HR+ Metastatik Meme Kanseri Tedavisinde Yeni Yaklaşımlar

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Ajanda

1. Giriş
2. MMK HT Tedavi
3. MMK HT Direnç/ CDK İnhibitörleri

Meme Kanseri Önemli Gelişmeler

Erken Evre

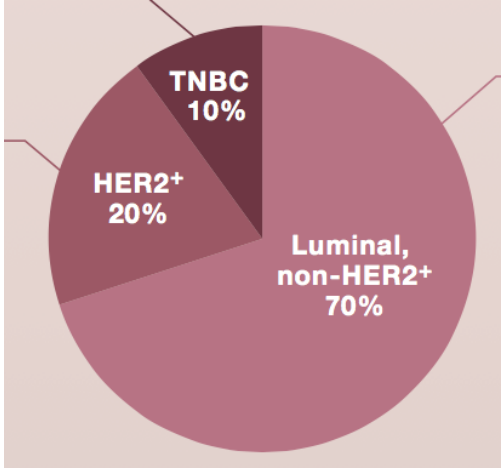
- Cerrahi yaklaşımlar
- Genomik Profilleme
- Anti-HER2 tedaviler

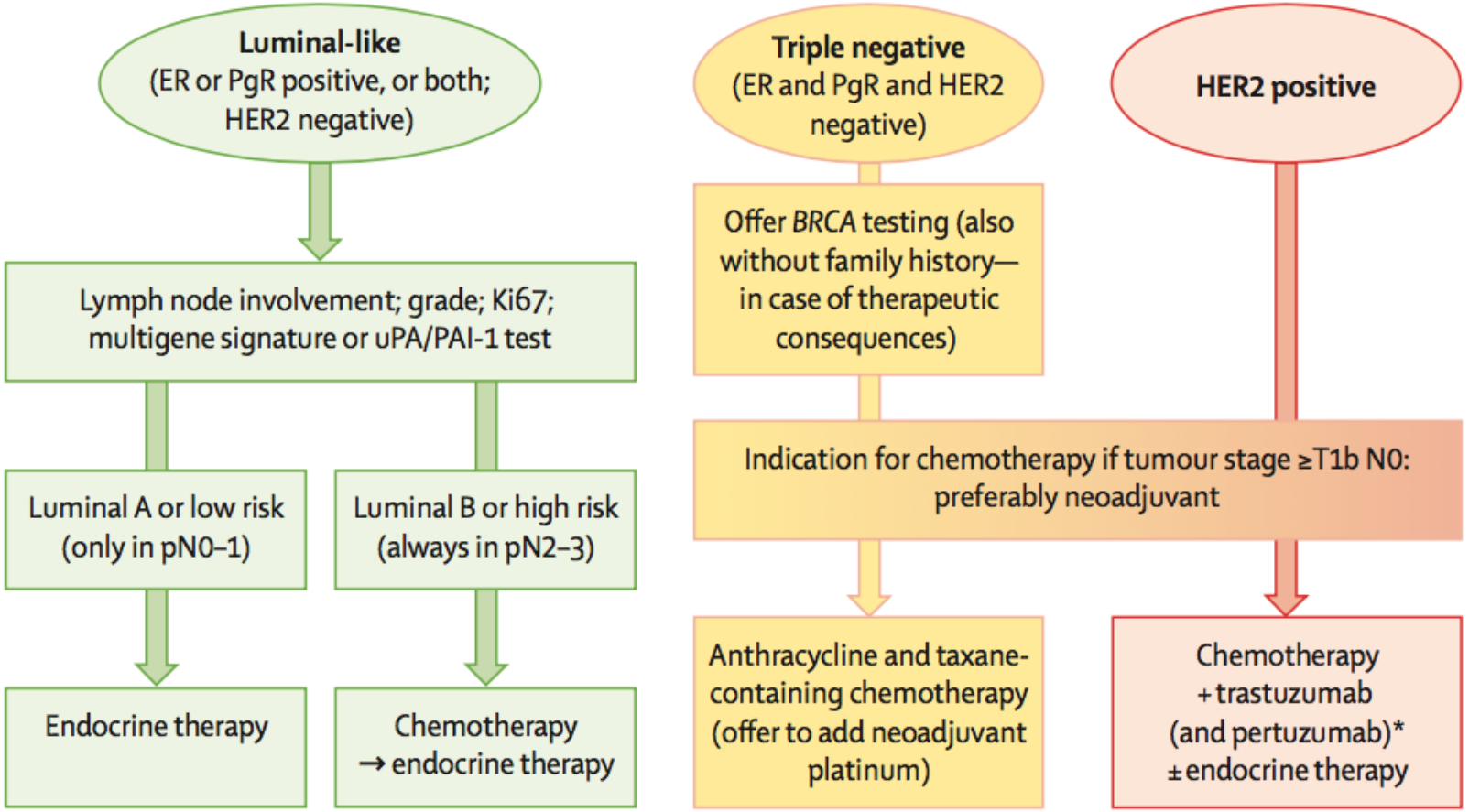
İleri Evre

- CDK4/6 inhibisyonu
- PARP İnhibitörleri
- Anti-HER2 tedaviler

Biyobenzerler

Meme Kanseri Alttipleri





Meme Kanseri & Sağkalım

Subtype	Stage	5 year OS (%)	10 year OS (%)
*DCIS	0	99	98
Luminal (non-HER2+)	I	98	95
	II	91	81
	III	72	54
	IV	33	17
**HER2+	I	98	95
	II	92	86
	III	85	75
	IV	40	15
TNBC	I	93	90
	II	76	70
	III	45	37
	IV	15	11

Polyak 2012

Luminal Meme Kanseri

- ER (+) ve/veya PR (+)
- HER2(-)/(+)
- Adj ET Relatif relaps riskini %40 azaltıyor
- CDK4/6 aşırı ekspresyonu veya Siklin D1 amplifikasyonu sık
  - CDK4/ CDK6 (cyclin-dependent kinases)
  - mTOR inhibitör

Endocrine-Based Therapies for Breast Cancer

Year	Agent	Mechanism
1977	**SERMs** Tamoxifen Toremifene	Antagonizes ER in breast tissue
1990s	**AIs** Anastrozole Exemestane Letrozole	Inhibit estrogen production in postmenopausal women
2000s	**ERD** Fulvestrant	Impairs ER dimerization, increases ER degradation, and disrupts nuclear localization of ER
2010s	**Combinations** Exemestane/everolimus Letrozole/palbociclib Fulvestrant/palbociclib	Blockade of estrogen signaling and prosurvival or cell cycle pathways

Lim E, et al. Oncology (Williston Park). 2012;26:688-694.
Croxtall JD, et al. Drugs. 2011;71:363-380.
Vidula N, et al. Clin Breast Cancer. 2016;16:8-17.
Mustonen MV, et al. World J Clin Oncol. 2014;5:393-405.

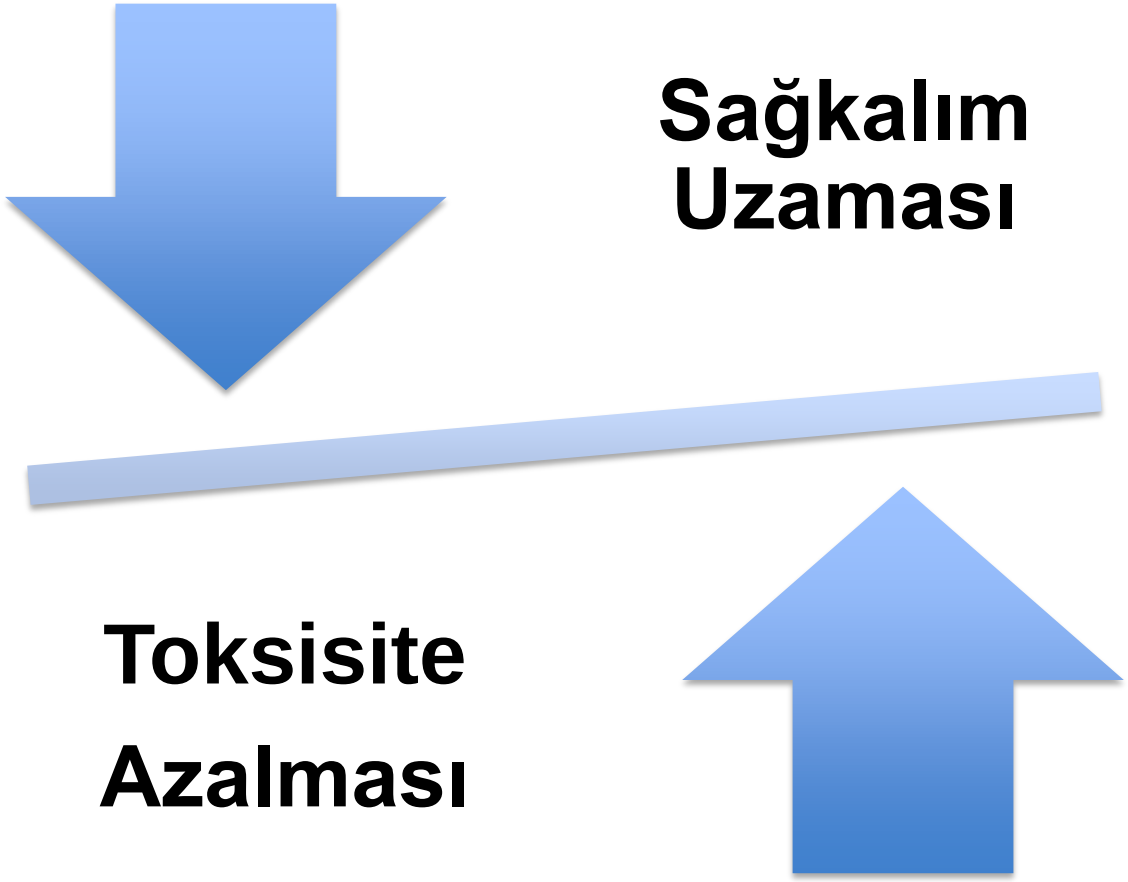
Slide credit: clinicaloptions.com

Metastatik Meme Kanseri (MMK)

İnkürabl

- MMK- Ortanca OS ~ 2-3 yıl
- MMK- 5 yıllık OS %25
- MMK- %77 hasta >50 yaş

MMK



Palyasyon

Olgu 1; 52y K

Cerrahiden konsulte ediliyor

- Cerrahi menapozal
- Özg: hipotiroidi, gastrit
- Sigara:(-) ilaç:(Euthyrox)
- Op:(1.5 yıl önce TAH BSO, tiroid op)
- Soyg: Ca öyküsü yok

Meme Kanseri Cerrahi & Adjuvan Tedavi

Temmuz 2012 Sol MRM

- Pat:
  - IDK gr 2,tm 2cm,
  - LVI+,PNI-,CS-,DCIS alanları+
  - ER+++,PR+++,HER2-
  - 4/14 met LN (üçünde yd invazyonu, EB 1.5cm)
- 6 TAC
- Tamoksifen 3 yıl

PETBT (Haziran 2016)

- Boyunda tiroid bezi her iki lob lokalizasyonunda SUVm 6.16
- Sağ aksiler LAPlarda tutulum yok
- Sağ AC’de ön planda enflamatuar değişiklikler ile uyumlu görünüm düşük FDG (RT sekonder)
- KC segment 2’de 11mm lezyonda SUVm 5.34 met lehine

Üst abdomen MR

- KC segm 2-3 de 7mm parankimal lezyon (kist?)

Tıbbi Onkoloji Klinik

KC kitlesinden bx (26.9.16)

- Pat:
  - Karsinom met, meme karsinomu ile uyumlu
  - ER%100,PR%80,HER2++
  - HER2 FISH ile NEGATİF

Tedavi ?

- AI
- Fulvestrant
- CDK+ AI
- CDK+ Fulvestrant
- mTOR+ Eksemestan
- Kemoterapi
- Diğer

Tedavi

- 20/10/2016 RF
- Fulvestrant başlandı
- Tedavinin 25. ayında

HR+ MMK Tedavi Yaklaşımı

- *Viseral kriz veya endokrin direnç kanıtı dışında* tüm hastalara **tüm kılavuzlarda endokrin tedavi**

Lobbezoo DJ, Ann Oncol 2016

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 28: 16–33, 2017
doi:10.1093/annonc/mdw544
Published online 5 December 2016

SPECIAL ARTICLE

3rd ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3)

F. Cardoso[1*], A. Costa[2], E. Senkus[3], M. Aapro[4], F. André[5], C. H. Barrios[6], J. Bergh[7], G. Bhattacharyya[8], L. Biganzoli[9], M. J. Cardoso[10], L. Carey[11], D. Corneliussen-James[12], G. Curigliano[13], V. Dieras[14], N. El Saghir[15], A. Eniu[16], L. Fallowfield[17], D. Fenech[18], P. Francis[19], K. Gelmon[20], A. Gennari[21], N. Harbeck[22], C. Hudis[23], B. Kaufman[24], I. Krop[25], M. Mayer[26], H. Meijer[27], S. Mertz[28], S. Ohno[29], O. Pagani[30], E. Papadopoulos[31], F. Peccatori[32], F. Penault-Llorca[33], M. J. Piccart[34], J. Y. Pierga[35], H. Rugo[36], L. Shockney[37], G. Sledge[38], S. Swain[39], C. Thomssen[40], A. Tutt[41], D. Vorobiof[42], B. Xu[43], L. Norton[44] & E. Winer[45]

Special article

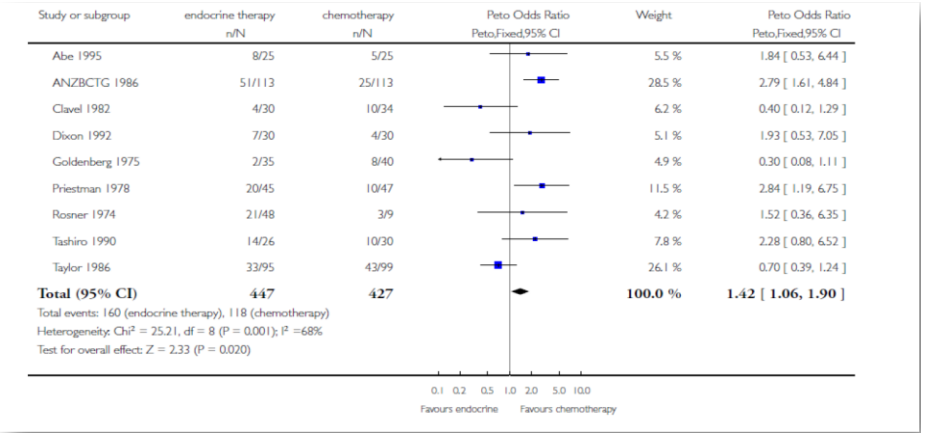
Annals of Oncology

SECTION 4. ER POSITIVE/HER-2 NEGATIVE (LUMINAL) ABC

GUIDELINE STATEMENT	LoE	Consensus
Endocrine therapy (ET) is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance.	1 A	Voters: 41 Yes: 93% (38) Abstain: 7% (3)
The preferred 1st line ET for postmenopausal patients depends on type and duration of adjuvant ET as well as time elapsed from the end of adjuvant ET; it can be an aromatase inhibitor, tamoxifen or fulvestrant.	1 A	Voters: 44 Yes: 84% (37) Abstain: 7% (3)

HR+ MMK; KT vs ET

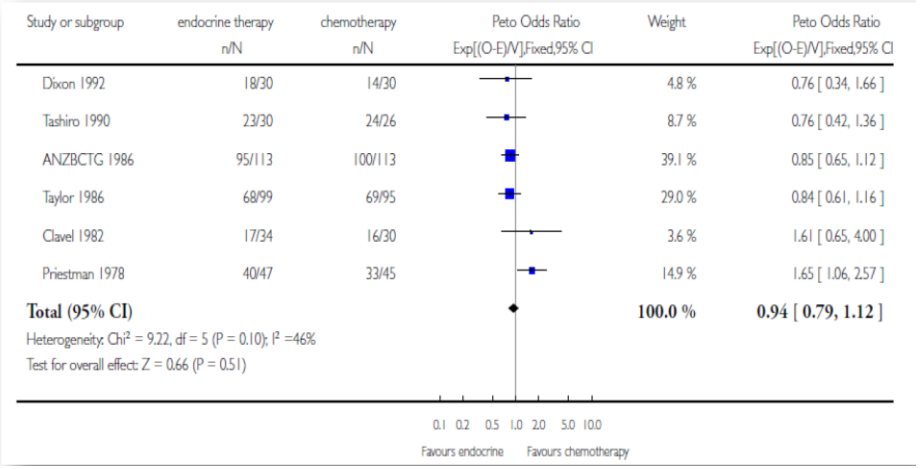
RR



Study or subgroup	endocrine therapy n/N	chemotherapy n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Abe 1995	8/25	5/25		5.5 %	1.84 [0.53, 6.44]
ANZBCTG 1986	51/113	25/113		28.5 %	2.79 [1.61, 4.84]
Clavel 1982	4/30	10/34		6.2 %	0.40 [0.12, 1.29]
Dixon 1992	7/30	4/30		5.1 %	1.93 [0.53, 7.05]
Goldenberg 1975	2/35	8/40		4.9 %	0.30 [0.08, 1.11]
Priestman 1978	20/45	10/47		11.5 %	2.84 [1.19, 6.75]
Rosner 1974	21/48	3/9		4.2 %	1.52 [0.36, 6.35]
Tashiro 1990	14/26	10/30		7.8 %	2.28 [0.80, 6.52]
Taylor 1986	33/95	43/99		26.1 %	0.70 [0.39, 1.24]
Total (95% CI)	**447**	**427**		**100.0 %**	**1.42 [1.06, 1.90]**

Total events: 160 (endocrine therapy), 118 (chemotherapy)
Heterogeneity: $Chi^2 = 25.21$, df = 8 (P = 0.001); $I^2 = 68\%$
Test for overall effect: Z = 2.33 (P = 0.020)

OS



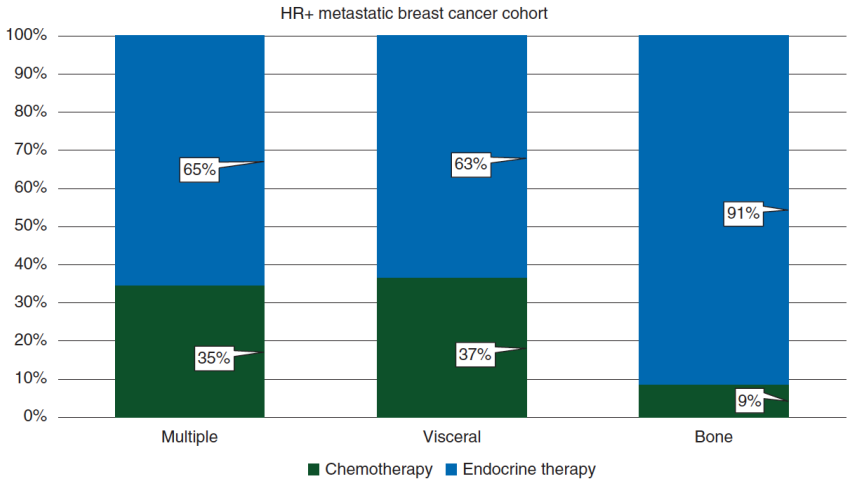
Study or subgroup	endocrine therapy n/N	chemotherapy n/N	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI	Weight	Peto Odds Ratio Exp[(O-E)/V],Fixed,95% CI
Dixon 1992	18/30	14/30		4.8 %	0.76 [0.34, 1.66]
Tashiro 1990	23/30	24/26		8.7 %	0.76 [0.42, 1.36]
ANZBCTG 1986	95/113	100/113		39.1 %	0.85 [0.65, 1.12]
Taylor 1986	68/99	69/95		29.0 %	0.84 [0.61, 1.16]
Clavel 1982	17/34	16/30		3.6 %	1.61 [0.65, 4.00]
Priestman 1978	40/47	33/45		14.9 %	1.65 [1.06, 2.57]
Total (95% CI)				**100.0 %**	**0.94 [0.79, 1.12]**

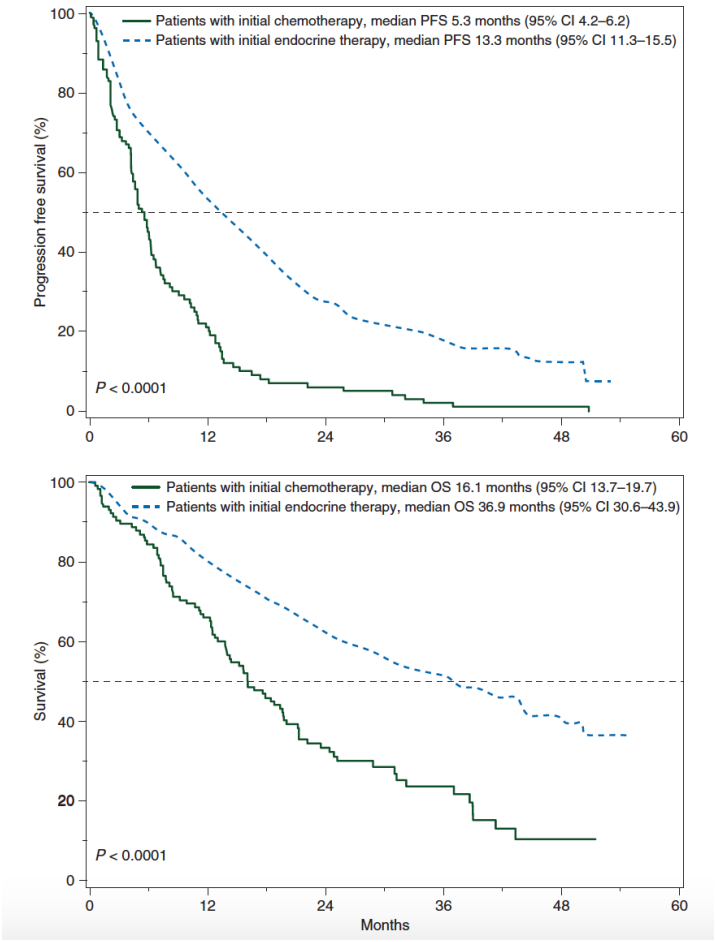
Heterogeneity: $Chi^2 = 9.22$, df = 5 (P = 0.10); $I^2 = 46\%$
Test for overall effect: Z = 0.66 (P = 0.51)

Wilcken 2009

KT vs ET

n= 520
8 merkez Avrupa

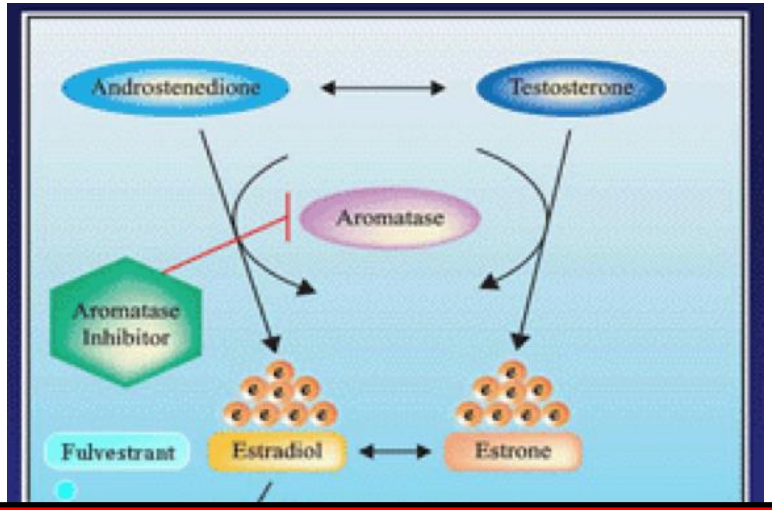




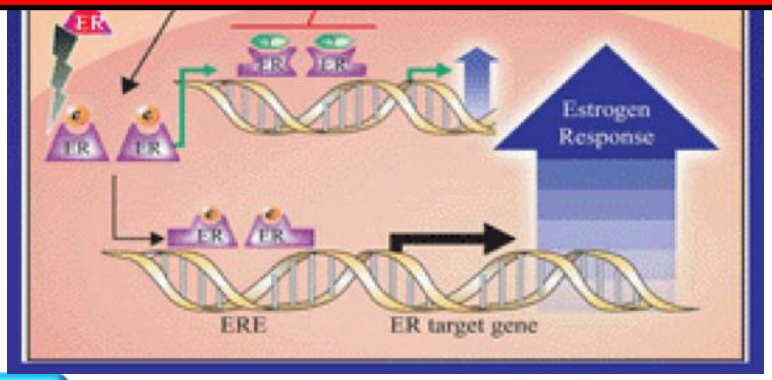
Lobbezoo 2016

MMK HR+ Tedavi

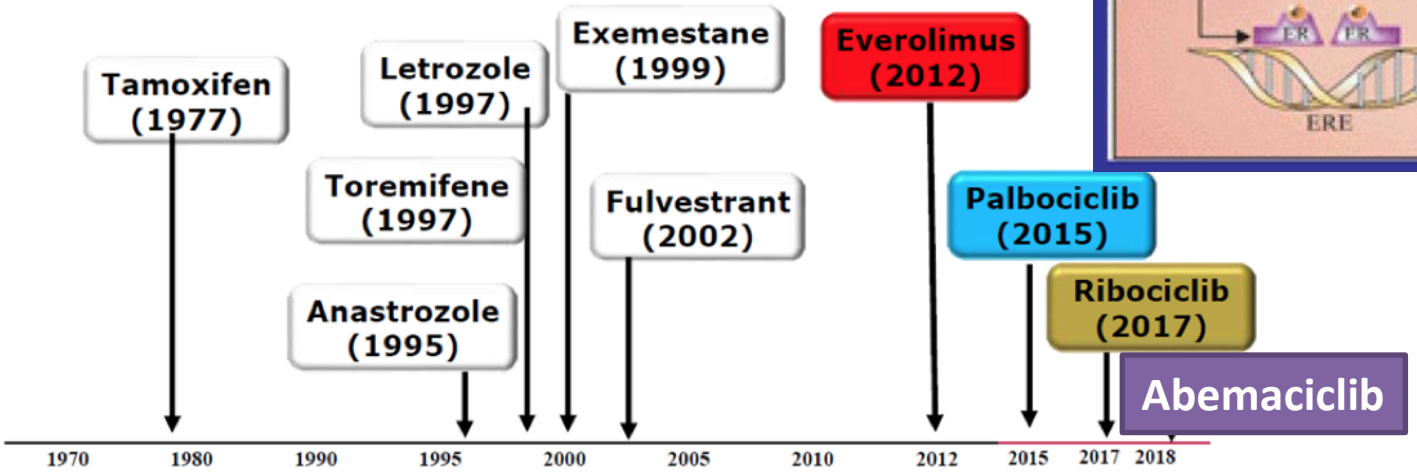
- Nonsteroidal AI (anastrozol,letrozol)
- Steroidal AI (ekzemestan)
- SERM (tamoksifen, toremifen)
- SERD (fulvestrant)
- Kombinasyon tedavileri



Östrojen Düzeyini/ Etkinliğini Azaltmak

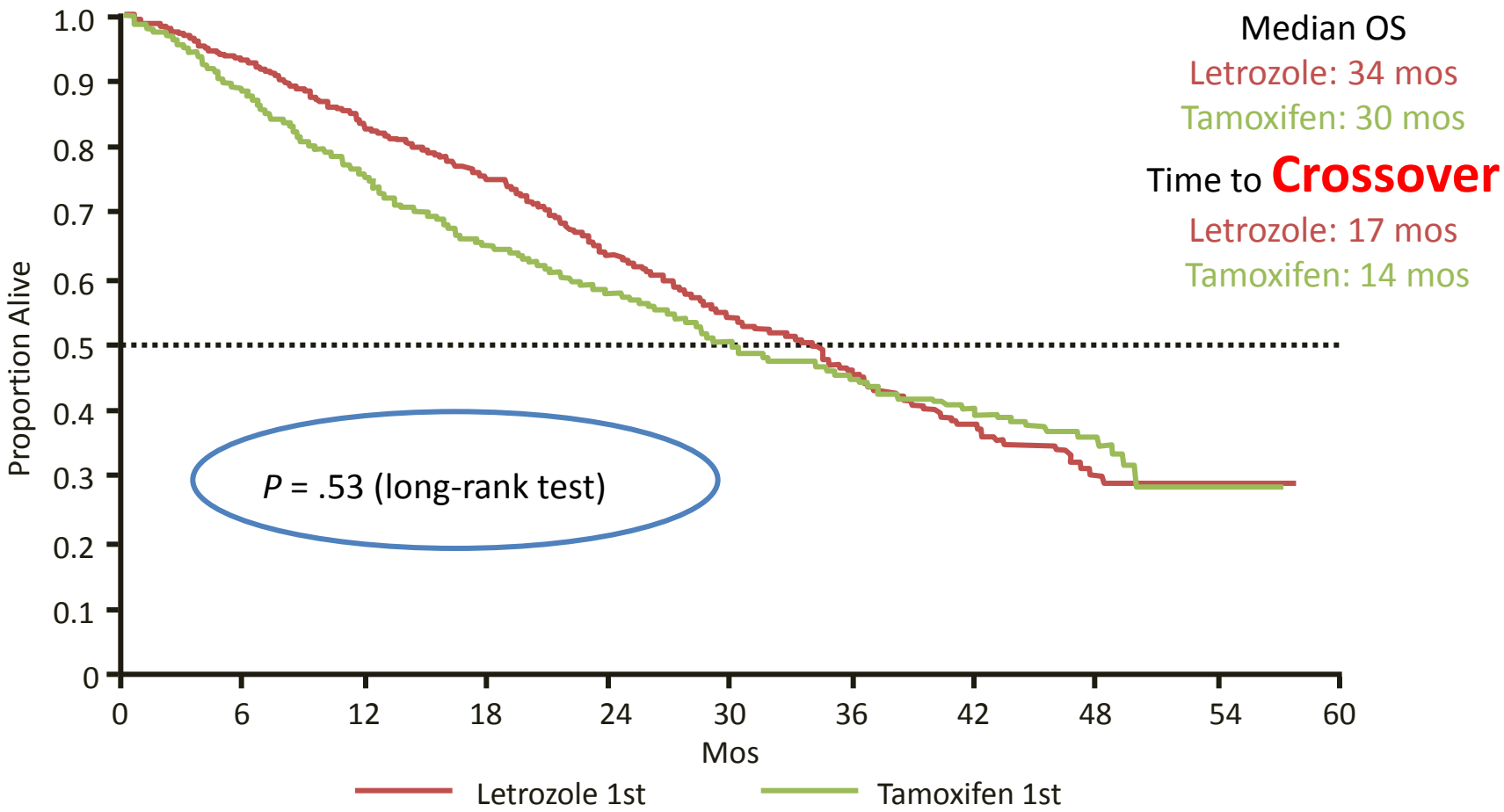


- CDKİ+ Fulvestrant
- CDKİ+ Tmx



Modified after Drugs@FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfn

MMK 1. basamak
Letrozole vs Tamoksifen



Mouridsen H, J Clin Oncol. 2003

Randomized Phase III Trials of AIs vs Tamoxifen as First-line Treatment of MBC

	Anastrozole	Anastrozole	Letrozole	Exemestane
No. patients	170 vs 182	340 vs 328	453 vs 454	182 vs 189
ORR, %	21 vs 17	33 vs 33	30 vs 20*	46 vs 31*
CBR, %	59 vs 46*	56 vs 56	49 vs 38*	66 vs 49*
TTP or PFS, months	11 vs 6*	8 vs 8	9 vs 6*	10 vs 6*
ER status unknown, %	11 vs 11	56 vs 54	34 vs 33	15 vs 11

ORR = overall response rate; CBR = clinical benefit rate; TTP = time to progression; PFS = progression-free survival; ER = estrogen receptor

* Statistically significantly different

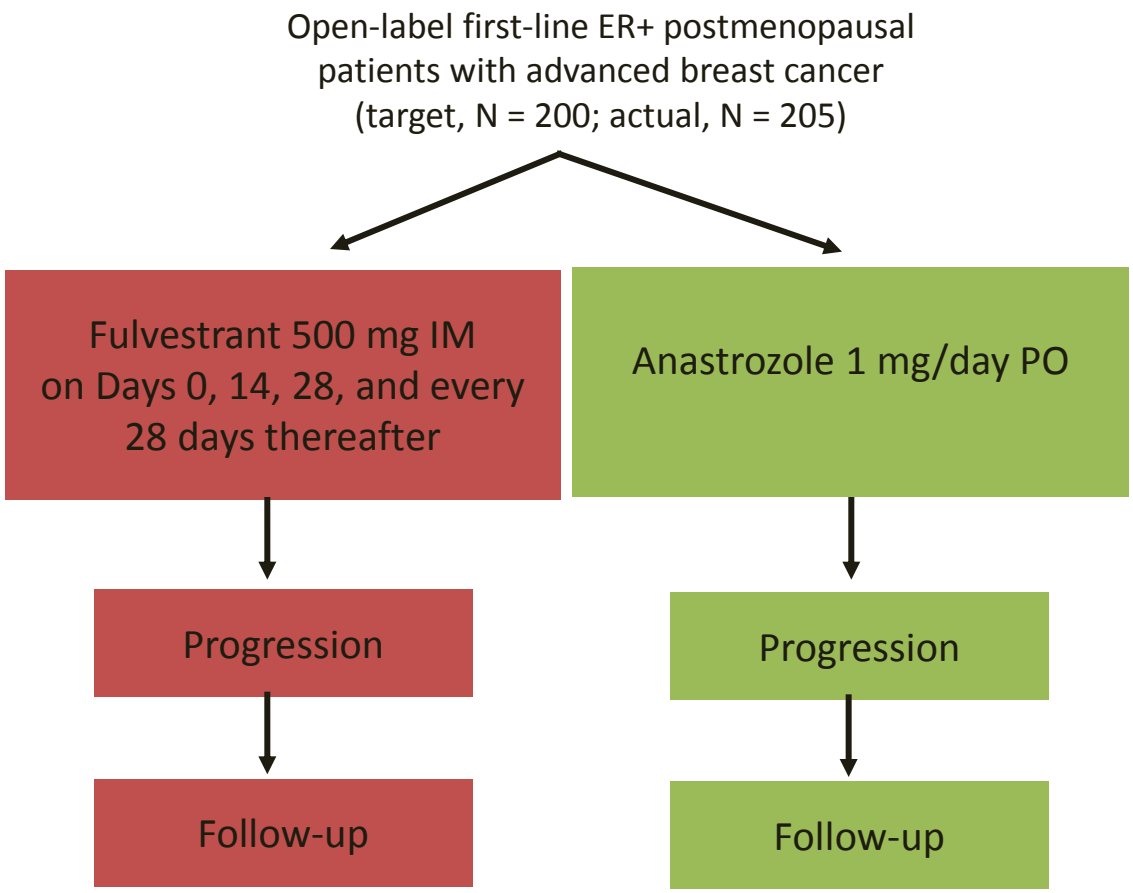
Nabholtz JM et al. *J Clin Oncol*, 2000;18:3758-3767.
Bonneterre J et al. *J Clin Oncol*. 2000;18:3748-3757.
Mouridsen H et al. *J Clin Oncol*, 2003;21:2101-2109.
Paridaens R et al. Presented at: American Society of Clinical Oncology, 2004; Abstract 515.

MMK & Anastrazol vs Letrazol

Efficacy parameter	Letrozole ($n = 356$)	Anastrozole ($n = 357$)	Adjusted P
Median TTP, months (90% CI)	5.7 (5.1–6.0)	5.7 (4.6–6.1)	0.92
ORR, no. (%)	68 (19.1)[a]	44 (12.3)[b]	0.013
CR	24 (6.7)	13 (3.6)	
PR	44 (12.4)	31 (8.7)	
NC ⩾ 6 months	28 (7.9)	38 (10.6)	
PD	203 (57.0)	222 (62.2)	
NE	57 (16.0)	53 (14.8)	
Median DOR, months	22	25	0.645
Clinical benefit (CR + PR + NC ⩾ 6 months), no. (%)	96 (27.0)	82 (23.0)	0.216
Median TTF, months (90% CI)	5.6 (4.4–5.8)	5.6 (4.0–6.0)	0.761
Treatment failures, no. (%)	315 (88.5)	322 (90.2)	
Median OS, months (90% CI)	22.0 (19.6–24.6)	20.3 (18.0–23.1)	0.624

Rose 2003

Faz 2 FIRST Çalışması



Endpoints at primary data cutoff

Primary endpoint

- Clinical benefit rate

Secondary endpoints

- ORR
- TTP
- Duration of response
- Duration of clinical benefit
- Safety

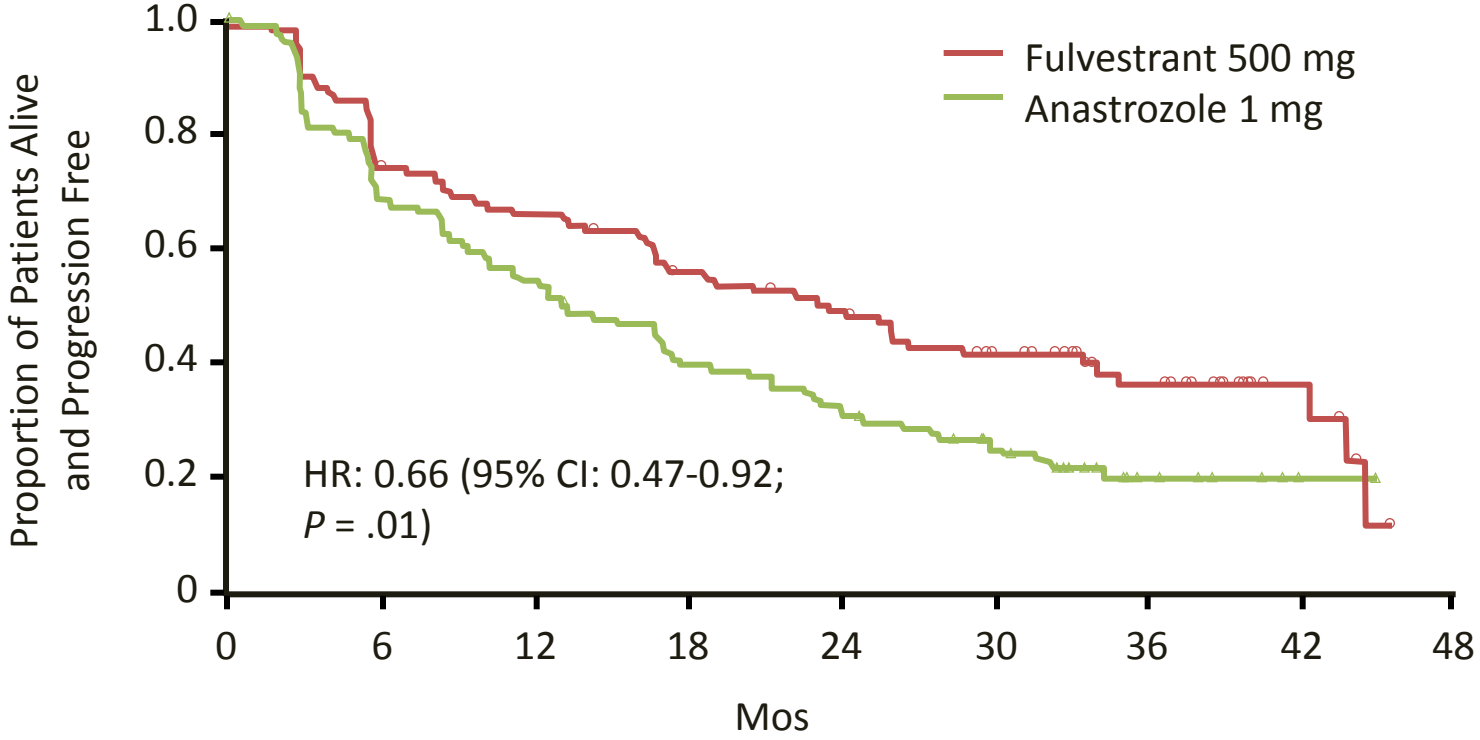
Exploratory endpoint

- Best response to subsequent therapy

Robertson JF, et al. Clin Oncol. 2009;27:4530-4535.

FIRST & TTP İzlem

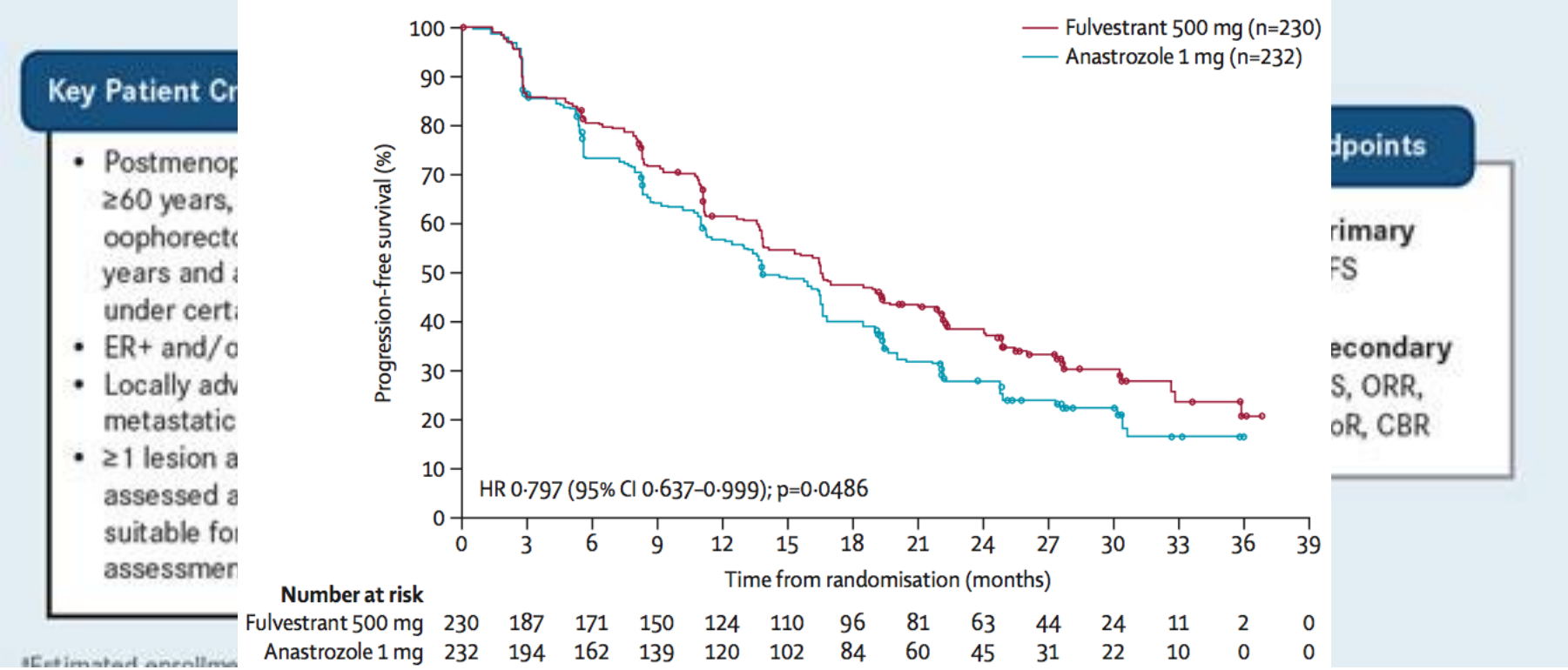
TTP: 13.1 ay vs 23.4 ay (p:0.01)
OS: 48.4 ay vs 54.1 ay (p:0.04)



Pts at Risk, n									
Fulvestrant 500 mg	102	74	65	52	45	34	20	6	0
Anastrozole 1 mg	103	69	55	39	30	21	8	2	0

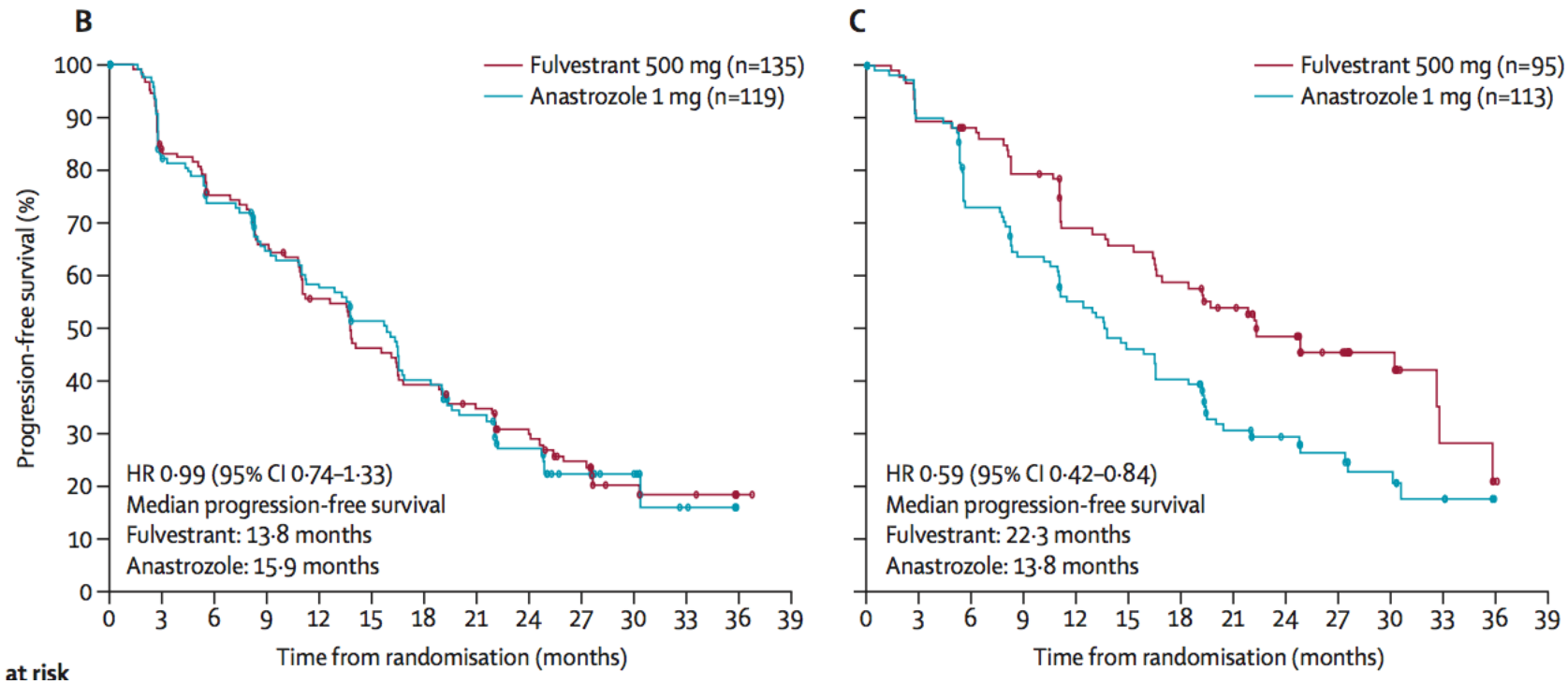
Robertson JF, et al. Breast Cancer Res Treat. 2012;136:503-511.

Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial



Ellis 2017

FALCON; PFS & Viseral Hastalık

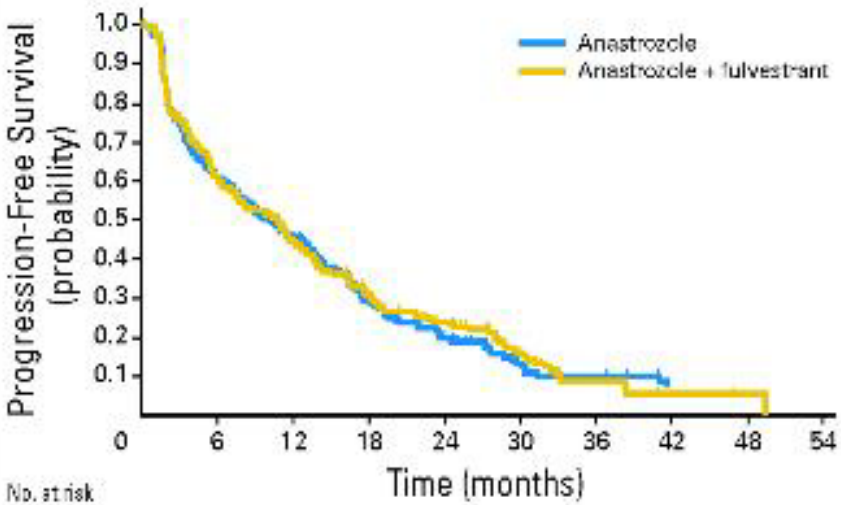


at risk

PFS: 13.8 ay vs 16.6 ay (p:0.04)
Viseral met-; PFS: 13.8 ay vs 22.3 ay

MBC 1. Basamak
Mono vs Kombo (Anastrazol vs Anastrazol+Fulvestran)

FACT: PFS



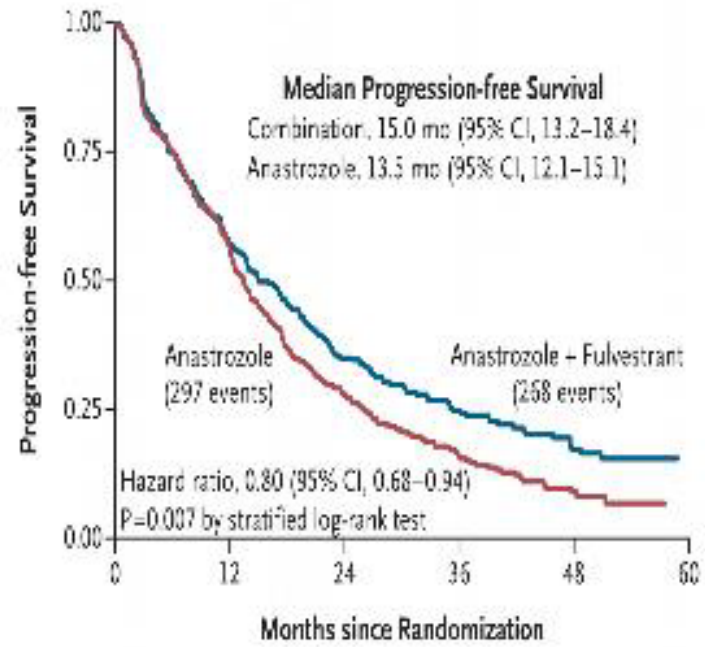
No. at risk

Anastrozole	258	140	100	57	31	18	10	5	4	1
Anastrozole + fulvestrant	258	149	107	55	40	20	6	2	1	0

	Fulvestrant + anastrozole (n = 258)	Anastrozole (n = 256)
No. of patients with progression (%)	200 (77.5)	200 (78.1)
Median TTP in months	10.8	10.2
Primary TTP analysis (log-rank test):		
Hazard ratio* (95% CI)	0.99 (0.81 to 1.20)	
P	0.91	

Bergh J et al. JCO 2012;30:1919-1925

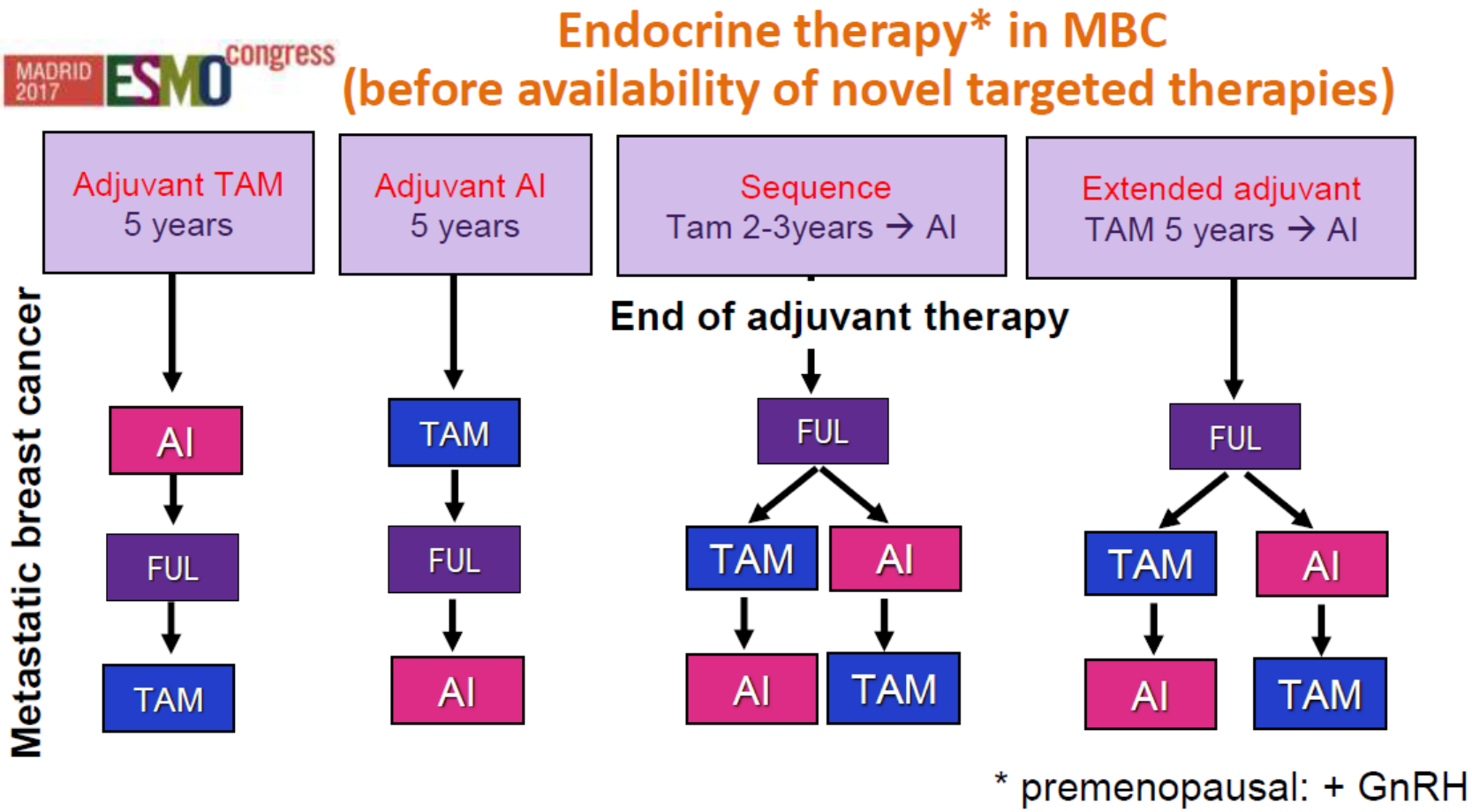
SWOG 0226: PFS



No. at Risk

Anastrozole + fulvestrant	349	199	114	53	21	8
Anastrozole	345	193	92	39	11	3

Mehta RS et al. N Engl J Med 2012;367:435-444.



AI, aromatase inhibitor; FUL, fulvestrant; GnRH, gonadotrophin-releasing hormone; MBC, metastatic breast cancer; TAM, tamoxifen

Olgu 2; 72y, E

1 yıldır sol memede akıntı

- Özg: İKH (PTCA 3 ay önce), PTE ?,DM, HT, hipotiroidi
- Sigara:(1p/g/ 30 yıl)
- ilaç:(lansor,desal,coversyl,coralan,cipralex,corum venotrek,glifor,ator,euthyrox,vastarel)
- Op:(TK araç içi- sağ el serçe parmak ampute)
- Soyg : Anne ve kızkardeş meme ca

Klinik

- 3 ay önce KAG sırasında sol meme kitlesi
- TAP BT:
  - mediastinal multipl LAP,
  - minimal perikardiyal ve plevral eff,
  - multipl EB 22mm AC nodülü
  - Sol meme lezyonu,T11 de sağ yarıda 2 cm lezyon

Klinik

- Meme US: sol meme ve aksillada lezyon
- Pat:
  - IDK,
  - ER ve PR kuvvetli pozitif, HER2-
  - ki67%25,
- PETBT: primer sol meme de ve kemik ve ac nodüllerinde artmış fdg
- TVKS T11de met ön planda lezyon

Tıbbi Onkoloji Başvuru

- AOH pat kons:
  - IDK gr2
  - gelen kesitte tm 1.2cm
  - ER %100, PR%80
  - HER2-
  - ki 67 %27
  - DCIS görülmemiştir

Fizik Muayene

- PS:1 GD iyi
- CVS ve SS doğal
- Batın rahat hsm yok traube açık.
- Sol memede ödemli cilt lezyonu
- Sol aksiller LAP+

- CA15.3 58,GFR 48,krea 1.44,

Tedavi ?

- AI
- Fulvestrant
- CDK+ AI
- CDK+ Fulvestrant
- mTOR+ Eksemestan
- Kemoterapi
- Diğer

MMK Tedavi

- Haziran 2017; Letrazol
- T10-12 palyatif RT
- Şubat 2018 Fulvestrant, zoledronik asid
- Mayıs 2018 Sağ kalçada ağrı, FM meme lezyonu benzer
  - CA15.3 212
- Temmuz 2018 Tm marker regrese
  - CA15.3: 172
- Ekim 2018 Progresif hastalık

MMK
Endokrin Direnç/ Yeni Tedaviler

ENDOKRİN DİRENÇ

Erken evre meme kanserinde %25
Metastatik meme kanserinde **%100**

- **Primer endokrin direnç**
  - Adjuvan ET'nin ilk 2 yılında
  - MMK ET'nin ilk 6 ayında
- **Sekonder endokrin direnç**
  - Adjuvan ET'nin ilk 2 yılından sonra
  - Adjuvan ET tamamlandıktan sonra 12 ay içinde
  - MMK ET'nin ilk 6 ayından sonra

Endokrin Direnç

1. Sinyal yolak aktivasyonu

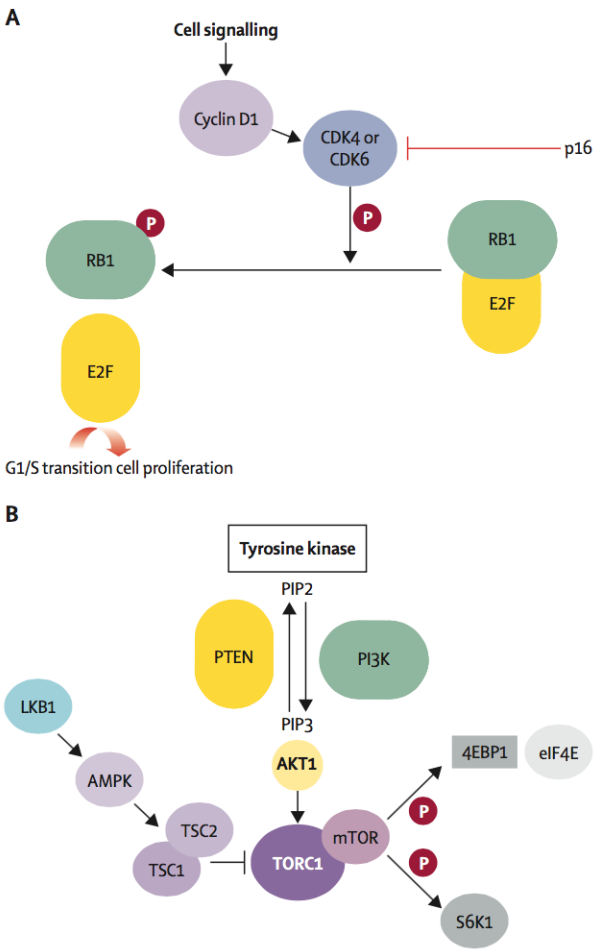
PI3K, HER2, FGFR, IGF-1R

2. Hücre döngü yolaklarının bozulması

Siklin D1 amplifikasyonu

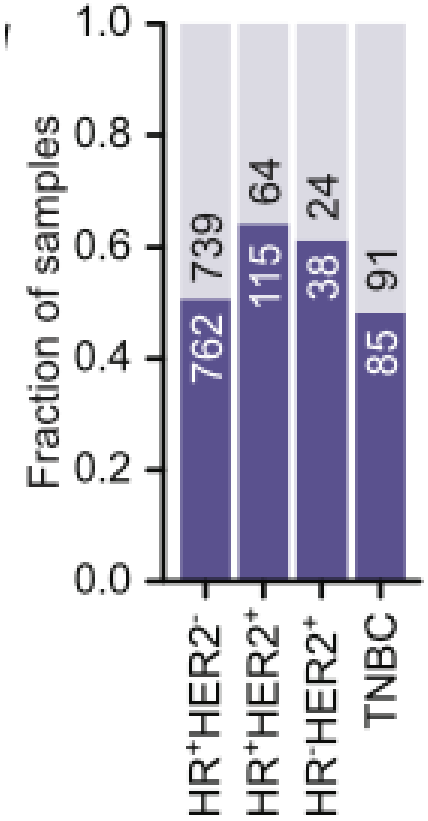
3. ER yolak regülasyonunun bozulması

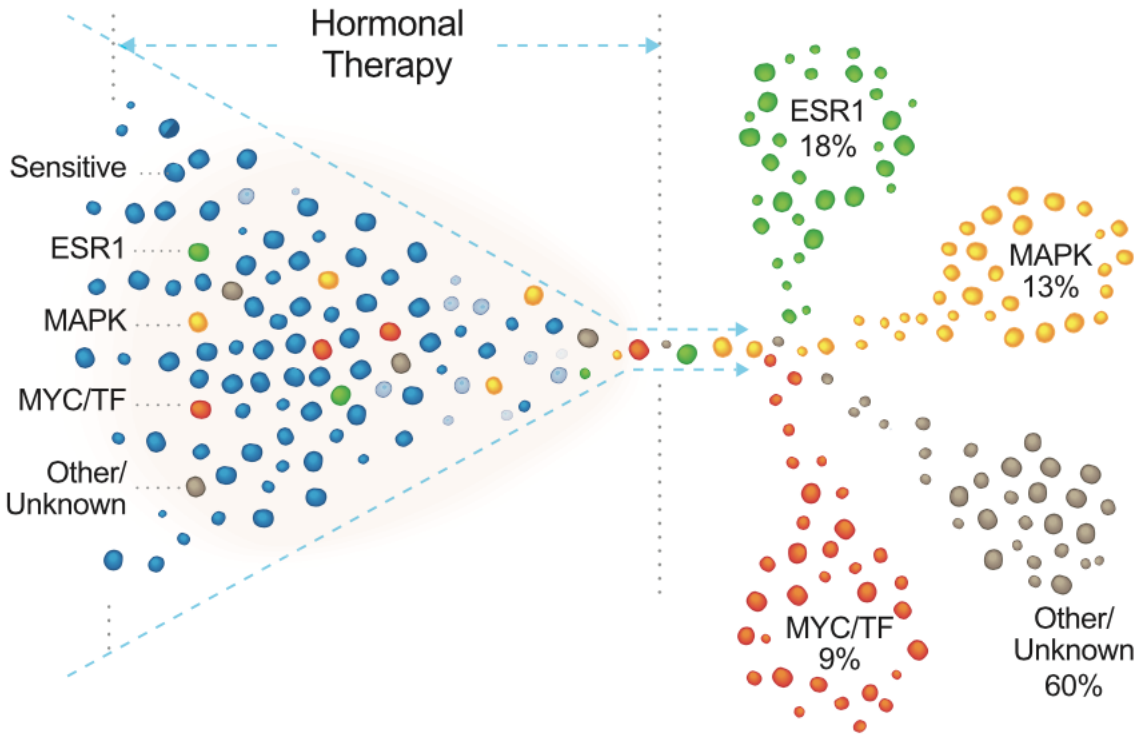
ESR1 aktive edici mutasyonlar



Cancer Cell

The Genomic Landscape of Endocrine-Resistant Advanced Breast Cancers





Razavi 2018

n= 1501 HR+ MMK
MAPK + TF alterasyonu %22 (Endokrin Direnç !)
ESR1 ile ‘mutually exclusive’

Endokrin Direnç

1. Sinyal yolak aktivasyonu

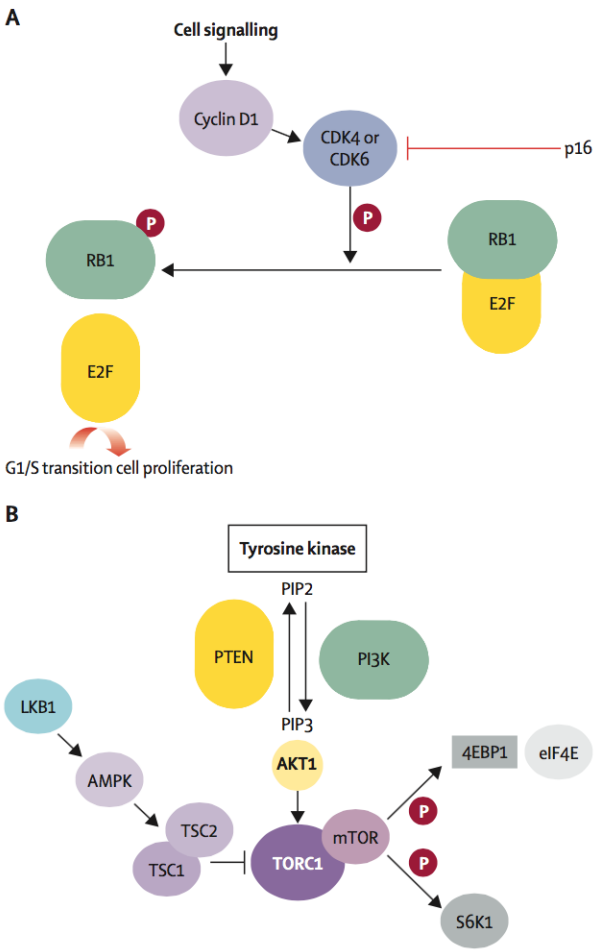
PI3K, HER2, FGFR, IGF-1R

2. Hücre döngü yolaklarının bozulması

Siklin D1 amplifikasyonu

3. ER yolak regülasyonunun bozulması

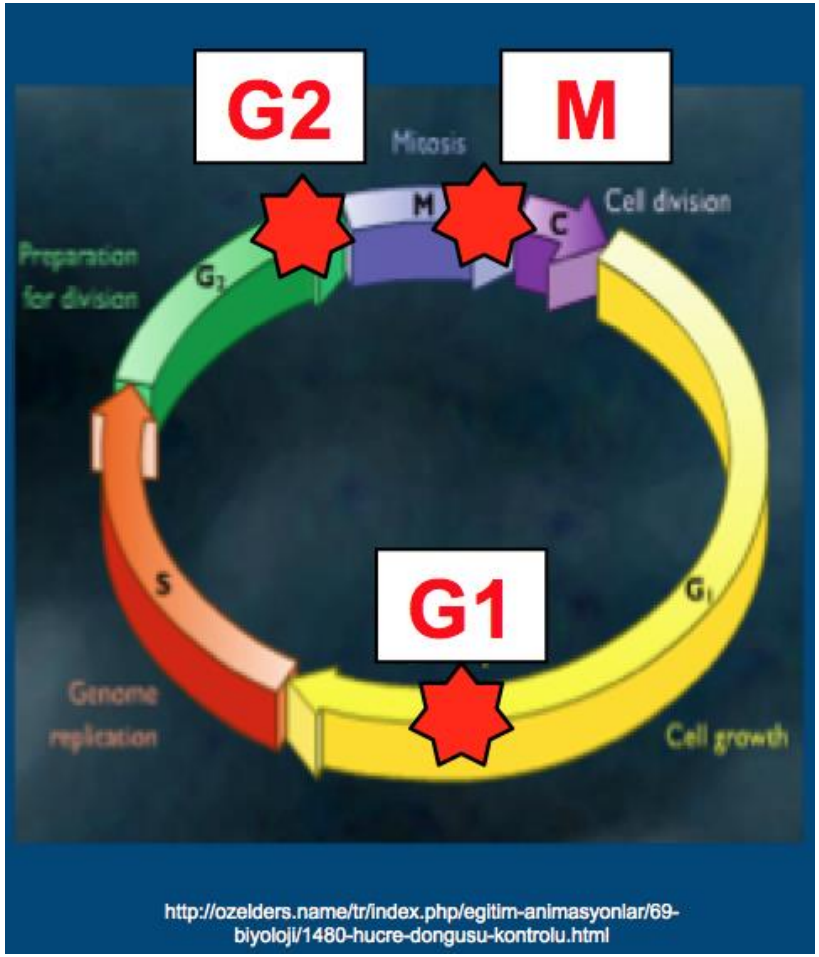
ESR1 aktive edici mutasyonlar



Hücre Döngüsü Kontrol

Her zaman S fazını M fazı takip etmeli

M fazı S fazı tamamlanmadan başlamamalı



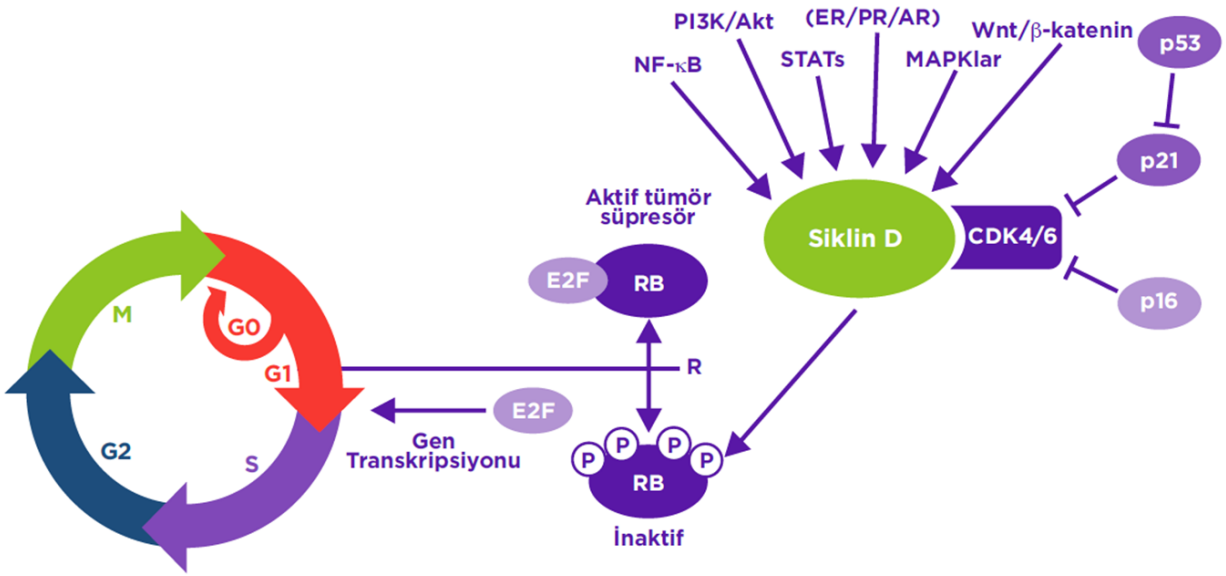
HÜCRE DÖNGÜSÜ PROTEİNLERİ

SİKLİNLER

SİKLİN-BAĞIMLI KİNAZLAR (CDK)

SİKLİN-BAĞIMLI KİNAZ İNHİBİTÖRLERİ (CDI)

Cell cycle proteins	
Cyclin	A (A1, A2) · B (B1, B2, B3) · D (D1, D2, D3) · E (E1, E2)
CDK	2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 · 10 · CDK-activating kinase
CDK inhibitor	INK4a/ARF (p14arf/p16, p15, p18, p19) · cip/kip (p21, p27, p57)



AR: Androgen Receptor (Androjen Reseptör). **ER:** Estrogen Receptor (Östrojen Reseptör). **MAPK:** Mitogen-Activated Protein Kinase (Mitojen Aktiveli Protein Kinaz). **NF-κB:** Nuclear Factor Kappa-Light-Chain Enhancer of Activated B Cells (Nükleer Faktör-Kappa B). **PI3K:** Phosphoinositide-3 Kinase (Fosfoinozitid-3 Kinaz). **PR:** Progesterone Receptor (Progesteron Reseptörü). **R:** Restriction Point (Restriksiyon Noktası). **RB:** Retinoblastoma (Retinoblastom). **STAT:** Signal Transducer and Activator of Transcription (Transkripsiyon Sinyal Dönüştürücü ve Aktivatörü).

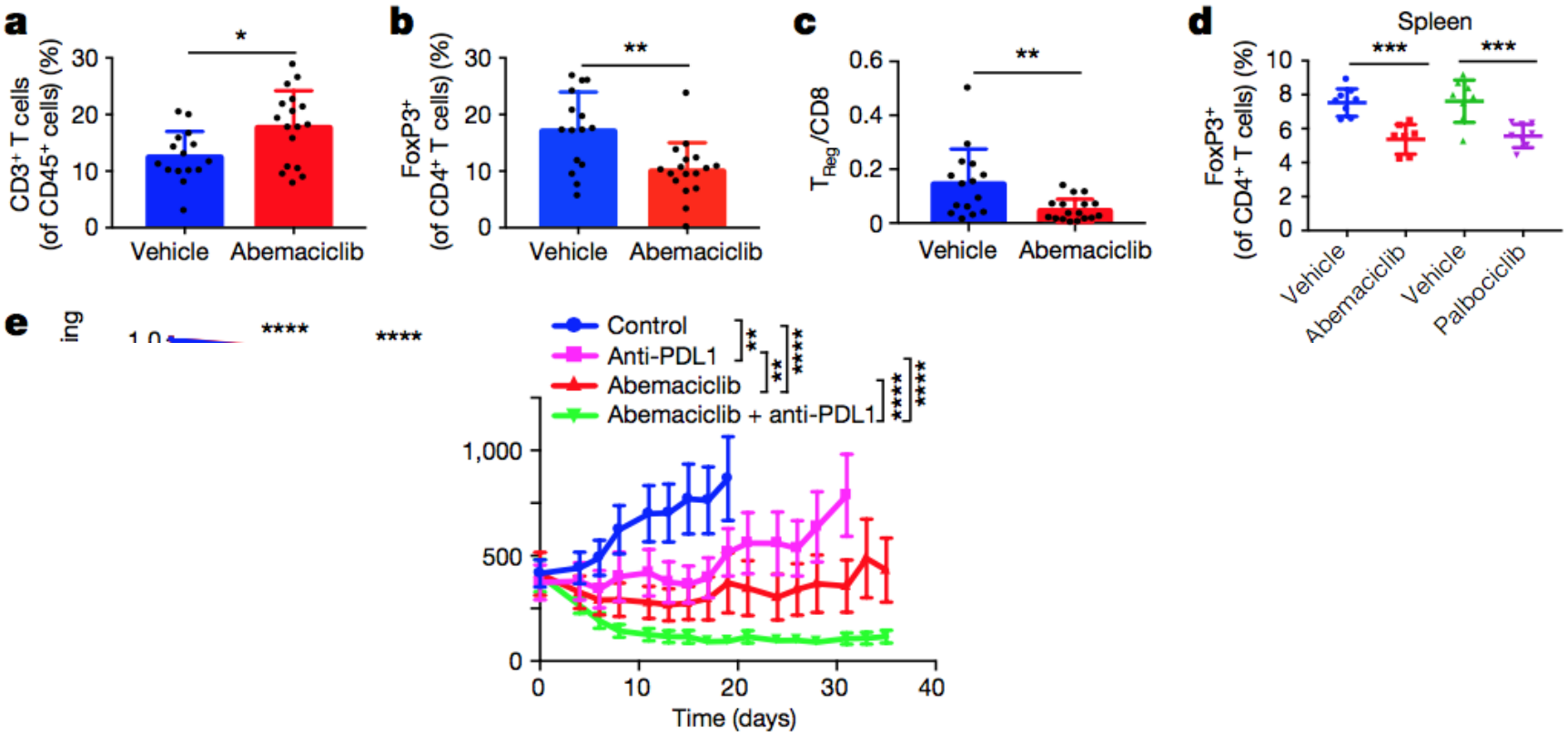
- Siklin-D amplifikasyonu, kaybı, mutasyonu,
- Rb kaybı ve mutasyonu,
- p 16 kaybı

• Meme kanserinde endokrin direnç ile ilişkili

LETTER

doi:10.1038/nature23465

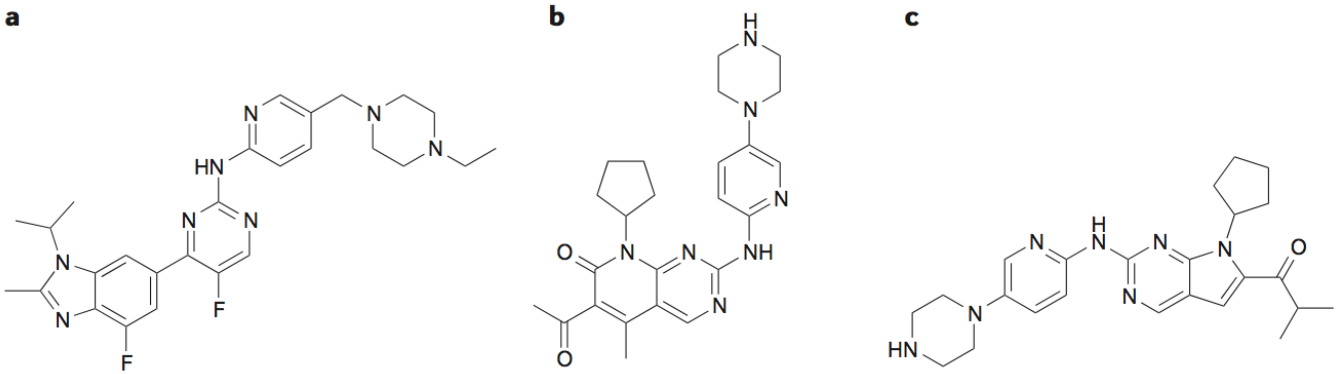
CDK4/6 inhibition triggers anti-tumour immunity



Goel 2018

CDK 4/6 İnhibitörleri

- Palbociclib (PD-0332991)
- Abemaciclib (LY2835219)
- Ribociclib (LEE011)



	Abemaciclib (LY-2835219)	Palbociclib (PD-0332991)	Ribociclib (LEE011)
IC_{50}	CDK1: >1 μM	CDK1: >10 μM	CDK1: >100 μM
	CDK2: >500 nM	CDK2: >10 μM	CDK2: >50 μM
	CDK4: 2 nM	CDK4: 9–11 nM	CDK4: 10 nM
	CDK5: ND	CDK5: >10 μM	CDK5: ND
	CDK6: 5 nM	CDK6: 15 nM	CDK6: 39 nM
	CDK7: 300 nM	CDK7: ND	CDK7: ND
	CDK9: 57 nM	CDK9: ND	CDK9: ND

CDK İnhibitör Doz & İzlem

Drug	Dose and Schedule	CBC and Differential	Liver Tests (AST, ALT, and Total Bilirubin)	Serum Electrolytes (K, Ca, Mg, P)	ECG
Palbociclib	125 mg daily, 3 wk on, 1 wk off	Baseline, every 2 wk for 2 m, monthly for next 4 mo, then every 3 mo[§]	NA	NA	NA
Ribociclib	600 mg daily, 3 wk on, 1 wk off	Baseline, every 2 wk for 2 mo, monthly for 4 mo	Baseline, every 2 wk for 2 mo, monthly for 4 mo	Baseline, monthly for 6 mo	Baseline, day 14 of cycle 1, day 1 of cycle 2
Abemaciclib	150 mg twice daily[†] OR 200 mg twice daily[‡]	Baseline, every 2 wk for 2 mo, monthly for 2 mo	Baseline, every 2 wk for 2 mo, monthly for 2 mo	NA	NA

Crugliano Mescape 2018

2014

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1 10

Palbociclib Shows Promising Results in Patients With Hormone Receptor-positive Metastatic Breast Cancer

4/6/2014

SAN DIEGO — The drug palbociclib, an inhibitor of cyclin-dependent kinases (CDK) 4 and 6, significantly improved progression-free survival when administered as a first-line treatment in patients with hormone receptor-positive, metastatic breast cancer, according to phase II results of the study PALOMA-1, presented here at the AACR Annual Meeting 2014, April 5-9.

PALOMA 1

The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study

Richard S Finn, John P Crown, Istvan Lang, Katalin Boer, Igor M Bondarenko, Sergey O Kulyk, Johannes Ettl, Ravindranath Patel, Tamas Pinter, Marcus Schmidt, Yaroslav Shparyk, Anu R Thummala, Nataliya L Voytko, Camilla Fowst, Xin Huang, Sindy T Kim, Sophia Randolph, Dennis J Slamon

Cohort 1 (n=66)
- Postmenopausal
- ER+, HER2− mBC
- **No prior treatment for advanced disease**

Cohort 2 (n=99)
- As above with: ***CCND1* amplification and/or loss of p16**

N=165

1:1

RANDOMISATION

Palbociclib (125 mg QD, 3/1 schedule) + letrozole (2.5 mg QD)

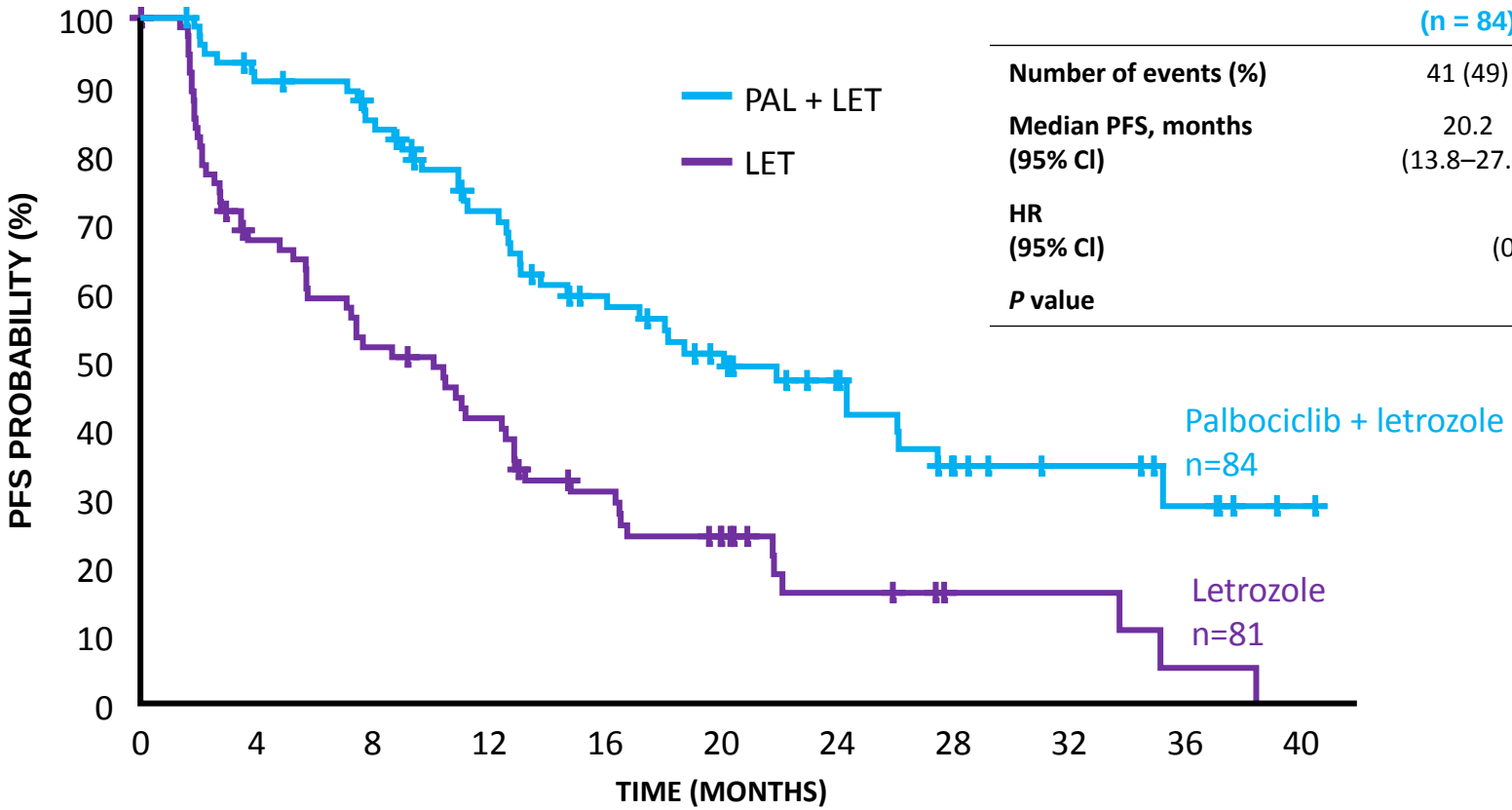
Letrozole (2.5 mg QD)

Primary endpoint: progression-free survival

Secondary/exploratory endpoints: response, overall survival, safety, biomarkers, patient-reported outcomes

Stratification factors: disease site, disease-free interval

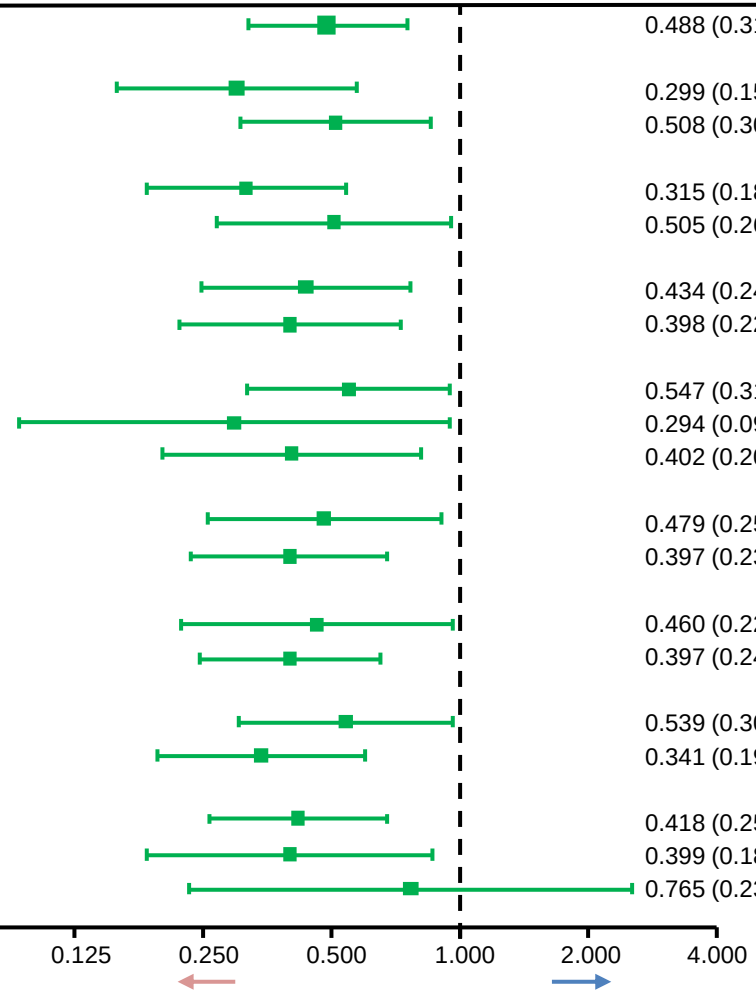
PALOMA 1 & PFS



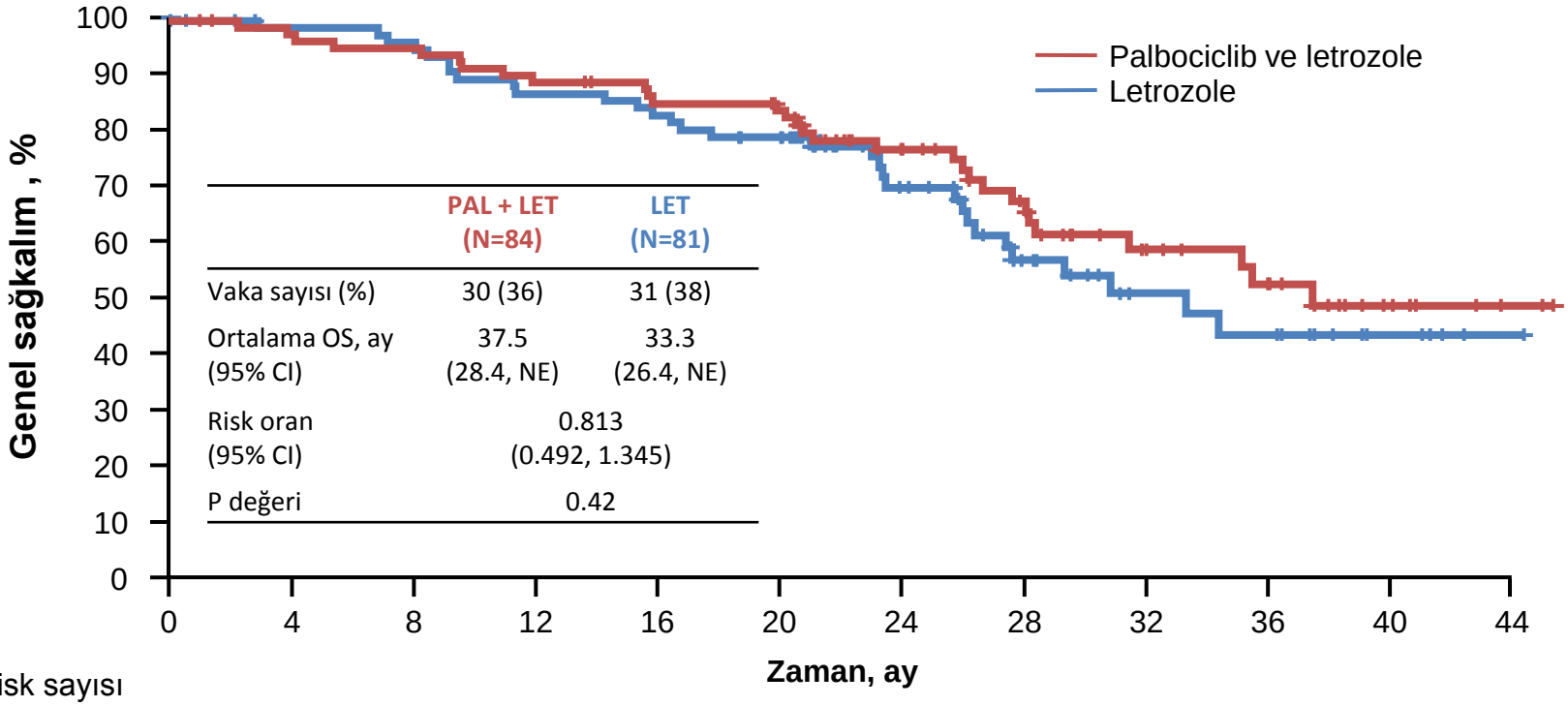
	PAL + LET (n = 84)	LET (n = 81)
Number of events (%)	41 (49)	59 (73)
Median PFS, months (95% CI)	20.2 (13.8–27.5)	10.2 (5.7–12.6)
HR (95% CI)	0.488 (0.319–0.748)	
***P* value**	0.0004	

PALOMA 1 – Subgrup Analizi

	PAL + LET		LET		Hazard ratio (95% CI)	Interaction P value*
	Patients	Events	Patients	Events		
All patients (intention-to-treat population)	84	41	81	59	0.488 (0.319–0.748)	
Cohort						
1	34	15	32	25	0.299 (0.156–0.572)	0.14
2	50	26	49	34	0.508 (0.303–0.853)	
Age group (years)						
<65 years	47	24	42	35	0.315 (0.184–0.539)	0.34
≥65 years	37	17	39	24	0.505 (0.269–0.948)	
Baseline ECOG performance status						
0	46	21	45	31	0.434 (0.246–0.766)	0.78
1	38	20	36	28	0.398 (0.220–0.721)	
Disease site						
Visceral	37	21	43	34	0.547 (0.317–0.944)	0.44
Bone Only	17	5	12	7	0.294 (0.092–0.945)	
Other	30	15	26	18	0.402 (0.200–0.808)	
Previous chemotherapy						
Yes	34	17	37	24	0.479 (0.255–0.898)	0.75
No	50	24	44	35	0.397 (0.234–0.671)	
Previous antihormonal therapy						
Yes	27	12	28	19	0.460 (0.222–0.956)	0.88
No	57	29	53	40	0.397 (0.244–0.646)	
Previous systemic therapy						
Yes	40	20	44	28	0.539 (0.302–0.962)	0.36
No	44	21	37	31	0.341 (0.194–0.599)	
Time from end of adjuvant treatment to disease recurrence						
≤12 months (including de-novo presentation)	59	31	51	39	0.418 (0.259–0.674)	0.95
>12 months	25	10	30	20	0.399 (0.185–0.858)	0.34
≤12 months (excluding de-novo presentation)	15	7	14	5	0.765 (0.232–2.523)	



PALOMA 1 – Genel Sağkalım (IA)



	PAL + LET (N=84)	LET (N=81)
Vaka sayısı (%)	30 (36)	31 (38)
Ortalama OS, ay (95% CI)	37.5 (28.4, NE)	33.3 (26.4, NE)
Risk oran (95% CI)	0.813 (0.492, 1.345)	
P değeri	0.42	

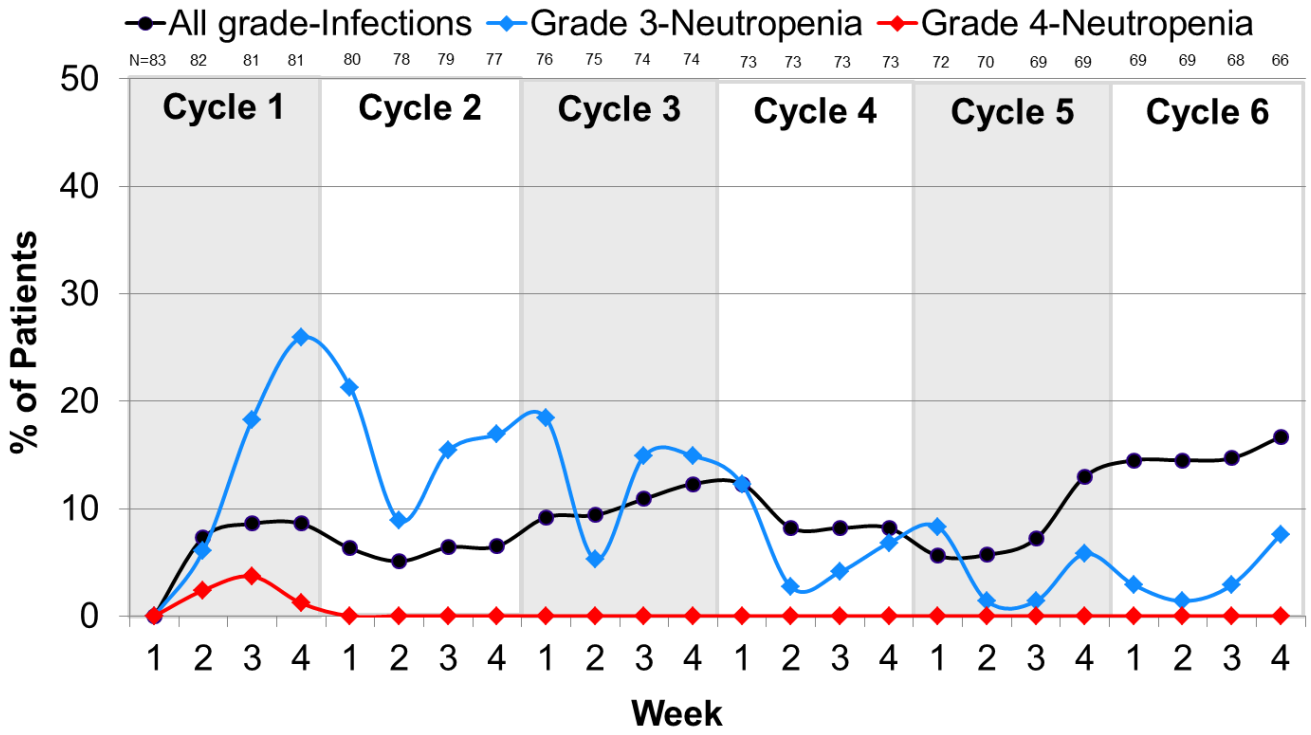
Risk sayısı

PAL + LET	84	80	78	73	68	65	47	35	22	17	7	2
LET	81	76	74	67	64	59	37	23	14	12	5	1

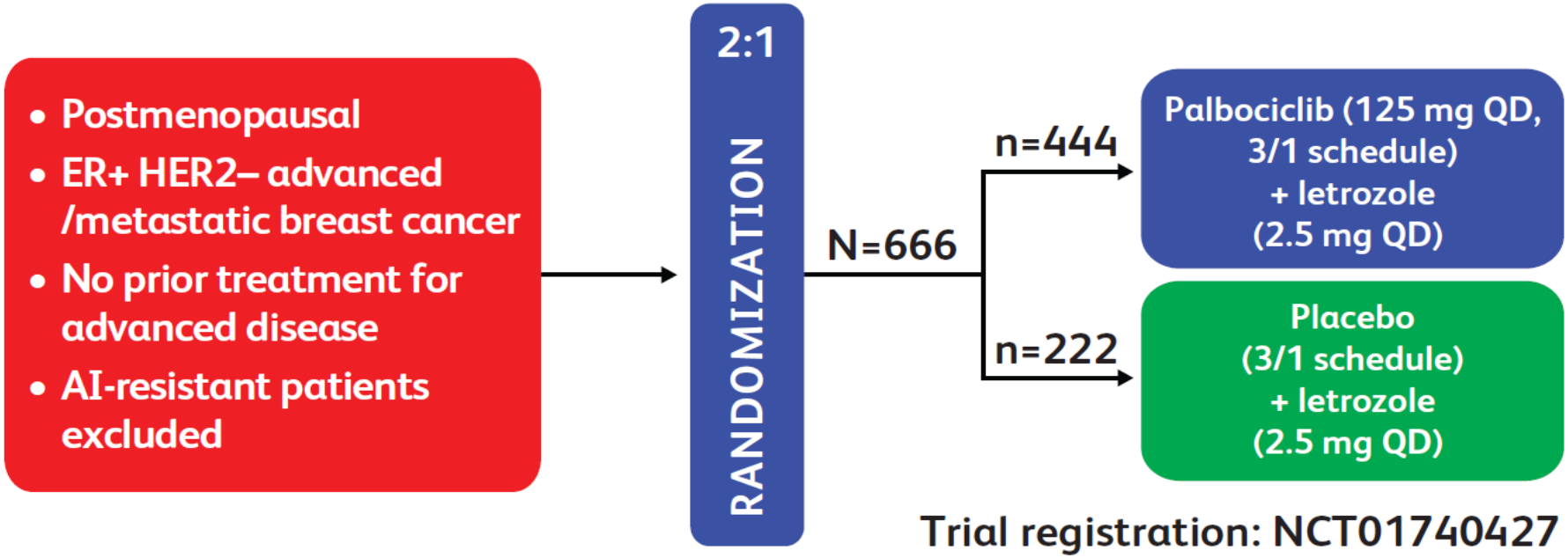
PALOMA 1 – Advers Olaylar

	Combined cohorts			
	PAL + LET (n=83)		LET (n=77)	
AE (%)	All grades	Grade 3/4	All grades	Grade 3/4
Any AE	99	76	84	21
Neutropenia	75	54	5	1
Leukopenia	43	19	3	0
Fatigue	41	5	23	1
Anemia	35	6	6	1
Nausea	25	2	13	1
Arthralgia	23	1	16	3
Alopecia	22	NA	3	NA
Diarrhea	20	4	10	0
Hot flush	21	0	12	0
Thrombocytopenia	17	2	1	0
Decreased appetite	16	1	7	0
Dyspnea	16	2	8	1
Nasopharyngitis	16	0	10	0
Back pain	11	0	16	1
Headache	14	0	10	0

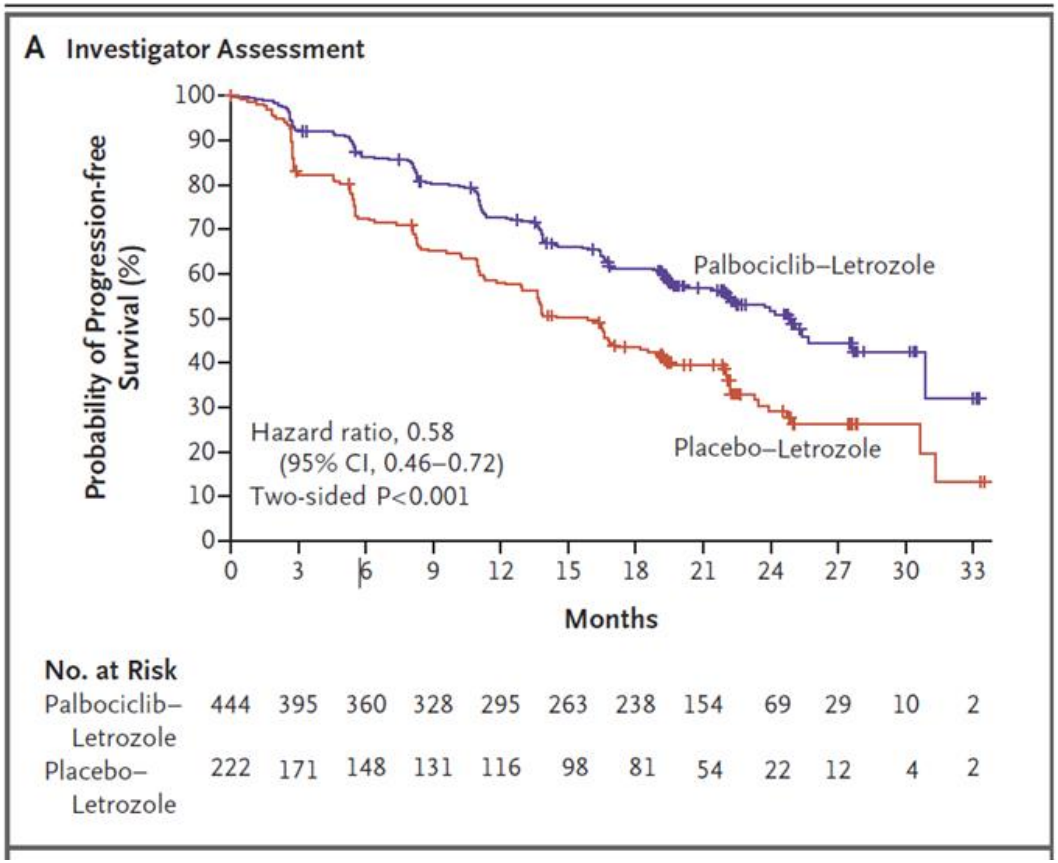
Gr 3-4 Nötropeni genellikle ilk sikluslarda görülmektedir



PALOMA - 2

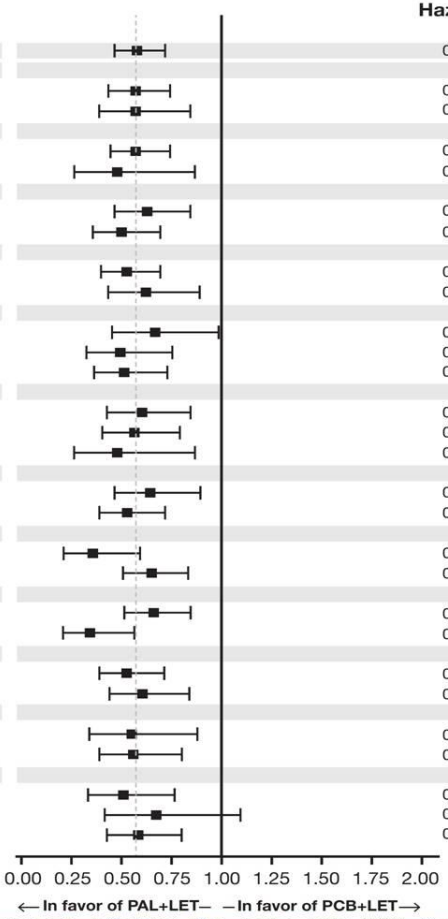

• Postmenopausal
• ER+ HER2– advanced /metastatic breast cancer
• No prior treatment for advanced disease
• AI-resistant patients excluded
2:1
RANDOMIZATION
N=666
n=444
n=222
Palbociclib (125 mg QD, 3/1 schedule) + letrozole (2.5 mg QD)
Placebo (3/1 schedule) + letrozole (2.5 mg QD)
Trial registration: NCT01740427

PALOMA 2 & PFS


A Investigator Assessment
Probability of Progression-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
Palbociclib–Letrozole
Placebo–Letrozole
Hazard ratio, 0.58
(95% CI, 0.46–0.72)
Two-sided P<0.001
0 3 6 9 12 15 18 21 24 27 30 33
Months
No. at Risk
Palbociclib–Letrozole 444 395 360 328 295 263 238 154 69 29 10 2
Placebo–Letrozole 222 171 148 131 116 98 81 54 22 12 4 2

Forest Plot of Subgroup Analysis of PFS (Investigator Assessment)

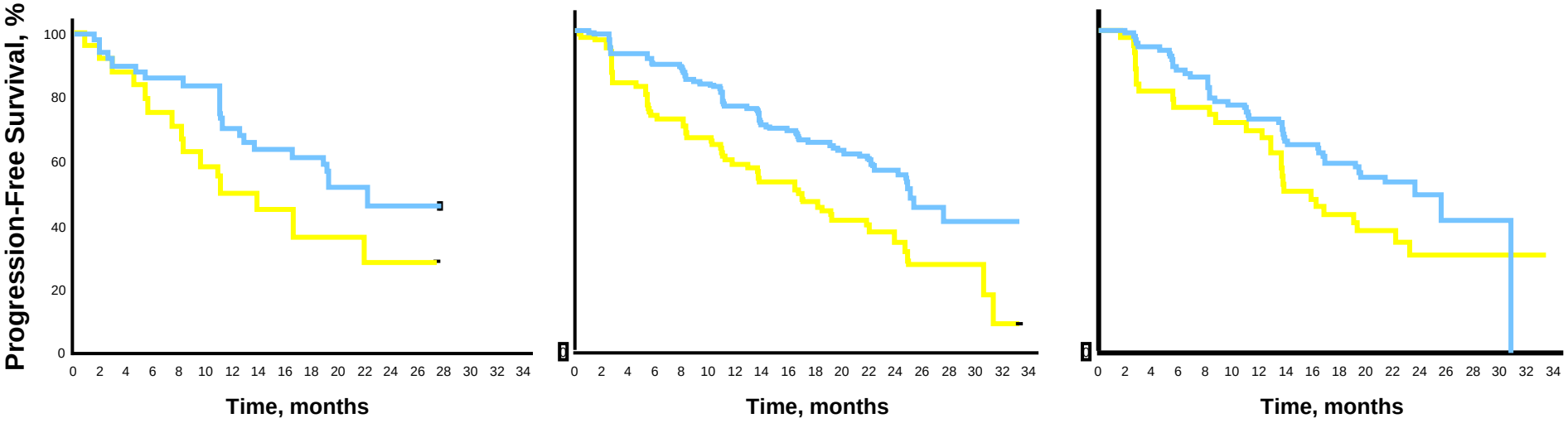
Subgroup	n (%)	Hazard Ratio (95%CI)
All randomized patients	666 (100)	0.576 (0.463 to 0.718)
Age		
<65 Years	404 (60.7)	0.567 (0.434 to 0.740)
≥65 Years	262 (39.3)	0.571 (0.386 to 0.843)
Race		
White	516 (77.5)	0.576 (0.450 to 0.739)
Asian	95 (14.3)	0.484 (0.269 to 0.871)
Site of metastatic disease		
Visceral	324 (48.6)	0.633 (0.472 to 0.849)
Non-visceral	342 (51.4)	0.502 (0.360 to 0.699)
Prior hormonal therapy		
Yes	375 (56.3)	0.528 (0.400 to 0.698)
No	291 (43.7)	0.628 (0.439 to 0.897)
Disease free interval		
De Novo Metastases	248 (37.2)	0.674 (0.457 to 0.993)
≤12 months	147 (22.1)	0.501 (0.329 to 0.761)
>12 months	271 (40.7)	0.516 (0.365 to 0.731)
Region		
North America	267 (40.1)	0.605 (0.431 to 0.849)
Europe	307 (46.1)	0.571 (0.410 to 0.796)
Asia/Pacific	92 (13.8)	0.486 (0.270 to 0.872)
ECOG performance status		
0	359 (53.9)	0.646 (0.466 to 0.896)
1/2	307 (46.1)	0.531 (0.393 to 0.718)
Bone-only disease at baseline		
Yes	151 (22.7)	0.363 (0.221 to 0.594)
No	515 (77.3)	0.654 (0.512 to 0.837)
Measurable Disease		
Yes	509 (76.4)	0.663 (0.517 to 0.849)
No	157 (23.6)	0.350 (0.215 to 0.568)
Prior chemotherapy		
Yes	322 (48.3)	0.533 (0.395 to 0.720)
No	344 (51.7)	0.611 (0.443 to 0.842)
Most recent therapy		
Aromatase inhibitor	135 (20.3)	0.549 (0.341 to 0.883)
Anti-estrogen	229 (34.4)	0.558 (0.390 to 0.799)
Number of disease sites		
1	204 (30.6)	0.511 (0.339 to 0.770)
2	169 (25.4)	0.679 (0.421 to 1.096)
≥3	293 (44.0)	0.587 (0.430 to 0.803)



ECOG=Eastern Cooperative Oncology Group; LET=letrozole; PAL=palbociclib; PCB=placebo.

ER pozitiflik düzeyi biyomarker olabilir mi?

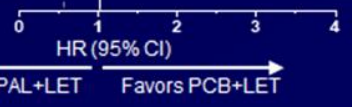
	≤25% 0< H-Score ≤40		>25% to <75% 40< H-Score <170		≥75% H-Score ≥170	
	PAL+LET (n=52)	PCB+LET (n=28)	PAL+LET (n=187)	PCB+LET (n=95)	PAL+LET (n=99)	PCB+LET (n=43)
mPFS, mo	22.2	11.1	25.1	16.8	23.7	14.9
HR (95% CI);	0.55		0.53		0.65	
P value	0.0587		0.0002		0.0760	



Subgroup Analysis of PFS by Biomarker

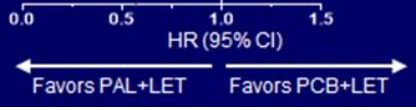
Qualitative Analysis

	n	HR (95% CI)
All patients	666	0.58 (0.46–0.72)
ER+	504	0.57 (0.44–0.74)
ER–	62	0.41 (0.22–0.75)
Rb+	512	0.53 (0.42–0.68)
Rb–	51	0.68 (0.31–1.48)
Cyclin D1+	549	0.56 (0.44–0.71)
Cyclin D1–	15	1.0 (0.29–3.46)
p16+	466	0.52 (0.40–0.67)
p16–	84	0.73 (0.39–1.36)
Ki-67 ≤20%	318	0.53 (0.38–0.74)
Ki-67 >20%	235	0.57 (0.41–0.79)

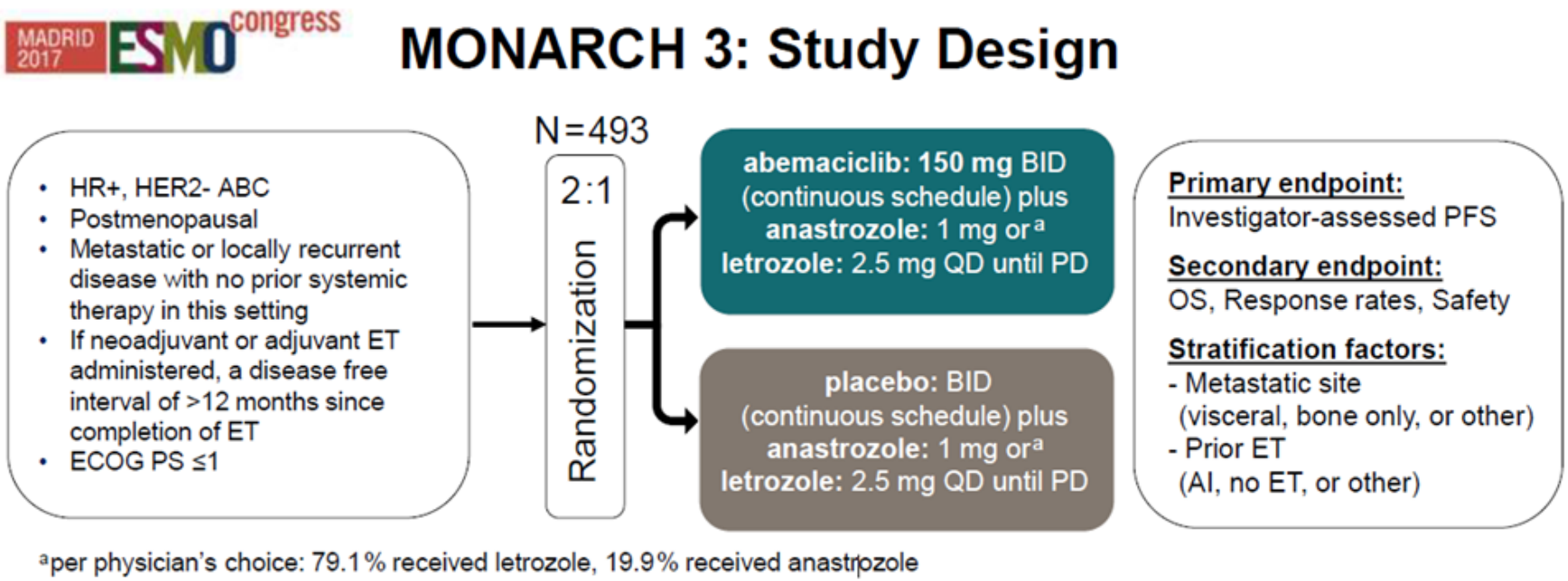


Quantitative Analysis

	Percentile	n	HR (95% CI)
All patients		666	0.58 (0.46–0.72)
ER status	≤25th	142	0.50 (0.32–0.78)
	>25th to <75th	282	0.53 (0.37–0.74)
	≥75th	142	0.65 (0.41–1.05)
Rb status	≤25th	154	0.57 (0.36–0.88)
	>25th to <75th	249	0.46 (0.32–0.67)
	≥75th	160	0.63 (0.42–0.95)
Cyclin D1 status	≤25th	141	0.41 (0.26–0.65)
	>25th to <75th	247	0.69 (0.48–1.00)
	≥75th	176	0.52 (0.34–0.78)
p16 status	≤25th	140	0.74 (0.46–1.20)
	>25th to <75th	258	0.62 (0.44–0.89)
	≥75th	152	0.33 (0.21–0.52)



MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer



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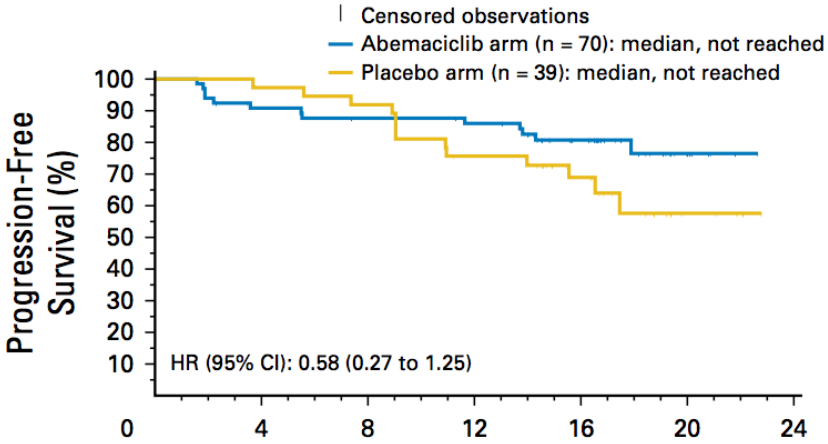
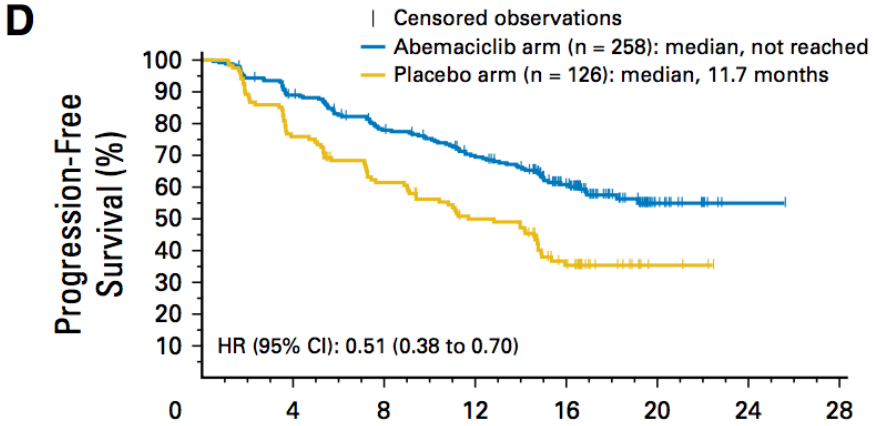
MONARCH 3 & Sadece Kemik Met





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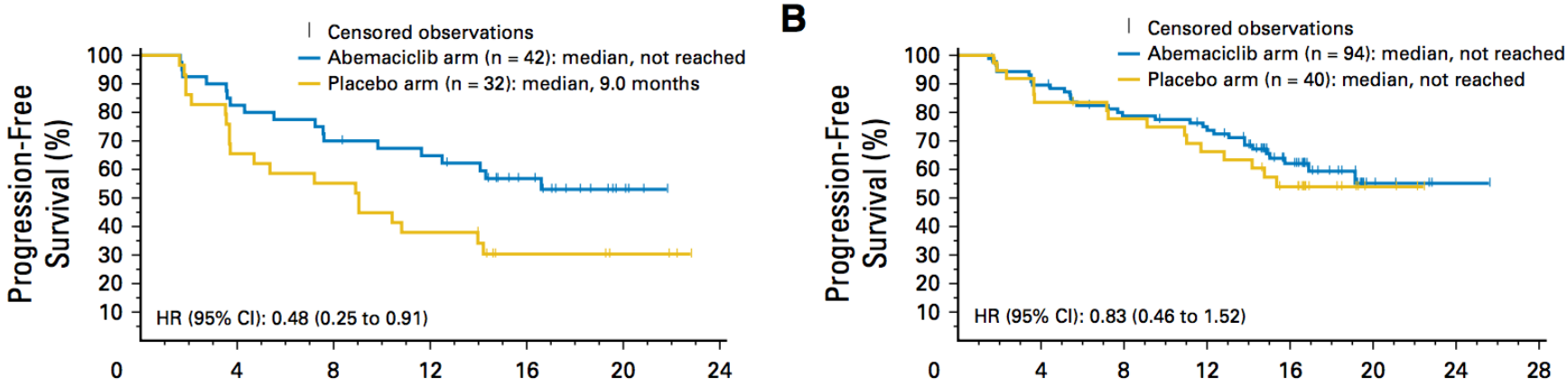
MONARCH 3 & Hastalıksız Sağkalım >36 ay

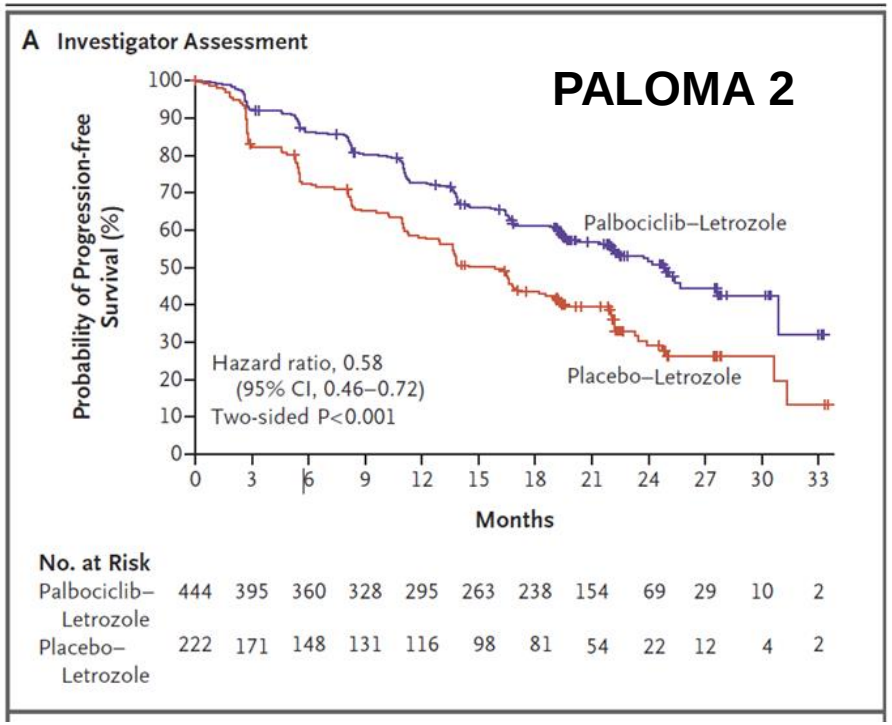


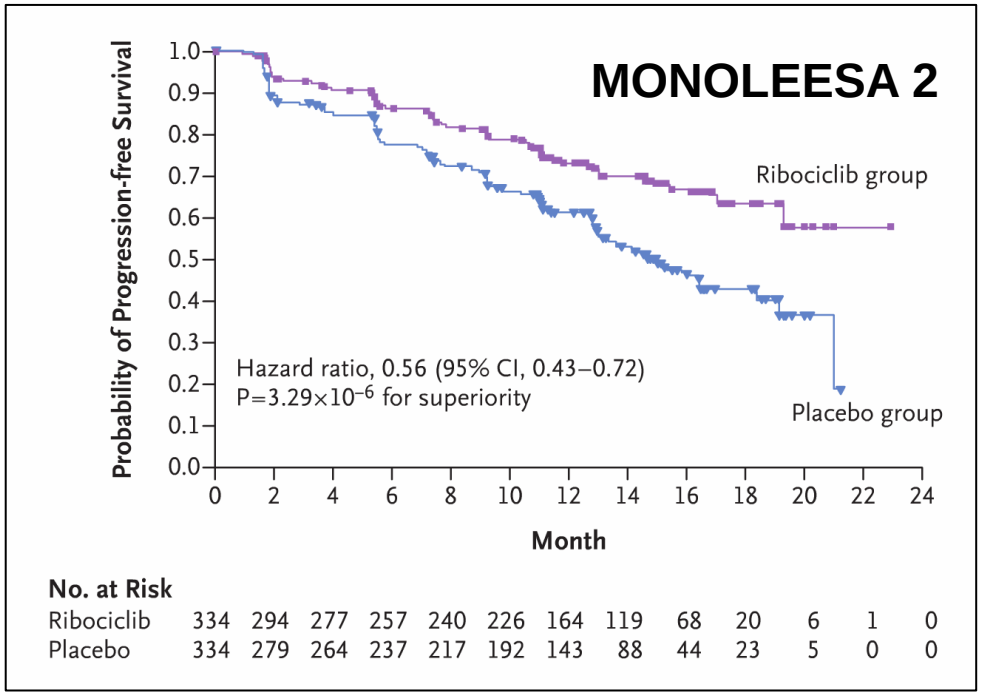
Di Leo JCO 2017

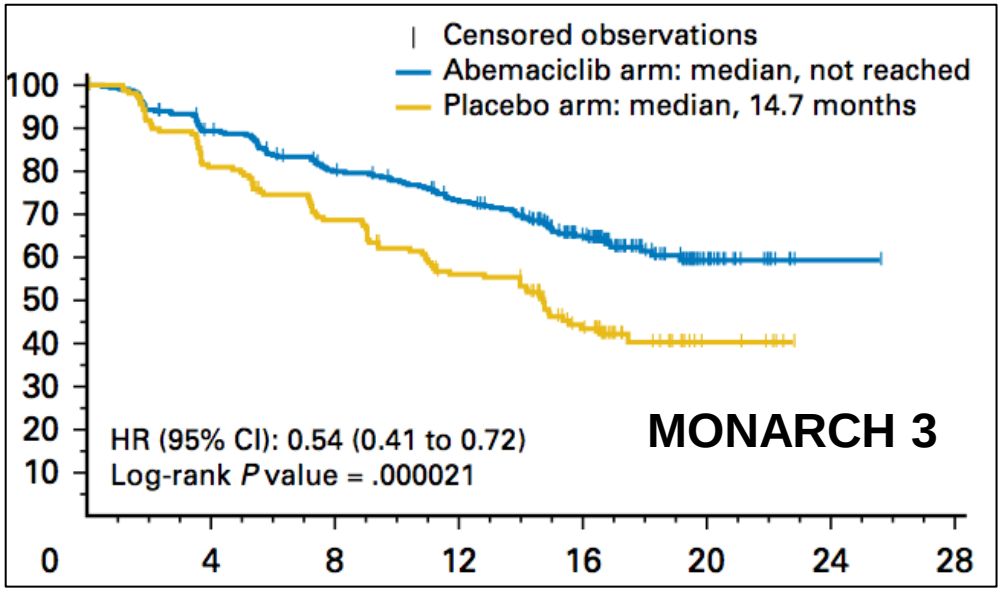
1. Basamak CDK4/6 İnh Çalışmaları

	PALOMA-2 trial	MONALEESA-2 trial	MONALEESA-7 trial	MONARCH-3 trial
cdk4/6inh	Palbociclib	Ribociclib	Ribociclib	Abemacicl
Number of patients AI + placebo arm	222	334	337	165
Median PFS AI + placebo arm	14.5 months	14.7 months	13 months	14.7 months
Number of patients AI + cdk4/6inh arm	444	334	337	328
Median PFS AI + cdk4/6inh arm	24.8 months	Not reached	23.8 months	Not reached
PFS hazard ratio [95%CI]	0.58 [0.46; 0.72]	0.56 [0.43; 0.72]	0.55[a]	0.54 [0.41; 0.72]

Progresyon Riskinde %45 Risk Azalması

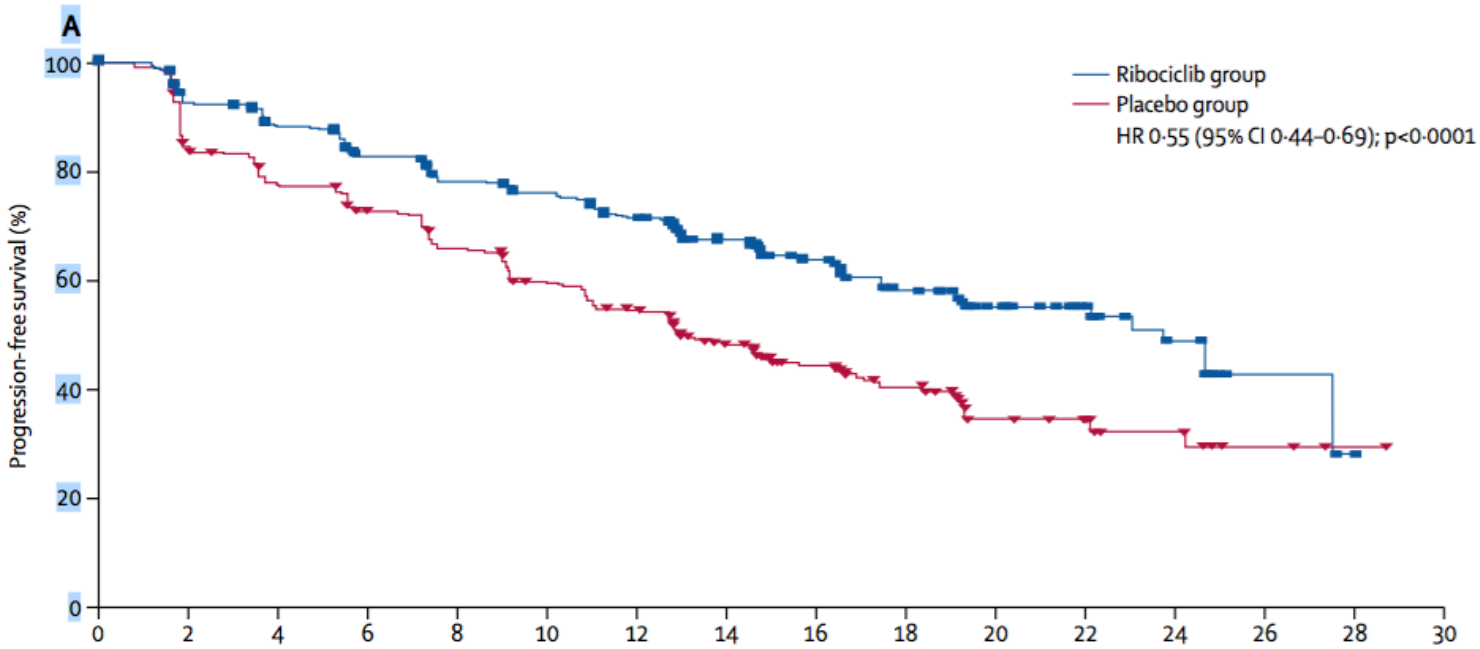

A Investigator Assessment
PALOMA 2
Probability of Progression-free Survival (%)
Palbociclib–Letrozole
Placebo–Letrozole
Hazard ratio, 0.58
(95% CI, 0.46–0.72)
Two-sided P<0.001
Months
No. at Risk
Palbociclib–Letrozole 444 395 360 328 295 263 238 154 69 29 10 2
Placebo–Letrozole 222 171 148 131 116 98 81 54 22 12 4 2


MONOLEESA 2
Probability of Progression-free Survival
Ribociclib group
Placebo group
Hazard ratio, 0.56 (95% CI, 0.43–0.72)
P=3.29×10−6 for superiority
Month
No. at Risk
Ribociclib 334 294 277 257 240 226 164 119 68 20 6 1 0
Placebo 334 279 264 237 217 192 143 88 44 23 5 0 0


Censored observations
Abemaciclib arm: median, not reached
Placebo arm: median, 14.7 months
HR (95% CI): 0.54 (0.41 to 0.72)
Log-rank P value = .000021
MONARCH 3

Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial

Debu Tripathy, Seock-Ah Im, Marco Colleoni, Fabio Franke, Aditya Bardia, Nadia Harbeck, Sara A Hurvitz, Louis Chow, Joohyuk Sohn, Keun Seok Lee, Saul Campos-Gomez, Rafael Villanueva Vazquez, Kyung Hae Jung, K Govind Babu, Paul Wheatley-Price, Michelino De Laurentiis, Young-Hyuck Im, Sherko Kuemmel, Nagi El-Saghir, Mei-Ching Liu, Gary Carlson, Gareth Hughes, Ivan Diaz-Padilla, Caroline Germa, Samit Hirawat, Yen-Shen Lu



Dirençli MMK & CDK İnhibitörleri

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 16, 2015 VOL. 373 NO. 3

Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer

Nicholas C. Turner, M.D., Ph.D., Jungsil Ro, M.D., Fabrice André, M.D., Ph.D., Sherene Loi, M.D., Ph.D., Sunil Verma, M.D., Hiroji Iwata, M.D., Nadia Harbeck, M.D., Sibylle Loibl, M.D., Cynthia Huang Bartlett, M.D., Ke Zhang, Ph.D., Carla Giorgetti, Ph.D., Sophia Randolph, M.D., Ph.D., Maria Koehler, M.D., Ph.D., and Massimo Cristofanilli, M.D.

PALOMA - 3

PALOMA 3

- HR+ HER2– ABC
- Pre-/peri-[a] or postmenopausal[b]
- Progressed on prior endocrine therapy:
  - On or within 12 mo of completion of adjuvant treatment
  - On or within 1 mo of treatment for ABC
- ≤1 prior chemotherapy regimen for advanced cancer

2:1 randomisation

N=521[c]

Stratification:

- Visceral metastases
- Sensitivity to prior hormonal therapy*
- Pre-/peri- vs. postmenopausal

n=347

Palbociclib
(125 mg QD;
3 wks on/1 wk off)
+
Fulvestrant[d]
(500 mg IM q4w)

n=174

Placebo
(3 wks on/1 wk off)
+
Fulvestrant[d]
(500 mg IM q4w)

- PEP: investigator-assessed PFS
- SEP: ORR, CBR (CR, PR, or SD for ≥ 24 wks), OS, PRO, safety

*Documented clinical benefit (≥24 weeks) to ≥1 prior HT in the met setting or ≥24 months of adjuvant hormonal therapy before recurrence.

PALOMA 3 & Hasta Özellikleri

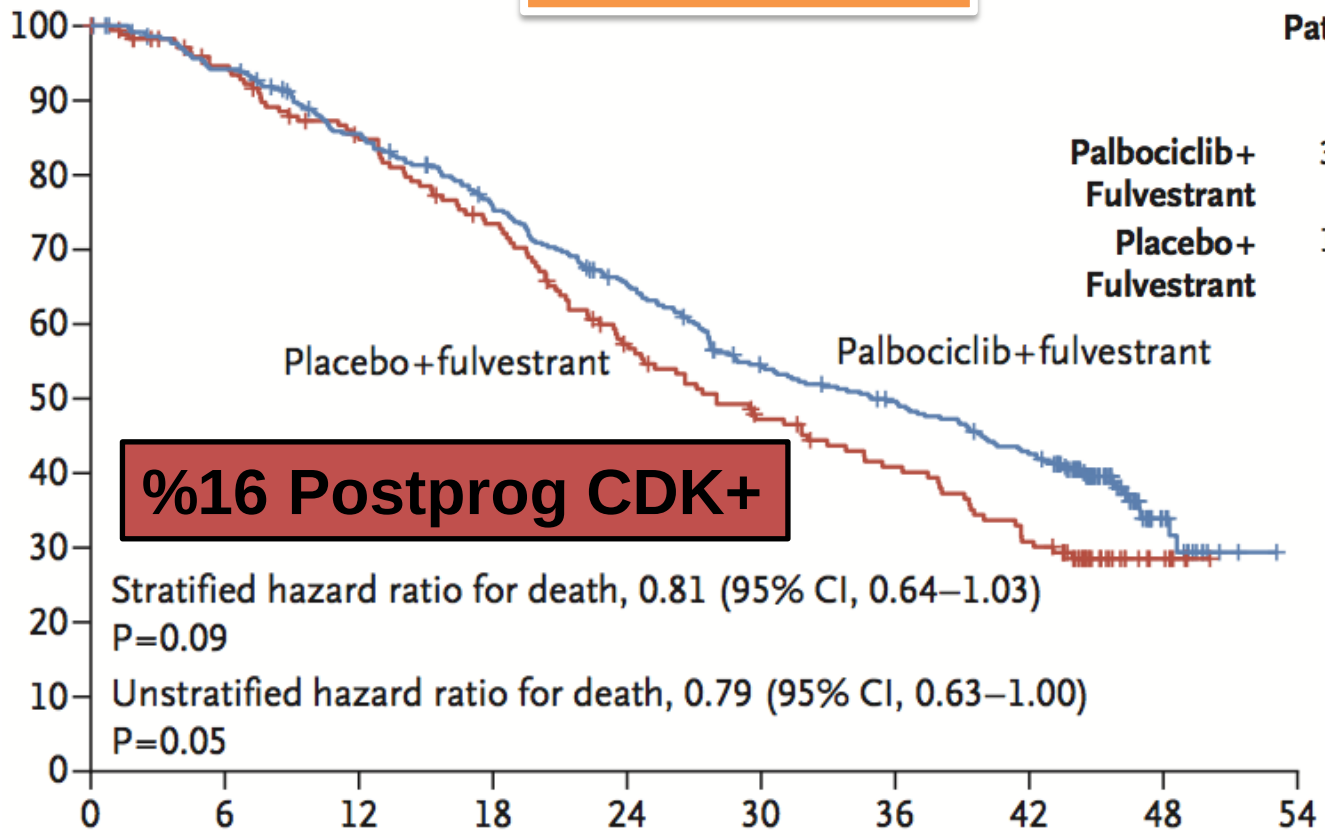
	Intention-to-treat population	
	Fulvestrant plus palbociclib (n=347)	Fulvestrant plus placebo (n=174)
Median age, years (range)	57 (30–88)	56 (29–80)
Self-reported race		
White	252 (73%)	133 (76%)
Asian	74 (21%)	31 (18%)
Black and others	21 (6%)	10 (6%)
ECOG performance status		
0	206 (59%)	116 (67%)
1	141 (41%)	58 (33%)
Menopausal status		
Premenopausal or perimenopausal	72 (21%)	36 (21%)
Postmenopausal	275 (79%)	138 (79%)
Non-measurable disease		
Bone	75 (22%)	36 (21%)
Others	4 (1%)	0
Measurable disease		
Any measurable disease	268 (77%)	138 (79%)
Visceral disease*	206 (59%)	105 (60%)
Lung involvement	100 (29%)	45 (26%)
Liver involvement	127 (37%)	81 (47%)
Peritoneal involvement	2 (1%)	1 (1%)
Brain or pleural involvement, or both	4 (1%)	2 (1%)
Number of previous lines of endocrine treatment		
1	160 (46%)	91 (52%)
2	140 (40%)	61 (35%)
≥3	47 (14%)	22 (13%)

	Intention-to-treat population	
	Fulvestrant plus palbociclib (n=347)	Fulvestrant plus placebo (n=174)
(Continued from previous page)		
Purpose of most recent treatment†		
Adjuvant therapy	74 (21%)	40 (23%)
Treatment of advanced or metastatic breast cancer	273 (79%)	133 (76%)
Disease-free interval‡		
Data available	233 (67%)	123 (71%)
>24 months	192 (82%)	101 (82%)
12–24 months	30 (13%)	19 (15%)
<12 months	11 (5%)	3 (2%)
Previous endocrine therapy		
Aromatase inhibitors	137 (39%)	70 (40%)
Tamoxifen	51 (15%)	23 (13%)
Aromatase inhibitors and tamoxifen	159 (46%)	81 (47%)
Previous chemotherapy		
Neoadjuvant or adjuvant therapy only§	139 (40%)	74 (43%)
Treatment of metastatic disease (with or without adjuvant or neoadjuvant)	113 (33%)	64 (37%)
Previous sensitivity to endocrine therapy¶		
Yes	274 (79%)	136 (78%)
No	73 (21%)	38 (22%)
Oestrogen-receptor or progesterone-receptor status confirmed by central laboratory testing		
Oestrogen-receptor and progesterone-receptor positive		
≥Median of distribution	81 (23%)	40 (23%)
<Median of distribution	71 (20%)	29 (17%)
Oestrogen-receptor or progesterone-receptor positive		
≥Median of distribution	179 (52%)	100 (57%)
<Median of distribution	165 (48%)	90 (52%)
Central laboratory tested, median H-score (IQR); mean (SD)‖		
Oestrogen receptor	110 (40–160); 107 (74)	114 (23–150); 99 (72)
Progesterone receptor	10 (0–100); 53 (68)	20 (0–100); 51 (62)

Cristofanilli Lancet 2016

PALOMA 3 & Final OS

ESMO 2018



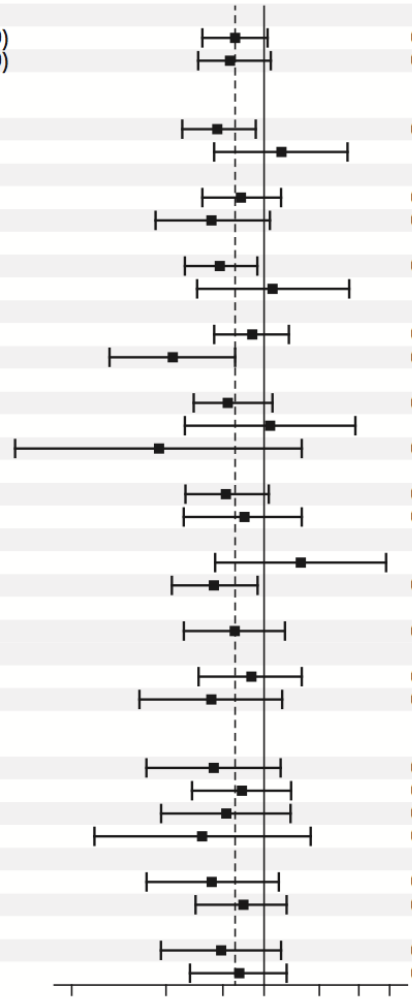
	No. of Patients	Median Overall Survival (95% CI)
		mo
Palbociclib+ Fulvestrant	347	34.9 (28.8–40.0)
Placebo+ Fulvestrant	174	28.0 (23.6–34.6)

%16 Postprog CDK+

Cristofanilli NEJM 2018

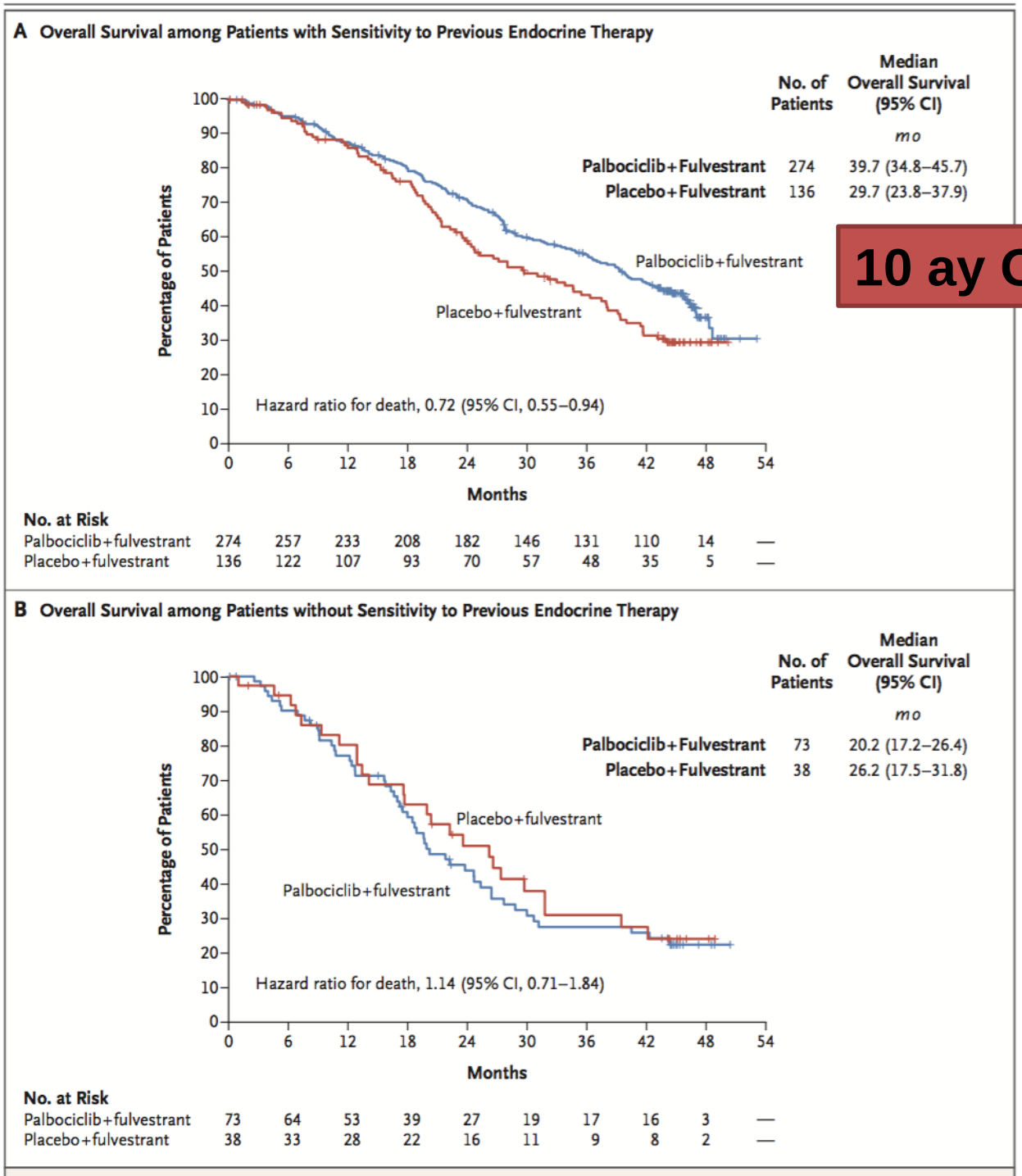
PALOMA 3 OS & Altgrup

Subgroup	No. of Patients (%)	Hazard Ratio for Death (95% CI)	Median Overall Survival (95% CI) Palbociclib+ fulvestrant (mo)	Median Overall Survival (95% CI) Placebo+ fulvestrant (mo)	P Value for Interaction
All patients					
Stratified analysis	521 (100)	0.81 (0.64–1.03)	34.9 (28.8–40.0)	28.0 (23.6–34.6)	
Unstratified analysis	521 (100)	0.79 (0.63–1.00)	34.9 (28.8–40.0)	28.0 (23.6–34.6)	
Sensitivity to previous hormonal therapy					0.12
Yes	410 (79)	0.72 (0.55–0.94)	39.7 (34.8–45.7)	29.7 (23.8–37.9)	
No	111 (21)	1.14 (0.71–1.84)	20.2 (17.2–26.4)	26.2 (17.5–31.8)	
Site of metastatic disease					0.44
Visceral	311 (60)	0.85 (0.64–1.13)	27.6 (24.4–31.2)	24.7 (20.8–31.8)	
Nonvisceral	210 (40)	0.69 (0.46–1.04)	46.9 (39.3–NE)	35.4 (24.6–NE)	
Menopausal status at study entry					0.25
Postmenopausal	413 (79)	0.73 (0.57–0.95)	34.8 (28.8–40.1)	27.1 (22.8–32.1)	
Premenopausal or perimenopausal	108 (21)	1.07 (0.61–1.86)	38.0 (24.4–NE)	38.0 (22.2–NE)	
Age					0.04
<65 yr	392 (75)	0.91 (0.70–1.20)	31.4 (27.4–39.3)	29.7 (24.0–38.0)	
≥65 yr	129 (25)	0.52 (0.33–0.82)	39.7 (30.7–47.0)	23.8 (20.0–33.8)	
Race or ethnic group					0.38
White	385 (74)	0.78 (0.60–1.01)	31.7 (27.6–38.9)	26.2 (21.4–32.1)	
Asian	105 (20)	1.04 (0.57–1.93)	43.7 (28.8–NE)	41.7 (29.7–NE)	
Black or other	29 (6)	0.47 (0.16–1.32)	37.3 (23.8–NE)	19.7 (4.4–NE)	
Hormone-receptor status					0.70
ER-positive and PR-positive	351 (67)	0.77 (0.57–1.03)	39.3 (32.0–45.7)	31.8 (24.0–39.1)	
ER-positive and PR-negative	142 (27)	0.86 (0.56–1.32)	27.6 (22.0–38.9)	24.3 (17.5–37.5)	
Disease-free interval					0.08
≤24 mo	62 (12)	1.31 (0.71–2.44)	19.9 (15.6–27.6)	20.3 (9.3–42.2)	
>24 mo	292 (56)	0.70 (0.52–0.96)	39.3 (31.7–44.5)	29.5 (22.8–38.1)	
Previous chemotherapy					0.66
Neoadjuvant or adjuvant treatment only	214 (41)	0.81 (0.56–1.17)	36.6 (28.9–42.3)	27.4 (22.2–39.5)	
Treatment for metastatic disease	177 (34)	0.91 (0.63–1.32)	25.6 (21.4–30.1)	26.2 (20.0–37.5)	
None	130 (25)	0.68 (0.41–1.15)	46.2 (36.5–NE)	29.7 (22.8–NE)	
Previous lines of therapy for metastatic disease					0.88
0	114 (22)	0.70 (0.43–1.14)	36.1 (27.6–43.7)	24.7 (19.5–34.6)	
1	225 (43)	0.86 (0.60–1.22)	38.0 (27.7–46.5)	33.8 (23.5–41.4)	
2	131 (25)	0.76 (0.48–1.22)	30.0 (23.0–40.1)	24.3 (20.0–29.7)	
≥3	51 (10)	0.64 (0.29–1.40)	34.8 (26.1–NE)	27.1 (5.3–NE)	
ESR1 mutation status					0.60
Positive	106 (20)	0.69 (0.43–1.12)	35.6 (23.6–42.0)	24.6 (19.7–33.0)	
Negative	289 (55)	0.85 (0.61–1.19)	36.5 (28.0–43.1)	31.8 (22.8–39.1)	
PIK3CA mutation status					0.64
Positive	133 (26)	0.74 (0.48–1.14)	28.6 (25.3–39.3)	22.2 (15.7–29.5)	
Negative	262 (50)	0.84 (0.59–1.18)	38.8 (28.9–44.5)	33.0 (24.3–41.6)	



Cristofanilli NEJM 2018

PALOMA 3
OS & Endokrin Duyarlı



10 ay OS FARKI

Cristofanilli NEJM 2018

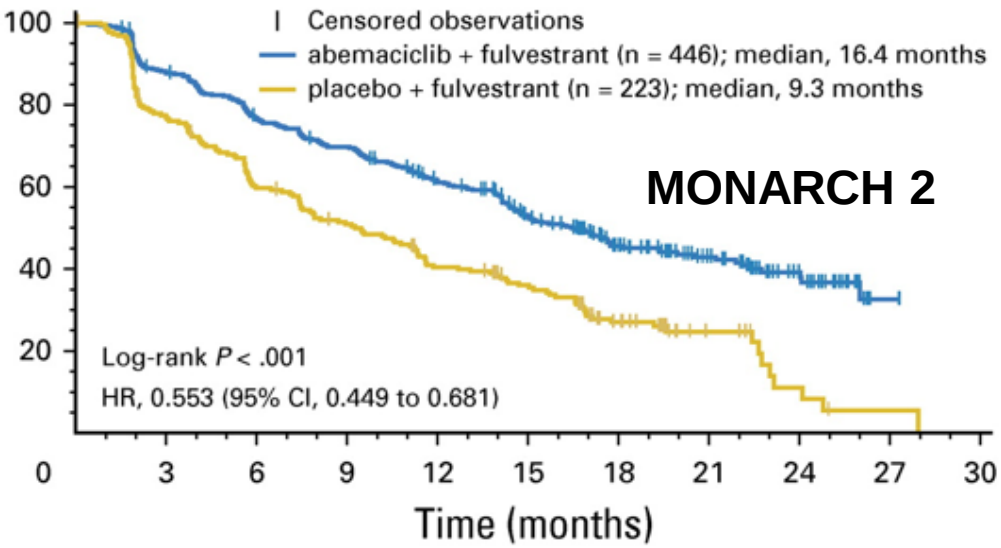
PALOMA-3: Grad ¾ Toksisite

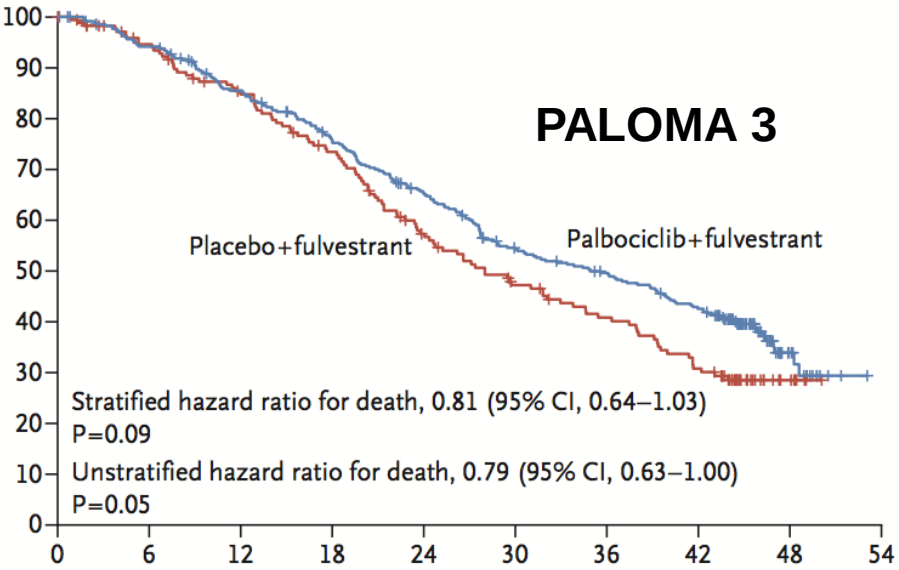
Nonhematologic AE, n	Palbociclib + Fulvestrant (n = 345)	Placebo + Fulvestrant (n = 172)
Infections	6	1
Fatigue	8	0
Headache	2	0
Vomiting	1	0
Decreased appetite	3	0
Rash	2	0
Back pain	4	0
Arthralgia	1	0
Stomatitis	2	0
Dizziness	1	0
Dyspnea	0	1
Pyrexia	1	0
Insomnia	1	0

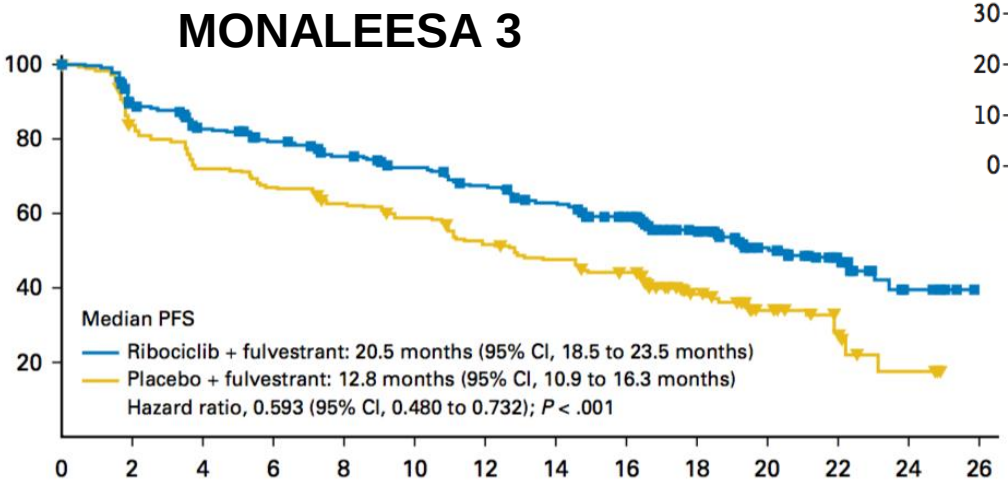
Hematologic Event, n (%)	Palbociclib + Fulvestrant (n = 345)	Placebo + Fulvestrant (n = 172)
Neutropenia	223 (65)	1 (< 1)
Anemia	10 (3)	3 (2)
Leukopenia	93 (27)	2 (1)
Thrombocytopenia	6 (2)	0

- FN benzer (0.9% vs 0.6%)
- Tedavi kesilmesi benzer (4% vs 2%)

Cristofanilli M, et al. SABCS 2015. Abstract P4-13-01.


MONARCH 2
Censored observations
abemaciclib + fulvestrant (n = 446); median, 16.4 months
placebo + fulvestrant (n = 223); median, 9.3 months
Log-rank P < .001
HR, 0.553 (95% CI, 0.449 to 0.681)
Time (months)


PALOMA 3
Placebo+fulvestrant
Palbociclib+fulvestrant
Stratified hazard ratio for death, 0.81 (95% CI, 0.64–1.03)
P=0.09
Unstratified hazard ratio for death, 0.79 (95% CI, 0.63–1.00)
P=0.05


MONALEESA 3
Median PFS
Ribociclib + fulvestrant: 20.5 months (95% CI, 18.5 to 23.5 months)
Placebo + fulvestrant: 12.8 months (95% CI, 10.9 to 16.3 months)
Hazard ratio, 0.593 (95% CI, 0.480 to 0.732); P < .001

MONARCH 1

Dirençli MMK, Abemasiklib monoterapisi

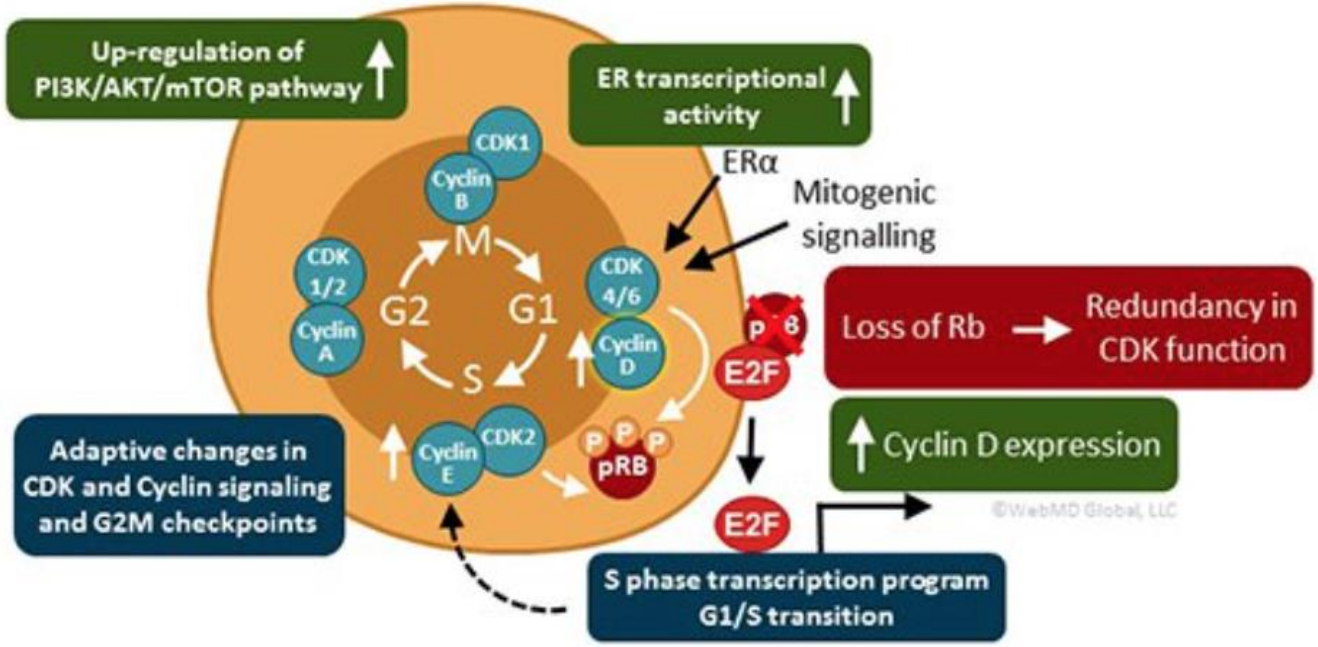
- ORR %19.7
- CBR %42.4
- mPFS 6 ay
- mOS 17.7 ay

CDK4/6 Resistance: Re-wiring of cell signalling pathways

Strategies against CDK4/6 resistance

1. Switch to other CDK4/6 + endocrine therapy
2. Target other cell cycle regulators (CDK1/2, CDK7, Wee-1)
3. Co-targeting other cell signalling pathways (mTOR)

Adaptive network changes make it difficult to identify dominant drivers



Dixon *N J Sci*. 2014

MADRID 2017 ESMO congress

Second line (and beyond) efficacy of endocrine ± targeted agents

Phase III trial	PALOMA 3 (n=521)	MONARCH 2 (n=669)	BOLERO 2 (n=724)
Targeted agent	Palbociclib	Abemaciclib	Everolimus
Endocrine agent	Fulvestrant	Fulvestrant	Exemestane
PFS	11.2 vs. 4.6 months	16.4 vs. 9.3 months	10.6 vs. 4.1 months
HR (PFS)	0.580	0.553	0.43
Most frequent G3/4 side effects	neutropenia, leukopenia, anaemia	Diarrhoea, neutropenia, leukopenia, anaemia, nausea, fatigue	Stomatitis, anaemia, dyspnea, hyperglycemia, fatigue, pneumonitis

Turner et al. SABCS 2016; Christofanilli et al. 2016; Sledge et al. 2017; Baselga et al. 2012

HR, hazard ratio; PFS, progression-free survival

Endokrin Tedavi & mTOR inh

	Treatment	Setting	Patient sample	Phase	n	Effect on primary endpoint
NCT00107016[46]	Letrozole with or without everolimus	Neoadjuvant	Endocrine naive	Phase 2	270	Clinical response: 68% *vs* 59% (p=0·06; prespecified significance <0·1)
TAMRAD[47]	Tamoxifen with or without everolimus	Metastatic	Resistant to aromatase inhibitor	Phase 2	111	Clinical benefit rate: 61% (95% CI 47–74) *vs* 42% (29–56)
BOLERO-2[8]	Exemestane with or without everolimus	Metastatic	Resistant to non-steroidal aromatase inhibitor	Phase 3 registration	724	Median PFS: 6·9 months *vs* 2·8 months (HR 0·43, 95% CI 0·35–0·54; p<0·001)

HR=hazard ratio. PFS=progression-free survival.

Turner 2015

Everolimus + Tmx

TAMRAD Faz 2 (n: 111)

- Önceden Aİ almış HR(+), HER2(-) MMK **tamoksifen** +/- everolimus (10mg/g)
- **Primer sonlanım**:
  - klinik yarar oranı %41 vs 61 (p= 0.04)
- **Sekonder sonlanım**:
  - TTP (4.5 vs 8.6 ay, p: .002)
  - OS yararı (32 vs NR, HR: 0.32, p .001)

Tabakalandırma:

Primer ED: adj horm ted sırasında veya met.ik hastalıkta ilk 6 ayda progresyon

Sekonder ED: adj ted sonrası geç nüks (>6ay) veya met evrede yanıt sonrası nüks

Bachelot T, JCO 2012

BOLERO - 2

Key Slides BOLERO-2 News

BOLERO-2 (Ph III)

Everolimus in advanced BC

N=724
- Postmenopausal ER+
- Unresectable locally advanced or metastatic BC
- Recurrence or progression after letrozole or anastrozole

R 2:1

EVE (10 mg daily) + **EXE** (25 mg daily) (n=485)

Placebo + **EXE** (25 mg daily) (n=239)

Endpoints
- Primary: PFS (local assessment)
- Secondary: OS, ORR, QOL, safety, bone markers, PK

Stratification
- sensitivity to prior hormone therapy and presence of visceral mestastases

BC: breast cancer; ER+: estrogen receptor-positive; EVE: everolimus; EXE: exemestane; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PK: pharmacokinetics; QOL: quality of life

NSAI %100, Tmx %48,

Fulvestrant %16, KT %68

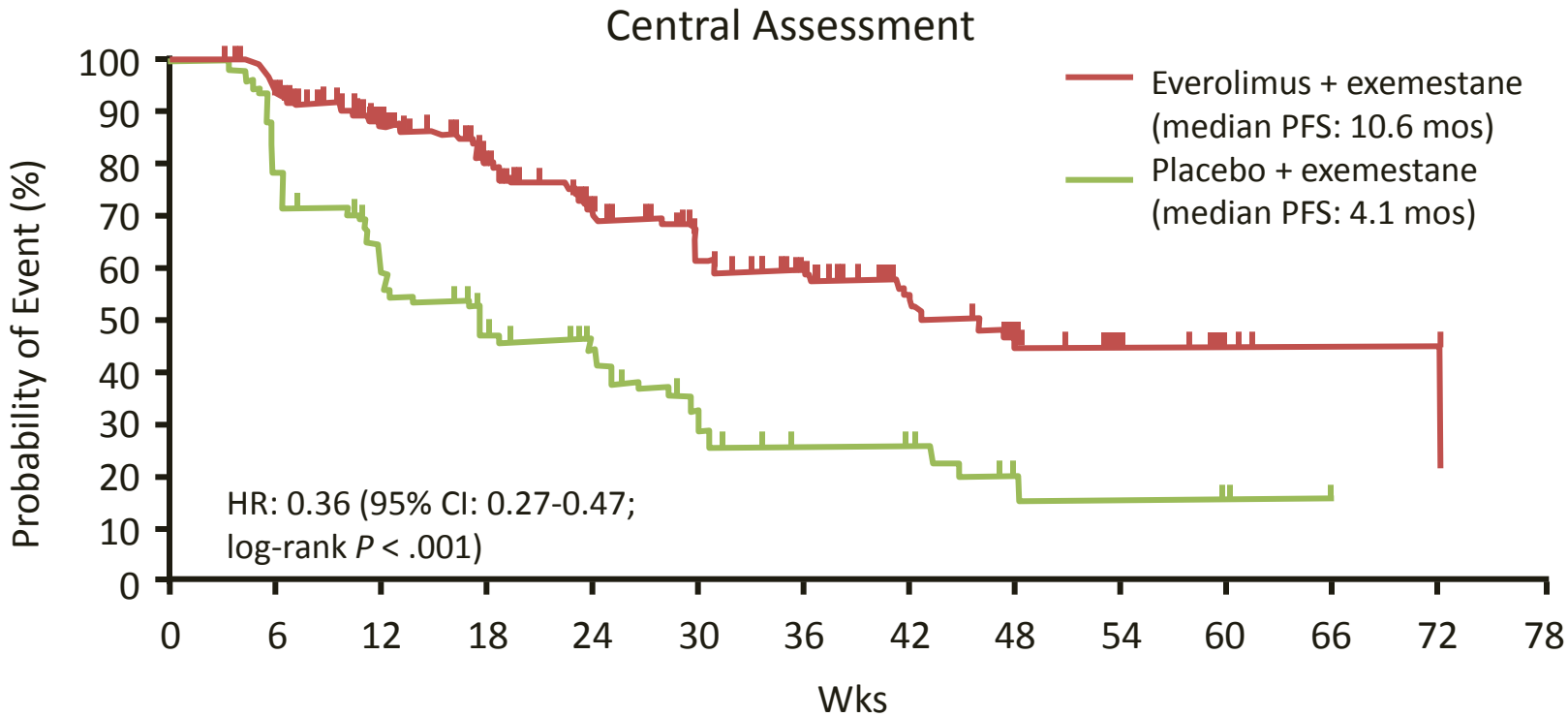
Mod. da Hortobagyi G, et al. SABCS 2011

© 2014 – FSE/ANM

Baselga J, et al. N Engl J Med. 2012

BOLERO-2 & PFS

ORR %1.3 vs 12.0 (p<.0001)



Everolimus	485	385	281	201	132	102	67	43	28	18	9	3	2	0
Placebo	239	168	94	55	33	20	11	11	6	3	3	1	0	0

Baselga J, et al. N Engl J Med. 2012

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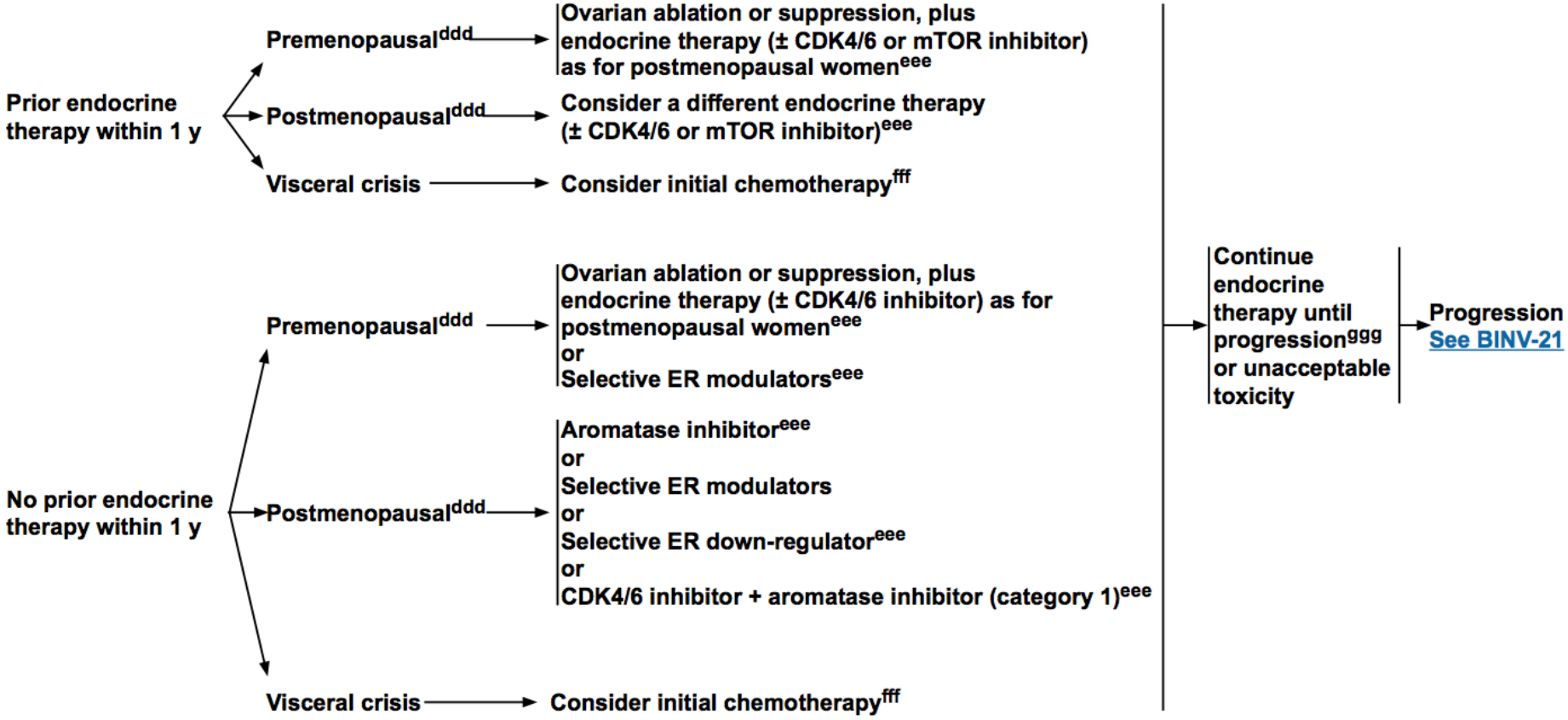
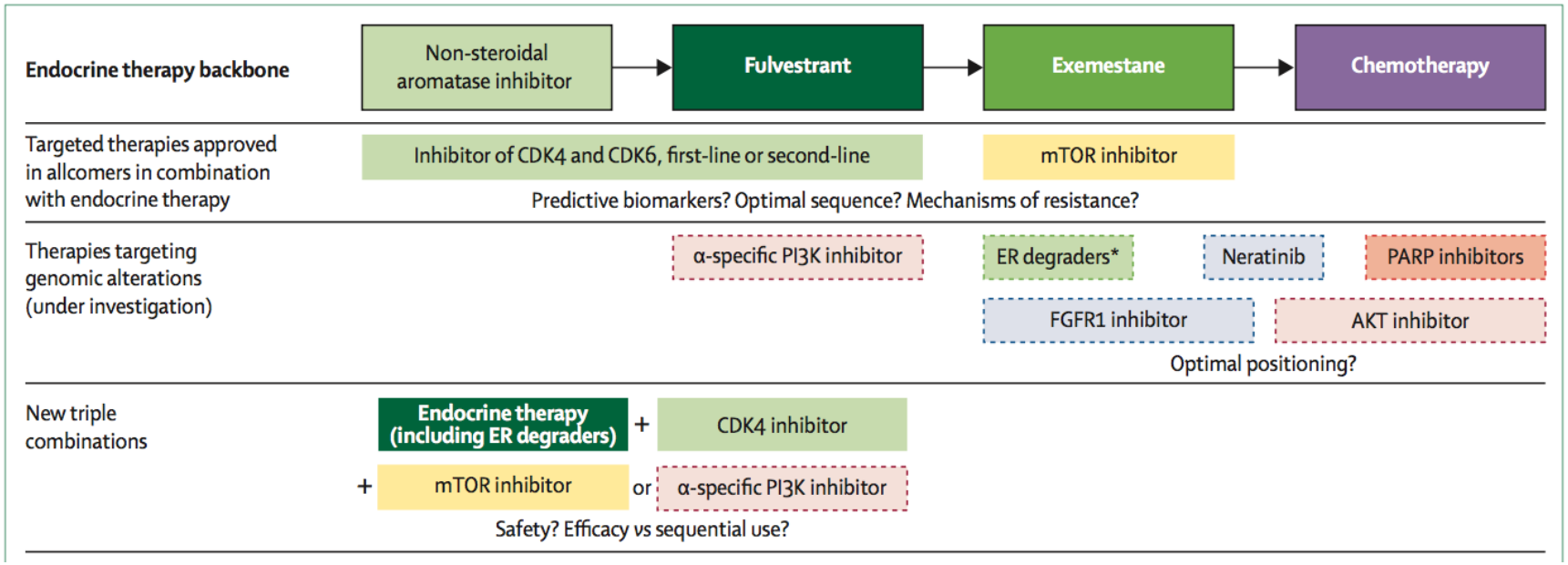
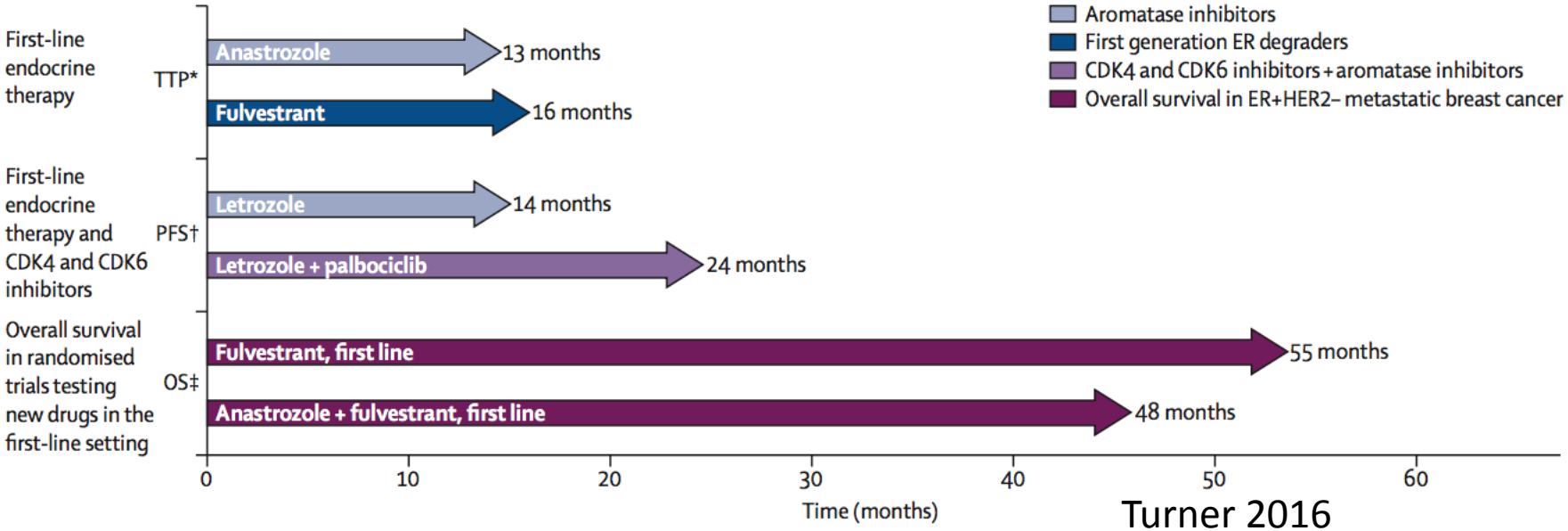
SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE ER AND/OR PR POSITIVE; HER2 NEGATIVE[c]



ET Algoritma





Turner 2016

HR+HER2- MMK: Özet

- Progresyonda endokrin temelli ardışık tedavi
- Hedefli tedavi eklemek etkinliği arttıran ve dirençte etkili
  - CDKİ/ mTOR
- Yeni tartışmalar
  - İlaca ulaşım
  - sekans
  - proaktif yan etki takibi yakın hasta-heki gerektirmekte,
  - ilaç-ilaç etkileşimi

Teşekkür ederim

Olgu; 47y, K

- Ekim 2014; Sağ memede kitle

- Özg: HT, G5P2Y2, toplam 3 yıl emzirmiş
- İlk adet yaşı:13, sat: 01/10/2014
- OKS 8 yıl kullanmış, HRT kullanmamış
- Soyg: Anne meme ca (50 yaşında tanı almış)

Primer Cerrahi ve Tedavi

- Eylül 2014 Meme bx
  - Pat; IDK, gr 2, ER%90, PR %90, HER2-, ki67 %20
- Eylül 2014 Sol MKC+ ALND
  - Pat; IDK, 32/33 met LN
  - T1N3M0
- Adjuvan 4 kür AC- 12hf Pakli
- Tamoksifen 3 yıl

Metastatik Hastalık - Mayıs 2017

- Toraks BT
  - Toraks duvarı sağ lateralde 6 mm LAP
  - Vertebral kolonda sklerotik met
  - KC 12 mm hipodens lezyon met?

- Abd Dinamik MR
  - KC segm 4-5-7’de EB 21 mm 3 adet hipervask met
  - sağ böbrek alt pol 2 cm met
  - sağ femur boynu ve sağ iliak kemikte L4 te met

Metastatik Hastalık - Mayıs 2017

- Torakolomber MR: C6, T7-8-9-12, L4,S2 vertebral met
- TVKS: sağ 9.kostada, sağ asetabulum, sağ sakroiliak, sağ femur dital yeni izlenen lezyonlar met ?
- C6 vertebra opere;
  - Karsinom met, ER %90, PR %70, HER2-, ki67 %50
- CA15-3: 86 U/ml, CEA 10ng/ml **
- Torakal MR (Eylül 2017): multipl vertebral met,T9 yükseklik kaybı,**kc de multipl met**
- T9 vertebra opere

Tedavi ?

- AI
- Fulvestrant
- CDK+ AI
- CDK+ Fulvestrant
- mTOR+ Eksemestan
- Kemoterapi
- Diğer

MMK 1. Basamak Tedavi

- Ribosiklib- Letrazol- Zoledronik asid
- Sırtta pigmentasyon cilt döküntüsü
  - RT recall fenomeni
- Nisan 2018 6. ay SD
- Ekim 2018 Yeni yanıt değerlendirme SD, Tm marker yanıt+