Küçük Hücreli Dışı Akciğer Kanserinde(KHDAK) Hedefe Yönelik Tedavi Seçenekleri

Dr. Deniz Tural
Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi
Tıbbi Onkoloji

KHDAK Hedefe Yönelik Tedavi Seçenekleri

DERS PLANI

- KHDAK insidans/mortalite
- KHDAK adjuvan/neoadjuvan tedavi
- Metastatik hasta gurubunda tedavi seçenekleri
- Hedefe yönelik tedaviler
- KHDAK yeni tedavi seçenekleri

Akciğer Kanserinde İnsidans ve Mortalite

	Common Types of Cancer	Estimated New Cases 2016	Estimated Deaths 2016
1.	Breast Cancer (Female)	246,660	40,450
2.	**Lung and Bronchus Cancer**	**224,390**	**158,080**
3.	Prostate Cancer	180,890	26,120
4.	Colon and Rectum Cancer	134,490	49,190
5.	Bladder Cancer	76,960	16,390
6.	Melanoma of the Skin	76,380	10,130
7.	Non-Hodgkin Lymphoma	72,580	20,150
8.	Thyroid Cancer	64,300	1,980
9.	Kidney and Renal Pelvis Cancer	62,700	14,240
10.	Leukemia	60,140	24,400

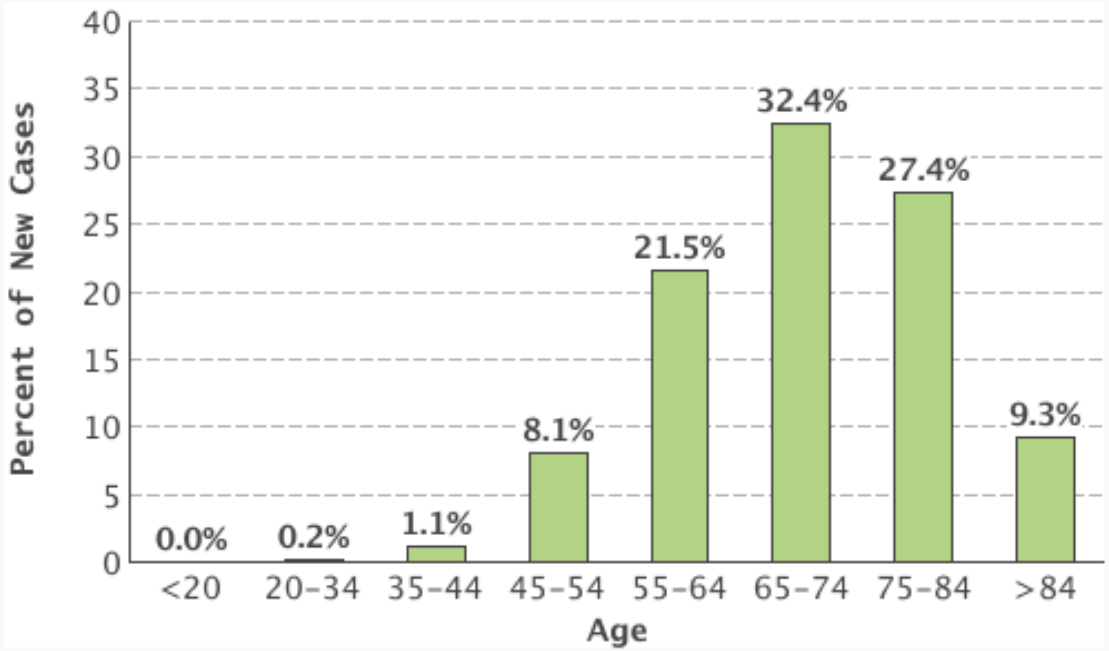
Lung and bronchus cancer represents 13.3% of all new cancer cases in the U.S.

13.3%

In 2016, it is estimated that there will be 224,390 new cases of lung and bronchus cancer and an estimated 158,080 people will die of this disease.

Akciğer Kanserinde İnsidans ve Mortalite

Percent of New Cases by Age Group: Lung and Bronchus Cancer



Lung and bronchus cancer is most frequently diagnosed among people aged 65–74.

Median Age At Diagnosis

70

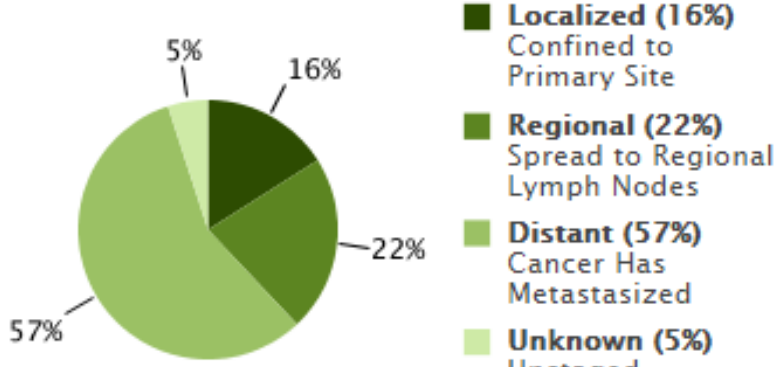
SEER 18 2009–2013, All Races, Both Sexes

Number of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Lung and Bronchus Cancer

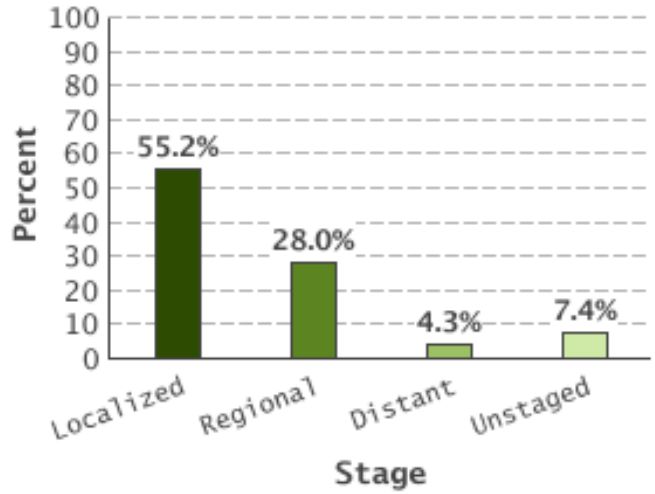
Akciğer Kanserinde İnsidans ve Mortalite

Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Lung and Bronchus Cancer

Percent of Cases by Stage

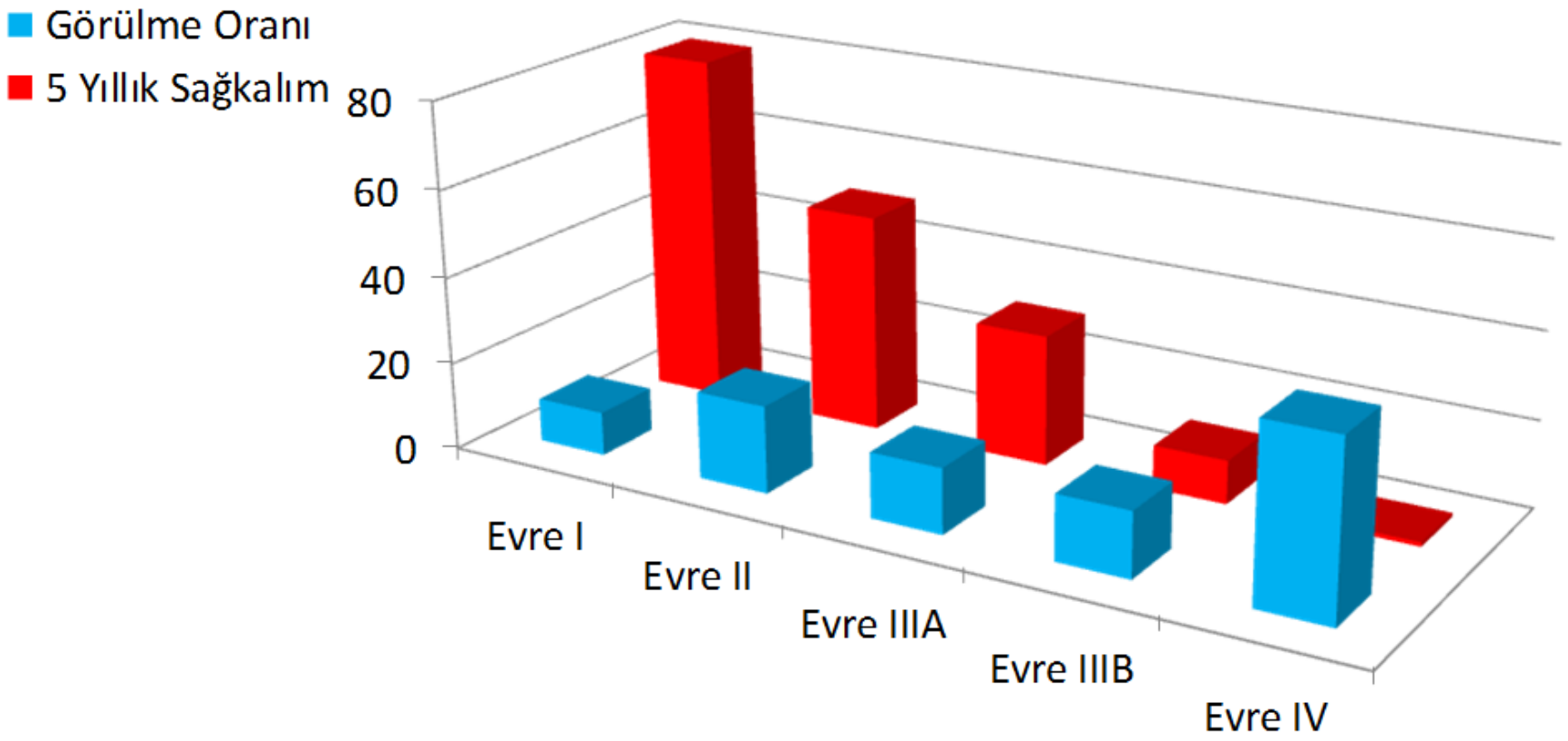


5-Year Relative Survival

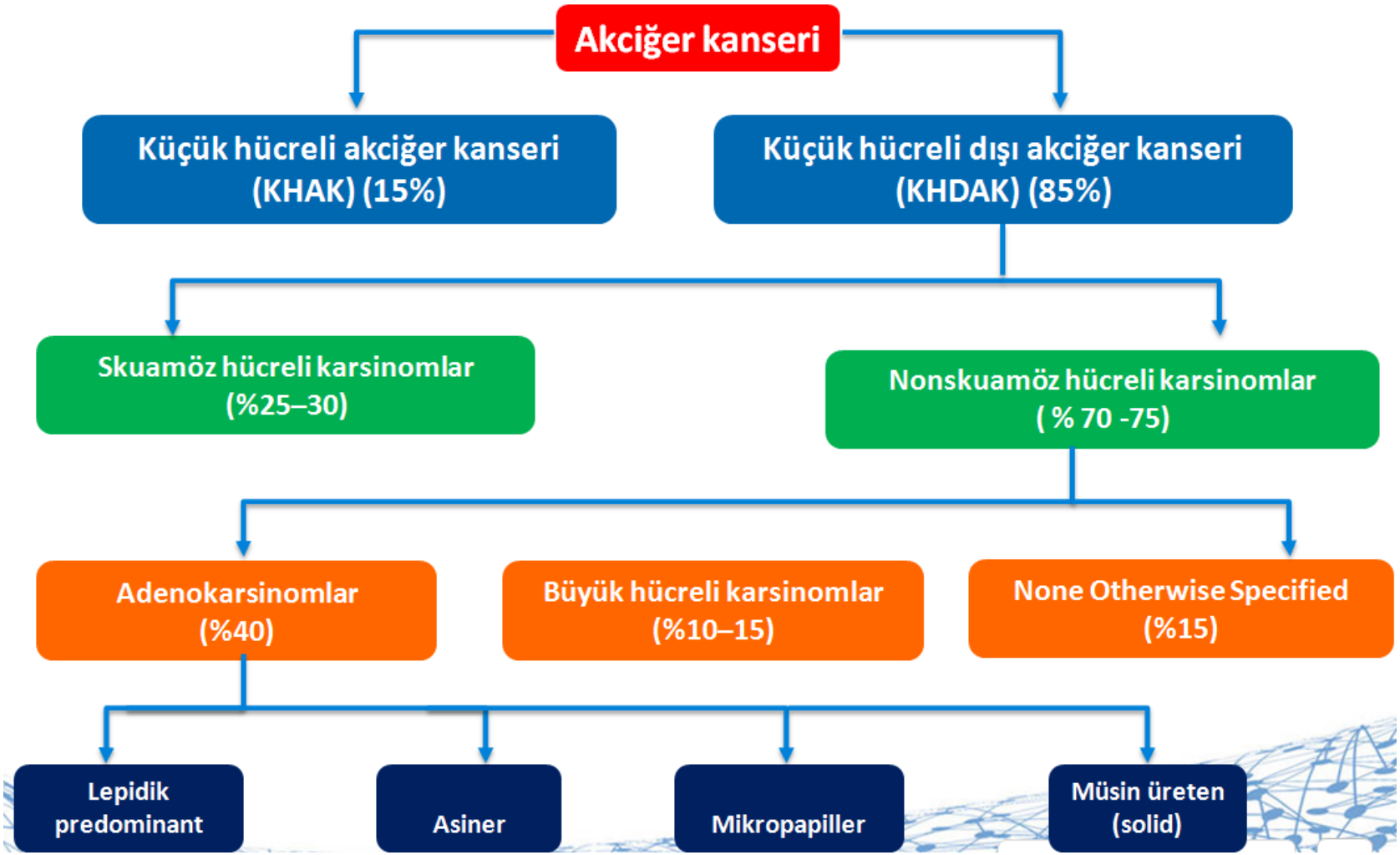


SEER 18 2006-2012, All Races, Both Sexes by SEER Summary Stage 2000

KHDAK'de Sağkalım



Akciğer Kanserinde Patolojik Sınıflandırma

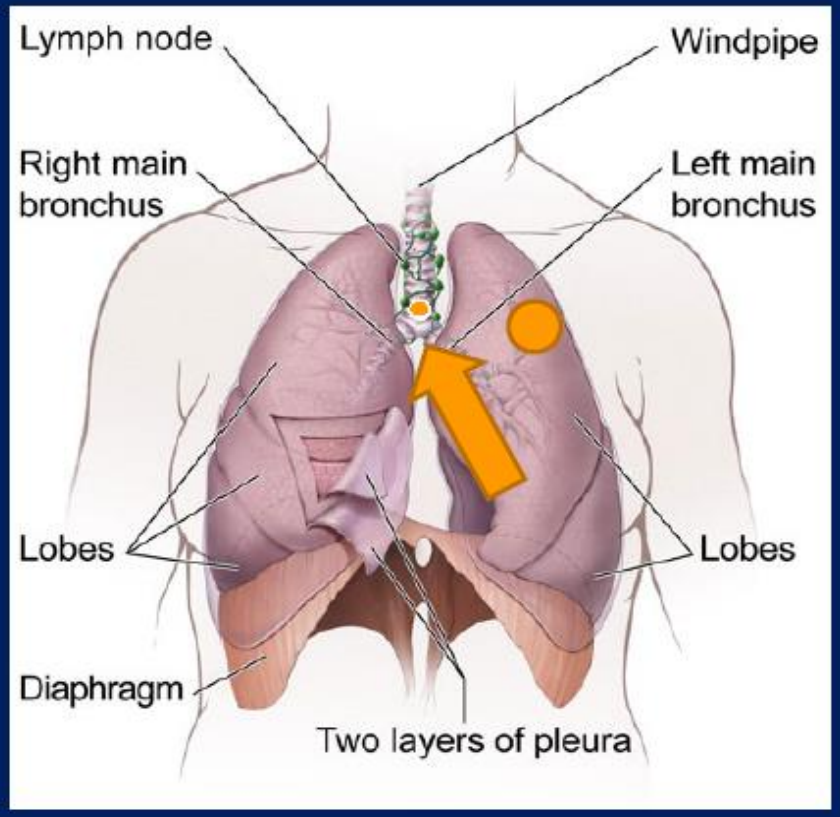


KHDAK Patolojik Sınıflandırma

- Adenocarcinoma of lung
  - TTF-1 (+), Cytokeratin 7/20 (+/-)
- Adenocarcinoma of GI tract
  - CDX 2 (+), Cytokeratin 7/20 (-/+)
- Squamous of lung
  - p63 and p40 (+)
- Mesothelioma
  - WT-1 (+), Calretinin (+), Cytokeratin 5/6 (+)

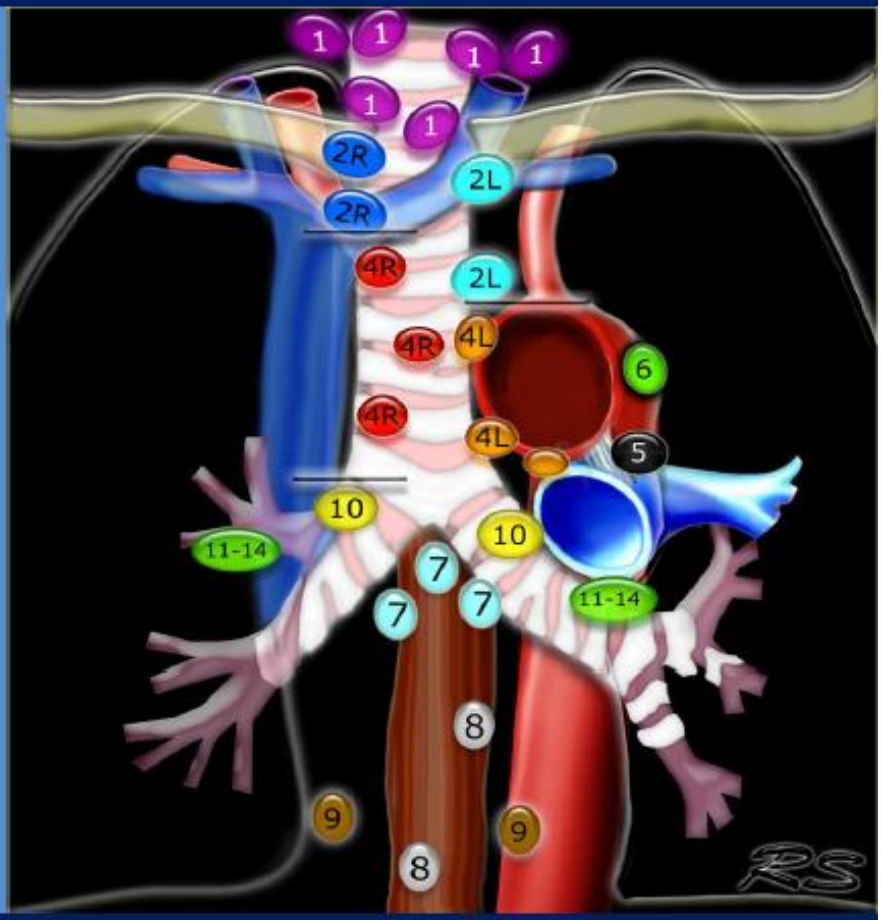
KHDAK Klinik Sınıflandırma

Stage III NSCLC: Mediastinal (N2/N3) LN



KHDAK Kanserinde Klinik Sınıflandırma

- **Right sided tumors:**
  - 2R, 4R, 7, 8, 9
- **Left sided tumors:**
  - 4L, 5, 6, 7, 8, 9



Single digit LN's are N2 (e.g. station 7)
Double digit LN's are N1 (e.g. station 11)

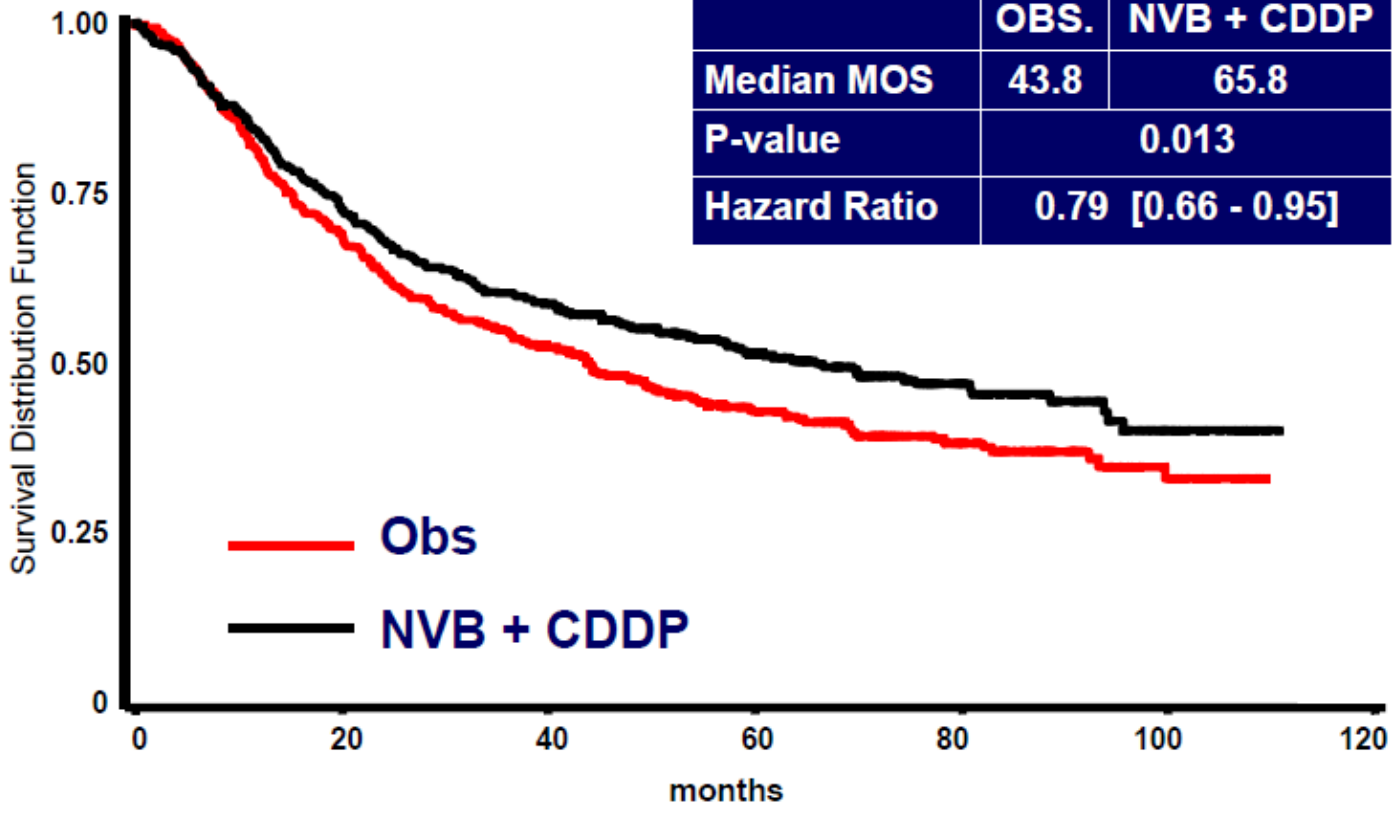
EBUS: 2, 4, 7, 10, hilar
EUS: 7, 8, 9

KDHAK Adjuvan Tedavi

Adjuvant Cisplatin/Vinorelbine in stage I-III NSCLC

Douillard et al, Lancet Oncol 2006;7:719-727

	OBS.	NVB + CDDP
Median MOS	43.8	65.8
P-value	0.013	
Hazard Ratio	0.79 [0.66 - 0.95]	

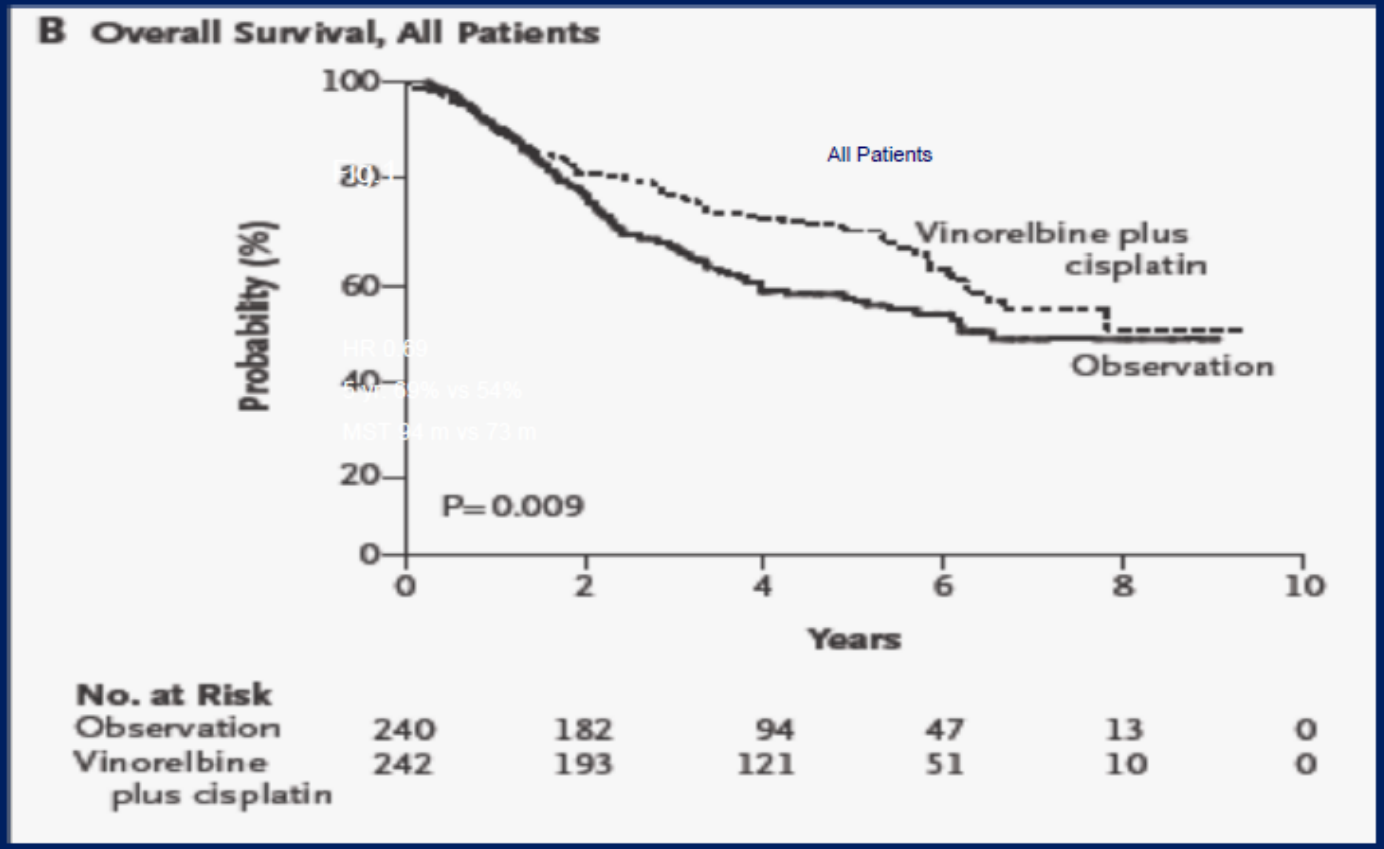


Radiation was allowed

KDHAK Adjuvan Tedavi

Adjuvant Cisplatin/Vinorelbine in stage Ib-II NSCLC

Winton et al, NEJM 2005;352:2589-2597



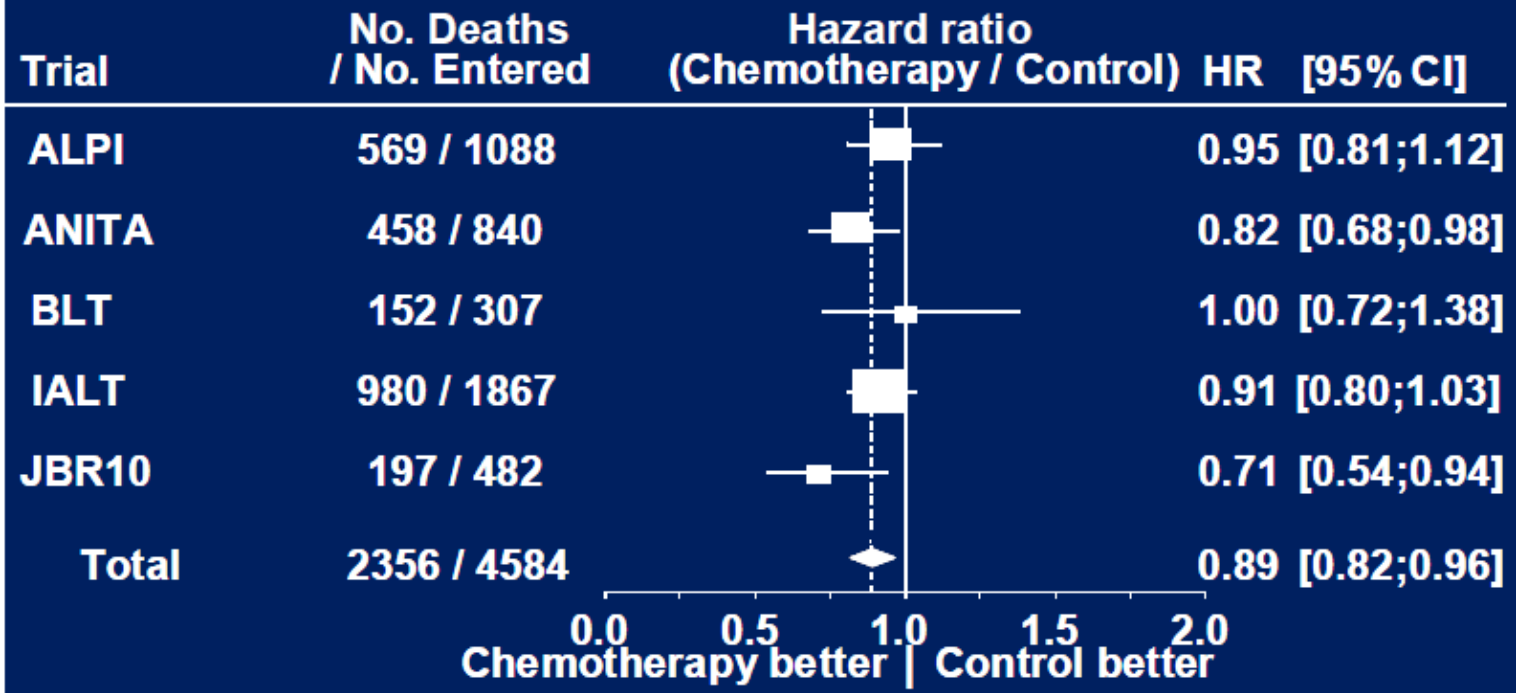
Absolute improvement in 5 yr OS = 15% (69% vs. 54%)

No radiation allowed

KDHAK Adjuvan Tedavi

LACE Meta-analysis: Cisplatin-based

Pignon JP et al, J Clin Oncol 2006; 24



Test for heterogeneity: p = 0.34

Chemotherapy effect: p= 0.004

ABSOLUTE survival benefit gain is SMALL (~5%)

KDHAK Evreleme

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017 Staging Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Table 3. Descriptors, T and M Categories, and Stage Grouping*

6th Edition T/M Descriptor	7th Edition T/M	N0	N1	N2	N3
T1 (≤2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (<2–3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (≤5 cm)	T2a	IB	**IIA**	IIIA	IIIB
T2 (<5–7 cm)	T2b	**IIA**	IIB	IIIA	IIIB
T2 (>7 cm)	T3	**IIB**	**IIIA**	IIIA	IIIB
T3 invasion		IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		**IIB**	**IIIA**	**IIIA**	IIIB
T4 extension	T4	**IIIA**	**IIIA**	IIIB	IIIB
M1 (ipsilateral lung)		**IIIA**	**IIIA**	**IIIB**	**IIIB**
T4 (pleural effusion	M1a	**IV**	**IV**	**IV**	**IV**
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Cells in bold indicate a change from the sixth edition for a particular TNM category.

KDHAK Adjuvan Tedavi

Adjuvant chemotherapy does not improve survival in stage IB

Trial	IA	IB	II	III
ALPI	NO	NO	NO	NO
IALT	NO	NO	NO	YES
BLT	NO	NO	NO	NO
JBR.10		NO	YES	
ANITA		NO	YES	YES
CALGB 9633		NO		
LACE (Meta)	NO	NO	YES	YES

KDHAK Adjuvan Tedavi

LACE Pooled Analysis

Stage	HR (<1 favor chemotherapy)
IA	1.41
IB	0.92 [0.78-1.10]
II	0.83 [0.73-0.95]
III	0.83 [0.73-0.95]

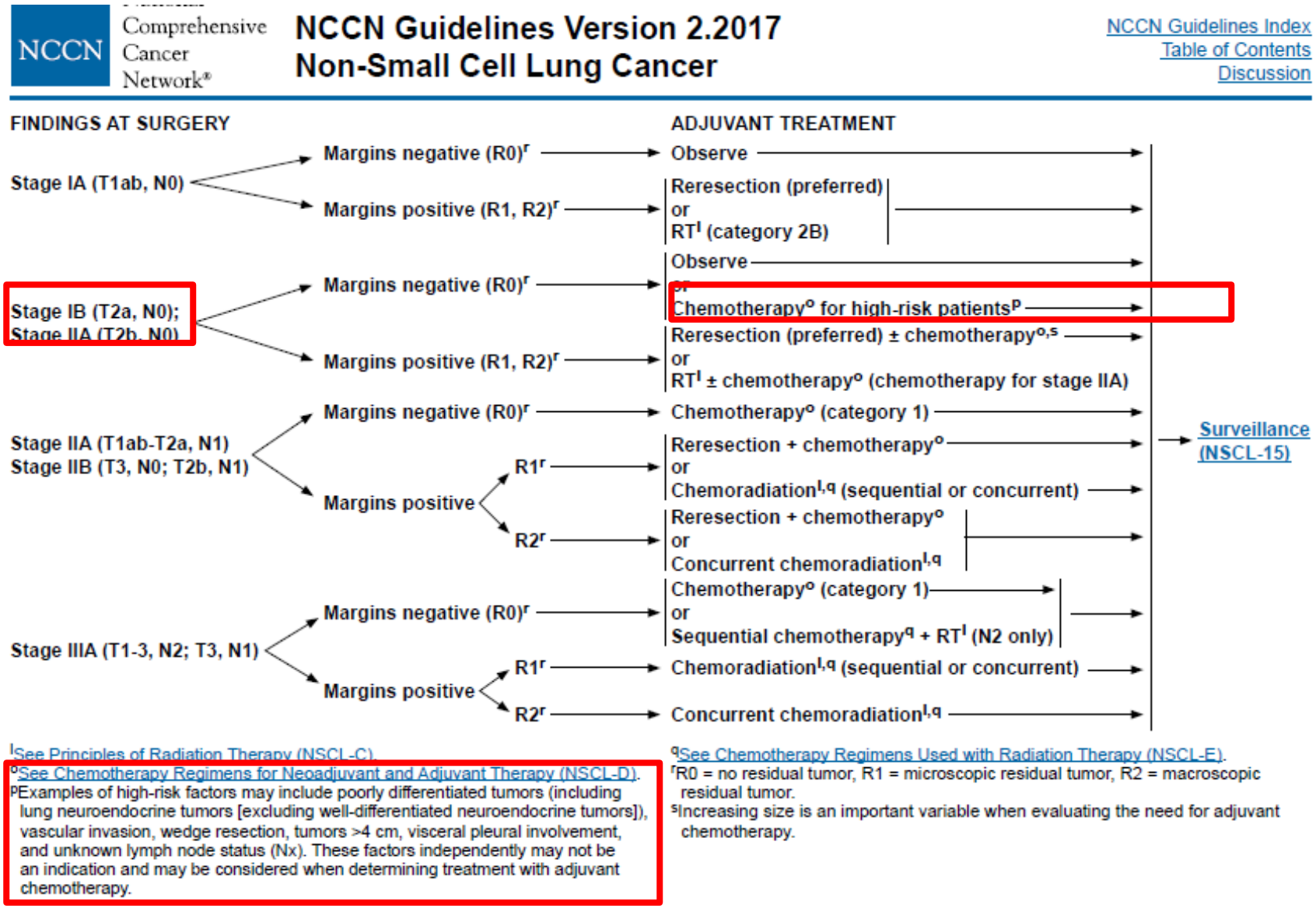
KDHAK Adjuvan Tedavi

Stage IB survival by tumor size

Strauss et al, ASCO 2011 (abst 7015)

Tumor size	HR
Tumors ≥4cm	HR=0.78, p 0.087
Tumors >7cm	**HR=0.52, p .048**

KDHAK Adjuvan Tedavi



KDHAK Adjuvan Tedavi

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

CHEMOTHERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, 22, every 28 days for 4 cycles[a]
- Cisplatin 100 mg/m² day 1; vinorelbine 30 mg/m² days 1, 8, 15, 22, every 28 days for 4 cycles[b,c]
- Cisplatin 75–80 mg/m² day 1; vinorelbine 25–30 mg/m² days 1 + 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1; etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles[b]
- Cisplatin 75 mg/m² day 1; gemcitabine 1250 mg/m² days 1, 8, every 21 days for 4 cycles[d]
- Cisplatin 75 mg/m² day 1; docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[e]
- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 for nonsquamous every 21 days for 4 cycles[f]

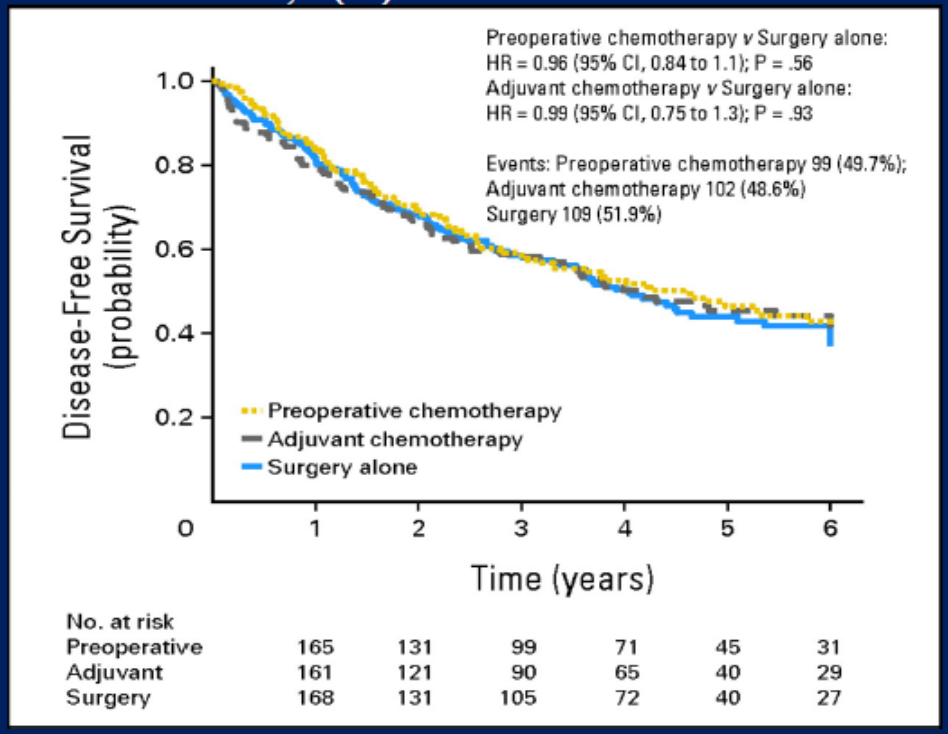
Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin

Paclitaxel 200 mg/m² day 1, carboplatin AUC 6 day 1, every 21 days[g]

KDHAK Adjuvan/Neoadjuvan Tedavi

Surgery vs. Surgery + Neoadjuvant or Adjuvant Carboplatin/Paclitaxel

J Clin Oncol 2010;28(19):3138-45



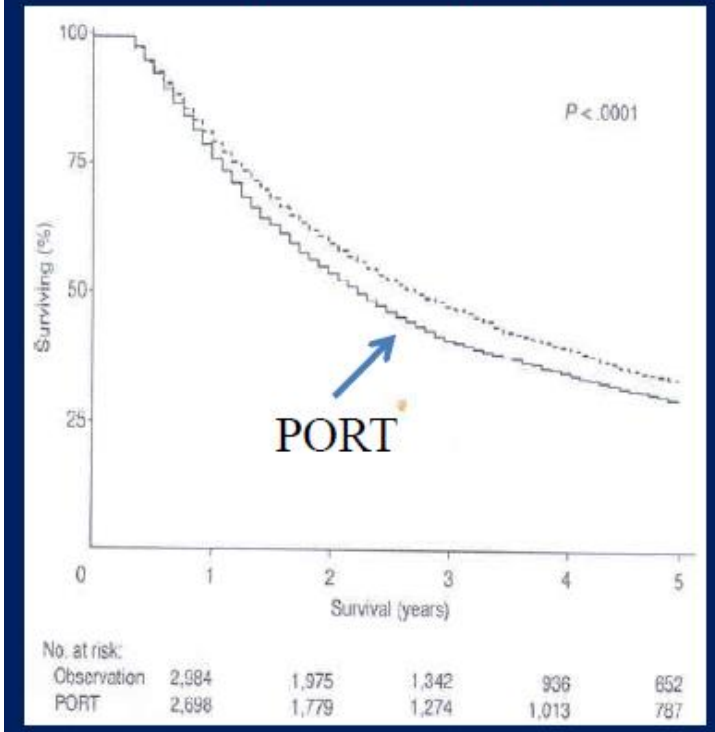
Over 70% had stage I disease where there was NO survival benefit
Survival gain for stage II and T3N1 disease

KDHAK Adjuvan Radyoterapi

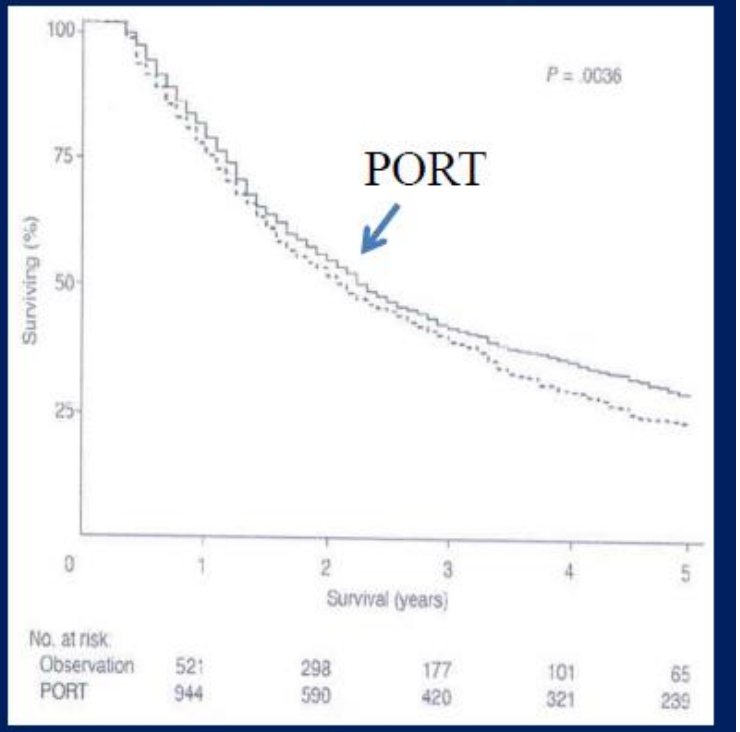
SEER data on PORT in NSCLC

Lally et al, JCO 2006;24:2998-3006

All patients (I-III)



N2 patients only

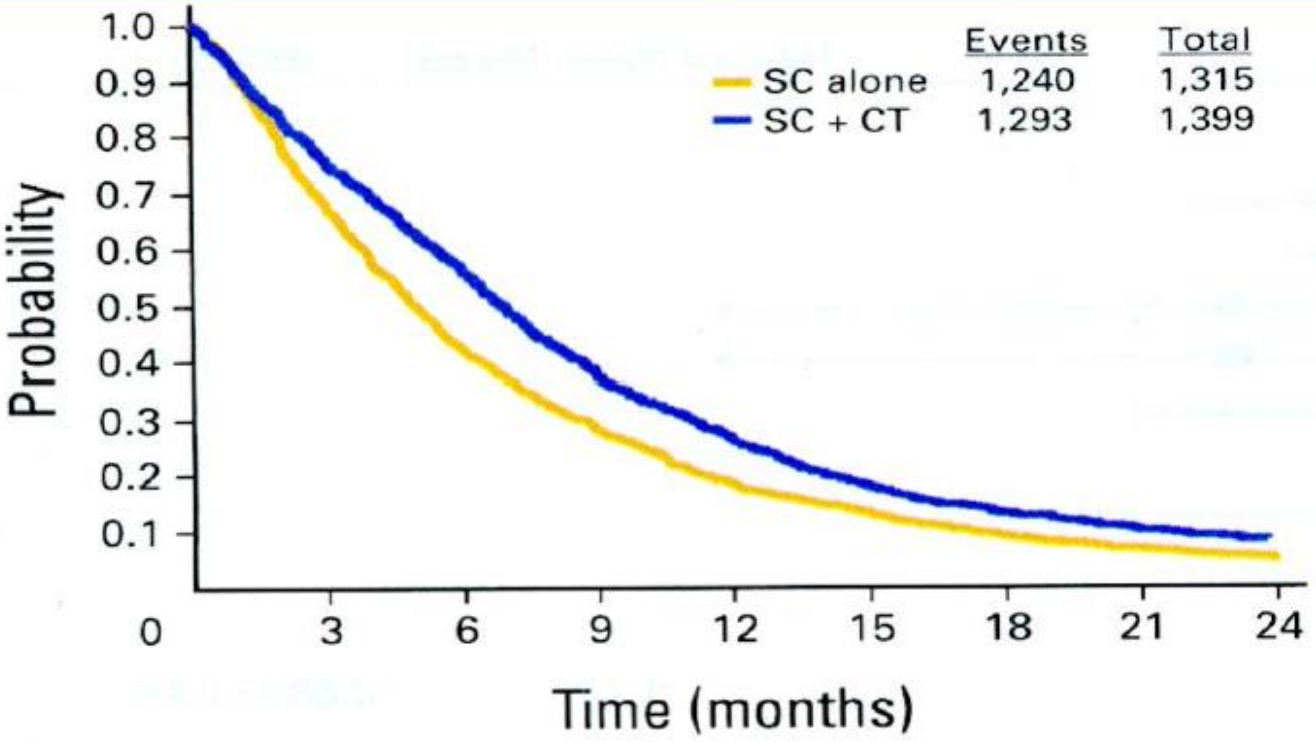


Most patients had not received adjuvant chemotherapy

Metastatik KHDAK Tedavi

Chemotherapy vs. Best supportive care

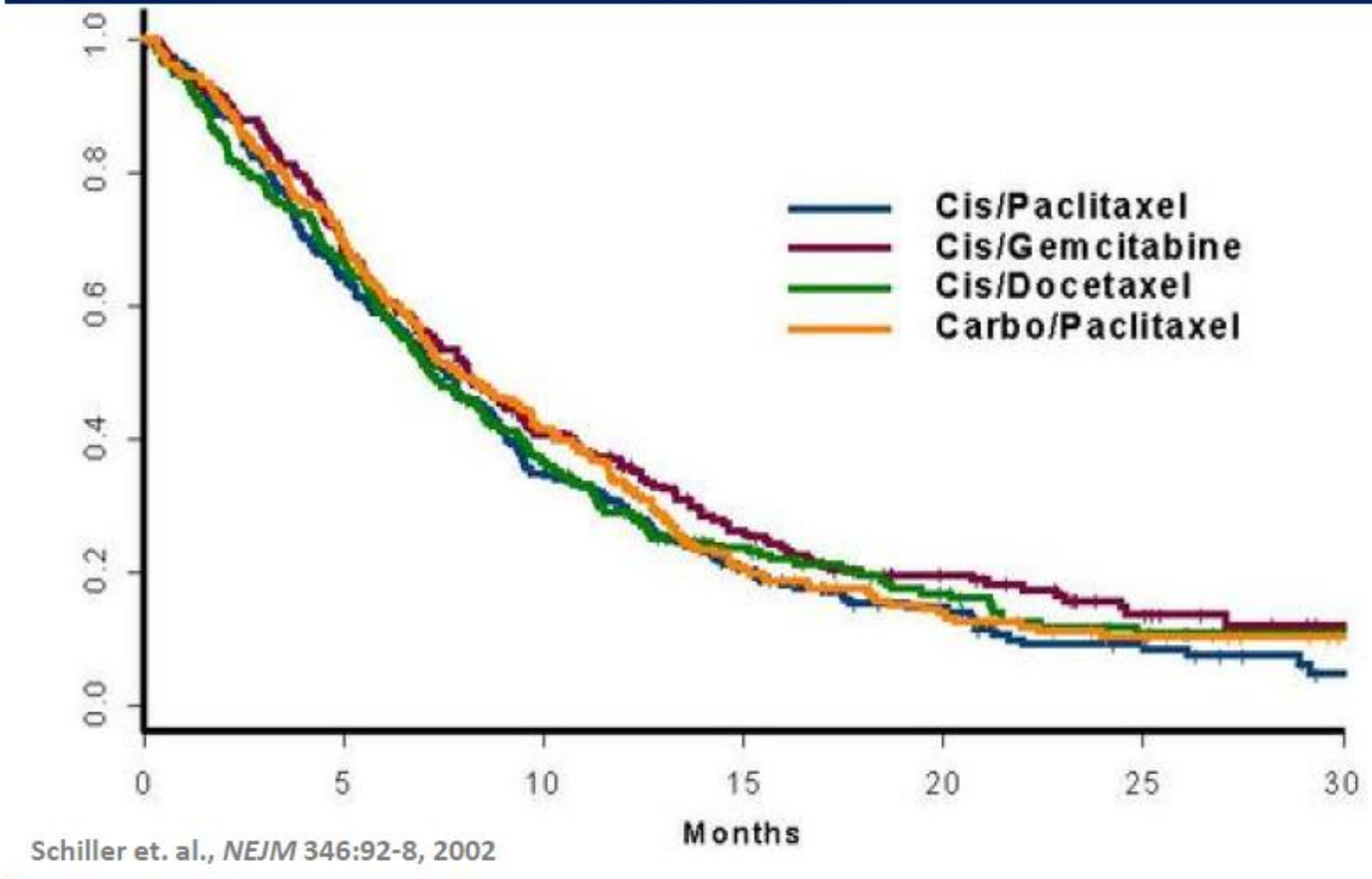
NSCLC Meta-Analyses Collaborative Group ; JCO 2008;26(28)



Patients at risk									
SC alone	1,315	884	552	363	231	161	107	77	55
SC + CT	1,399	1,052	779	519	349	233	165	115	91

Metastatik KHDAK Tedavi

Platinum-Doublets in stage IV NSCLC

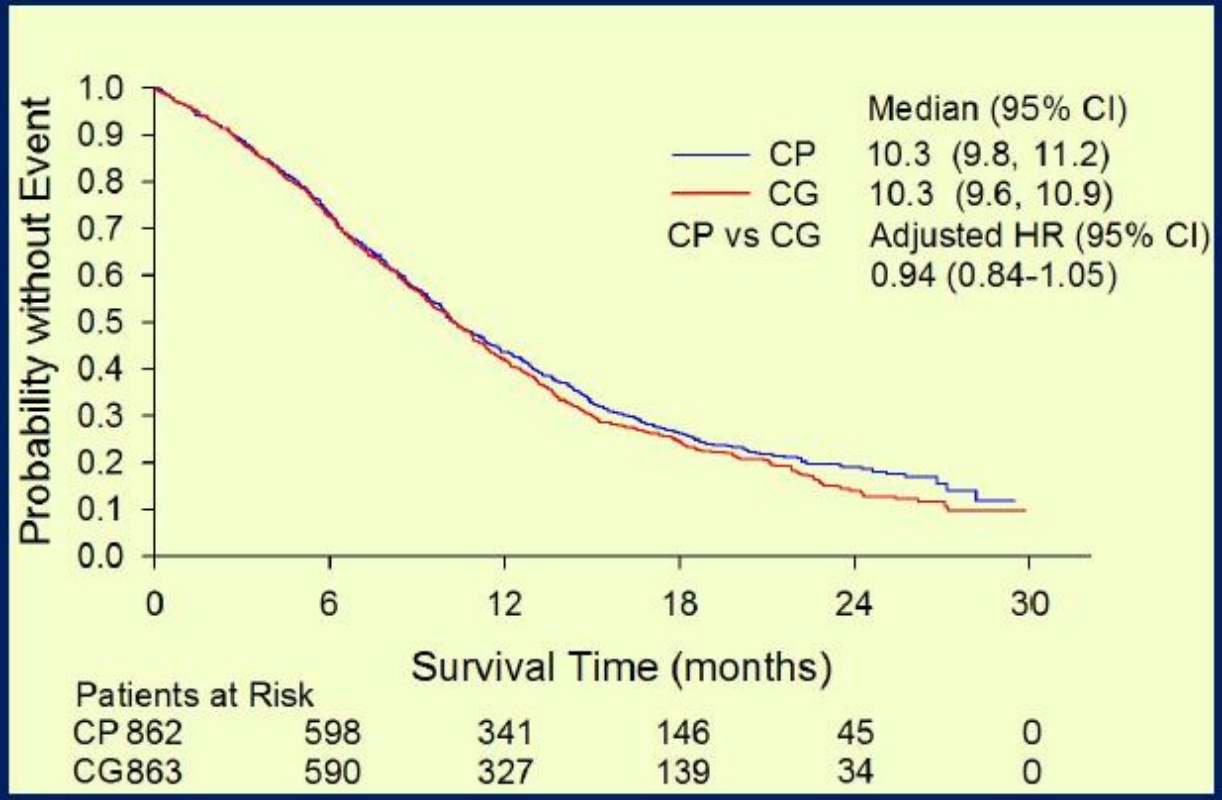


Schiller et. al., *NEJM* 346:92-8, 2002

Metastatik KHDAK Tedavi
Patolojik Alt Tipe Göre

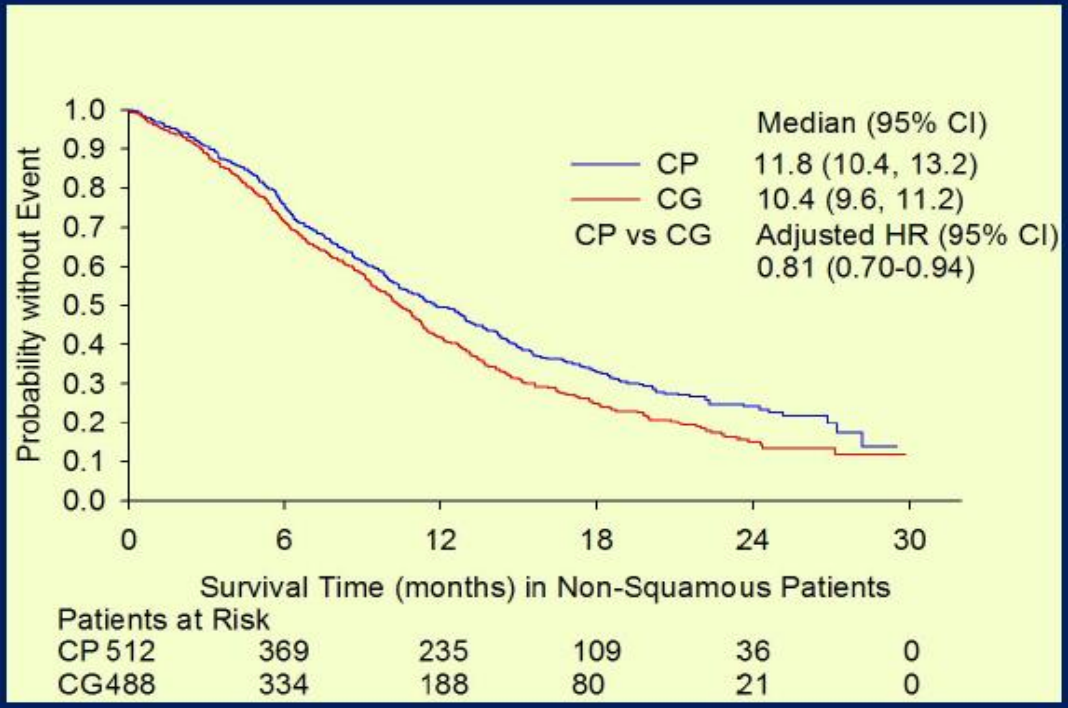
Cisplatin + Gemcitabine or Pemetrexed

Scagliotti et al, JCO 2008; 26(21): 3543-51



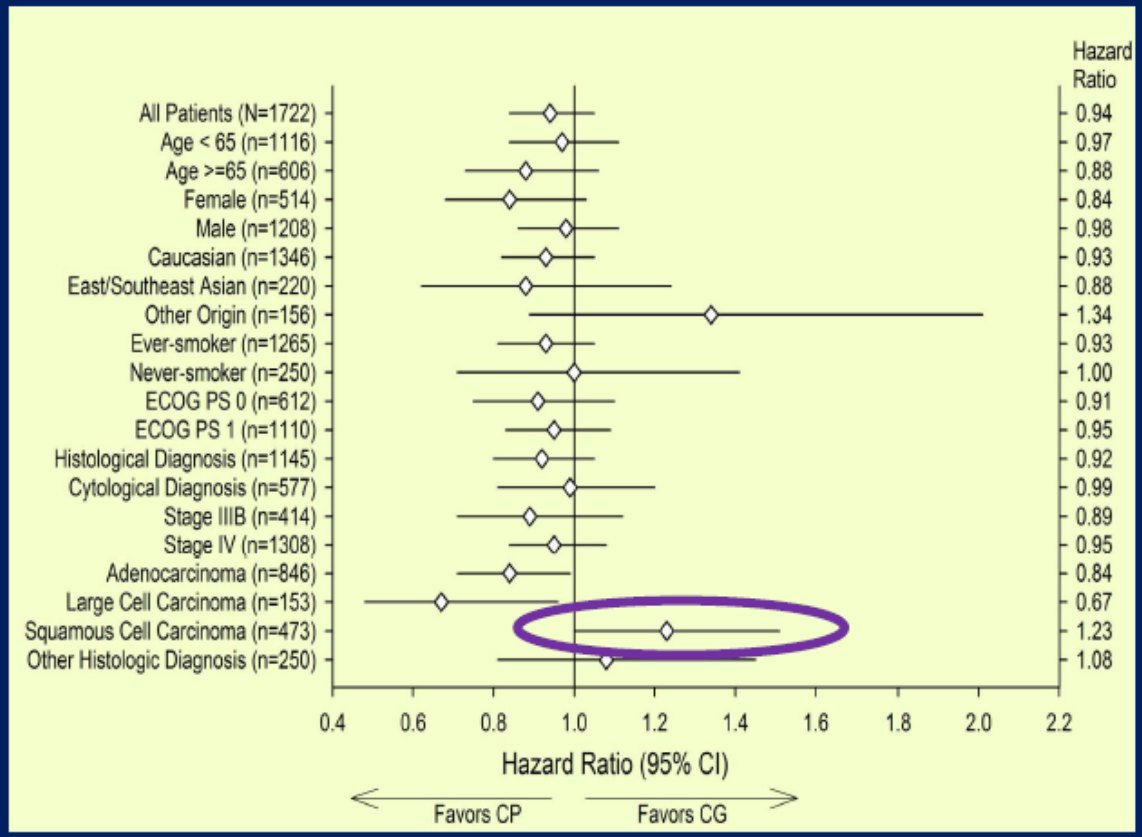
Metastatik KHDAK Tedavi
Patolojik Alt Tipe Göre

Cis/Pem favored in non-squamous



Metastatik KHDAK Tedavi Patolojik Alt Tipe Göre

Cis/Gem favored in squamous

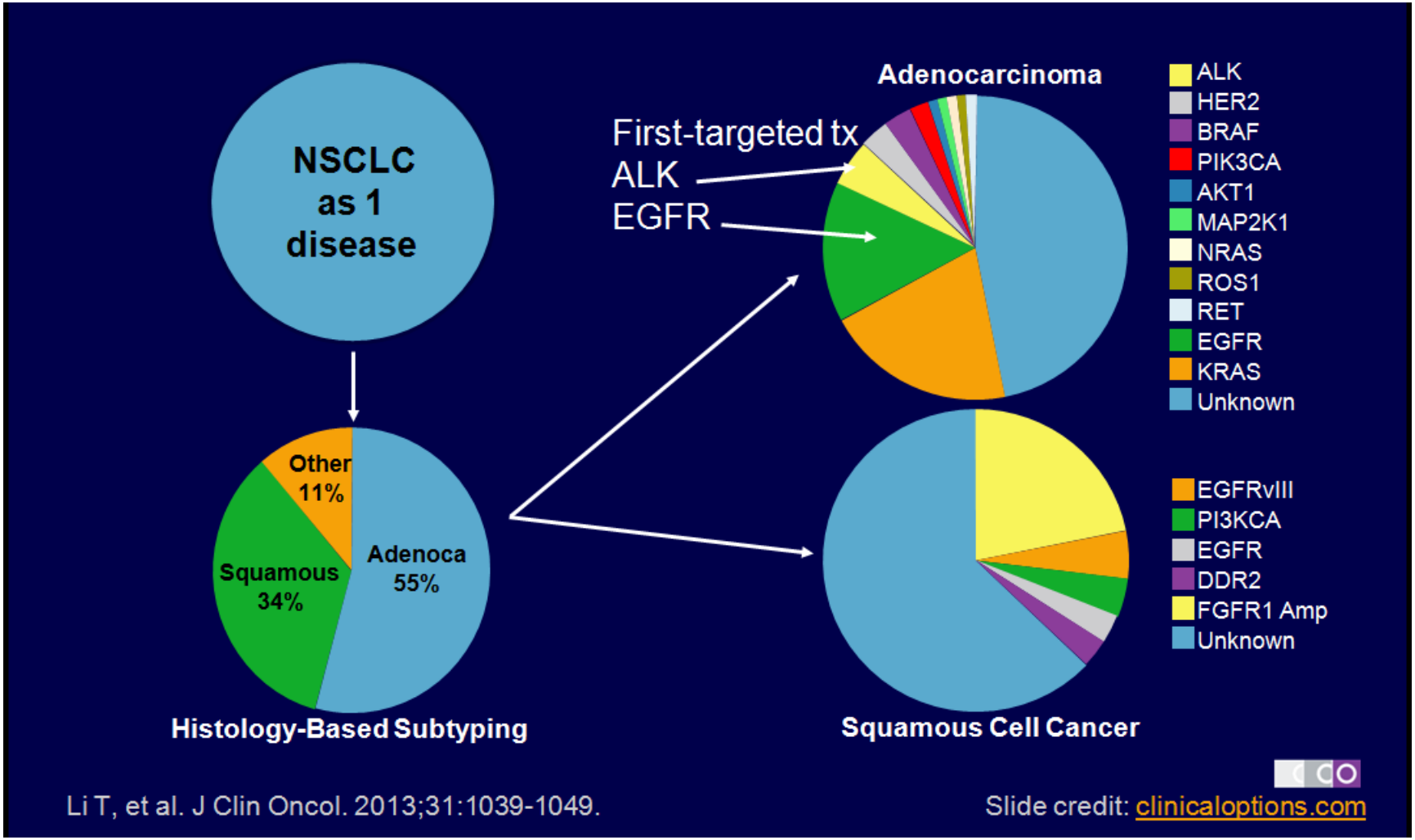


Metastatik KHDAK Tedavi

PLATİN BAZLI KEMOTERAPİK AJANLARIN

- Cevap oranları: %30–40
- Medyan sağkalım: 8–10 ay
- 1-yıllık sağkalım: %30–40

Metastatik KHDAK Tedavi
Hedefe Yönelik Tedaviler



Metastatik KHDAK
Hedefe Yönelik Tedaviler

Swanton C, Govindan R. N Engl J Med 2016;374:1864-1873

Alteration	Adeno	Squamous	Small Cell
p53 mutation	46%	91%	92%
RB mutation		7%	75%
Kras mutation	33%		
EGFR mutation	14%		
RAF mutation	10%		
MET mutation	8%		
NF1 mutation	11%		
PI3KCA mutation	7%	16%	
STK11 mutation	17%		
PTEN mutation		8%	5%
ALK translocation	3-8%		
ROS-1 translocation	2%		
RET translocation	1%		
MYC amplification			16%
CDKN2A amplification	20%	27%	

Lung Cancer Mutation Consortium I

- Goals: Run a panel of molecular tests on consecutive patients with advanced lung adenocarcinoma and then put as many patients with molecular drivers on molecular therapy to determine the value of the testing and treatment.

Lung Cancer Mutation Consortium I

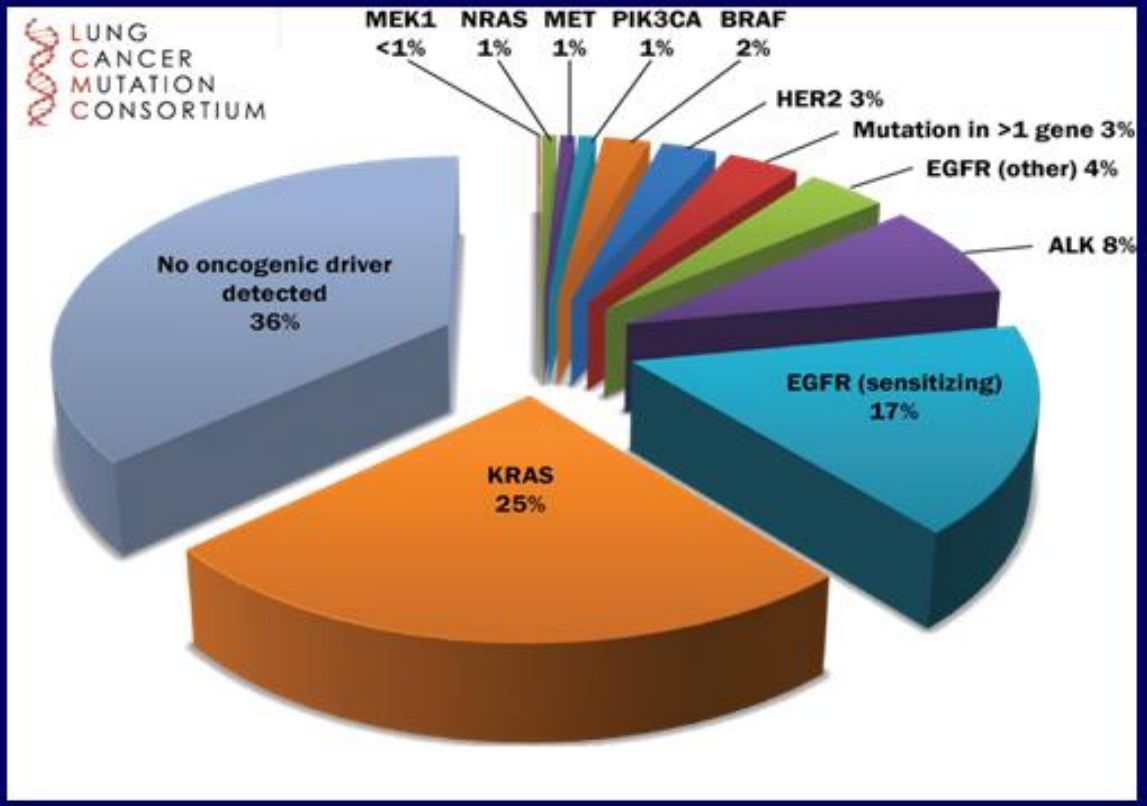
LCMC protocols linked to specific molecular lesions detected

Target	Agent	LCMC Lead
MEK1	GSK1120212 Trametinib	P Jänne
BRAF (V600E)	GSK2118434 Dabrafenib	B Johnson
BRAF (not V600E)	GSK1120212	P Jänne
HER2	Dacomitinib	M Kris
PIK3CA	BKM120	J Engelman
EGFR	Erlotinib + OSI 906 Erlotinib + MM 121	C Rudin L Sequist
KRAS *NRAS*	Tivantinib + Erlotinib Trametinib	J Schiller, P Jänne G Blumenschein
MET Amplification	Crizotinib	R Camidge
ALK	Crizotinib	R Camidge
ROS	Crizotinib	R Camidge

Metastatik KHDAK Hedefe Yönelik Tedaviler

Lung Cancer Mutation Consortium

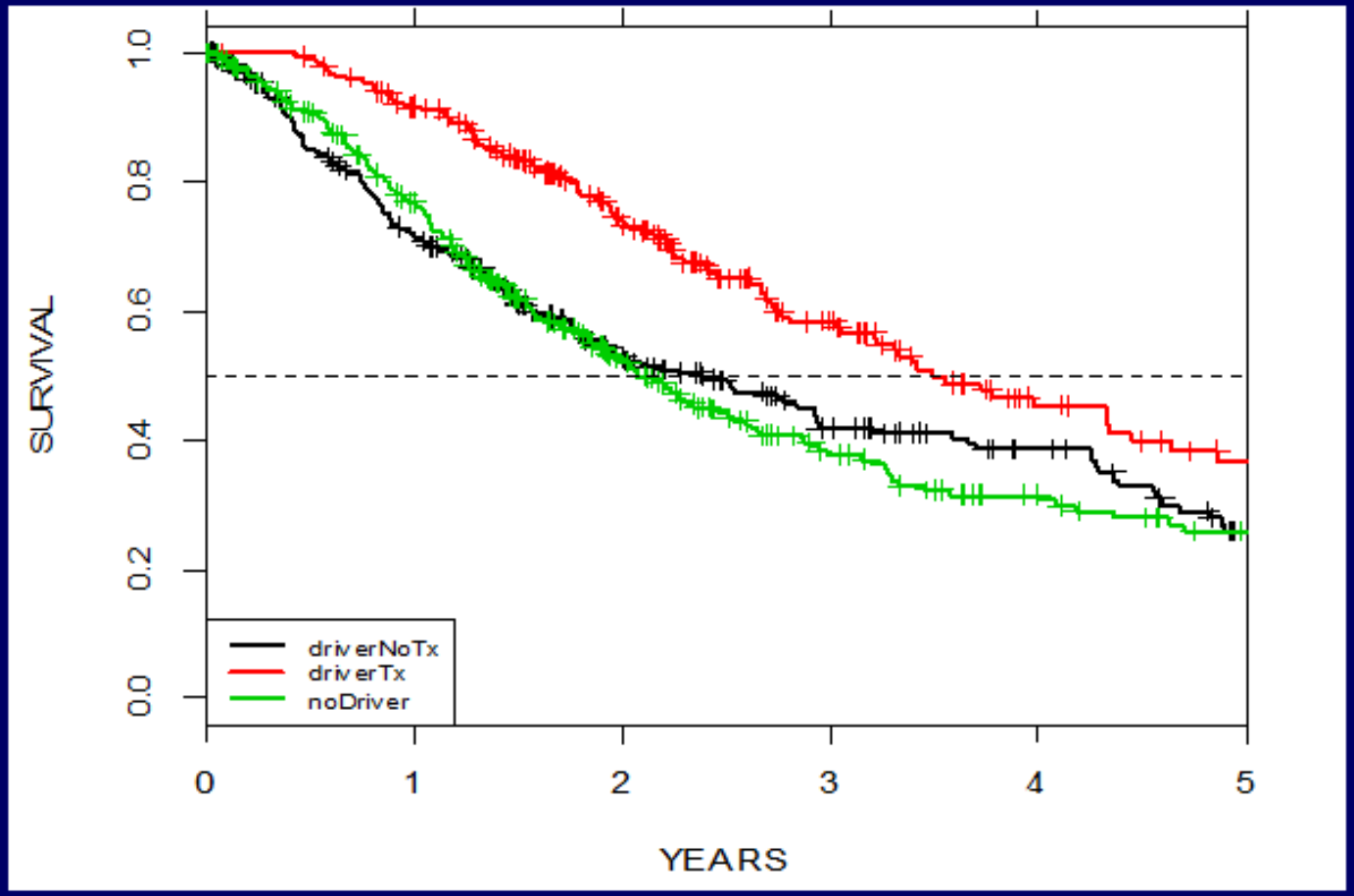
Incidence of Single Driver Mutations



Kris M, et al. *JAMA*. 2014 May 21; 311(19): 1998–2006.

Metastatik KHDAK Hedefe Yönelik Tedaviler

Lung Cancer Mutation Consortium I: Survival by Group

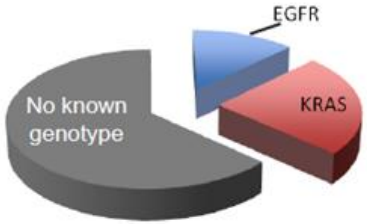


Kris M, et al. *JAMA*. 2014 May 21; 311(19): 1998–2006

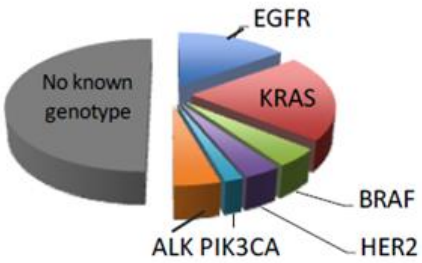
Metastatik KHDAK
Hedefe Yönelik Tedaviler

Akciğer Kanserinde Mutasyonlar

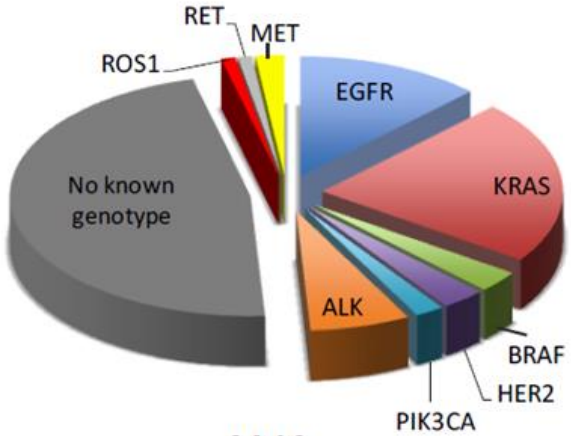
1984–2003



2004

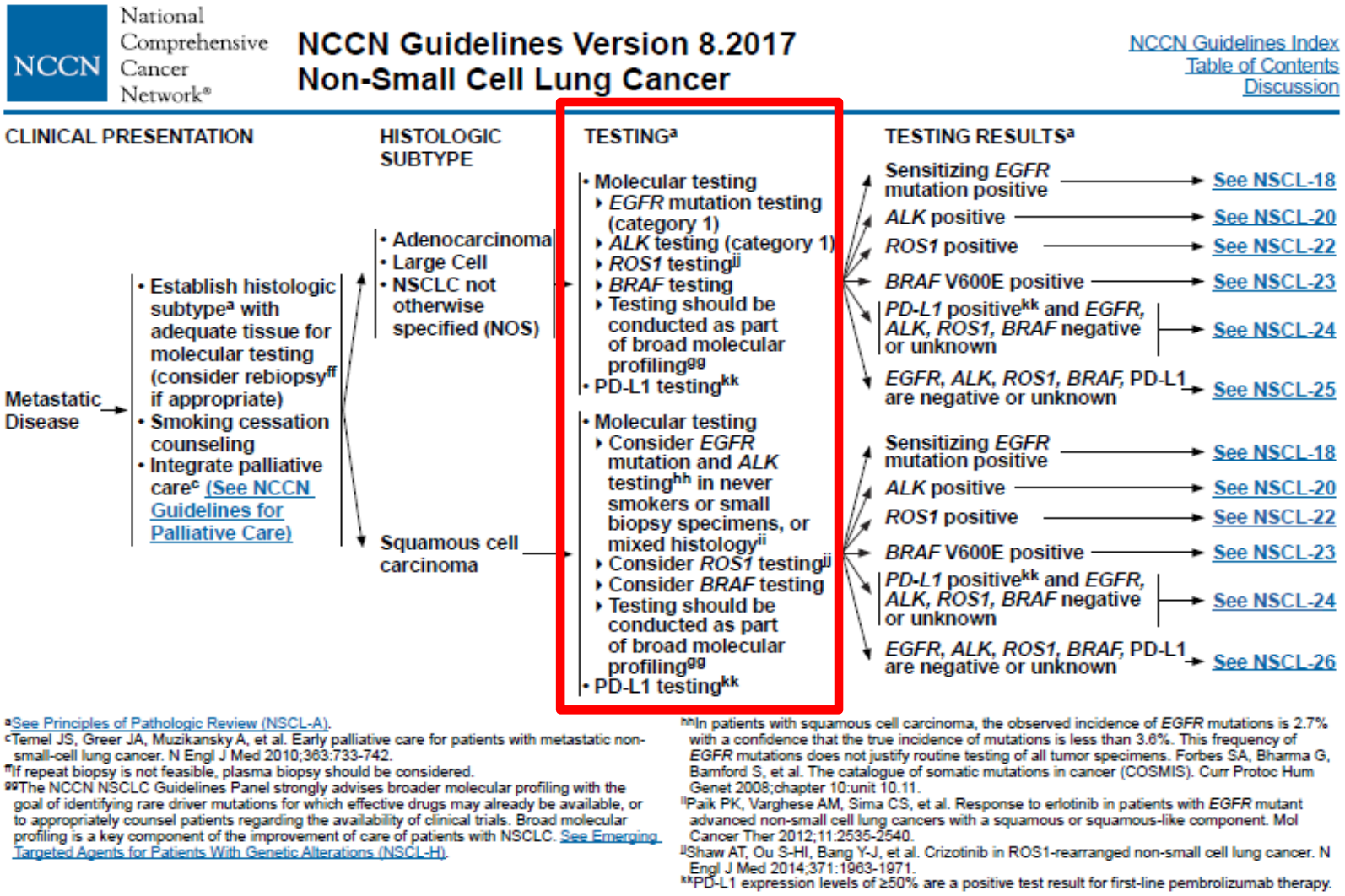


2009



2013

Metastatik KHDAK Hedefe Yönelik Tedaviler



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

[c] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.

[ff] If repeat biopsy is not feasible, plasma biopsy should be considered.

[gg] The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).

[hh] In patients with squamous cell carcinoma, the observed incidence of *EGFR* mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of *EGFR* mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.

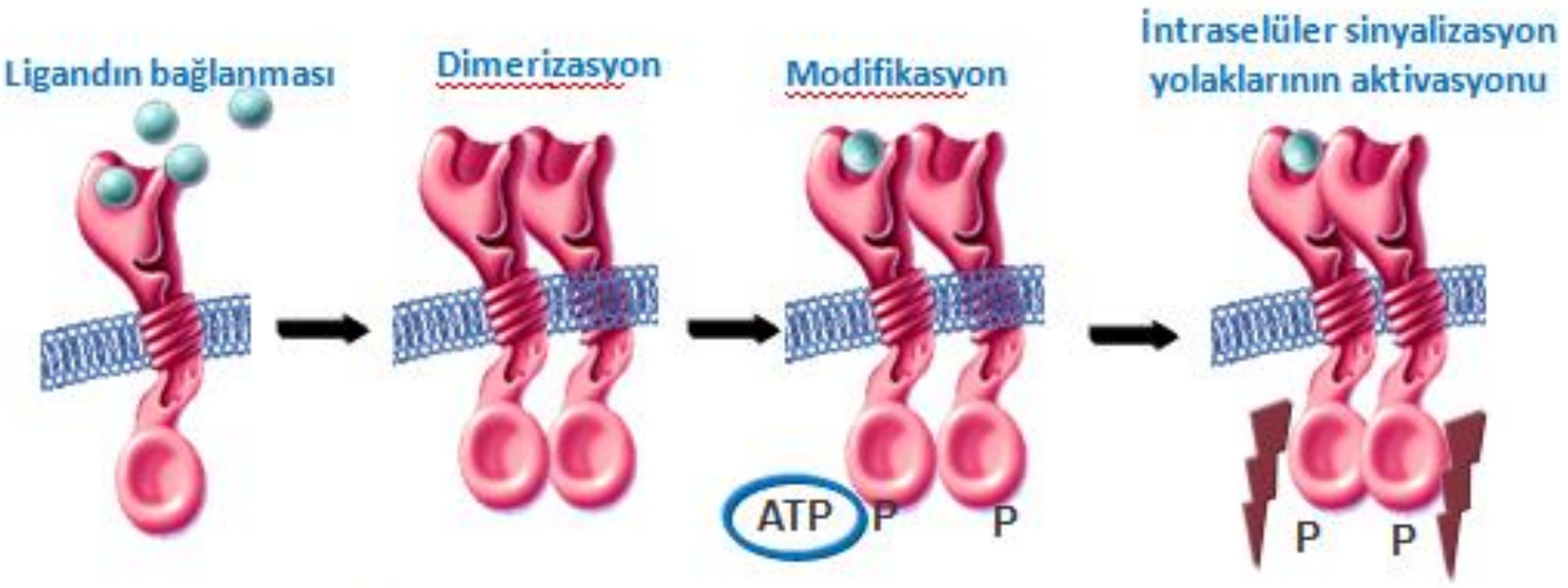
[ii] Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with *EGFR* mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther 2012;11:2535-2540.

[jj] Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.

[kk] PD-L1 expression levels of ≥50% are a positive test result for first-line pembrolizumab therapy.

Metastatik KHDAK Hedefe Yönelik Tedaviler

EGFR: Sinyalizasyon



Ekstraselüler bölgeye spesifik ligand bağlanır

Yapısal değişiklikler ve dimerizasyon meydana gelir

- Homodimerizasyon
- Heterodimerizasyon

Reseptörlerden birinin intraselüler TK bölgesi diğer reseptörün TK bölgesini fosforiller (ATP)

Proliferasyon, sağkalım, migrasyo adezyon ve diferansiyasyon

Metastatik KHDAK Hedefe Yönelik Tedaviler

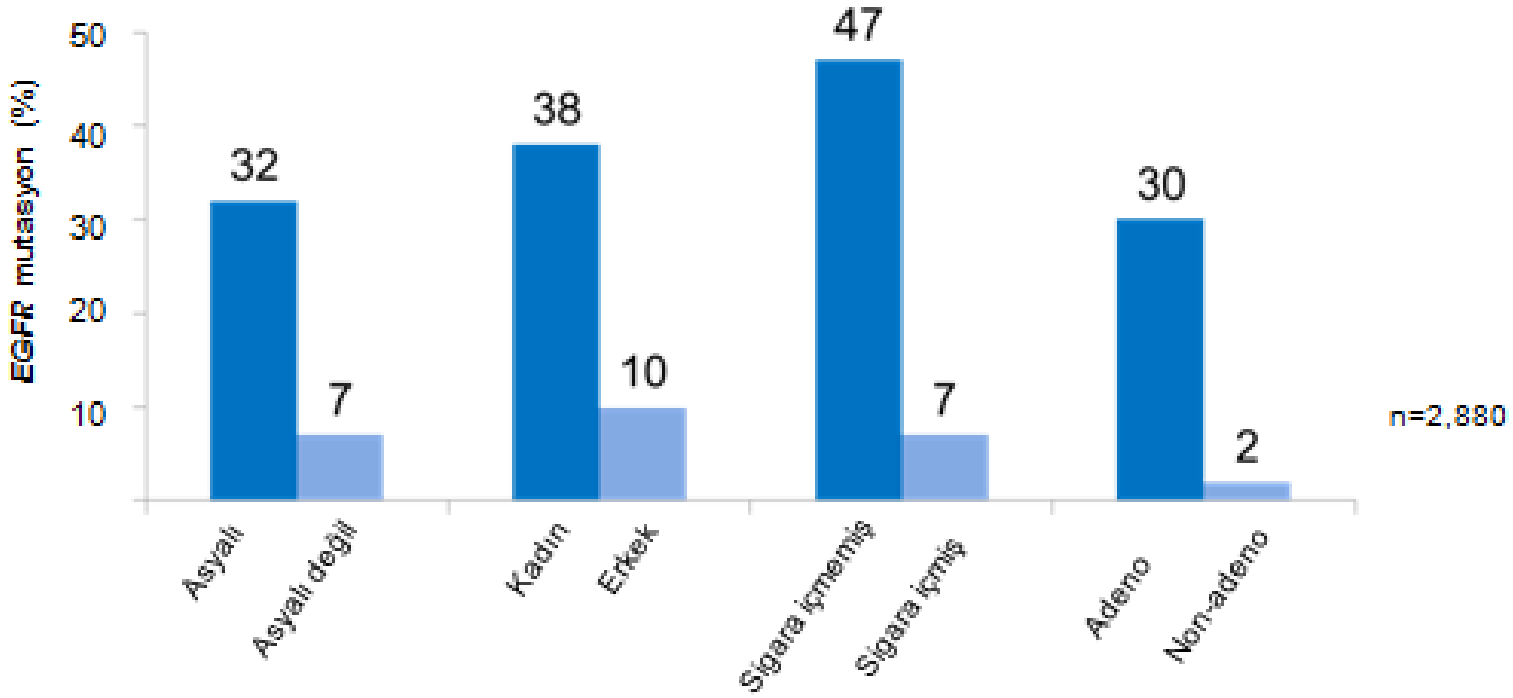
- Found in 10% to 30% of NSCLC pts[1]
- More common in neversmokers, adenocarcinomas, females, Asians[1,2]
- Predominantly located in *EGFR* exons 18-21[2]
  - ~ 85% of *EGFR* mutations are either deletions in exon 19 or a single-point mutation in exon 21 (L858R)
- Specific *EGFR* mutation identified is important
  - There are sensitive mutations, primary resistance mutations (often exon 20), and acquired resistance mutations (T790M)

1. Pao W, et al. J Clin Oncol. 2005;23:2556-2568.
2. Wu YL, et al. J Thorac Oncol. 2007;2:430-439.

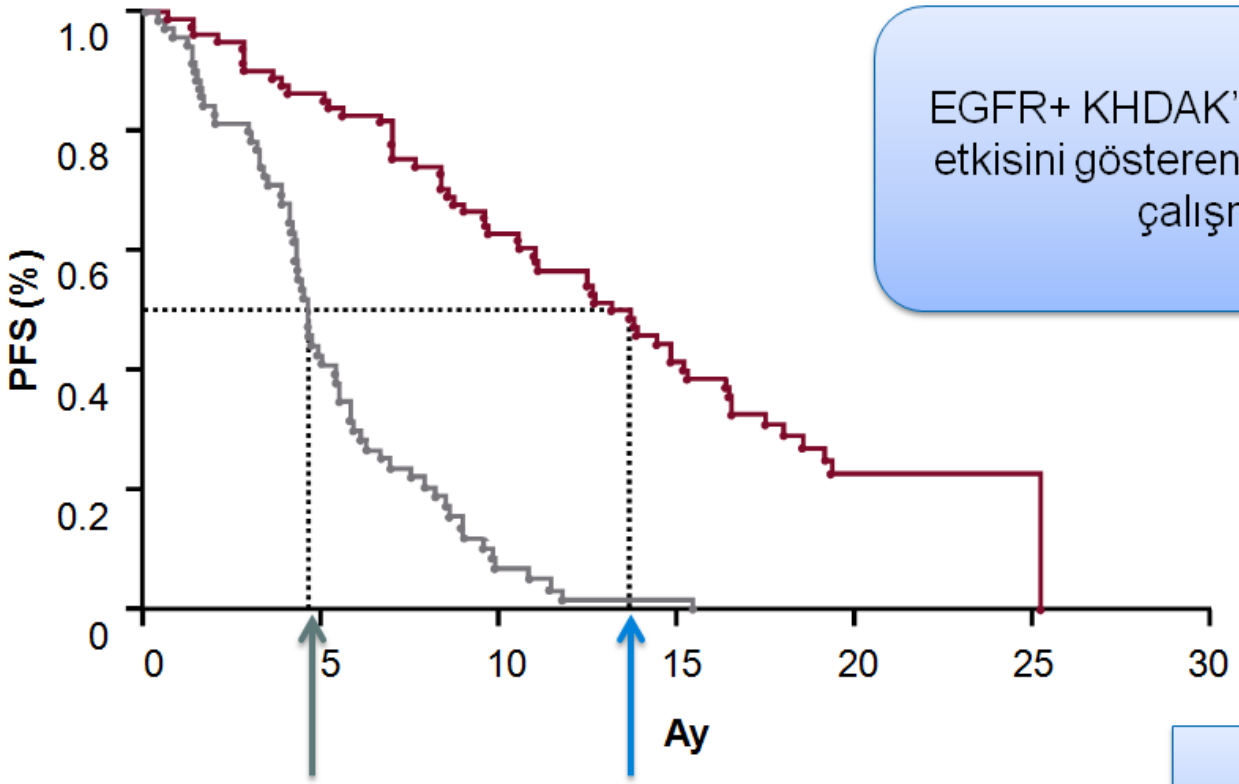
Metastatik KHDAK Hedefe Yönelik Tedaviler

EGFR & Hasta Özellikleri

Hastanın EGFR TKI almasına karar verilirken klinik karekteristikler kullanılmamalıdır



Metastatik KHDAK Hedefe Yönelik Tedaviler



EGFR+ KHDAK'de Erlotinib'in etkisini gösteren ilk prospektif çalışma

G/C medyan PFS: 4.6 ay

Erlotinib medyan PFS: **13.7 ay**

HR=0.16 p<0.0001

x3

OPTIMAL ÇALIŞMASI

Metastatik KHDAK Hedefe Yönelik Tedaviler

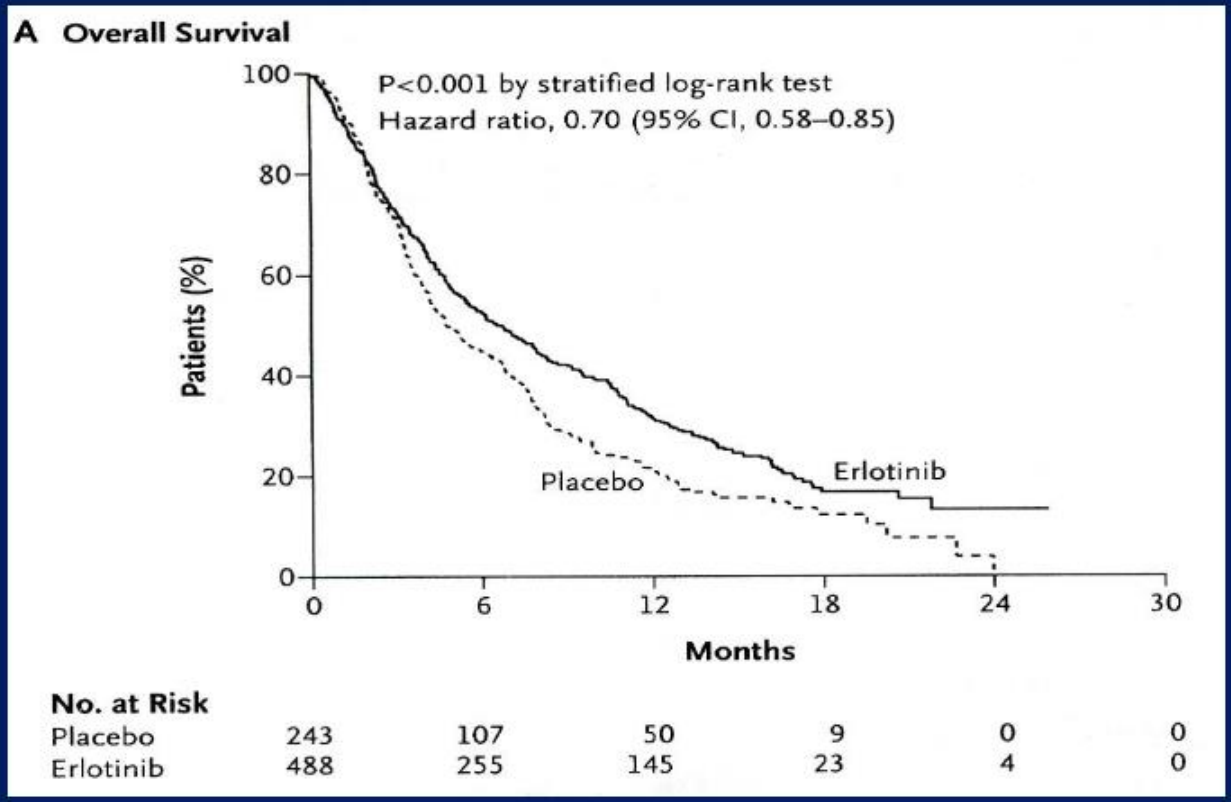
First line EGFR TKI vs. chemotherapy in EGFR mut + NSCLC

	RR (%)		Median PFS (mo)	
Trial	TKI	Chemo	TKI	Chemo
IPASS [Gefitinib]	71	47	9.5	6.3
First-SIGNAL [Gefitinib]	84	37	8.4	6.7
WJTOG [Gefitinib]	62	32	9.2	6.3
NEJ002 [Gefitinib]	73	30	10.8	5.4
OPTIMAL [Erlotinib]	83	36	13.7	4.6
EURTAC [Erlotinib]	58	15	9.7	5.2
LUX-Lung 3 [Afatinib]	56	22	11.1	6.9
LUX-Lung 6 [Afatinib]	67	23	11	5.6

Metastatik KHDAK Hedefe Yönelik Tedaviler

2nd or 3rd line: Erlotinib vs. Placebo

Shepherd FA, et al.: NEJM (353) 2005; 123-32



Metastatik KHDAK Hedefe Yönelik Tedaviler

Summary of EGFR Tki vs. Chemotherapy 2nd line in EGFR WT

Study	PFS Chemo	PFS TKI	OS Chemo	OS TKI
INTEREST	2.6 mos	1.7 mos	6 mos	6.4 mos
TAILOR	3.4 mos	2.4 mos	8.2 mos	5.4 mos
DELTA	2.9 mos	1.3 mos	10.1 mos	9 mos

Kim et al, The Lancet Oncol 2008;372; Douillard et al. JCO 2010;28; Grassino et al, Lancet 2013; Kawaguchi T et al. JCO 2014;32:1902-08.

Kraniyal Metastatik KHDAK Hedefe Yönelik Tedaviler

Trials evaluating the activity of 1st and 2nd Generation EGFR TKIs in Brain Metastases

Treatment	N	Selection	Brain RR	OS	Reference
Erlotinib	17	*EGFR* mutated	82%	NS	Porta *et al.* (7)
Gefitinib or erlotinib	28	*EGFR* mutated	83%	15.9 months	Park *et al.* (8)
Gefitinib	9	*EGFR* mutated	89%	NS	Li (19)
Gefitinib or erlotinib	23	Asian never-smokers	74%	18.8 months	Kim *et al.* (20)
Erlotinib	40	Unselected	86%	11.8 months	Welsh *et al.* (21)
Gefitinib	41	*EGFR* mutated	88%	21.9 months	Iuchi *et al.* (22)
Afatinib	32	*EGFR* mutated, TKI-pretreated	35%	9.8 months	Hoffknecht *et al.* (23)

NS: Not stated; EGFR: epidermal growth factor receptors; OS: overall survival; RR: response rate.

- EGFR TKIs can cross the blood brain barrier but concentrations may be low
- Due to this though, brain mets in EGFR mutant disease may not develop secondary resistance mutations despite their occurrence elsewhere in the body

Dempke W et al Anticancer Research 35: 5797-5806

Kraniyal Metastatik KHDAK Hedefe Yönelik Tedaviler

CSF penetration of 1st and 2nd generation EGFR TKIs

- Mixed data — Higher CSF concentration may be achieved with erlotinib compared to gefitinib due to higher peak plasma concentrations. However, this has not borne an increase in responses.
- Erlotinib CSF levels ~ 5% of plasma levels but adequate for receptor inhibition
- Gefitinib CSF levels ~1% of plasma levels considered inadequate for inhibition
- Afatinib data are limited
- Osimertinib: ~ 10-fold higher levels in CNS than gefitinib in preclinical models and evidence of CNS activity in phase 1 trial

Dempke W et al Anticancer Research 35: 5797-5806
Kim D Ann Oncol 25(Suppl 4) iv146-164, 2014, Janne P et al ASCO 2015

Kraniyal Metastatik KHDAK Hedefe Yönelik Tedaviler

What about combining EGFR TKI with radiation?

- Phase 2 study
  - Erlotinib x 1 wk 150 mg PO q day x 1 wk followed by concurrent WBRT to 35 Gy followed by erlotinib maintenance.
  - Results — EGFR mutated (N = 9) RR 89% and Median OS 19.1 months.
  - No neurotoxicity of grade 4 events.
- Phase 1 Study
  - Increase cerebral efficacy is to boost exposure by increasing the erlotinib dose
  - Twice weekly pulse dose (1200 mg days 1-2) and low daily dose (50 mg days 3-7)
  - 12 pts with CNS disease and none developed progressive disease

Welch JW et al JCO 31:895-902, 2013, Yu HA et al JCO 33(Suppl15s): 426s, 2015

Metastatik KHDAK Hedefe Yönelik Tedaviler

MADRID 2017 ESMO congress

OSIMERTINIB VS STANDARD-OF-CARE EGFR-TKI AS FIRST-LINE TREATMENT IN PATIENTS WITH EGFRm ADVANCED NSCLC: FLAURA

Ramalingam SS[1], Reungwetwattana T[2], Chewaskulyong B[3], Dechaphunkul A[4], Lee KH[5], Imamura F[6], Nogami N[7], Ohe Y[8], Cheng Y[9], Cho BC[10], Cho EK[11], Vansteenkiste J[12], Voon PJ[13], Zhou C[14], Gray JE[15], Hodge R[16], Rukazenkov Y[16], Soria JC[17]

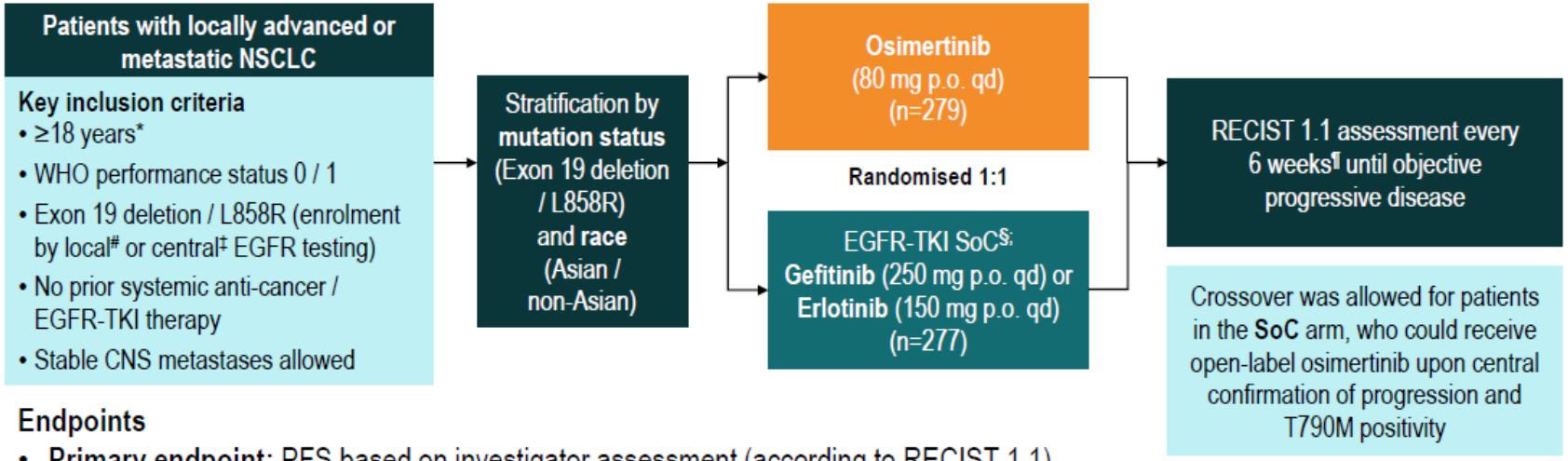
[1]Emory University, Winship Cancer Institute, Atlanta, GA, USA; [2]Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [3]Oncology Unit, Department of Medicine, Chiang Mai University, Chiang Mai, Thailand; [4]Prince of Songkla University, Songkhla, Hat-Yai, Thailand; [5]Division of Medical Oncology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheong-ju, Korea; [6]Department of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan; [7]Department of Thoracic Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan; [8]Department of Internal Medicine, National Cancer Center Hospital, Tokyo, Japan; [9]Jilin Provincial Cancer Hospital, Changchun, China; [10]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [11]Division of Hematology and Oncology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, Republic of Korea; [12]University Hospital KU Leuven, Leuven, Belgium; [13]Hospital Umum Sarawak, Kuching, Malaysia; [14]Pulmonary Hospital of Tongji University, Shanghai, China; [15]Department of Thoracic Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; [16]AstraZeneca, Cambridge, United Kingdom; [17]Gustave Roussy Cancer Campus and University Paris-Sud, Villejuif, France

Presented by SS Ramalingam at the European Society of Medical Oncology Congress 2017

Metastatik KHDAK Hedefe Yönelik Tedaviler

MADRID 2017 ESMO congress

FLAURA DOUBLE-BLIND STUDY DESIGN



Endpoints

- **Primary endpoint**: PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints**: objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

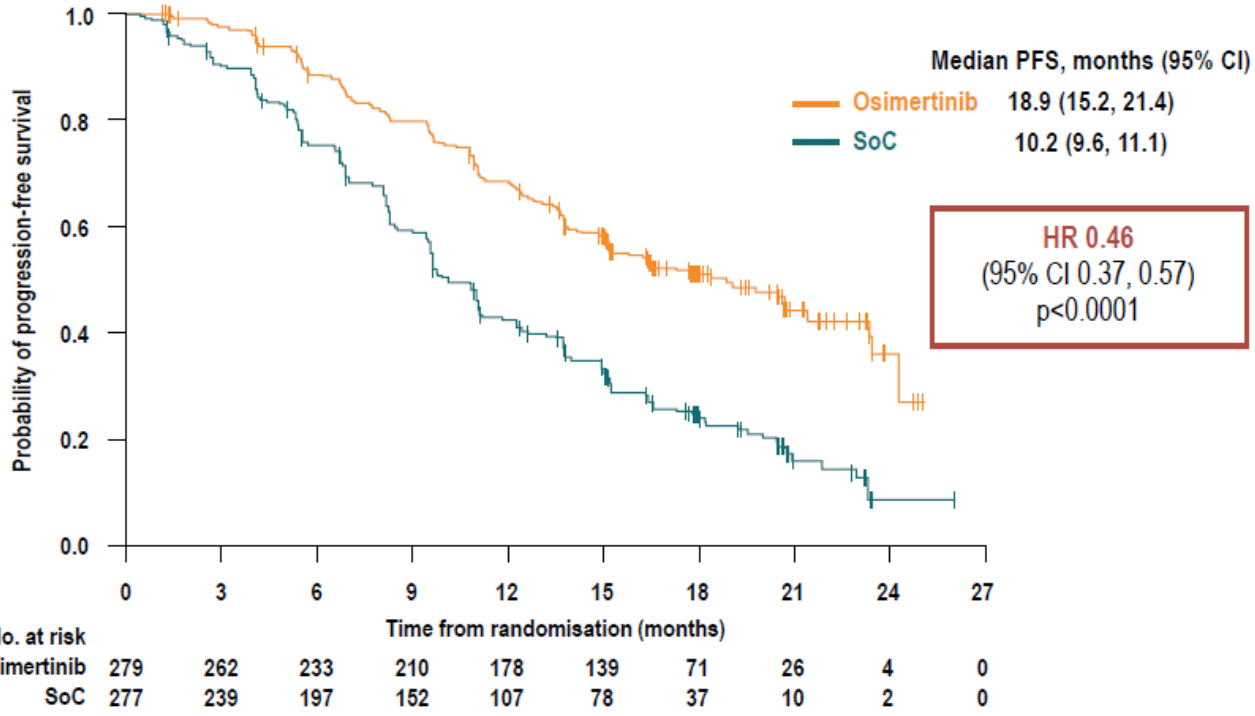
FLAURA data cut-off: 12 June 2017; NCT02296125
*≥20 years in Japan; #With central laboratory assessment performed for sensitivity; ‡cobas EGFR Mutation Test (Roche Molecular Systems); §Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; ¶Every 12 weeks after 18 months
CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; p.o., orally; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; qd, once daily; SoC, standard-of-care; TKI, tyrosine kinase inhibitor; WHO, World Health Organization

Metastatik KHDAK Hedefe Yönelik Tedaviler

MADRID 2017 ESMO congress

PRIMARY ENDPOINT: PFS BY INVESTIGATOR ASSESSMENT

342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)

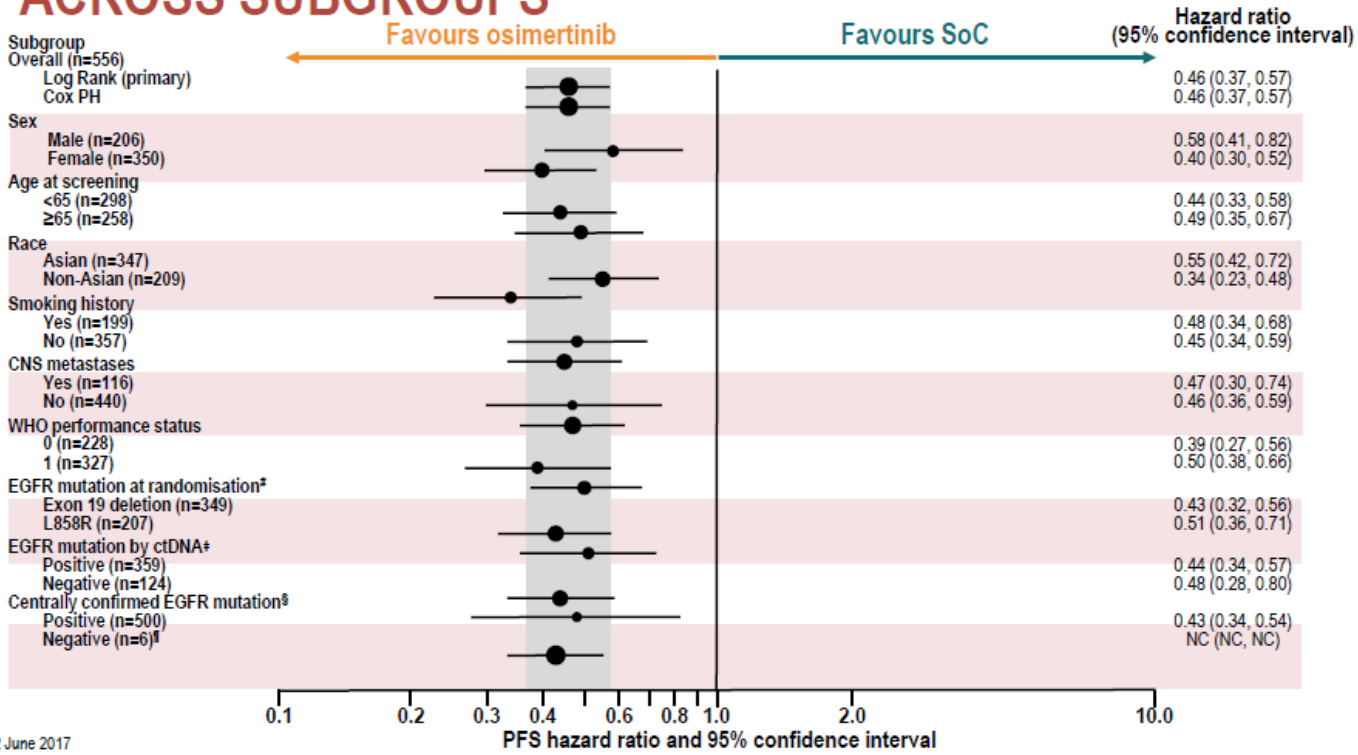


LAURA data cut-off: 12 June 2017
ick marks indicate censored data;
I, confidence interval; DCO, data cut-off; HR, hazard ratio; SoC, standard-of-care; PFS, progression-free survival

Metastatik KHDAK Hedefe Yönelik Tedaviler

MADRID 2017 ESMO congress

PFS* ACROSS SUBGROUPS



FLAURA data cut-off: 12 June 2017

Hazard ratio <1 implies a lower risk of progression on osimertinib 80 mg. Size of circle is proportional to the number of events

*By Investigator assessment; ‡Local or central test; §Result missing for 36 patients in the osimertinib arm and 37 patients in the SoC arm; ¶Result missing for 21 patients in the osimertinib arm and 29 patients in the SoC arm; ¶Subgroup categories with less than 20 events were excluded from the analysis

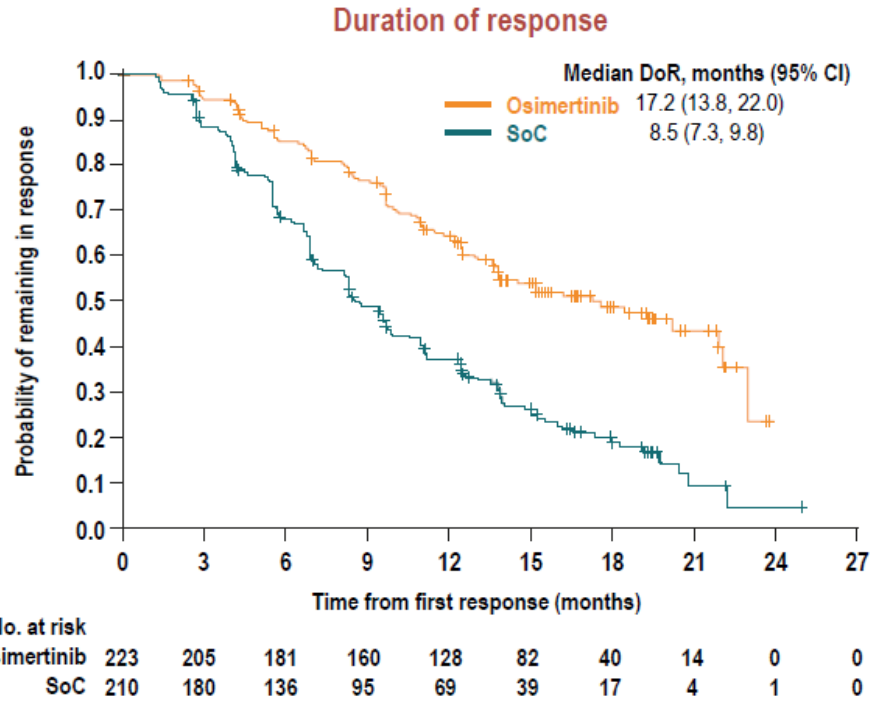
CNS, central nervous system; ctDNA, circulating tumour DNA; EGFR, epidermal growth factor receptor; PFS, progression-free survival; SoC, standard-of-care; WHO, World Health Organization

Metastatik KHDAK Hedefe Yönelik Tedaviler

MADRID 2017 ESMO congress

OBJECTIVE RESPONSE RATE*

	Osimertinib (n=279)	SoC (n=277)
ORR (95% CI)	80% (75, 85)	76% (70, 81)
Odds ratio# (95% CI)	1.28 (0.85, 1.93); p=0.2335	
Complete response‡, n (%)	7 (3)	4 (1)
Partial response‡, n (%)	216 (77)	206 (74)
Stable disease ≥6 weeks, n (%)	47 (17)	46 (17)
Progression, n (%)	3 (1)	14 (5)
Not evaluable, n (%)	6 (2)	7 (3)
Estimated remaining in response§, (95% CI)		
12 months	64% (58, 71)	37% (31, 44)
18 months	49% (41, 56)	19% (13, 26)



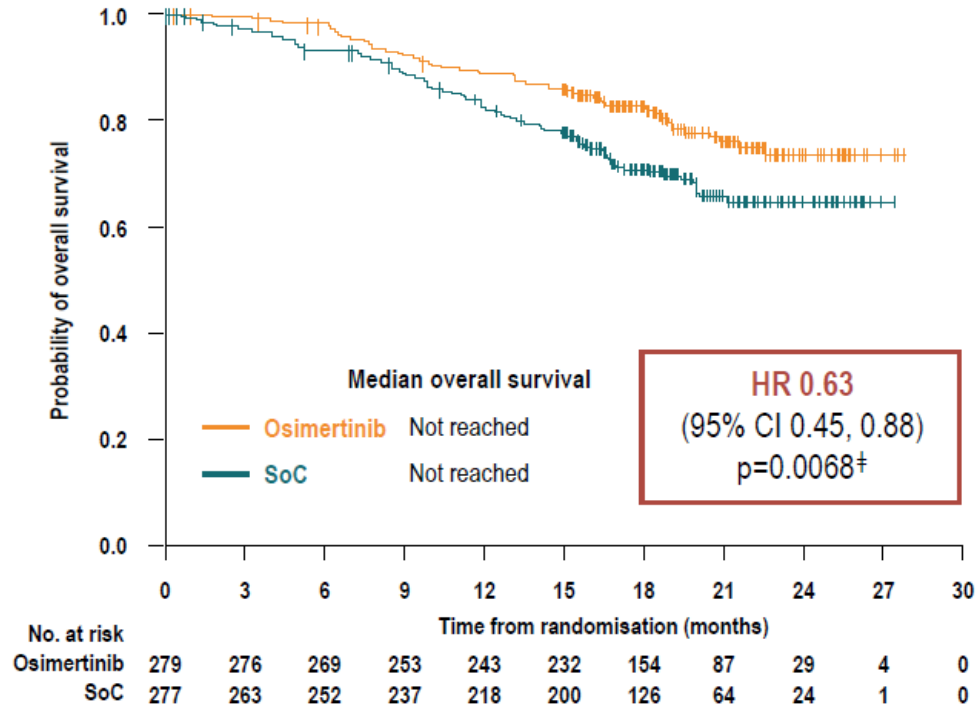
FLAURA data cut-off: 12 June 2017
Tick marks indicate censored data
*By investigator assessment #Analysis performed using a logistic regression stratified by race (Asian versus Non-Asian) and mutation type (Exon 19 deletion versus L858R); ‡Response did not require confirmation; §Calculated using Kaplan-Meier approach
CI, confidence interval; DoR, duration of response; ORR, objective response rate; SoC, standard-of-care

Metastatik KHDAK Hedefe Yönelik Tedaviler

MADRID 2017 ESMO congress

OVERALL SURVIVAL INTERIM ANALYSIS

141 deaths in 556 patients at DCO: 25% maturity; osimertinib: 58 deaths (21%), SoC: 83 deaths (30%)



‡A p-value of <0.0015 was required for statistical significance at current maturity

FLAURA data cut-off: 12 June 2017; Tick marks indicate censored data
CI, confidence interval; DCO, data cut-off; HR, hazard ratio; SoC, standard-of-care

Metastatik KHDAK Hedefe Yönelik Tedaviler

MADRID 2017 ESMO congress

FLAURA SAFETY SUMMARY

AE, any cause*, n (%)	Osimertinib (n=279)	SoC (n=277)
Any AE	273 (98)	271 (98)
Any AE Grade ≥3	94 (34)	124 (45)
Any AE leading to death	6 (2)	10 (4)
Any serious AE	60 (22)	70 (25)
Any AE leading to discontinuation	37 (13)	49 (18)
AE, possibly causally related#, n (%)		
Any AE	253 (91)	255 (92)
Any AE Grade ≥3	49 (18)	78 (28)
Any AE leading to death	0	1 (<1)
Any serious AE	22 (8)	23 (8)

FLAURA data cut-off: 12 June 2017

*Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category counted once in each of those categories; #As assessed by the investigator. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication

AE, adverse event; SoC, standard-of-care

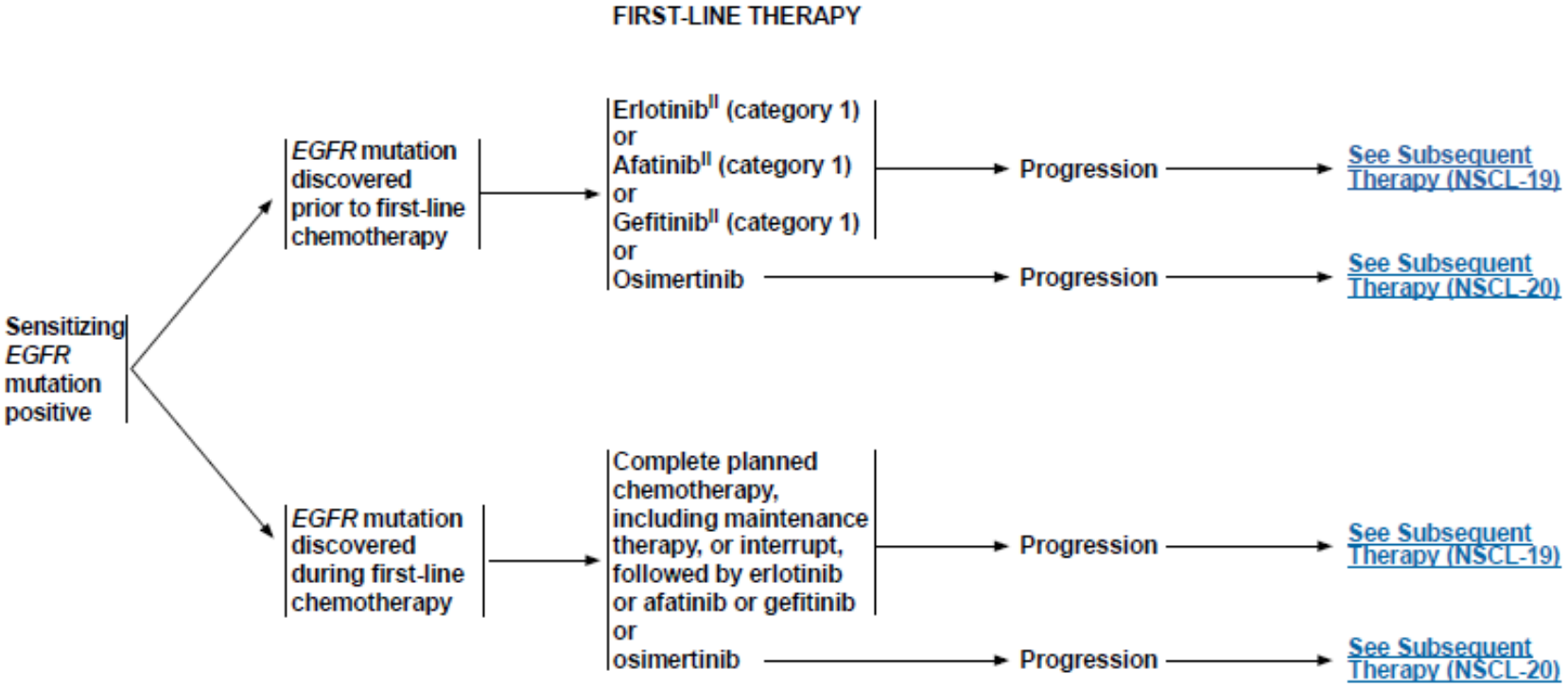
Metastatik KHDAK Hedefe Yönelik Tedaviler

National Comprehensive Cancer Network®

NCCN Guidelines Version 9.2017
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SENSITIZING EGFR MUTATION POSITIVE[a]



Metastatik KHDAK Hedefe Yönelik Tedaviler Direnç Mekanizmaları

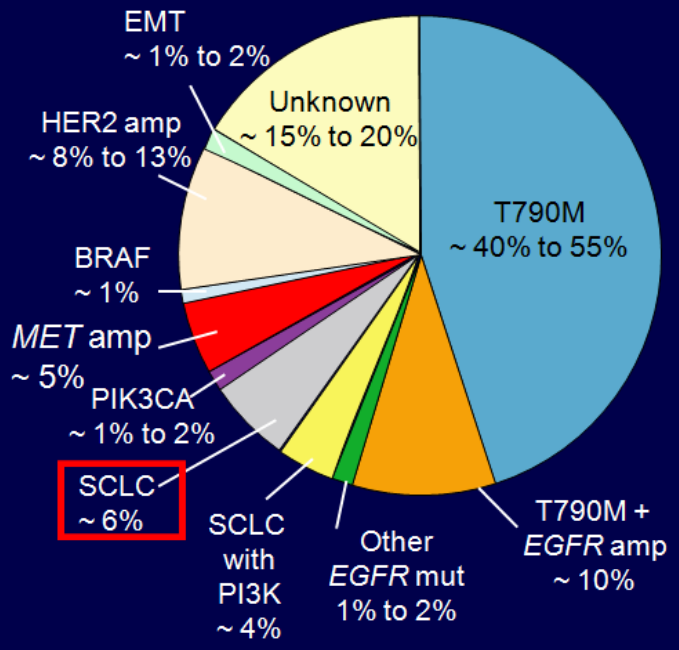
Disease Progression on EGFR TKI in NSCLC With *EGFR* Sensitizing Mutations

PD: Clinical characteristics

- Rapid global progression
- Slow growth globally
- Growth in several areas, but not all

PD: Molecular characteristics

- Unknown (other pathways)
- *EGFR* T790M (exon 20)
- *MET* amplification
- PIK3CA

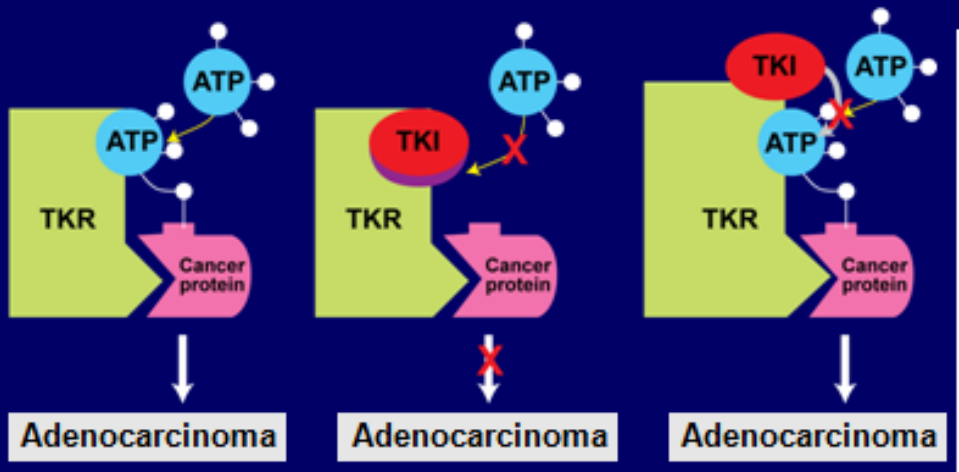


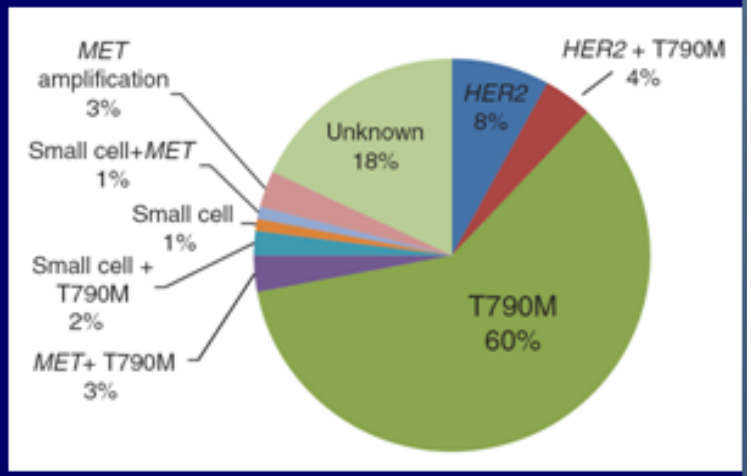
Camidge DR, et al. Nat Rev Clin Oncol. 2014;11:473-481.

Slide credit: clinicaloptions.com

Metastatik KHDAK Hedefe Yönelik Tedaviler
Direnç Mekanizmaları

Tyrosine Kinase Inhibitor Resistance





Metastatik KHDAK Hedefe Yönelik Tedaviler
Direnç Mekanizmaları

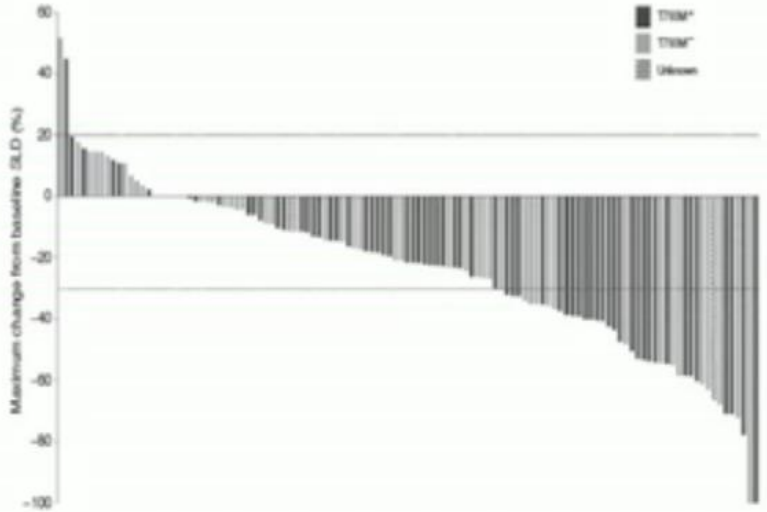
EGFR resistance

Tan et al, JTO 2016;11:946-963

- **T790M in 50-60% of patients**
- Bypass pathways:
  - MET amplification (5-30%)
  - HER-2 amplification (12%)
  - PI3KCA mutation (5%)
  - BRAF mutation (1%)
  - Others (e.g. EMT, AXL overexpression)

Metastatik KHDAK Hedefe Yönelik Tedaviler
Yeni Moleküler

Afatinib + Cetuximab in EGFR TKI Resistant Disease



RESULTS

MTD – Afatinib 40 mg PO q day
+ Cetuximab 500 mg/m^2 q 2 wks

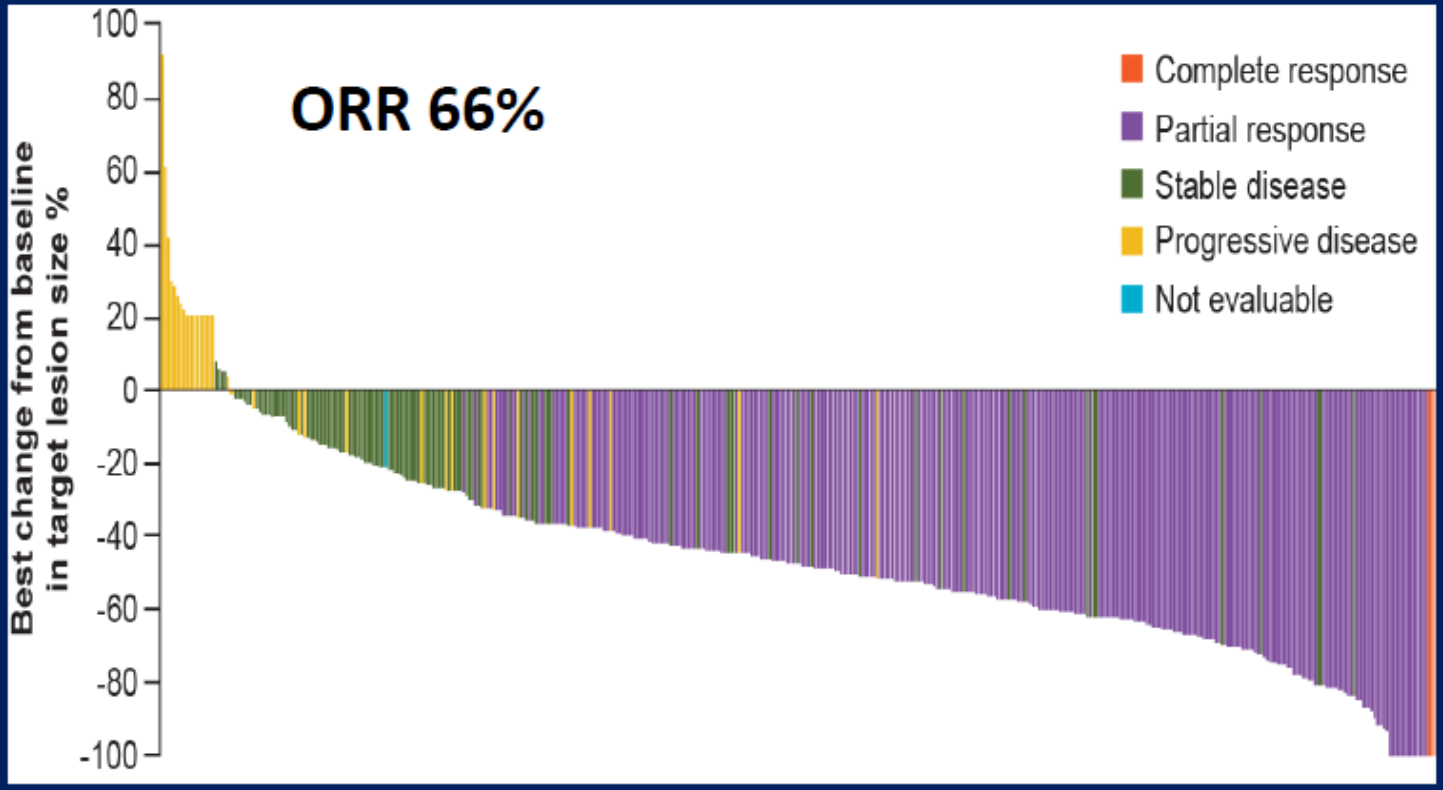
T790M mutation negative
ORR 25%
Median PFS – 4.6 mo

Grade 3 toxicity – 44%

Janjgian Y et al Cancer Discov 4(9);1036-45, 2014.

Metastatik KHDAK Hedefe Yönelik Tedaviler Yeni Moleküler

Osimertinib is standard for T790M +



Poster #365 presented by Glenwood D. Goss at the ECC 2015 European Cancer Congress

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

Third Generation EGFR TKIs

Agent	N	RR, % T790M-	RR, % T790M+	PFS, mos	Toxicity
Osimertinib[1]	253	21	61	~ 8.2	Diarrhea
Rociletinib[2,3]	130	29 (17)	59 (45)	13.1 (6.1)	Hyperglycemia
Olmutinib[4]	62	NR	55	NR	Dyspnea/rash
EGF816[5]	53	–	60	NR	Rash
ASP8273[6]	47	~ 33	61	NR	Hyponatremia/ diarrhea

1. Jänne PA, et al. N Engl J Med. 2015;372:1689-1699. 2. Sequist LV, et al. N Engl J Med. 2015;372:1700-1709. 3. Sequist LV, et al. N Engl J Med. 2016;374:2296-2297. 4. Park K, et al. ASCO 2015. Abstract 8084. 5. Tan DS, et al. ASCO 2015. Abstract 8013. 6. Goto Y, et al. ASCO 2015. Abstract 8014.

Slide credit: clinicaloptions.com

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

Randomized Studies of First Line EGFR TKI in Patients with EGFR Mutations

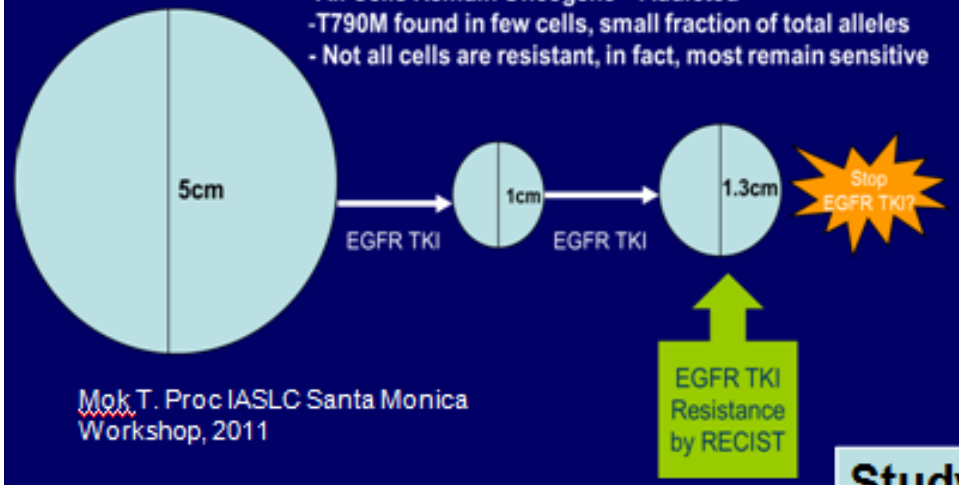
Author	Study	Agent	N (EGFRm+)	RR	Median PFS (months)	Median OS (months)
Mok et al.	IPASS	Gef	261	71.2% vs 47.3%	9.8 vs 6.4	21.6 vs 21.9
Lee et al.	First-SIGNAL	Gef	42	84.6% vs 37.5%	8.4 vs 6.7	27.2 vs 25.6
Mitsudomi et al.	WJTOG 3405	Gef	177	62.1% vs 32.2%	9.2 vs 6.3	35.5 vs 38.8
Maemondo et al.	NEJGSG002	Gef	230	73.7% vs 30.7%	10.8 vs 5.4	30.0 vs 23.6
Zhou et al.	OPTIMAL	Erl	154	83% vs 36%	13.1 vs 4.6	22.6 vs 28.8
Rosell et al.	EURTAC	Erl	154	54.5% vs 10.5%	9.2 vs 5.4	19.3 vs 19.5
Yang et al.	LUX-Lung 3	Afat	345	56% vs 23%	13.6 vs 6.9	31.6 vs 28.2
Wu et al.	LUX-Lung 6	Afat	364	67% vs 23%	11.0 vs 5.6	23.6 vs 23.5

Mok et al. *N Engl J Med.* 2009;361:947-57
Lee et al. WCLC 2009
Mitsudomi et al. *Lancet Oncol.* 2010;11;121-8
Maemondo et al. *N Engl J Med.* 2010;262:2380-88
Zhou et al. ESMO 2010
Rosell et al. ASCO 2011
Yang et al. ASCO 2012, Sequist IASLC 2012
Wu et al. ASCO 2013

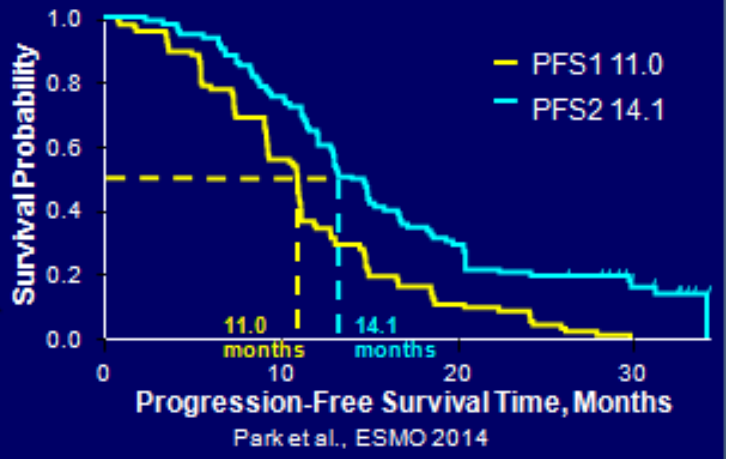
Cross-over to an EGFR TKI in the control groups felt to reduce detectability of any possible OS benefit (all mutations)

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

Post EGFR TKI Recist progression: Continue or Local Therapy



Mok T. Proc IASLC Santa Monica Workshop, 2011

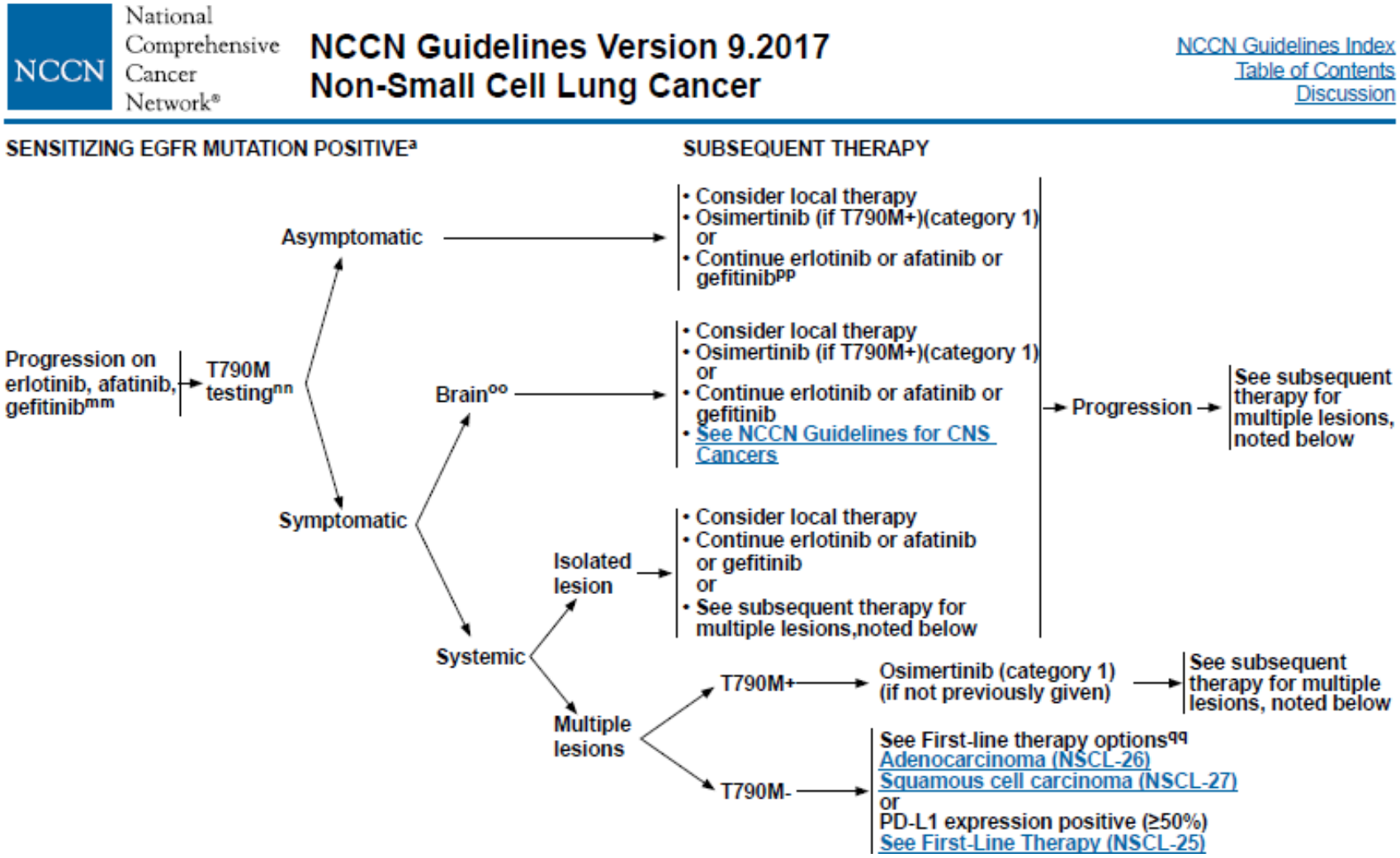


Park et al., ESMO 2014

Study	N pts	PFS1	PFS2
Colorado	25	10	6.2
MSKCC	18	19	10

Weickhardt A et al, Proc ASCO 2012 # 7526
Yu A et al, Proc ASCO 2012 # 7527

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler



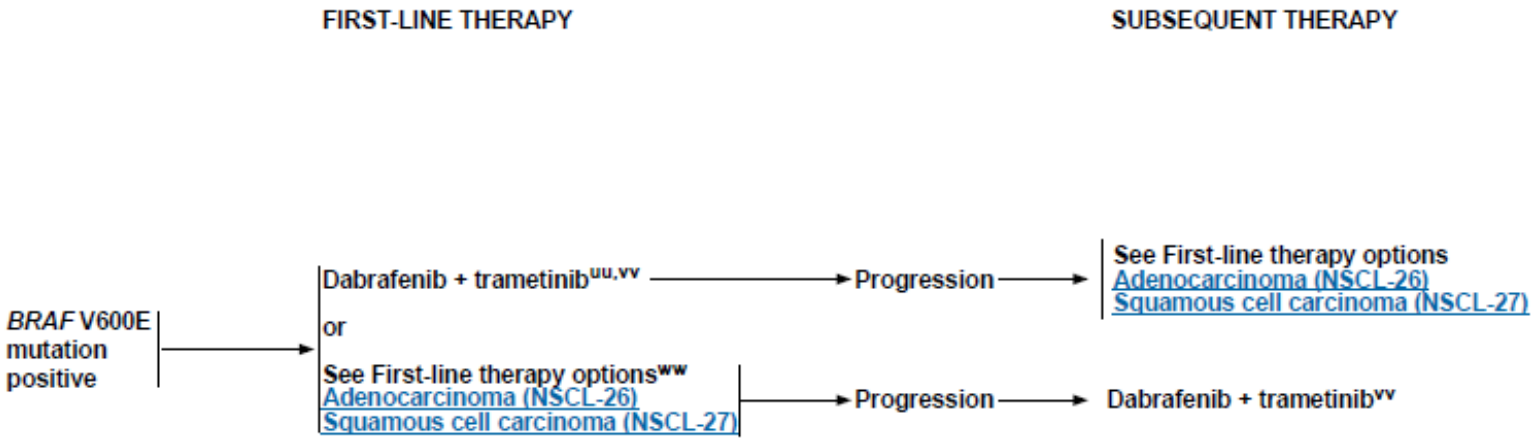
Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

National Comprehensive Cancer Network®

NCCN Guidelines Version 9.2017
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

BRAF V600E MUTATION POSITIVE



[uu]At this point, there are no published data on the progression-free survival (PFS) of patients treated in the first-line setting.
[vv]Single-agent vemurafenib or dabrafenib are treatment options if the combination of dabrafenib + trametinib is not tolerated.
[ww]Although it may be reasonable to treat *BRAF* V600E positive tumors with first-line pembrolizumab if PD-L1 ≥ 50%, there are no data of its efficacy in this subgroup of patients. The data in the second-line setting suggest that immunotherapy is less effective, irrespective of PD-L1 expression, in tumors with an actionable mutation.

Metastatik KHDAK Hedefe Yönelik Tedaviler

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

EMERGING TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
BRAF V600E mutation* *Non-V600E mutations have variable kinase activity and response to these agents.	vemurafenib[1,2] dabrafenib[2,3] dabrafenib + trametinib[4]
High-level *MET* amplification or MET exon 14 skipping mutation	crizotinib[5-9]
RET rearrangements	cabozantinib[10,11] vandetanib[12]
HER2 mutations	trastuzumab[13] (category 2B) afatinib[14] (category 2B)

Metastatik KHDAK Hedefe Yönelik Tedaviler

Recommendations for Molecular Testing in NSCLC Beyond *EGFR*, *ALK*, and *ROS1*

Emerging Targeted Agents for Pts With Lung Cancer and Genetic Alterations	
Genetic Alteration (Driver Event)	**Available Targeted Agents Against Driver Event in Lung Cancer**
BRAF V600E mutation*	Vemurafenib Dabrafenib Dabrafenib + trametinib
High-level *MET* amplification or MET exon 14 skipping mutation	Crizotinib
RET rearrangements	Cabozantinib
HER2 mutations	Trastuzumab (category 2b) Afatinib (category 2b)

*Non-V600E mutations have variable kinase activity and response to these agents.

NCCN. Clinical practice guidelines in oncology: non-small-cell lung cancer. v4.2016.

Slide credit: clinicaloptions.com

Metastatik KHDAK Hedefe Yönelik Tedaviler

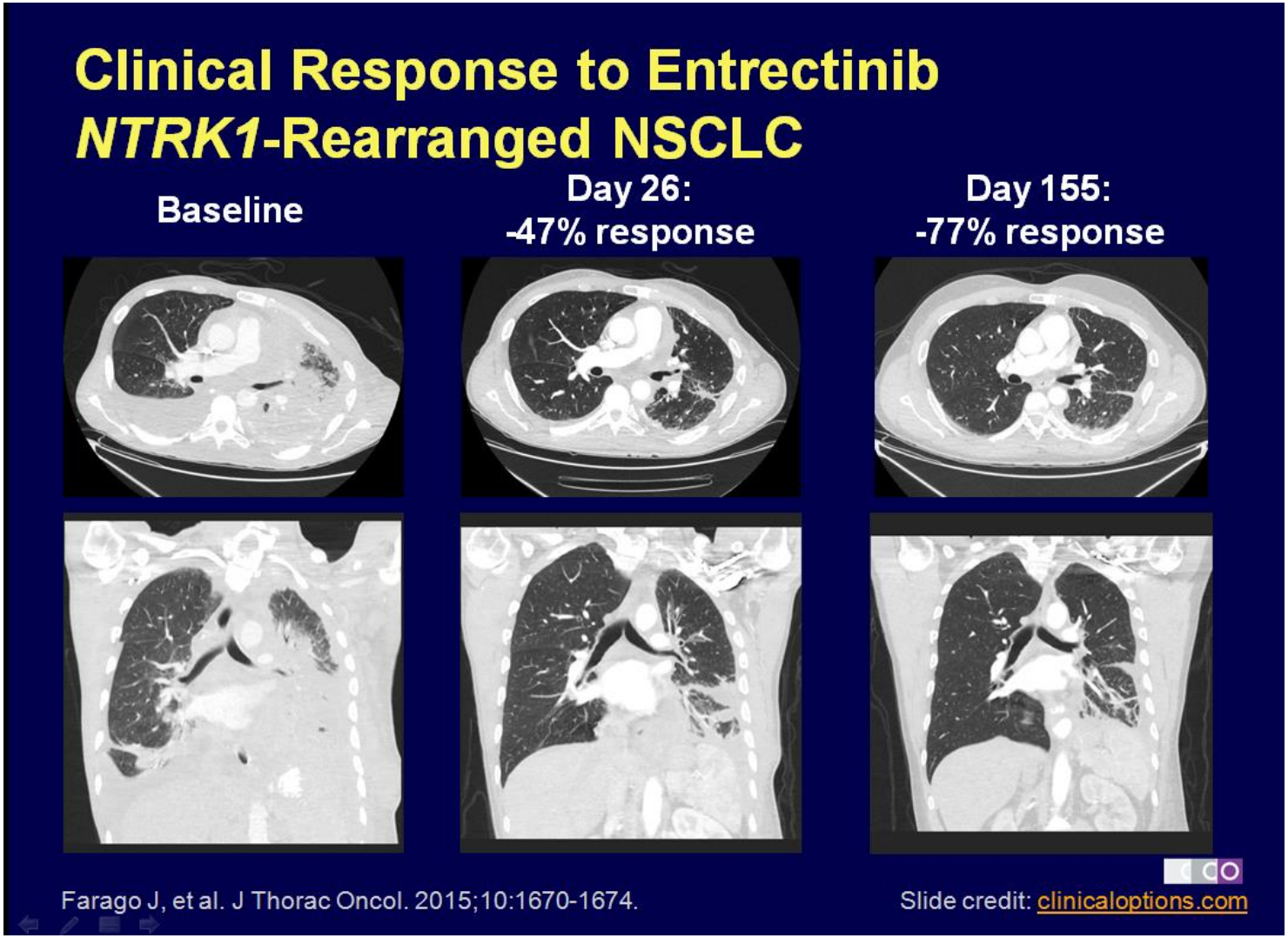
Neurotrophic Tyrosine Kinase (NTRK) and Tropomysin-Related Kinases A, B, C

- TrkA, TrkB, and TrkC: receptor tyrosine kinases encoded by *NTRK1, NTRK2, NTRK3* genes
  - Implicated in neuronal development
- Mutations or fusions in TK domain lead to constitutive activation
  - Several fusions described in lung cancer primarily involving *NTRK1* and *NTRK2*

Barbacid M. J Neurobiol. 1994;25:1386-1403. Vaishnavi A, et al. Nature Med. 2013;19:1469-1472. Farago J, et al. J Thorac Oncol. 2015;10:1670-1674.

Slide credit: clinicaloptions.com

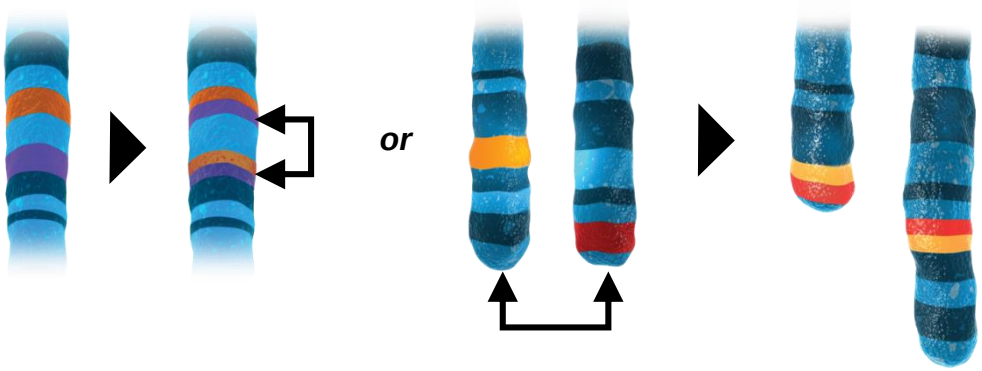
Metastatik KHDAK Hedefe Yönelik Tedaviler

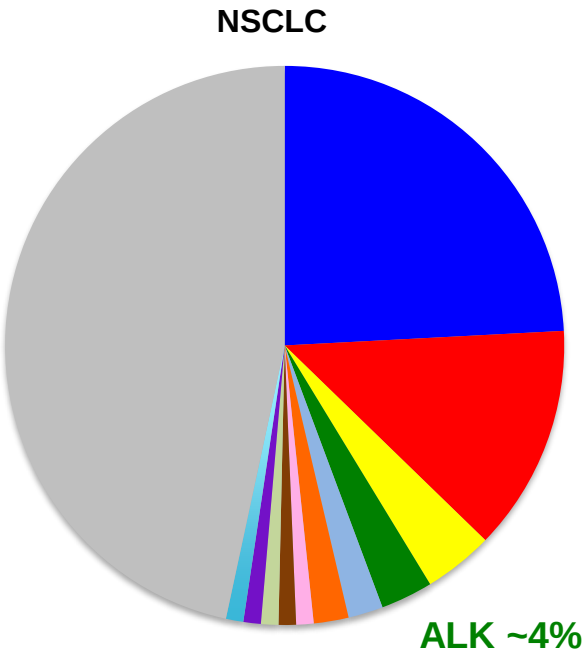


ALK-Rearranged NSCLC

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda, Young Lim Choi, Munehiro Enomoto, Shuji Takada, Yoshihiro Yamashita, Shunpei Ishikawa, Shin-ichiro Fujiwara, Hideki Watanabe, Kentaro Kurashina, Hisashi Hatanaka, Masashi Bando, Shoji Ohno, Yuichi Ishikawa, Hiroyuki Aburatani, Toshiro Niki, Yasunori Sohara, Yukihiko Sugiyama & Hiroyuki Mano





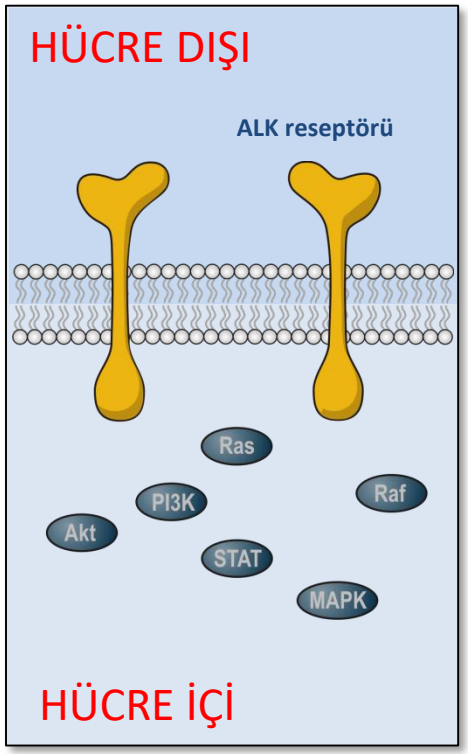
Common features:
Younger age
Neversmoking history
Adenocarcinoma
CNS metastasis
Sensitivity to ALK TKis

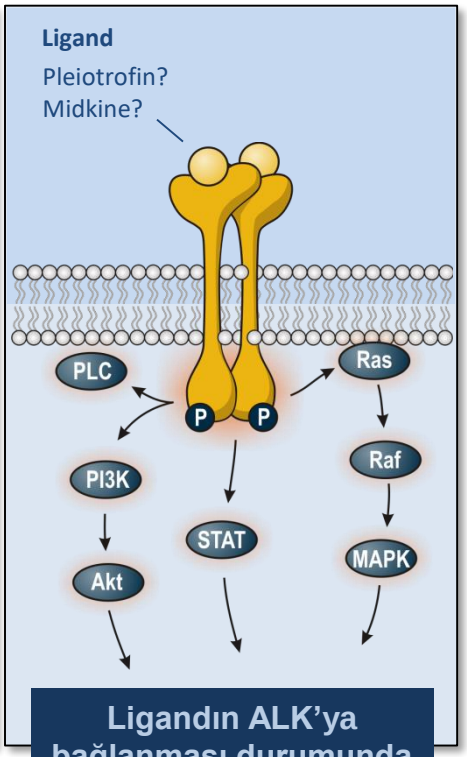
Soda et al., Nature 448: 561-7, 2007

Metastatik KHDAK Hedefe Yönelik Tedaviler

Krizotinib etki mekanizması

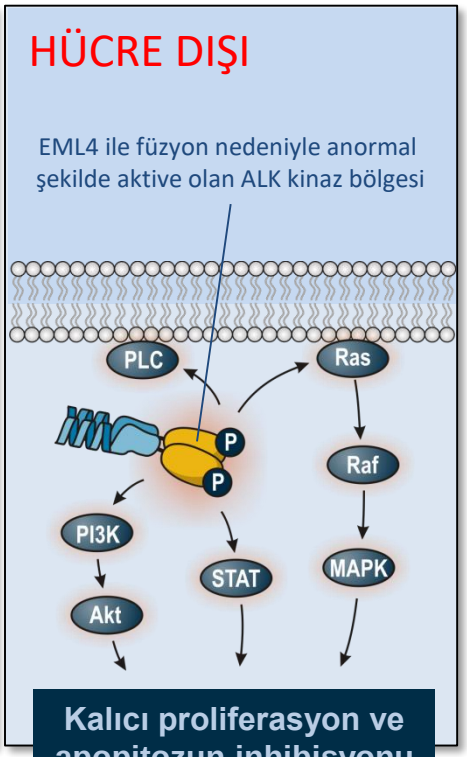
Normal ALK sinyal iletimi





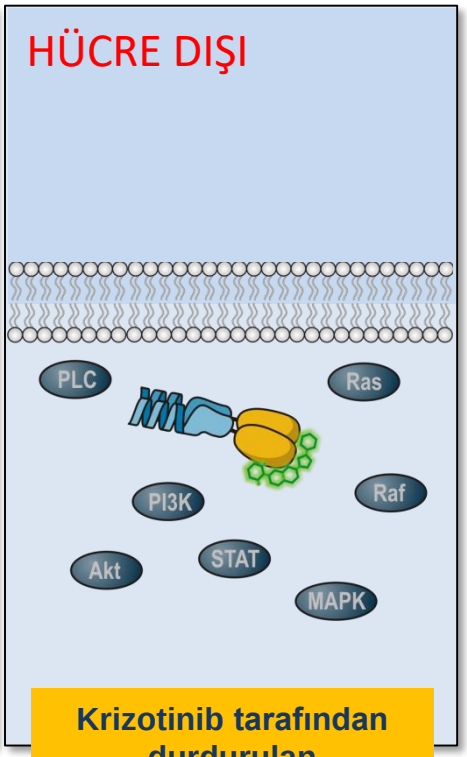
Ligandın ALK'ya bağlanması durumunda proliferasyon ve sağkalım

Patolojik ALK sinyal iletimi



Kalıcı proliferasyon ve apopitozun inhibisyonu

Krizotinibin etki şekli

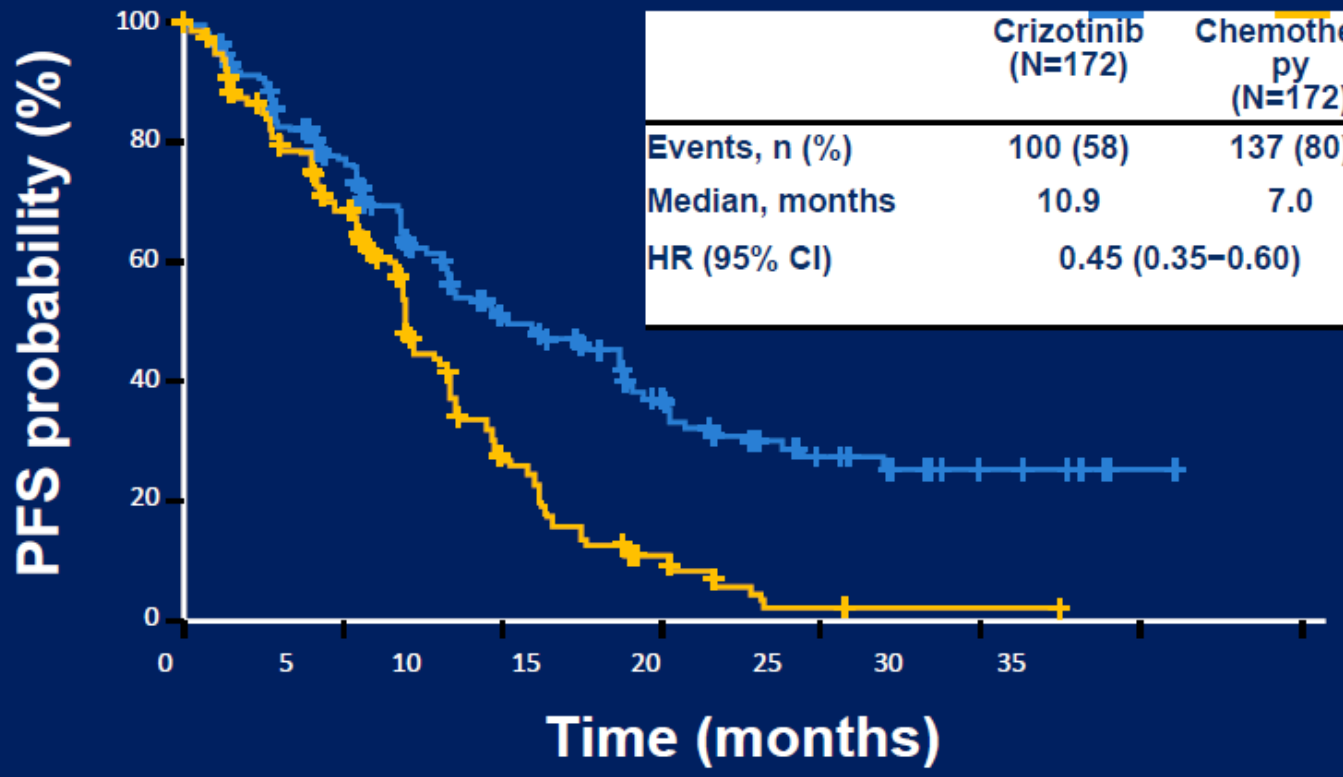


Krizotinib tarafından durdurulan EML4-ALK füzyonu

Metastatik KHDAK Hedefe Yönelik Tedaviler

1st line Crizotinib prolongs PFS compared to platinum/pemetrexed

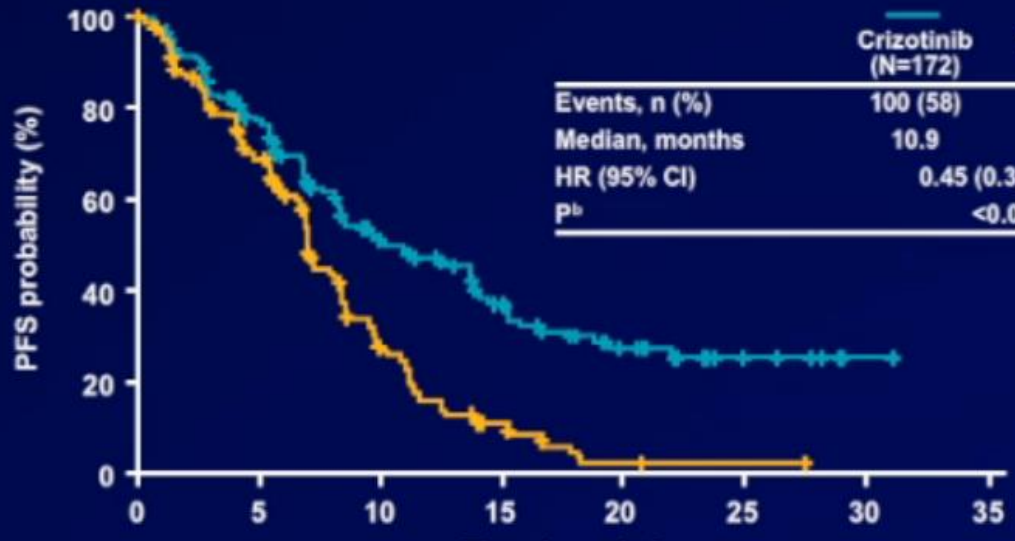
Mok et al, ASCO 2014, abstr 8002



	Crizotinib (N=172)	Chemotherapy (N=172)
Events, n (%)	100 (58)	137 (80)
Median, months	10.9	7.0
HR (95% CI)	0.45 (0.35–0.60)	

Metastatik KHDAK Hedefe Yönelik Tedaviler

Crizotinib Is Superior to Platinum Combination Chemotherapy in First-Line ALK+ NSCLC



	Crizotinib (N=172)	Chemotherapy (N=171)
Events, n (%)	100 (58)	137 (80)
Median, months	10.9	7.0[a]
HR (95% CI)	0.45 (0.35–0.60)	
P[b]	<0.001	

No. at risk								
Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

- Median duration of treatment: crizotinib, 10.9 months; chemotherapy, 4.1 months

Data cutoff: November 30, 2013

[a]As-treated population: pemetrexed–cisplatin, 6.9 months (n=91; HR: 0.49; P<0.0001); pemetrexed–carboplatin, 7.0 months (n=78; HR: 0.45; P<0.0001)

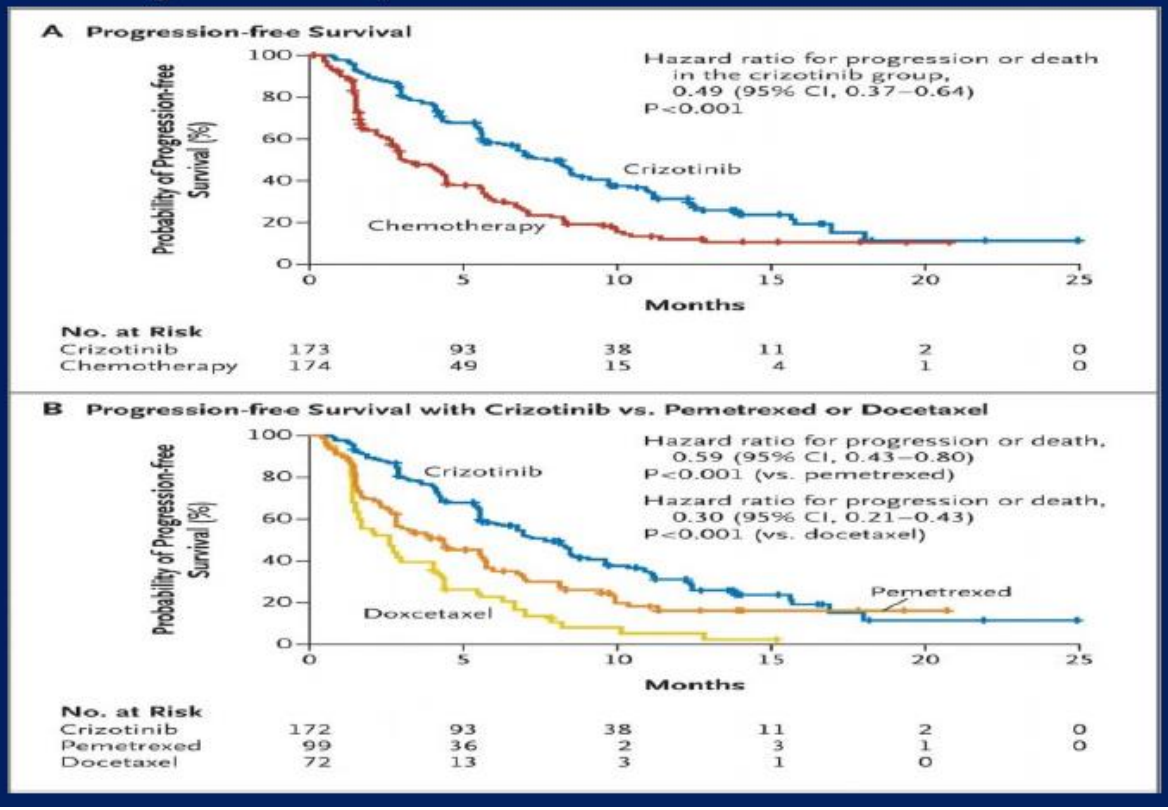
[b]2-sided stratified log-rank test

Solomon et al., NEJM 371(23): 2167-77, 2014

Metastatik KHDAK Hedefe Yönelik Tedaviler

2nd line Crizotinib vs. Docetaxel or Pemetrexed in ALK + patients

Shaw et al. N Engl J Med 2013;368:2385-2394



Metastatik KHDAK Hedefe Yönelik Tedaviler

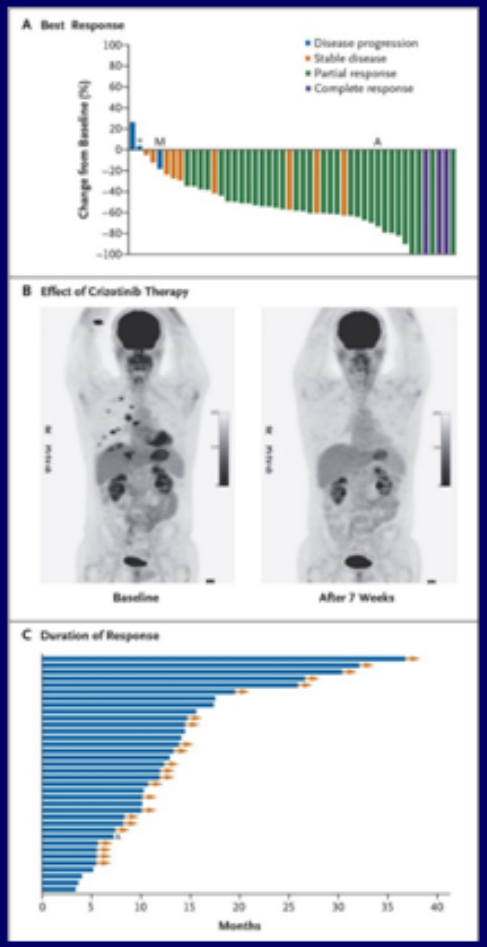
Crizotinib Is a Standard Therapy for Patients with Metastatic ALK+ NSCLC

	PROFILE 1001[1] (N=143)	PROFILE 1005[2] (N=259)	PROFILE 1007[3] (N=172)	PROFILE 1014[4] (N=172)
Phase	1	2	3	3
Line of therapy	Any line	2nd line and beyond	2nd line	1st line
Response rate	61%	60%	65%	74%
PFS, median (mos)	9.7	8.1	7.7	10.9
Survival probability at 12 mos	75%	NA	70%	84%

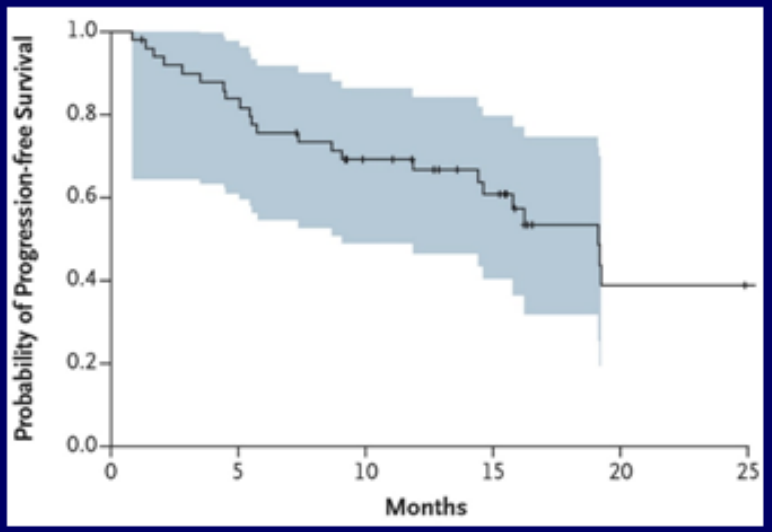
[1]Camidge et al., Lancet Oncol 13(10): 1011-9, 2012
[2]Kim et al., ASCO 2012
[3]Shaw et al., NEJM 368(25): 2385-94 , 2013
[4]Solomon et al., NEJM 371(23): 2167-77, 2014

Metastatik KHDAK Hedefe Yönelik Tedaviler

Crizotinib in *ROS1*-Rearranged NSCLC



PFS

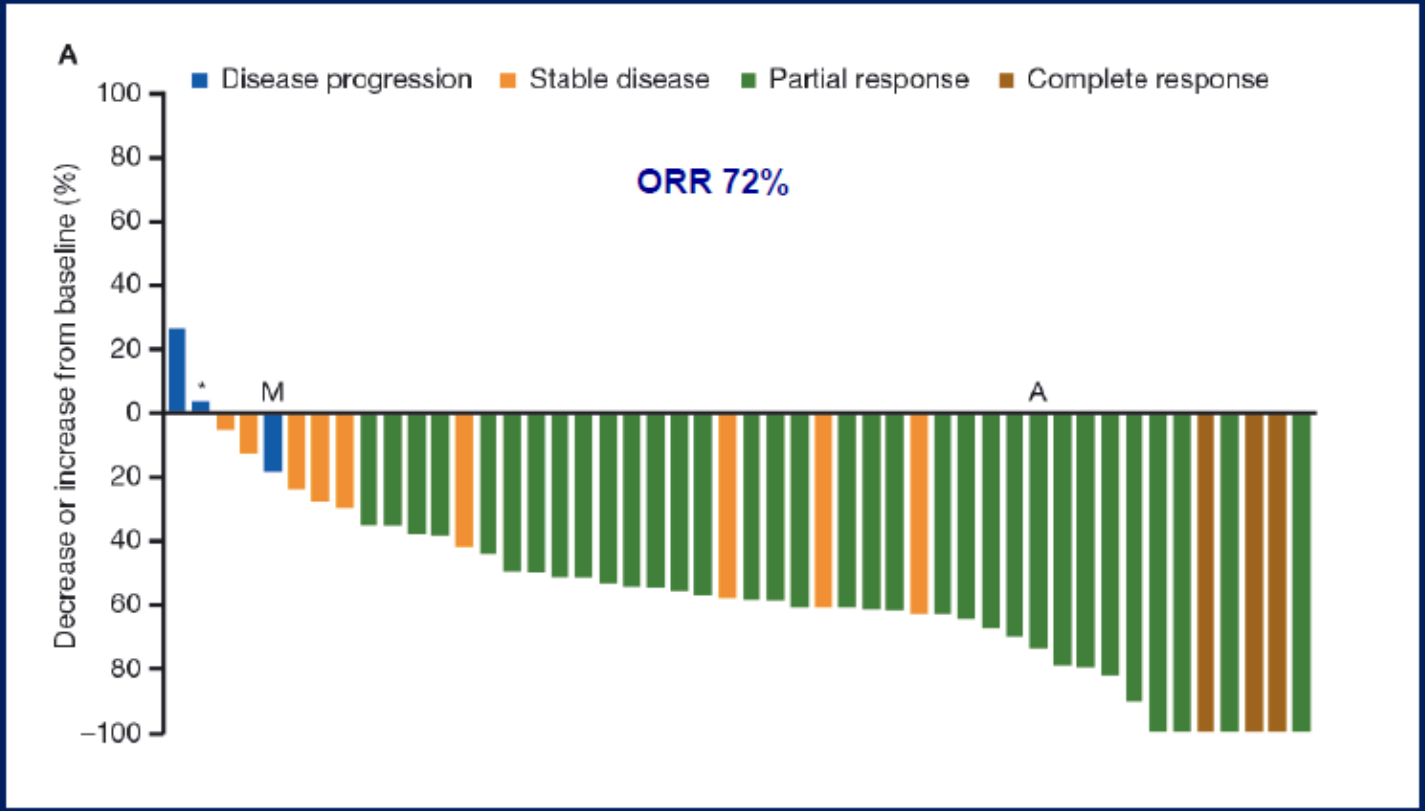


Shaw A, et al. *N Engl J Med*. 2014; 371 (21):1963-1971.

Metastatik KHDAK Hedefe Yönelik Tedaviler

ROS1+ NSCLC: Crizotinib is standard

Shaw et al. NEJM 371(21): 1963-71, 2014



İlk Seri ALK İnhibitörlerinde Direnç

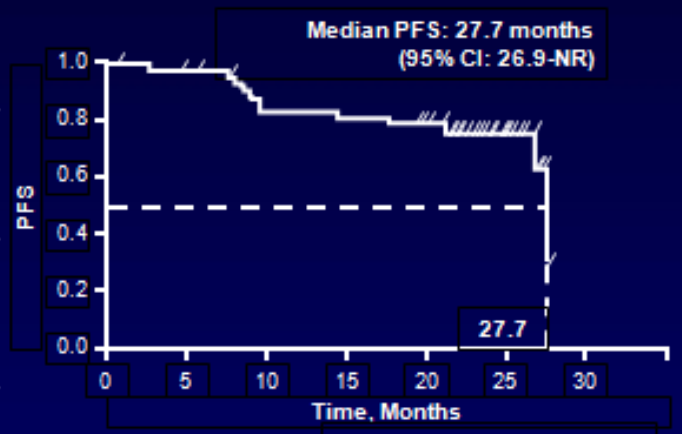
Next Generation ALK Inhibitors

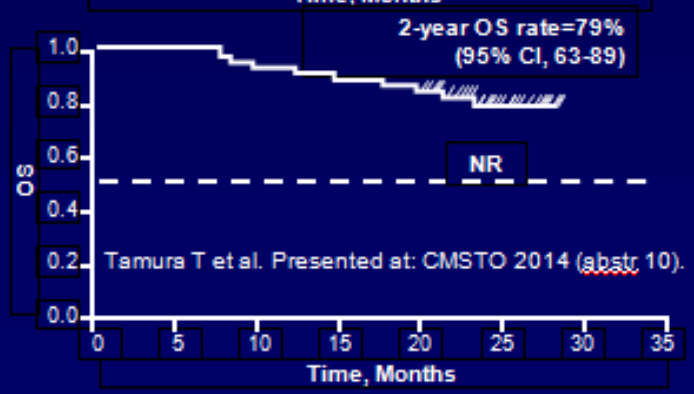
In Crizotinib Resistance

	Status	ORR	PFS, mo	DR, mo	CNS RR
Ceritinib[1] (LDK378)	Approved	55% (N = 163)	6.9	7.4	Yes (50%)
Alectinib[2] (CH5424802)	Approved	50% (N = 122)	8.9	11.2	Yes (57%)
Brigatinib[3] (AP26113)	Phase II	71% (N = 70)	13.4	9.3	Yes (53%)
PF-06463922[4]	Phase I/II	44% (N = 34)	NR	NR	Yes (36%)

1. Kim D-W, et al. *J Clin Oncol* 2014;32(5S): Abstract 8003; 2. Ou S-H, et al. *J Clin Oncol* 2015;33(Suppl): Abstract 8008; 3. Camidge DR, et al. *J Clin Oncol* 2015;33(Suppl): Abstract 8062; 4. Shaw AT, et al. *J Clin Oncol* 2015;33(Suppl): Abstract 8018.

1st Line





İlk Seri ALK İnhibitörlerinde Direnç

ALK kinase domain mutations – drug efficacy

	1st gen	2nd gen			3rd gen
	Crizotinib	Alectinib	Brigatinib	Ceritinib	Lorlatinib
G1123S	Res	Sens[2]	N/D	Res[2]	N/D
1151Tins	Res	Res[3]	N/D	Res[7]	Sens[9]
L1152P/R	Res	Sens	N/D	Res[7]	Sens[9]
C1156Y/T	Res	Sens	N/D	Res[7]	Sens[9]
I1171T/N	Res	Res[4,5]	N/D	Sens[4,5,7]	N/D
F1174C/L/V	Res	Sens	Sens[6]	Res[7]	Sens[9]
V1180L	Res	Res [4]	N/D	Sens[4]	N/D
L1196M	Res	Sens[3]	Sens[6]	Sens[7]	Sens[9]
L1198F	Sens [1]	Res[1]	Res[1]	Res[1]	Res[1]
G1202R	Res	Res[3]	N/D	Res[7]	Sens[9]
S1206C/Y	Res	Sens[3]	Res[6]	Sens[7]	Sens[9]
F1245C	Res[8]	N/D	N/D	Sens[8]	N/D
G1269A/S	Res	Sens	N/D	Sens[7]	Sens[9]

REFERENCES

1. Shaw NEJM 2016
2. Toyokawa JTO 2015
3. Katayama STM 2012
4. Katayama CCR 2014
5. Ou Lung Cancer 2015
6. Ceccon MCR 2014
7. Friboulet Cancer Discov 2014
8. Kodityal Lung Cancer 2016
9. Zou Cancer Cell 2015
10. Bayliss Cel Mol Lif Sci 2015

Slide courtesy of Dr. Christine Lovly

Metastatik KHDAK Hedefe Yönelik Tedaviler

MADRID 2017 ESMO congress

OVERALL SURVIVAL (OS) FOR FIRST-LINE CRIZOTINIB VERSUS CHEMOTHERAPY IN ALK+ LUNG CANCER

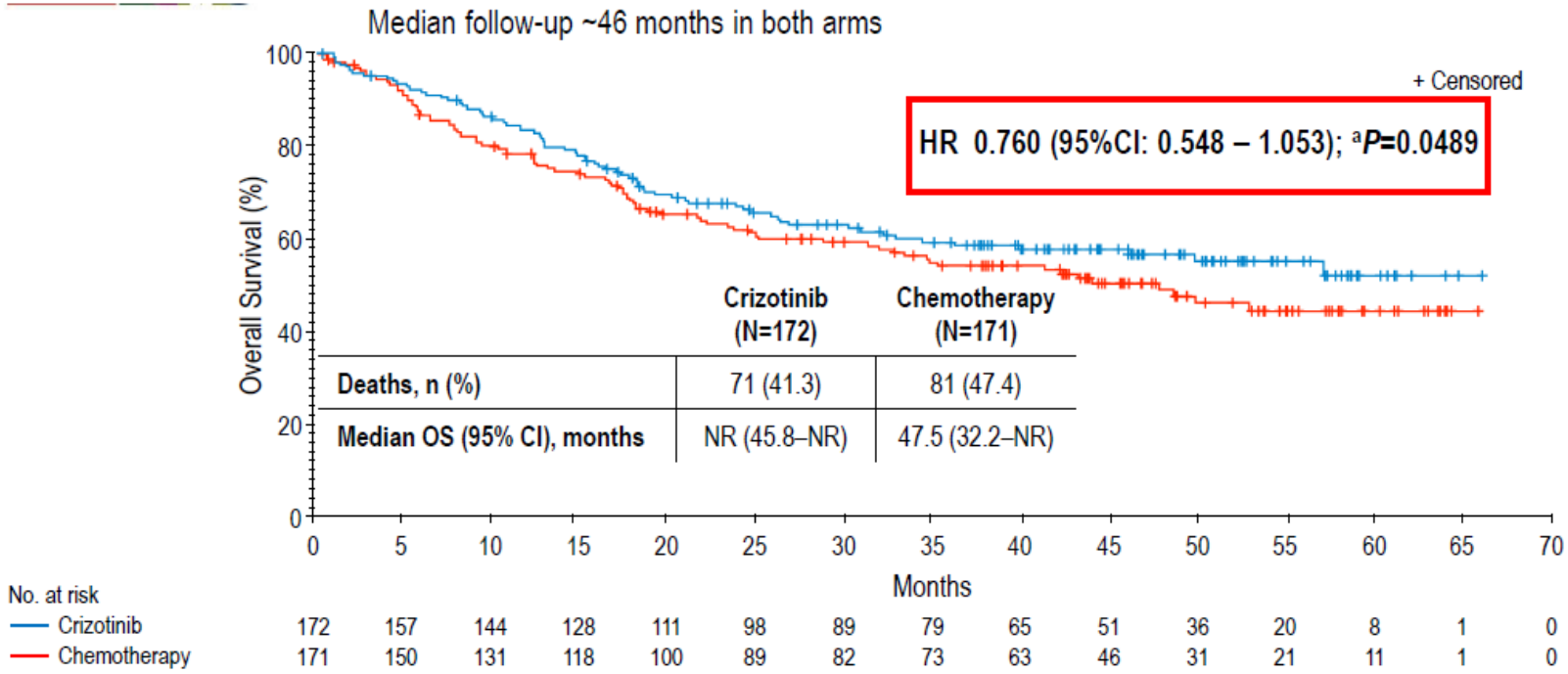
Updated Results from PROFILE 1014

Tony S. Mok,[1] Dong-Wan Kim,[2] Yi-Long Wu,[3] Kazuhiko Nakagawa,[4] Tarek Mekhail,[5] Enriqueta Felip,[6] Federico Cappuzzo,[7] Jolanda Paolini,[8] Tiziana Usari,[8] Keith Wilner,[9] Fiona Blackhall,[10] Benjamin J. Solomon[11]

[1]The Chinese University of Hong Kong, Hong Kong, China;[2]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [3]Guangdong General Hospital & Guangdong Academy of Medical Sciences; [4]Kindai University, Osaka Japan; [5]Department of Hematology/Oncology, Florida Hospital, Orlando, FL, USA; [6]Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain; [7]Medical Oncology Department, AUSL Della Romagna, Ravenna, Italy; [8]Pfizer Oncology, Milan, Italy; [9]Pfizer Oncology, La Jolla, CA, USA; [10]Institute of Cancer Sciences, Manchester University and Christie Hospital NHS Foundation Trust, Manchester, UK; [11]Peter MacCallum Cancer Centre, Melbourne, Australia

Metastatik KHDAK Hedefe Yönelik Tedaviler

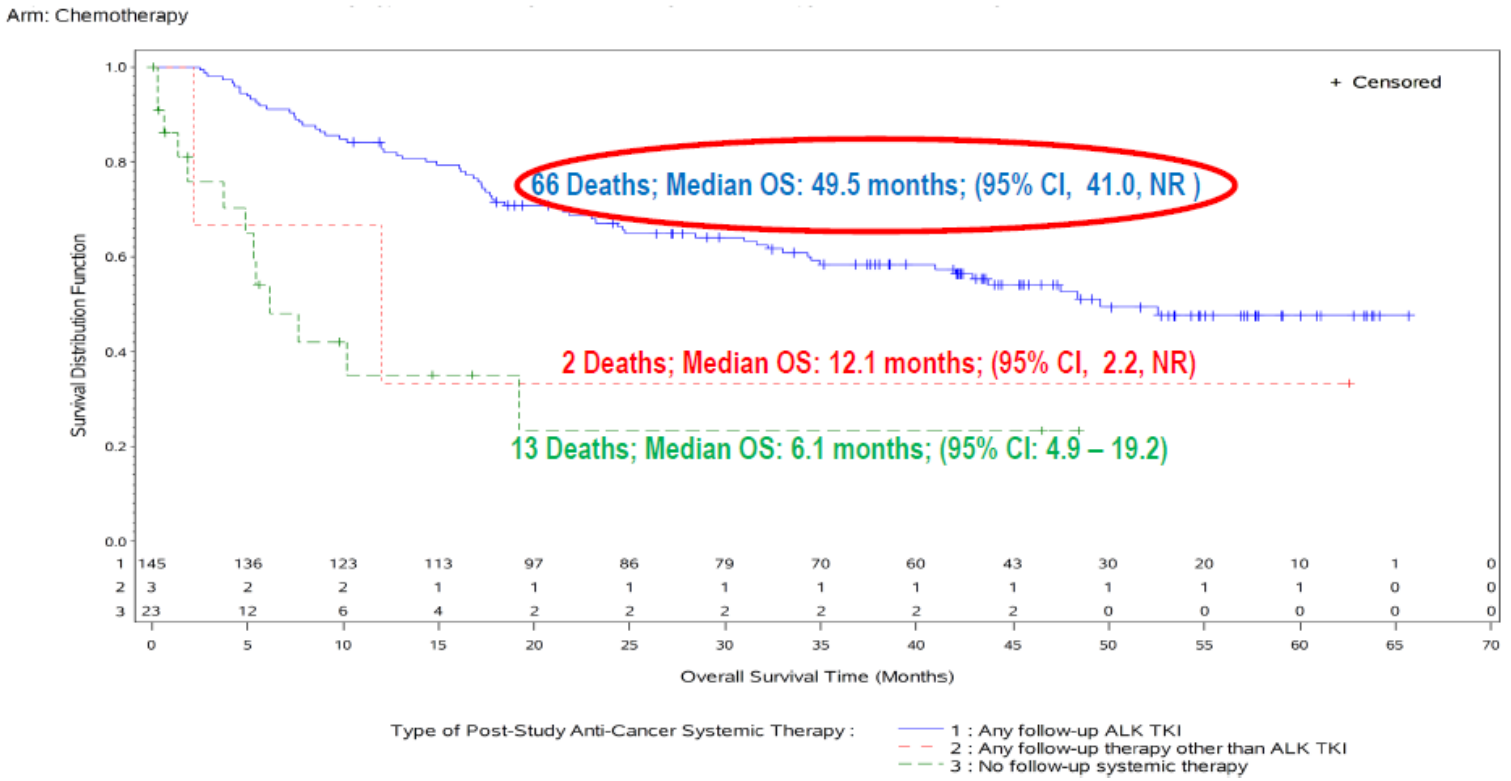
Final Primary OS Analysis (ITT Population)



[a]1-sided stratified log-rank test. *P* value <0.05 is not statistically significant as it was 1-sided

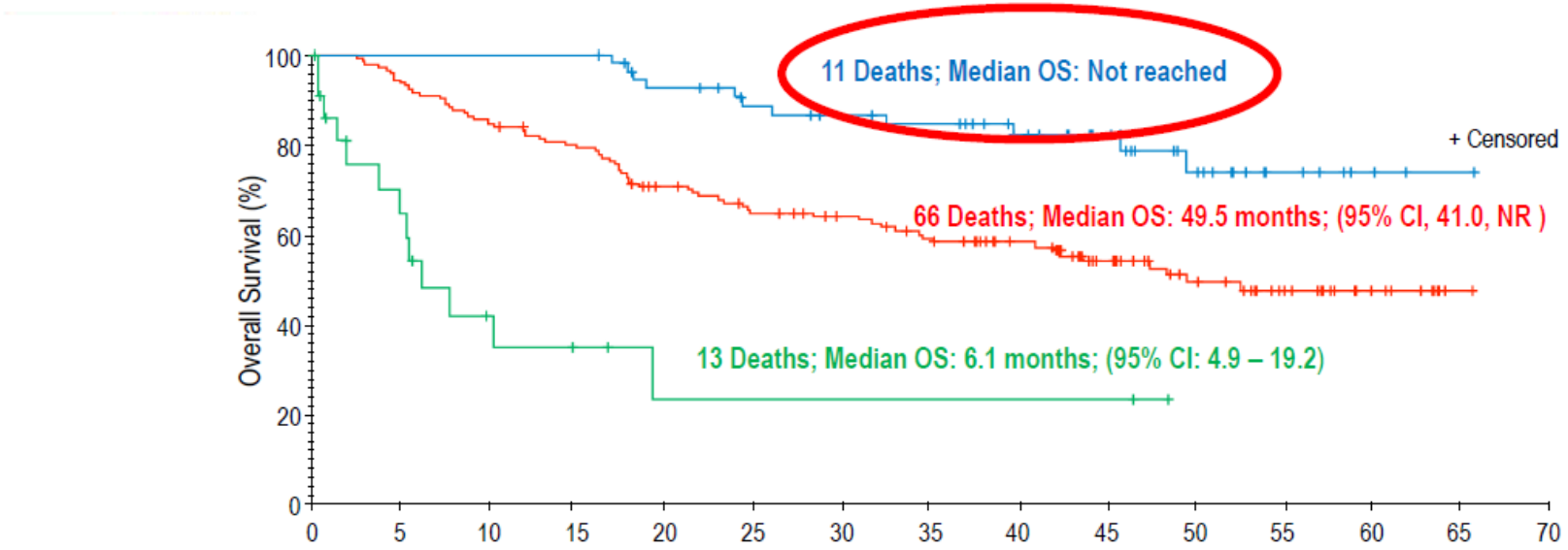
Metastatik KHDAK Hedefe Yönelik Tedaviler

Impact on OS of Subsequent ALK TKI, Other Than ALK TKI or No Treatment After Randomized Phase of Study: Chemotherapy Arm



Metastatik KHDAK Hedefe Yönelik Tedaviler

Impact on OS of Subsequent ALK TKI, Other Than ALK TKI or No Systemic Treatment After Randomized Phase of Study



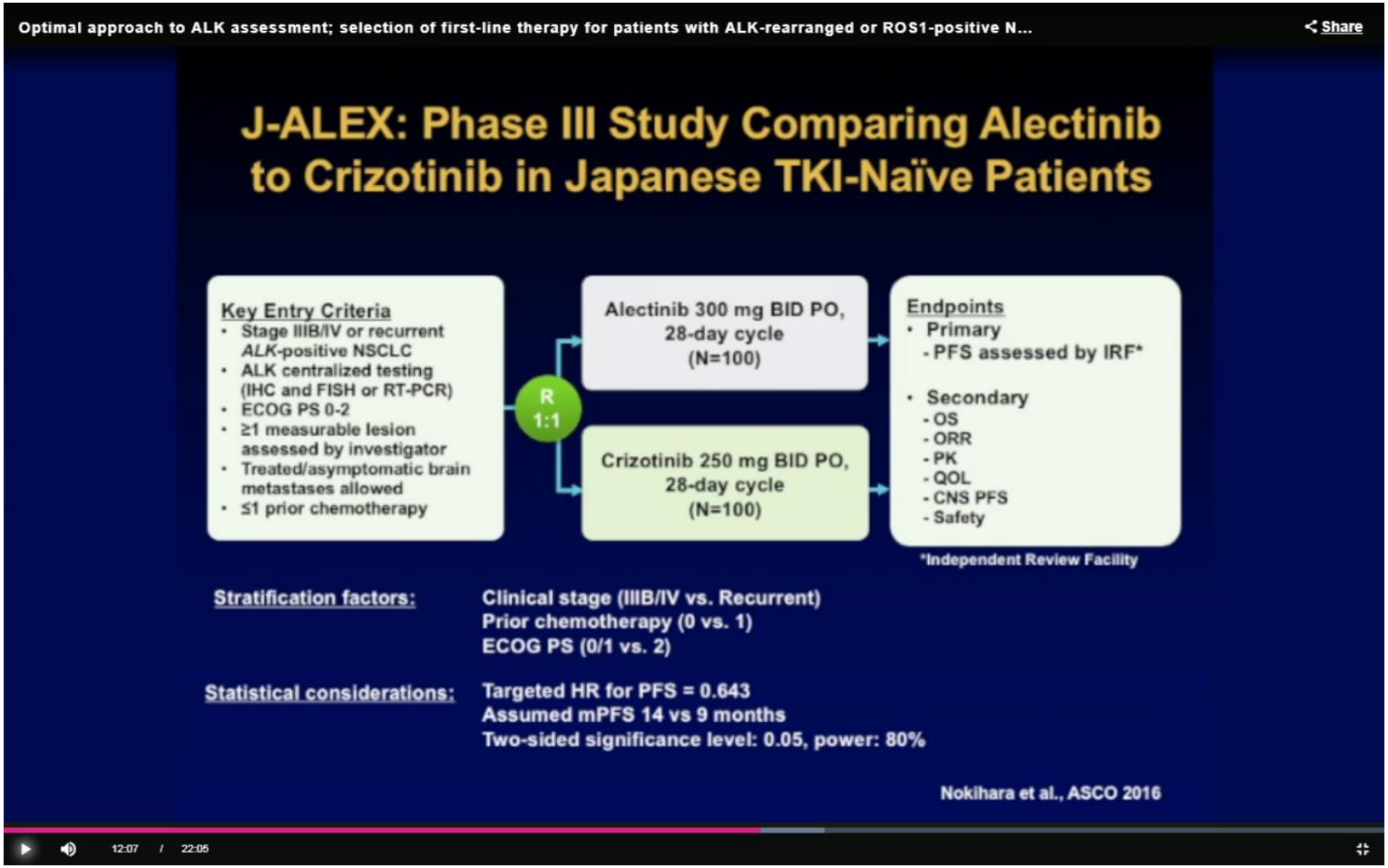
No. at risk														
Crizotinib Followed by any ALK TKI	57	57	57	57	50	45	42	40	33	25	16	8	3	1	0
Chemotherapy Followed by any ALK TKI	145	136	123	113	97	86	79	70	60	43	30	20	10	1	0
Chemotherapy Followed by No Systemic Therapy	23	12	6	4	2	2	2	2	2	2	0	0	0	0	0

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

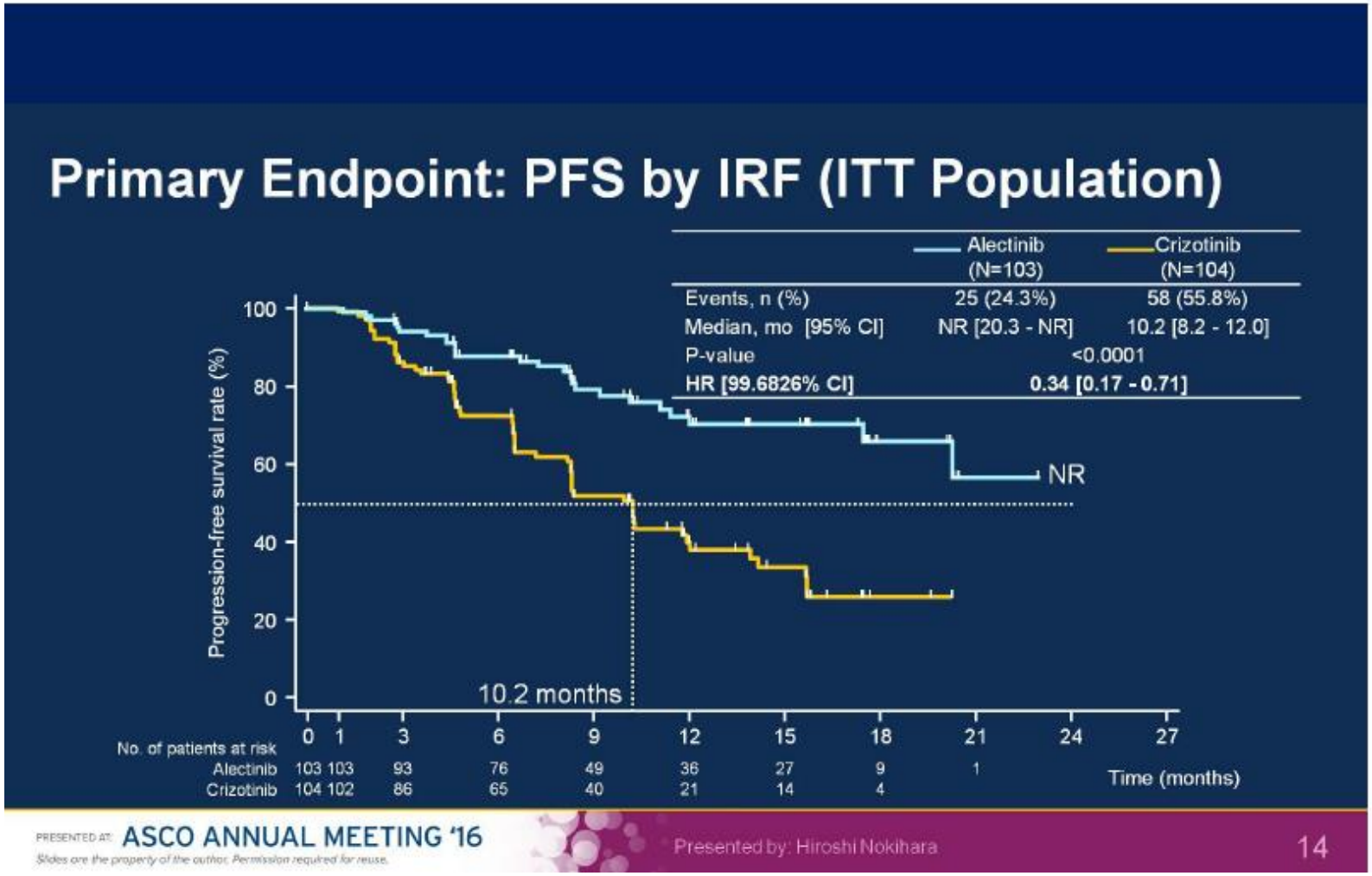
Other ALK inhibitors: 2nd line and beyond

- Ceritinib FDA approved in ALK + patients previously treated with Crizotinib
  - Response Rate: 56%
- Alectinib FDA approved in ALK + patients previously treated with Crizotinib
  - Response Rate: 50%; brain met RR: 57%

Shaw et al, NEJM 2013;368:2385-94
Shaw et al, NEJM 2014;370:1189-97
Abstract 8008, ASCO 2015


J-ALEX: Phase III Study Comparing Alectinib to Crizotinib in Japanese TKI-Naïve Patients
Key Entry Criteria
• Stage IIIB/IV or recurrent ALK-positive NSCLC
• ALK centralized testing (IHC and FISH or RT-PCR)
• ECOG PS 0-2
• ≥1 measurable lesion assessed by investigator
• Treated/asymptomatic brain metastases allowed
• ≤1 prior chemotherapy
R
1:1
Alectinib 300 mg BID PO, 28-day cycle (N=100)
Crizotinib 250 mg BID PO, 28-day cycle (N=100)
Endpoints
• Primary
- PFS assessed by IRF*
• Secondary
- OS
- ORR
- PK
- QOL
- CNS PFS
- Safety
*Independent Review Facility
Stratification factors:
Clinical stage (IIIB/IV vs. Recurrent)
Prior chemotherapy (0 vs. 1)
ECOG PS (0/1 vs. 2)
Statistical considerations:
Targeted HR for PFS = 0.643
Assumed mPFS 14 vs 9 months
Two-sided significance level: 0.05, power: 80%
Nokihara et al., ASCO 2016

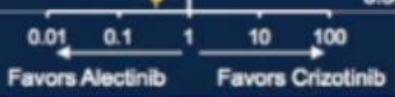
Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler



Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

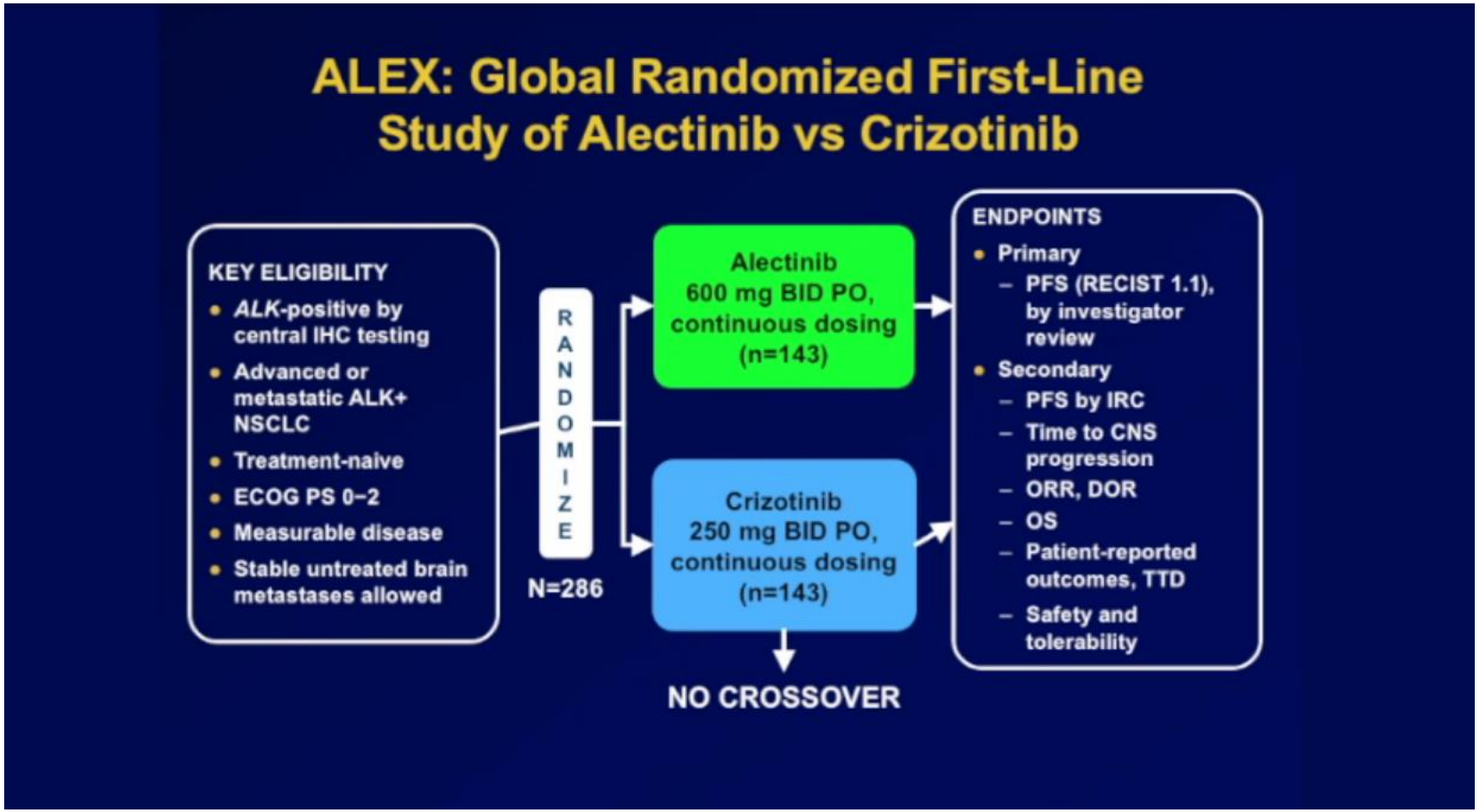
Subgroup Analysis of PFS by IRF

Subgroup		Alectinib (N=103) n	Alectinib (N=103) Events	Crizotinib (N=104) n	Crizotinib (N=104) Events	HR [95% CI]
Overall		103	25	104	58	0.34 [0.21 - 0.54]
ECOG performance status	0/1	101	24	102	57	0.33 [0.20 - 0.53]
	2	2	1	2	1	1.41 [0.08 - 23.57]
Prior chemotherapy	0	66	15	67	35	0.30 [0.17 - 0.56]
	1	37	10	37	23	0.39 [0.18 - 0.83]
Clinical stage	Postoperative recurrence	24	6	26	13	0.49 [0.18 - 1.30]
	Stage IIIB/IV	79	19	78	45	0.31 [0.18 - 0.52]
Age group	≥75	12	3	10	5	0.28 [0.06 - 1.19]
	<75	91	22	94	53	0.34 [0.21 - 0.56]
Smoking status	Never smoker	56	18	61	33	0.50 [0.28 - 0.89]
	Past or Current smoker	47	7	43	25	0.18 [0.06 - 0.42]
Brain metastases at baseline	Yes	14	1	29	16	0.08 [0.01 - 0.61]
	No	89	24	75	42	0.39 [0.23 - 0.64]
ALK testing method	IHC and FISH	96	21	94	52	0.30 [0.18 - 0.50]
	RT-PCR	7	4	10	6	0.80 [0.22 - 2.90]
Sex	Female	62	16	63	37	0.31 [0.17 - 0.57]
	Male	41	9	41	21	0.35 [0.16 - 0.77]



Nokihara et al., ASCO 2016

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler



Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

MADRID 2017 ESMO congress

ALECTINIB VS CRIZOTINIB IN TREATMENT-NAÏVE *ALK*+ NSCLC: CNS EFFICACY RESULTS FROM THE ALEX STUDY

[1]Shirish Gadgeel, [2]Solange Peters, [3]Tony Mok, [4]Alice T. Shaw, [5]Dong-Wan Kim, [6]Sai-Hong Ignatius Ou, [7]Maurice Pérol, [8]Rafal Dziadziuszko, [9]Jin Seok Ahn, [10]Rafael Rosell, [11]Ali Zeaiter, [11]Emmanuel Mitry, [11]Eveline Nueesch, [11]Bogdana Balas, [12]D. Ross Camidge

[1]University of Michigan, Ann Arbor, MI, USA; [2]Lausanne University Hospital, Lausanne, Switzerland; [3]State Key Laboratory of South China, Chinese University of Hong Kong, Shatin, New Territories, Hong Kong; [4]Massachusetts General Hospital, Boston, MA, USA; [5]Seoul National University Hospital, Seoul, South Korea; [6]Chao Family Comprehensive Cancer Center, University of California, Irvine School of Medicine, Orange, CA, USA; [7]Department of Medical Oncology, Léon Bérard Cancer Center, Lyon, France; [8]Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland; [9]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [10]Catalan Institute of Oncology, Barcelona, Spain; [11]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [12]University of Colorado, Denver, CO, USA

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

BASELINE CNS DISEASE

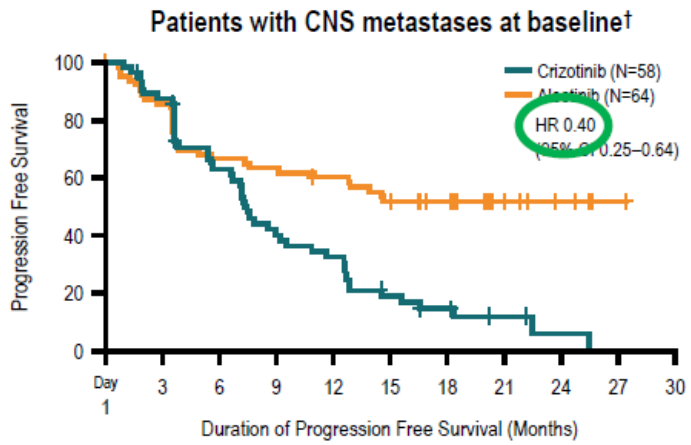
		ITT population (n=303)	
Patient characteristics		**Crizotinib (n=151)**	**Alectinib (n=152)**
CNS metastases by IRC (%)	Present	58 (38)	64 (42)
	Absent	93 (62)	88 (58)
CNS metastases treatment (%)	n	58	64
	None	36 (62)	37 (58)
	Whole brain RT	16 (28)	17 (27)
	Radiosurgery	4 (7)	5 (8)
	Other*	1 (2)	4 (6)
	Brain surgery	1 (2)	1 (2)

*1 patient in the alectinib arm received both radiosurgery and whole brain radiotherapy; 1 patient in the crizotinib arm and 3 patients in the alectinib arm had brain surgery combined with radiotherapy
IRC = independent review committee; ITT = intent to treat; RT = radiotherapy

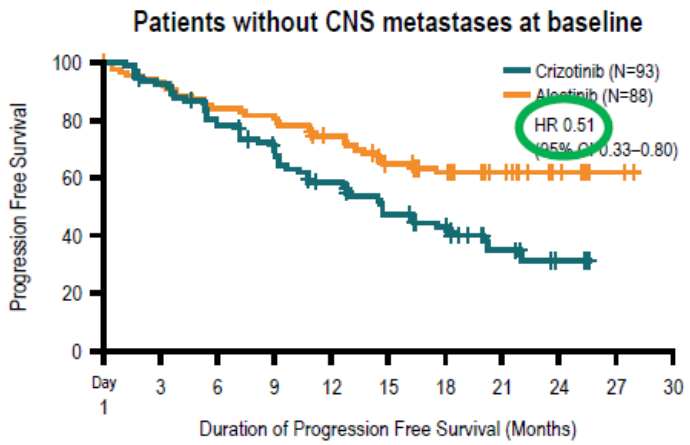
Peters, et al. NEJM 2017

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

PFS BY BASELINE CNS METASTASES STATUS*



Patients at Risk										
Crizotinib	58	48	66	22	17	9	6	3	1	
Alectinib	64	54	41	39	36	31	24	10	4	1



Patients at Risk										
Crizotinib	93	84	71	62	48	37	29	13	4	
Alectinib	88	81	72	70	61	50	43	25	11	2

*investigator-assessed; †All patients with CNS metastases at baseline, irrespective of radiotherapy

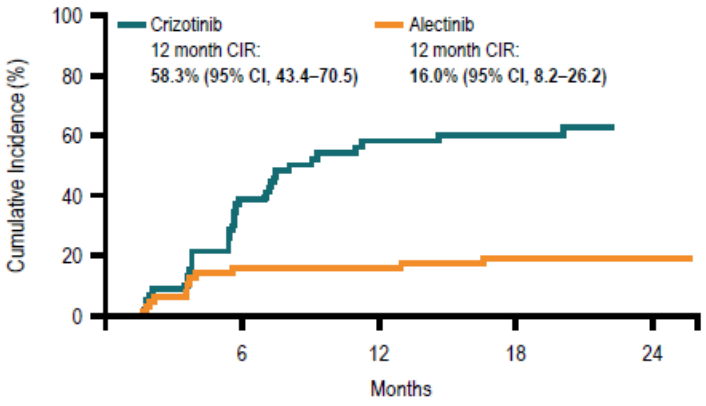
Shaw, et al. ASCO 2017

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

TIME TO CNS PROGRESSION BY CNS METS AT BASELINE (IRC, ITT)

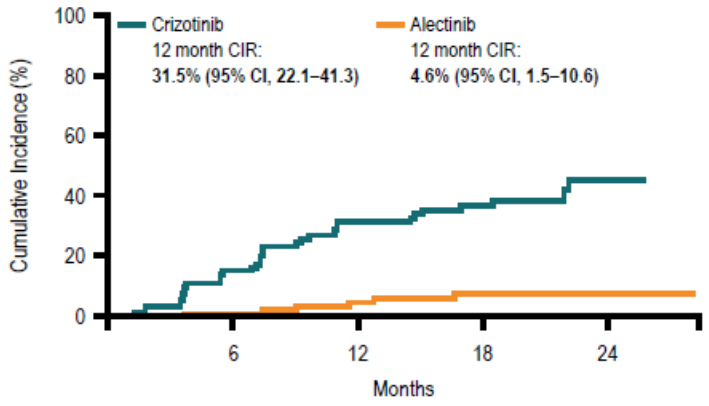
- A competing risk analysis with CNS progression, non-CNS progression and death as competing events was conducted for each patient, the first event of CNS progression, non-CNS progression or death was counted
- Alectinib delayed the time to CNS progression in patients with and without CNS metastases at baseline compared with crizotinib

Patients with CNS metastases at baseline



	Crizotinib (N=58)	Alectinib (N=64)
Cause-specific HR (95% CI)	0.18	
P-value (log-rank test)	P<0.0001	

Patients without CNS metastases at baseline



	Crizotinib (N=88)	Alectinib (N=93)
Cause-specific HR (95% CI)	0.14	
P-value (log-rank test)	P<0.0001	

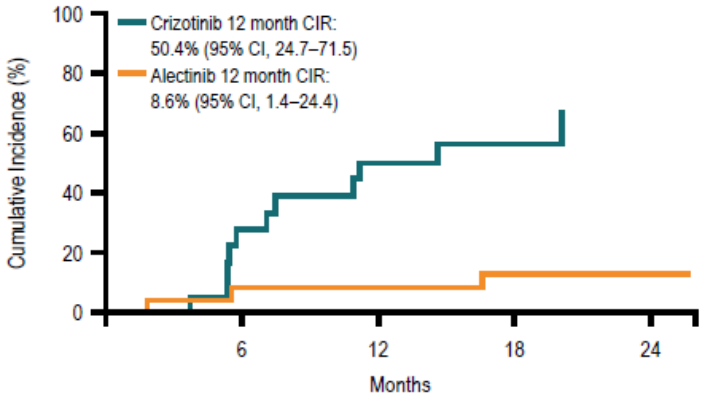
CIR = cumulative incidence rate

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

TIME TO CNS PROGRESSION BY PRIOR BRAIN RT*

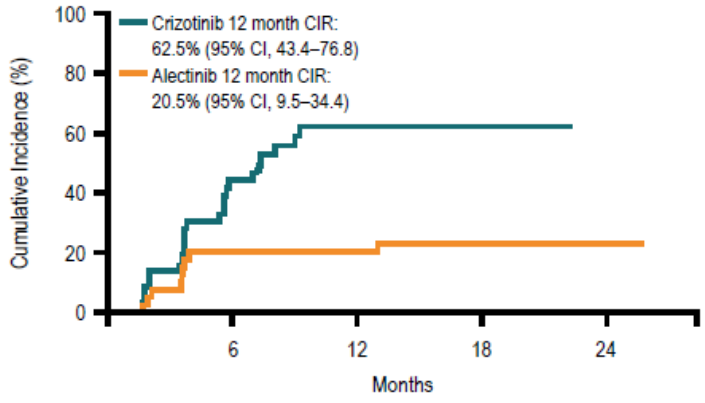
- A competing risk analysis with CNS progression, non-CNS progression and death as competing events was conducted for each patient, the first event of CNS progression, non-CNS progression or death was counted

Patients who had received prior RT



	Crizotinib (N=21)	Alectinib (N=25)
Cause-specific HR (95% CI)	0.11 (0.03–0.42)	
P-value (log-rank test)	P0.0002	

Patients who had not received prior RT



	Crizotinib (N=37)	Alectinib (N=39)
Cause-specific HR (95% CI)	0.22	
P-value (log-rank test)	P<0.0001	

*in patients with brain mets at baseline as determined by IRC
RT= radiotherapy (includes both stereotactic radiosurgery and whole-brain radiotherapy)

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

CNS RESPONSE BY IRC RECIST

	Patients with measurable CNS disease at baseline*				Patients with measurable and non-measurable CNS disease at baseline			
	Patients who had received prior RT		Patients who had not received prior RT		Patients who had received prior RT		Patients who had not received prior RT	
	Crizotinib (n=7)	Alectinib (n=7)	Crizotinib (n=15)	Alectinib (n=14)	Crizotinib (n=21)	Alectinib (n=25)	Crizotinib (n=37)	Alectinib (n=39)
CNS responders, % (95% CI)	71.4 (29.0–96.3)	85.7 (41.2–99.6)	40.0 (16.3–67.7)	78.6 (49.2–95.3)	28.6 (11.3–52.2)	36.0 (18.0–57.5)	24.3 (11.8–41.2)	74.4 (57.9–87.0)
CNS CR, %	0 (0–41.0)	28.6 (3.7–71.0)	6.7 (0.2–32.0)	42.9 (17.7–71.1)	4.8 (0.1–23.8)	20.0 (6.8–40.1)	10.8 (3.0–25.4)	61.5 (44.6–76.6)
CNS DoR, median months (95% CI)	17.3 (2.1–18.1)	NE (14.8–NE)	4.6 (1.9–6.8)	17.3 (1.9–NE)	11.1 (3.7–18.1)	NE (14.8–NE)	3.7 (2.3–5.5)	NE (13.4–NE)

CR = complete response
*Tumour lesions at baseline were considered measurable if they had the following minimum size; 10mm by CT or MRI scan, 10mm caliper measurement by clinical examination, 20mm by chest x-ray

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

MADRID 2017 ESMO congress

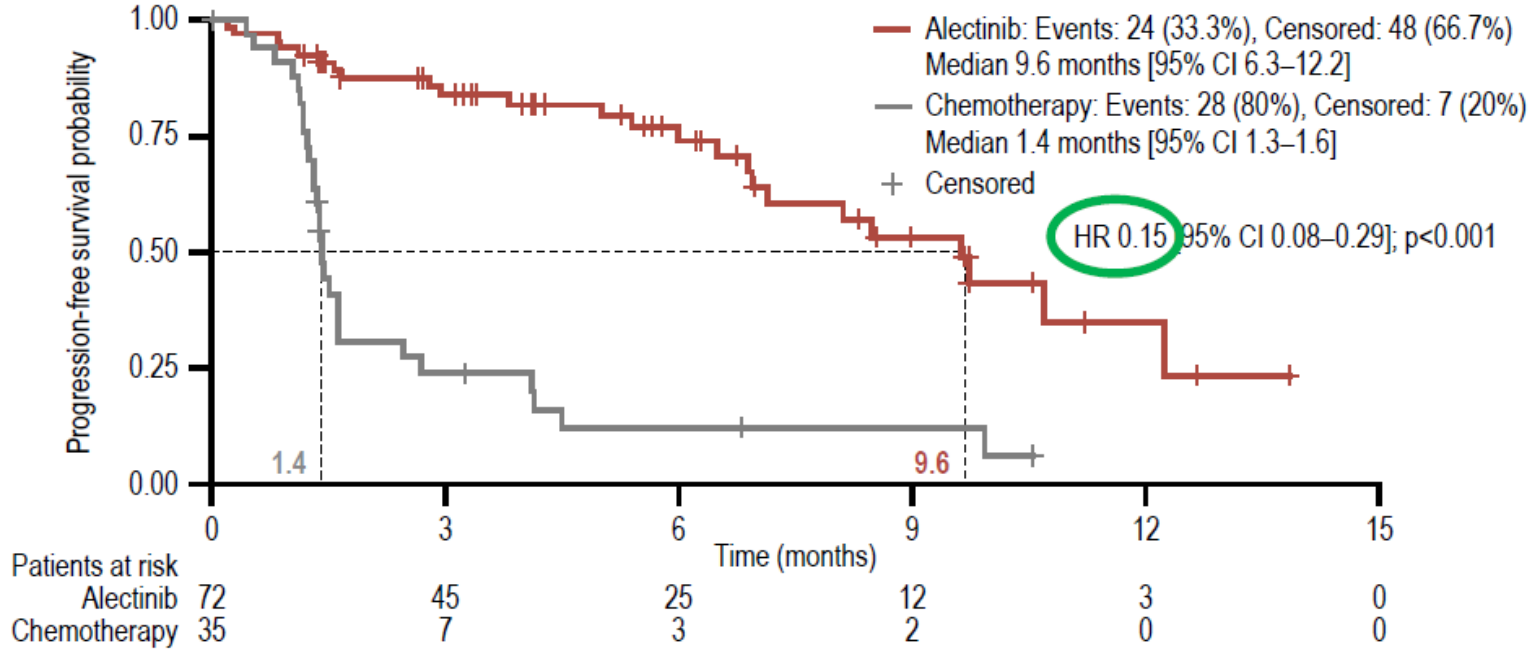
PRIMARY RESULTS FROM THE PHASE III ALUR STUDY OF ALECTINIB VERSUS CHEMOTHERAPY IN PREVIOUSLY TREATED *ALK*+ NON-SMALL-CELL LUNG CANCER (NSCLC)

Silvia Novello,[1] Julien Mazières,[2] In-Jae Oh,[3] Javier de Castro,[4] Maria Rita Migliorino,[5] Aslaug Helland,[6] Rafal Dziadziuszko,[7] Frank Griesinger,[8] Ahmed Kotb,[9] Ali Zeaiter,[9] Andres Cardona,[9] Bogdana Balas,[9] Hrefna Johannsdottir,[9] Ashis Das-Gupta,[9] Jurgen Wolf[10]

[1]Department of Oncology, University of Turin, Turin, Italy; [2]Toulouse University Hospital, Toulouse, France; [3]Department of Internal Medicine, Chonnam National University Hwasun Hospital, Jeonnam, South Korea; [4]Department of Medical Oncology, University Hospital, La Paz, Madrid; [5]A.O. San Camillo Forlanini, Rome, Italy; [6]Department of Cancer Genetics, Institute for Cancer Research, Oslo University Hospital, Radiumhospitalet, Oslo, Norway, and Department of Oncology, Oslo University Hospital, Radiumhospitalet, Oslo, Norway; [7]Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland; [8]Department of Hematology and Oncology, Pius Hospital, University of Oldenburg, Oldenburg, Germany; [9]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [10]Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

PRIMARY ENDPOINT: PFS, INVESTIGATOR-ASSESSED



- At data cut-off (26.01.17), median follow-up was 6.5 months with alectinib and 5.8 months with chemotherapy
- Median time on treatment was 20 weeks (95% CI 0.4–62.1) in the alectinib arm and 6 weeks (95% CI 1.9–47.1) in the chemotherapy arm

CI, confidence interval

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

Ceritinib as First ALK TKI in Advanced ALK+ NSCLC

	ASCEND-1[a] (FAS, N=83, by investigator)	ASCEND-3[b] (FAS, N=124, by BIRC)
ORR (95% CI), %	72 (61-82)	63.7 (54.6-72.2)
Median DOR (95% CI), months	17.0 (11.3-NE)	23.9 (16.6-NE)
DCR (95% CI), %	74 (67-81)	86.3 (79.0-91.8)
Median PFS (95% CI), months	18.4 (11.1-NE)	18.4 (10.9-26.3)
Median OS (95% CI), months	Not reached (19.6 – NE)	NE

BIRC, Blinded Independent Review Committee; DCR, disease control rate; DOR, duration of response; FAS, full analysis set; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

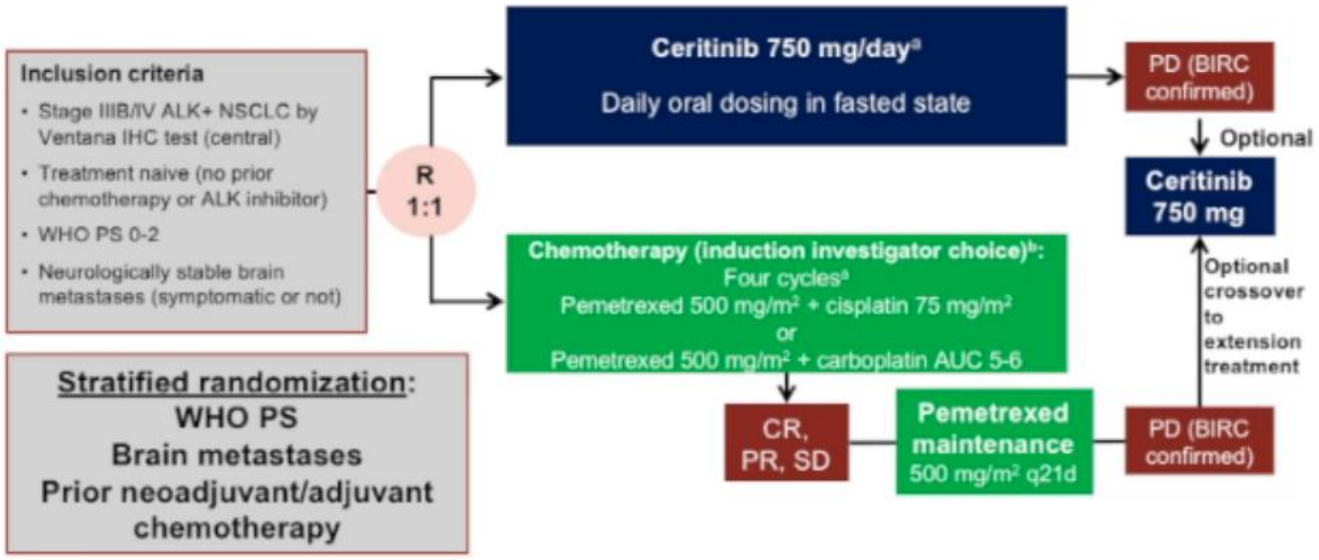
[a]81% of patients had at least 1 prior line of chemotherapy.

[b]98.4% of patients had at least 1 prior line of chemotherapy.

Kim DW et al. *Lancet Oncol* 2016;17(4):452-463; Felip E et al. Presented at: European Society for Medical Oncology Annual Meeting October 7-11, 2016, Copenhagen, Denmark [abstract 1208O].

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

ASCEND-4: Randomized Phase 3 Study Comparing First-Line Ceritinib with Chemo

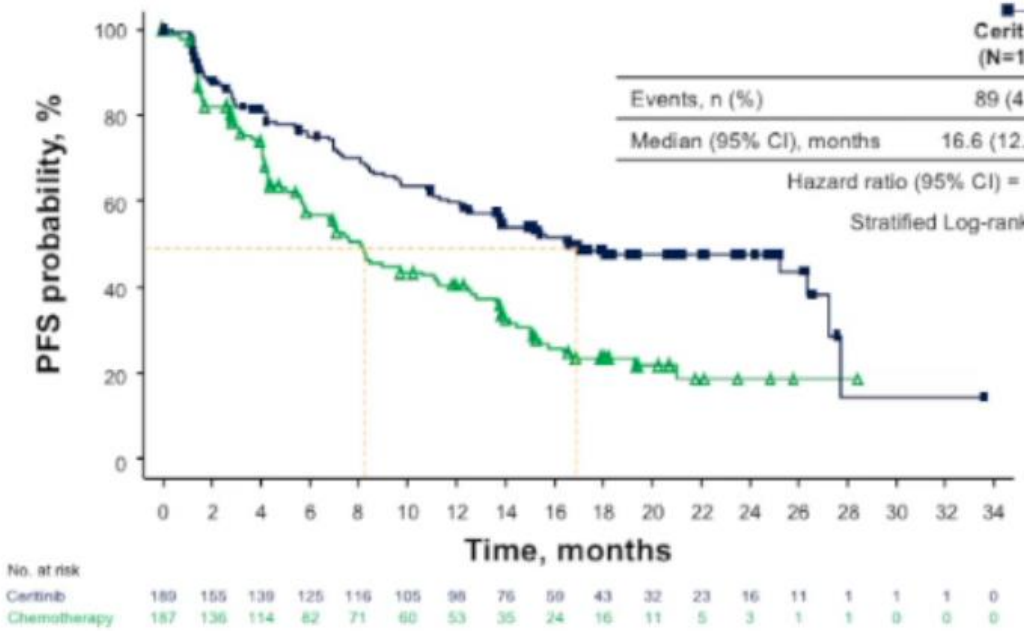


IHC, immunohistochemistry; PD, progressive disease; PS, performance status; WHO, World Health Organization.
[a]One cycle = 21 days.
[b]At the time when ASCEND-4 was designed and initiated, pemetrexed-platinum chemotherapy followed by pemetrexed maintenance was the standard of care in patients with non-squamous advanced NSCLC.
de Castro G, et al. Presented at WCLC 2016.

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

Primary Endpoint: PFS by BIRC

Ceritinib demonstrated an estimated 45% risk reduction vs chemotherapy



	Ceritinib (N=189)	Chemotherapy (N=187)
Events, n (%)	89 (47.1)	113 (60.4)
Median (95% CI), months	16.6 (12.6-27.2)	8.1 (5.8-11.1)

Hazard ratio (95% CI) = 0.55 (0.42-0.73)

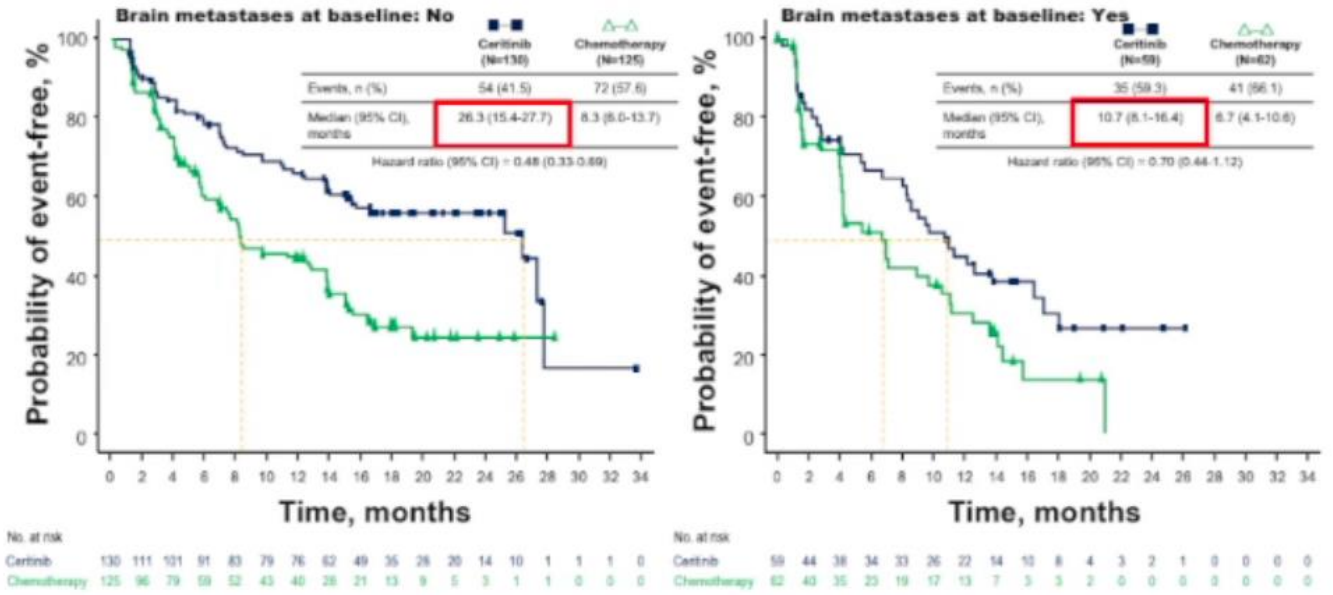
Stratified Log-rank *P*<0.001

de Castro G, et al. Presented at WCLC 2016

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

PFS by BIRC in Patients Without and With Brain Metastases

Ceritinib achieved better PFS in patients without and with brain metastases



de Castro G, et al. Presented at WCLC 2016

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

Summary

- Crizotinib is the current first-line therapy for patients with newly diagnosed, metastatic ALK+ NSCLC
- Second-generation ALK inhibitors are approved for patients who previously received crizotinib
- Second-generation ALK TKIs are highly effective in the first-line setting
  - Alectinib: mPFS NR (vs crizotinib)
  - Ceritinib: mPFS 16.6 mos (vs chemo)
- Alectinib is particularly active in the CNS
- Side effect profiles will impact selection of first-line ALK inhibitor

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

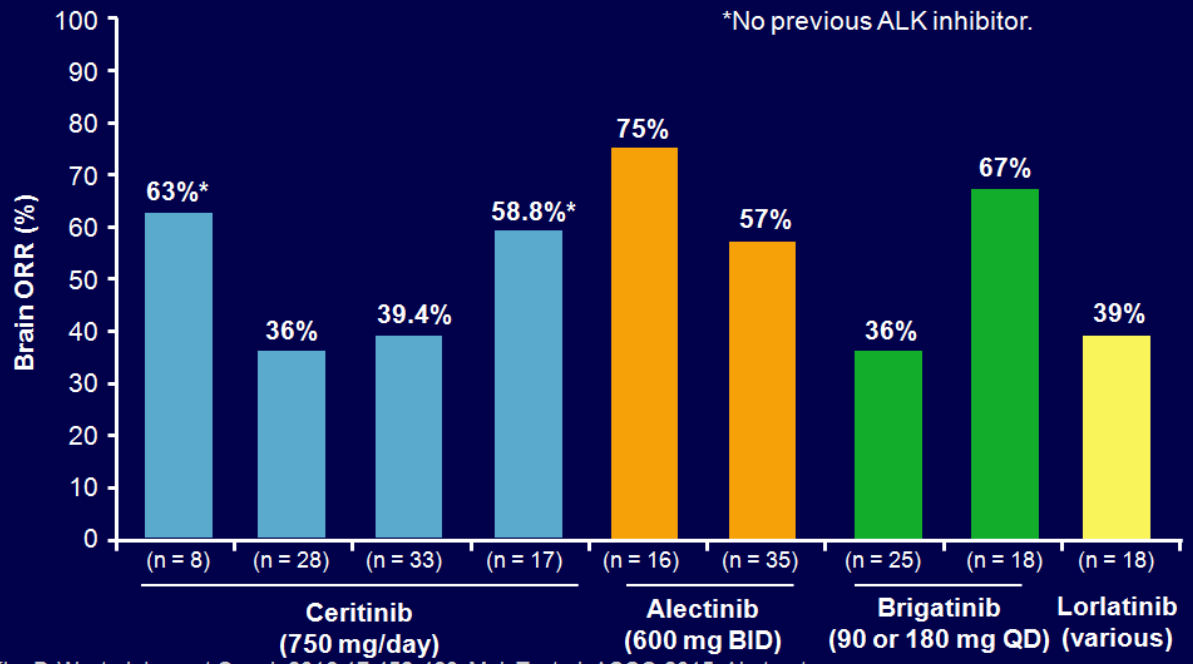
Second-Generation ALK Inhibitors

	N	Phase	Prior Cri?	ORR, %	Median PFS, Mos
Ceritinib					
▪ ASCEND-1[1]	163	I	Yes	56	6.9
	83	I	No	72	18.4
▪ ASCEND-2[2]	140	II	Yes	38.6	5.7
▪ ASCEND-3[3]	124	II	No	63.7	11.1
Alectinib					
▪ Shaw[4]	87	II	Yes	48	8.1
▪ Ou[5]	138	II	Yes	50	8.9
Brigatinib[6]	222	II	Yes	45 (90 mg QD) 54 (180 mg QD)	15.6 (90 mg QD) NR (180 mg QD)
Lorlatinib[7]	54	I/II	Yes (40/41 pts)	46	11.4

1. Kim DW, et al. Lancet Oncol. 2016;17:452-63. 2. Mok T, et al. ASCO 2015. Abstract 8059. 3. Felip E, et al. ASCO 2015. Abstract 8060. 4. Shaw AT, et al. Lancet Oncol. 2016;17:234-242. 5. Ou SH, et al. J Clin Oncol. 2016;34:661-668. 6. Kim DW, et al. ASCO 2016. Abstract 9008. 7. Solomon BJ, et al. ASCO 2016. Abstract 9009.

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

Second-Generation ALK Inhibitor CNS Activity



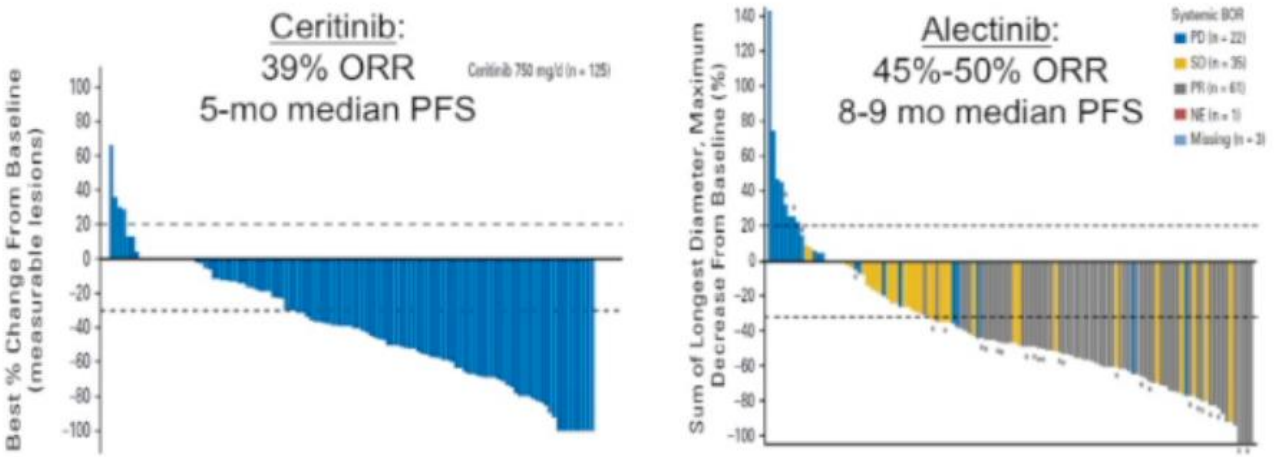
Kim D-W, et al. Lancet Oncol. 2016;17:452-463. Mok T, et al. ASCO 2015. Abstract 8059. Felip E, et al. ASCO 2015. Abstract 8060. Shaw AT, et al. Lancet Oncol. 2016;17:234-242. Ou S, et al. J Clin Oncol. 2016;34:661-668. 5. Kim D-W, et al. ASCO 2016. Abstract 9007. Solomon BJ, et al. ASCO 2016. Abstract 9009.

Slide credit: clinicaloptions.com

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

Second-generation ALK TKI

- Ceritinib and alectinib both FDA approved after failure of crizotinib
  - 39%-50% ORR, 5-9 mo median PFS, CNS activity



DANA-FARBER CANCER INSTITUTE

Crino et al. JCO 2016;
Shaw et al. Lancet Oncol 2016; Ou et al. JCO 2016.

HARVARD MEDICAL SCHOOL

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

Second-generation ALK TKI

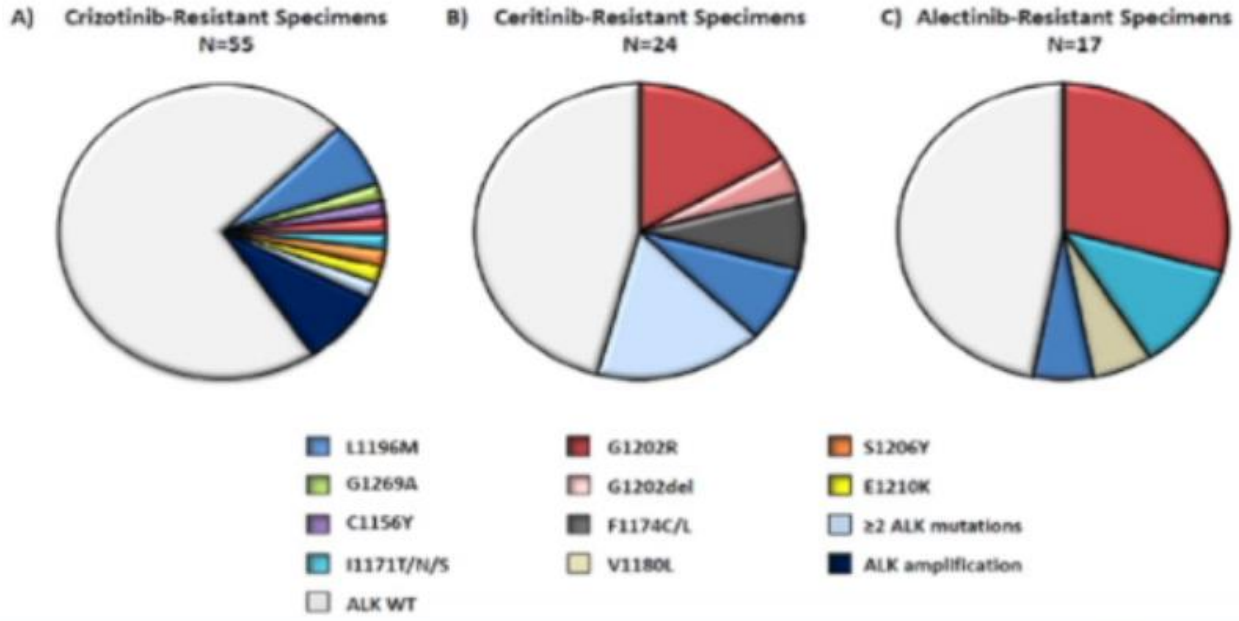
- Alectinib has generally been better tolerated than ceritinib
  - Ceritinib phase II trial reported 46% incidence of grade 3-4 drug-related AE (LFT, N/V, diarrhea), with dose reduction in 54% of patients
  - Alectinib phase II trials reported low incidence of grade 3-4 drug-related AE, with dose reduction in 16%-20% of patients
- Alternate ceritinib dosing (with light snack) is being studied and is better tolerated

Crino et al. JCO 2016;
Shaw et al. Lancet Oncol 2016; Ou et al. JCO 2016.

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

ALK resistance

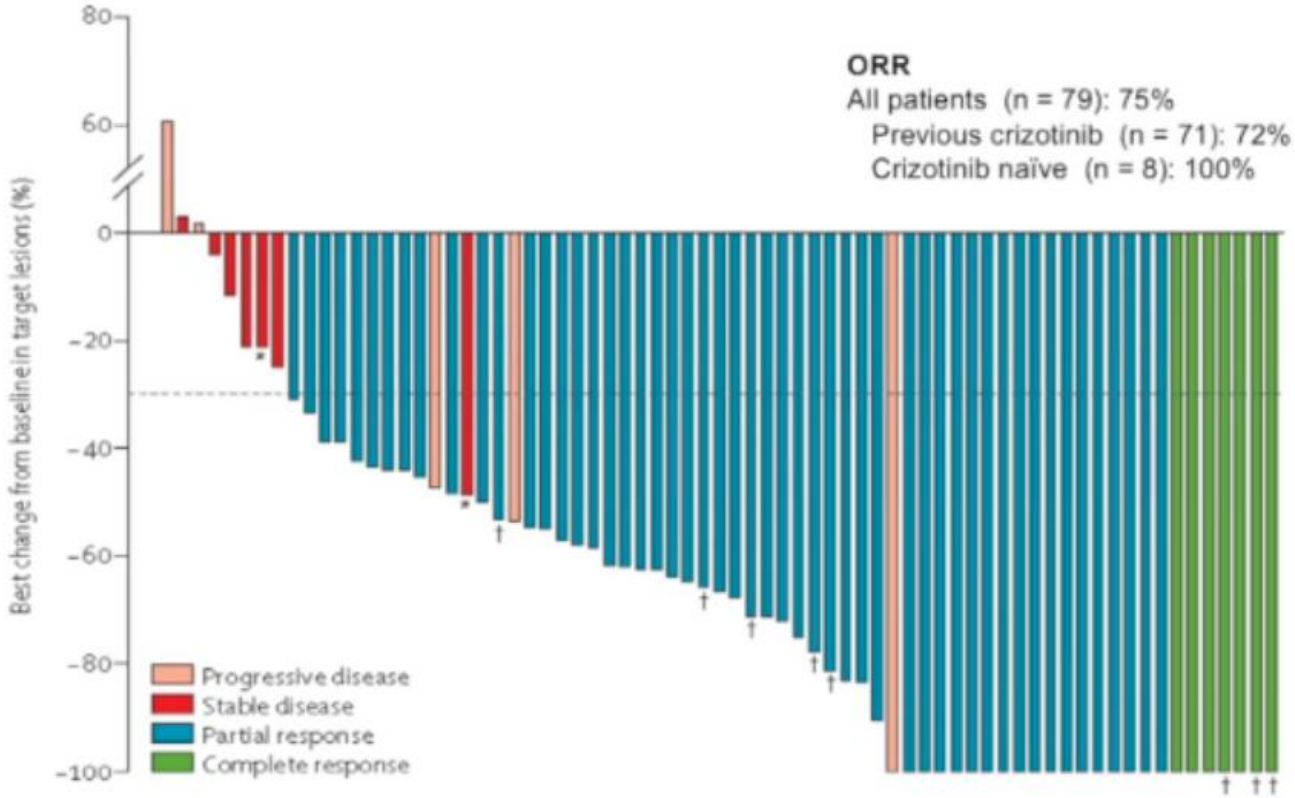
- Emerging data suggests that newer ALK inhibitors alter the spectrum of resistance mutations, inducing more ALK resistance mutations



Gainor et al. Cancer Disc 2016.

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

Response to Brigatinib in ALK+ NSCLC



DANA-FARBER CANCER INSTITUTE

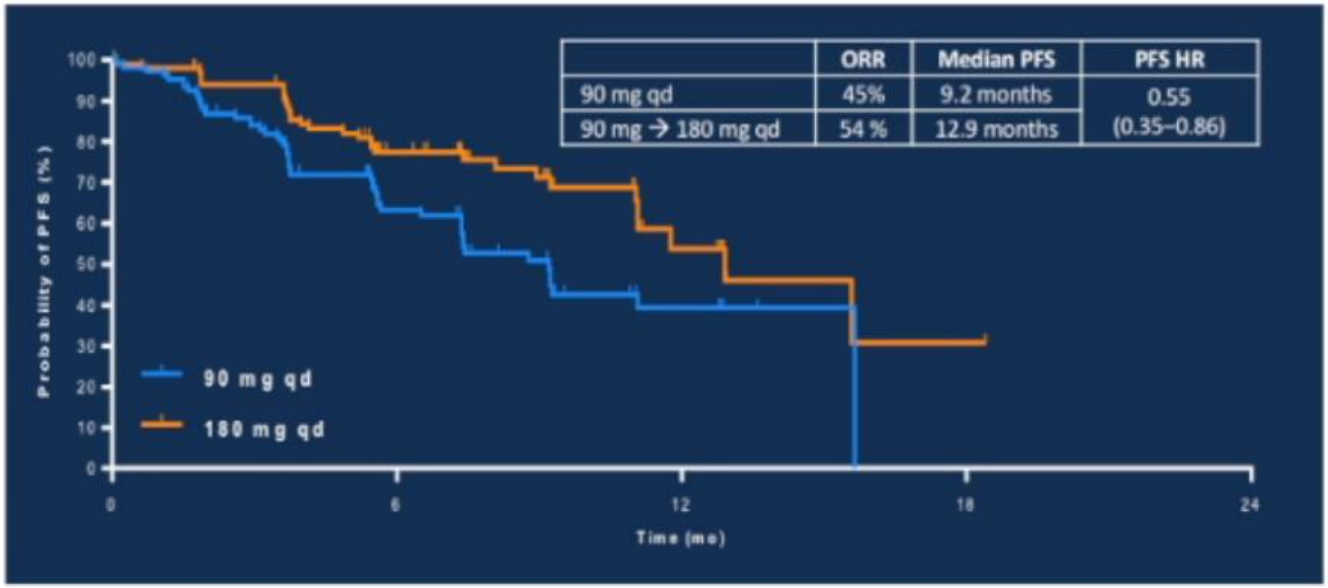
Gettinger SN et al. Lancet Oncol 2016;17(12):1683-96.

HARVARD MEDICAL SCHOOL

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

Brigatinib

- Broad activity against a range of resistance mutations
- ALTA trial randomized 222 patients with NSCLC with crizotinib resistance to two different doses:



	ORR	Median PFS	PFS HR
90 mg qd	45%	9.2 months	0.55 (0.35–0.86)
90 mg → 180 mg qd	54 %	12.9 months	

Gettinger et al. Lancet Oncol 2016; Kim et al. ASCO 2016; Zhang et al. CCR 2016.

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

ALTA: Select Adverse Events

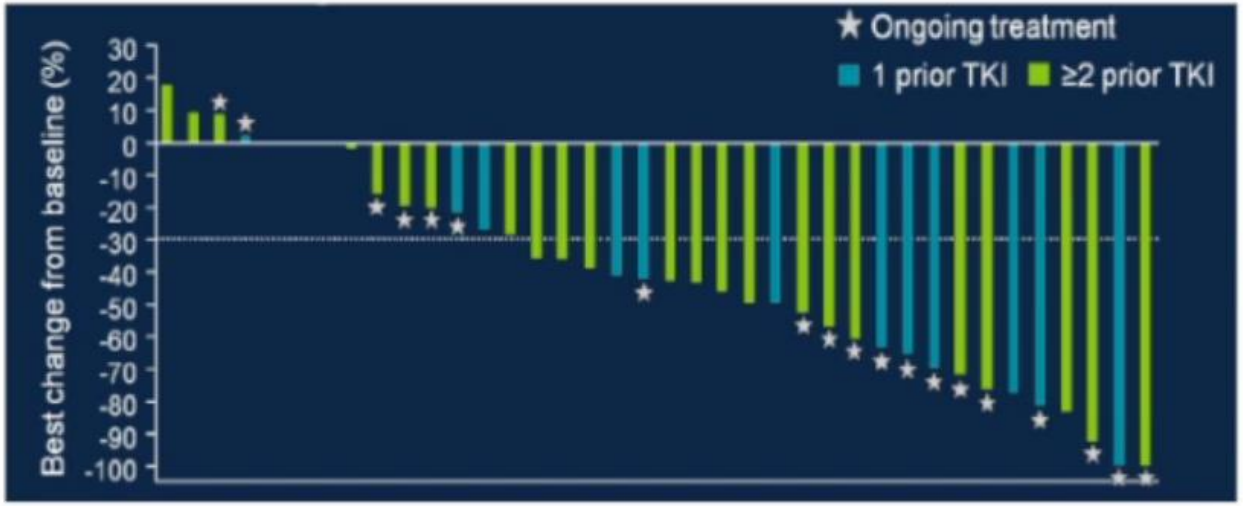
Any grade AE (≥10% of patients)	Brigatinib 90 mg qd (n=109)	Brigatinib 180 mg qd (n=110)
Nausea	33%	40%
Diarrhea	19%	38%
Cough	18%	34%
Dyspnea	21%	21%
Hypertension	11%	21%

A subset of pulmonary AEs with early onset (including dyspnea, hypoxia, cough, pneumonia, pneumonitis) occurred in 14 (6%) of patients, before dose escalation to 180 mg

Kim D et al. ASCO 2016;17:Abstract 9007.

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

Phase I study of Lorlatinib in ALK+ NSCLC



Lorlatinib demonstrated robust clinical activity in patients with ALK+ and patients with ROS1+ NSCLC, most of whom had brain metastases and had received ≥ 1 prior ALK TKI

Solomon BJ et al. Proc ASCO 2016;Abstract 9009.

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

Phase I/II Trial of Ensartinib (X-396) in ALK+ NSCLC

Response	All patients (n=27)	Crizotinib treated (n=12)
Partial response	19 (70%)	10 (83%)
Stable disease	2 (7%)	1 (8%)

Most adverse events were grade 1/2 and included rash, nausea, vomiting and fatigue

Lovly CM et al. Proc AACR 2016;Abstract CT088.

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

Lots of ALK inhibitors

	Crizotinib	Ceritinib	Alectinib	Brigatinib
Indication	ALK+ NSCLC	ALK resistance	ALK resistance	(Not yet approved)
Highly active	Yes	Yes	Yes	Yes
Tolerability	Good	Moderate	Good	Good
CNS activity	Some	Good	Good	Good
Potency against resistance	Poor	Moderate	Moderate	Good

- Potent CNS activity of newer ALK inhibitors, combined with favorable toxicity profile, means that patients can stay on therapy for a durable period
- Moving potent ALK inhibitors into first line to prevent resistance is intuitive

DANA-FARBER CANCER INSTITUTE

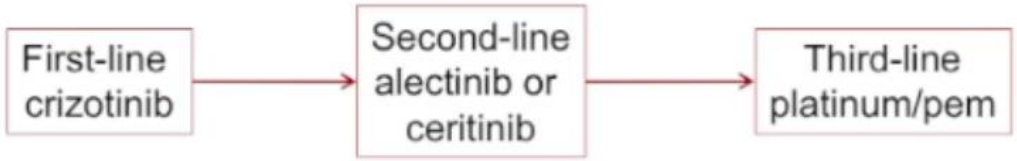
Kwak et al. NEJM 2010; Awad et al. Clin Adv Hematol Oncol 2014; Kodama et al. MCT 2014; Solomon et al. JCO 2016.

HARVARD MEDICAL SCHOOL

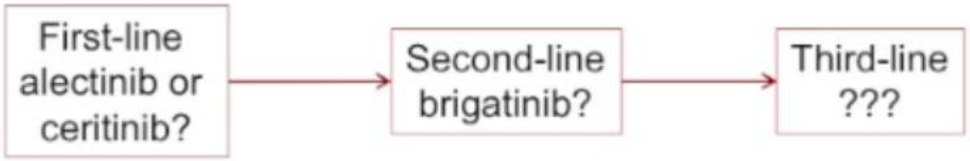
Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

Summary

- **Current standard approach for ALK+ NSCLC:**



- **Future approach envisioned for ALK+ NSCLC?**



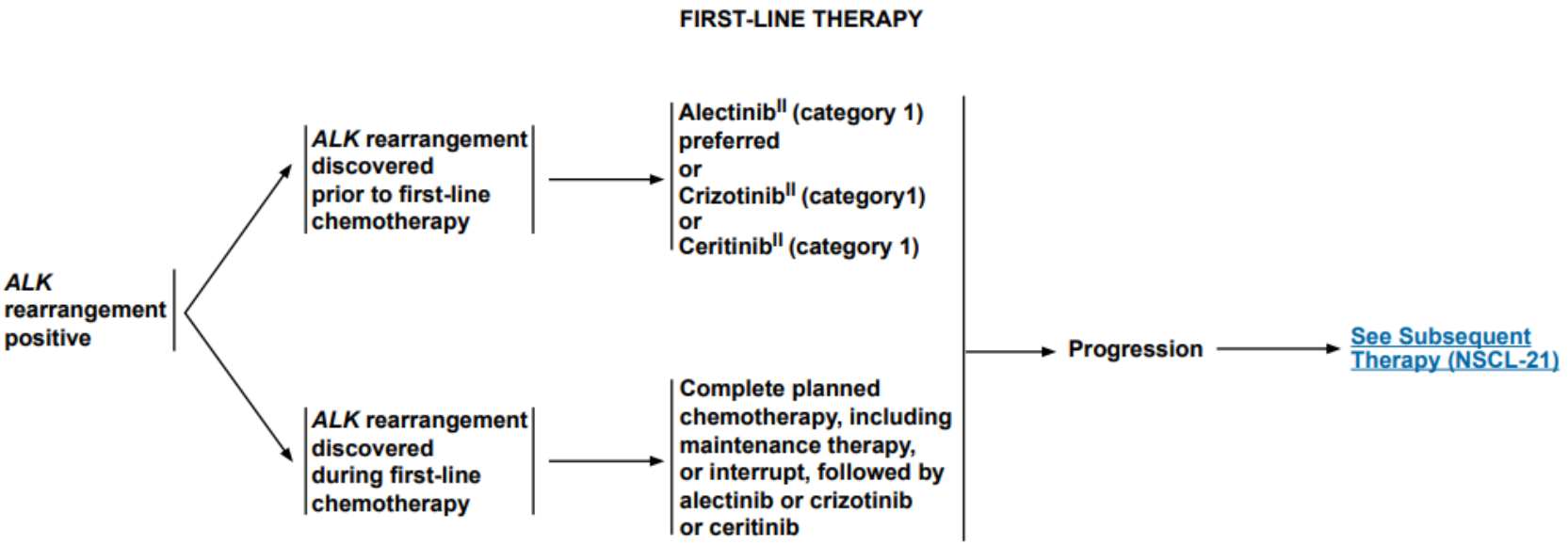
Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

National Comprehensive Cancer Network®

NCCN Guidelines Version 8.2017
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

ALK REARRANGEMENT POSITIVE[a]



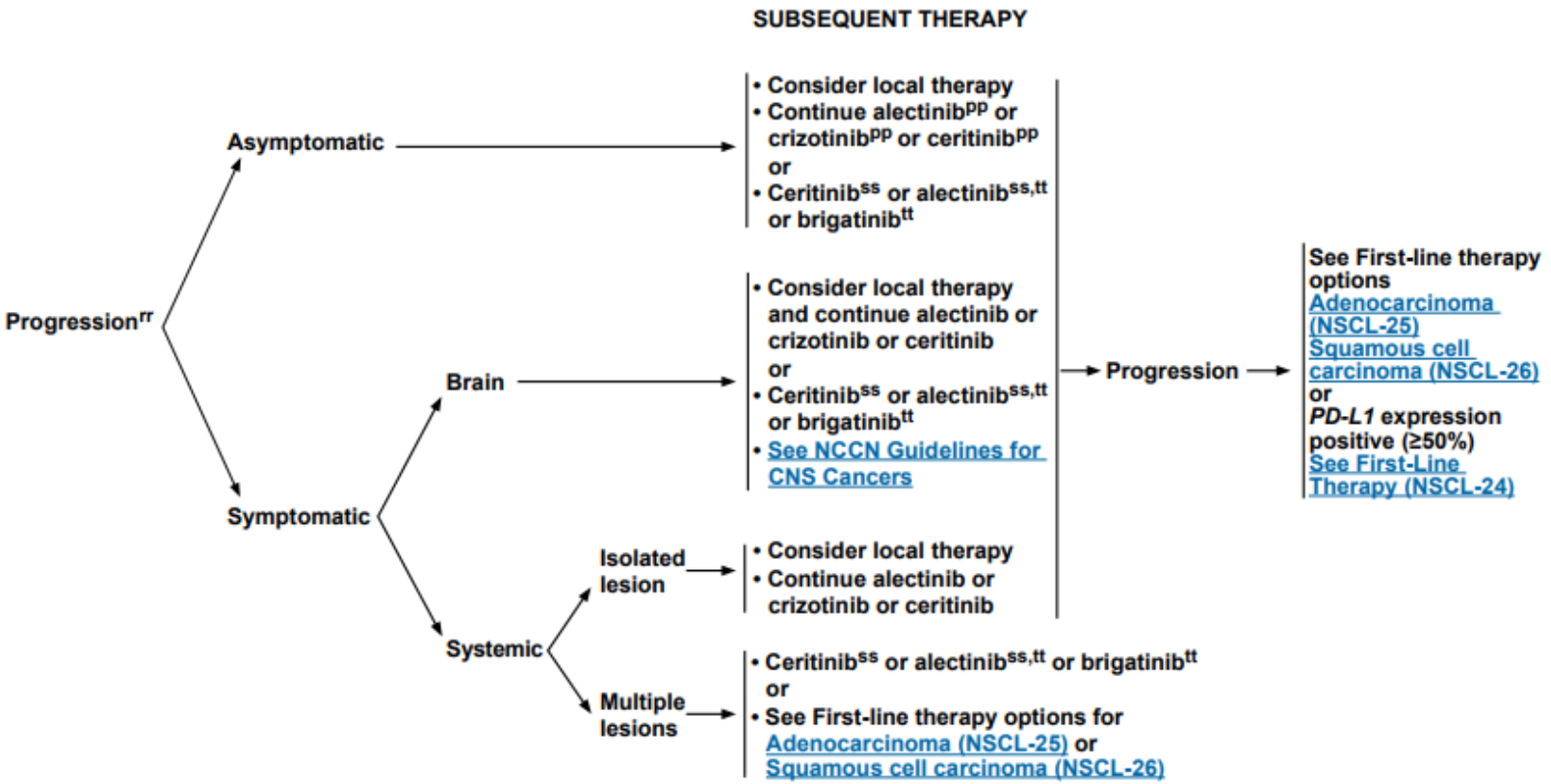
Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

National Comprehensive Cancer Network®

NCCN Guidelines Version 8.2017
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

ALK REARRANGEMENT POSITIVE[a]



[a] See Principles of Pathologic Review (NSCL-A).
[pp] For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.
[rr] Patients who are intolerant to crizotinib may be switched to ceritinib, alectinib, or brigatinib.
[ss] If not previously given.
[tt] Alectinib or brigatinib are treatment options for patients with ALK-positive metastatic NSCLC that have progressed on crizotinib.

Metastatik KHDAK Hedefe Yönelik Tedaviler

Mechanisms for acquired resistance to EGFR, ALK-TKIs

		EGFR-TKI	ALK-TKI
Target modification	seconday mutation	T790M	L1196M
		others (rare) L747S, D761Y, T854A	others (common) 1151Tins, L1152R, C1156Y, F1196L, G1202R, S1206Y, G1269A
	amplification/loss	EGFR amp/loss	ALK amp
Bypass/ accessory pathway	bypass track	c-MET, HER2, HER3, IGF1R, AXL, DAPK, HER3, JAK HGF, FGF, VEGF	EGFR (exp, , HER2,3, EGFR mutation HGF/c-Met Kit EGF ligands
	down stream pathway	BRAF、CRKL, PIK3CA, PTEN, MEK1, NF-kB, PUMA	KRAS mutation
Histologic transformation		EMT (TGFb, MED12, AXL, Notch1)	EMT
		SCLC	

Metastatik KHDAK Hedefe Yönelik Tedaviler

Molecularly Targeted Therapy

- EGFR activating mutation [exon 19 or 21]
  - Erlotinib, Afatinib and Gefitinib are FDA approved 1st line
- EGFR resistance mutation [exon 20 T790M]
  - Osimertinib is FDA approved
- EGFR wild type
  - Erlotinib approved 2nd/3rd line regardless of EGFR status
  - Afatinib approved 2nd line squamous cell histology
- ALK gene-rearranged (+)
  - Crizotinib is approved any line ALK + only
  - Ceritinib and Alectinib approved as 2nd line ALK
- ROS-1 gene re-arranged (+)
  - Crizotinib

Metastatik KHDAK Hedefe Yönelik Tedaviler

Tedavi Şekli	Medyan Sağkalım (ay)
Destek tedavisi	3-4
Eski KT rejimleri	6-8 ay
Güncel ikili kombinasyonlar	8-10 ay
İkili KT+hedefe yönelik ajan	12
Histolojiye göre KT	12
1.basamak sonrası idame	14-16
EGFR TKI, ALK TKI	+28

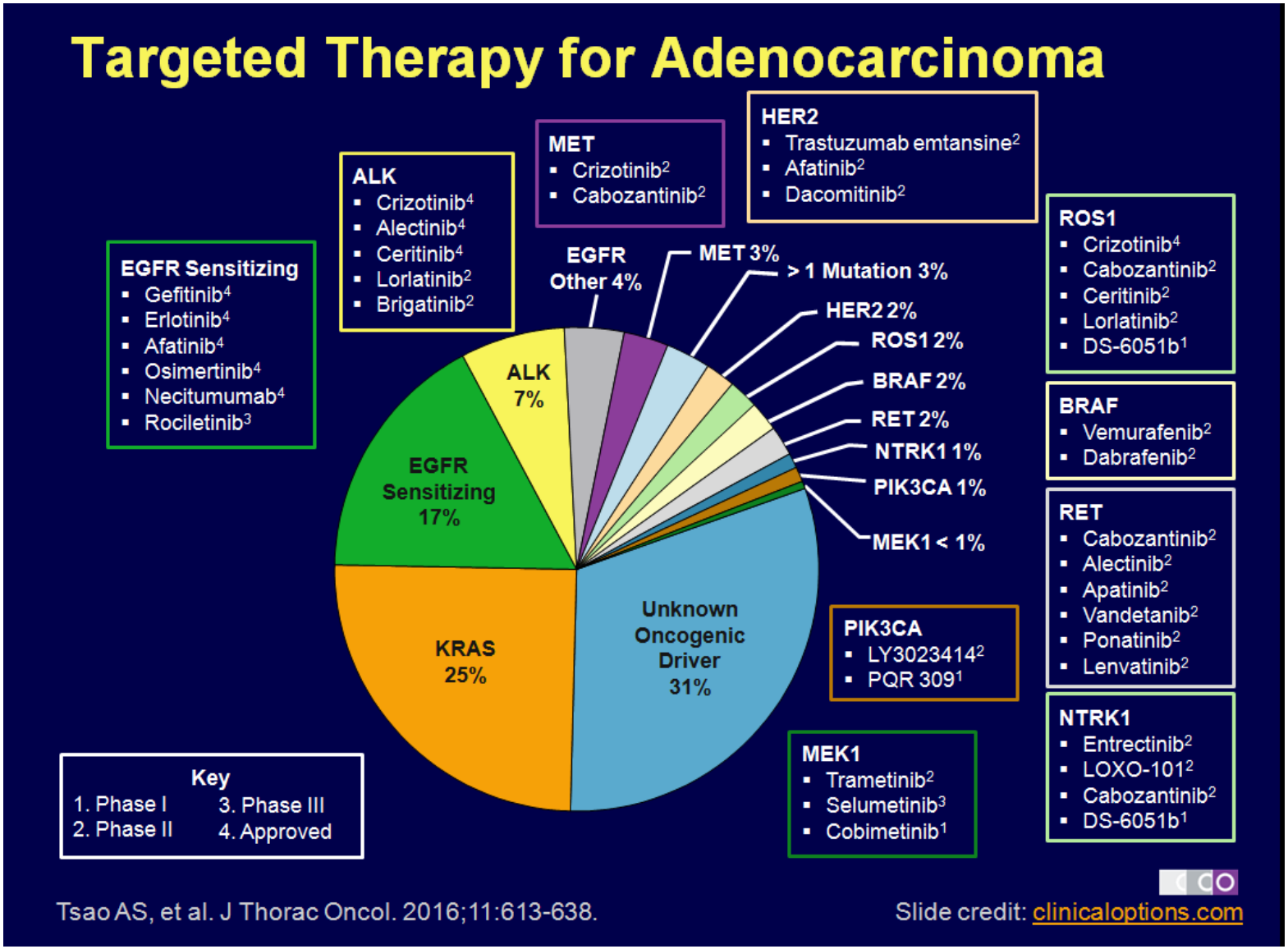
Metastatik KHDAK Hedefe Yönelik Tedaviler

What should we test for?

Target	IHC	Translocation	Amplification	Mutation
EGFR	No	No	No	YES
HER-2	No	No	No	YES
ALK	YES	YES	No	No
ROS-1	No	YES	No	No
KRAS	No	No	No	YES
BRAF	No	No	No	YES
RET	No	YES	No	YES
MET	No	No	No	YES
PDL-1	YES	No	No	No

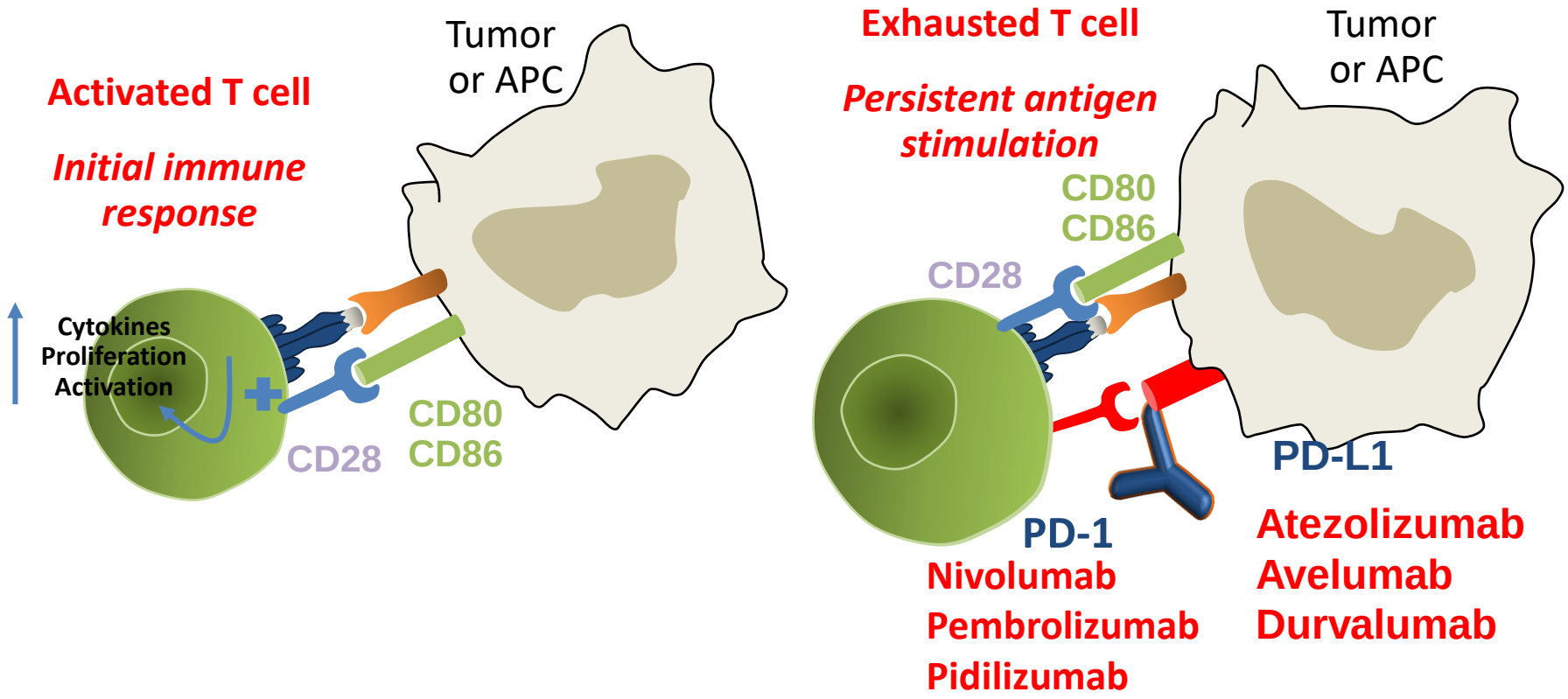
- I favor NGS in most of my patients, rather than looking for individual gene abnormalities

Metastatik KHDAK Hedefe Yönelik Tedaviler



Akciğer Kanserinde İmmünoterapi

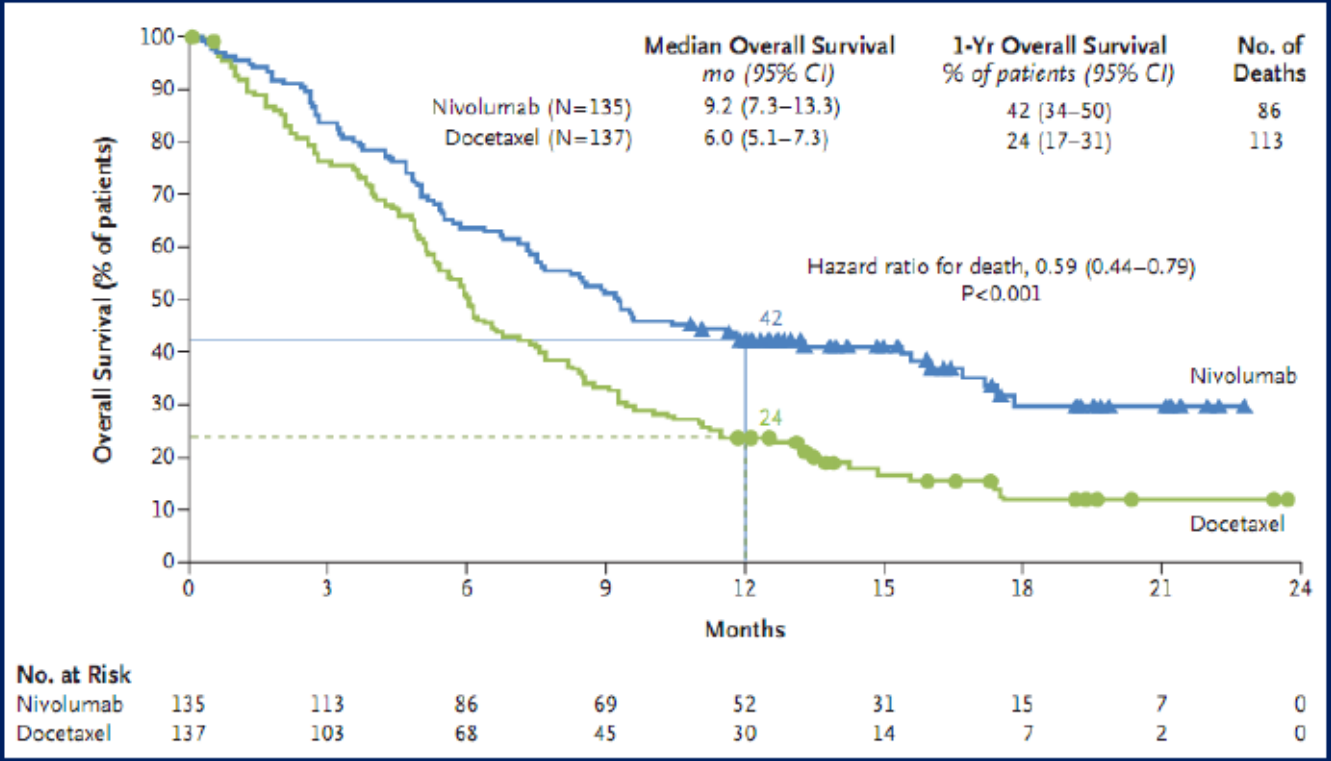
PD-1 as a Target in Cancer Therapy



McDermott DF, et al. Cancer Med. 2013;2:662-673

Akciğer Kanserinde İmmünoterapi

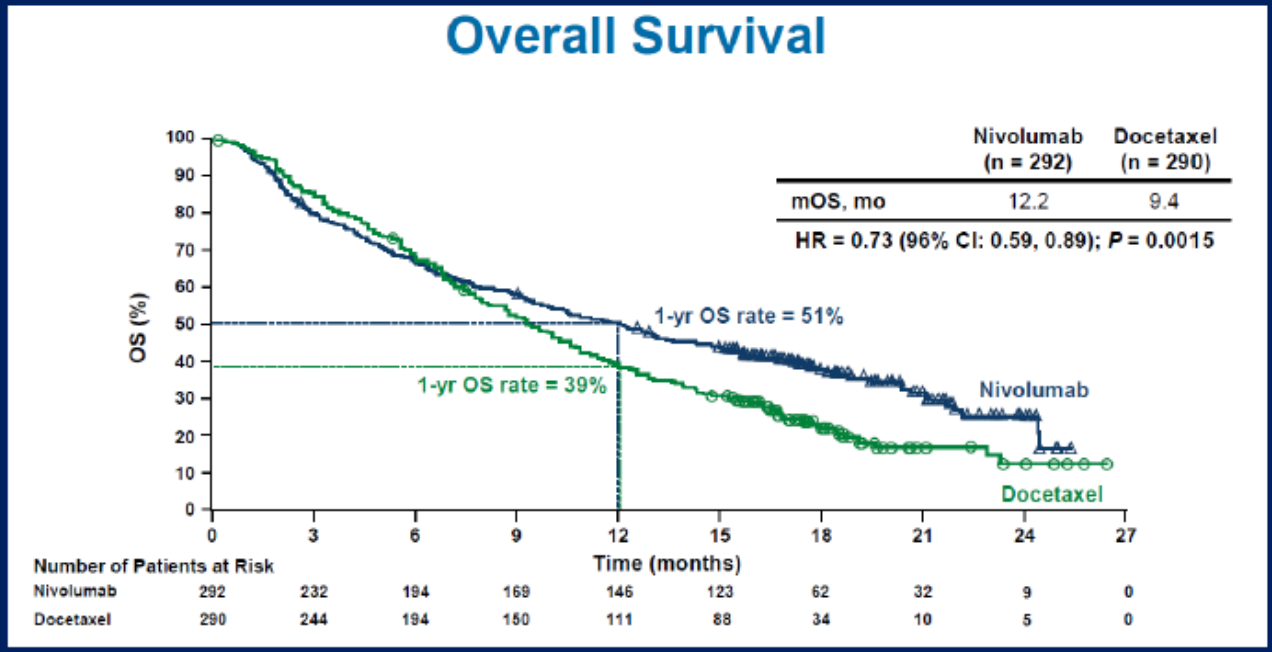
Squamous Cell Carcinoma
Nivolumab vs. Docetaxel 2nd line



Brahmer J, et al. *N Engl J Med*. 2015;373(2):123-135.

Akciğer Kanserinde İmmünoterapi

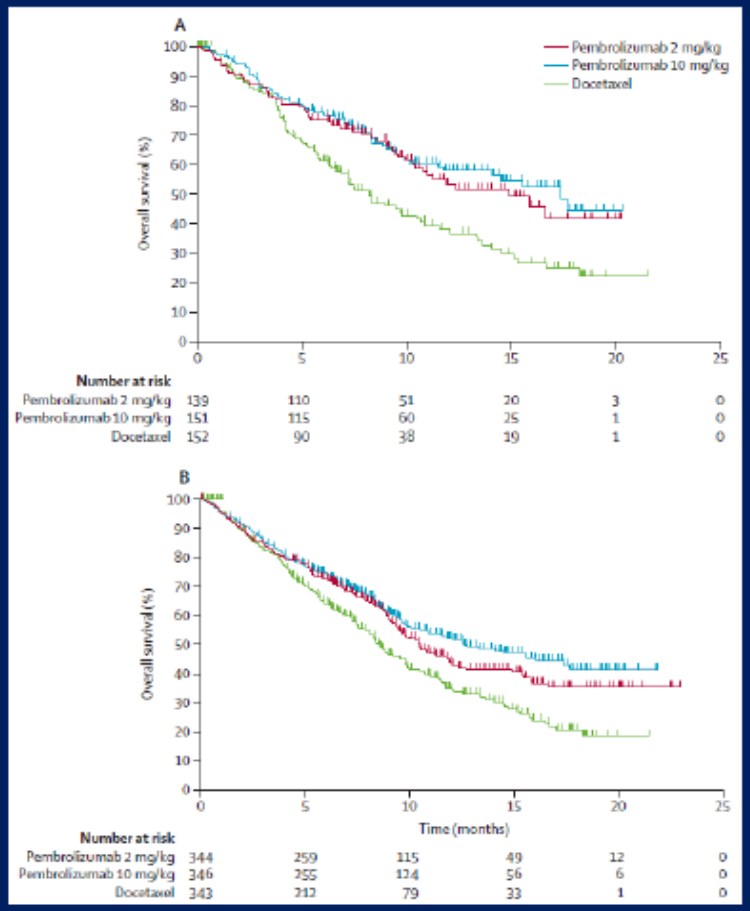
Non-Squamous NSCLCs
Nivolumab vs. Docetaxel 2nd line



Borghaei H, et al. *N Engl J Med*. 2015;373(17):1627-1639

Akciğer Kanserinde İmmünoterapi

Pembrolizumab vs. Docetaxel



Herbst R et al Lancet. 2015;375: 1540-50

Median Overall Survival

Patients with 50% tumor proportion score:

- **14.9 months for pembro 2 mg/kg**
- **17.3 months for pembro 10 mg/kg**
- **8.2 months for docetaxel**

Overall Population:

- **10.4 months for pembro 2 mg/kg**
- **12.7 months for pembro 10 mg/kg**
- **8.5 months for docetaxel**

Updated Data on OS based TPS

1-24% HR 0.74
25-49% HR 0.86
50-74% HR 0.58
≥ 75% HR 0.51

ASCO 2016, Abstract 9015

Akciğer Kanserinde İmmünoterapi

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csőszi, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators*

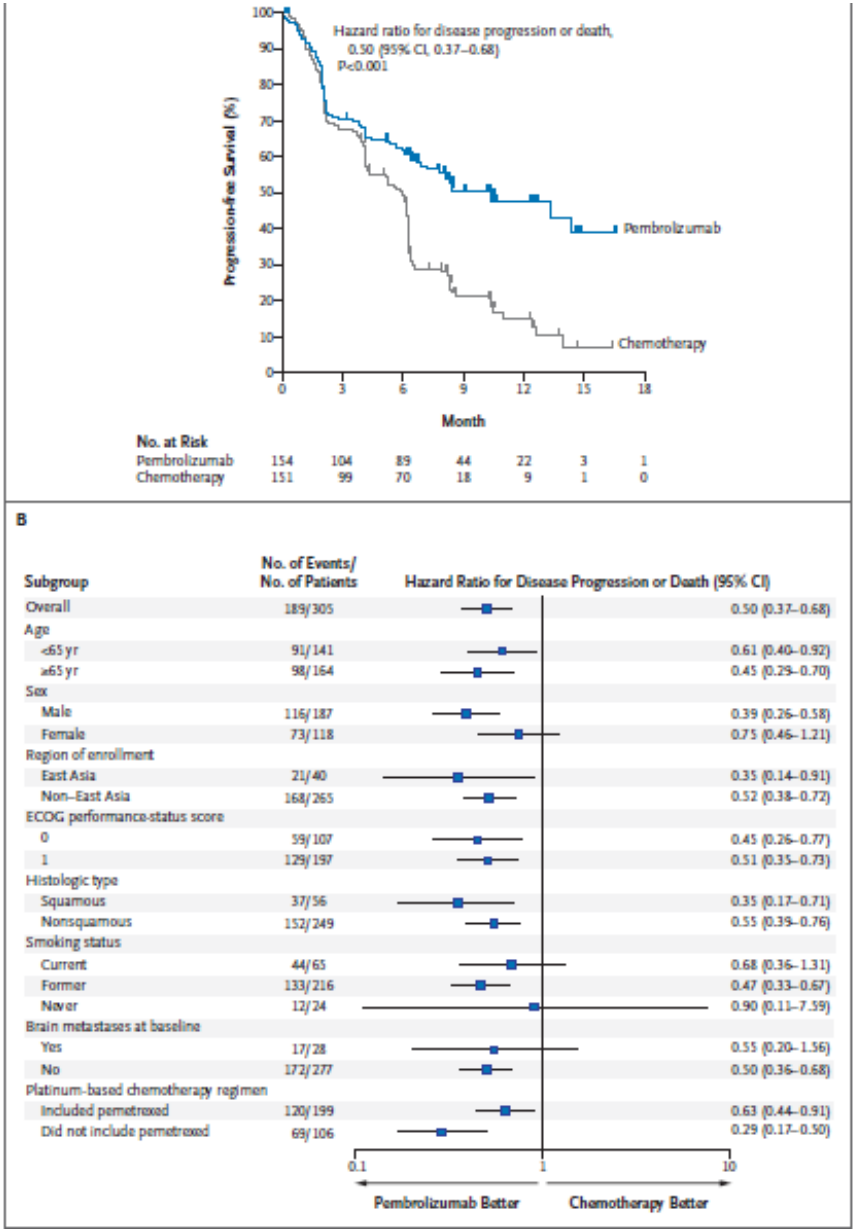
ABSTRACT

BACKGROUND

Pembrolizumab is a humanized monoclonal antibody against programmed death 1 (PD-1) that has antitumor activity in advanced non–small-cell lung cancer (NSCLC), with increased activity in tumors that express programmed death ligand 1 (PD-L1).

From Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany (M.R.); Hospital Universitario Insular de

Akciğer Kanserinde İmmünoterapi



KHDAK Tedavi Algoritması Nasıl Olacak?

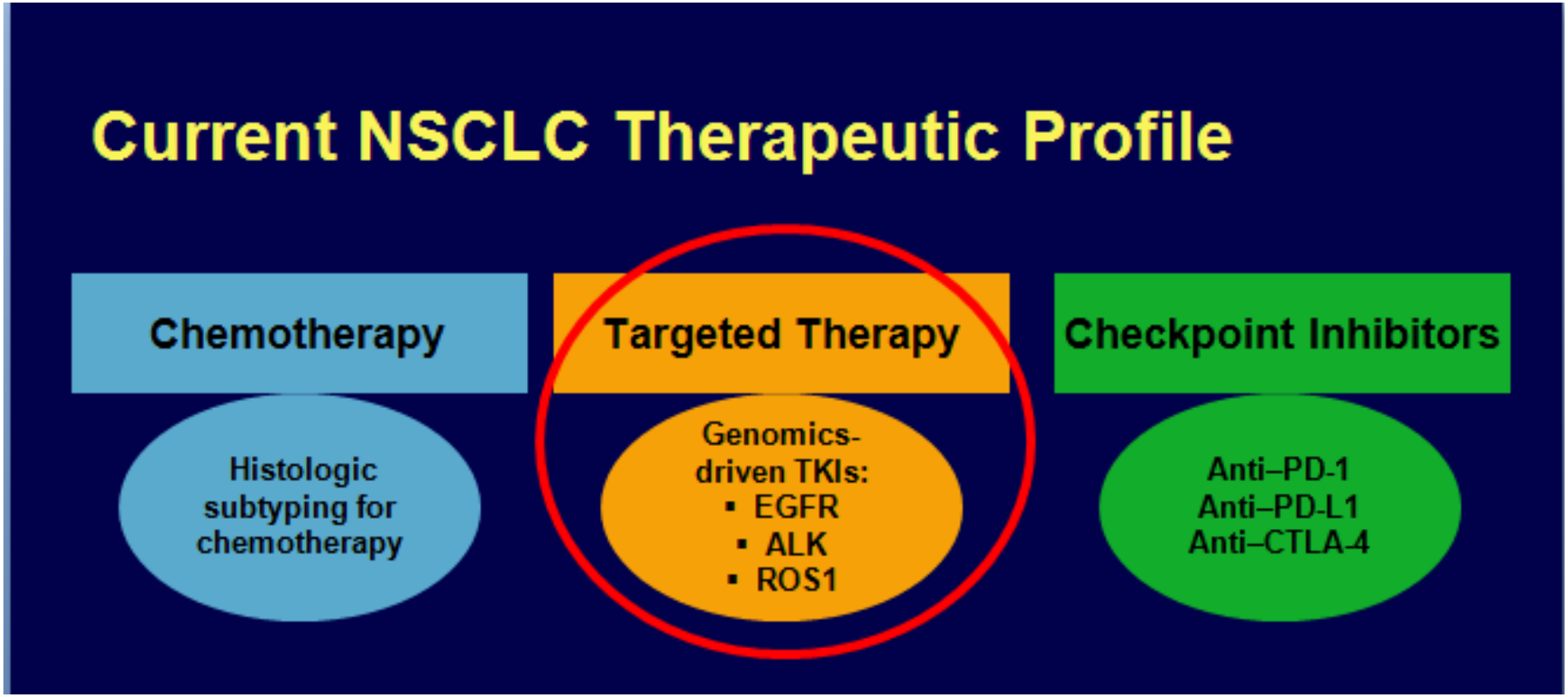
Ongoing Phase III Trials of Combination Therapy with Checkpoint Inhibitors in Nonsquamous Metastatic NSCLC

Checkpoint Inhibitor	Trial Identifier	N	Combination Evaluated
Nivolumab Ipilimumab	CheckMate 227 (NCT02477826)	1,980	Nivolumab + ipilimumab Nivolumab + platinum doublet
Pembrolizumab	KEYNOTE-189 (NCT02578680)	570	Cisplatin/pemetrexed + pembrolizumab
Atezolizumab	NCT02657434	680	Atezolizumab + carboplatin Atezolizumab + cisplatin/pemetrexed
	IMpower 130 (NCT02367781)	550	Atezolizumab + carboplatin/paclitaxel
	IMpower 150 (NCT02366143)	1,200	Atezolizumab + carboplatin/paclitaxel ± bevacizumab
Durvalumab (MEDI 4736)	NEPTUNE (NCT02542293)	800	Durvalumab + tremelimumab (1st line, Primary endpoint: OS)
	MYSTIC (NCT02453282)	675	Durvalumab + tremelimumab (1st line, Primary endpoint: PFS)
	ARCTIC (NCT02352948)	730	Durvalumab + tremelimumab (≥3rd line)

SARAH CANNON

www.clinicaltrials.gov, Feb 10, 2016

KHDAK Tedavi Algoritması



Avelumab in First-line Non-Small Cell Lung Cancer (JAVELIN Lung 100)

This study is currently recruiting participants. (see Contacts and Locations)

Verified November 2016 by EMD Serono

Sponsor:
EMD Serono

Collaborator:
Merck KGaA

Information provided by (Responsible Party):
EMD Serono

ClinicalTrials.gov Identifier:
NCT02576574

First received: October 13, 2015
Last updated: November 9, 2016
Last verified: November 2016
History of Changes

Purpose

The purpose of this study is to demonstrate superiority with regard to progression free survival (PFS) based on an Independent Review Committee (IRC) assessment of avelumab versus platinum-based doublet in non-small cell lung cancer (NSCLC) subjects with Programmed death ligand 1+ (PD-L1+) tumors.

Metastatik KHDAK Hedefe Yönelik Tedaviler

2017 Treatment Algorithm

Determine Performance Status, Histology, PD-L1 status and Presence of Driver Mutations

	Adenoca with Driver PS 0-3	Adeno PD-L1>49% PS0-3?	Adenoca No Driver PD-L1<50% PS 0-2	Squamous PD-L1<50 PS 0-2	Squamous PD-L1>49 PS 0-23?
1st Line	EGFR + Gefitinib, Erlotinib, Afatinib,osimertinib ALK/ROS1+ Crizotinib,Alectinib BRAF+ Debrafenib/Trametinib RET, MET, HER2, NTRK+ specific TKI	Pembrolizumab	Platinum doublet (Pem,Taxane) ± Bevacizumab	Platinum doublet (Gem, Taxane) ± Necitumumab	Pembro
Maintenance	Continue TKI	Pembrolizumab	Bev, Pem, Erlotinib or none	None? Doce, Gem, Erlotinib	Pembro
2nd/3rd Line	2nd/3rd-generation TKI then chemo	Platinum Doublet +/-bev Doce+/-ram	Nivo,Pembro,Atezo Doce ± Ramucirumab	Nivolumab, Doce ± Ram	Plat. Doublet+/- Bev

LCNE, Large cell neuroendocrine (LCNE) carcinomas; TKI, tyrosine kinase inhibitor; Pem, pemetrexed; Gem, gemcitabine; Etop, etoposide; Doce, docetaxel; Ram, ramucirumab