Dr Dilşen Çolak
Başkent Üniversitesi Tıp Fakültesi
Tıbbi Onkoloji Kliniği

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

Sara M. Tolaney, M.D., M.P.H., William T. Barry, Ph.D., Chau T. Dang, M.D., Denise A. Yardley, M.D., Beverly Moy, M.D., M.P.H., P. Kelly Marcom, M.D., Kathy S. Albain, M.D., Hope S. Rugo, M.D., Matthew Ellis, M.B., B.Chir., Ph.D., Iuliana Shapira, M.D., Antonio C. Wolff, M.D., Lisa A. Carey, M.D., Beth A. Overmoyer, M.D., Ann H. Partridge, M.D., M.P.H., Hao Guo, M.S., Clifford A. Hudis, M.D., Ian E. Krop, M.D., Ph.D., Harold J. Burstein, M.D., Ph.D., and Eric P. Winer, M.D.

N Engl J Med 2015;372:134-41.

HER-2 (+) hastalık

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

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

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

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

Dahil edilme kriterleri

- HER 2 3+ yada FISH +
- Tm </= 3 cm
- Histolojik olarak kanıtlı aksilla negatif tümör, Nımic (AD tamamlanmış olacak)
- HR+/- olabilir

N Engl J Med 2015;372:134-41.

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

- Paklitaksel haftalık 80 mg 12 hafta
- Trastuzumab haftada bir 12 hafta ,
  sonrasında haftalık ya da 3 haftalık toplam 1 yıl
- HR (+) hastalarda paclitaxel sonrası HT
- RT
  - Parsiyel meme ışınlaması /protokol öncesinde
  - Tüm meme ışınlaması / paclitaxel bitiminde

N Engl J Med 2015;372:134-41.

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

- Etkinlik ölçütü: invaziv hastalık (rekürrens veya yeni invaziv hastalık)
- Alt grup analizleri
  - ✓ (≤1 cm vs >1 cm)
  - ✓ Hormon-reseptör durumu (İHB ER ve/veya PR ≥ %1)

N Engl J Med 2015;372:134-41.

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

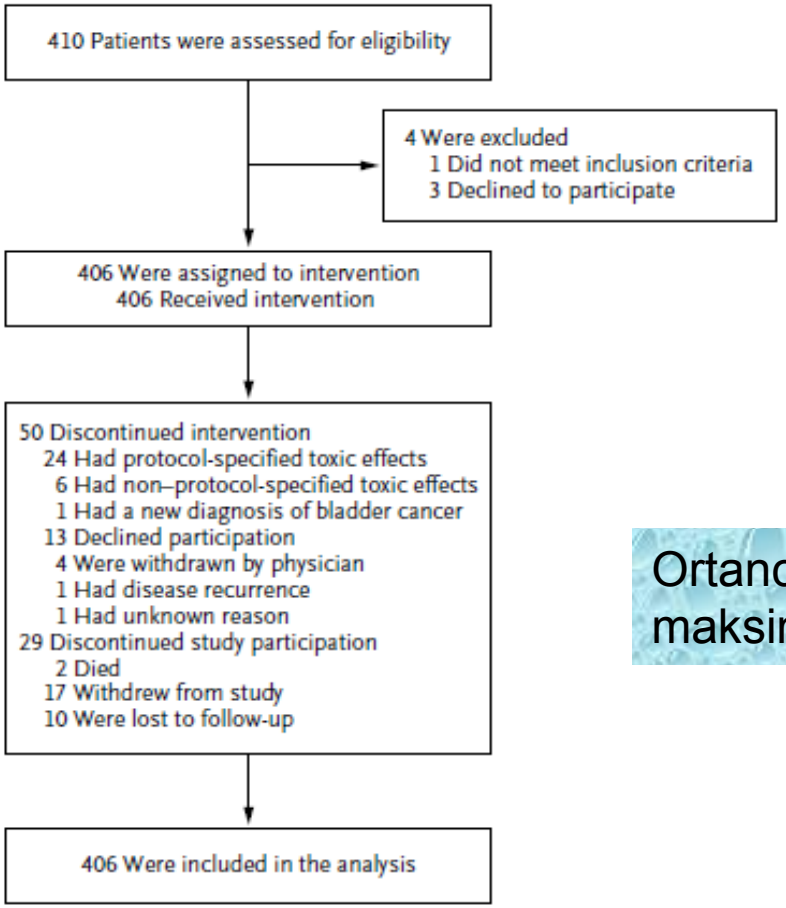


Figure 1. Enrollment and Follow-up.

Ortanca takip süresi: 4 yıl, maksimum 6.2 yıl

N Engl J Med 2015;372:134-41.

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Patients (N = 406)
	no. (%)
Age group	
<50 yr	132 (32.5)
50–59 yr	137 (33.7)
60–69 yr	96 (23.6)
≥70 yr	41 (10.1)
Sex	
Female	405 (99.8)
Male	1 (0.2)
Race†	
White	351 (86.5)
Black	28 (6.9)
Asian	11 (2.7)
Other	16 (3.9)
Primary tumor	
Size	
T1mic: ≤0.1 cm	9 (2.2)
T1a: >0.1 to ≤0.5 cm	68 (16.7)
T1b: >0.5 to ≤1.0 cm	124 (30.5)
T1c: >1.0 to ≤2.0 cm	169 (41.6)
T2: >2.0 to ≤3.0 cm	36 (8.9)
Nodal status	
N0	400 (98.5)
N1mic	6 (1.5)
Histologic grade	
I: well-differentiated	44 (10.8)
II: moderately differentiated	131 (32.3)
III: poorly differentiated	228 (56.2)
Unknown	3 (0.7)
Hormone-receptor status	
Positive	272 (67.0)
Negative	134 (33.0)

N Engl J Med 2015;372:134-41.

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

Table 2. Events Observed for the Primary End Point of Disease-free Survival.

Event	Patients (N = 406)	Time to Event
	no. (%)	*mo*
Any recurrence or death	12 (3.0)	
Local or regional recurrence*		
Ipsilateral axilla, HER2-positive	3 (0.7)	12, 20, 54
Ipsilateral breast, HER2-positive	1 (0.2)	37
New contralateral primary breast cancer		
HER2-positive	1 (0.2)	56
HER2-negative	3 (0.7)	12, 37, 59
Distant recurrence*		
Skeletal tissue, HER2-positive	1 (0.2)	27
Soft tissue, HER2-negative	1 (0.2)	46
Death		
Breast-cancer–related	0	
Not breast-cancer–related	2 (0.5)	13, 71

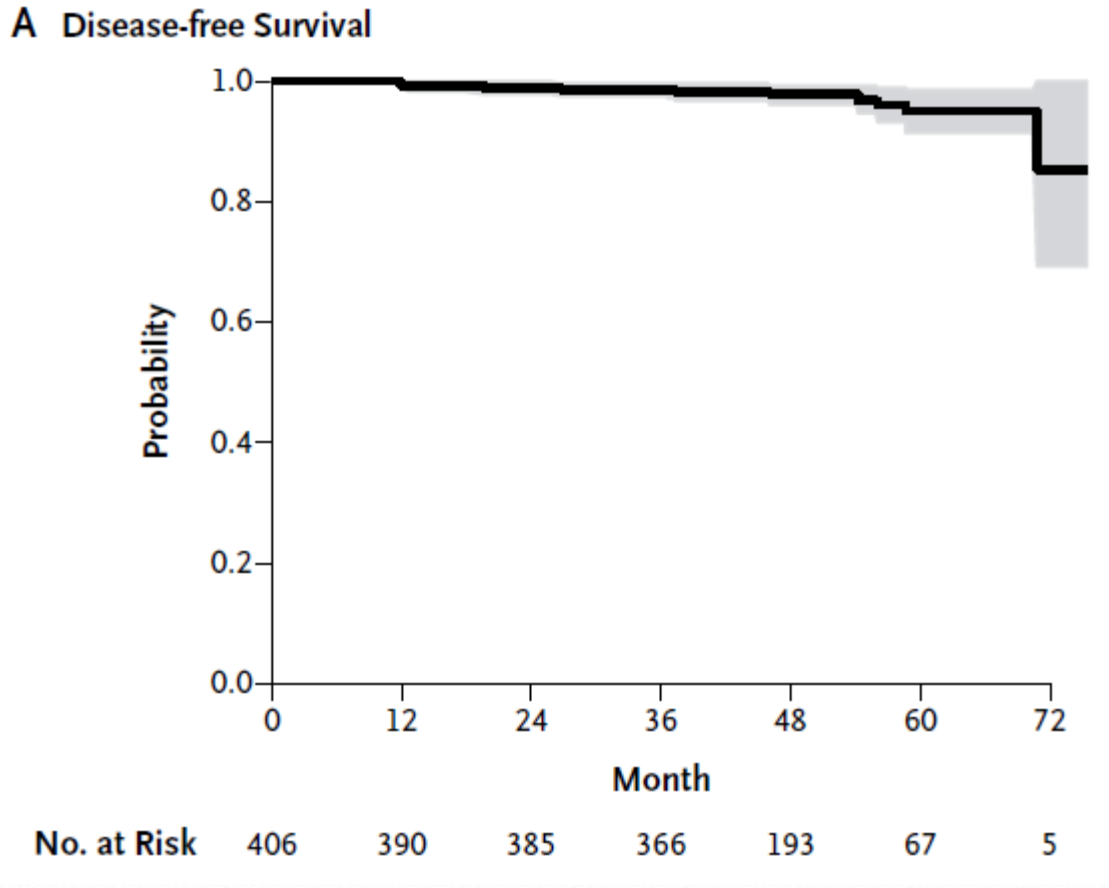
N Engl J Med 2015;372:134-41.

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

- %87,7 52 haftalık tedaviyi tamamlamış.
- Takipte
  - ✓ 2 hastada uzak metastaz
  - ✓ 4 lokal-rejyonel nüks
  - ✓ 4 karşı meme kanseri
  - ✓ 1 over kanseri
  - ✓ 1 stroke
- 3 yıllık DFS %98.7; 3 yıllık RFS %99,2

N Engl J Med 2015;372:134-41.

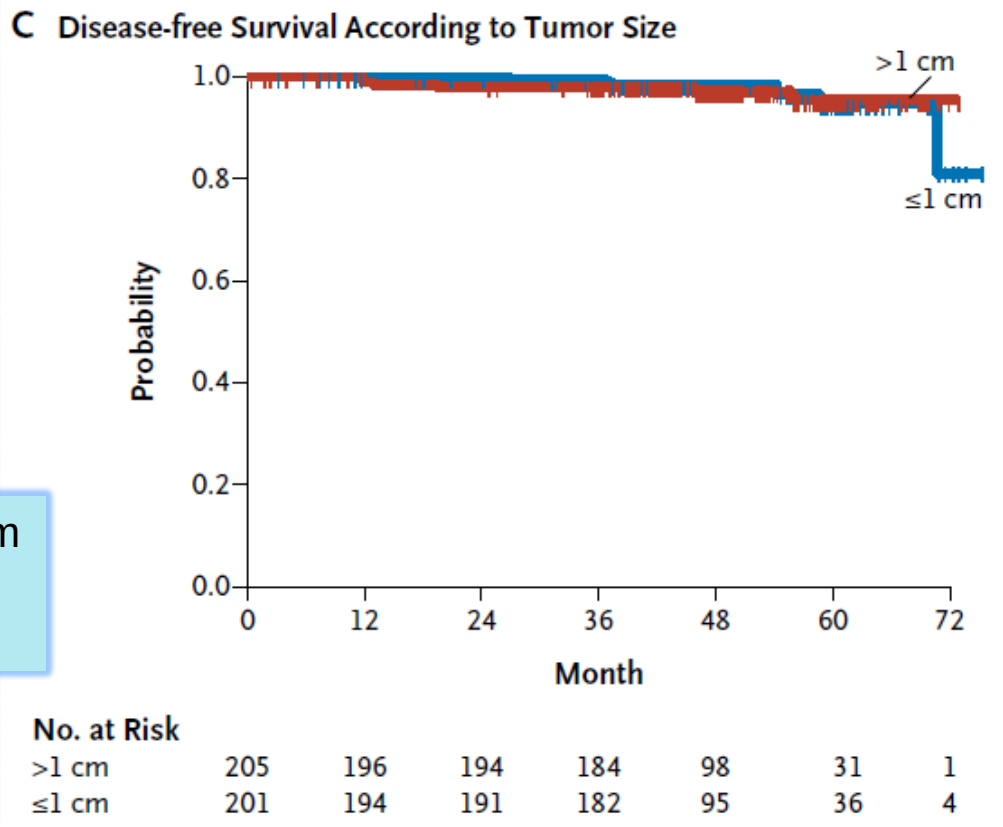
Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer



DFS %98.7

N Engl J Med 2015;372:134-41.

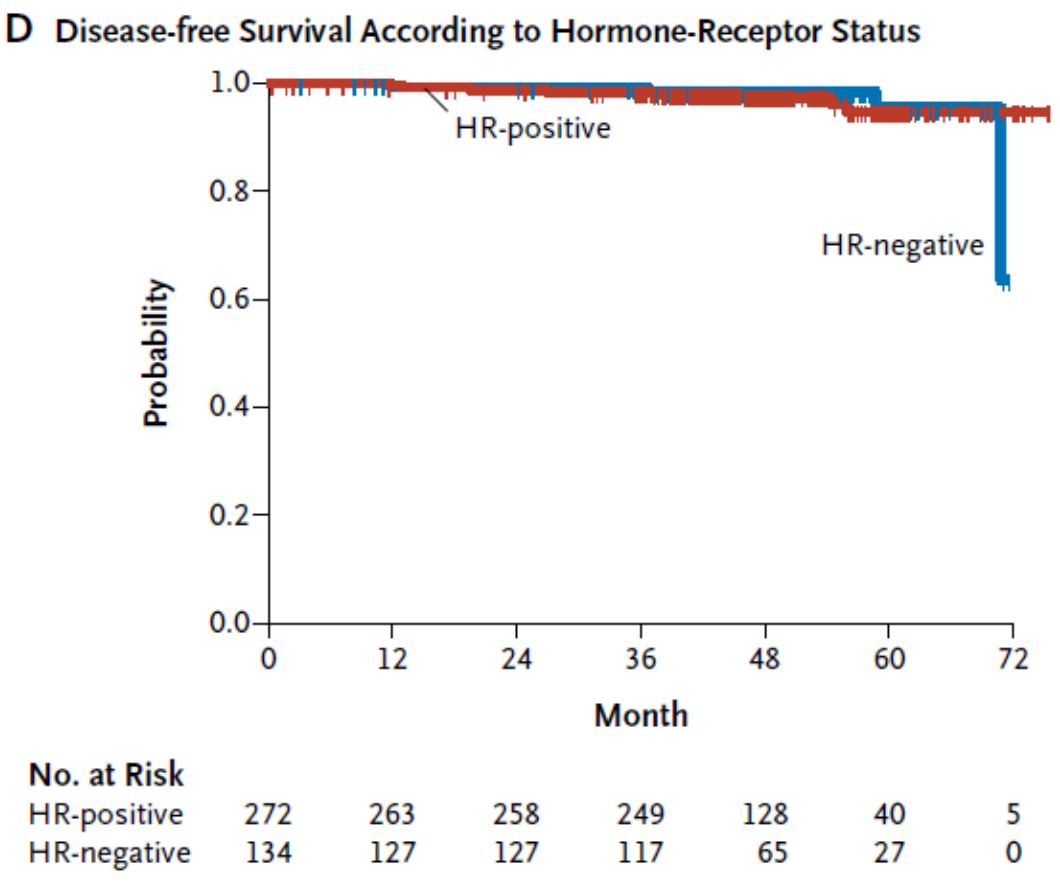
Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer



HR+,-, <=1 cm ya da >1 cm gruplarında rekürrens düşük oranda

N Engl J Med 2015;372:134-41.

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer



N Engl J Med 2015;372:134-41.

Adjuvant Paclitaxel and Trastuzumab for Node-Negative, HER2-Positive Breast Cancer

Yan etkiler

- %3,2 grad 3 nöropati, grad 4 yok
- 2 hastada grad 3 sistolik disfonksiyon; her ikisi de 4 haftalık ara sonrası düzelmiş
- 13 hastada asemptomatik EF düşüklüğü (%3,2)
- 2 hastada EF normale gelmemiş
- 7 hastada grad 3-4 alerjik rxn

OXFORD JOURNALS Annals of Oncology

Ann Oncol. 2015 Aug; 26(8): 1533–1546.
Published online 2015 May 4. doi: 10.1093/annonc/mdv221
Editor's choice

PMCID: PMC4511219

Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015

A. S. Coates,[1] E. P. Winer,[2] A. Goldhirsch,[3,*] R. D. Gelber,[4] M. Gnant,[5] M. Piccart-Gebhart,[6] B. Thürlimann,[7] and H.-J. Senn[8], Panel Members[†]

St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015

Any patient with HER2+ Stage I BC and candidate to chemo with a tumor of maximum 1 cm. Preferred regimen:

- anthracyclines followed by taxanes and trastuzumab 27%
- Paclitaxel-trastuzumab 64.9%
- Other 8.1%
- Abstain 0

St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015

Any patient with HER2+ Stage I BC and candidate to chemo with a tumor >1 cm.

Preferred regimen:

- anthracyclines followed by taxanes and trastuzumab 50%
- Paclitaxel-trastuzumab 37.5%
- Other 9.4%
- Abstain 0

St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015

HER2-positive Stage 2

Should chemotherapy always be given to patients with stage 2 disease who require anti-HER2 therapy? 97/3/0

Should the chemotherapy regimen for these patients preferably contain anthracyclines? 88.9/7.4/3.7 1Y/ 2N/ 9A

Should the chemotherapy regimen for these patients contain taxanes? 97.2/2.8/0 1Y/ 2N/ 9A

Should anti-HER2 therapy start concurrent with taxane? 97.3/2.7/0 1Y/ 2N/ 9A

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Invasive Breast Cancer

NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

PREOPERATIVE/ADJUVANT THERAPY REGIMENS [1,2,3,4]

Regimens for HER2-negative disease[5]

Preferred regimens:

- **Dose-dense AC** (doxorubicin/cyclophosphamide) **followed by paclitaxel every 2 weeks**
- **Dose-dense AC** (doxorubicin/cyclophosphamide) **followed by weekly paclitaxel**
- **TC** (docetaxel and cyclophosphamide)

Other regimens:

- **Dose-dense AC** (doxorubicin/cyclophosphamide)
- **AC** (doxorubicin/cyclophosphamide) **every 3 weeks** (category 2B)
- **CMF** (cyclophosphamide/methotrexate/fluorouracil)
- **AC followed by docetaxel every 3 weeks**
- **AC followed by weekly paclitaxel**
- **EC** (epirubicin/cyclophosphamide)
- **FEC/CEF followed by T** (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel) **or** (fluorouracil/epirubicin/cyclophosphamide followed by weekly paclitaxel)
- **FAC followed by T** (fluorouracil/doxorubicin/cyclophosphamide followed by weekly paclitaxel)
- **TAC** (docetaxel/doxorubicin/cyclophosphamide)

Regimens for HER2-positive disease[6,7,8]

Preferred regimens:

- **AC followed by T + trastuzumab ± pertuzumab**[9] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)
- **TCH** (docetaxel/carboplatin/trastuzumab) **± pertuzumab**

Other regimens:

- **AC followed by docetaxel + trastuzumab ± pertuzumab**[9]
- **Docetaxel + cyclophosphamide + trastuzumab**
- **FEC followed by docetaxel + trastuzumab + pertuzumab**[9]
- **FEC followed by paclitaxel + trastuzumab + pertuzumab**[9]
- **Paclitaxel + trastuzumab**[10]
- **Pertuzumab + trastuzumab + docetaxel followed by FEC**[9]
- **Pertuzumab + trastuzumab + paclitaxel followed by FEC**[9]

[10]Paclitaxel + trastuzumab may be considered for patients with low-risk stage I, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.

- Over fonksiyonlarının supreyonu (OFS)?
- Premenapozal hastada OFS + Aromataz inhibitörü?

The International Breast Cancer Study Group

- Adjuvan endokrin tedavi
  - Over fonksiyonlarının supreyonu (OFS)?
  - Premenapozal hastada OFS + Aromataz inhibitörü?
- The **S**upression of **O**varian **F**unction (SOFT) **T**rial
- The **T**amoxifen and **Ex**emestane (TEXT) **T**rial

Faz III Çalışmalar

Over Supresyonu (GnRH, cerrahi veya radyoterapi)

TEXT & SOFT

Tamoksifen + OFS vs. Ekzemestan + OFS

Stratified by trial, use of chemotherapy, nodal status

TEXT

Premenopausal, HR+ BC
≤ 12 wks after surgery
N = 2672

- **Tamoxifen 20 mg/day + OFS*** (n = 1338)
- **Exemestane 25 mg/day + OFS*** (n = 1334)

SOFT

- Premenopausal HR+ BC ≤ 12 wks after surgery (if no chemo) *or*
- ≤ 8 mos after chemo if premen status confirmed
- N = 3066

- **Tamoxifen 20 mg/day + OFS*** (n = 1024)
- **Exemestane 25 mg/day + OFS*** (n = 1021)
- **Tamoxifen 20 mg/day**

Joint Analysis

Tamoxifen + OFS*

N = 2344

- Median follow up: 68 months
- 42% N+
- Neo/Adjuvant chemotherapy: 58%

Exemestane+ OFS*

N = 2346

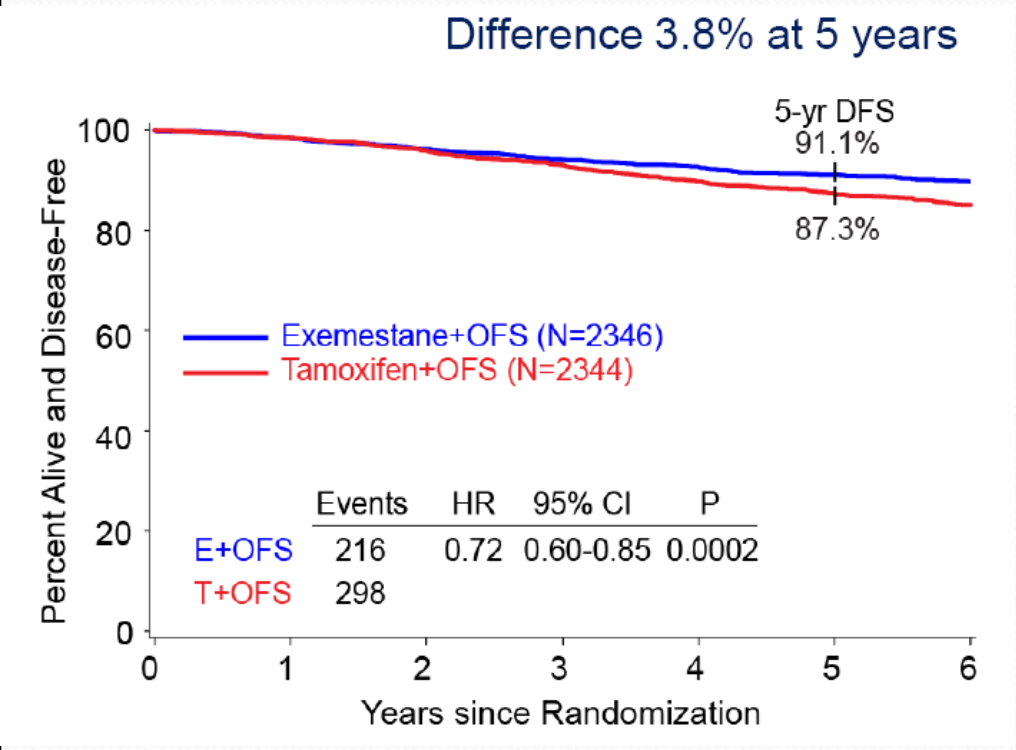
OFS

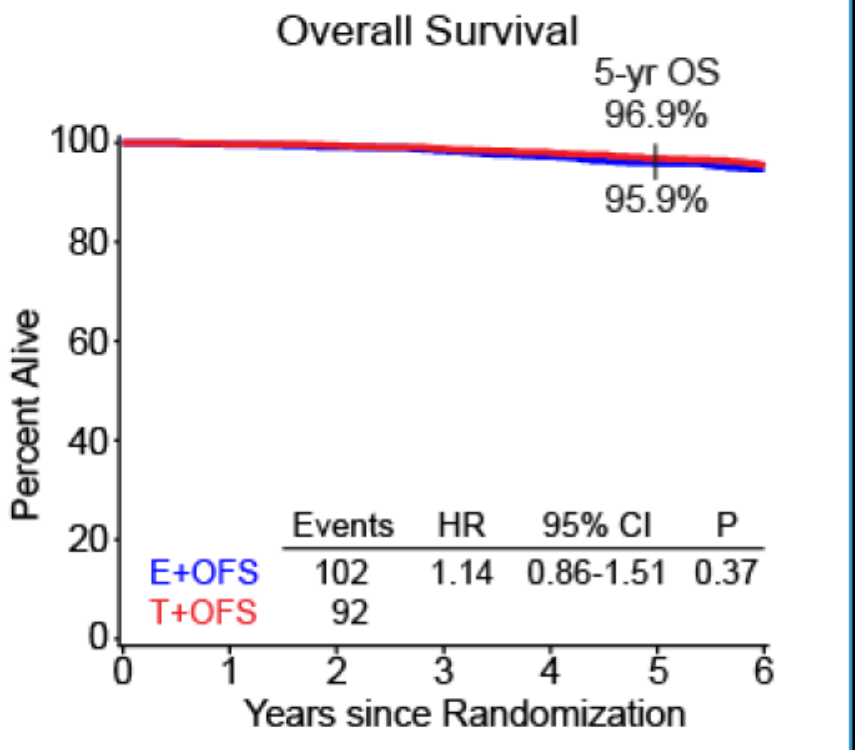
- TEXT: triptorelin 3.75 mg IM every 28 days for 6-8 weeks prior to initiation of HT or concurrently with chemotherapy
- SOFT: triptorelin, bilateral oophorectomy or Ovarian irradiation

Pagani O, et al. NEJM July 2014.

SOFT/TEXT birleşik analizi

Exemestane + OFS ile DFS daha iyi





Ortanca takip 5.7 yıl

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Ovarian Suppression in Premenopausal Breast Cancer

Prudence A. Francis, M.D., Meredith M. Regan, Sc.D., Gini F. Fleming, M.D., István Láng, M.D., Eva Ciruelos, M.D., Meritxell Bellet, M.D., Hervé R. Bonnefoi, M.D., Miguel A. Climent, M.D., Gian Antonio Da Prada, M.D., Harold J. Burstein, M.D., Ph.D., Silvana Martino, D.O., Nancy E. Davidson, M.D., Charles E. Geyer, Jr., M.D., Barbara A. Walley, M.D., Robert Coleman, M.B., B.S., M.D., Pierre Kerbrat, M.D., Stefan Buchholz, M.D., James N. Ingle, M.D., Eric P. Winer, M.D., Manuela Rabaglio-Poretti, M.D., Rudolf Maibach, Ph.D., Barbara Ruepp, Pharm.D., Anita Giobbie-Hurder, M.S., Karen N. Price, B.S., Marco Colleoni, M.D., Giuseppe Viale, M.D., Alan S. Coates, M.D., Aron Goldhirsch, M.D., and Richard D. Gelber, Ph.D., for the SOFT Investigators and the International Breast Cancer Study Group*

N Engl J Med 2015;372:436-46

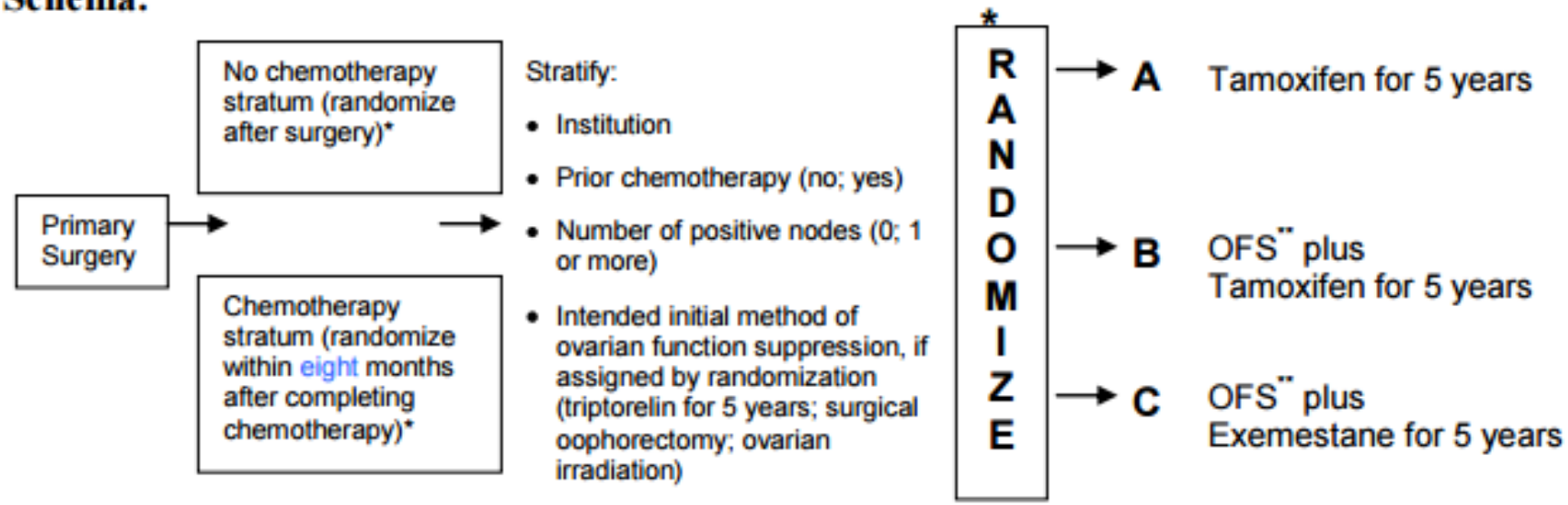
The **S**upression of **O**varian **F**unction (SOFT) **T**rial

- Adjuvan veya neo-adjuvan kemoterapi sonrası premenapozal kalan *veya*

  adjuvan tamoxifen'in tek başına yeterli olacağı düşünülen premenapozal kadınlar
- Dahil edilme kriterleri
  - ✓ Dökümante (serum E2 düzeyi ile) premenapozal statü
  - ✓ Operabıl meme kanseri (total mastektomi veya meme koruyucu cerrahi)
  - ✓ Aksiller dxn veya Sentinal LN bx
  - ✓ ER veya PR pozitif hastalık (en az %10)

SOFT Trial

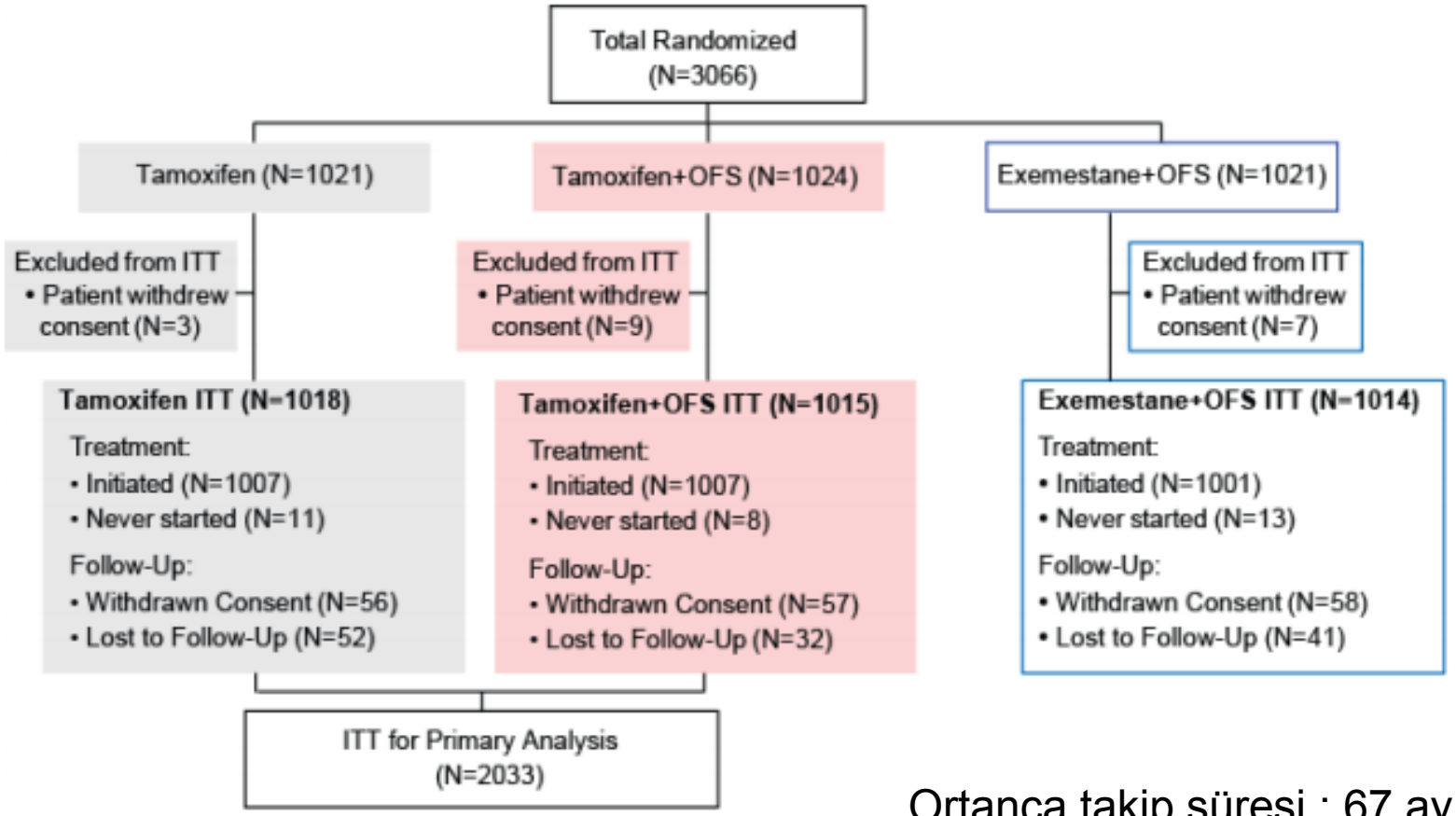
Schema:



* Patients may have received tamoxifen or anti-aromatase agent prior to randomization

** OFS = ovarian function suppression (triptorelin for 5 years OR surgical oophorectomy OR ovarian irradiation)

SOFT Trial



Ortanca takip süresi : 67 ay

SOFT Trial

Table 1. Characteristics of Patients in the Primary Analysis, Overall and According to Chemotherapy Cohort.*

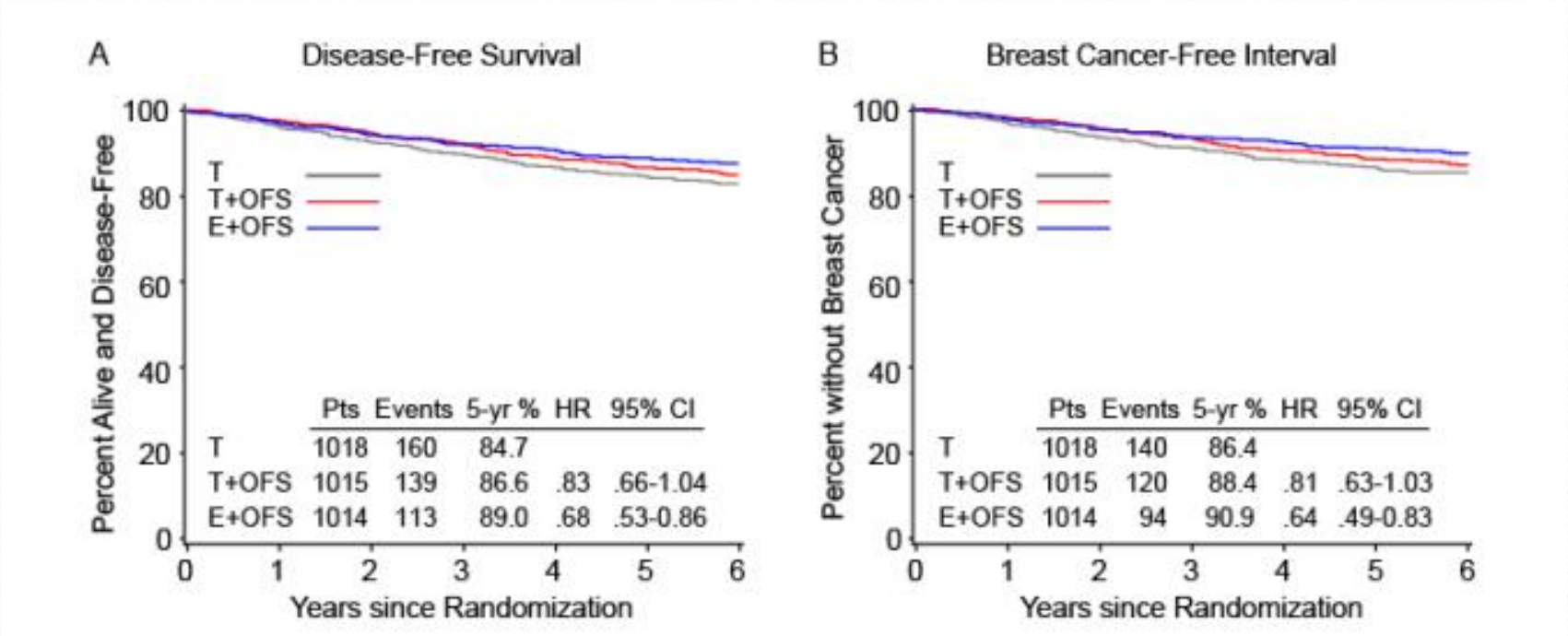
Characteristic	No Chemotherapy (N=949)	Prior Chemotherapy (N=1084)	Overall (N=2033)
Age at randomization			
Median — yr	46	40	43
Distribution — no. (%)			
<35 yr	14 (1.5)	219 (20.2)	233 (11.5)
35–39 yr	78 (8.2)	309 (28.5)	387 (19.0)
40–49 yr	702 (74.0)	522 (48.2)	1224 (60.2)
≥50 yr	155 (16.3)	34 (3.1)	189 (9.3)
Lymph-node status — no. (%)			
Negative	861 (90.7)	463 (42.7)	1324 (65.1)
Positive	88 (9.3)	621 (57.3)	709 (34.9)
Tumor size — no. (%)†			
≤2 cm	806 (84.9)	526 (48.5)	1332 (65.5)
>2 cm	136 (14.3)	513 (47.3)	649 (31.9)
Tumor grade — no. (%)‡			
1	389 (41.0)	151 (13.9)	540 (26.6)
2	483 (50.9)	523 (48.2)	1006 (49.5)
3	65 (6.8)	374 (34.5)	439 (21.6)
HER2-positive — no. (%)	40 (4.2)	196 (18.1)	236 (11.6)
Interval from surgery to randomization — mo			
Median	1.8	8.0	3.2
Interquartile range	1.2–2.4	5.8–10.3	1.7–8.33
Endocrine therapy before randomization — no. (%)§	47 (5.0)	475 (43.8)	522 (25.7)

* A more complete summary is provided in Table S1 in the Supplementary Appendix. Characteristics were well balanced according to treatment assignment (Table S2 in the Supplementary Appendix). The statistical analysis plan did not specify hypothesis testing regarding comparisons between these groups. HER2 denotes human epidermal growth factor receptor 2.
† Data were missing for 7 patients who did not receive chemotherapy and for 45 who had received chemotherapy previously.
‡ Data were missing for 12 patients who did not receive chemotherapy and for 36 who had received chemotherapy previously.
§ Oral endocrine therapy before randomization was allowed while premenopausal status was established or reestablished.

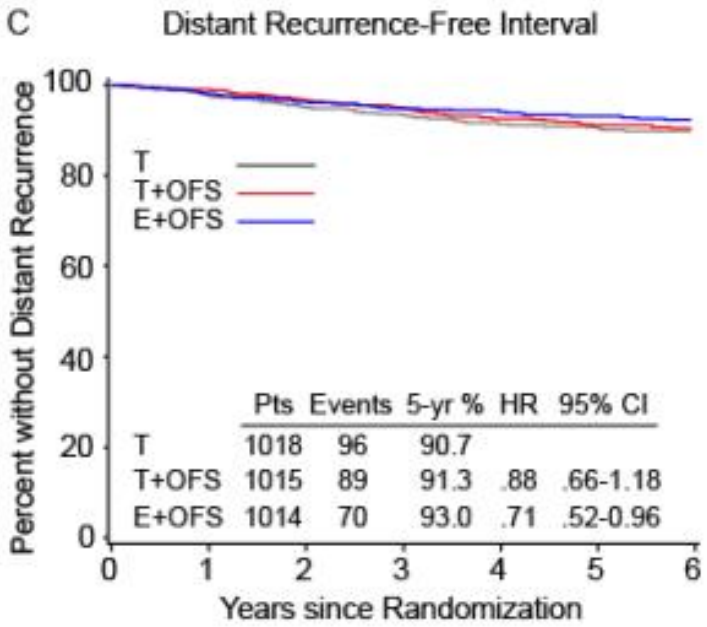
SOFT Trial

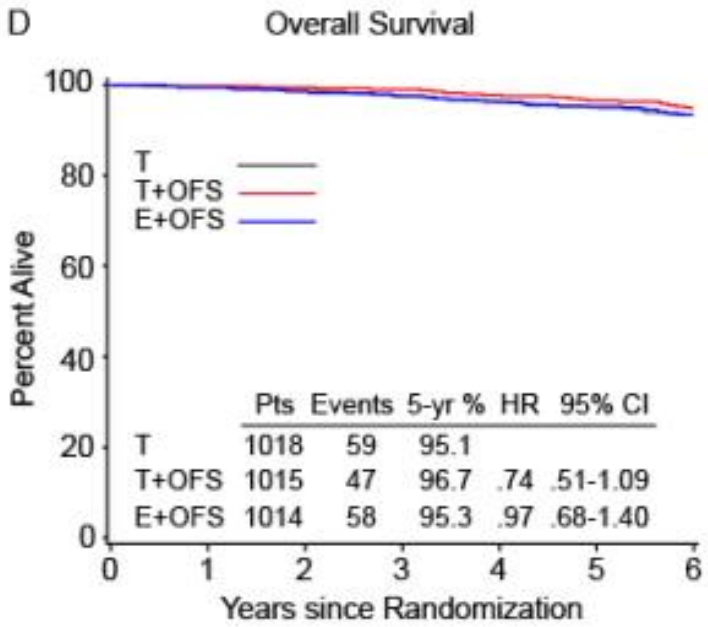
- Birincil sonlanım noktası: Hastalıksız sağ kalım (DFS)
- İkincil sonlanım noktaları:
  - ✓ Genel sağ kalım
  - ✓ Sistemik hastalıksız sağ kalım
  - ✓ Yaşam kalitesi
  - ✓ Tedavi başarısızlığının yeri
  - ✓ Erken menapozun uzun dönem yan etkileri
  - ✓ İkinci (meme dışı) kanser insidansı
  - ✓ Kanser dışı ölüm nedenleri

SOFT Trial

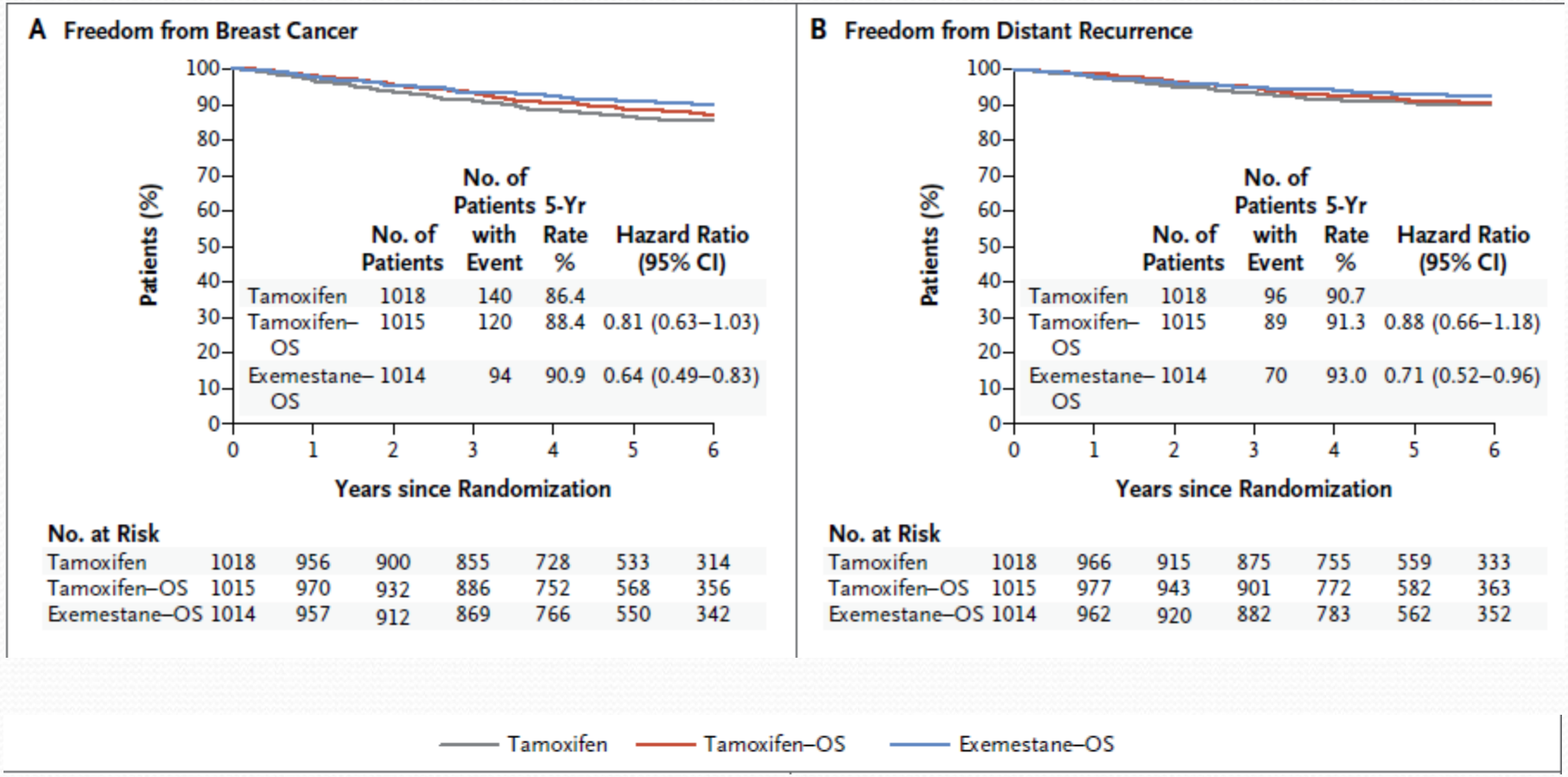

A
Disease-Free Survival
Percent Alive and Disease-Free
100
80
60
40
20
0
T
T+OFS
E+OFS
Pts Events 5-yr % HR 95% CI
T 1018 160 84.7
T+OFS 1015 139 86.6 .83 .66-1.04
E+OFS 1014 113 89.0 .68 .53-0.86
0 1 2 3 4 5 6
Years since Randomization
B
Breast Cancer-Free Interval
Percent without Breast Cancer
100
80
60
40
20
0
T
T+OFS
E+OFS
Pts Events 5-yr % HR 95% CI
T 1018 140 86.4
T+OFS 1015 120 88.4 .81 .63-1.03
E+OFS 1014 94 90.9 .64 .49-0.83
0 1 2 3 4 5 6
Years since Randomization

SOFT Trial


C
Distant Recurrence-Free Interval
Percent without Distant Recurrence
100
80
60
40
20
0
T
T+OFS
E+OFS
Pts Events 5-yr % HR 95% CI
T 1018 96 90.7
T+OFS 1015 89 91.3 .88 .66-1.18
E+OFS 1014 70 93.0 .71 .52-0.96
0 1 2 3 4 5 6
Years since Randomization


D
Overall Survival
Percent Alive
100
80
60
40
20
0
T
T+OFS
E+OFS
Pts Events 5-yr % HR 95% CI
T 1018 59 95.1
T+OFS 1015 47 96.7 .74 .51-1.09
E+OFS 1014 58 95.3 .97 .68-1.40
0 1 2 3 4 5 6
Years since Randomization

SOFT


A Freedom from Breast Cancer
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6
Years since Randomization
No. of Patients
No. of Patients with Event
5-Yr Rate %
Hazard Ratio (95% CI)
Tamoxifen 1018 140 86.4
Tamoxifen–OS 1015 120 88.4 0.81 (0.63–1.03)
Exemestane–OS 1014 94 90.9 0.64 (0.49–0.83)
No. at Risk
Tamoxifen 1018 956 900 855 728 533 314
Tamoxifen–OS 1015 970 932 886 752 568 356
Exemestane–OS 1014 957 912 869 766 550 342
B Freedom from Distant Recurrence
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6
Years since Randomization
No. of Patients
No. of Patients with Event
5-Yr Rate %
Hazard Ratio (95% CI)
Tamoxifen 1018 96 90.7
Tamoxifen–OS 1015 89 91.3 0.88 (0.66–1.18)
Exemestane–OS 1014 70 93.0 0.71 (0.52–0.96)
No. at Risk
Tamoxifen 1018 966 915 875 755 559 333
Tamoxifen–OS 1015 977 943 901 772 582 363
Exemestane–OS 1014 962 920 882 783 562 352
Tamoxifen
Tamoxifen–OS
Exemestane–OS

SOFT

Multivariable cox propotional-hazard modeline göre

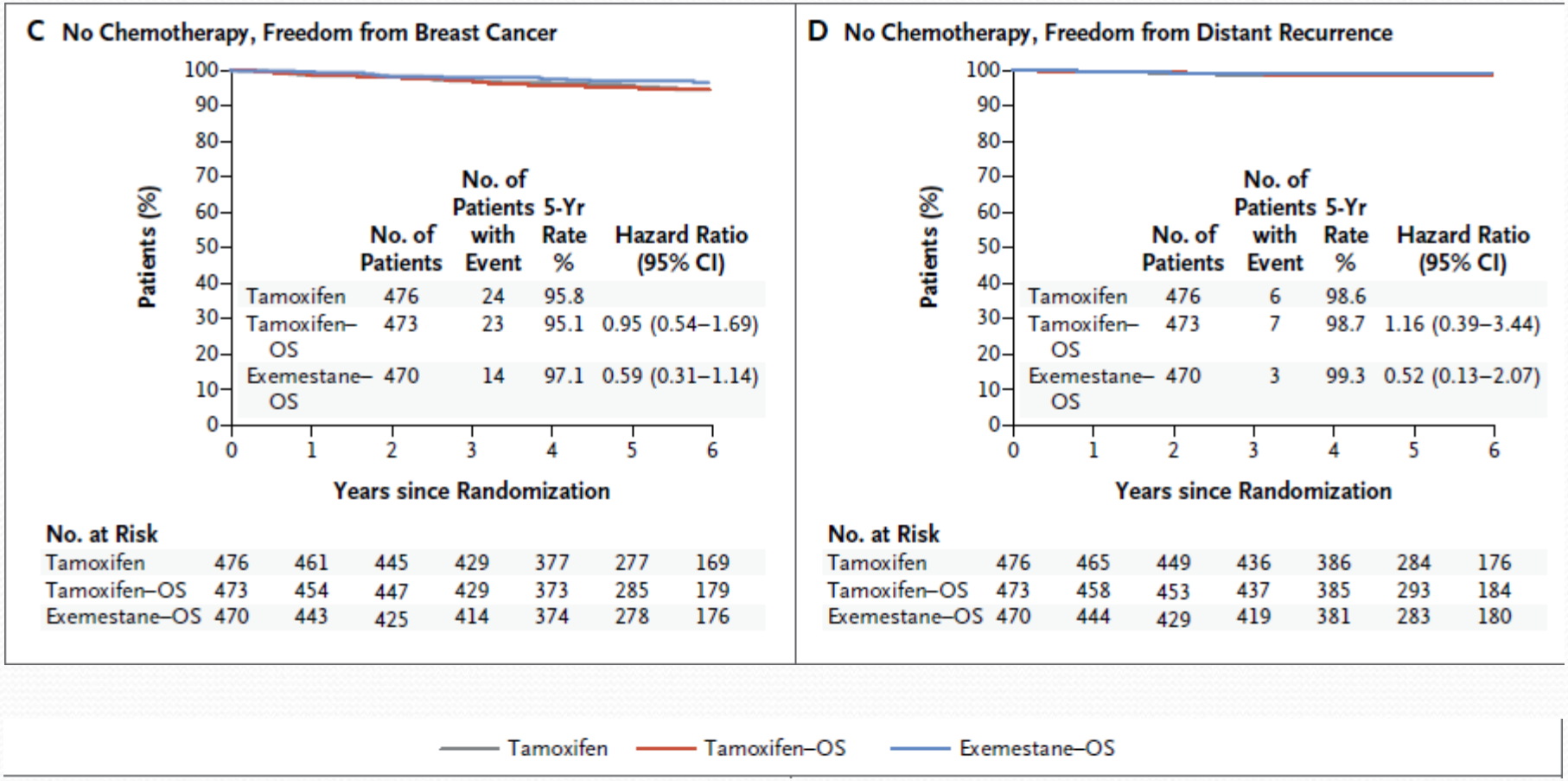
Meme kanseri nüksü

- Tamoxifen+OFS vs tamoxifen

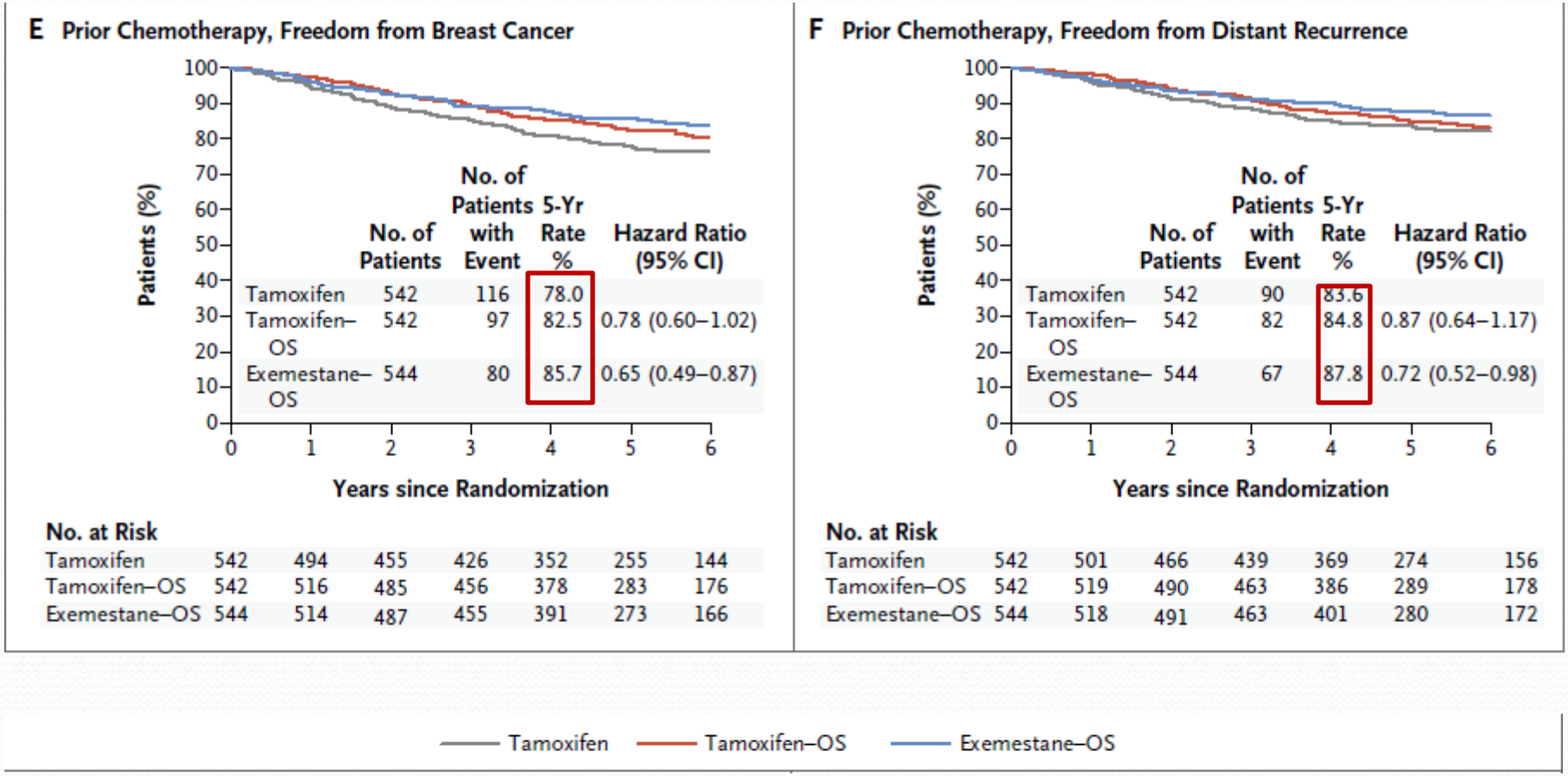
  (HR, 0.75; %95 CI 0.59-0.96; p=0.02)

  Tamoxifen+OFS lehine

SOFT


C No Chemotherapy, Freedom from Breast Cancer
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6
Years since Randomization
No. of Patients
No. of Patients with Event
5-Yr Rate %
Hazard Ratio (95% CI)
Tamoxifen 476 24 95.8
Tamoxifen–OS 473 23 95.1 0.95 (0.54–1.69)
Exemestane–OS 470 14 97.1 0.59 (0.31–1.14)
No. at Risk
Tamoxifen 476 461 445 429 377 277 169
Tamoxifen–OS 473 454 447 429 373 285 179
Exemestane–OS 470 443 425 414 374 278 176
D No Chemotherapy, Freedom from Distant Recurrence
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6
Years since Randomization
No. of Patients
No. of Patients with Event
5-Yr Rate %
Hazard Ratio (95% CI)
Tamoxifen 476 6 98.6
Tamoxifen–OS 473 7 98.7 1.16 (0.39–3.44)
Exemestane–OS 470 3 99.3 0.52 (0.13–2.07)
No. at Risk
Tamoxifen 476 465 449 436 386 284 176
Tamoxifen–OS 473 458 453 437 385 293 184
Exemestane–OS 470 444 429 419 381 283 180
Tamoxifen
Tamoxifen–OS
Exemestane–OS

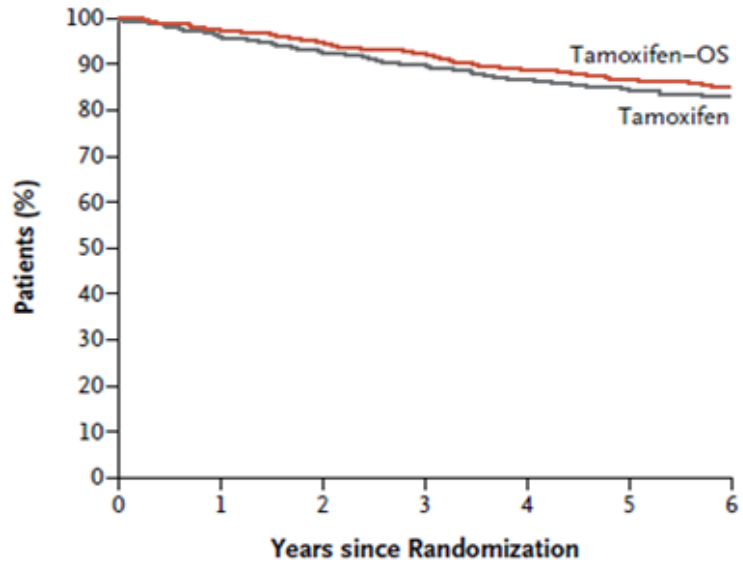
SOFT


E Prior Chemotherapy, Freedom from Breast Cancer
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6
Years since Randomization
No. of Patients
No. of Patients with Event
5-Yr Rate %
Hazard Ratio (95% CI)
Tamoxifen 542 116 78.0
Tamoxifen–OS 542 97 82.5 0.78 (0.60–1.02)
Exemestane–OS 544 80 85.7 0.65 (0.49–0.87)
No. at Risk
Tamoxifen 542 494 455 426 352 255 144
Tamoxifen–OS 542 516 485 456 378 283 176
Exemestane–OS 544 514 487 455 391 273 166
F Prior Chemotherapy, Freedom from Distant Recurrence
Patients (%)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6
Years since Randomization
No. of Patients
No. of Patients with Event
5-Yr Rate %
Hazard Ratio (95% CI)
Tamoxifen 542 90 83.6
Tamoxifen–OS 542 82 84.8 0.87 (0.64–1.17)
Exemestane–OS 544 67 87.8 0.72 (0.52–0.98)
No. at Risk
Tamoxifen 542 501 466 439 369 274 156
Tamoxifen–OS 542 519 490 463 386 289 178
Exemestane–OS 544 518 491 463 401 280 172
Tamoxifen
Tamoxifen–OS
Exemestane–OS

SOFT trial

Tamoxifen vs Tamoxifen + OFS

A Disease-free Survival



No. at Risk							
Tamoxifen	1018	951	895	847	719	525	309
Tamoxifen–OS	1015	966	927	878	742	556	349

	No. of Patients	No. of Patients with Event	5-Yr Rate %
Tamoxifen	1018	160	84.7
Tamoxifen–OS	1015	139	86.6

Hazard ratio for recurrence, second invasive cancer, or death, 0.83 (95% CI, 0.66–1.04)

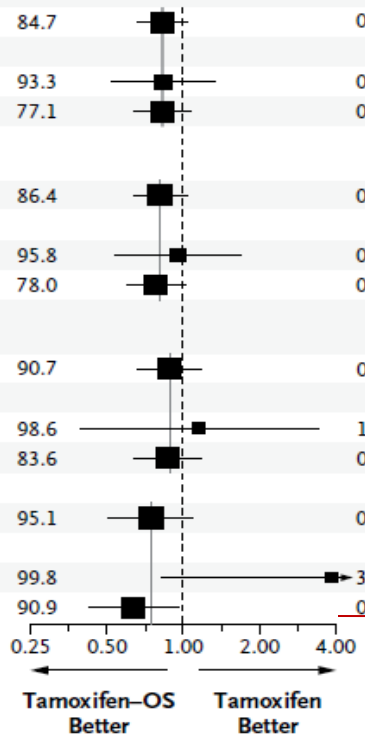
P=0.10

SOFT trial

Tamoxifen vs Tamoxifen + OFS

B End Points, Overall and According to Chemotherapy Cohort

End Point	No. of Patients		No. of Patients with Event		5-Yr Rate (%)		Hazard Ratio (95% CI)	P Value
	Tamoxifen–OS	Tamoxifen	Tamoxifen–OS	Tamoxifen	Tamoxifen–OS	Tamoxifen		
Disease-free survival								
All patients	1015	1018	139	160	86.6	84.7	0.83 (0.66–1.04)	0.10
Prior chemotherapy								
No	473	476	32	38	93.4	93.3	0.83 (0.52–1.34)	0.96
Yes	542	542	107	122	80.7	77.1	0.82 (0.64–1.07)	
Freedom from breast cancer								
All patients	1015	1018	120	140	88.4	86.4	0.81 (0.63–1.03)	0.09
Prior chemotherapy								
No	473	476	23	24	95.1	95.8	0.95 (0.54–1.69)	0.54
Yes	542	542	97	116	82.5	78.0	0.78 (0.60–1.02)	
Freedom from distant recurrence								
All patients	1015	1018	89	96	91.3	90.7	0.88 (0.66–1.18)	0.40
Prior chemotherapy								
No	473	476	7	6	98.7	98.6	1.16 (0.39–3.44)	0.62
Yes	542	542	82	90	84.8	83.6	0.87 (0.64–1.17)	
Overall survival								
All patients	1015	1018	47	59	96.7	95.1	0.74 (0.51–1.09)	0.13
Prior chemotherapy								
No	473	476	8	2	99.2	99.8	3.84 (0.81–18.08)	0.03
Yes	542	542	39	57	94.5	90.9	0.64 (0.42–0.96)	



SOFT Trial

- Ölümlerin ≥ %90'ı kemoterapi alan hastalarda
- Kemoterapi alan hastalarda

5 yıllık sağ kalım:

Tamoxifen + OFS kolunda %94.5 (%95 CI, 92.0 - 96.2)

Tamoxifen kolunda %90.9 (% 95 CI, 87.9 - 93.2)

(HR, 0.64; %95 CI, 0.42 - 0.96)

SOFT Trial

< 35 yaş hastalar (%11.5)

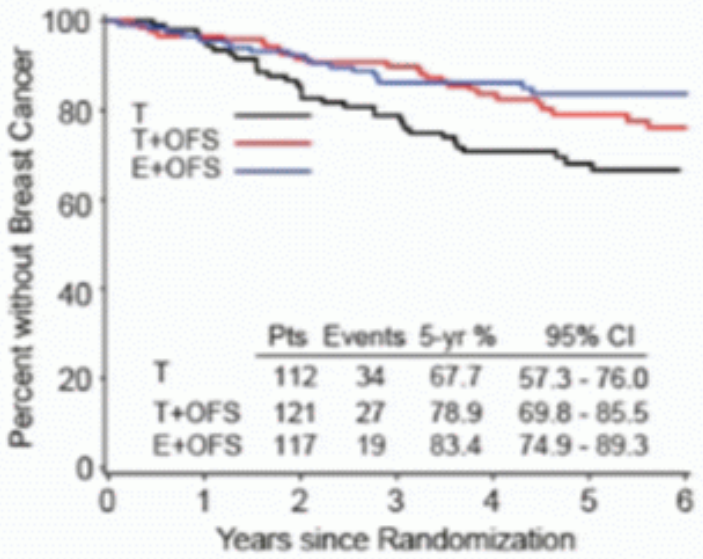
- 350 hastanın 233'ü 35 yaş altında
- %94'ü daha önce KT almış

- 5. yılda *'freedom from breast cancer'*

Tamoxifen kolunda %67.7

Tamoxifen + OFS %78.9

Exemestane + OFS %83.4



St. Gallen/Vienna 2015

Factors arguing for including ovarian function suppression (OFS) are:

- Age <= 35 years 81%/19%/0 1Y/ 2N/ 9A
- Premenopausal oestrogen level after adjuvant chemotherapy 73.7/26.3/0 1Y/ 2N/ 9A
- Grade 3 55.9/38.2/0 1Y/ 2N/ 9A
- Involvement of 4 or more nodes 89.7/10.3/0 1Y/ 2N/ 9A
- Adverse result of multi-gene test 60/24.4/15.6% 1Y/ 2N/ 9A

St. Gallen/Vienna 2015

Factors arguing for use of OFS + AI rather than OFS + tamoxifen are:

- Age <= 35 years 59.4/37.5/3.1 1Y/ 2N/ 9A
- Premenopausal oestrogen level after adjuvant chemotherapy 43.9/51.2/4.9 1Y/ 2N/ 9A
- Grade 3 57.1/35.7/7.1 1Y/ 2N/ 9A
- Involvement of 4 or more nodes 92.5/5/2.5%1Y/ 2N/ 9A
- Adverse result of multi-gene test 65.8/31.6/2.6% 1Y/ 2N/ 9A

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression

Harold J. Burstein, Christina Lacchetti, Holly Anderson, Thomas A. Buchholz, Nancy E. Davidson, Karen E. Gelmon, Sharon H. Giordano, Clifford A. Hudis, Alexander J. Solky, Vered Stearns, Eric P. Winer, and Jennifer J. Griggs

Published online ahead of print at www.jco.org on February 16, 2016.

Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression

The Panel notes that two prospective studies did not show overall clinical benefit for the addition of ovarian suppression to tamoxifen in premenopausal, ER-positive breast cancer. However, in a large subset of women with higher-risk cancers, nearly all of whom received chemotherapy but remained premenopausal, ovarian suppression added to tamoxifen reduced the risk of breast cancer recurrence. Because of the design of the clinical trials, there are few definitive criteria by which to define risk.

1.2 Women with stage II or stage III breast cancers who would ordinarily be advised to receive adjuvant chemotherapy should receive ovarian suppression in addition to endocrine therapy.

1.3 Women with stage I or II breast cancers at higher risk of recurrence, who might consider chemotherapy, may also be offered ovarian suppression in addition to endocrine therapy.

1.4 Women with stage I breast cancers not warranting chemotherapy should receive endocrine therapy but not receive ovarian suppression.

1.5 Women with node-negative cancers 1 cm or less (T1a, T1b) should receive endocrine therapy but not receive ovarian suppression.

[Benefits: increasing disease-free survival (DFS), freedom from breast cancer, and freedom from distance recurrence. Harms: worse menopausal symptoms and sexual functioning, including hot flashes, sweating, weight gain, vaginal dryness, and decreased libido.]

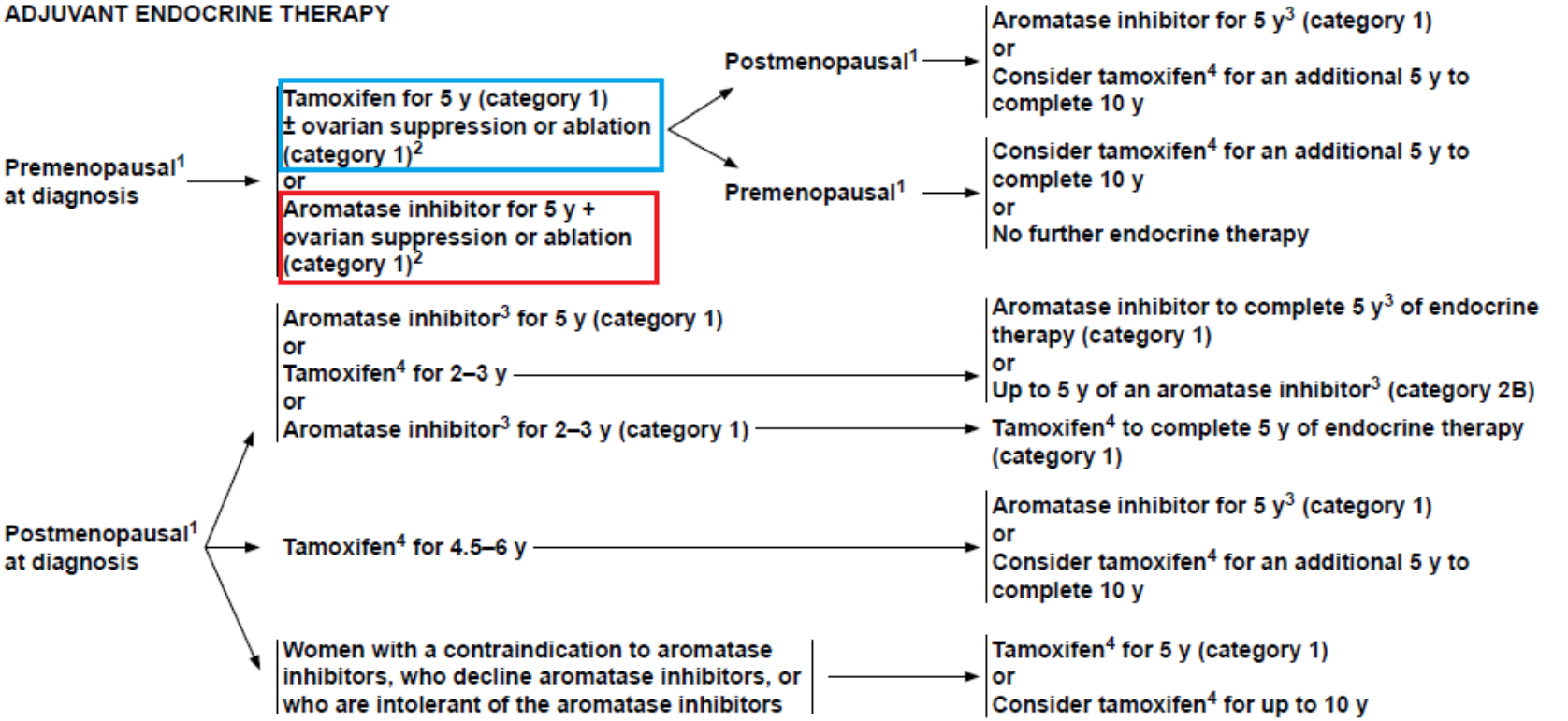
Evidence quality: Intermediate
Recommendation type: Evidence based and consensus
Recommendation strength: Moderate

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Invasive Breast Cancer

NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

ADJUVANT ENDOCRINE THERAPY

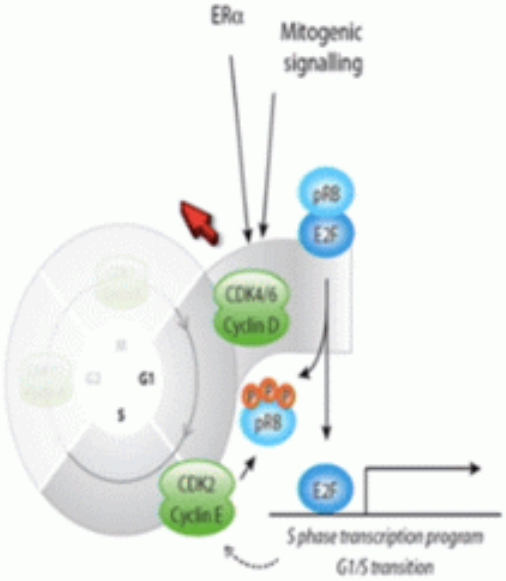


[1] See Definition of Menopause (BINV-M).
[2] Aromatase inhibitor or tamoxifen for 5 y plus ovarian suppression should be considered, based on SOFT and TEXT clinical trial outcomes, for premenopausal women at higher risk of recurrence (ie, young age, high-grade tumor, lymph node involvement, Pagani, NEJM 2014, Prudence, NEJM 2014).Survival data still pending.
[3] The panel believes the three selective aromatase inhibitors (ie, anastrozole, letrozole, exemestane) have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and preoperative settings. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.

Yeni umutlar

CDK4/6 in Breast Cancer

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



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

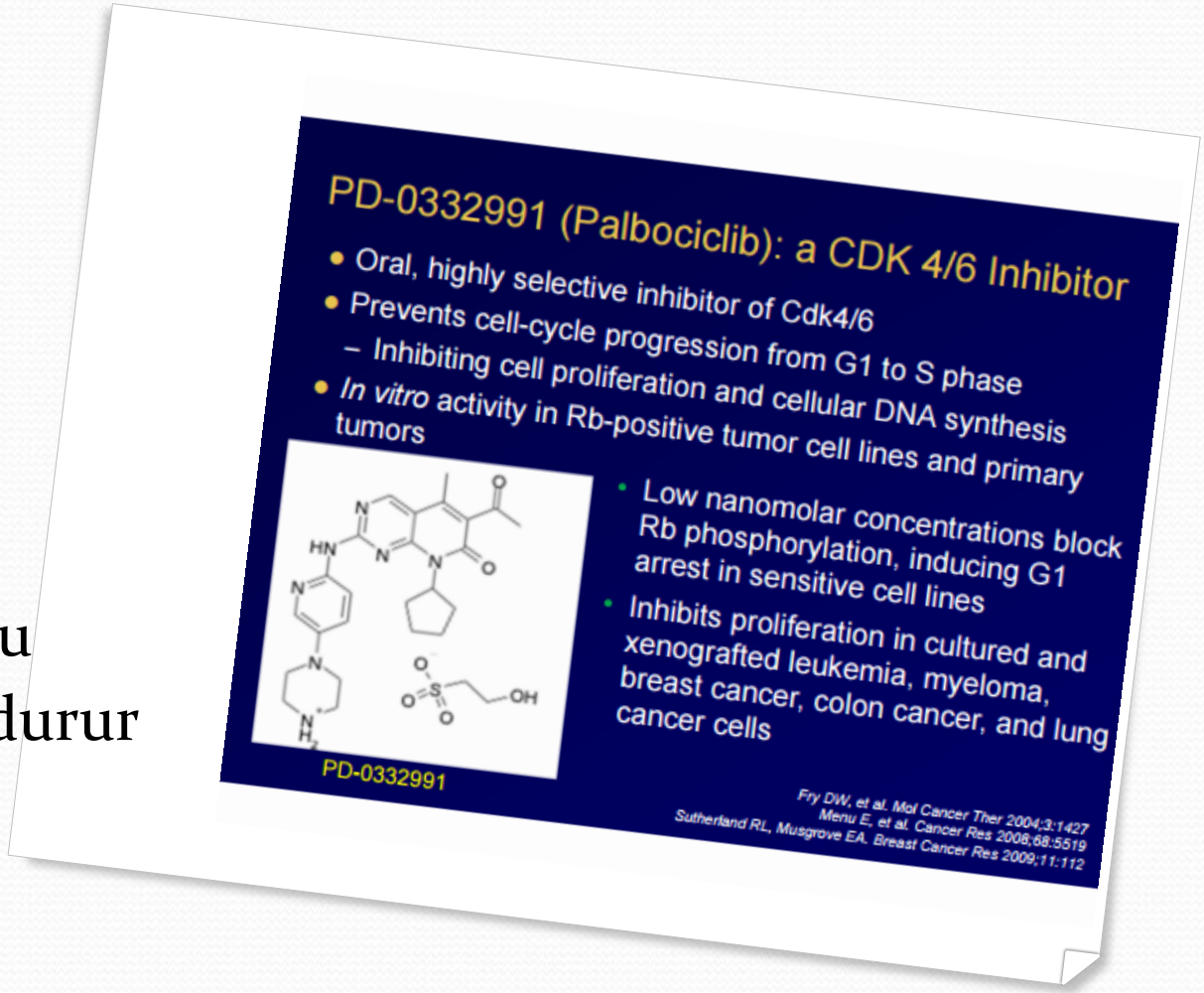
1. Asghar U, et al. *Nat Rev Drug Discov*. 2015;14:130-46.
2. Thangavel C, et al. *Endocr Relat Cancer*. 2011;18:333-45.

Palbociclib

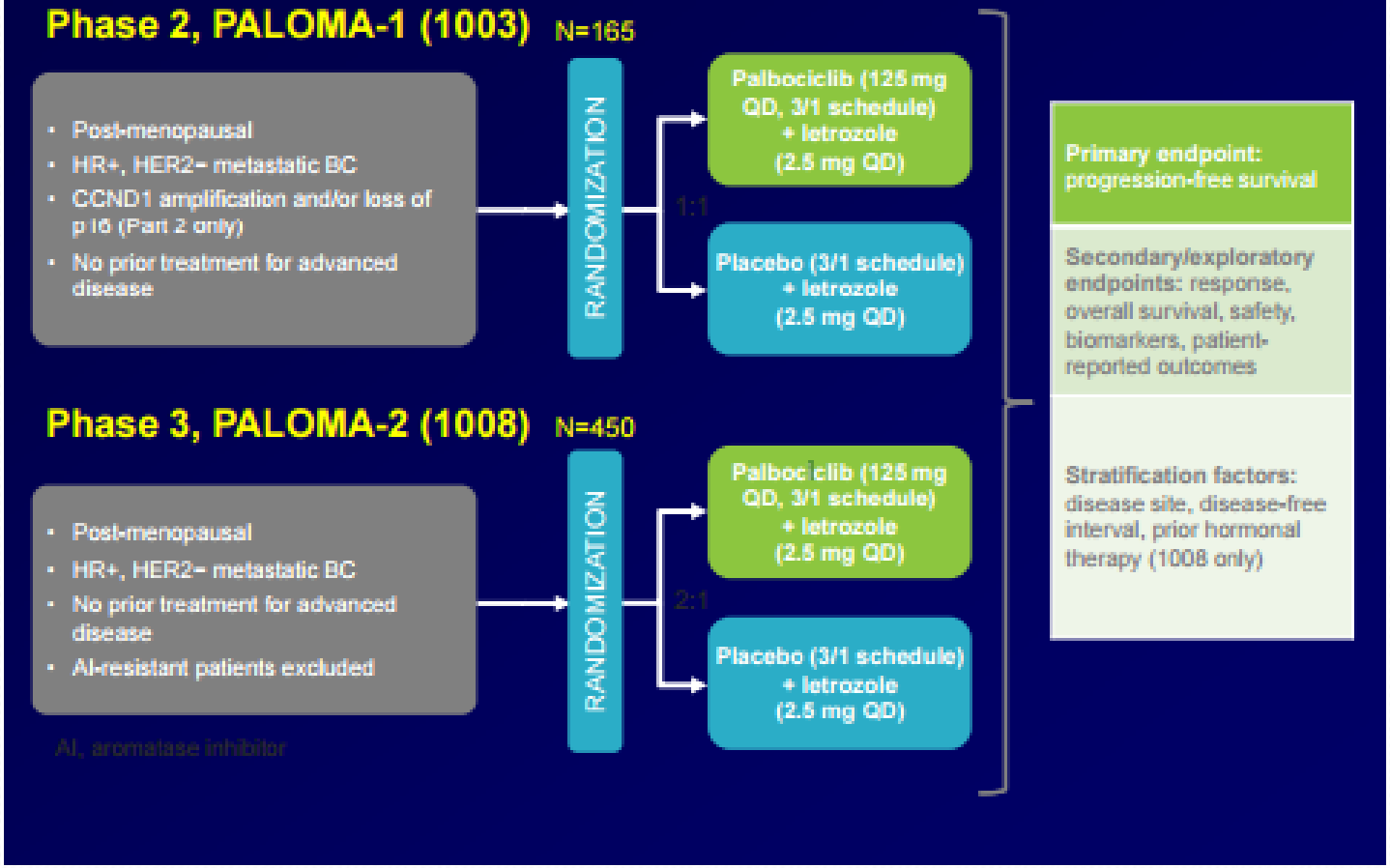
✓Oral Cdk 4/6 inhibitörü

✓Hücre siklusunu G1-S fazında durdurur

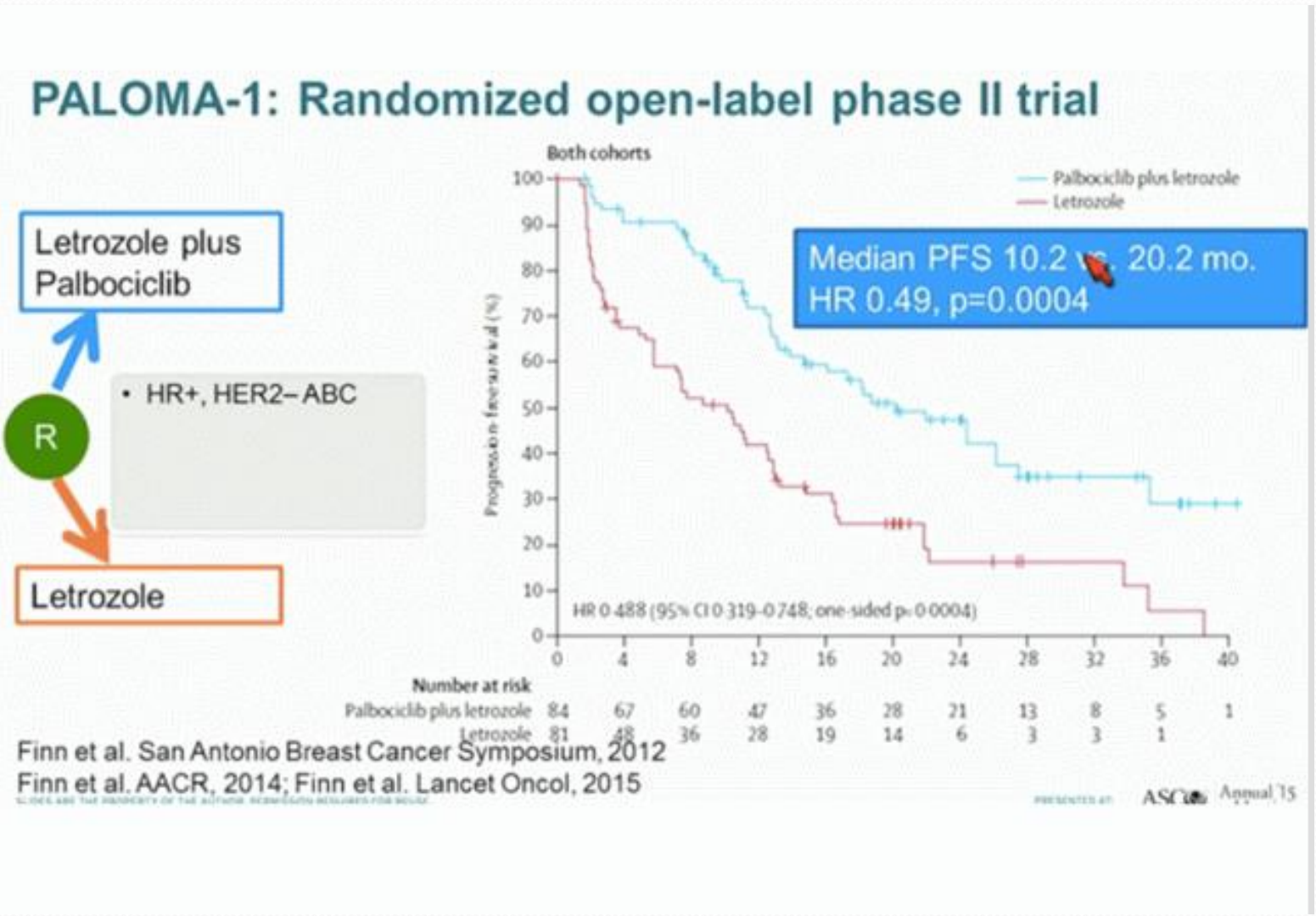
✓125 mg ¾ hafta



Phase 2 and 3 Studies of Palbociclib in Endocrine-sensitive Metastatic BC



PALOMA-1: Randomized open-label phase II trial



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

Şubat 2015'de FDA onayı aldı

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

- HR (+) HER2(-) ileri evre meme kanseri
- Endokrin tedavi altında relaps veya progresyon
- ER, PR ve HER2 en son doku örneğinde çalışılmış

PALOMA 3

- Post-menapozal

AI altında progresyon

  - Metastatik hastalıkta AI altında veya tedavi bitiminden 1 ay içinde
  - Adjuvan tedavi sırasında veya tedavi bitiminden 12 ay içinde

Women with premenopausal

- Pre / perimenapozal
  - Metastatik hastalıkta endokrin tedavi sırasında veya tedavi bitiminden 1 ay içinde progresyon
  - Adjuvan tedavi sırasında veya tedavi bitiminden 12 ay içinde progresyon
- 1 basamak KT almış olabilir

PALOMA 3

- Primer sonlanım noktası; PFS
- İkincil sonlanım noktaları
  - Genel sağ kalım
  - 1.,2. ve 3. yıl sağ kalım olasılığı
  - Objektif yanıt
  - Yanıt süresi
  - Klinik fayda

PALOMA 3

- Çift kör, faz 3 çalışma
- 2:1 randomizasyon
- Palbociclib + fulvestrant vs Placebo+fulvestrant
- Palbociclib 125 mg/gün ¾ hafta
- Pre / perimenapozal hastalar: goserelin
  (randomizasyondan en az 4 hafta önce başlanıp, 4 haftada bir)
- Tabakalama: viseral metastaz, menapoz durumu ve endokrin duyarlılık
  (metastatik hastalık OR veya SD ≥ 24 hafta, adjuvan tedavide 24 aydan sonra nüks)

PALOMA 3

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)

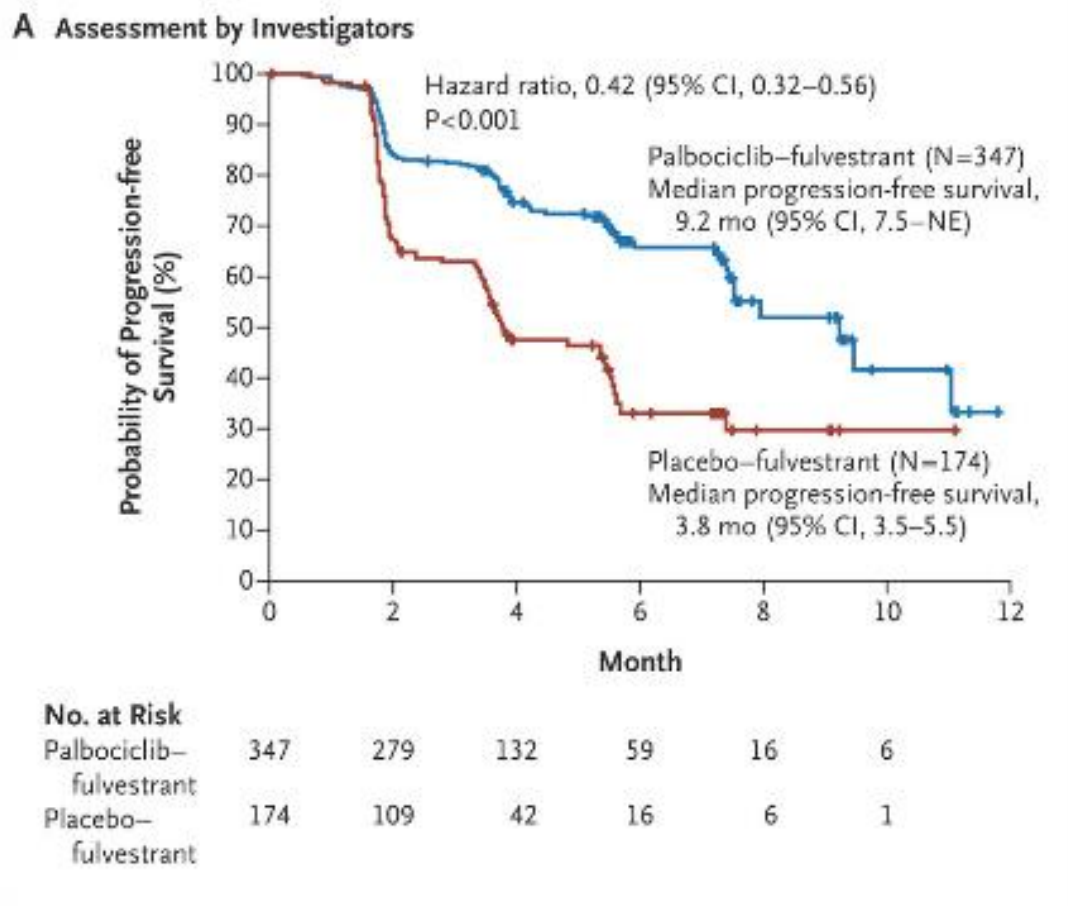
PALOMA 3

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)

PALOMA 3

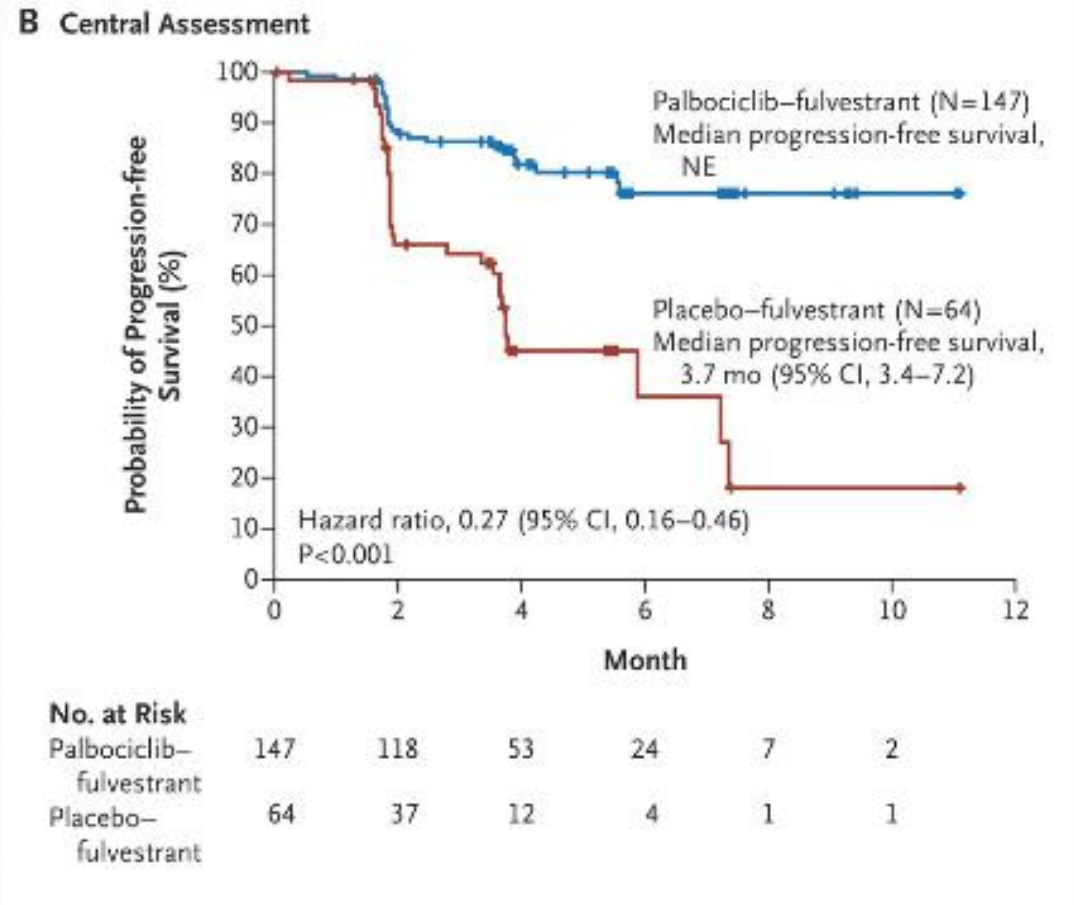
No. of disease sites — no. of patients (%)‡‡		
1	111 (32.0)	60 (34.5)
2	99 (28.5)	50 (28.7)
≥3	135 (38.9)	62 (35.6)
Prior endocrine therapy — no. (%)§§		
Aromatase inhibitor with or without GnRH agonist	296 (85.3)	151 (86.8)
Tamoxifen with or without GnRH agonist	211 (60.8)	104 (59.8)
Most recent therapy — 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)

PALOMA-3



Median PFS 3.8 vs 9.2 mo
HR 0.42 p<0.001

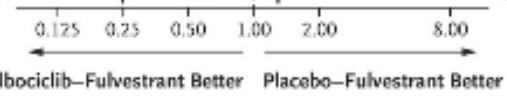
PALOMA-3



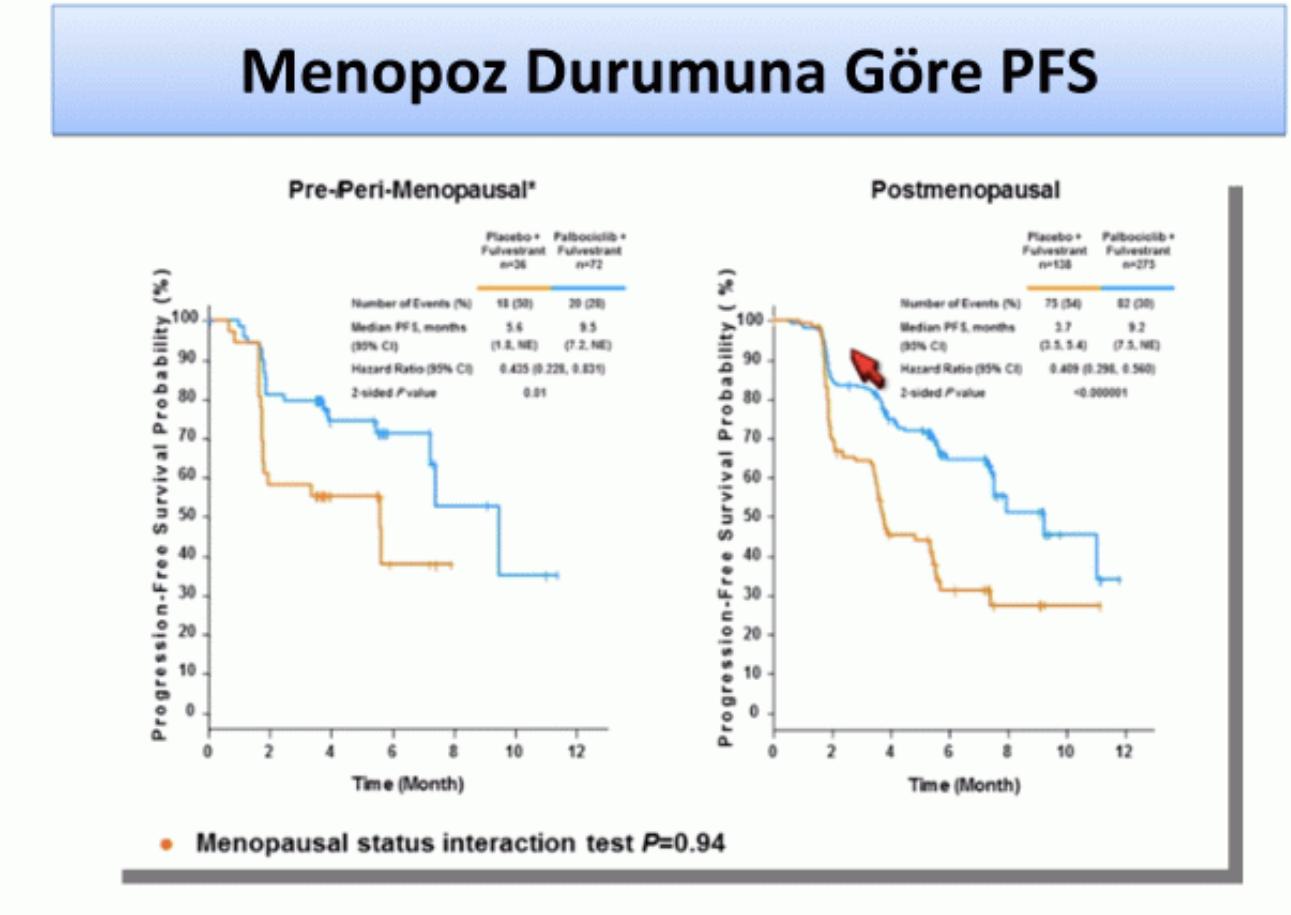
Median PFS 3.7 vs NE
HR 0.27 p<0.001
NE: not estimable

PALOMA-3

Subgroup	Patients no. (%)	Hazard Ratio for Disease Progression or Death (95% CI)	P Value for Interaction
All randomly assigned patients: intention-to-treat population	521 (100)	0.42 (0.32–0.56)	
Age			0.48
<65 yr	392 (75.2)	0.44 (0.32–0.61)	
≥65 yr	129 (24.8)	0.35 (0.19–0.62)	
Race			0.41
White	385 (73.9)	0.38 (0.27–0.52)	
Asian	105 (20.2)	0.64 (0.31–1.31)	
Black or other	29 (5.6)	0.44 (0.12–1.57)	
Menopausal status at study entry			0.94
Premenopausal or perimenopausal	108 (20.7)	0.44 (0.23–0.83)	
Postmenopausal	413 (79.3)	0.41 (0.30–0.56)	
Site of metastatic disease			0.62
Visceral	311 (59.7)	0.45 (0.32–0.63)	
Nonvisceral	210 (40.3)	0.36 (0.22–0.60)	
Sensitivity to previous hormonal therapy			0.30
Yes	410 (78.7)	0.39 (0.28–0.53)	
No	111 (21.3)	0.55 (0.31–0.98)	
Hormone-receptor status			0.88
ER-positive and PR-positive	349 (67.0)	0.46 (0.32–0.66)	
ER-positive and PR-negative	139 (26.7)	0.46 (0.28–0.77)	
Disease-free interval			0.15
≤24 mo	65 (12.5)	0.84 (0.41–1.75)	
>24 mo	281 (53.9)	0.45 (0.30–0.67)	
Prior chemotherapy			0.43
Neoadjuvant or adjuvant treatment only	219 (42.0)	0.51 (0.33–0.79)	
Metastatic treatment	170 (32.6)	0.42 (0.26–0.67)	
None	132 (25.3)	0.28 (0.15–0.53)	
Prior lines of therapy in context of metastatic disease			0.68
0	129 (24.8)	0.40 (0.23–0.70)	
1	202 (38.8)	0.47 (0.29–0.76)	
2	133 (25.5)	0.30 (0.17–0.53)	
≥3	57 (10.9)	0.57 (0.25–1.29)	



PALOMA-3


Menopoz Durumuna Göre PFS
Pre-Peri-Menopausal*
Placebo + Fulvestrant n=36
Palbociclib + Fulvestrant n=72
Number of Events (%) 18 (50) 20 (28)
Median PFS, months (95% CI) 5.6 (1.8, NE) 9.5 (7.2, NE)
Hazard Ratio (95% CI) 0.435 (0.228, 0.831)
2-sided P value 0.01
Progression-Free Survival Probability (%)
Time (Month)
Postmenopausal
Placebo + Fulvestrant n=138
Palbociclib + Fulvestrant n=273
Number of Events (%) 75 (54) 82 (30)
Median PFS, months (95% CI) 3.7 (3.5, 5.4) 9.2 (7.5, NE)
Hazard Ratio (95% CI) 0.409 (0.296, 0.560)
2-sided P value <0.000001
Progression-Free Survival Probability (%)
Time (Month)
Menopausal status interaction test P=0.94

PALOMA-3

Grad 3-4 advers olaylar;

- Nötropeni (%62 vs 0.6)
- Lökopeni (%25.2 vs %0.6)
- Anemi (%2.6 vs %1.2)

Plasebo-fulvestrant lehine

Febril nötropeni (%0.6 vs %0.06

Table 2. **Adverse Events with an Incidence of 10% or More in the Palbociclib–Fulvestrant Group, Regardless of Relationship to Study Drugs.***

Event	Palbociclib–Fulvestrant (N=345)			Placebo–Fulvestrant (N=172)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Any adverse event	337 (97.7)	202 (58.6)	37 (10.7)	153 (89.0)	28 (16.3)	3 (1.7)
Neutropenia	272 (78.8)	184 (53.3)	30 (8.7)	6 (3.5)	0	1 (0.6)
Leukopenia	157 (45.5)	85 (24.6)	2 (0.6)	7 (4.1)	0	1 (0.6)
Fatigue	131 (38.0)	7 (2.0)	0	46 (26.7)	2 (1.2)	0
Nausea	100 (29.0)	0	0	45 (26.2)	1 (0.6)	0
Anemia	90 (26.1)	9 (2.6)	0	17 (9.9)	3 (1.7)	0
Headache	73 (21.2)	1 (0.3)	0	30 (17.4)	0	0
Thrombocytopenia	67 (19.4)	6 (1.7)	2 (0.6)	0	0	0
Upper respiratory infection†	67 (19.4)	1 (0.3)	0	28 (16.3)	0	0
Diarrhea	66 (19.1)	0	0	30 (17.4)	1 (0.6)	0
Constipation	58 (16.8)	0	0	24 (14.0)	0	0
Alopecia	51 (14.8)‡	NA	NA	10 (5.8)	NA	NA
Hot flushes	51 (14.8)	0	0	28 (16.3)	0	0
Vomiting	50 (14.5)	1 (0.3)	0	21 (12.2)	1 (0.6)	0
Arthralgia	45 (13.0)	1 (0.3)	0	28 (16.3)	0	0
Cough	45 (13.0)	0	0	18 (10.5)	0	0
Decreased appetite	44 (12.8)	3 (0.9)	0	13 (7.6)	0	0
Stomatitis	40 (11.6)	2 (0.6)	0	4 (2.3)	0	0
Back pain	39 (11.3)	3 (0.9)	0	26 (15.1)	4 (2.3)	0
Dizziness	37 (10.7)	1 (0.3)	0	16 (9.3)	0	0
Dyspnea	37 (10.7)	0	1 (0.3)	11 (6.4)	1 (0.6)	0
Pain in extremity	34 (9.9)	0	0	19 (11.0)	3 (1.7)	0

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer

TO THE EDITOR: In the PALOMA3 study, Turner et al. (July 16 issue)[1] report that the addition of palbociclib to fulvestrant improved progression-free survival as compared with fulvestrant alone in patients with advanced breast cancer, with similar discontinuation rates because of adverse effects (2.6% and 1.7%, respectively). However, molecularly targeted therapies have moderate toxic effects that may become unacceptable over the long term and result in a deterioration in the quality of life, as shown in a previous report.[2,3] The PALOMA1 administration of the combination therapy or hamper the use of subsequent therapies.

Akihiko Ozaki, M.D.
Minamisoma Municipal General Hospital
Fukushima, Japan
ozakiakihiko@gmail.com

Tetsuya Tanimoto, M.D.
Jyoban Hospital
Fukushima, Japan

Shigehira Saji, M.D., Ph.D.
Fukushima Medical University
Fukushima, Japan

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Invasive Breast Cancer

NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion

ENDOCRINE THERAPY FOR RECURRENT OR STAGE IV DISEASE

Premenopausal patients with hormone-receptor positive disease should have ovarian ablation/suppression and follow postmenopausal guidelines

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

[2]Palbociclib in combination with letrozole may be considered as a treatment option for first-line therapy for postmenopausal patients with hormone-receptor positive, HER2-negative metastatic breast cancer.

[3]For postmenopausal women or for premenopausal women receiving ovarian suppression with an LHRH agonist, with hormone-receptor positive and HER2-negative metastatic breast cancer that has progressed on endocrine therapy.

TEŞEKKÜRLER