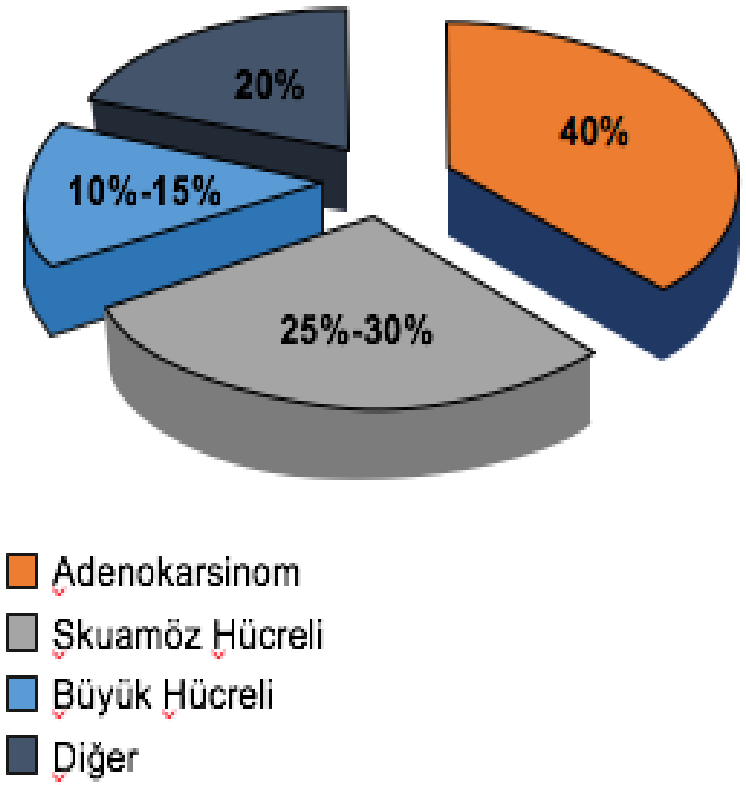
Küçük Hücreli Dışı Akciğer Kanserinde Hedefe Yönelik Tedaviler

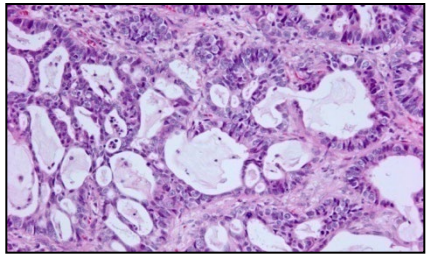
Doç Dr Hande Turna

Medikal Onkoloji Bilim Dalı

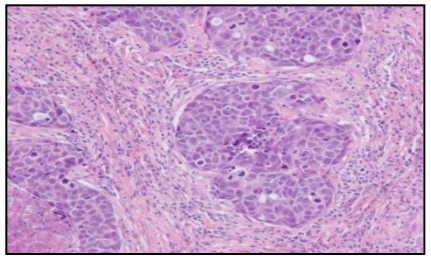
İstanbul Üniversitesi-Cerrahpaşa Tıp Fakültesi

KHDAK'de Histolojik Sınıflama

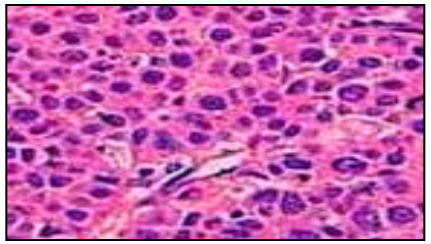




Adenokarsinom

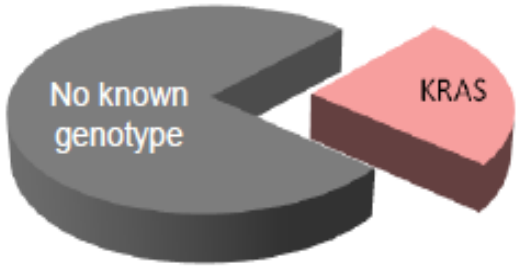


Skuamöz Hücreli

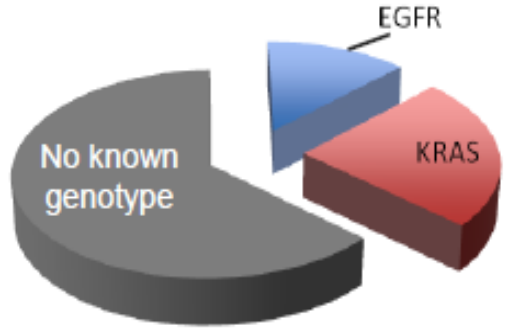


Büyük Hücreli

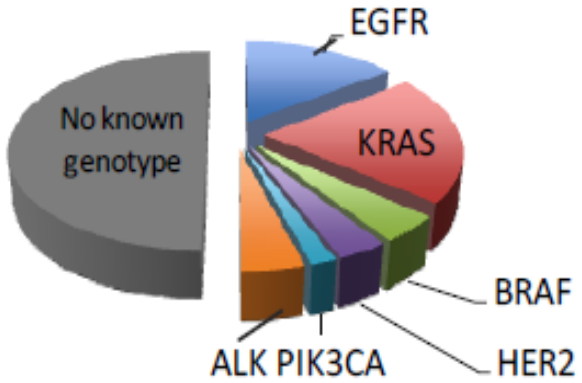
American Cancer Society database. www.cancer.org 2014.



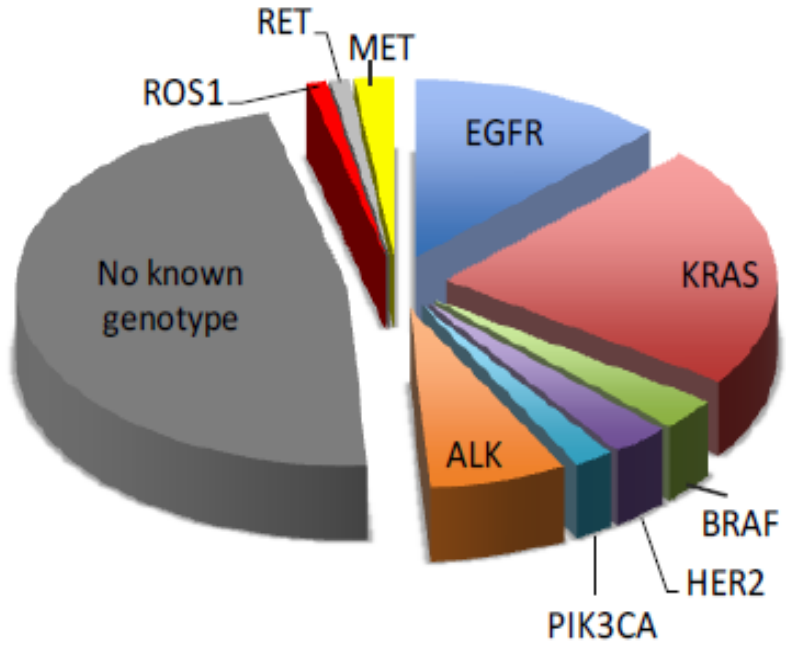
1984–2003



2004

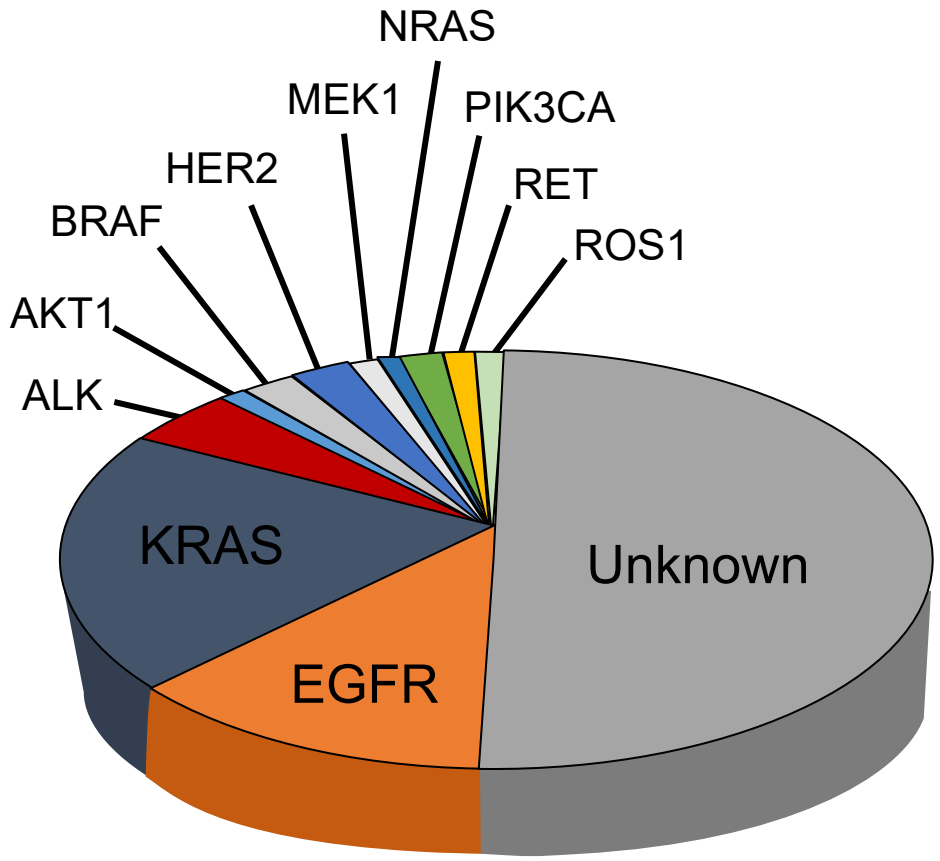


2009



2013

KHDAK'nin Moleküler Alt tipleri ve Tetikleyici Mutasyonlar(*driver mutations*)



KHDAK'de tetileyici mutasyon sıklığı %	
AKT1	1
ALK	3-7
BRAF	1-3
EGFR	10-35
HER2	2-4
KRAS	15-25
MEK1	1
NRAS	1
PIK3CA	1-3
RET	1-2
ROS1	1

www.mycancergenome.org **Lindeman 2013; Scheffler 2015; Platt 2015; Cardarella 2013**.

Lung Cancer Mutation Consortium

Mutasyonların %97'si tek olarak bulunuyor

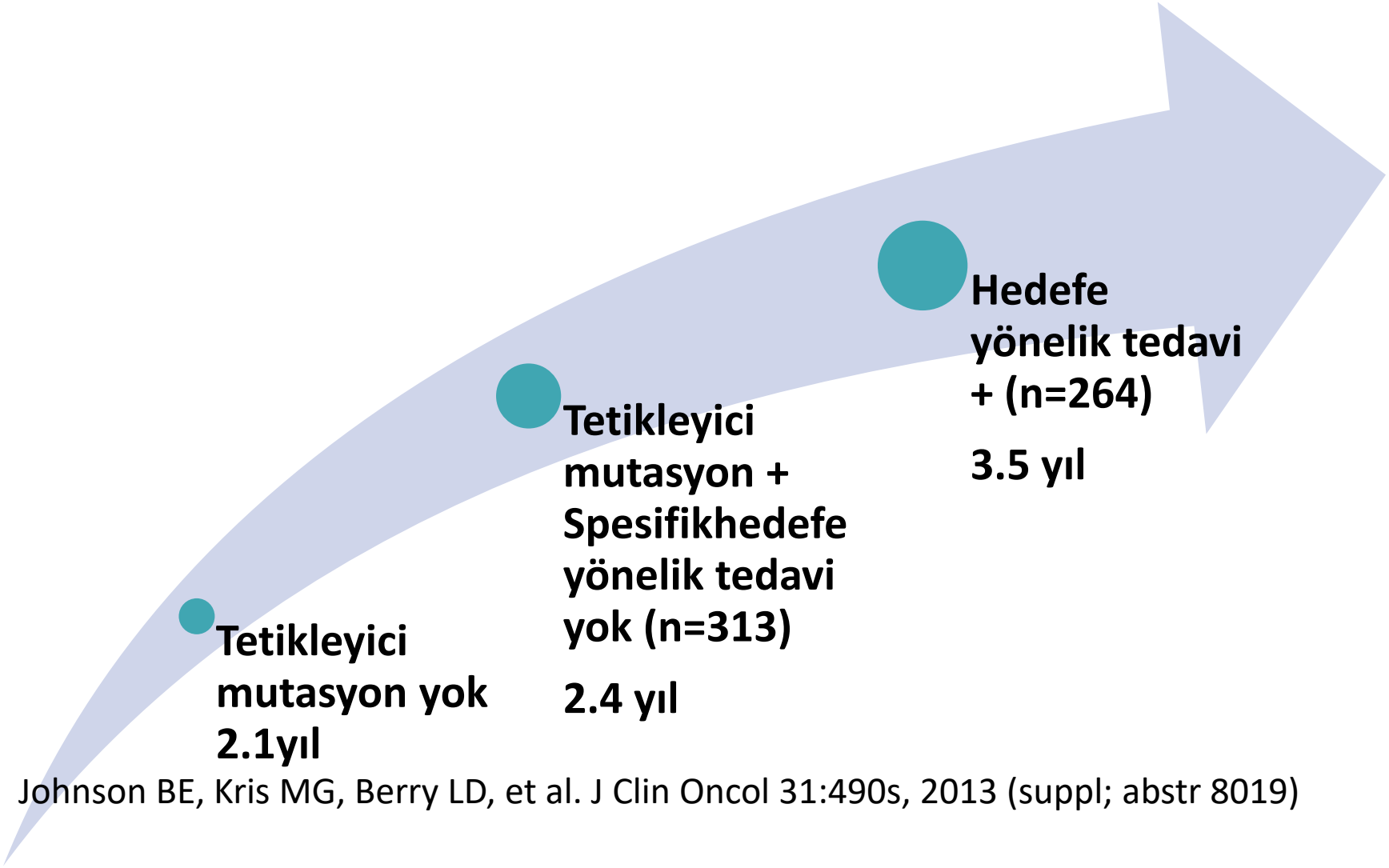
# Single Mutations	ALK	ALT	BRAF	EGFR	HER2	KRAS	MEK1	MET	NRAS	PIK3CA
ALK (38)	X		1	2		1		1		
AKT 1 (0)		X								
BRAF (9)			X							1
EGFR (89)				X				1		3
HER2 (3)					X					
KRAS (114)						X		1		1
MEK1 (2)							X	1		1
MET AMP (3)								X		
NRAS (2)									X	
PIK3CA (6)										X

Kris MG, et al. ASCO 2011. Abstract CRA7506.

Metastatik KHDAK

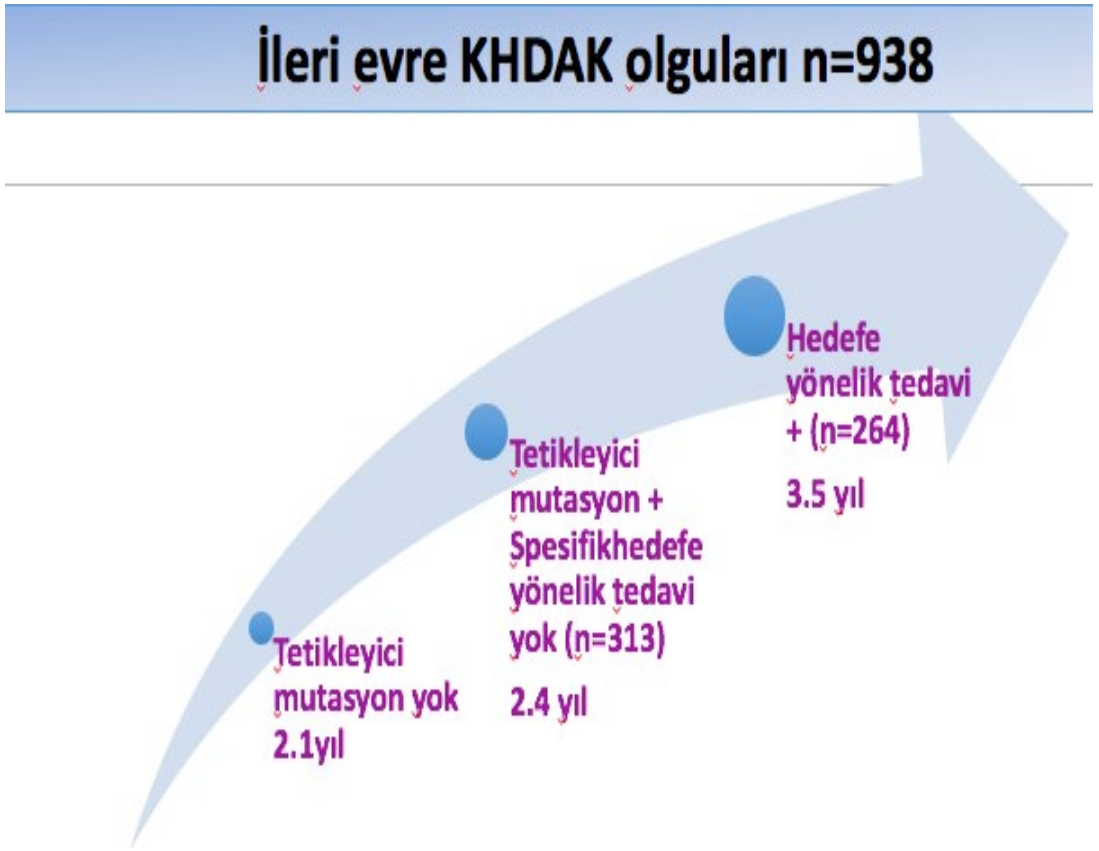
Tedavi stratejileri	Medyan sağkalım
• Destek tedavi	3-4 ay
• Eski kemoterapi rejimleri	6-8 ay
• Güncel ikili kombinasyonlar	8-10 ay
• İkili kemo. + hedefe yönelik ajan	12 ay
•Histolojiye göre kemoterapi	12 ay
•1. basamak sonrası idame	14-16 ay
• EGFR TKI , ALK TKI	+28 ay

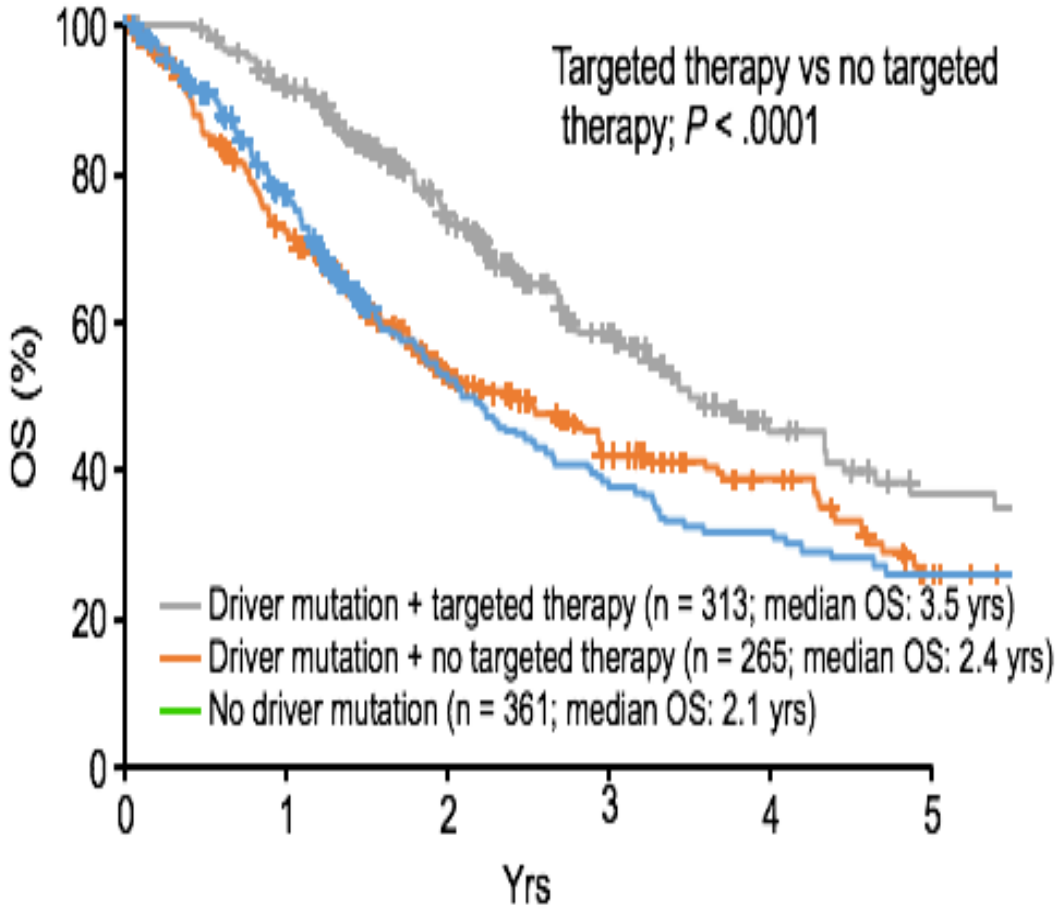
İleri evre KHDAK olguları n=938



Johnson BE, Kris MG, Berry LD, et al. J Clin Oncol 31:490s, 2013 (suppl; abstr 8019)

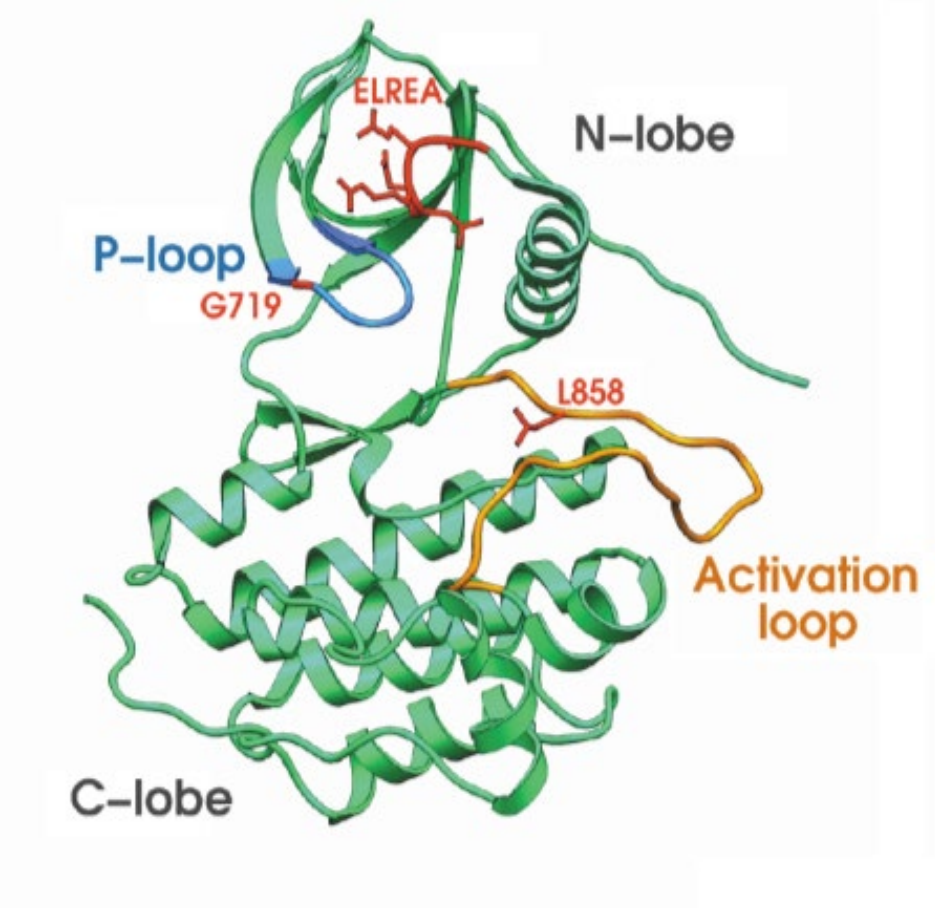
Lung Cancer Mutation Consortium

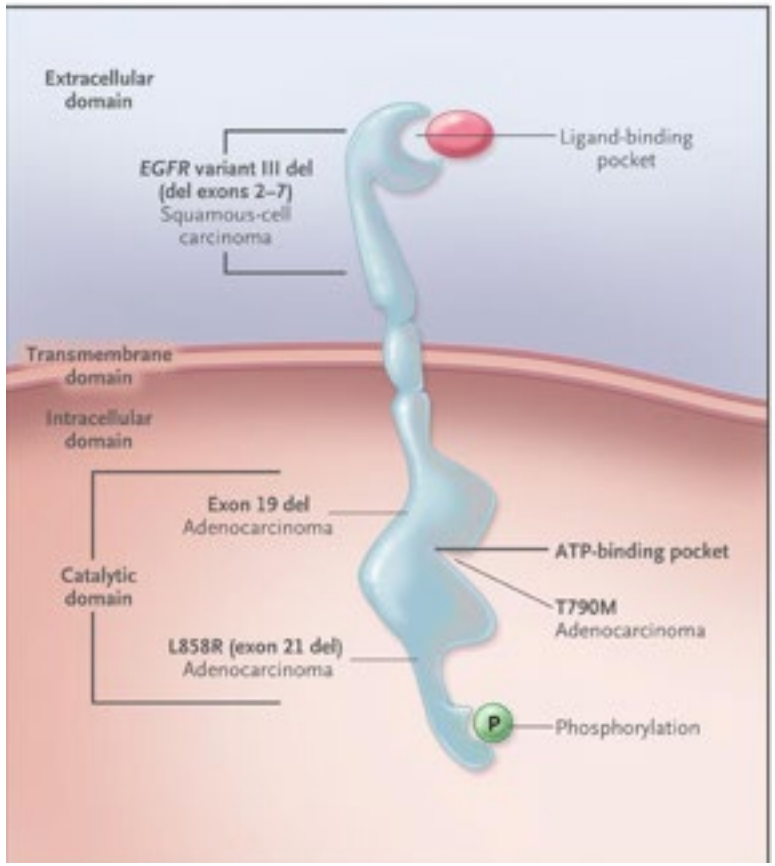




Johnson BE, Kris MG, Berry LD, et al. J Clin Oncol 31:490s, 2013 (suppl; abstr 8019)

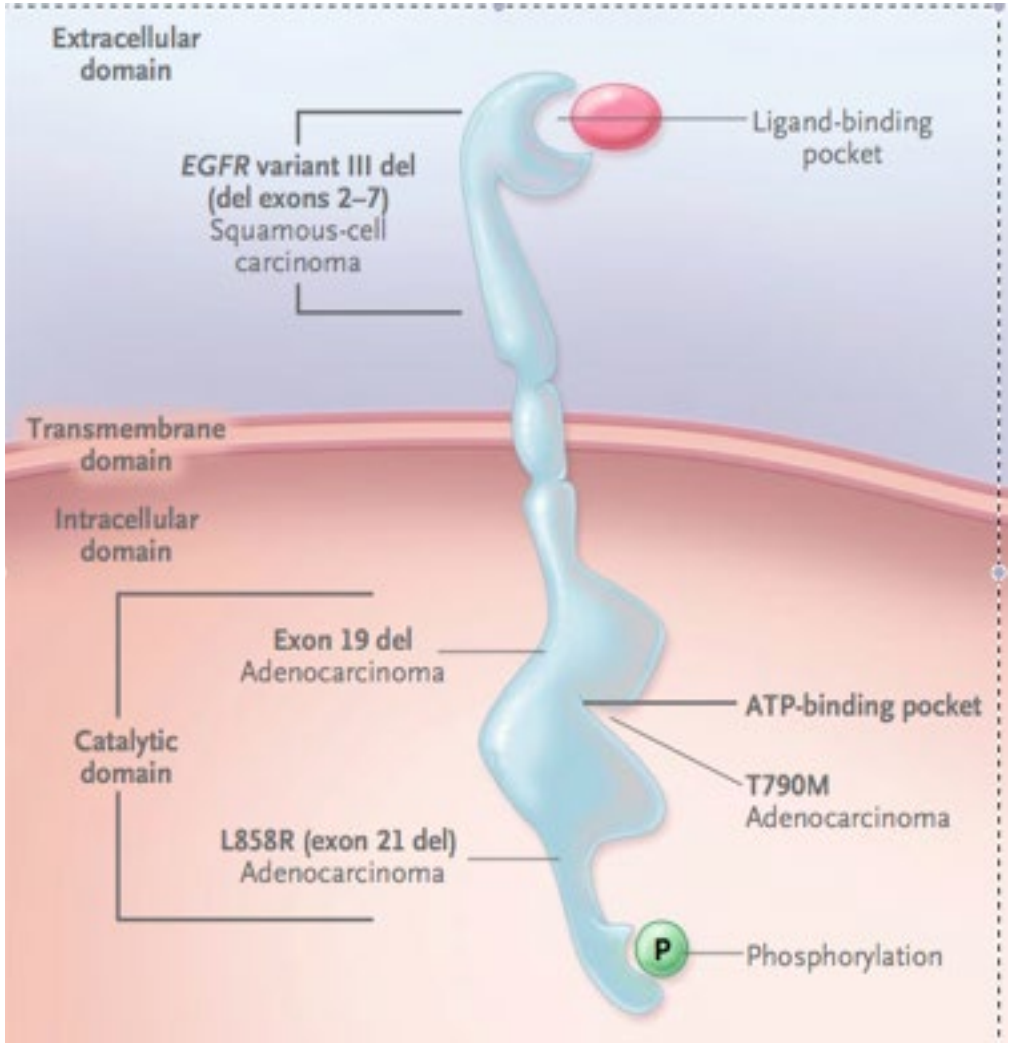
EGFR MUTASYONLARI





Lynch TJ, et al. N Engl J Med. 2004;350:2129-2139. Paez JG, et al. Science. 2004;304:1497-1500.

EGFR Mutasyonları



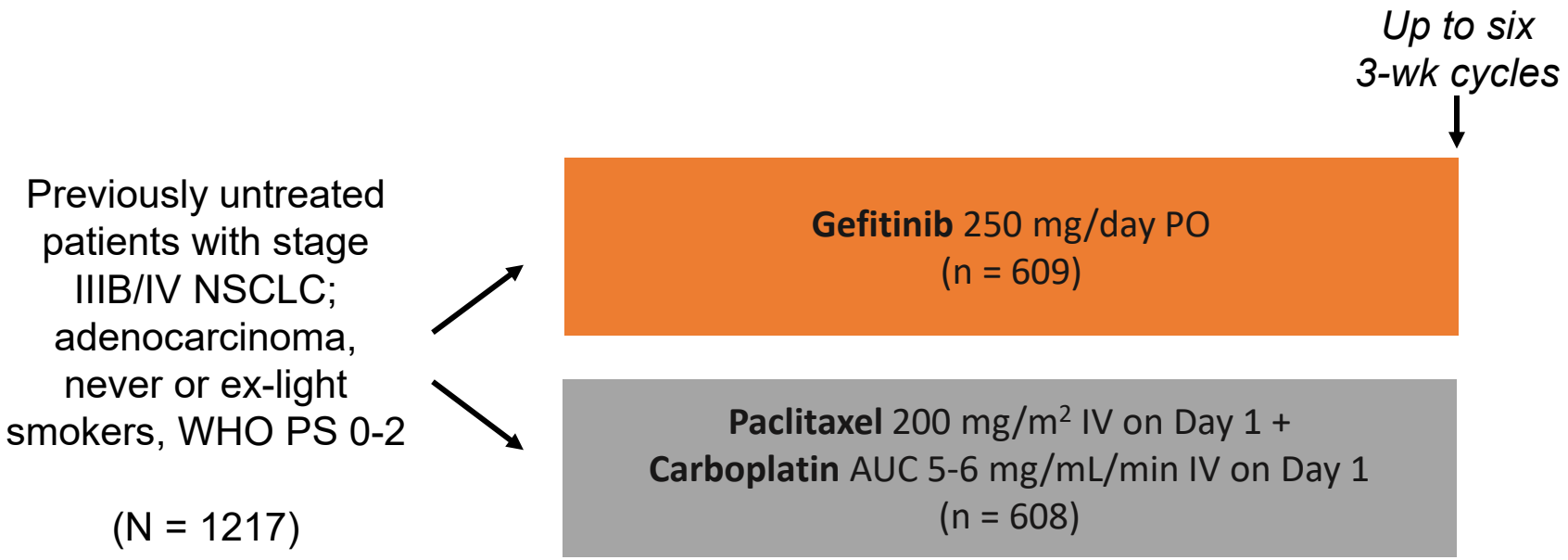
- Doğu Asya Kökenli kişilerde %50
- Mutasyonların %60-70 sigara içmemiş veya az içmiş kişilerde
- Kuzey Amerika da %15

<u>Duyarlılaştıran Mutasyonlar</u>

- **Exon 19 delesyonu (LREA)**
  %45
  RR %53
- **Exon 21(L858R)**
  %40
  RR %26
- %55-80 RR
- 9-13 aylık PFS
- **Exon 21 (L861Q)**
- **Exon 18(GX17X)**
- **(S768I)**
  RR %21

Herbst RS, Heymach JV, Lippman SM.N Engl J Med. 2008
Rosell RN Engl J Med. 2009
Shi YJ Thorac Oncol. 2014

IPASS Faz III Çalışması

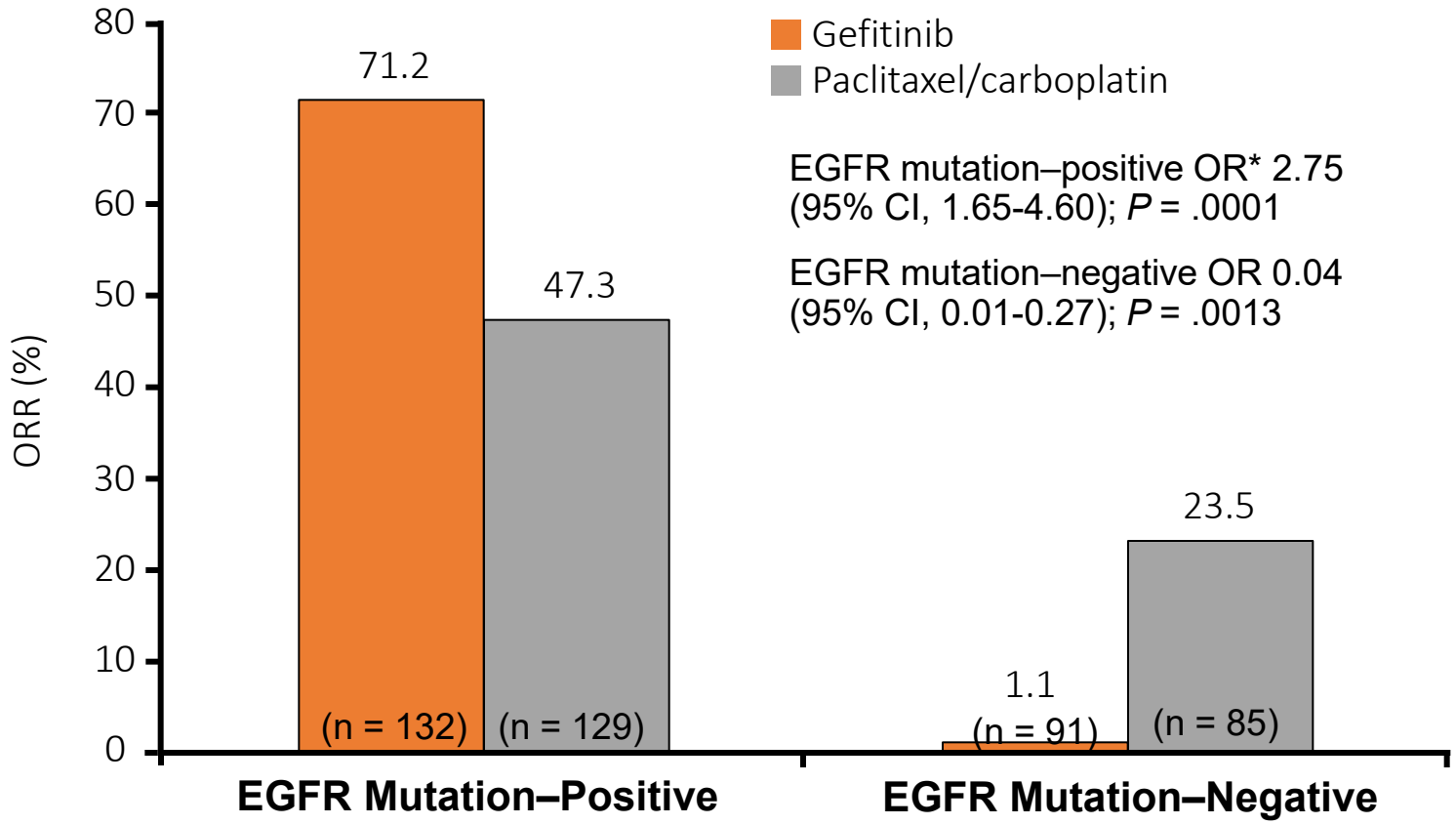


- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, quality of life, symptom reduction, safety
- Study conducted in China, Japan, Thailand, Taiwan, Indonesia, Malaysia, Philippines, Hong Kong, and Singapore

Mok TS, et al. N Engl J Med. 2009;361:247-257.

IPASS

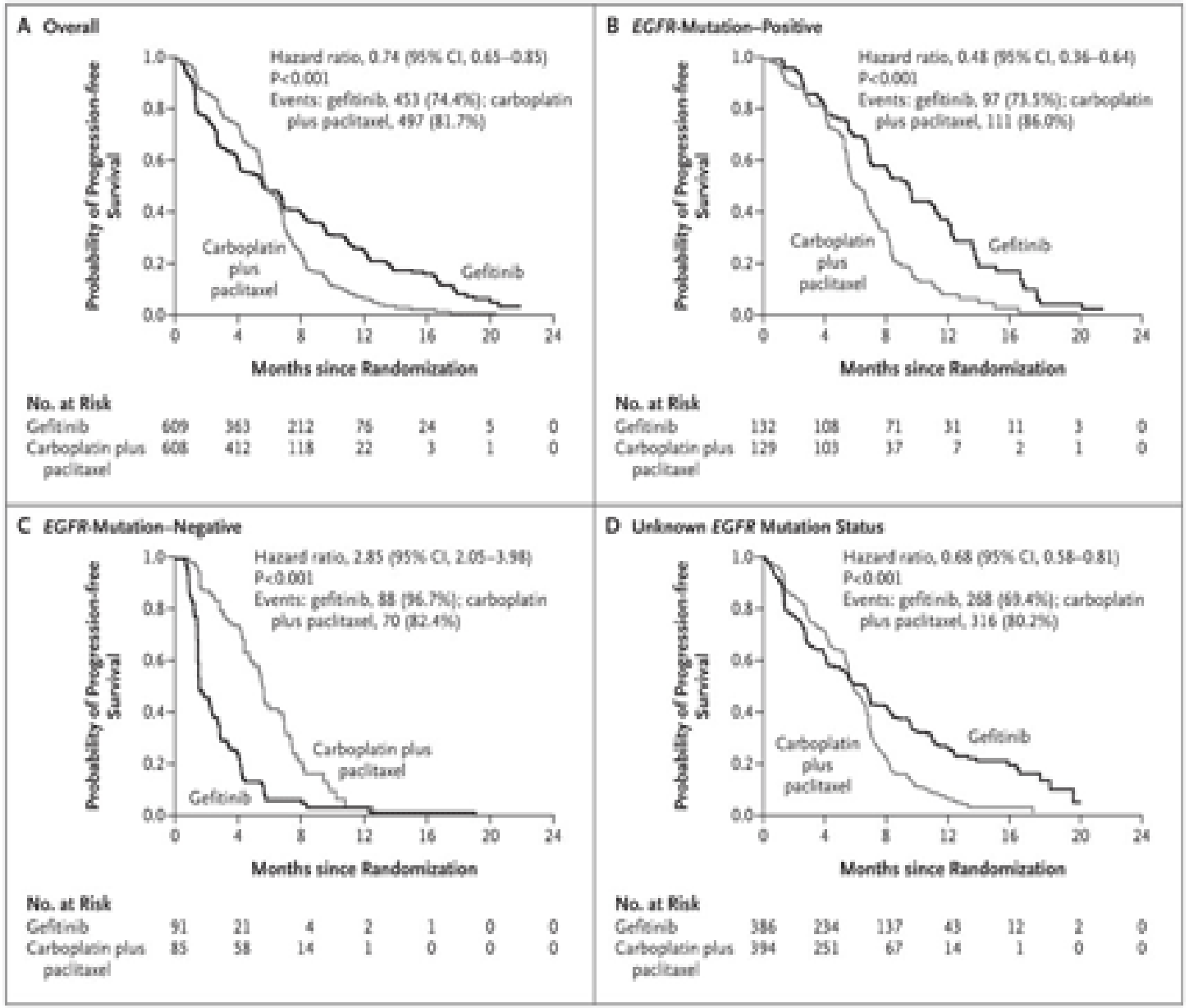
EGFR Mutasyonu Pozitif ve Negatif Olgularda Cevap Oranları



*OR > 1 suggests greater chance of response on gefitinib.

Mok TS, et al. N Engl J Med. 2009;361:947-957.

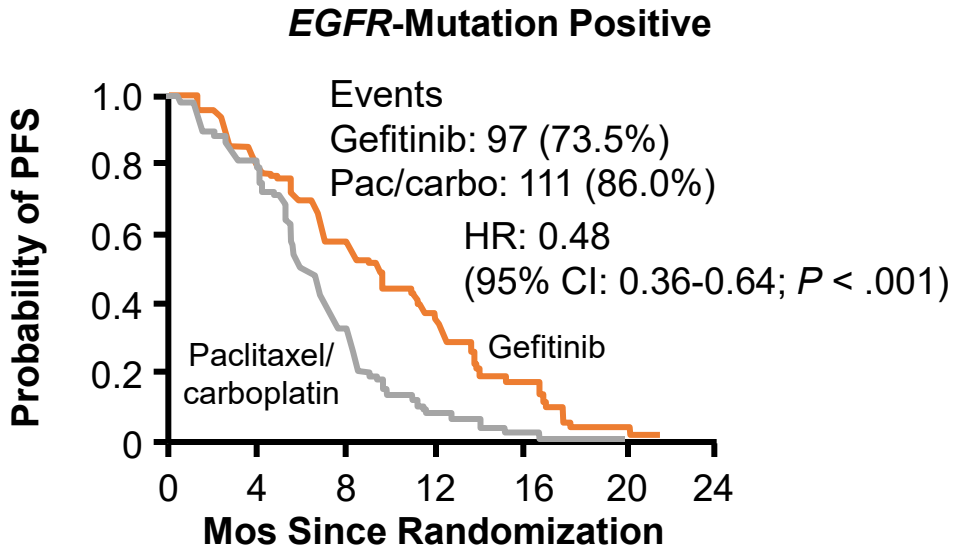
IPASS

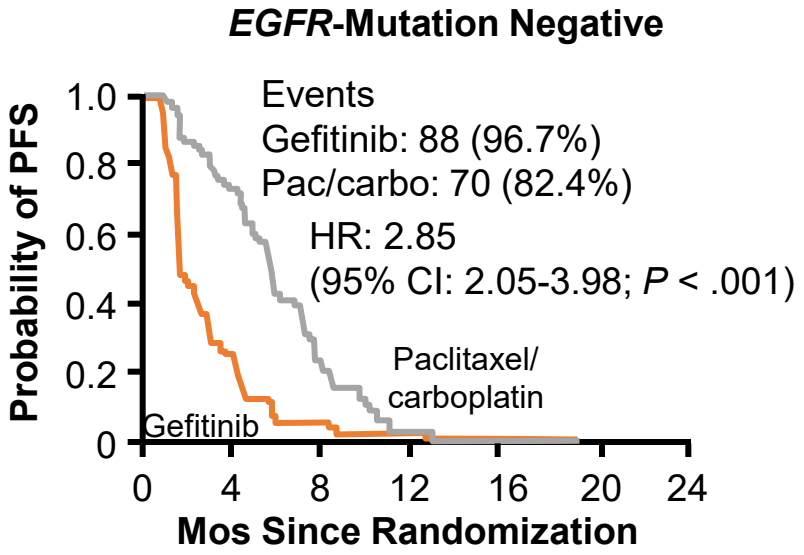


Mok TS et al.
NEJM 2009;

IPASS : *EGFR* Mutasyon Durumuna Göre PFS

- In *EGFR* mutation–positive subgroup, significantly longer PFS with gefitinib (HR: 0.48; 95% CI: 0.36-0.64; *P* < .001)
- In *EGFR* mutation–negative subgroup, significantly shorter PFS with gefitinib (HR: 2.85; 95% CI: 2.05-3.98; *P* < .001)





Mok TS, et al. N Engl J Med. 2009;361:247-257.

Birinci Jenerasyon EGFR Tirozin Kinaz İnhibitörleri

Erlotinib

- Optimal
- Eurtac
- Ensure

9-13ay PFS
27 aya varan GSK

Gefitinib

- IPASS
- West Japan Oncology Oncology Group 172 Çalışması
- North-East Japan Study Group 002 çalışması

Meta-Analiz: 6 çalışma

- **ENSURE, EURTAC, NEJ002, OPTIMAL, WJTOG 3405, IPASS**
- **3 erlotinib, 3 gefitinib çalışması**

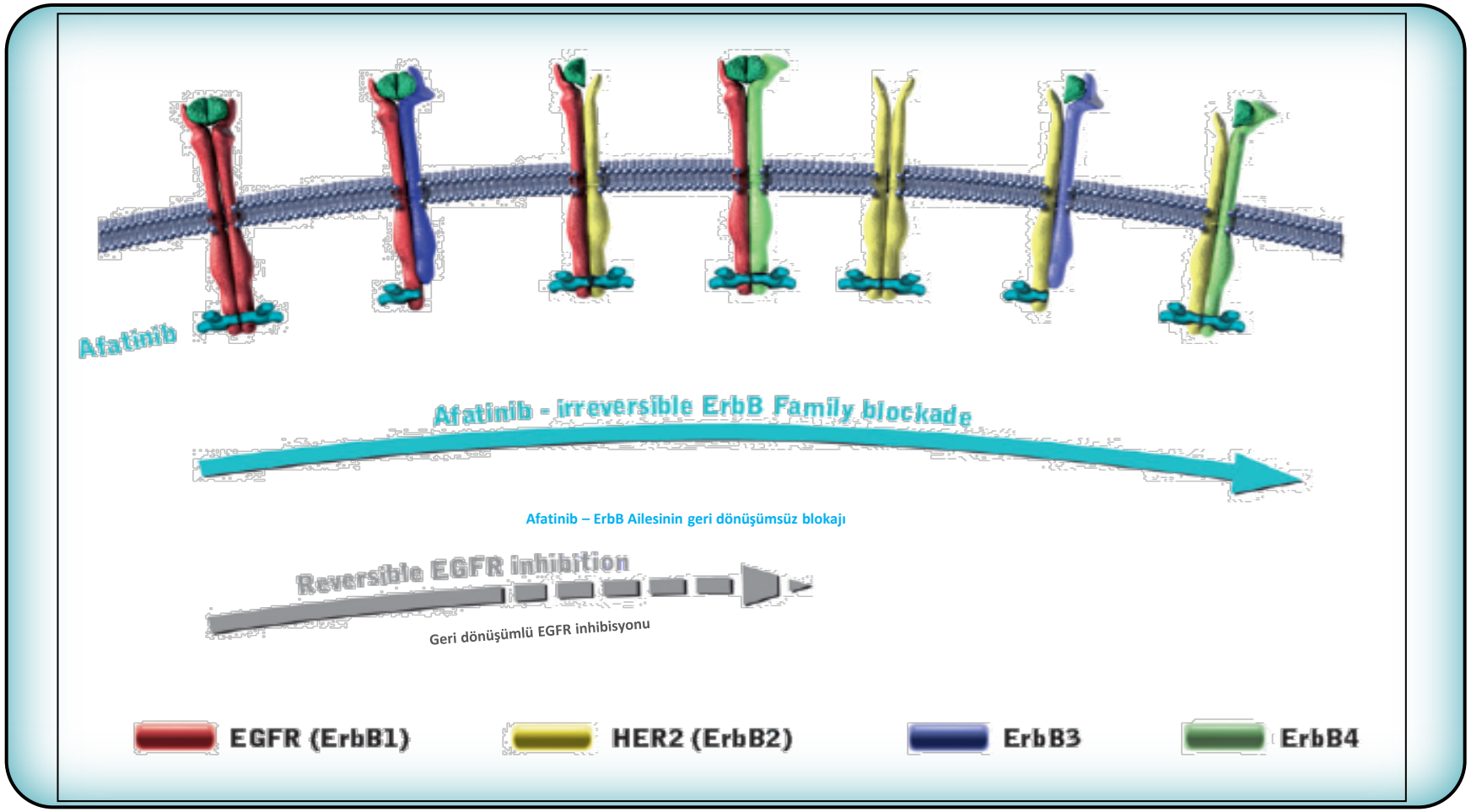
- n: **1231**
  - **EGFR TKI: 632**
  - **Kemoterapi: 599**

- **Kemoterapi sonrası Erlo/gefi: %73.8**
- **Erlo/gefi sonrası kemoterapi: %65.9**

Lee et al. JNCI 2017; 109 (6)

Afatinib

Tüm ErbB Ailesi Homo- ve Hetero-dimerlerinin
Geri Dönüşümsüz İnhibitörü



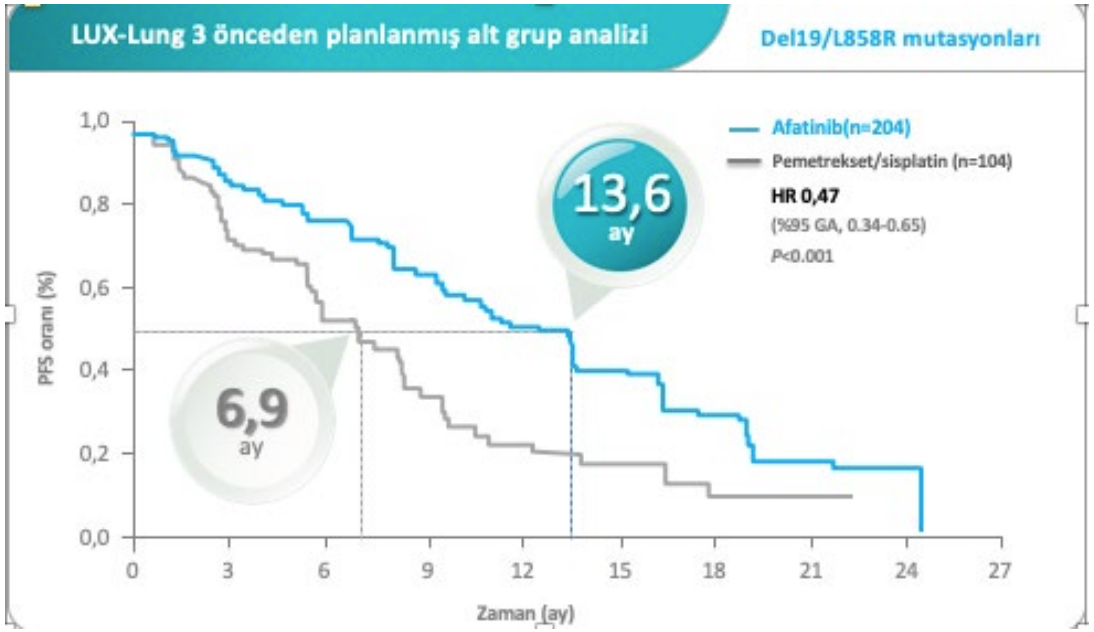
Solca F *ve ark.* J Pharmacol Exp Ther 2012;343:342-350.

İkinci Jenerasyon EGFR Tirozin Kinaz İnhibitörü Afatinib

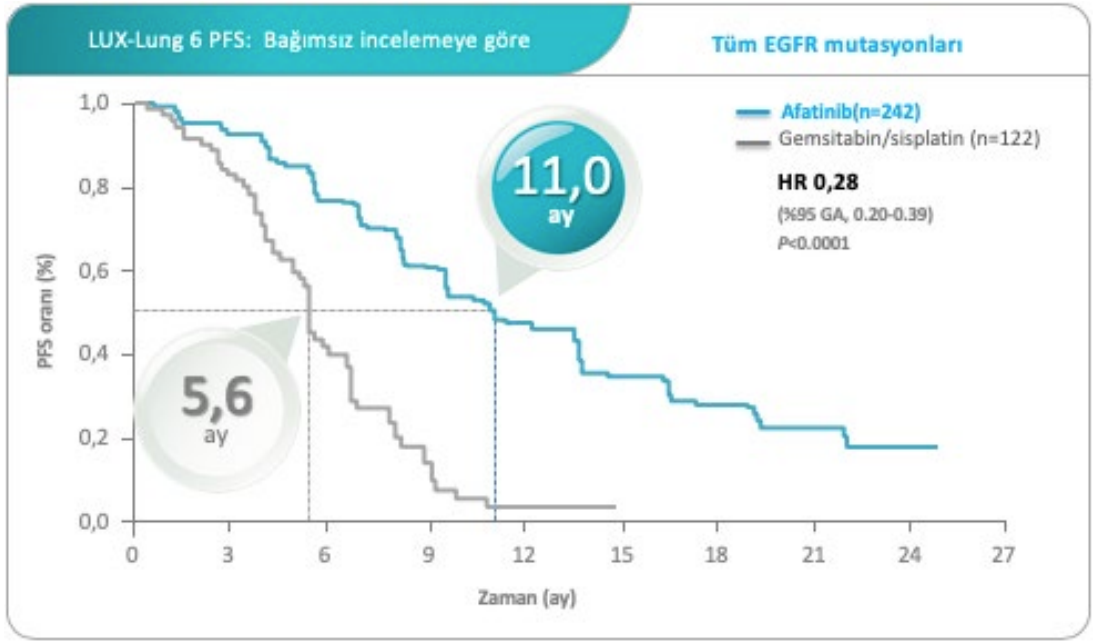
Trial	Regimen	n	RR, %	OS, mos
LUX-Lung 1[Miller 2012]	Afatinib 50 mg/day	390	7.0	10.8
	Placebo	195	< 1.0	12.0
LUX-Lung 3[Sequist 2013; Yang 2015]	Afatinib 40 mg/day	230	56.1	28.2*
	Pemetrexed/cisplatin	115	22.6	28.2
LUX-Lung 6[Wu 2014; Yang 2015]	Afatinib 40 mg/day	242	66.9	23.1*
	Gemcitabine/cisplatin	122	23.0	23.5
LUX-Lung 8[Soria 2015]	Afatinib 40 mg/day	392	5.5	7.9
	Erlotinib 150 mg	395	2.8	6.8

LUX-LUNG 3 ve 6 Progresyonsuz Sağkalım

LUX-Lung 3 (Cispaltin-Pemetrexed)

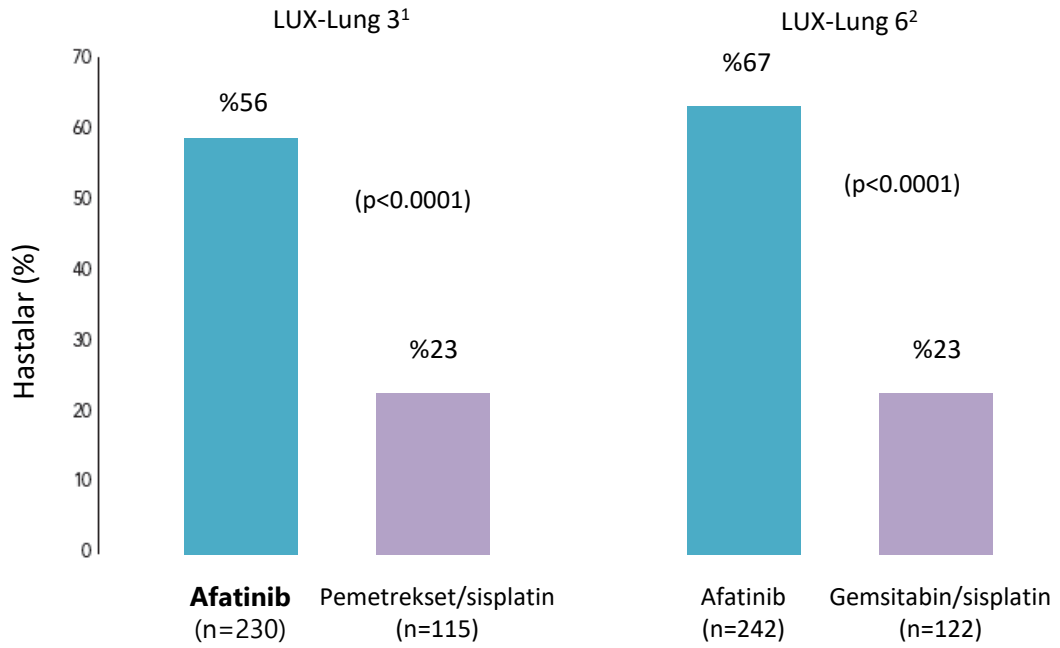


Lux-Lung 6 (Cisplatin-Gemsitabine)



Afatinib
LUX-Lung 3 ve LUX-Lung 6

LUX-Lung 3 ve 6'da Objektif Yanıt Oranları
(CR + PR, ikincil sonlanım noktaları, bağımsız inceleme ile değerlendirilmiştir)



Hastalık kontrolü (CR+PR+SD)	%90 vs %81	%93 vs %76

1. Sequist LV *ve ark*. J Clin Oncol. 2013;31(27):3327-3334.
2. Wu YL *ve ark.* Lancet Oncol. 2014;15(2):213-22.

LUX-Lung 3 ve 6 Kombine analiz

Afatinib versus cisplatin-based chemotherapy for *EGFR* mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials

James Chih-Hsin Yang, Yi-Long Wu*, Martin Schuler, Martin Sebastian, Sanjay Popat, Nobuyuki Yamamoto, Caicun Zhou, Cheng-Ping Hu, Kenneth O'Byrne, Jifeng Feng, Shun Lu, Yunchao Huang, Sarayut L Geater, Kye Young Lee, Chun-Ming Tsai, Vera Gorbunova, Vera Hirsh, Jaafar Bennouna, Sergey Orlov, Tony Mok, Michael Boyer, Wu-Chou Su, Ki Hyeong Lee, Terufumi Kato, Dan Massey, Mehdi Shahidi, Victoria Zazulina, Lecia V Sequist*

Summary

Background We aimed to assess the effect of afatinib on overall survival of patients with *EGFR* mutation-positive lung adenocarcinoma through an analysis of data from two open-label, randomised, phase 3 trials.

Methods Previously untreated patients with *EGFR* mutation-positive stage IIIB or IV lung adenocarcinoma were enrolled in LUX-Lung 3 (n=345) and LUX-Lung 6 (n=364). These patients were randomly assigned in a 2:1 ratio to receive afatinib or chemotherapy (pemetrexed-cisplatin [LUX-Lung 3] or gemcitabine-cisplatin [LUX-Lung 6]), stratified by *EGFR* mutation (exon 19 deletion [del19], Leu858Arg, or other) and ethnic origin (LUX-Lung 3 only). We planned analyses of mature overall survival data in the intention-to-treat population after 209 (LUX-Lung 3) and 237 (LUX-Lung 6) deaths. These ongoing studies are registered with ClinicalTrials.gov, numbers NCT00949650 and NCT01121393.

Findings Median follow-up in LUX-Lung 3 was 41 months (IQR 35–44); 213 (62%) of 345 patients had died. Median follow-up in LUX-Lung 6 was 33 months (IQR 31–37); 246 (68%) of 364 patients had died. In LUX-Lung 3, median overall survival was 28·2 months (95% CI 24·6–33·6) in the afatinib group and 28·2 months (20·7–33·2) in the pemetrexed-cisplatin group (HR 0·88, 95% CI 0·66–1·17, p=0·39). In LUX-Lung 6, median overall survival was 23·1 months (95% CI 20·4–27·3) in the afatinib group and 23·5 months (18·0–25·6) in the gemcitabine-cisplatin group (HR 0·93, 95% CI 0·72–1·22, p=0·61). However, in preplanned analyses, overall survival was significantly longer for patients with del19-positive tumours in the afatinib group than in the chemotherapy group in both trials: in LUX-Lung 3, median overall survival was 33·3 months (95% CI 26·8–41·5) in the afatinib group versus 21·1 months (16·3–30·7) in the chemotherapy group (HR 0·54, 95% CI 0·36–0·79, p=0·0015); in LUX-Lung 6, it was 31·4 months (95% CI 24·2–35·3) versus 18·4 months (14·6–25·6), respectively (HR 0·64, 95% CI 0·44–0·94, p=0·023). By contrast,

Lancet Oncol 2015; 16: 141–51

Published Online January 12, 2015 http://dx.doi.org/10.1016/S1470-2045(14)71173-8

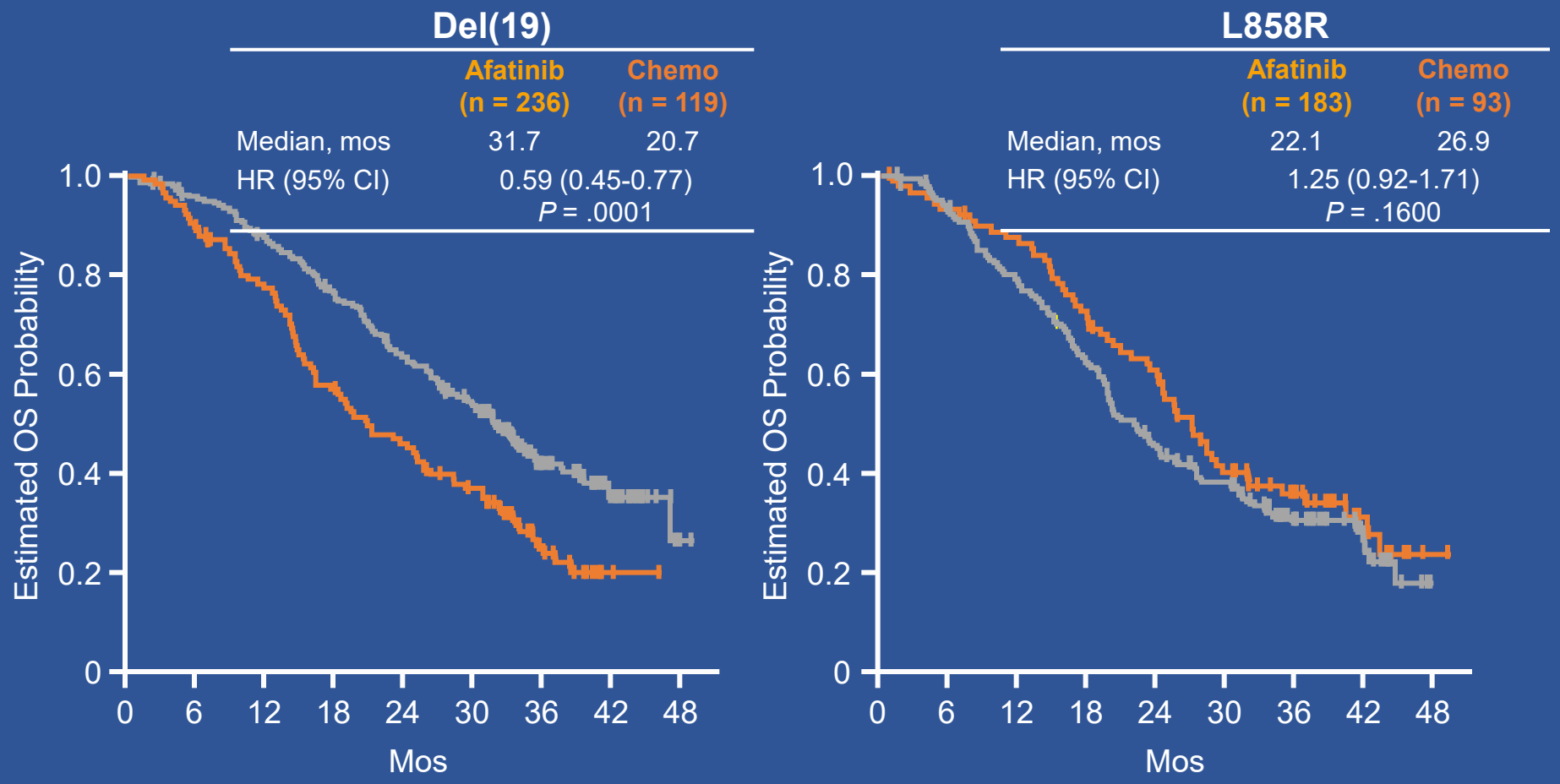
See Comment page 118

*Contributed equally

National Taiwan University Hospital and National Taiwan University, Taipei, Taiwan (Prof J C-H Yang MD); Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China (Prof Y-L Wu MD); West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Essen, Germany (Prof M Schuler MD); Johann Wolfgang Goethe University Medical Center, Frankfurt am Main, and University Medical Center of

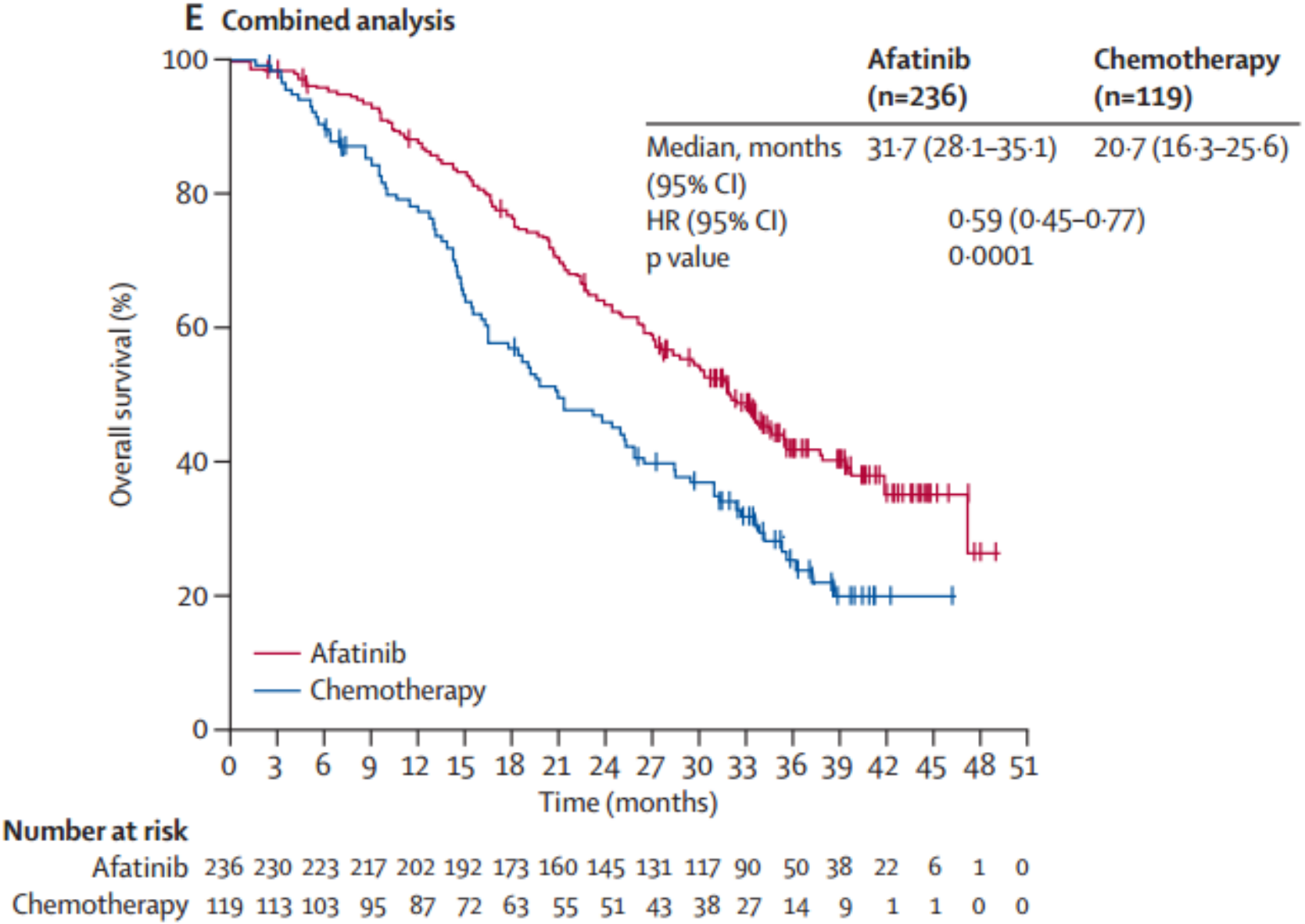
Yang JC *ve ark.* Lancet Oncol. 2015;16(2):141-51.

LUX-Lung 3+6: del(19) and L858R Mutasyon Durumuna Göre Sağkalım



Yang JCH, et al. Lancet Oncol. 2015;16:141-151.

Del 19 Populasyonunda Genel Sağkalım



Yang JC *ve ark.* Lancet Oncol. 2015;16(2):141-51.

Dacomitinib- 2.jenerasyon Geridönüşümsüz TKI

Format: Abstract Send to

Lancet Oncol. 2017 Nov;18(11):1454-1466. doi: 10.1016/S1470-2045(17)30608-3. Epub 2017 Sep 25.

Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial.

Wu YL[1], Cheng Y[2], Zhou X[3], Lee KH[4], Nakagawa K[5], Niho S[6], Tsuji F[7], Linke R[8], Rosell R[9], Corral J[10], Migliorino MR[11], Pluzanski A[12], Sbar EI[13], Wang T[14], White JL[14], Nadanaciva S[14], Sandin R[15], Mok TS[16].

Author information

Abstract

BACKGROUND: Dacomitinib is a second-generation, irreversible EGFR tyrosine kinase inhibitor. We compared its efficacy and safety with that of the reversible EGFR tyrosine kinase inhibitor gefitinib in the first-line treatment of patients with advanced EGFR-mutation-positive non-small-cell lung cancer (NSCLC).

METHODS: In this international, multicentre, randomised, open-label, phase 3 study (ARCHER 1050), we enrolled adults (aged ≥18 years or ≥20 years in Japan and South Korea) with newly diagnosed advanced NSCLC and one EGFR mutation (exon 19 deletion or Leu858Arg) at 71 academic medical centres and university hospitals in seven countries or special administrative regions. We randomly assigned participants (1:1) to receive oral dacomitinib 45 mg/day (in 28-day cycles) or oral gefitinib 250 mg/day (in 28-day cycles) until disease progression or another discontinuation criterion was met. Randomisation, stratified by race and EGFR mutation type, was done with a computer-generated random code assigned by a central interactive web response system. The primary endpoint was progression-free survival assessed by masked independent review in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, number NCT01774721, and is ongoing but no longer recruiting patients.

FINDINGS: Between May 9, 2013, and March 20, 2015, 452 eligible patients were randomly assigned to receive dacomitinib (n=227) or gefitinib (n=225). Median duration of follow-up for progression-free survival was 22·1 months (95% CI 20·3-23·9). Median progression-free survival according to masked independent review was 14·7 months (95% CI 11·1-16·6) in the dacomitinib group and 9·2 months (9·1-11·0) in the gefitinib group (hazard ratio 0·59, 95% CI 0·47-0·74; p<0·0001). The most common grade 3-4 adverse events were dermatitis acneiform (31 [14%] of 227 patients given dacomitinib vs none of 224 patients given gefitinib), diarrhoea (19 [8%] vs two [1%]), and raised alanine aminotransferase levels (two [1%] vs 19 [8%]). Treatment-related serious adverse events were reported in 21 (9%) patients given dacomitinib and in ten (4%) patients given gefitinib. Two treatment-related deaths occurred in the dacomitinib group (one related to untreated diarrhoea and one to untreated cholelithases/liver disease) and one in the gefitinib group (related to sigmoid colon diverticulitis/rupture complicated by pneumonia).

INTERPRETATION: Dacomitinib significantly improved progression-free survival over gefitinib in first-line treatment of patients with EGFR-mutation-positive NSCLC and should be considered as a new treatment option for this population.

PFS: Dacomıtınib 14.7 ay
Gefitinib 9.2 ay

JOURNAL OF CLINICAL ONCOLOGY RAPID COMMUNICATION

Improvement in Overall Survival in a Randomized Study That Compared Dacomitinib With Gefitinib in Patients With Advanced Non–Small-Cell Lung Cancer and *EGFR*-Activating Mutations

Tony S. Mok, Yang Cheng, Xiangdong Zhou, Ki Hyeong Lee, Kazuhiko Nakagawa, Seiji Niho, Min Lee, Rolf Linke, Rafael Rosell, Jesus Corral, Maria Rita Migliorino, Adam Pluzanski, Eric I. Sbar, Tao Wang, Jane Liang White, and Yi-Long Wu

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on June 4, 2018.

Processed as a Rapid Communication manuscript.

Clinical trial information: NCT01774721.

Corresponding author: Yi-Long Wu, MD, Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, 106 Zhongshan Er Rd, Guangzhou, Guangdong 510080, China; email: syylwu@live.cn.

0732-183X/18/3622w-2244w/$20.00

ABSTRACT

Purpose

ARCHER 1050, a randomized, open-label, phase III study of dacomitinib versus gefitinib in treatment-naive patients with advanced non–small-cell lung cancer (NSCLC) and activating mutations in *EGFR*, reported significant improvement in progression-free survival with dacomitinib. The mature overall survival (OS) analysis for the intention-to-treat population is presented here.

Patients and Methods

In this multinational, multicenter study, patients age 18 years or older (≥ 20 years in Japan and Korea) who had an Eastern Cooperative Oncology Group performance status of 0 or 1 and newly diagnosed NSCLC with activating mutations in *EGFR* (exon 19 deletion or exon 21 L858R) were enrolled and randomly assigned in a 1:1 manner to dacomitinib (n = 227) or gefitinib (n = 225). Random assignment was stratified by race (Japanese, Chinese, other East Asian, or non-Asian) and *EGFR* mutation type. The final OS analysis was conducted with a data cutoff date of February 17, 2017; at that time 220 deaths (48.7%) were observed.

Results

During a median follow-up time of 31.3 months, 103 (45.4%) and 117 (52.0%) deaths occurred in the dacomitinib and gefitinib arms, respectively. The estimated hazard ratio for OS was 0.760 (95% CI, 0.582 to 0.993; two-sided $P = .044$). The median OS was 34.1 months with dacomitinib versus 26.8 months with gefitinib. The OS probabilities at 30 months were 56.2% and 46.3% with dacomitinib and gefitinib, respectively. Preliminary subgroup analyses for OS that are based on baseline characteristics were consistent with the primary OS analysis.

Conclusion

In patients with advanced NSCLC and *EGFR* activating mutations, dacomitinib is the first second-generation epidermal growth factor receptor tyrosine kinase inhibitor (TKI) to show significant improvement in OS in a phase III randomized study compared with a standard-of-care TKI. Dacomitinib should be considered one of the standard treatment options for these patients.

GSK: Dacomitinib 34.1 ay
Gefitinib 26.8 ay

Osimertinib 3. Jenerasyon TKI

- T790M-pozitif ve diğer EGFR TKI tedavilerine yanıt alınmayan KHDAK (Aralık 2015 FDA onayı)

- EGFR T790M-pozitif olgularda cevap oranı 59% to 61%

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 11, 2018 VOL. 378 NO. 2

Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

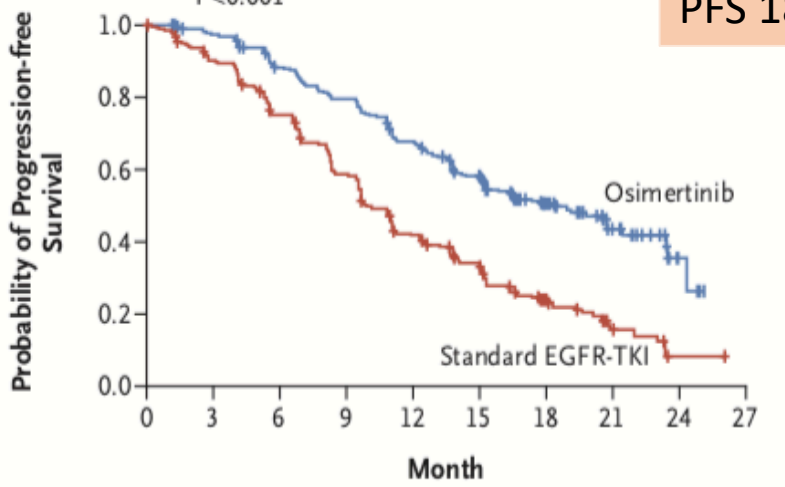
J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam, for the FLAURA Investigators*

FLAURA Çalışması
Osimertinib / Gefitinib-Erlotinib

A Progression-free Survival in Full Analysis Set

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001



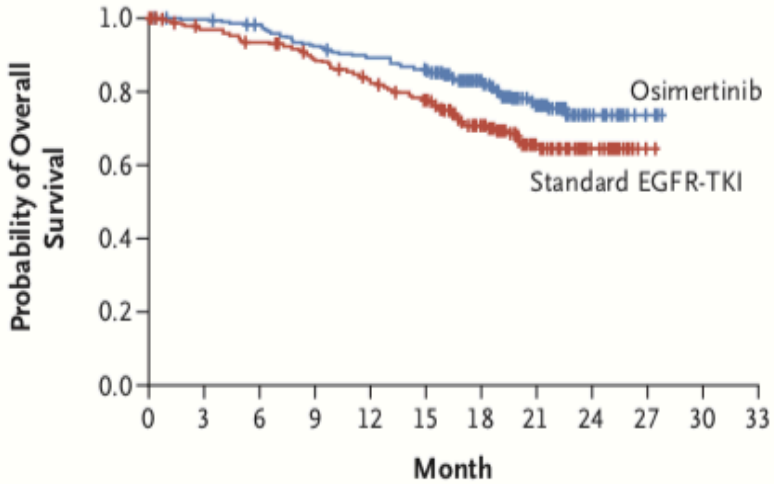
PFS 18.9 ay

No. at Risk										
Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

D Overall Survival

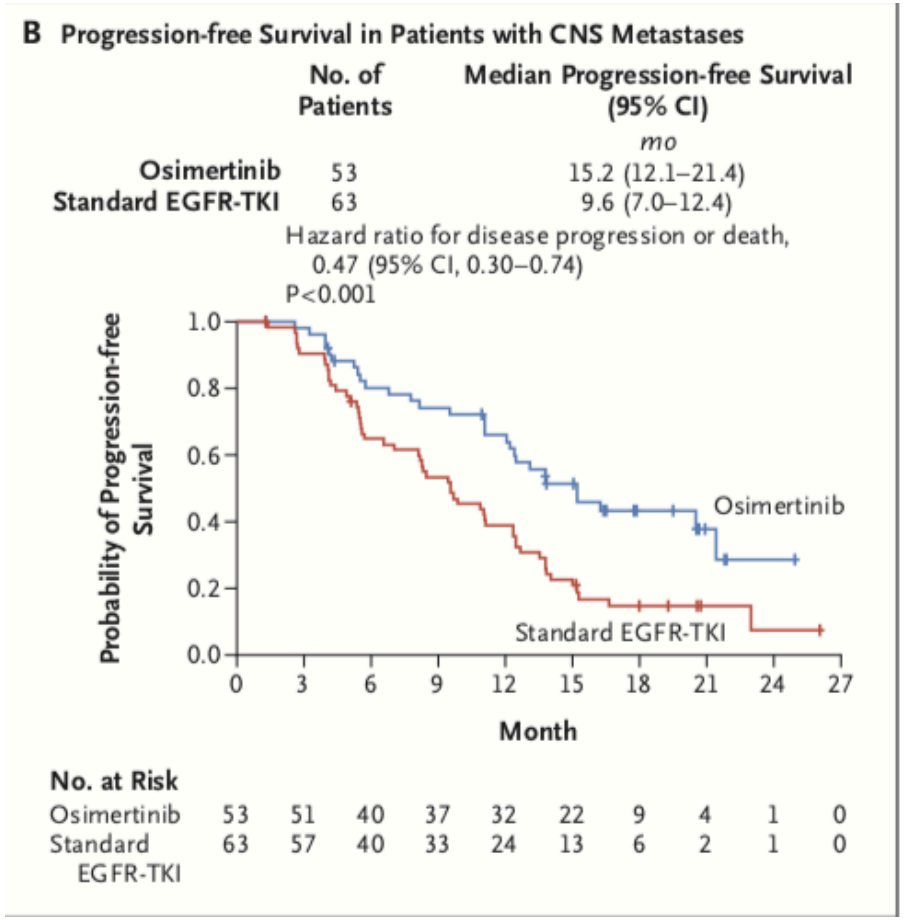
	No. of Patients	Median Overall Survival (95% CI)
		mo
Osimertinib	279	NC (NC–NC)
Standard EGFR-TKI	277	NC (NC–NC)

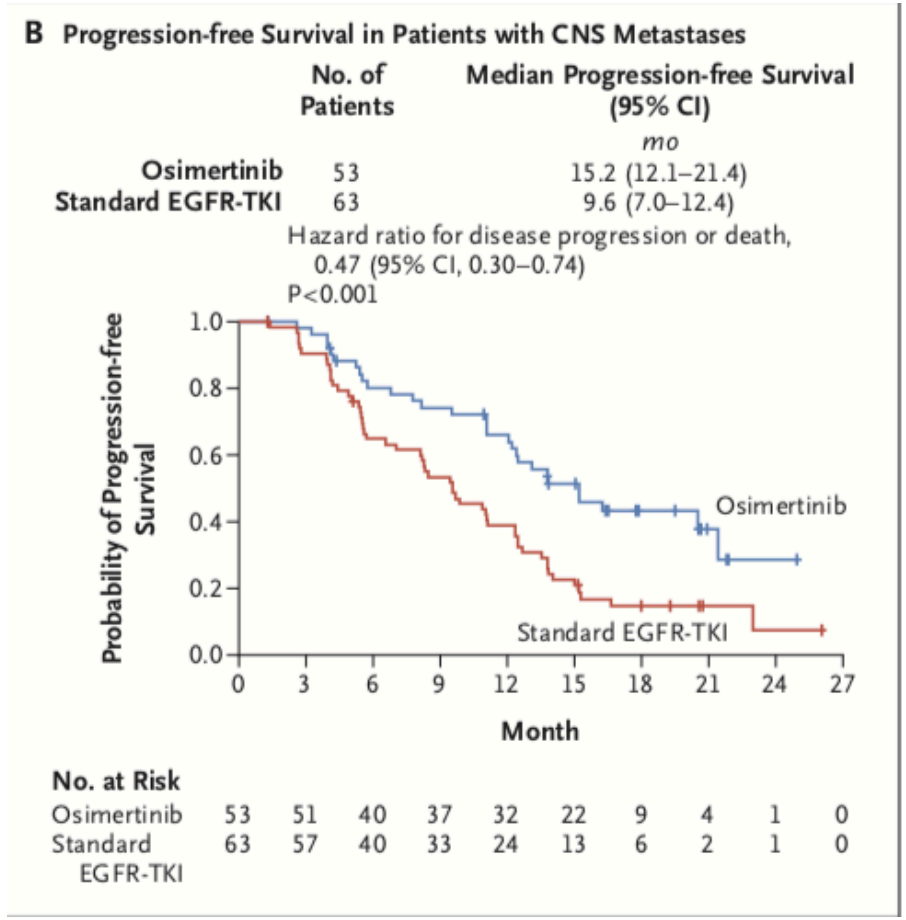
Hazard ratio for death, 0.63 (95% CI, 0.45–0.88)
P=0.007



No. at Risk												
Osimertinib	279	276	269	253	243	232	154	87	29	4	0	0
Standard EGFR-TKI	277	263	252	237	218	200	126	64	24	1	0	0

Osimertinib –Beyin Metastazları





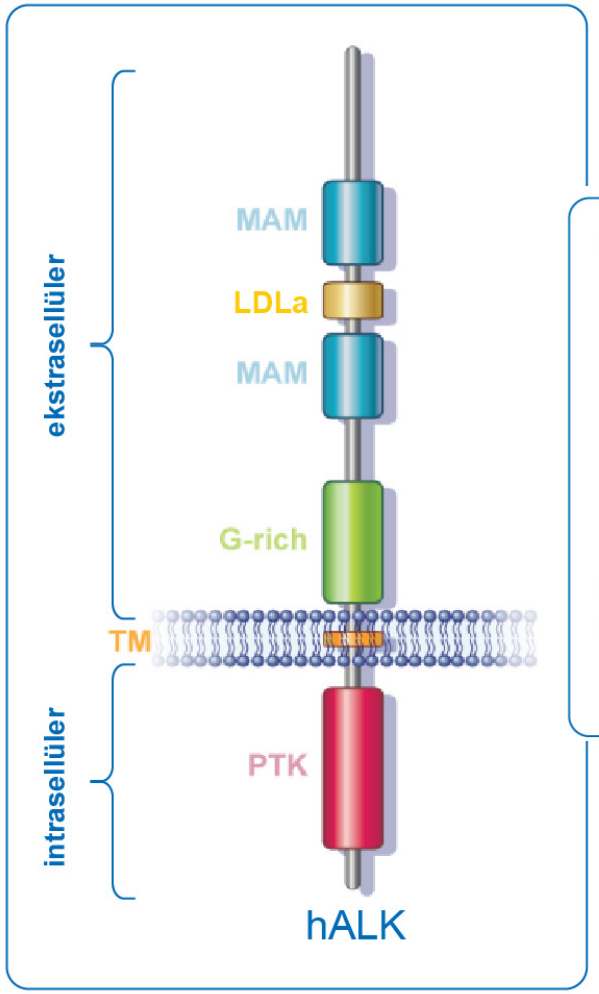
NCCN 2019 (2.versiyon)

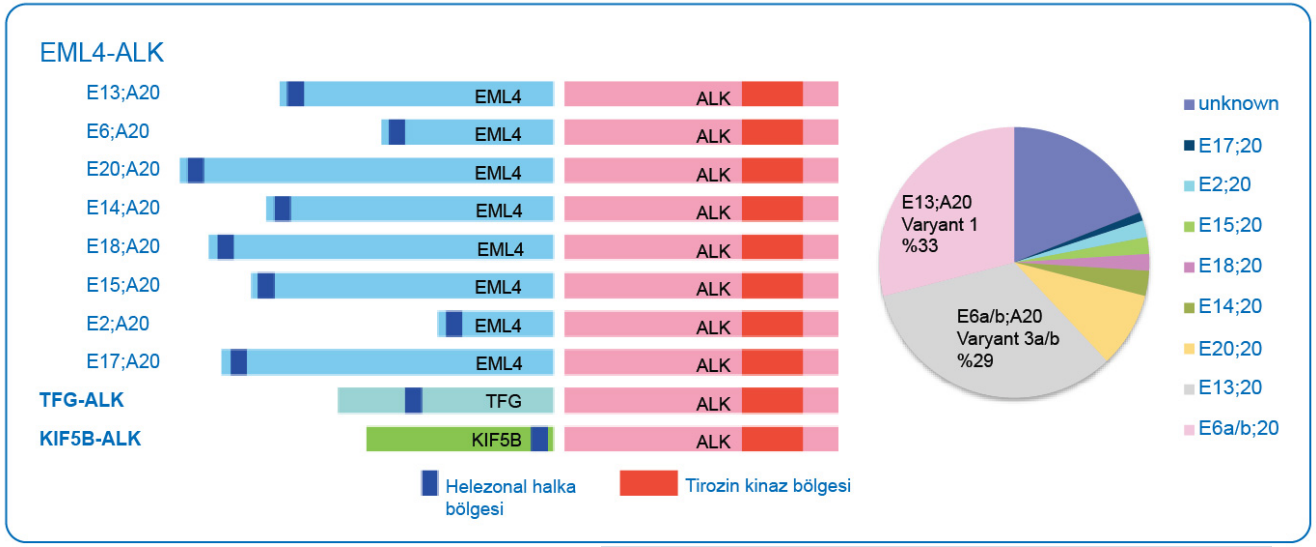
Sensitizing *EGFR* Mutation Positive

- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6]
- Subsequent therapy
  - Osimertinib[7]

*__Osimertinib-__
T790M
En uzun PFS 18.9 ay
*__Afatinib__
* Del 19 GSK avantajı
*__Dacomitinib__
GSK avantajı

Anaplastic lymphoma kinase (ALK) rearrangement (ALK-EML4)
ALK fusion oncogene (ALK-echinoderm microtubule-associated protein-like 4)





KHDAK' lerinin %2-7

Sigara içmemiş veya az içmiş

Daha sık olarak erkek

Palmer ve ark., *Biochem J* 2009; 420:345-361

Drexler ve ark., *Leukemia* 2000; 14:1533-1559

Kwak ELN Engl J Med. 2010

ALK Tirozin Kinaz İnhibitörleri- 1. seri tedavi

Crizotinib (ALK,ROS,MET)

- PROFİLE 1014

Alectinib (ALK,RET)

- ALEX
- J-ALEX

Ceritinib (ALK,ROS,IGF-1)

- ASCEND-4

Brigantinib (ALK)

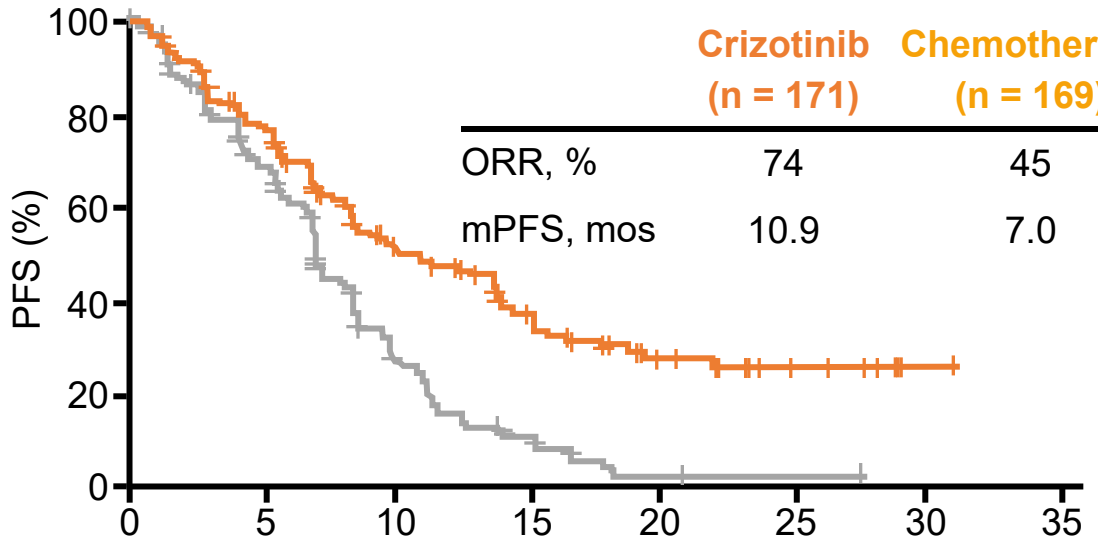
- ALTA-IL

ALK Pozitif KHDAK
Crizotinib vs Pemetrexed/ Platin

nonsquamous NSCLC not previously treated (N = 343)

- Crizotinib 250 mg BID
- Pemetrexed + Cisplatin or Carboplatin q3w x 6 cycles

Primary endpoint: PFS



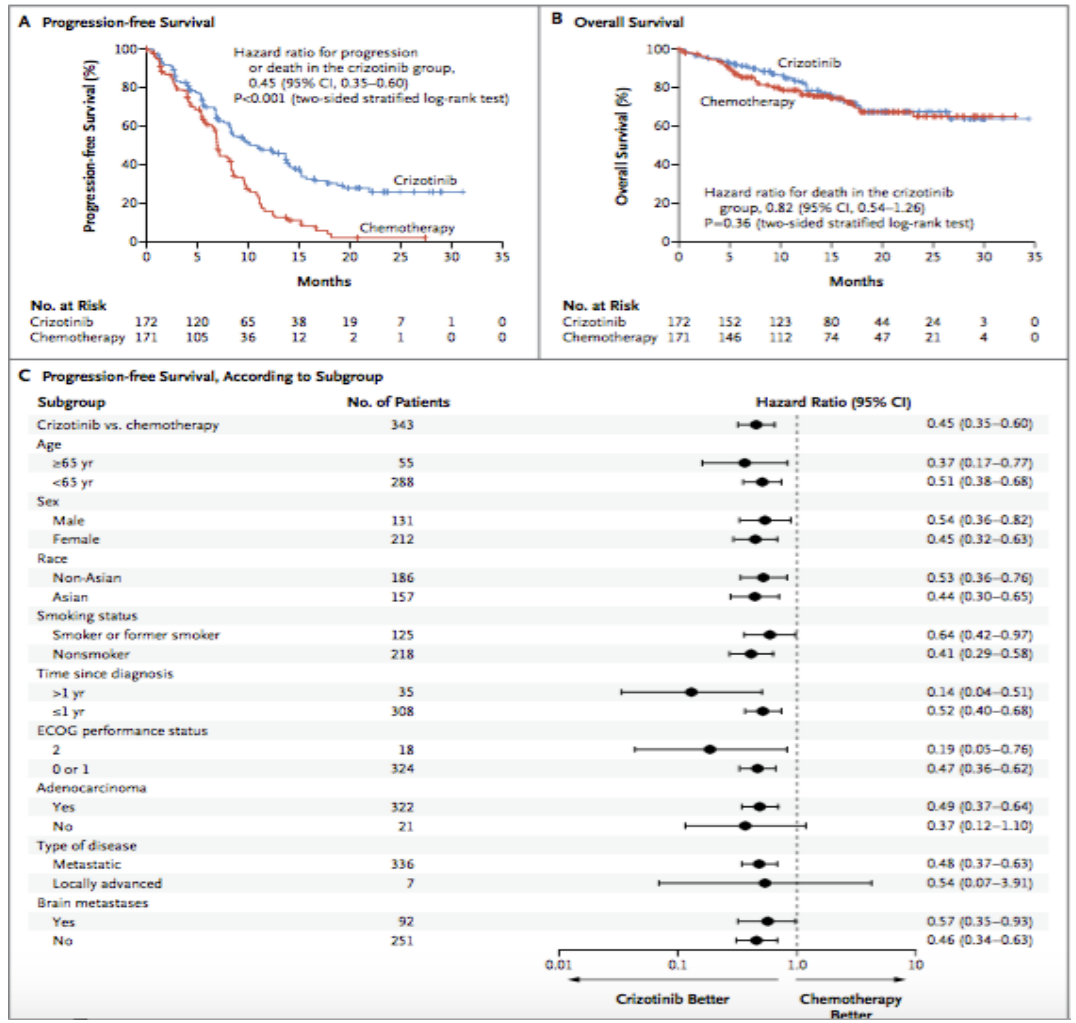
	Crizotinib (n = 171)	Chemotherapy (n = 169)	HR (95% CI)	*P* Value
ORR, %	74	45		
mPFS, mos	10.9	7.0	0.45 (0.35-0.60)	

Solomon BJ, et al. N Engl J Med. 2014;371:2167-2177. Mok T, et al. ASCO 2014. Abstract 8002.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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



The NEW ENGLAND JOURNAL of MEDICINE

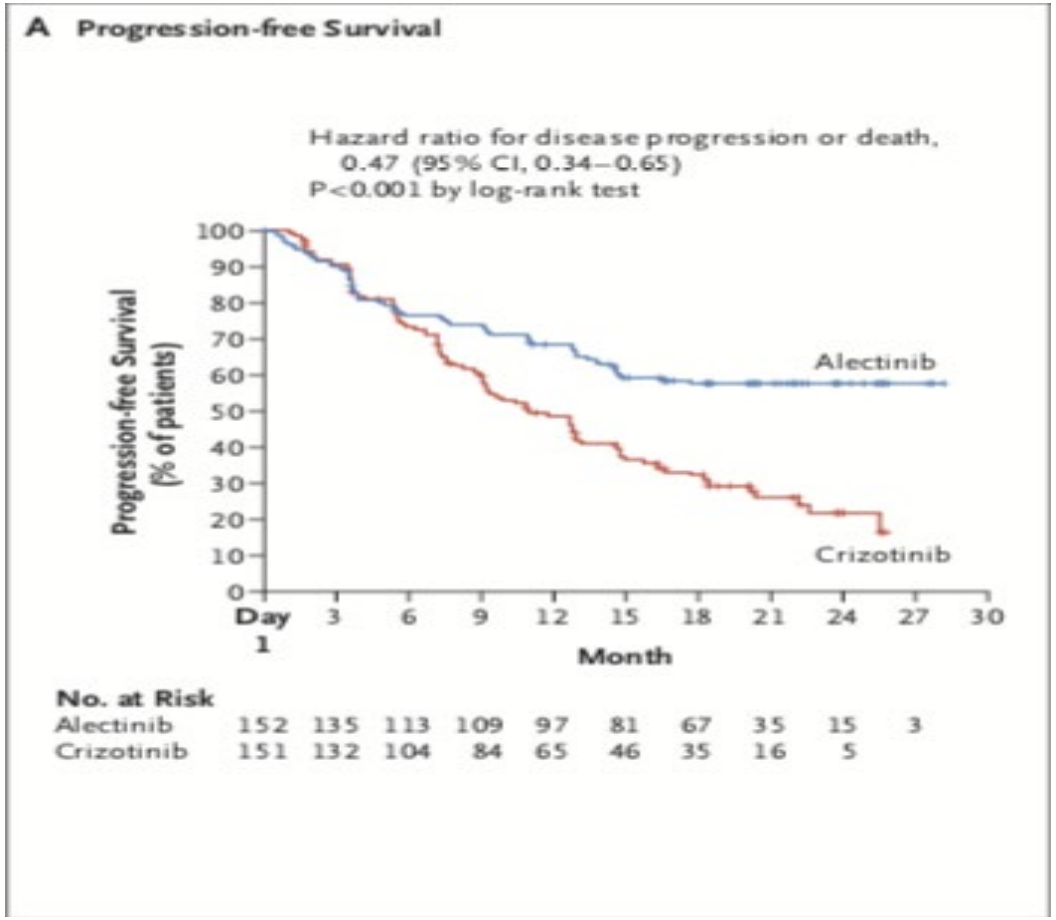
ORIGINAL ARTICLE

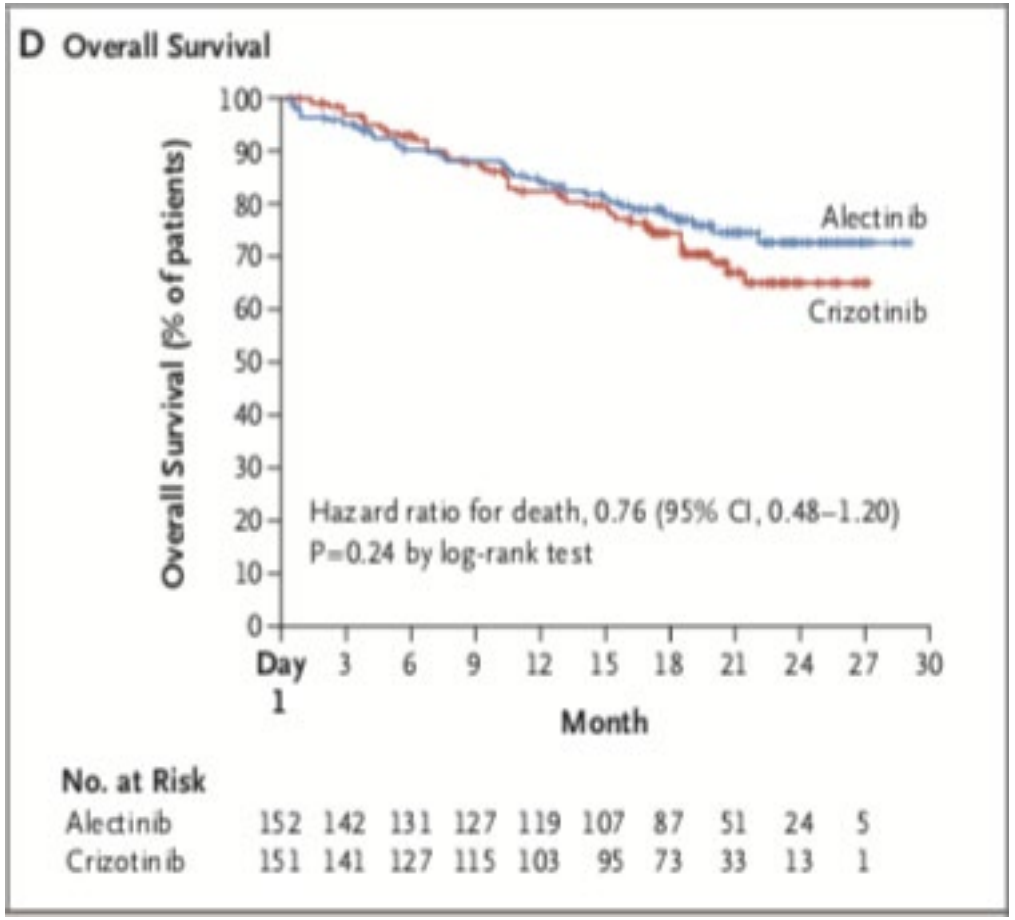
Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

Solange Peters, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Shirish Gadgeel, M.D., Jin S. Ahn, M.D., Dong-Wan Kim, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Maurice Pérol, M.D., Rafal Dziadziuszko, M.D., Rafael Rosell, M.D., Ph.D., Ali Zeaiter, M.D., Emmanuel Mitry, M.D., Ph.D., Sophie Golding, M.Sc., Bogdana Balas, M.D., Johannes Noe, Ph.D., Peter N. Morcos, Pharm.D., and Tony Mok, M.D., for the ALEX Trial Investigators*

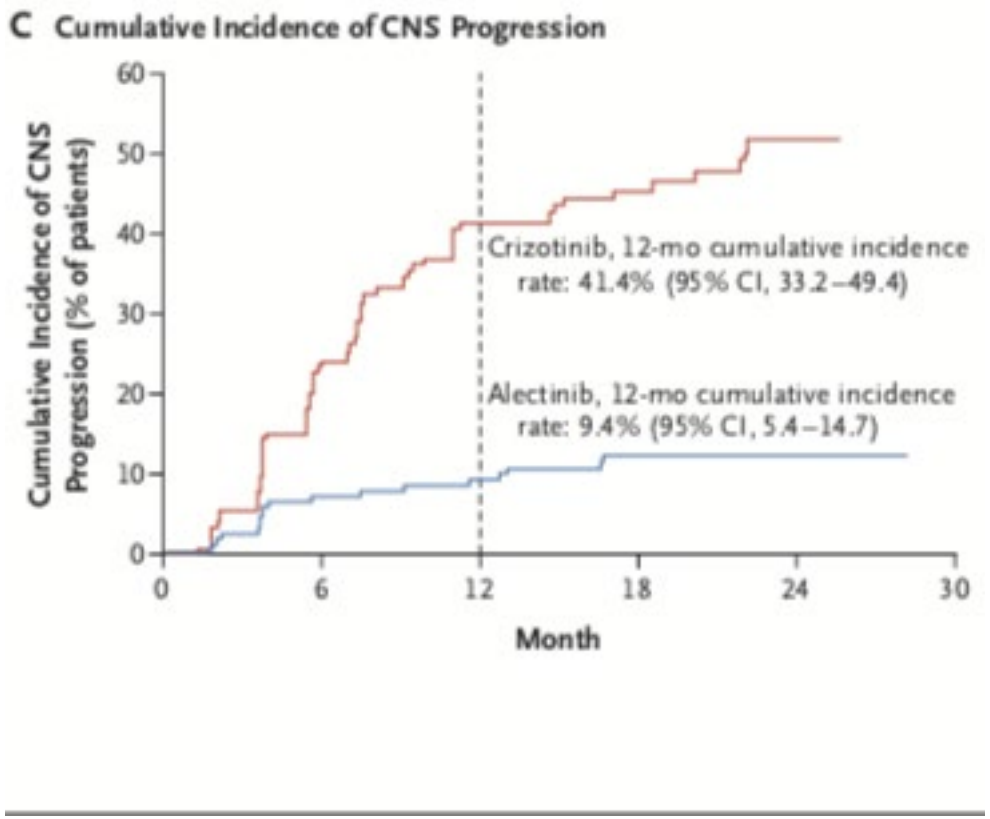
Nejm 2017 Aug 377;9

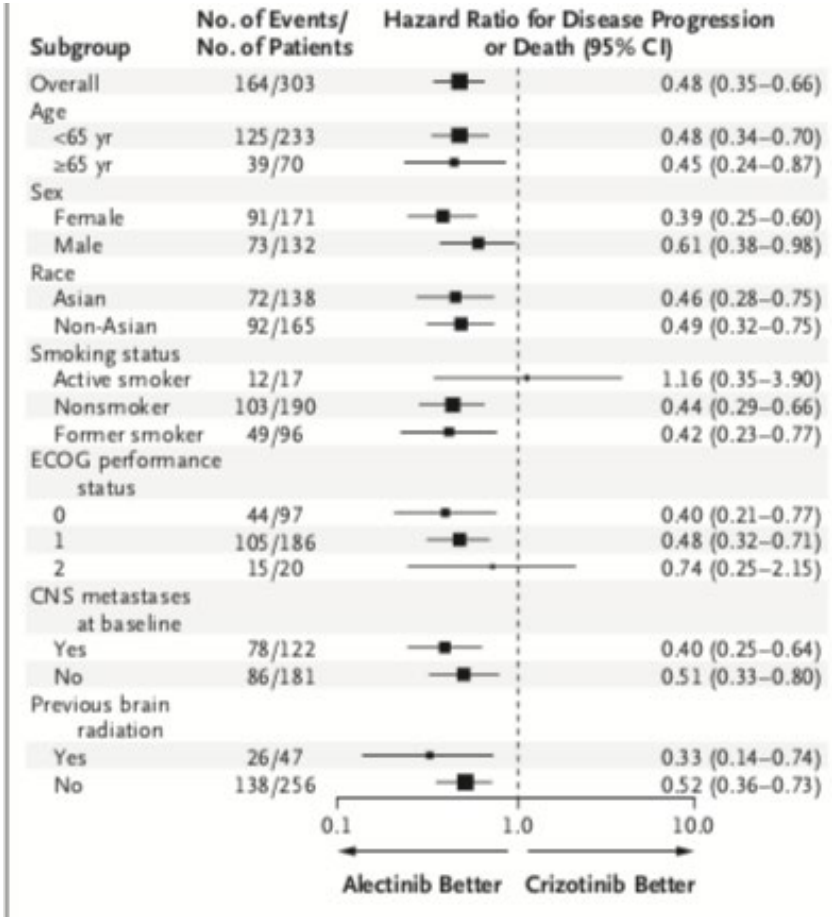
ALEX Çalışması (Alectinib/ Crizotinib)





ALEX Çalışması (Alectinib/ Crizotinib)





CERITINIB (ALK,ROS, IGF-1)- ASCEND 4

First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study.

Soria JC[1], Tan DSW[2], Chiari R[3], Wu YL[4], Paz-Ares L[5], Wolf J[6], Geater SL[7], Orlov S[8], Cortinovis D[9], Yu CJ[10], Hochmair M[11], Cortot AB[12], Tsai CM[13], Moro-Sibilot D[14], Campelo RG[15], McCulloch T[16], Sen P[16], Dugan M[16], Pantano S[17], Branle F[17], Massacesi C[17], de Castro G Jr[18].

Author information

Erratum in

Department of Error. [Lancet. 2017]

Abstract

BACKGROUND: The efficacy of ceritinib in patients with untreated anaplastic lymphoma kinase (ALK)-rearranged non-small-cell lung cancer (NSCLC) is not known. We assessed the efficacy and safety of ceritinib versus platinum-based chemotherapy in these patients.

METHODS: This randomised, open-label, phase 3 study in untreated patients with stage IIIB/IV ALK-rearranged non-squamous NSCLC was done in 134 centres across 28 countries. Eligible patients were assigned via interactive response technology to oral ceritinib 750 mg/day or platinum-based chemotherapy ([cisplatin 75 mg/m^2 or carboplatin AUC 5-6 plus pemetrexed 500 mg/m^2] every 3 weeks for four cycles followed by maintenance pemetrexed); randomisation was stratified by World Health Organization performance status (0 vs 1-2), previous neoadjuvant or adjuvant chemotherapy, and presence of brain metastases as per investigator's assessment at screening. Investigators and patients were not masked to treatment assignment. The primary endpoint was blinded independent review committee assessed progression-free survival, based on all randomly assigned patients (the full analysis set). Efficacy analyses were done based on the full analysis set. All safety analyses were done based on the safety set, which included all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT01828099.

FINDINGS: Between Aug 19, 2013, and May 11, 2015, 376 patients were randomly assigned to ceritinib (n=189) or chemotherapy (n=187). Median progression-free survival (as assessed by blinded independent review committee) was 16·6 months (95% CI 12·6-27·2) in the ceritinib group and 8·1 months (5·8-11·1) in the chemotherapy group (hazard ratio 0·55 [95% CI 0·42-0·73]; p<0·00001). The most common adverse events were diarrhoea (in 160 [85%] of 189 patients), nausea (130 [69%]), vomiting (125 [66%]), and an increase in alanine aminotransferase (114 [60%]) in the ceritinib group and nausea (in 97 [55%] of 175 patients), vomiting (63 [36%]), and anaemia (62 [35%]) in the chemotherapy group.

INTERPRETATION: First-line ceritinib showed a statistically significant and clinically meaningful improvement in progression-free survival versus chemotherapy in patients with advanced ALK-rearranged NSCLC.

PFS: Ceritinib 16.6 ay
KT 8.1 ay

Lancet 2017 Mar 4;389(10072):917-929

ORIGINAL ARTICLE FREE PREVIEW

Brigatinib versus Crizotinib in ALK-Positive Non–Small-Cell Lung Cancer

D. Ross Camidge, M.D., Ph.D., Hye Ryun Kim, M.D., Ph.D., Myung-Ju Ahn, M.D., Ph.D., James Chih-Hsin Yang, M.D., Ph.D., Ji-Youn Han, M.D., Ph.D., Jong-Seok Lee, M.D., Maximilian J. Hochmair, M.D., Jacky Yu-Chung Li, M.B., B.S., Gee-Chen Chang, M.D., Ph.D., Ki Hyeong Lee, M.D., Ph.D., Cesare Gridelli, M.D., Angelo Delmonte, M.D., Ph.D., et al.

ALTA IL Çalışması

PFS Brigatinib % 67
Crizotinib % 43
HR: =o.49

N Engl J Med 2018; 379:2027-2039

NCCN 2019 (2.versiyon)

***ALK* Rearrangement Positive**

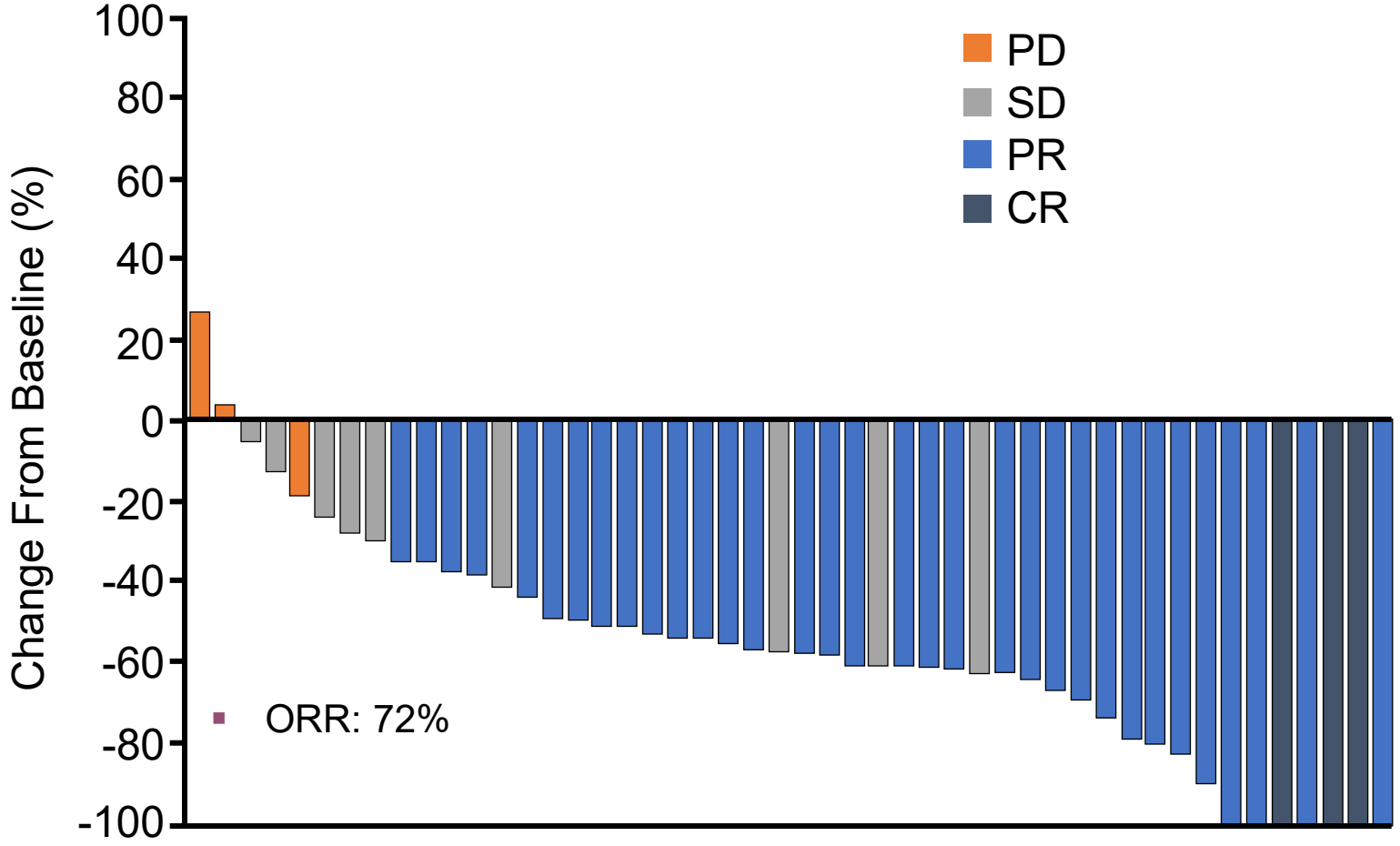
- First-line therapy
  - Alectinib[8,9]
  - Brigatinib[10]
  - Ceritinib[11]
  - Crizotinib[12,13]
- Subsequent therapy
  - Alectinib[14,15]
  - Brigatinib[16]
  - Ceritinib[17]
  - Lorlatinib[18]

ROS1

- ROS1 re-aranjmanları KHDAK'nin yaklaşık %1-3'de bulunur.
- Nispeten genç ve daha önce sigara içmemiş hastalarda daha fazla gözlenir.
- Genellikle KRAS, EGFR ve ALK ile eşzamanlı bulunmaz.

Bergethon K J Clin Oncol. 2012
Takeuchi KNat Med. 2012

ROS1 Re-aranjmanı Olan KHDAK'de Crizotinib



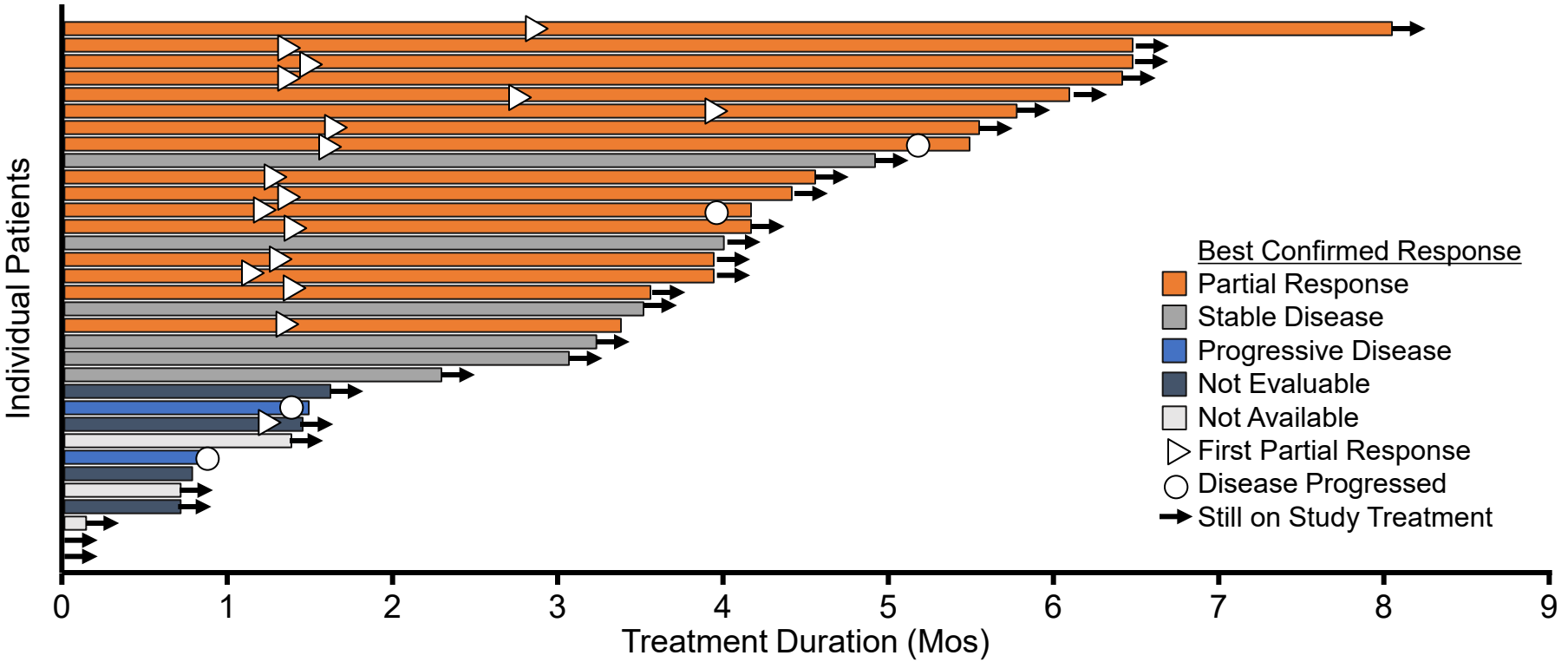
Shaw AT, et al. N Engl J Med. 2014;371:1963-1971.

NCCN 2019 (2.versiyon)

***ROS1* Rearrangement Positive**

- First-line therapy
  - Ceritinib[19]
  - Crizotinib[20]

B-Raf(V600 E) mutasyonu + KHDAK Dabrafenib +Trametinib Cevap Oranları



*1st-line patient (protocol deviation)

- Median time on study treatment (dabrafenib and trametinib) = 108 days (range, 1 to 244 days)

Planchard D, et al. ASCO 2015. Abstract 8006. Reprinted with permission.

Lancet Oncol. 2016 Jul;17(7):984-993. doi: 10.1016/S1470-2045(16)30146-2. Epub 2016 Jun 6.

Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial.

Planchard D[1], Besse B[2], Groen HJM[3], Souquet PJ[4], Quoix E[5], Baik CS[6], Barlesi F[7], Kim TM[8], Mazieres J[9], Novello S[10], Rigas JR[11], Upalawanna A[12], D'Amelio AM Jr[13], Zhang P[13], Mookerjee B[13], Johnson BE[14].

Author information

Abstract

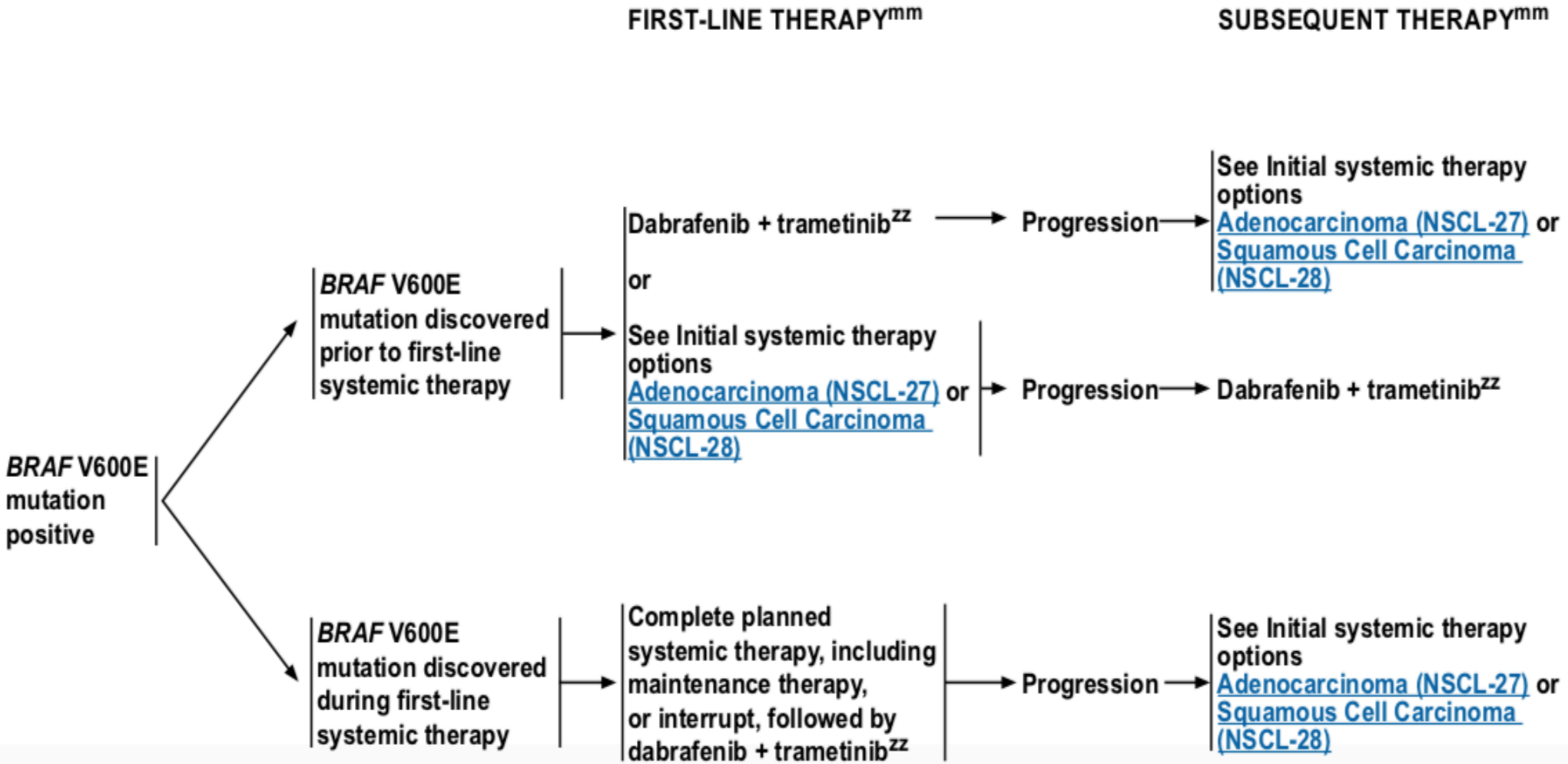
BACKGROUND: BRAF mutations act as an oncogenic driver via the mitogen-activated protein kinase (MAPK) pathway in non-small cell lung cancer (NSCLC). BRAF inhibition has shown antitumour activity in patients with BRAF(V600E)-mutant NSCLC. Dual MAPK pathway inhibition with BRAF and MEK inhibitors in BRAF(V600E)-mutant NSCLC might improve efficacy over BRAF inhibitor monotherapy based on observations in BRAF(V600)-mutant melanoma. We aimed to assess the antitumour activity and safety of dabrafenib plus trametinib in patients with BRAF(V600E)-mutant NSCLC.

METHODS: In this phase 2, multicentre, non-randomised, open-label study, we enrolled adult patients (aged ≥18 years) with pretreated metastatic stage IV BRAF(V600E)-mutant NSCLC who had documented tumour progression after at least one previous platinum-based chemotherapy and had had no more than three previous systemic anticancer therapies. Patients with previous BRAF or MEK inhibitor treatment were ineligible. Patients with brain metastases were allowed to enrol only if the lesions were asymptomatic, untreated (or stable more than 3 weeks after local therapy if treated), and measured less than 1 cm. Enrolled patients received oral dabrafenib (150 mg twice daily) plus oral trametinib (2 mg once daily) in continuous 21-day cycles until disease progression, unacceptable adverse events, withdrawal of consent, or death. The primary endpoint was investigator-assessed overall response, which was assessed by intention to treat in the protocol-defined population (patients who received second-line or later treatment); safety was also assessed in this population and was assessed at least once every 3 weeks, with adverse events, laboratory values, and vital signs graded according to the Common Terminology Criteria for Adverse Events version 4.0. The study is ongoing but no longer recruiting patients. This trial is registered with ClinicalTrials.gov, number NCT01336634.

FINDINGS: Between Dec 20, 2013, and Jan 14, 2015, 59 patients from 30 centres in nine countries across North America, Europe, and Asia met eligibility criteria. Two patients who had previously been untreated due to protocol deviation were excluded; thus, 57 eligible patients were enrolled. 36 patients (63·2% [95% CI 49·3–75·6]) achieved an investigator-assessed overall response. Serious adverse events were reported in 32 (56%) of 57 patients and included pyrexia in nine (16%), anaemia in three (5%), confusional state in two (4%), decreased appetite in two (4%), haemoptysis in two (4%), hypercalcaemia in two (4%), nausea in two (4%), and cutaneous squamous cell carcinoma in two (4%). The most common grade 3–4 adverse events were neutropenia in five patients (9%), hyponatraemia in four (7%), and anaemia in three (5%). Four patients died during the study from fatal adverse events judged to be unrelated to treatment (one retroperitoneal haemorrhage, one subarachnoid haemorrhage, one respiratory distress, and one from disease progression that was more severe than typical progression, as assessed by the investigator).

INTERPRETATION: Dabrafenib plus trametinib could represent a new targeted therapy with robust antitumour activity and a manageable safety profile in patients with BRAF(V600E)-mutant NSCLC.

BRAF V600E MUTATION POSITIVE[hh]



KRAS Mutasyonu

- Akciğer adenokarsinomlarında de en sık görülen mutasyon (%30)
- EGFR tirozin kinaz inhibitörlerine cevapsızlıkta rolü var
- Pozitifliğinde diğer mutasyonların bakılmasına gerek yok

- SELUMETİNİB(Mek1/Mek2 inhibitörü
- Faz II çalışma

Shigematsu HJ Natl Cancer Inst. 2005
Riely GJProc Am Thorac Soc. 2009

Skuamöz Hücreli Karsinomlarda

PIK3CA mutations	3.6-6.5	No association seen	GDC-0941 XL147 BKM120
FGFR1 amplification	9.7-21.0	Never-smokers	Brivanib (BMS-582664) Dovitinib (TKI258) Ponatinib (AP24534) E3810
DDR2 mutations	2.2	No association seen	Dasatinib Imatinib Nilotinib

KHDAK Tedavisinde Birinci Seri Tedaviyi Belirlerken .....

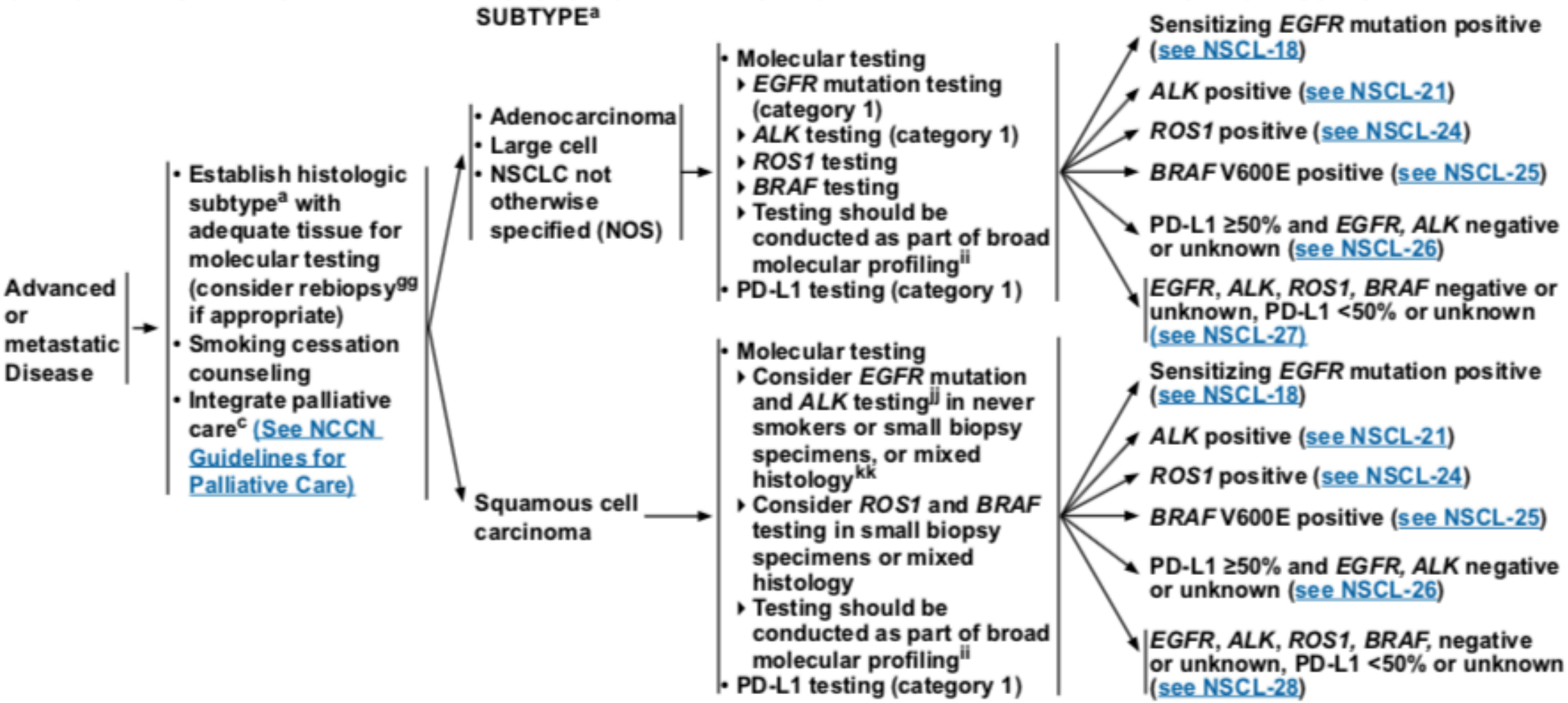
- EGFR mutasyonları
- ALK/EML4
- ROS
- B-RAF

- PDL1

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion



Anti EGFR TKİ –Direnç Gelişimi

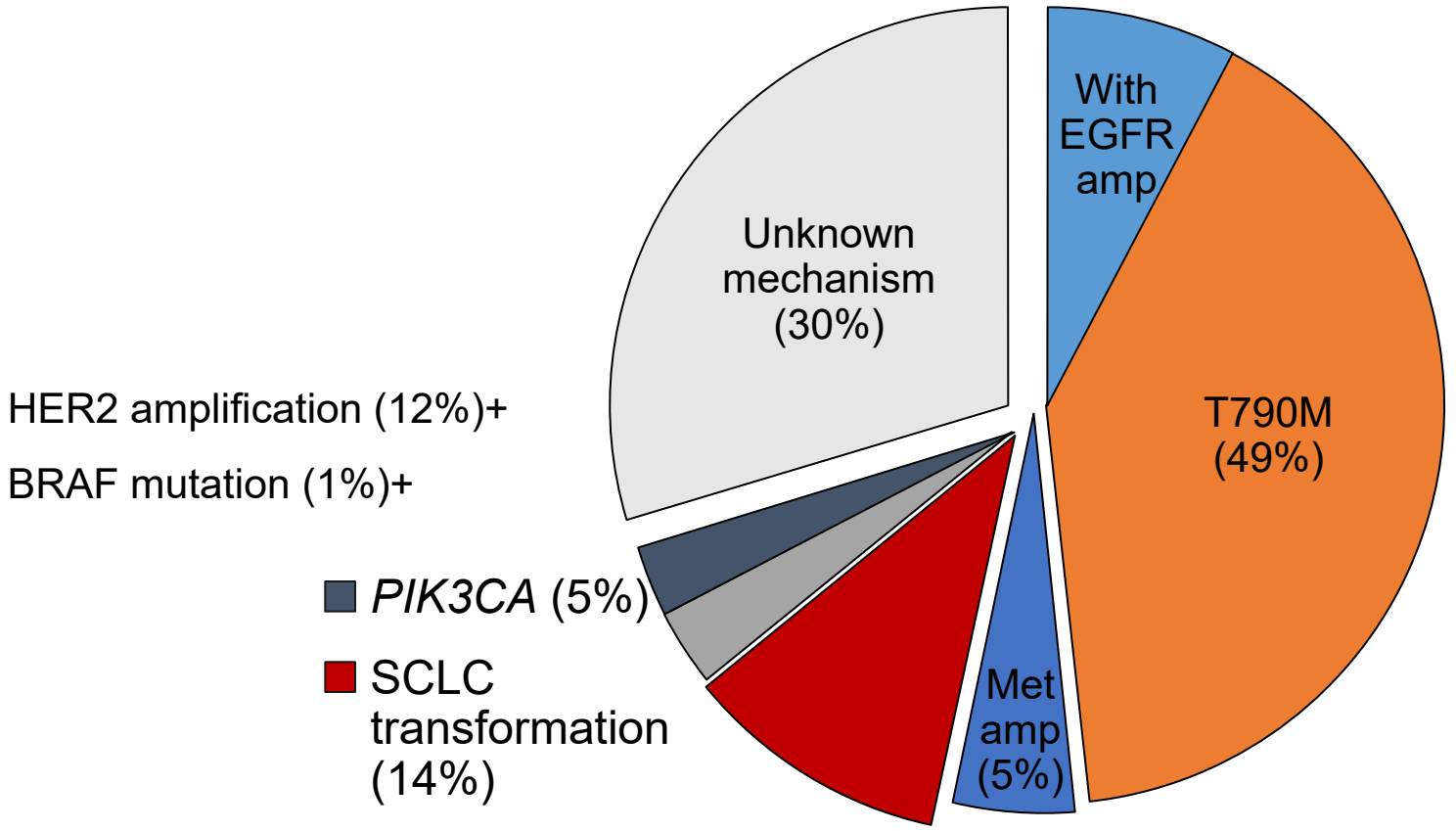
Primer direnç

- Kras mutasyonu
- Exon 20 insersiyon mutasyonu

Edinsel direnç

- T790M (tedaviye yanıt sonrası progresyonun %60'I)
- 8-16 ay içinde
- KHDAK----KHAK
- Epitelyal- mezenkimal transizyon

Edinsel Direnç Mekanizmaları



Sequist LV, et al. Sci Trans Med. 2011;3:75ra26. Oxnard GR, et al. Clin Cancer Res. 2011;17:1616-1622. Ohashi K, et al. Proc Nat Acad Sci USA. 2012;109:E2127-E2133. Takezawa K, et al. Cancer Discov. 2012;2:922-933.

Osimertinib 3. Jenerasyon TKI

- T790M-pozitif ve diğer EGFR TKI tedavilerine yanıt alınmayan KHDAK (Aralık 2015 FDA onayı)

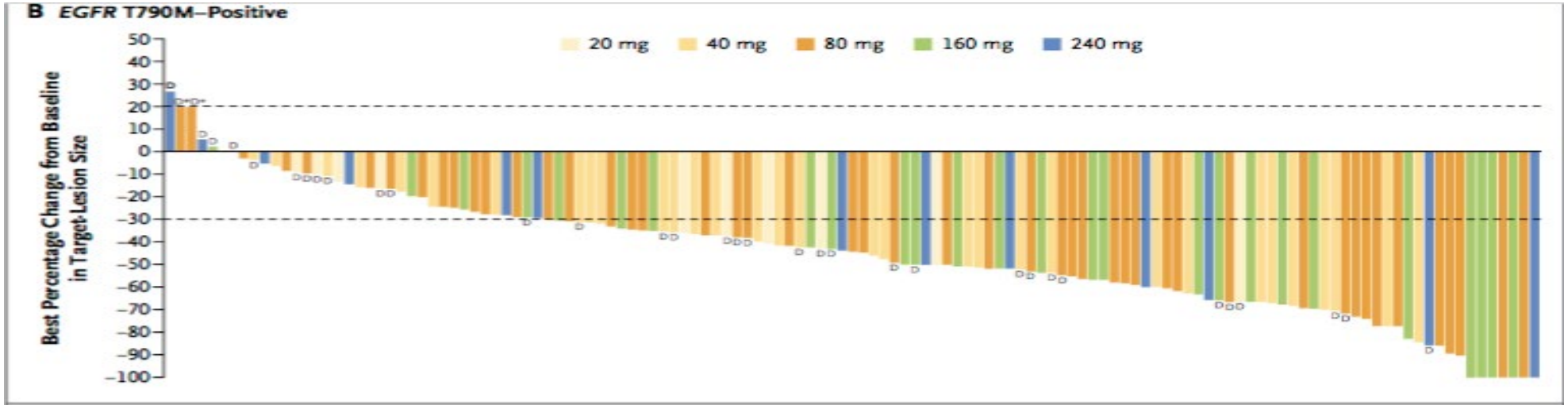
- EGFR T790M-pozitif olgularda cevap oranı 59% to 61%

The NEW ENGLAND JOURNAL of MEDICINE

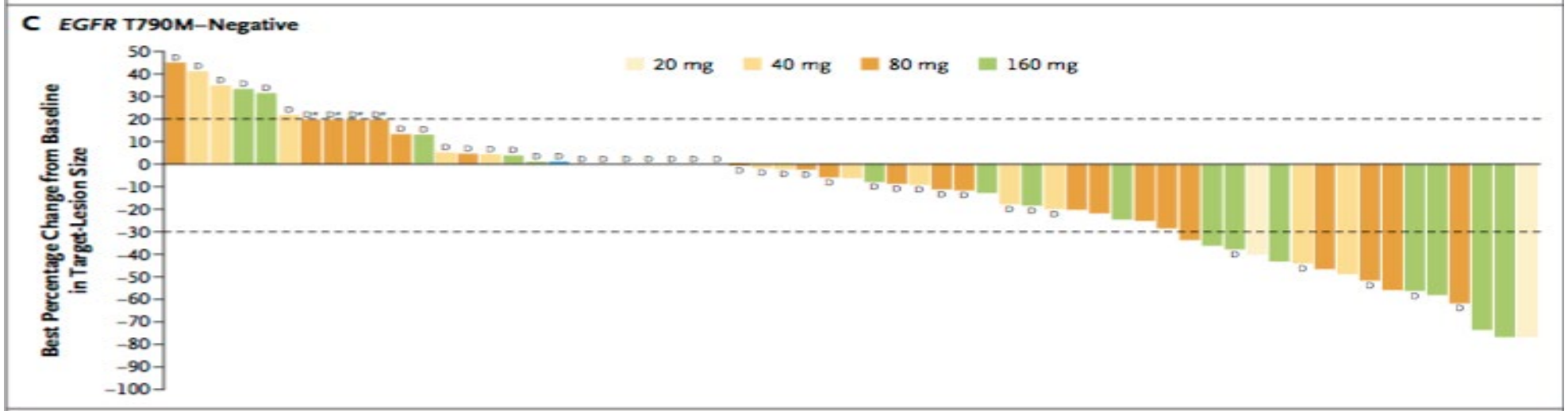
ESTABLISHED IN 1812 APRIL 30, 2015 VOL. 372 NO. 18

AZD9291 in EGFR Inhibitor–Resistant Non–Small-Cell Lung Cancer

Pasi A. Jänne, M.D., Ph.D., James Chih-Hsin Yang, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D.,



Cevap Oranı %61



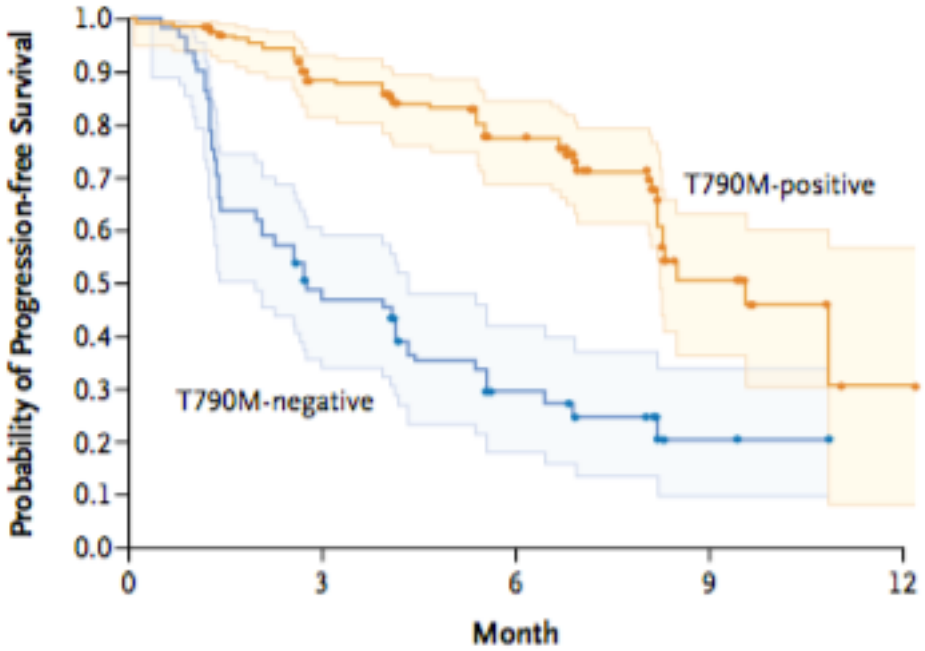
Cevap Oranı %21

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 30, 2015 VOL. 372 NO. 18

AZD9291 in EGFR Inhibitor–Resistant Non–Small-Cell Lung Cancer

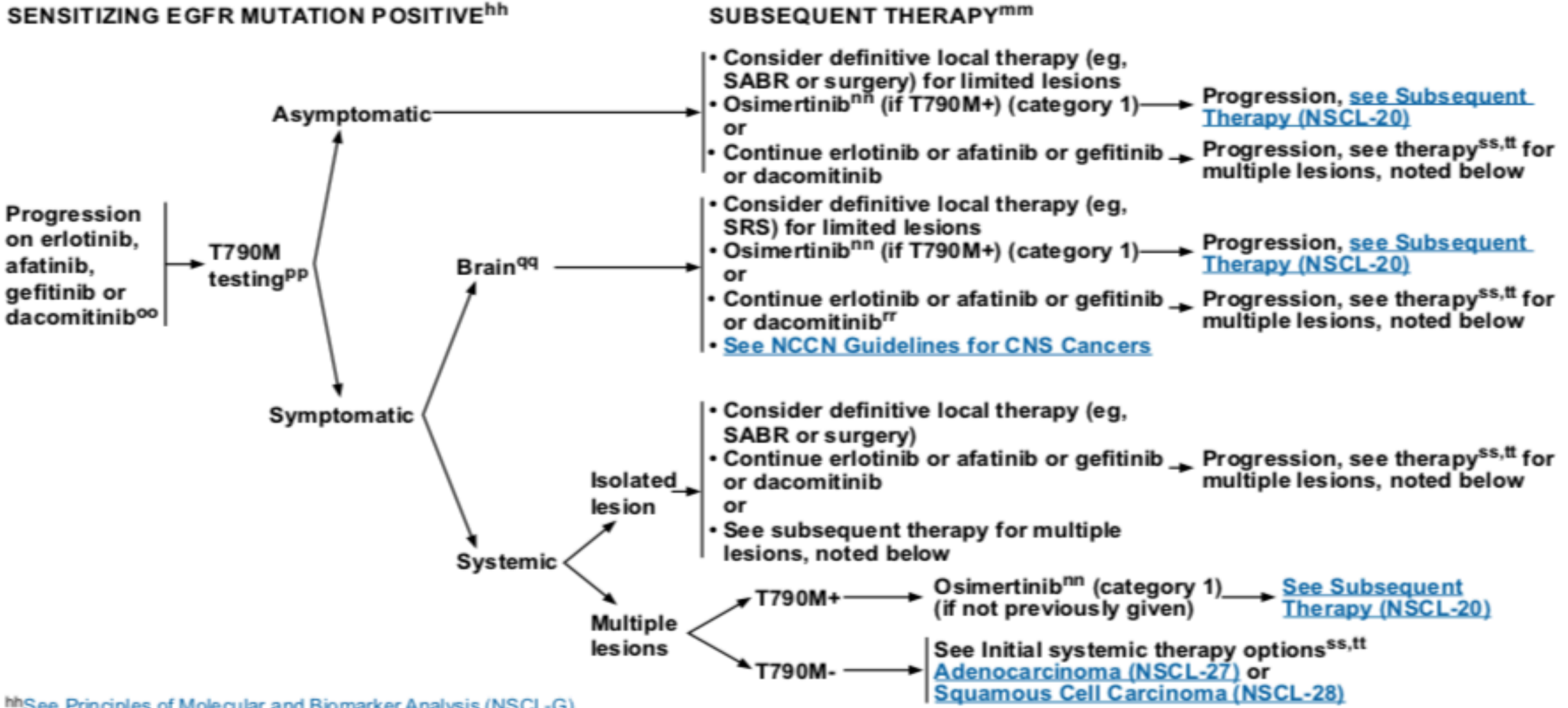
Pasi A. Jänne, M.D., Ph.D., James Chih-Hsin Yang, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D.,



No. at Risk					
T790M-positive	138	100	70	14	1
T790M-negative	62	27	13	3	0

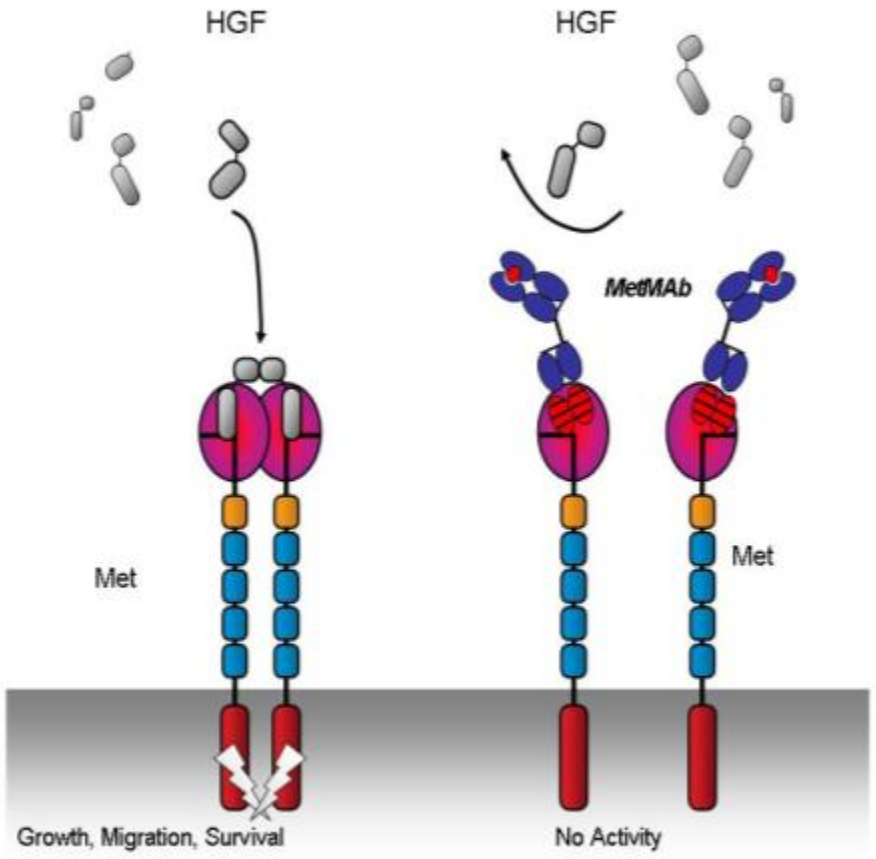
PFS:9.6 ay

PFS: 2.8 ay



[hh] See Principles of Molecular and Biomarker Analysis (NSCL-G).
[mm] See Targeted Therapy for Advanced or Metastatic Disease (NSCL-I).
[nn] For performance status 0-4.

Met



- Bir çok tümörde MET amplifikasyonu, mutasyonu, aşırı ekspresyonu var
- MET ekspresyonu bir çok tümör ve KHDAK için kötü bir prognostik özellik
  - Amplifikasyonu
  - Exon14 mutasyonları
- MET aktivasyonu erlotinib/gefitinib direncinde rol oynuyor

Spigel DR, et al. ASCO 2011. Abstract 7505.

EMERGING BIOMARKERS TO IDENTIFY NOVEL THERAPIES FOR PATIENTS WITH METASTATIC NSCLC

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
High-level MET amplification or MET exon 14 skipping mutation	Crizotinib[1-5]
RET rearrangements	Cabozantinib[6,7] Vandetanib[8]
ERBB2 (HER2) mutations	Ado-trastuzumab emtansine[9]
Tumor mutational burden (TMB)*	Nivolumab + ipilimumab[10] Nivolumab[11]

*TMB is an evolving biomarker that may be helpful in selecting patients for immunotherapy. There is no consensus on how to measure TMB.

Teşekkürler