Meme Kanseri:
Pratiği Değiştiren Çalışmalar

Ne biliyorduk; Ne değişti??

Prof. Dr. Yeşim ERALP
İÜ Onkoloji Enstitüsü

- Endokrin tedavi
  - Adjuvan
  - Metastatik
- Hedefe yönelik tedavi
  - HER-2 (+) hastalık
- Adjuvan sistemik tedavi
  - Doz yoğun tedavi
- Neoadjuvan tedavi

Pratik yaklaşımımızdaki veriler güçlendi ☺)

ADJUVAN KEMOTERAPİ

2010'lara doğru nod negatif erken evre meme kanserinde standartlar…

4 AC
4 TC

Düşük riskli nod negatif hastalık

NSABP B15 & B23
USO 9735
JCO 1990; Fisher JCO 2001
Jones, JCO 2006

CMF

6 FAC
6 TAC
4 FAC-8 hft PAC

Yüksek riskli nod negatif hastalık

Hutchinson JCO 2005
GEICAM 9805; Martin NEJM 2010
GEICAM 2003/02; Martin JCO 2013

6 FEC

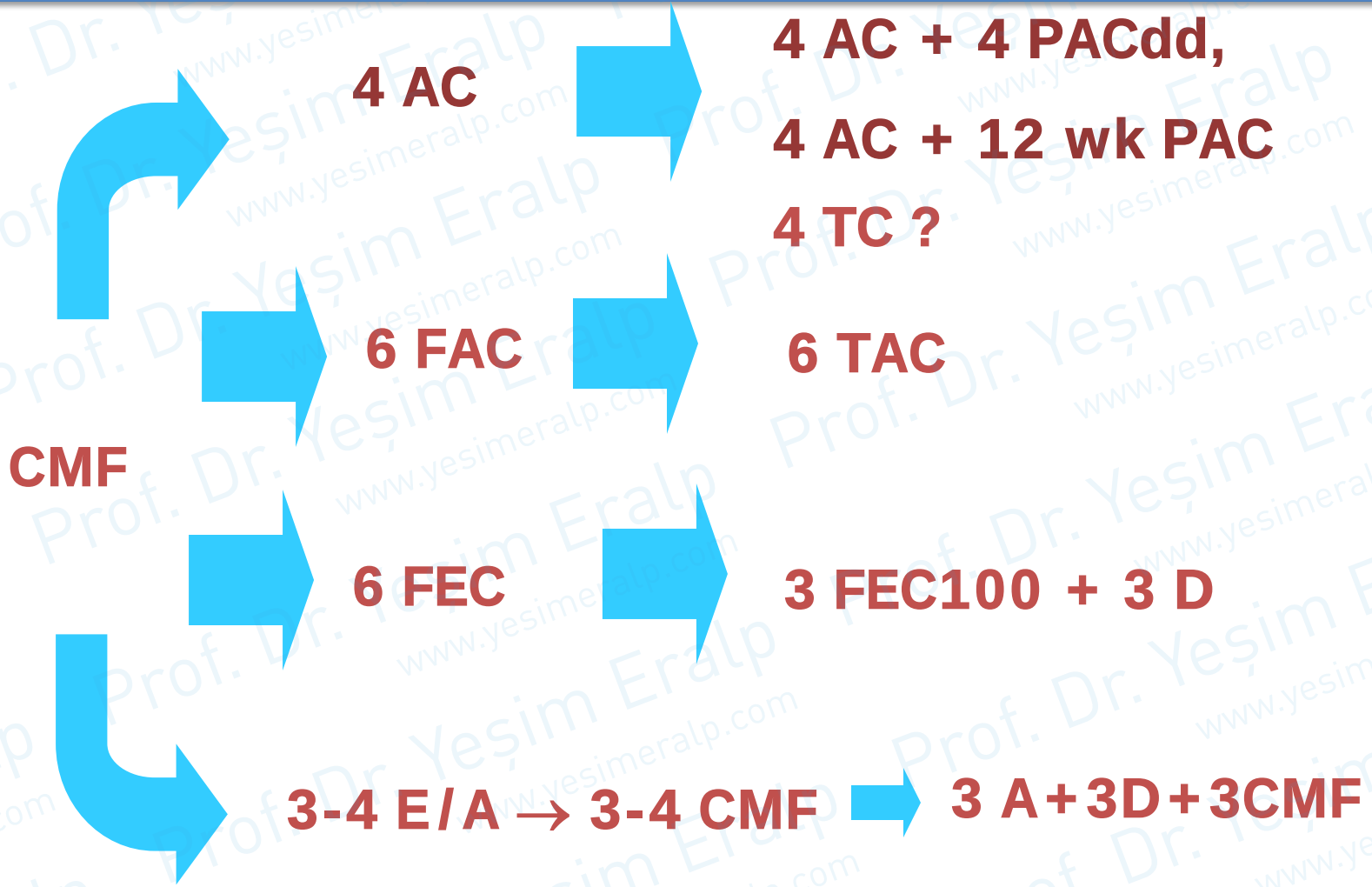
SWOG 8897;
Hutchinson JCO 2005
NSABP B36; SABCS 2014

3-4 E/A → 3-4 CMF

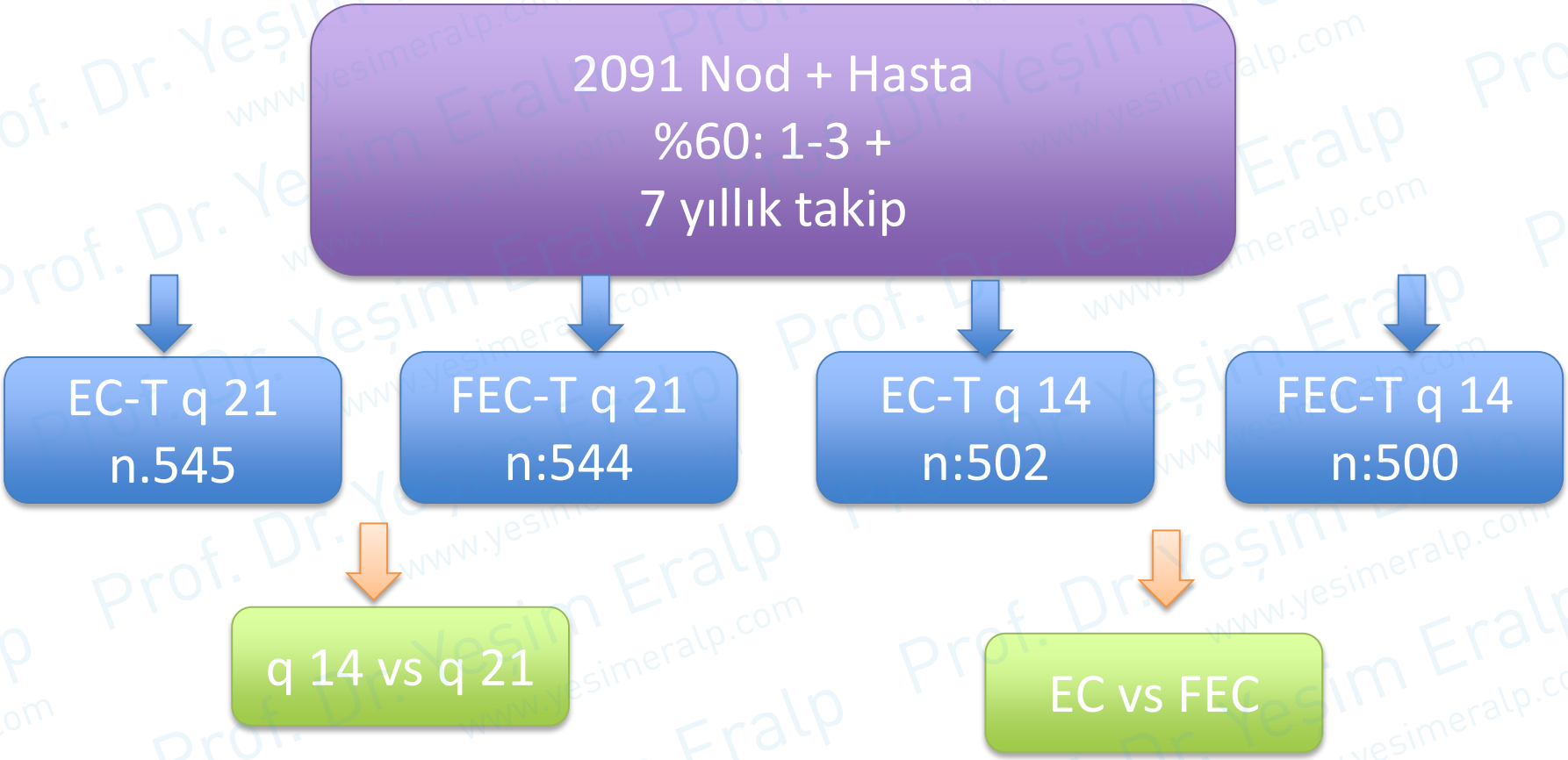
UK-TACT;
Ellis, Lancet 2009

Tm> 2 cm
HR:-
Grad 2-3
Yaş <35

2010'lara doğru Her-2 negatif & nod pozitif erken evre meme kanserinde standartlar…



GIM-2



Cognetti, SABCS 2013

GIM-2

q 14 vs q 21

FEC-T q 14
n:500

=

EC-T q 14
n:502

FEC-T q 21
n:544

=

EC-T q 21
n.545

	Q 14	Q 21	HR; p
DFS	%81	%76	0.78; 0.002
OS	%94	%89	0.69; p:0.0001

Doz yoğun bazı alt gruplarda yararlı olabilir:

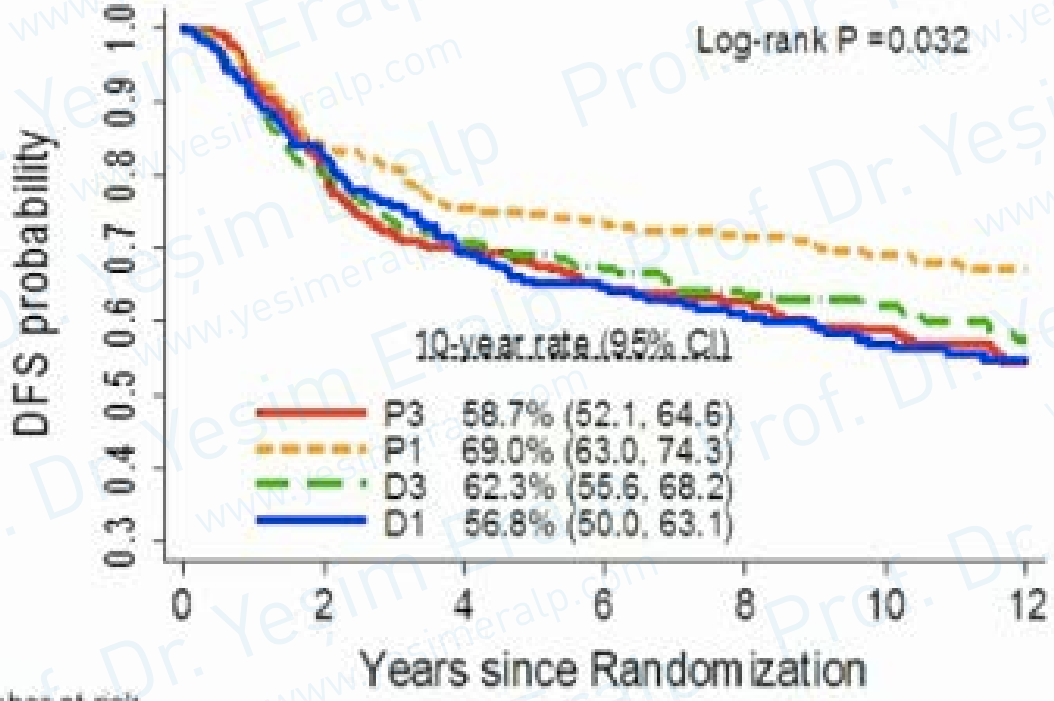
ER, PR:-

>4 LN:+

Genç yaş

Cognetti, SABCS 2013

E 1199: Triple Negatif Alt-grup



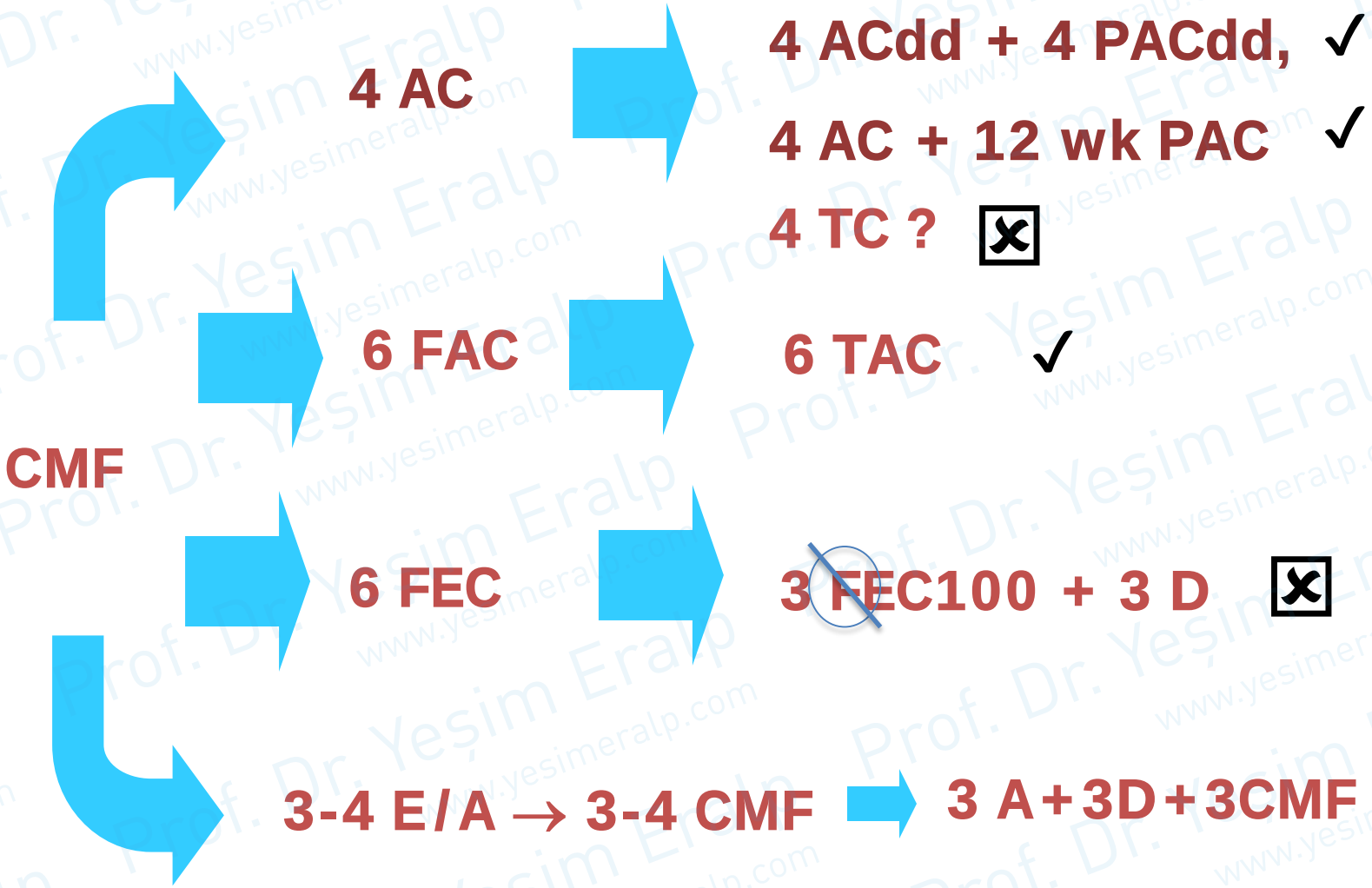
Number at risk

P3	261	207	166	138	126	102	47
P1	274	226	197	175	159	127	61
D3	248	195	160	134	120	106	52
D1	243	197	160	133	109	88	49

TNBC subset

Sparano J, et al. SABCS 2014.

Her-2 negatif & nod pozitif erken evre meme kanserinde standartlar: 2015



ADJUVAN HEDEFE YÖNELİK TEDAVİ

Her-2 pozitif hastalık

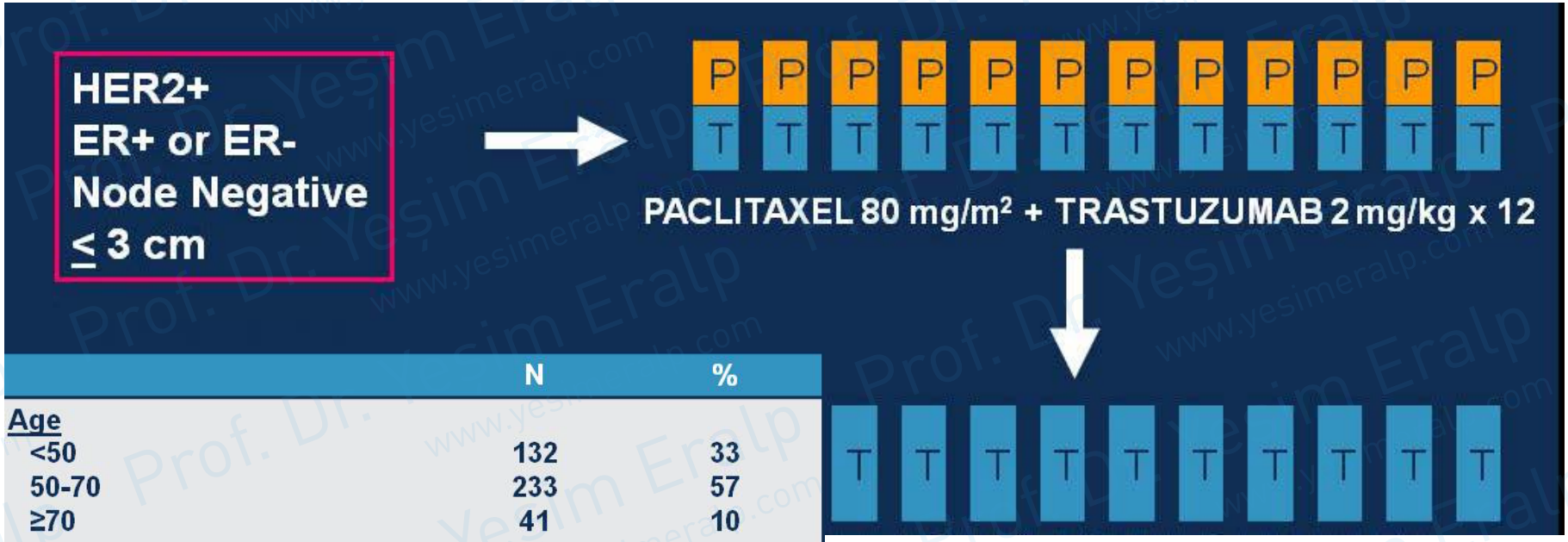
- T1a,b tümörlerde adjuvan trastuzumab
- Trastuzumab süresi
- Farklı ajanlar
  - Neratinib

- İlk 5 yılda nüks riski → Hormon reseptörü ilişkili
  - T1a: %2-10
  - T1b: %5-15
  - T1c: %10-25

- Riski belirledik; Hangi Tedavi..??
  - AC-TH
  - TCH
  - Hormon + Trastuzumab
  - Başka KT

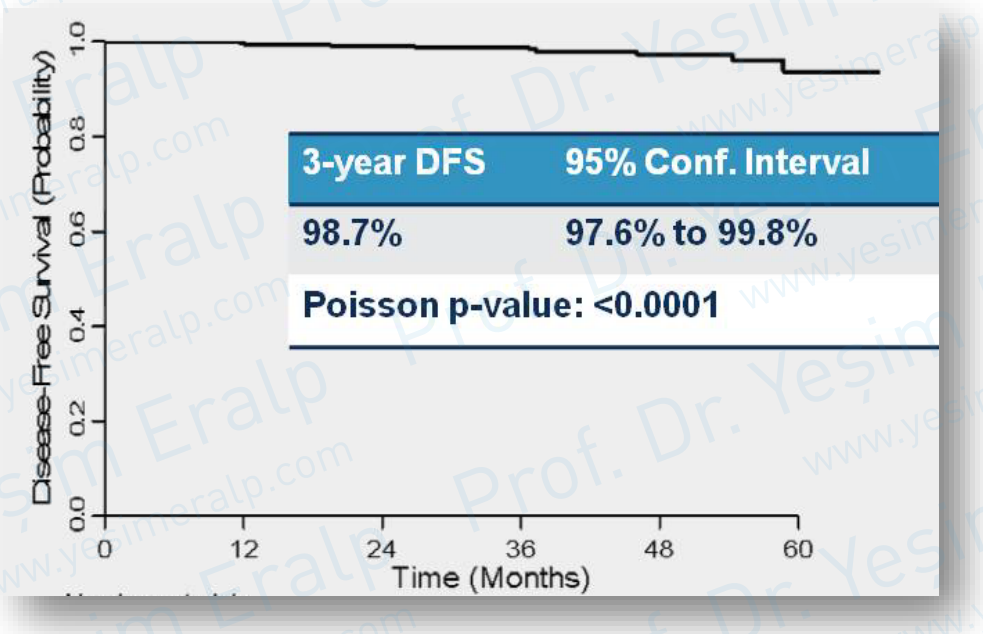
	Ciddi Kardiak Yan-etki	AML
AC-TH	%2	%0.4
TCH	%0.4	%0.1

APT Çalışması



	N	%	
Age			
<50	132	33	
50-70	233	57	
≥70	41	10	
Size of Primary Tumor			
T1a ≤0.5 cm	77	19	50%
T1b >0.5-≤1.0	124	31	
T1c >1.0-≤2.0	169	42	50%
T2 >2.0-≤3.0	36	9	
Histologic Grade			
I Well differentiated	44	11	
II Moderately differentiated	131	32	
III Poorly differentiated	228	56	
HR Status (ER and/or PR)			
Positive	272	67	
Negative	134	33	

Tolaney, SABCS 2013



- ↑ HR + hasta oranı; Uzun süreli takipte nüksler ??

- Özellikle T1a veya düşük riskli T1b hastalık için uygun bir seçenek
  - Düşük kardiyak yan-etki
  - Uzun dönem myeloid toksisite yok

- Yüksek riskli hastalar için standart antrasiklinli KT halen düşünülmeli
  - AC-TH vs TCH: %3 DFS farkı
  - TCH = TH (metastatik hastalık ekstrapolasyonu)

T1N0 Her-2 (+) Hastalık
Adjuvan Tedavi

	0.1-0.5 cm	0.6-1.0 cm	>1.0 cm
HR+	SEÇİLMİŞ HASTA GRUBUNA ÖNERİLEBİLİR**	ADJ KT* + TRAST İÇİN DEĞERLENDİR	KT* + TRAST
HR–	SEÇİLMİŞ HASTA GRUBUNA ÖNERİLEBİLİR**	KT* + TRAST	KT + TRAST

*: non-antrasiklin bazlı KT
**: yaş<35; grad 2-3

Phare: 6 vs 12 ay trastuzumab

156 merkez, 3300 hasta
Hedef sonlanım: DFS; Non-inferiority; HR:1.15

	12-month group		6-month group		Hazard ratio (95% CI)
	Events/ patients	Disease-free survival at 2 years (95% CI)	Events/ patients	Disease-free survival at 2 years (95% CI)	
Total population	1690	93·8% (92·6–94·9)	1690	91·1% (89·7–92·4)	1·28 (1·05–1·56)
Oestrogen-receptor status					
Negative	92/716	91·2% (88·8–93·1)	117/696	87·7% (85·0–89·9)	1·34 (1·02–1·76)
Positive*	83/974	95·7% (94·3–96·9)	102/994	93·6% (91·9–95·0)	1·23 (0·92–1·65)
Timing of administration of chemotherapy and trastuzumab					
Sequential*	84/729	92·5% (90·3–94·2)	117/747	89·5% (87·0–91·5)	1·41 (1·06–1·86)
Concomitant	91/961	94·8% (93·2–96·1)	102/943	92·5% (90·6–94·0)	1·15 (0·87–1·53)
Oestrogen-receptor status and timing of chemotherapy and trastuzumab					
Negative—sequential	46/312	89·8% (85·8–92·7)	69/314	84·5% (80·0–88·1)	1·57 (1·08–2·28)
Positive—sequential	38/417	94·5% (91·8–96·4)	48/433	93·1% (90·2–95·1)	1·25 (0·81–1·91)
Negative—concomitant	46/404	92·3% (89·2–94·6)	48/382	90·3% (86·8–92·9)	1·10 (0·73–1·65)
Positive—concomitant	45/557	96·7% (94·8–97·9)	54/561	94·0% (91·6–95·7)	1·23 (0·83–1·82)

Xavier Pivot, Lancet Oncol 2013; 14: 741–48

Phare: 6 vs 12 ay trastuzumab

156 merkez, 3300 hasta

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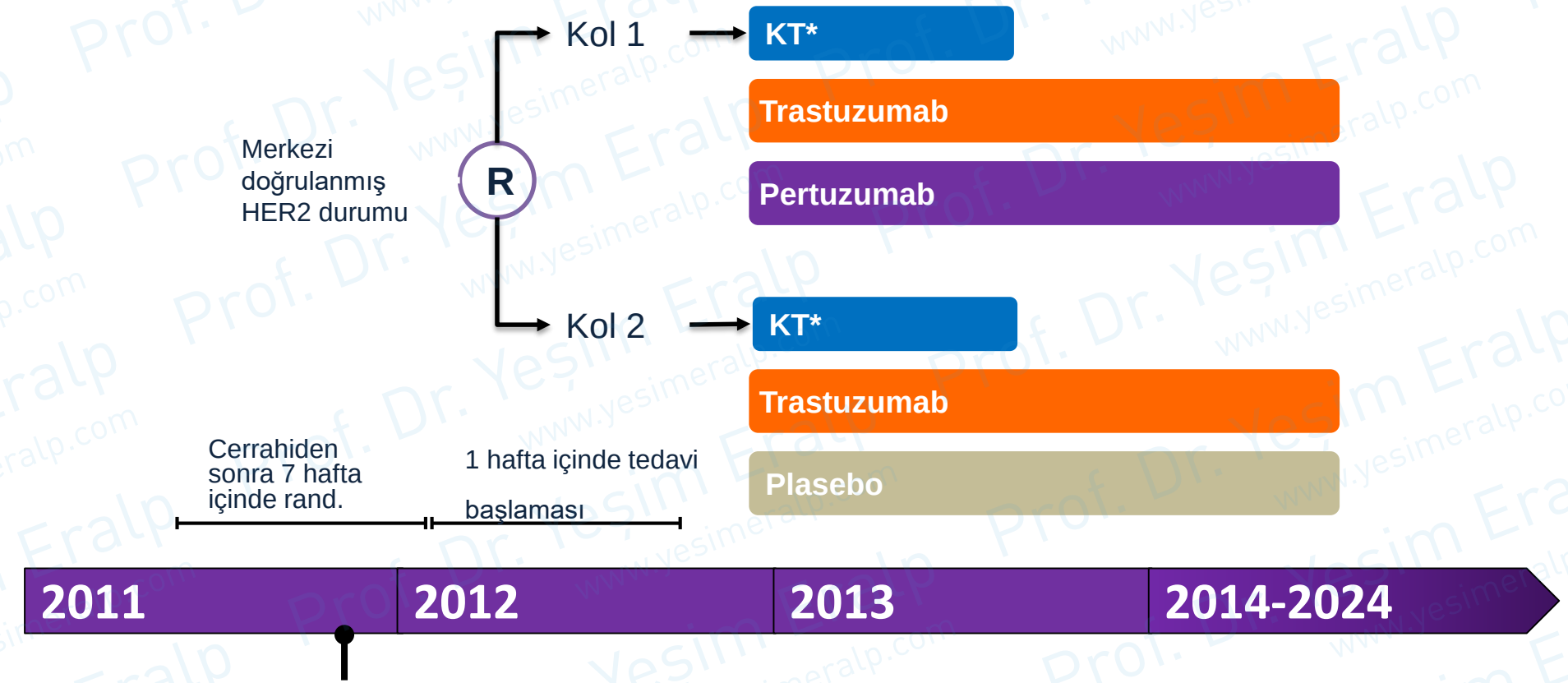
Positive—concomitant	45/557	96·7% (94·8–97·9)	54/561	94·0% (91·6–95·7)	1·23 (0·83–1·82)

ADJUVAN TRASTUZUMAB TEDAVİSİ 12 AY BOYUNCA SÜRDÜRÜLMELİ

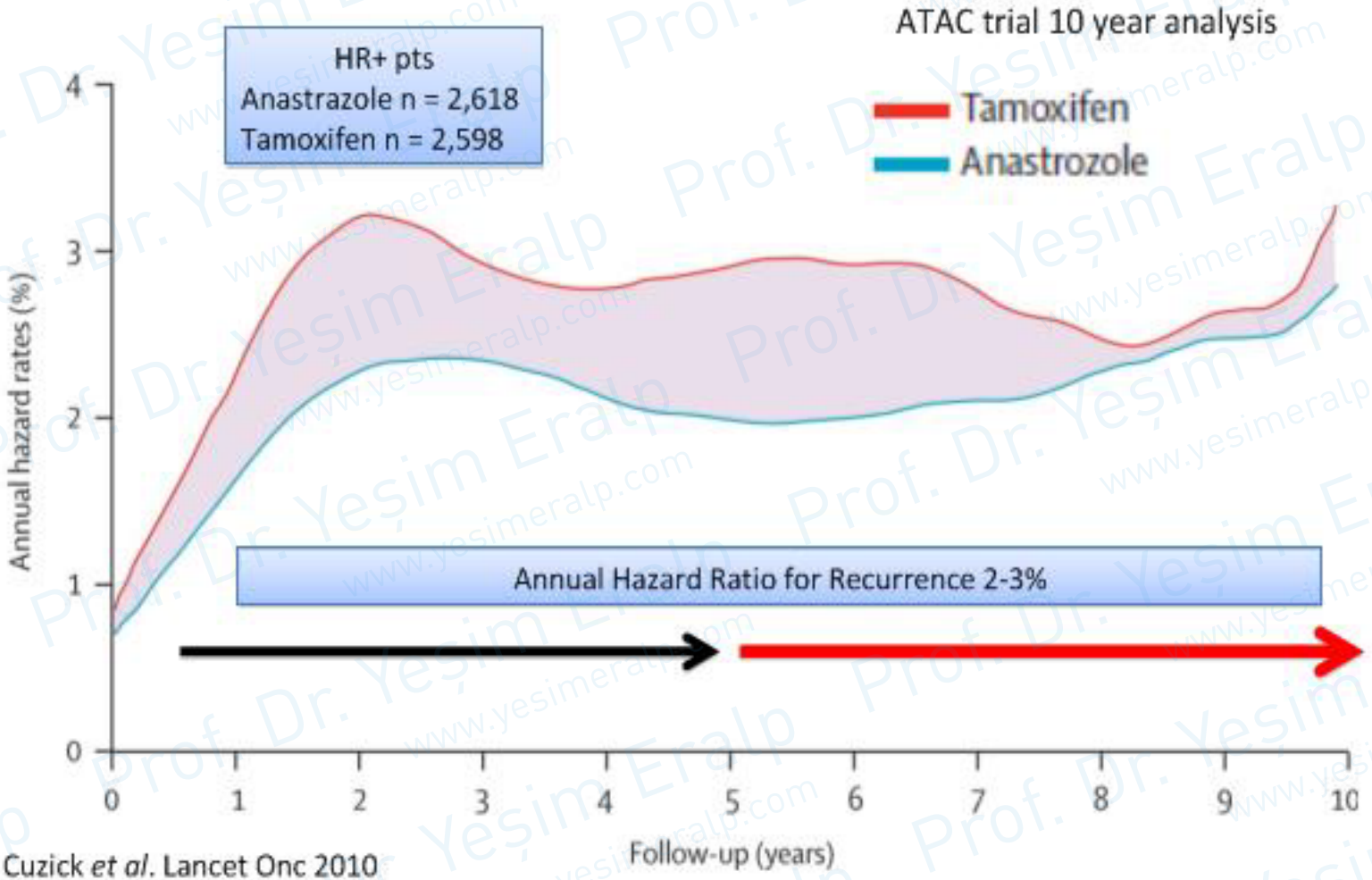
APHINITY Faz III Çalışma



ADJUVAN HORMONAL TEDAVİ

- Uzatılmış adjuvan endokrin tedavi
- Premenapozal hastada aromataz inhibitörlerinin rolü
- Over supresyonunun rolü

Chemotherapy and Endocrine Therapy Prevents Early Recurrence, But Late Recurrence Remains a Challenge Despite Carryover Effect of Endocrine Therapy



Cuzick *et al*. Lancet Onc 2010

Uzatılmış AI çalışmaları

MA.17[30,33]	5,187	Postmenopausal HR+ EBC who had received 4.5 to 6 yr of adjuvant T therapy	0.68 (0.56, 0.83), p < 0.001	0.99 (0.79, 1.24), p = 0.83
Double-Blind	64-mo follow-up		IPCW 0.52 (0.45, 0.61), p < 0.001	IPCW 0.61 (0.52, 0.71), p < 0.001
L vs. Placebo			SCC[a] 0.58 (0.47 -0.72), p < 0.001	SCC* 0.76 (0.60, 0.96), p = 0.02
ABCSG Trial 6a[37]	856	Postmenopausal HR+ EBC who had received 5 yr of adjuvant T, with or without AG, for the first 2 yr of therapy	0.62 (0.40, 0.96), p = 0.031	0.89 (0.59, 1.34), p = 0.57
Open-Label	62.3-mo follow-up			
A (3 yr) vs. No Further Treatment				
NSABP-33[38]	1,598	Postmenopausal HR+ T1-3N1M0 EBC who were disease-free after 5 yr of adjuvant T	0.68, p = 0.07	NA
Double-Blind	30-mo follow-up			
E (5 yr) vs. Placebo (5 yr)				

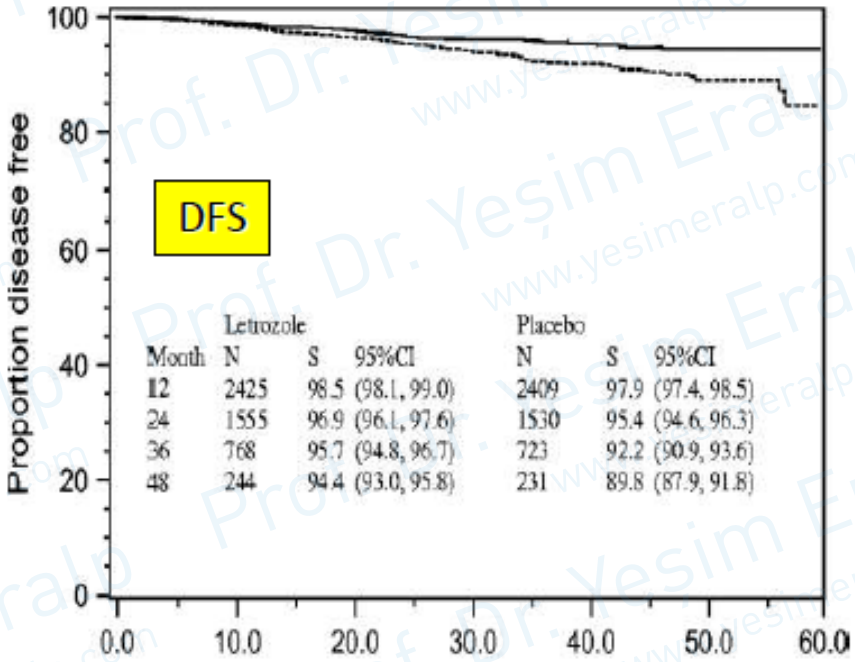
MA 17

Tamoxifen for 4.5-6 yrs
Postmenopausal
N=5,187

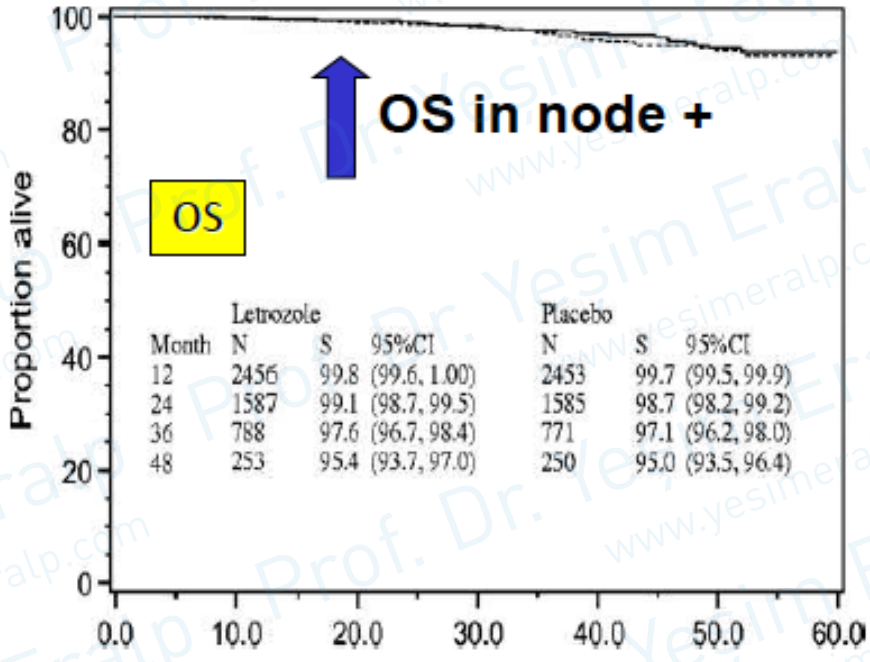
PLACEBO

5 yrs rx planned

LETROZOLE

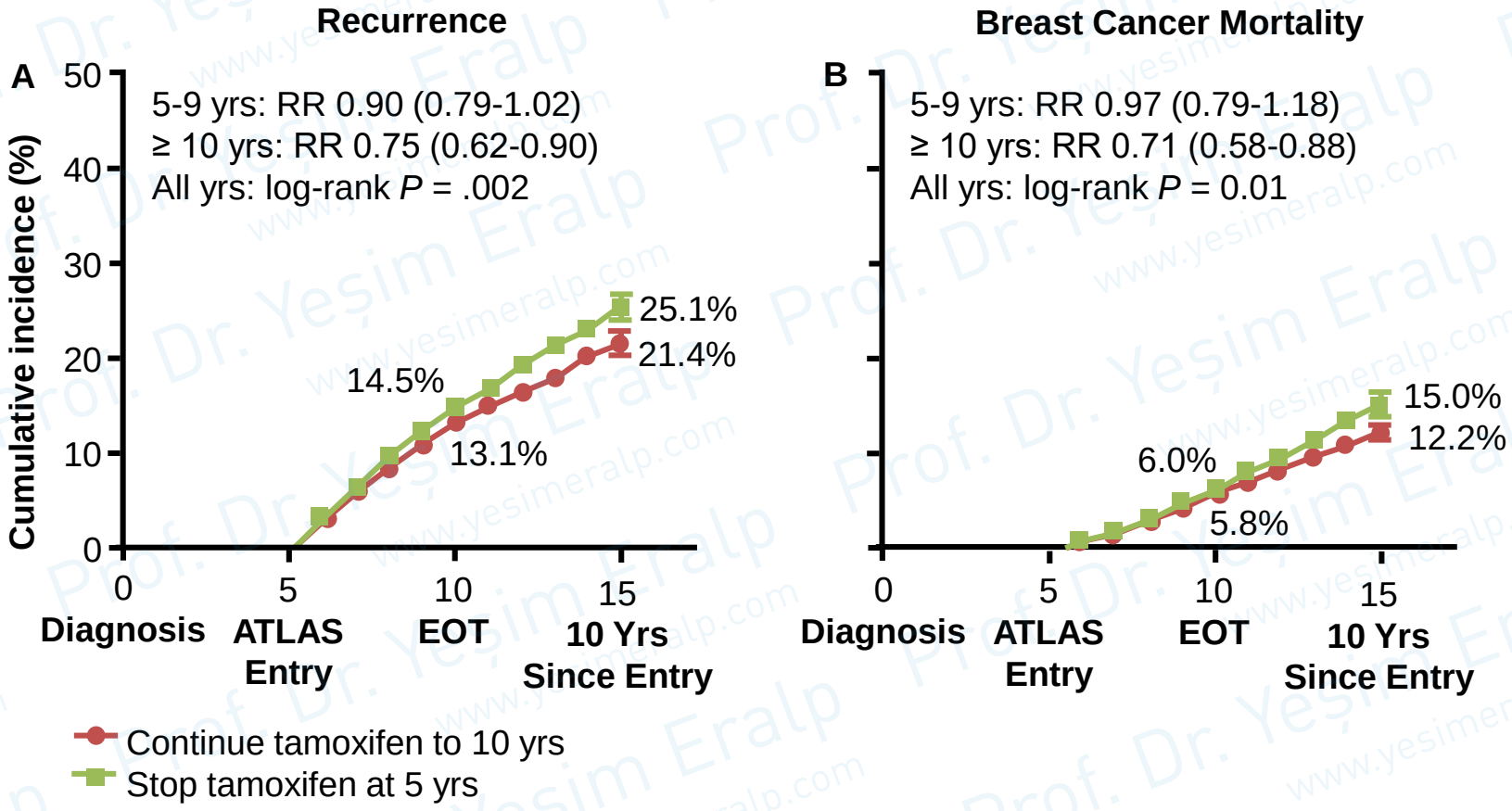


	Letrozole			Placebo		
Month	N	S	95%CI	N	S	95%CI
12	2425	98.5	(98.1, 99.0)	2409	97.9	(97.4, 98.5)
24	1555	96.9	(96.1, 97.6)	1530	95.4	(94.6, 96.3)
36	768	95.7	(94.8, 96.7)	723	92.2	(90.9, 93.6)
48	244	94.4	(93.0, 95.8)	231	89.8	(87.9, 91.8)



	Letrozole			Placebo		
Month	N	S	95%CI	N	S	95%CI
12	2456	99.8	(99.6, 1.00)	2453	99.7	(99.5, 99.9)
24	1587	99.1	(98.7, 99.5)	1585	98.7	(98.2, 99.2)
36	788	97.6	(96.7, 98.4)	771	97.1	(96.2, 98.0)
48	253	95.4	(93.7, 97.0)	250	95.0	(93.5, 96.4)

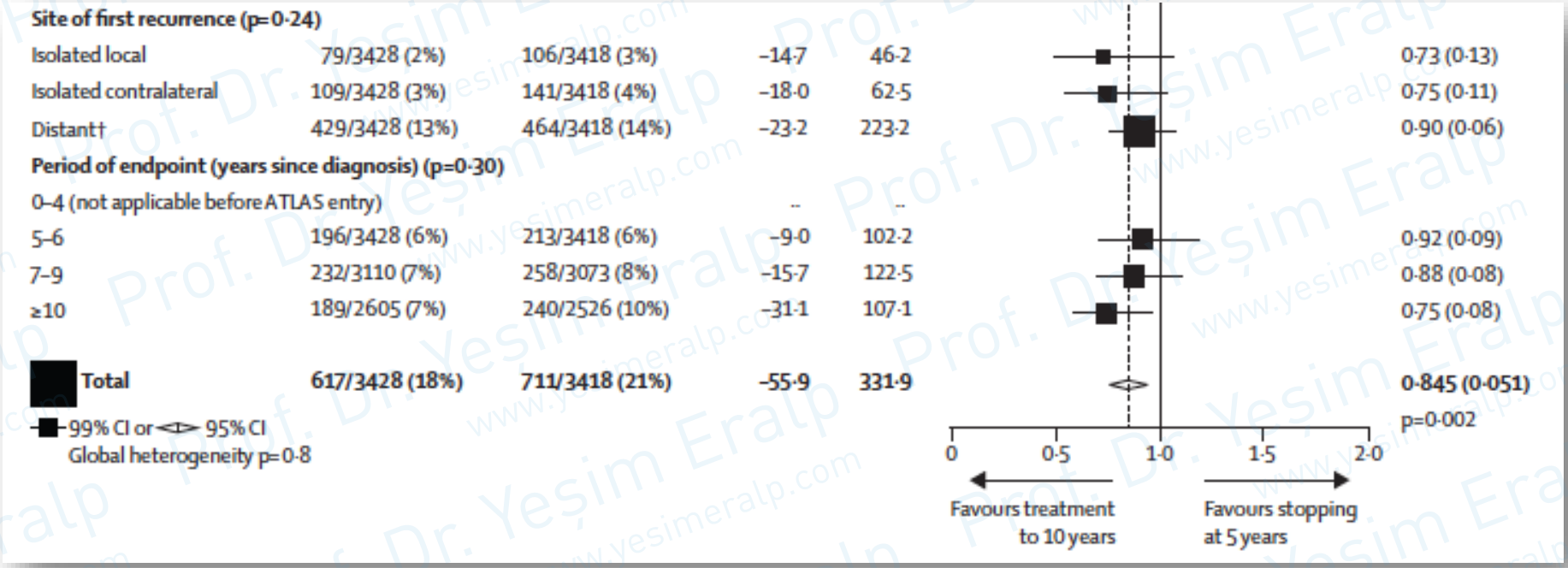
ATLAS: 5 vs 10 Yıl Tamoxifen



Davies C, et al. SABCS 2012. Abstract S1-2. Davies C, et al. Lancet. 2012

ATLAS

Yaş, tm çapı, nodal tutulum, TMX kullanım süresi, mastektomi gibi tüm alt gruplarda uzun tedaviden farklı yararlanan bir grup gösterilemedi….



Christina Davies, *Lancet* 2013; 381: 805–16

aTTom & ATLAS Kombine Analiz

	Breast Cancer Mortality			OS
	10 yrs tam. vs 5: aTTom trial (n=6934 ER+/UK)	10 yrs tam. vs 5: ATLAS trial* (n=10,543 ER+/UK)	10 yrs tam. vs 5: aTTom & ATLAS combined (n=17,477 ER+/UK)	10 yrs tam. vs 5: aTTom & ATLAS combined (n=17477 ER+/UK)
years 5-9	1.08 (0.85-1.38)	0.92 (0.77-1.09)	0.97 (0.84-1.15)	0.99 (0.89-1.10)
years 10+	0.75† (0.63-0.90)	0.75§ (0.63-0.90)	0.75† (0.65-0.86)	0.84† (0.77-0.93)
All years	0.88‡ (0.74-1.03)	0.83‡ (0.73-0.94)	0.85‡ (0.77-0.94)	0.91‡ (0.84-0.97)
	†p=0.007 ‡p=0.1	§p=0.002 ‡p=0.004	†p=0.00004 ‡p=0.001	†p=0.0007 ‡p=0.008

*Inverse-variance-weighted estimate of the effect in ER+.(ATLAS, *Lancet* 2013)

Uzatılmış Adjuvan ET için yüksek riskli grubun belirlenmesi: Genomik Analizler

References	Endocrine treatment	Patient population	Nodal status	Biomarker assessed	Group at high risk for late relapse
Dubsky *et al*, 2013	Tamoxifen or tamoxifen followed by anastrozole	ABCSG-06 ABCSG-08	Node negative and positive (96% G1 or G2)	EndoPredict (EP) EPciln (including tumour size and nodal status)	High EP High EPclin
Bianchini *et al*, 2013	Tamoxifen	Public data sets	Node negative and positive	Combination of proliferation (MKS, GGI) and estrogen-related genes (ERS) markers	High-proliferation/ high ERS Low-proliferation/low ERS
Zhang *et al*, 2013	Tamoxifen (2 or 5 years)	Stockholm TAM and institutional cohorts	Node negative	Breast Cancer Index (BCI) (linear combination model)	Intermediate/high BCI
Sgroi *et al*, 2013b	Tamoxifen or anastrozole	ATAC	Node negative	BCI (linear combination model) HOXB13/IL17BR (H/I) MGI IHC4 RS	Intermediate/high BCI High HOXB13/ IL17BR (H/I)
Sgroi *et al*, 2013a	Tamoxifene	MA.17	Node negative and positive	HOXB13/IL17BR (H/I)	High HOXB13/ IL17BR (H/I)
Sestak *et al*, 2013	Tamoxifen or anastrozole	ATAC	Node negative and positive	IHC4 RS ROR (from PAM50)	High ROR

G Bianchini www.bjcancer.com | DOI:10.1038/bjc.2013.707

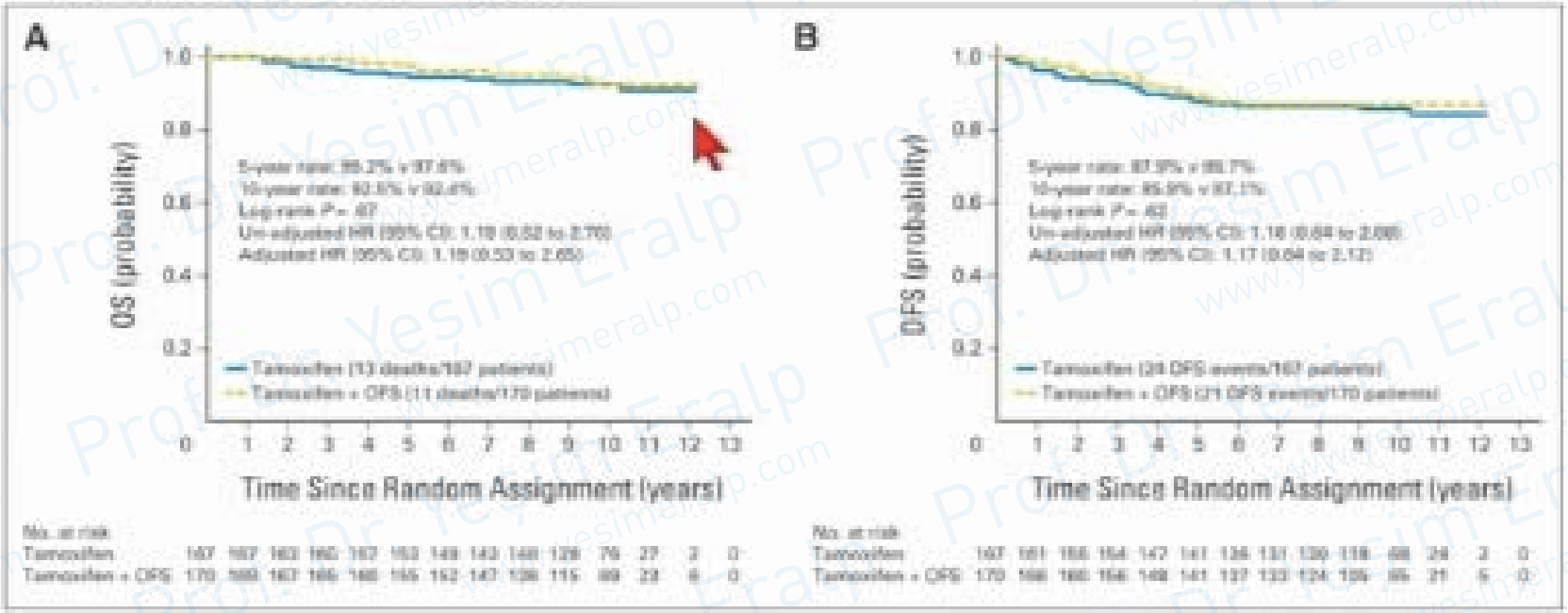
MAKSİMAL HORMON BLOKAJI: OVER SUPRESYONU + TMX/AI

Tamoxifen +/- OFS: ECOG E3193

Premenopausal
ER and/or PR +
T≤ 3 cm, N0
N=345
Median followup = 9.9 yr

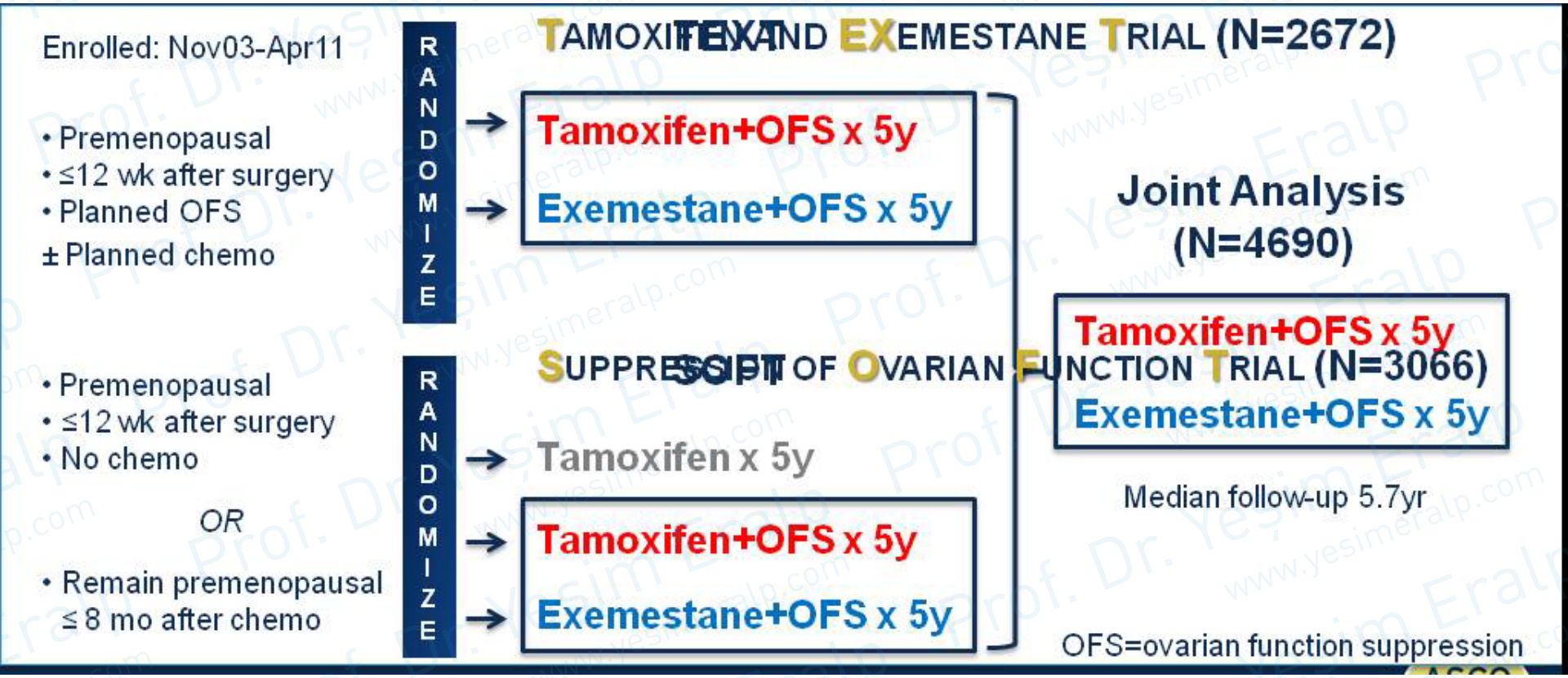
→ **Tamoxifen X 5 yr**

→ **Tamoxifen + OFS X 5 yr**



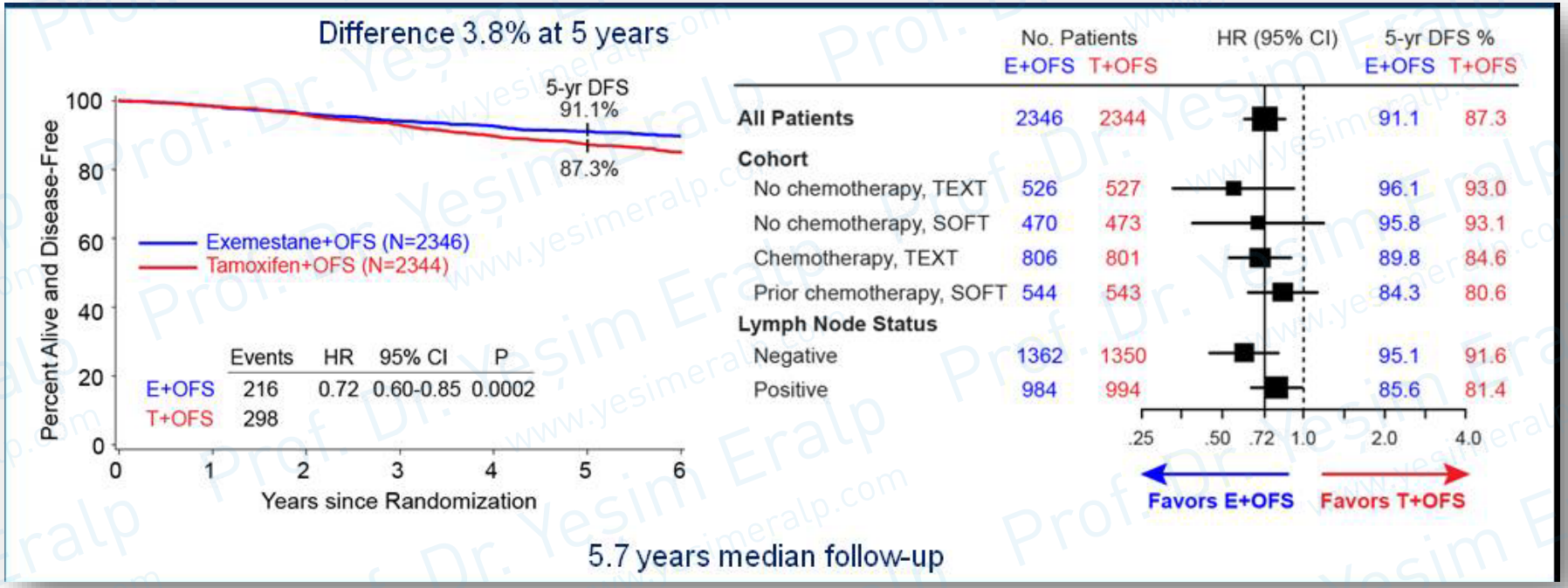
Tevaarwerk et al, J Clin Oncol, 2014

TEXT & SOFT Çalışma Kurgusu



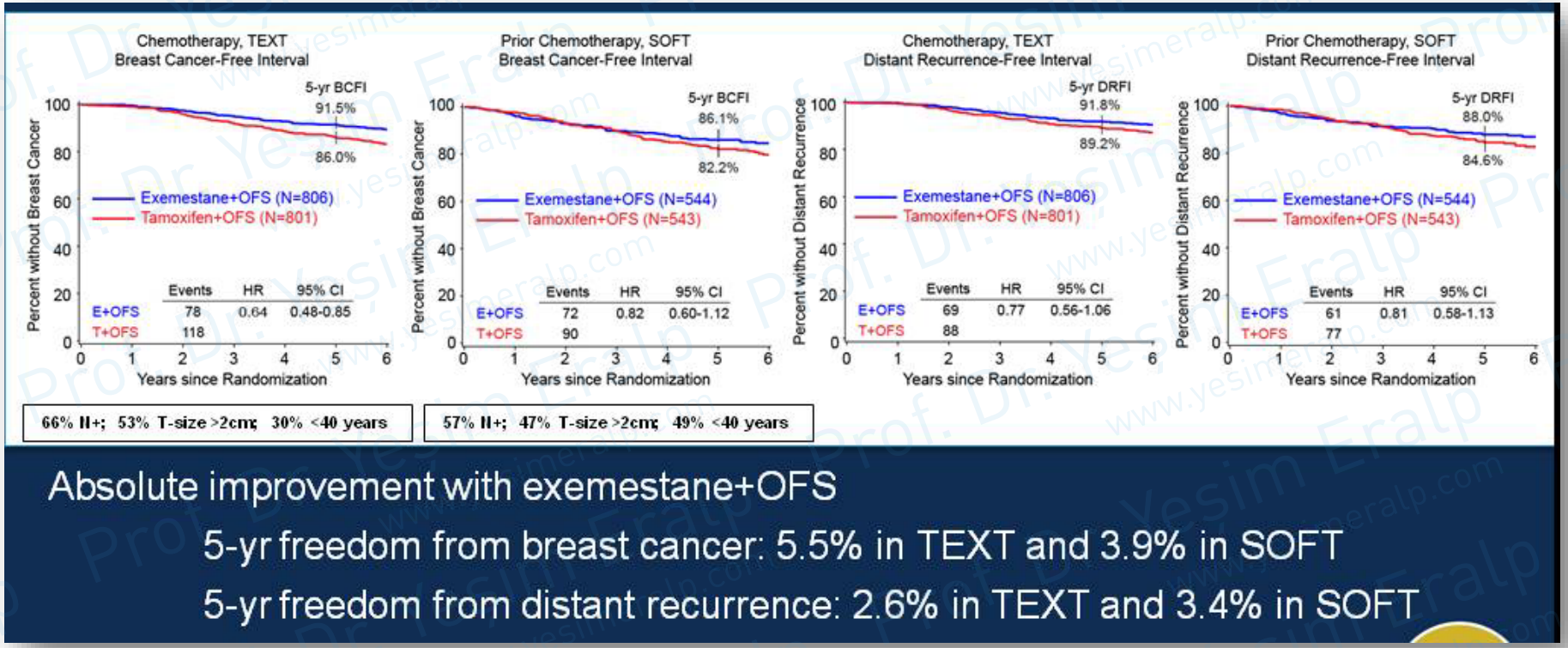
Olivia Pagani **N Engl J Med 2014;371:107-18.**

Exemestane+OFS vs TMX + OFS: DFS yararı



Olivia Pagani **N Engl J Med 2014;371:107-18.**

KT Uygulanan Hastalarda DFS Yararı



Absolute improvement with exemestane+OFS

5-yr freedom from breast cancer: 5.5% in TEXT and 3.9% in SOFT

5-yr freedom from distant recurrence: 2.6% in TEXT and 3.4% in SOFT

Olivia Pagani **N Engl J Med 2014;371:107-18.**

SOFT & TEXT Kombine Analiz

Medyan takip süresi: 5.7 yıl

Outcome	HR (95% CI)	P
DFS	0.72 (0.60-0.85)	0.0002
BCFI	0.66 (0.55-0.80)	<0.0001
DDFI	0.78 (0.62-0.97)	0.02
OS	1.14 (0.86-1.51)	0.37

Olivia Pagani N Engl J Med 2014;371:107-18.

SOFT: SUPPRESSION of OVARIAN FUNCTION TRIAL

Premenopausal ER+ve and/or PR+ve Breast Cancer

3047 Patients Randomized in ITT, Dec 2003 - Jan 2011

Primary Analysis (n= 2033)
Median follow-up 5.6 years

Two Patient Cohorts (stratified)

No Chemotherapy (47%)
Premenopausal, within 12 weeks of surgery
(Median time since surgery = **1.8 months**)

Prior Chemotherapy (53%)
Premenopausal* after completing chemotherapy;
Randomization within 8 months of completion
(Median time since surgery = **8.0 months**)

RANDOMIZE

→ **Tamoxifen x 5y** (n=1018)

→ **Tamoxifen+OFS x 5y** (n=1015)

→ **Exemestane+OFS x 5y** (n=1014)

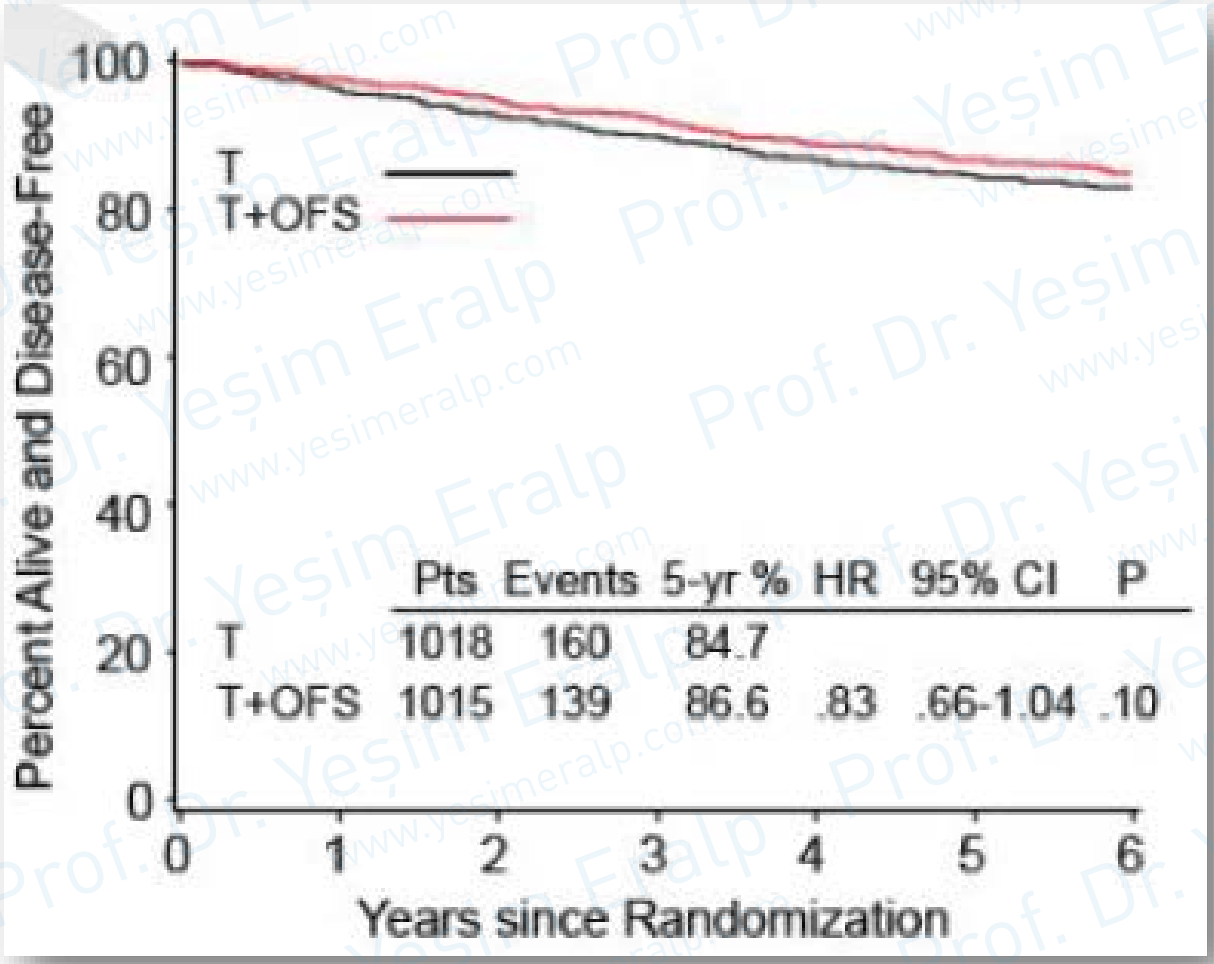
OFS=ovarian function suppression
(GnRH triptorelin, oophorectomy or irradiation)

*According to locally-determined Elevel in premenopausal range

Primary Analysis: Patient Characteristics

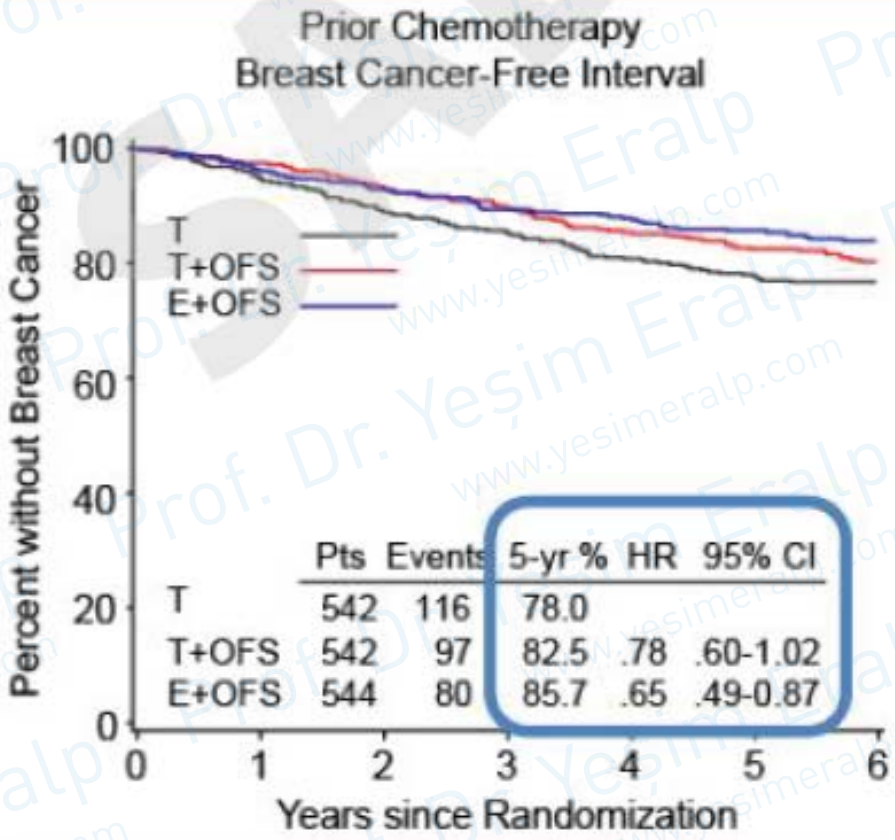
	No chemo 47% (n=949)	Prior Chemo 53% (n=1084)	Overall (n=2033)
Median age	46 y	40 y	43 y
Lymph Node +ve	9%	57%	35%
Tumor > 2 cm	14%	47%	32%
Grade 1	41%	14%	27%
Grade 3	7%	35%	22%
HER2+ve	4%	18%	12%
Median time since surgery	1.8 mo	8.0 mo	3.2 mo

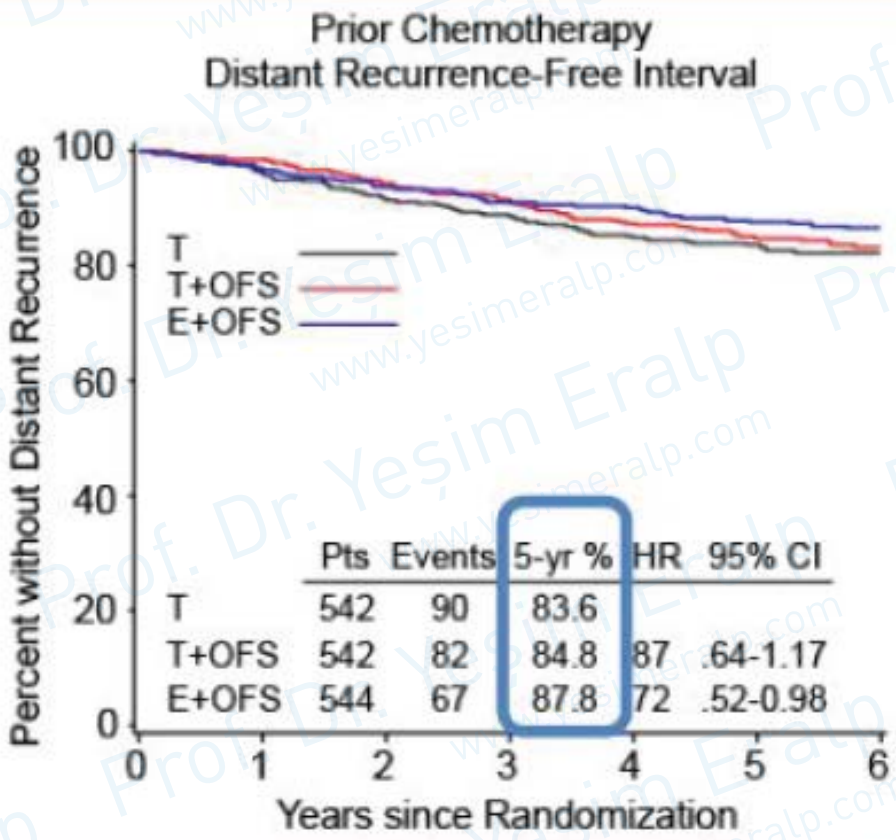
SOFT: DFS



Francis, N Engl J Med 2014

SOFT:
KT sonrası premenapozal hastalarda yarar

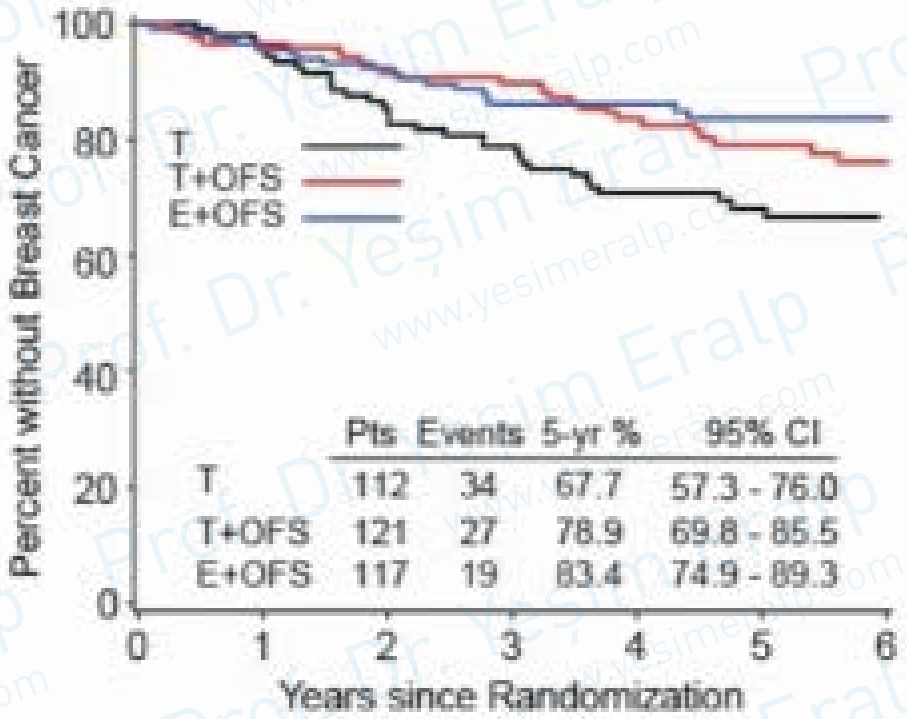




T+OFS v T: Absolute improvement in 5-yr BCFI of 4.5%

E+OFS v T: Absolute improvement in 5-yr BCFI of 7.7% and 5-yr DRFI of 4.2%

SOFT: 35 yaş altı hastalarda yarar



	Pts	Events	5-yr %	95% CI
T	112	34	67.7	57.3 - 76.0
T+OFS	121	27	78.9	69.8 - 85.5
E+OFS	117	19	83.4	74.9 - 89.3

- **350 patients (11.5%) under age 35**
- **94% received chemotherapy in this age group**

Francis et al, N Engl J Med, 2014

Premenapozal Hastada Adjuvan Tedavi Seçenekleri

- TMX 5-10 yıl
- TMX 5 yıl + AI 3-5 yıl (MA 17)
- OS + TMX / EXE

- Henüz uzun dönem takip oluşmadı
- OS farkı gösterilemedi
- Farklı toksisite profili ve “drop-out”
  - Endokrin
  - Osteoporoz
  - Kardiyak
  - Psikolojik
- Yarar-zarar dengesi iyi gözetilerek karar verilmeli

HR Pozitif Premenapoze Hastalarda Adjuvan Endokrin Tedavi :

Düşük Risk

Küçük tm çapı
Nod negatif
Grad 1
Yaş >40 (?)

TMX 5 yıl
10 yıl ?

Orta Risk

Düşük gradlı ve;
Daha büyük tm çapı
Veya
Nod Pozitif

KT + OS + TMX / EXE ?
OS + ET

Yüksek Risk

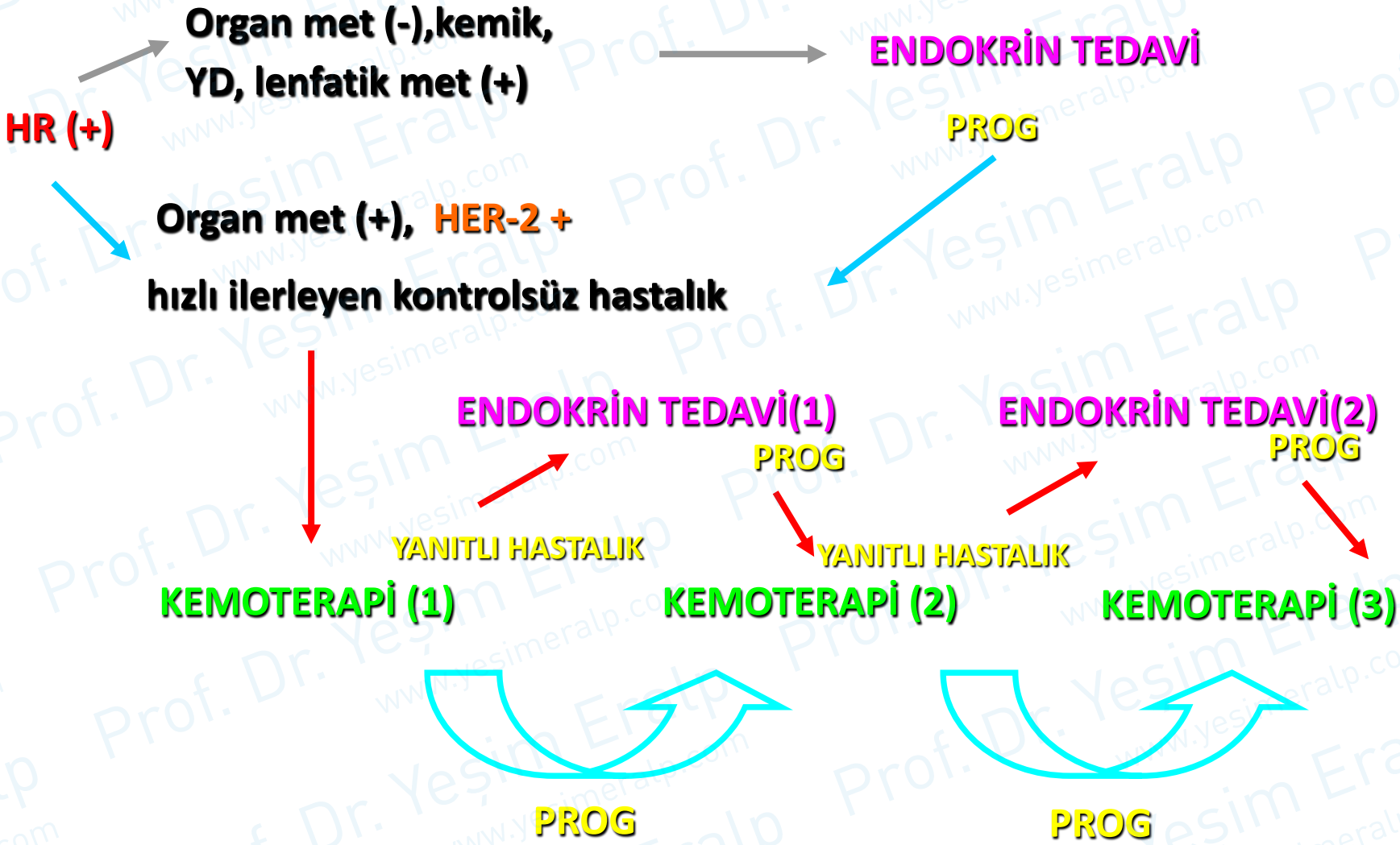
Büyük tm çapı
Nod Pozitif
Çoklu nodal tutulum
Grad 3
Yaş <35

KT + OS + EXE

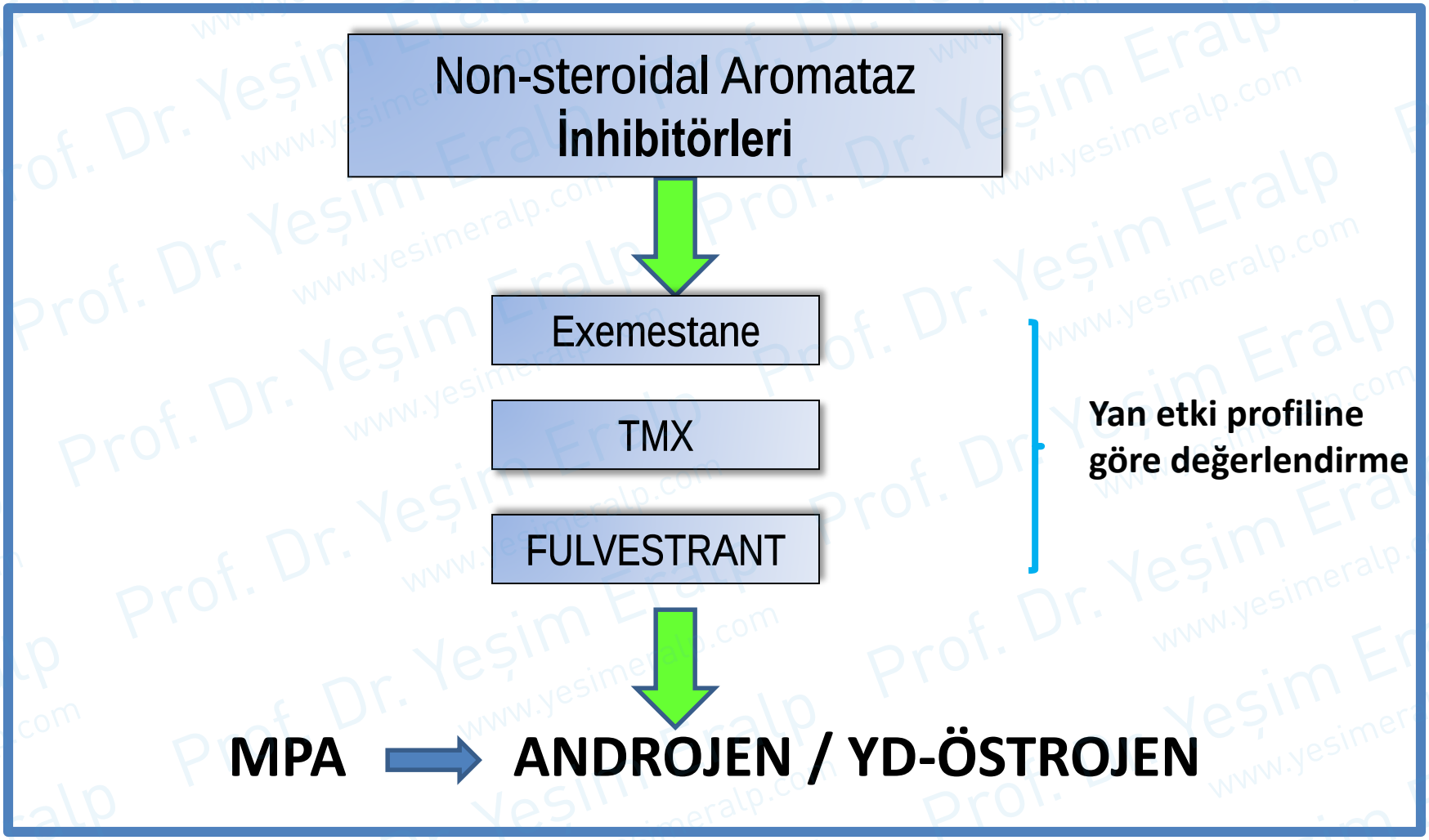
5-10. yıllar arası uzatılmış TMX/AI

METASTATİK HASTALIK

TEDAVİ ALGORİTMASI

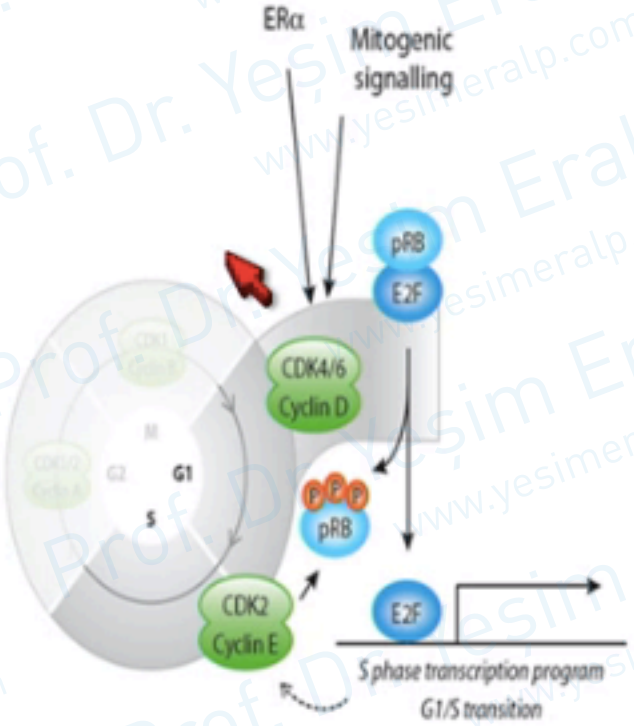


Post-menapozal ER (+), HER 2 (-) Hastada HT seçenekleri: 2011



CDK4/6 in Breast Cancer

- Resistance to endocrine therapy presents a major clinical challenge
- The growth of HR+ breast cancer is dependent on cyclin D1, a direct transcriptional target of ER.
- Cyclin D1 activates CDK 4/6 resulting in G1-S phase transition and entry into the cell cycle.[1]



CDK=cyclin-dependent kinase; ER=estrogen receptor; HR+=hormone receptor-positive;

1. Asghar U, et al. *Nat Rev Drug Discov*. 2015;14:130-46.
2. Thangavel C, et al. *Endocr Relat Cancer*. 2011;18:333-45.

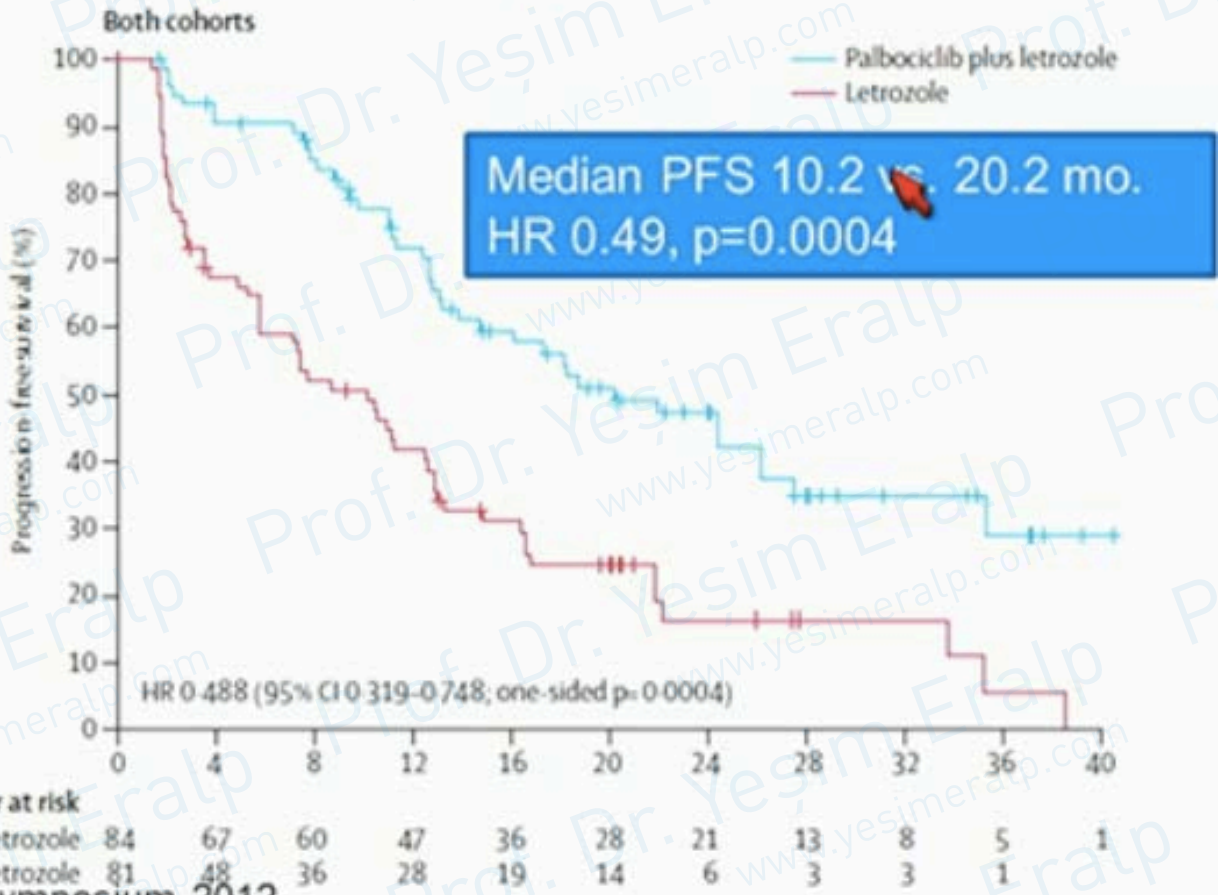
PALOMA-1: Randomized open-label phase II trial

Letrozole plus Palbociclib

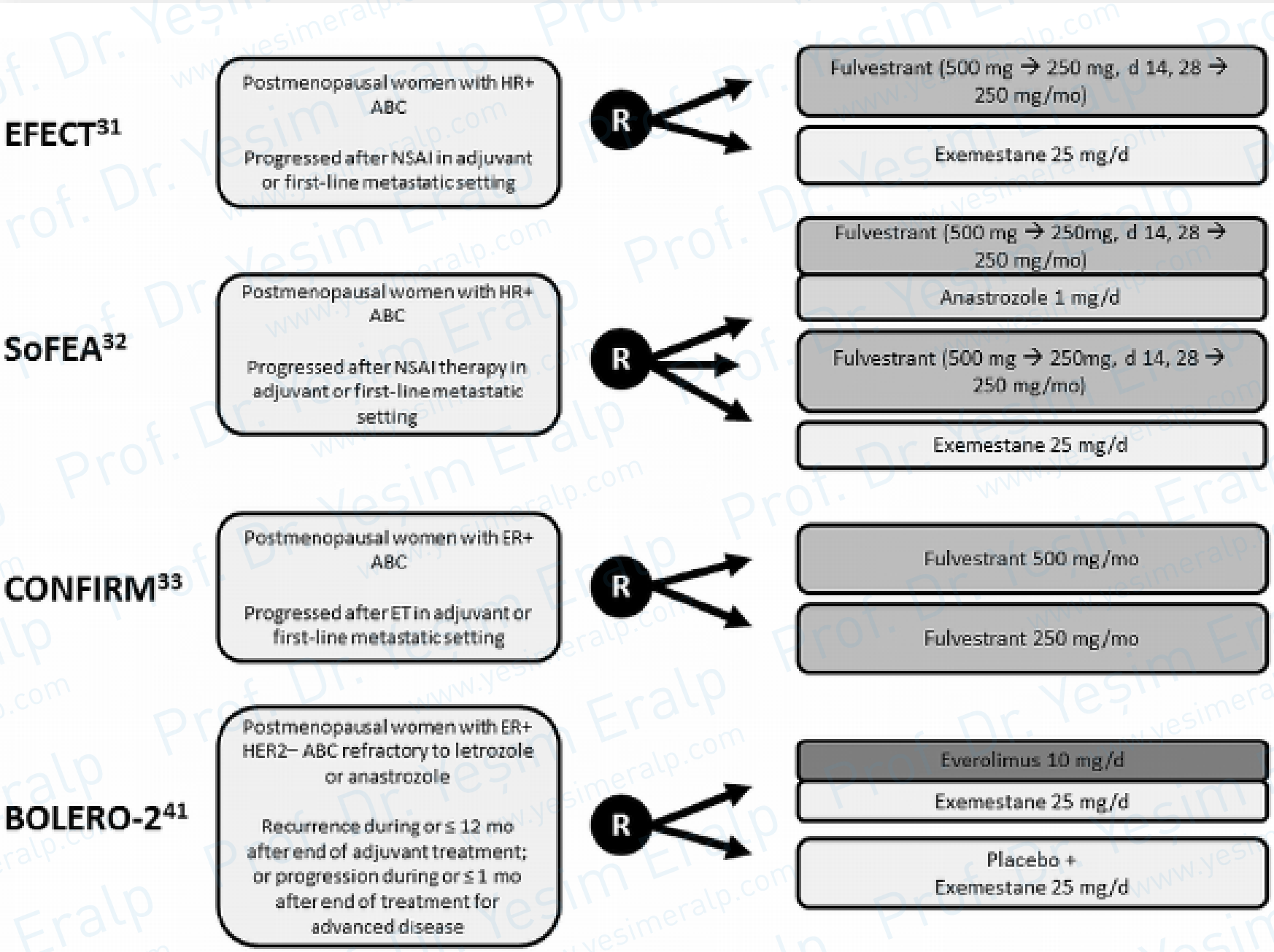
R

Letrozole

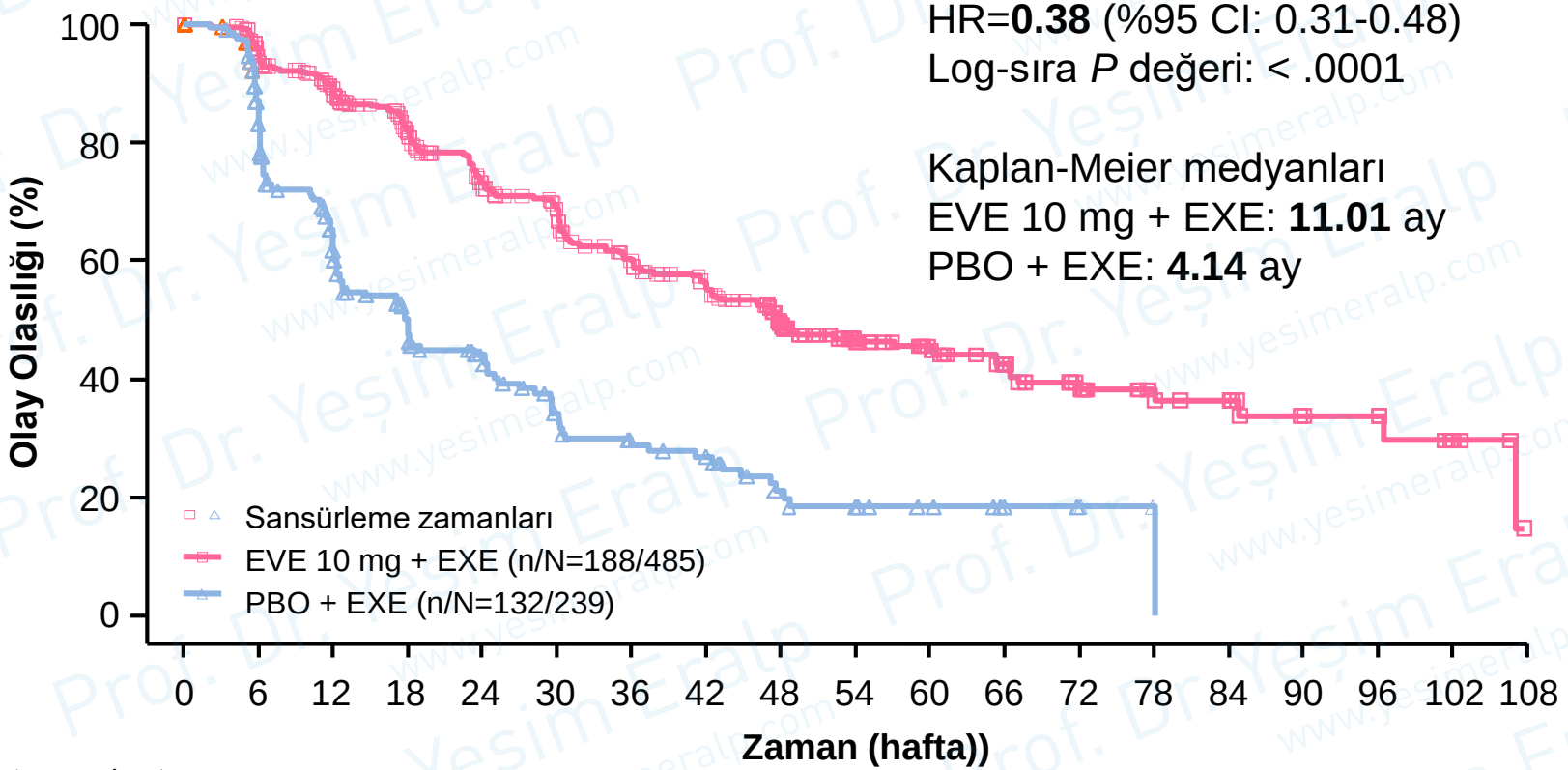
- HR+, HER2– ABC



Finn et al. San Antonio Breast Cancer Symposium, 2012
Finn et al. AACR, 2014; Finn et al. Lancet Oncol, 2015


EFECT[31]
Postmenopausal women with HR+ ABC
Progressed after NSAI in adjuvant or first-line metastatic setting
R
Fulvestrant (500 mg → 250 mg, d 14, 28 → 250 mg/mo)
Exemestane 25 mg/d
SoFEA[32]
Postmenopausal women with HR+ ABC
Progressed after NSAI therapy in adjuvant or first-line metastatic setting
R
Fulvestrant (500 mg → 250mg, d 14, 28 → 250 mg/mo)
Anastrozole 1 mg/d
Fulvestrant (500 mg → 250mg, d 14, 28 → 250 mg/mo)
Exemestane 25 mg/d
CONFIRM[33]
Postmenopausal women with ER+ ABC
Progressed after ET in adjuvant or first-line metastatic setting
R
Fulvestrant 500 mg/mo
Fulvestrant 250 mg/mo
BOLERO-2[41]
Postmenopausal women with ER+ HER2– ABC refractory to letrozole or anastrozole
Recurrence during or ≤ 12 mo after end of adjuvant treatment; or progression during or ≤ 1 mo after end of treatment for advanced disease
R
Everolimus 10 mg/d
Exemestane 25 mg/d
Placebo + Exemestane 25 mg/d

BOLERO-2: PFS (18-Aylık Takip, Merkezi)



Halen risk taşıyan hasta sayısı

EVE 10 mg + EXE	485	427	359	292	239	211	166	140	108	77	62	48	32	21	18	11	10	5	0
PBO + EXE	239	179	114	76	56	39	31	27	16	13	9	6	4	1	0	0	0	0	0

- **Steroidal aromataz inhibitörleri**
  - Exemestan

- **SERD**
  - Fulvestrant

- **EFECT**
- **SOFEA**
- **CONFIRM**
- **BOLERO 2**

→ **EXE =FUL (500/250)**

→ **FUL 500 > FUL 250**

→ **EXE + EVE > EXE**

Deleo et al, S1-4, SABCS 2012 and J Clin Oncol. 2010 Oct 20;28(30):4594-600.

J Clin Oncol 26:1664-1670. © 2008

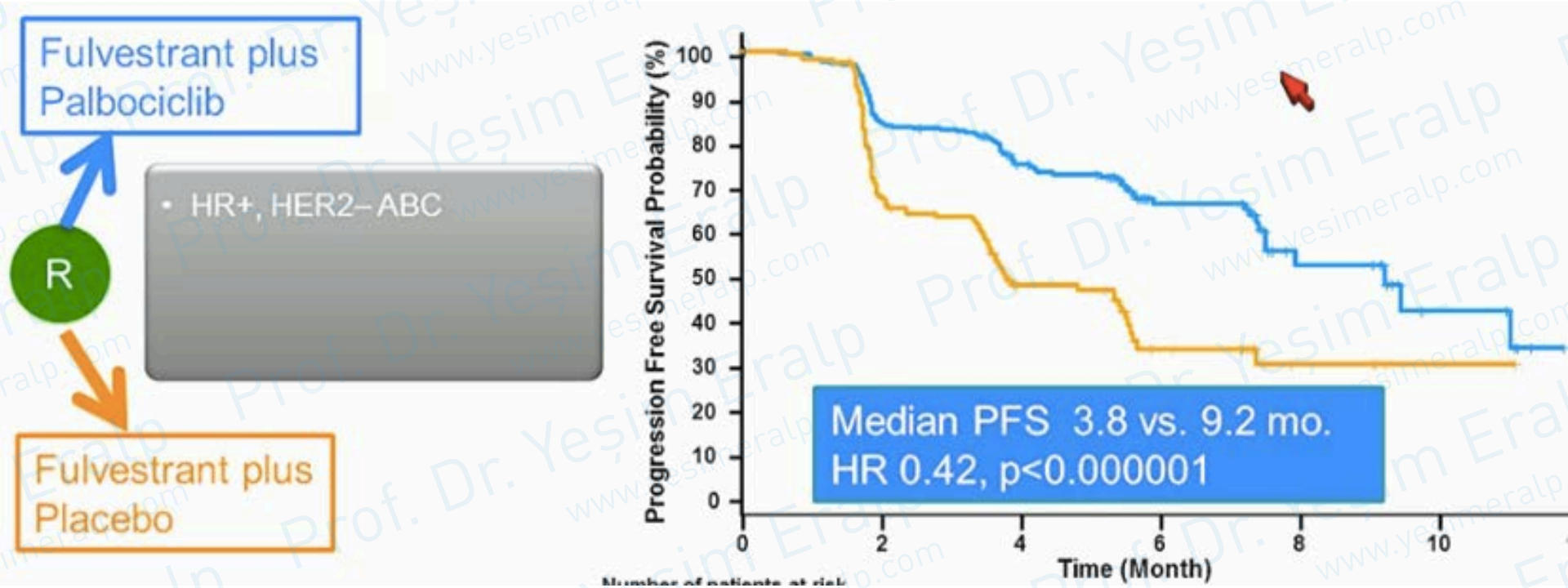
	EFECT	SOFEA	CONFIRM	BOLERO 2
ENDOKRİN DİRENÇLİ	≤6 ay adj NSAI sonrası 1. Seçim NSAI 6 ay içinde P	≤12 ay adj ET sonrası 1. Seçim NSAI 6 ay içinde	≤24 ay adj ET içinde 1. Seçim NSAI 6 ay içinde P	≤24 ay adj ET içinde 1. Seçim NSAI 6 ay içinde P

BAŞLANGIÇTA:
≈%30 hasta primer endokrin dirençli
Diğerleri ilk seçimden sonra sekonder direnç geliştirir

Reference (study name)	*Regimen*	*Prior ET*	*Sensitivity to prior ET*		*Progression-free survival*	
			Definition	*Proportion (%)*	*Prior sensitivity*	*Prior resistance*
Fulvestrant						
Chia *et al.*, 2008[31] (EFECT)	Fulvestrant 250 mg vs. exemestane	NSAI	≥6 Months before recurrence or progression	61–64	HR: 0.90 (95% CI: 0.73 to 1.08)[a] (TTP, *n*=434)	HR: 1.01 (95% CI: 0.79 to 1.35)[a] (TTP, *n*=259)
Johnston *et al.*, 2012[32] (SoFEA)	Fulvestrant 250 mg vs. exemestane	NSAI	>1 Year before progression	1–2 Years: 26–35 >2 Years: 27–31	HR: 0.75 (95% CI: 0.54 to 1.06) (1–2 years, *n*=149)[b] HR: 1.06 (95% CI: 0.75 to 1.50) (>2 years, *n*=139)[b]	HR: 1.27 (95% CI: 0.84 to 1.91)[c] (*n*=100)
Di Leo *et al.*, 2010[33] (CONFIRM)	Fulvestrant 500 mg vs. fulvestrant 250 mg	Tamoxifen or AI	>2 Years before recurrence ≥6 Months before progression	63–67	HR: 0.86 (95% CI: 0.72 to 1.05)[a]	HR: 0.72 (95% CI: 0.57 to 0.93)[a,d]
Everolimus						
Baselga *et al.*, 2012[41] (BOLERO-2)	Everolimus plus exemestane vs. exemestane	NSAI	≥2 Years before recurrence ≥6 Months before progression	84	HR: 0.43 (95% CI: 0.34 to 0.54)[a] (*n*=610)	HR: 0.49 (95% CI: 0.30 to 0.81)[a] (*n*=114)

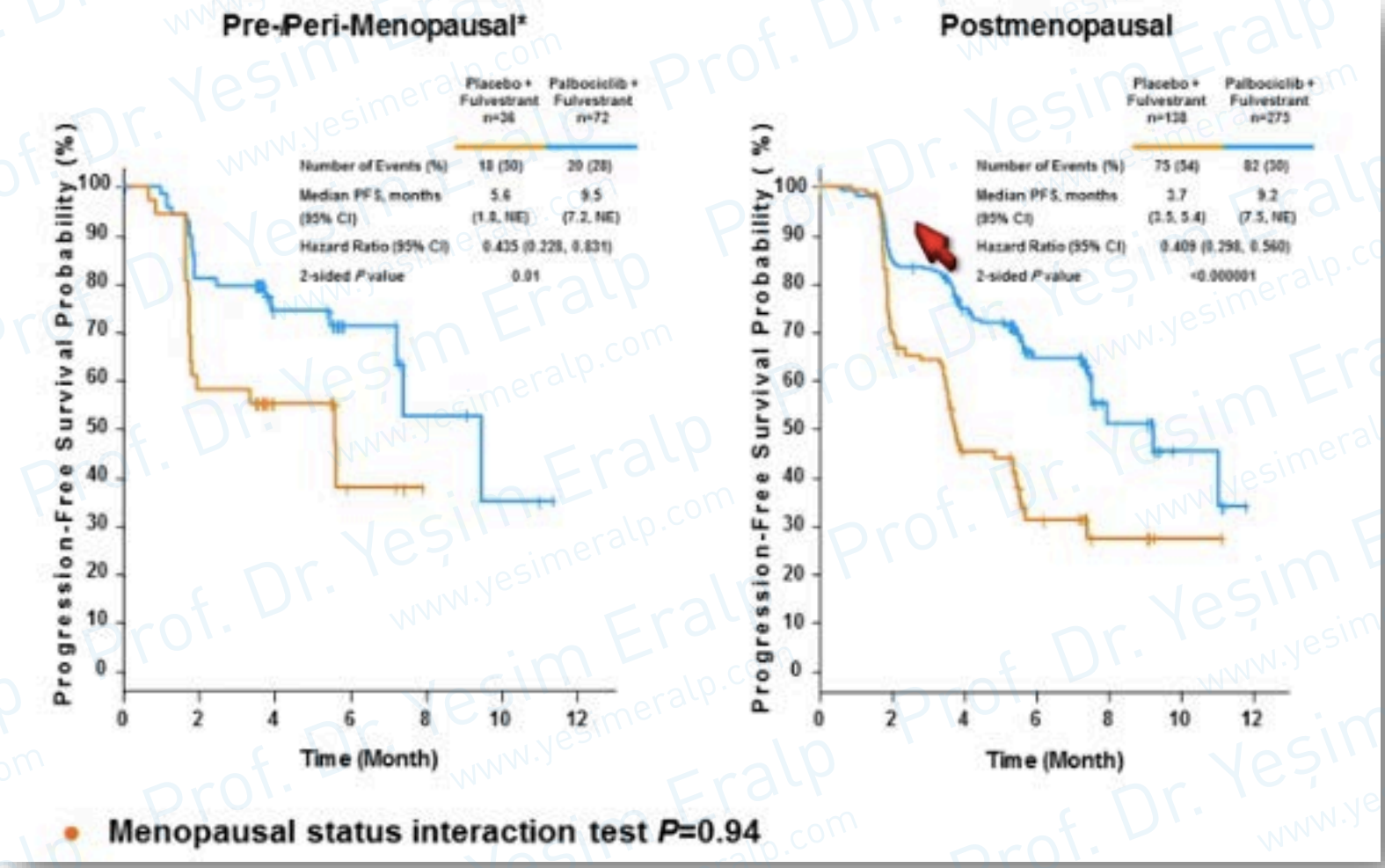
PALOMA 3: İkinci seçim ET-Faz III

%85 hasta daha önce AI uygulanmış;
%60 organ metastazı mevcut



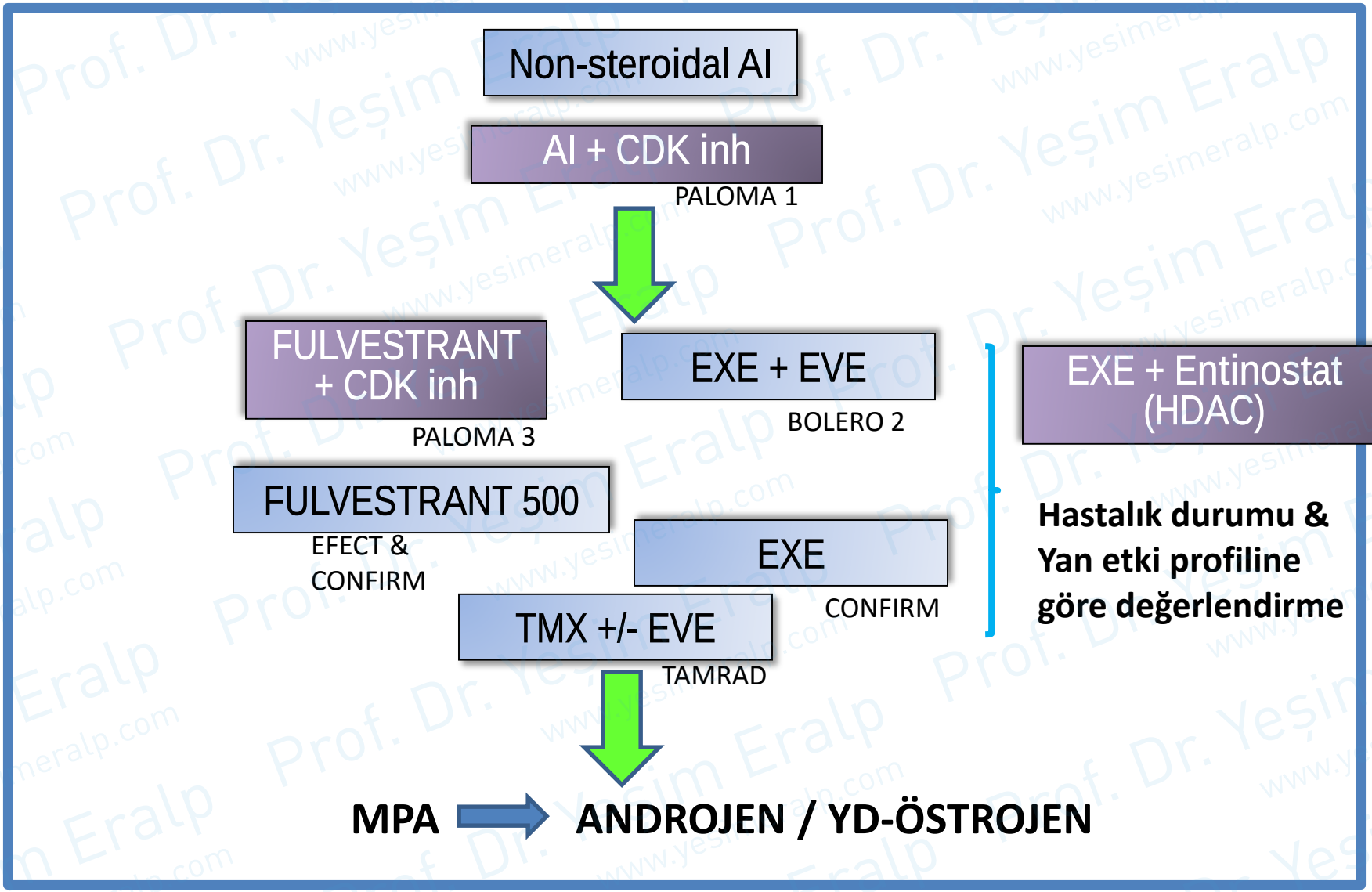
Turner, ASCO 2015

Menopoz Durumuna Göre PFS



Turner, ASCO 2015

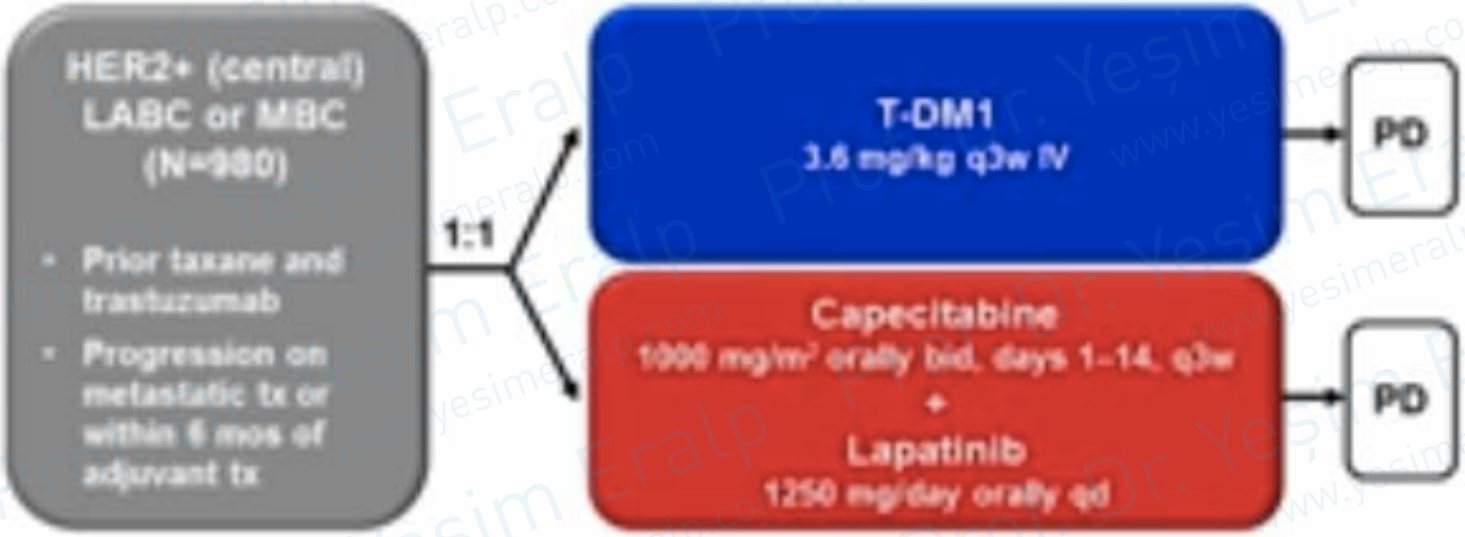
Post-menapozal ER (+), HER 2 (-) Hastada HT seçenekleri: 2015



*: endokrin duyarlı hastalık

HER 2 POZİTİF HASTALIK

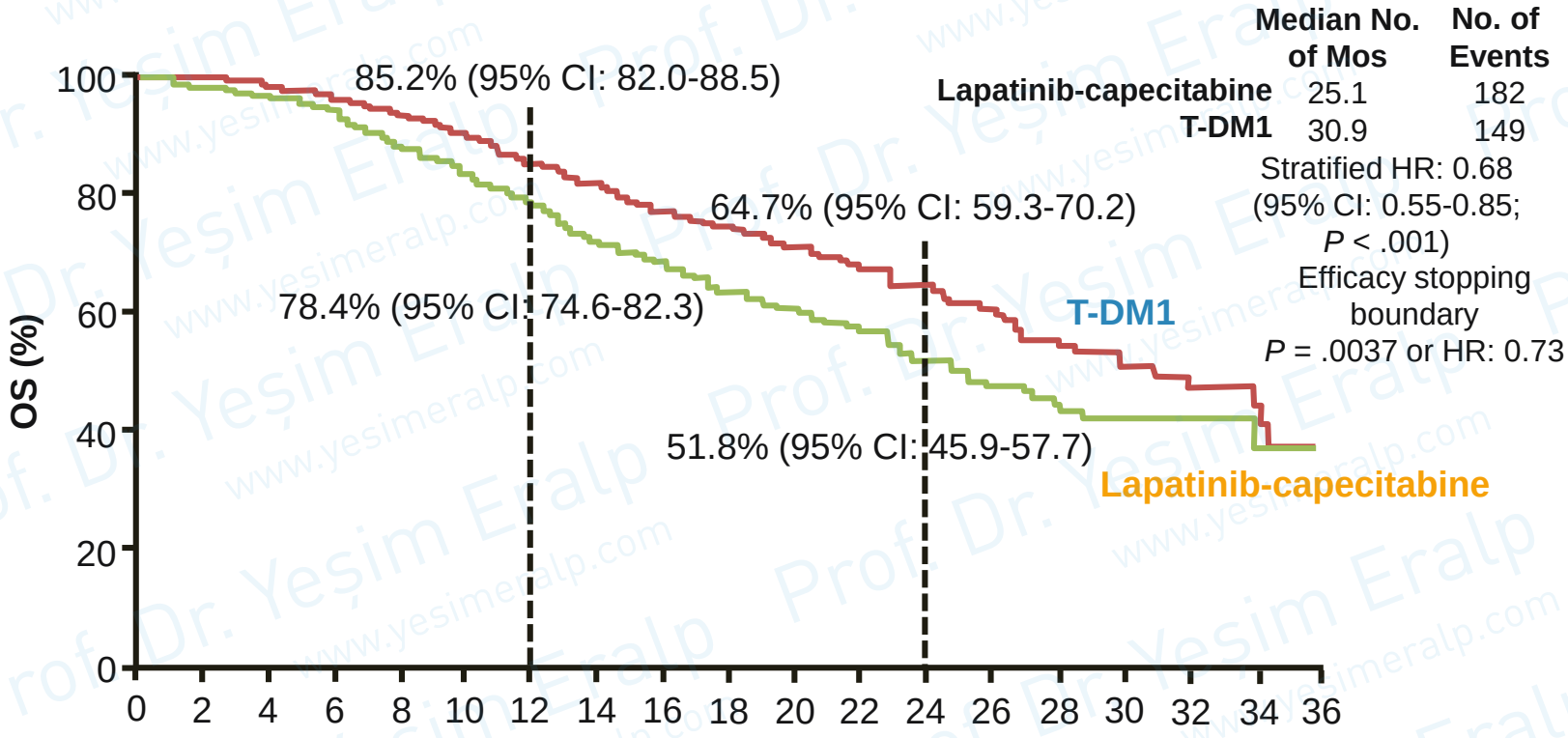
EMILIA: Faz III



- 991 hasta
- %16 hasta adjuvan trastuzumab sonrası 6 ay içinde progresyon

N Engl J Med 2012;367:1783-91.

Genel Sağkalım



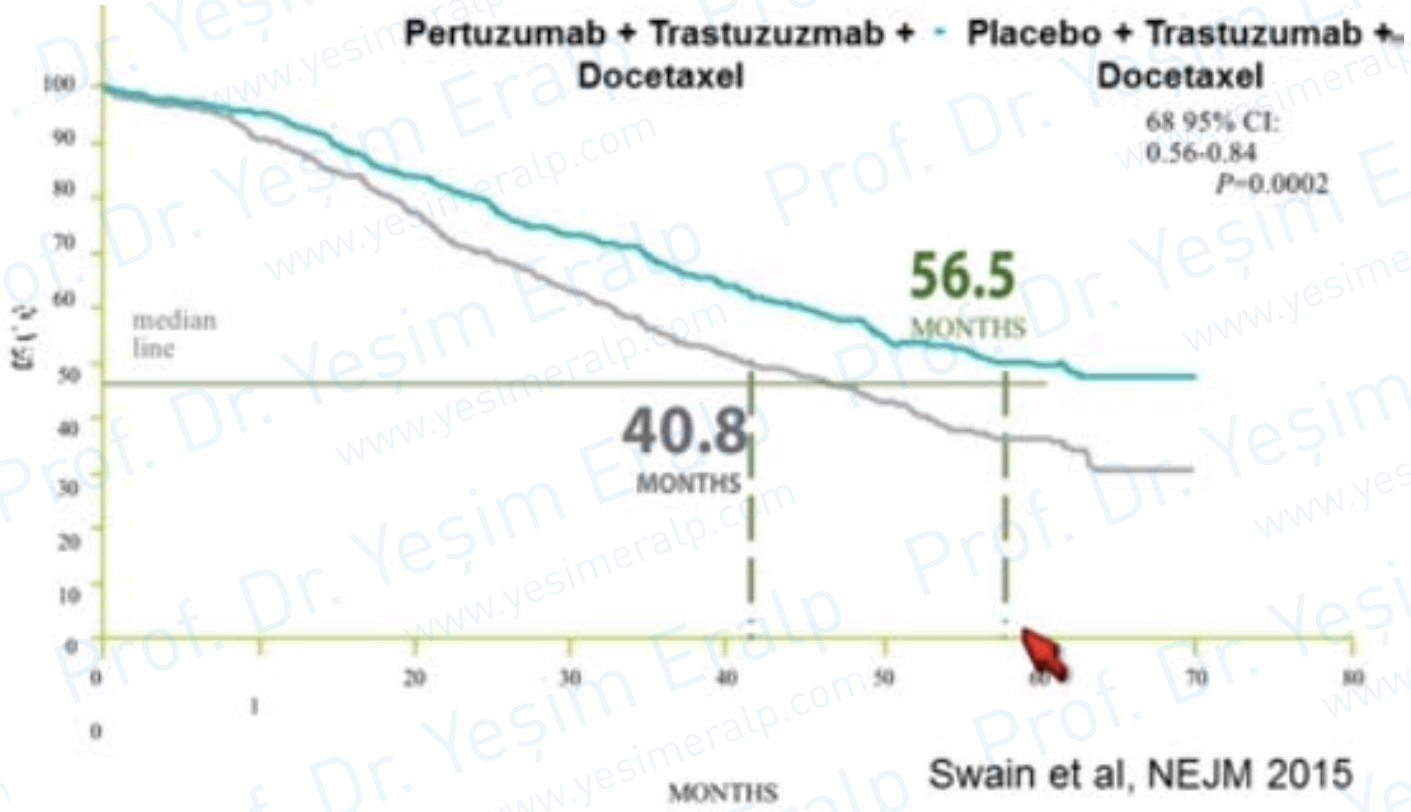
Pts at Risk, n																			
Lapatinib-capecitabine	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

Data cutoff July 31, 2012; median follow-up: 18.6 mos.

Verma S, et al. N Engl J Med. 2012;367:1783-1791.

CLEOPATRA-1. Seçim Tedavi Faz III

N:808 hasta; %80 organ metastazı
%10 hasta adjuvan Trastuzumab kullanmış;12 ay sonrasında progresyon olanlar dahil edilmiş



MARIANNE: 1. Seçim Faz III

- HER2-positive (central) LABC[a] or MBC
- No prior chemotherapy for LABC/MBC
- >6 months from prior (neo)adjuvant vinca alkaloid or taxane chemotherapy

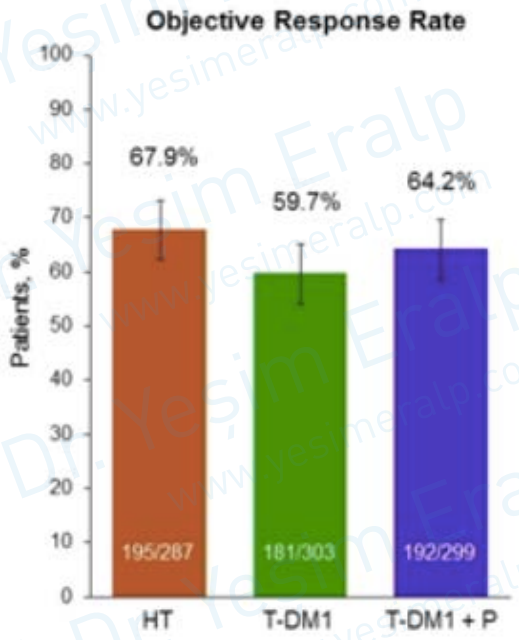
N = 1095

Trastuzumab + docetaxel
(8 mg/kg LD then 6 mg/kg + 100 or 75 mg/m² q3w) **OR**
Trastuzumab + paclitaxel
(4 mg/kg LD then 2 mg/kg + 80 mg/m² qw)

T-DM1 + placebo[b]
(3.6mg/kg + 840 mg LD then 420 mg q3w)

T-DM1 + pertuzumab
(3.6mg/kg + 840 mg LD then 420 mg q3w)

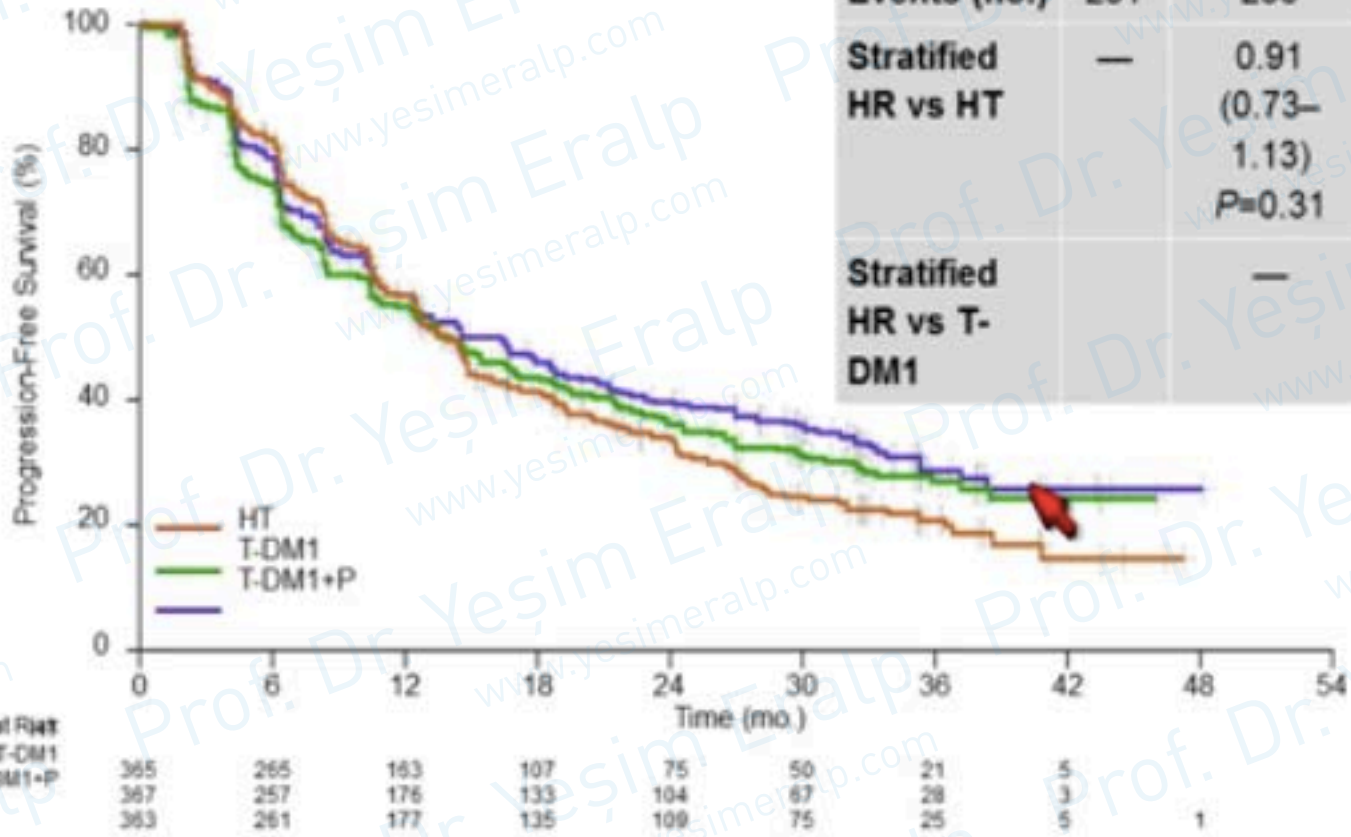
- **Primary end point**: PFS by independent review facility (IRF), non-inferiority a
- **Key secondary end points**: OS, PFS by investigator, ORR, Safety, Patient-re



Ellis P, ASCO 2015

Progression-Free Survival by IRF

	HT	T-DM1	T-DM1+P
Median PFS (mo.)	13.7	14.1	15.2
Events (no.)	231	236	217
Stratified HR vs HT	—	0.91 (0.73–1.13) *P*=0.31	0.87 (0.69–1.08) *P*=0.14
Stratified HR vs T-DM1		—	0.91 (0.73–1.13)



HER 2 (+) Hastada Hastalık Yönetimi: 2015

HR (-) / (+)

Trastuzumab +

Pertuzumab+

Taksan

CLEOPATRA

↓

TDM-1

EMILIA

↓

Kullanılmadıysa Pertuzumab + Taksan veya TDM-1

Lapatinib+ Kapesitabin

Lapatinib+Trastuzumab

Trastuzumab+VNR / Gem

HR (+)

Lapatinib+Letrozol

Trastuzumab + TMX / AI

HER2 + Hastalıkta ET ile GS avantajı gösterilemiştir
Hastalık durumu &
Yan etki profiline göre değerlendirme !

↓

HR (-) hastalık yönetimi

pCR ORANINI ARTTIRMA ÇABALARI….

NEOADJUVAN TEDAVİ

- Sitotoksik ajanlar
  - TN hastalıkta Carboplatin
- Biyolojik ajanlar
  - Her-2
    - Pertuzumab
  - Anjiogenez
    - Bevacizumab

TNBC & Carboplatin: pCR oranları

	Çalışma kolları	n	pCR (ypT0/is N0) %
CALGB 40603	PAC-ddAC	212	41
	PAC+CARBO-ddAC	221	54*
GEPAR-SIXTO	PAC-LIP DOX+ Bev	157	37.9
	PAC-LIPDOX-CARBO + Bev	158	58.7*

Prediction of Carboplatin Effect on pCR

%	PM (N=146)	PMCb (N=149)	OR	*p*
No risk factor	34.5	46.0	1.61	*0.13*
	Δ 11.5			
Family history of BC/OC without alteration	30.8	57.5	3.04	*0.02*
	Δ 26.7			
g*BRCA/RAD* alteration with/without family history	43.5	66.7	2.60	*0.13*
	Δ 23.2			

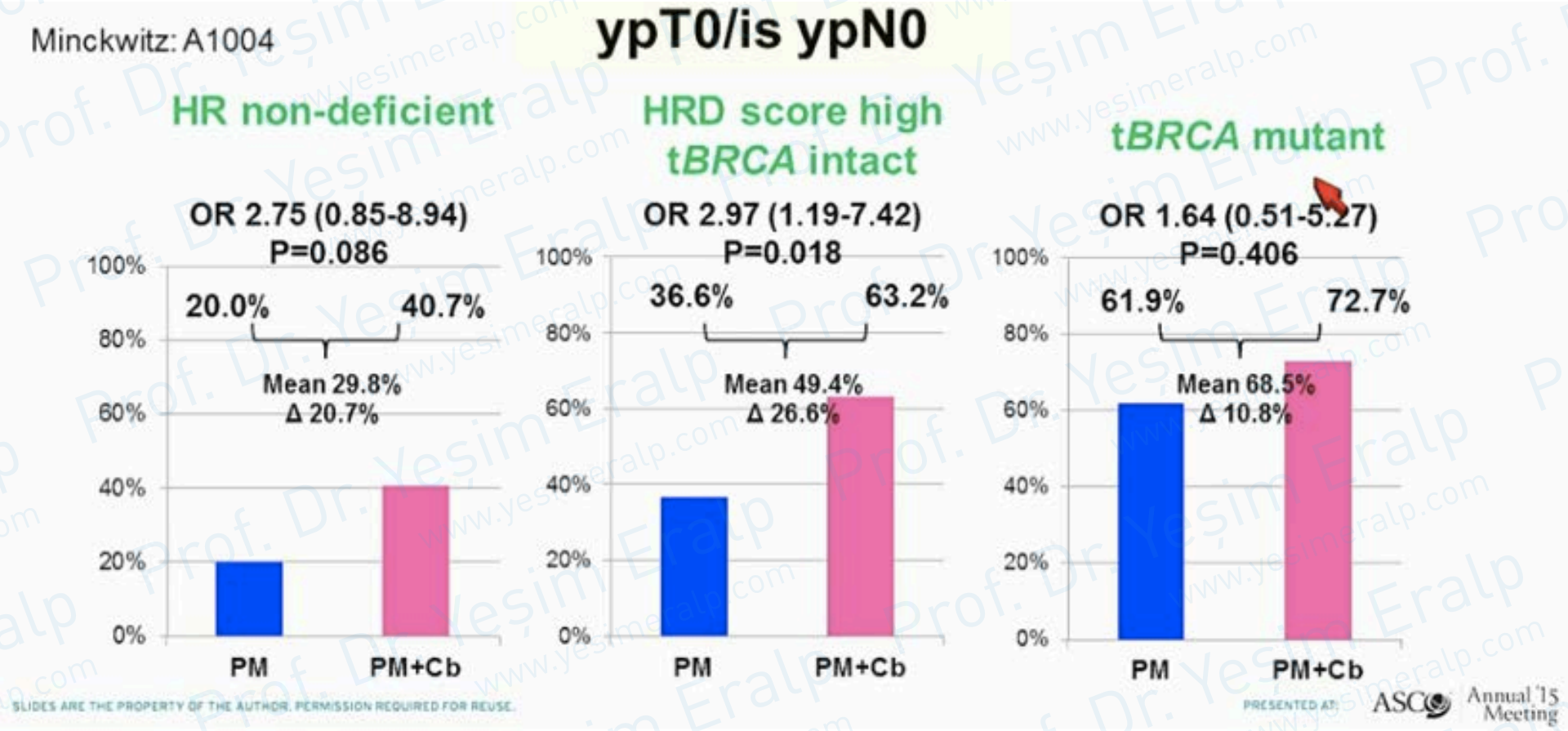
AGO-B BREAST STUDY GROUP

ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

Presented at the 2014 ASCO Annual Meeting by Gunter von Minckwitz, M.D..
Presented data is the property of GBG and AGO-B.

GBG GERMAN BREAST GROUP

Triple Negatif Hastalıkta Carboplatin Yararı: Alt-grup Analizi



Triple Negatif Hastalıkta Carboplatin Yararı:

- Giderek artan sayıda çalışmada seçilmiş TN hastalıkta platin yararı mevcut
  - BRCAm & RAD51C
  - Kuvvetli aile hikayesi
  - HRD +

Riskli Hastalıkta Değerlendirilmeli

Background

NeoSphere: Study design and main results

TH (n=107)
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)

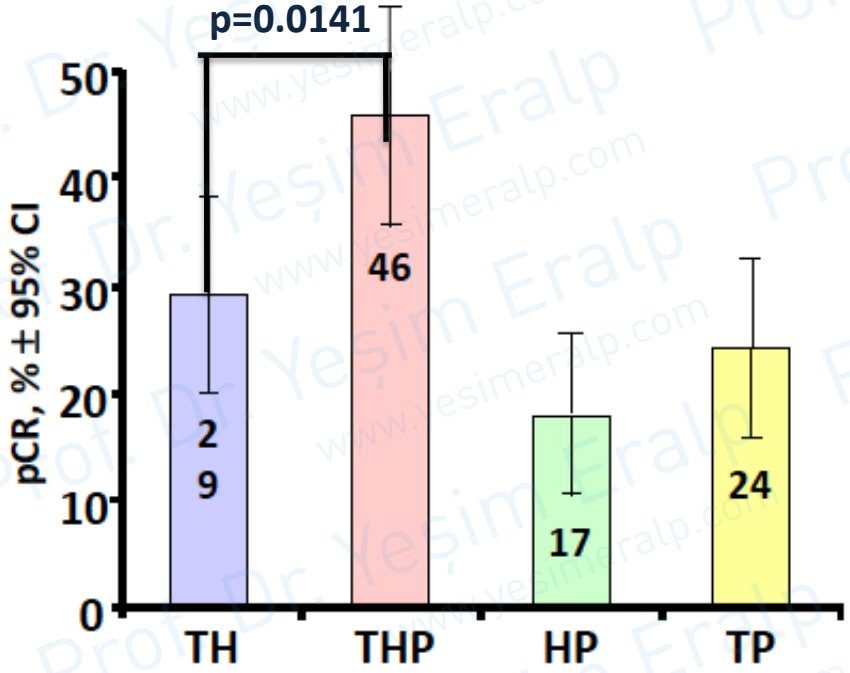
THP (n=107)
docetaxel (75→100 mg/m²)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

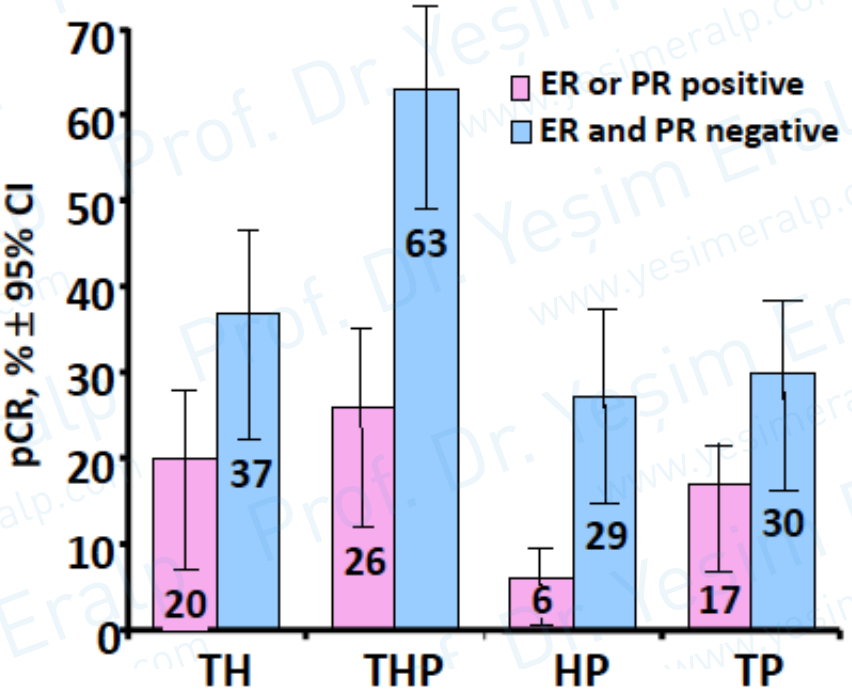
HP (n=107)
trastuzumab (8→6 mg/kg)
pertuzumab (840→420 mg)

TP (n=96)
docetaxel (75→100 mg/m²)
pertuzumab (840→420 mg)

SURGERY

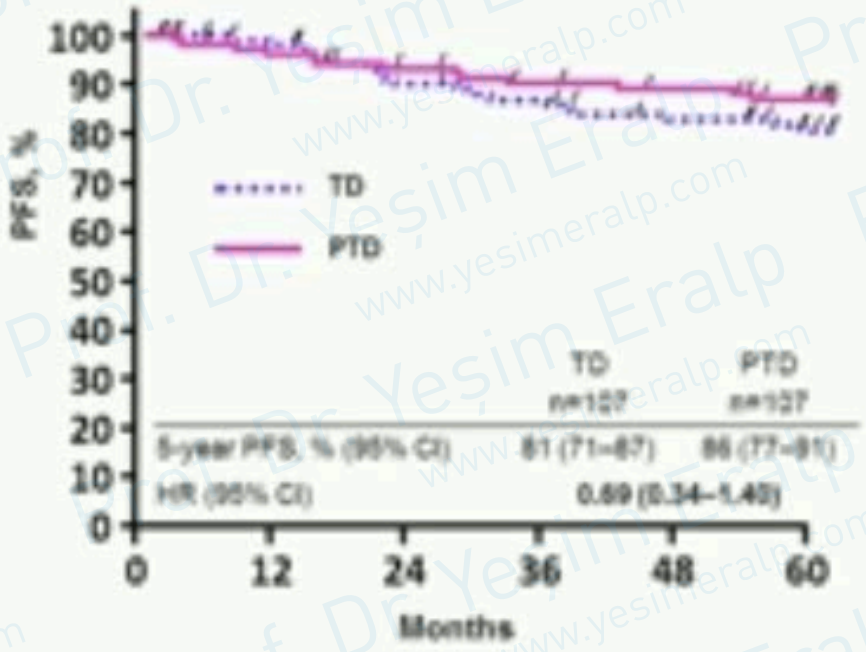
Study dosing: q3w x 4

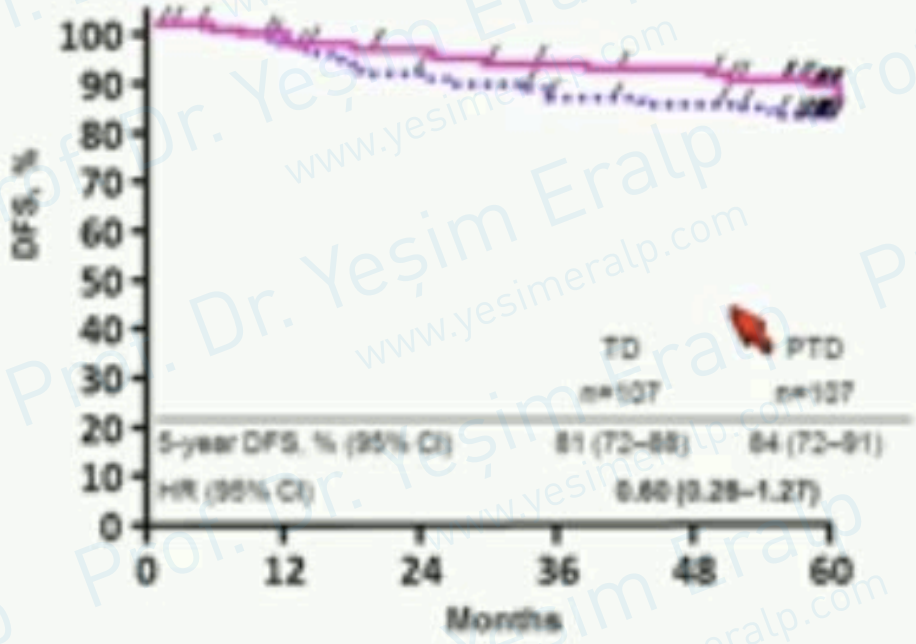




Gianni L, et al. Lancet Oncol 2011 DOI:10.1016/S1470-2045(11)70336-9

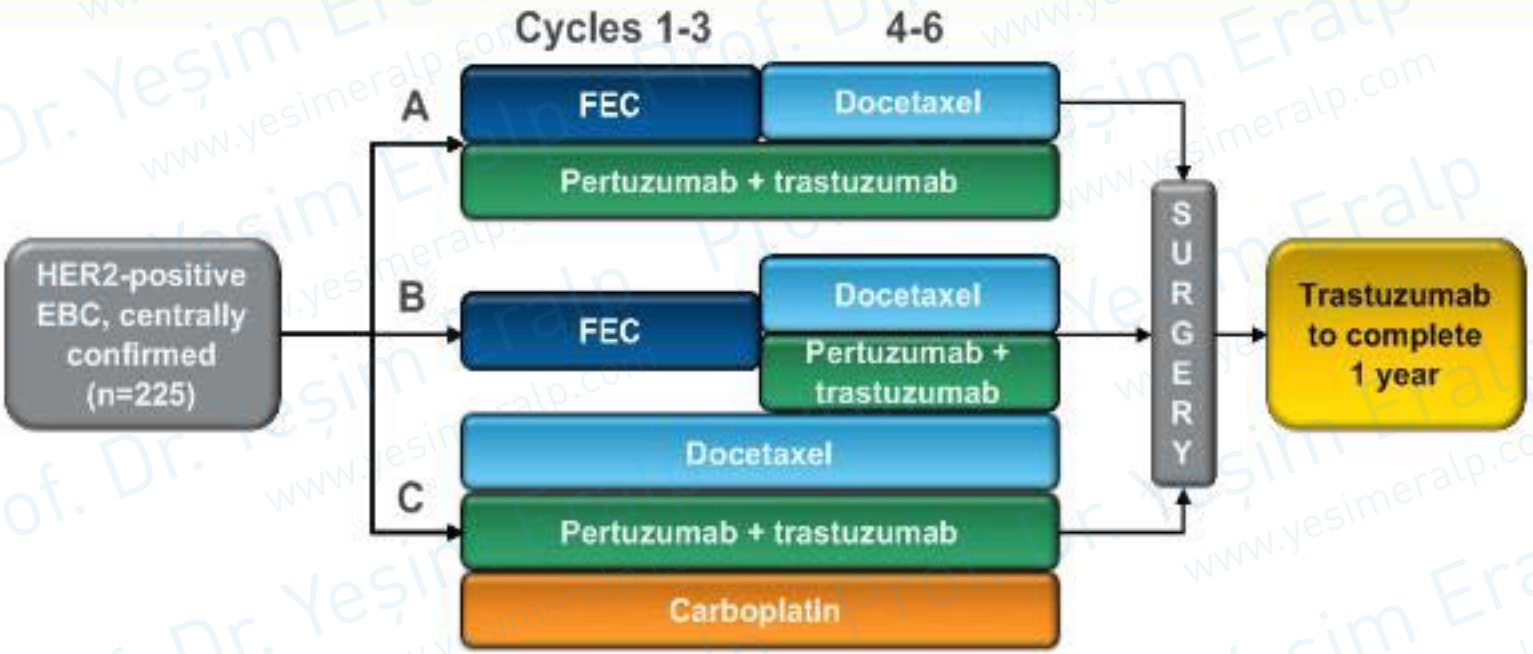
PFS and DFS for PTD vs TD, ITT population





Trial is underpowered for this analysis but results are suggestive of a benefit from the addition of pertuzumab to docetaxel + trastuzumab

TRYPHAENA* Phase II Neoadjuvant Trastuzumab and Pertuzumab in HER2-Positive EBC: Study Design

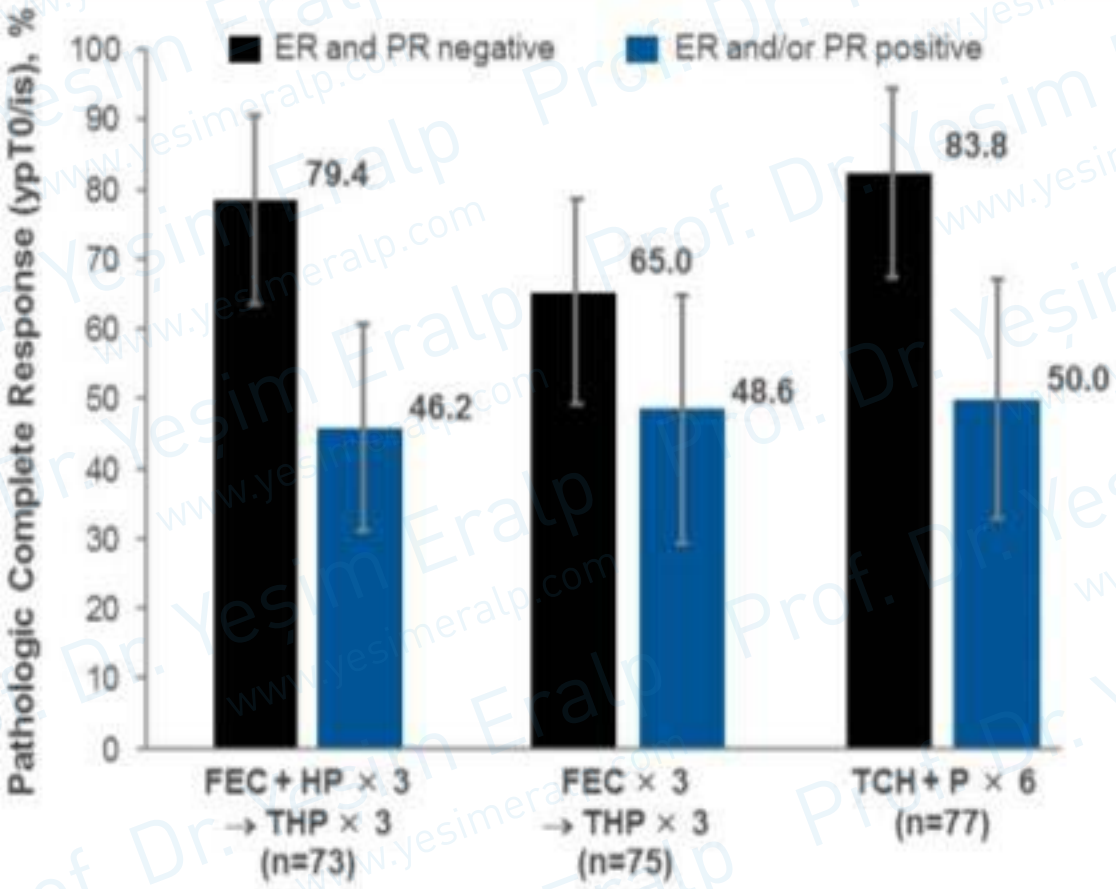


- All 3 arms were experimental
- Study dosing q3w:
  - FEC: 500 mg/m^2, 100 mg/m^2, 600 mg/m^2
  - Carboplatin: AUC 6
  - Trastuzumab: 8 mg/kg loading dose, 6 mg/kg maintenance
  - Pertuzumab: 840 mg loading dose, 420 mg maintenance
  - Docetaxel: 75 mg/m^2 (escalating to 100 mg/m^2 if tolerated, in Arms A and B only)
- Stratification:
  - Operable, locally advanced, and inflammatory breast cancer
  - Hormone receptor positivity

EBC=early-stage breast cancer; FEC=5-fluorouracil, epirubicin, cyclophosphamide

Schneeweiss A, et al. Ann Oncol. 2013 May 22 [Epub ahead of print].

TRYPHAENA* Phase II Neoadjuvant Trastuzumab and Pertuzumab in HER2-Positive EBC: **Pathologic Complete Response by Hormone Receptor Status**



C=carboplatin; EBC=early-stage breast cancer; ER=estrogen receptor; FEC=5-fluorouracil, epirubicin, cyclophosphamide; H=trastuzumab; P=pertuzumab; PR=progesterone receptor; T=docetaxel

Schneeweiss A, et al. Ann Oncol. 2013 May 22 [Epub ahead of print].

*Genentech/Roche Sponsored Study

Acclerated FDA Approval

(Product Information Brochure)

- **Approved Regimens:** Pertuzumab … every 3 weeks for 3 to 6 cycles as part of one of the following … regimens ... :
  - ***4 preoperative cycles (of pertuzmab).. with trastuzumab and docetaxel*** followed by 3 postoperative cycles of … FEC.. in Study 2 (NeoSphere)
  - ***3 preoperative cycles of FEC alone followed by 3 preoperative cycles of pertuzumab in combination with docetaxel and trastuzumab*** …. in Study 3 (Tryphaena).
  - ***6 preoperative cycles … with …TCH*** … Study 3 (Tryphaena)
  - Following surgery, .. Continue … trastuzumab to complete 1 year of treatment. ….***insufficient evidence to recommend continued use of pertuzumab for greater than 6 cycles***…
- **Limitations of Use:**
  - The safety … as part of a doxorubicin-containing regimen has not been established….

2014 yılına girerken neoadjuvan KT: Standart nedir ? Ne değişti?

- Her-2 + hastalıkta → KT eş-zamanlı Trastuzumab
  - Sağkalım pCR ile ilişkili → hız onay prosedürü
  - Dual blokaj pCR'ı arttırır; EFS ve GS avantajı sağlayabilir → pertuzumab+trastuzumab
- TN hastalık:
  - herkese Carboplatin eklenmeli mi?
    - (GEPARSIXTO & CALGB 40603)
    - Seçilmiş hastada neden olmasın? (doz youğunluğu !!)
  - Bevacizumab: TN hastalıkta artan pCR
    - CALGB 40603
    - Sağkalım yararı açısından konfirmasyon gerekli