

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

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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

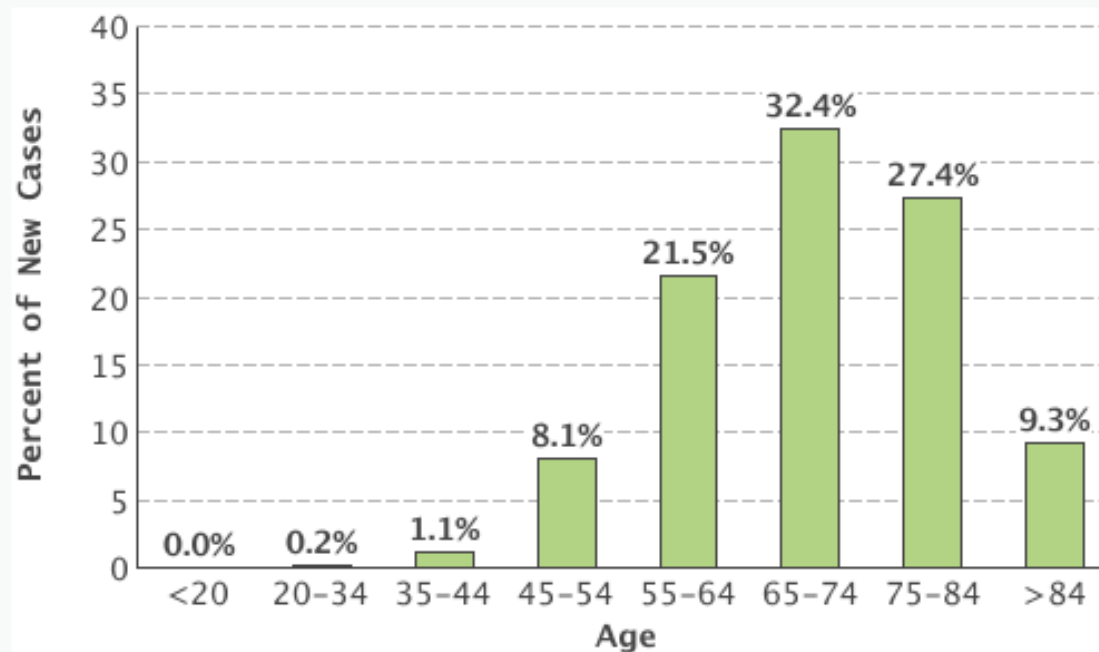
Lung and bronchus cancer represents 13.3% of all new cancer cases in the U.S.



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

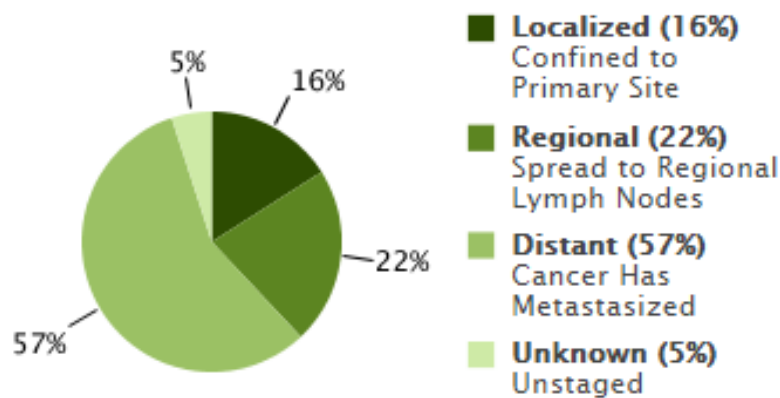
SEER 18 2009-2013, All Races, Both Sexes

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

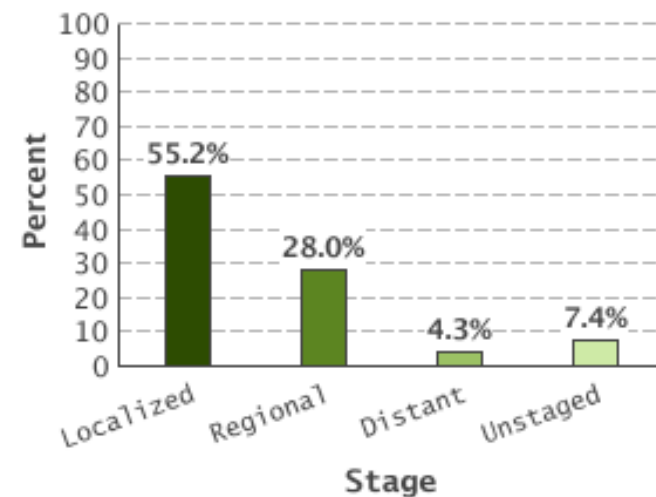
Akciğer Kanserinde insidans ve Mortalite

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

Percent of Cases by Stage



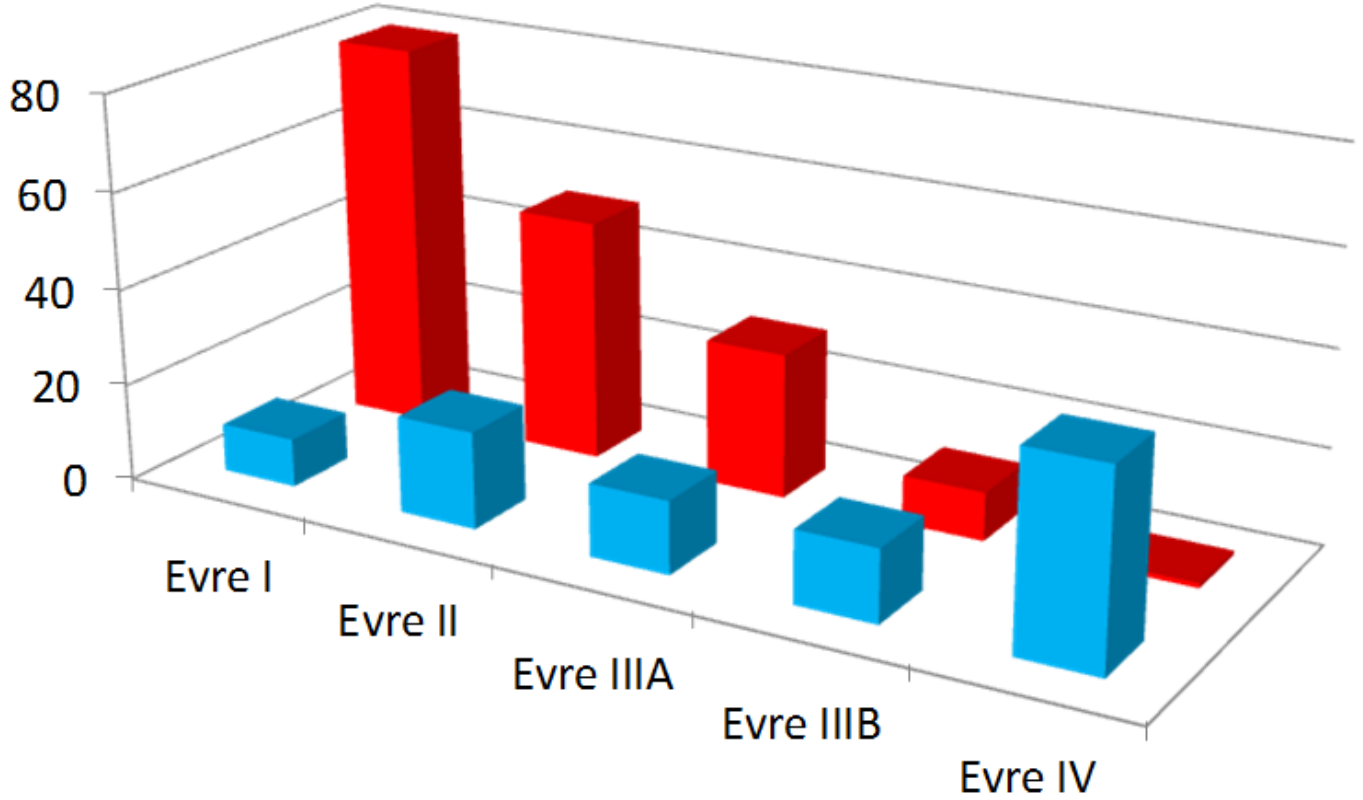
5-Year Relative Survival



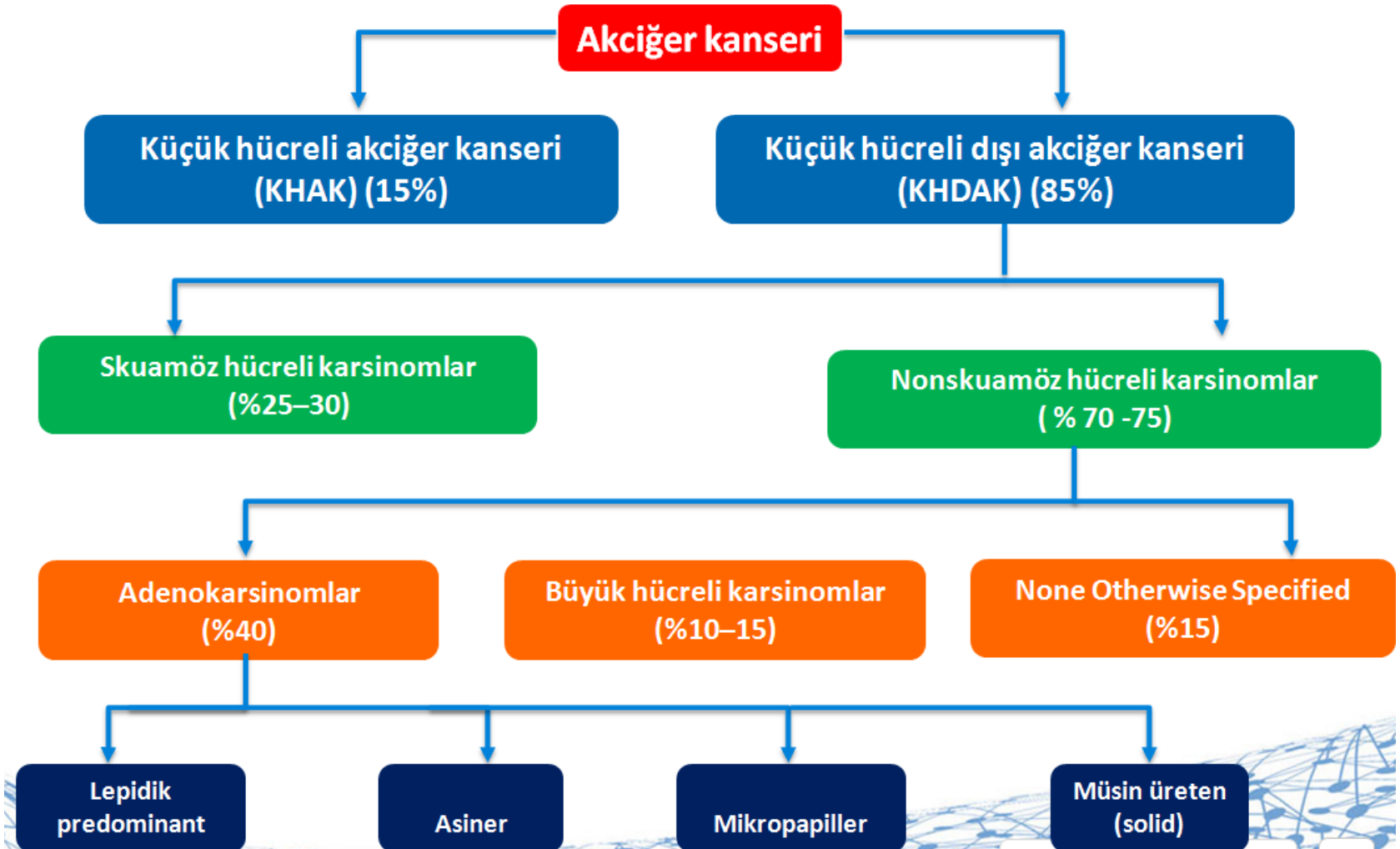
SEER 18 2006-2012, All Races, Both Sexes by SEER Summary Stage 2000

KHDAK'de Saękalım

■ Görölme Oranı
■ 5 Yıllık Saękalım



Akciğer Kanserinde Patolojik Sınıflandırma

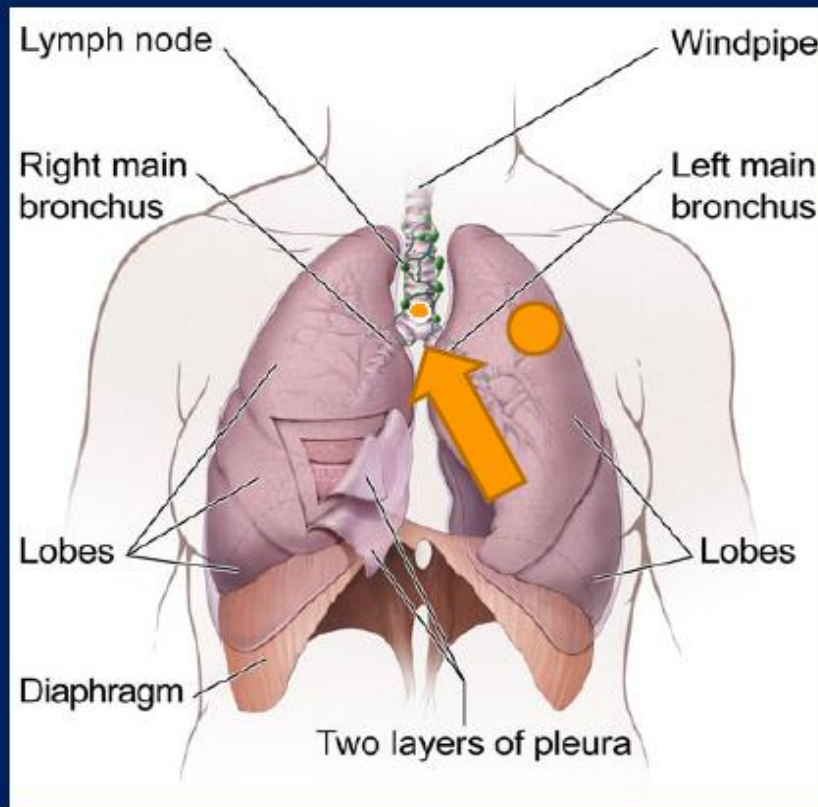


KHDAK Patolojik Sınıflandırma

- 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 (+)

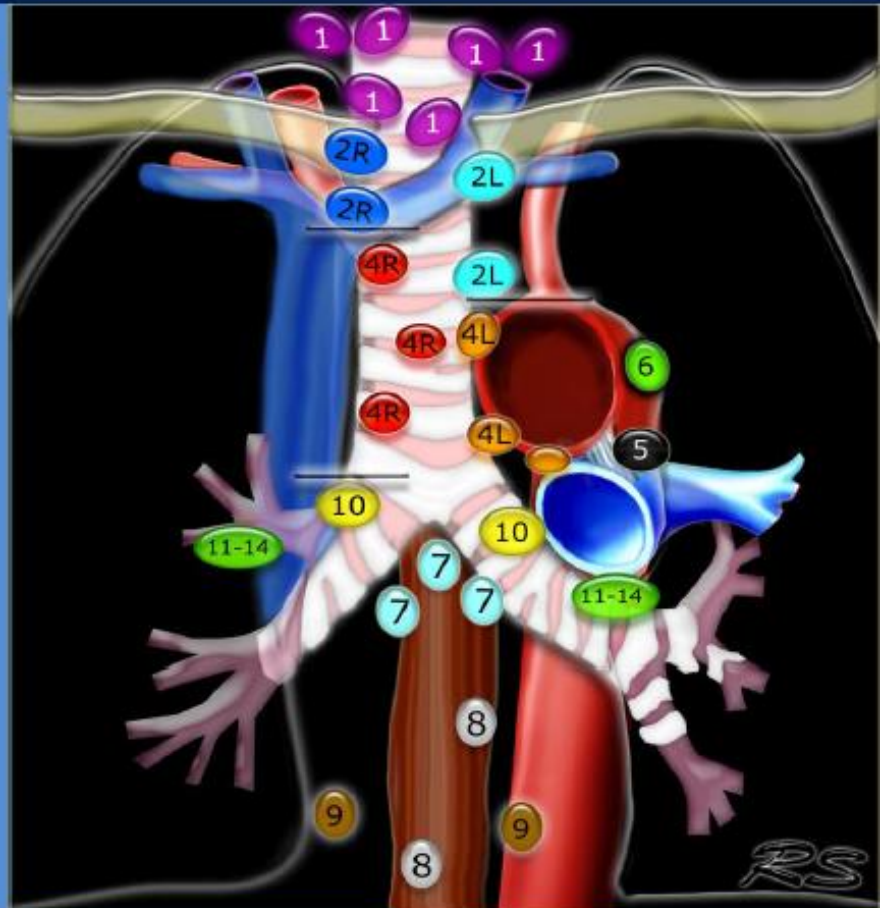
KHDAK Klinik Sınıflandırma

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)

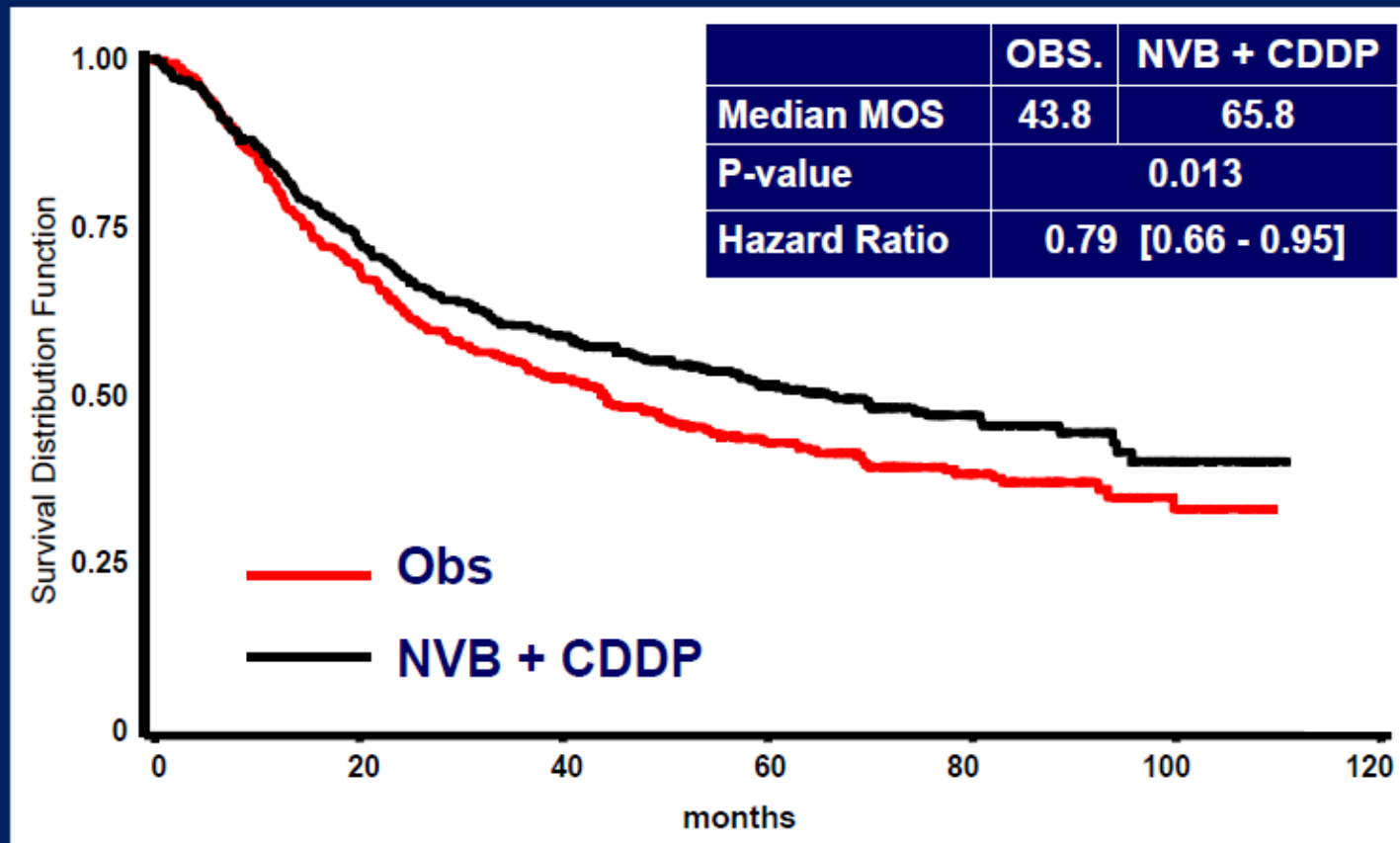
EBUS: 2, 4, 7, 10, hilar

EUS: 7, 8, 9

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Adjuvant Cisplatin/Vinorelbine in stage I-III NSCLC

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

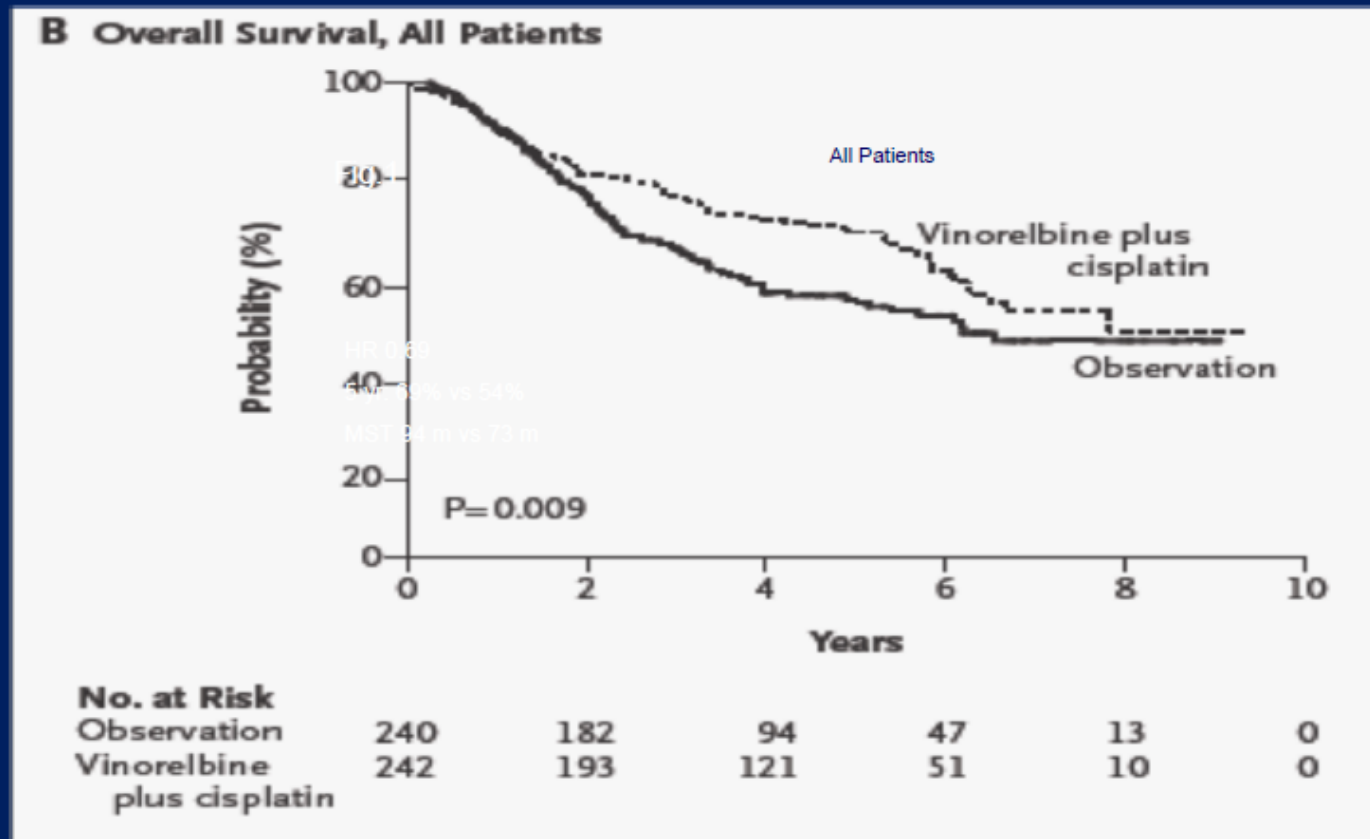


Radiation was allowed

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Adjuvant Cisplatin/Vinorelbine in stage Ib-II NSCLC

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



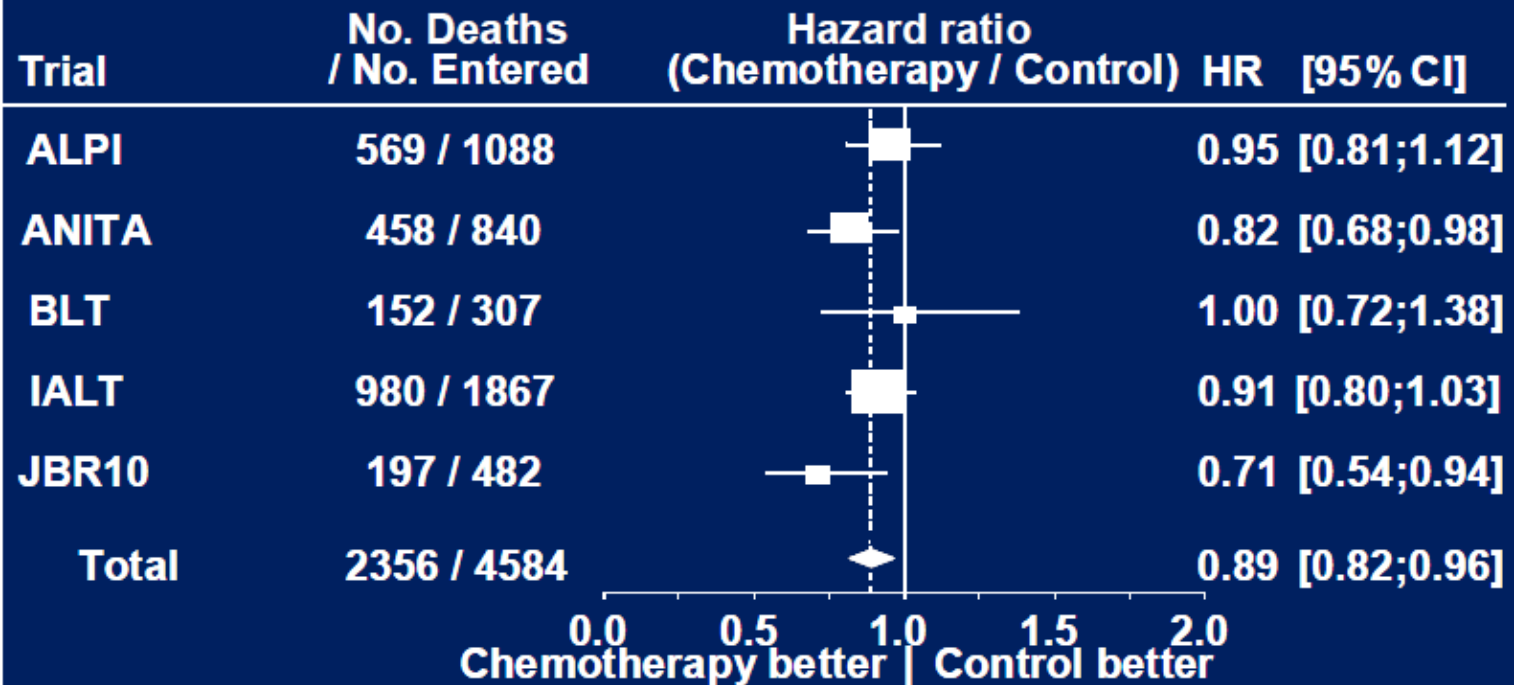
Absolute improvement in 5 yr OS = 15% (69% vs. 54%)

No radiation allowed

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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

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.

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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

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LACE Pooled Analysis

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

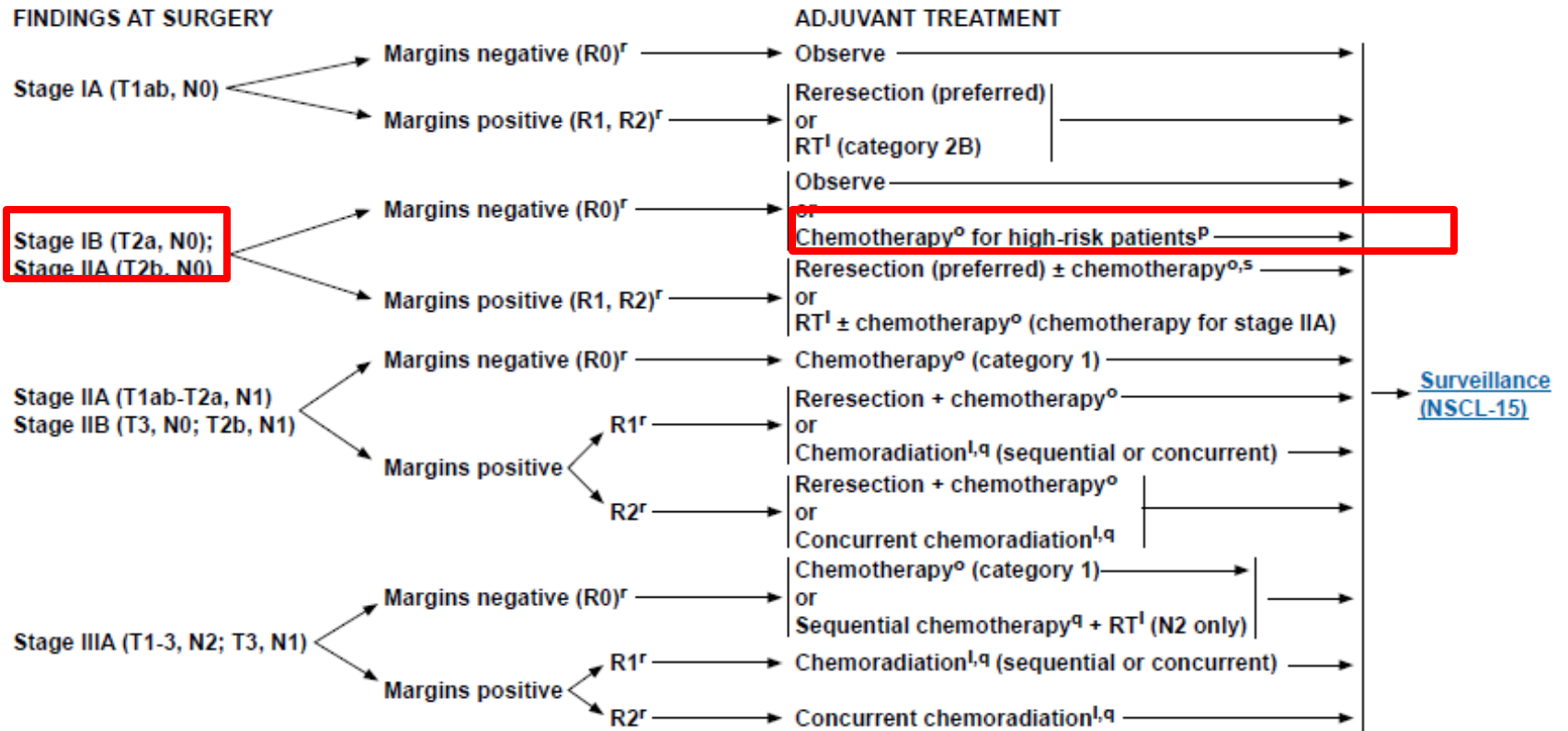
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Stage IB survival by tumor size

Strauss et al, ASCO 2011 (abst 7015)

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

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^lSee Principles of Radiation Therapy (NSCL-C).

^oSee Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).

^pExamples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and unknown lymph node status (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.

^qSee Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

^rR0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

^sIncreasing size is an important variable when evaluating the need for adjuvant chemotherapy.

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National
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Cancer
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NCCN Guidelines Version 2.2017 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)
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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

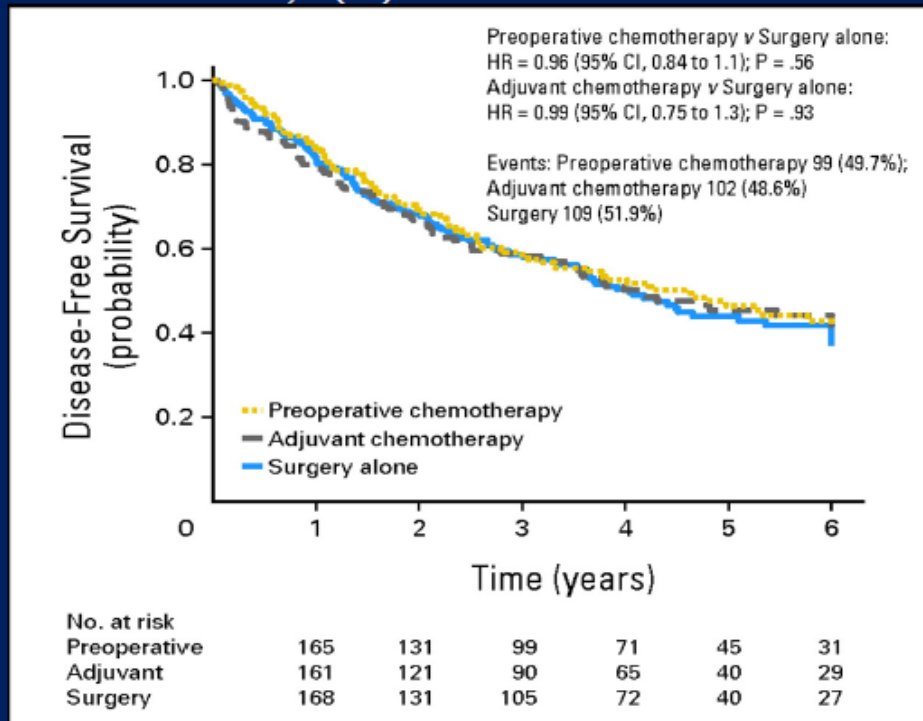
Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin

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



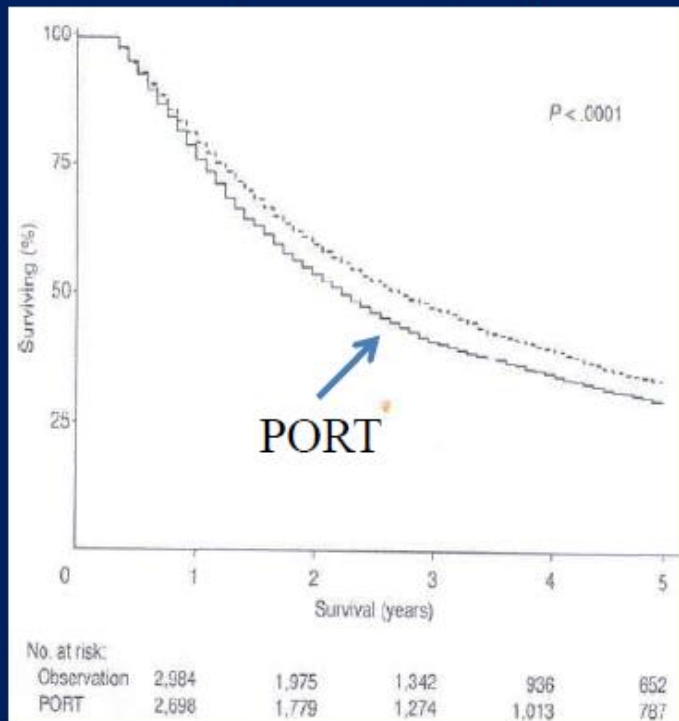
**Over 70% had stage I disease where there was NO survival benefit
Survival gain for stage II and T3N1 disease**

KDHAK Adjuvan Radyoterapi

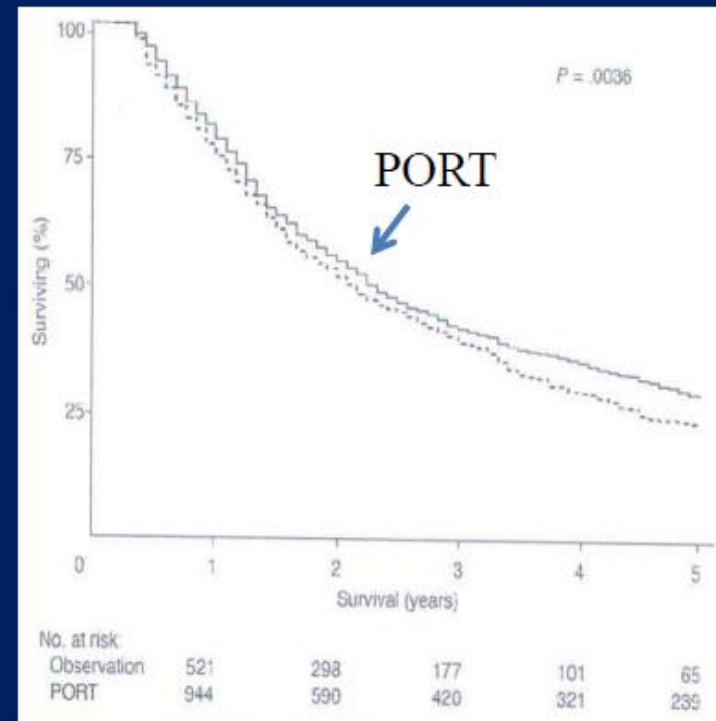
SEER data on PORT in NSCLC

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

All patients (I-III)



N2 patients only

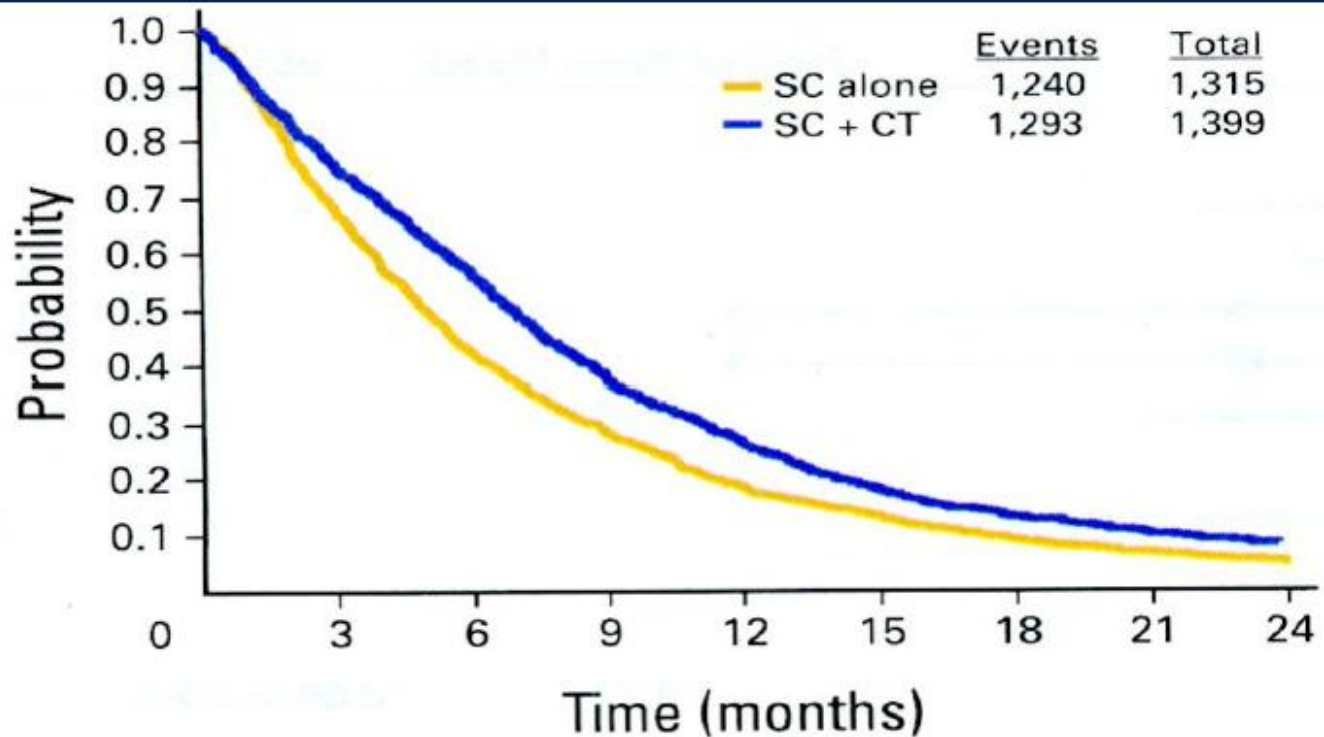


Most patients had not received adjuvant chemotherapy

Metastatik KHDAK Tedavi

Chemotherapy vs. Best supportive care

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

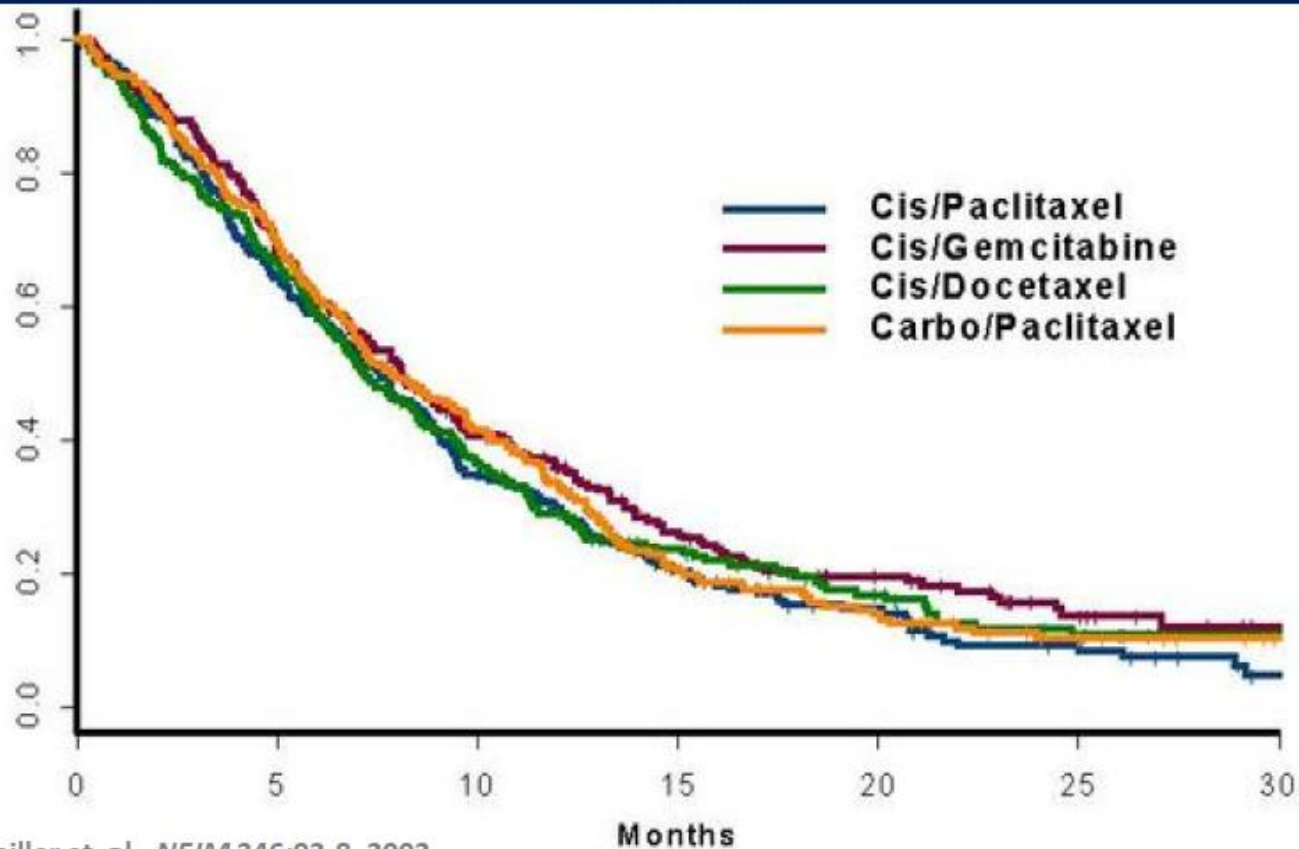


Patients at risk

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

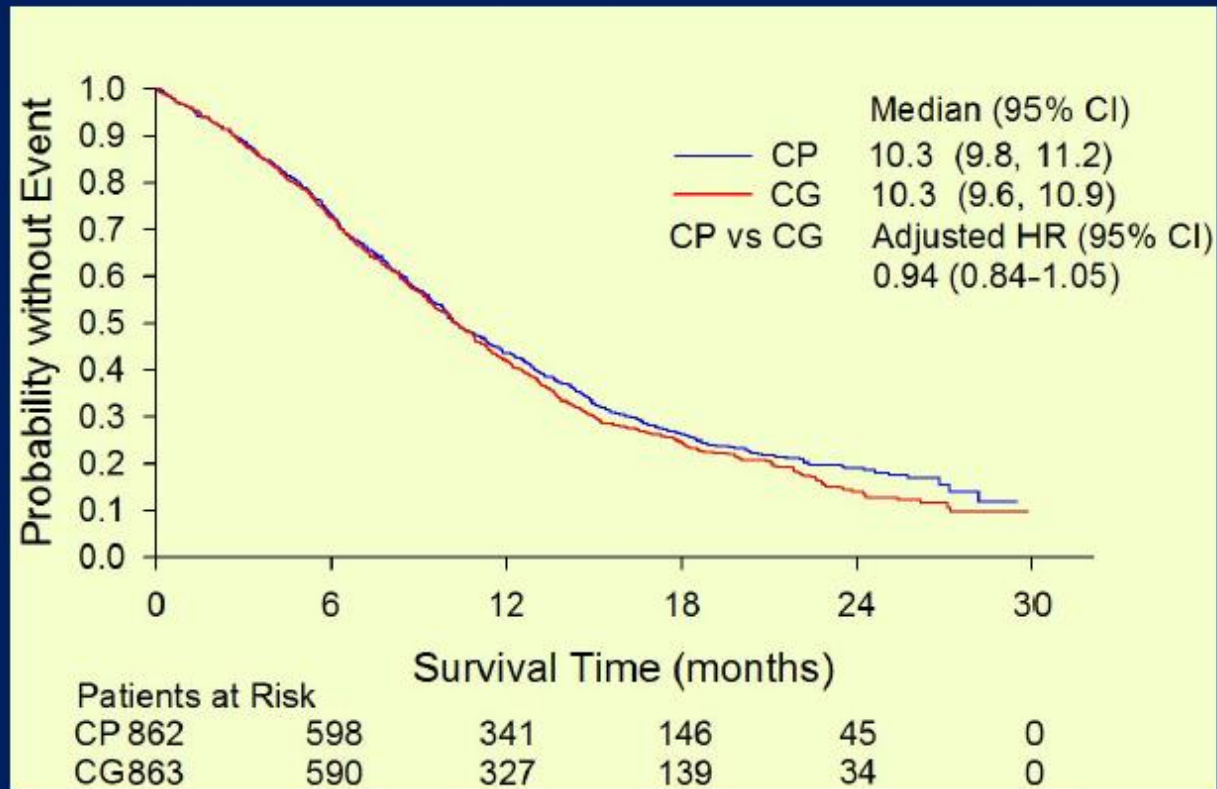
Platinum-Doublets in stage IV NSCLC



Metastatik KHDAK Tedavi Patolojik Alt Tipe Göre

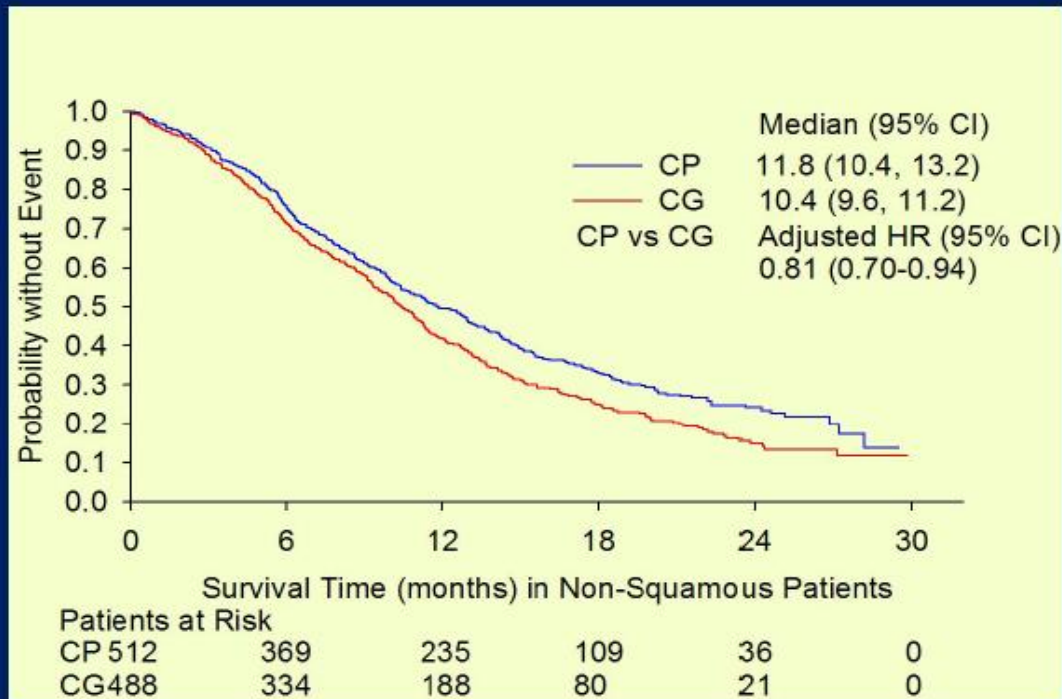
Cisplatin + Gemcitabine or Pemetrexed

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



Metastatik KHDAK Tedavi Patolojik Alt Tipe Göre

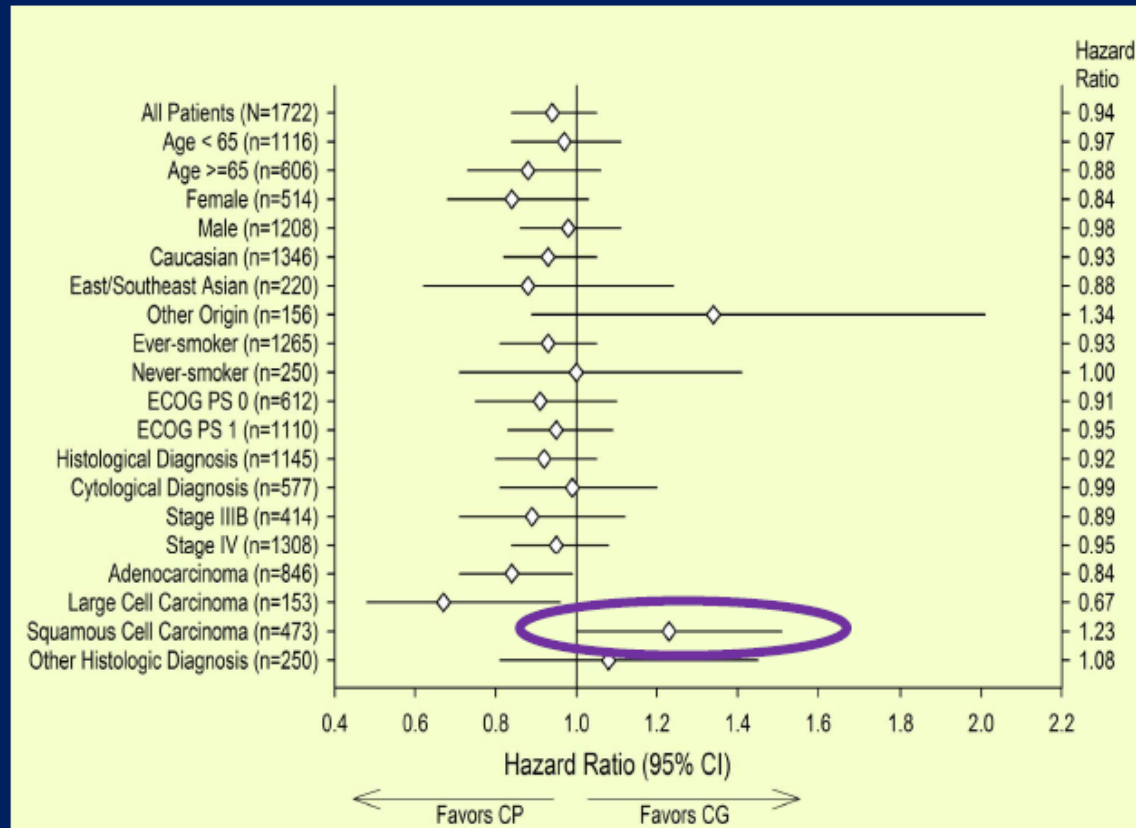
Cis/Pem favored in non-squamous



Metastatik KHKDAK Tedavi

Patolojik Alt Tipe Göre

Cis/Gem favored in squamous



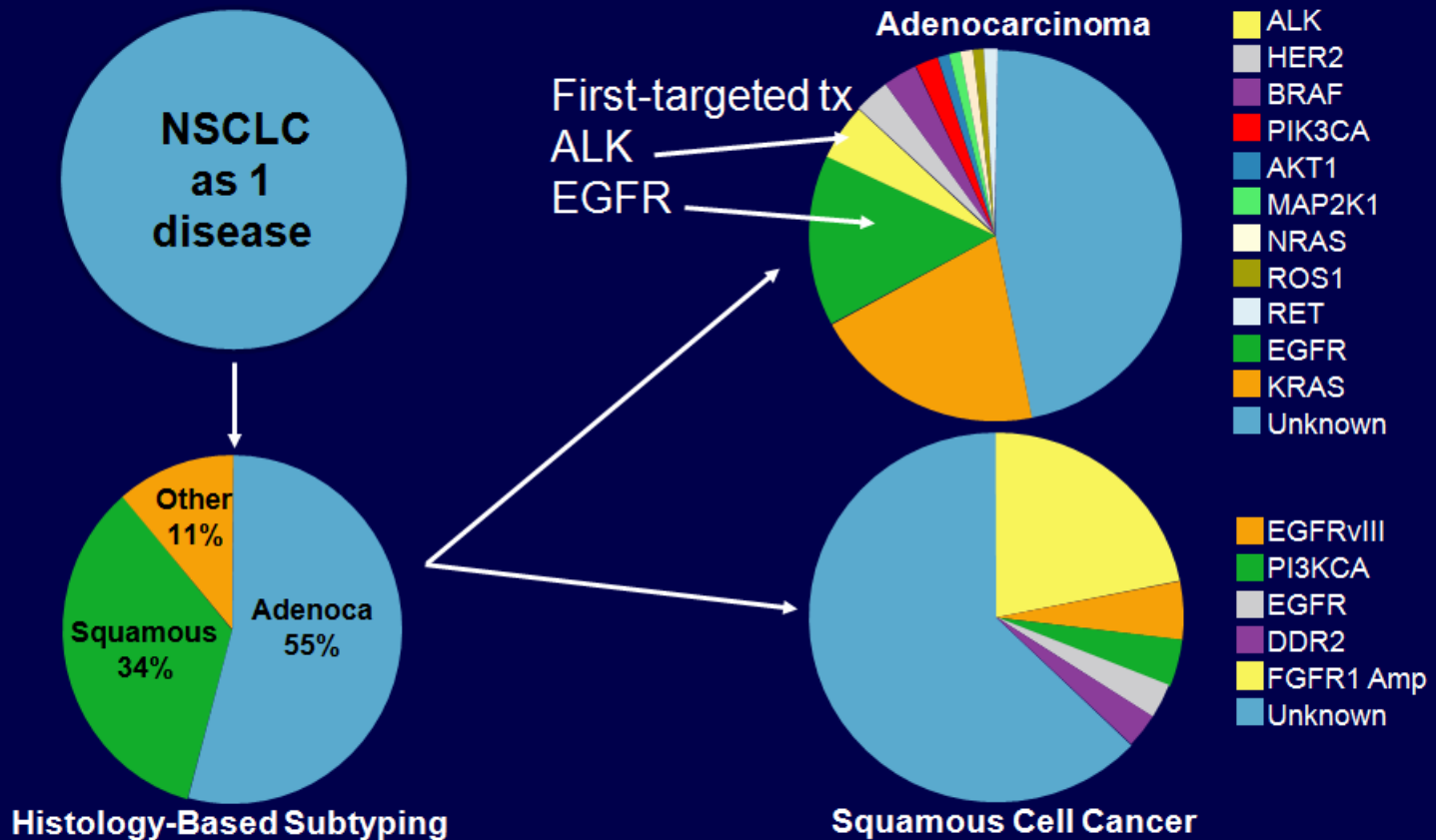
Metastatik KHDAK Tedavi

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

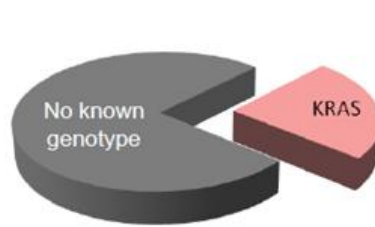
Swanton C, Govindan R. N Engl J Med 2016;374:1864-1873

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%	

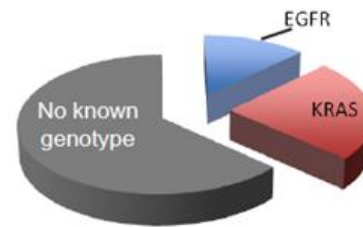
Metastatik KHDAK

Hedefe Yönelik Tedaviler

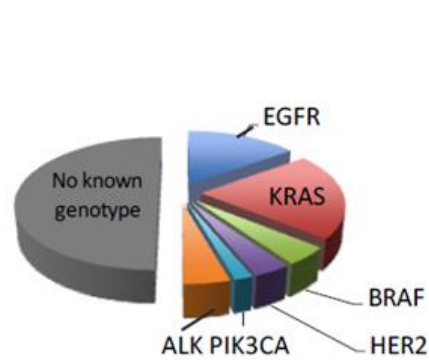
Akciğer Kanserinde Mutasyonlar



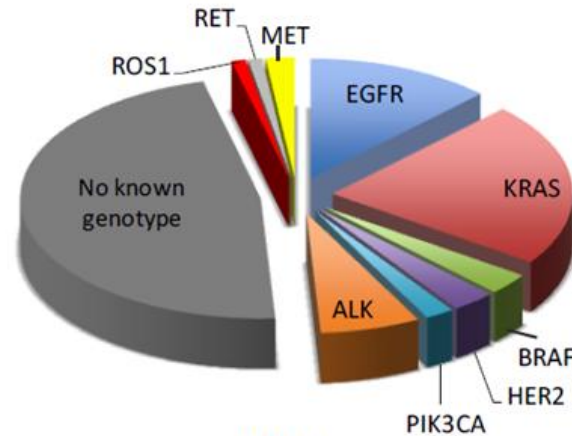
1984–2003



2004



2009

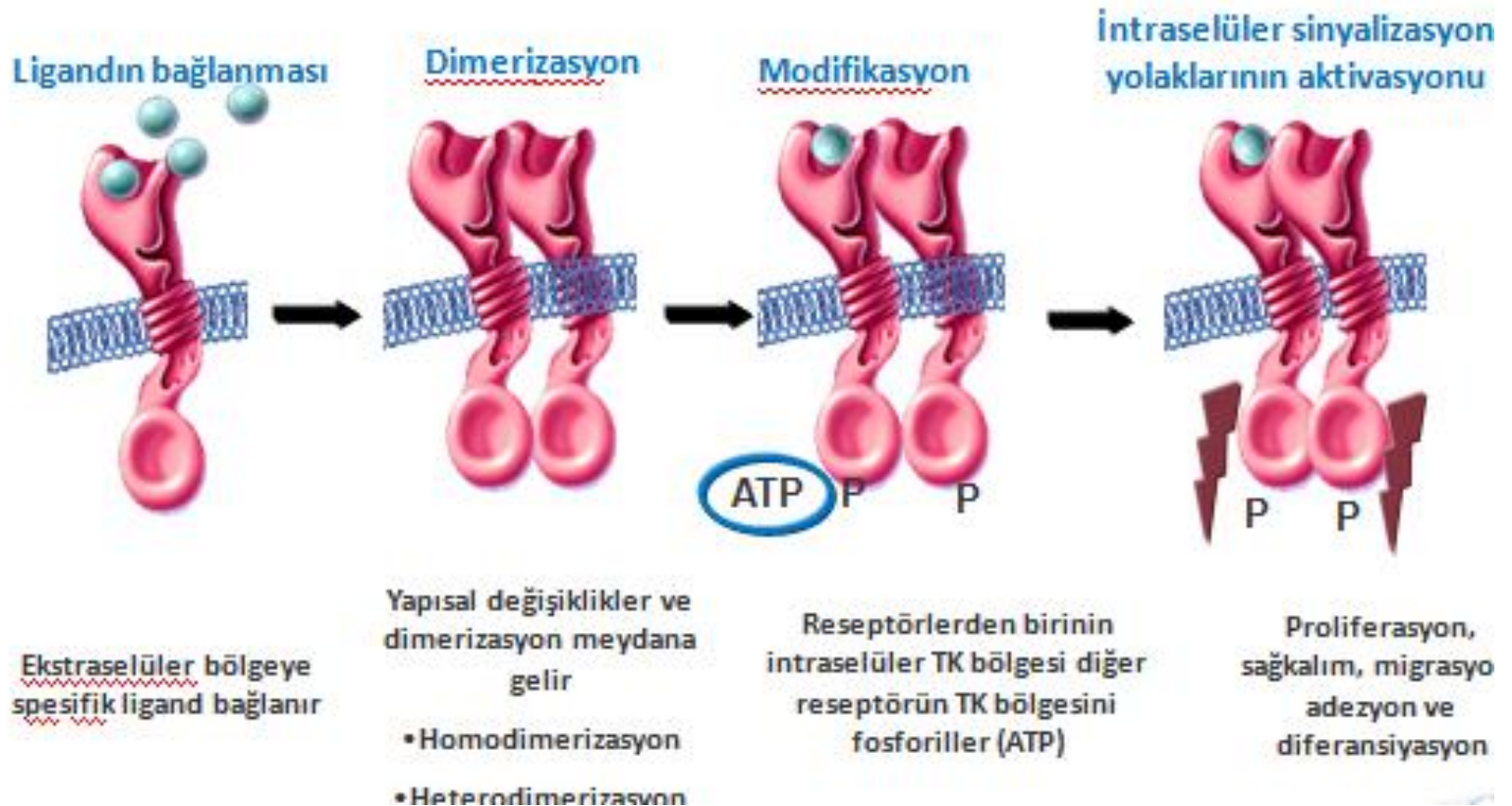


2013



Metastatik KHDAK Hedefe Yönelik Tedaviler

EGFR: Sinyalizasyon



Metastatik KHKDAK Hedefe Yönelik Tedaviler

- Found in 10% to 30% of NSCLC pts^[1]
- More common in never-smokers, 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.

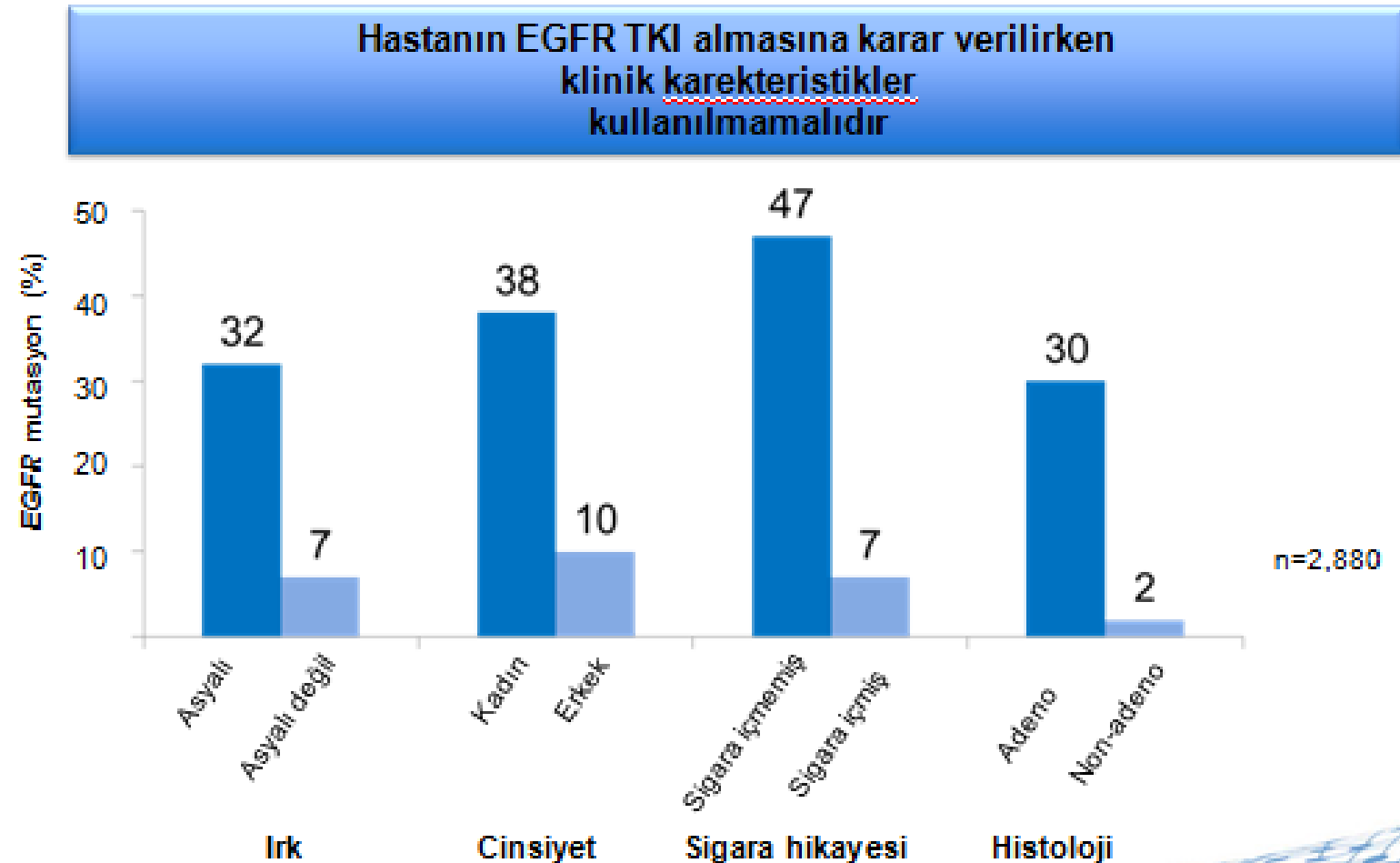
2. Wu YL, et al. J Thorac Oncol. 2007;2:430-439.

1. Pao W, et al. J Clin Oncol. 2005;23:2556-2568.

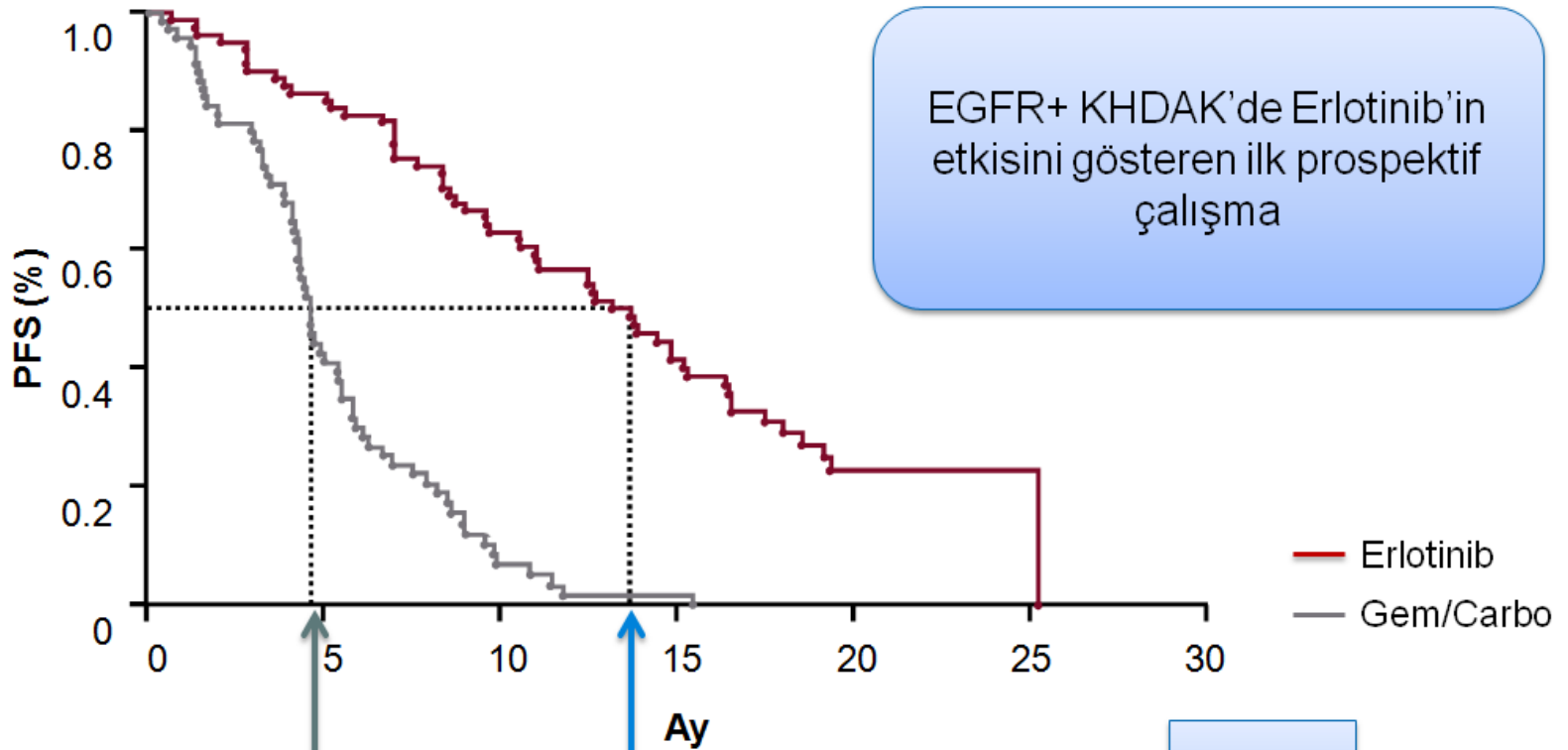
2. Wu YL, et al. J Thorac Oncol. 2007;2:430-439.

Metastatik KHDAK Hedefe Yönelik Tedaviler

EGFR & Hasta Özellikleri



Metastatik KHDAK Hedefe Yönelik Tedaviler



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

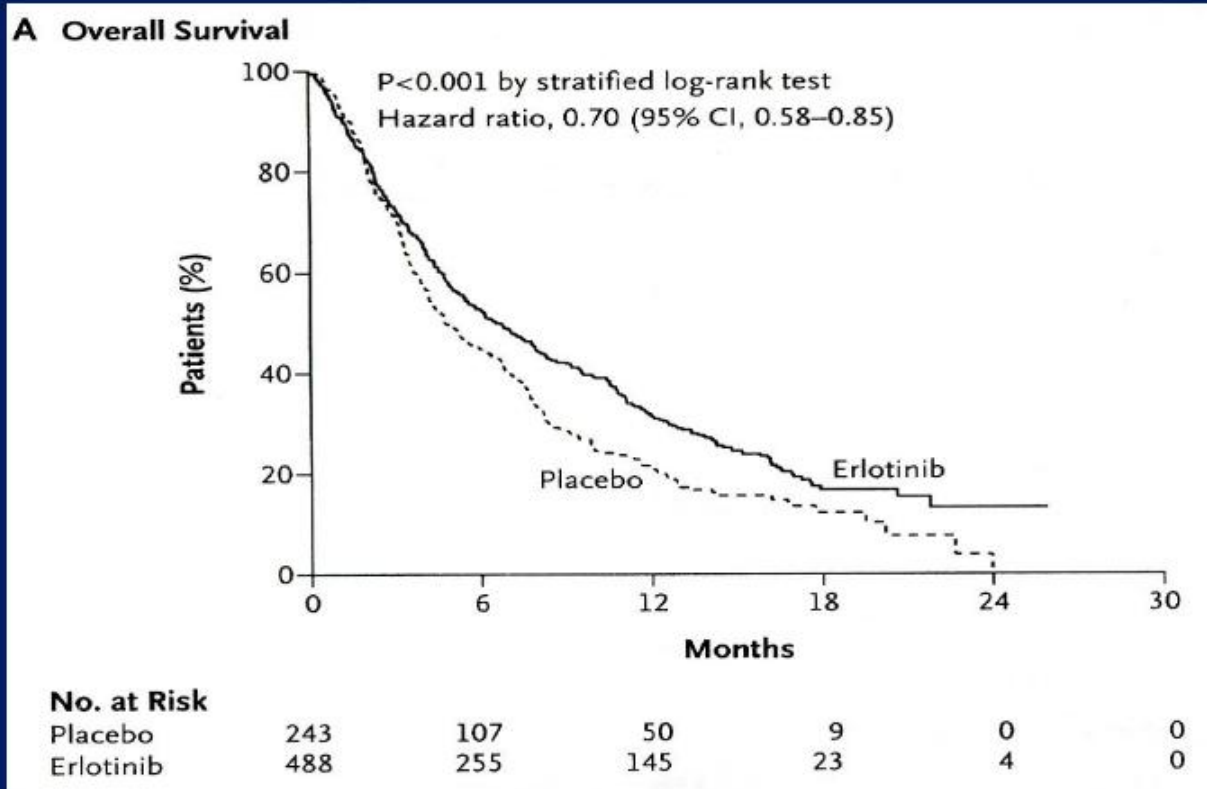
First line EGFR TKI vs. chemotherapy in EGFR mut + NSCLC

Trial	RR (%)		Median PFS (mo)	
	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 <i>et al.</i> (7)
Gefitinib or erlotinib	28	EGFR mutated	83%	15.9 months	Park <i>et al.</i> (8)
Gefitinib	9	EGFR mutated	89%	NS	Li (19)
Gefitinib or erlotinib	23	Asian never-smokers	74%	18.8 months	Kim <i>et al.</i> (20)
Erlotinib	40	Unselected	86%	11.8 months	Welsh <i>et al.</i> (21)
Gefitinib	41	EGFR mutated	88%	21.9 months	Iuchi <i>et al.</i> (22)
Afatinib	32	EGFR mutated, TKI-pretreated	35%	9.8 months	Hoffknecht <i>et al.</i> (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

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

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 Direnç Mekanizmaları

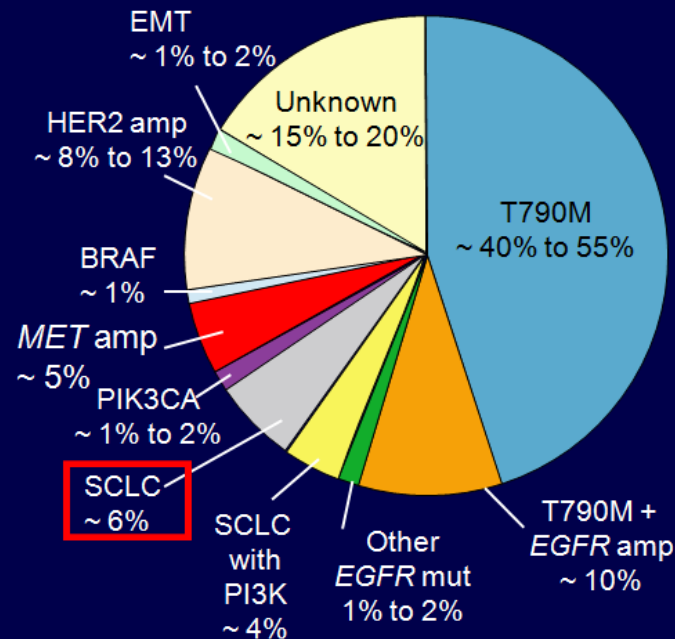
Disease Progression on EGFR TKI in NSCLC With *EGFR* Sensitizing Mutations

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



Metastatik KHDAK Hedefe Yönelik Tedaviler Direnç Mekanizmaları

EGFR resistance

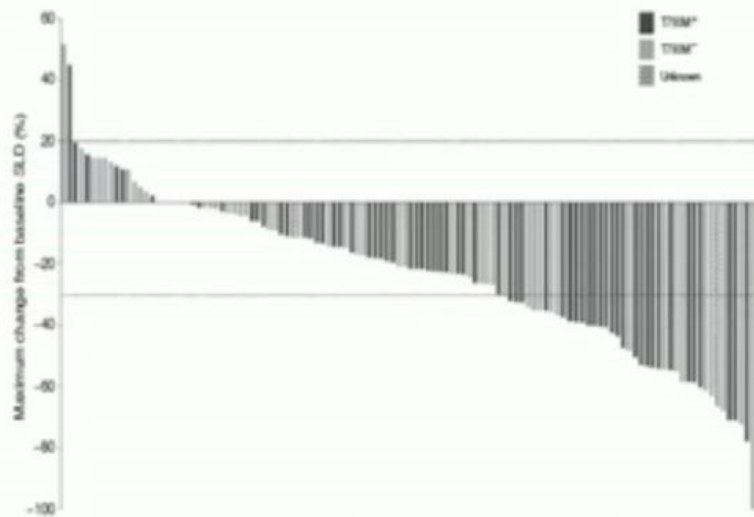
Tan et al, JTO 2016;11:946-963

- **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/m² q 2 wks

T790M mutation negative

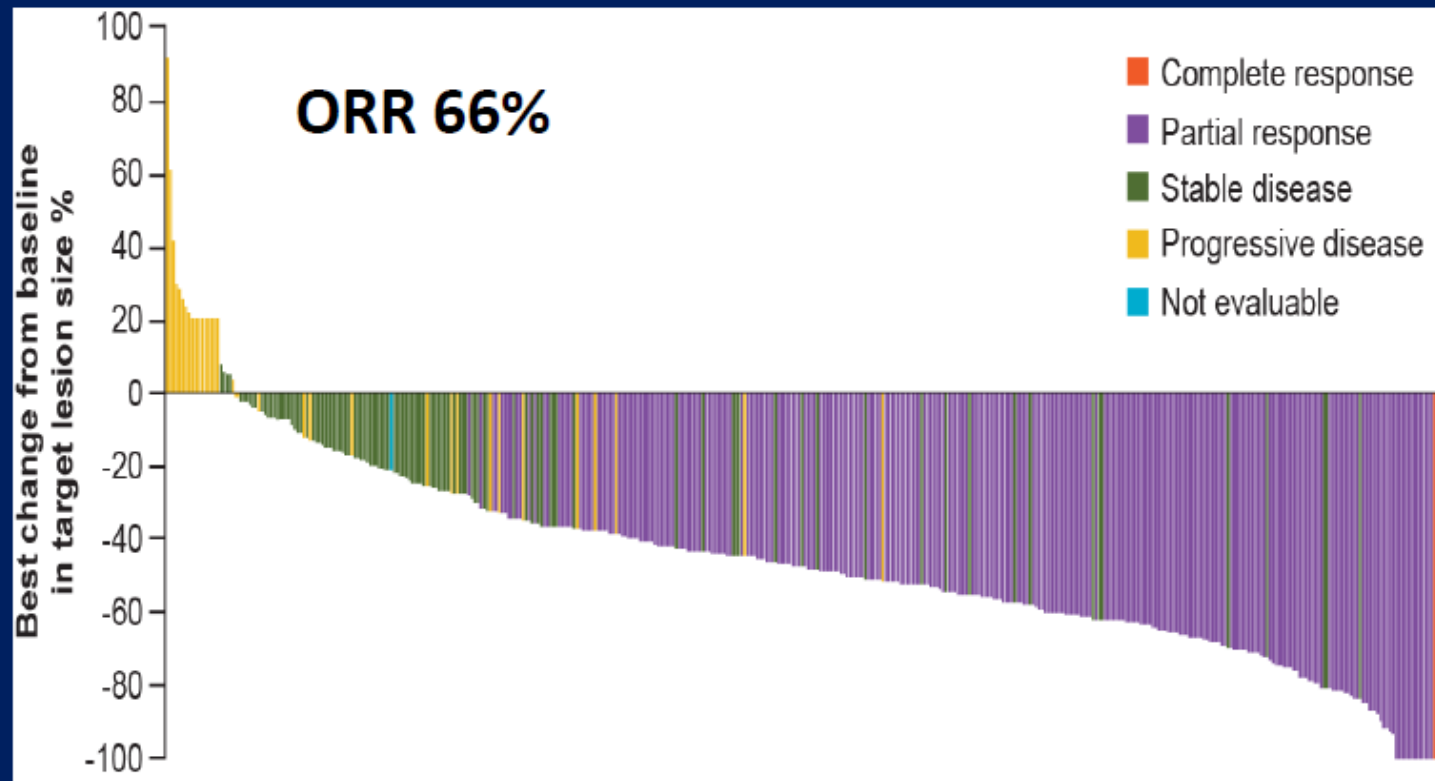
ORR 25%

Median PFS – 4.6 mo

Grade 3 toxicity – 44%

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.

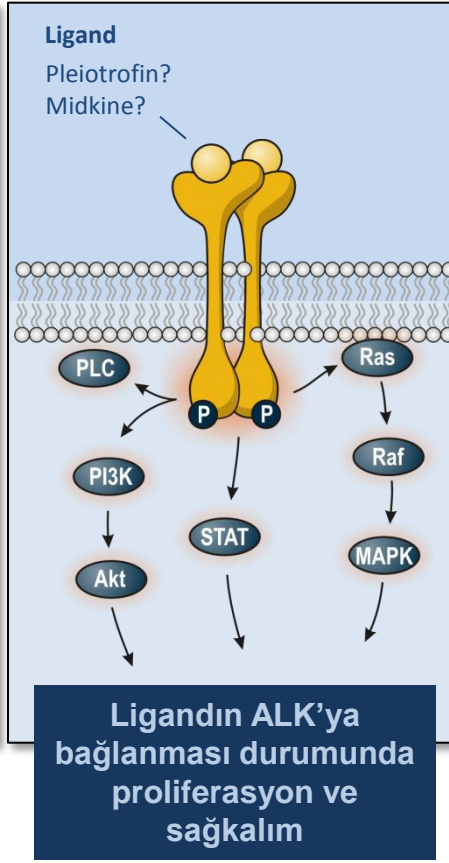
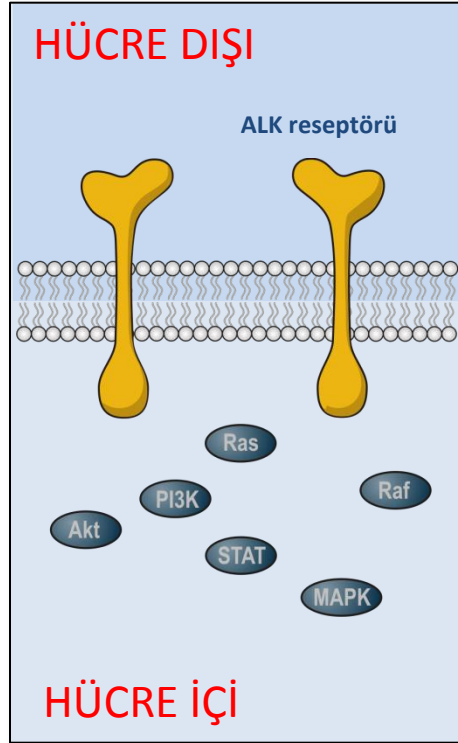


Slide credit: clinicaloptions.com

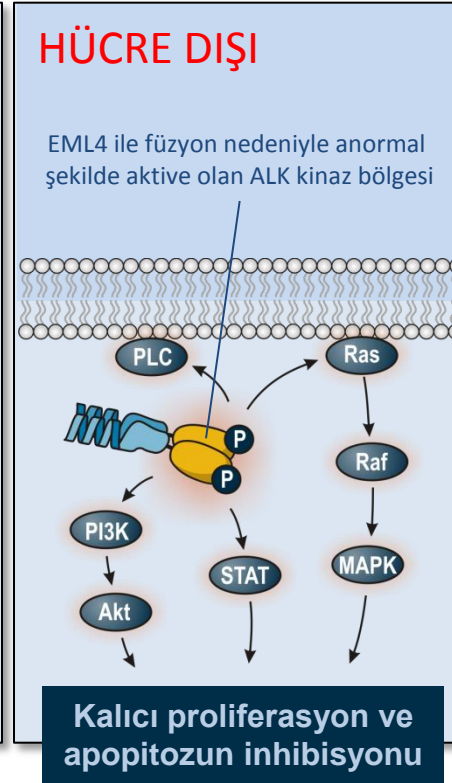
Metastatik KHDAK Hedefe Yönelik Tedaviler

Krizotinib etki mekanizması

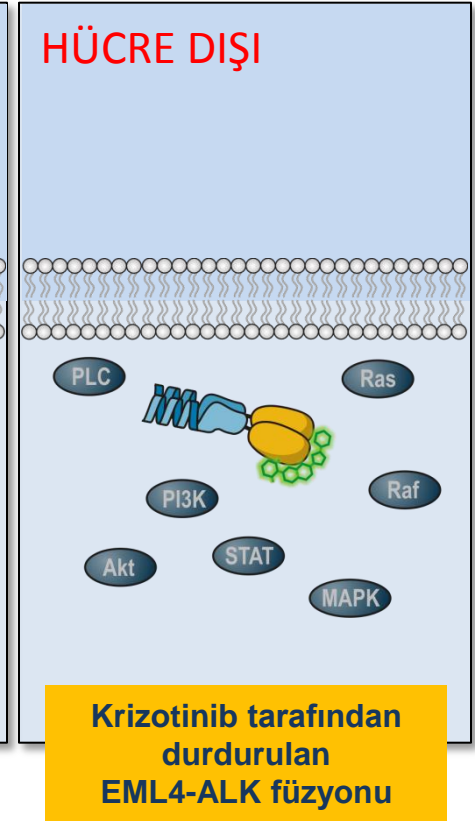
Normal ALK sinyal iletimi



Patolojik ALK sinyal iletimi



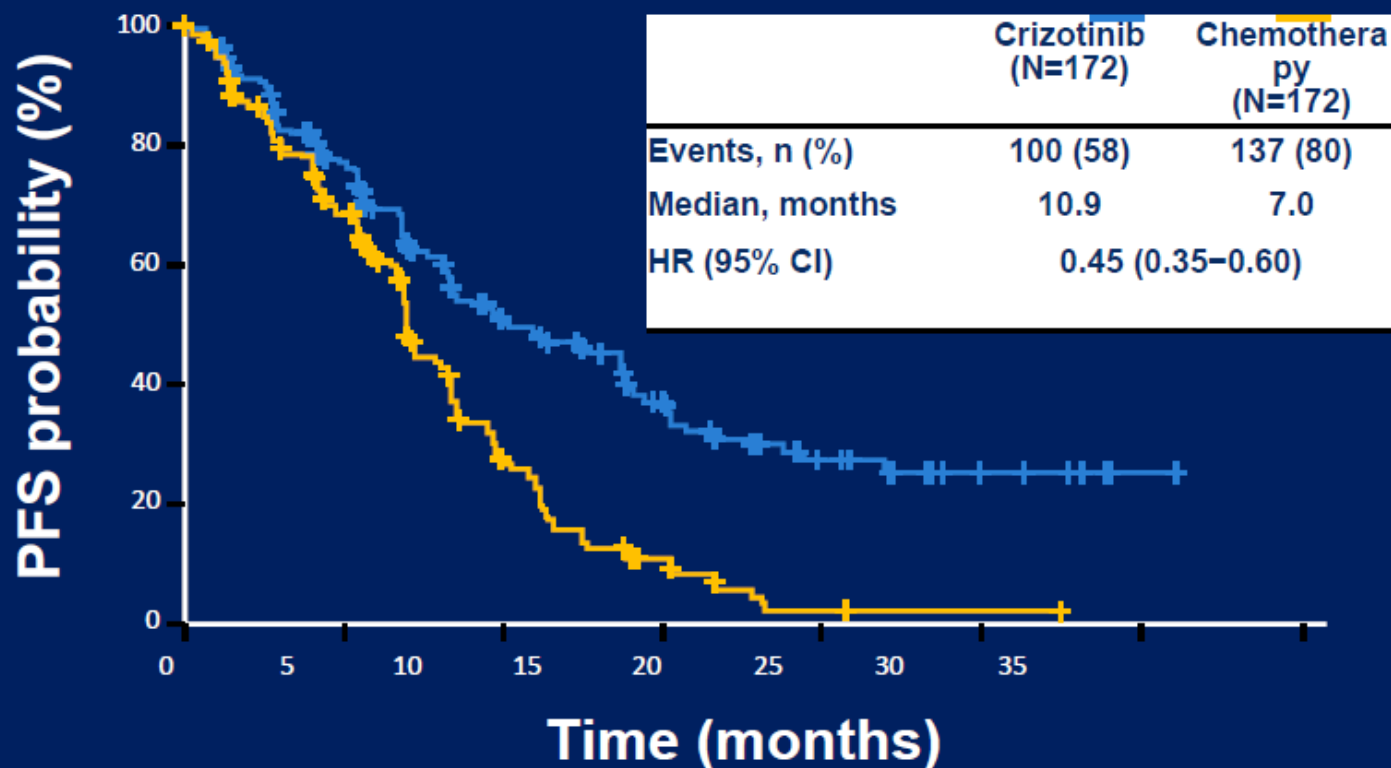
Krizotinibin etki şekli



Metastatik KHDAK Hedefe Yönelik Tedaviler

1st line Crizotinib prolongs PFS compared to platinum/pemetrexed

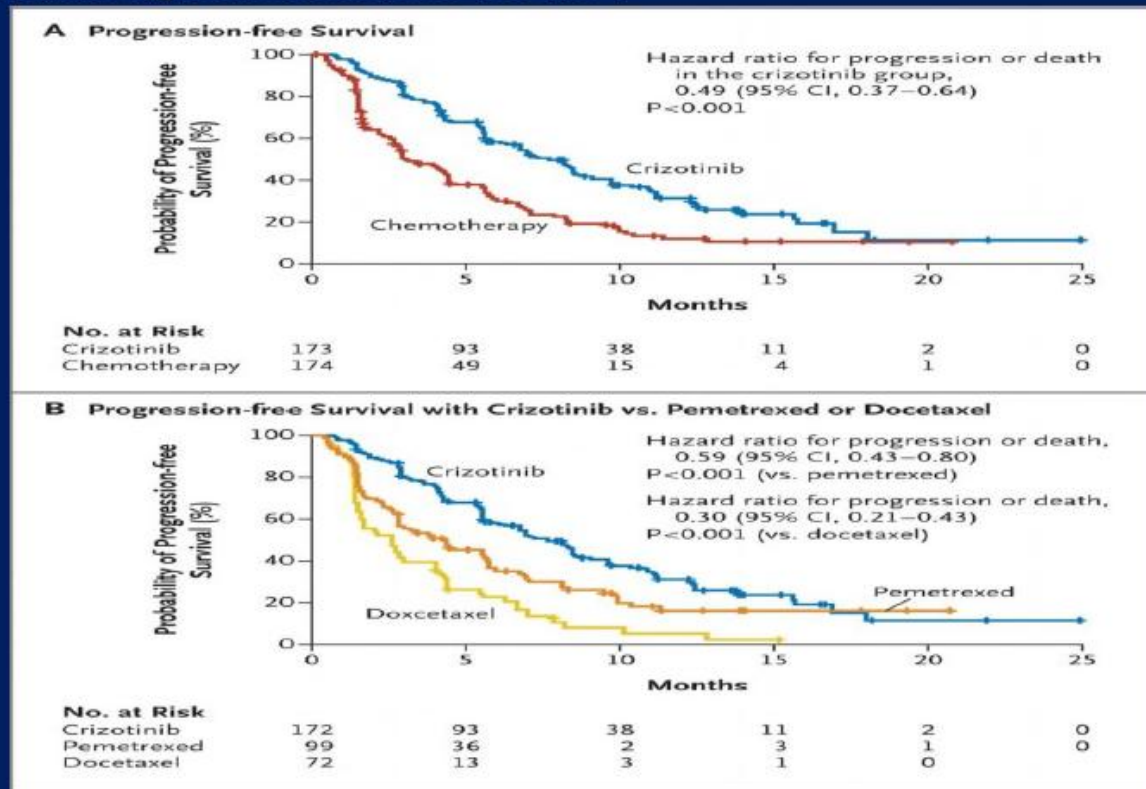
Mok et al, ASCO 2014, abstr 8002



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 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%

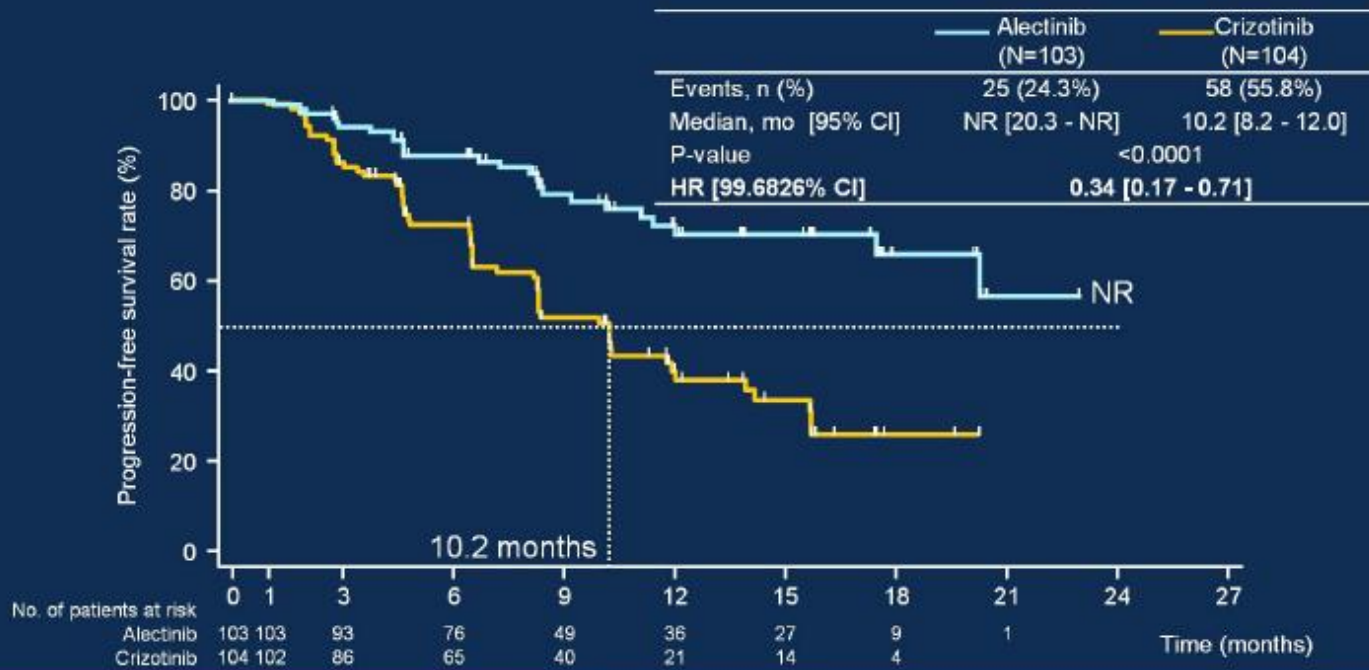
Shaw et al, NEJM 2013;368:2385-94

Shaw et al, NEJM 2014;370:1189-97

Abstract 8008, ASCO 2015

Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

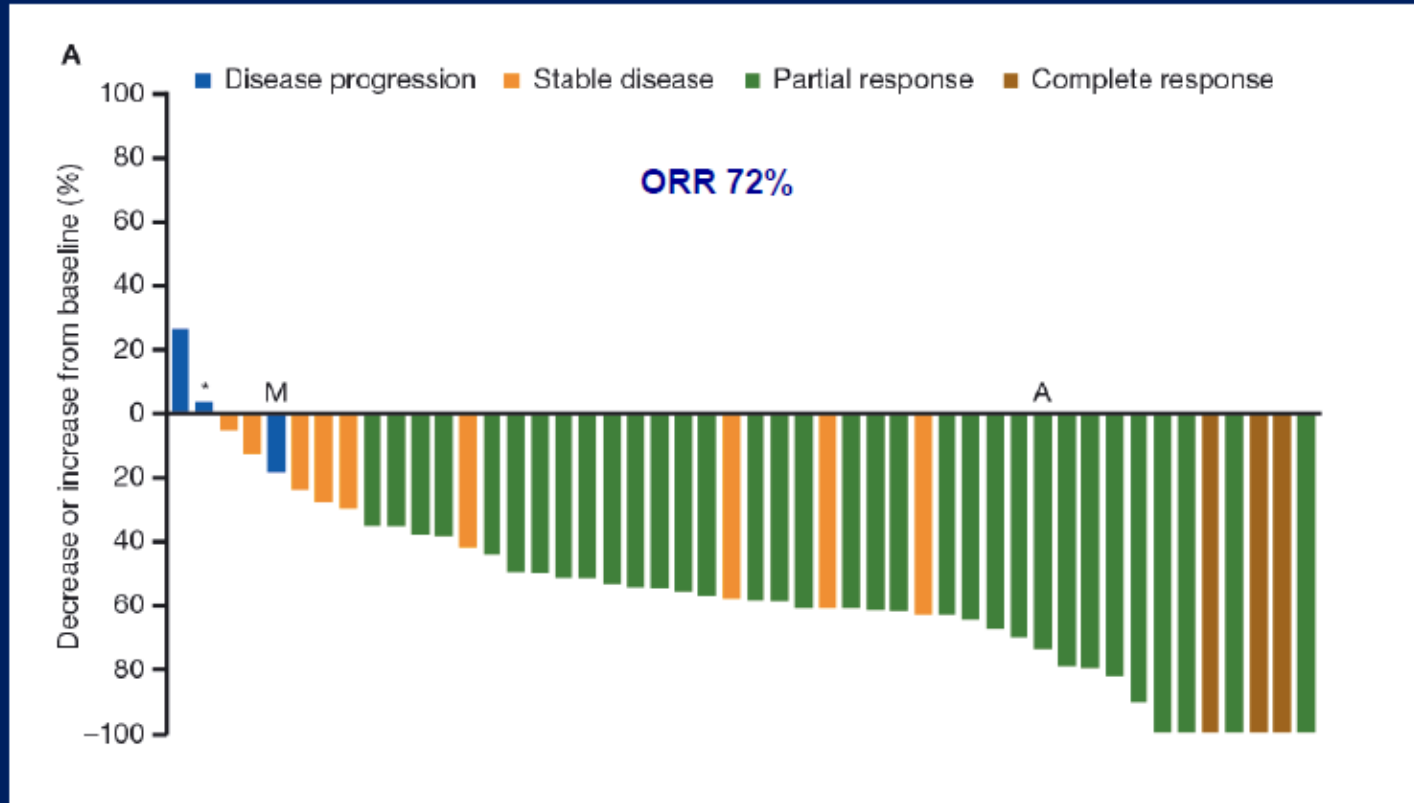
Primary Endpoint: PFS by IRF (ITT Population)



Metastatik KHDAK Hedefe Yönelik Tedaviler

ROS1+ NSCLC: Crizotinib is standard

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



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

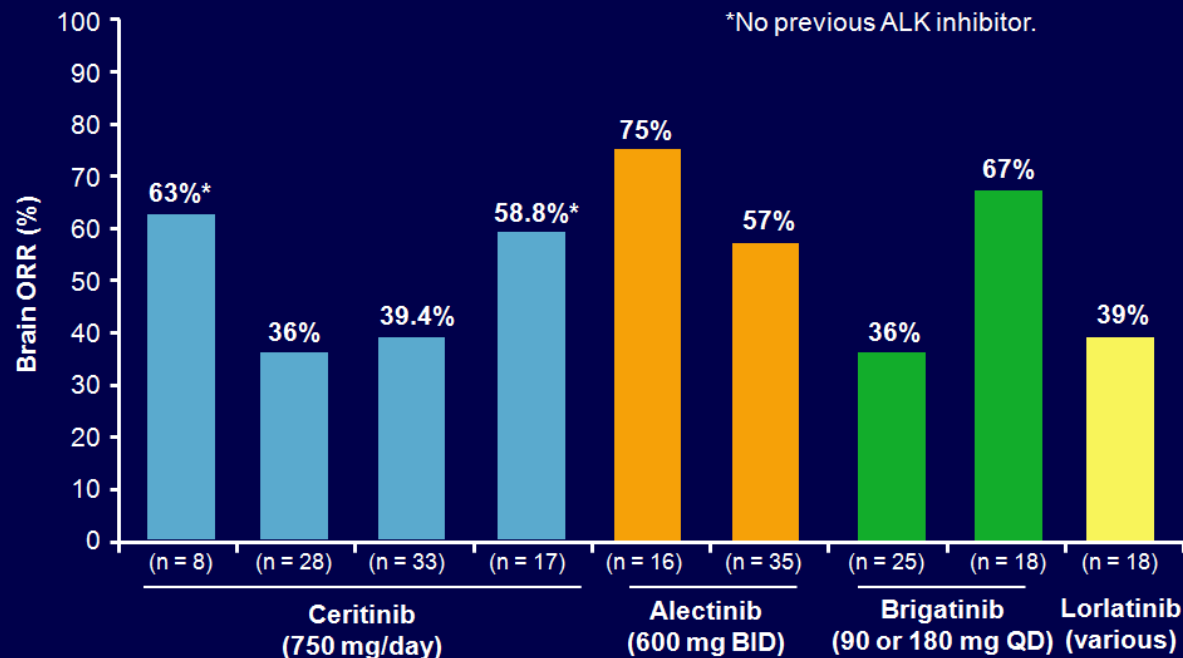
1. Kim DW, et al. Lancet Oncol. 2016;17:452-63. 2. Mok T, et al. ASCO 2015. Abstract 8059.
3. Felip E, et al. ASCO 2015. Abstract 8060. 4. Shaw AT, et al. Lancet Oncol. 2016;17:234-242.
5. Ou SH, et al. J Clin Oncol. 2016;34:661-668. 6. Kim DW, et al. ASCO 2016. Abstract 9008. 7. Solomon BJ, et al. ASCO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



Slide credit: clinicaloptions.com

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 KHDAK Hedefe Yönelik Tedaviler

Mechanisms for acquired resistance to EGFR, ALK-TKIs

		EGFR-TKI	ALK-TKI
Target modification	secondary 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 KHDAAK Hedefe Yönelik Tedaviler

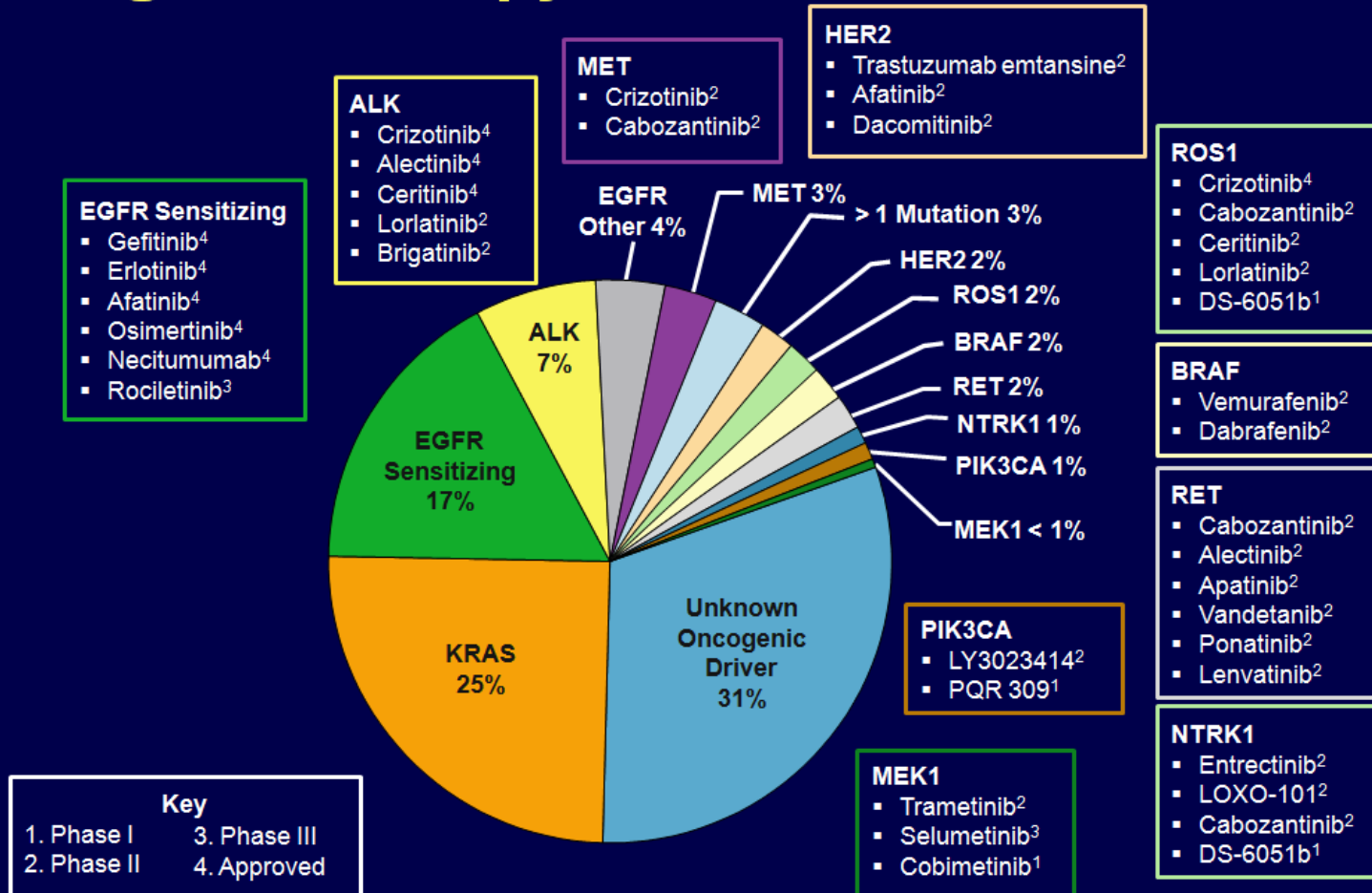
What should we test for?

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

Targeted Therapy for Adenocarcinoma



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
<i>BRAF</i> V600E mutation*	Vemurafenib Dabrafenib Dabrafenib + trametinib
High-level <i>MET</i> amplification or <i>MET</i> exon 14 skipping mutation	Crizotinib
<i>RET</i> rearrangements	Cabozantinib
<i>HER2</i> mutations	Trastuzumab (category 2b) Afatinib (category 2b)

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

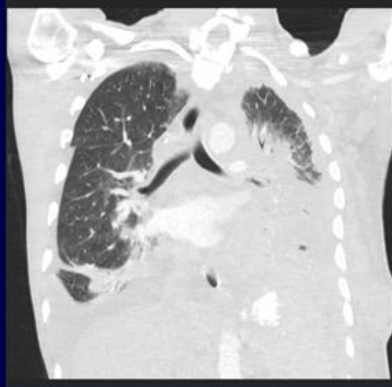
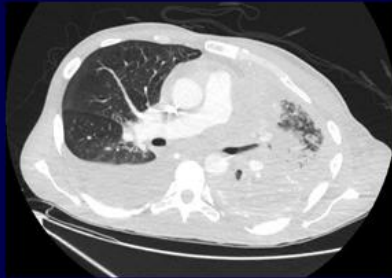
Neurotrophic Tyrosine Kinase (NTRK) and Tropomyosin-Related Kinases A, B, C

- 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*

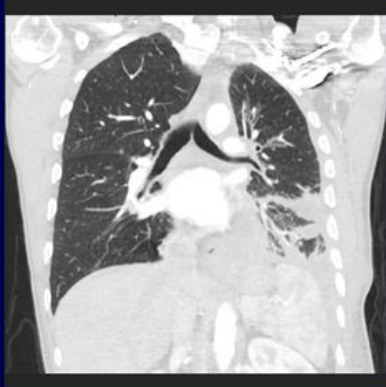
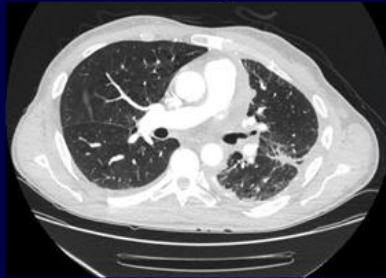
Metastatik KHDAK Hedefe Yönelik Tedaviler

Clinical Response to Entrectinib *NTRK1*-Rearranged NSCLC

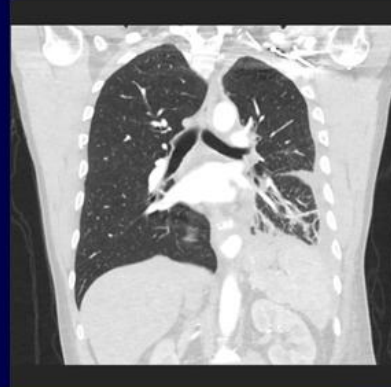
Baseline



Day 26:
-47% response



Day 155:
-77% response



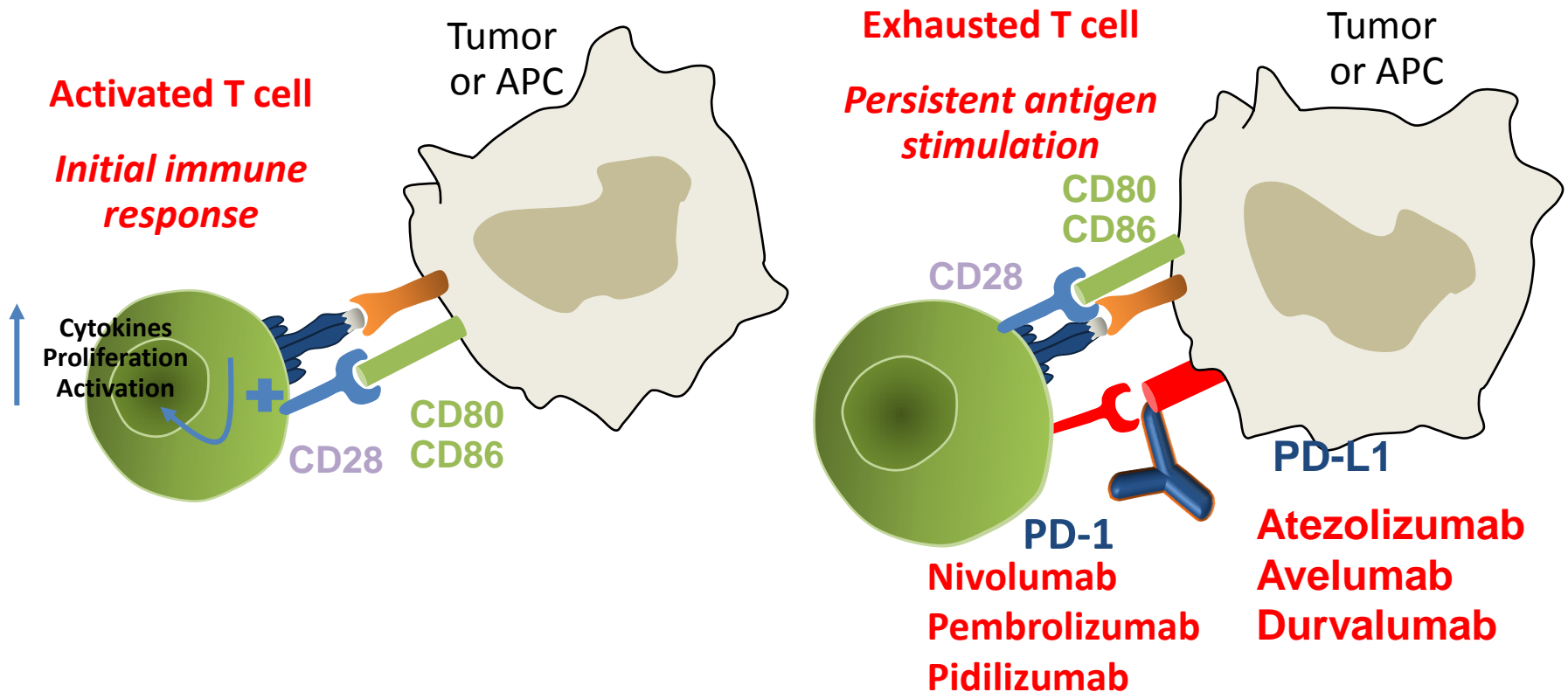
Metastatik KHDAK Hedefe Yönelik Tedaviler

EMERGING TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

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

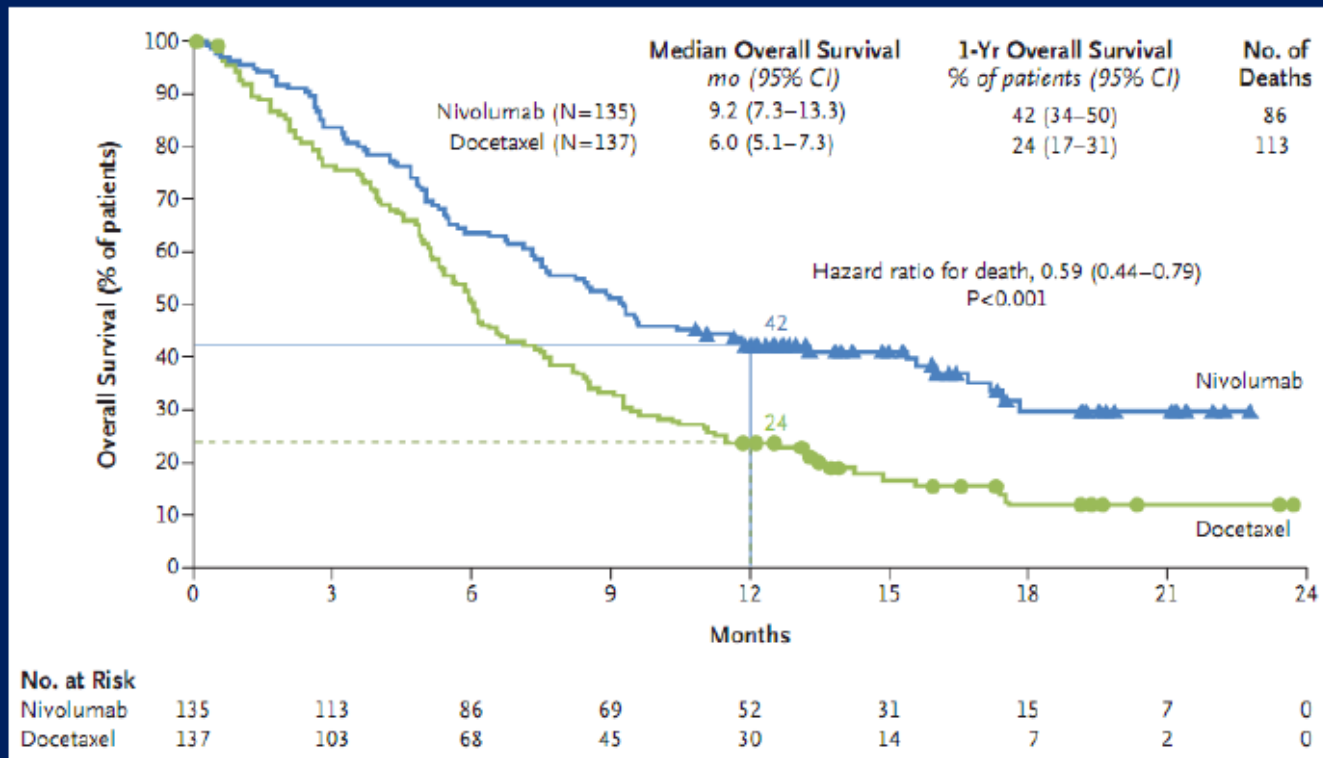
Akciğer Kanserinde İmmünoterapi

PD-1 as a Target in Cancer Therapy



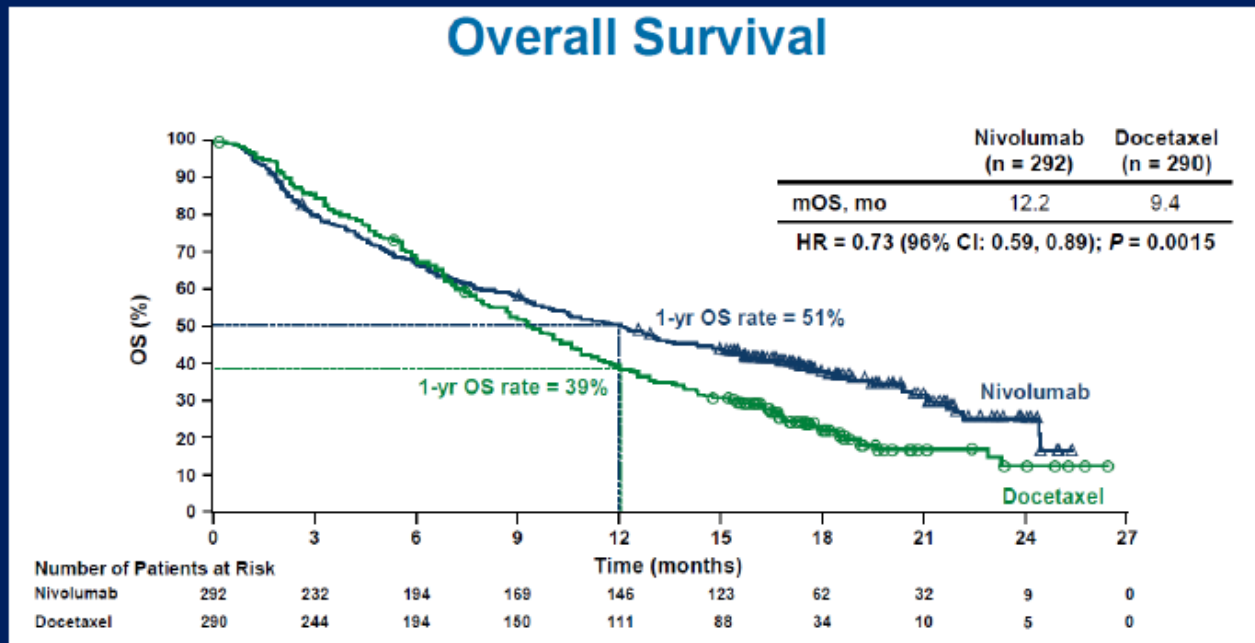
Akciğer Kanserinde İmmünoterapi

Squamous Cell Carcinoma Nivolumab vs. Docetaxel 2nd line



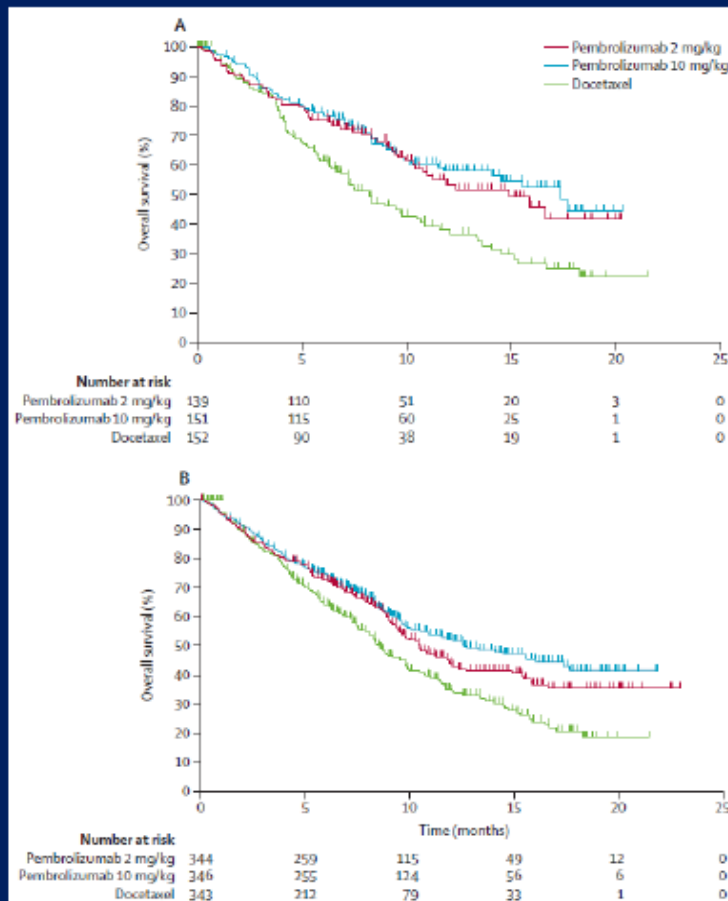
Akciğer Kanserinde İmmünoterapi

Non-Squamous NSCLCs Nivolumab vs. Docetaxel 2nd line



Akciğer Kanserinde İmmünoterapi

Pembrolizumab vs. Docetaxel



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*

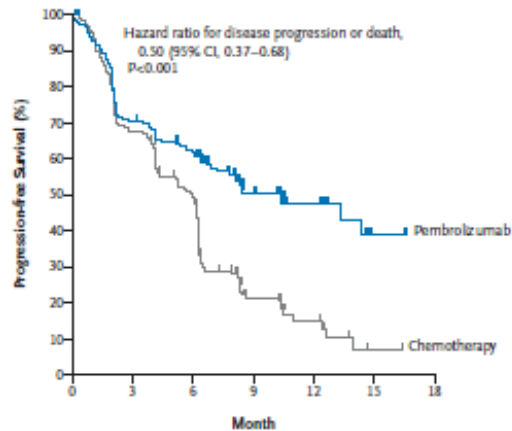
ABSTRACT

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).

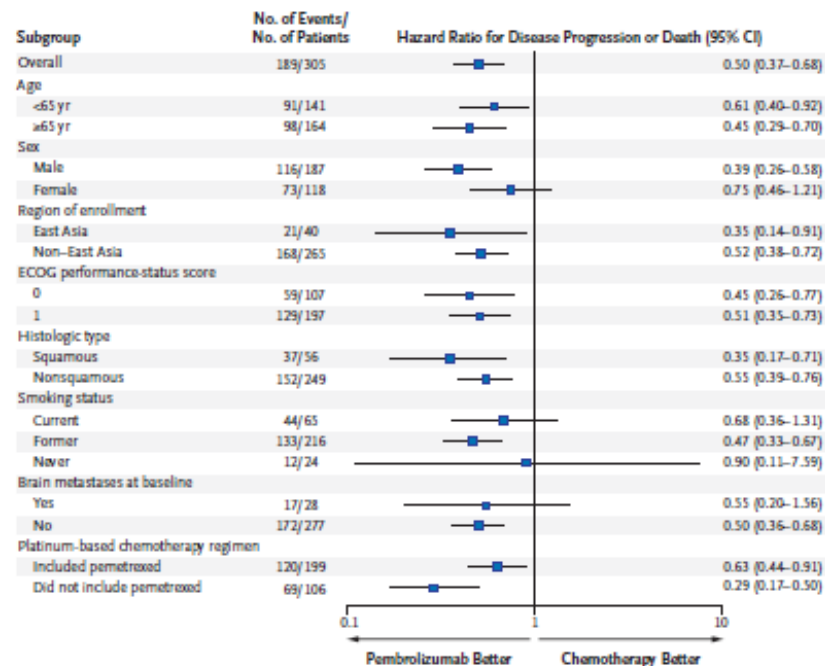
From Lung Clinic Grosshansdorf, Airway Research Center North, German Center of Lung Research, Grosshansdorf, Germany (M.R.); Hospital Universitario Insular de

Akciğer Kanserinde İmmünoterapi



No. at Risk	0	3	6	9	12	15	18
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0

B



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 (1 st line, Primary endpoint: OS)
	MYSTIC (NCT02453282)	675	Durvalumab + tremelimumab (1 st line, Primary endpoint: PFS)
	ARCTIC (NCT02352948)	730	Durvalumab + tremelimumab (≥3 rd line)

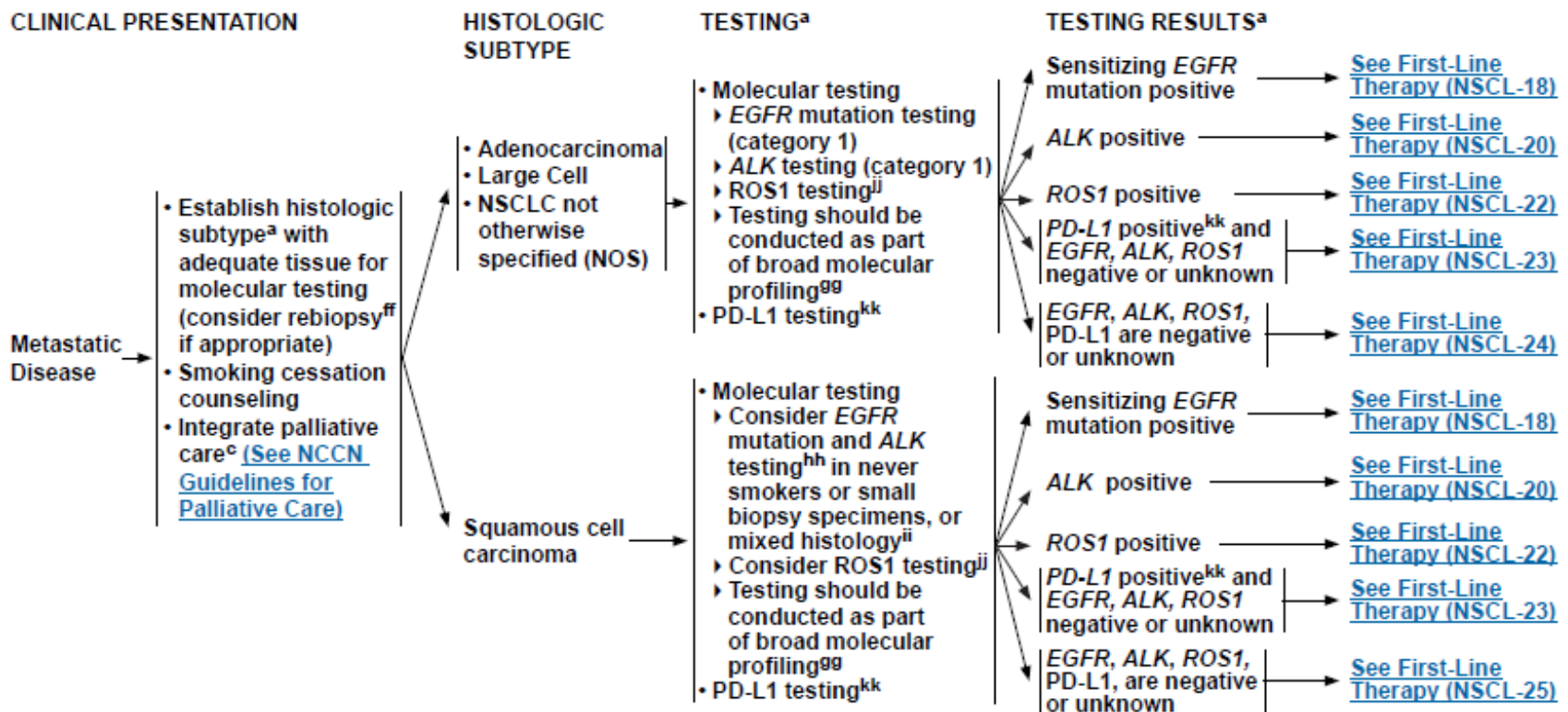
Metastatik KHDAK Hedefe Yönelik Tedaviler



National
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NCCN Guidelines Version 2.2017 Non-Small Cell Lung Cancer

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[Discussion](#)



KHDAK Tedavi Algoritması

Current NSCLC Therapeutic Profile

Chemotherapy

Histologic
subtyping for
chemotherapy

Targeted Therapy

Genomics-
driven TKIs:
▪ EGFR
▪ ALK
▪ ROS1

Checkpoint Inhibitors

Anti-PD-1
Anti-PD-L1
Anti-CTLA-4

Now Available: [Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting](#)

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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](#)

[Full Text View](#)

[Tabular View](#)

[No Study Results Posted](#)

[Disclaimer](#)

[How to Read a Study Record](#)

▶ 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.