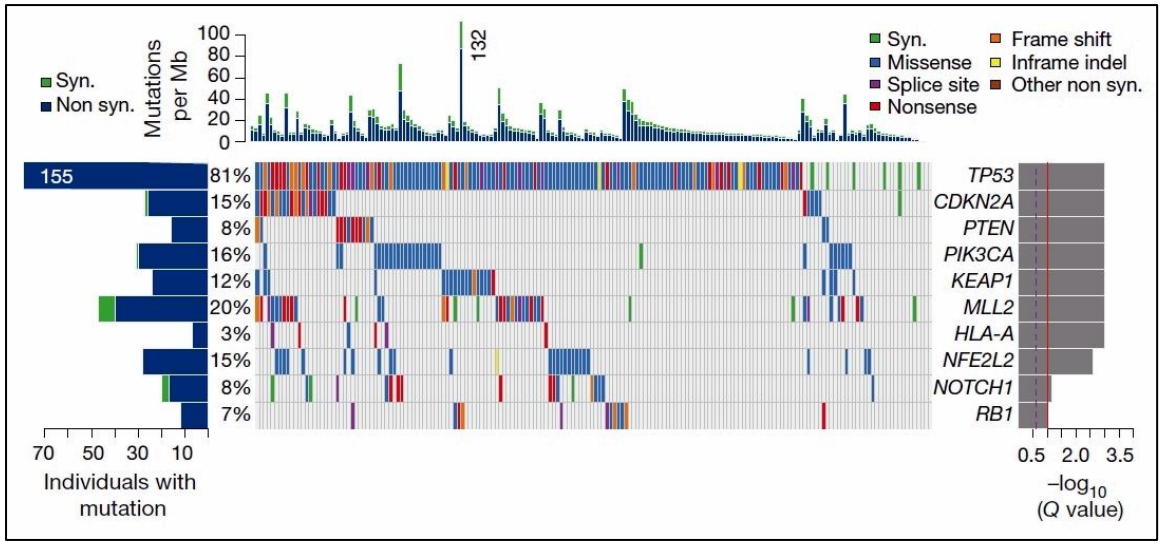
Clinical features

Carcinogenesis

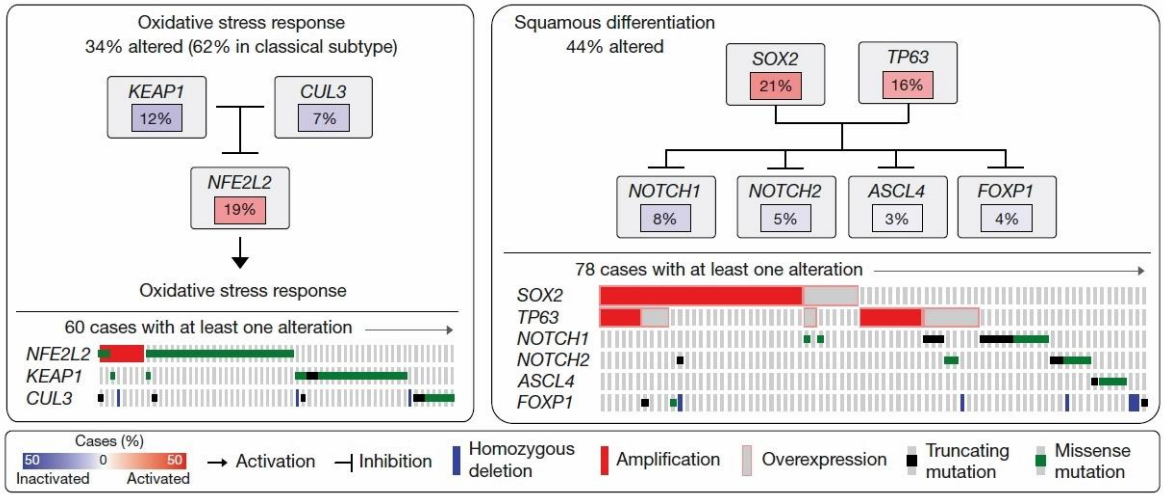
**Targetable driver mutations**

Clinical trials

# Significantly mutated genes and pathways in SQCLC

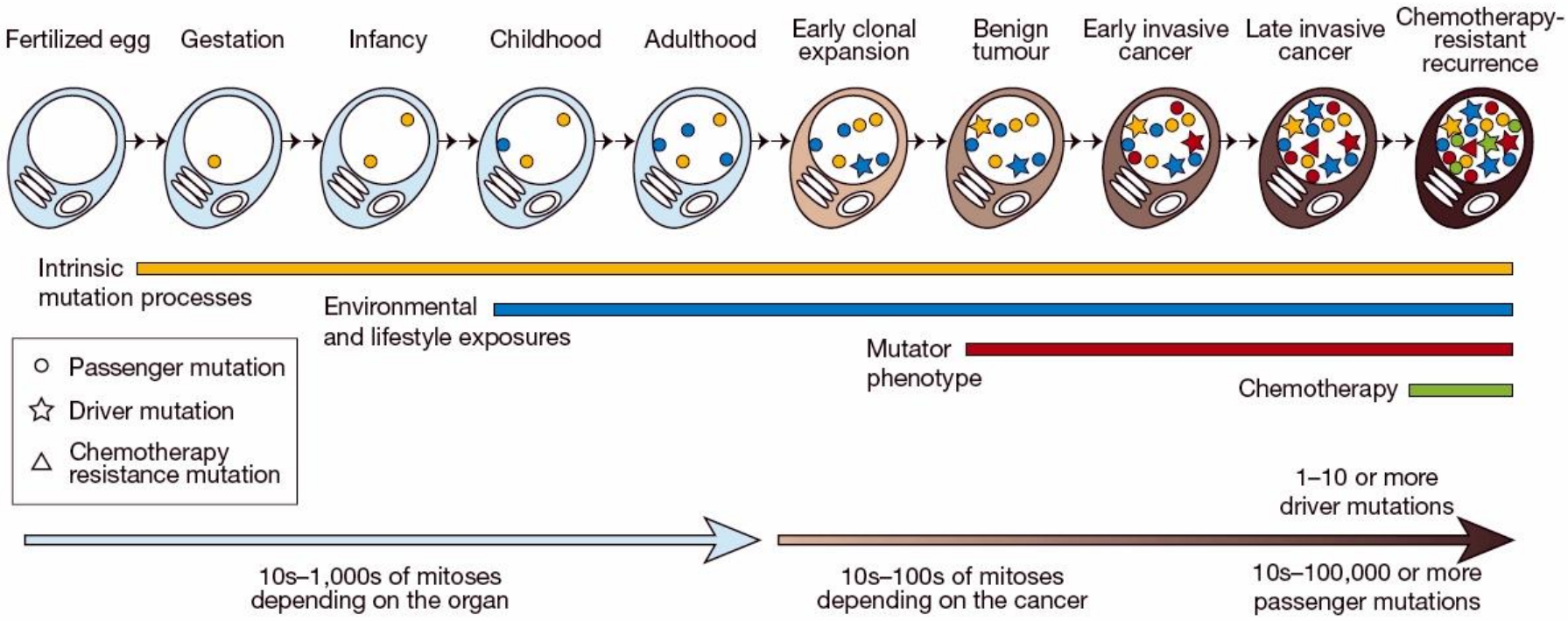



- Tumor samples from 178 pt
- High overall mutation rate : 8.1 mutations/Mb
- Marked genomic complexity



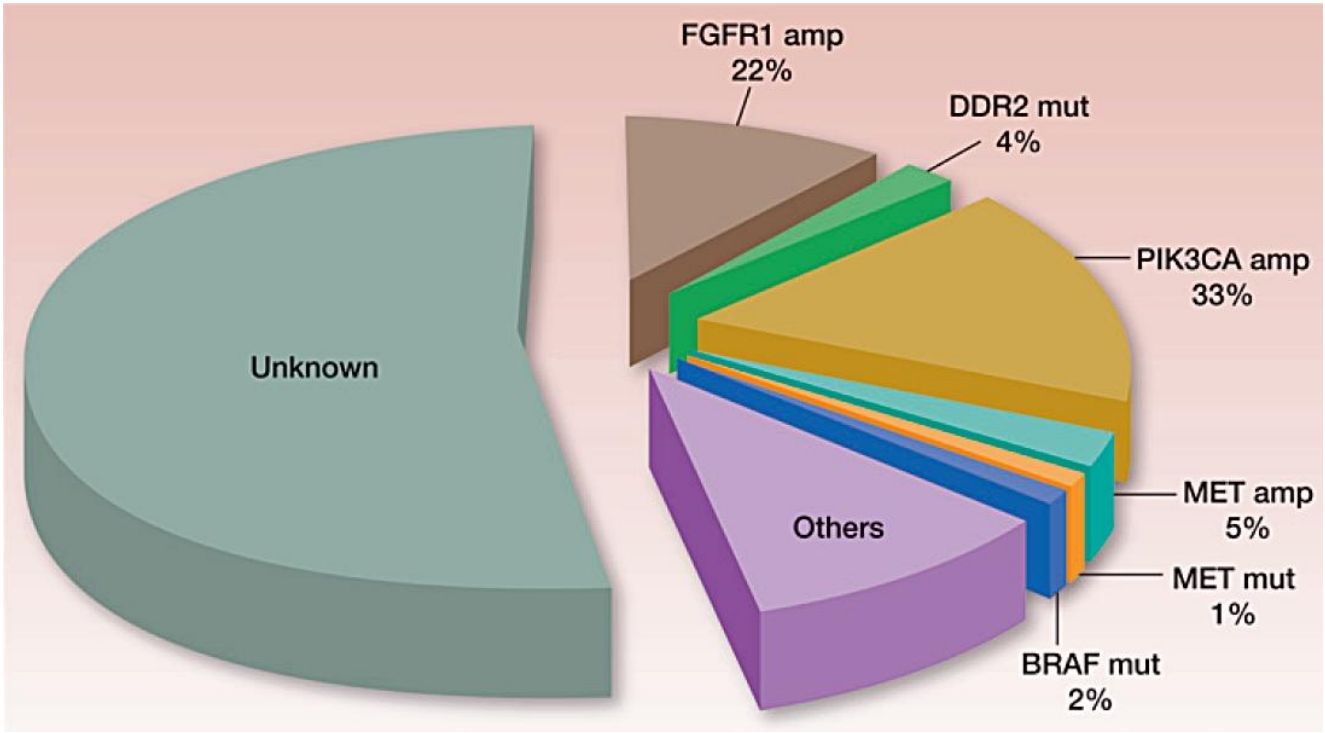

The Cancer Genome Atlas Research Network. Nature 2012;489:519-25.

# Passenger or driver?




Stratton MR, et al. Nature 2009;458:719-24.

# Frequencies of potentially targetable genetic abnormalities in SQCLC

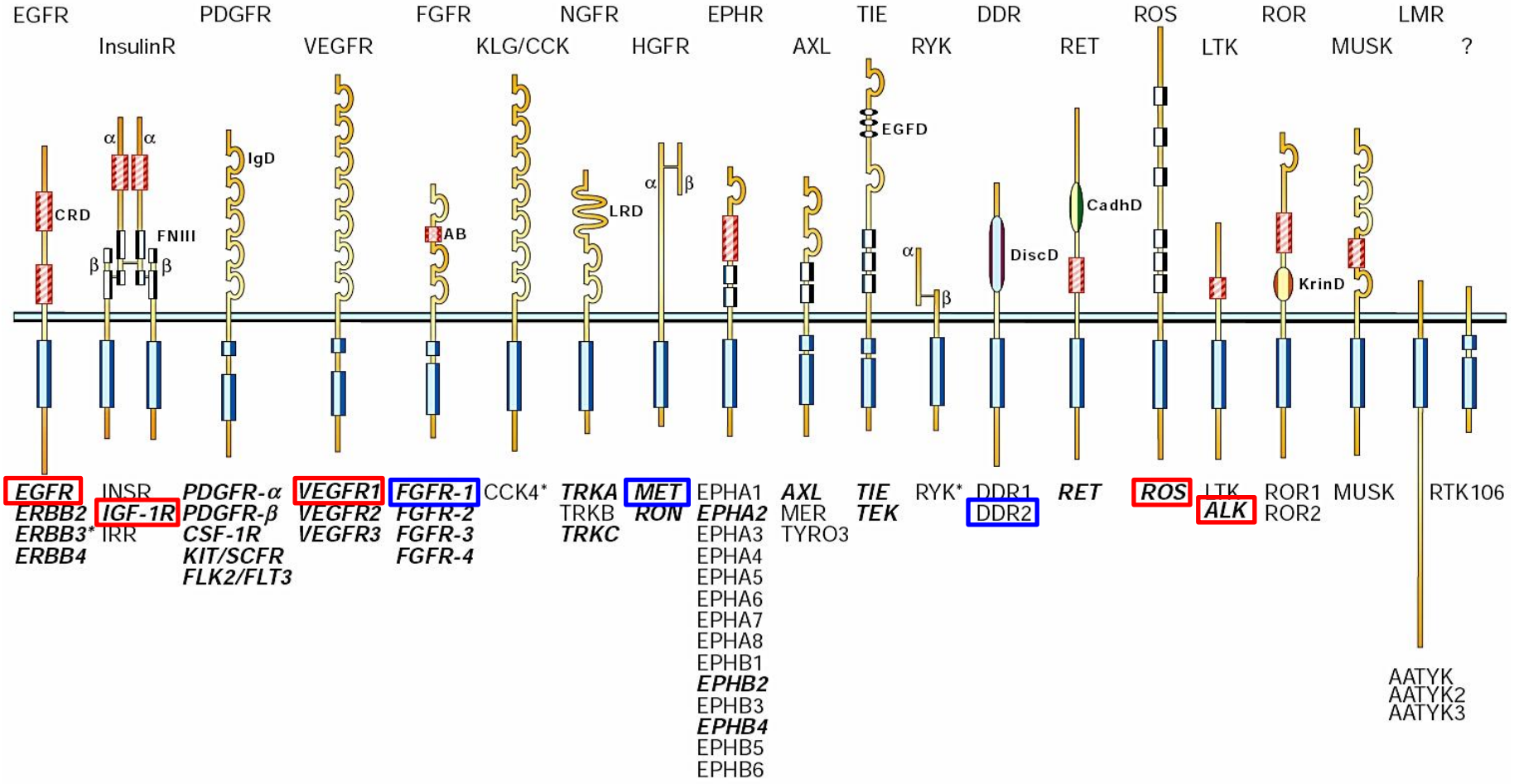



Perez-Moreno P, et al. Clin Cancer Res 2012;18:2443-51.

# Classification of molecular alterations present in SQCLC

| Membrane receptor alterations |
| --- |
| – **FGFR1** amplification<br>– **DDR2** mutation<br>– **MET** amplification |
| **Signaling pathway alterations** |
| – **PIK3CA** amplification and mutation<br>– **AKT1** mutation<br>– **PTEN** loss<br>– **BRAF** mutation |
| **Transcriptional factor alterations** |
| – **p53** mutation<br>– **SOX2** amplification |

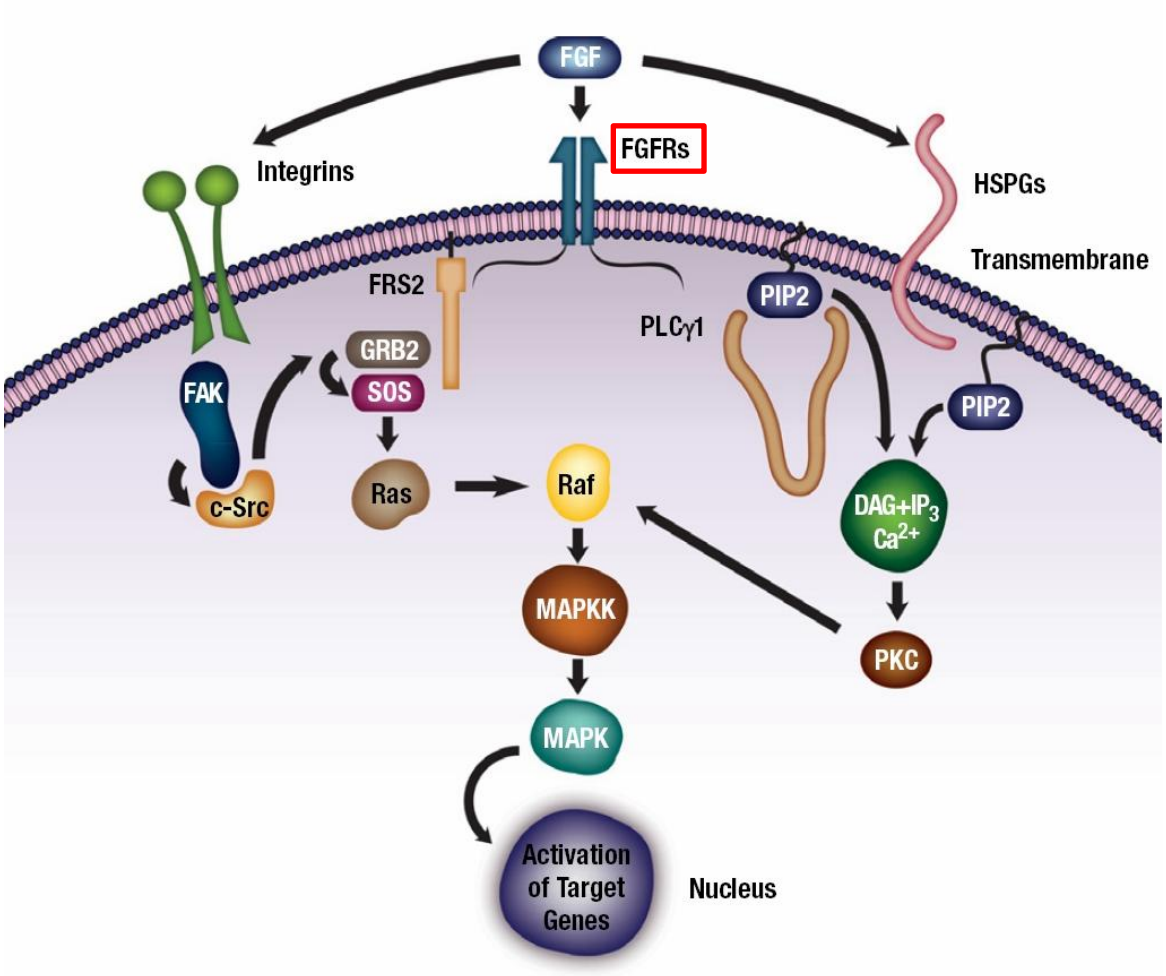
# Human receptor protein-tyrosine kinases




Blume-Jensen P & Hunter T. Nature 2001;411:355-65.

FGFR1

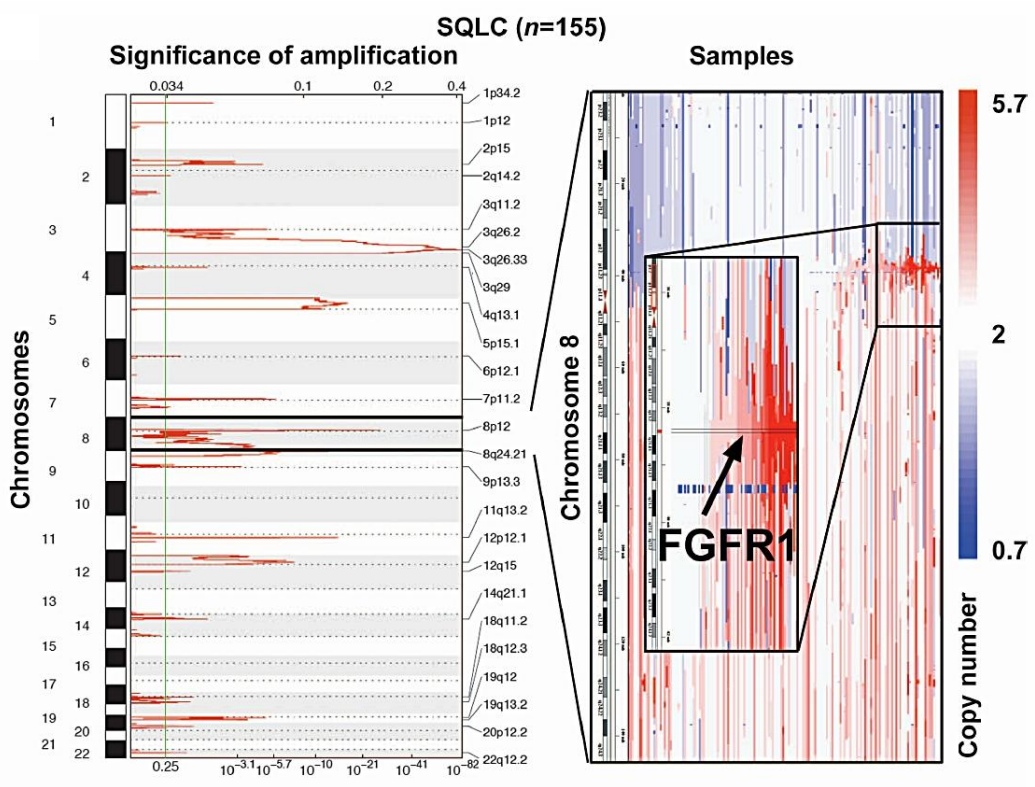
# Fibroblast growth factor signaling

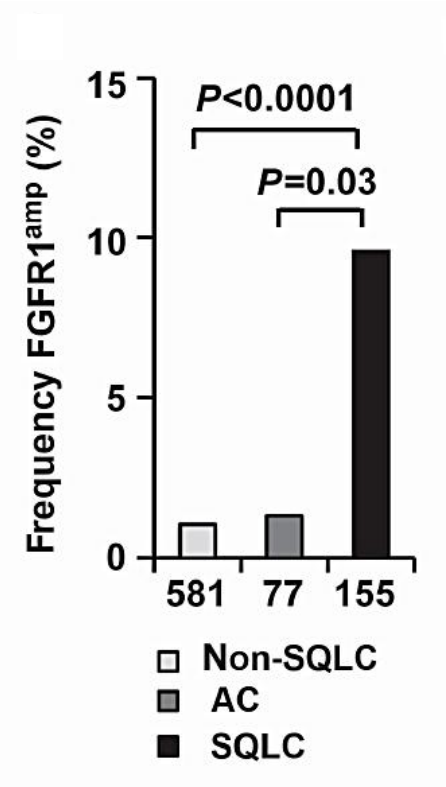


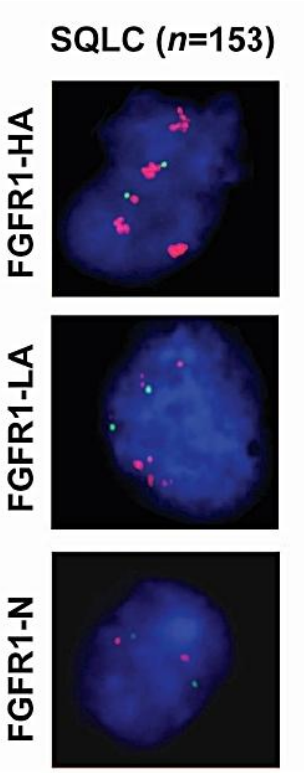

Semrad TJ & Mack PC. Clinical Lung Cancer 2012;13:90-5.

FGFR1

# FGFR1 is amplified in SQCLC



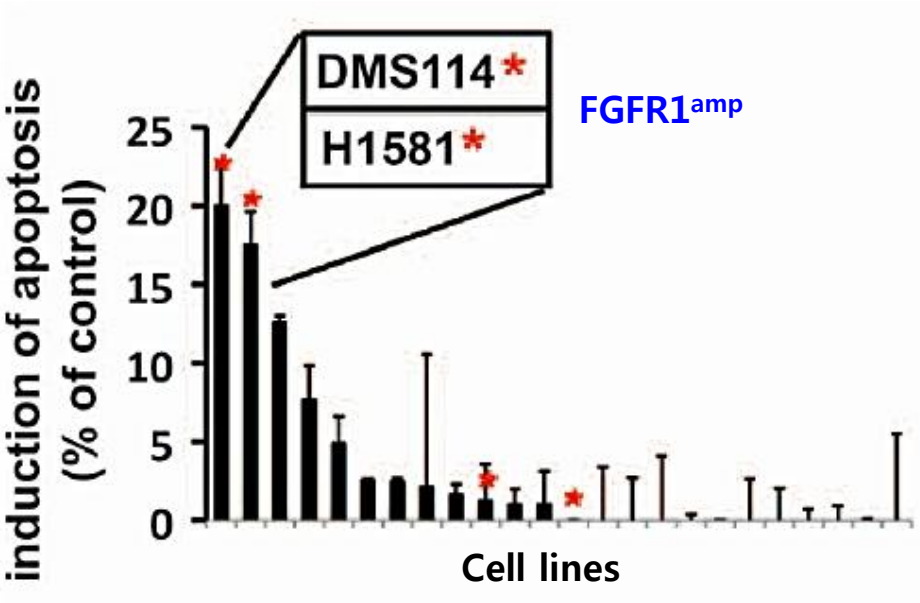



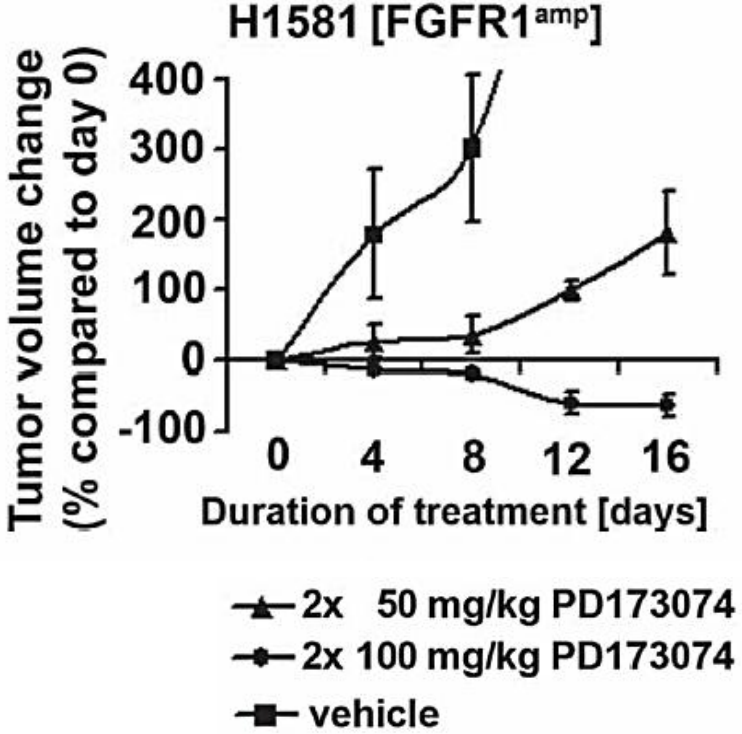

Weiss J, et al. Sci Transl Med 2010;2:62ra93.

FGFR1

# FGFR1 amplifications are associated with FGFR inhibitor activity

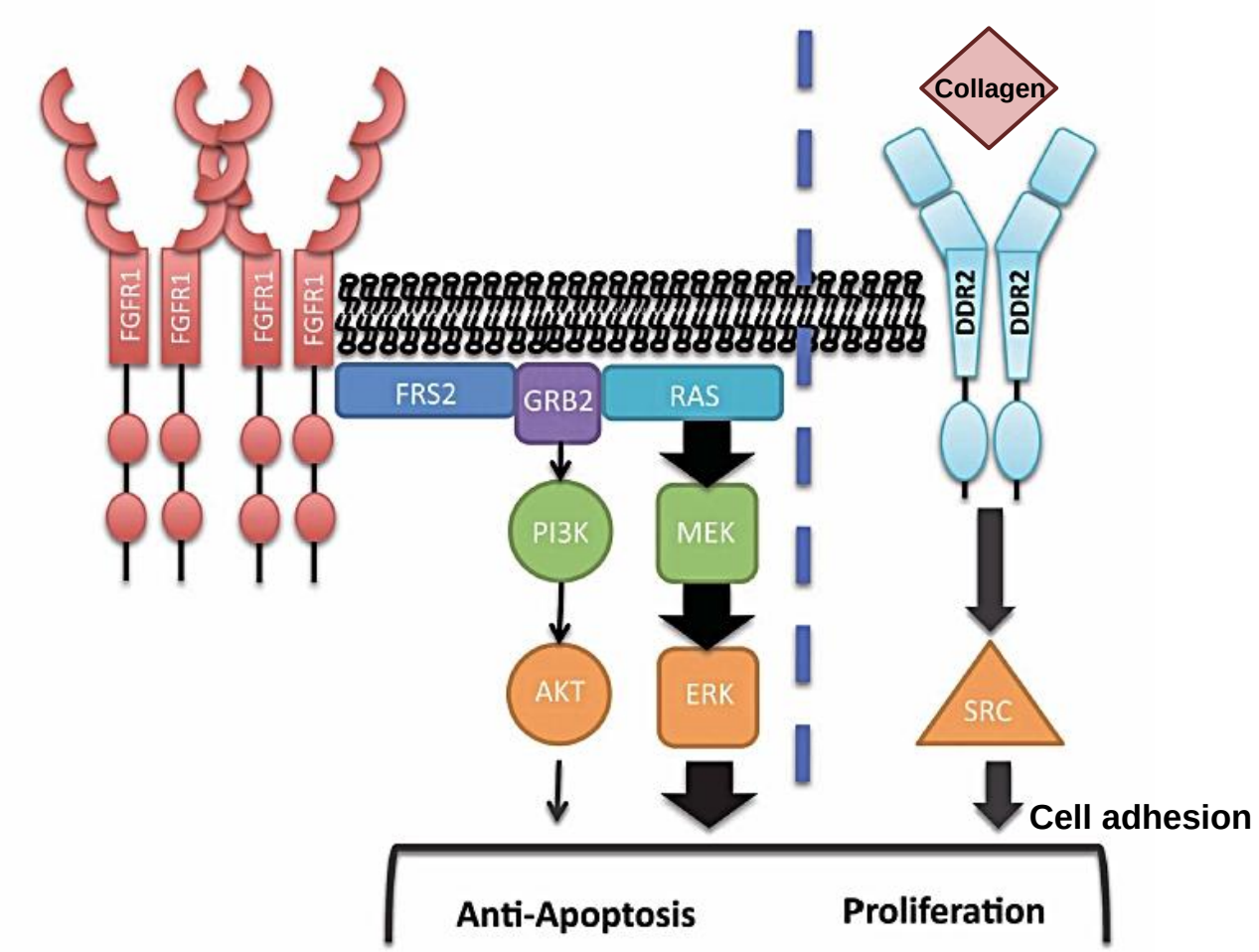



PD173074: FGFR inhibitor




Weiss J, et al. Sci Transl Med 2010;2:62ra93.

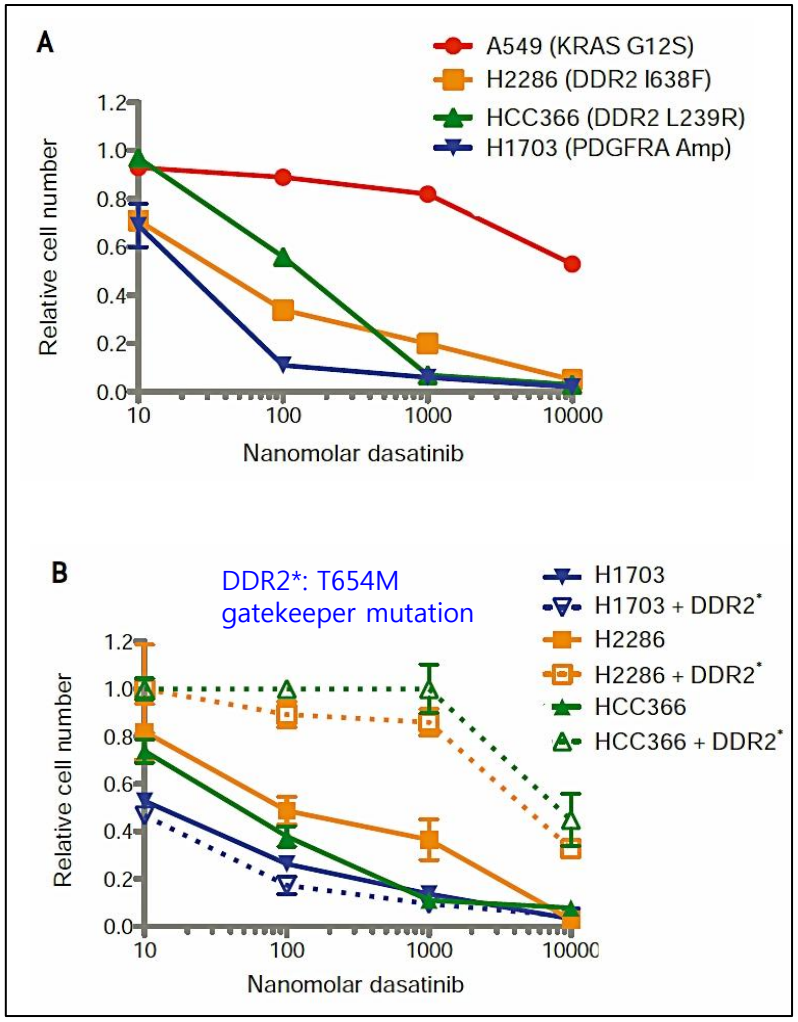
# Signaling pathway engaged by amplified FGFR1 and mutant DDR2 in SQCLC

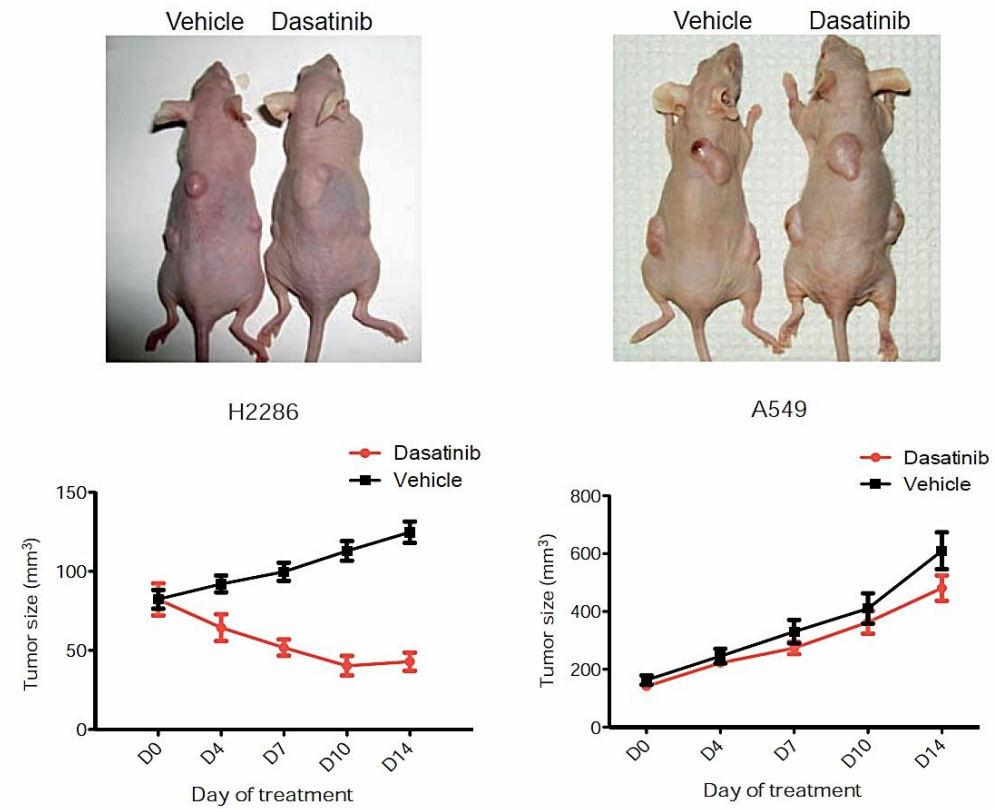



Sos ML & Thomas RK. Oncogene 2012;31:4811-4.

DDR2

# Lung cancer cells with *DDR2* mutations are sensitive to a DDR2 inhibitor

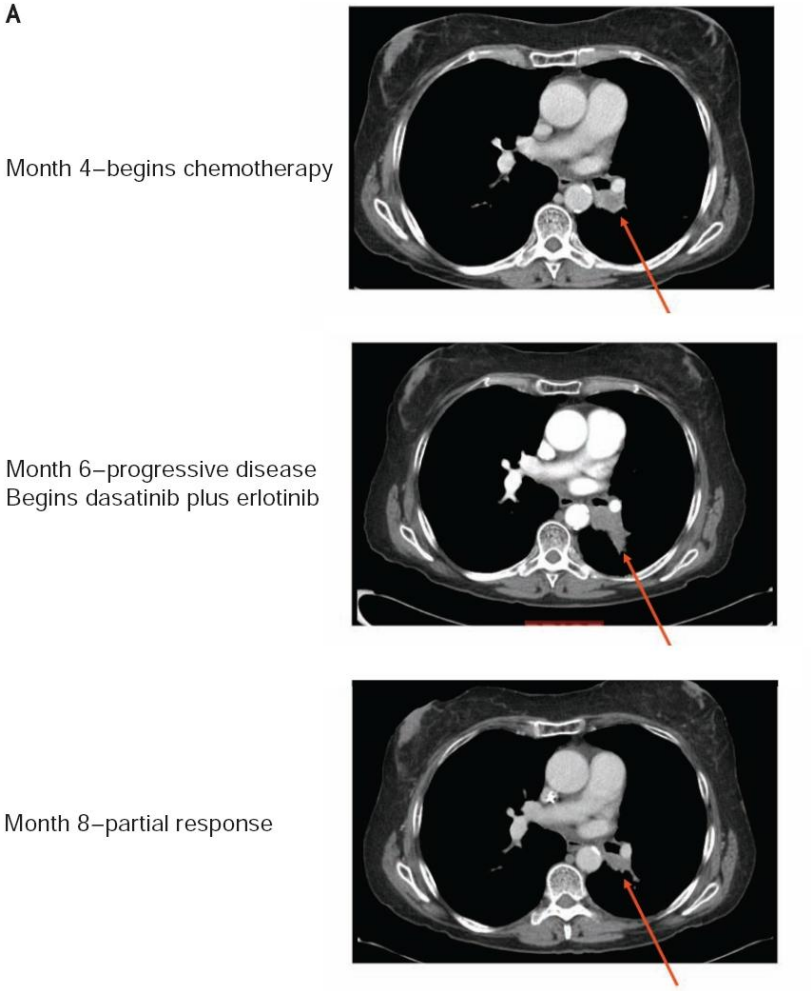



Hammerman PS, et al. Cancer Discovery 2011;1:78-89.

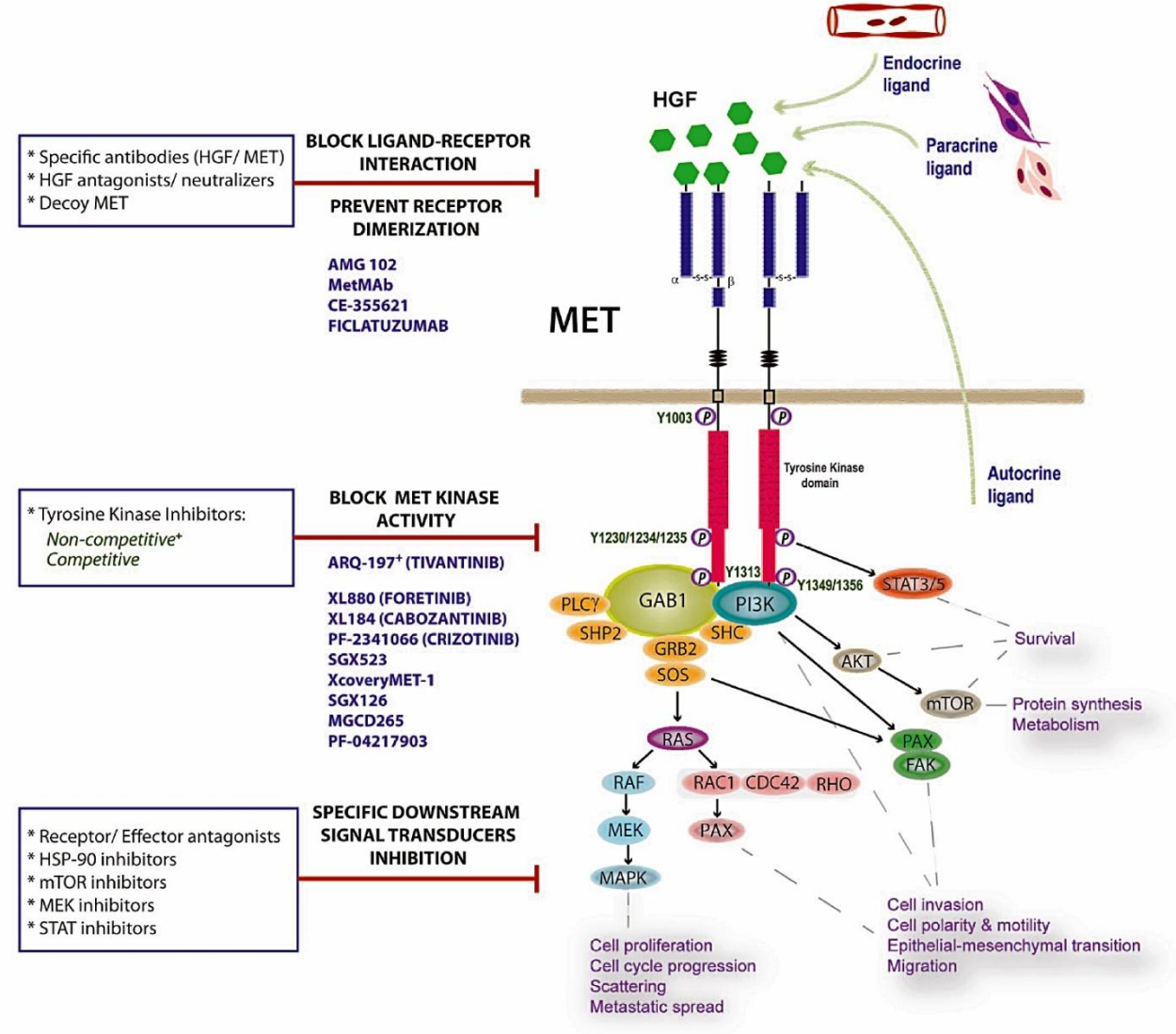
DDR2

# Response of a patient with a S768R *DDR2* mutation treated with dasatinib plus erlotinib



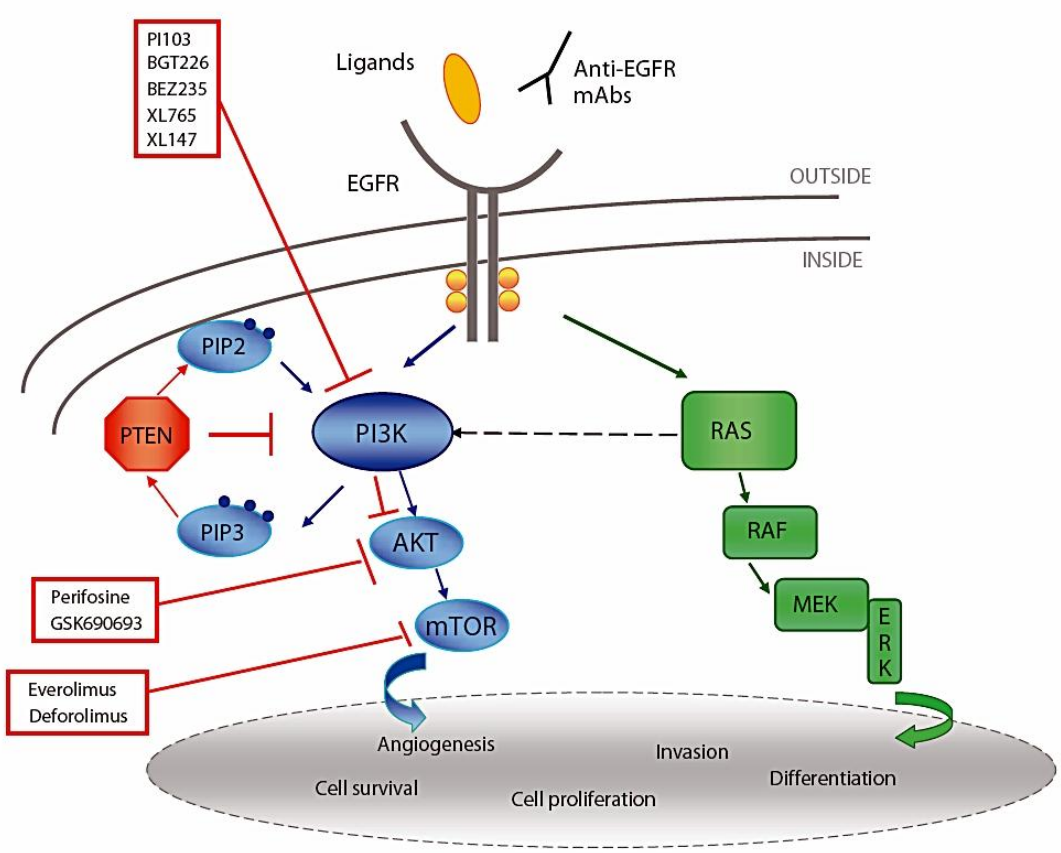

Hammerman PS, et al. Cancer Discovery 2011;1:78-89.

# MET signaling and strategies of therapeutic inhibition in lung cancer




Feng Y, et al. J Thorac Oncol 2012;7:459–67.

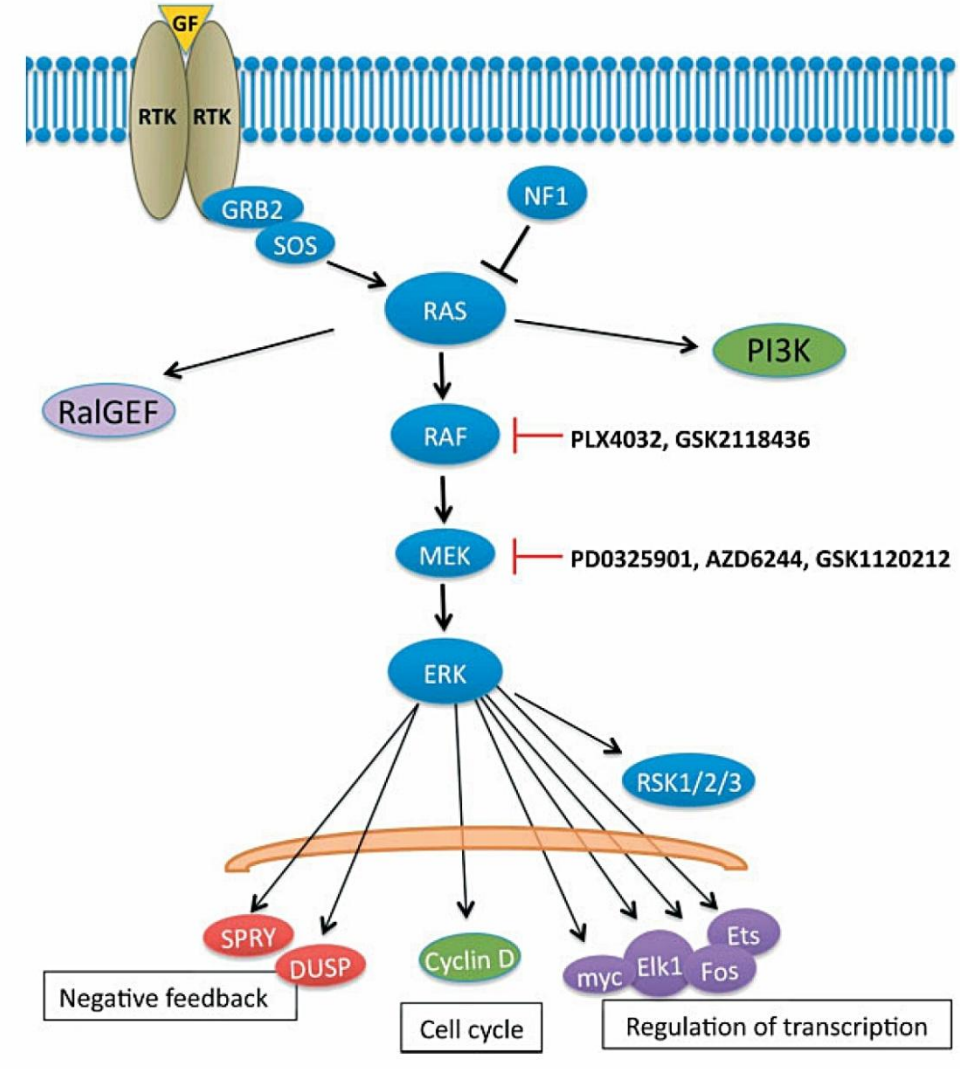
# Inhibitors targeting PI3K/AKT/mTOR pathway




| | SQCLC | Adeno |
|---|---|---|
| **PIK3CA amplification** | | |
| Ji 2011 | 42.4% | 0.1% |
| Okudela 2007 | 42.9% | 9.6% |
| Yamamoto 2008 | 33.1% | 6.2% |
| **PIK3CA mutation** | | |
| Rekhtman 2012 | 4.2% | NA |
| Yamamoto 2008 | | |
| Cell lines | 7.1% | 2.0% |
| Tumors | 3.6% | 2.6% |
| Kawano 2006 | 6.5% | 1.5% |
| **PTEN mutation** | | |
| Jin 2010 | 10.2% | 1.7% |
| **AKT1 mutation (E17K)** | | |
| Rekhtman 2012 | 1.1% | NA |
| Malanga 2008 | 5.5% | 0% |
| Do 2008 | 7.1% | 0% |

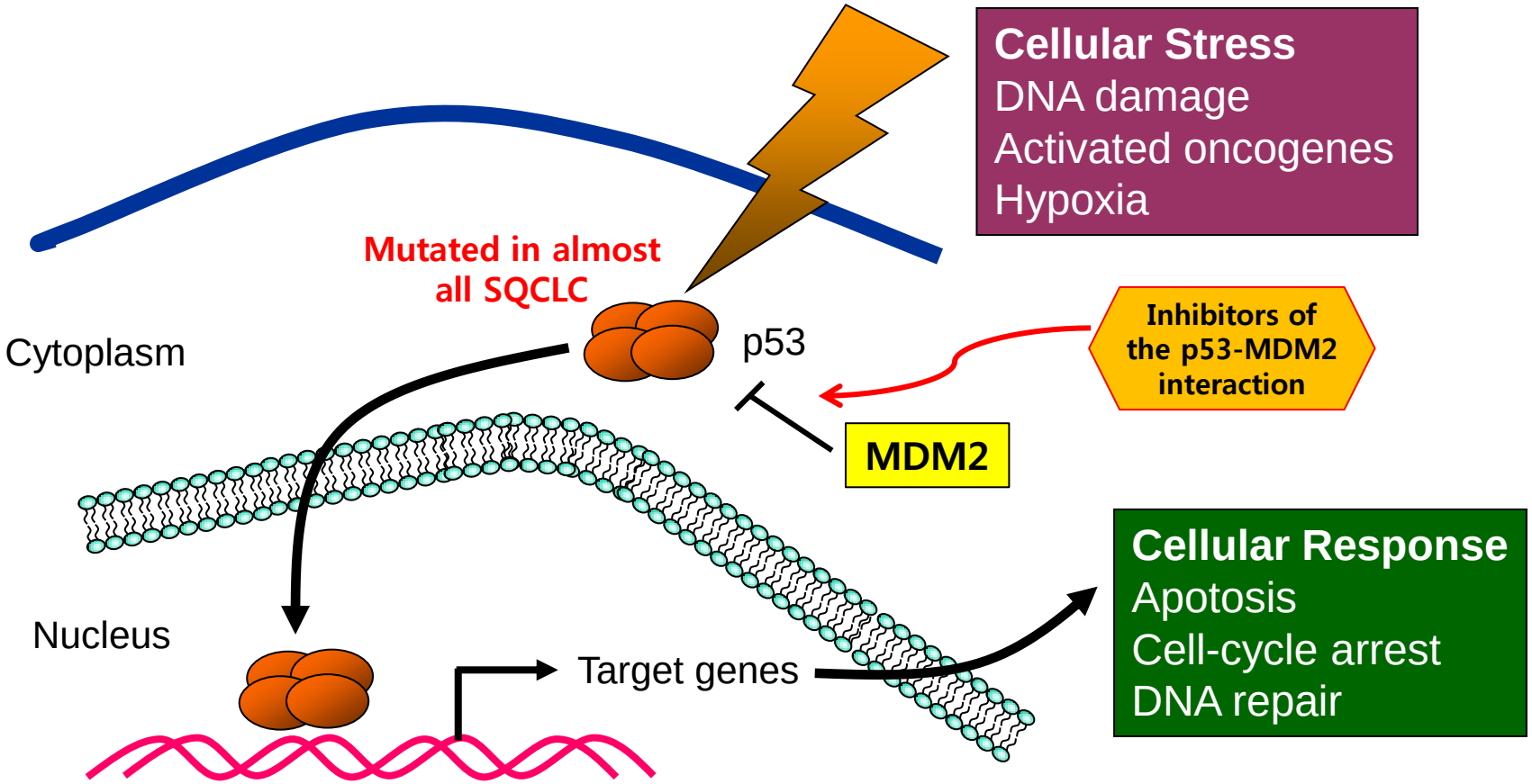
Silvestris N et al. Oncology 2009;77(suppl 1):69–74.
Drilon A, et al. Lancet Oncol 2012;13:e418–26.

# Therapeutic strategies for inhibiting oncogenic BRAF signaling in lung cancer

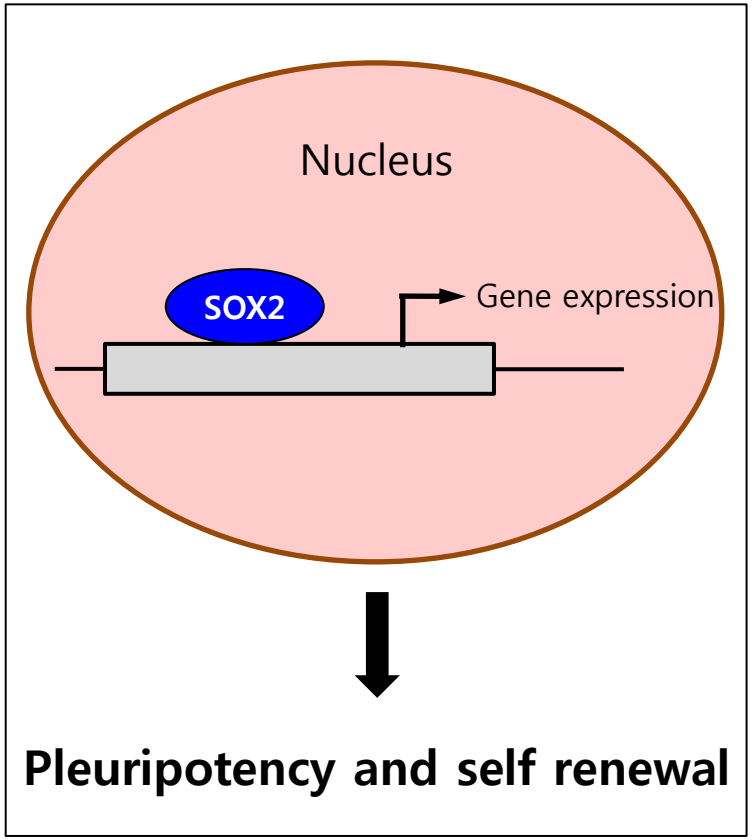


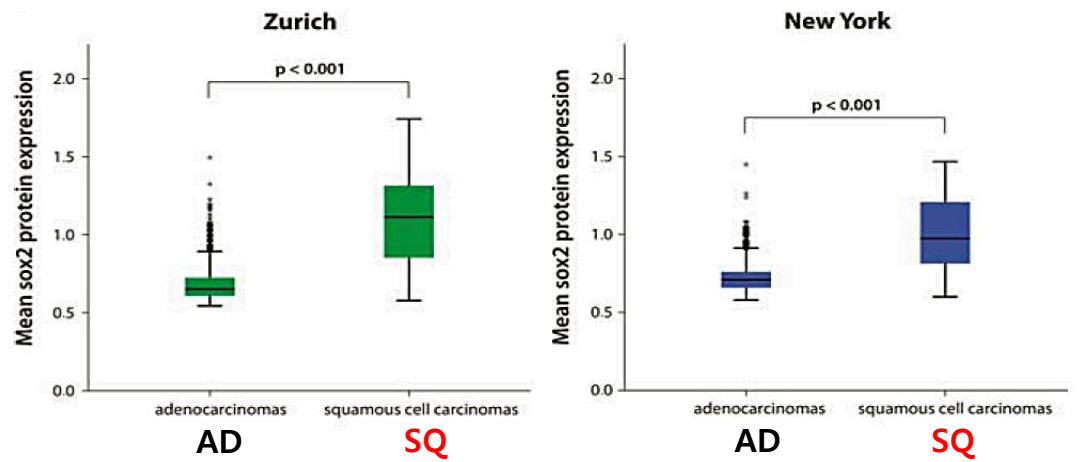

Vakiani E & Solit DB. J Pathol 2011;223:219–29.

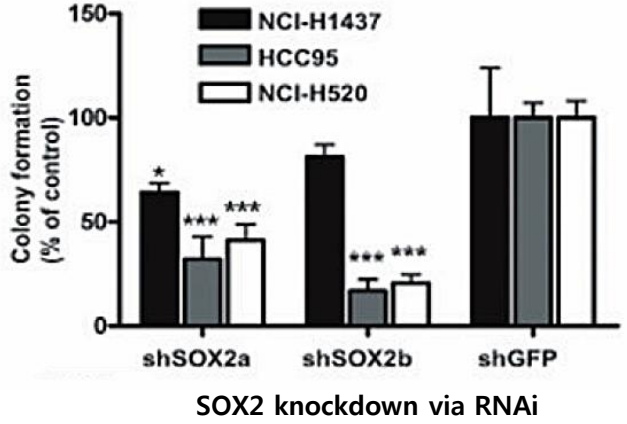
# The loss of p53 allows the proliferation of damaged cells



# SOX2 amplification in NSCLC from two independent cohorts




SOX2 knockdown via RNAi

Wilbertz T, et al. Modern Pathology 2011;24:944–53.
Bass AJ, et al. Nat Genet 2009;41:1238–42.

Clinical features

Carcinogenesis

Targetable driver mutations

**Clinical trials**

# Phase II trial of pazopanib in patients with stage I/II resectable NSCLC

- Stage I/II NSCLC
- PS ≤ 1
- Treatment-naive

N=35

**Pazopanib**

800 mg daily
2-6 weeks

Continue until surgery

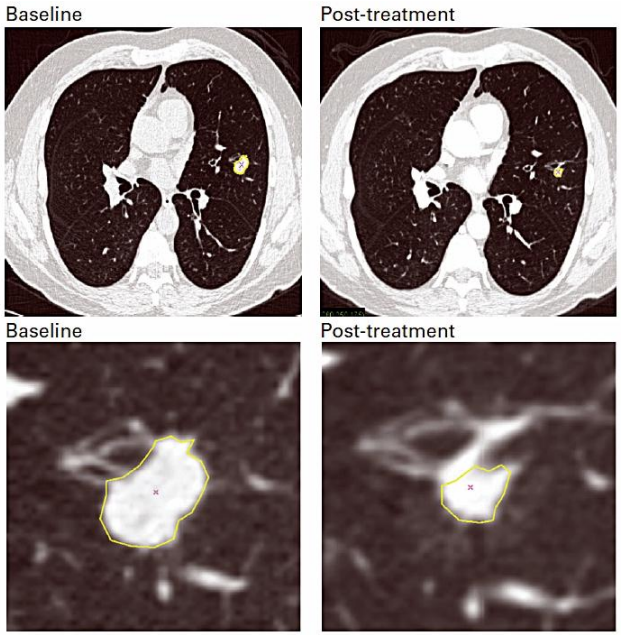
(surgery performed after a washout period of 1 week after the last dose)

Primary objective: volumetric tumor response rate
(50% tumor-volume reduction determined by HRCT)
Secondary objectives: RR determined by RECIST
safety and tolerability

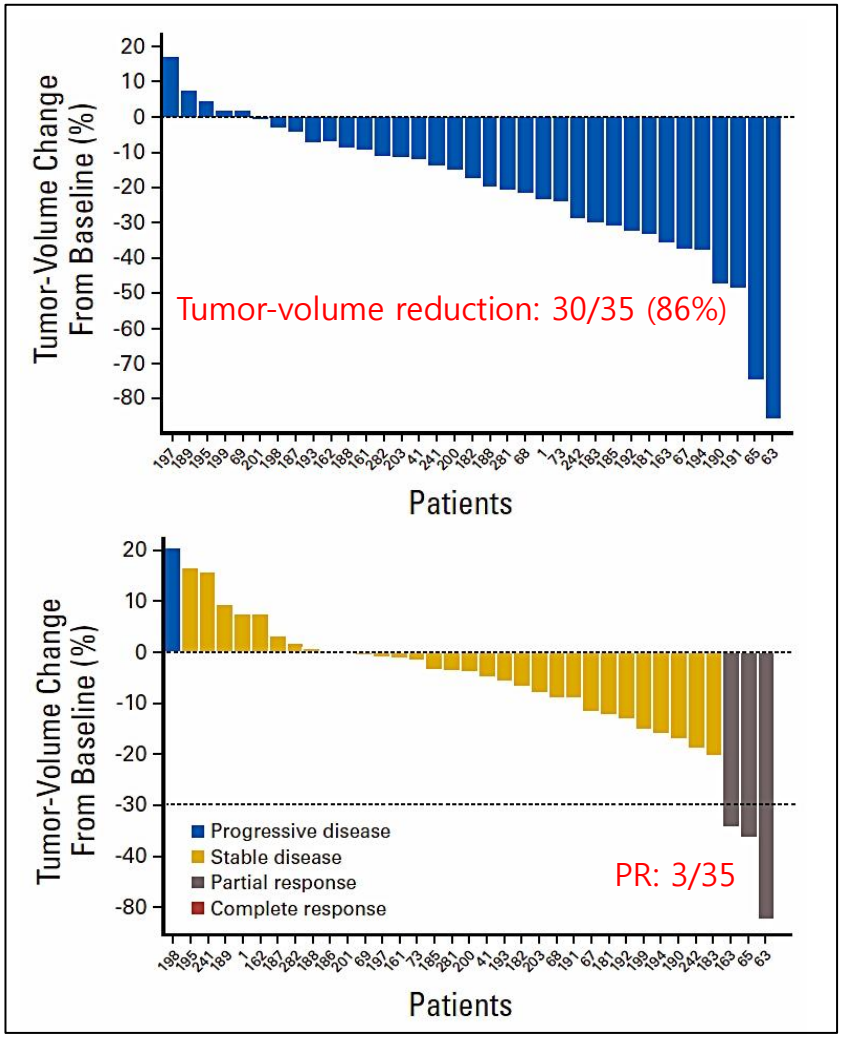
**Pazopanib:** a selective multi-targeted RTK inhibitor of VEGFRs, PDGFRs, c-kit, and FGFRs

Altorki N, et al. J Clin Oncol 2010;28:3131-7.

# Pazopanib was generally well tolerated and demonstrated single-agent activity in patients with early-stage NSCLC




| Event | Total | | Grade 1/2 | | Grade 3 | | Grade 4 | |
|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % |
| Any | 33 | 94 | 27 | 77 | 5 | 14 | 1 | 3 |
| Hypertension | 15 | 43 | 15 | 43 | 0 | | 0 | |
| Diarrhea | 13 | 37 | 13 | 37 | 0 | | 0 | |
| Fatigue | 13 | 37 | 13 | 37 | 0 | | 0 | |
| Nausea | 12 | 34 | 12 | 34 | 0 | | 0 | |
| ALT increased | 8 | 23 | 6 | 17 | 2 | 6 | 0 | |
| Headache | 8 | 23 | 8 | 23 | 0 | | 0 | |




Altorki N, et al. J Clin Oncol 2010;28:3131-7.

# Phase II/III study of cediranib with standard CRx as initial therapy for advanced NSCLC

- Stage IIIB/IV NSCLC
- PS ≤ 1
- Permissible prior Tx:
  Adjuvant CRx, EGFR inhibitors, RT, surgery

RANDOMIZE

N=251

**Cediranib + TC**
(N=126)

**Cediranib**: 30 mg daily until PD or intolerable toxicity

**TC**: Paclitaxel 200 mg/m$^2$ and Carboplatin AUC 6
Every 3 weeks for 6-8 cycles

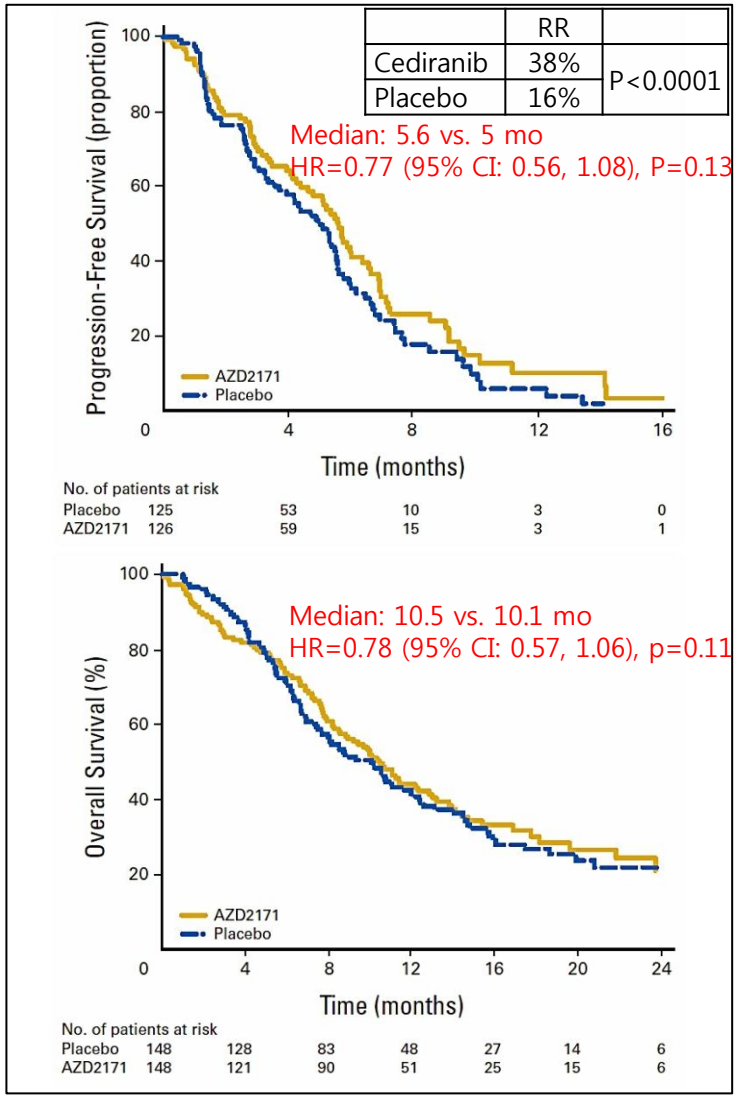
**Placebo + TC**
(N=125)

Phase II objective: PFS, RR, and toxicity
Phase III
Primary objective: OS
Secondary objectives: PFS, RR, toxicity, health economics, tissue markers, QoL

**Cediranib (AZD2171):** a inhibitor of VEGFRs and FGFR1

Goss GD, et al. J Clin Oncol 2010;28:49-55.

# Efficacy and safety of cediranib (30-mg dose) with carboplatin/paclitaxel

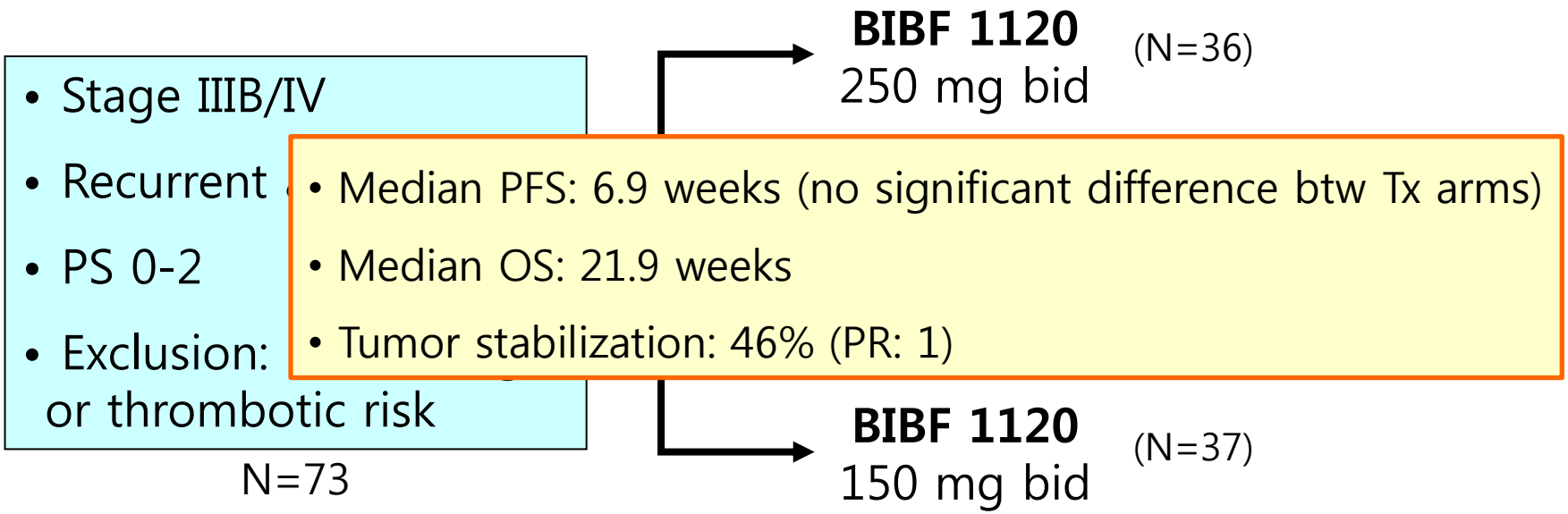



| Adverse Event | Cediranib (%) (n = 126) | | Placebo (%) (n = 123) | |
|---|---|---|---|---|
| | All Grades | Grade ≥ 3 | All Grades | Grade ≥ 3 |
| Hypertension | 38 | 19 | 10 | 2 |
| Diarrhea | 79 | 15 | 36 | 2 |
| Anorexia | 61 | 6 | 41 | 3 |
| Stomatitis | 41 | 6 | 19 | 0 |
| Fatigue | 88 | 29 | 84 | 19 |
| Dyspnea | 75 | 10 | 65 | 13 |
| Sensory neuropathy | 63 | 3 | 67 | 5 |
| Hand-foot syndrome | 15 | 2 | 6 | 1 |
| Bleeding | 25 | 3 | 11 | 1 |
| Hemoptysis | 12 | 2 | 9 | 0 |
| Venous thromboembolism | 4 | 4 | 4 | 2 |
| Increased TSH (≥ 2 × ULN) | 45 | 27 | 7 | 0 |
| Febrile neutropenia | 10 | 4 | | |
| Grade 3 or 4 neutropenia | 65 | 49 | | |
| G-CSF usage | 10 | 2 | | |
| Grade 3 or 4 thrombocytopenia | 15 | 4 | | |
| Hospitalization (any) | 34 | 24 | | |
| Serious adverse events | 51 | 20 | | |
| Serious adverse events leading to hospitalization | 33 | 15 | | |
| Fatal serious adverse events | 10 | 2 | | |
| Death ≤ 30 days of last dose of protocol therapy | 16 | 7 | | |

Abbreviation: TSH, thyroid-stimulating hormone; ULN, upper limit of normal; G-CSF, granulocyte colony-stimulating factor.

Goss GD, et al. J Clin Oncol 2010;28:49-55.

# Phase II study of BIBF 1120 in patients with relapsed advanced NSCLC




Primary objective: PFS, RR
Secondary objectives: evaluation of SD, PR, CR; OS; QoL

**BIBF 1120:** a triple angiokinase inhibitor which blocks VEGFs, PDGFRs and FGFRs

Reck M, et al. Annals of Oncology 2011;22:1374–81.

# Phase II trial of dasatinib in advanced SQCLC

- Stage IIIB/IV
- Squamous cell histology
- 1 prior systemic therapy
- Tissue available

**Dasatinib**

100 mg daily
Continuous

Continue until disease progression or development of toxicity

Primary objective: response rate

Secondary objectives: types/frequencies of DDR2 mutations, correlation of DDR2 mutations with RR, PFS, OS and toxicity

Johnson B. Dana-Farber Cancer Institute DF/HCC #11-142.

# On-going clinical trials with targeted agents in SQCLC

| Compound | Targets | Mechanism of action | Monotherapy/ Combined therapy | Phase of clinical development | Molecularly enriched | Histologic selection or stratification | NCTID |
|---|---|---|---|---|---|---|---|
| **FGFR1** | | | | | | | |
| **BGJ398** | Pan FGFR | Kinase inhibitor | Monotherapy | 1 | Yes | No | NCT01004224 |
| **AZD4547** | Pan FGFR | Kinase inhibitor | Monotherapy | 1 | Yes | No | NCT00979134 |
| **E-3810** | Pan FGFR, VEGFR | Kinase inhibitor | Monotherapy | 1 | No | No | NCT01283945 |
| **FP-1039** | FGF | Antibody | Monotherapy | 1 | No | No | NCT00687505 |
| **TKI258** | FGFR, VEGFR, PDGFR | Kinase inhibitor | Monotherapy | 1 | No | No | NCT01270906 |
| **DDR2** | | | | | | | |
| **Dasatinib** | BCR/ABL, SRC, c-Kit, DDR1–2 | Kinase inhibitor | Monotherapy | 2 | No | No | NCT00787267<br>NCT00459342 |
| **BRAF** | | | | | | | |
| **GSK2118436** | BRAF | Kinase inhibitor | Monotherapy | 2 | Yes | No | NCT01336634 |
| **PI3KCA** | | | | | | | |
| **PF-04691502** | PI3K, mTOR | Kinase inhibitor | Monotherapy | 1 | No | No | NCT00927823 |
| **XL147** | PI3K | Kinase inhibitor | Combined therapy | 1 | No | No | NCT00756847 |
| **BKM120** | PI3K | Kinase inhibitor | Monotherapy | 2 | Yes | Yes | NCT01297491 |
| **BYL719** | PI3K | Kinase inhibitor | Monotherapy | 1 | Yes | No | NCT01219699 |
| **XL765** | PI3K, mTOR | Kinase inhibitor | Monotherapy | 1 | No | No | NCT00485719 |
| **PX866** | PI3K | Kinase inhibitor | Combined therapy | 1 | No | No | NCT01204099 |
| **GDC-0941** | PI3K | Kinase inhibitor | Combined therapy | 1 | No | No | NCT00975182 |
| **AKT1** | | | | | | | |
| **MK2206** | Pan AKT | Kinase inhibitor | Combined therapy<br>Combined therapy | 1<br>2 | No | No | NCT01147211<br>NCT01294306 |
| **GDC-0068** | Pan AKT | Kinase inhibitor | Monotherapy | 1 | No | No | NCT01090960 |
| **MET** | | | | | | | |
| **Crizotinib** | MET, ALK | Kinase inhibitor | Monotherapy<br>Combined therapy | 1 | No | No | NCT00585195<br>NCT01121575 |
| **XL184** | MET, RET, VEGFR2 | Kinase inhibitor | Monotherapy<br>Combined therapy | 2 | No | No | NCT00940225<br>NCT00596648 |
| **MetMAb** | MET | Antibody | Combined therapy | 3 | Yes | No | NCT01456325 |
| **Arq197** | MET | Kinase inhibitor | Combined therapy | 2 | Yes | No | NCT01395758 |
| **ERBB2** | | | | | | | |
| **MGAH22** | Her2 | Antibody | Monotherapy | 1 | Yes | | NCT01148849 |
| **Lapatinib** | EGFR, HER2 | Kinase inhibitor | Combined therapy | 1 | No | | NCT01184482 |

NCTID, National Cancer Trial Identification

# Summary

- Detailed genomic analysis of squamous cell lung cancers has identified several new potential therapeutic targets
- We can now identify a possible therapeutic target in most SQCLC samples
- Targets will need to be validated in pre-clinical models
- FGFR1/2, PIK3CA and DDR2 inhibitor trials are planned or ongoing