Sottogruppi luminali in stadio avanzato: lo standard

Alessandro Minisini

Dipartimento di Oncologia
Azienda Sanitaria Universitaria Integrata
Udine

AGENDA

- Some definitions
- Guidelines
- ET + CDK inhibitors: recent data
- After CDK inhibitors?

Advanced breast cancer

- Advanced breast cancer (ABC) mainly incurable
  - 5 years OS about 25%

- In luminal (HER-2 negative) subgroup ABC endocrine therapy (ET) should be first choice
  - Unless visceral crisis
  - Concern of endocrine resistance

Cardoso et al, Ann Oncol 2018

Visceral crisis

- **Visceral crisis**:
  - severe organ dysfunction as assessed by signs and symptoms, laboratory studies and rapid progression of disease
    - Not merely visceral disease
    - Need for rapid tumor shrinkage
    - Therapy at progression probably not possible

Cardoso et al, Ann Oncol 2018

Endocrine resistance

- **Primary endocrine resistance**:
  - relapse while on the first 2 years of adjuvant ET, or PD within first 6 months of first-line ET for ABC, while on ET.
- **Secondary endocrine resistance**:
  - relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or PD ≥ 6 months after initiating ET for ABC, while on ET.

Cardoso et al, Ann Oncol 2018

Advanced breast cancer

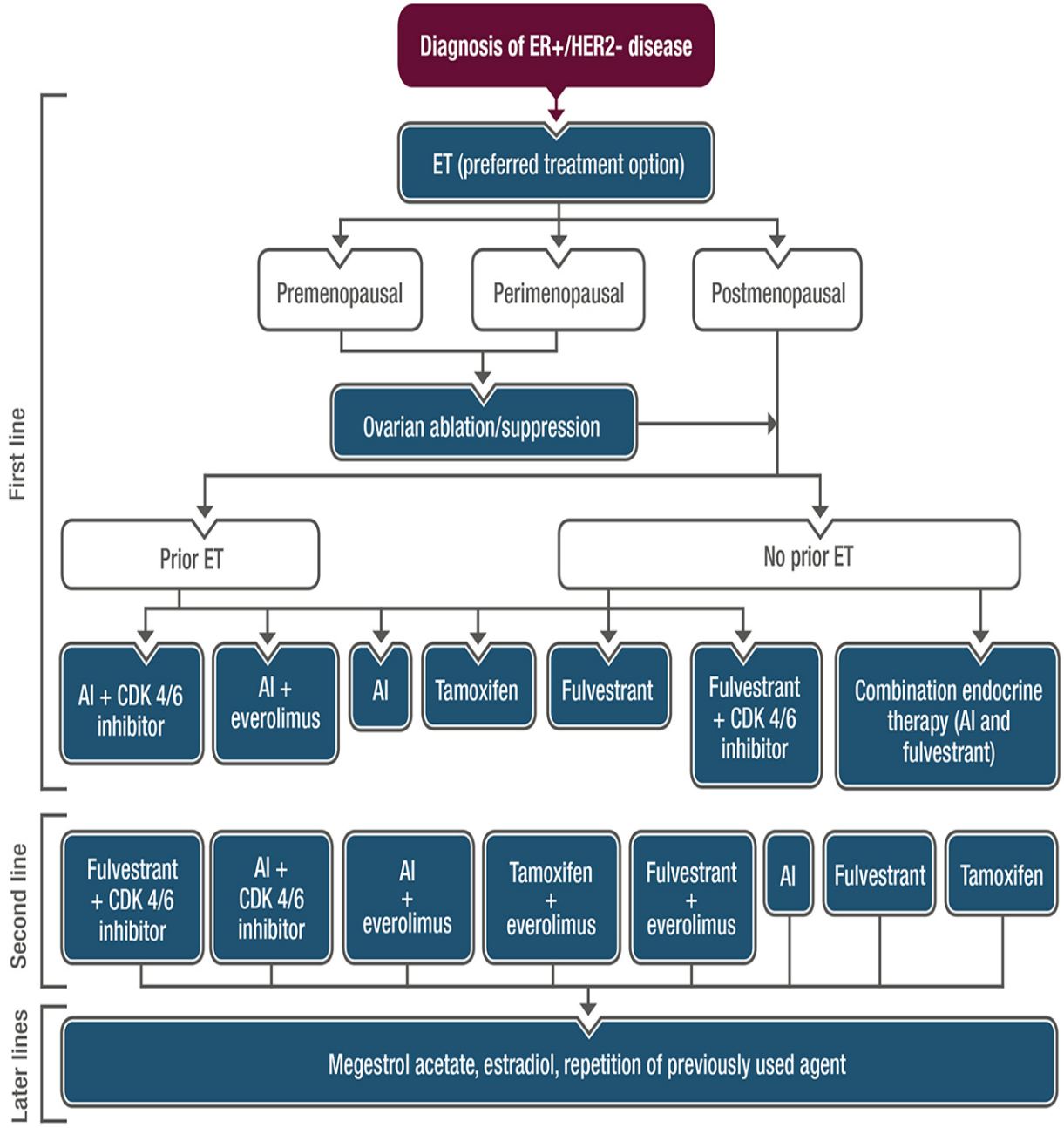
- **Treatment choice should take into account**
  - HR and HER2 status,
  - previous therapies and their toxicities,
  - DFI,
  - tumour burden (defined as number and site of metastases),
  - biological age,
  - PS,
  - comorbidities (including organ dysfunctions),
  - menopausal status (for ET),
  - need for a rapid disease/symptom control,
  - socio-economic and psychological factors,
  - patient's preferences.

Cardoso et al, Ann Oncol 2018

CLINICAL PRACTICE GUIDELINES

Treatment of ER-positive / HER2-negative ABC

Endocrine Therapy (ET)



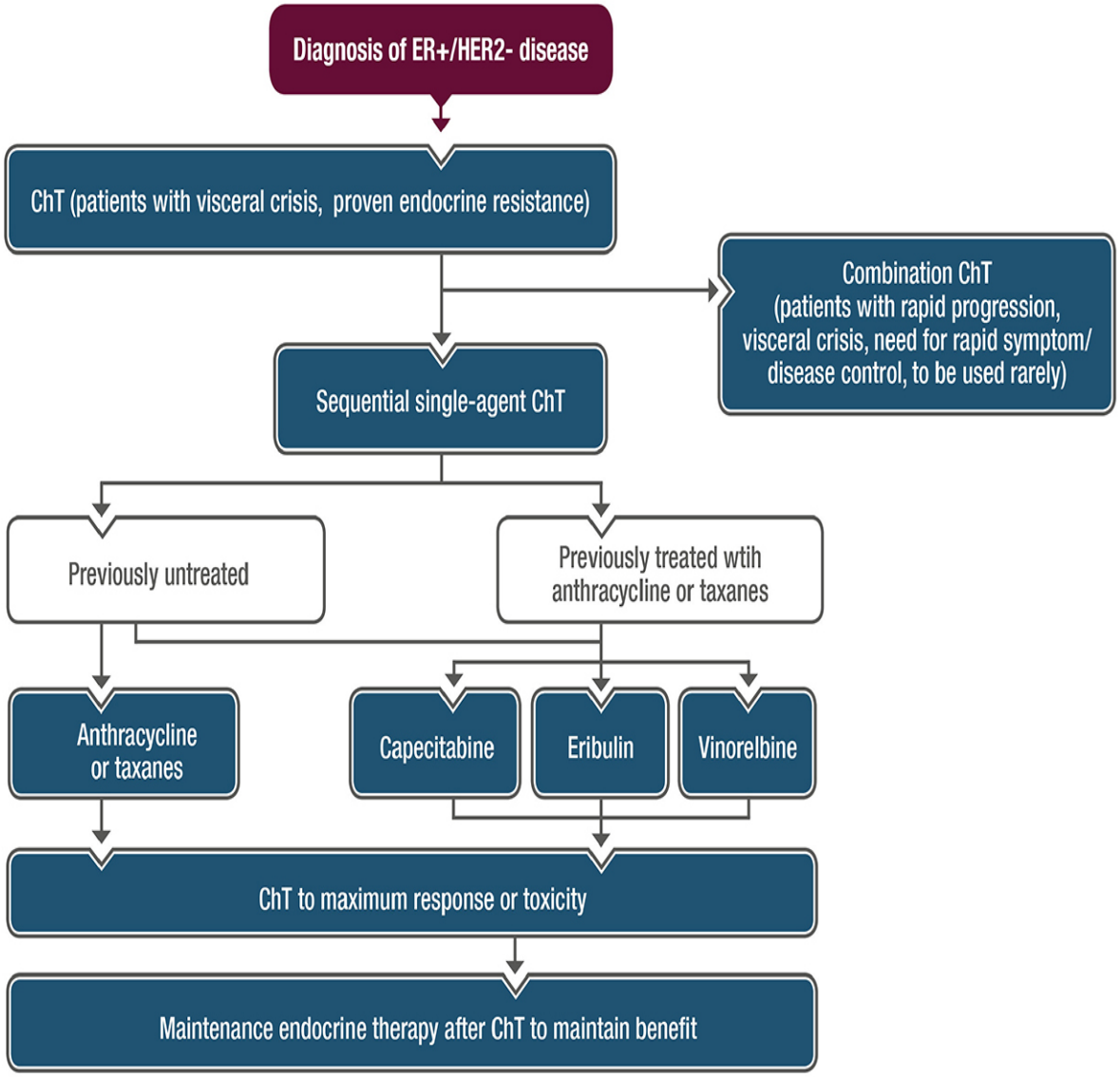
Genetic counselling and *BRCA* mutation status testing to be discussed with selected patients

ESMO

CLINICAL PRACTICE GUIDELINES

Treatment of ER-positive / HER2-negative ABC

Chemotherapy (ChT)

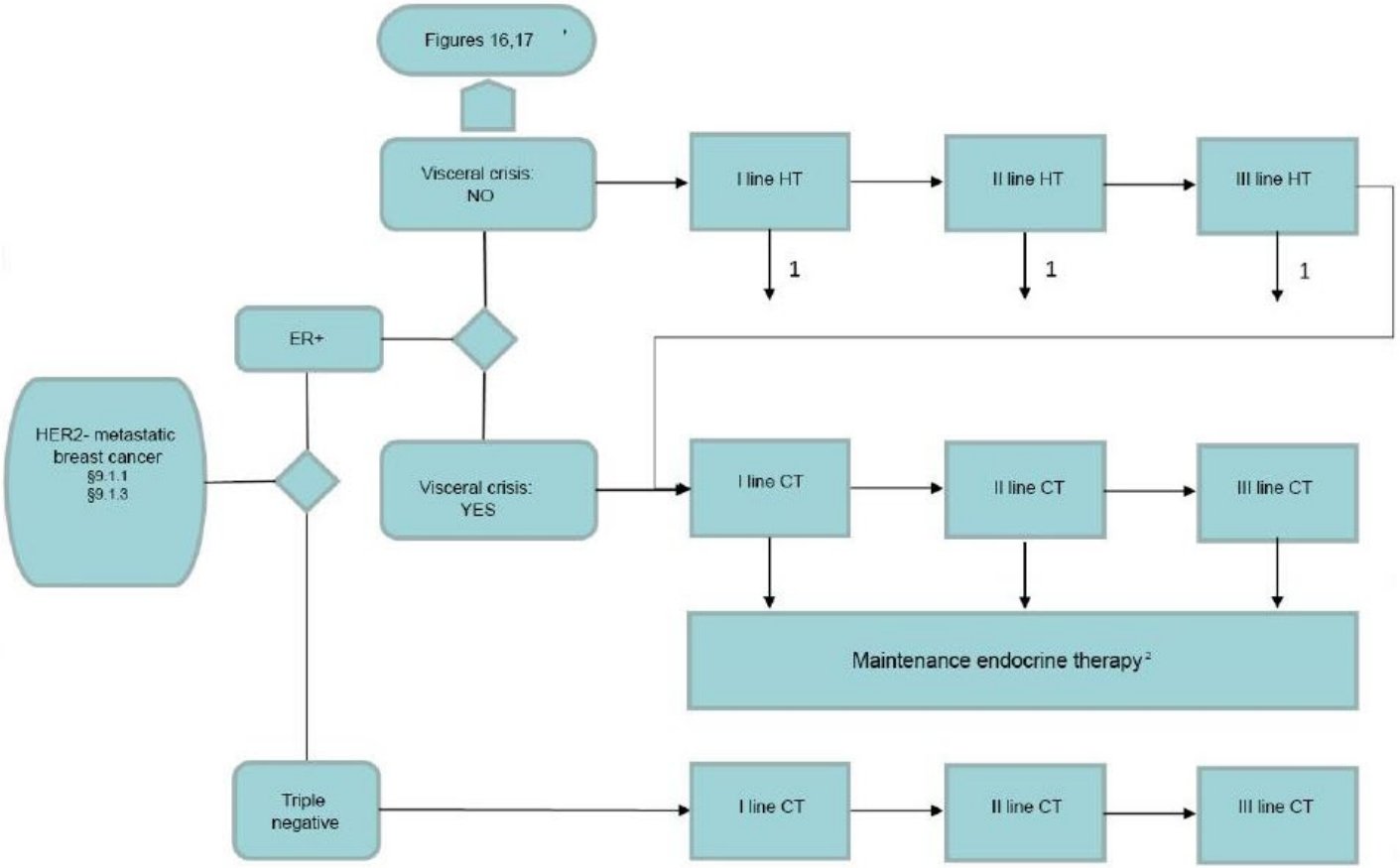


Genetic counselling and *BRCA* mutation status testing to be discussed with selected patients

ESMO

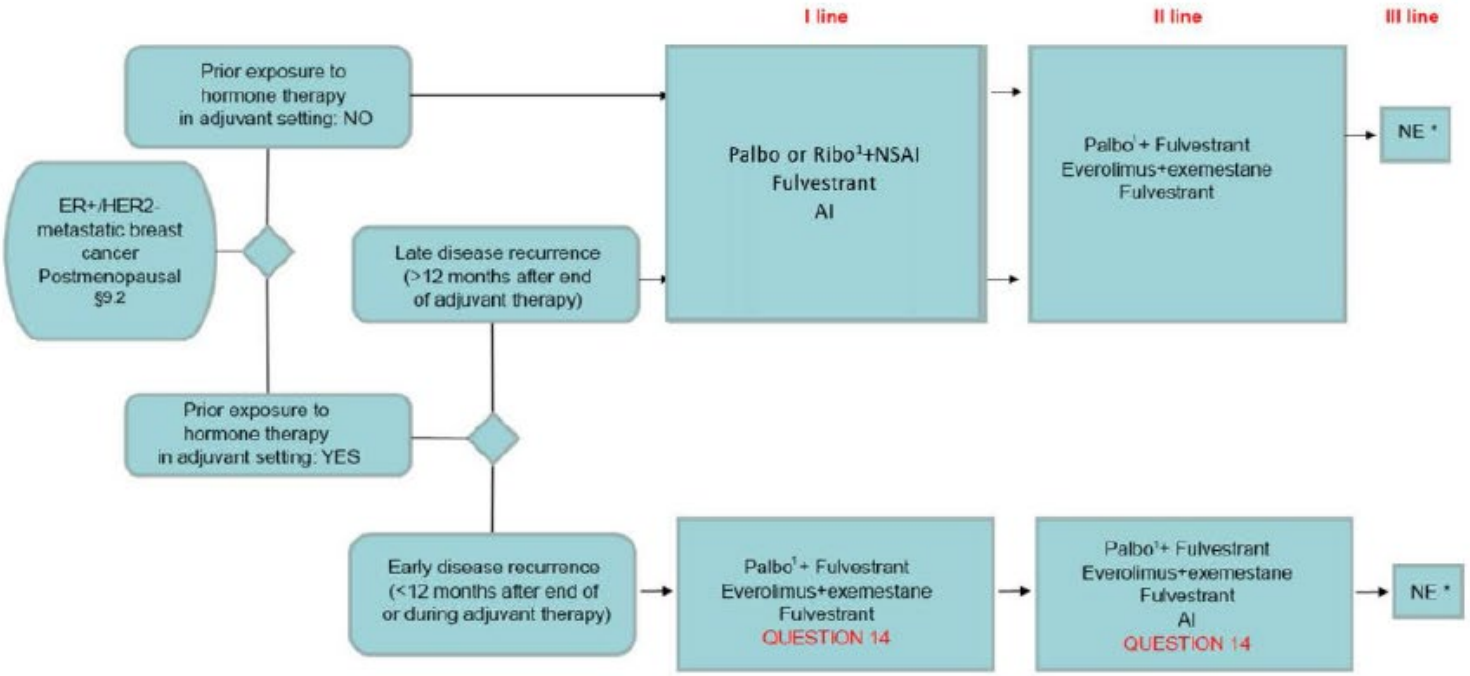
AIOM guidelines 2018

Figure 12 - HER2-NEGATIVE METASTATIC BREAST CANCER: Medical therapy based on pathological and clinical characteristics



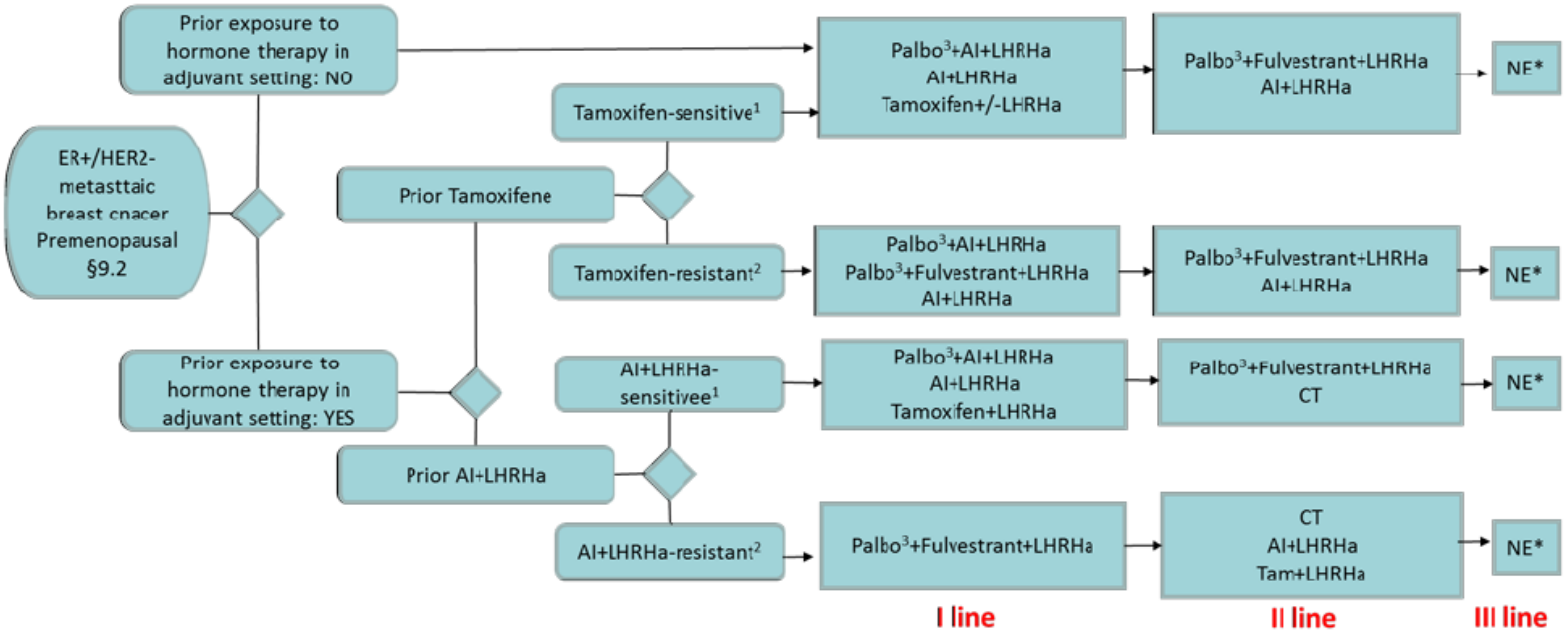
AIOM guidelines 2018

Figure 14 - ER+/HER2- METASTATIC BREAST CANCER: Postmenopausal hormone therapy



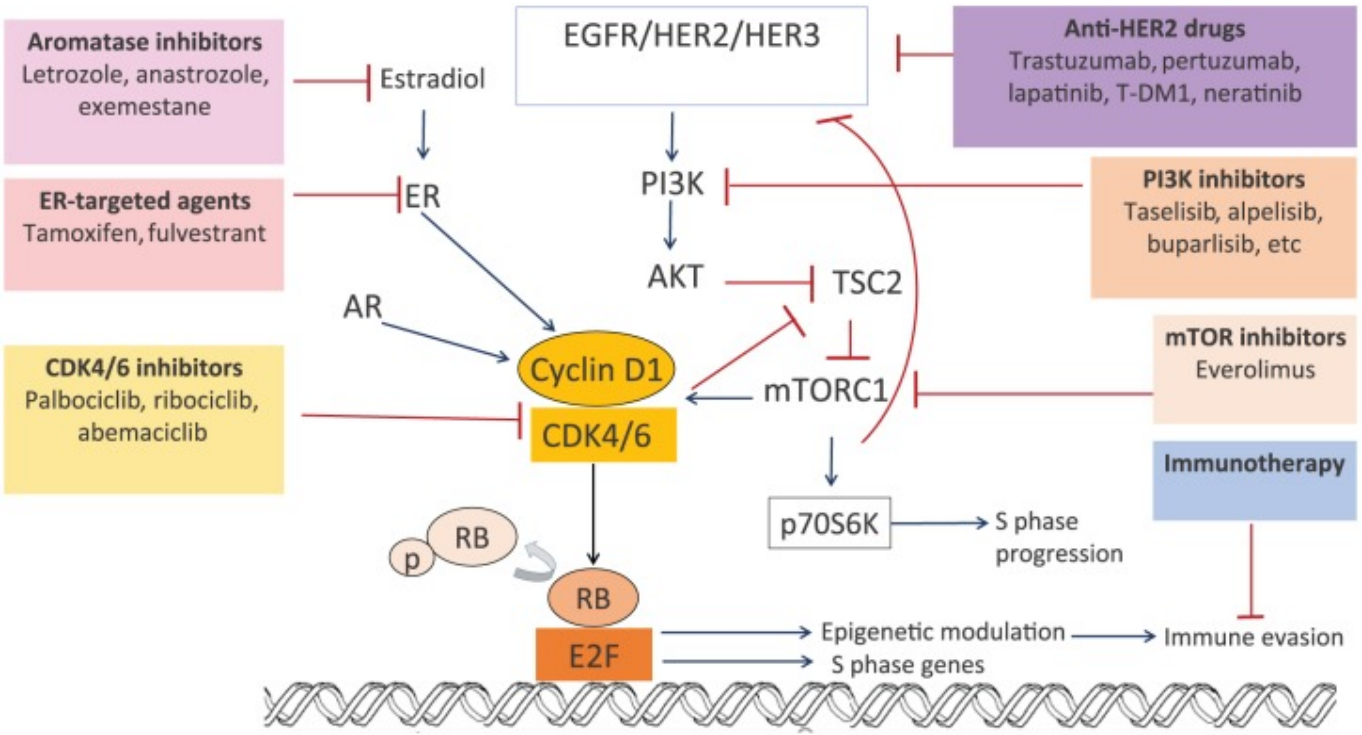
AIOM guidelines 2018

Figure 13 – ER+/HER2- METASTATIC breast cancer: Hormone therapy in premenopausal women



Note 1 - Interval between end of adjuvant treatment and occurrence of metastases > 12 months
Note 2 - Occurrence of metastases during adjuvant treatment or within 12 months after the end of adjuvant treatment

Cyclin D1–CDK4/6–RB pathway in BC



Pernas et al, Ther Adv Med Oncol 2018

CDK inhibitors

- **Palbociclib**
  - IC 50= 11mM (CDK4), 15mM (CDK6)
  - 125 mg QD 3 weeks on 1 week off
  - Neutropenia

- **Ribociclib**
  - IC 50= 10mM (CDK4), 40mM (CDK6)
  - 600 mg QD 3 weeks on 1 week off
  - Neutropenia, liver tox, QT

- **Abemaciclib**
  - IC 50= 2mM (CDK4), 10mM (CDK6) → more potent
  - 150 mg BID
  - Diarrhea

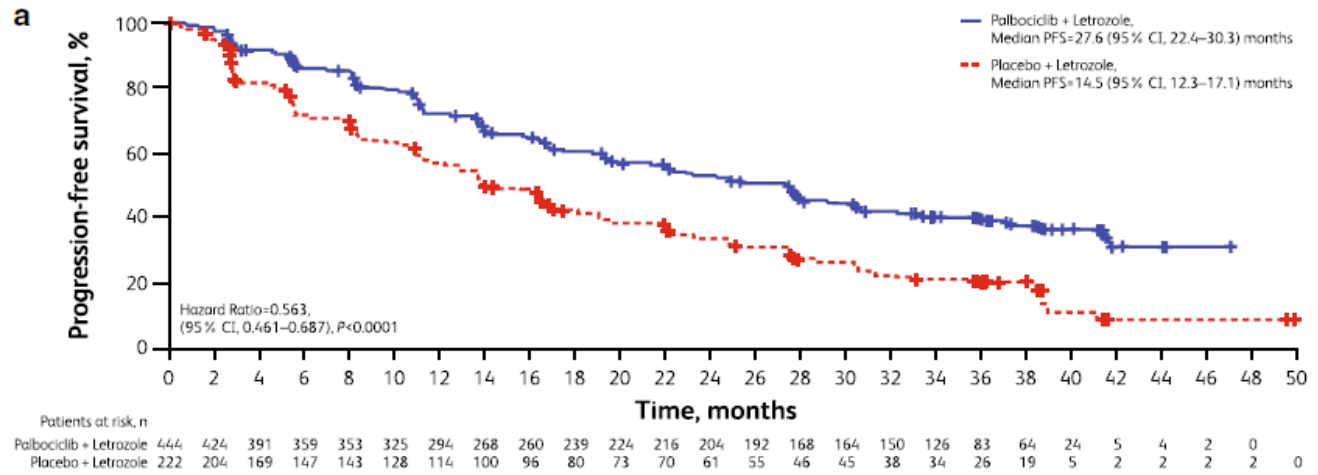
First-(ET)line CDKi trials

	PALOMA-1	PALOMA-2	MONALEESA-2	MONARCH-3	MONALEESA-7
Design	Phase 2	Phase 3	Phase 3	Phase 3	Phase 3
Treatment arms	Letro +/- palbo	Letro +/- palbo	Letro +/- ribo	NSAI +/- abema	Tam/NSAI + LHRH +/- ribo
Patients (n)	165	666	668	493	672
Median PFS (m)	20.2 vs 10.2	27.6 vs 14.5	25.3 vs 16	28.8 vs 14.7	23.8 vs 13
PFS HR	0.49	0.56	0.56	0.54	0.55
RR (%)	55 vs 49	55 vs 44	53 vs 37	59 vs 44	51 vs 36
CBR (%)	81 vs 58	85 vs 70	80 vs 73	78 vs 71.5	80 vs 67

External consistency!

Palbociclib + letrozole: 1° line

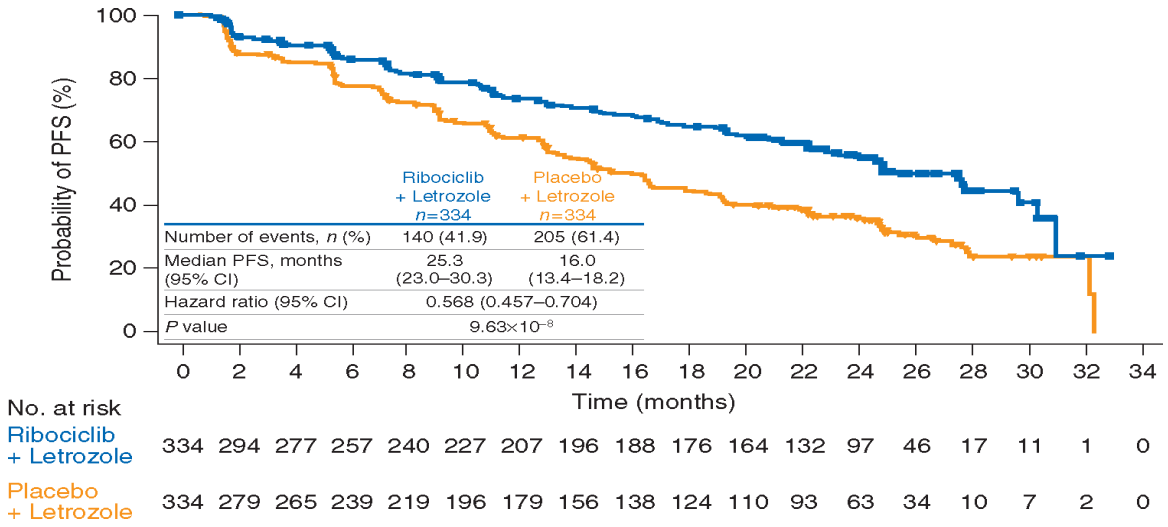
- Paloma 2 trial
  - 38 months follow-up update
    - PFS: HR=0.56
      - Median 27.6 vs 14.5 m



Rugo et al. Breast Cancer Res Treat 2019

Ribociclib + letrozole: 1° line

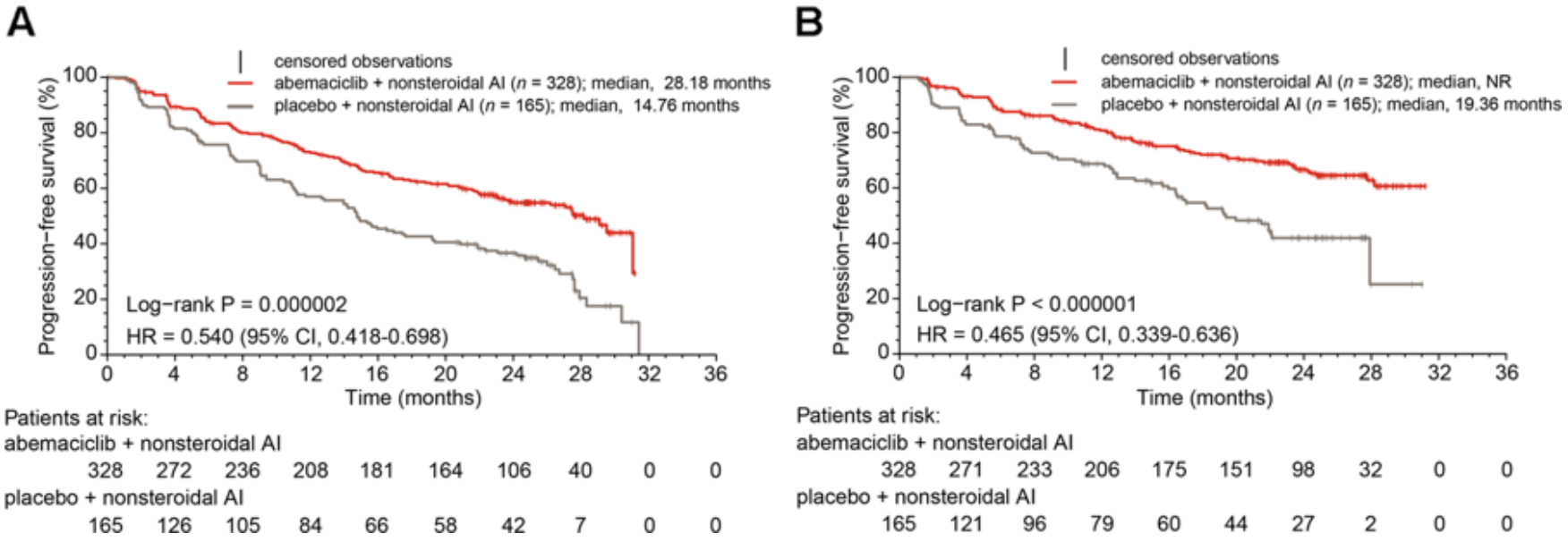
- Monaleesa 2 trial
  - 26.4 months follow-up update
    - PFS: HR=0.56
      - Median 25.3 vs 16.9 m



Hortobagy et al, Ann Oncol 2018

Abemaciclib + letrozole: 1° line

- Monarch 3 trial
  - 26.7 months follow-up update
    - PFS: HR=0.54
      - Median 28.8 vs 14.7 m

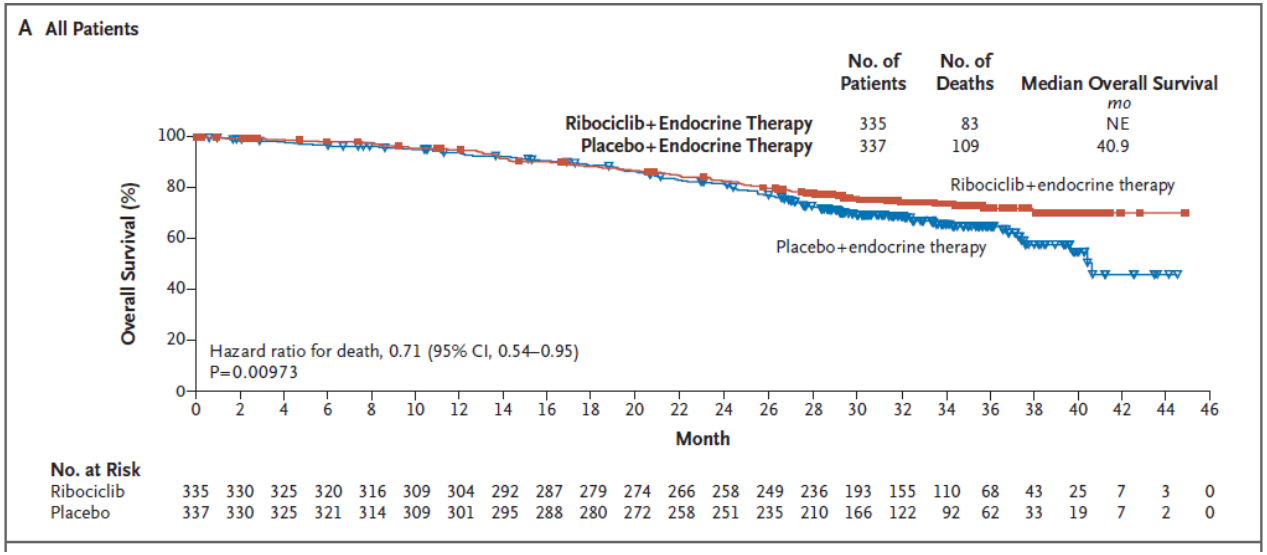


A: investigator assessed
B: central review

Johnston S et al, NPJ Breast Cancer 2019

Ribociclib + Ais/Tam + GnRH in premenopasal: 1° ET line

- Monaleesa 7 trial
  - 14% previous CT; median follow-up 34.6 m
  - OS benefit



42 m: 70.2% vs 46.0% → +24.2 %

Im SA et al, NEJM 2019

Ribociclib + Ais/Tam + GnRH in premenopasal: 1° ET line

- Monaleesa 7 trial
  - First subsequent therapy

Table 2. First Subsequent Antineoplastic Therapy among Patients Who Discontinued the Trial Regimen.

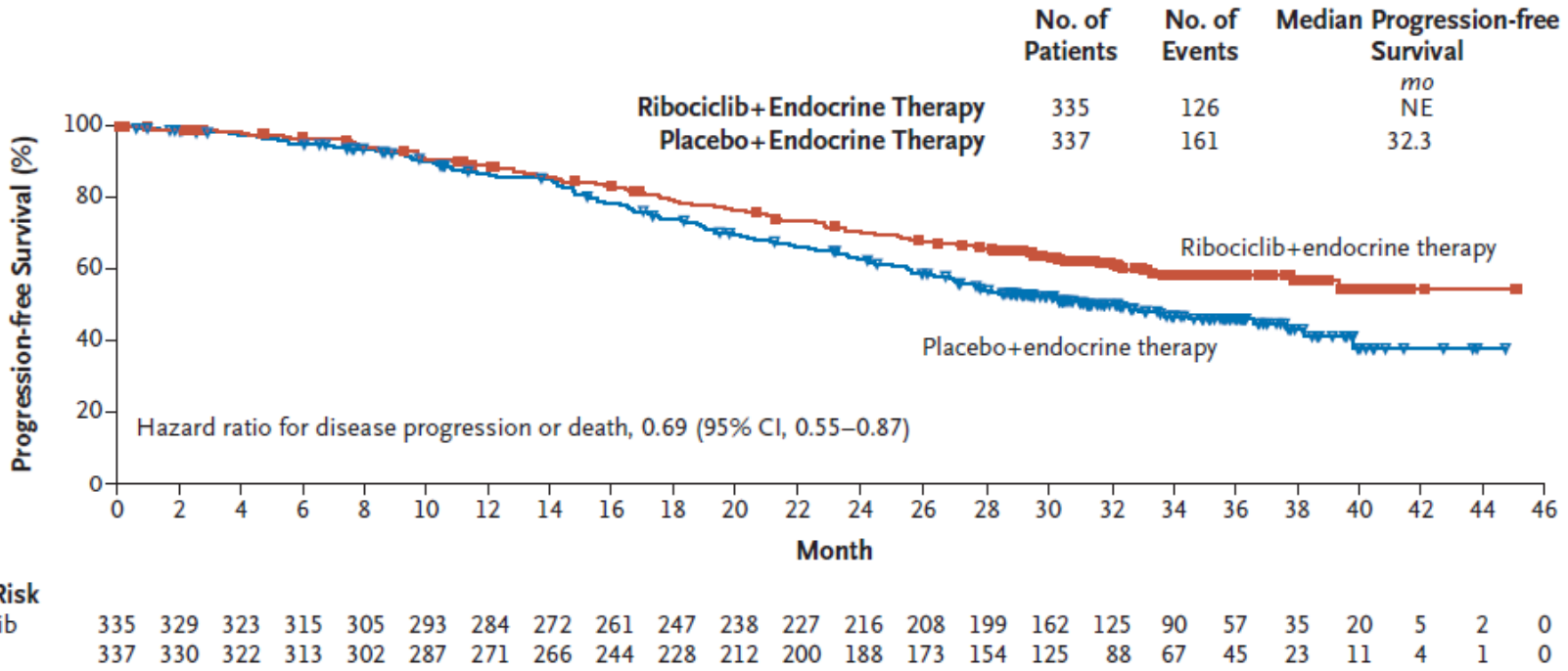
Variable	Ribociclib Group (N=335)	Placebo Group (N=337)
No. of patients who discontinued the trial regimen	219	280
Patients who received any subsequent therapy — no. (%)	151 (68.9)	205 (73.2)
Chemotherapy alone	49 (22.4)	80 (28.6)
Chemotherapy plus hormone therapy or other therapy*	18 (8.2)	22 (7.9)
Hormone therapy alone	49 (22.4)	57 (20.4)
Hormone therapy plus other therapy†	31 (14.2)	41 (14.6)
Other	4 (1.8)	5 (1.8)

* This category includes patients who received chemotherapy in combination with any nonchemotherapy.
† This category includes patients who received hormone therapy plus another medication without chemotherapy.

Im SA et al, NEJM 2019

Ribociclib + Ais/Tam + GnRH in premenopasal: 1° ET line

- Monaleesa 7 trial
  - 2° line PFS



Im SA et al, NEJM 2019

ET + CDK inhibitors: 1° ET line

- Benefit in terms of
  - RR
  - PFS
    - Similar for all CDK inhibitors
    - No relevant difference in subgroups
      - Even bone only disease
  - OS
    - ribociclib in pre/perimenopausal pts
      - PFS benefit → OS benefit
      - No detrimental effect on second line therapies

First line luminal ABC

- **CDK inhibitors + ET should be considered a standard in first line**
  - No CT regimen better than ET+ CDKi
    - Network meta-analysis

Giuliano et al, Lancet Oncol 2019

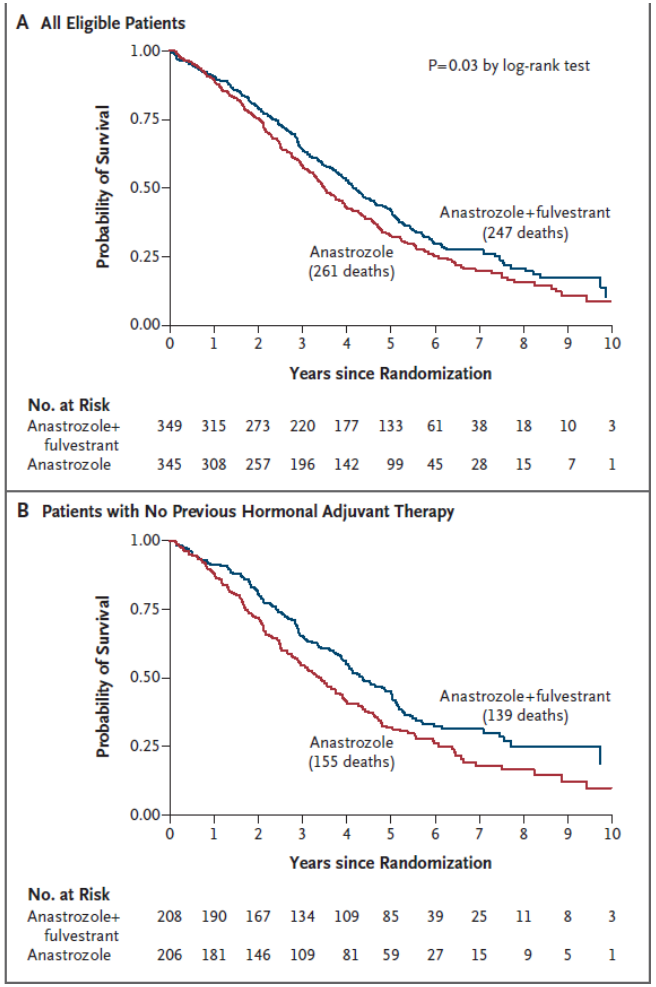
- **Is there a subset of patients deriving no benefit from ET+CDKi?**
  - A priori not

- **Could a subset of patients be spared from CDKi?**
  - To be further investigated
  - CDKi seems to be effective but more toxic in elderly patients
    - Be careful of compliance and drug interactions

Singh H et al, SABCS 2017

Fulvestrant + anastrozole: 1° line

- S0226 trial 7 yrs update
  - Phase III Fulv+Ana vs Ana
  - OS: HR =0.82, p=0.03
    - Median 49.8 vs 42 m
  - Higher benefit in pts who were not previously treated with adjuvant Tam
    - HR=0.73, 95% CI 0.58-0.92
      - Median 50.2 vs 40.3 m
    - Interaction test p=0.09
  - Higher benefit in endocrine sensitive pts (90%)
    - HR=0.79, p <0.05
      - Median 50.7 vs 42.3m
    - No significant interaction test
- Some concerns
  - Fulvestrant dose
  - Patient enrollment 2004-2009
  - Previous adjuvant Tam (40%)
  - HER-2 pos: 8-10%



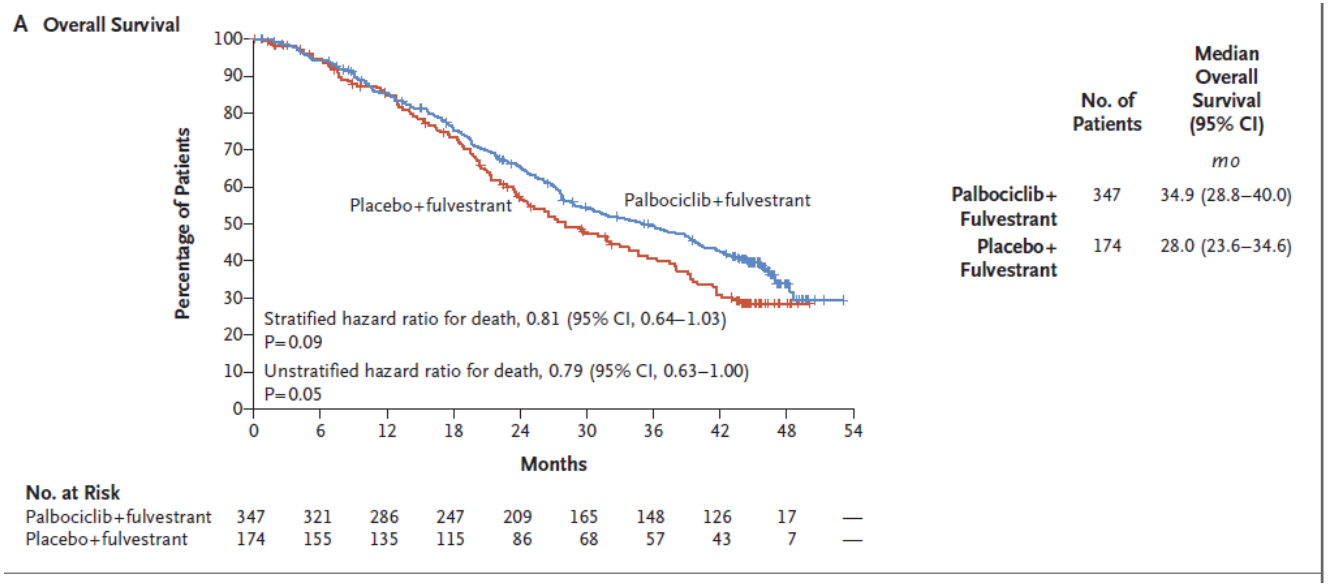
Mehta et al, NEJM 2019

Further lines CDKi trials

	PALOMA-3	MONARCH-2	MONALEESA-3	MONARCH-1
Design	Phase-3, 2°-… line	Phase-3, 2° line	Phase-3, 1-2° line	Phase-2
Treatment arms	F +/- palbo	F +/- abema	F +/- ribo	abema
Patients n	521	669	725	132
Patient population	≤ 1 prior CT for ABC; any previous ET line	No prior CT for ABC; 1 previous ET line	No prior CT for ABC; ≤ 1 ET line (49% 1° line)	≤ 2 prior CT for ABC; any previous ET line
Median PFS (m)	9.5 vs 4.6 HR=0.46	16.4 vs 9.3 HR=0.55	20.5 vs 12.8 HR=0.59	6.0
ORR (%)	25 vs 11	35 vs 16.1	40.9 vs 28.7	20
CBR (%)	67 vs 40	72 vs 56	70.2 vs 62.8	42.4

Palbociclib + fulvestrant: further lines

- Paloma 3 trial
  - OS data
    - Median follow-up 44m
    - ITT: mOS= 34.9 vs 28.0; HR= 0.81 (95% CI, 0.64 to 1.03; P=0.09)

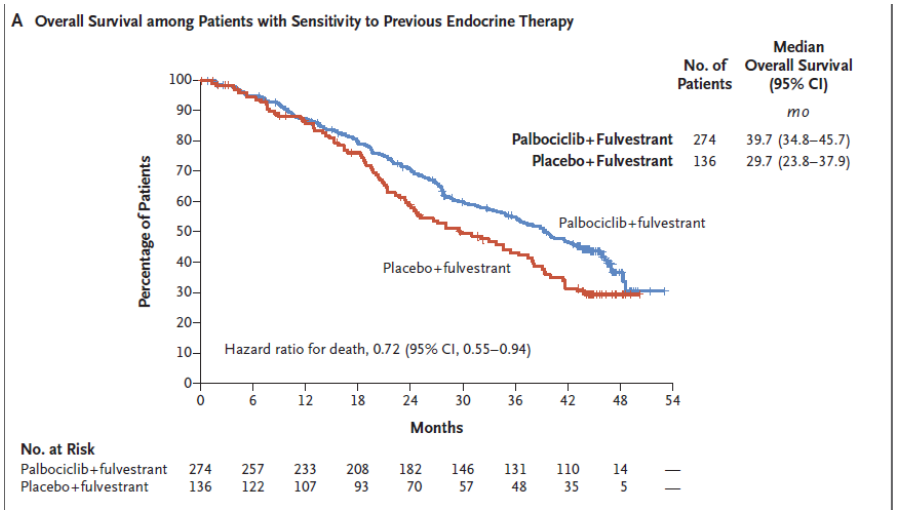


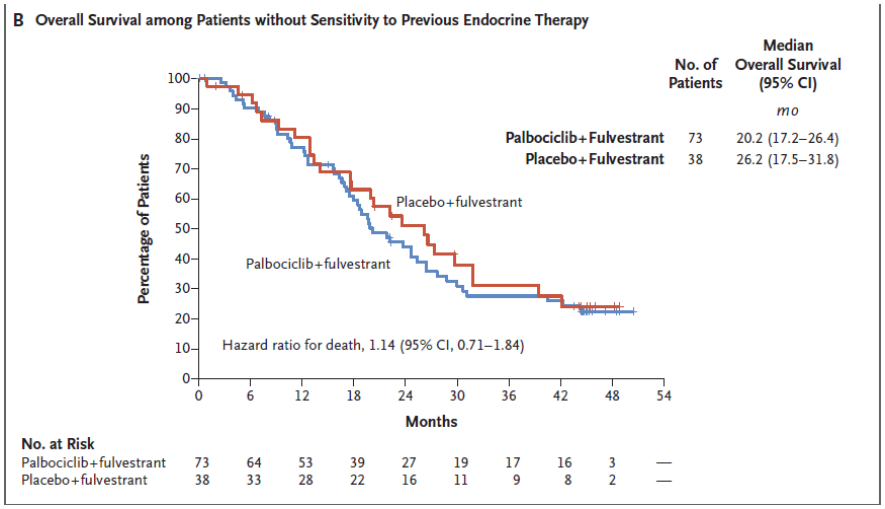
Cross-over with CDKi in 16% of placebo arm

Turner NC et al, NEJM 2018

Palbociclib + fulvestrant: further lines

- Better in endocrine sensitive
  - 79% of pts
    - HR: 0.72
    - mOS: 29.7 vs 39.7
  - No OS difference in endocrine not sensitive
- Better in postmenopausal
  - 79% of pts
    - HR:0.73
  - Higher not endocrine sensitive in premenopausal
    - 32% vs 19%



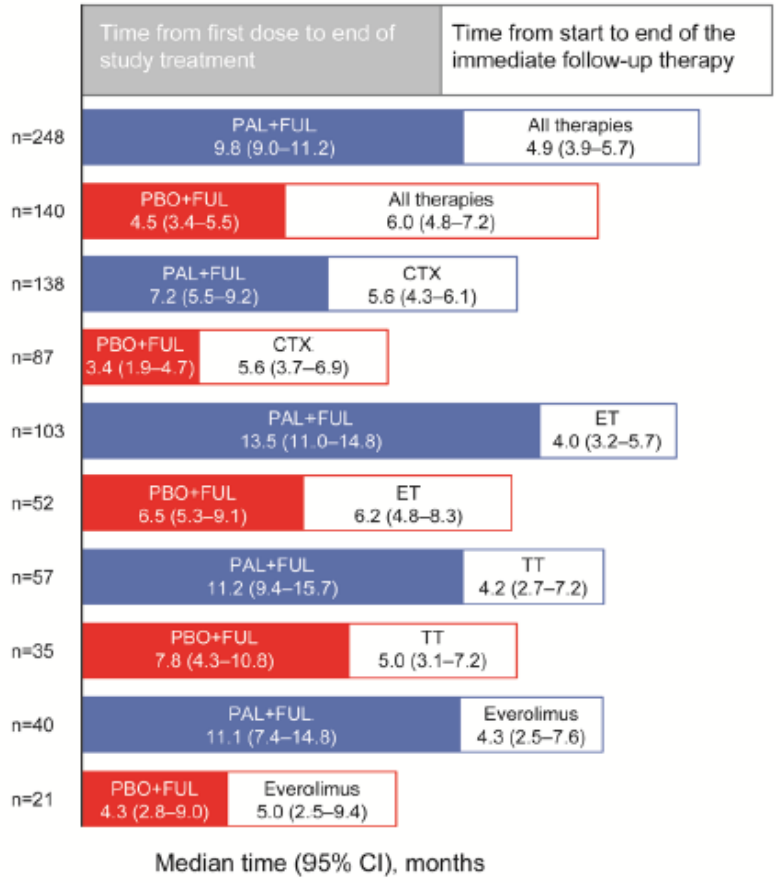


Turner NC et al, NEJM 2018

Palbociclib + fulvestrant: further lines

- At progression
  - 40% further ET
- No detrimental effect of CDKi in further therapy efficacy
- Time to CT (from Random)
  - 17 vs 8 m

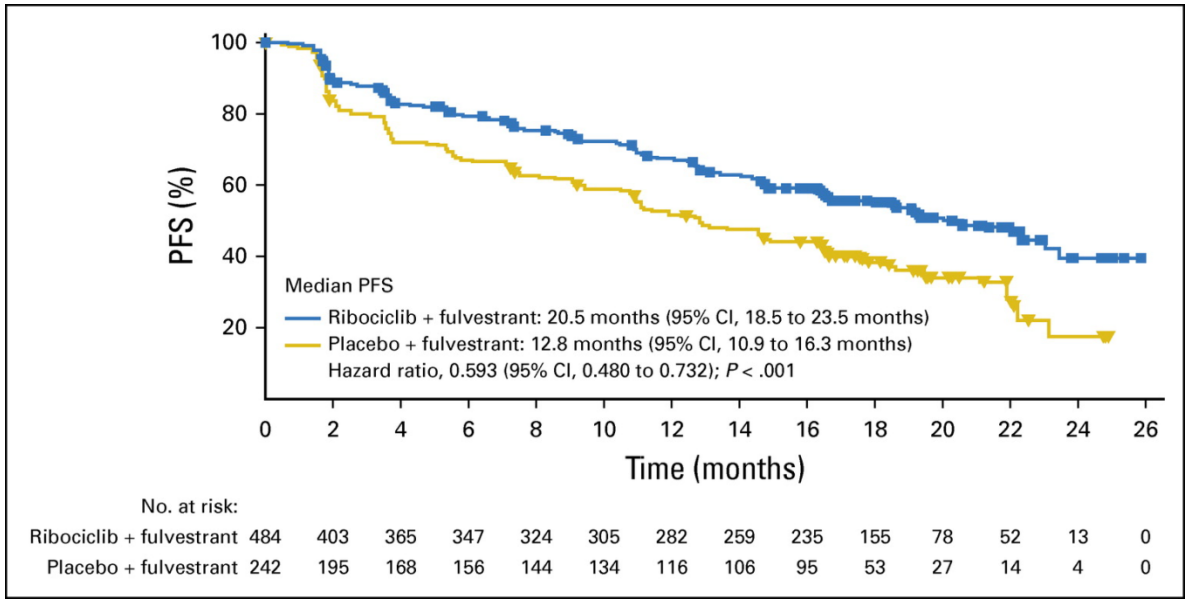
Fig. S5. Kaplan-Meier Estimated Median Duration of Immediate Subsequent Line of Therapy Postprogression. CI=confidence interval; ET=endocrine therapy; FUL=fulvestrant; PAL=palbociclib; PBO=placebo; TT=targeted therapy.



Turner NC et al, NEJM 2018 suppl

Ribociclib + fulvestrant: further lines

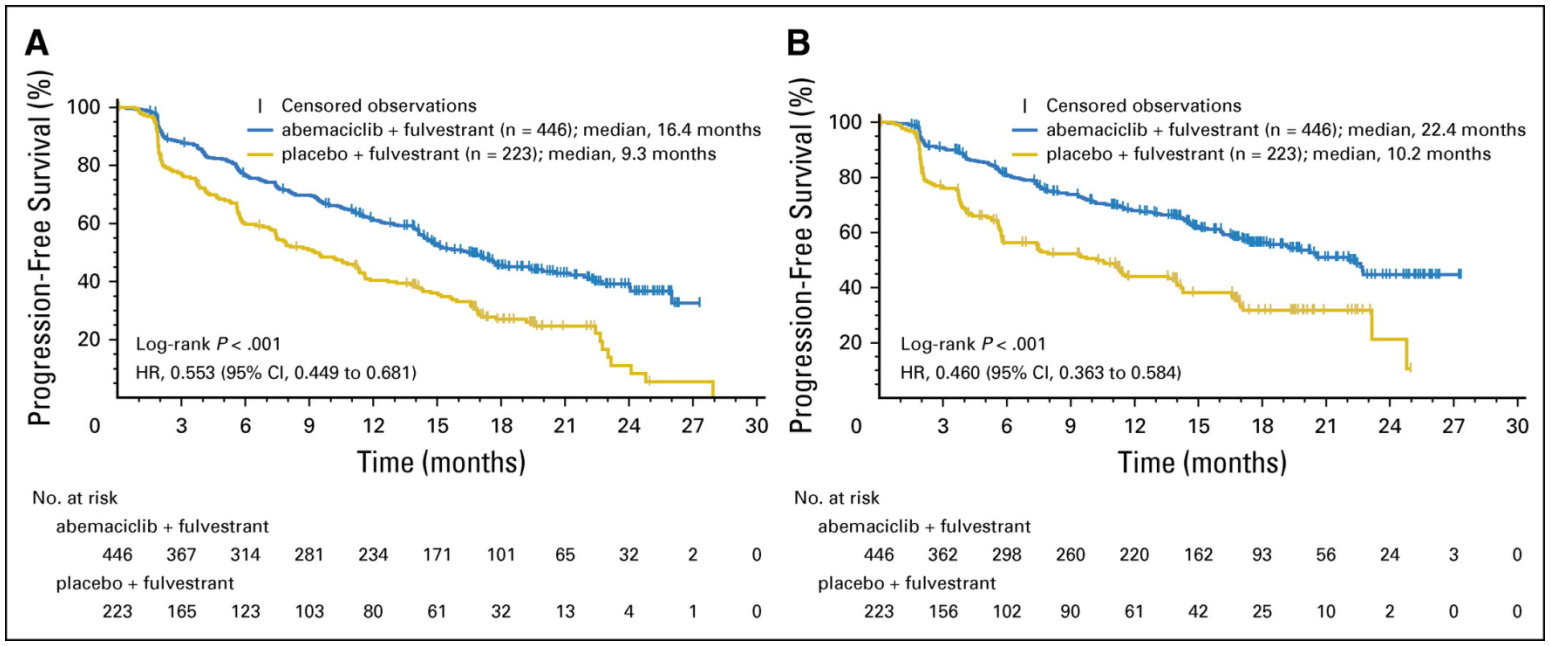
- Monaleesa 3 trial
  - **Press release: improvement in OS**
  - No prior ET: 49%; *de novo* ABC: 20%
  - PFS: HR=0.59



Slamon J et al, J Clin Oncol 2018

Abemaciclib + fulvestrant: further lines

- Monarch 2 trial
  - **Press release: improvement in OS**
  - PFS (inv): HR=0.55



Sledge et al, J Clin Oncol 2017

After CDK inhibitor failure?

- **Lack of high quality evidence in this setting**
- **A standard still not exists**
  - Resistance deserves further investigation
    - Loss of Rb1, CyclineE, AKT mut
  - CDKi beyond progression still under investigation
- **Everolimus + exemestane could be an option**
  - BOLERO-2 trial
    - Final PFS (inv) analysis: 7.8 vs 3.2m
- **Chemotherapy in case of**
  - Visceral crisis
  - Low probability of endocrine sensitivity
    - Sequential monotherapy

Metronomic chemotherapy

- Metronomic CT is a reasonable treatment option for patients not requiring rapid tumour response.
  - CM or other regimens are being evaluated (e.g. capecitabine and vinorelbine).
    - VICTOR-2: cape + vnb
      - CBR= 45.7% (1° line), 51.1% (2° line)

Cazzaniga et al, BCRT 2016

- Randomised trials are needed to accurately compare metronomic ChT with standard dosing regimens.

Cardoso et al, Ann Oncol 2018

CONCLUSIONS

- **ET first option in most Luminal (HER-2 neg) ABC**
  - Choose wisley taking into consideration tumor and patient's characteristics
  - Treat premenenopausal pts with OFS + ET as for postmenopausal
- **CDK inhibitors impact on OS**
  - Standard
- **After CDK inhibitors a standard still not exists**
  - Consider available options
- **Modest improvement in CT benefit in the last years**
  - Sequential single agents