2019
CARCINOMA MAMMARIO
I TRAGUARDI RAGGIUNTI E LE NUOVE SFIDE

ROMA 4 - 5 OTTOBRE
STARHOTELS METROPOLE

AIOM

# CDK 4/6 INHIBITORS NELL'UOMO CON MALATTIA METASTATICA: QUALI EVIDENZE?

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**Marta Bonotto**
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# BC in men: epidemiology


| INCIDENZA | Maschi | | | Femmine | | |
|---|---|---|---|---|---|---|
| | Nord | Centro | Sud e isole | Nord | Centro | Sud e isole |
| Mammella | 1,9 | 1,5 | 1,6 | 161,9 | 141,7 | 124,9 |

**TABELLA 15. AIRTUM 2010-2015. Tassi di incidenza standardizzati sulla popolazione nuova europea per area geografica e sesso (x 100.000).** Nota: è stata utilizzata la nuova popolazione standard europea (Eurostat 2013)

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In the U.S and U.K: 0.5-1% of all cancer diagnosis in men

In areas of Central Africa: 6% of all cancer diagnosis in men

# BC in men: epidemiology


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In the U.S and U.K: 0.5-1% of all cancer diagnosis in men

In areas of Central Africa: 6% of all cancer diagnosis in men

**Men tend to be approximately 5-10 years older than women (at time of diagnosis)**
**The annual incidence appears to be rising: +26% in 25 years**

# BC in men: characteristics

| | Period of diagnosis | | | | Total ($N$ = 1483) | Total | Test for trend over time |
|---|---|---|---|---|---|---|---|
| | 1990–1995 ($N$ = 225) $N$ (%) | 1996–2000 ($N$ = 317) $N$ (%) | 2001–2005 ($N$ = 457) $N$ (%) | 2006–2010 ($N$ = 484) $N$ (%) | $N$ (%) | (% excl. Missing) | |
| Age at diagnosis | | | | | | | No significant trend |
| ≤40 | 5 (2.2) | 4 (1.3) | 8 (1.8) | 7 (1.4) | 24 (1.6) | | ($P$= 0.589) |
| 41–50 | 18 (8.0) | 31 (9.8) | 28 (6.1) | 40 (8.3) | 117 (7.9) | | |
| 51–65 | 63 (28.0) | 97 (30.6) | 144 (31.5) | 148 (30.6) | 452 (30.5) | | |
| 66–75 | 77 (34.2) | 93 (29.3) | 134 (29.3) | 147 (30.4) | 451 (30.4) | | |
| >75 | 62 (27.6) | 92 (29.0) | 143 (31.3) | 142 (29.3) | 439 (29.6) | | |
| Median | 69.0 | 67.9 | 69.1 | 67.9 | 68.4 | | |
| M status at diagnosis | | | | | | | No significant trend |
| M0 | 135 (60.0) | 185 (58.4) | 344 (75.3) | 390 (80.6) | 1054 (71.1) | (94.9) | ($P$= 0.105) |
| M1 | 7 (3.1) | 16 (5.0) | 19 (4.2) | 15 (3.1) | 57 (3.8) | (5.1) | |
| Mx | 83 (36.9) | 116 (36.6) | 94 (20.6) | 79 (16.3) | 372 (25.1) | | |
| For M0 patients (at diagnosis): | ($N$=135) | ($N$=185) | ($N$= 344) | ($N$=390) | ($N$=1054) | | No significant trend |
| pN status | | | | | | | ($P$= 0.962) |
| pN0 | 75 (55.6) | 99 (53.5) | 184 (53.5) | 234 (60.0) | 592 (56.2) | | |
| pN1 | 40 (29.6) | 49 (26.5) | 112 (32.6) | 120 (30.8) | 321 (30.5) | | |
| pN2 | 7 (5.2) | 9 (4.9) | 20 (5.8) | 17 (4.4) | 53 (5.0) | | |
| pN3 | 2 (1.5) | 7 (3.8) | 8 (2.3) | 13 (3.3) | 30 (2.8) | | |
| Nx | 11 (8.1) | 21 (11.4) | 20 (5.8) | 6 (1.5) | 58 (5.5) | | |
| For M1 patients (at diagnosis): | ($N$=7) | ($N$=16) | ($N$=19) | ($N$=15) | ($N$=57) | | |
| Site *of M* | | | | | | | |
| Bone | 1 (14.3) | 1 (6.3) | 4 (21.1) | 4 (26.7) | 10 (17.5) | | |
| Lung | 0 (0.0) | 0 (0.0) | 3 (15.8) | 3 (20.0) | 6 (10.5) | | |
| Soft tissue | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) | 1 (1.8) | | |
| Distant lymph node | 0 (0.0) | 2 (12.5) | 1 (5.3) | 0 (0.0) | 3 (5.3) | | |
| Skin/subcutaneous | 0 (0.0) | 1 (6.3) | 0 (0.0) | 1 (6.7) | 2 (3.5) | | |
| Other | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (6.7) | 1 (1.8) | | |
| Combination | 3 (42.9) | 6 (37.5) | 7 (36.8) | 6 (40.0) | 22 (38.6) | | |
| Missing | 3 (42.9) | 6 (37.5) | 3 (15.8) | 0 (0.0) | 12 (21.1) | | |

Cardoso F, Ann Oncol. 2018;29(2):405.

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| | 1990–1995 ($N = 225$) *N* (%) | 1996–2000 ($N = 317$) *N* (%) | 2001–2005 ($N = 457$) *N* (%) | 2006–2010 ($N = 484$) *N* (%) | *N* (%) | (% excl. Missing) | |
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| Bone | 1 (14.3) | 1 (6.3) | 4 (21.1) | 4 (26.7) | 10 (17.5) | | |
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Cardoso F, Ann Oncol. 2018;29(2):405.

# BC in men: subtypes

| Clinico-pathological subtypes (2013 St Gallen consensus) | |
|---|---|
| Luminal A | 417 (39.6) |
| Luminal B HER2− | 483 (45.8) |
| Luminal B HER2+ | 89 (8.4) |
| HER2 positive (nonluminal) | 2 (0.2) |
| Basal | 3 (0.3) |
| Not defined (ER−, PR+) | 0 (0.0) |
| Missing | 60 (5.7) |

Cardoso F. Ann Oncol. 2018;29(2):405.

# BC in men: subtypes

| | | |
|---|---|---|
| ER+ | 99% | 77% |
| PR+ | 82% | 64% |
| AR+ | 97% | 77% |
| HER2+ | 9% | 11% |
| TNBC | 0.3% | 11% |

| Clinico-pathological subtypes (2013 St Gallen consensus) | |
|---|---|
| Luminal A | 417 (39.6) |
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| Luminal B HER2+ | 89 (8.4) |
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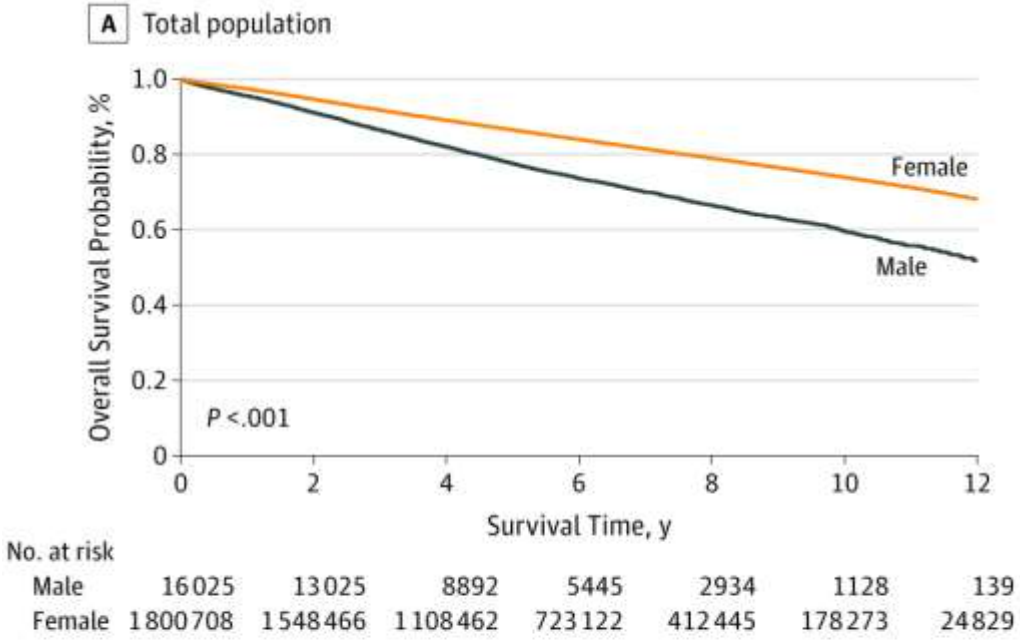
Gucalp. Breast Cancer Research and Treatment. 2019;173(1):37. Cardoso F. Ann Oncol. 2018;29(2):405.

# BC Overall survival: men vs women




No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Male | 16025 | 13025 | 8892 | 5445 | 2934 | 1128 | 139 |
| Female | 1800708 | 1548466 | 1108462 | 723122 | 412445 | 178273 | 24829 |

| Survival | Male, % | Female, % |
|---|---|---|
| 3 y | 86.4 (95% CI, 85.9-87.0) | 91.7 (95% CI, 91.7-91.8) |
| 5 y | 77.6 (95% CI, 76.8-78.3) | 86.4 (95% CI, 86.4-86.5) |
| Overall | 45.8 (95% CI, 49.5-54.0) | 60.4 (95% CI, 58.7-62.0) |

3yOS HR* 1.15; 95%CI 1.10-1.21
5yOS HR* 1.19; 95%CI 1.14-1.23
*adjusted for age, clinical and treatment factors, race and acces to care

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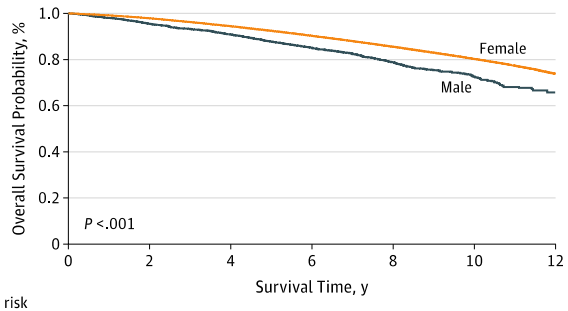
# BC Overall survival: men vs women

C Stage I

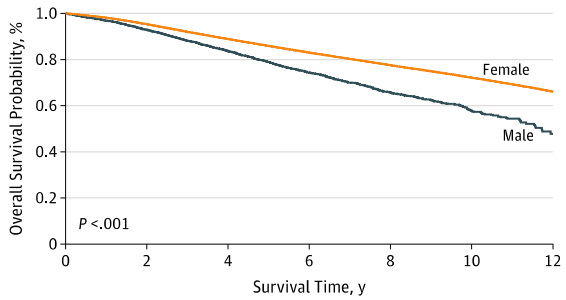



No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Male | 4817 | 4101 | 2918 | 1800 | 961 | 393 | 61 |
| Female | 698509 | 621387 | 448437 | 289708 | 165333 | 71810 | 10056 |

| Survival | Male, % | Female, % |
|---|---|---|
| 3 y | 93.3 (95% CI, 92.5-94.0) | 96.3 (95% CI, 96.2-96.3) |
| 5 y | 87.8 (95% CI, 86.7-88.8) | 92.5 (95% CI, 92.4-92.5) |
| Overall | 65.8 (95% CI, 62.0-69.3) | 64.3 (95% CI, 60.9-67.4) |

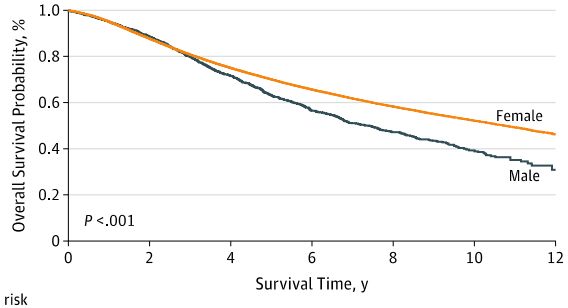
D Stage II




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 5313 | 4408 | 3000 | 1813 | 977 | 371 | 33 |
| | 458364 | 399725 | 284829 | 186560 | 106397 | 46110 | 6392 |

| Survival | Male, % | Female, % |
|---|---|---|
| 3 y | 88.2 (95% CI, 87.3-89.1) | 92.1 (95% CI, 92.0-92.1) |
| 5 y | 78.9 (95% CI, 77.7-80.2) | 85.9 (95% CI, 85.8-86.0) |
| Overall | 47.8 (95% CI, 43.1-52.3) | 58.0 (95% CI, 54.7-61.1) |

E Stage III

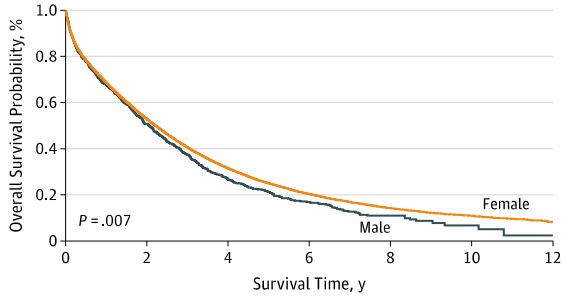



No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Male | 2240 | 1816 | 1129 | 628 | 324 | 109 | 16 |
| Female | 160710 | 131028 | 87391 | 54222 | 29869 | 12282 | 1666 |

| Survival | Male, % | Female, % |
|---|---|---|
| 3 y | 80.0 (95% CI, 78.2-81.6) | 80.9 (95% CI, 80.7-81.1) |
| 5 y | 63.3 (95% CI, 61.0-65.5) | 70.1 (95% CI, 69.8-70.3) |
| Overall | 30.9 (95% CI, 25.5-36.5) | 40.5 (95% CI, 37.0-43.9) |

F Stage IV




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 928 | 427 | 162 | 66 | 22 | 4 | 1 |
| | 67704 | 32154 | 13964 | 5960 | 2381 | 817 | 116 |

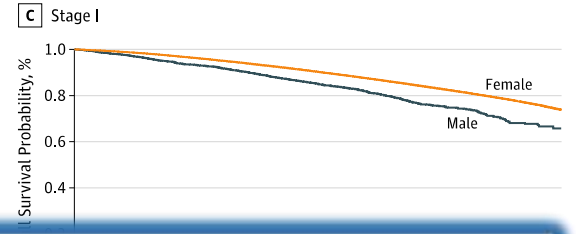
| Survival | Male, % | Female, % |
|---|---|---|
| 3 y | 37.5 (95% CI, 34.2-40.1) | 40.6 (95% CI, 40.2-41.0) |
| 5 y | 21.4 (95% CI, 18.4-24.5) | 25.1 (95% CI, 24.7-25.5) |
| Overall | 2.5 (95% CI, 0.4-9.2) | 8.3 (95% CI, 7.7-8.9) |

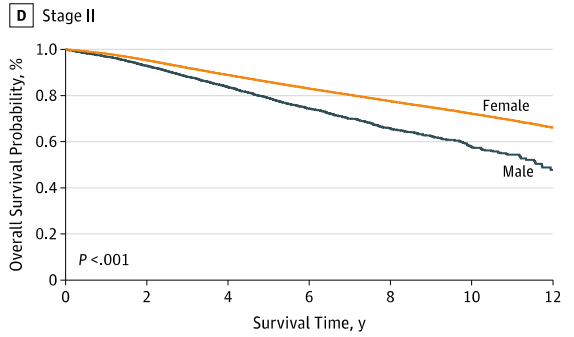
Wang. JAMA Oncol. September 19, 2019

# BC Overall survival: men vs women

**Table 10.1** Stage at presentation in larger MBC series

| Author | Country | N | Stage I | Stage II | Stage III | Stage IV |
|---|---|---|---|---|---|---|
| Ramantanis 1980 [1] | Greece | 120 | 44 (37%) | 37 (31%) | 27 (22.5%) | 12 (10%) |
| Ribeiro 1985 [2] | England | 292 | 111 (38%) | 61 (21%) | 76 (26%) | 44 (15%) |
| Gough 1993 [3] | USA | 105 | 21 (20%) | 27 (26%) | 43 (41%) | 14 (13%) |
| Yildirim 1999 [4] | Turkey | 121 | 3 (2%) | 35 (30%) | 67 (55%) | 16 (13%) |
| Bourhafour 2011 [5] | Morocco | 127 | 6 (5%) | 20 (16%) | 64 (50%) | 37 (29%) |
| Thuler 2014 [6] | Brazil | 1189 | 170 (14%) | 455 (38%) | 406 (34%) | 158 (13%) |




| Survival | Male, % | Female, % |
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| 3 y | 88.2 (95% CI, 87.3-89.1) | 92.1 (95% CI, 92.0-92.1) |
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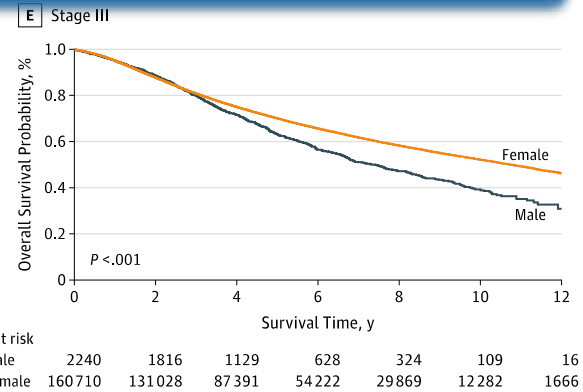
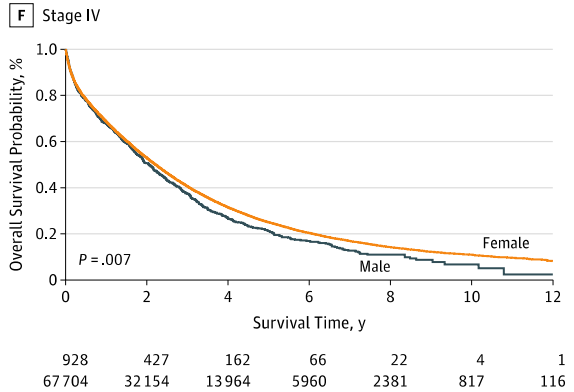



| Survival | Male, % | Female, % |
|---|---|---|
| 3 y | 80.0 (95% CI, 78.2-81.6) | 80.9 (95% CI, 80.7-81.1) |
| 5 y | 63.3 (95% CI, 61.0-65.5) | 70.1 (95% CI, 69.8-70.3) |
| Overall | 30.9 (95% CI, 25.5-36.5) | 40.5 (95% CI, 37.0-43.9) |

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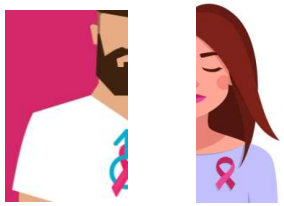
Wang. JAMA Oncol. September 19, 2019, Fentiman. Male Breast Cancer (eBOOK). DOI 10.1007/978-3-319-04669-3

# BC in men: genetics



| | | |
|---|---|---|
| Genetic/epigenetic alterations | | |
| *CYP17* gene aberration | Common | Rare [37, 38] |
| Klinefelter's syndrome (XXY) | BC rates increase 20- to 50-fold compared to XY males [4] | None [4] |
| Hypermethylation of *BRCA1, BRCA2, CD44, ESR1, STK11, RARB*, and *ATM* promoter regions | Rare [40] | Common [40] |
| *BRCA1* germline mutation | Rare (~1%) [30] | Rare (~5–10%) [48] |
| *BRCA2* germline mutation | Common (~12%) (60–76% in male BC patients with multiple family members with BC) [30]; pathogenic variants increase risk 13.9-fold [49] | Rare (~5%) [48] |
| *CHEK2* mutations | Pathogenic variants increase risk 3.7-fold [49] | |
| *CHEK2* 1100delC deletion | Deletion increases risk 3.13-fold [50] | Deletion increases risk 2.88-fold [50] |
| *PALB2* mutations | Pathogenic variants increase risk 6.6-fold [49] | |

Gucalp. Breast Cancer Research and Treatment. 2019;173(1):37.

# BC in men: Treatment of Advanced Disease

# BC in men: Treatment of Advanced Disease

**Table 10.9** Response of metastatic MBC to aromatase inhibitors

| Author | AI | N | Response | Comment |
|---|---|---|---|---|
| Giordano 2002 [51] | A | 5 | 60% | SD 3, PD 2 |
| Italiano 2004 [52] | A | 1 | 100% | CR |
| Zabolotny 2005 [53] | L | 1 | 100% | CR 12 months |
| Arriola 2007 [54] | L | 1 | 100% | |
| Carmona-Bayonas 2007 [55] | A | 1 | 100% | Concomitant herceptin |
| Doyen 2010 [56] | A | 15 | 40% | CR 2, PR, 4, SD 2, PD 7 |
| Visram 2010 [57] | A<br>L | 5<br>5 | 3 (60%)<br>5 (100%) | |
| Zagouri 2013 [58] | A/L | 6 | 3 (50%) | PR 3, SD 2, PD 1 |
| Kuba 2016 [59] | L | 3 | 2 (67%) | PR2, PD 1 |

*CR* complete response, *PR* partial response, *SD* static disease, *PD* progressive disease

**Table 10.10** Response of metastatic MBC to fulvestrant

| Author | N | Response | Comment |
|---|---|---|---|
| Agrawal 2007 [63] | 2 | 100% | First line treatment |
| Rodrigues 2009 [64] | 1 | 100% | Prior chemotherapy |
| Masci 2011 [65] | 5 | 20% | PR 1. SD 2. PD 2 |
| Zagouri 2013 [58] | 14 | 21% | PR 3 SD 7 PD 4 |

Fentiman. Male Breast Cancer (eBOOK). DOI 10.1007/978-3-319-04669-3

# BC in men: Treatment of Advanced Disease

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| Doyen 2010 [56] | A | 15 | 40% | CR 2, PR, 4, SD 2, PD 7 |
| Visram 2010 [57] | A<br>L | 5<br>5 | 3 (60%)<br>5 (100%) | |
| Zagouri 2013 [58] | A/L | 6 | 3 (50%) | PR 3, SD 2, PD 1 |
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*CR* complete response, *PR* partial response, *SD* static disease, *PD* progressive disease

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| Masci 2011 [65] | 5 | 20% | PR 1. SD 2. PD 2 |
| Zagouri 2013 [58] | 14 | 21% | PR 3 SD 7 PD 4 |

Fentiman. Male Breast Cancer (eBOOK). DOI 10.1007/978-3-319-04669-3

# CDK4/6i and prescribing information: FDA

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use IBRANCE safely and effectively. See full prescribing information for IBRANCE.**

**IBRANCE® (palbociclib) capsules, for oral use**
**Initial U.S. Approval: 2015**

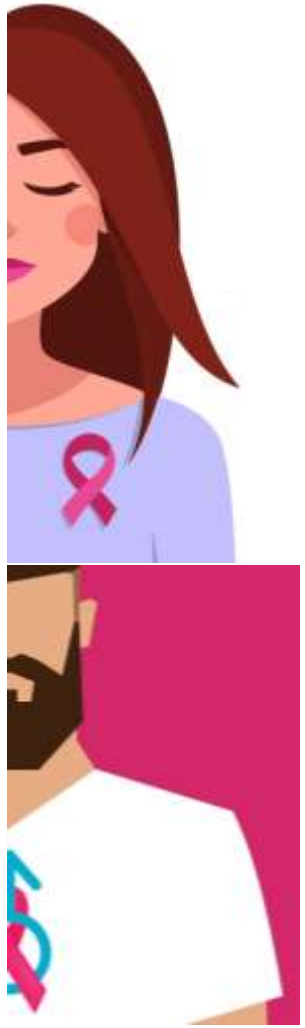
**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Indications and Usage (1) | 4/2019 |

**---------- INDICATIONS AND USAGE----------**

IBRANCE is a kinase inhibitor indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men; or
- fulvestrant in patients with disease progression following endocrine therapy. (1)



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*… but abemaciclib or ribociclib are appropriate off-label substitutes.*

# CDK4/6i and prescribing information: EMA

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

IBRANCE is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer:

- in combination with an aromatase inhibitor;
- in combination with fulvestrant in women who have received prior endocrine therapy (see section 5.1).

In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Verzenios is indicated for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.

In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

**4. CLINICAL PARTICULARS**

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Kisqali is indicated for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.

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# CDK4/6i and prescribing information: EMA

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# CDK4/6i and prescribing information: EMA

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# CDK4/6i and prescribing information: EMA

4.6 Fertility, pregnancy and lactation

Fertility

There were no effects on oestrous cycle (female rats) or mating and fertility in rats (male or female) in nonclinical reproductive studies. However, no clinical data have been obtained on fertility in humans. Based on male reproductive organ findings (seminiferous tubule degeneration in testis, epididymal hypospermia, lower sperm motility and density, and decreased prostate secretion) in nonclinical safety studies, male fertility may be compromised by treatment with palbociclib (see section 5.3). Thus, men may consider sperm preservation prior to beginning therapy with IBRANCE.

5.2 Pharmacokinetic properties

Special populations

*Age, gender, and body weight*

Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age ranging from 22 to 89 years, and body weight ranging from 38 to 123 kg), gender had no effect on the exposure of palbociclib, and age and body weight had no clinically important effect on the exposure of palbociclib.

# CDK4/6 Inhibitors in MBC: first-line Trials

| Trial | Regimen | Phase | N | ORR,* % | PFS, Mos | HR | 95% CI |
|---|---|---|---|---|---|---|---|
| PALOMA-1[1] | Letrozole ± palbociclib | II | 165 | 39 vs 55 | 10.2 vs 20.2 | 0.49 | 0.22-0.75 |
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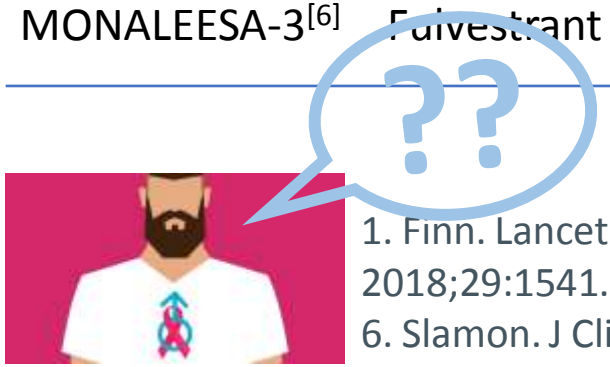


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# CDK4/6 Inhibitors in MBC: post first-line Trials

| Trial | Regimen | Phase | N | ORR*, % | PFS, Mos | HR | 95% CI |
|---|---|---|---|---|---|---|---|
| PALOMA-3[1] | Fulvestrant ± palbociclib | III | 521 | 6 vs 10 | 4.6 vs 9.5 | 0.46 | 0.36-0.59 |
| MONARCH-2[2] | Fulvestrant ± abemaciclib | III | 669 | 21 vs 48 | 9.3 vs 16.4 | 0.55 | 0.45-0.68 |
| MONALEESA-3[3] | Fulvestrant ± ribociclib | III | 345 | 29 vs 41 | 12.8 vs 20.5 | 0.59 | 0.48-0.73 |
| MONARCH-1[4] | Abemaciclib monotherapy | II | 132 | 20 | 6.0 | -- | -- |

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# CDK4/6 Inhibitors in MBC

**The rarity of BC in men limits the feasibility of randomized clinical studies in this population.**

**THE REAL-WORLD DATA SOURCES USED IN THIS STUDY SUPPORT THAT MEN WITH MBC DERIVE CLINICAL BENEFIT FROM THE ADDITION OF PAL TO ET**


Bartlett. Journal of Clinical Oncology 2019 37:15_suppl, 1055-1055

# CDK4/6 Inhibitors in MBC: REAL WORLD

**Two retrospective analysis (2015-2017):**

1. of pharmacy and medical claims data from IQVIA Inc. **– 1139 pts - 147 male**
2. of data derived from electronic health records in the Flatiron Health database. **- 12 pts**

**FIRST LINE SETTING:**

mDOT PAL (n=37) vs non-PAL (n=214): 8.5 vs 4.3 mo

mDOT PAL + LET (n=26) vs LET alone (n=63): 9.4 vs 3.0 mo

**ACROSS ALL LINES:**

maximum response rate in the PAL + ET (n=12) vs ET alone (n=8): 33.3% (2 complete responses [CR], 2 partial responses [PR]) vs 12.5% (0 CR, 1 PR)

Safety database consistent with known safety profile of palbociclib

Bartlett. Journal of Clinical Oncology 2019 37:15_suppl, 1055-1055

# CDK4/6 Inhibitors in MBC: REAL WORLD

328P **Ribociclib (RIB) plus letrozole (LET) in male patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor-2–negative (HER2–) advanced breast cancer (ABC) from the CompLEEment-1 trial**

M. Campone[1], M. De Laurentiis[2], C. Zamagni[3], I. Kudryavcev[4], M. Agterof[5], U. Brown-Glaberman[6], M. Palácová[7], S. Chatterjee[8], L. Menon-Singh[9], J. Wu[10], K. Zhou[11], M. Martin[12]

mDOT 8m
ORR 34.4% (95% CI, 18.6- 53.2)

Safety:

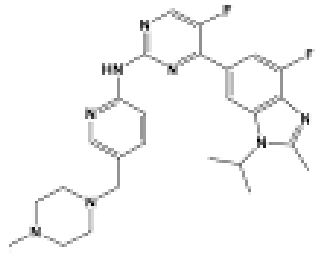
- No fatal SAEs
- Most common Aes: neutropenia,  hot flashes, diarrea, fatigue
- 1 pts with at least 1 dose adjustment of RIB
- pts permanently discontinued treatment: 7 due to progressive disease and 4 due to AEs.

# CDK4/6 Inhibitors in MBC: post first-line Trials

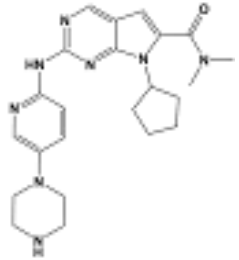
Dr Richard Pazdur, director of the FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research said:

***"Some approved indications for breast cancer treatments do not distinguish by gender, but in certain cases if there is a concern that there may be a difference in efficacy or safety results between men and women, then further data may be necessary to support a labeling indication for male patients."***

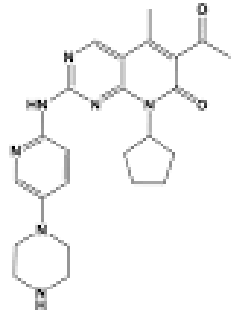
# Conclusions



Abemaciclib
LY2835219



Ribociclib
LEE011



Palbociclib
PD-332991


# Conclusions

Forbes

Aug 28, 2019, 08:25am

**FDA Urges Inclusion Of Men In Breast Cancer Clinical Trials**

28 agosto 2019

la Repubblica

**Tumore al seno, Fda: "Includere anche gli uomini nella ricerca"**


## Male Breast Cancer: Developing Drugs for Treatment

### Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2019
Clinical/Medical

FDA encourages sponsors to discuss their breast cancer drug development plan early in development with CDER or CBER, as applicable, and recommends the following:

- Scientific rationale should be included in the protocol when proposing to exclude males from breast cancer trials. FDA does not intend to consider low expected accrual rates of male patients with breast cancer to be a sufficient scientific rationale for excluding them from a clinical trial.
- Further data may be necessary to support extrapolation of findings to support an FDA-approved indication for male patients with breast cancer where there is a concern for differential efficacy or safety between males and females. In breast cancer, this may be relevant when a drug results in or relies upon manipulation of the hormonal axis, as with endocrine therapy. The additional data to support efficacy and safety for male patients with breast cancer can be generated through a variety of trial designs using different data sources, including small-single arm trials and studies using real-world data sources.

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