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

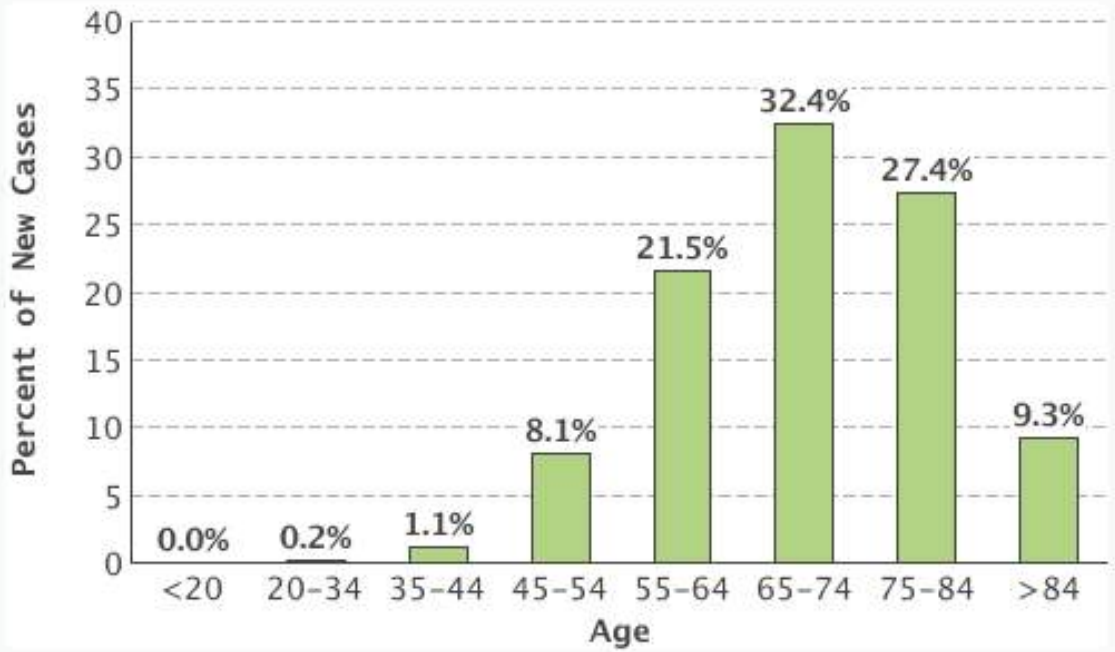
	Common Types of Cancer	Estimated New Cases 2016	Estimated Deaths 2016
1.	Breast Cancer (Female)	246,660	40,450
2.	**Lung and Bronchus Cancer**	**224,390**	**158,080**
3.	Prostate Cancer	180,890	26,120
4.	Colon and Rectum Cancer	134,490	49,190
5.	Bladder Cancer	76,960	16,390
6.	Melanoma of the Skin	76,380	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

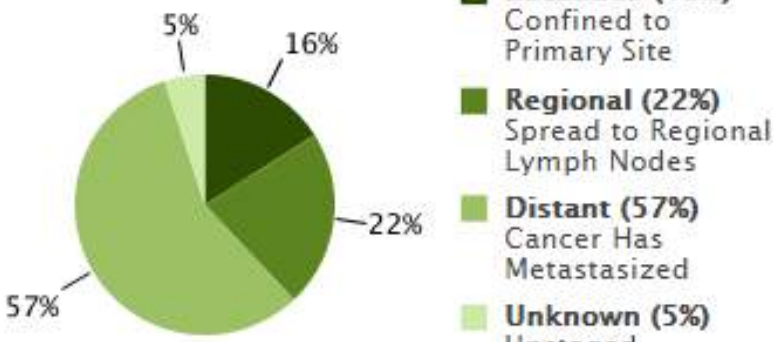
SEER 18 2009-2013, All Races, Both Sexes

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

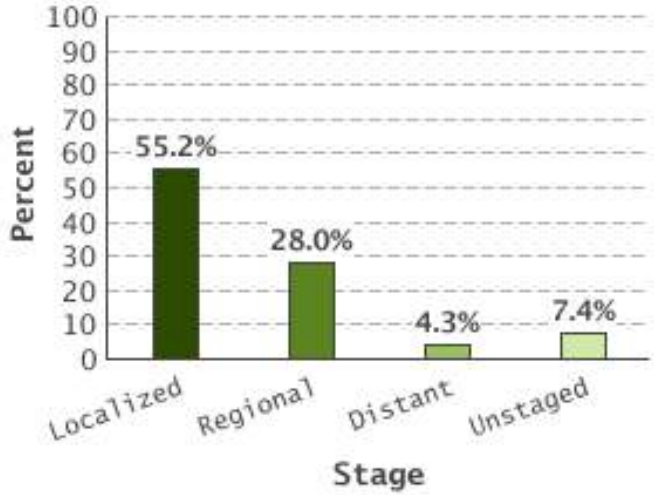
Akciğer Kanserinde İnsidans ve Mortalite

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

Percent of Cases by Stage

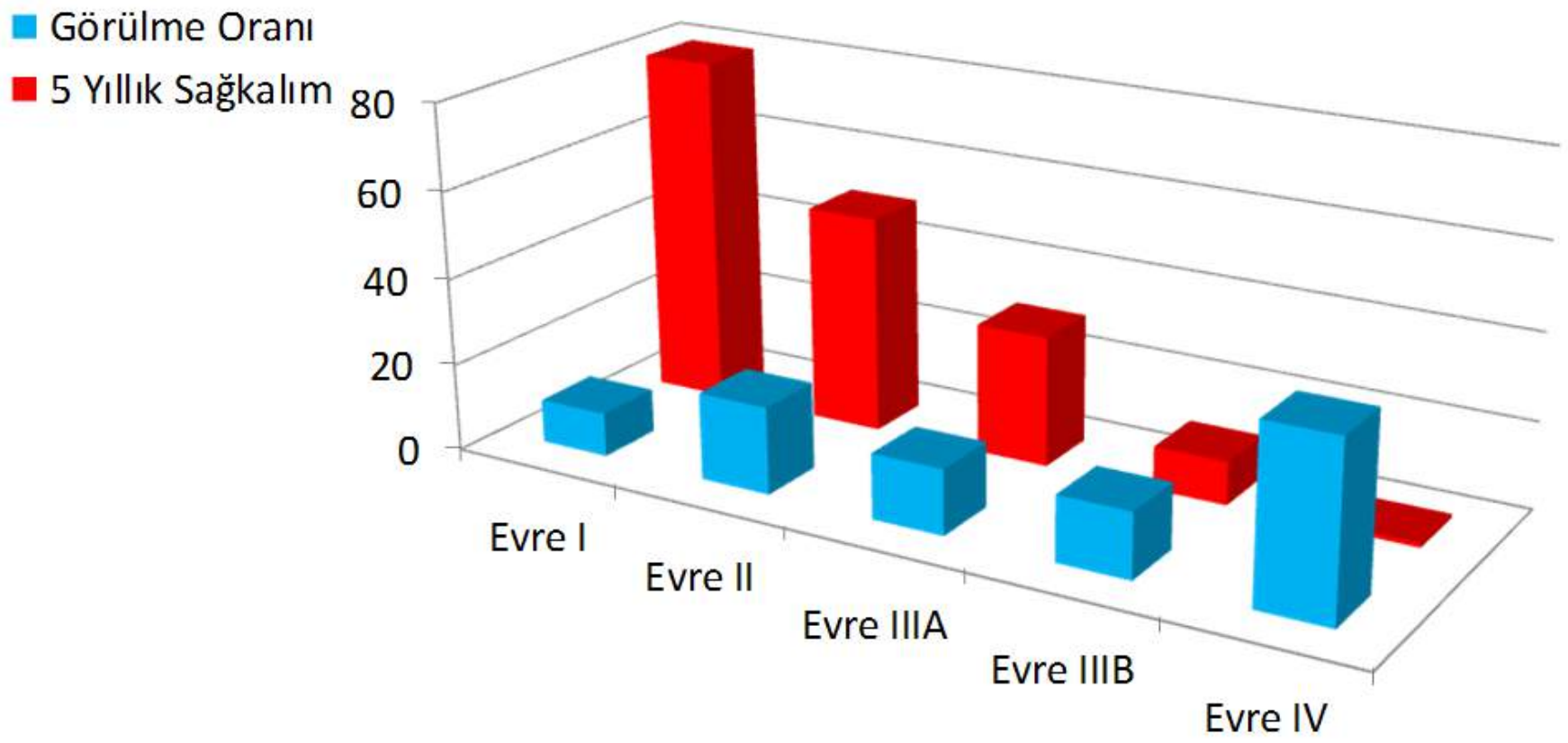


5-Year Relative Survival

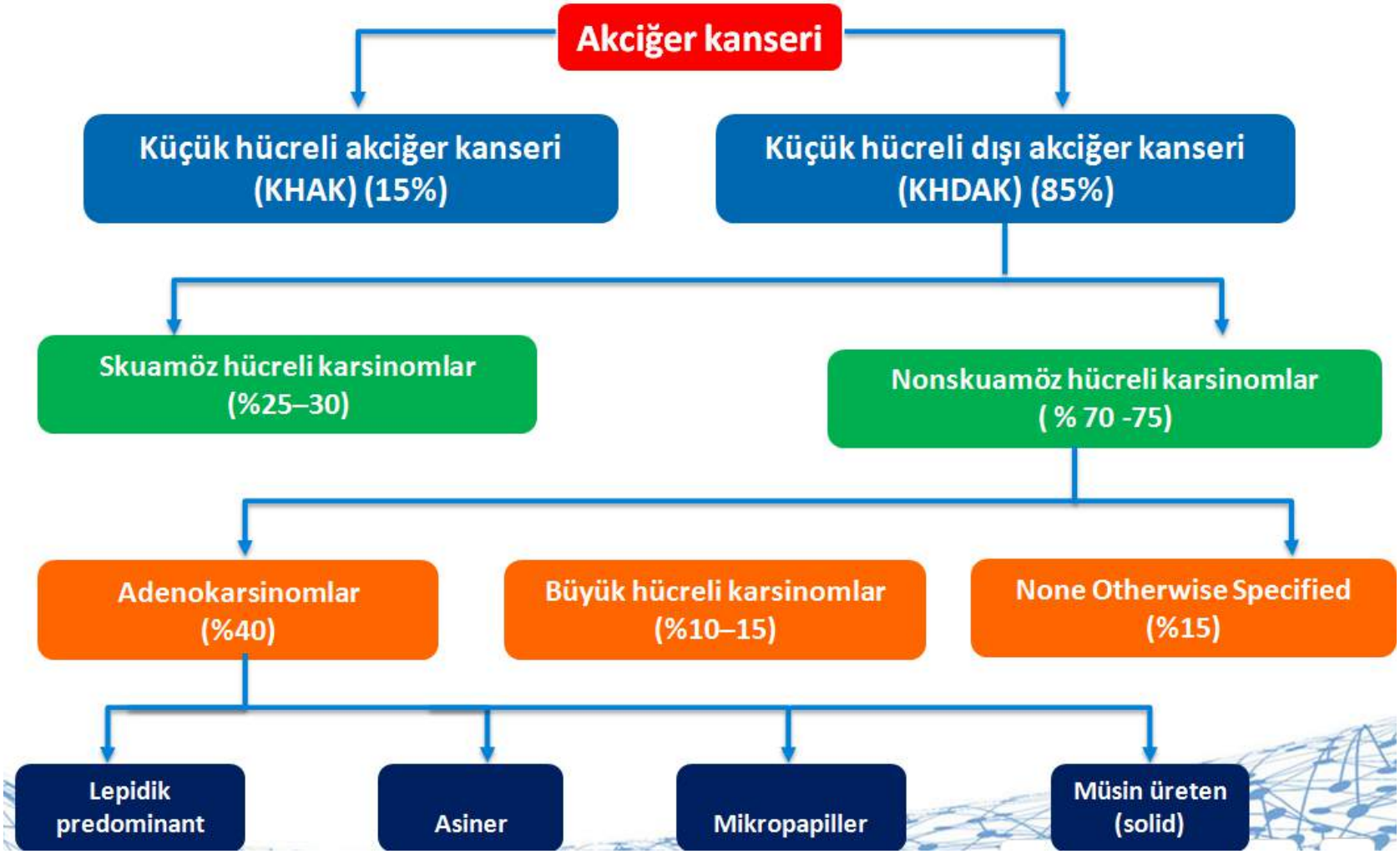


SEER 18 2006-2012, All Races, Both Sexes by SEER Summary Stage 2000

KHDAK'de Sağkalım



Akciğer Kanserinde Patolojik Sınıflandırma

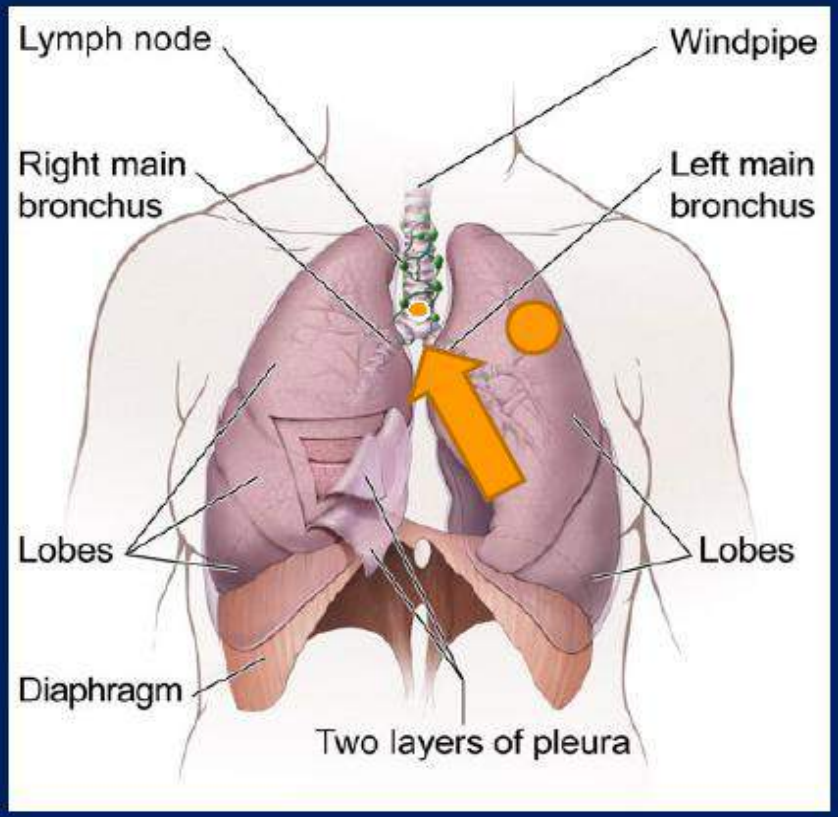


KHDAK Patolojik Sınıflandırma

- 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 (+)

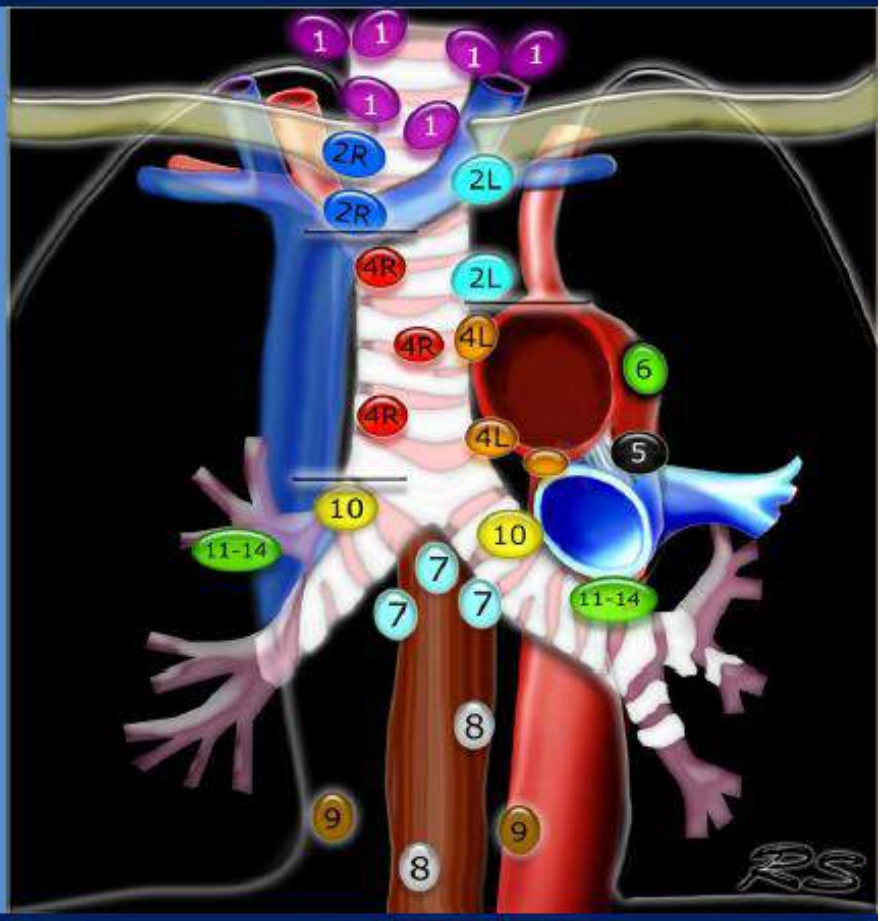
KHDAK Klinik Sınıflandırma

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

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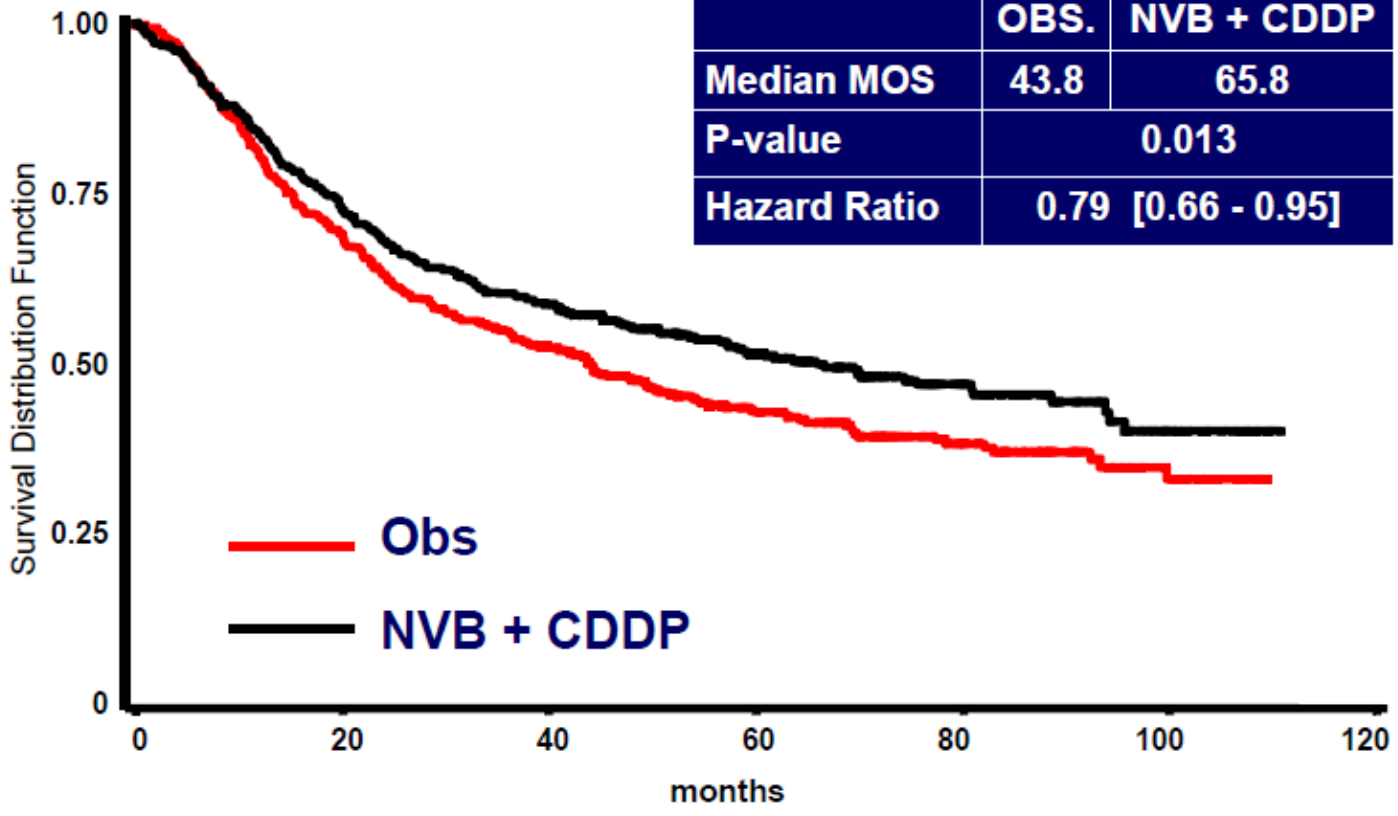
Adjuvant Cisplatin/Vinorelbine in stage I-III NSCLC

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

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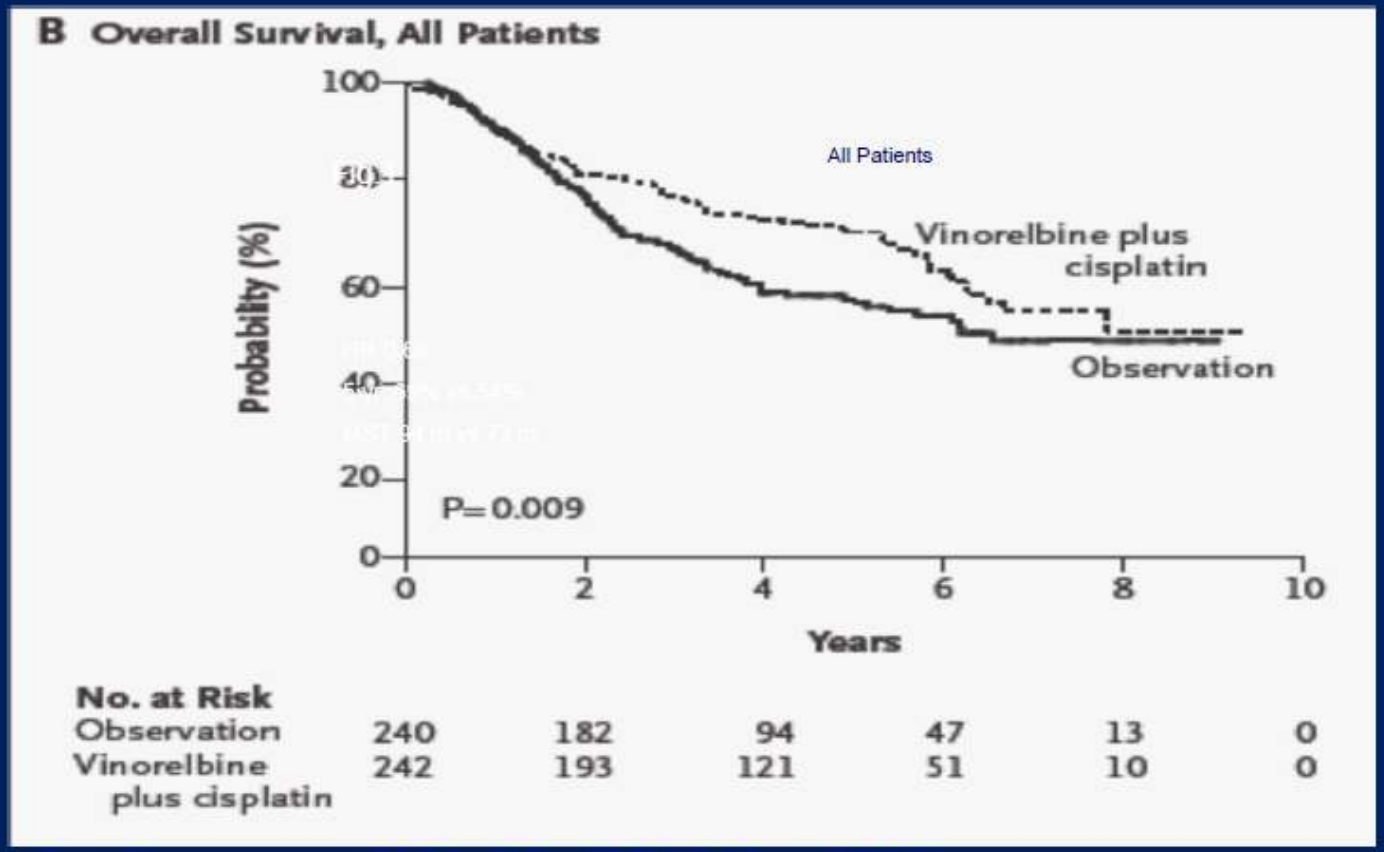
Adjuvant Cisplatin/Vinorelbine in stage Ib-II NSCLC

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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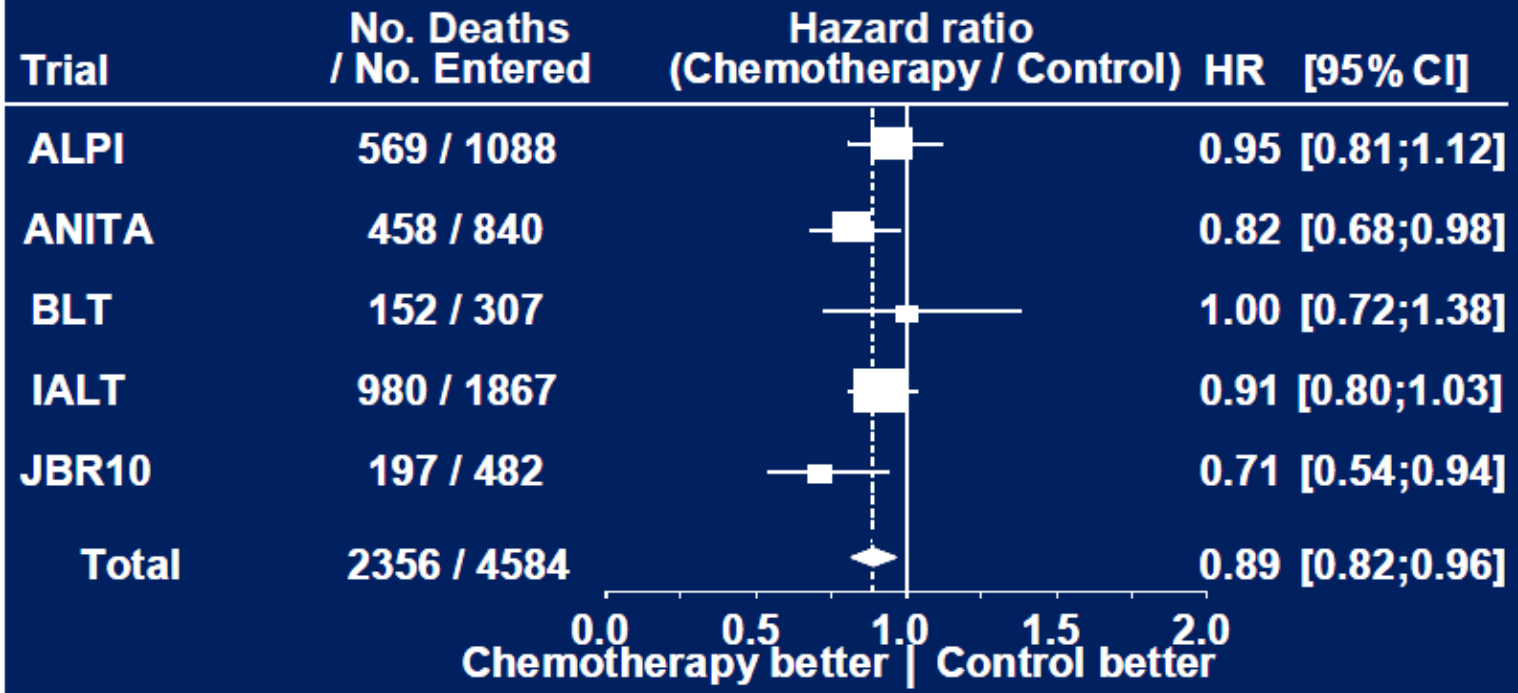
LACE Meta-analysis: Cisplatin-based

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017 Staging Non-Small Cell Lung Cancer

NCCN Guidelines Index
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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

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]

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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**

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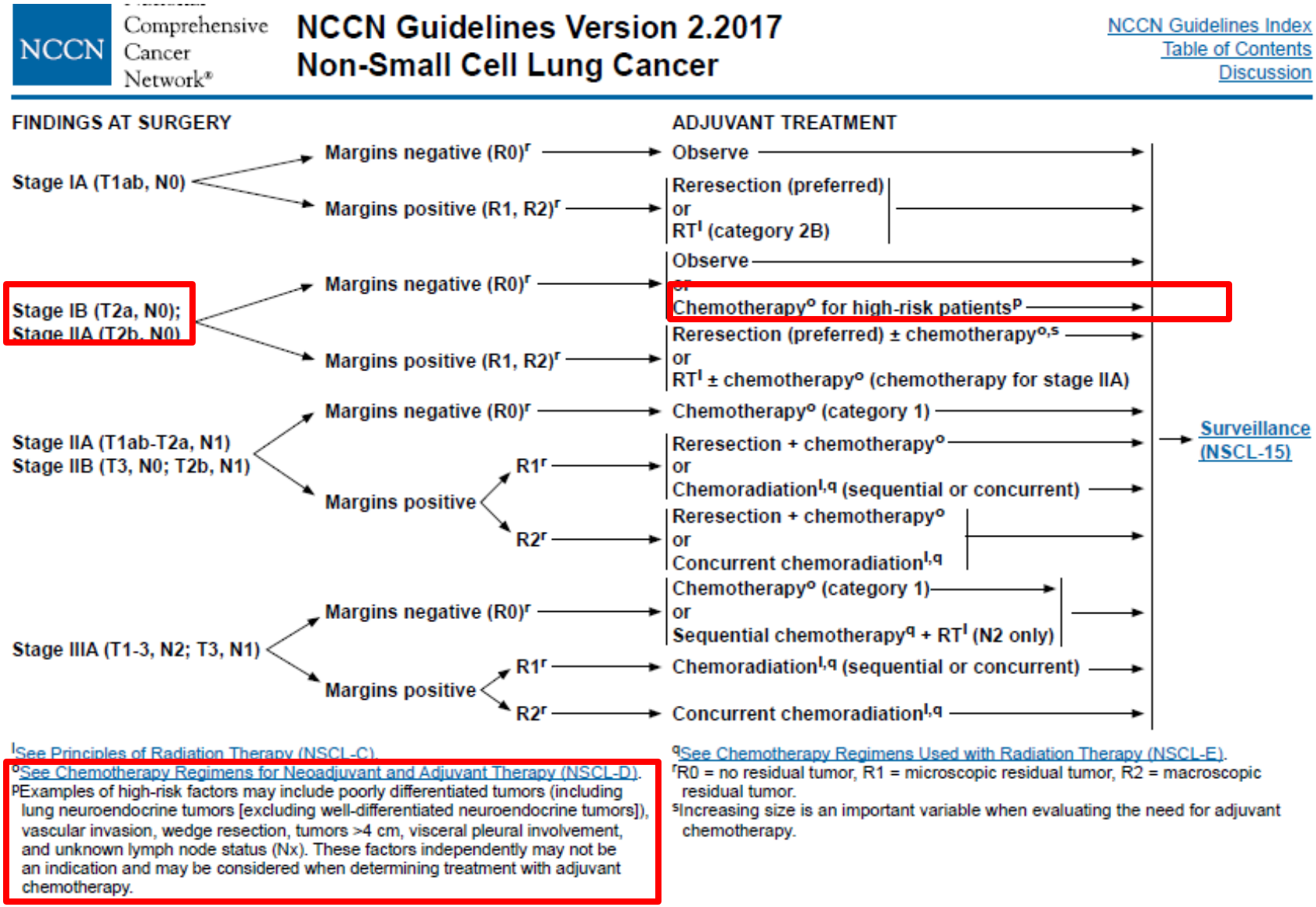

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NCCN Guidelines Version 2.2017
Non-Small Cell Lung Cancer

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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]

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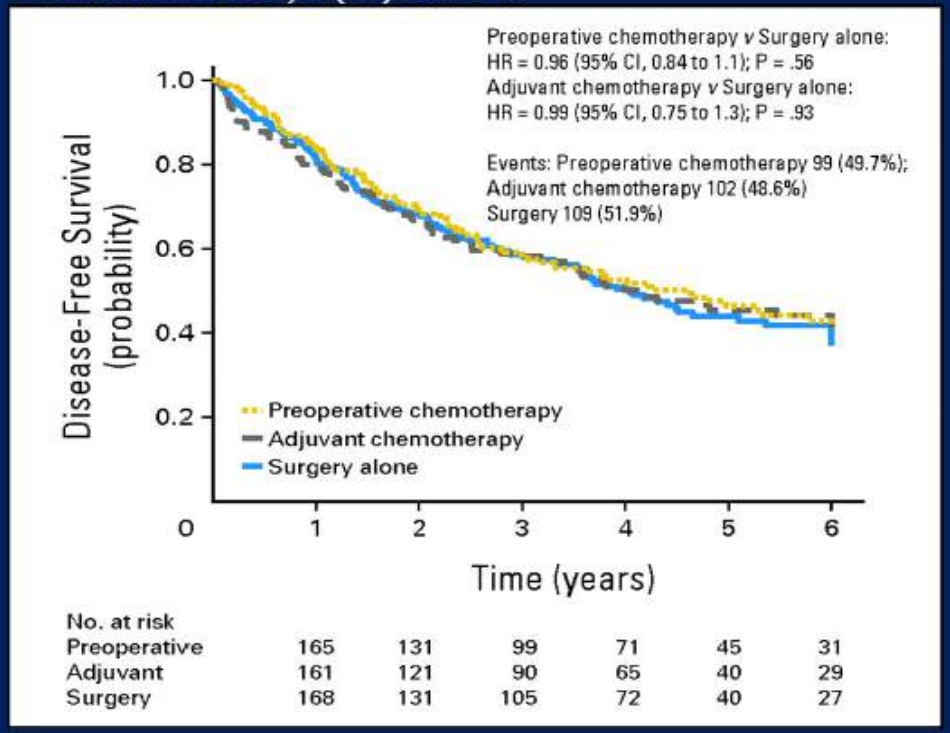
Surgery vs. Surgery + Neoadjuvant or Adjuvant Carboplatin/Paclitaxel

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

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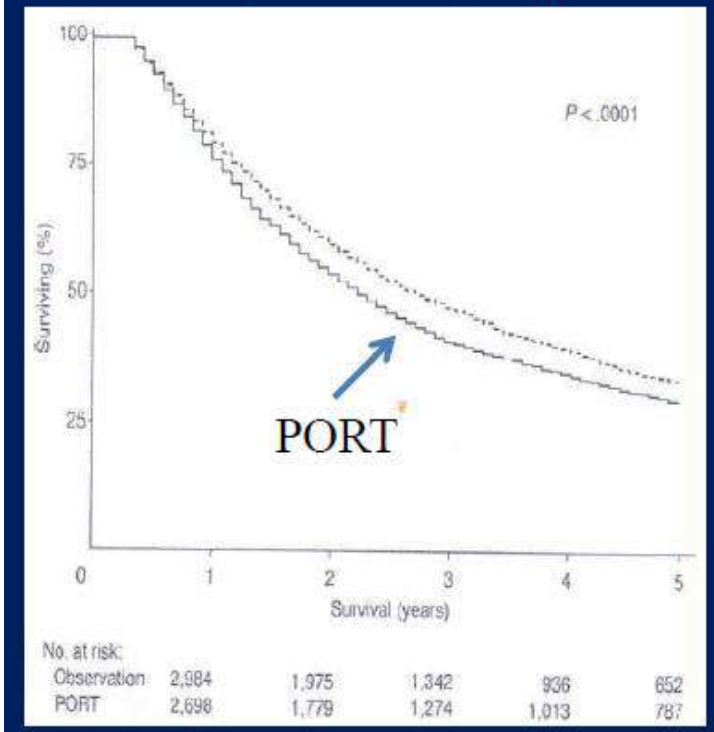
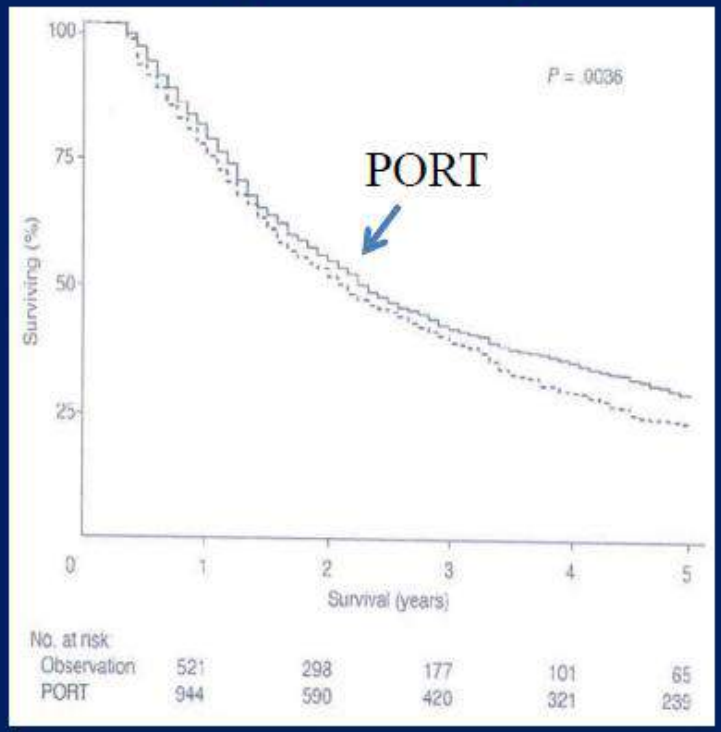
SEER data on PORT in NSCLC

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

All patients (I-III)



N2 patients only

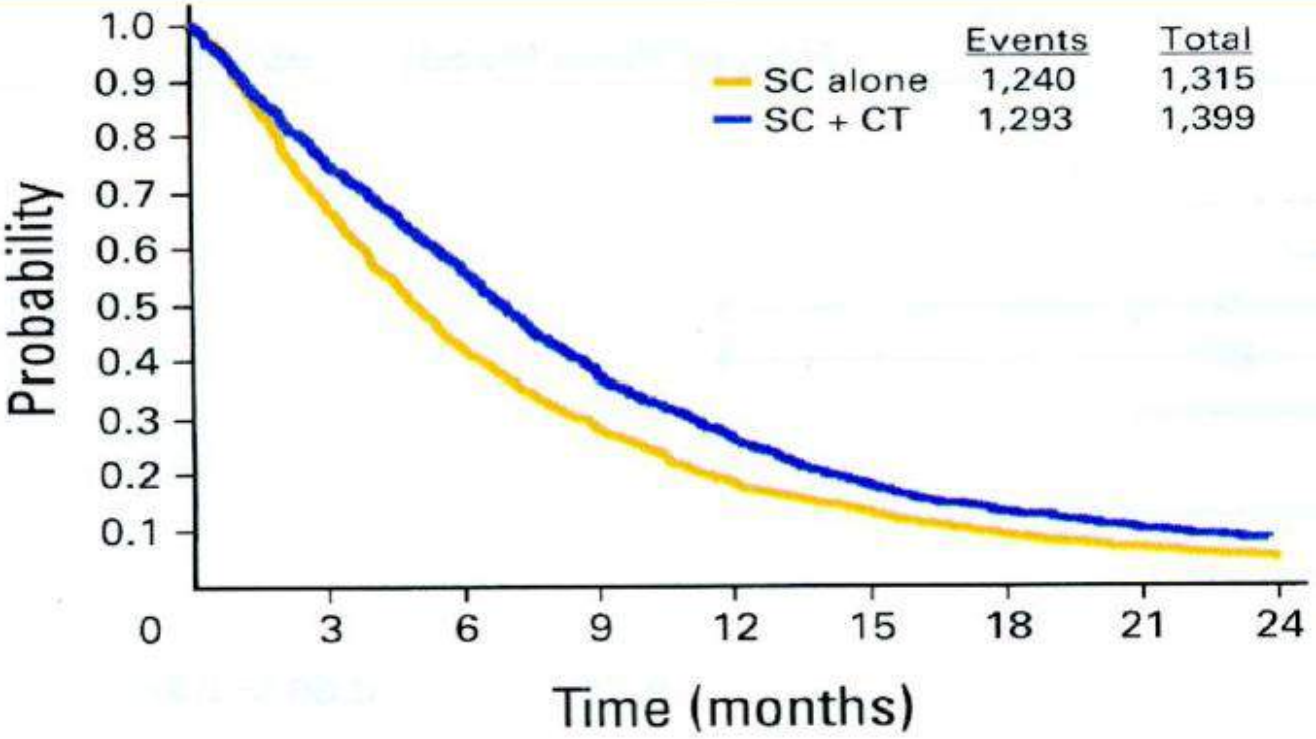


Most patients had not received adjuvant chemotherapy

Metastatik KHDAK Tedavi

Chemotherapy vs. Best supportive care

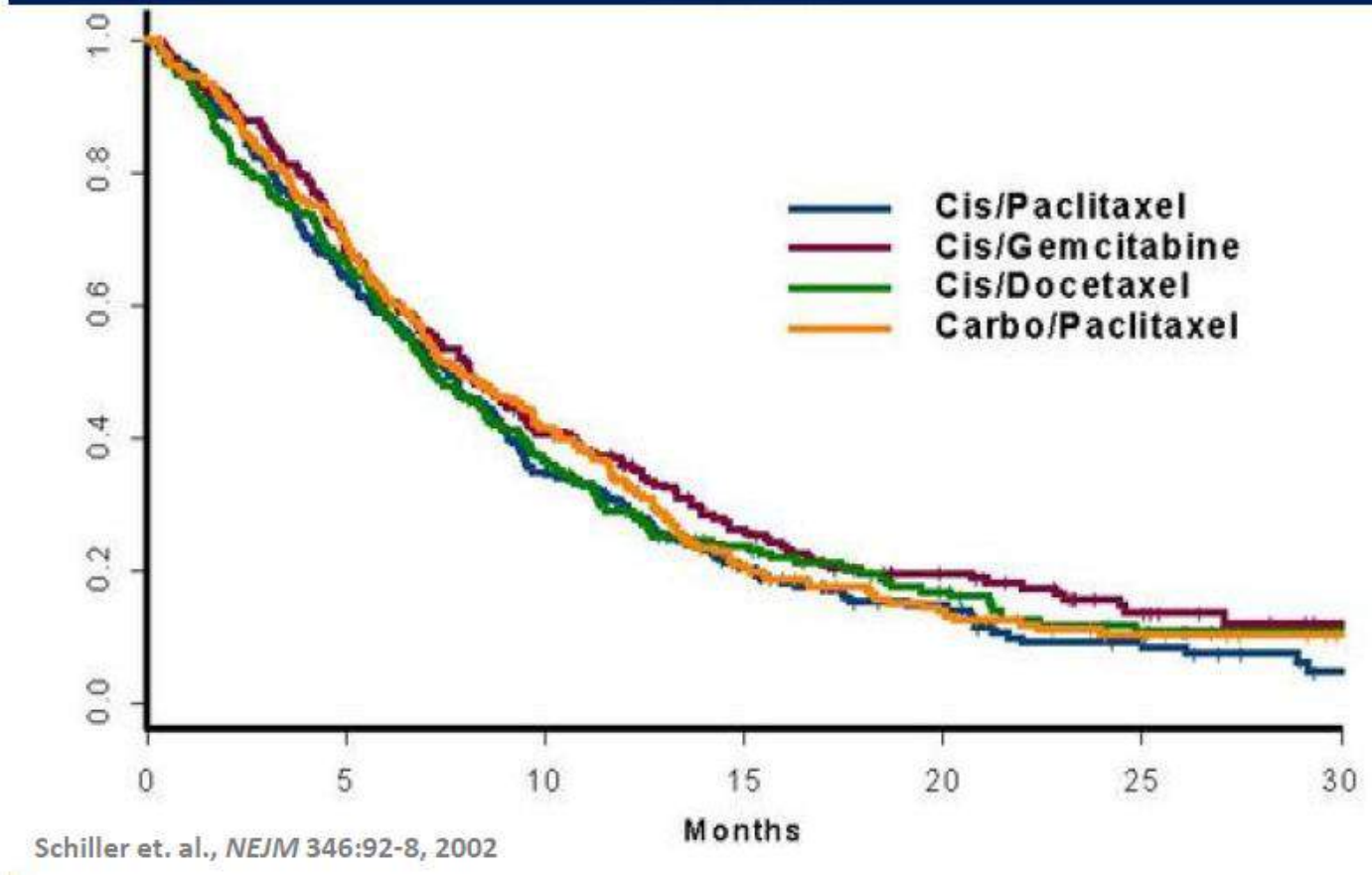
NSCLC Meta-Analyses Collaborative Group ; JCO 2008;26(28)



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

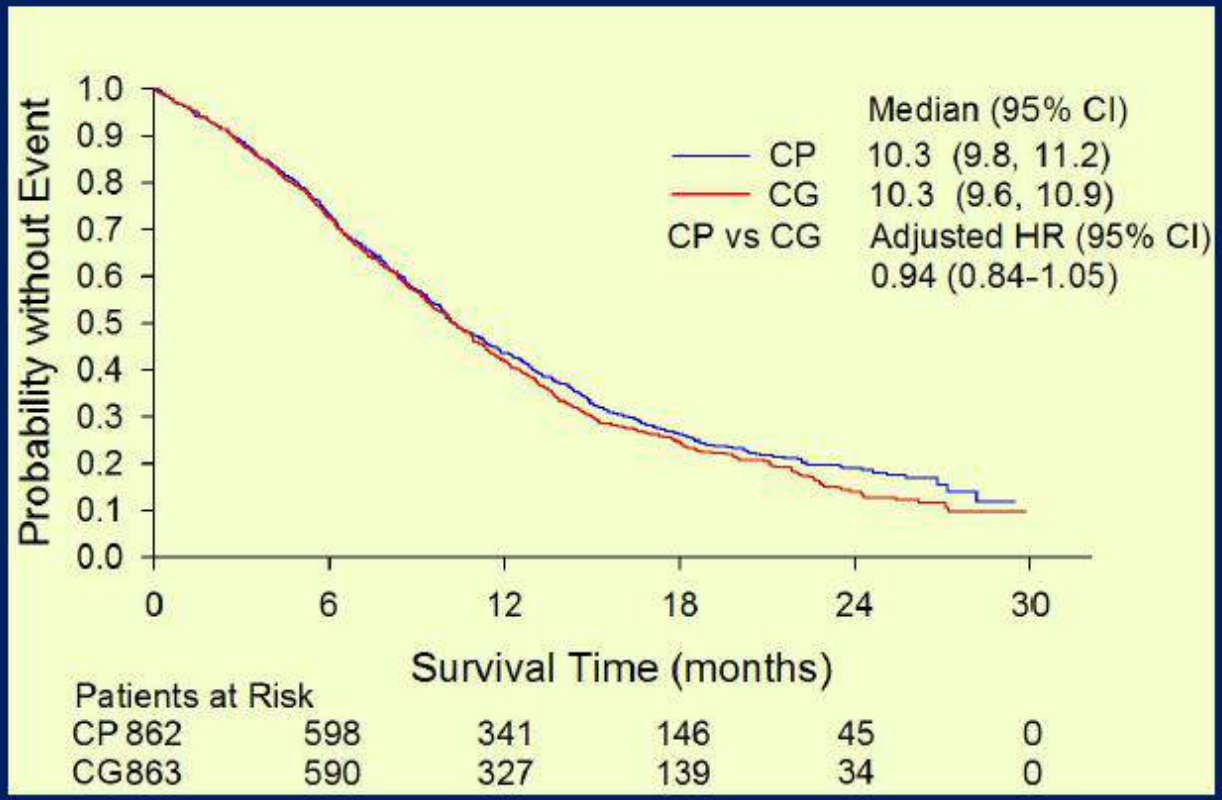


Schiller et. al., *NEJM* 346:92-8, 2002

Metastatik KHDAK Tedavi
Patolojik Alt Tipe Göre

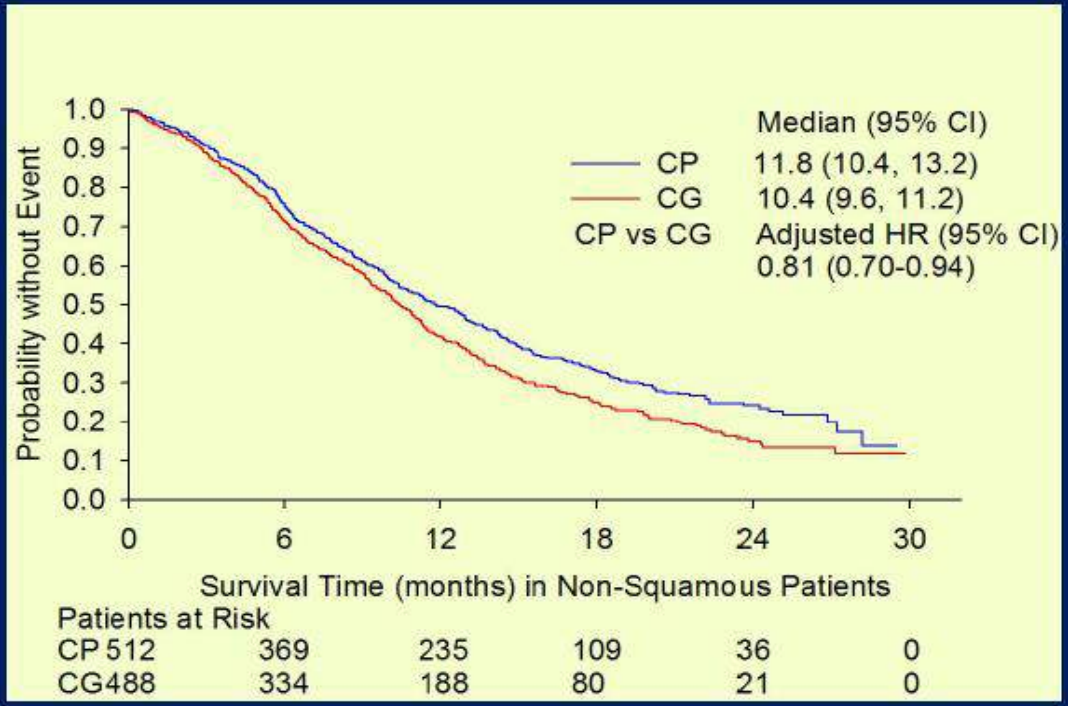
Cisplatin + Gemcitabine or Pemetrexed

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



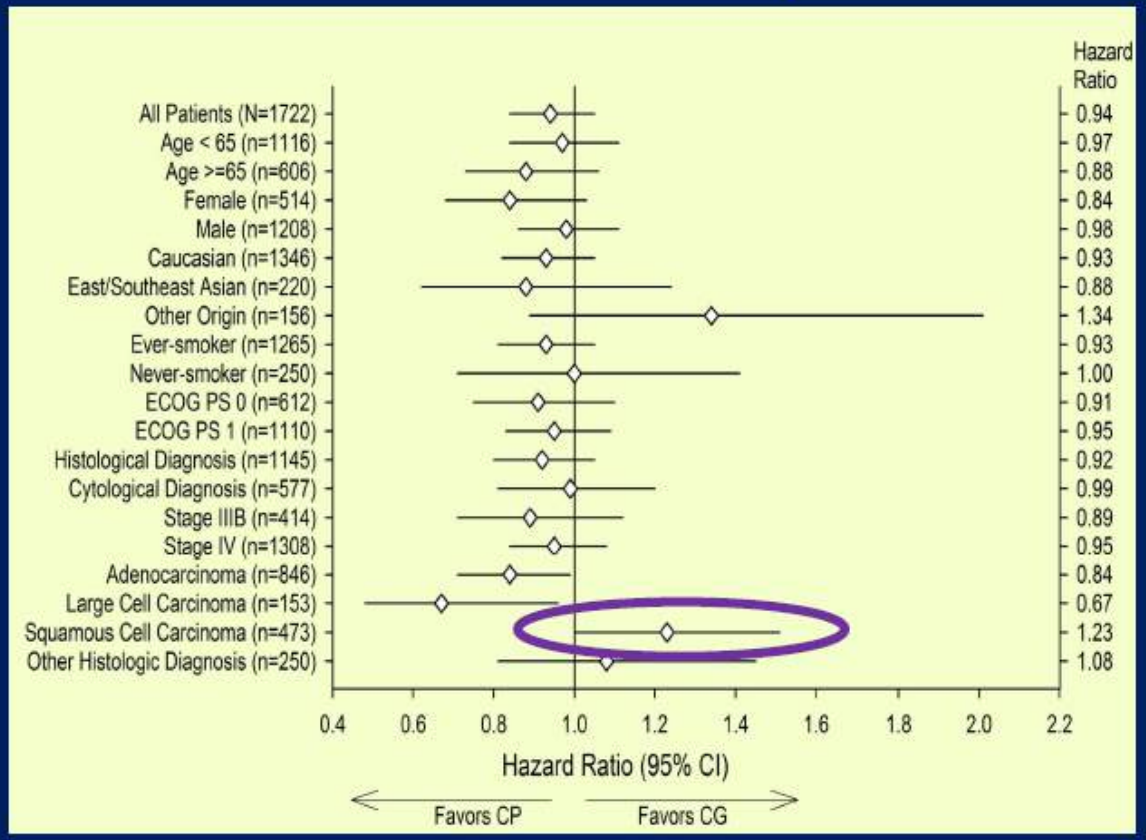
Metastatik KHDAK Tedavi
Patolojik Alt Tipe Göre

Cis/Pem favored in non-squamous



Metastatik KHDAK Tedavi Patolojik Alt Tipe Göre

Cis/Gem favored in squamous

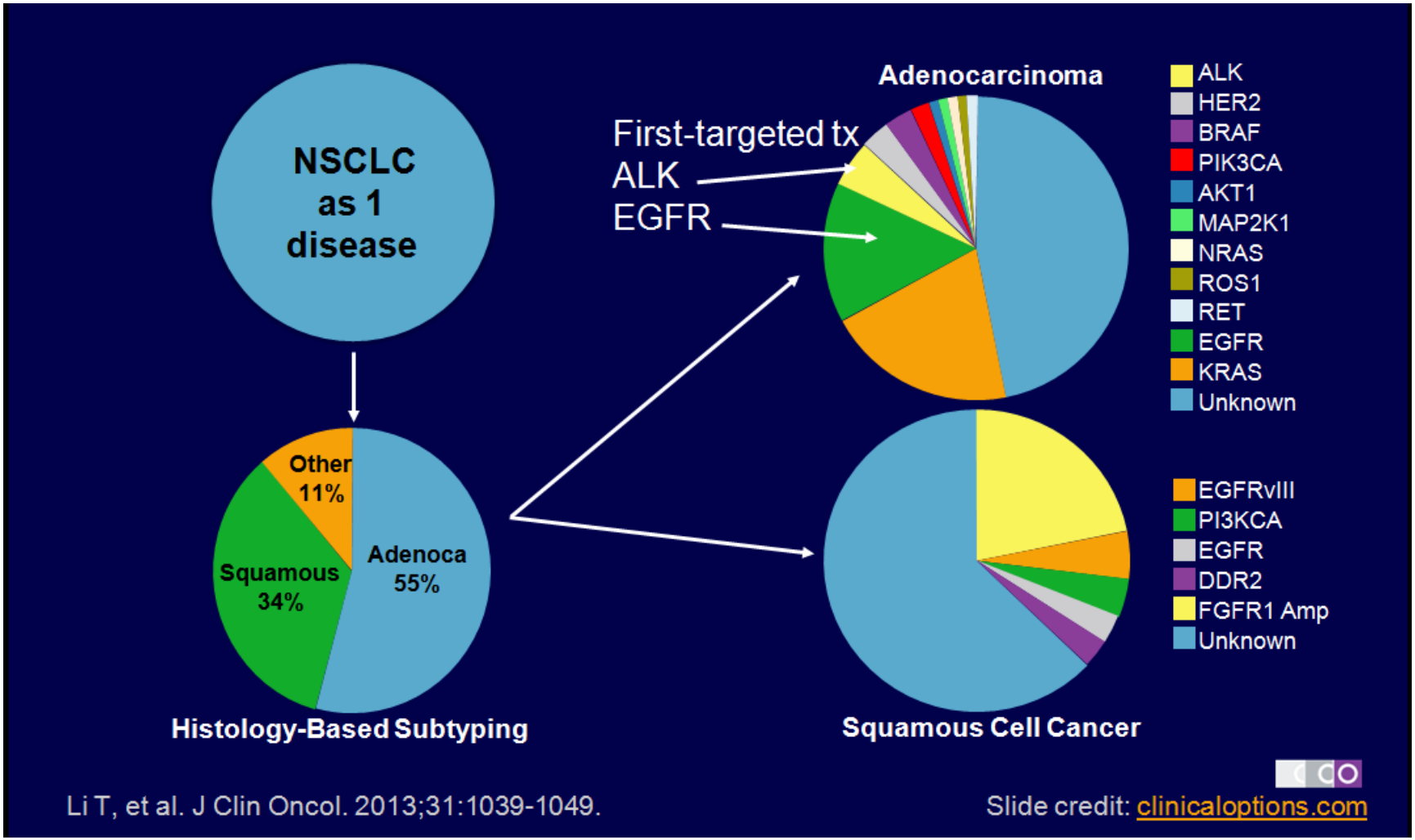


Metastatik KHDAK Tedavi

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

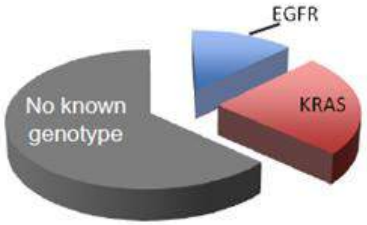
Swanton C, Govindan R. N Engl J Med 2016;374:1864-1873

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%	

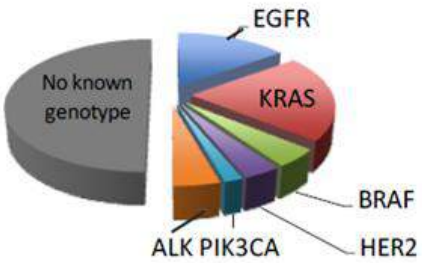
Metastatik KHDAK
Hedefe Yönelik Tedaviler

Akciğer Kanserinde Mutasyonlar

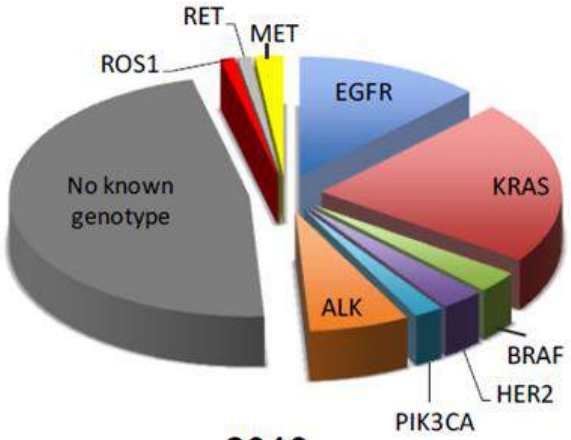
1984–2003



2004



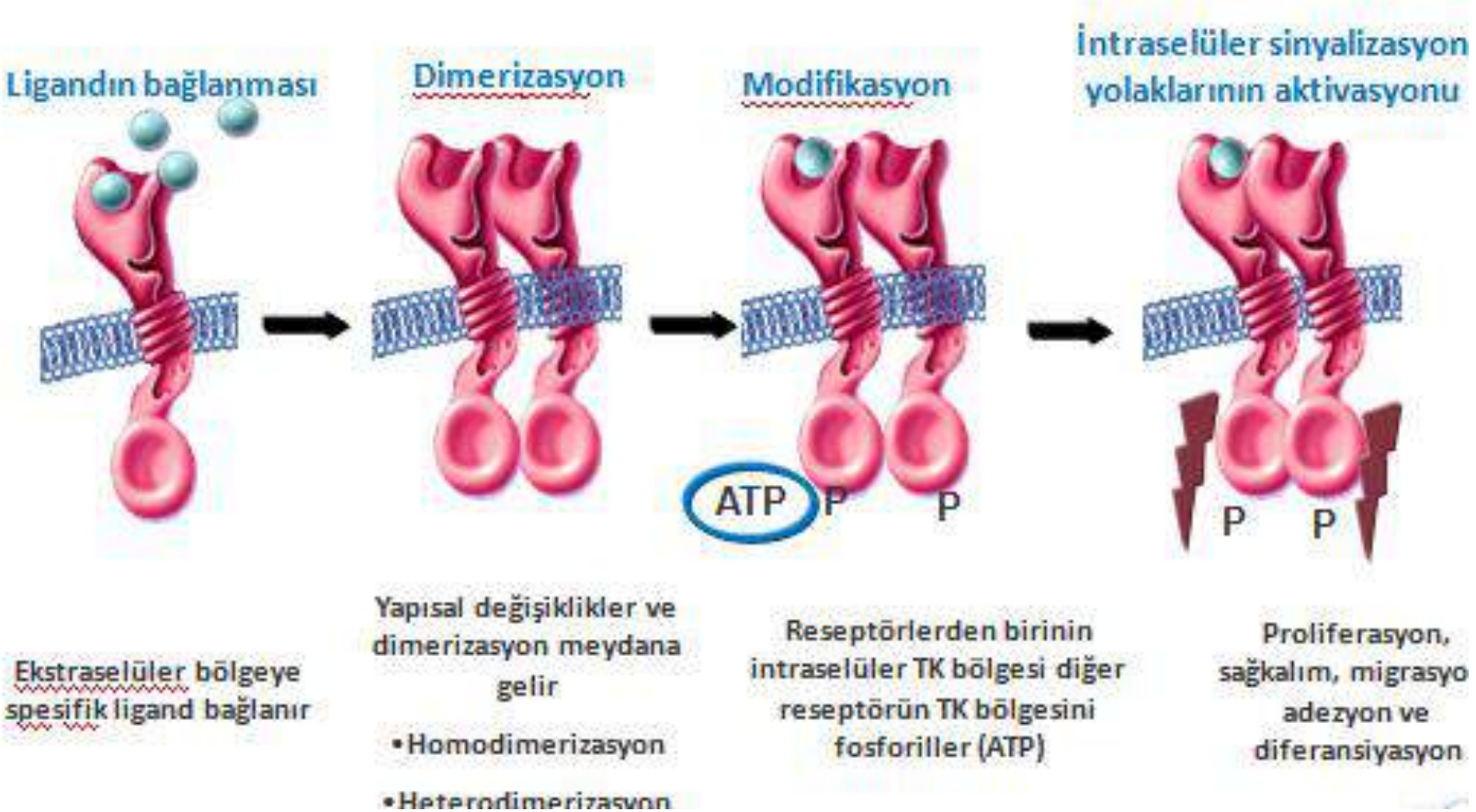
2009



2013

Metastatik KHDAK Hedefe Yönelik Tedaviler

EGFR: Sinyalizasyon



Metastatik KHDAK Hedefe Yönelik Tedaviler

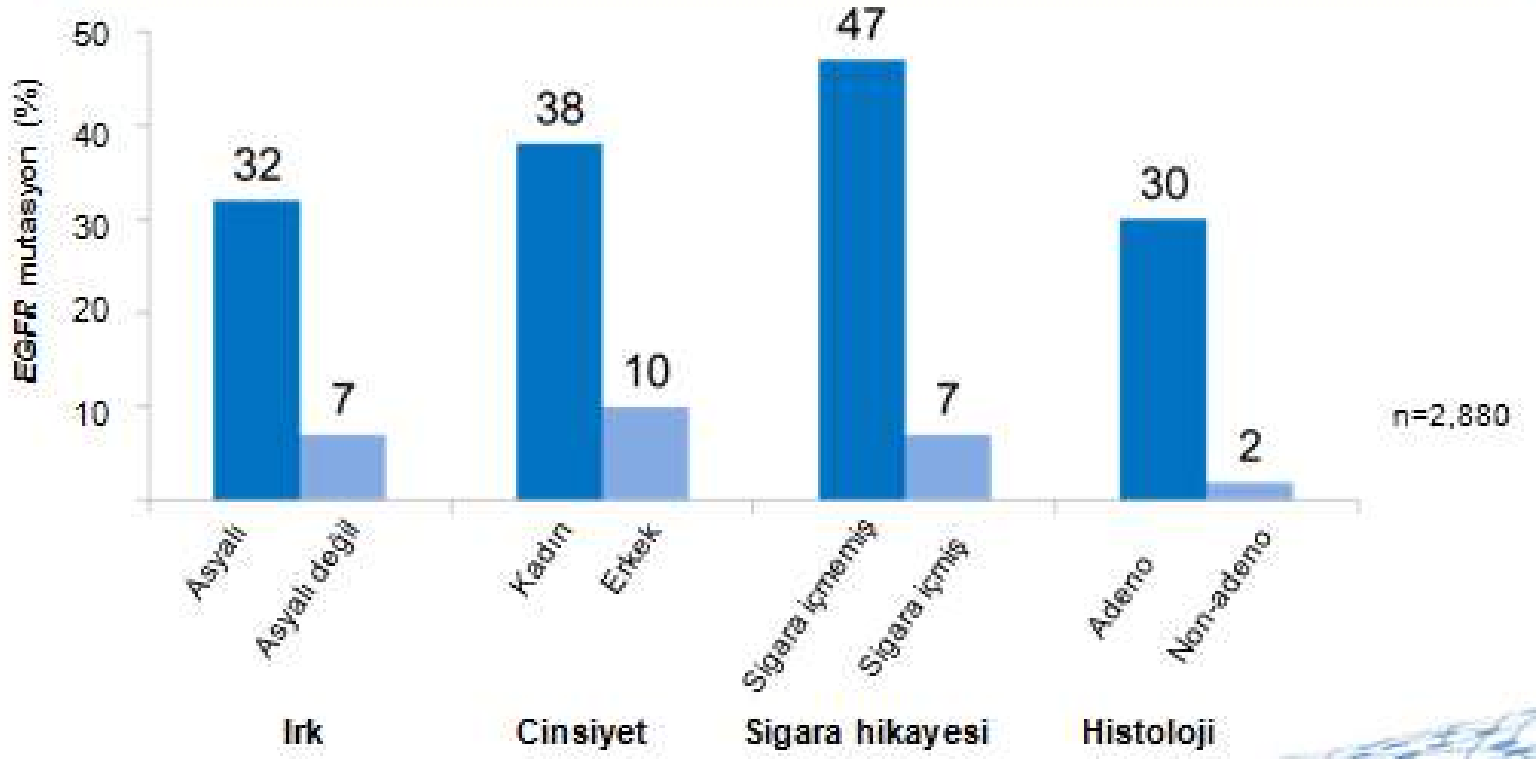
- Found in 10% to 30% of NSCLC pts[1]
- More common in never-smokers, adenocarcinomas, females, Asians[1,2]
- Predominantly located in *EGFR* exons 18-21[2]
  - ~ 85% of *EGFR* mutations are either deletions in exon 19 or a single-point mutation in exon 21 (L858R)
- Specific *EGFR* mutation identified 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.

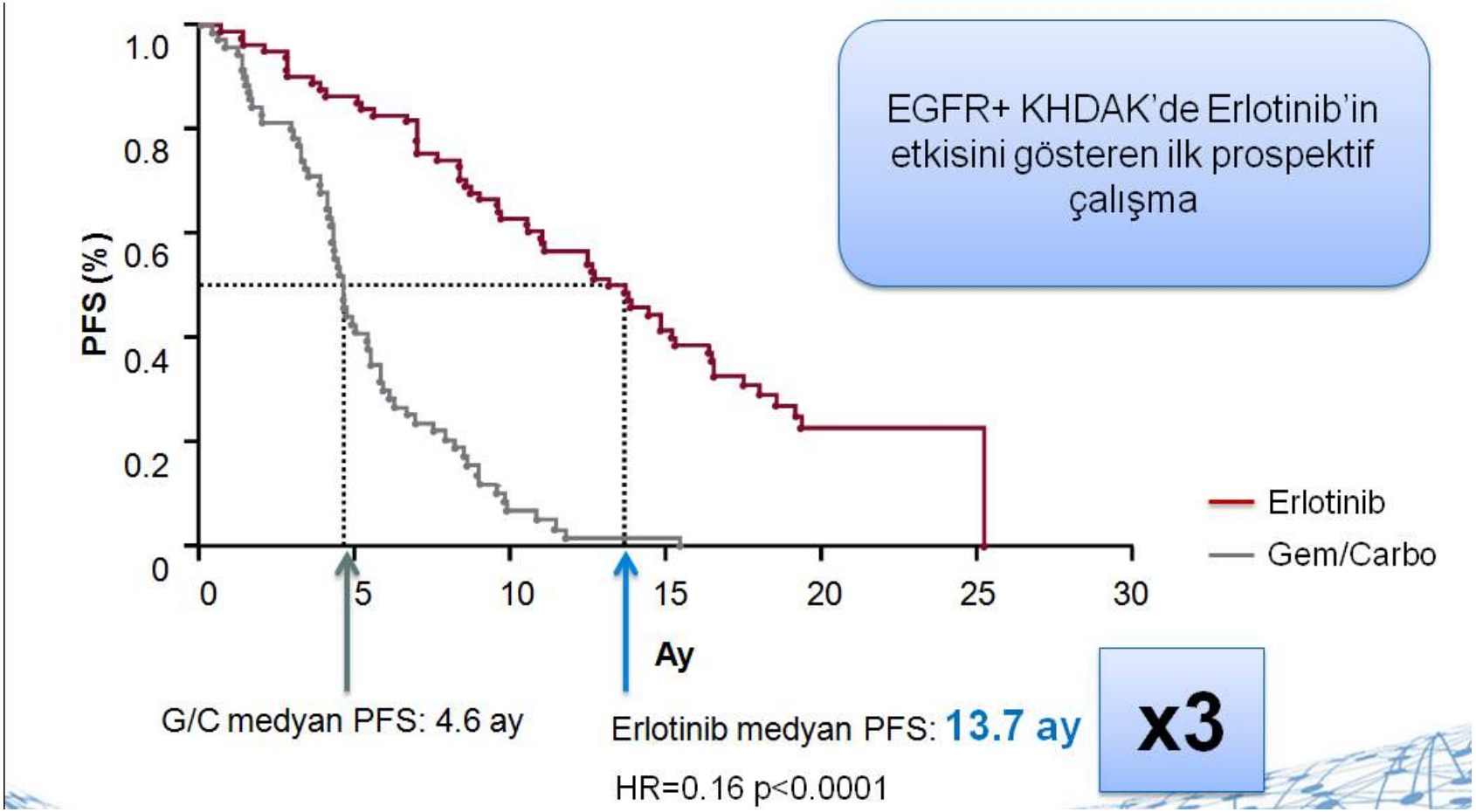
Metastatik KHDAK Hedefe Yönelik Tedaviler

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

OPTIMAL ÇALIŞMASI

Metastatik KHDAK Hedefe Yönelik Tedaviler

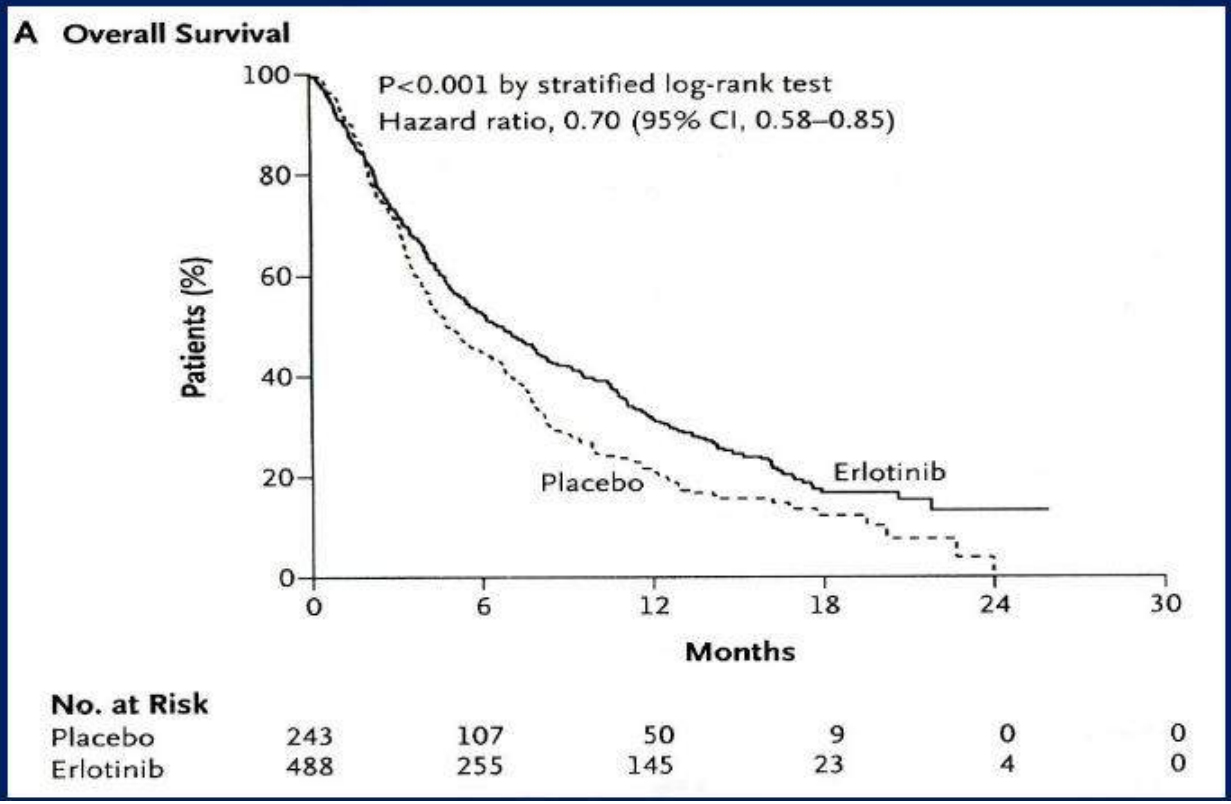
First line EGFR TKI vs. chemotherapy in EGFR mut + NSCLC

	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 Direnç Mekanizmaları

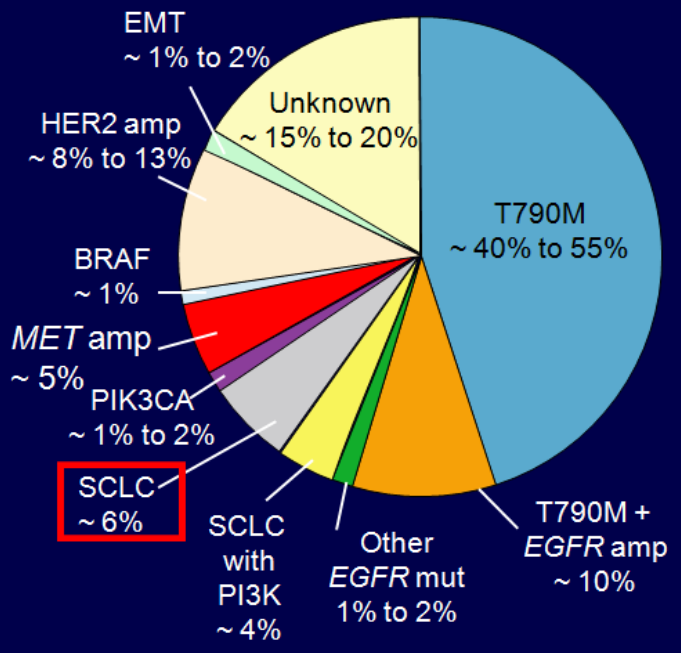
Disease Progression on EGFR TKI in NSCLC With *EGFR* Sensitizing Mutations

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

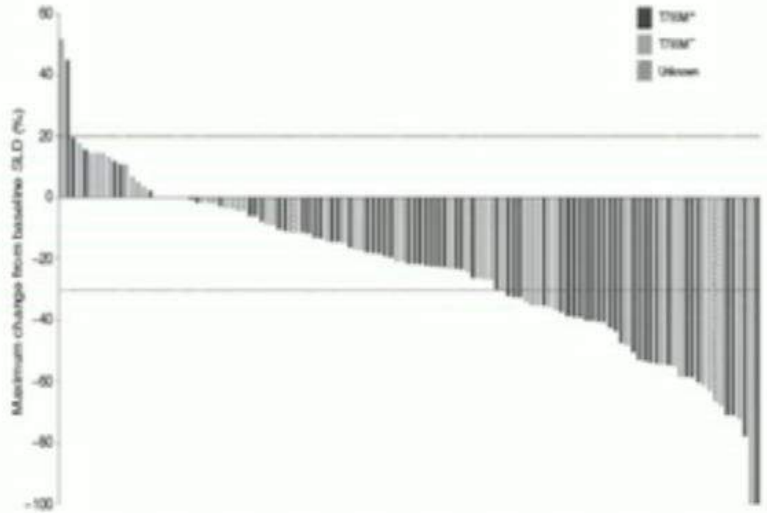
EGFR resistance

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

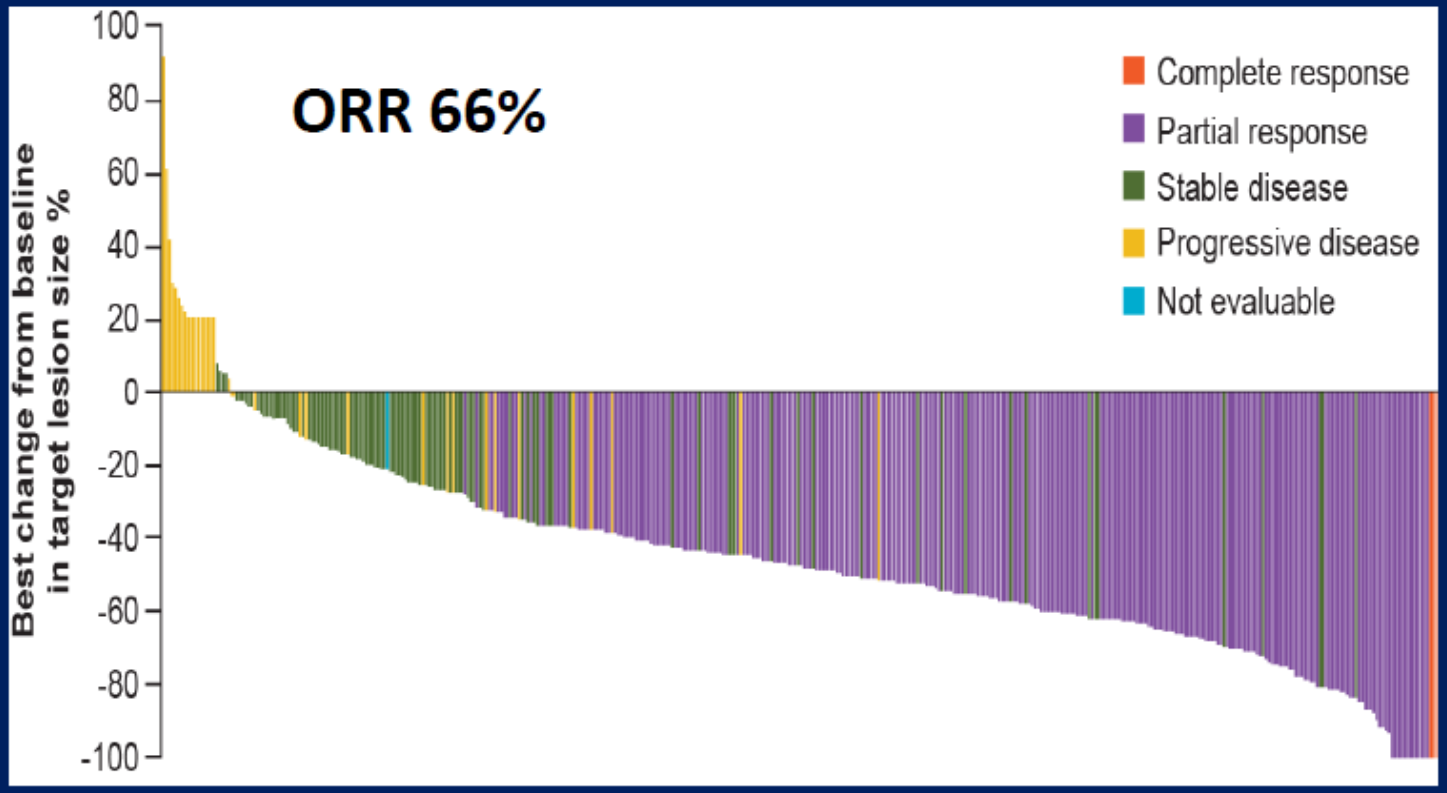
T790M mutation negative
ORR 25%
Median PFS – 4.6 mo

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

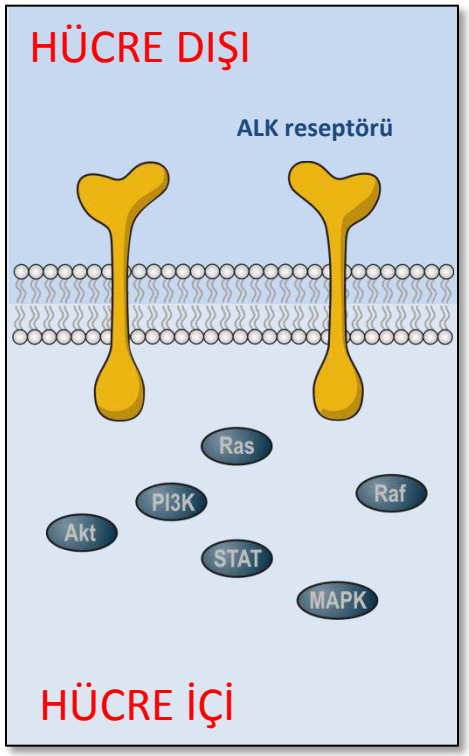
1. Jänne PA, et al. N Engl J Med. 2015;372:1689-1699. 2. Sequist LV, et al. N Engl J Med. 2015;372:1700-1709. 3. Sequist LV, et al. N Engl J Med. 2016;374:2296-2297. 4. Park K, et al. ASCO 2015. Abstract 8084. 5. Tan DS, et al. ASCO 2015. Abstract 8013. 6. Goto Y, et al. ASCO 2015. Abstract 8014.

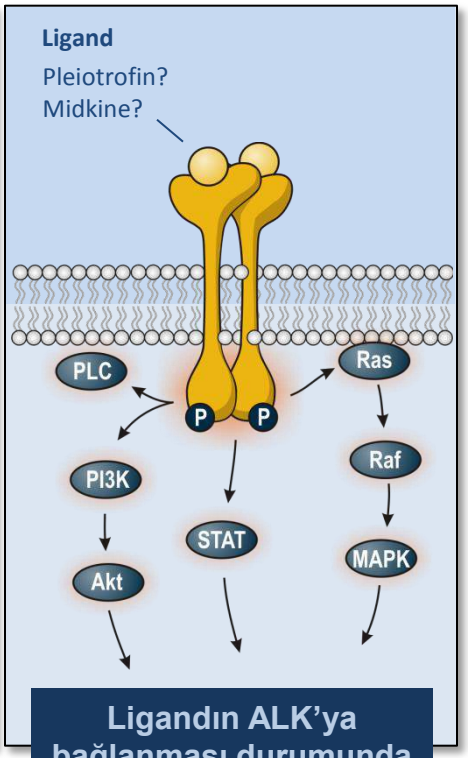
Slide credit: clinicaloptions.com

Metastatik KHDAK Hedefe Yönelik Tedaviler

Krizotinib etki mekanizması

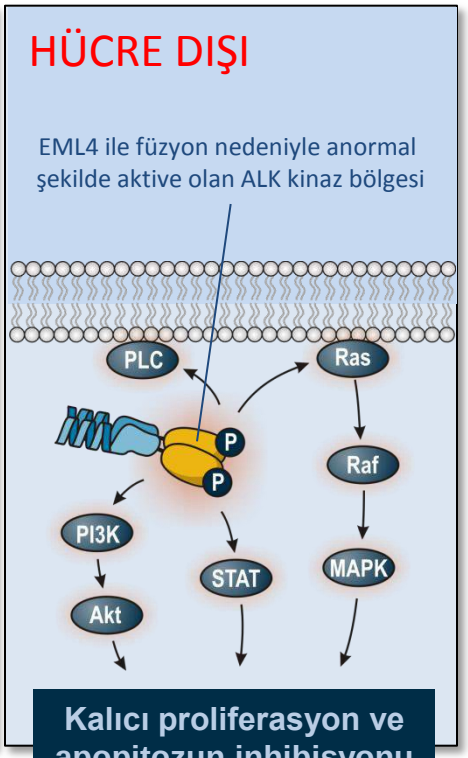
Normal ALK sinyal iletimi





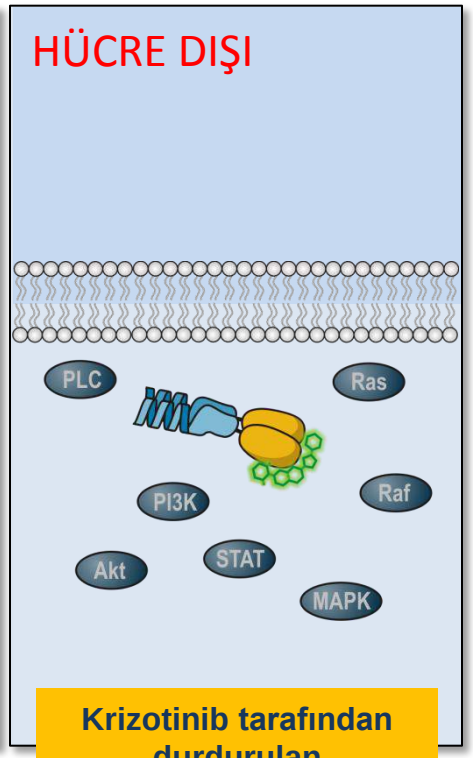
Ligandın ALK'ya bağlanması durumunda proliferasyon ve sağkalım

Patolojik ALK sinyal iletimi



Kalıcı proliferasyon ve apopitozun inhibisyonu

Krizotinibin etki şekli

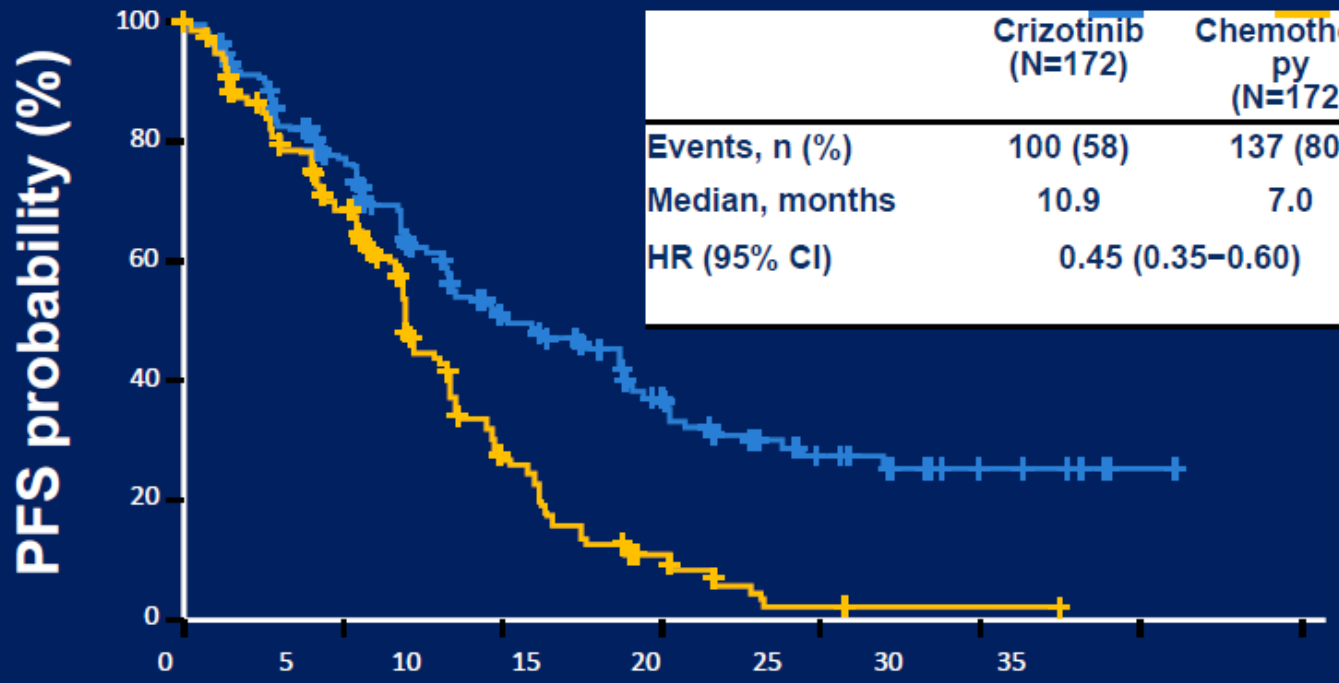


Krizotinib tarafından durdurulan EML4-ALK füzyonu

Metastatik KHDAK Hedefe Yönelik Tedaviler

1st line Crizotinib prolongs PFS compared to platinum/pemetrexed

Mok et al, ASCO 2014, abstr 8002

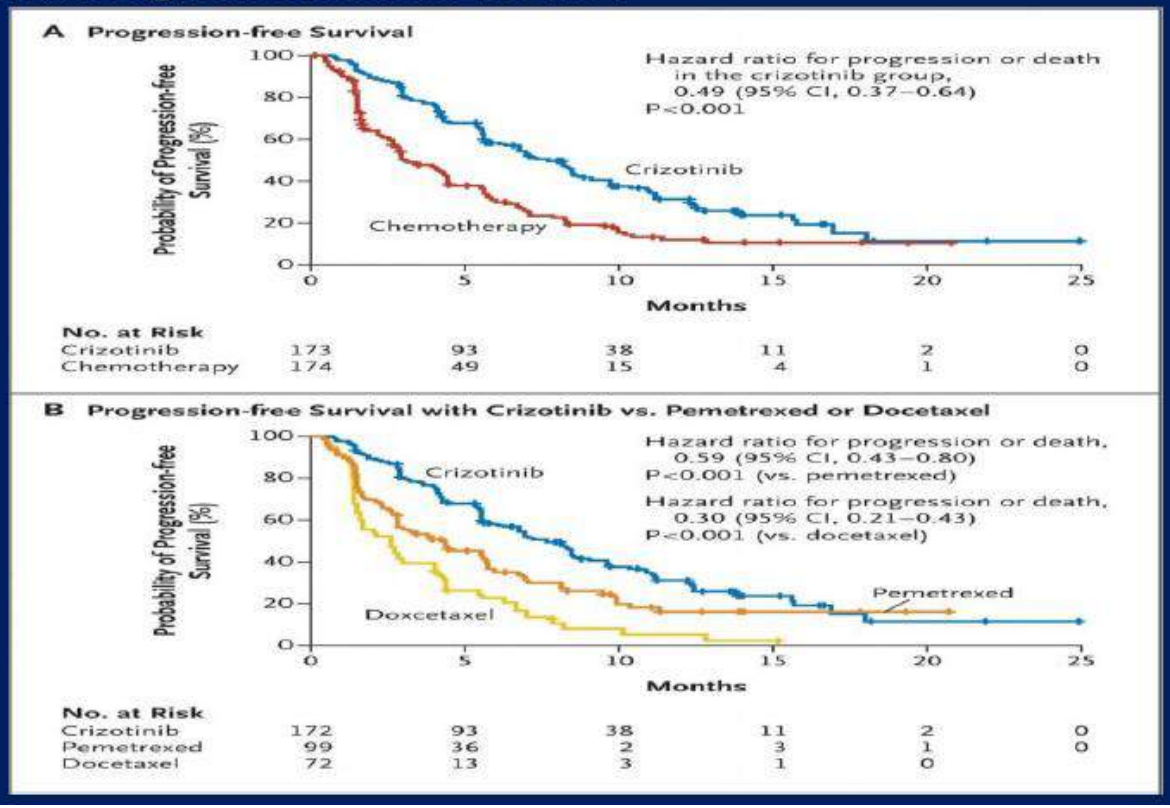


	Crizotinib (N=172)	Chemotherapy (N=172)
Events, n (%)	100 (58)	137 (80)
Median, months	10.9	7.0
HR (95% CI)	0.45 (0.35–0.60)	

Metastatik KHDAK Hedefe Yönelik Tedaviler

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

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



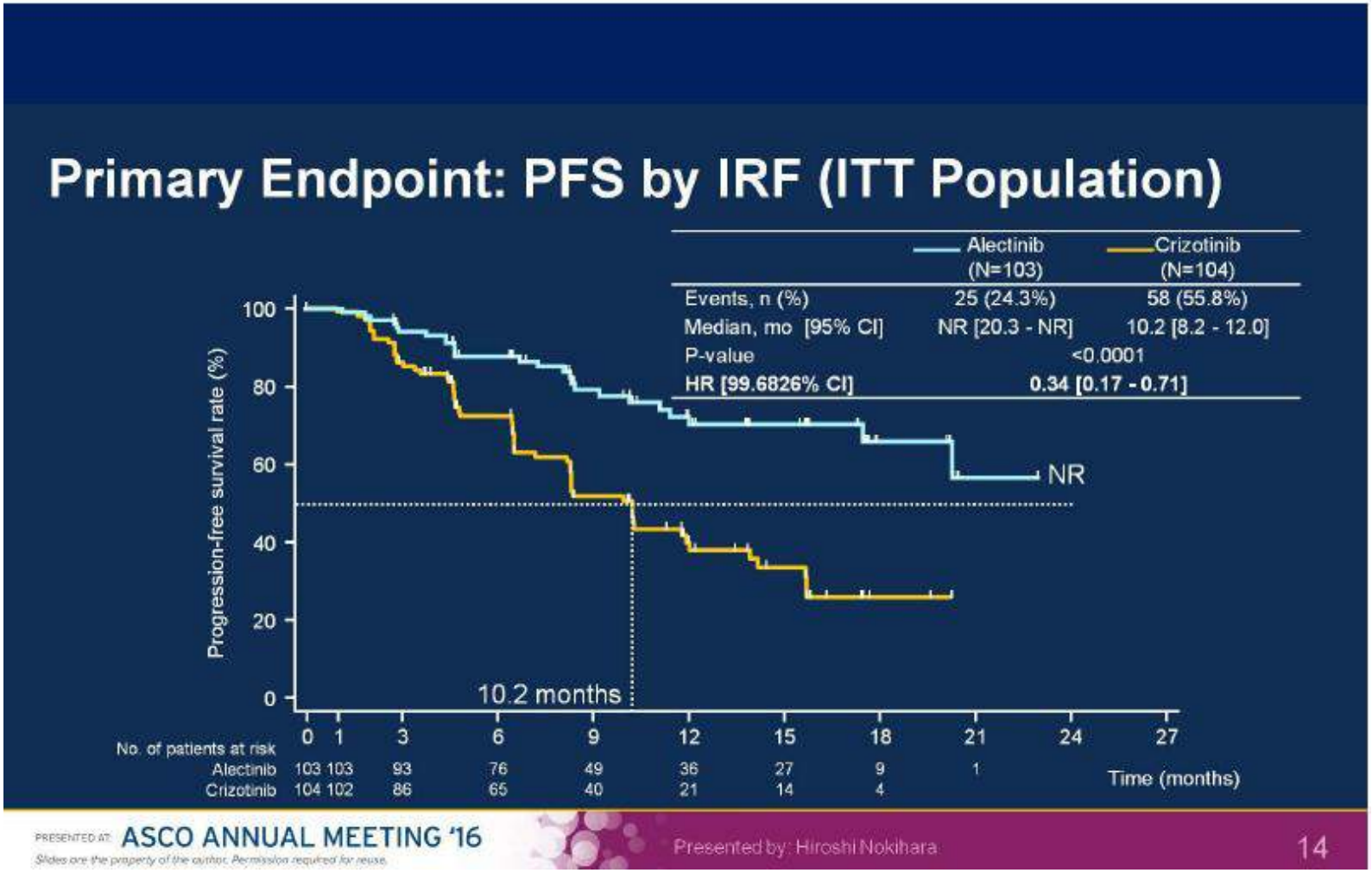
Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler

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

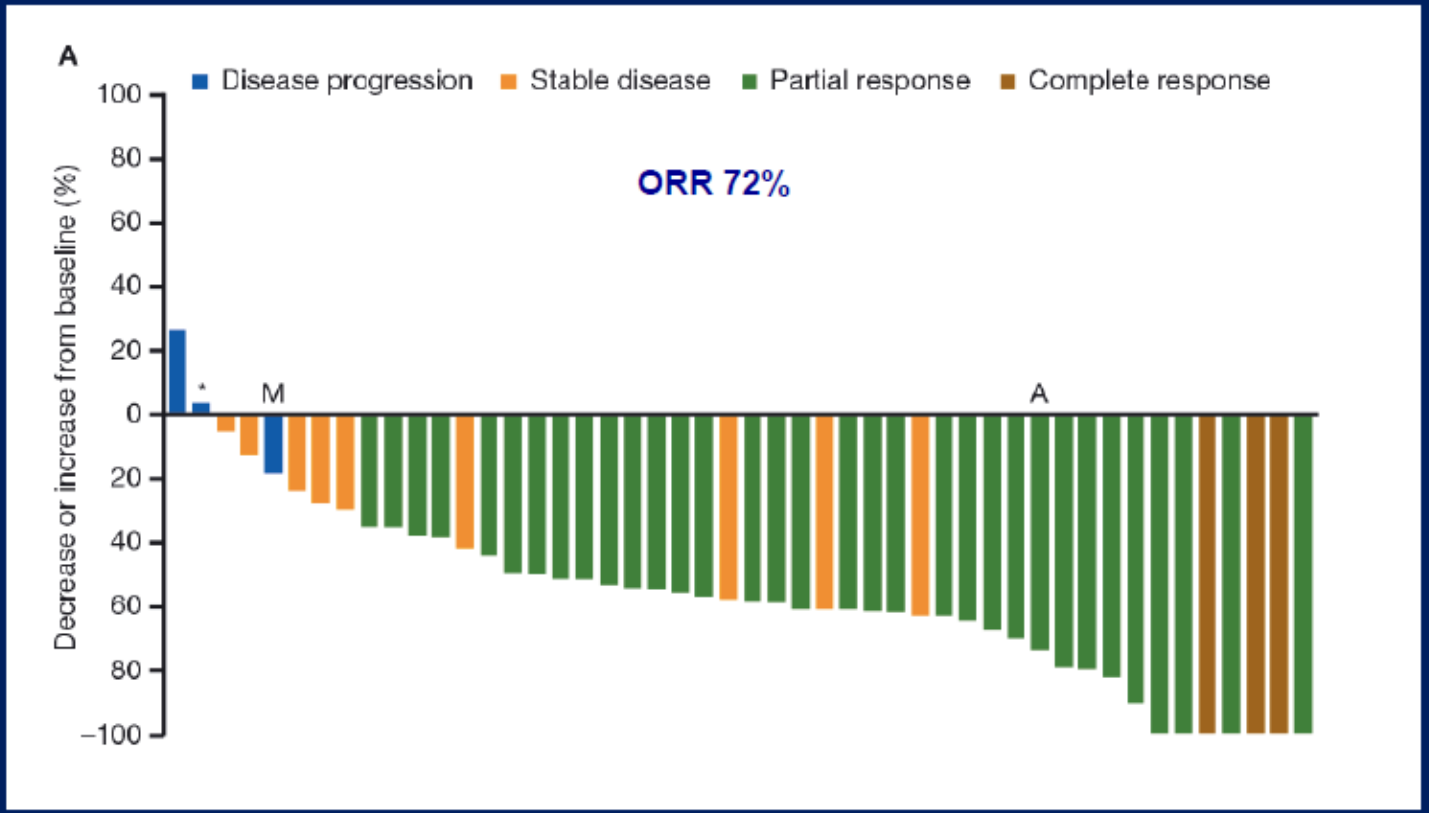
Metastatik KHDA Kanserinde Hedefe Yönelik Tedaviler



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

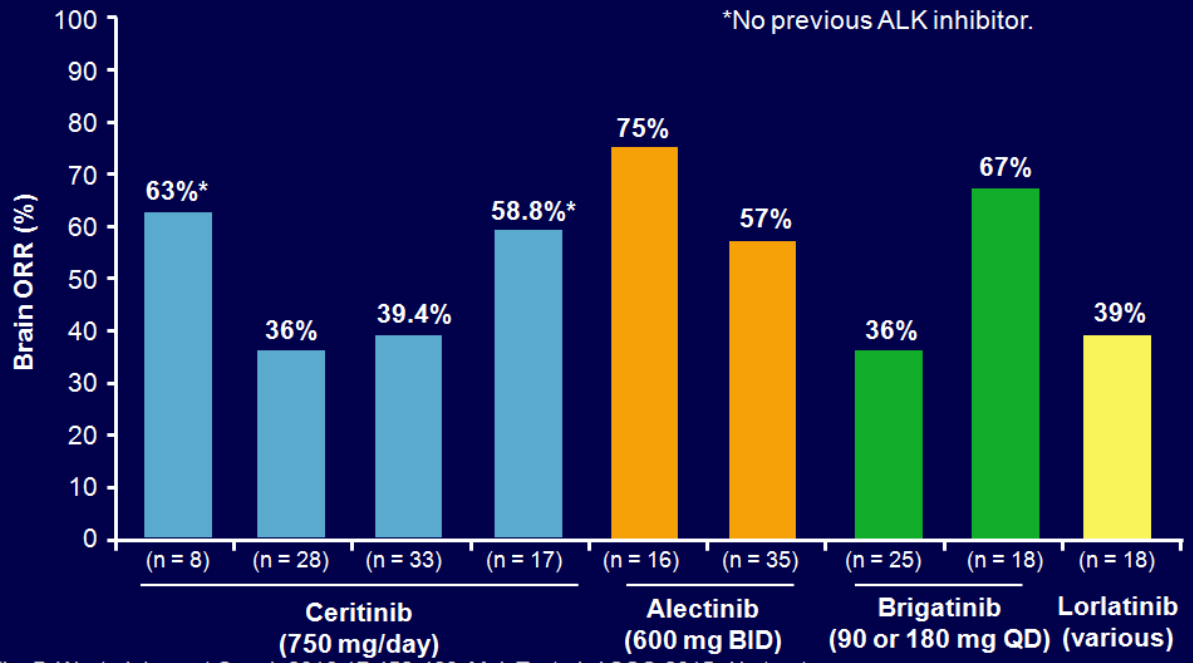
Second-Generation ALK Inhibitors

	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.

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	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

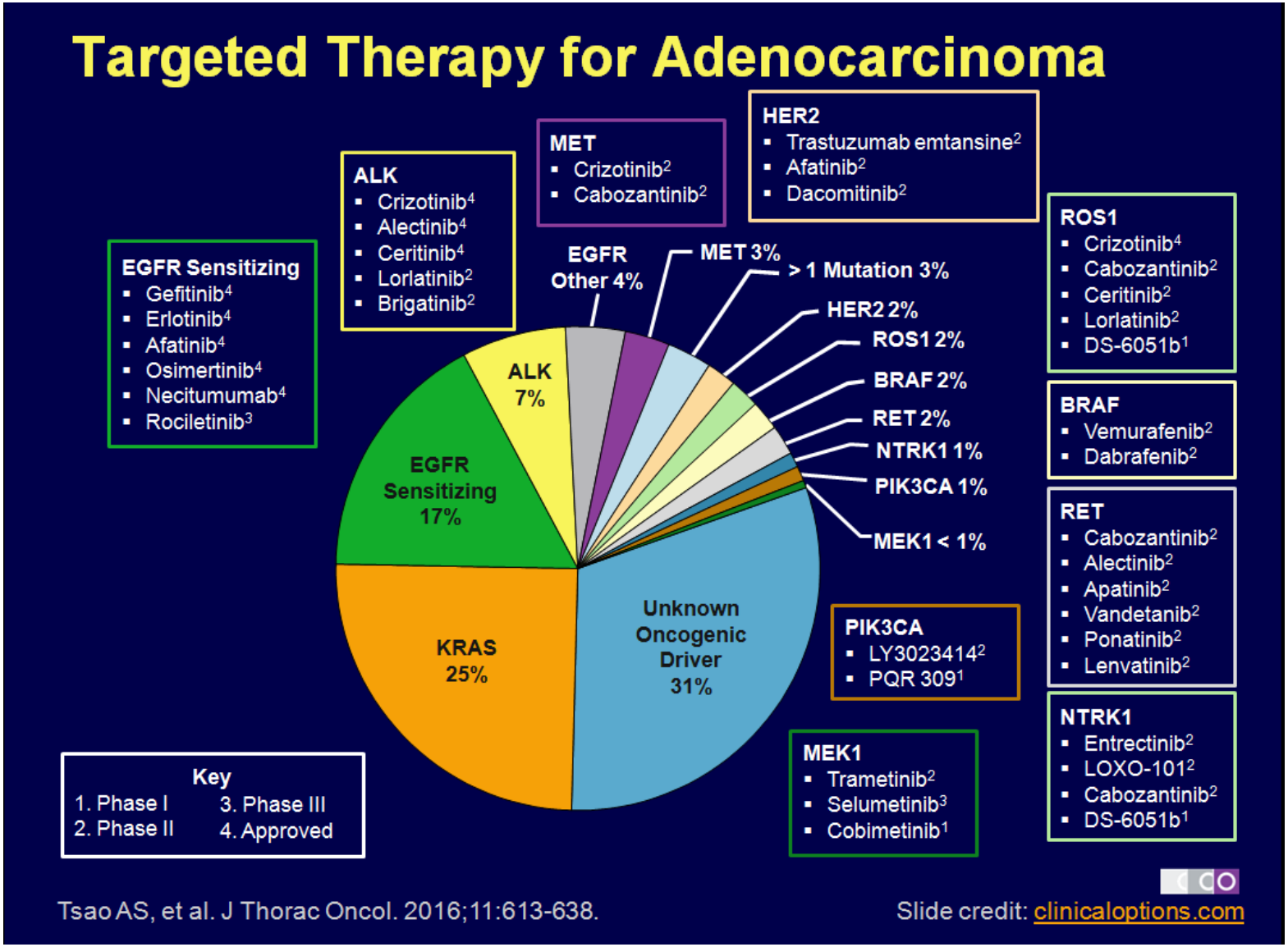
Metastatik KHDAK Hedefe Yönelik Tedaviler

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



Tsao AS, et al. J Thorac Oncol. 2016;11:613-638.

Slide credit: clinicaloptions.com

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

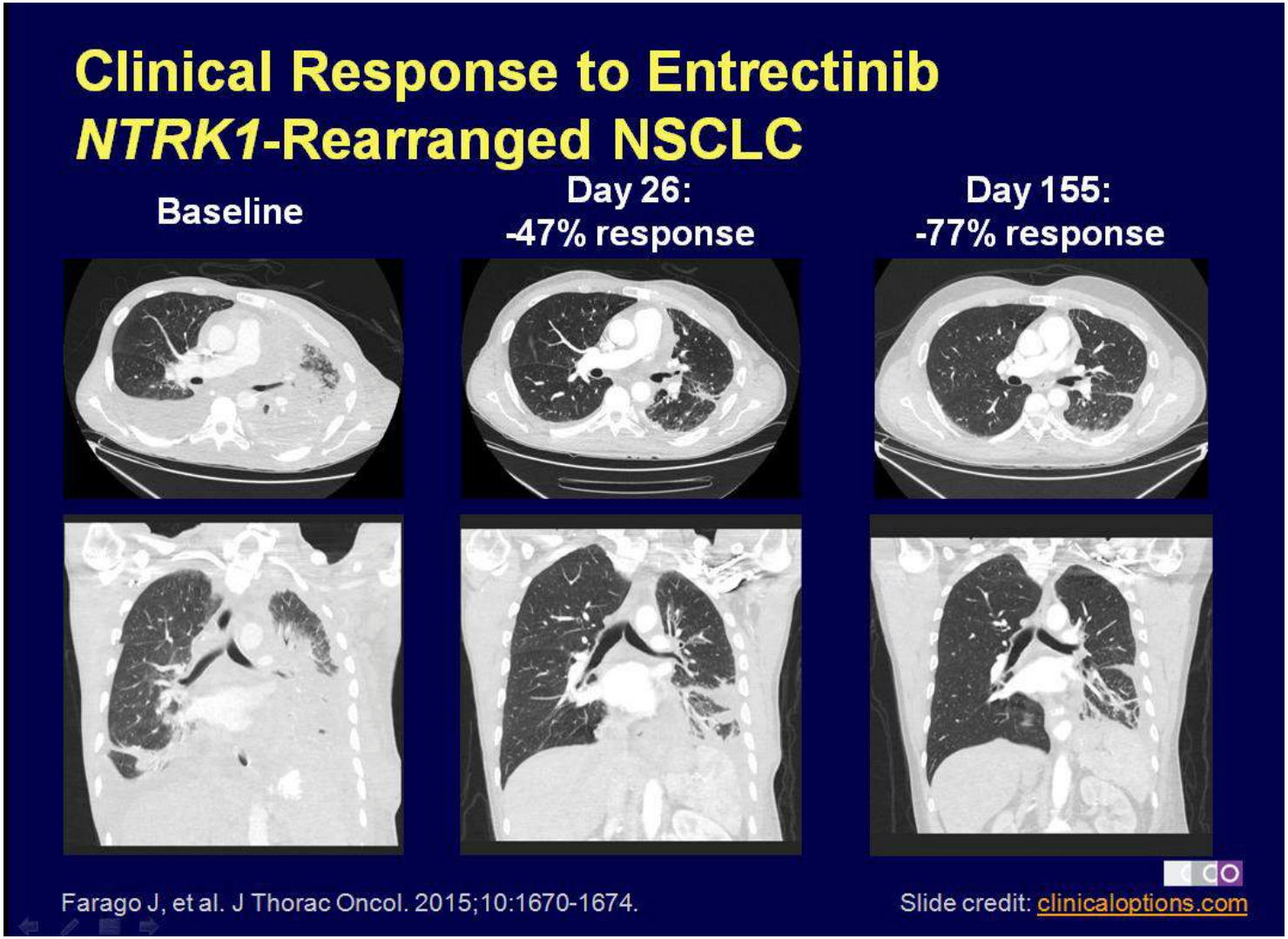
Neurotrophic Tyrosine Kinase (NTRK) and Tropomysin-Related Kinases A, B, C

- 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



Metastatik KHDAK Hedefe Yönelik Tedaviler

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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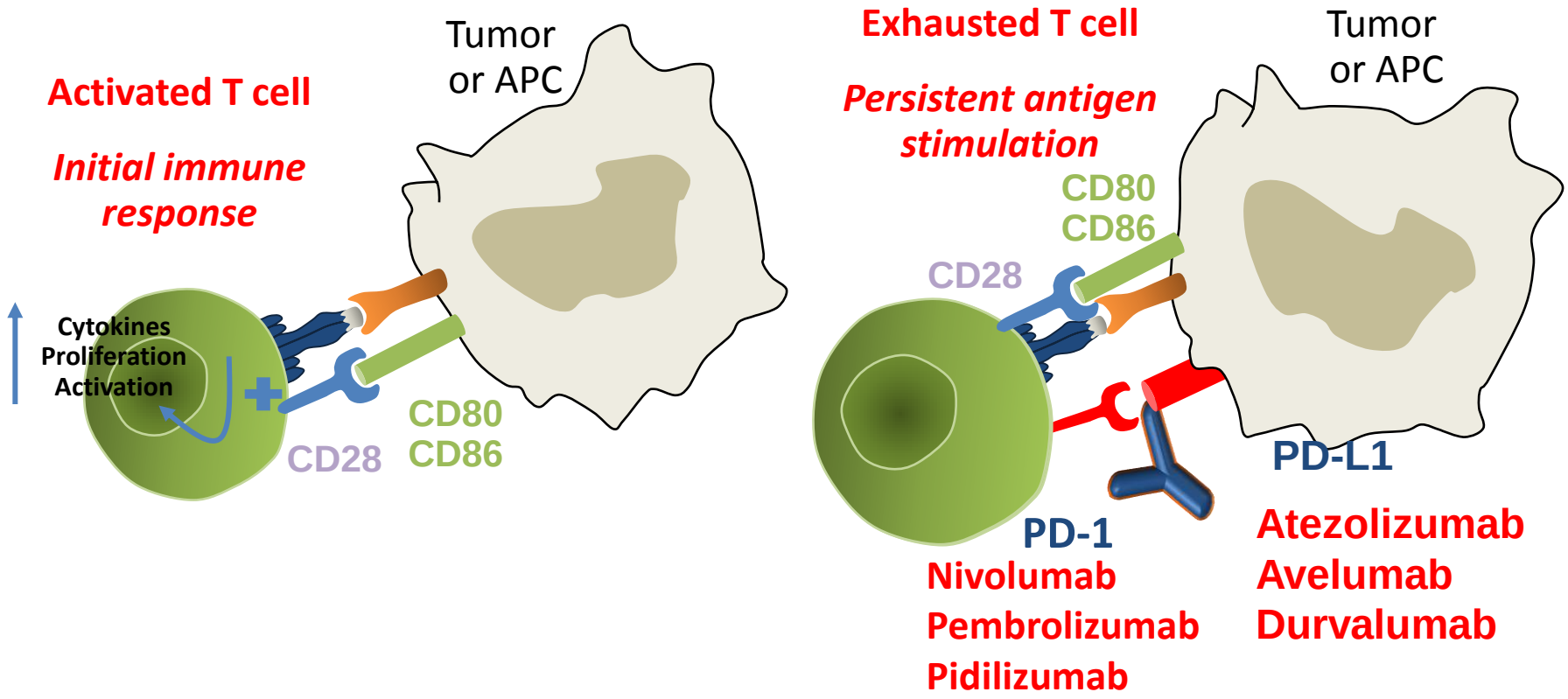
Discussion

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)

Akciğer Kanserinde İmmünoterapi

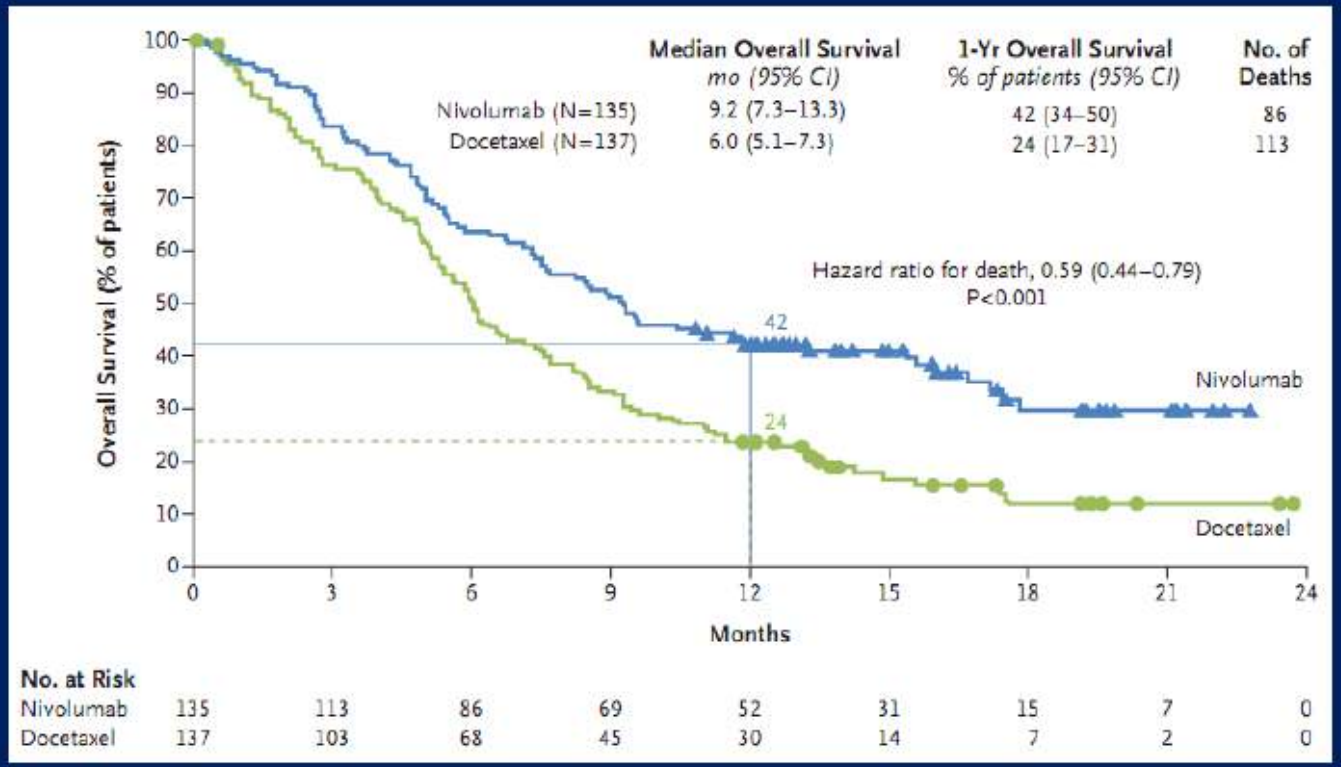
PD-1 as a Target in Cancer Therapy



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

Akciğer Kanserinde İmmünoterapi

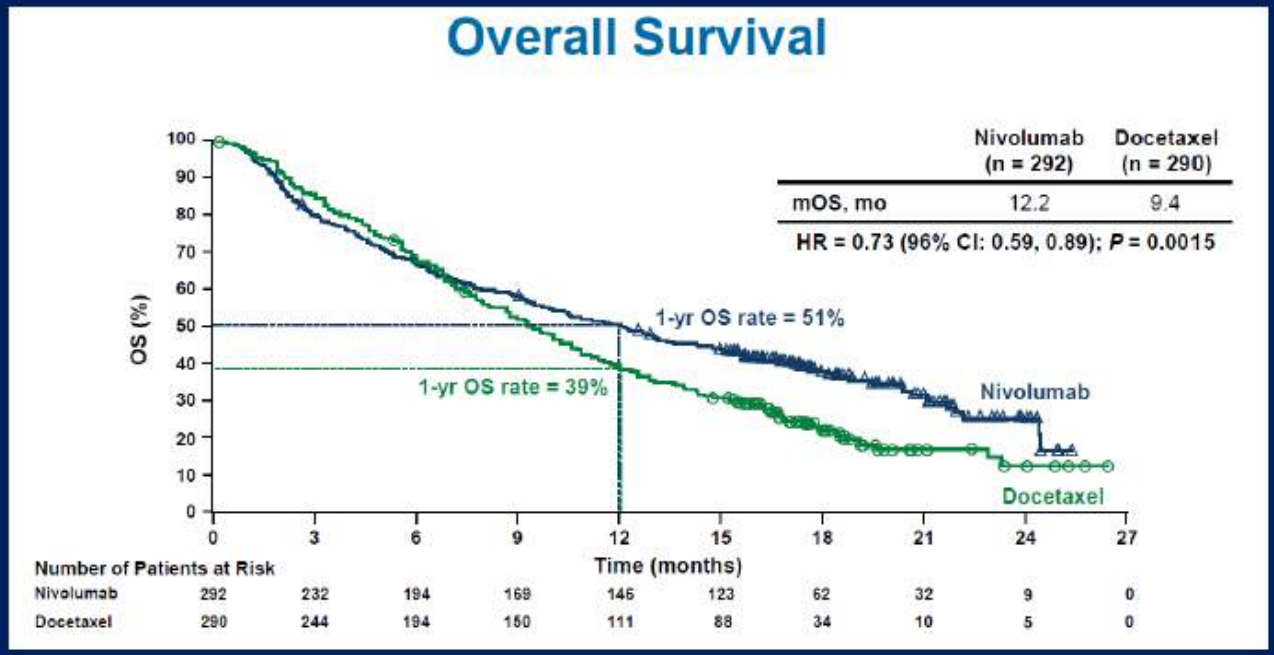
Squamous Cell Carcinoma
Nivolumab vs. Docetaxel 2nd line



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

Akciğer Kanserinde İmmünoterapi

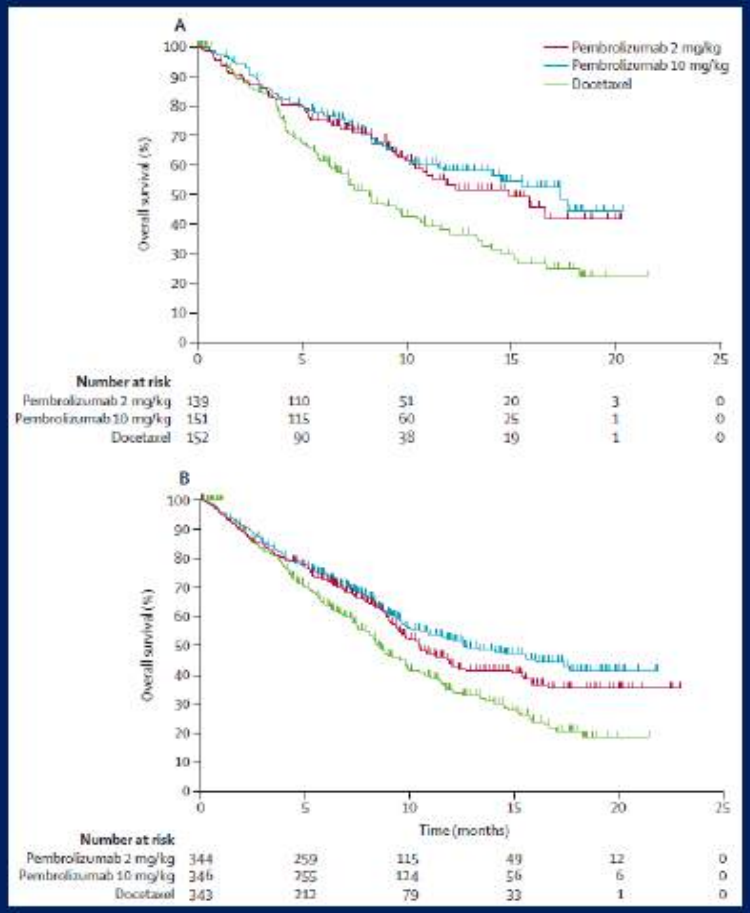
Non-Squamous NSCLCs
Nivolumab vs. Docetaxel 2nd line



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*

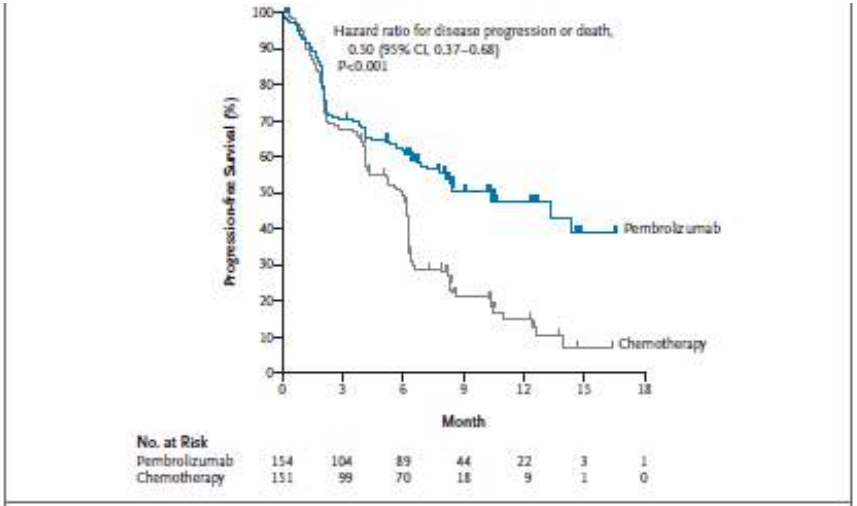
ABSTRACT

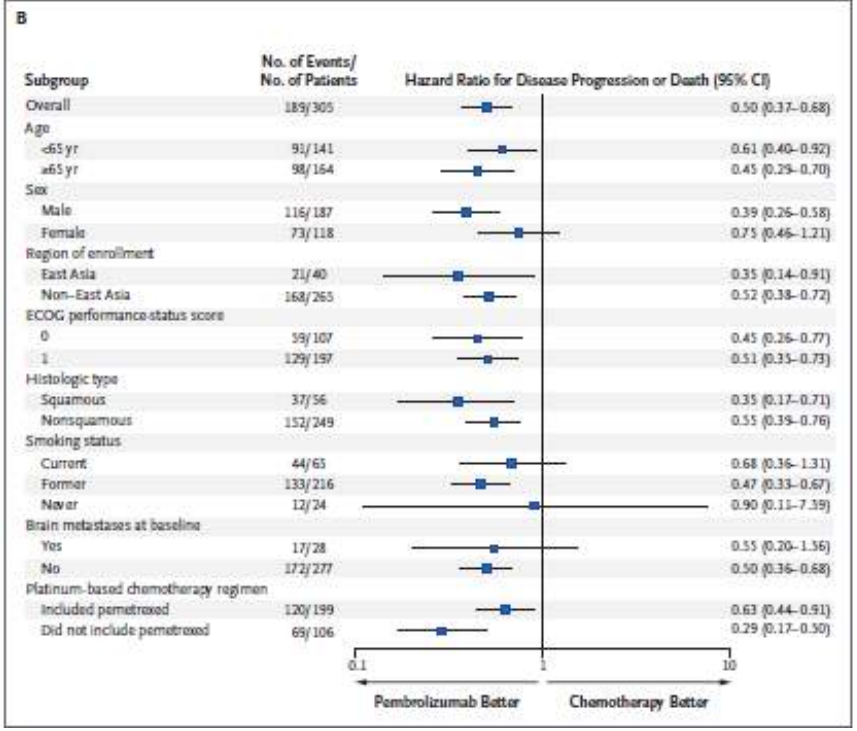
BACKGROUND

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?

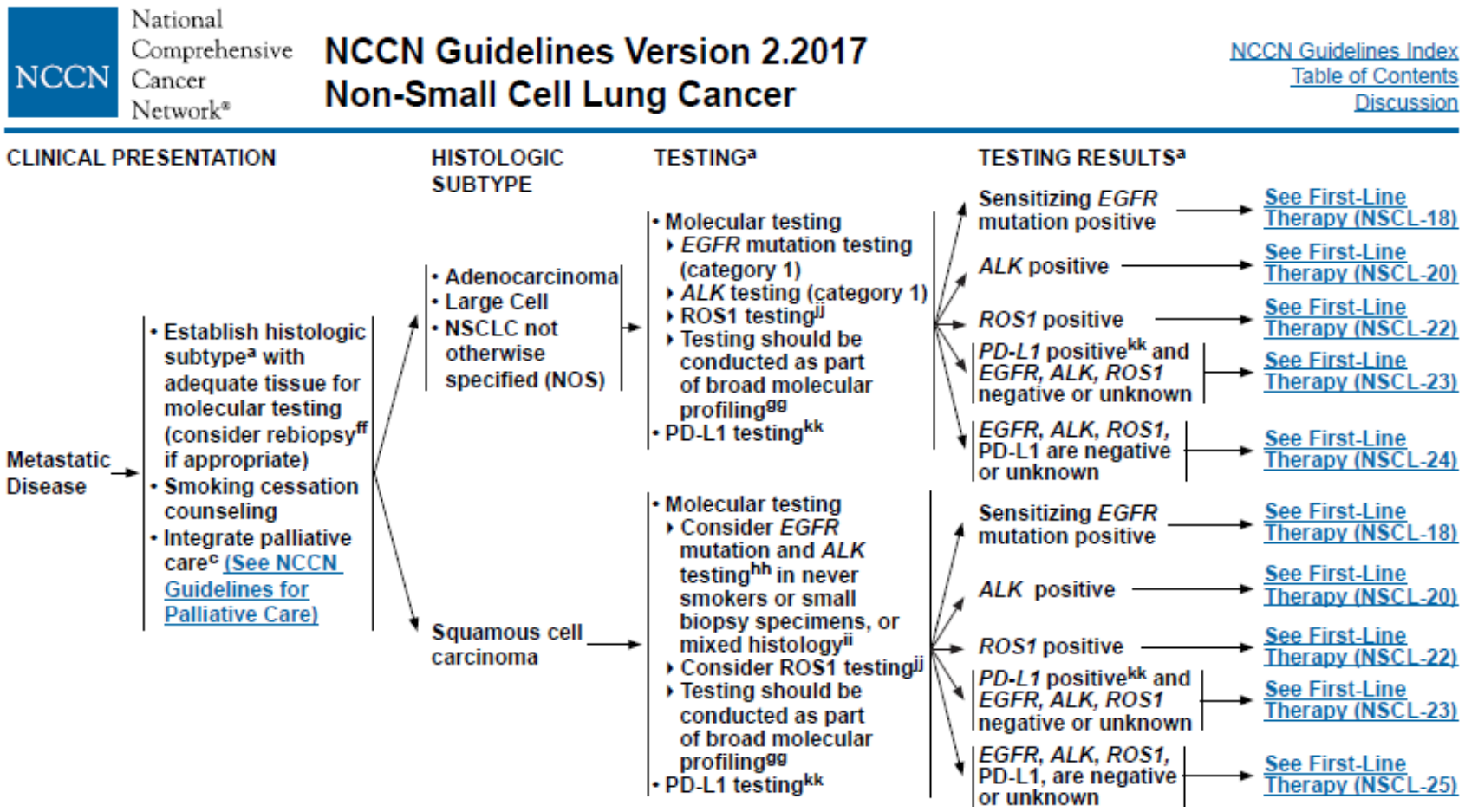
Ongoing Phase III Trials of Combination Therapy with Checkpoint Inhibitors in Nonsquamous Metastatic NSCLC

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)

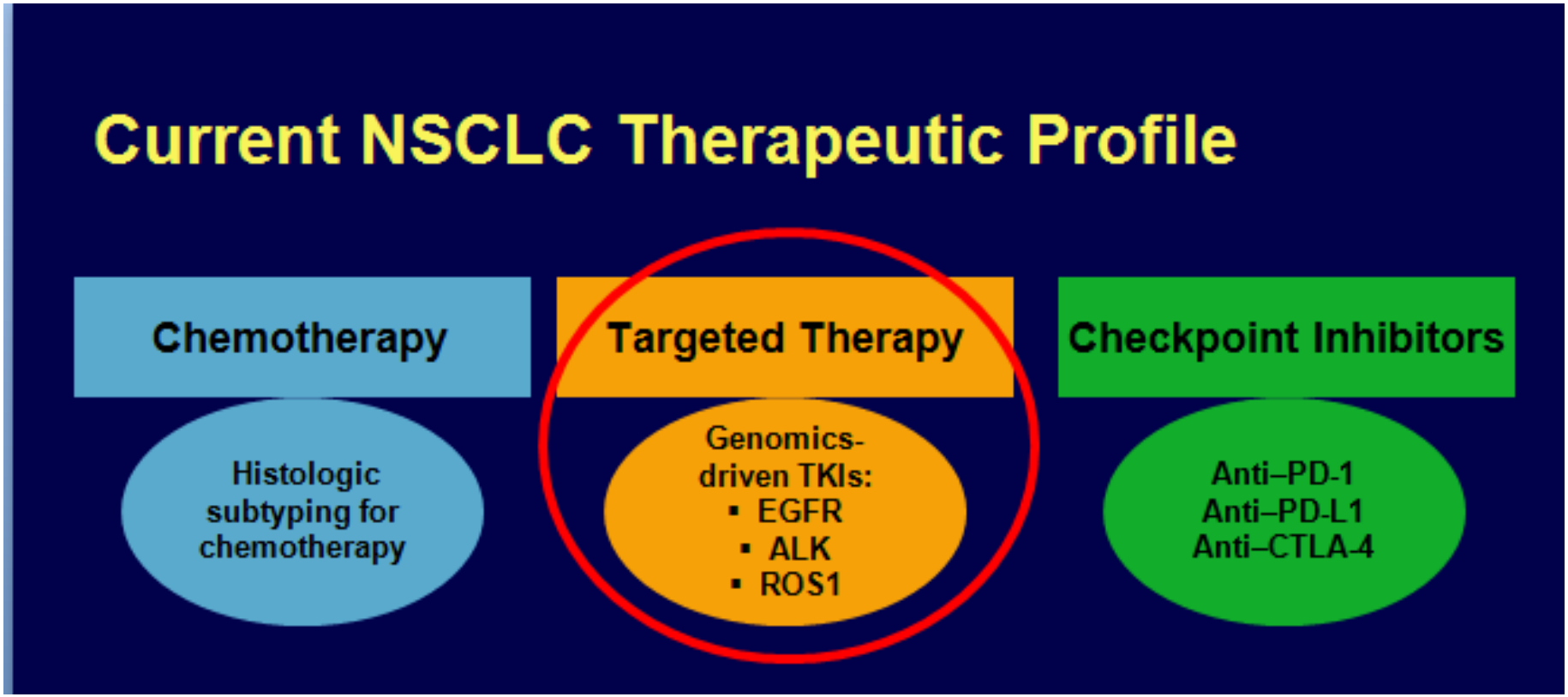
SARAH CANNON

www.clinicaltrials.gov, Feb 10, 2016

Metastatik KHDAK Hedefe Yönelik Tedaviler



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.