KHDAK SİSTEMİK TEDAVİDE YENİLİKLER

Dr. Yeşim ERALP

- Erken Evre & Adjuvan kemoterapi
- Erken evre/ lokal ileri hastalık & Neo-adjuvan tedavi
- Metastatik hastalık & palyatif KT

Adjuvan KEMOTERAPİ– 2014

- Evre II & III
- Evre IB + tm. ≥ 4 cm.

PS:0-1
Kilo kaybı<10%

  - Viseral plevral invazyon, LVI, yüksek grad, sublobar rezeksiyon, Nx
  - T2N0 hastalık: Genomik profil: prospektif validasyon

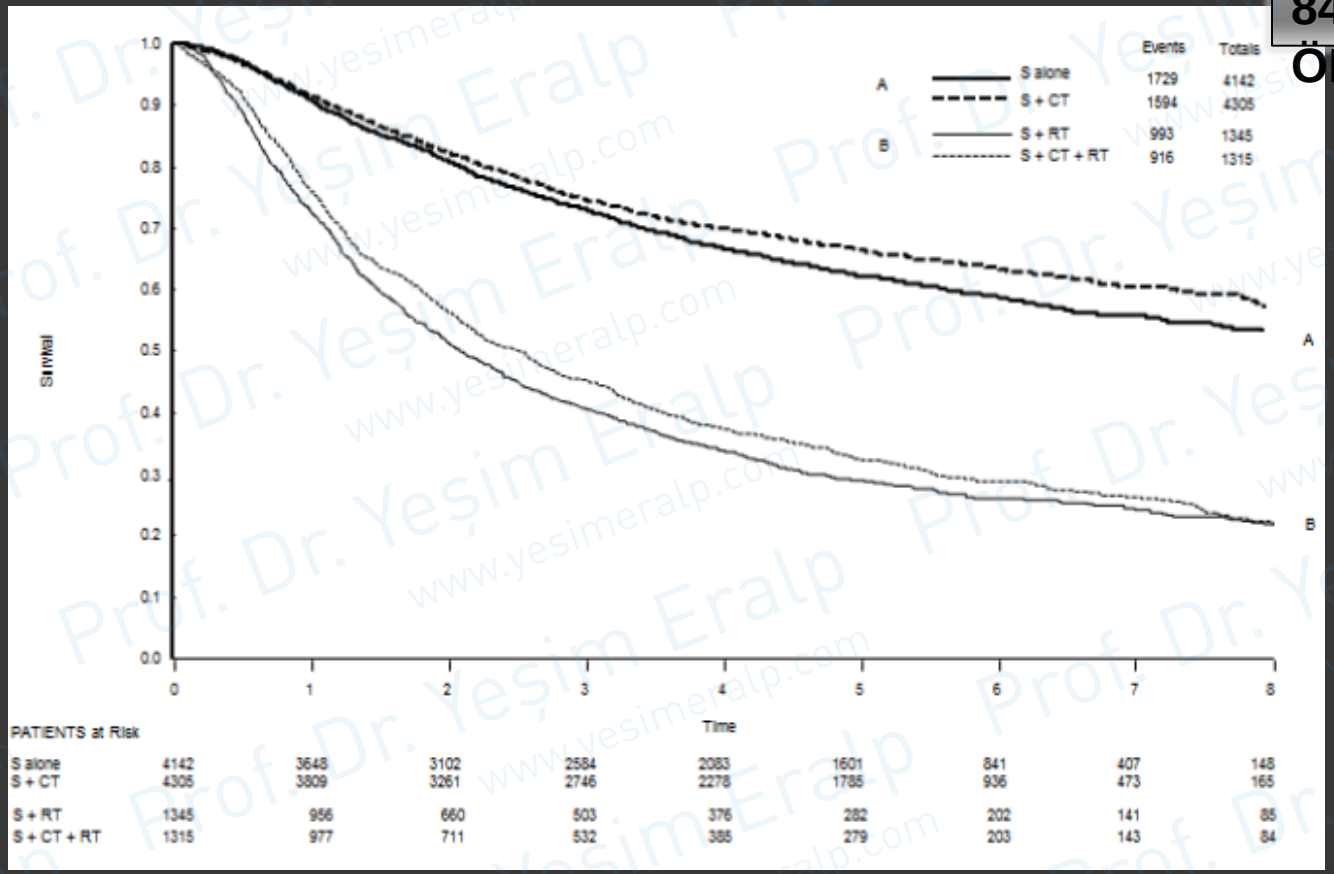
- Cisplatin & vinorelbin x 4
- Carboplatin & paclitaxel x 4*
- Hedefe yönelik ajanlar için kanıt yok

*: yaşlı & komorbid durumu olan hasta

Adjuvant chemotherapy for resected early-stage non-small cell lung cancer (Review)

Non-Small Cell Lung Cancer Collaborative Group

34 ÇALIŞMA
8447 HASTA; 3323 ÖLÜM



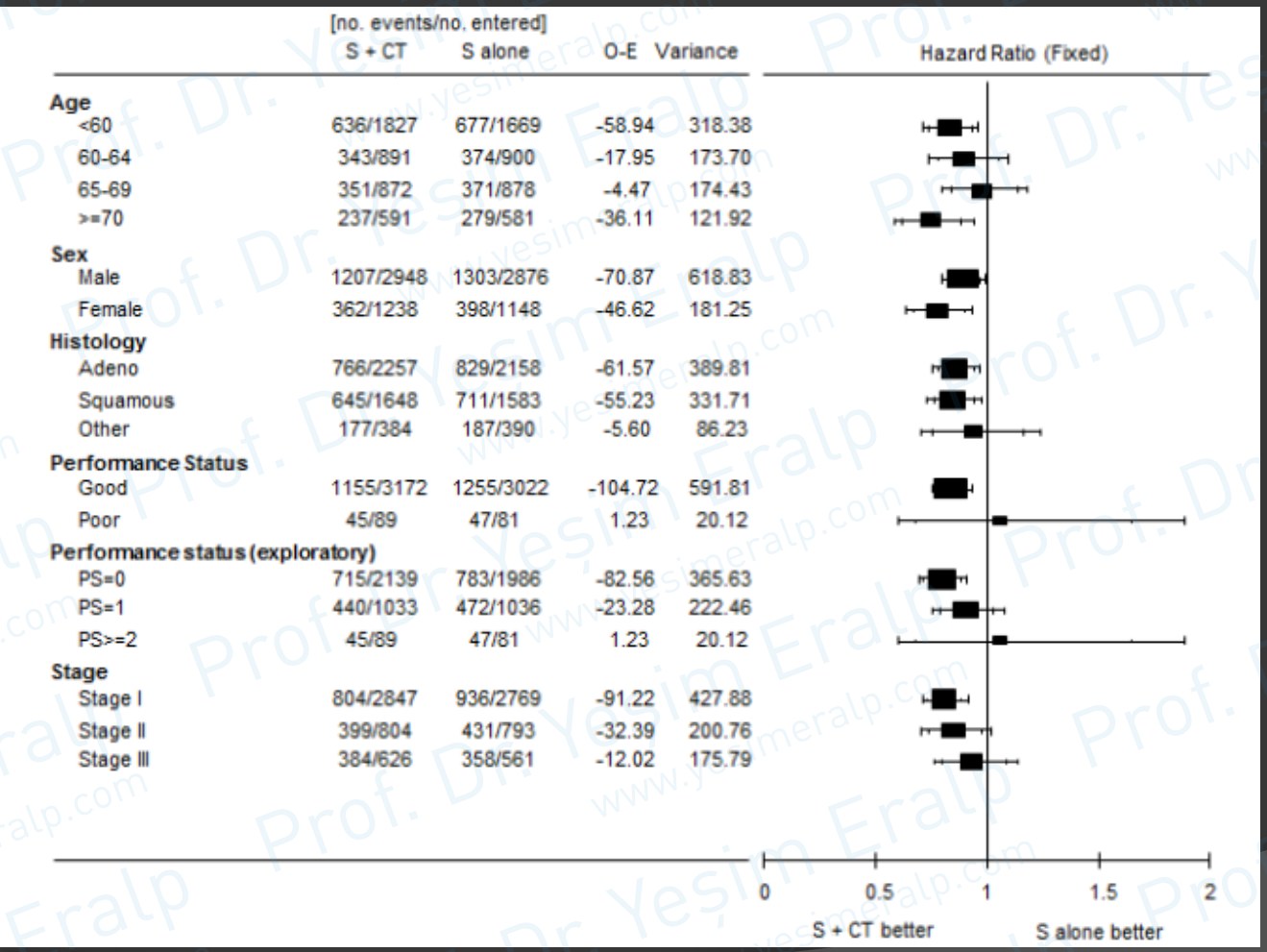
5 YIL SAĞKALIM:

%60 → %64

Burdett S. *Cochrane Database of Systematic Reviews* 2015

Adjuvant chemotherapy for resected early-stage non-small cell lung cancer (Review)

Non-Small Cell Lung Cancer Collaborative Group



5 YIL SAĞKALIM:

%60 → %64

EVRE IA: %80 → %82

EVRE IB: %75 → %78

EVRE II: %40 → %45

EVRE III: %30 → %35

Burdett S. *Cochrane Database of Systematic Reviews* 2015

Evre I hastalık:
Nüks için prognostik faktörler

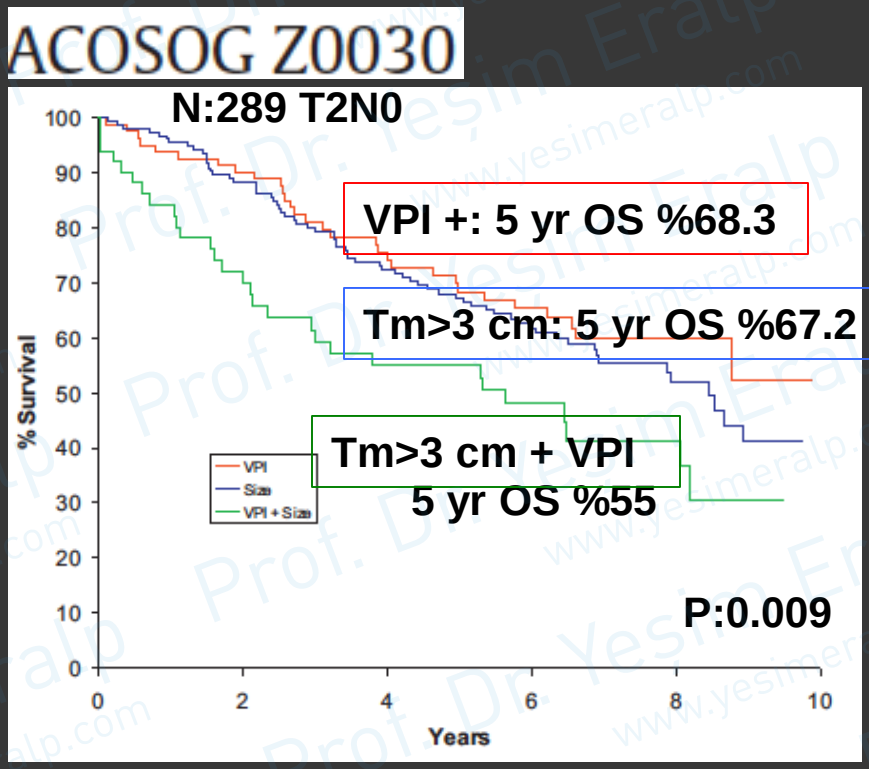
n:1477

CHEST 2011; 140(6):1494–1502

Characteristic	No. of Patients	Freedom From Recurrence Rate, 5 y, %	Univariate *P* Value	Multivariate Analysis		
				HR	95% CI	*P* Value
Overall	1,477	84.2	…			
Age, y			.005[a]			
≤65	724	87.4		1	…	…
>65	753	80.9		1.296	0.988-1.698	.061
Sex			.002[a]			
Female	635	87.5		1	…	…
Male	842	81.6		1.078	0.745-1.559	.69
Smoking habits			<.001[a]			
Never smoker	574	88.9		1	…	…
Ever smoker	903	81.9		1.149	0.764-1.728	.504
CEA			.001[a]			
Within normal range	1,034	86.4		1	…	…
Elevated	441	79.2		1.06	0.804-1.399	1.244
Not examined	2					
Tumor size, cm			<.001[a]			
≤3.0	1,056	87.5		1	…	…
>3.0	421	76		1.244	0.940-1.648	.127
Histologic type			<.001[a]			
Adenocarcinoma	1,112	86.3		1	…	…
[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]
Histologic differentiation			<.001[a]			
Well differentiated	538	94.1		1	…	…
Moderately/poorly differentiated	939	77.8		1.916	1.292-2.841	.001[a]
Vessel invasion			<.001[a]			
Absent	902	92.6		1	…	…
Present	575	71.7		2.715	1.952-3.778	<.001[a]
VPI			<.001[a]			
Absent	1,196	88.3		1	…	…
Present	281	66.7		1.768	1.326-2.357	<.001[a]

T1-2 Tümörler & VPI (PI-1 / PI-2):

Metanaliz 5 yıl OS beklentisi: %75



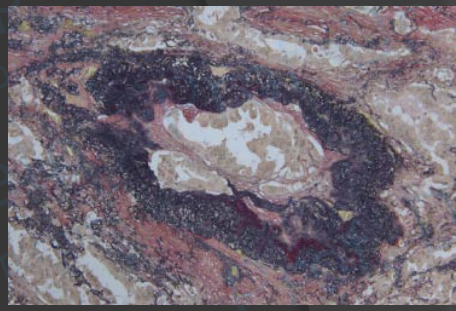
J.J. Fibla et al. / Lung Cancer 78 (2012) 259–262

		n	5-y OS	p-value		
A	≤ 3 cm, non-VPI	415	86.6		0.12	
B	≤ 3 cm, VPI	74	75.9		0.96	
C	3.1-5 cm, non-VPI	143	79.4		*0.003	0.07
D	3.1-5 cm, VPI	47	66.4		0.94	
E	5.1-7 cm, non-VPI	16	59.7		0.98	0.77
F	5.1-7 cm, VPI	13	46.2			

Y. Kudo et al. / Lung Cancer 78 (2012) 153–160

Evre I & Mikro-vasküler invazyon:

n:694 Evre I hasta
n:201: damar invazyonu mevcut



Group	n	5yOS	p-value	7th Edition stage (N0M0)	Our proposal stage (N0M0)
T1a/non-BVI	227	94.5%	< 0.0001	IA	IA
T1a/BVI	38	87.5 %	NS (0.2604)	IA	**IB**
T1b/non-BVI	125	82.7%	0.034	IA	**IB**
T1b/BVI	39	65.9%	0.0002	IA	**IIA**
T2a/non-BVI	145	90.9%	< 0.0001	IB	IB
T2a/BVI	130	61.8%	NS (0.2394)	IB	**IIA**
T2b	36	68.7%		IIA	IIA

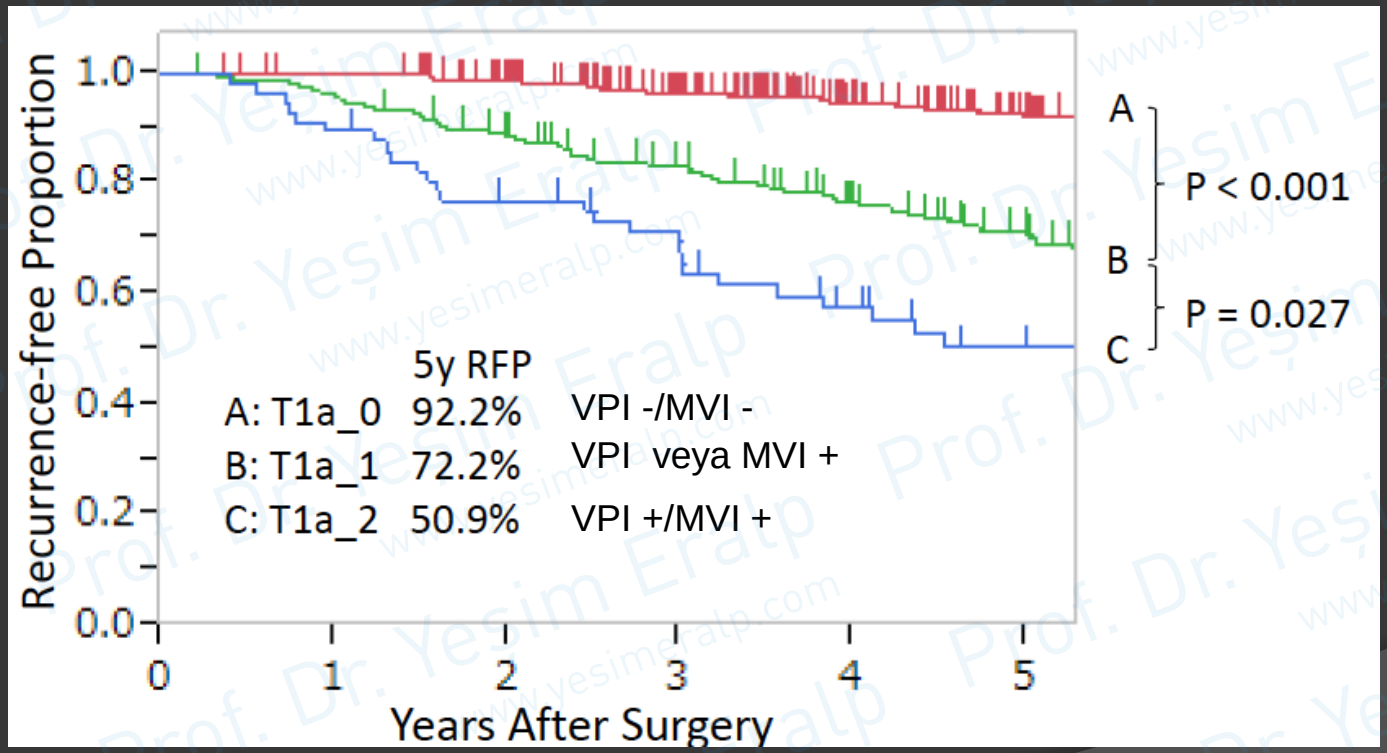
NS (0.0753)

NS (0.7364)

Y. Kudo et al. / Lung Cancer 81 (2013) 187–193

Prognostic Impact of Microscopic Vessel Invasion and Visceral Pleural Invasion in Non–Small Cell Lung Cancer

N: 2657; T1a--n: 1478

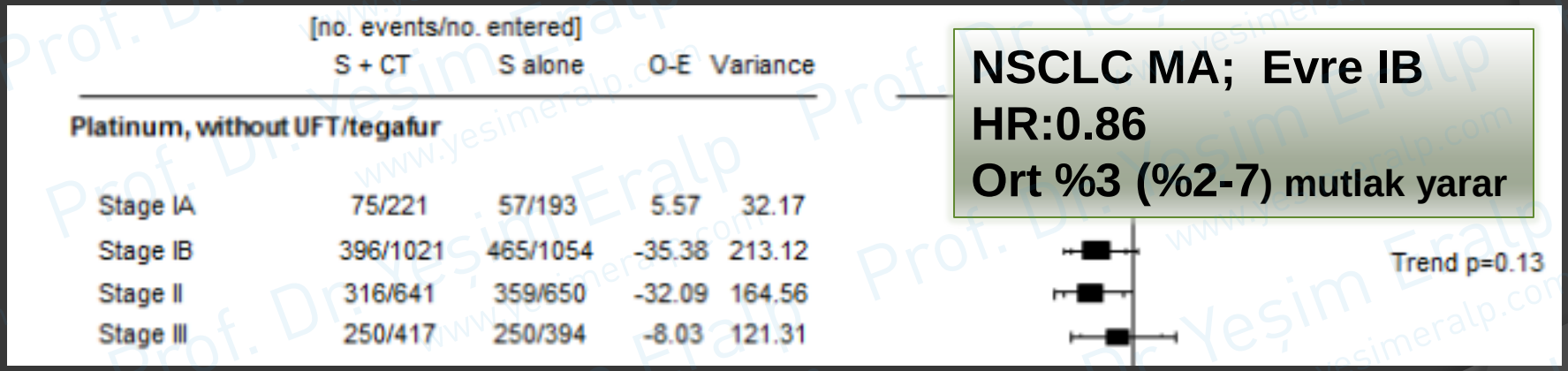


Shinya Neri, *Ann Surg* 2014;260:383–388

T1-2N0 yüksek riskli hastalık & Adjuvan Kemoterapi

- >2cm +
  - Visceral plevra invazyonu
  - Mikro-vasküler invazyon

%25-50
NÜKS RİSKİ !!
5 yıl OS: %55-70



	[no. events/no. entered] S + CT	S alone	O-E	Variance
Platinum, without UFT/tegafur				
Stage IA	75/221	57/193	5.57	32.17
Stage IB	396/1021	465/1054	-35.38	213.12
Stage II	316/641	359/650	-32.09	164.56
Stage III	250/417	250/394	-8.03	121.31

NSCLC MA; Evre IB
HR:0.86
Ort %3 (%2-7) mutlak yarar

- **GD uygun hastalar adjuvan KT için değerlendirilmeli..**

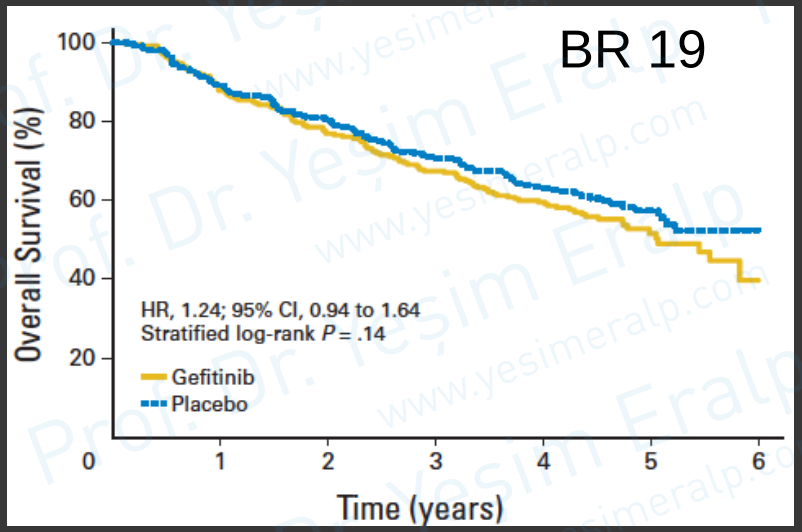
Adjuvant chemotherapy for resected early-stage non-small cell lung cancer (Review)

Non-Small Cell Lung Cancer Collaborative Group

7). Since we did not collect data for tumour size, patients with larger stage IB tumours, who would be classed as stage II in the 7th edition of the TNM staging system (IASLC 2009) and might achieve a greater benefit from adjuvant chemotherapy are potentially included. In the absence of comorbidities and contraindications to chemotherapy, our findings show that adjuvant platinum-based chemotherapy may be considered as a treatment option for patients at high risk of recurrence, ie, those with stage IB, II, or III disease.

Burdett S, *Cochrane Database of Systematic Reviews* 2015

Adjuvan hedefe yönelik tedaviler



J Clin Oncol 31:3320-3326. © 2013

RADIANT: n:973; 2:1
EGFR IHC + / FISH +

Rand: adj KT +/- sonrası 2 yıl

DFS EGFR mut+: HR: 0.61, P.0.04

OS: med ulaşılamadı; NS

Shepherd, ASCO 2014

- BR 19: EGFR mut + sadece 19 hasta
- RADIANT: kollar arasında dağılım eşitsizliği (KT var/yok; tm çapı; mut varlığı vb) öngörülen DFS hedefine ulaşılamadı…

Standart olarak önerilemiyor

Neo-Adjuvan Tedavi

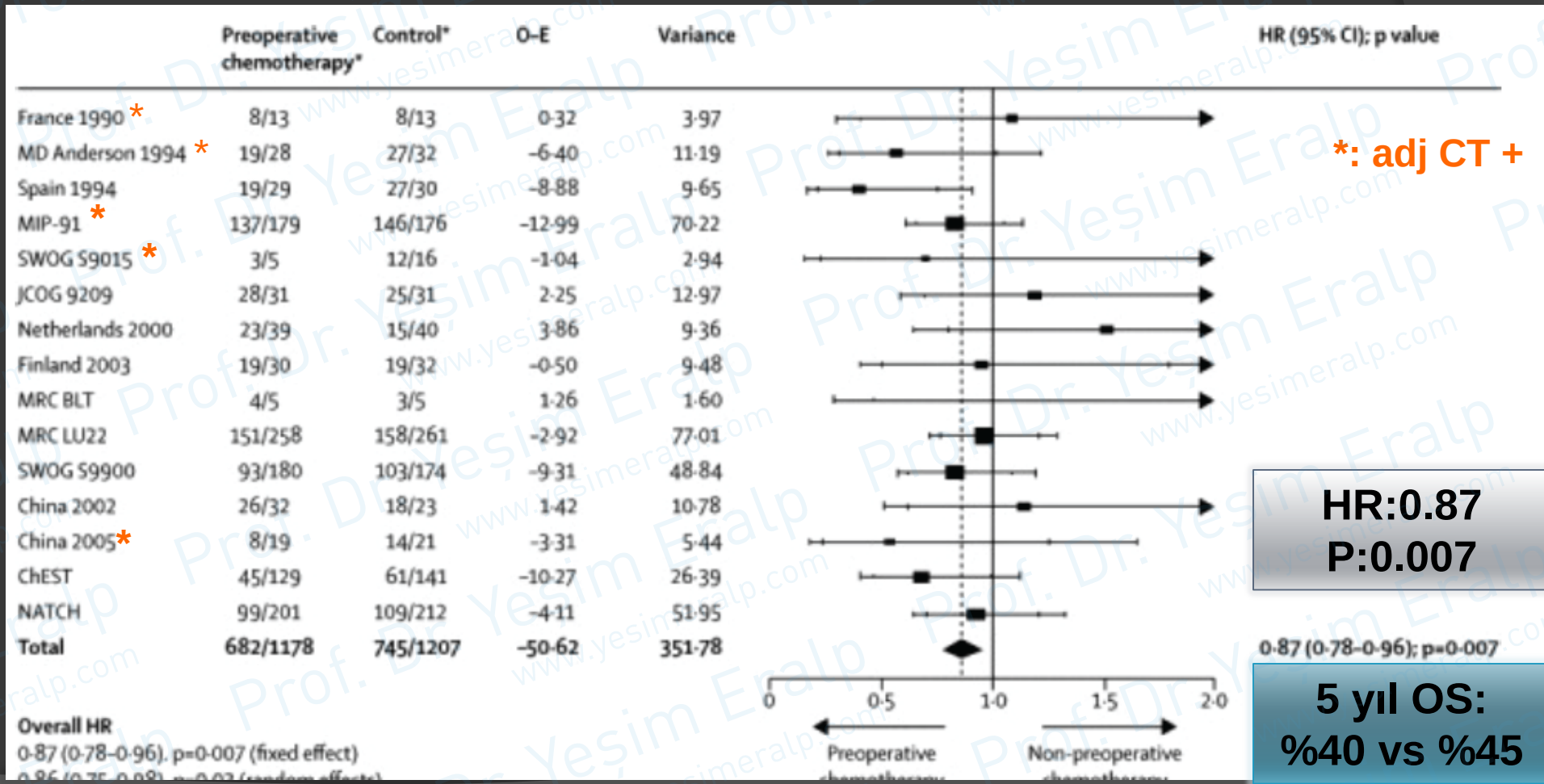
Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data

OPERABL HASTALIK !

NSCLC Meta-analysis Collaborative Group†

Lancet. 2014 May 3; 383(9928): 1561–1571.

15 randomised controlled trials (2385 patients, 1427 deaths)



	Preoperative chemotherapy*	Control*	O-E	Variance
France 1990 *	8/13	8/13	0·32	3·97
MD Anderson 1994 *	19/28	27/32	-6·40	11·19
Spain 1994	19/29	27/30	-8·88	9·65
MIP-91 *	137/179	146/176	-12·99	70·22
SWOG S9015 *	3/5	12/16	-1·04	2·94
JCOG 9209	28/31	25/31	2·25	12·97
Netherlands 2000	23/39	15/40	3·86	9·36
Finland 2003	19/30	19/32	-0·50	9·48
MRC BLT	4/5	3/5	1·26	1·60
MRC LU22	151/258	158/261	-2·92	77·01
SWOG S9900	93/180	103/174	-9·31	48·84
China 2002	26/32	18/23	1·42	10·78
China 2005*	8/19	14/21	-3·31	5·44
ChEST	45/129	61/141	-10·27	26·39
NATCH	99/201	109/212	-4·11	51·95
Total	**682/1178**	**745/1207**	**-50·62**	**351·78**

Overall HR
0·87 (0·78–0·96), p=0·007 (fixed effect)

*: adj CT +

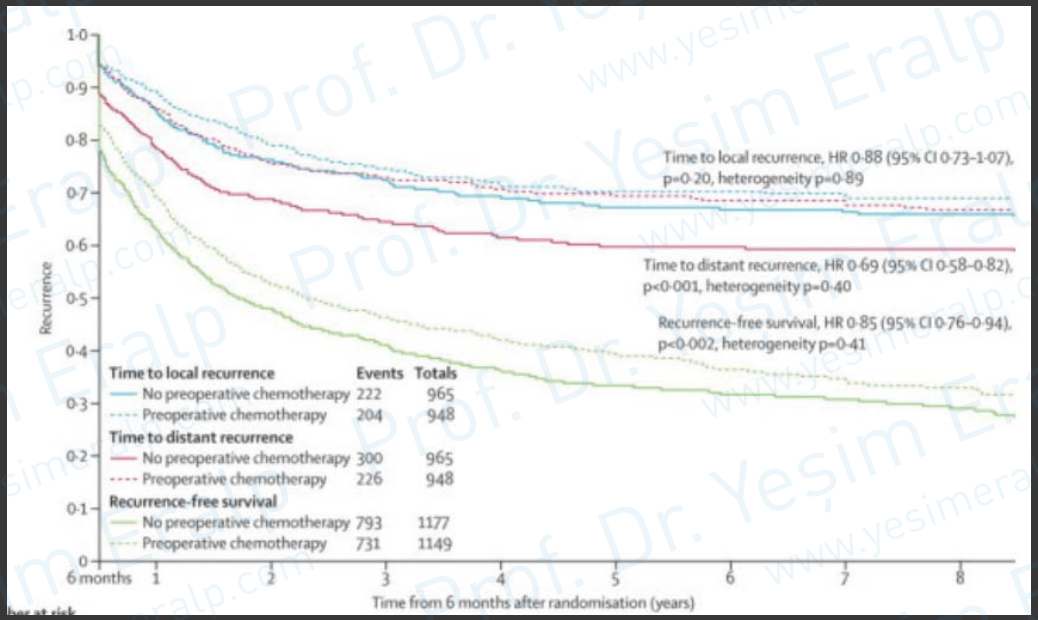
HR:0.87
P:0.007

5 yıl OS:
%40 vs %45

Pre-op Kemoterapi+ Cerrahi vs Cerrahi

	Number of trials	Number of deaths/patients	Hazard ratio (95%CI), p value	Heterogeneity p value	F ratio p value	Interaction p value
Survival by planned chemotherapy schedule (n=15 trials)					0·32	0·23
Preoperative chemotherapy only	10	1045/1883	0·90 (0·80–1·02), 0·09	0·10		
Preoperative and postoperative chemotherapy (to responders)	5	382/502	0·78 (0·64–0·95), 0·02	0·62		

Lancet. 2014 May 3; 383(9928): 1561–1571.



improvement in time to distant recurrence of 10% at 5 years (from 60% to 70%).

	Pre-op KT		Pre-op + Post-op KT		Interaction p
	HR	p	HR	p	
Lokal Nüks	0.94	0.6	0.73	0.11	0.26
Uzak Metastaz	**0.78**	**0.02**	**0.53**	**<0.001**	**0.05**

Lancet. 2014 May 3; 383(9928): 1561–1571.

Potansiyal rezektabl N2 hastalık: Neoadjuvan KT-RT vs KT-RT

	INT 0139		EORTC 08941		GLCCG	
TEDAVİ	**KT/RT –C**	**KT/RT**	**KT-C**	**KT-RT**	**KT/RT-C**	**KT-C-RT**
N	202	194	167	166	245	236
KT ŞEMASI	Cis-Vp	Cis-Vp	Platin bazlı	Platin bazlı	Cis-vp /carbo-Vds	Cis-vp
RT doz	**45**	**61**	**-**	**60**	**45**	**54**
R0 rezeksiyon	**71**	**-**	**50**	**-**	**45**	**50**
Mortalite %	**8**	**2**	**4**	**<1**	**6**	**5**
pCR (%)	**15**	**-**	**5**	**-**	**-**	**-**
PFS (ay)	**12.8**	**10.5**	**9.0**	**11.3**	**10**	**10**
OS (ay)	**23**	**22.2**	**16.4**	**17.5**	**15**	**17**

Treatment of Stage III Non-small Cell Lung Cancer

2.3.3. In patients with infiltrative stage III (N2,3) NSCLC, performance status 0-1, and minimal weight loss being considered for curative-intent treatment, concurrent chemoradiotherapy is recommended over sequential chemoradiotherapy (Grade 1A).

3.5.2. In patients with discrete N2 involvement by NSCLC identified preoperatively (IIIA), either definitive chemoradiation therapy or induction therapy followed by surgery is recommended over either surgery or radiation alone (Grade 1A).

CHEST 2013; 143(5)(Suppl):e314S–e340S

Neo-adjuvan tedavi & sorunlar...

- ?? Daha sınırlı rezeksiyon

- Chest: pn/lobektomi (neo CT): %17 vs %25
- INT 119: pCR hastaların 45%'ine pnömonektomi yapılmış...!

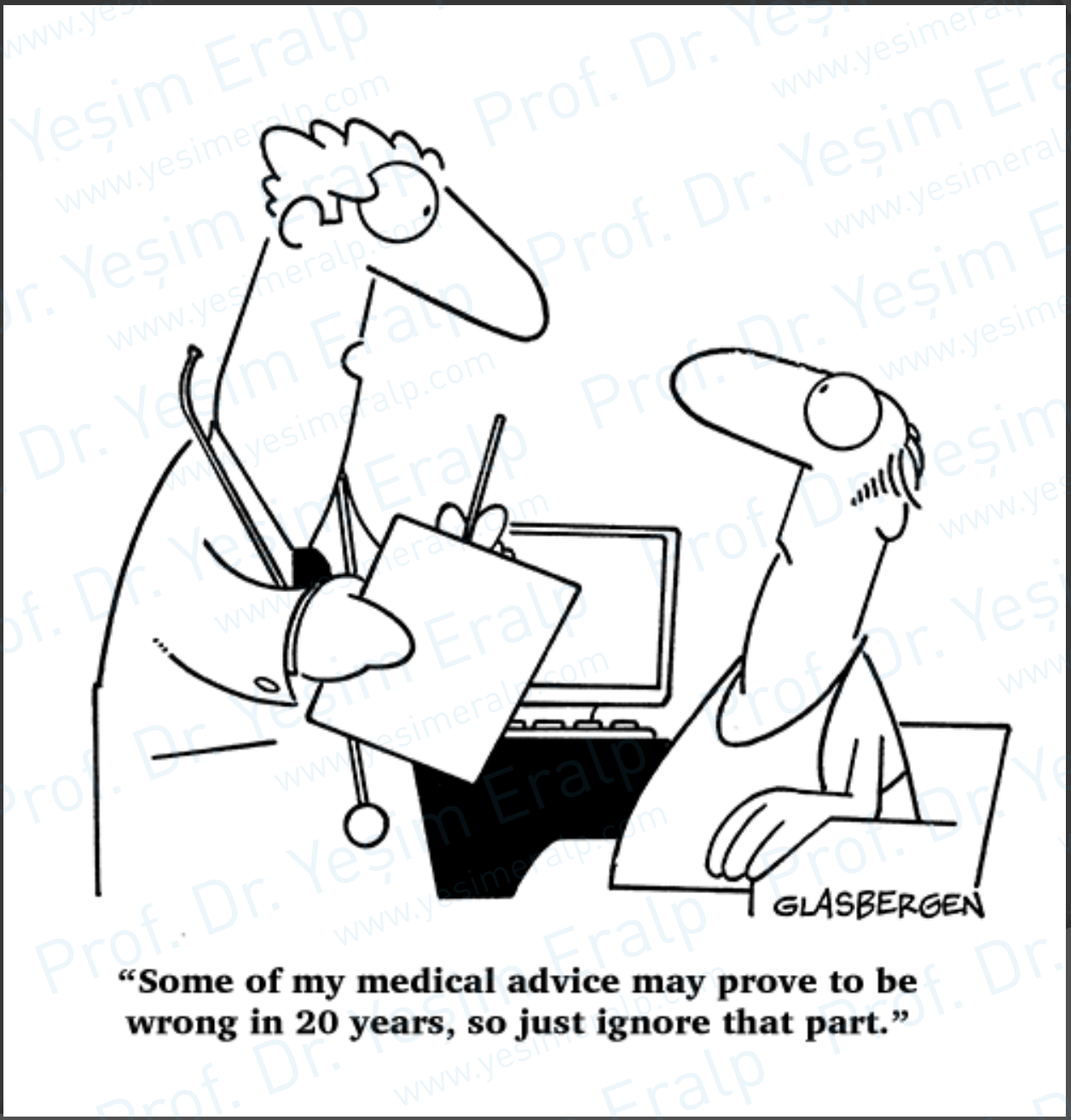
Neo-adjuvan tedavi & sorunlar...

- ?? Daha sınırlı rezeksiyon

Potansiyal zarar:

- 8-10 % progresyon
- Artmış morbidite & mortalite

Olgu bazlı dikkatli klinik değerlendirme & deneyim



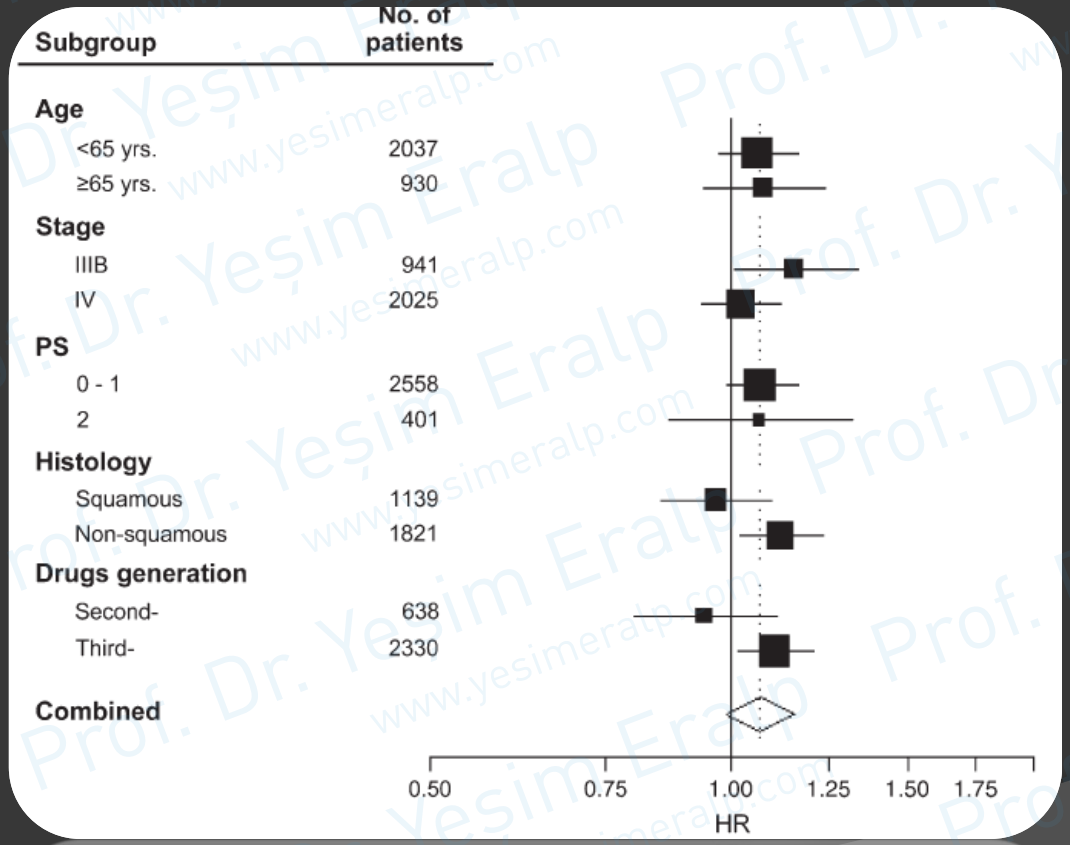
"Some of my medical advice may prove to be wrong in 20 years, so just ignore that part."

METASTATİK KHDAK

"GELİŞMEKTE OLAN" TEDAVİ ALGORİTMALARI

CISCA Meta-analizi

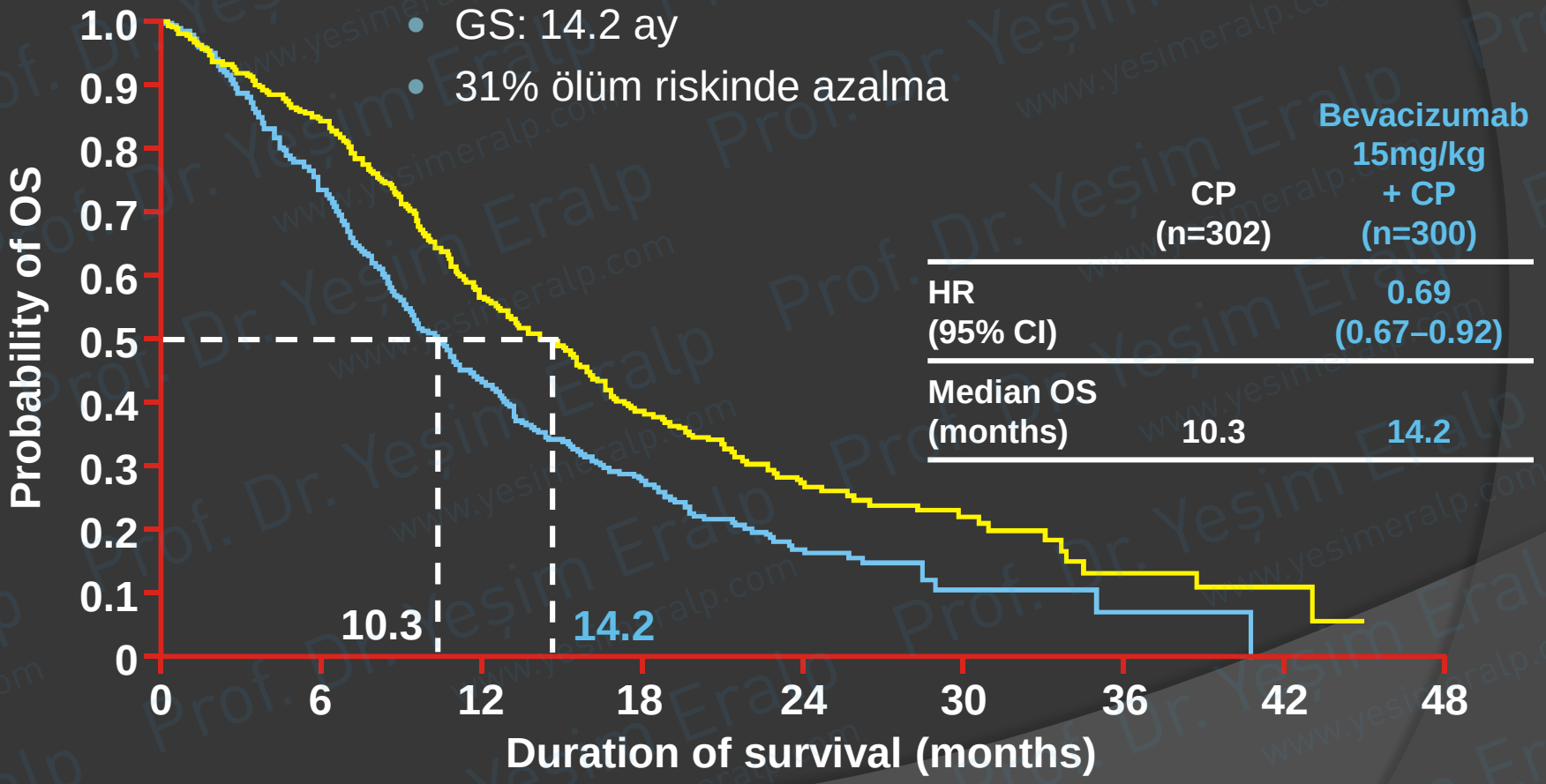
OLGU BAZLI META-ANALİZ: 9 FAZ III ÇALIŞMA; n: 2968 hasta verisi



Andrea Ardizzoni, J Natl Cancer Inst 2007;99:847–57

Bevacizumab: adenokarsinom & sağkalım

- Bevacizumab:
  - GS: 14.2 ay
  - 31% ölüm riskinde azalma



	CP (n=302)	Bevacizumab 15mg/kg + CP (n=300)
HR (95% CI)		0.69 (0.67–0.92)
Median OS (months)	10.3	14.2

Note: preplanned subgroup analysis in E4599

Sandler, et al. JTO 2008;3(Suppl 4):S283 (Abs. 133)

KHD AC KANSERİNDE TEDAVİ ALGORİTMALARI: 2008

EPİDERMOİD

PLATİN + GEMSİTABİN

CİSPLATİN + VİNORELBİN

+ Cetuximab

FLEX

NON-**EPİDERMOİD**

PLATİN + PEMETREXED

+ Bevacizumab

ECOG 4599
AVAIL

Carboplatin + **PAKLİTAKSEL**

2. SEÇİM TEDAVİ

ERLOTİNİB / GEFİTİNİB

NON-EPİDERMOİD

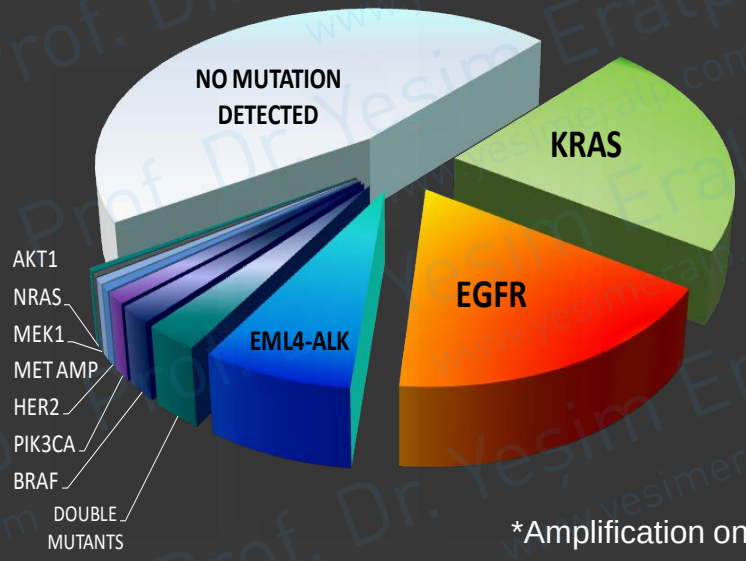
>6 AY

PLATİN-BAZLI İKİLİ KOMBİNASYON

DOSETAKSEL

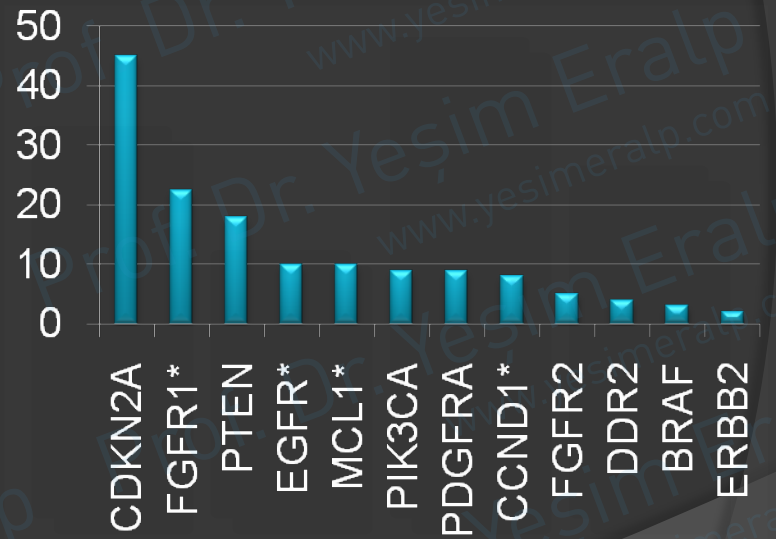
KHDAK & Genom Projesi

Lung Cancer Mutation Consortium (Adenocarcinomas)[2]



*Amplification only

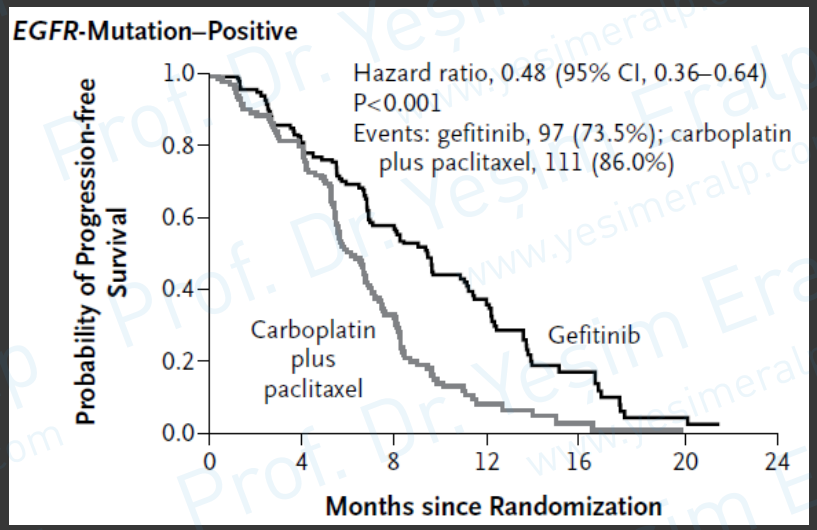
The Cancer Genome Atlas project (Squamous Cell Carcinoma)[3]



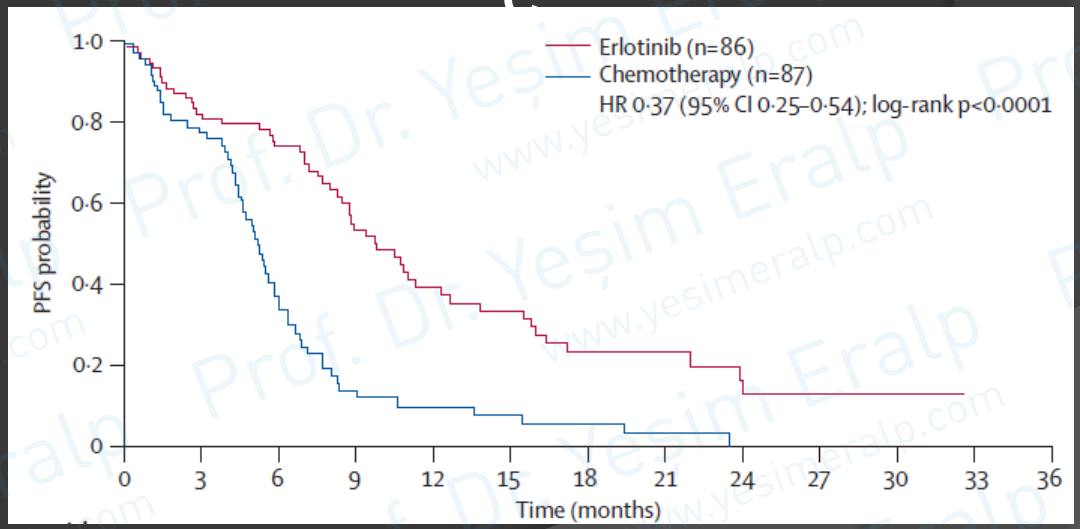
1. Pao and Girard, *Lancet Oncol* 2011; 12:175–80
2. Kris et al., ASCO 2011; Abs #7506
3. Sivachenko et al., IASLC 2011; Abs #PRS.1

- EGFR mutasyon olan hastalarda 1. seçim tedavide EGFR-TKI standart tedavi seçeneğidir..

IPASS



EURTA C

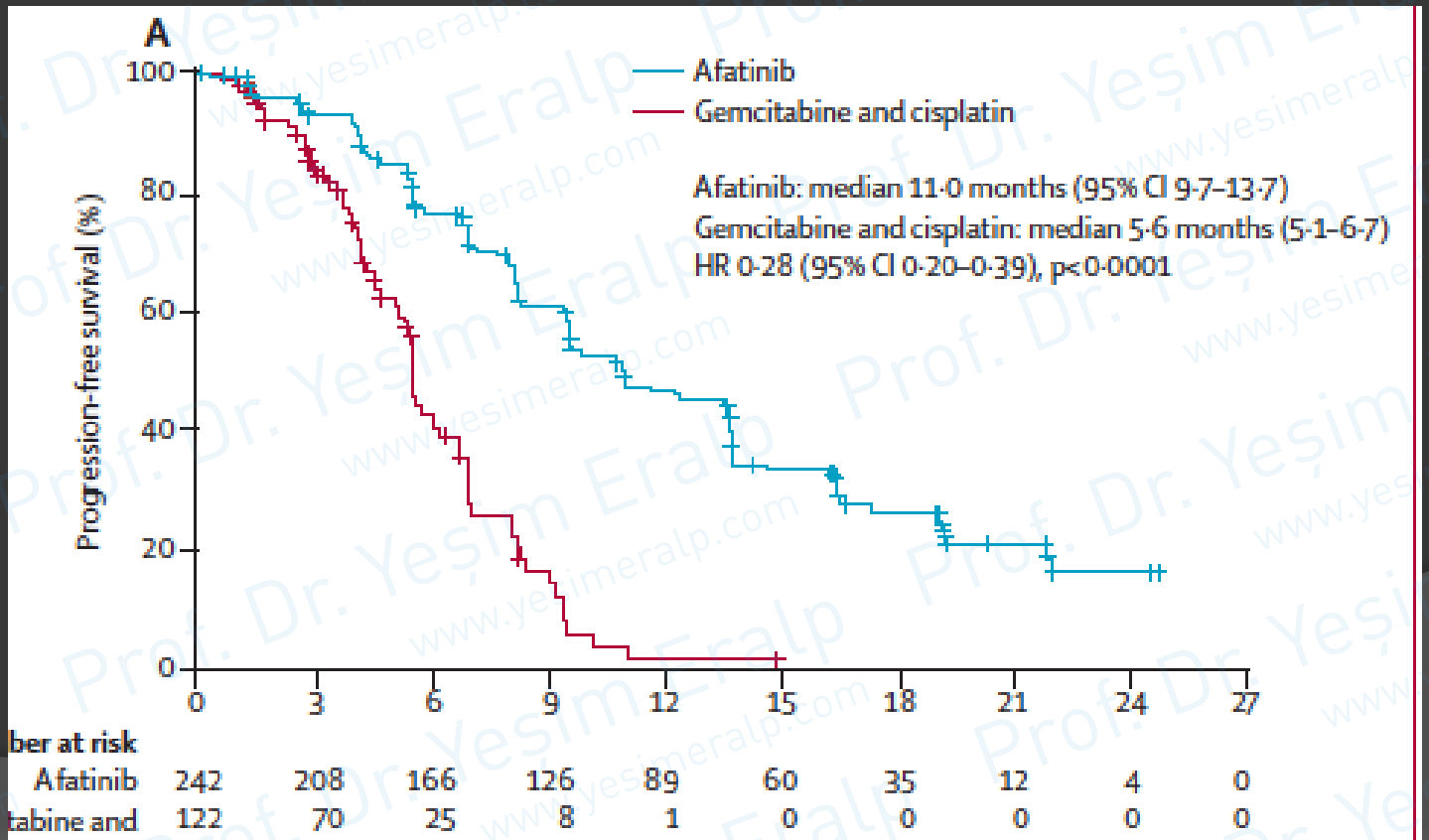


Tony S. Mok N Engl J Med 2009;361:947-57.

Rafael Rosell, Lancet Oncol 2012; 13: 239–46

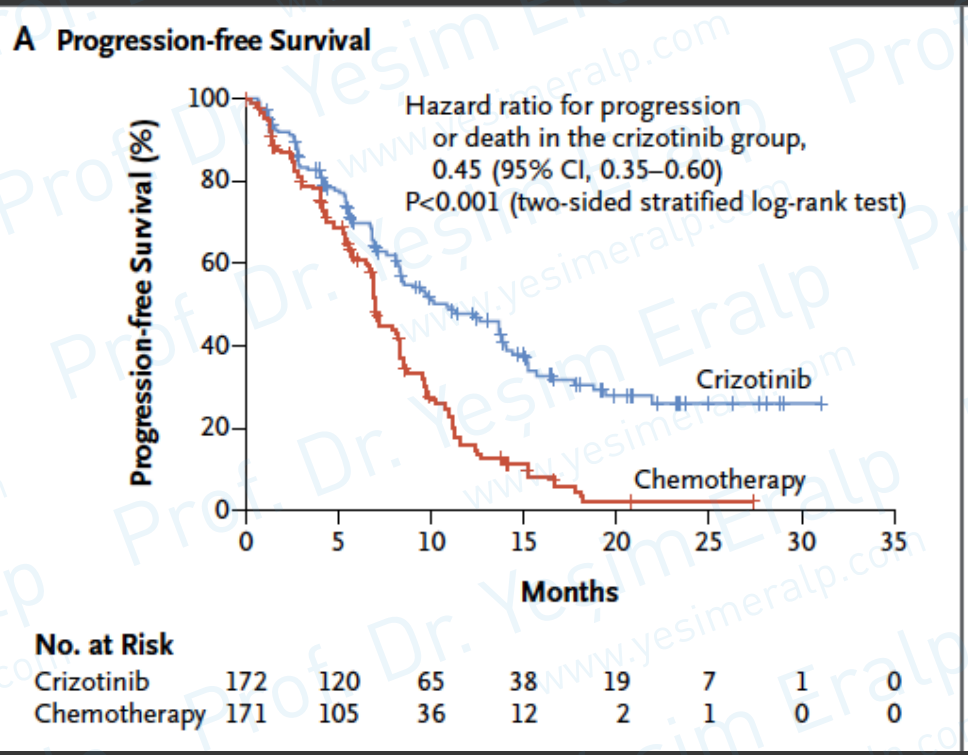
LUX-L6:
1. seçim tedavide Afatinib

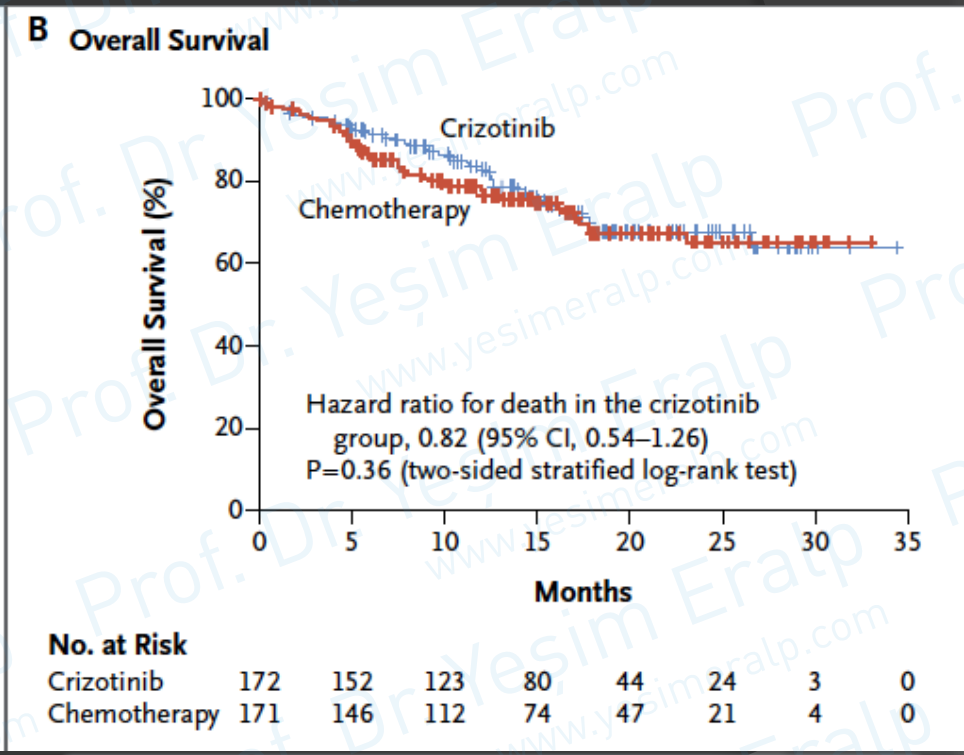
- Irreversibl Pan-EGFR inhibitörü
- EGFR mutasyonu + ; n:364; 2:1 randomizasyon



Yi-Long Wu,
Lancet Oncol 2014; 15: 213–22

PROFILE 1014:
ALK + hastalık & Crizotinib (1. seçim tedavi)

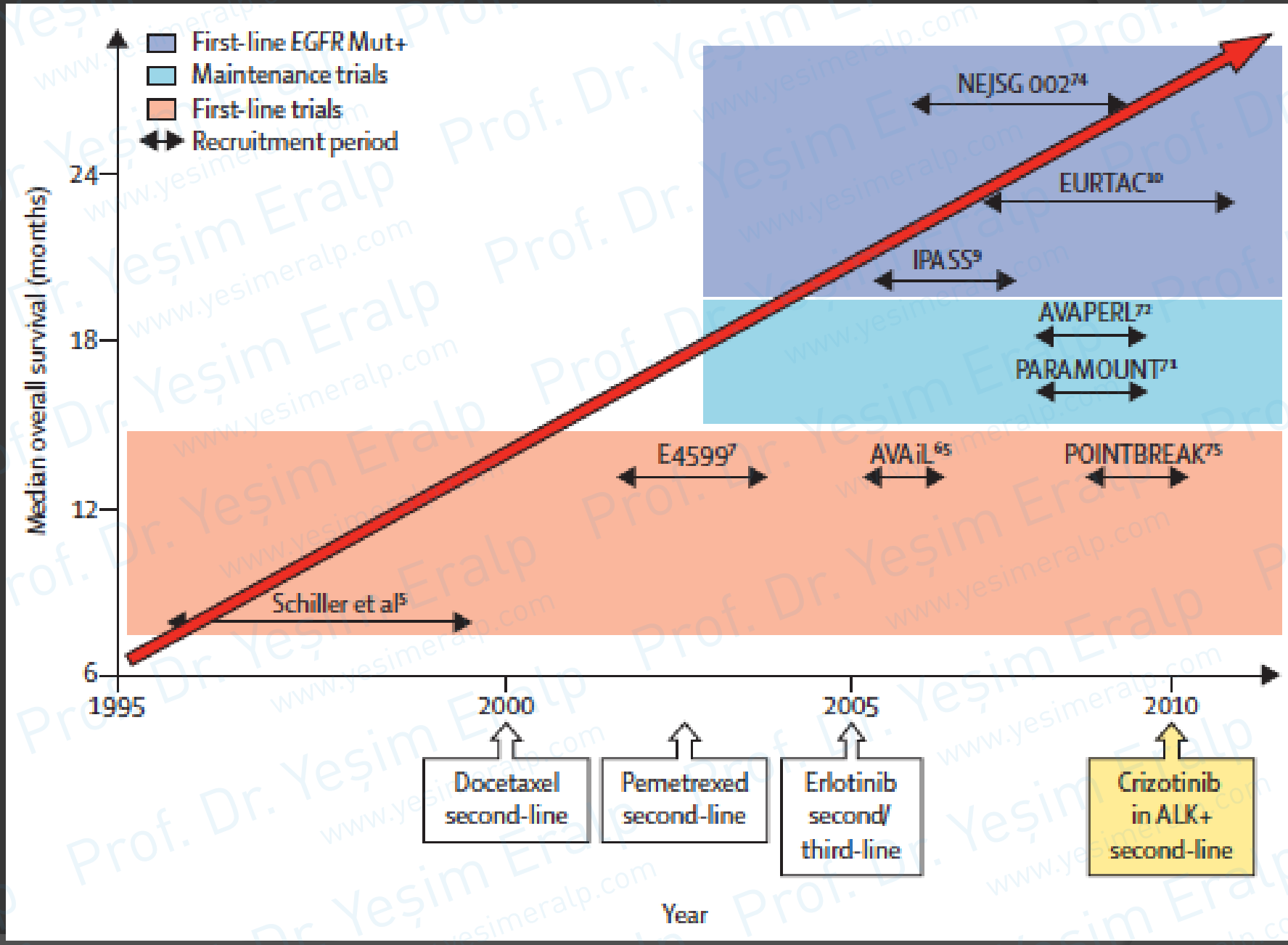




%26 ölüm olayı
170 hastanın 121'I 2. seçim crizotinib koluna cross-over

Benjamin J. Solomon

N Engl J Med 2014;371:2167-77

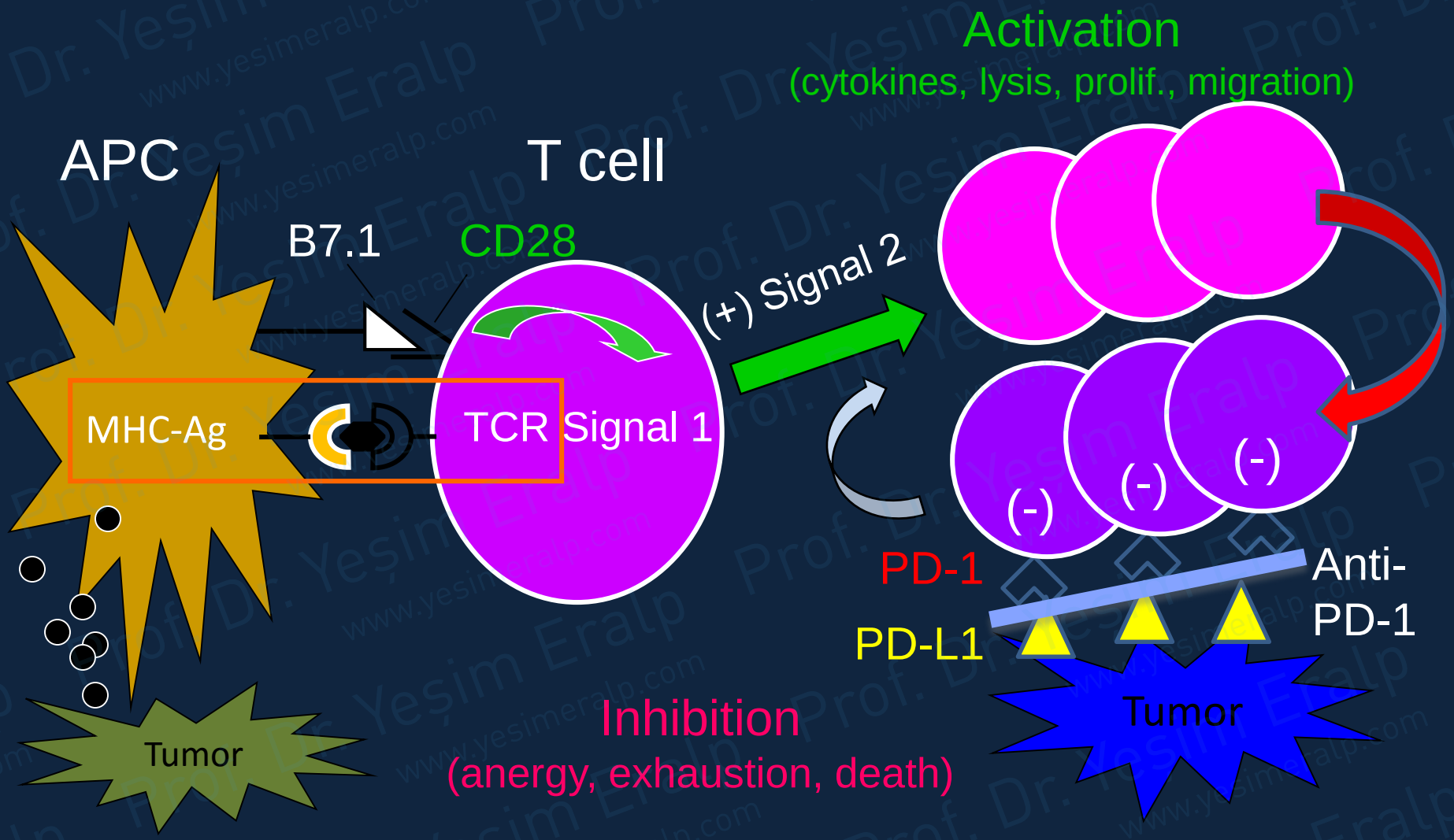


Lancet 2013; 382: 709–19

The seventh fundamental hallmark of cancer

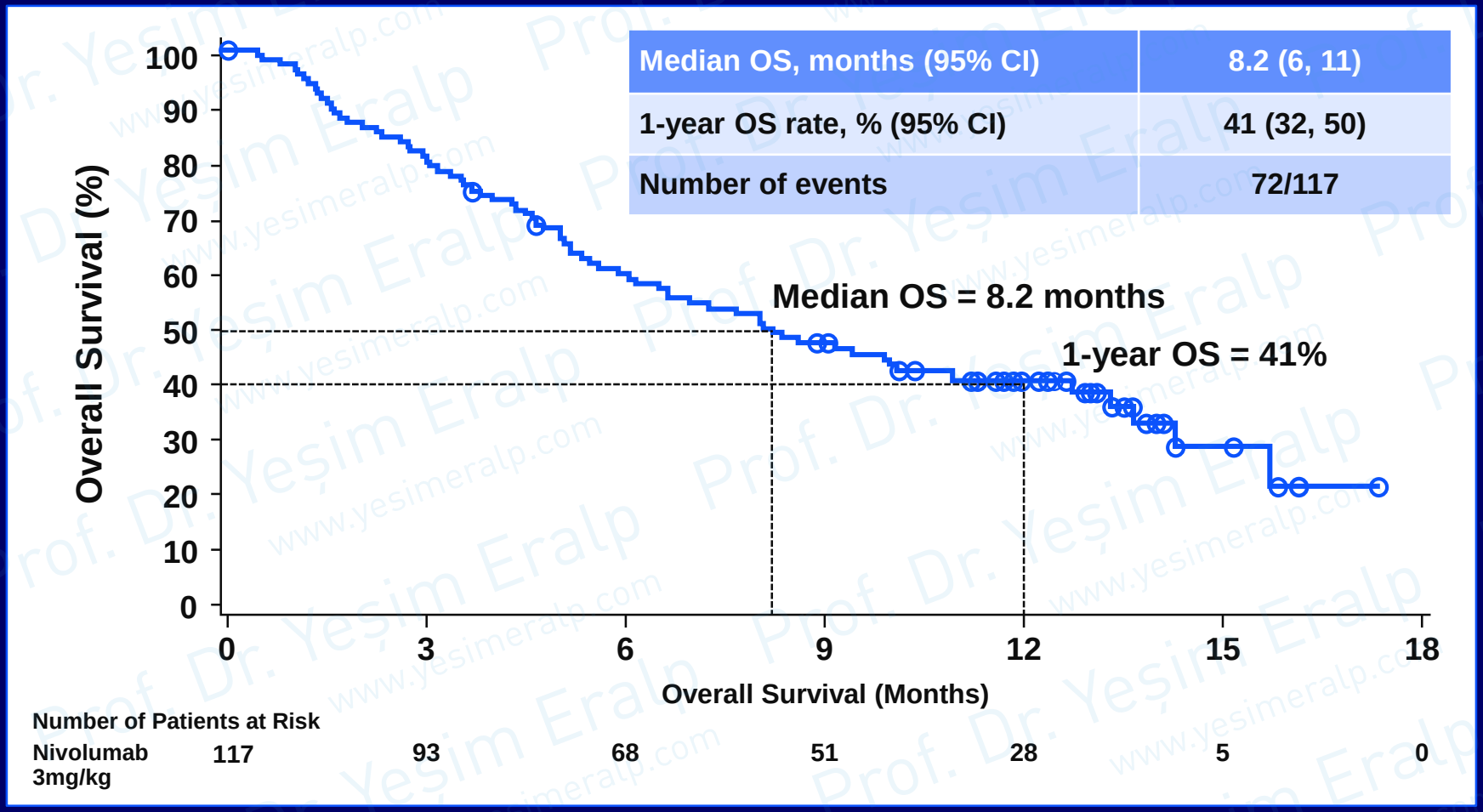
Dunn, G.P., Old, L.J., and Schreiber, R.D. 2004. *Annu Rev Immunol* 22:329-360.
Zitvogel, L., Tesniere, A., and Kroemer, G. 2006. *Nat Rev Immunol* 6:715-727.
T. J. Curiel. 2007 *J Clin Invest,* 117(5):1167-1174.

Role of PD-1 in Suppressing Antitumor Immunity



Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

Nivolumab Overall Survival (OS)



- Median follow-up for survival: 8 months (range, 0–17 months)

[a]Based on July 2014 DBL; Symbols represent censored observations

Pembrolizumab: NSCLC Clinical Activity

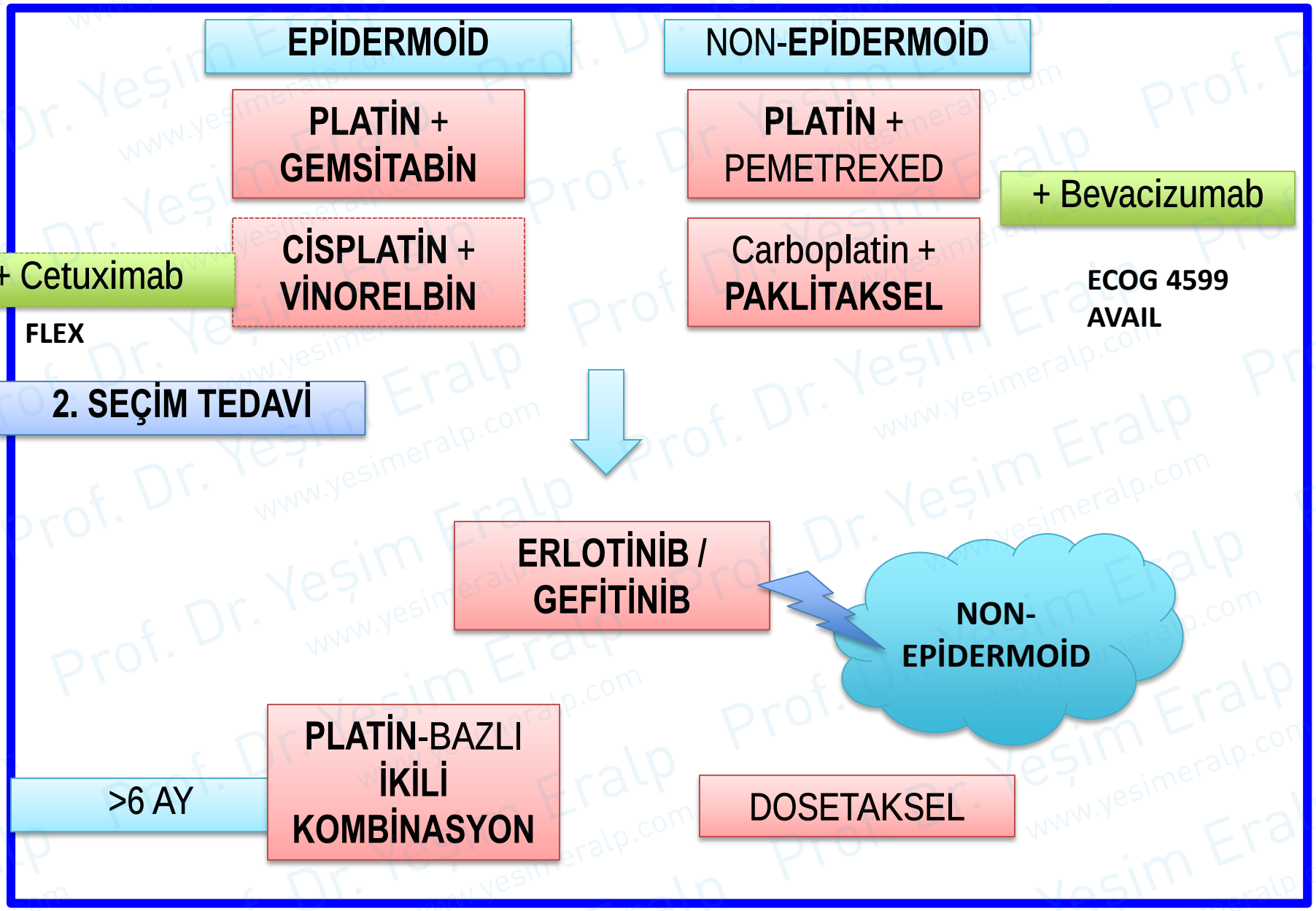
	First-line[1]	Previously treated[2]	
	PD-L1+ (n = 42)	PD-L1+ (n = 159)	PD-L1 – (n = 35)
ORR*, %	26	23	9
DCR*, %	64	42	31
Median duration of response, wks	NR	31	NR

*RECIST v1.1

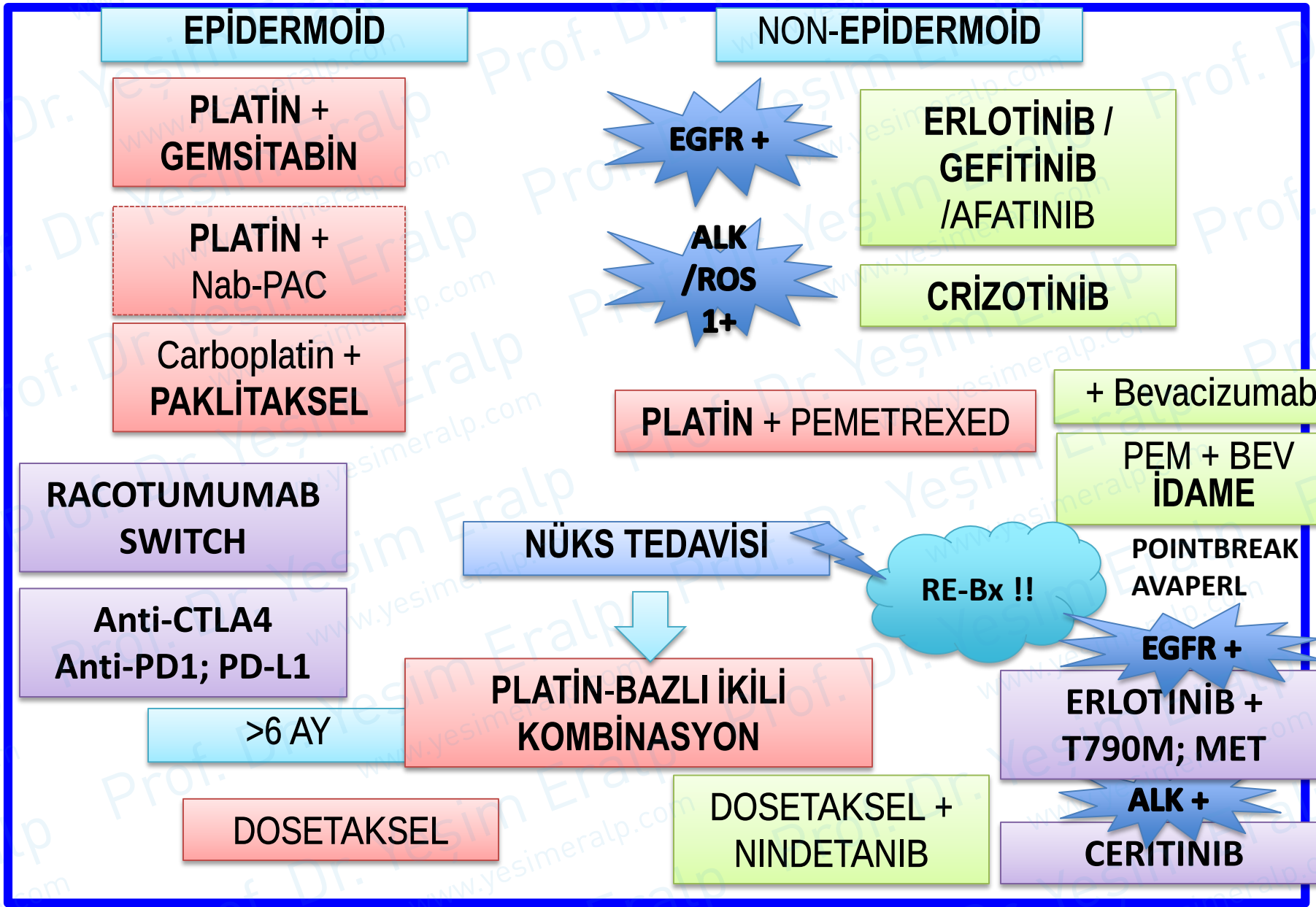
- ~ 80% of screened patients in each study were PD-L1+
- Among previously treated patients with NSCLC, ORR was 26% in current/former smokers and 9% in never smokers

1. Rizvi N, et al. ASCO 2014. Abstract 8007. 2. Garon E, et al. ASCO 2014. Abstract 8020.

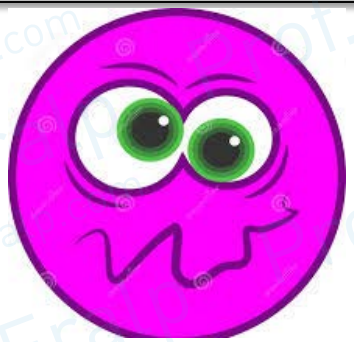
KHD AC KANSERİNDE TEDAVİ ALGORİTMALARI: 2008



KHD AC KANSERİNDE TEDAVİ ALGORİTMALARI: 2014



SONUÇ:
KHDAK Hedefe Yönelik Tedaviler



- Birçok molekül; Değişken etkinlik

- Hedef ne olmalı: Genel sağkalım vs PFS
  Klinik anlamlılık ??
  Maliyet-Yarar Analizi ??

- Sorun: ALK, ROS1 & EGFR dışında;
  - Biyobelirteç yokluğu
  - Karsinogenezin temelinde yatan kilit hedefin bulunamamış olması

Genotipe Dayalı Tedavi

Gelecek için Hedefe Yönelik Tedavi