HR Pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

Dr. Deniz Tural
Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi
Tıbbi Onkoloji

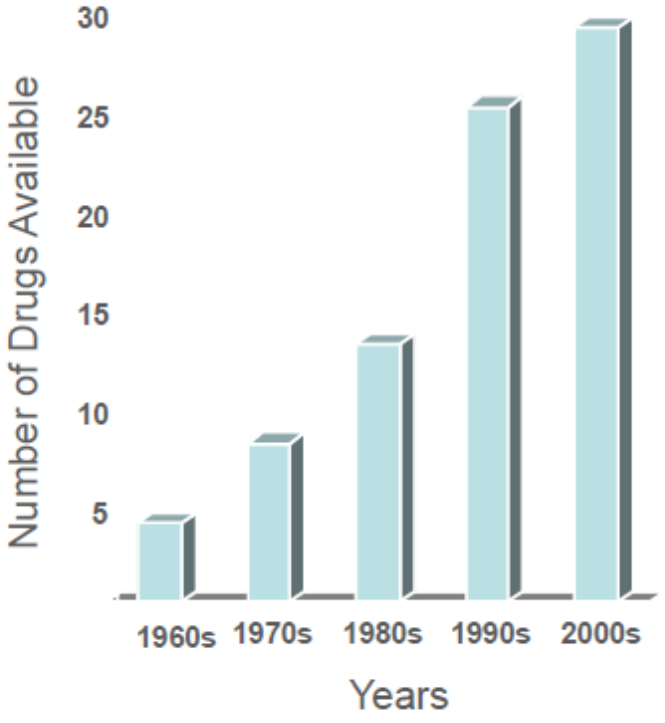
İnsidans ve Epidemiyoloji

	Common Types of Cancer	Estimated New Cases 2016	Estimated Deaths 2016
1.	**Breast Cancer (Female)**	**246,660**	**40,450**
2.	Lung and Bronchus Cancer	224,390	158,080
3.	Prostate Cancer	180,890	26,120
4.	Colon and Rectum Cancer	134,490	49,190
5.	Bladder Cancer	76,960	16,390
6.	Melanoma of the Skin	76,380	10,130
7.	Non-Hodgkin Lymphoma	72,580	20,150
8.	Thyroid Cancer	64,300	1,980
9.	Kidney and Renal Pelvis Cancer	62,700	14,240
10.	Leukemia	60,140	24,400

Female breast cancer represents 14.6% of all new cancer cases in the U.S.

14.6%

İnsidans ve Epidemiyoloji



1950s: Cyclophosphamide, methotrexate

1960s: 5-fluorouracil

1970s: Doxorubicin, tamoxifen

1980s: Mitoxantrone, megestrol acetate, goserelin, leuprolide

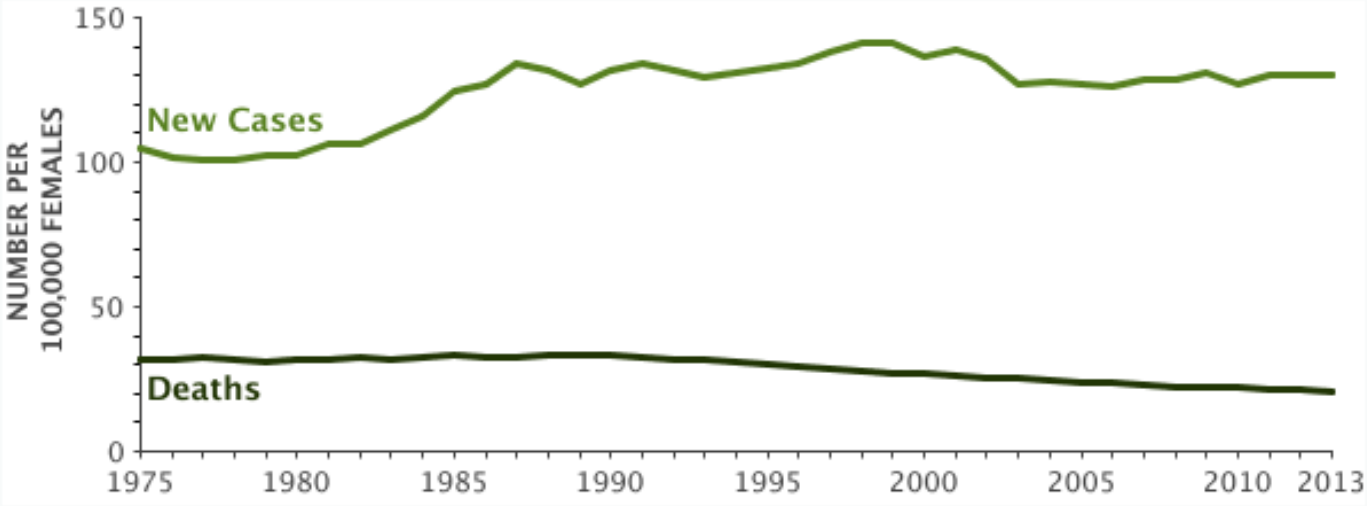
1990s: Paclitaxel, docetaxel, vinorelbine, trastuzumab, capecitabine, gemcitabine, epirubicin, toremifene, anastrozole, letrozole, exemestane

2000s: *nab*-paclitaxel, lapatinib, ixabepilone, eribulin, denosumab, everolimus, palbociclib, fulvestrant, T-DM1, pertuzumab…

İnsidans ve Epidemiyoloji

New Cases, Deaths and 5-Year Relative Survival

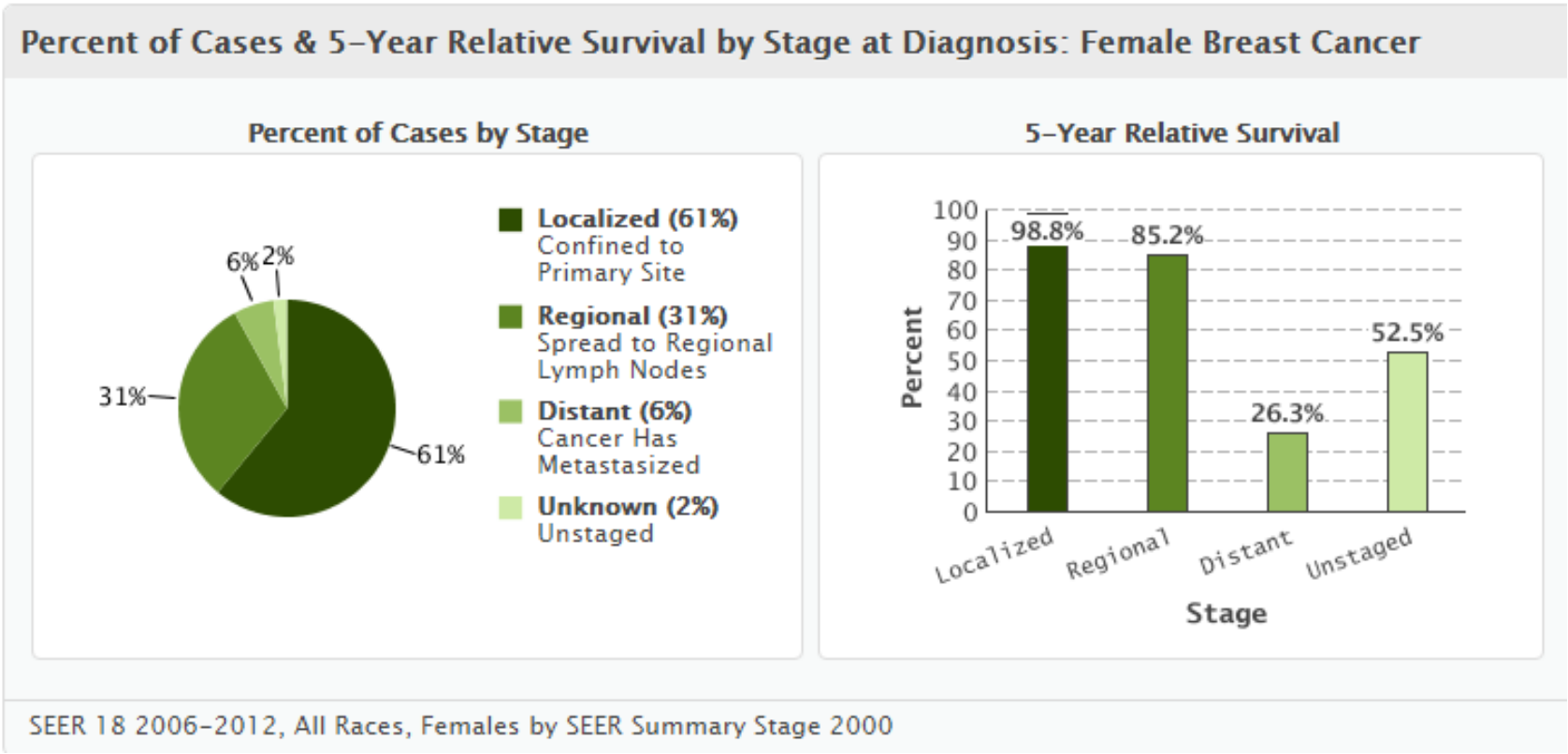
View Data Table



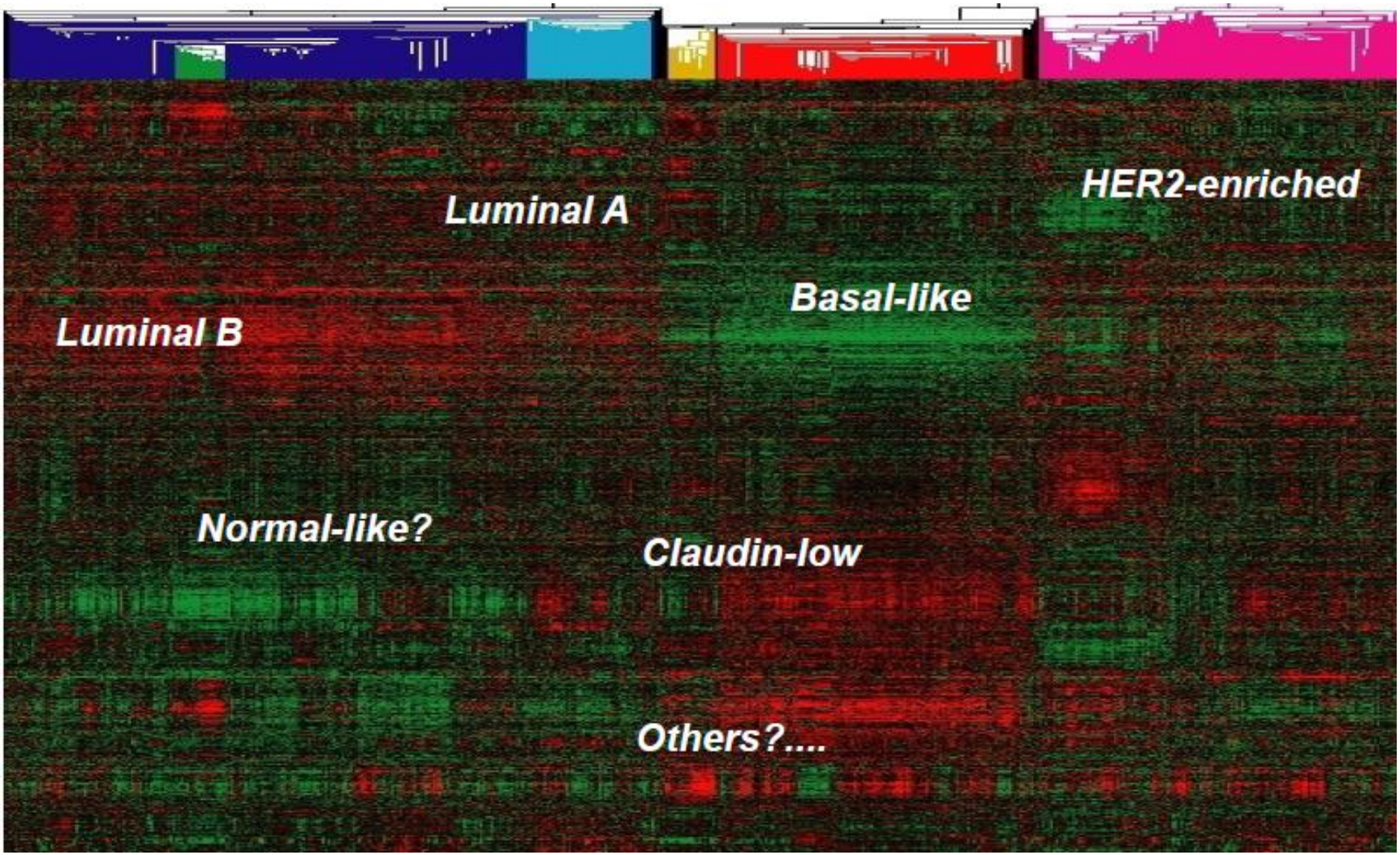
Year	1975	1980	1985	1990	1995	2000	2004	2008
5-Year Relative Survival	75.2%	74.9%	78.4%	84.6%	86.8%	90.2%	89.9%	90.6%

SEER 9 Incidence & U.S. Mortality 1975-2013, All Races, Females. Rates are Age-Adjusted.

İnsidans ve Epidemiyoloji

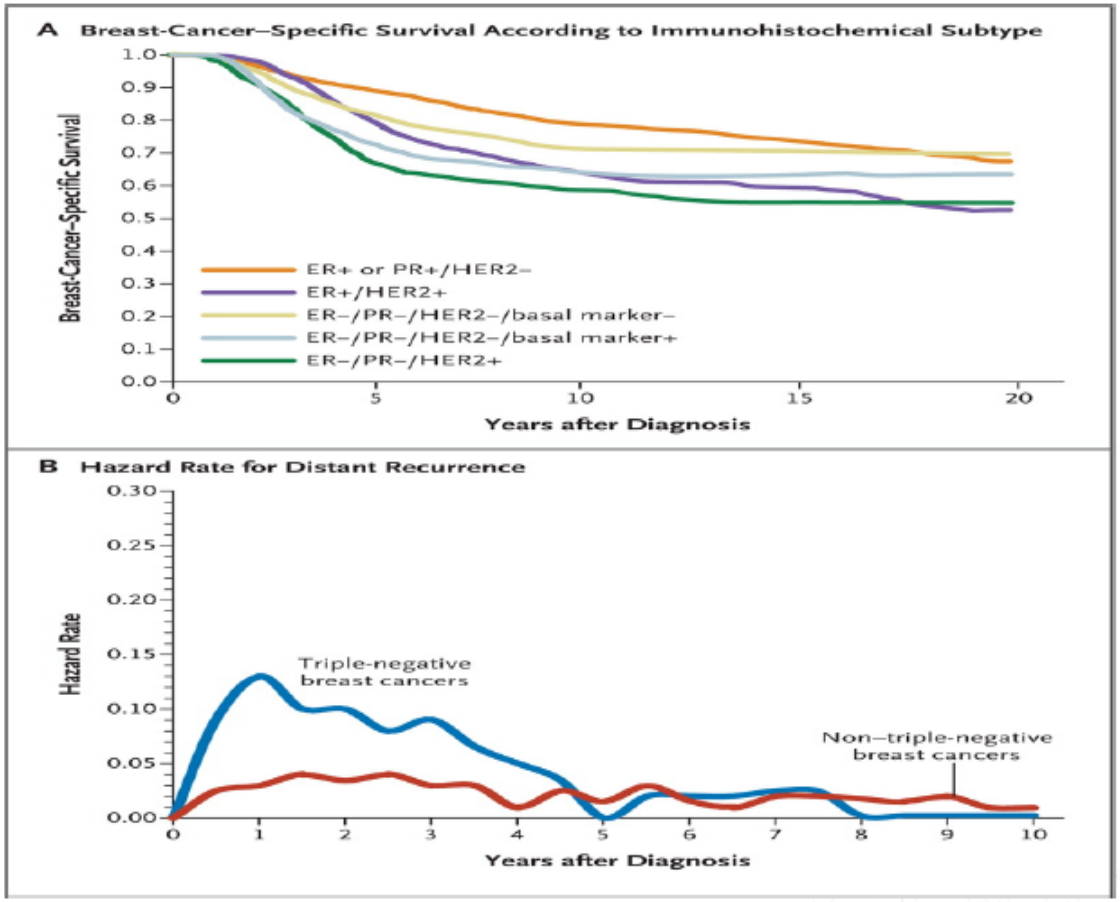


Meme Kanseri Moleküler Alt Grupları



Meme Kanseri Moleküler Alt Grupları

Breast Cancer Recurrences Occur Late



Foulkes WD et al. N Engl J Med 2010;363:1938-1948.

Meme Kanseri Moleküler Alt Grupları

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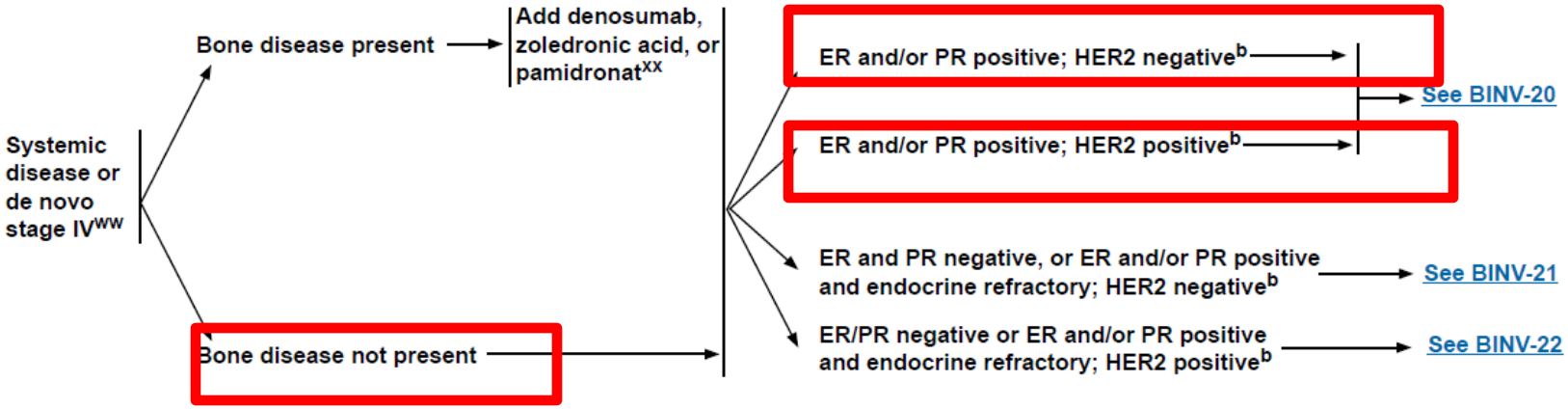
TREATMENT OF STAGE IV DISEASE



Meme Kanseri Moleküler Alt Grupları

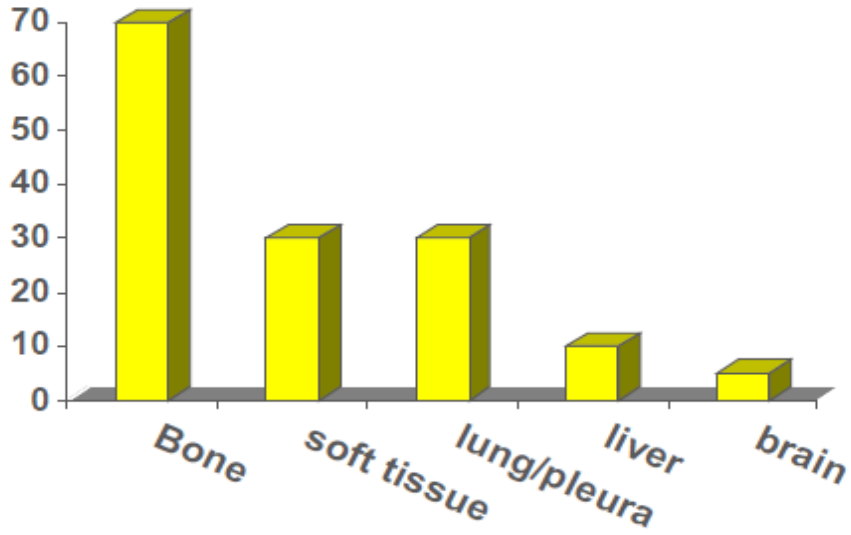
New Patients With Metastatic Breast Cancer in U.S.

Subtype	Percentage
HER2+	~15-20% (↓ing)
Triple Neg	~ 15-20%
ER+ and HER2-	~ 60-70%

About 50% of total HR+ are highly sensitive to endocrine Rx

Meme Kanseri Metastaz Bölgeleri

Metastatic Sites

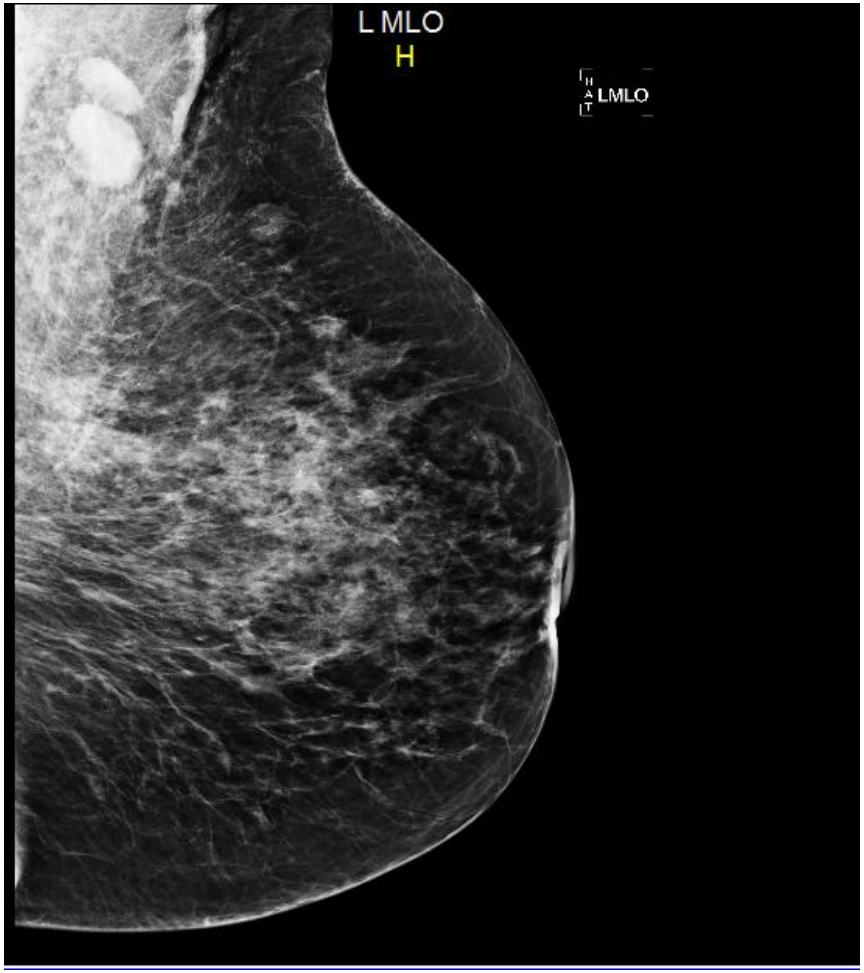


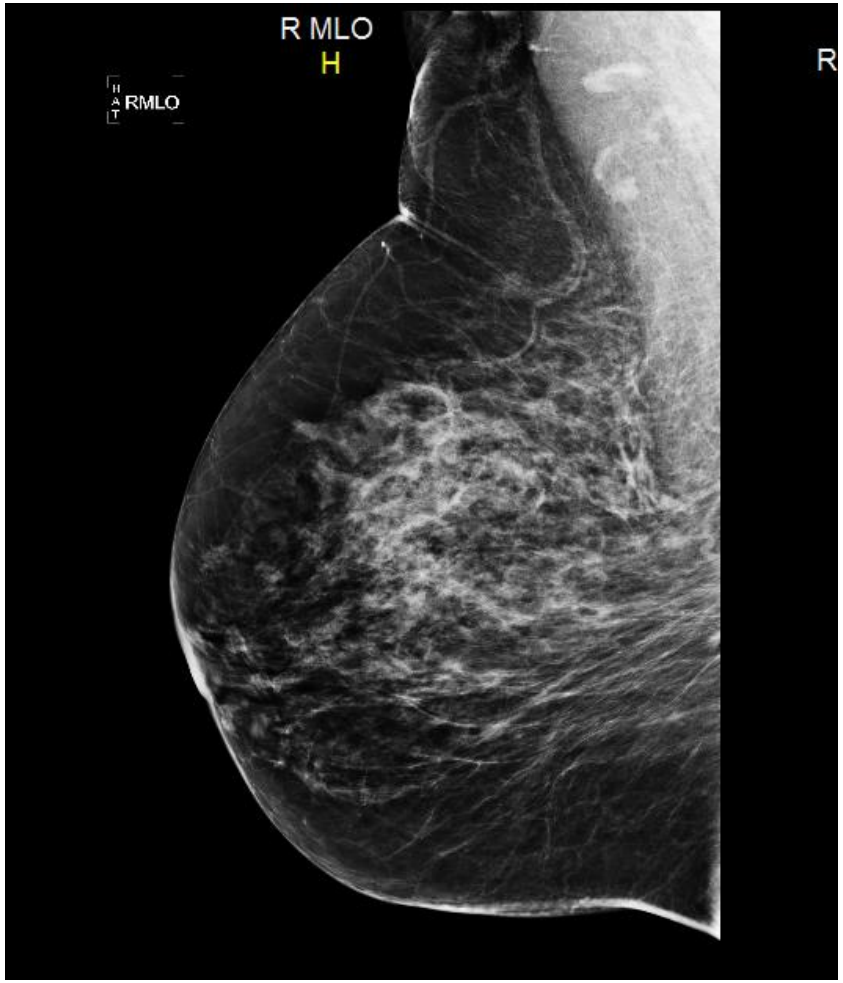
Breast cancer tropisms differ by subtype
Bone more dominant in hormone receptor positive
Visceral and CNS in hormone receptor negative

Sırt ağrısı ile başvuran kadın hasta

- 67 yaşında, kadın hasta, ev hanımı
- Sırt ağrısı ile başvurdu
- Bilinen hastalık öyküsü yok
- Aile öyküsünde bilinen özelik yok
- Sigara, alkol alışkanlığı yok
- Sürekli kullandığı ilaç yok
- 15 yıl önce TAH+BSO operasyonu geçirmiş

Mamografi ile Tarama





Meme Tru-cut Biyopsi

MAKROSKOPİK BULGULAR : LEZYON 1 KAYITLI ; EN BÜYÜĞÜ 0.6X0.1 CM, EN KÜÇÜĞÜ 0.2X0.1 CM ÖLÇÜLERİNDE SARI RENKTE 4 ADET TRU - CUT BİYOPSİ MATERYALİNİN TAMAMI 4P 1K.
LEZYON 2 KAYITLI(a) ; ENJEKTÖR İÇERİSİNDEKİ MATERYALDEN TP 1 + 2 ADET HAZIR YAYMA PREPARAT.
LEZYON 3 KAYITLI (b) ; 0.2 CC HACİMDE KANAMALI GÖRÜNÜMDE ASPİRASYON MATERYALİNDEN TP 1 + 2 ADET HAZIR YAYMA PREPARAT + HB YAPILDI.

TANI : İNVAZİV LOBÜLER KARSİNOM ;
SOL MEME (lezyon 1 kayıtlı)
TRU - CUT BİYOPSİ

E- KADERİN : (-)
ÖSTROJEN RESEPTÖRÜ : invaziv tümör hücrelerinin % 90 ında şiddetli intranükleer pozitif boyanma izlendi.
PROGESTERON RESEPTÖRÜ : invaziv tümör hücrelerinin % 90 nında şiddetli intranükleer pozitif boyanma izlendi.
Cerb - B2 : invaziv tümör hücrelerinde sitoplazmik membranöz boyanma izlenmedi (skor 0) .

MALİGNİTE AÇISINDAN ŞÜPHELİ YAYMA ;
SOL MEME (lezyon 2 kayıtlı)
İİAB

KAN ELEMANLARI ;
SOL AKSİLLA (lezyon 3 kayıtlı)
İİAB

NOT : * SOL MEME LEZYON 2 KAYITLI DOKU ÖRNEKLERİNDE SİTOMORFOLOJİK BULGULAR MALİGNİTE AÇISINDAN ŞÜPHELİ OLARAK DEĞERLENDİRİLMİŞTİR. ANCAK MEVCUT MATERYAL İLE DAHA İLERİ YORUM YAPILAMAMIŞTIR.
* SOL AKSİLLA KAYITLI DOKU ÖRNEKLERİNDE KAN ELEMANLARI DIŞINDA HÜCRESEL ELEMAN İZLENMEMİŞTİR.

PET-CT

- Sol meme üst dış kadranda 2.5x1.5 cm kitlesel lezyon
- Sol supraklaviküler , sol pektoral , aksiler 1.7 cm varan multiple LAP
- Tüm vertebral kolonda yaygın tutulum ve pelvik kemiklerde tutulum
- Bilateral femur, bilateral humerus kemiklerinde tutulum

Tedavi Seçenekleri

HR+, HER2- negatif, çok sayıda kemik metastazı olan, ağrı semptomu mevcut, ECOG PS1 hasta

1- RT sonrası,tekli kemoterapi(paklitaksel), Zolendronik asid/ Denasumumab

2-RT sonrası, kombine kemoterapi(CAF), Zolendronik asid /Denasumumab

4- RT+Letrazole+paclociblib(yada Ameciblib/Ribociclib)+Denasumumab/Zolendronik asid

5-RT+ Letrazole(Anastrazole)+Everolimus+ Denasumumab/Zolendronik asid

6-RT+Fulvestran+zolendronik asid

7-RT+Letrazole(Anastrazole)+Zolendronik asid

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

Heterogeneity of Metastatic Breast Cancer

Disease Characteristics

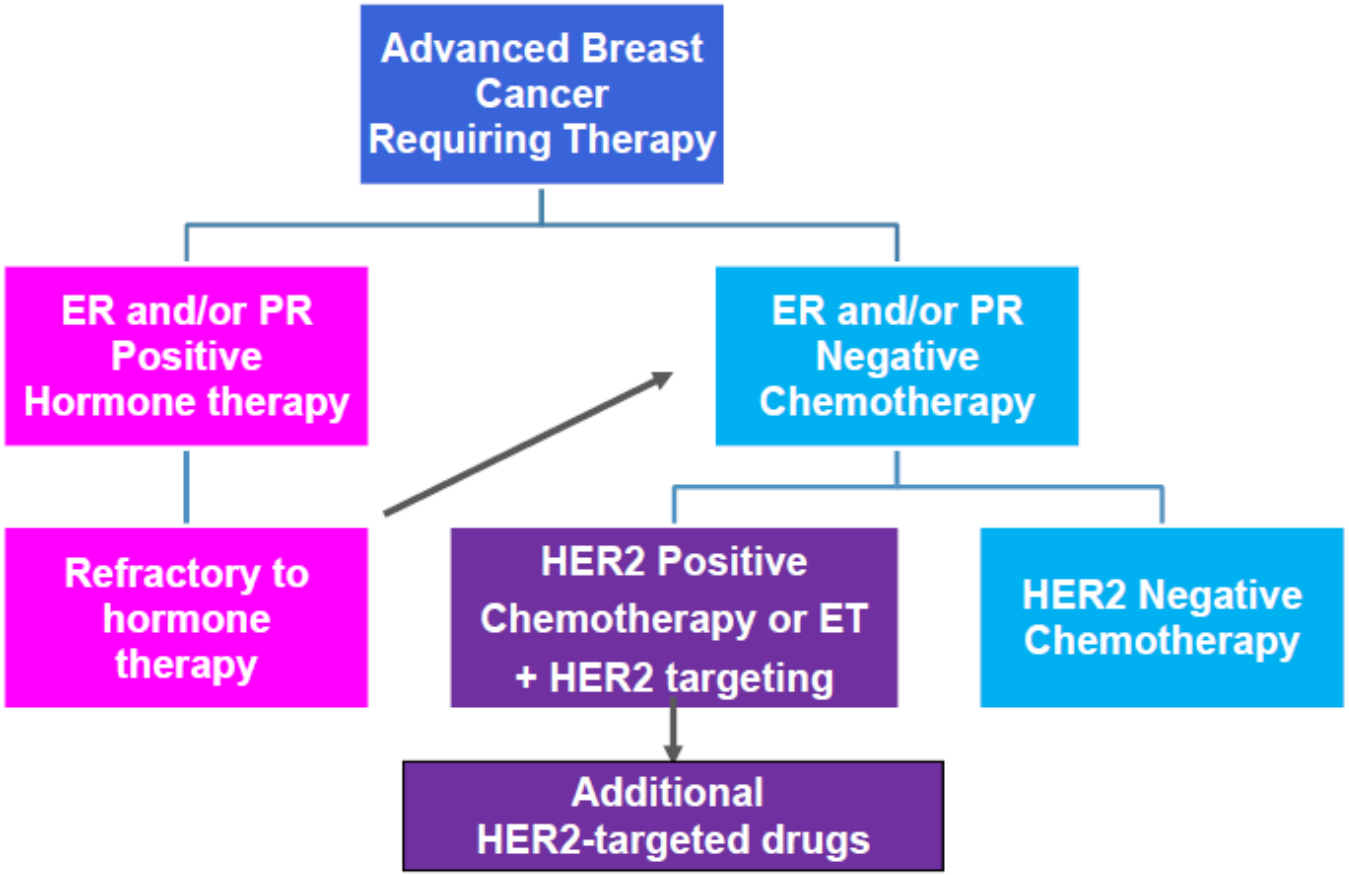
- Disease-free interval
- Sites and volume of disease
- Tempo of disease
- Prior therapy
- ER and PR status
- HER-2 status

Patient Characteristics

- Performance status
- Comorbidity
- Host factors
  - ? Immune response
  - ? Drug metabolism

Meme Kanseri Moleküler Alt Gruplara Göre Tedavi

Treatment Based on Tumor Phenotype



Meme Kanseri Moleküler Alt Gruplara Göre Tedavi

ASCO Guidelines

Chemotherapy and Targeted Therapy for Women With HER2–Negative (or unknown) ABC: ASCO Clinical Practice Guideline.
Endocrine Therapy for Hormone Receptor Positive Metastatic Breast Cancer: ASCO Clinical Oncology Guideline.

1. Endocrine therapy is preferable to chemotherapy as first-line treatment for patients with ER+ MBC unless improvement is medically necessary (eg, immediately life-threatening disease).
   - Evolving use of targeted agents: palbociclib, everolimus, others
2. Single agent chemotherapy is preferable to combination; longer duration improves outcome but must be balanced against toxicity.
   - There is no single optimal 1st or subsequent line chemotherapy; choice of treatment will be determined by multiple factors including prior therapy, toxicity, performance status, comorbid conditions, and patient preference.
   - The role of bevacizumab remains controversial. Other targeted therapies have not so far been shown to enhance chemotherapy outcome in HER2-negative BC
3. HER2+ MBC separate topic.

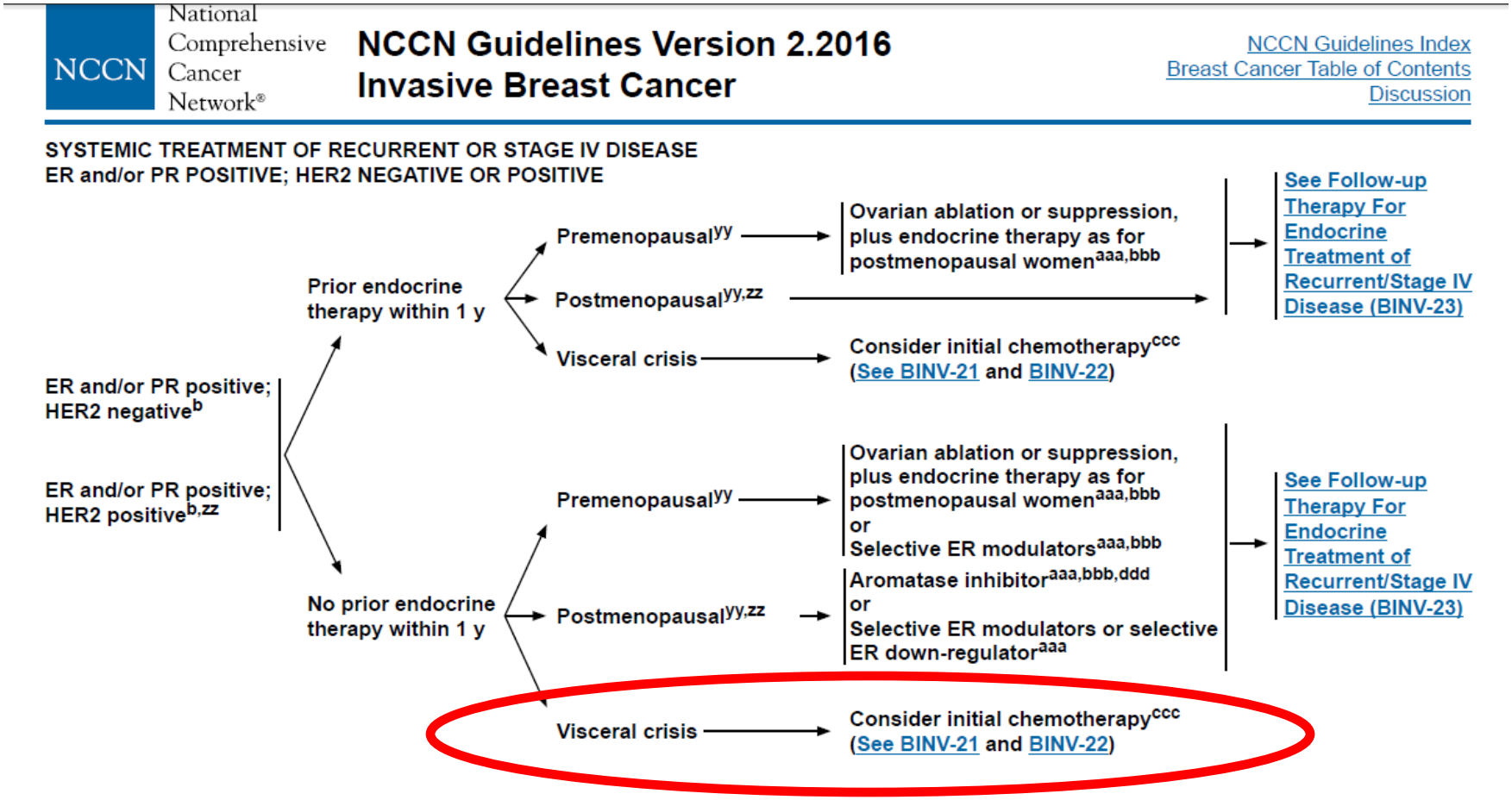
Partridge et al, JCO 2014; Rugo et al, JCO 2016

Meme Kanseri Moleküler Alt Gruplara Göre Tedavi

ESO-ESMO Konsensus Kılavuzu

Guideline statement	LoE	Consensus
VISCERAL CRISIS is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases, but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.	Expert opinion	95.0% (38) Yes 5.0% (2) Abstain (40 voters)

Meme Kanseri Moleküler Alt Gruplara Göre Tedavi



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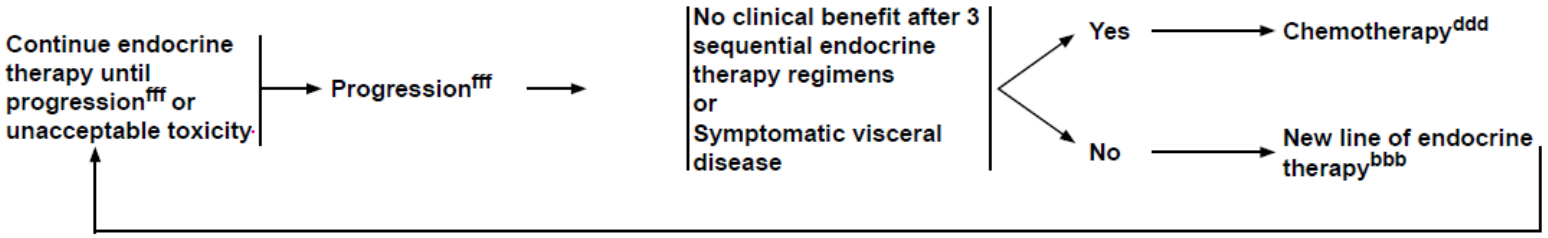
FOLLOW-UP THERAPY FOR ENDOCRINE TREATMENT OF RECURRENT OR STAGE IV DISEASE



HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

Hormonal Therapy Options

- Premenopausal
  - Tamoxifen
  - Oophorectomy (OA)/LHRH agonist (OS)
  - OA/OS + the postmenopausal options
- Postmenopausal
  - Nonsteroidal aromatase inhibitor (AI*)
  - AI plus palbociclib
  - Steroidal AI
  - Steroidal AI + everolimus
  - Tamoxifen
  - Fulvestrant
  - Fulvestrant + palbociclib
  - Estradiol

Nonsteroidal AI = letrozole, anastrozole; Steroidal AI = exemestane

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

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ENDOCRINE THERAPY FOR RECURRENT OR STAGE IV DISEASE

Premenopausal Patients

- **Selective ER modulators or ovarian ablation/suppression plus endocrine therapy as for postmenopausal women.**

Postmenopausal Patients

- **Non-steroidal aromatase inhibitor (anastrozole, letrozole)**
- **Steroidal aromatase inactivator (exemestane)**
- **Exemestane + everolimus[1]**
- **Palbociclib + letrozole[2]**
- **Palbociclib + fulvestrant (category 1)[3]**
- **Fulvestrant[4]**
- **Tamoxifen or toremifene**
- **Megestrol acetate**
- **Fluoxymesterone**
- **Ethinyl estradiol**

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

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DEFINITION OF MENOPAUSE

Clinical trials in breast cancer have utilized a variety of definitions of menopause. Menopause is generally the permanent cessation of menses, and as the term is utilized in breast cancer management includes a profound and permanent decrease in ovarian estrogen synthesis. Reasonable criteria for determining menopause include any of the following:

- Prior bilateral oophorectomy
- Age ≥60 y
- Age <60 y and amenorrheic for 12 or more months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and follicle-stimulating hormone (FSH) and estradiol in the postmenopausal range
- If taking tamoxifen or toremifene, and age <60 y, then FSH and plasma estradiol level in postmenopausal ranges

It is not possible to assign menopausal status to women who are receiving an LHRH agonist or antagonist. In women premenopausal at the beginning of adjuvant chemotherapy, amenorrhea is not a reliable indicator of menopausal status as ovarian function may still be intact or resume despite anovulation/amenorrhea after chemotherapy. For these women with therapy-induced amenorrhea, oophorectomy or serial measurement of FSH and/or estradiol are needed to ensure postmenopausal status if the use of aromatase inhibitors is considered as a component of endocrine therapy.

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

AI vs Tamoxifen: 1st Line Postmenopausal

	Anastrozole	Letrozole	Exemestane
N	353	907	371
CR+PR	21% vs 17%	30% vs 20%	45% vs 30%
CR+PR+SD	59% vs 46%	49% vs 38%	--
TTP (mo)	11.1 vs 5.6	9.4 vs 6.0	9.9 vs 5.8

AI at least as good as tamoxifen
Anastrozole = Letrozole = Exemestane

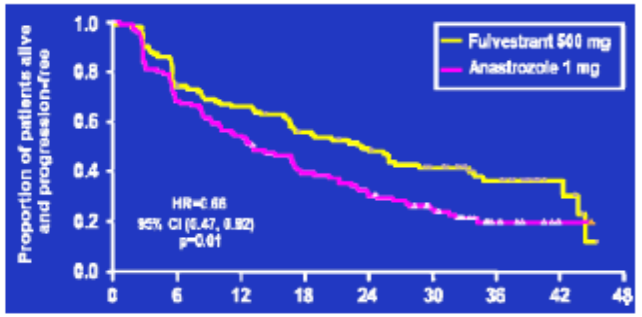
Nabholtz et al; Mouridsen et al, Paridaens et al

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

Fulvestrant vs AI: 1st Line

FIRST study: Phase II trial

	Fulvestrant	Anastrozole	P-value
CR+ PR	31.4%	32.1%	NS
CBR*	72.5%	67.0%	NS
TTP	23.4m	13.1m	0.01
OS	54.1m	48.4m	0.04



* Primary endpoint=CBR

Robertson et al, JCO 2009; BCRT 2012

Confirmatory Phase III FALCON trial pending, but "positive" press release by AZ May 27, 2016

Fulvestrant reasonable 1st line endocrine Rx; may become one of preferred Rx

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

FALCON – Trial Design and Patient Characteristics

- Postmenopausal women
- Locally advanced or metastatic breast cancer
- ER+ and/or PgR+
- Endocrine therapy-naïve

Stratification factors:
- Prior chemo for MBC
- Measurable disease
- Locally advanced vs. MBC

Fulvestrant 500 mg (500 mg IM on days 0, 14, 28 then every 28 days) + Placebo

Anastrozole 1 mg + Placebo

Primary endpoint: PFS

Secondary: OS, ORR, CBR, DoR, DoCB, HRQol, Safety

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- N = 450 patients for 306 progression events;
- If true PFS HR was 0.69 this would provide 90% power at the 5% two-sided level (log-rank test)
- Subgroup analysis of PFS for pre-defined baseline covariates

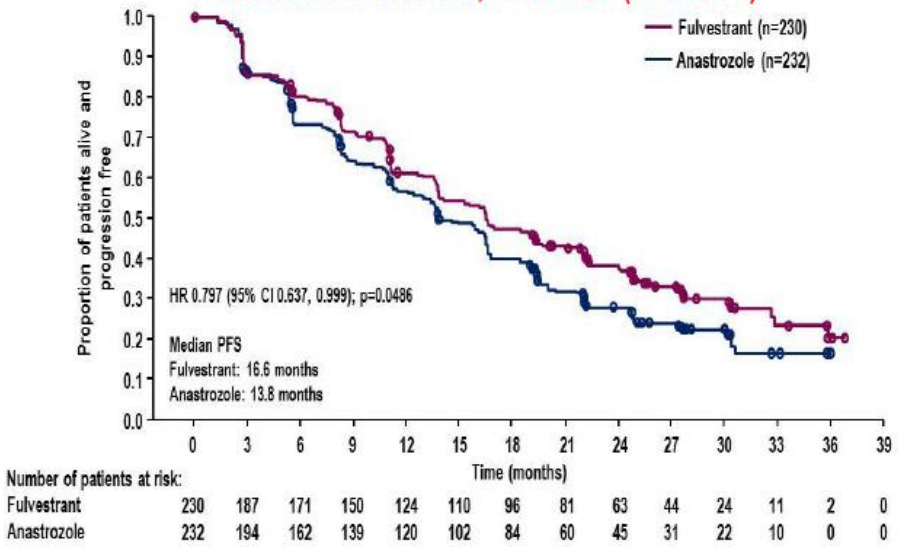
	Total (N=462)	
Any prior chemotherapy, n (%)	160	(34.6%)
Advanced disease	79	(17.1%)
Adjuvant / neoadjuvant	62 / 27	(13.4 %/ 5.8%)
Receptor status, n (%)		
ER+ / PgR+	354	(76.6%)
ER+ / PgR-	87	(18.8%)
Unknown	17	(3.7%)
Overall disease classification, n (%)		
Locally advanced disease	60	(13.0%)
Metastatic disease	402	(87.0%)
Visceral disease, n (%)	254	(55.0%)
Measurable disease, n (%)	389	(84.2%)

Ellis et al. ESMO 2016. LBA-14 Slide courtesy of Peter Schmid

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

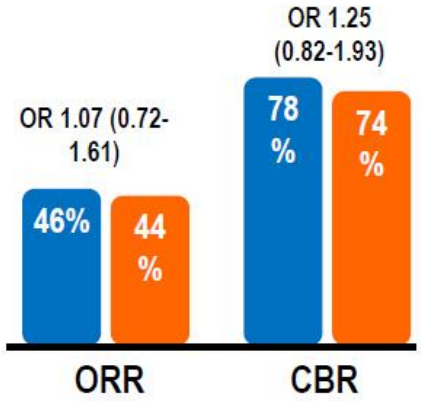
FALCON Study: Efficacy

Primary Endpoint met: Benefit in PFS
16.6 vs 13.8 months, HR 0.797 (not 0.69!)



No Survival Benefit (yet?) but survival data immature (31%)

No difference in response



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Ellis et al. ESMO 2016. LBA-14 Slide courtesy of Peter Schmid

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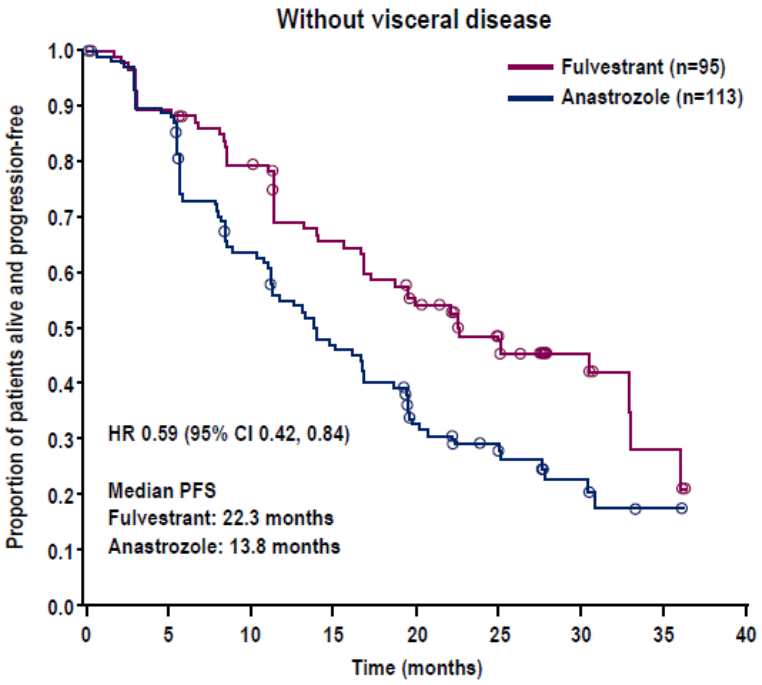
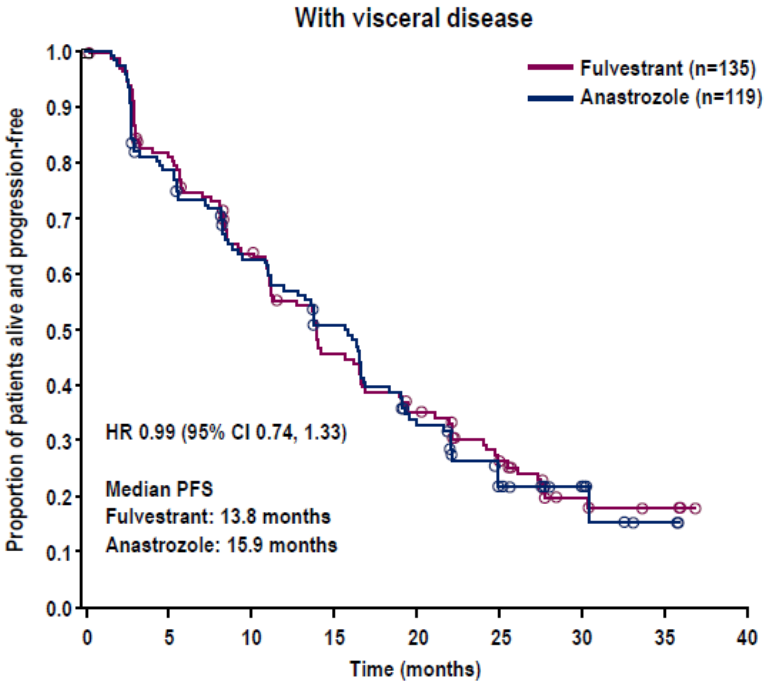
FALCON: PFS In Patients With/Without Visceral Disease





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A circle represents a censored observation
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Ellis et al, ESMO 2016 LBA 14.

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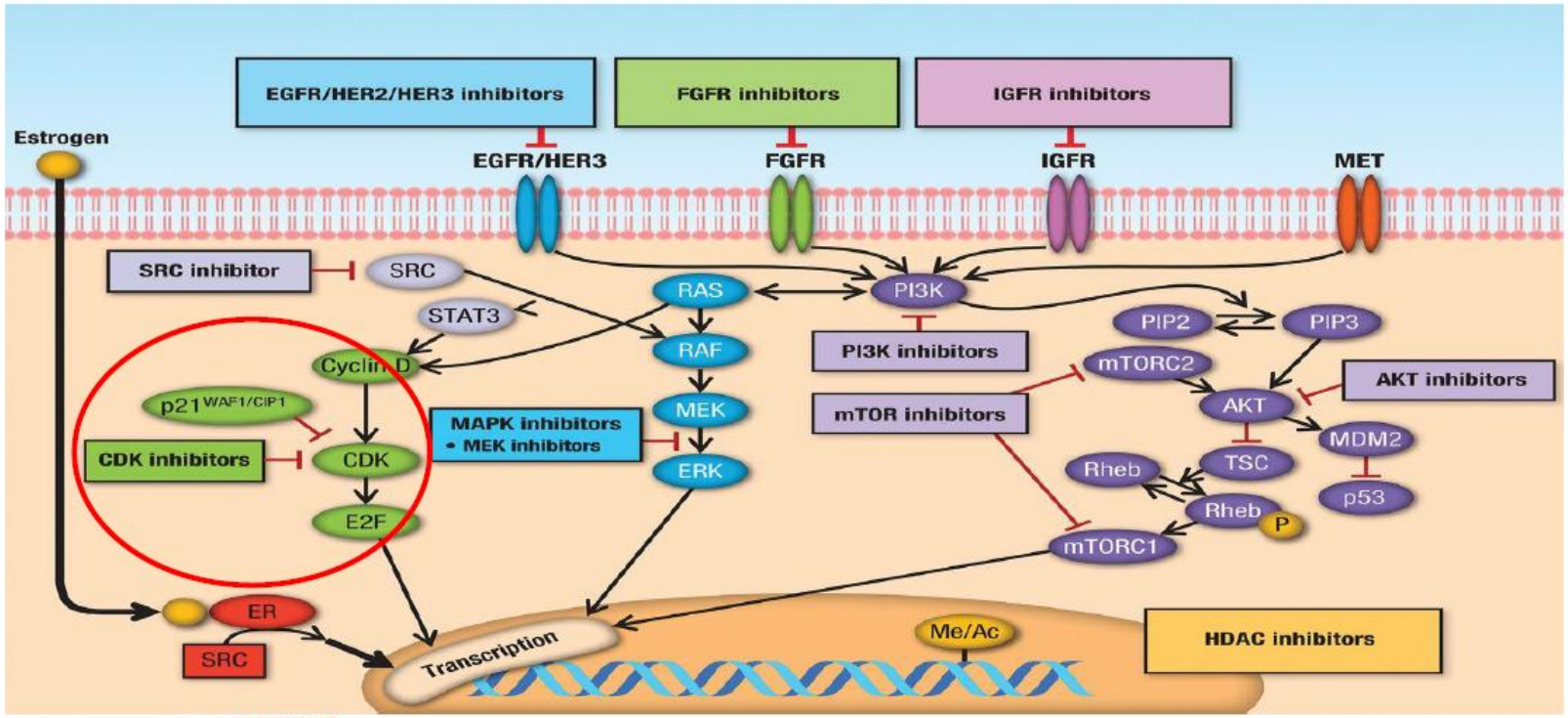
Targeted Therapy Pathways For ER+ Advanced Breast Cancer.



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Johnston SRD. J Natl Cancer Inst 2015; Aug 6;107(10). 107:djv212

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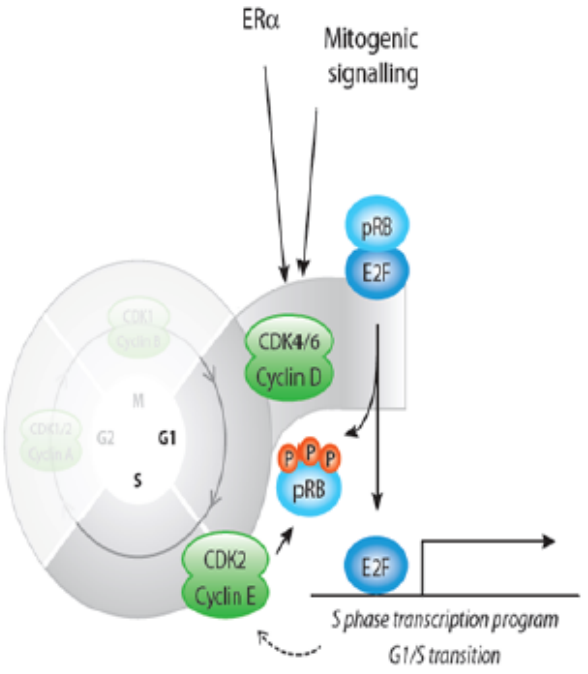
Cyclin Dependent Kinase 4/6 Inhibitors

Role in HR+ breast cancer

- **Growth of HR+ BC depends on cyclin D1, a transcriptional target of ER**
- **Cyclin D1 activates CDK 4/6 causing G1-S phase transition and cell cycle entry**

Major area drug development

- **Palbociclib**
- **Abemaciclib**
- **Ribaciclib**



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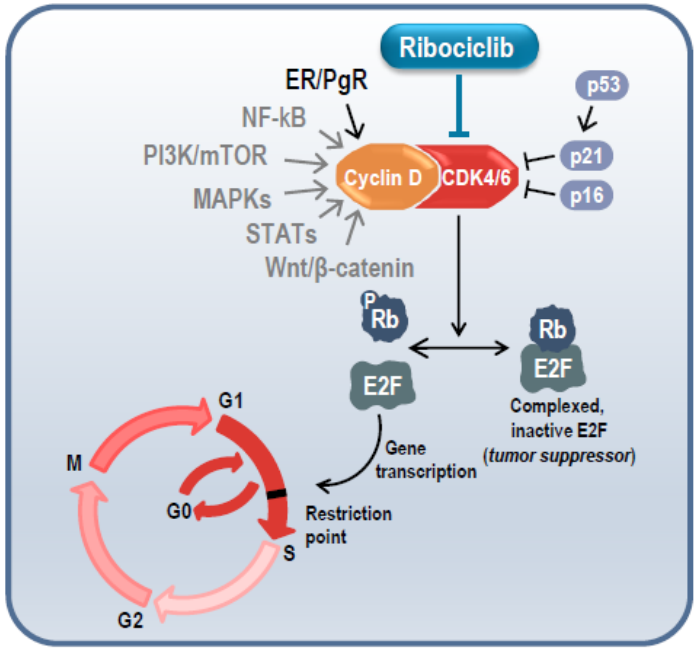
The Role of CDK4/6 in HR+ Breast Cancer



- Rb binding inactivates E2F, which regulates genes important for transition through the G1/S cell cycle restriction point[1,2]
- Phosphorylation of Rb by CDK4/6 leads to dissociation of E2F from Rb and cell cycle progression[1,2]
- Increased CDK4/6 activity driven by perturbations of other pathways is associated with endocrine therapy resistance[1,2]

CDK, cyclin-dependent kinase; Rb, retinoblastoma.

1. Hosford S, Miller T. *Pharmgenomics Pers Med* 2014;7:203–215; 2. Thangavel C, *et al. Endocr Relat Cancer* 2011;18:333–345;.

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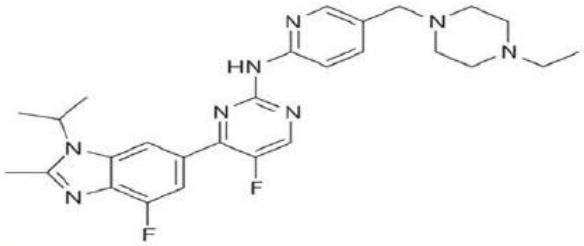
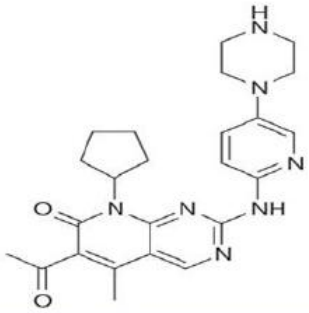
Selective CDK 4/6 Inhibitors

The University Of Sheffield.

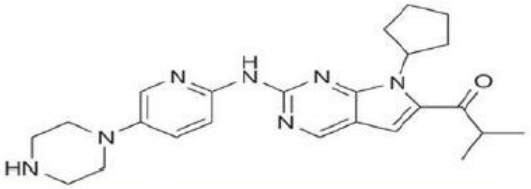
Abemaciclib



Palbociclib



Ribociclib



	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

Nature Reviews | Clinical Oncology

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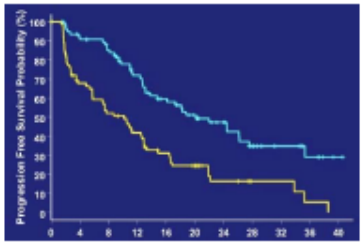
O'Leary B, et al. Nat Rev Clin Oncol. 2016;13(7):417–430.

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

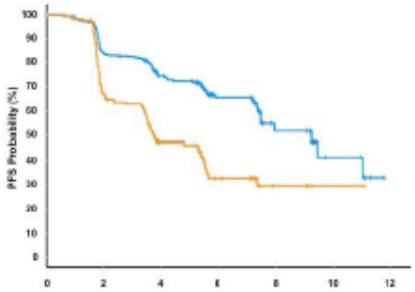
Palbociclib Trials in HR+ Disease

PALOMA-1: Phase II letrozole ± palbo in 1st line HR+/HER2-



PFS: 20m vs 10m, p=0.0004
(OS secondary: 37m vs 33m, ns)
Accelerated FDA approval 2015:
Letrozole + palbo in 1st line

PALOMA-3: Phase III fulvestrant ± palbo in 2nd+ line HR+/HER2-

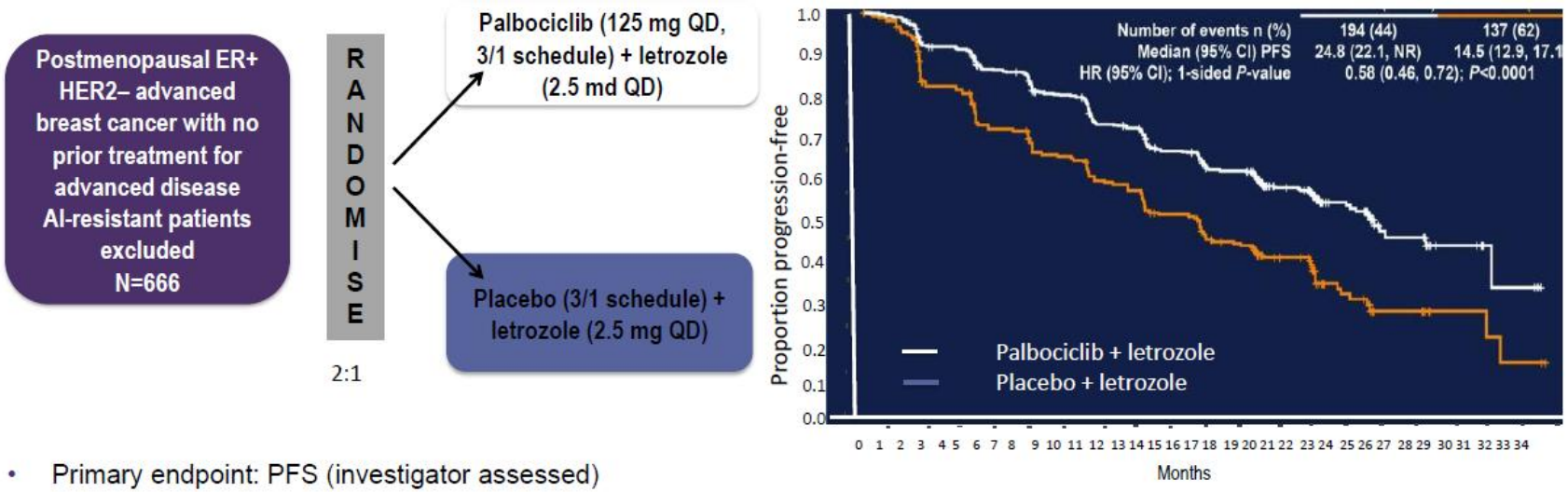


PFS: 9m vs 4m, p<0.0001
(OS immature)
Accelerated FDA approval 2016:
Fulvestrant + palbo in pretreated (no prior palbo)

Key AE: neutropenia, infections, anemia (needs monitoring ET doesn't)

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

PALOMA-2: Biomarker Evaluation



- Primary endpoint: PFS (investigator assessed)
- Secondary endpoints: Response, OS, safety, biomarkers, PROs

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Finn R, et al. ASCO 2016, Abstract 504 (oral abstract)

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

PALOMA-2: A Phase III Trial of First-Line Palbociclib with Letrozole

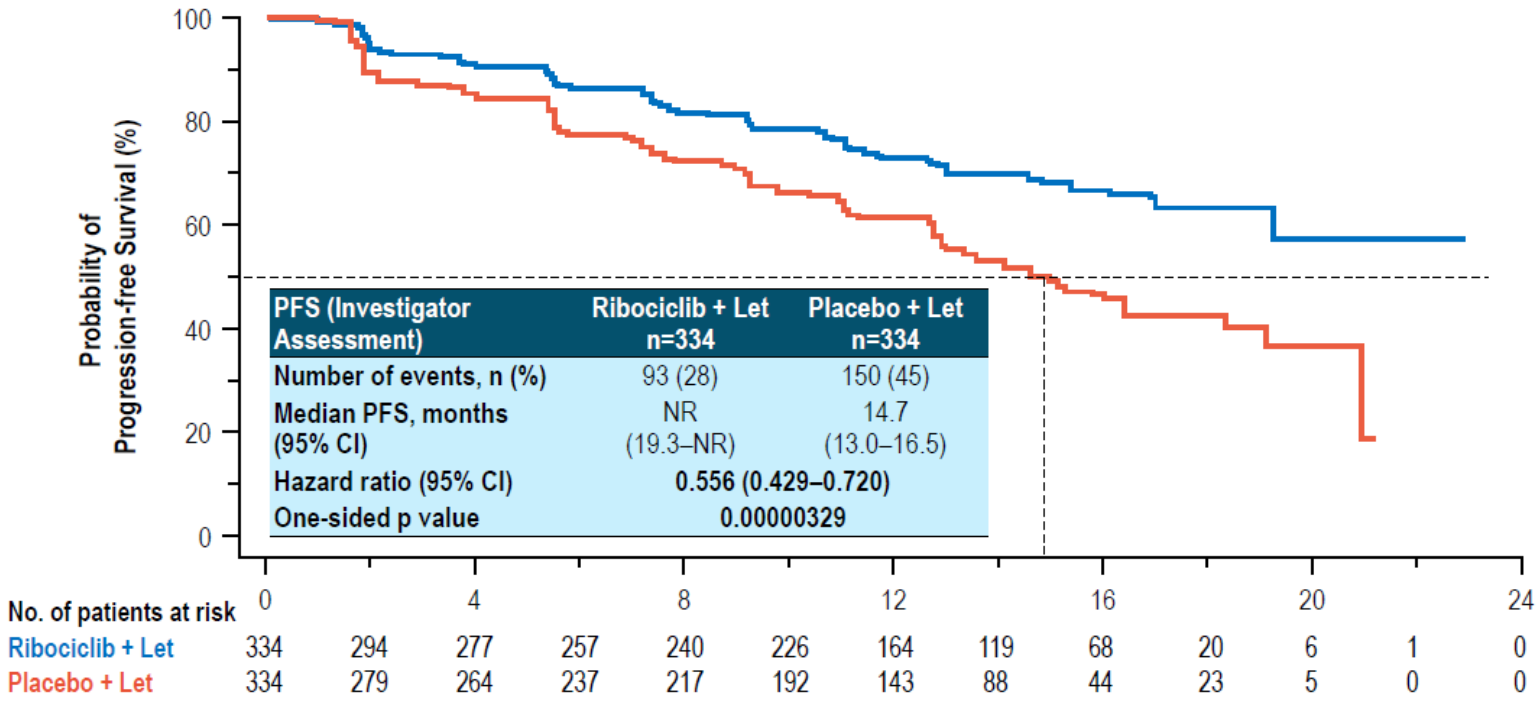
	Palbociclib + letrozole (n = 444)	Placebo + letrozole (n = 222)	HR (*p*-value)
Median PFS	24.8 mo	14.5 mo	0.58 (<0.000001)

Hematologic AEs, %	Palbociclib + letrozole (n = 444)			Placebo + letrozole (n = 222)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Neutropenia	80	56	10	6	1	<1
Leukopenia	39	24	1	2	0	0
Anemia	24	5	<1	9	2	0
Thrombocytopenia	16	1	<1	1	0	0

Finn RS et al. *Proc ASCO* 2016;Abstract 507.

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

MONALEESA - Primary Endpoint



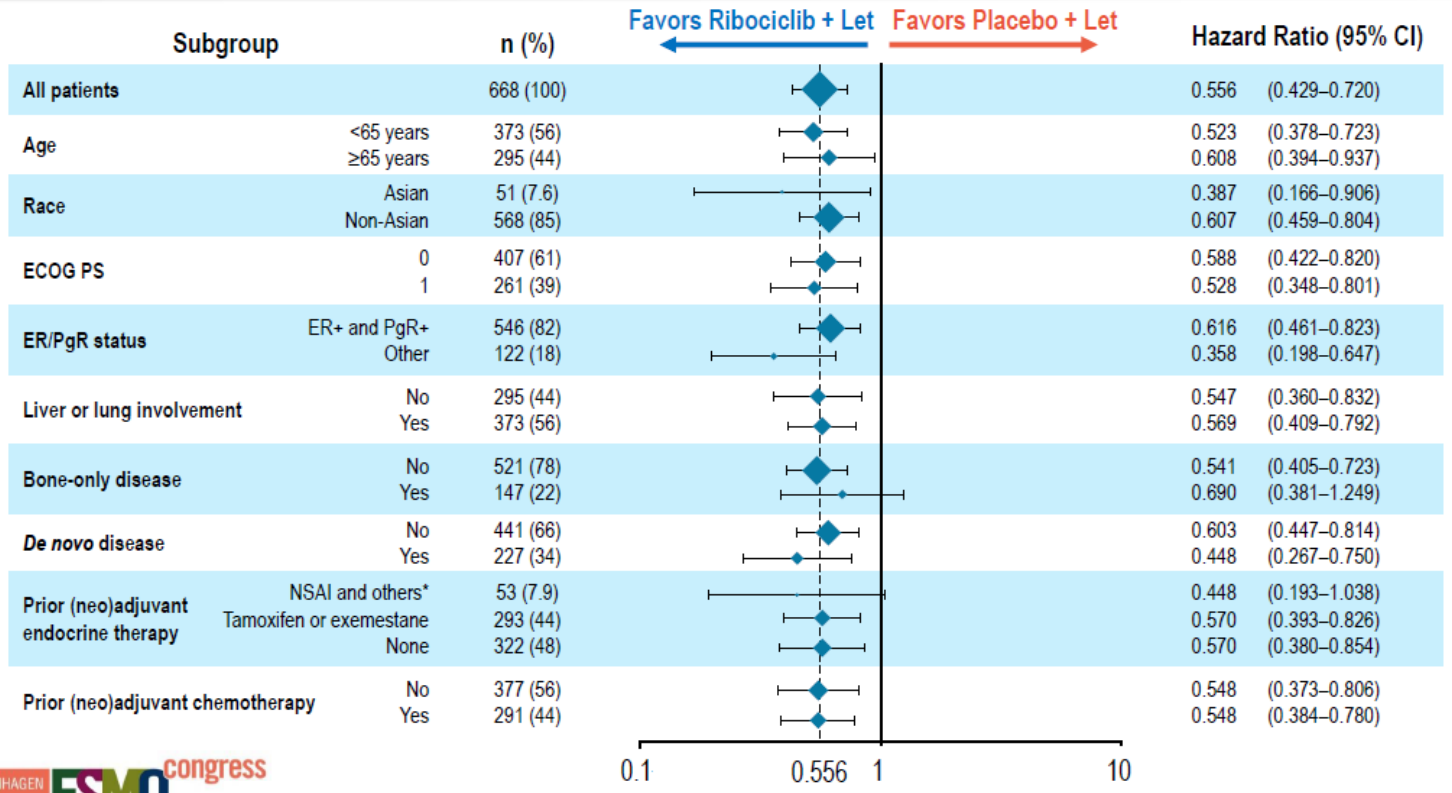
PFS results by independent central review: hazard ratio 0.592 (95% CI: 0.412–0.852; p=0.002)

- Let, letrozole; NR, not reached.

Hortobagyi G et al ESMO

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

MONALEESA - Subgroup Analysis



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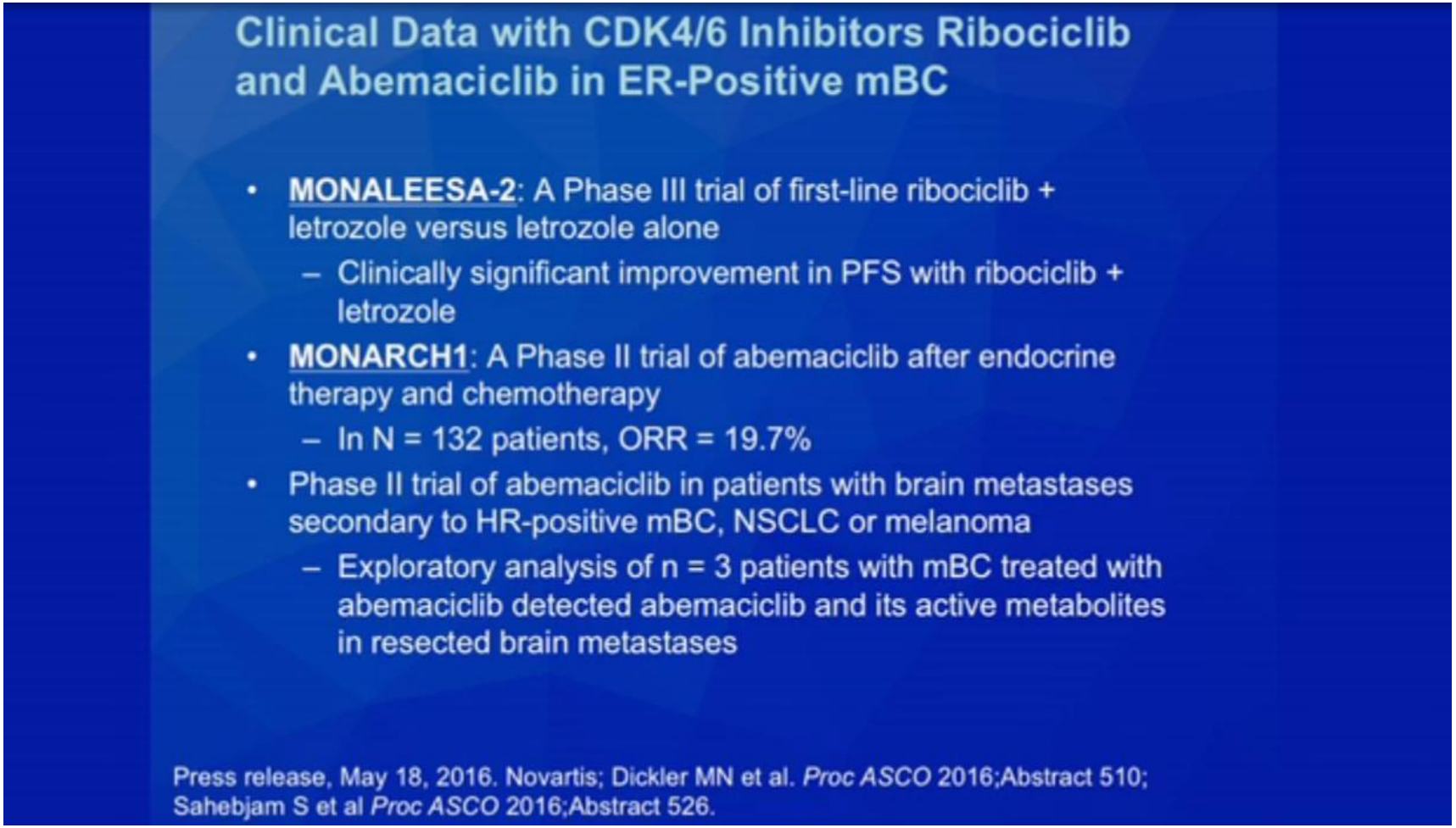
- NSAI, non-steroidal aromatase inhibitor.
- *Excludes patients who had received tamoxifen.

Hortobagyi G et al ESMO 2016 LBA 1

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi



HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

MONARCH-1: A Phase II Study of Single-Agent Abemaciclib in HR+/HER2-Negative mBC After Chemotherapy

In N = 132 heavily pretreated patients, abemaciclib demonstrated single-agent activity:

- ORR = 19.7%
- Median PFS = 6.0 mo
- Median OS = 17.7 mo

Select most common AEs	All grade	Grade 3	Grade 4
Creatinine increased	98.5%	0.8%	0
Diarrhea	90.2%	19.7%	0
Neutrophil decreased	87.7%	22.3%	4.6%
Platelet count decreased	41.4%	2.3%	0

Dickler MN et al. *Proc ASCO* 2016;Abstract 510.

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

BOLERO-4 Study Design

The University Of Sheffield.

Open-label, single-arm, phase 2 study of EVE + endocrine therapy in the first- and second-line setting for postmenopausal women with HR+, HER2− locally advanced or metastatic BC

First line (N = 202)

EVE
(10 mg orally QD)
+
LET
(2.5 mg orally QD)

→ **Disease progression** →

Second line[a]

EVE
(10 mg orally QD)
+
EXE
(25 mg orally QD)

Treatment until disease progression, intolerable toxicity, or withdrawal of consent

End points[b]

Primary
PFS first line per RECIST v1.0

Secondary
ORR, CBR
OS
Safety and tolerability[c]

Enrollment is complete

Primary analysis data cutoff: Dec 17, 2015
Estimated study completion: Dec 17, 2016

[a] Patients who progress on first-line treatment have the option to receive EVE + EXE in the second-line setting. [b]Additional first- and second-line end points to be reported separately as data become available. [c]Assessed according to Common Terminology Criteria for Adverse Events v4.0.

CBR, clinical benefit rate (CR + PR + SD ≥ 24 weeks); CR, complete response; LET, letrozole; ORR, overall response rate (CR + PR); OS, overall survival; PFS, progression-free survival; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease.

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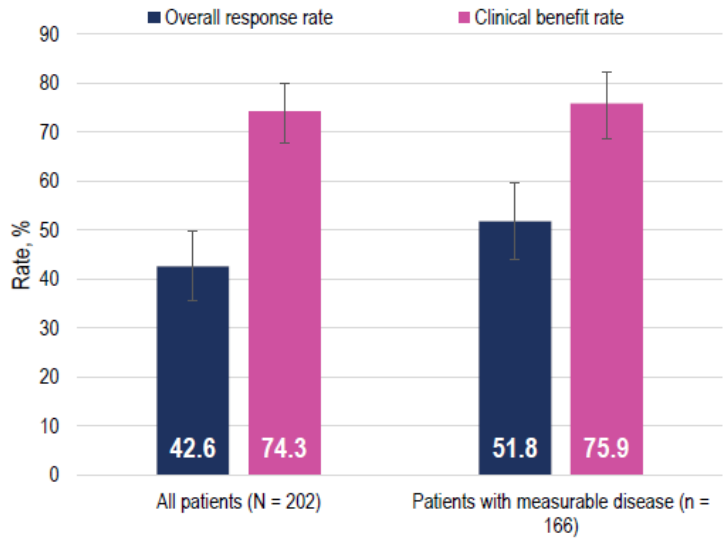
Royce M ESMO 2016 Abstract 2220

Tam dolu (%100)

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

BOLERO-4: Secondary End Points



Data are the rates and associated 95% confidence intervals.

Best Overall Response in the First Line

Patients, n (%)	All N = 202	Measurable Disease[a] n = 166
Best overall response[b]		
Complete response	3 (1.5)	3 (1.8)
Partial response	83 (41.1)	83 (50.0)
Stable disease	91 (45.0)	59 (35.5)
Progressive disease	14 (6.9)	12 (7.2)
Unknown	11 (5.4)	9 (5.4)
Overall response rate	86 (42.6)	86 (51.8)
Clinical benefit rate	150 (74.3)	126 (75.9)

[a] Patients with measurable disease at baseline based on local assessment.
[b] Best overall response in the first line based on local assessment.

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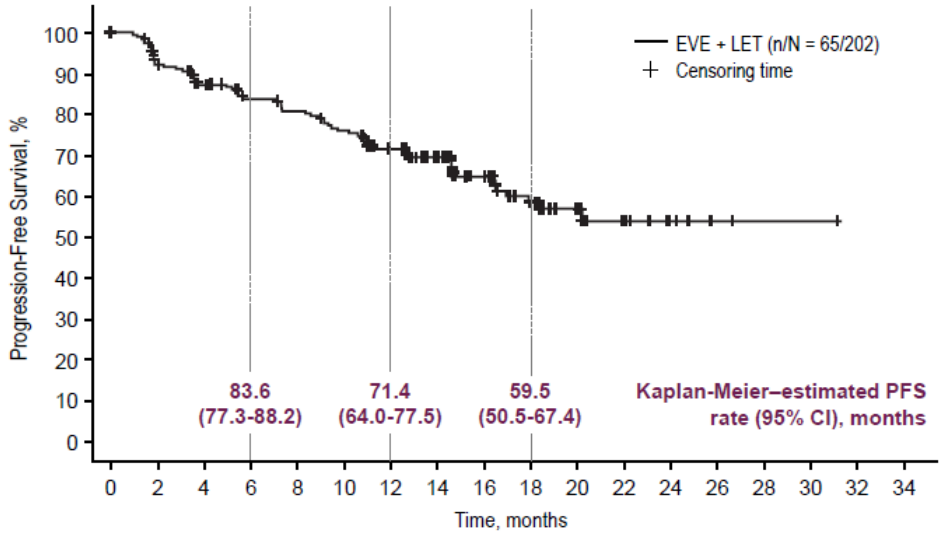
HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

BOLERO-4: Primary End Point: PFS in the First Line

- Locally assessed median PFS in the first line was not yet reached with a median follow-up of 17.5 months



No. of patients still at risk:

EVE + LET	202	172	153	140	134	125	105	82	61	43	26	13	6	2	1	1	0	0
Months	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34

EVE + LET N = 202	
PFS events, n (%)	65 (32.2)
Progression, n (%)	62 (30.7)
Death, n (%)	3 (1.5)
Censored, n (%)	137 (67.8)
Percentile, months (95% CI)	
75th percentile	NE (NE-NE)
Median	NE (18.0-NE)
25th percentile	10.7 (7.4-14.7)

NE, not estimable.

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Royce M ESMO 2016 Abstract 2220

Tedavi Seçenekleri

HR+, HER2- negatif, çok sayıda kemik metastazı olan, ağrı semptomu mevcut, ECOG PS1 hasta

1- RT sonrası,tekli kemoterapi(paklitaksel), Zolendronik asid/ Denasumumab

2-RT sonrası, kombine kemoterapi(CAF), Zolendronik asid /Denasumumab

3- RT+Letrazole+paclociblib(ya da Ameciblib/Ribociclib)+Denasumumab/Zolendronik asid

4-RT+ Letrazole(Anastrazole)+Everolimus+ Denasumumab/Zolendronik asid

5-RT+Fulvestran+zolendronik asid

6-RT+Letrazole(Anastrazole)+Zolendronik asid

PET-CT; 3. Ay Yanıt değerlendirmesi

Kontrol PET-CT

- Sağ kaput humeride hafif tutulum
- Sağ akciğer subkarinal posteriyorda buzlu cam

TAMA YAKIN YANIT

HR+, HER2- ,Yaygın Kemik metastazı olan Meme Kanseri 1. Basamak Tedavi

- Palyatif RT sonrası
- Letrazole 2.5 mg/gün
- Zolendronik asdi 4mg/28 günde bir
- Üç aylık yanıt değerlendirilmesinde tama yakın yanıt
- 9 aylık PFS sonrası, kemik lezyonlarında progresyon saptandı

PET-CT; 9. Ay Yanıt değerlendirmesi

PET-CT

- Sağ aksilada yeni lenf nodu
- Sağ kaput humeri progrese
- Sol akromion, sol humerus, sağ kaput humeri, sol 7 kot lateral, sol iliyak posteriyorda yeni gelişen kemik metastazları

Tedavi Seçenekleri

HR+, HER2- negatif, yeni kemik metastazı olan, belirgin semptomu olmayan , 1 basamak hormon tedavisi sonrası kadın hasta, ECOG PS0-1 hasta

1- RT sonrası,tekli kemoterapi(paklitaksel), Zolendronik asid/ Denasumumab

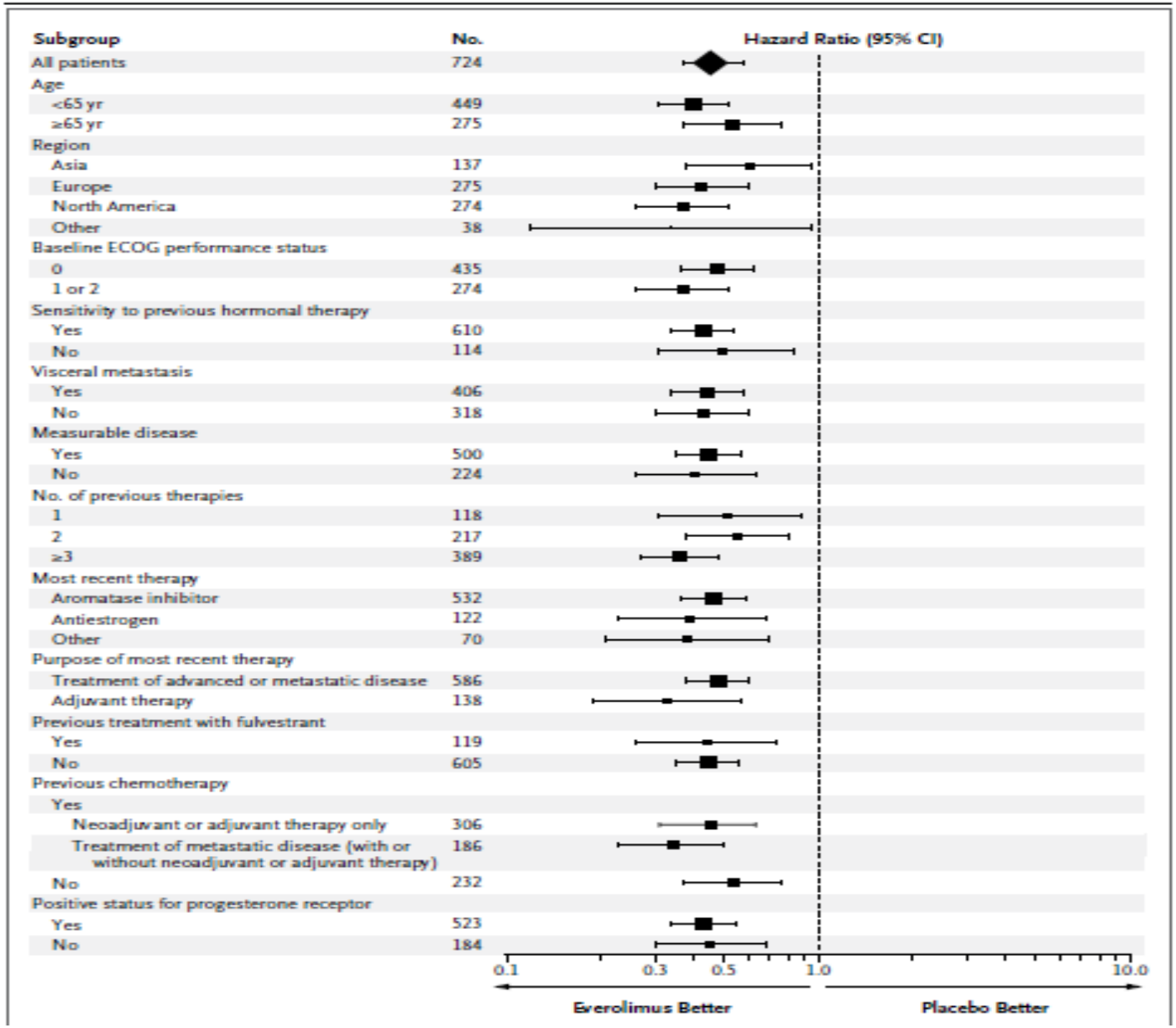
2-RT sonrası, kombine kemoterapi(CAF), Zolendronik asid /Denasumumab

3-RT+Exemestane+ Denasumumab/Zolendronik asid

4-RT+ Exemestane+Everolimus+ Denasumumab/Zolendronik asid

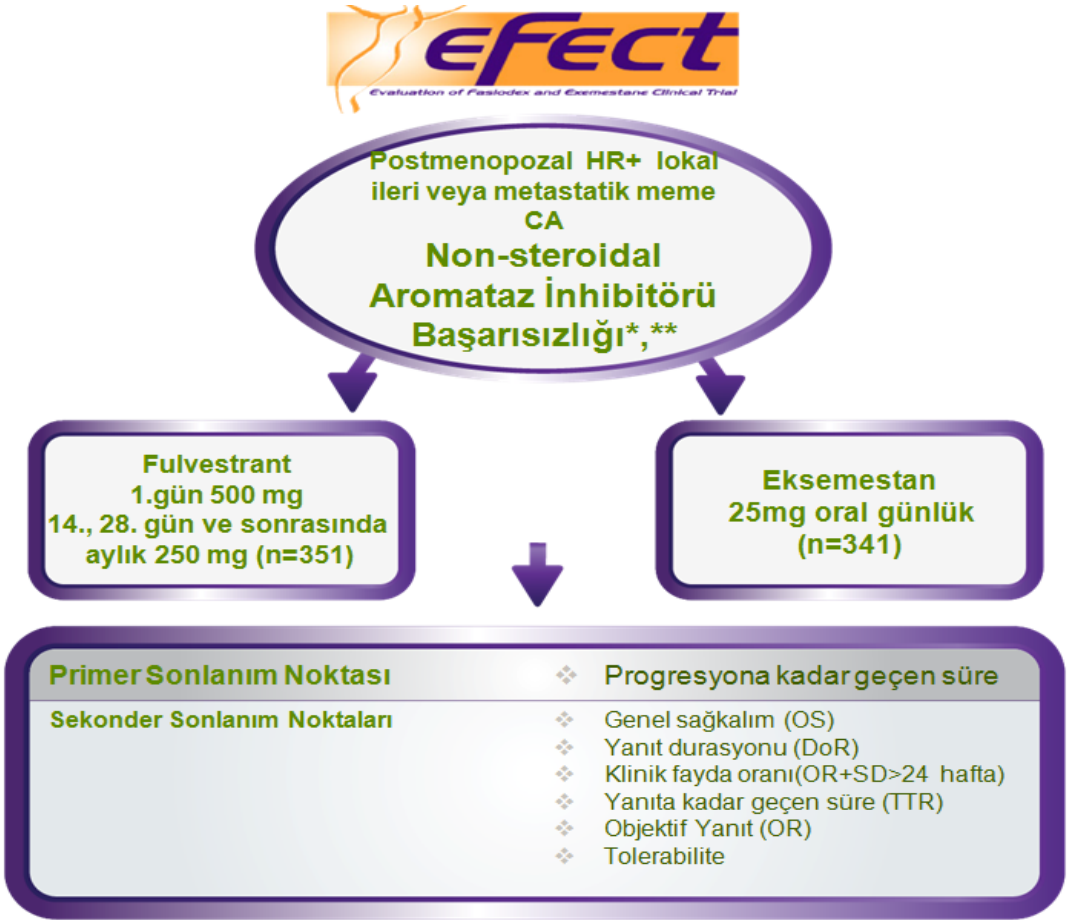
5-RT+Fulvestrane+paclociblib+Denasumumab/Zolendronik asid

6-RT+Fulvestran+zolendronik asid



Johnston S et al, Lancet Oncol 2013; Baselga J et al, NEJM 2011; Piccart M et al, Ann Oncol 2014

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi



580 olayın (progresyon ya da Ölüm) ardından analiz[2]

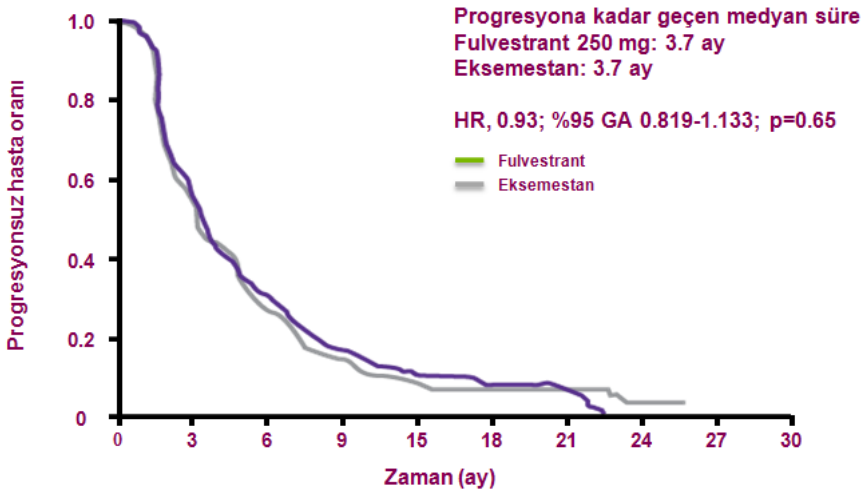
edavisi sırasında veya sonrasındaki ilk 6 ay içinde progrese olmuş hastalar
staların Al öncesi tamoksifen kulanmış olmasına izin verildi.

1.Mauriac L,et al.Breast Cancer Res Treat.2009 sep;117(1):69-75
2.Chia S,et al.J Clin Oncol.2008 Apr 1;26(10):1664-70

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

EFECT Çalışması
Progresyona Kadar Geçen Süre

Fulvestrant 250 mg ve eksemestan ile progresyona kadar geçen süre benzerdir.

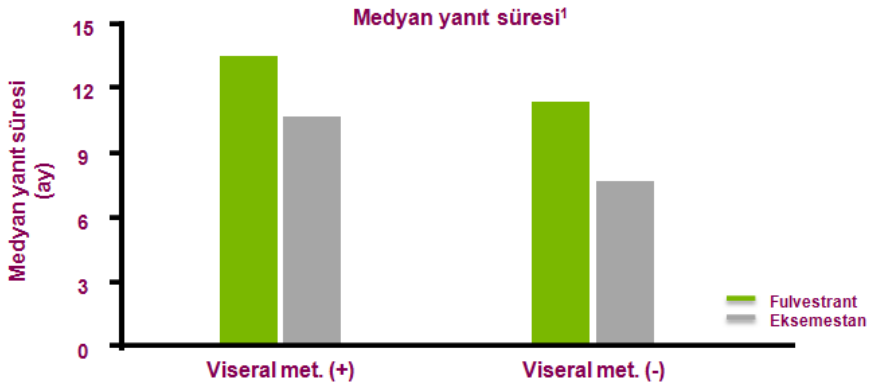


Chia S, et al. J Clin Oncol. 2008 Apr 1;26(10):1664-70

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

Efect Çalışması
Medyan Yanıt Süresi

Viseral metastazı olan hastalarda, medyan yanıt süresi sayısal olarak fulvestrant kolu lehinedir.[1]



Fulvestrant kolunda başlangıçta viseral metastazı olan HR+ hasta oranı: %69 ; eksemestan kolunda %56.6[1]

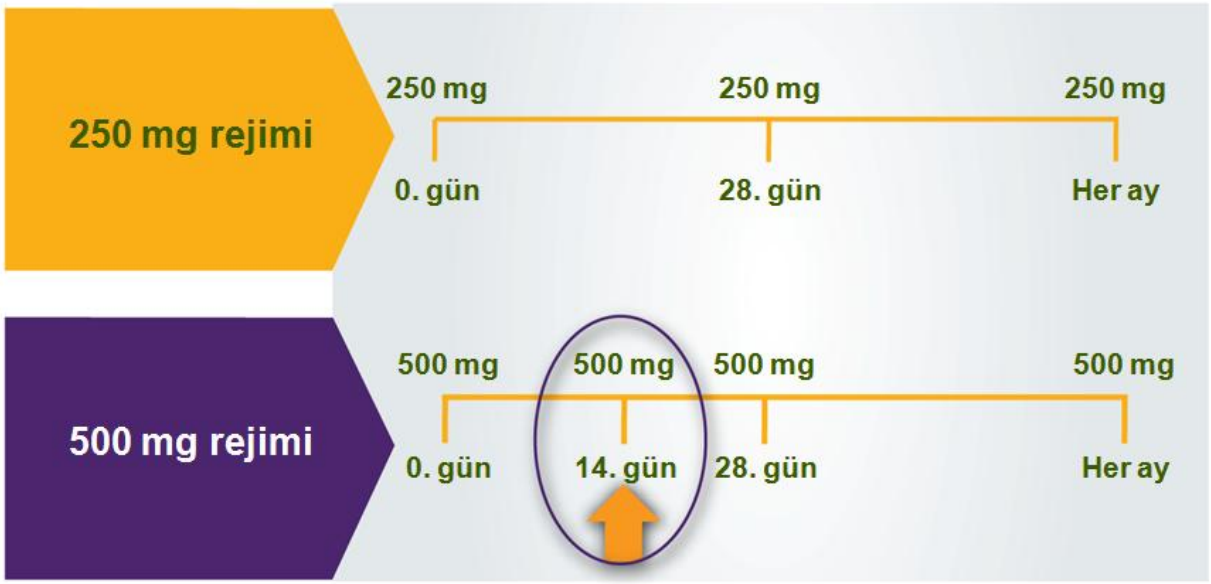
NCNN 2015 Meme Kanseri Klavuzu

Hormon reseptör pozitif non-viseral veya asemptomatik viseral tümörü olan hastalarda düşük toksisite nedeniyle endokrin tedavi düşünülebilir.[2]

1. Chia S, et al. J Clin Oncol. 2008 Apr 1;26(10):1664-70
2. NCCN Clinical Practice Guidelines in Oncology - Breast Cancer. Version 2.2015. NCCN.org

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

CONFIRM
Fulvestrant Doz Şeması



Di Leo A et al. J Clin Oncol 2010; 28: 4594-4600

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

CONFIRM
Hasta Özellikleri

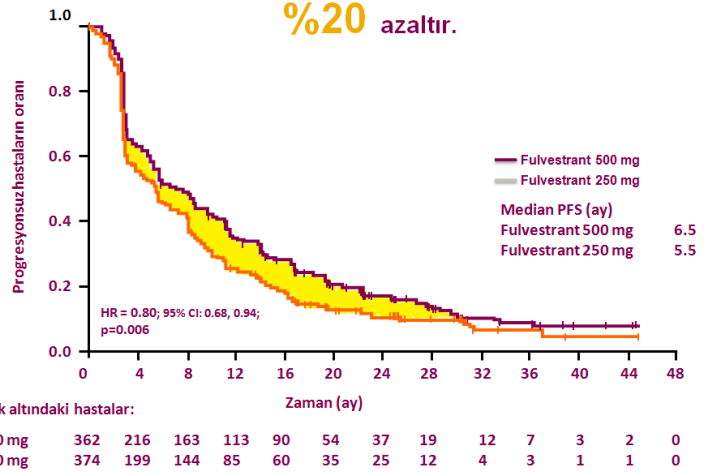
Özellik	Faslodex 500 mg (n=362)		Faslodex 250 mg (n=374)	
Medyan yaş	61		61	
ER pozitif (n,%)	362	%100	374	%100
PgR durumu				
Pozitif	241	%66.6	266	%71.1
Negatif	92	%25.4	96	%25.7
Bilinmiyor	29	%8	12	%3.2
Lokal ileri hastalık	4	%1.1	11	%2.9
Metastatik hastalık	358	%98.9	363	%97.1
Viseral tutulum	239	%66	232	%62

Di Leo A et al. J Clin Oncol 2010; 28: 4594-4600;

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

CONFIRM – PROGRESYONSUZ SAĞKALIM

Fulvestrant 500mg progresyon riskini 250mg'a göre anlamlı olarak **%20** azaltır.



Risk altındaki hastalar:

500 mg	362	216	163	113	90	54	37	19	12	7	3	2	0
250 mg	374	199	144	85	60	35	25	12	4	3	1	1	0

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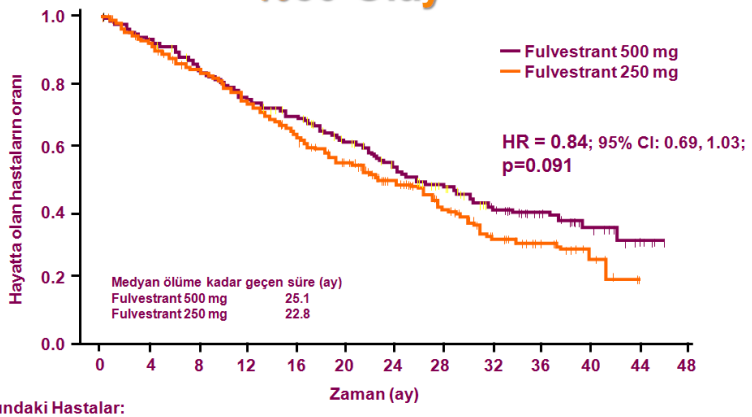
Di Leo A et al. J Clin Oncol 2010; 28: 4594-4600

Sekonder Sonlanım: Genel Sağkalım %50 Olay



Risk Altındaki Hastalar:

500 mg	362	330	285	251	223	165	116	74	46	29	16	6	0
250 mg	374	338	299	260	222	157	107	61	34	18	10	2	0

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Di Leo A et al. J Clin Oncol 2010; 28: 4594-4600

Table 1. Clinical and Pathological Characteristics of the Patients.*

Characteristic	Palbociclib–Fulvestrant (N=347)	Placebo–Fulvestrant (N=174)
Age		
Median — yr	57	56
Range — yr	30–88	29–80
<65 yr — no. (%)	261 (75.2)	131 (75.3)
≥65 yr — no. (%)	86 (24.8)	43 (24.7)
Race — no. (%)†		
White	252 (72.6)	133 (76.4)
Asian	74 (21.3)	31 (17.8)
Black or other	20 (5.8)	9 (5.2)
Hormone-receptor status — no. (%)		
ER-positive and PR-positive	238 (68.6)	111 (63.8)
ER-positive and PR-negative	91 (26.2)	48 (27.6)
ECOG performance status — no. (%)‡		
0	207 (59.7)	115 (66.1)
1	140 (40.3)	59 (33.9)
Disease-free interval§		
Median — mo	48	51
≤24 mo — no./total no. (%)	42/235 (17.9)	23/124 (18.5)
>24 mo — no./total no. (%)	186/235 (79.1)	95/124 (76.6)
Menopausal status at study entry — no. (%)		
Premenopausal or perimenopausal	72 (20.7)	36 (20.7)
Postmenopausal	275 (79.3)	138 (79.3)
Documented sensitivity to prior hormonal therapy — no. (%)¶		
Yes	274 (79.0)	136 (78.2)
No	73 (21.0)	38 (21.8)
Visceral metastasis — no. (%)‖	206 (59.4)	105 (60.3)
Measurable disease — no. (%)	268 (77.2)	138 (79.3)
Disease stage at study entry — no. (%)**		
Recurrent locally advanced††	49 (14.1)	25 (14.4)
Metastatic	296 (85.3)	146 (83.9)
No. of disease sites — no. of patients (%)‡‡		
1	111 (32.0)	60 (34.5)
2	99 (28.5)	50 (28.7)
≥3	135 (38.9)	62 (35.6)
Prior endocrine therapy — no. (%)§§		
Aromatase inhibitor with or without GnRH agonist	296 (85.3)	151 (86.8)
Tamoxifen with or without GnRH agonist	211 (60.8)	104 (59.8)
Most recent therapy — no. (%)		
Aromatase inhibitor with or without GnRH agonist	238 (68.6)	118 (67.8)
Tamoxifen with or without GnRH agonist	63 (18.2)	30 (17.2)

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi-PALOMA 3

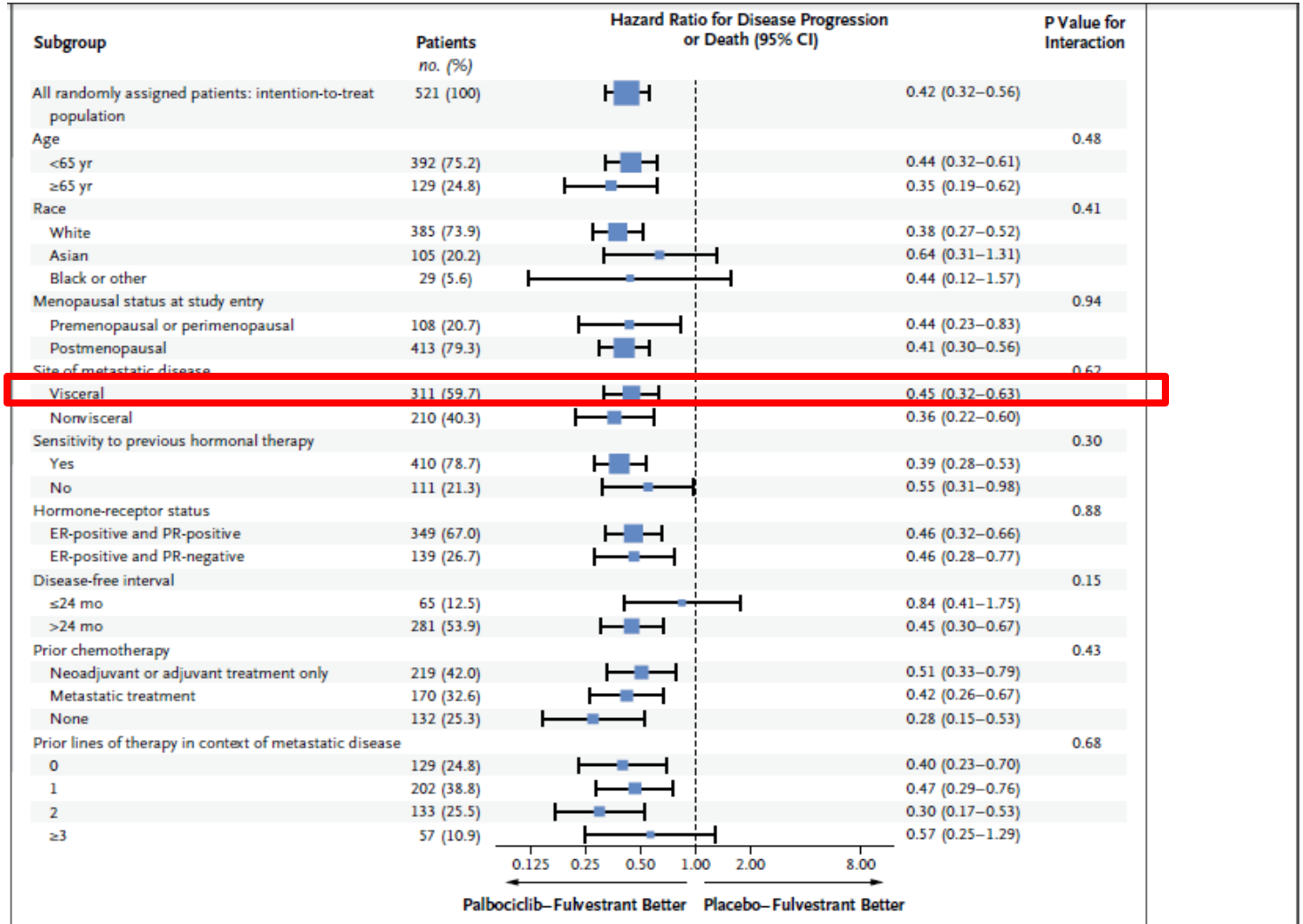


Figure 2. Subgroup Analysis of Progression-free Survival.

The blue boxes represent the hazard ratios with 95% confidence intervals (horizontal lines); the size of each box is proportional to the size of the corresponding subgroup. ER denotes estrogen receptor, and PR progesterone receptor.

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi

Efficacy of Palbociclib and Fulvestrant in Patients with mBC and ESR1 Mutations

- N = 395 patients with successful ESR1 mutation analysis from PALOMA-3 trial
- ESR1 mutations were strongly associated with acquired resistance to prior aromatase inhibitors

	Median PFS (months)		
	Palbociclib + fulvestrant	Placebo + fulvestrant	HR (*p*-value)
ESR1-positive (n = 67; 39)	9.4	4.1	0.524 (0.0052)
ESR1-negative (n = 198; 91)	9.5	3.8	0.438 (<0.0001)

- Palbociclib offers high efficacy regardless of ESR1 mutation status

Turner NC et al. *Proc ASCO* 2016;Abstract 512.

Tedavi Seçenekleri

HR+, HER2- negatif, yeni kemik metastazı olan, belirgin semptomu olmayan , 1 basamak hormon tedavisi sonrası kadın hasta, ECOG PS0-1 hasta

1- RT sonrası,tekli kemoterapi(paklitaksel), Zolendronik asid/ Denasumumab

2-RT sonrası, kombine kemoterapi(CAF), Zolendronik asid /Denasumumab

3-RT+Exemestane+ Denasumumab/Zolendronik asid

4-RT+ Exemestane+Everolimus+ Denasumumab/Zolendronik asid

5-RT+Fulvestrane+paclociblib+Denasumumab/Zolendronik asid

6-RT+Fulvestran+zolendronik asid

PET-CT; 3. Ay Yanıt değerlendirmesi

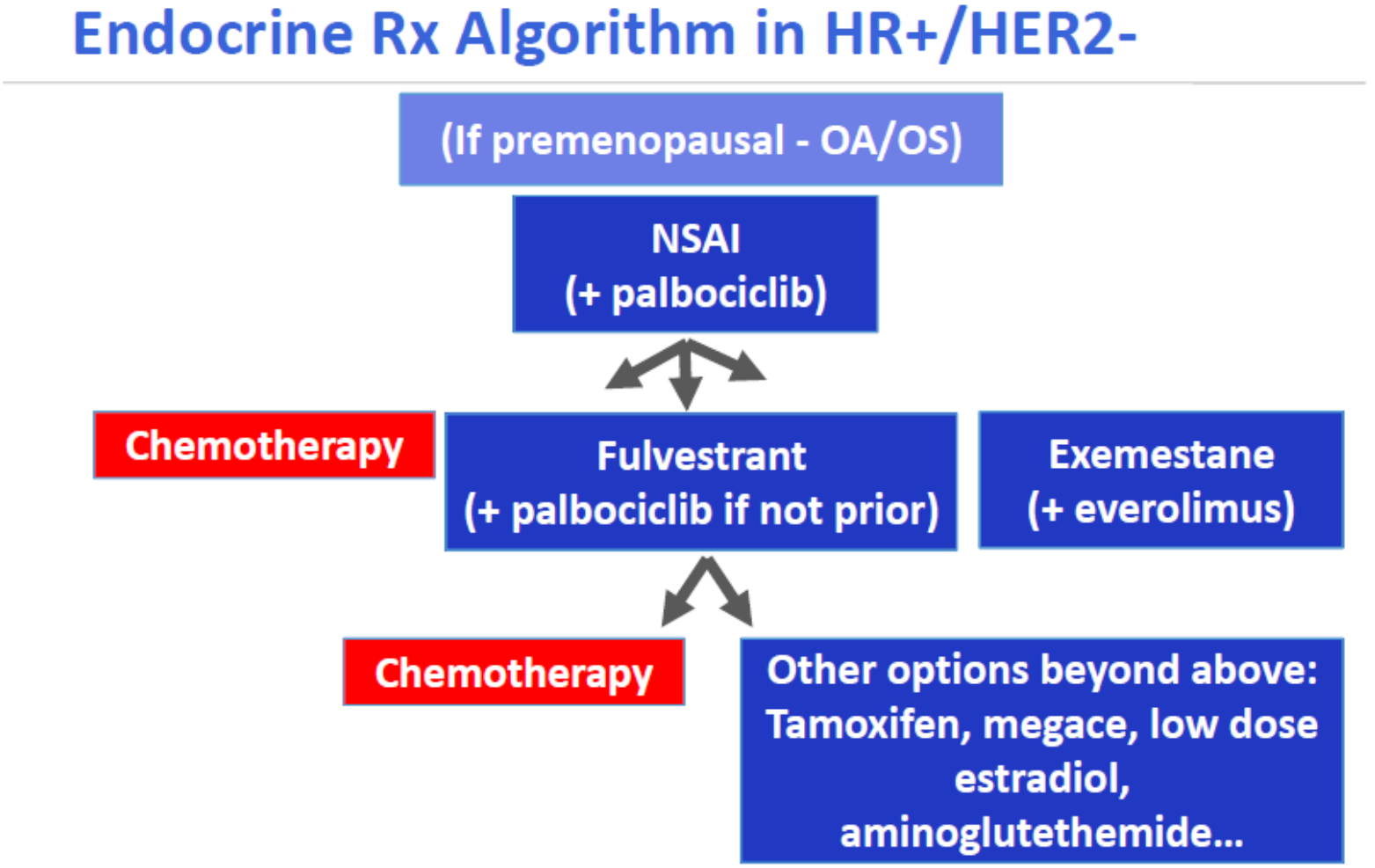
3. Aylık PET-CT kontrolde;

- Sağ aksila lenf nodunun gözlenmediği
- kemik metastazlarında belirgin regresyon saptandı

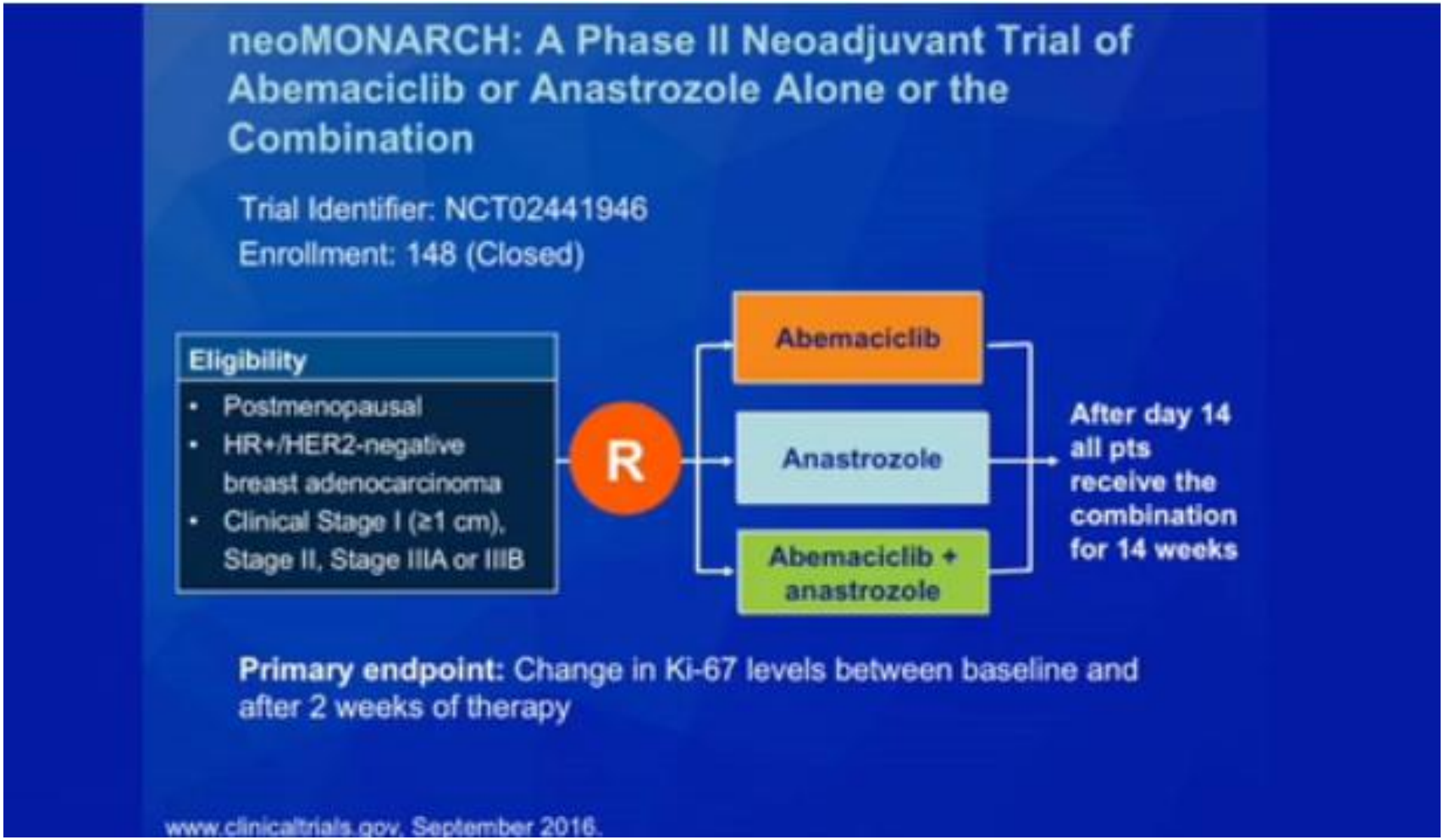
HR+, HER2- ,Yaygın Kemik metastazı olan Meme Kanseri 2. Basamak Tedavi

- Fulvestran 500 mg yükleme dozu sonrası(1, 14, 28. gün), 28 günde bir başlandı
- Zolendronik asid 4 mg/ 28 gün devam edildi
- 3. Aylık PET-CT kontrolde; Sağ aksila lenf nodunun gözlenmediği, kemik metastazlarında belirgin regresyon saptan
- Hasta 6. ayında progresyonsuz izleniyor

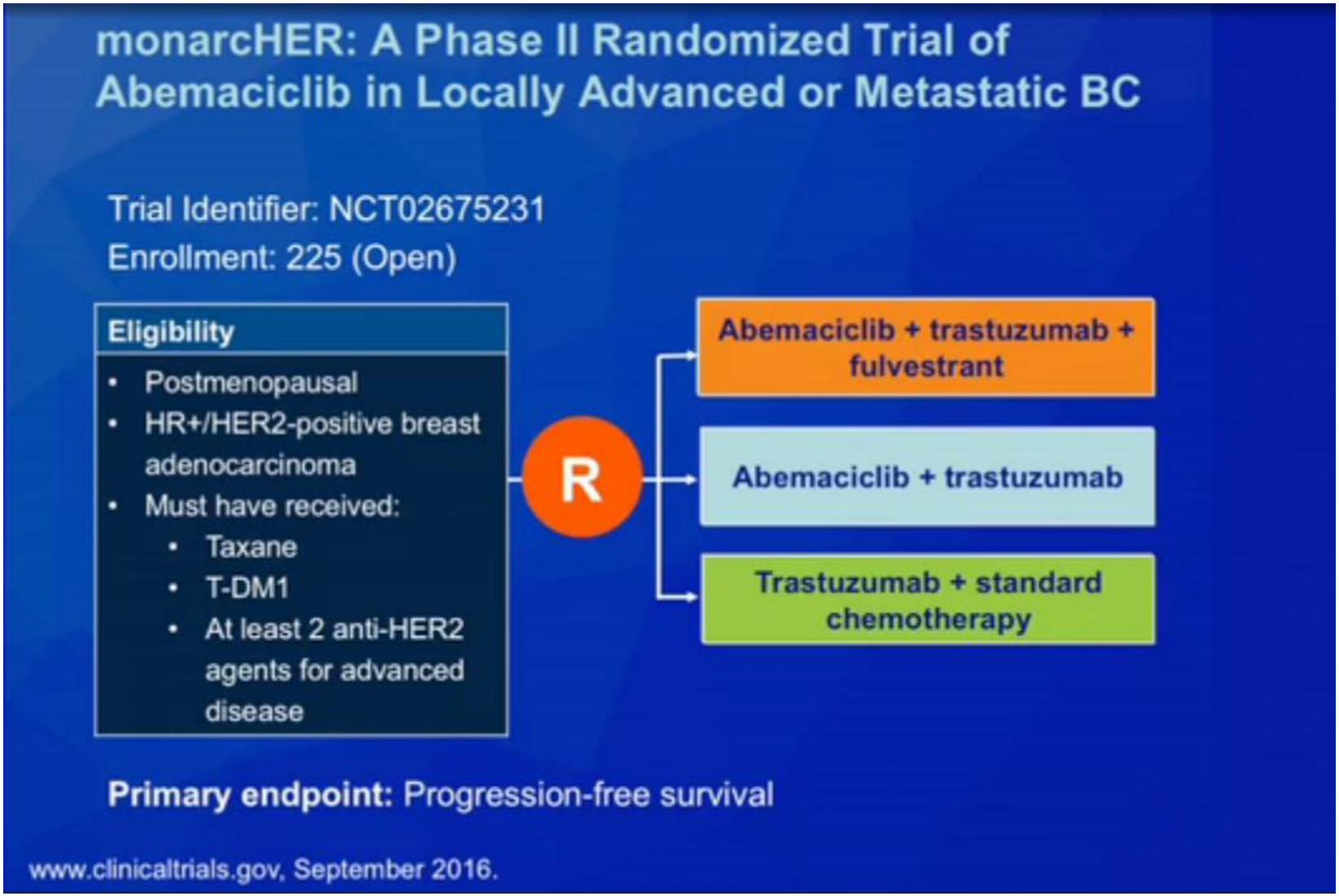
HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi



HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi



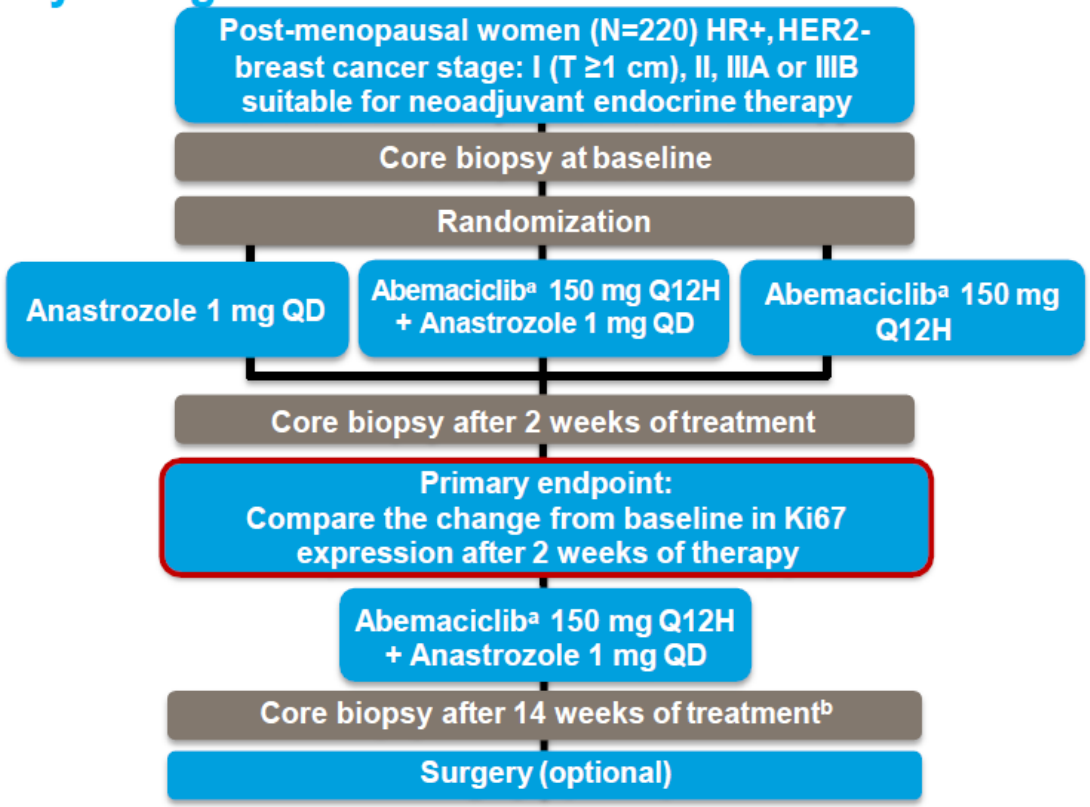
HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi



HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi Nereye Gidiyor

neoMONARCH: Phase II study design

- Abemaciclib 150 mg BID is tolerable when dosed on a continuous schedule with endocrine therapy[1]
- The most common adverse event has been diarrhea
  - Typically occurred within the first 7 days of treatment
  - Manageable with use of loperamide or dose reduction
- Loperamide was administered prophylactically for the first 28 days then at discretion of investigator



[1]Patnaik A et al. *Cancer Discovery* 2016;6:740-5

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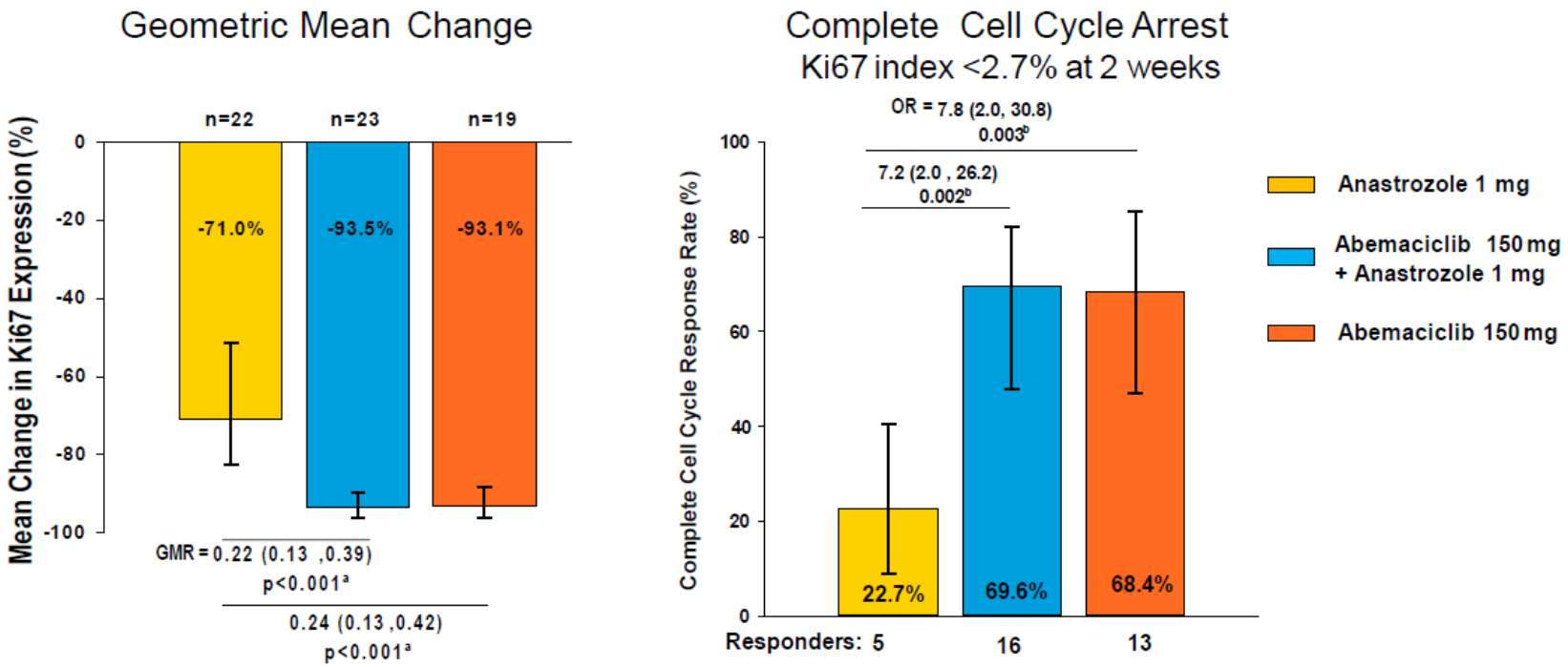
Abbreviations: HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; Q12H = every 12 hours; QD = once daily
[a]Participants receive loperamide with each dose of abemaciclib
[b]Participants who experience benefit following 14 weeks may remain on neoadjuvant therapy for up to 8 additional weeks

HR pozitif, HER2 negatif Metastatik Meme Kanserinde Tedavi Nereye Gidiyor

neoMONARCH: Change in Ki67 expression and Ki67 response

- Study met the boundary for statistical significance at the interim analysis (boundary p <0.03)



Abbreviations: GMR = geometric mean ratio, OR = odds ratio

[a]Geometric Mean Ratio (GMR), 2-sided 90% confidence interval (CI), p-value. p-values are based on a one-sided hypothesis test from a linear model with treatment, PR status (positive versus negative/unknown) and tumor size (<2 cm versus ≥2 cm and <5 cm versus ≥5 cm) as fixed effects.

[b]A responder is identified as a patient with a ln(Ki67) value of less than 1. Odds ratio (OR), 2-sided 90% CI, p value. p-value is calculated by Fisher's Exact test of a one-sided hypothesis.

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