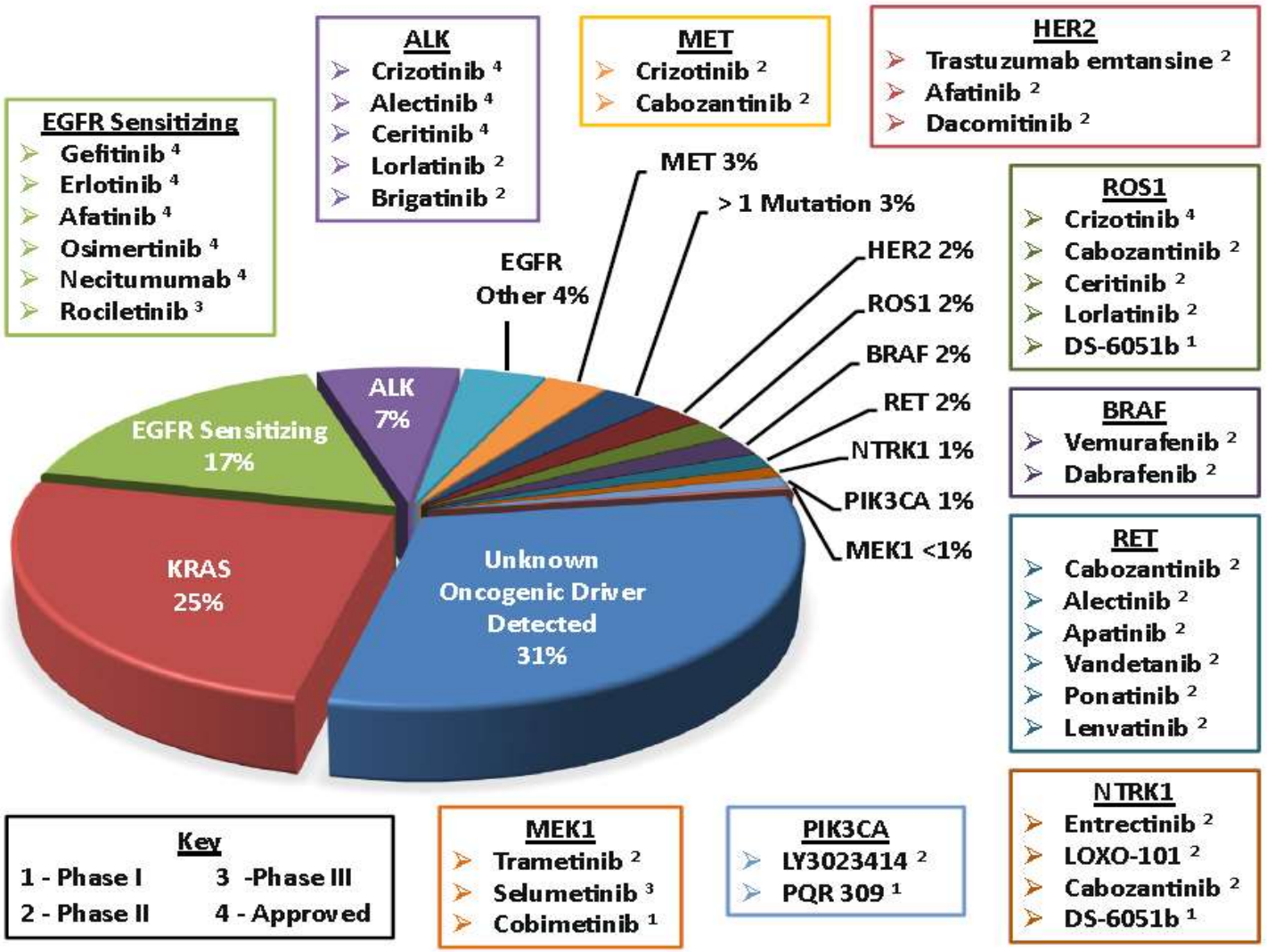
Current and emerging targets for personalized treatment for advanced NSCLC

11/11/2016

2004 → 2016


ALK
Crizotinib 4
Alectinib 4
Ceritinib 4
Lorlatinib 2
Brigatinib 2
MET
Crizotinib 2
Cabozantinib 2
HER2
Trastuzumab emtansine 2
Afatinib 2
Dacomitinib 2
EGFR Sensitizing
Gefitinib 4
Erlotinib 4
Afatinib 4
Osimertinib 4
Necitumumab 4
Rociletinib 3
MET 3%
> 1 Mutation 3%
EGFR Other 4%
HER2 2%
ROS1 2%
BRAF 2%
RET 2%
NTRK1 1%
PIK3CA 1%
MEK1 <1%
ALK 7%
EGFR Sensitizing 17%
KRAS 25%
Unknown Oncogenic Driver Detected 31%
ROS1
Crizotinib 4
Cabozantinib 2
Ceritinib 2
Lorlatinib 2
DS-6051b 1
BRAF
Vemurafenib 2
Dabrafenib 2
RET
Cabozantinib 2
Alectinib 2
Apatinib 2
Vandetanib 2
Ponatinib 2
Lenvatinib 2
Key
1 - Phase I
2 - Phase II
3 -Phase III
4 - Approved
MEK1
Trametinib 2
Selumetinib 3
Cobimetinib 1
PIK3CA
LY3023414 2
PQR 309 1
NTRK1
Entrectinib 2
LOXO-101 2
Cabozantinib 2
DS-6051b 1

Personalized therapy

- Individuals respond differently to drugs
- Differences in DNA that alter the expression or function of proteins (driver mutations) that are targeted by drugs can contribute significantly to variation in the responses of individuals
- This intersection of genomics and medicine is the basis of personalized therapy

Driver genotype

- The term ‘driver’ genotype refers to
  - crucial necessary biologic change (usually a gain of function)
  - imparted by a gene mutation, amplification or translocation
  - Is oncogenic and plays a critical role in the signaling that drives malignant phenotype of the cancer
  - typically not found in the germline (noncancer) genome of the host and
  - are usually mutually exclusive

Driver genotype

- Hence the driver mutation is the most useful biomarkers for predicting the efficacy of targeted therapy in advanced NSCLC

Personalized therapy

- Driver mutations are typically
  - Transformative→initiate the evolution of a noncancerous cell to malignancy
  - Oncogene addicted biology→ the mutated protein engenders reliance within the cancer cell to receive a signal from the driver in order to survive

Personalized therapy

- The complete reliance of downstream growth and survival pathways in the cell upon a single upstream signal that is "stuck in the on position" serves as an Achilles' heel, making the cancer uniquely susceptible to downregulation of signal originating from the driver

Personalized therapy

- Screening for driver mutations is thus a standard part of the diagnostic workup for NSCLC

Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT)

- Patients with advanced NSCLC, who were routinely screened for *driver mutations*
- a 1-year period (April, 2012, to 2013)
- 18 679 molecular analyses of 17 664 patients with NSCLC were done
- The median interval between the initiation of analysis and provision of the written report was 11 days
- A genetic alteration was recorded in about 50% of the analyses
- Compared with absence of a genetic alteration, presence of a genetic alteration was also associated with improved first-line progression-free survival (10·0 months [95% CI 9·2–10·7] *vs 7·1 months [6·1–7·9]; p<0·0001)*

Lancet. 2016 Apr 2;387(10026):1415-26

Original Investigation

Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs

- To determine the frequency of oncogenic drivers in patients NSCLC
- From 2009 through 2012, patients with metastatic lung adenocarcinomas were tested for 10 drivers
- 1007 patients were tested for at least 1 gene and 733 for 10 genes
- An oncogenic driver was found in 466 of 733 patients (64%)
- Results were used to select a targeted therapy or trial in 275 of 1007 patients (28%).

JAMA. 2014 May 21;311(19):1998-2006

Molecular testing

- Whenever feasible, patients with advanced NSCLC should have tumor assessed for the presence of a driver mutation

Molecular testing

SPECIAL ARTICLE

Molecular Testing Guideline for Selection of Lung Cancer Patients for EGFR and ALK Tyrosine Kinase Inhibitors

Guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology

The Journal of Molecular Diagnostics, Vol. 15, No. 4, July 2013

Molecular testing

- When Should Molecular Testing of Lung Cancers Be Performed?
  - Which patients
  - When
  - How rapidly
- How Should EGFR Testing Be Performed?
- How Should ALK Testing Be Performed?
- Should Other Genes Be Routinely Tested in Lung Adenocarcinoma?

- Recommend analysis of either the primary tumor or of a metastasis for EGFR and ALK for all patients whose tumor contains an element of adenocarcinoma, regardless of the clinical characteristics of the patient and the results should be available with in 2 weeks (10 working days)

Molecular testing: techniques

- Methods are continuously evolving and no

• Utilize clinically available samples (formalin fixed, paraffin embedded tissue)
•Are relatively inexpensive
•Have clinically relevant turnaround times
•Are semi-automated so that they are not reliant upon a single operator
•Tissue efficient

Molecular testing

- Multiplexed genotype testing allows an entire panel of genotypes of interest to be queried at a single time from a single tissue sample instead of doing the tests sequentially one by one
- Most tissue efficient approach
- Most time efficient process for screening

EGFR receptor

- Cell surface membrane receptors
  - →control intracellular signal transduction pathways
    - → regulating cell proliferation, apoptosis, angiogenesis, adhesion, and motility
      - →Tumor growth and progression

EGFR receptor

- EGFR exists as a monomer on the cell surface, and it must dimerize to activate the TK
- Normal cells→ activity tightly controlled
- Malignant cells →Usual intracellular inhibitory mechanisms escaped

EGFR

- Molecular pathogenesis

https://www.youtube.com/watch?v=-MaWFedVGCA

EGFR mutation as a predictor of responsiveness

- NSCLCs that contains characteristic mutations in EGFR are highly sensitive to EGFR TKIs
- Analysis for the presence or absence of a driver mutation in EGFR is the standard approach to decide whether or not to use an EGFR TKI for the initial treatment of a patient with advanced NSCLC

Epidemiology Of EGFR mutation

A Prospective, Molecular Epidemiology Study of *EGFR* Mutations in Asian Patients with Advanced Non–Small-Cell Lung Cancer of Adenocarcinoma Histology (PIONEER)

Untreated stage IIIB/IV adenocarcinoma were screened for *EGFR* mutation

- 1482 patients were screened from seven Asian regions
- 746 [51.4%] positive; 704 [48.6%] negative
  - Country
  - Ethnicity
  - Smoking status and
  - histology type ($p = 0.016$) correlated significantly with *EGFR* mutation frequency.
- Mutation frequency was 61.1% in females, 44.0% in males; lower in patients from India (22.2%) compared with other areas
- Sex was not significant when adjusted for smoking status

J Thorac Oncol. 2014 Feb;9(2):154-62

EGFR Mutations

TABLE 4. Summary of Individual *EGFR* Mutation Types (Including Multiple Mutations)

	n	%
Patients with an evaluable *EGFR* mutation test	1450	100.0
Sensitizing mutations alone	671	46.3
G719X	15	1.0
G719X, deletion	4	0.3
G719X, L861Q	2	0.1
Deletion	321	22.1
Deletion, L858R	11	0.8
L858R	303	20.9
L858R, L861Q	2	0.1
L861Q	13	0.9
Resistance mutations	42	2.9
T790M	5	0.3
S768I	14	1.0
S768I, exon 20 other (insertion)	4	0.3
Exon 20 other (insertion)	19	1.3

J Thorac Oncol. 2014 Feb;9(2):154-62

EGFR detection in blood

- The level of circulating DNA in blood has been found to be higher in lung cancer patients than cancer-free patients
- Most of the excess circulating DNA is believed to be released from dying lung cancer cells at primary and/or metastatic sites
- Therefore, blood is a potential substitute for tumor tissues to provide a noninvasive, easily accessible, and repeatedly measurable source of genotypic information that may predict response and prognosis after treatment

Medicine (Baltimore). 2015 May;94(21):e775

EGFR detection in blood

OPEN

Blood as a Substitute for Tumor Tissue in Detecting *EGFR* Mutations for Guiding EGFR TKIs Treatment of Nonsmall Cell Lung Cancer

A Systematic Review and Meta-Analysis

This systematic review included 25 studies with 2605 patients
The pooled overall sensitivity, specificity, and concordance rate were 0.61, 0.90, and 0.79, respectively
Hence, EGFR mutation positivity in blood can be used to recommend EGFR TKIs treatment, but the absence of blood positivity should not necessarily be construed with confirmed negativity

Medicine (Baltimore). 2015 May;94(21):e775

Efficacy Of EGFR TKIS

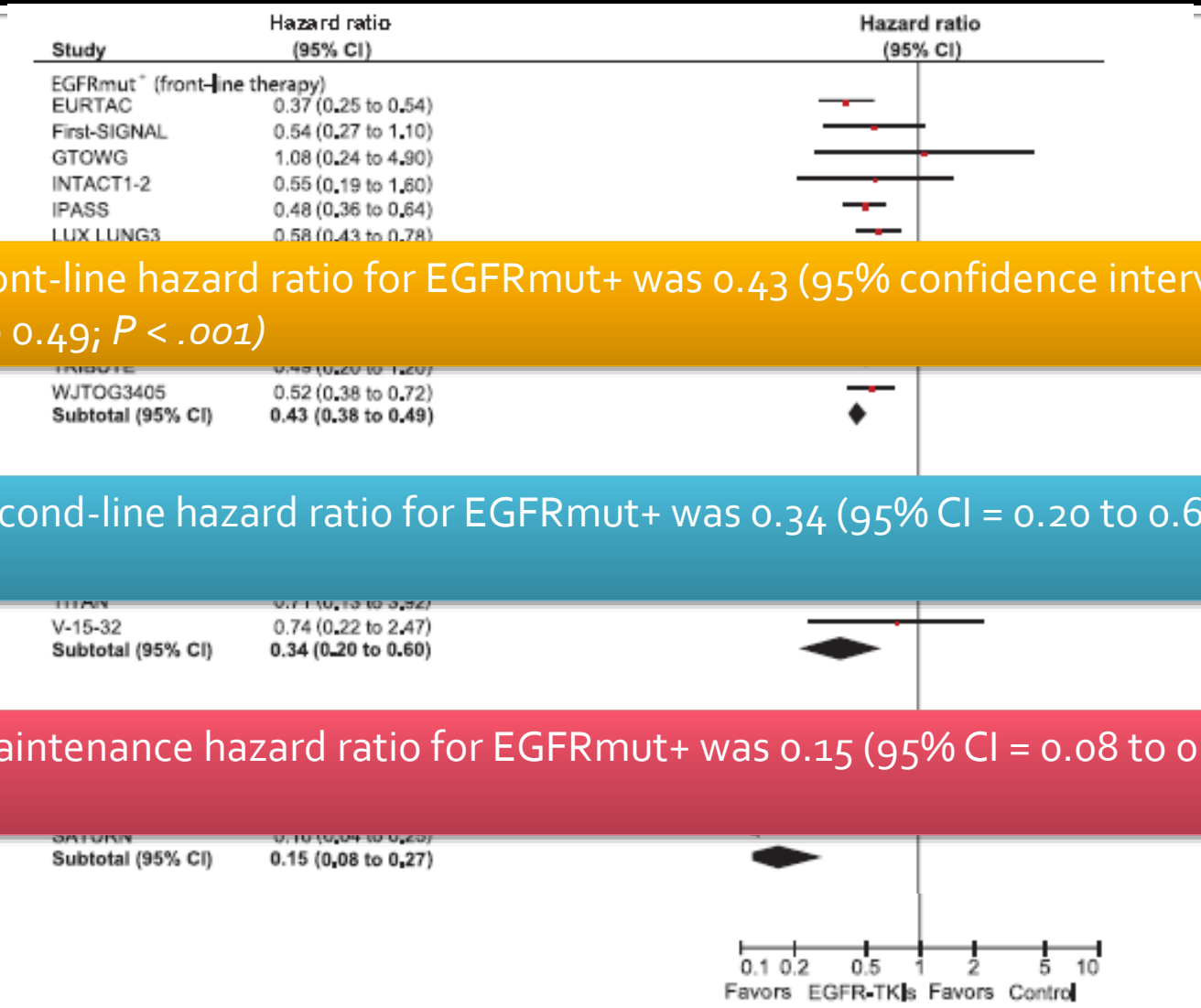
Table 1. Demographic characteristics of patients*

Study name (year) (reference)	Treatment comparison	EGFR mutation assessment method	No. of EGFR+ patients (%)	No. of EGFR- patients (%)	No. of EGFR unknown patients (%)	Age, y, median	Asian, %	Males, %	Present/ former smokers, %	Adeno-carcinoma, %
Front-line treatment										
INTACT 1 (2004) (24,43)	Gefitinib + CisG vs CisG	Direct sequencing	32 (2)	280 (13)	1818 (85)	60	6	74	NK	46
INTACT 2 (2004) (25,43)	Gefitnib + CP vs CP					62	NK	60	NK	55
TRIBUTE (2005) (22)	Erlotinib + CP vs CP	Direct sequencing	29 (3)	198 (18)	851 (79)	63	3	61	89	61
TALENT (2007) (26,37)	Erlotinib + CisG vs CisG	NK	NK	NK	NK	61	4	77	NK	38
IPASS (2009) (19,20)	Gefitinib vs CP	ARMS	261 (21)	176 (15)	780 (64)	57	100	21	6	96
NEJ002 (2010) (17,38)	Gefitinib vs CP	PCR clamp	228 (100)	0	0	63‡	100	36	38	94
GTOWG† (2010) (27)	Erlotinib vs CV	Direct sequencing	10 (4)	75 (26)	199 (70)	76	NK	68	83	50
TOPICAL (2010) (36,43)	Erlotinib vs placebo	SequenomOncoCarta Panel	28 (4)	362 (54)	280 (42)	77	2	61	95	38
WJTOG3405* (2010) (21,33)	Gefitinib vs CisD	Direct sequencing, PCR clamp	172 (100)	0	0	64	100	31	31	97
OPTIMAL* (2011) (16,35)	Erlotinib vs CG	Direct sequencing	154 (100)	0	0	58	100	41	29	87
First-SIGNAL (2012) (23)	Gefitinib vs CisG	Direct sequencing	43 (14)	54 (17)	212 (69)	57	100	11	NK	NK
EURTAC* (2012) (18)	Erlotinib vs platinum-G or platinum-D	Direct sequencing	173 (100)	0	0	65	0	27	31	92
LUX Lung 3† (2012) (34)	Afatinib vs CisPem	TheraScreen EGFR29	345 (100)	0	0	61	72	35	32	100
Maintenance therapy										
IFCT-GFPC 0502* (2010) (32)	Erlotinib or G vs placebo	NK	8 (3)	106 (34)	196 (63)	58	0	73	90	65
SATURN (2010) (13)	Erlotinib vs placebo	Direct sequencing	49 (6)	388 (44)	452 (50)	60	15	74	83	45
INFORM (2011) (30)	Gefitinib vs placebo	NK	30 (10)	49 (17)	217 (73)	55	100	59	46	71
Second-line/subsequent treatment										
ISEL (2005) (41)	Gefitinib vs placebo	Direct sequencing, ARMS	26 (2)	189 (11)	1477 (87)	62	20	67	78	45
BR21 (2005) (39,40)	Erlotinib vs placebo	Direct sequencing, ARMS	34 (5)	170 (23)	527 (72)	61	13	65	75	50
INTEREST (2008) (28,29)	Gefitinib vs D	Direct sequencing	44 (3)	253 (17)	1169 (80)	61	22	65	80	54
V-15–32 (2008) (31)	Gefitinib vs D	Direct sequencing	31 (6)	26 (6)	432 (88)	NK	100	62	68	78
TITAN (2012) (12)	Erlotinib vs pemetrexed or D	Direct sequencing	11 (3)	149 (35)	264 (62)	59	13	76	83	50
TAILOR† (2012) (14)	Erlotinib vs D	Direct sequencing	0	219 (100)	0	67	0	68	77	69
KCSG-LU08-01 (2012) (42)	Gefitinib vs Pem	Direct sequencing	33 (24)	38 (28)	64 (48)	61	100	15	0	100

* ARMS = amplification refractory mutation system; CG = carboplatin-gemcitabine; CisD = cisplatin-docetaxel; CisG = cisplatin-gemcitabine; CisPem = cisplatin-pemetrexed; CP = carboplatin-paclitaxel; CV = carboplatin-vinorelbine; D = docetaxel; EGFR+ = presence of epidermal growth factor receptor mutation; EGFR- = absence of epidermal growth factor receptor mutation; G = gemcitabine; NK = not known; PCR = polymerase chain reaction; PEM = pemetrexed.

J Natl Cancer Inst. 2013 May 1;105(9):595-605

HR comparing PFS in subgroups of EGFR positive

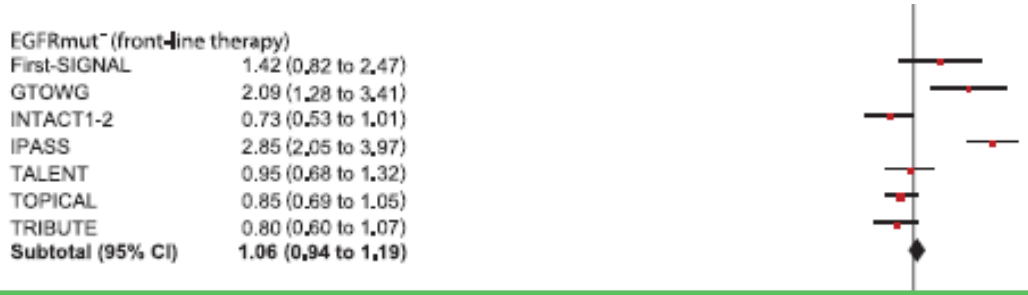


The front-line hazard ratio for EGFRmut+ was 0.43 (95% confidence interval [CI] = 0.38 to 0.49; *P* < *.001)*

The second-line hazard ratio for EGFRmut+ was 0.34 (95% CI = 0.20 to 0.60; *P* < *.001*

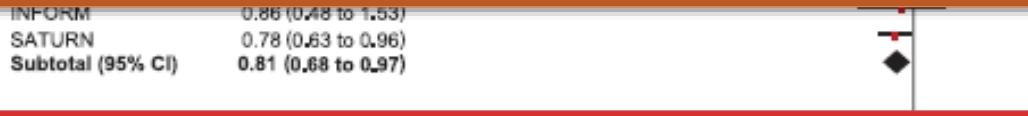
The maintenance hazard ratio for EGFRmut+ was 0.15 (95% CI = 0.08 to 0.27; *P* < *.001)*

HR comparing PFS in subgroups of EGFR positive



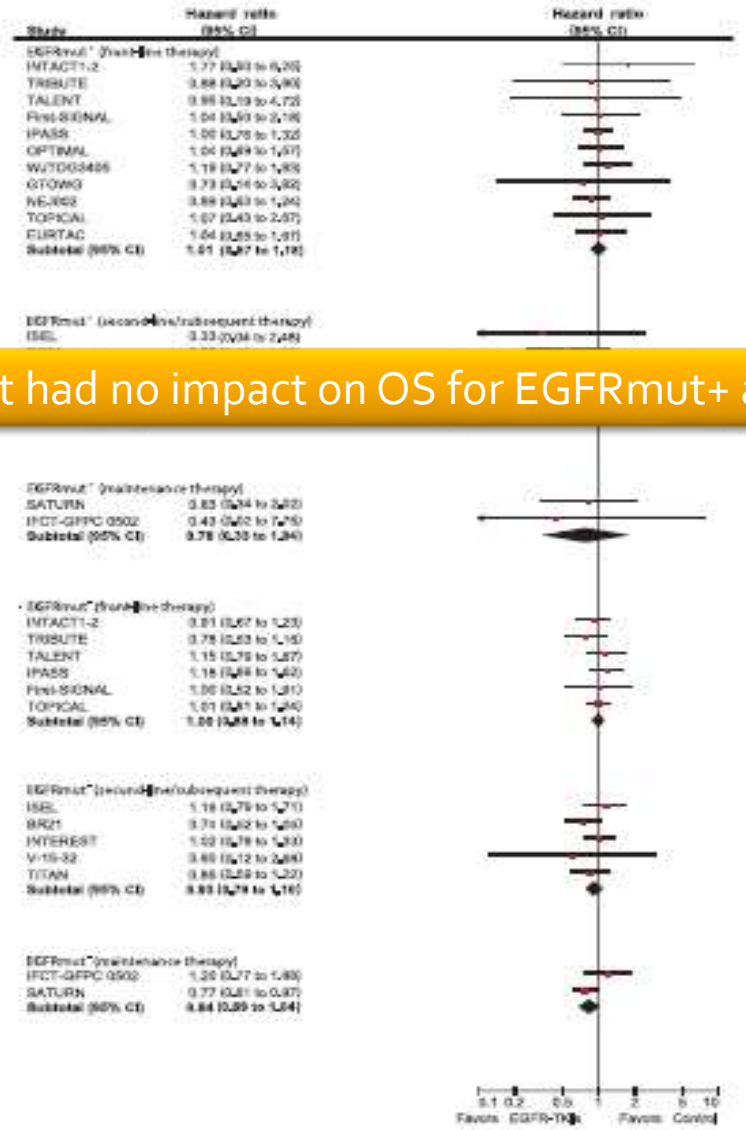
The front-line hazard ratio for EGFRmut– was 1.06 (95% CI = 0.94 to 1.19; *P* = *.35; Pinteraction < .001)*

The second-line hazard ratio for EGFRmut– was 1.23 (95% CI = 1.05 to 1.46; *P = .01; Pinteraction < .001).*



Maintenance hazard ratio for EGFRmut– was 0.81 (95% CI = 0.68 to 0.97; *P = .02; Pinteraction < .001*

HR comparing OS in subgroups of EGFR positive



EGFR-TKIs treatment had no impact on OS for EGFRmut+ and EGFRmut– patients

Individual TKIs: Erlotinib

Lancet Oncol. 2011 Aug;12(8):735-42. doi: 10.1016/S1470-2045(11)70184-X. Epub 2011 Jul 23.

Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study.

Zhou C[1], Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zhang L, Hu C, Hu C, Luo Y, Chen L, Ye M, Huang J, Zhi X, Zhang Y, Xiu Q, Ma J, Zhang L, You C.

Lancet Oncol. 2012 Mar;13(3):239-46. doi: 10.1016/S1470-2045(11)70393-X. Epub 2012 Jan 26.

Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial.

Rosell R[1], Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez JM, Porta R, Cobo M, Garrido P, Longo F, Moran T, Insa A, De Marinis F, Corre R, Bover I, Illiano A, Dansin E, de Castro J, Milella M, Reguart N, Altavilla G, Jimenez U, Provencio M, Moreno MA, Terrasa J, Muñoz-Langa J, Valdivia J, Isla D, Domine M, Molinier O, Mazieres J, Baize N, Garcia-Campelo R, Robinet G, Rodriguez-Abreu D, Lopez-Vivanco G, Gebbia V, Ferrera-Delgado L, Bombaron P, Bernabe R, Bearz A, Artal A, Cortesi E, Rolfo C, Sanchez-Ronco M, Drozdowskyj A, Queralt C, de Aguirre I, Ramirez JL, Sanchez JJ, Molina MA, Taron M, Paz-Ares L; Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica.

Ann Oncol. 2015 Sep;26(9):1883-9. doi: 10.1093/annonc/mdv270. Epub 2015 Jun 23.

First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study.

Wu YL[1], Zhou C[2], Liam CK[3], Wu G[4], Liu X[5], Zhong Z[6], Lu S[7], Cheng Y[8], Han B[7], Chen L[9], Huang C[10], Qin S[11], Zhu Y[12], Pan H[13], Liang H[14], Li E[15], Jiang G[16], How SH[17], Fernando MC[18], Zhang Y[19], Xia F[19], Zuo Y[19].

Individual TKIs: Erlotinib

Name	n	comparison	outcome
OPTIMAL	154	erlotinib or gemcitabine plus carboplatin	**Improved PFS** (13.1 versus 4.6 months, HR 0.16, 95% CI 0.10-.26)
EURTAC	174	erlotinib or a platinum based doublet	**Improved PFS** (9.7 versus 5.2 months, HR 0.37, 95% CI 0.250.54)
ENSURE	275	erlotinib or gemcitabine plus cisplatin	**Improved PFS** (11.0 versus 5.5 months, HR 0.34, 95% CI 0.220.51)

Individual TKIs: Gefitinib

In this phase 3, open-label study, previously untreated patients in East Asia who had advanced pulmonary adenocarcinoma and who were nonsmokers or former light smokers were randomly assigned to receive gefitinib or carboplatin plus paclitaxel

- PFS :hazard ratio for progression or death, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001
- In the subgroup of **261 patients EGFR mutation positive**,PFS was significantly longer among those who received gefitinib than among those who received carboplatin–paclitaxel (hazard ratio for progression or death, 0.48; 95% CI, 0.36 to 0.64; P<0.001)
- In the subgroup of 176 patients who were **negative for the mutation**, PFS was significantly longer among those who received carboplatin–paclitaxel (hazard ratio for progression or death with gefitinib, 2.85; 95% CI, 2.05 to 3.98; P<0.001)

N Engl J Med. 2009 Sep 3;361(10):947-57

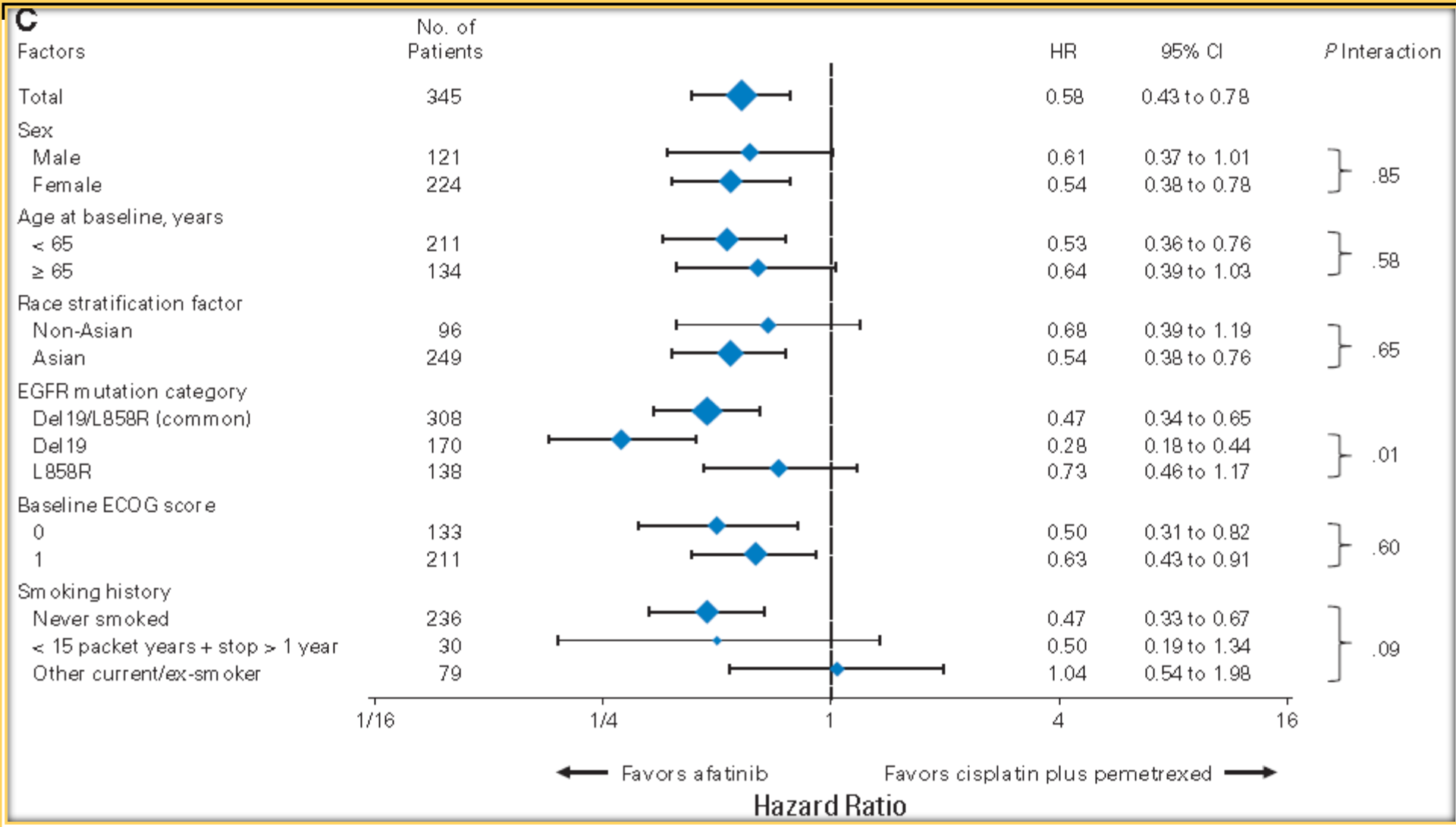
Individual TKIs:Gefitinib

- Two additional phase III trials were conducted exclusively in patients with EGFR mutations (the West Japan Oncology Group 172 trial and the North East Japan Study Group 002 trial)
- The overall results and magnitude of the benefit were essentially the same as in the IPASS trial

N Engl J Med. 2010;362(25):2380.

Lancet Oncol. 2010;11(2):121

Individual TKIs: Afatinib



J Clin Oncol. 2013 Sep 20;31(27):3327-34

Individual TKIs: Afatinib

- A second phase III trial was conducted in 364 Asian patients (Lux Lung 6), in which afatinib was compared with gemcitabine plus cisplatin
- Similar results were observed with afatinib resulting in an increased PFS (11.0 versus 5.6 months)

Lancet Oncol. 2014 Feb;15(2):213-22

Individual TKIs: Afatinib

- In a combined analysis of these two trials (n = 709), the **median overall survival was not significantly increased** for patients assigned to afatinib compared wit chemotherapy (median 25.8 versus 24.5 months, HR for death 0.91, 95% CI 0.75-1.11)
- When the combined trial data were analyzed based upon the specific mutation present, **a statistically significant benefit was observed in overall and progression free survival in patients with exon 19 deletion**.

Lancet Oncol. 2015;16(2):14

Comparisons of EGFR TKIs

- Choice of EGFR TKI can be individualized according to patient and provider preferences
- Available data suggest that erlotinib, gefitinib, and afatinib all have efficacy in EGFR mutant lung cancer and are generally well tolerated
- Some data suggest that afatinib may yield the strongest disease outcomes but may also cause the most side effects
- Gefitinib may be the best tolerated of the agents
- Cost is an important consideration

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase III Study Comparing Gefitinib With Erlotinib in Patients With Previously Treated Advanced Lung Adenocarcinoma: WJOG 5108L

Yoshiko Urata, Nobuyuki Katakami, Satoshi Morita, Reiko Kaji, Hiroshige Yoshioka, Takashi Seto, Miyako Satouchi, Yasuo Iwamoto, Masashi Kanehara, Daichi Fujimoto, Norihiko Ikeda, Haruyasu Murakami, Haruko Daga, Tetsuya Oguri, Isao Goto, Fumio Imamura, Shunichi Sugawara, Hideo Saka, Naoyuki Nogami, Shunichi Negoro, Kazuhiko Nakagawa, and Yoichi Nakanishi

Previously treated patients with lung adenocarcinoma were randomly assigned to receive gefitinib or erlotinib.

Median PFS and overall survival times for gefitinib and erlotinib were 6.5 and 7.5 months (hazard ratio [HR], 1.125; 95% CI, 0.940 to 1.347; P = .257) and 22.8 and 24.5 months (HR, 1.038; 95% CI, 0.833 to 1.294; P = .768), respectively

The study **did not demonstrate noninferiority of gefitinib compared with erlotinib** in terms of PFS in patients with lung adenocarcinoma according to the predefined criteria

Afatinib versus gefitinib as first-line treatment of patients with *EGFR* mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial

Treatment-naive patients with stage IIIB or IV NSCLC and a common *EGFR* mutation (exon 19 deletion or Leu858Arg) were randomly assigned (1:1) to receive afatinib (40 mg per day) or gefitinib (250 mg per day) until disease progression, or beyond if deemed benefi cial by the investigator

Afatinib significantly improved outcomes in treatment-naive patients with *EGFR-mutated NSCLC* compared with gefi tinib, with a manageable tolerability profi le.

- Progression-free survival (median 11·0 months with afatinib *vs 10·9 months with gefi tinib*
- Serious treatment-related adverse events occurred in 17 (11%) patients in the afatinib group and seven (4%) in the gefi tinib group

COST

Brand name	Company	Cost/30 tablets
Erlocip (100 mg)	CIPLA	Rs.6600
Erlocip (150 mg)	CIPLA	Rs.30000
Erleva (25 mg)	Glenmark	Rs. 1725
Erleva (100 mg)	Glenmark	Rs 19500
Erleva (150 mg)	Glenmark	Rs 30000
Loritinib (150 mg)		Rs 33000

Brand name	Company	Cost/30 tablets
Gefticip (250 mg)	Cipla	4500
Chemoressa (250 mg)	Biochem pharma	9600
Geftinat (250mg)	Natco	5900
Xefta (250 mg)	Dr Reddy	12000
Kabigef	Fresinius Kabi	5400

Duration of therapy

- Treatment with an EGFR TKI is generally continued until there is disease progression
- When chemotherapy is initiated, treatment with EGFR TKI generally should be discontinued

Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial

Chemotherapy-naive, stage IIIB-IV EGFR-mutation-positive advanced NSCLC with previous disease control with first-line gefitinib and recent disease progression

Participants were randomly assigned (1:1) by central block randomisation to oral gefitinib 250 mg or placebo once daily in tablet form
All patients also received the platinum-based doublet chemotherapy

Continuation of gefitinib after radiological disease progression on first-line gefitinib did not prolong progression-free survival in patients who received platinum-based doublet chemotherapy as subsequent line of treatment

Lancet Oncol. 2015 Aug;16(8):990-8

RESISTANCE TO EGFR TKIS

https://www.youtube.com/watch?v=5pMguzuSP1c

RESISTANCE TO EGFR TKIS

- Almost all patients who initially respond to an EGFR TKI subsequently develop disease progression
- The causes of acquired resistance are not fully understood, but include
  - secondary mutations in EGFR (50%) and
  - amplification of the MET (20%)
  - histologic transformation of NSCLC into small cell lung cancer

N Engl J Med. 2005 Feb 24;352(8):786-92

Management of acquired resistance

- Osimertinib has activity against T790M EGFR mutated NSCLC and was granted accelerated approval by the US FDA for use in patients with NSCLC harboring a T790M mutation whose disease progressed on other EGFR inhibiting therapy
- Other agents are rociletinib and HM61713
- AZD9291 is a third-generation EGFR-TKI

J Clin Oncol. 2016 Oct 1;34(28):3375-82

Management of acquired resistance

- The irreversible EGFR TKI afatinib may also have some activity in patients with acquired resistance to gefitinib or erlotinib

(abstract). European Society of Medical Oncology 2014 meeting

Primary resistance

- The T790M mutation has also been identified in a small percentage of patients with activating mutations of EGFR at presentation
- These patients appear to have a clinical course more typical of those with wild type EGFR

COMBINATION REGIMENS

- EGFR inhibition plus bevacizumab
  - One phase II trial to suggest combination may have some benefit over erlotinib alone
  - Median PFS was 16·0 months (95% CI 13·9-18·1) with combination and 9·7 months (5·7-11·1) with erlotinib alone (hazard ratio 0·54, 95% CI 0·36-0·79; log-rank test p=0·0015)

Lancet 2011; 377:1846

COMBINATION REGIMENS

- EGFR inhibition plus chemotherapy

Trial	n	combination	conclusion
TRIBUTE	526+533	erlotinib or placebo with up to of carboplatin and paclitaxel	did not confer a survival advantage
Tarceva Lung Cancer Trial	1172	erlotinib or placebo with up to of cisplatin and gemcitabine	no survival benefit
INTACT 1	1093	Gefitinib or placebo with gemcitabine and cisplatin	did not have improved efficacy
INTACT 2	1037	Gefitinib or placebo with paclitaxel and carboplatin	no added benefit

J Clin Oncol. 2005;23(25):5892
J Clin Oncol. 2007;25(12):1545

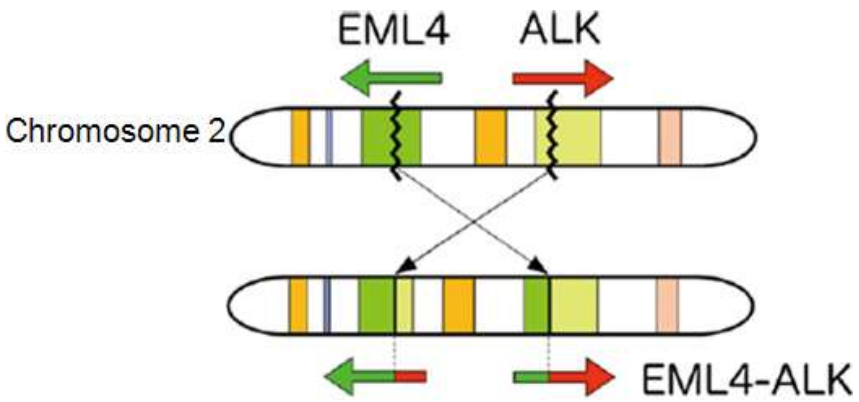
J Clin Oncol. 2004;22(5):777
J Clin Oncol. 2004;22(5):785

Side effects

- Important toxicities associated with inhibition of the EGFR pathway include
  - Dermatologic
    - dry skin and an acneiform rash
    - due to high levels of EGFR expression in the basal layer of the epidermis
    - Managed with antihistaminics, increasing the gap between two doses
  - Gastrointestinal
    - Up to 60 % of patients
    - Managed easily with loperamide
  - Hepatic toxicity with erlotinib

ALK fusion oncogene

- The echinoderm microtubule associated protein like 4 anaplastic lymphoma kinase (EML4 ALK) fusion oncogene arises from an inversion on the short arm of chromosome 2 (Inv(2)(p21p23)) that joins exons 1-13 of EML4 to exons 20-29 of ALK



ALK fusion oncogene

- The resulting chimeric protein, EML4ALK, contains an N terminus derived from EML4 and a C terminus containing the entire intracellular tyrosine kinase domain of ALK.
- For EML4ALK, the EML4 fusion partner mediates ligand independent dimerization and/or oligomerization of ALK, resulting in constitutive kinase activity

ALK fusion oncogene

- Cancer cell lines harboring the EML4ALK translocation are effectively inhibited by small molecule inhibitors that target the ALK tyrosine kinase supporting the notion that ALK driven cancers are "addicted" to the fusion oncogene

Diagnosis

- Anaplastic lymphoma kinase (ALK) gene rearrangements or the resulting fusion proteins may be detected in tumor specimens using
  - fluorescence in situ hybridization (FISH)
  - immunohistochemistry (IHC), and
  - reverse transcription polymerase chain reaction of cDNA (RTPCR)

IHC

- The biological premise for testing ALK mutation by IHC is that the inversion of part of the ALK gene leads to over-expression of the ALK protein
- The over expressed protein can be detected immunohistochemically

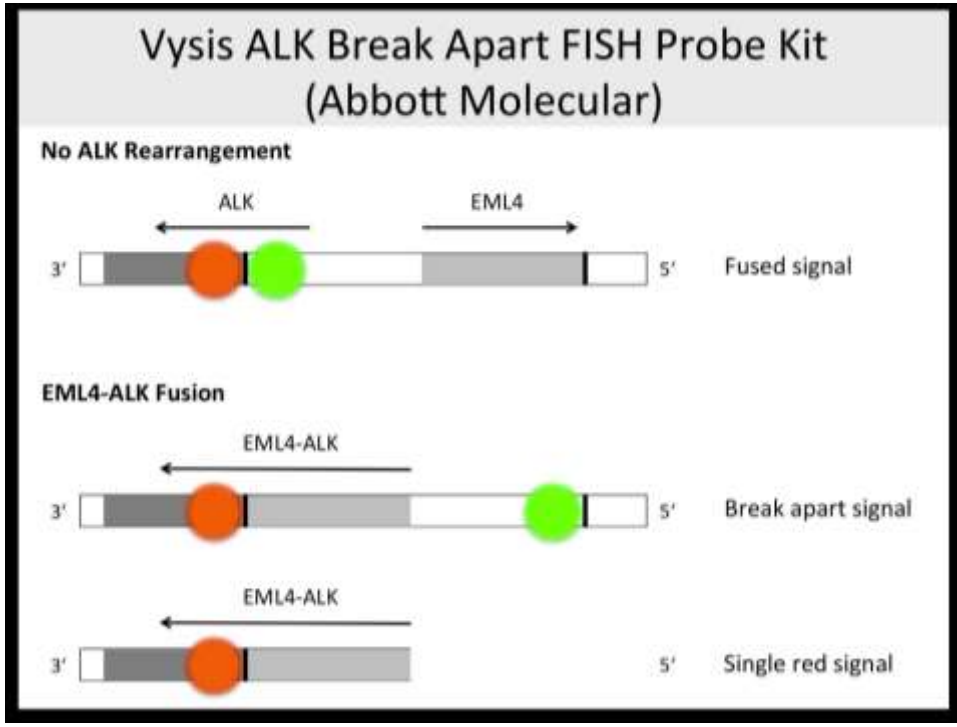
IHC

- Advantages
  - Cheap
  - Rapid
  - Easily integrated into a diagnostic protocol
  - Familiar to all pathologists
- The FDA has approved the Ventana ALK (D5F3) IHC assay as a companion diagnostic test to detect ALK rearrangement in NSCLC

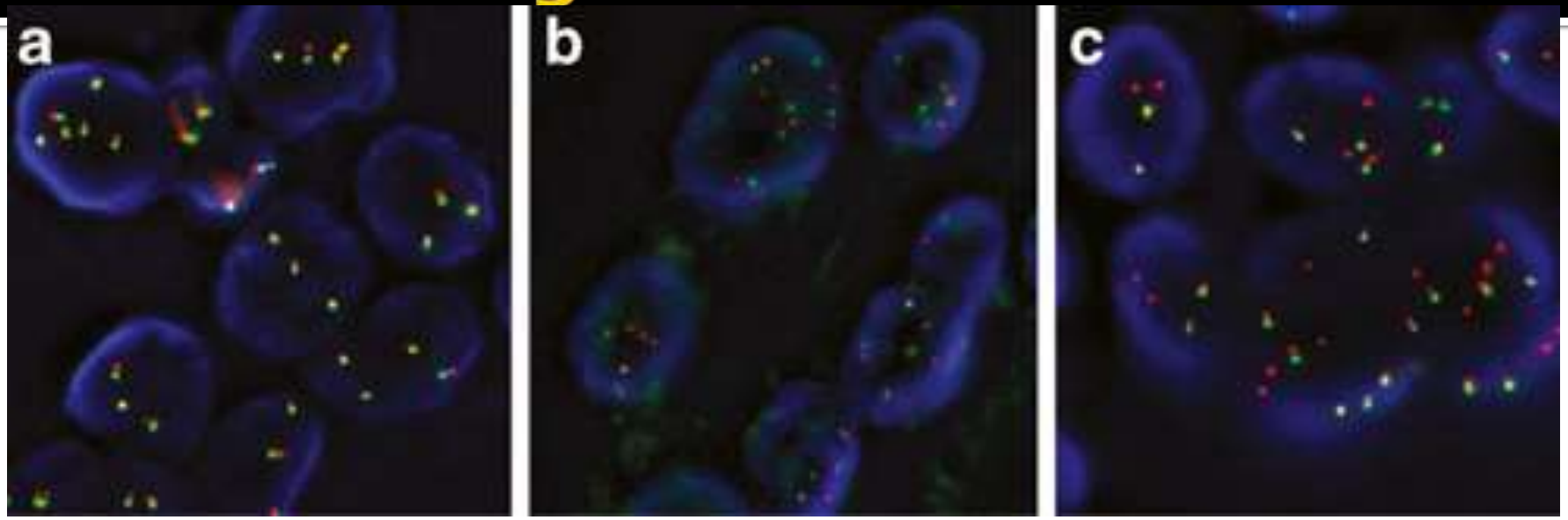
http://www.fda.gov/medicaldevices/productsandmedicalprocedures/deviceapprovalsandclearances/recently-approveddevices/ucm454476.htm

FISH

- The commercial break apart probes include two differently colored (red and green) probes that flank the highly conserved translocation breakpoint within ALK
- In non rearranged cells, the overlying red and green probes result in a yellow (fused) signal; in the setting of an ALK rearrangement, these probes are separated, and splitting of the red and green signals is observed



Representative examples of ALK FISH findings



a) Normal signals→no rearrangement
b) One or two break apart signals per nucleus, indicative of inversion
c) Single red signals, indicative of inversion and deletion

Cells are considered ALK FISH positive when there is: (1) ≥1 set of red and green signals that are ≥2 signal diameters apart, or
(2) a single red signal without a corresponding green signal in addition to fused (normal) signals

A sample is considered
- negative if <5 cells (<10 %) are positive and
- positive if >25 cells (>50 %) are positive
- equivocal if 5–25 cells (10–50 %) are positive

Epidemiology

- About 4% in non selected NSCLC
- Tend to be independent of EGFR or RAS mutation
- Increased prevalence in never/light smokers
- Younger patients
- 97% adenocarcinomas, rarely in squamous

CHEMOTHERAPY VERSUS TARGETED THERAPY

- Advanced NSCLC associated with ALK fusion oncogene is highly sensitive to ALK tyrosine kinase (TK) inhibitors

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Crizotinib versus Chemotherapy in Advanced *ALK*-Positive Lung Cancer

An open-label trial comparing crizotinib with chemotherapy in 347 patients with locally advanced or metastatic *ALK-positive lung cancer who* had received one prior platinum-based regimen.

The median progression-free survival was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group Crizotinib is superior to standard chemotherapy in patients with previously treated, advanced non–small-cell lung cancer with *ALK rearrangement*

N Engl J Med. 2013 Jun 20;368(25):2385-94

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

phase 3 trial comparing crizotinib with chemotherapy in 343 patients with advanced *ALK-positive nonsquamous NSCLC who had* received no previous systemic treatment for advanced disease

Progression-free survival was significantly longer with crizotinib than with chemotherapy (median, 10.9 months vs. 7.0 months)
Crizotinib was superior to standard first-line pemetrexed-plus-platinum chemotherapy in patients with previously untreated advanced *ALK-positive NSCLC.*

N Engl J Med. 2014 Dec 4;371(23):2167-77

Waiting time

- If systemic treatment is required before the results of genotype testing are available, systemic chemotherapy rather than targeted therapy is indicated
- Treatment plan should be reassessed when the results of genotype testing become available
- Optimal timing of ALK inhibitors in patients who have already started on chemotherapy is not known

ALK inhibitors

- Three TKIs have established roles in the treatment of ALK fusion oncogene positive NSCLC
  - crizotinib, ceritinib, and alectinib
  - Additional are under investigation

Duration of treatment

- continued until there is evidence of disease progression
- Switch to second generation ALK inhibitor

Resistance

- almost all patients develop resistance to the drug
  - acquired a secondary mutation within the ALK tyrosine kinase domain
  - amplification of the ALK fusion gene
  - alternative or bypass signaling pathways

CERITINIB

- Ceritinib is a second generation TKI of ALK
  - 20 times more potent
  - is approved for patients who have progressed on or are intolerant of crizotinib

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 27, 2014 VOL. 370 NO. 13

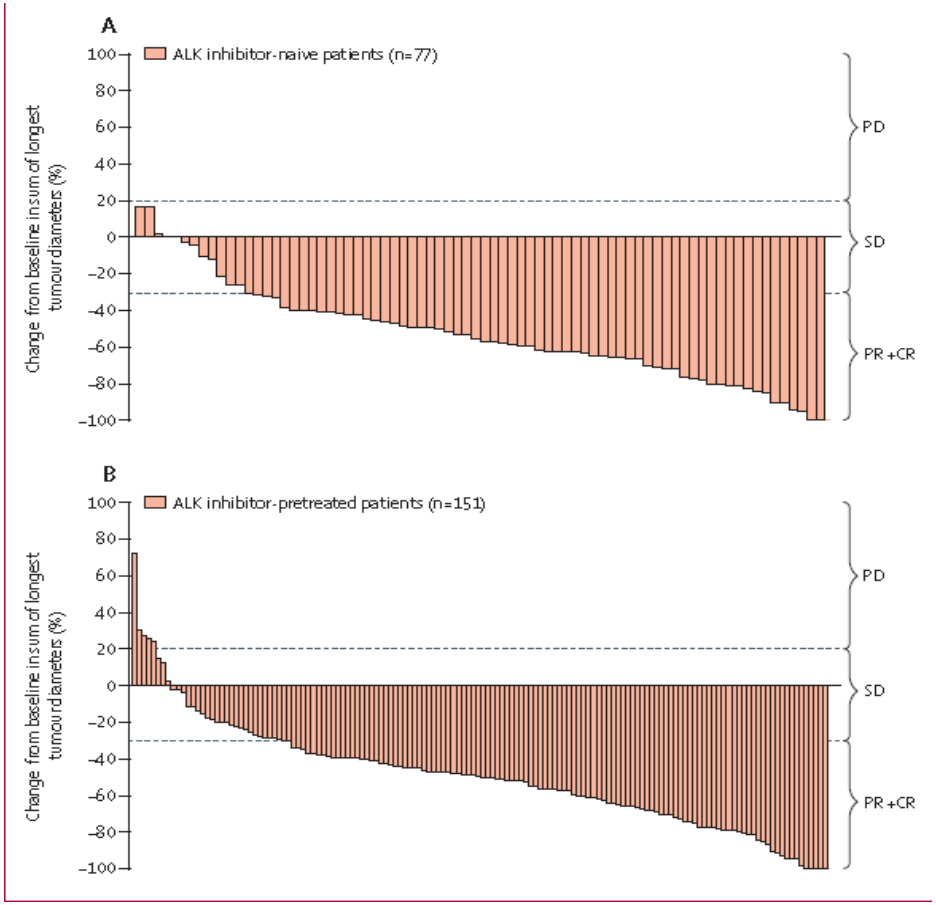
Ceritinib in *ALK*-Rearranged Non–Small-Cell Lung Cancer

- Phase 1 study, oral ceritinib in doses of 50 to 750 mg once daily was administered to patients with advanced cancers harboring genetic alterations in *ALK*
- Among 114 patients who received at least 400 mg of ceritinib per day, the

Ceritinib was highly active in patients with advanced, *ALK-rearranged NSCLC, including* those who had had disease progression during crizotinib treatment, regardless of the presence of resistance mutations in *ALK*

N Engl J Med. 2014 Mar 27;370(13):1189-9

Activity and safety of ceritinib in patients with *ALK*-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial



An overall response was reported in 60 (72% [95% CI 61–82]) of 83 ALK inhibitor naive pati ents and 92 (56% [49–64]) of 163 ALK inhibitor-pretreated patients

Lancet Oncol. 2016 Apr;17(4):452-63

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Multicenter Phase II Study of Whole-Body and Intracranial Activity With Ceritinib in Patients With *ALK*-Rearranged Non–Small-Cell Lung Cancer Previously Treated With Chemotherapy and Crizotinib: Results From ASCEND-2

Lucio Crinò, Myung-Ju Ahn, Filippo De Marinis, Harry J.M. Groen, Heather Wakelee, Toyoaki Hida, Tony Mok, David Spigel, Enriqueta Felip, Makoto Nishio, Giorgio Scagliotti, Fabrice Branle, Chetachi Emeremni, Massimiliano Quadrigli, Jie Zhang, and Alice T. Shaw

Lucio Crinò, University Medical School of

- All 140 patients enrolled had received two or more previous treatment regimens, and all patients had received crizotinib
- overall response rate was 38.6%

Consistent with its activity in ASCEND-1, ceritinib treatment provided clinically meaningful and durable responses with manageable tolerability in chemotherapy- and crizotinib-pretreated patients

J Clin Oncol. 2016 Aug 20;34(24):2866-73

Trial record **1 of 1** for: NCT01828112

Previous Study | Return to List | Next Study

LDK378 Versus Chemotherapy in ALK Rearranged (ALK Positive) Patients Previously Treated With Chemotherapy (Platinum Doublet) and Crizotinib

This study is ongoing, but not recruiting participants.

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:
NCT01828112

First received: April 2, 2013
Last updated: September 9, 2016
Last verified: September 2016
History of Changes

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Search Results > Study Record Detail Text Size

Trial record **1 of 1** for: NCT01828099

Previous Study | Return to List | Next Study

LDK378 Versus Chemotherapy in Previously Untreated Patients With ALK Rearranged Non-small Cell Lung Cancer

This study is ongoing, but not recruiting participants.

Sponsor:
Novartis Pharmaceuticals

Information provided by (Responsible Party):
Novartis (Novartis Pharmaceuticals)

ClinicalTrials.gov Identifier:
NCT01828099

First received: April 3, 2013
Last updated: November 3, 2016
Last verified: November 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

ALECTINIB

- It is another second generation ALK inhibitor that has activity in crizotinib resistant disease with
- Two phase II studies, both demonstrating response rates to alectinib of approximately 50 percent in patients with ALK positive locally advanced or metastatic NSCLC who had progressed on crizotinib

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Alectinib in Crizotinib-Refractory *ALK*-Rearranged Non–Small-Cell Lung Cancer: A Phase II Global Study

Sai-Hong Ignatius Ou, Jin Seok Ahn, Luigi De Petris, Ramaswamy Govindan, James Chih-Hsin Yang, Brett Hughes, Hervé Lena, Denis Moro-Sibilot, Alessandra Bearz, Santiago Viteri Ramirez, Tarek Mekhail, Alexander Spira, Walter Bordogna, Bogdana Balas, Peter N. Morcos, Annabelle Monnet, Ali Zeaiter, and Dong-Wan Kim

Sai-Hong Ignatius Ou, University of California Irvine School of Medicine, Orange, CA; Jin Seok Ahn, Sungkyunkwan University School of Medicine; Luigi De Petris, Karolinska

Articles

Alectinib in *ALK*-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial

*Alice T Shaw, Leena Gandhi, Shirish Gadgeel, Gregory J Riely, Jeremy Cetnar, Howard West, D Ross Camidge, Mark A Socinski, Alberto Chiappori, Tarek Mekhail, Bo H Chao, Hossein Borghaei, Kathryn A Gold, Ali Zeaiter, Walter Bordogna, Bogdana Balas, Oscar Puig, Volkmar Henschel, Sai-Hong Ignatius Ou, on behalf of the study investigators**

J Clin Oncol. 2016 Mar 1;34(7):661-8

Lancet Oncol. 2016 Feb;17(2):234-4

ALECTINIB

Alectinib (ALC) versus crizotinib (CRZ) in ALK-inhibitor naive *ALK*-positive non-small cell lung cancer (*ALK*+ NSCLC): Primary results from the J-ALEX study.

Subcategory:
Metastatic Non-Small Cell Lung Cancer

Category:
Lung Cancer—Non-Small Cell Metastatic

Meeting:
2016 ASCO Annual Meeting

Session Type and Session Title:
Oral Abstract Session, Lung Cancer—Non-Small Cell Metastatic

At J-ALEX IA, ALC demonstrated significantly prolonged PFS compared with CRZ and was well tolerated with a favorable AE profile

Citation:
J Clin Oncol 34, 2016 (suppl; abstr 9008)

Other ALK inhibitors

- Brigatinib is an investigational ALK inhibitor that is not yet approved for clinical use
- Preliminary results of a phase II study of 222 patients with crizotinib refractory, ALKpositive NSCLC demonstrated PFS of 8.8 and 11.1 months among those receiving a lower and higher dose of the agent, respectively, with low incidence of grade ≥3 toxicities in both arms

J Clin Oncol. 2016;34S: ASCO #9007

Other ALK inhibitors

- Lorlatinib is another investigational ALK inhibitor that has shown promising activity in a phase I study.
- Activity against tumor that harbor the highly resistant mutation ALK G1202R
- This mutation confers resistance to other next generation ALK inhibitors, including ceritinib, alectinib, and brigatinib

J Clin Oncol. 2016;34S:ASCO #9009

Safety and efficacy of lorlatinib (PF-06463922) from the dose-escalation component of a study in patients with advanced ALK+ or ROS1+ non-small cell lung cancer (NSCLC).

Subcategory:
Metastatic Non-Small Cell Lung Cancer

Category:
Lung Cancer—Non-Small Cell Metastatic

Meeting:
2016 ASCO Annual Meeting

Session Type and Session Title:
Clinical Science Symposium, Raising the Bar for Targeted Therapies for Lung Cancers

Abstract Number:
9009

Citation:
J Clin Oncol 34, 2016 (suppl; abstr 9009)

Brain metastasis

- For the patient who presents with newly diagnosed, ALKpositive NSCLC with CNS metastases alectinib is preferred over crizotinib because of
  - frequent CNS relapses on crizotinib
  - its poor penetration of the CNS
  - alectinib's excellent CNS penetration
  - high overall response rate and duration of response

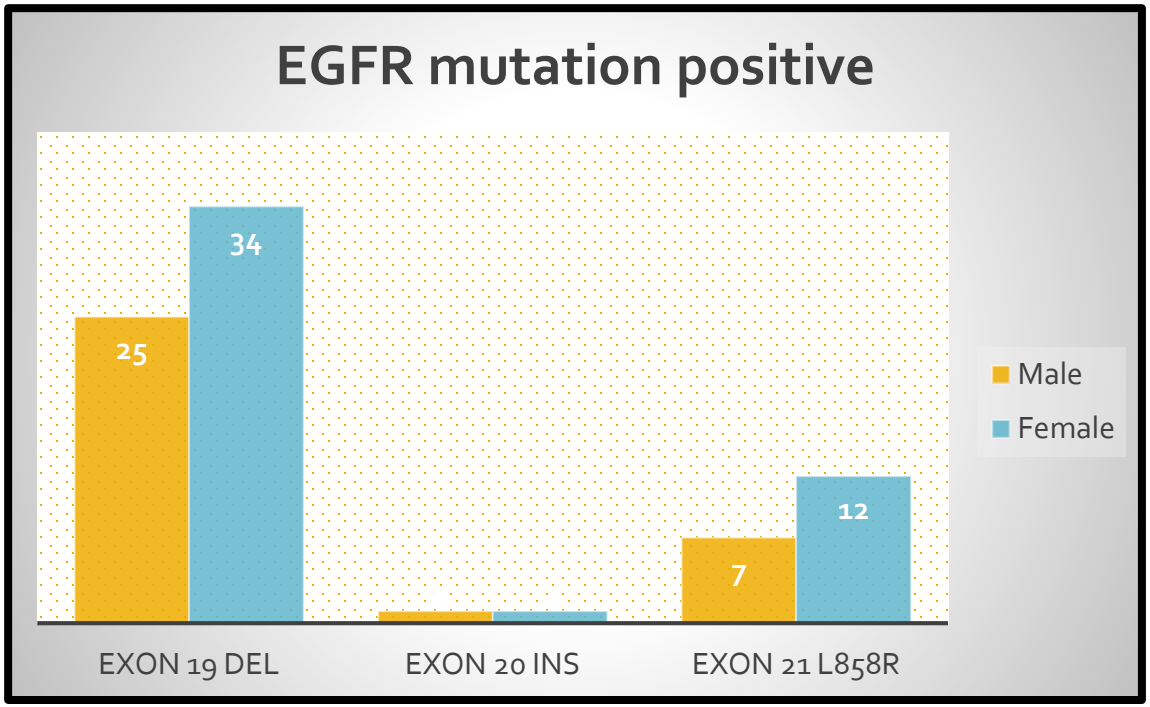
Toxicity

- Treatment with the anaplastic lymphoma kinase (ALK) inhibitors is generally well tolerated
- Toxicities may require dose modification
  - Gastrointestinal side effects — Nausea, vomiting, and diarrhea are common with both crizotinib and ceritinib
  - Hepatotoxicity — Liver function test abnormalities are occasionally seen with crizotinib. Hepatoxicity can progress and may require dose modification or discontinuation. (See "Chemotherapy
  - Pneumonitis — Severe, life threatening pneumonitis has been reported

Ther Adv Med Oncol. 2016 Jan;8(1):32-4

PGIMER experience

- ≅450 patients tested Jan 2012 – Aug 2016:
  - ~20% positive; mean age ≈ 60 years
  - Exon 19 del : Exon 21 L858R = ≈ 3 : 1
  - F : M = 1.4 : 1



EGFR & ALK: PGIMER experience

	No. tested	Interpretable results	Positive (%)	Mean age (Years)
EGFR	436	378 (86.7%)*	80 (18.3%) 80 (21.2%)	59.8
ALK	314	284 (90.4%)^	24 (7.6%) 24 (8.5%)	50.7

*** 92.5% with Real Time ARMS-PCR vs. 81.4% with Gene Sequencing**

^ 92.5% with D5F3 IHC vs. 79.6% with Break Apart FISH

EGFR & ALK: PGIMER experience

	EGFR	ALK
Overall	21.2%	8.5%
Adenocarcinoma only	22.8%	9.1%
Females vs. males	38.5% vs. 12.9%	13.7% vs. 5.8%
Non-Smokers vs. Smokers	34.3% vs. 10.3%	12.4% vs. 4.8%
Females & Non-smokers	40.2%	13.3%
Males & Non-smokers	24.6%	11.1%
Males & Smokers	9.5%	4.1%
Females & Adenocarcinoma	41.0%	14.3%
Method used for Testing	24.9% Real Time ARMS-PCR vs. 16.7% Gene Sequencing	9.4% D5F3 IHC vs. 2.6% Break Apart FISH

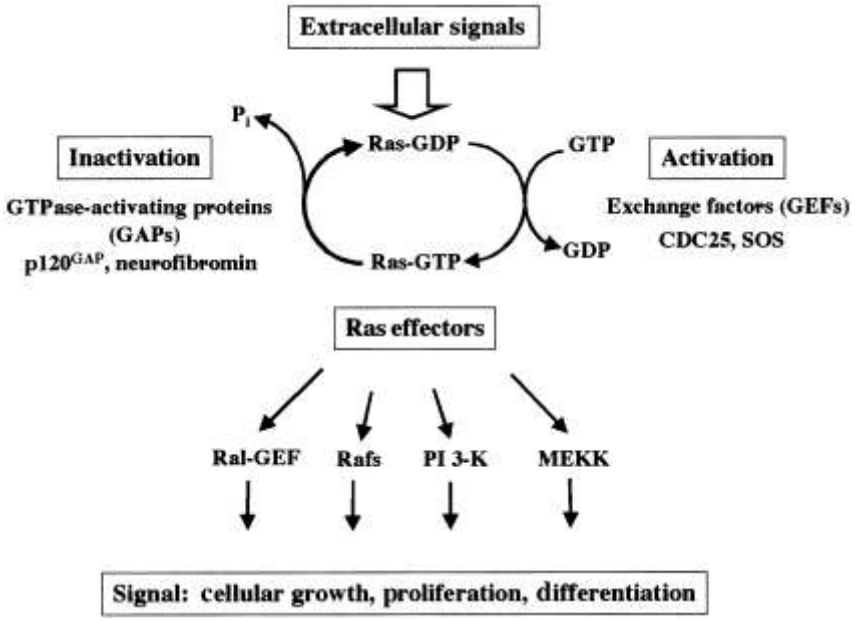
PGIMER Experience

- Retrospective analysis (n=186 over 3 years; 2012-14):
  - Of the patients with interpretable mutation status, EGFR mutations were detected in 26 (16.6%) and WT in 131. EGFR mutation status was uninterpretable (EGFR unknown) in 29 patients (15.6%).
    - Female sex (P = 0.002)
    - never smoking status (P = 0.002),
    - metastatic disease (P = 0.032), and
    - nonsolid subtype of ADC (P = 0.001)
  - Median OS was higher in patients with EGFR M (750 days) as compared to EGFR-WT (459 days) for overall population and in patients with Stage IV disease (750 days vs. 278 days for EGFR-WT, P = 0.024)

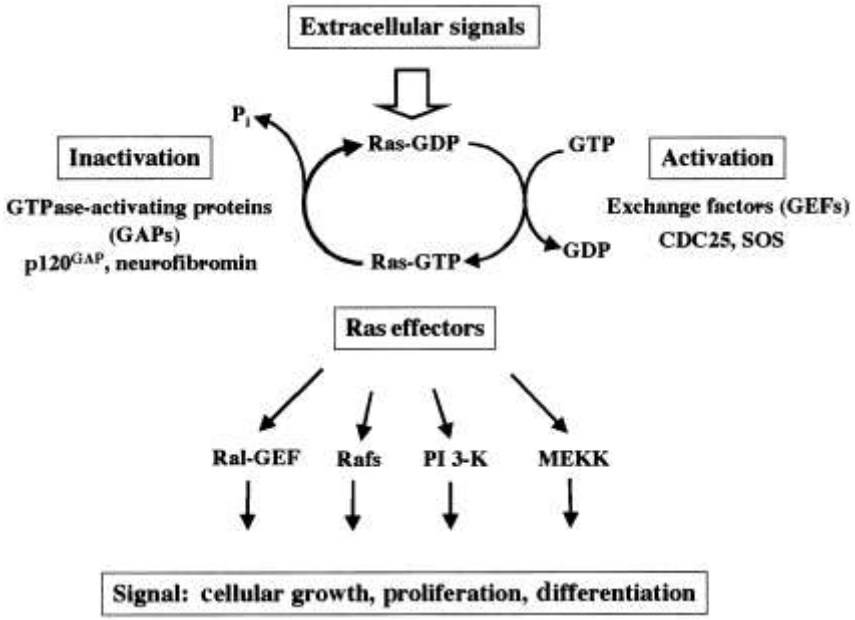
Maturu VN, Singh N et al. Lung India 2016; 33: 257-66

RAS mutations

- As a membrane bound intracellular GTPase, the RAS family of proteins is a central mediator of the
  - mitogen activated protein kinase (MAPK),
  - signal transducer and activator of transcription (STAT), and
  - phosphoinositide 3 kinase (PI3K) signaling
- These pathways together control cell proliferation and apoptosis



- Oncogenic RAS mutations cause constitutive activity of RAS independent of upstream signals by impairing the function of the RAS GTPase.



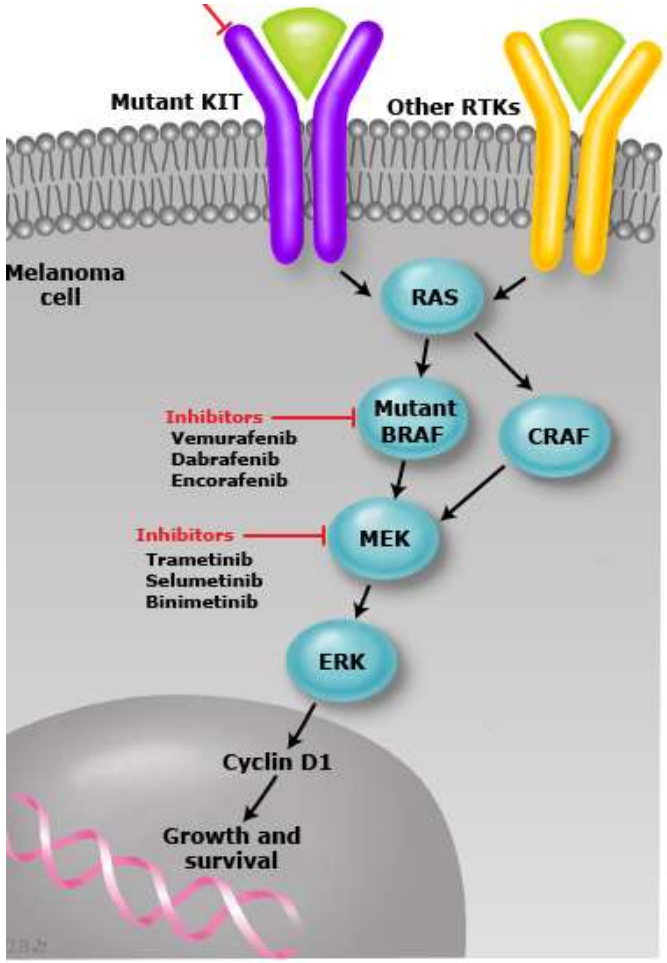
KRAS mutation

- More common in smokers (20-25% adeno, 4% squmous)
- No established targeted therapies for KRAS mutations
- The current focus of targeted therapeutics for patients with KRAS mutated lung cancer is against downstream effectors of activated KRAS
- The presence of a KRAS mutation appears to be associated with a worse prognosis

Cancer. 2001;92(6):1525

Evidence for targeted therapy against downstream targets

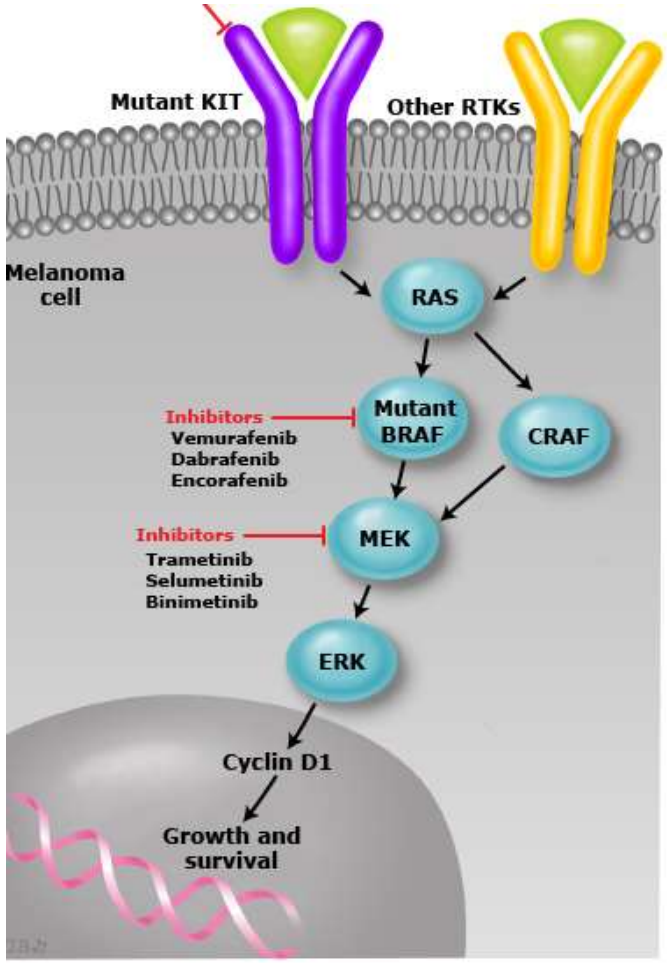
- MEK inhibition with selumetinib: 87 previously treated patients with KRAS mutant NSCLC were randomly assigned to docetaxel with or without selumetinib
- The addition of selumetinib significantly improved progression free survival (median 5.3 mo versus 2.1 mo, HR 0.58 80% CI 0.420.79)



Lancet Oncol. 2013 Jan;14(1):38-47

Evidence for targeted therapy against downstream targets

- MEK inhibition with trametinib
  - The combination of trametinib, a MEK inhibitor, plus either pemetrexed or docetaxel showed promising activity



N Engl J Med. 2012;367(2):107

KRAS mutation

- The activity of MEK inhibitors appears to be similar in patients with KRAS mutant and wild-type NSCLC suggesting KRAS mutation status is not a reliable biomarker for efficacy hence KRAS mutation status alone does not appear to be a biomarker of MEK inhibitor efficacy

Lancet Oncol. 2013 Jan;14(1):38-47

ROS1 translocation

- ROS1 is a receptor tyrosine kinase of the insulin receptor family that acts as a driver oncogene in 1 to 2 percent of NSCLC via a genetic translocation between ROS1 and other genes, the most common of which is CD74
  - Adenocarcinoma histology
  - Younger patients
  - Never smokers

ROS1 translocation

- High degree of homology between the ALK and ROS tyrosine kinase domains
- Identified by a FISH break apart assay
- The ROS1 tyrosine kinase is highly sensitive to crizotinib

J Clin Oncol. 2012 Mar;30(8):863-70

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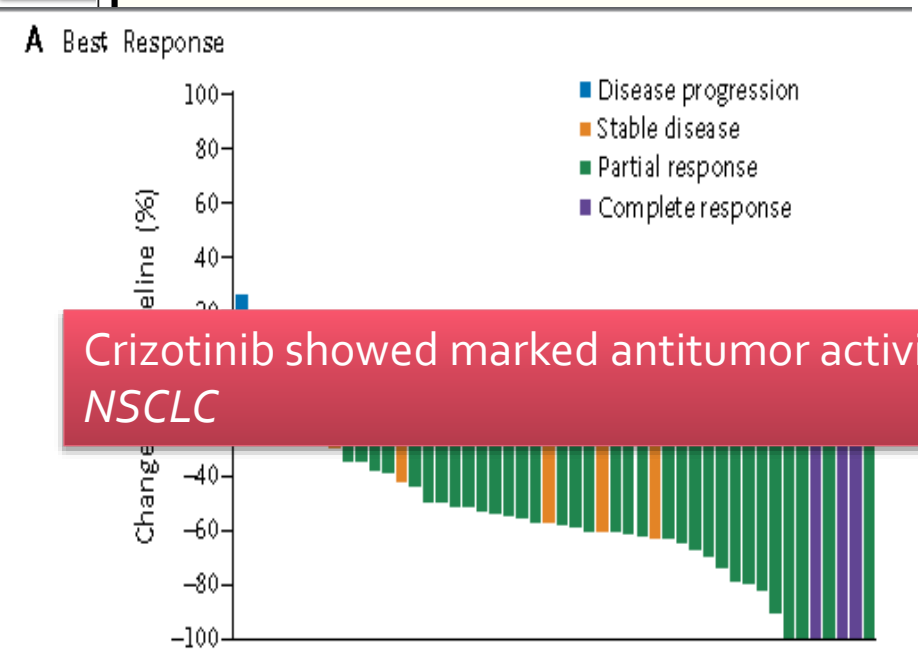
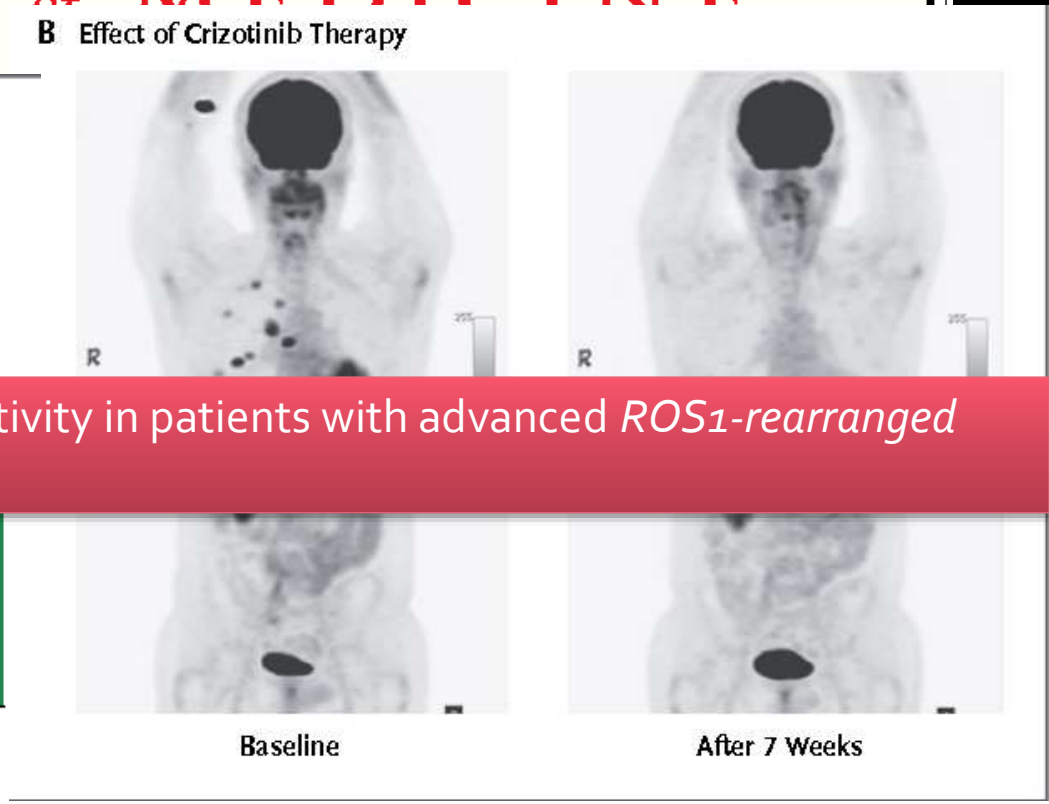




Crizotinib showed marked antitumor activity in patients with advanced *ROS1-rearranged NSCLC*

The objective response rate was 72% (95% confidence interval [CI], 58 to 84), with 3 complete responses and 33 partial responses

N Engl J Med. 2014 Nov 20;371(21):1963-71

ROS1 translocation

- Only case reports for ceritinib in ROS1 translocations

HER2 mutation

- HER2 (ERBB2) is an EGFR family receptor tyrosine kinase.
- Mutations in HER2 have been detected in approximately 1 to 2 percent of NSCLC tumors
- They usually involve small in frame insertions in exon 20
  - Adenocarcinoma
  - Never smokers
  - women

HER2 mutation

- There is no obvious association between HER2 amplification and HER2 mutations, and previous trials demonstrated no benefit for trastuzumab in HER2 amplified NSCLC
- Case series suggest that patients with tumors harboring HER2 insertions often respond to
  - trastuzumab and chemotherapy or
  - Afatinib or
  - irreversible pan HER inhibitor neratinib
- Larger clinical trials are ongoing

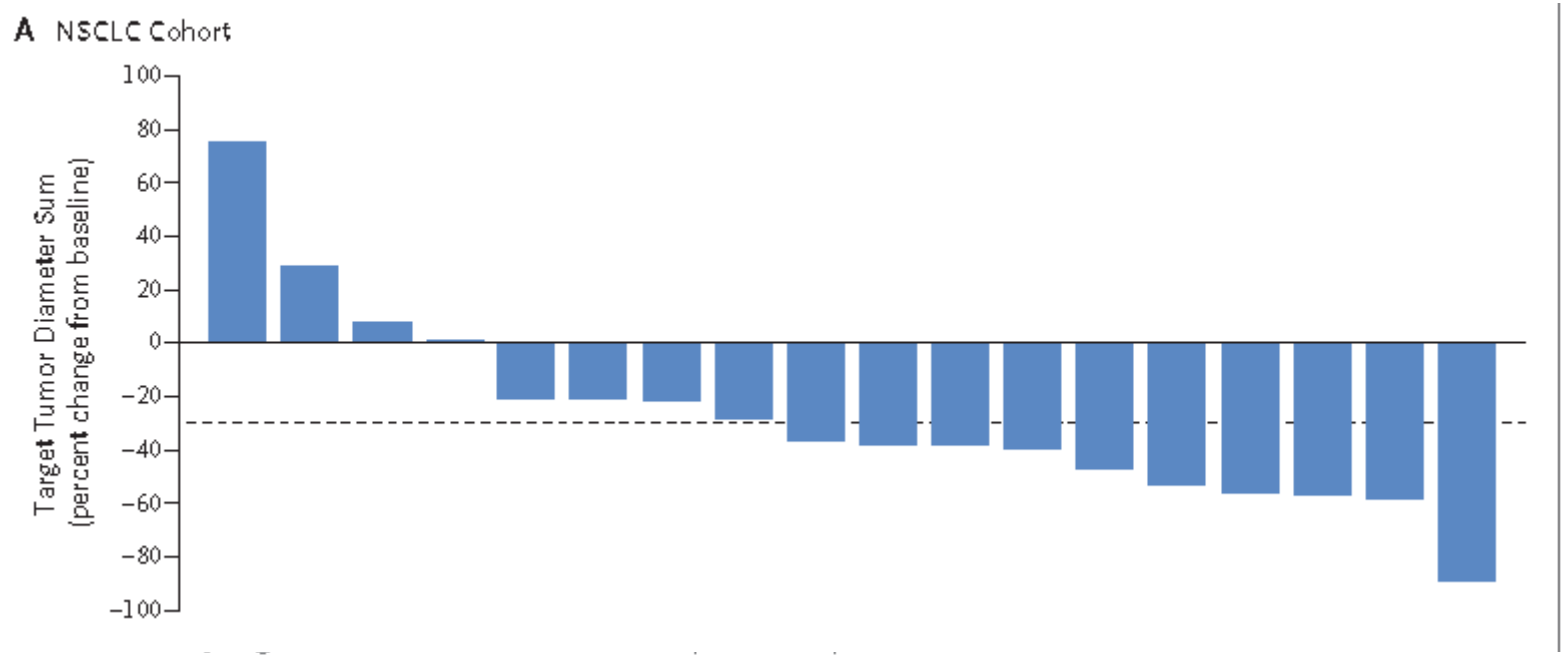
N Engl J Med. 2006 Jun 15;354(24):2619-21

J Clin Oncol. 2014 Jan 10;32(2):68-75

BRAF mutation

- BRAF is a downstream signaling mediator of KRAS which activates the MAP kinase pathway
  - 1-3% of NSCLC
  - Smoking history
  - Adenocarcinoma
- Activating BRAF mutations occur at the V600 position of exon 15

BRAF inhibitors



Antoine Hollebecque, M.D., Radj Gervais, M.D.,

In the cohort with non–small-cell lung cancer, the response rate was 42% (95% confidence interval [CI], 20 to 67) and median progression-free survival was 7.3 months (95% CI, 3.5 to 10.8)

N Engl J Med. 2015 Aug 20;373(8):726-36

BRAF inhibitors

Dabrafenib in patients with *BRAF*^{V600E}-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial

Previously treated and untreated patients with stage IV metastatic *BRAFV600E-positive NSCLC*

C Martin Curtis Jr, Bruce E Johnson

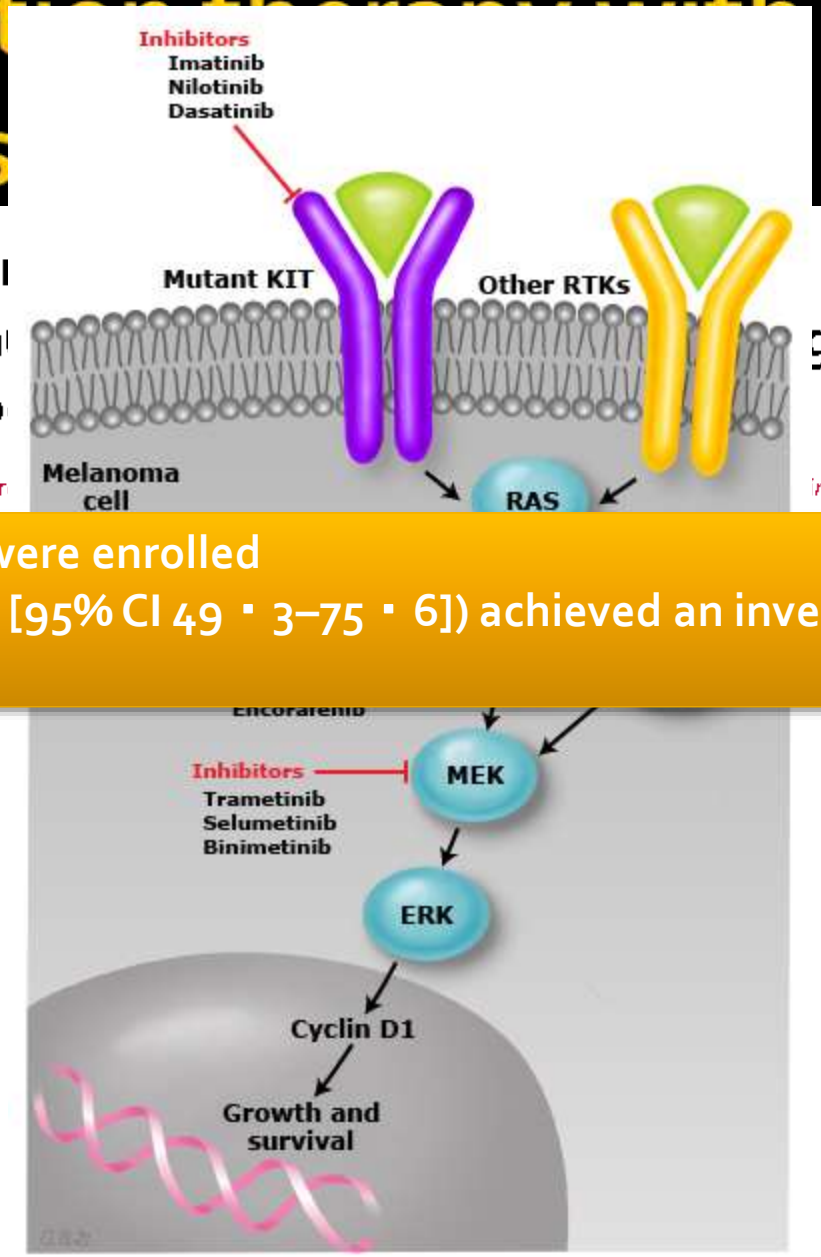
26 of the 78 previously treated patients achieved an investigator-assessed overall response (33% [95% CI 23–45])

Lancet Oncol. 2016 May;17(5):642-50

Combinat… therapy with BRAF inhibitors

Dabrafenib plus tra… treated *BRAF*^{V600E}-m… cancer: an open-lab…

David Planchard, Benjamin Besse, Harry J M Gr… …m,



57 eligible patients were enrolled
36 patients (63 · 2% [95% CI 49 · 3–75 · 6]) achieved an investigator-assessed overall response

Lancet Oncol. 2016 Jul;17(7):984-93

MET abnormalities

- MET is a tyrosine kinase receptor for hepatocyte growth factor
- Abnormalities associated with MET include
  - overexpression due to gene amplification and
  - exon 14 skipping mutations
- The MET exon 14 skipping mutation reduces degradation of the MET protein, causing it to behave as an oncogenic driver
  - 3-4% of NSCLC

MET inhibitors

- MET amplification
  - crizotinib is also a potent MET inhibitor
  - In a group of 12 patients with intermediate or high MET gene amplification crizotinib demonstrated responses in 5 and stable disease in 5 patients

abstract 8001. 2014 American Society of Clinical Oncology meeting

MET inhibitors

- MET exon 14 skipping mutations
  - Crizotinib
  - Cabozantinib

Cancer Discov. 2015 Aug;5(8):842-9

MET and EGFR comutations

Erlotinib, cabozantinib, or erlotinib plus cabozantinib as second-line or third-line treatment of patients with *EGFR* wild-type advanced non-small-cell lung cancer (ECOG-ACRIN 1512): a randomised, controlled, open-label, multicentre, phase 2 trial

*Joel W Neal, Suzanne E Dahlberg, Heather A Wakelee, Seena C Aisner, Michaela Bowden, Ying Huang, David P Carbone, Gregory J Gerstner, Rachel E Lerner, Jerome L Rubin, Taofeek K Owonikoko, Philip J Stella, Preston D Steen, Ahmed Ali Khalid, Suresh S Ramalingam, for the ECOG-ACRIN 1512 Investigators**

Compared with erlotinib alone (median 1·8 months [95% CI 1·7–2·2]), PFS was significantly improved in the cabozantinib group (4·3 months [3·6–7·4] and in the erlotinib plus cabozantinib group (4·7 months [2·4–7·4]

Lancet Oncol. 2016 Nov 4

RET translocation

- Recurrent translocations between RET and the various fusion partners have been identified in 1 to 2 percent of patients with adenocarcinoma or adenosquamous carcinoma of the lung
- Drugs inhibiting RET TK are
  - Vandetanib
  - Sorafenib
  - Sunitinib

RET translocation

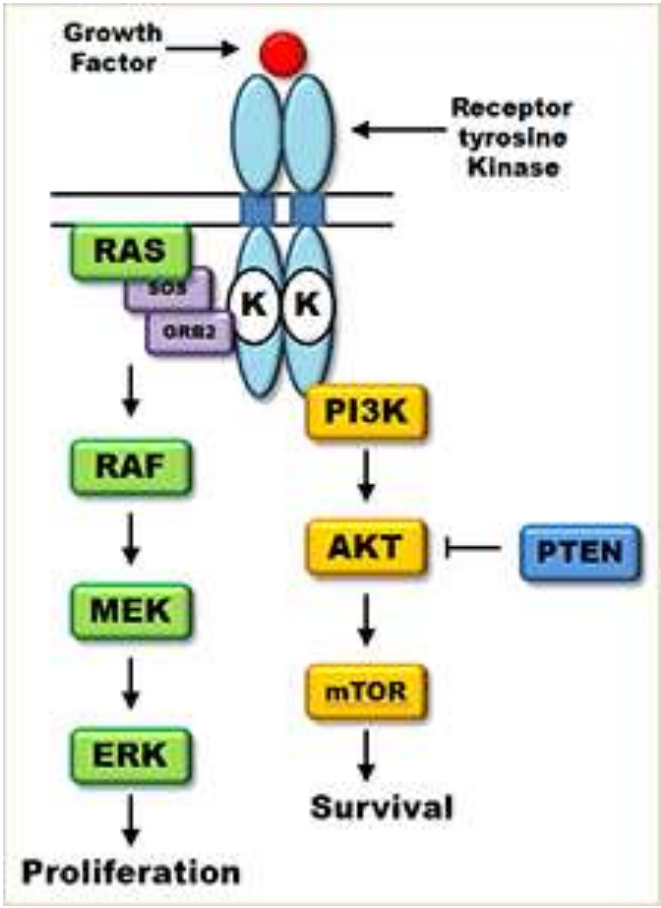
- Case reports have described responses to both vandetanib and cabozantinib in patients whose tumors contained a RET translocation
  - Patients with RET translocation were treated with cabozantinib
  - 16 evaluable patients, 7 had partial responses and 9 had stable disease

J Thorac Oncol. 2013;8(5):e43.
J Clin Oncol. 2016;34(15):e141

J Clin Oncol 33, 2015 (suppl; abstr 8007)

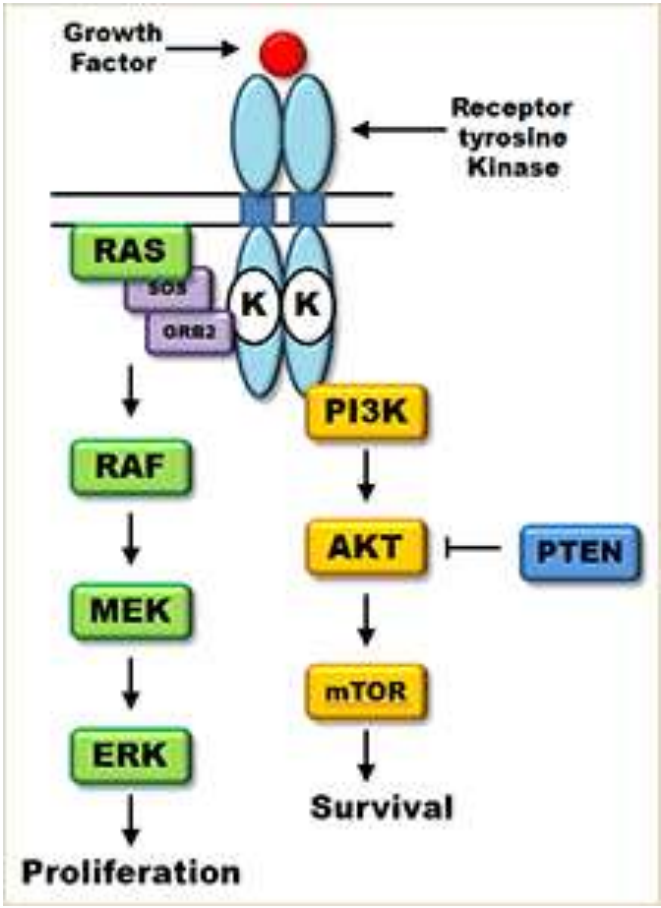
PIK3CA, AKT1, PTEN alterations

- PIK3CA encodes the catalytic subunit of phosphatidyl 3kinase (PI3K), which is an intracellular central mediator of cell survival signals
- AKT1 acts immediately downstream of PI3K
- PTEN inhibits AKT by dephosphorylation.



PIK3CA, AKT1, PTEN alterations

- Oncogenic alterations
  - Gain of function mutations in PIK3CA and AKT1
  - Loss of PTEN function
- Alterations frequent in squamous cell carcinoma



PIK3CA, AKT1, PTEN alterations

REVIEW

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Targeting the PI3K/AKT/mTOR pathway: potential for lung cancer treatment

Haiying Cheng*[1], Marina Shcherba[1], Gopichand Pendurti[1], Yuanxin Liang[1], Bilal Piperdi[1] & Roman Perez-Soler[1]

Lung Cancer Manag. 2014 Jan 1; 3(1): 67–75.

Others

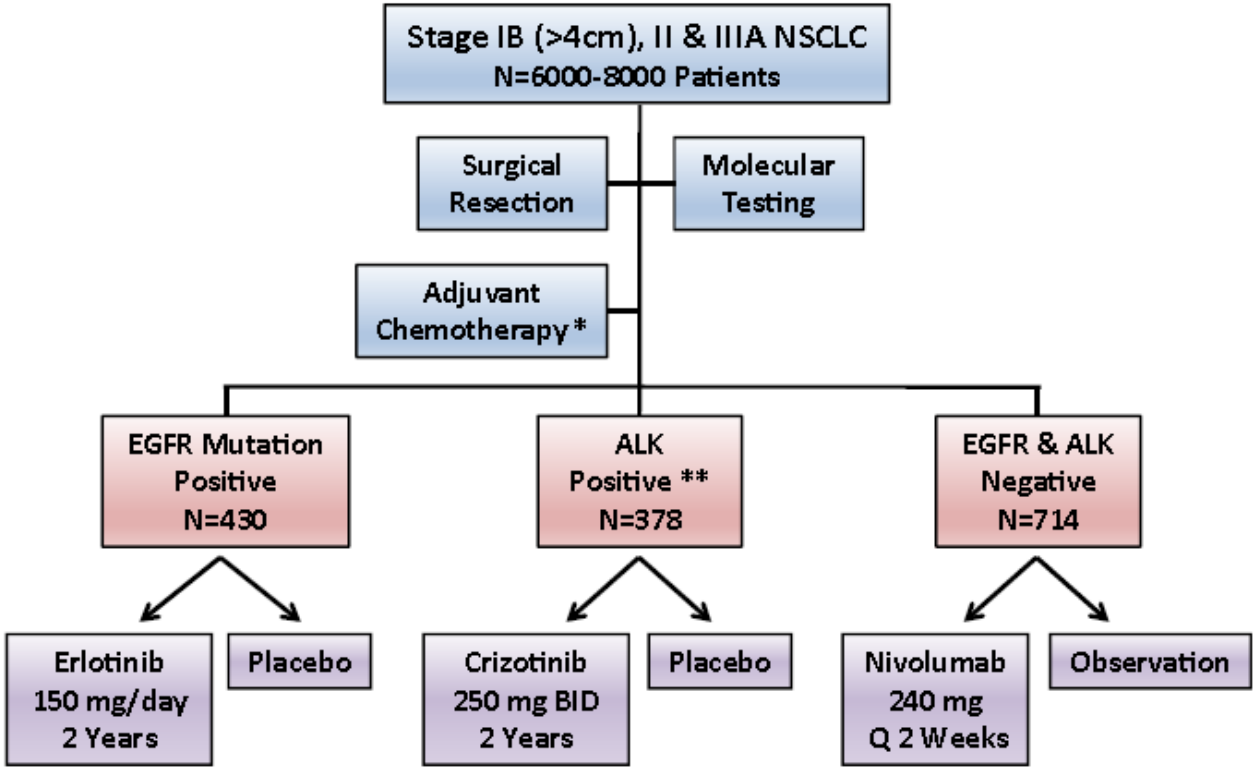
Target	Frequency	Molecule
FGFR1 amplification	13% Squamous cell ca	BGJ398
Bcatenin mutation	2% NSCLC	Clinical development
DDR2 mutation	4% Squamous cell ca	Dasatinib
MEK1 mutation	1% adenoca	Clinical development

abstract 8034, 2014 American Society of Clinical Oncology meeting
Sci Transl Med. 2011 Mar;3(75):75ra26
Cancer Res. 2008 Jul;68(14):5524-

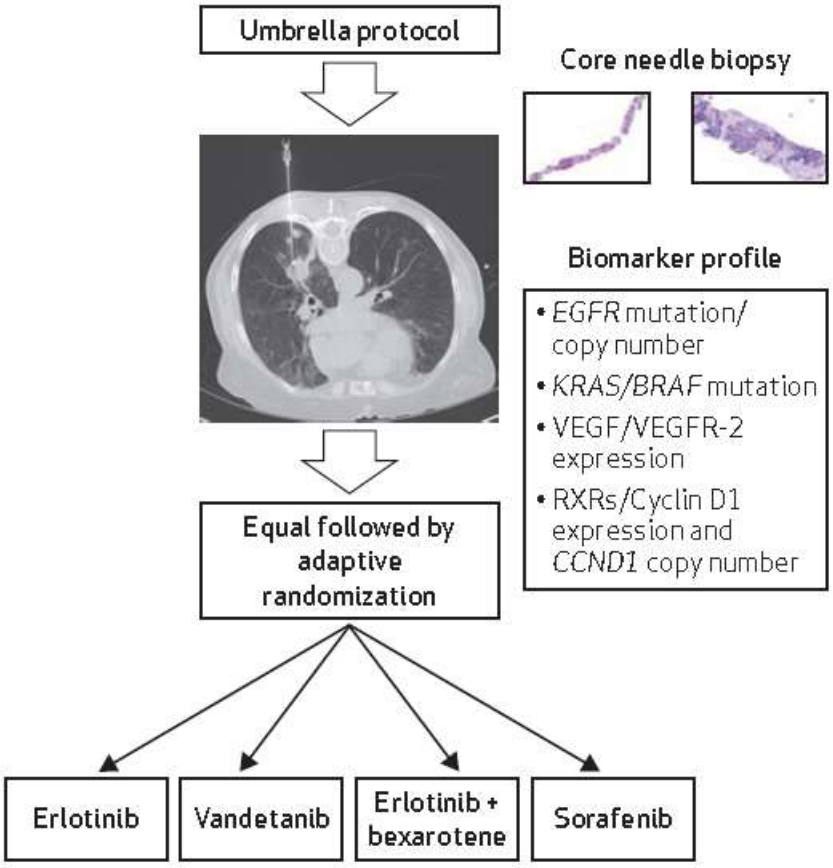
New Challenges

- Because many of the known genetically determined NSCLC subtypes represent small subsets of NSCLC, novel clinical trial designs have been used.
- Innovative and complex large umbrella trials, which can study multiple arms/strategies in parallel

ALCHEMIST study



BATTLE study



BATTLE establishes the feasibility of a new paradigm for a personalized approach to lung cancer clinical trials

Take home message

- Whenever feasible, patients with advanced NSCLC should have tumor assessed for the presence of a driver mutation

Practical points

- Antacid therapy should not be used when patient is on TKI
- All efforts to test for relevant mutations in Lung cancer patients, during treatment

Drug	Research molecule	Price/ month	Local price
Gefitinib	Iressa	10,000	3000
Erlotinib	Tarceva	50,000	6,900
Afatinib	Xovoltib/Gilotrif	50,000	50,000
Crizotinib	Xalkori	75,000	75,000