Il carcinoma mammario metastatico HR+/HER2- negativo: i nuovi algoritmi alla luce delle nuove opzioni terapeutiche

# Sessione 2:

# CASO CLINICO

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Negrar, 16 Aprile 2018

# History & Clinical Presentation

- 53 year-old female patient
- Post-menopause
- Never smoker, BMI=22
- No family history of breast or ovarian cancer
- Comorbidities:
  - Gilbert's Syndrome
  - Atrial septal aneurysm
- March 2017: Low back pain since December 2016, uncontrolled with anti-inflammatory drugs
  - ✓ Lumbar spine and pelvic bone MRI: multiple bone lesions suspected for metastases
  - ✓ Oncologic Visit (April 24th 2017): PS ECOG: 2 (disabling pain); palpable mass in right breast; reactive depressive symptoms
  - ✓ US-mammography: single nodule in the upper-exterior quadrant of right breast (21 mm)

# Diagnosis

- Core Biopsy of the right breast nodule: B5.
- Histology:
  - **Breast invasive carcinoma with solid and colloid aspects**
  - **Grading 3 (solid)**
  - **Ki67: 25%**
  - **ER: 90%**
  - **PgR: 20%**
  - **HER2-negative [IHC (HERcep test) score 1+]**
  - Grading 2 (colloid)
  - Vascular invasion

# Staging

**CT scan:**

– Right breast nodule

– **Multiple bone metastases**

– **No visceral metastases**

**$^{18}$FDG PET-CT:**

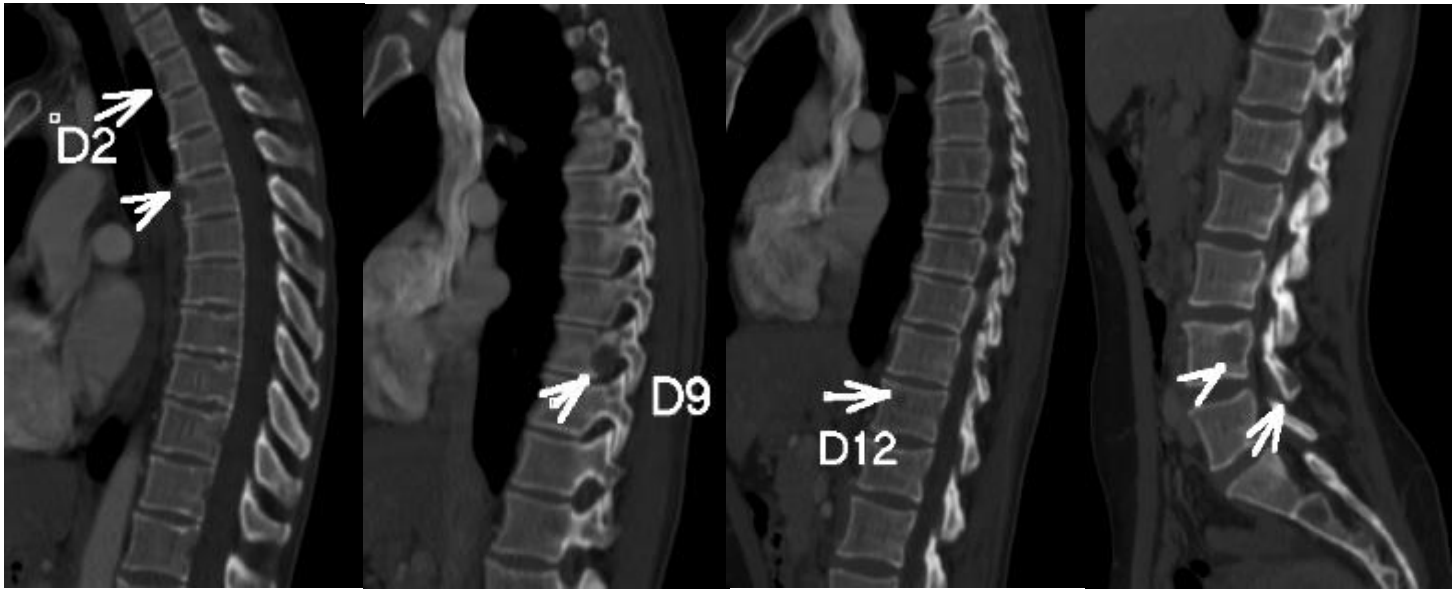
– Metabolic-active area in the right breast (25 mm);

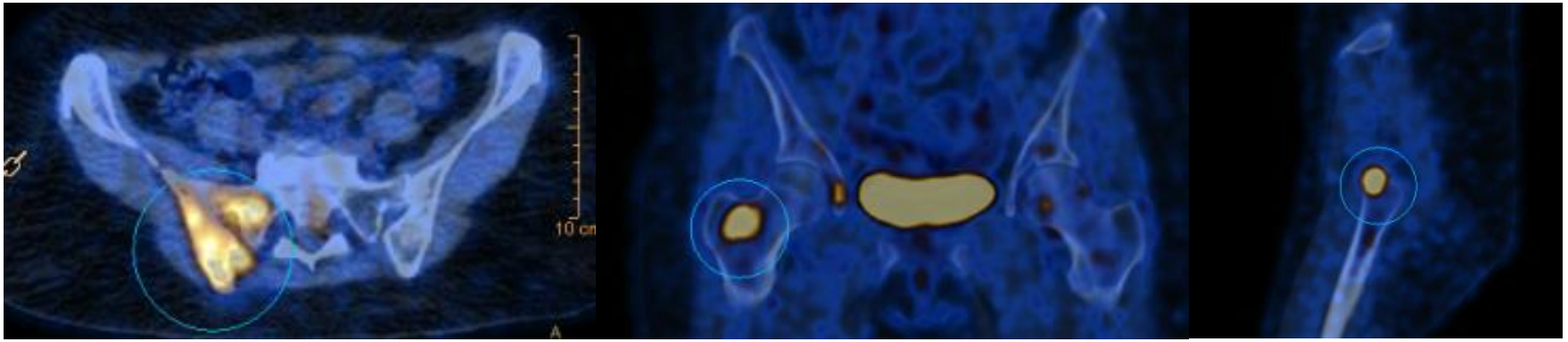
– **Multifocal osteolytic bone metastases:**

- Spine, Pelvic Bone, Ribs, Femurs, Skull

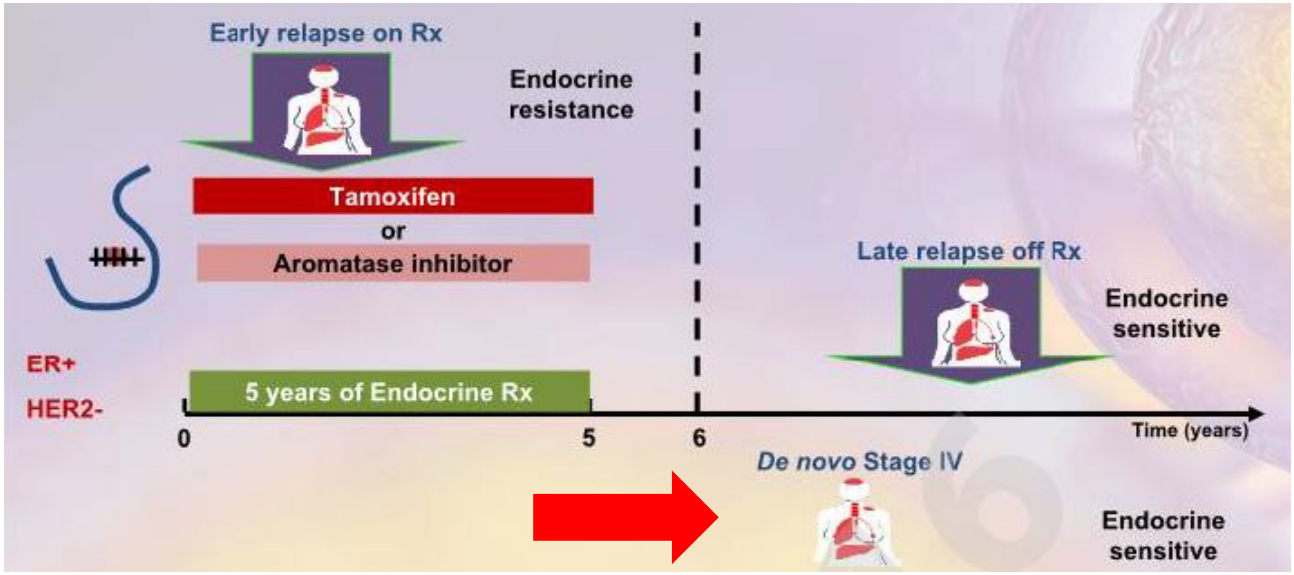
**cT2 cN0 M1 Stage IV (*De novo*)**
**Luminal-like, HER2-negative disease**

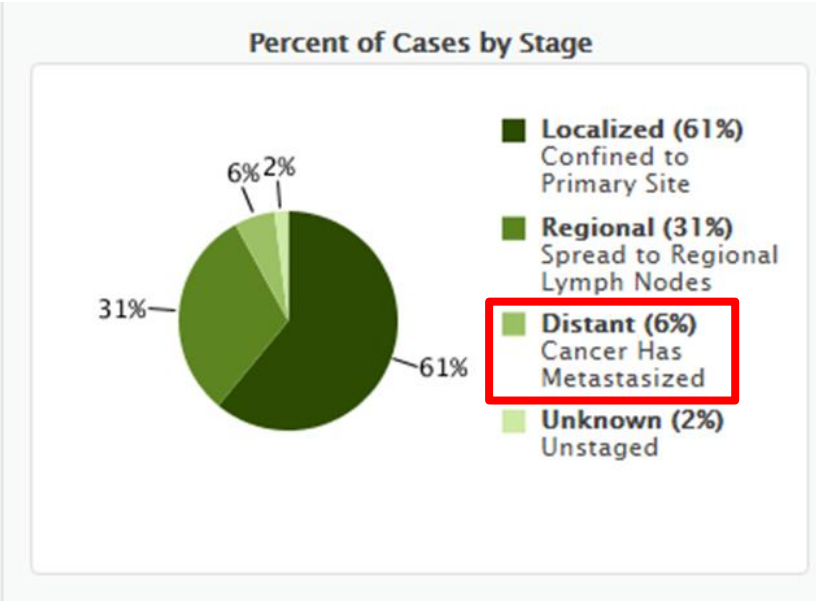
# Baseline CT and $^{18}$FDG PET-CT



# De Novo Stage IV in real-life




SEER 2006-2012[1]:

~6% *De Novo* Stage IV

AIOM-AIRTUM 2017[2]:

~ 3,000 new *De Novo* Stage IV cases in 2017

*1National Cancer Institute. SEER stat fact sheet. Accessed October 21st, 2017*

*2AIOM-AIRTUM: i numeri del cancro in Italia 2017*

# How many of these patients are represented in modern Phase III trials with new drugs?

| | MONALEESA-2 (n=668) | PALOMA-2 (n=666) | SWOG-0226 (n=707) | FALCON (n=462) | MONARCH-3 (n=493) |
|---|---|---|---|---|---|
| **Disease Free Interval** | | | | | |
| De Novo MBC | 34 % | 36% | 39% | LABC 18 % | 41% |
| < 12 mo | 2 % | 22 % | nil | MBC 87 % | NR |
| > 12 mo | 64 % | 42 % | (> 10 yr) 28% | | NR |
| **Prior Treatment** | | | | | |
| Adjuvant Endocrine Rx | 52 % | 56 % | 40 % | nil | 46% |
| Adjuvant Chemotherapy | 37 % | 48% | 33 % | 19 % | 38% |
| Chemotherapy for MBC | nil | nil | nil | 17 % | nil |
| **Site of Disease** | | | | | |
| Visceral | 59 % | 49 % | 54 % | 55 % | 52% |
| Bone only | 22 % | 22 % | 22 % | NR | 21% |
| Median PFS for AI (control arm) (95 % CI) | 14.7 mo (13.0 – 16.5) | 14.5 mo (12.9 - 17.1) | 13.5 mo (12.1 – 15.1) | 13.8 mo (NR) | 14.7 mo 11.9 – 16.5 |

*Updated - Johnston S, ESMO 2016*

# ABC: Treatment Goals

**Delay time to disease progression**

- **Maximum control of symptoms**
- **Maintain or improve quality of life**
- **Prevent serious complications**

**Efficacy** **Toxicity**

**Overall goal is to improve survival duration and quality of life**

# Multidisciplinary Strategy

## Multidisciplinary discussion:

1) **Pain management**
   - Opioid and non-steroidal anti-inflammatory analgesics
   - Bone palliative Radiotherapy
   - Orthopedic evaluation
2) **Psychological support**
   - Patient & relatives
3) **Bone stabilizing agent**
   - Prevention of SREs
4) **Oncologic systemic treatment**

# Treatment Tailoring in ABC

**Treatment choice should consider AT LEAST these factors:**

- HR and HER2 status
- Previous therapies and their toxicities
- Disease-free interval
- Tumor burden (defined as number and site of metastases)
- Biological age
- Performance status
- Comorbidities (including organ dysfunctions)
- Menopausal status (for ET)
- Need for a rapid disease/symptom control
- Patient preferences
- Socio-economic and psychological factors
- Available therapies in the patient's country

*Cardoso F et al., AO 2017*

**LoE: Expert Opinion (Consensus: 100%)**

# Guidelines for Luminal ABC

- **Endocrine therapy (ET) is the preferred option for luminal disease**, unless there is visceral crisis or concern/proof of endocrine resistance.

  **All guidelines are in agreement with this recommendation**

- Sequential hormone therapy is the preferential treatment.
- The preferred 1st line ET for post-menopausal patients depends on type and duration of adjuvant ET as well as time relapsed from the end of adjuvant ET; it can be an aromatase inhibitor, (tamoxifen) or fulvestrant.
- The addition of the CDK4/6 inhibitor to an aromatase inhibitor, as 1st line therapy, for post-menopausal patients represents one of the preferred treatment options.

# Systemic Treatment Options

- **ET**
  - Aromatase Inhibithor
  - Fulvestrant
- **ET + CDK4/6 inhibitor**
  - Letrozole + Palbociclib (CNN)
  - Clinical Trial
    - COMPLEEMENT-1 (Phase IIIb, Single Arm Trial) Letrozole + Ribociclib

# A.I. *vs* Tamoxifene *vs* Fulvestrant+A.I.

## PFS / TTP of AIs as 1st-line endocrine therapy trials in HR+ MBC

| Trial | Date | AI (months) | Tamoxifen (months) | AI + fulvestrant 250mg (months) | Hazard Ratio |
|---|---|---|---|---|---|
| Nabholtz et al *Anastrozole vs tamoxifen* | 2000 | 11.1 | 5.6 | - | 0.81 |
| Bonneterre et al *Anastrozole vs tamoxifen* | 2001 | 8.2 | 8.3 | - | 0.99 |
| Mouridsen et al *Letrozole vs tamoxifen* | 2001 | 9.4 | 6.0 | - | 0.72 |
| Chernozemsky et al *Exemestane vs tamoxifen* | 2007 | 12.0 | 8.3 | - | - |
| Paridaens et al *Exemestane vs tamoxifen* | 2008 | 9.9 | 5.8 | - | 0.84 |
| Mehta et al *Anastrozole vs anastrozole + fulvestrant 250mg* | 2012 | 13.5 | - | 15.0 | 0.80 |
| Bergh et al *Anastrozole vs anastrozole + fulvestrant 250mg* | 2012 | 10.2 | - | 10.8 | 0.99 |
| Range | | 8–13 | 6–8 | 10–15 | |

*Johnston S, SABCS 2016*

# A.I. as comparator in recent 1st-Line Phase III Trials

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*Updated - Johnston S, ESMO 2016*

# Fulvestrant [500mg] *vs* A.I.

## FALCON

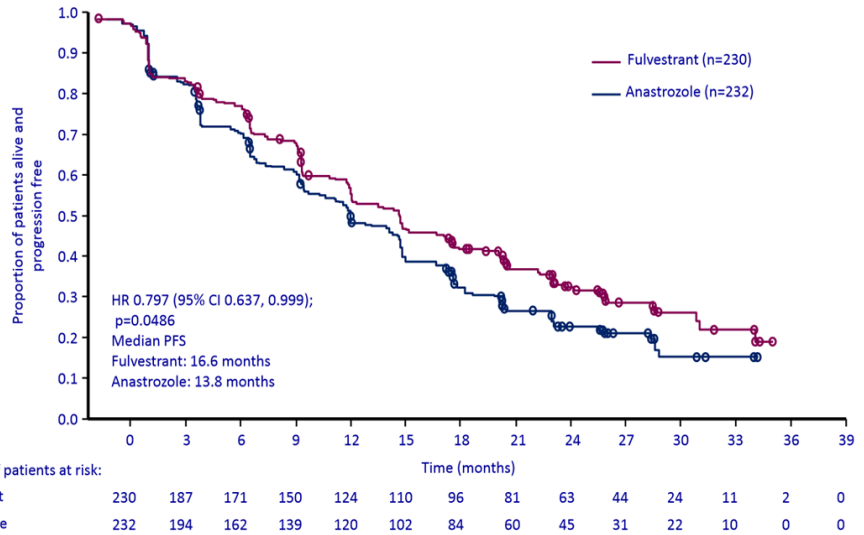
- Randomized, double-blind, multicenter, phase 3 trial
- Postmenopausal women with inoperable locally advanced or metastatic ER-positive/HER2-negative breast cancer (N = 462)
- No prior hormone therapy
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, DOR, EDOR, CBR, DOCB, EDOCB, HRQoL, safety

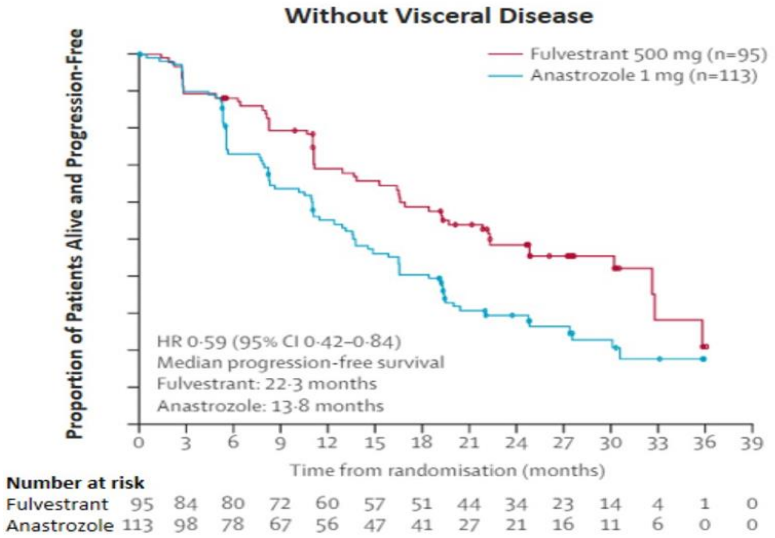
**Fulvestrant 500 mg IM days 0, 14, 28, then monthly thereafter (n = 230)**

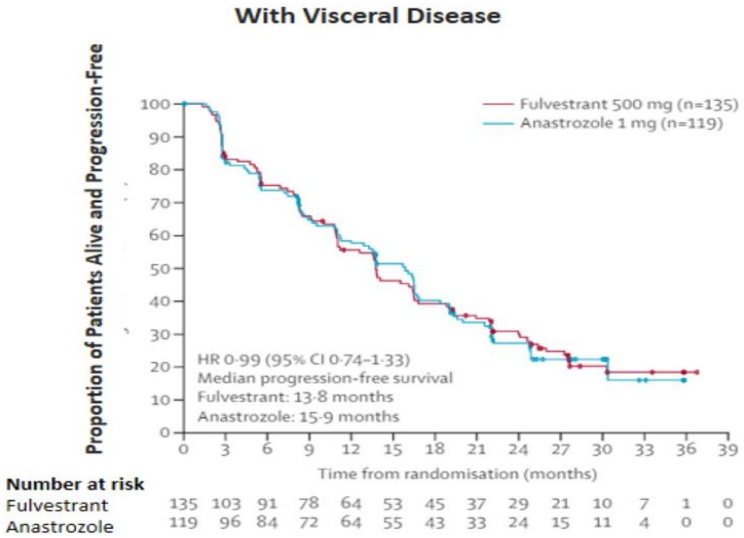
OR

**Anastrozole 1 mg every day (n = 232)**

**Patients allowed 1 line of chemotherapy**

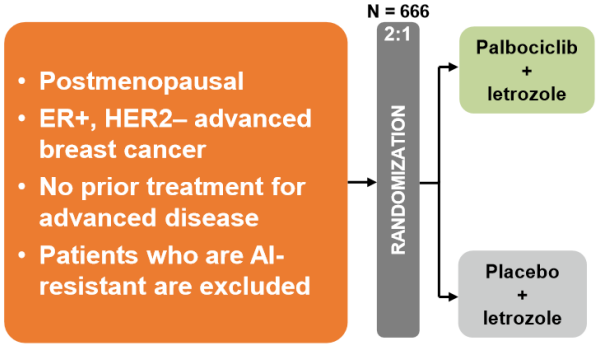


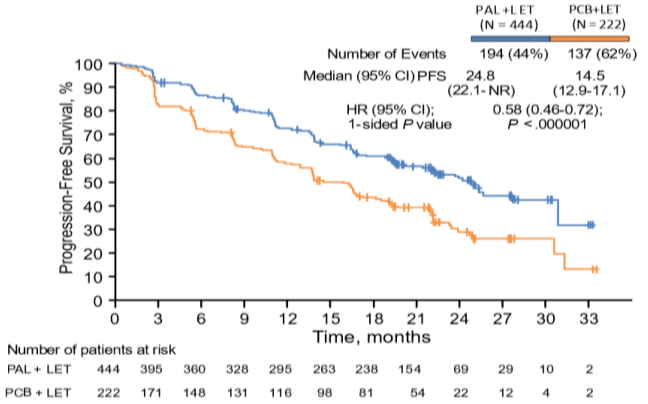

*Robertson J et al., Lancet 2016*

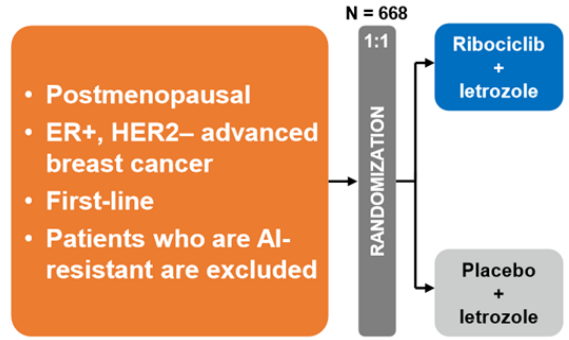
# Consistency of data favouring the addition of CDK4/6 inhibitors to AIs




- Postmenopausal
- ER+, HER2– advanced breast cancer
- No prior treatment for advanced disease
- Patients who are AI-resistant are excluded

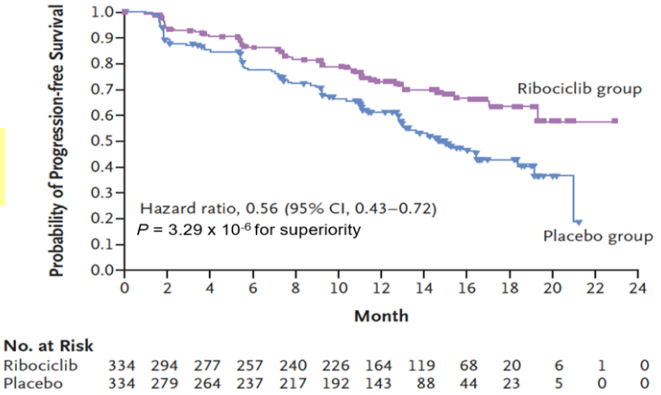
**PALOMA-2[1]**

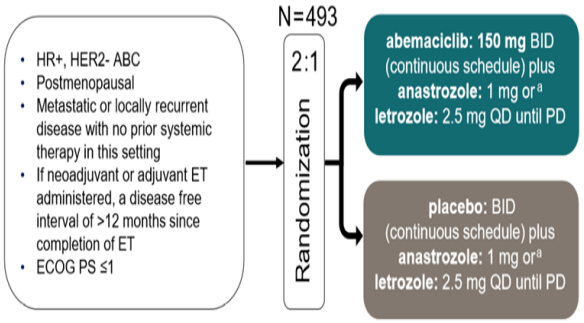



- Postmenopausal
- ER+, HER2– advanced breast cancer
- First-line
- Patients who are AI-resistant are excluded

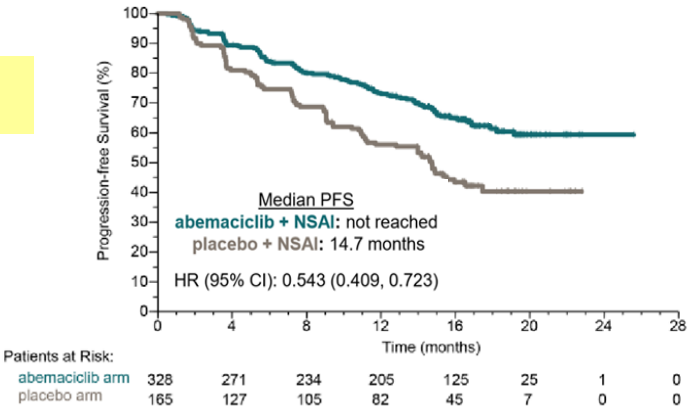
**MONALEESA-2[2]**




- HR+, HER2- ABC
- Postmenopausal
- Metastatic or locally recurrent disease with no prior systemic therapy in this setting
- If neoadjuvant or adjuvant ET administered, a disease free interval of >12 months since completion of ET
- ECOG PS ≤1

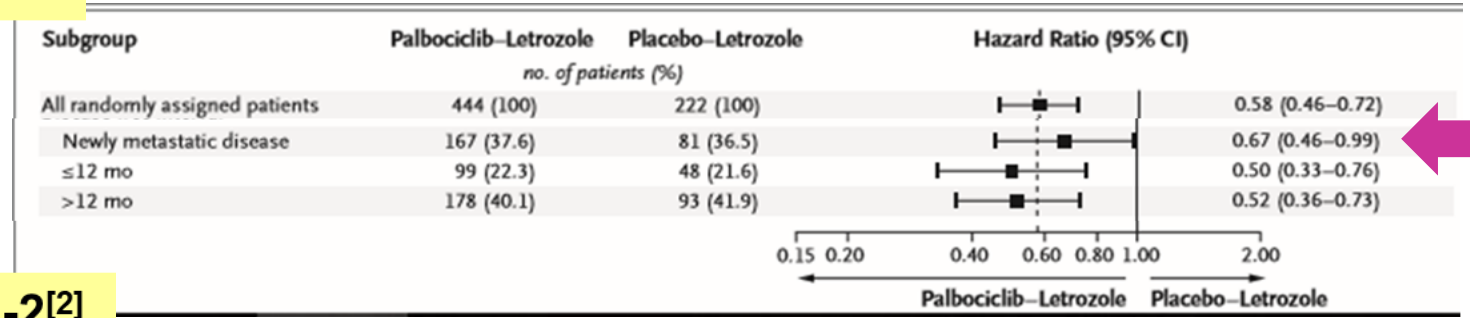
**MONARCH-3[3]**



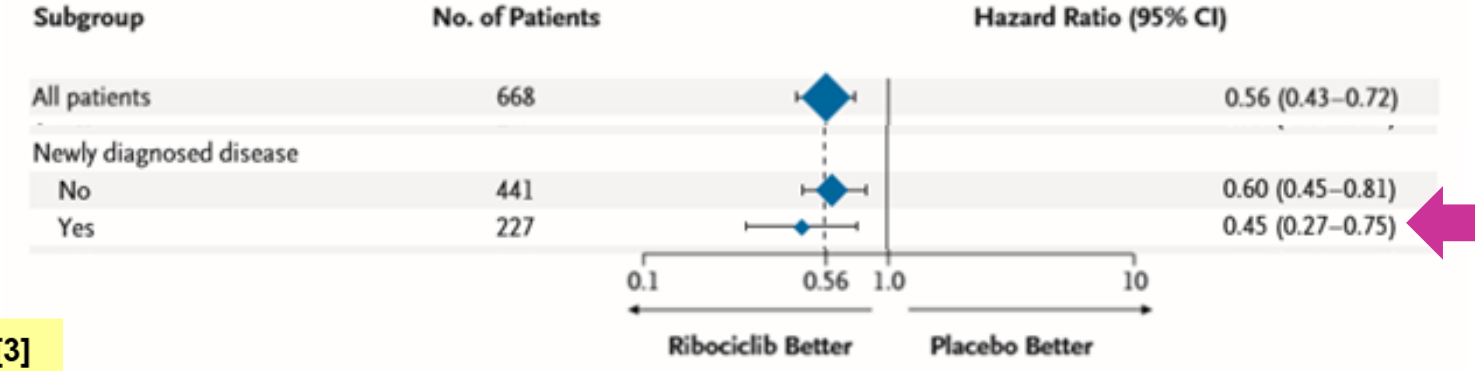

*1] Finn RS et al., NEJM 2016; 2] Hortobagyi GN et al., NEJM 2016; 3] Goetz MP et al., JCO 2017*

# Focus on *De Novo* ABC

## PALOMA 2[1]




## MONALEESA-2[2]

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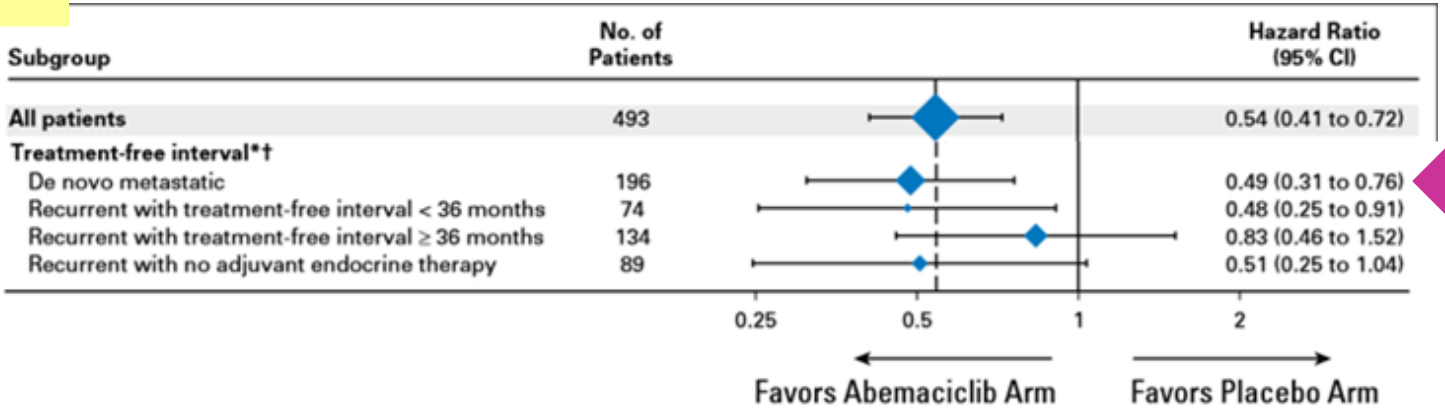
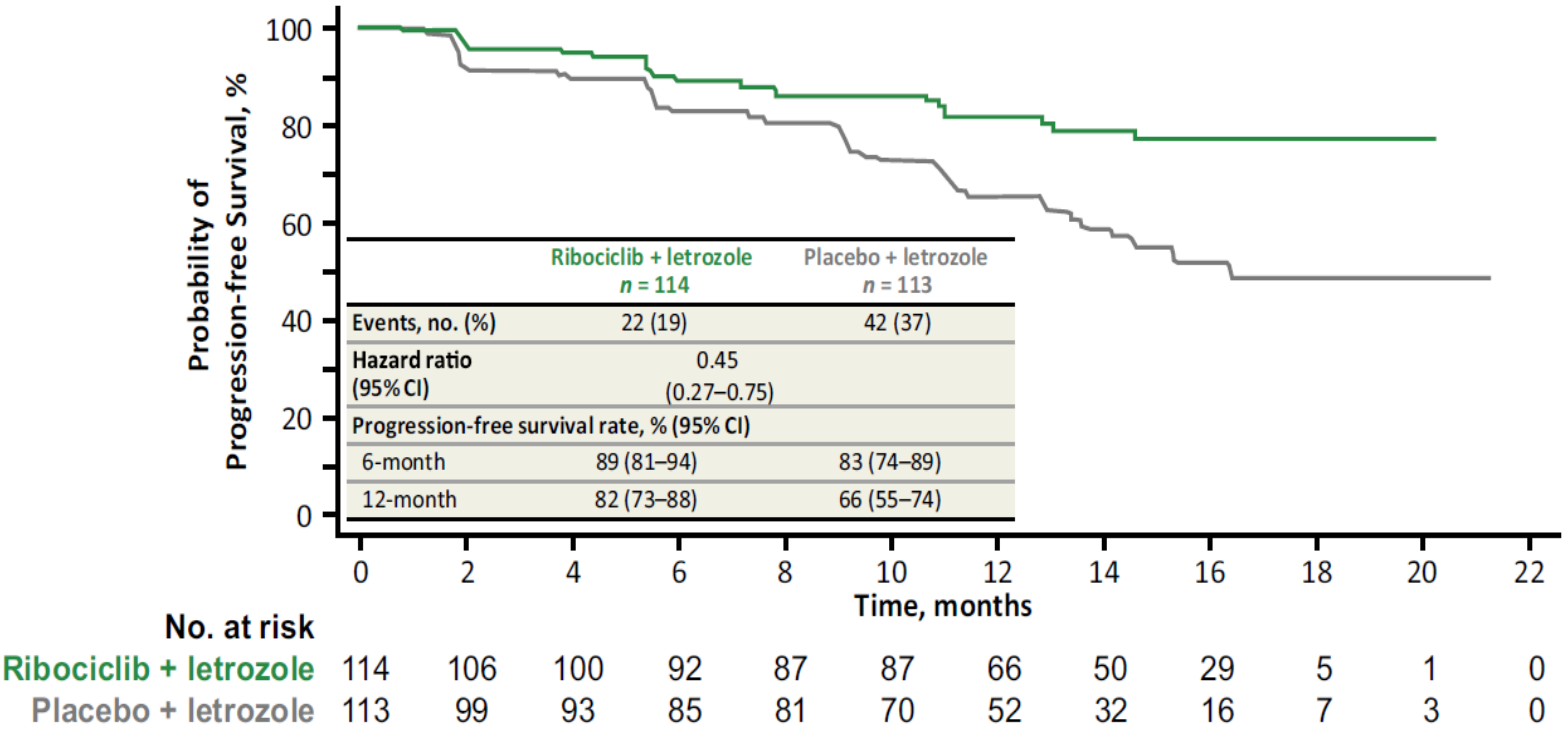



*1] Finn RS et al., NEJM 2016; 2] Hortobagyi GN et al., NEJM 2016; 3] Goetz MP et al., JCO 2017*

# *De Novo* ABC in MONALEESA-2




| | Ribociclib + letrozole *n* = 114 | Placebo + letrozole *n* = 113 |
|---|---|---|
| Events, no. (%) | 22 (19) | 42 (37) |
| Hazard ratio (95% CI) | 0.45 (0.27–0.75) | |
| Progression-free survival rate, % (95% CI) | | |
| 6-month | 89 (81–94) | 83 (74–89) |
| 12-month | 82 (73–88) | 66 (55–74) |

*O'Shaughnessy J et al., Breast Cancer Research and Treatment 2018*

# How many patients with bone only disease are represented in modern Phase III trials?

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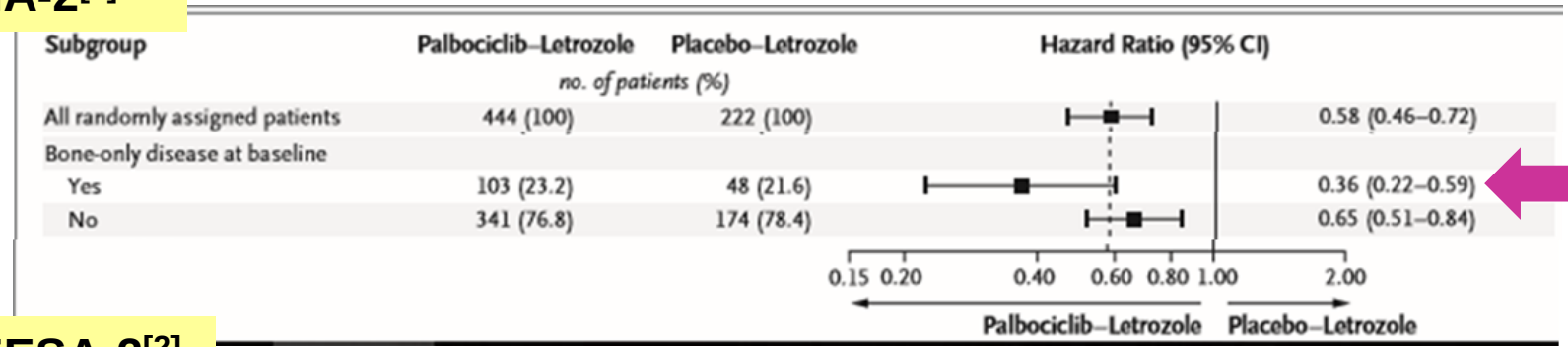
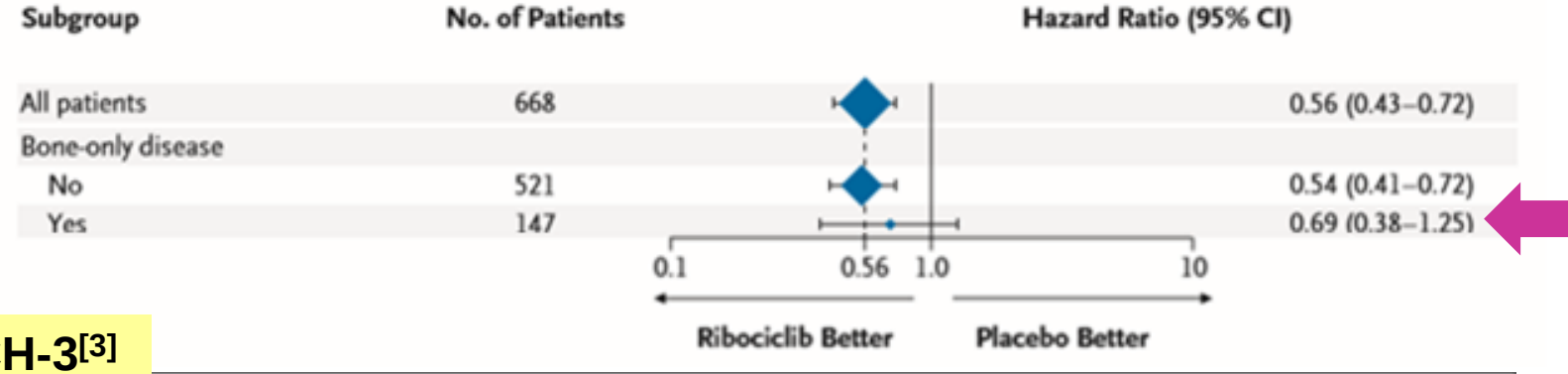
*Updated - Johnston S, ESMO 2016*

# Focus on *Bone only Disease*

## PALOMA-2[1]




## MONALEESA-2[2]

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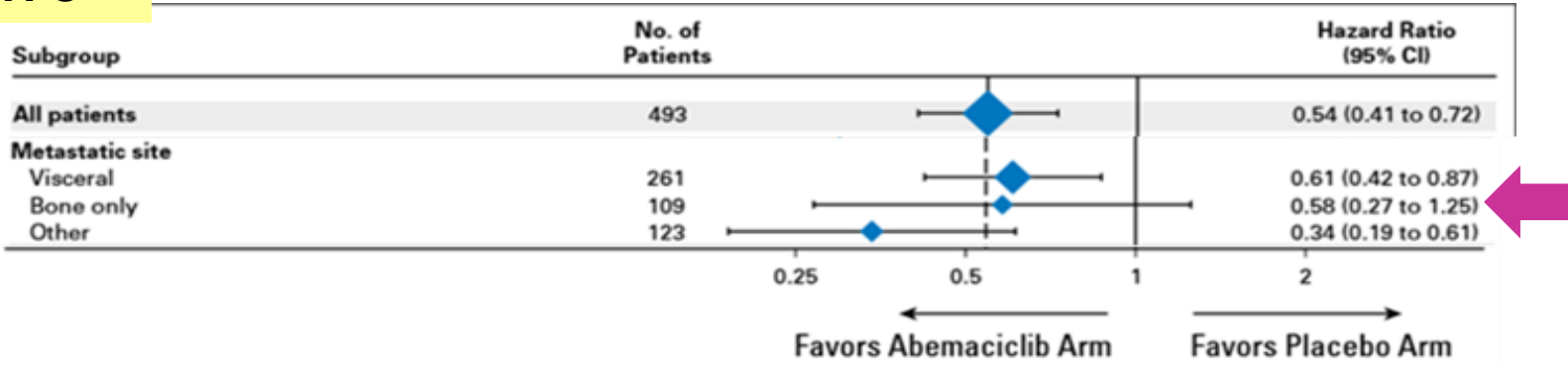
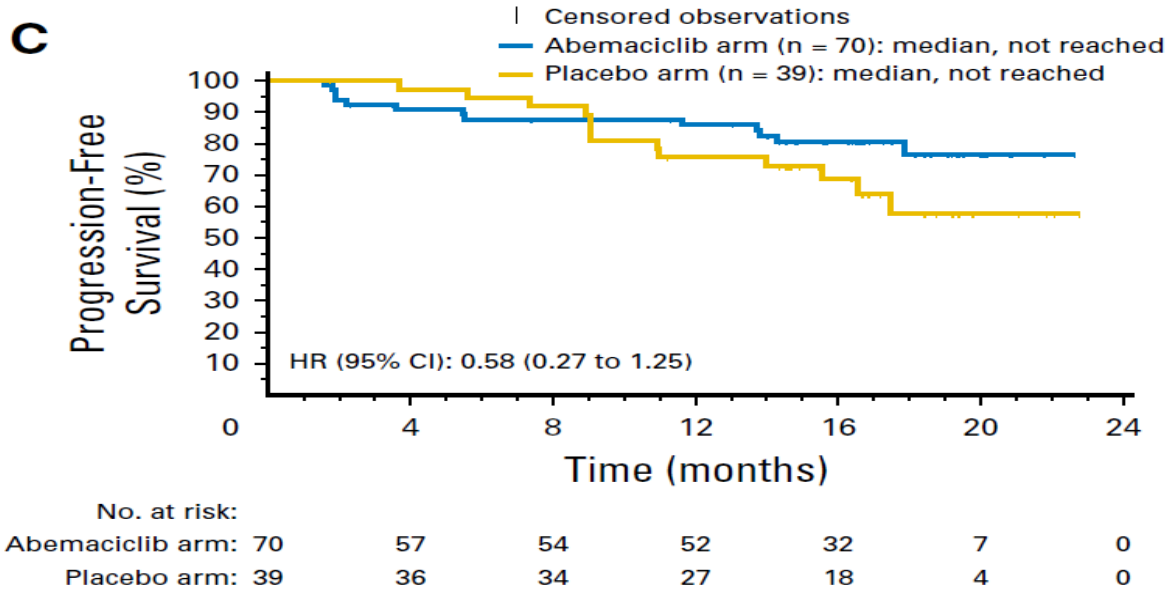


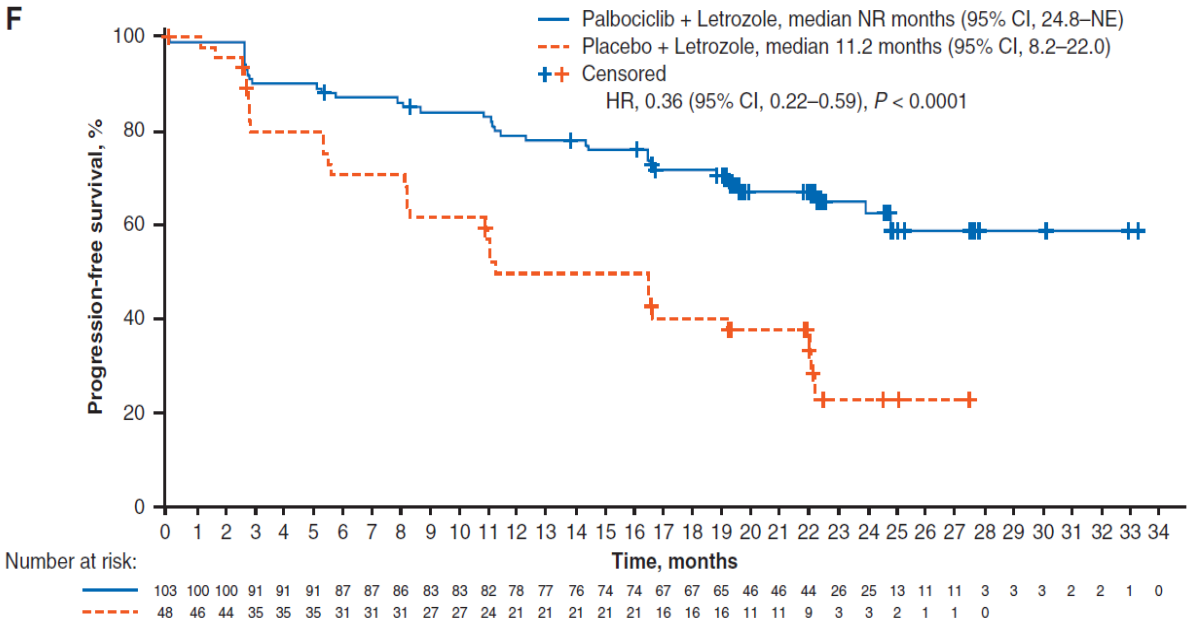

*1] Finn RS et al., NEJM 2016; 2] Hortobagyi GN et al., NEJM 2016; 3] Goetz MP et al., JCO 2017*

# *Bone only Disease* PFS *in MONARCH-3 & PALOMA-2*

**MONARCH-3[1]**




**PALOMA-2[2]**




*1] Goetz MP et al., JCO 2017 2] Turner NC et al., AO 2018*

# Summary

## Treatment choice should consider AT LEAST these factors:

| | |
|---|---|
| – HR and HER2 status | Luminal |
| – Previous therapies and their toxicities | No previous treatment |
| – Disease-free interval | |
| – Tumor burden (defined as number and site of metastases) | High |
| – Biological age | Young |
| – Performance status | Poor (due to disease) |
| – Comorbidities (including organ dysfunctions) | NO |
| – Menopausal status (for ET) | Post-menopausa |
| – Need for a rapid disease/symptom control | Synthomatic |
| – Patient preferences | Discussion the options |
| – Socio-economic and psychological factors | Depression |
| – Available therapies in the patient's country | New drugs available |

*Cardoso F et al., AO 2017*

**LoE: Expert Opinion (Consensus: 100%)**

# Clinical Course -1

- May 11th 2017: COMPLEEMENT-1 study
- The patient started:
  - **Letrozole** (2.5 mg daily)
  - **Ribociclib** (600 mg daily d1-21, q4w)
  - **Zoledronic acid** (4 mg q4w) + vitamin D supplementation
- After 1st cycle (d28):
  - **G4 Neutropenia (asymptomatic)**
  - **G2 Nausea**
  - **G1 Vomiting**
  - G1 Anemia
  - No bilirubin alterations
  - No EKG alterations

# Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer

| Adverse Event | Ribociclib Group (N=334) | | | Placebo Group (N=330)† | | |
|---|---|---|---|---|---|---|
| | Any Grade | Grade 3 | Grade 4 | Any Grade | Grade 3 | Grade 4 |
| | *number of patients (percent)* | | | | | |
| Any adverse event | 329 (98.5) | 221 (66.2) | 50 (15.0) | 320 (97.0) | 105 (31.8) | 3 (0.9) |
| Neutropenia‡ | 248 (74.3) | 166 (49.7) | 32 (9.6) | 17 (5.2) | 3 (0.9) | 0 |
| Nausea | 172 (51.5) | 8 (2.4) | 0 | 94 (28.5) | 2 (0.6) | 0 |
| Infections | 168 (50.3) | 12 (3.6) | 2 (0.6) | 140 (42.4) | 7 (2.1) | 1 (0.3) |
| Fatigue | 122 (36.5) | 7 (2.1) | 1 (0.3) | 99 (30.0) | 3 (0.9) | 0 |
| Diarrhea | 117 (35.0) | 4 (1.2) | 0 | 73 (22.1) | 3 (0.9) | 0 |
| Alopecia | 111 (33.2) | NA | NA | 51 (15.5) | NA | NA |
| Leukopenia | 110 (32.9) | 66 (19.8) | 4 (1.2) | 13 (3.9) | 2 (0.6) | 0 |
| Vomiting | 98 (29.3) | 12 (3.6) | 0 | 51 (15.5) | 3 (0.9) | 0 |

*Hortobagyi GN et al., NEJM 2016*

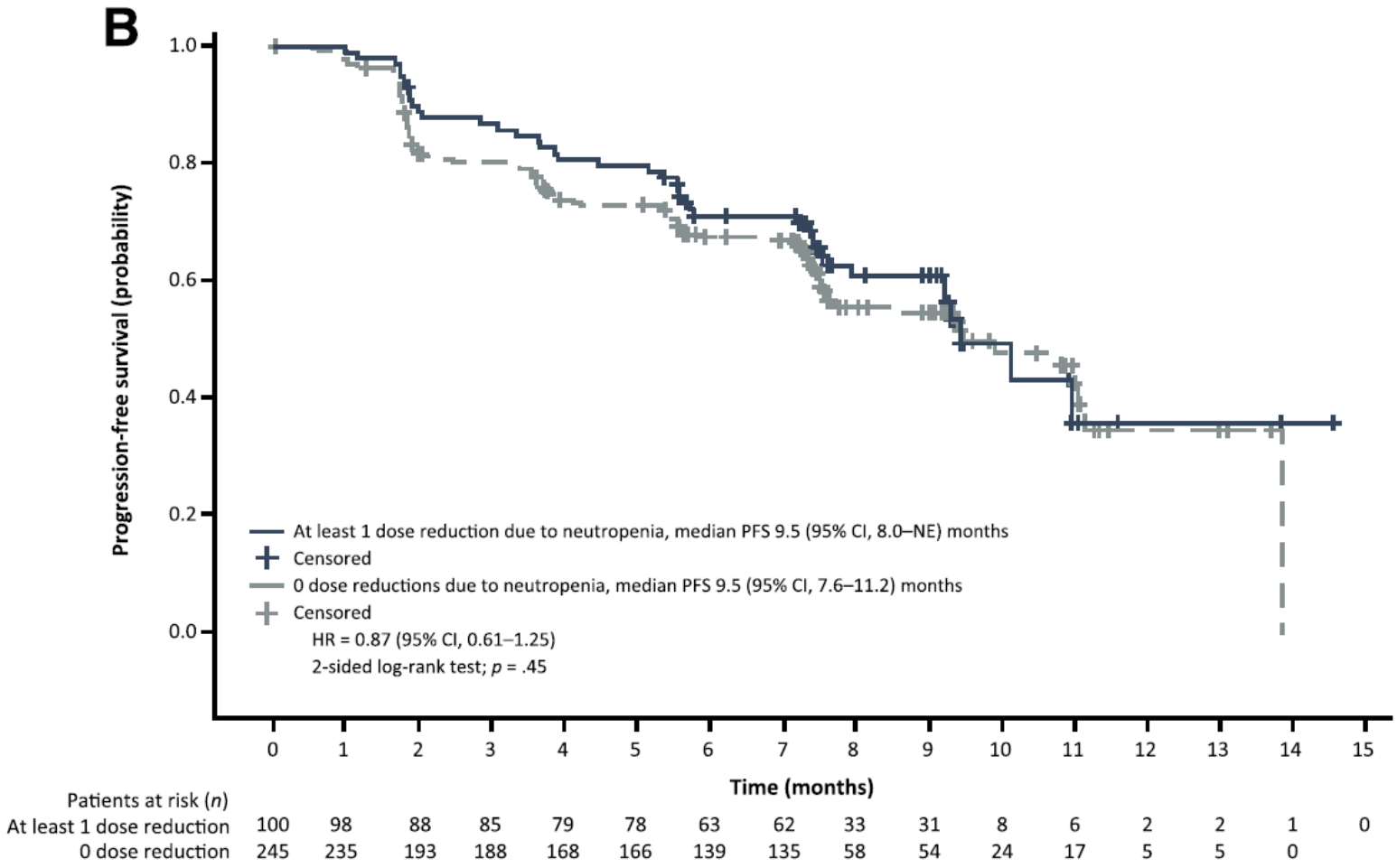
# Treatment exposure and dose adjustments

| | Ribociclib + Letrozole n=334 | | Placebo + Letrozole n=330 | |
|---|---|---|---|---|
| | Ribociclib | Letrozole | Placebo | Letrozole |
| **Treatment exposure** | | | | |
| Median duration of exposure, months | 12 | 13 | 12 | 12 |
| Median relative dose intensity, % | 88 | 100 | 100 | 100 |
| **Dose adjustments** | | | | |
| Dose interruptions, n (%) | 257 (77) | 132 (40) | 134 (41) | 107 (32) |
| Dose reductions due to AEs, n (%) | 169 (51) | – | 14 (4.2) | – |

| | Ribociclib + Letrozole n=334 | Placebo + Letrozole n=334 |
|---|---|---|
| **Treatment ongoing, n (%)** | 195 (58) | 154 (46) |
| **Treatment discontinued, n (%)** | 139 (42) | 180 (54) |
| **Primary reason for treatment discontinuation, n (%)** | | |
| Disease progression | 87 (26) | 146 (44) |
| Adverse events | 25 (7.5) | 7 (2.1) |
| Patient decision | 12 (3.6) | 13 (3.9) |
| Physician decision | 10 (3.0) | 13 (3.9) |
| Protocol deviation | 3 (0.9) | 1 (0.3) |
| Death | 2* (0.6) | 0 |

*Hortobagyi GN et al., ESMO 2016*

# PFS according to dose reductions in PALOMA-3




*Verma S et al., The Oncologist 2016*

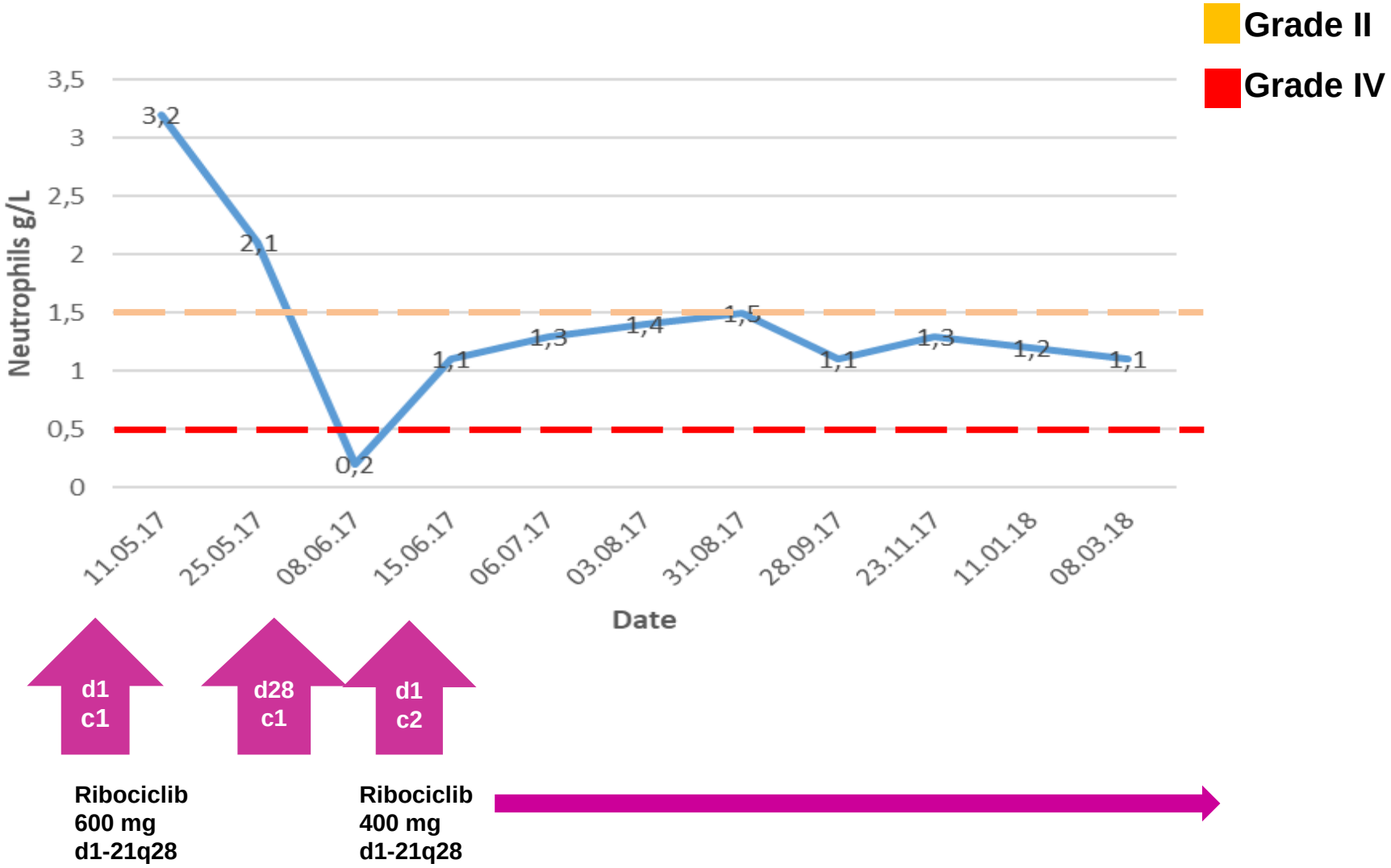
# Clinical Course -2

- 2nd cycle: Dose delay and next lower dose of ribociclib
  - The patient reduced **Ribociclib** (400 mg daily)
- June 2017: **Palliative Radiotherapy**
  - 30 Gy Right femur and pelvic bone
- After 2nd and 3rd cycle:
  - No Nausea and Vomiting
  - G2 Neutropenia
  - No bilirubin alterations
  - **Excellent pain control**
  - **PS ECOG: 0**
  - **Improved Health-related Quality of Life** (FACT-B questionnaire)
  - Clinical evaluation → breast nodule initial response
- July 2017: After 3 months of treatment the CT scan showed:
  - **Stable disease (bone metastases and right breast nodule)**

# Clinical Course -3

- The patient continued **Ribociclib** (400 mg daily d1-21, q4w), Letrozole and Zoledronic Acid
- After 4th cycle:
  - G2 Neutropenia
  - No bilirubin alterations
  - **Antalgic drugs interruption**
  - PS ECOG: 0
  - Clinical evaluation → breast nodule initial response
- April 2018: After 11 months of treatment the CT scan showed:
  - **Stable disease (bone metastases and right breast nodule)**
- The patient is still ongoing with the same treatment

# Neutrophils Count



# Second Line Treatment Options

- Best sequence still unknown
  - [*No reliable data with regard to therapeutic benefit of subsequent treatments after CDK4/6 inhibitors after progression; only PALOMA-3 available*][1]
- Options for 2nd line treatment:
  - Exemestane + Everolimus
  - Fulvestrant
  - CT?
  - Clinical Trial [ex. GIM16]: Exemestane+Everolimus → Fulvestrant or Fulvestrant → Exemestane+Everolimus

*Turner NC et al., SABCS 2016*

# Conclusion

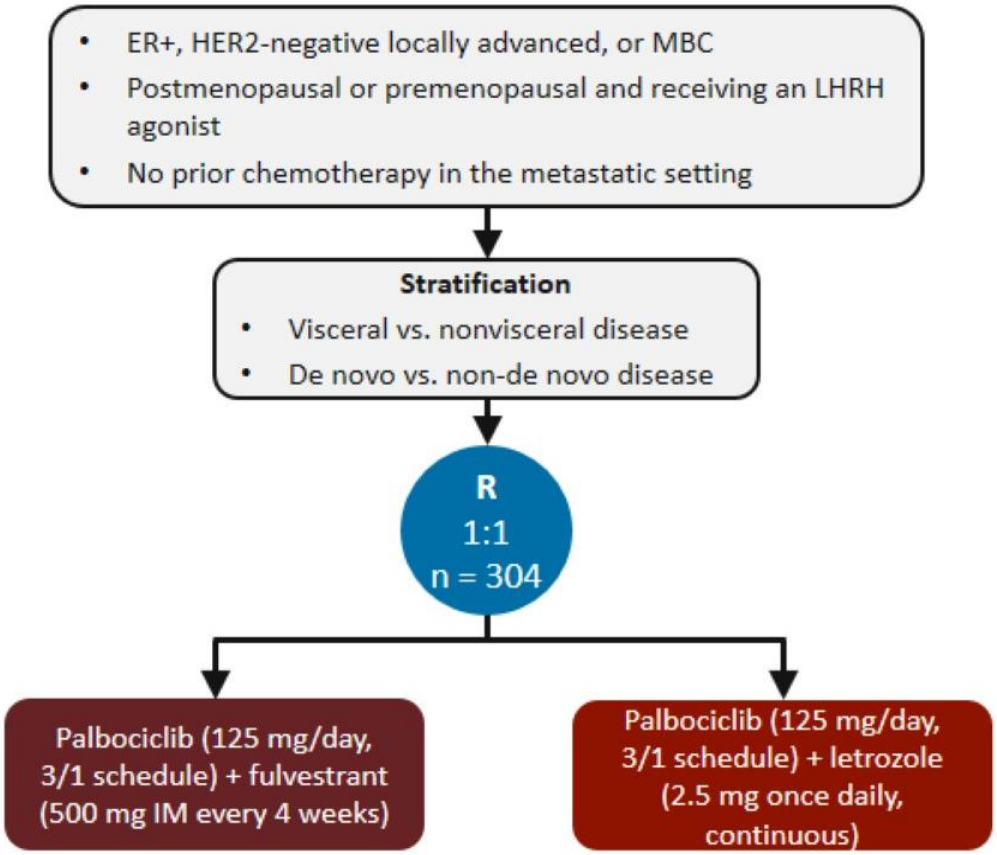
- Multidisciplinary approach was crucial
- The combination of ET with a CDK4/6 inhibitor seems a valuable treatment option for this patient
  - PS improvement
    - …with a improved QoL
  - Good safety profile
  - Disease control

# Discussion

- Should the combination of a ET with CDK4/6 inhibitor be offered as the 1st-line treatment to the majority of patients with luminal ABC?
- What optimal sequential strategy to give CDK4/6 inhibitors?
  - Ongoing CDK4/6 inhibitors trials in patients who progressed on CDK4/6 inhibitors containing therapy
  - Novel agents that inhibit mechanisms of ET resistance mechanisms are in clinical trial
- To date, no clear factors to identify patients for whom ET alone is enough
- What ET is the best partner for CDK4/6?

# PARSIFAL Trial

- Phase II, open-label, first-line setting




[Enrollment completed]

ClinicalTrials.gov. NCT02491983.

*Thank you for your attention*