Mazandaran University of Medical Sciences

Endocrine treatment for ER+ MBC

Dr. Mohammad Eslamijouybari
Hematologist & Medical Oncologist

Inserm

ESMO FACULTY
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE
European Society for Medical Oncology

AROME
CORE FACULTY
Association de Radiothérapie et d'Oncologie de laMéditérannéE
« Knowledge is the only value that increases with sharing »

ESO European School of Oncology
Learning to care
CORE FACULTY

HOW TO TREAT ER+/HER2 neg (LUMINAL) MBC:

Main Questions:

1. Do we need Chemotherapy (CT)?
2. If Endocrine Therapy (ET): which agent?
3. Is a targeted agent also necessary or is ET alone sufficient?
4. If CT: combination vs. sequential monotherapy?
5. If CT: which agent(s)?

ABC, advanced breast cancer; ER+, estrogen receptor-positive; HER2, human epidermal growth factor receptor-2.

Patients with low (1-10%) ER (and PR) positive, HER2 negative ABC should not be considered for endocrine therapy exclusively.

Patients with low (1-10%) ER (and PR) positive, HER2 negative ABC can be considered as patients with triple negative ABC, for clinical trials.

(LoE/GoR: III/B) (95%)

PRIMARY ENDOCRINE RESISTANCE is defined as:

Relapse while on the first 2 years of adjuvant ET, or

PD within first 6 months of 1st line ET for MBC, while on ET

SECONDARY (ACQUIRED) ENDOCRINE RESISTANCE is defined as:

Relapse while on adjuvant ET but after the first 2 years, or

Relapse within 12 months of completing adjuvant ET, or

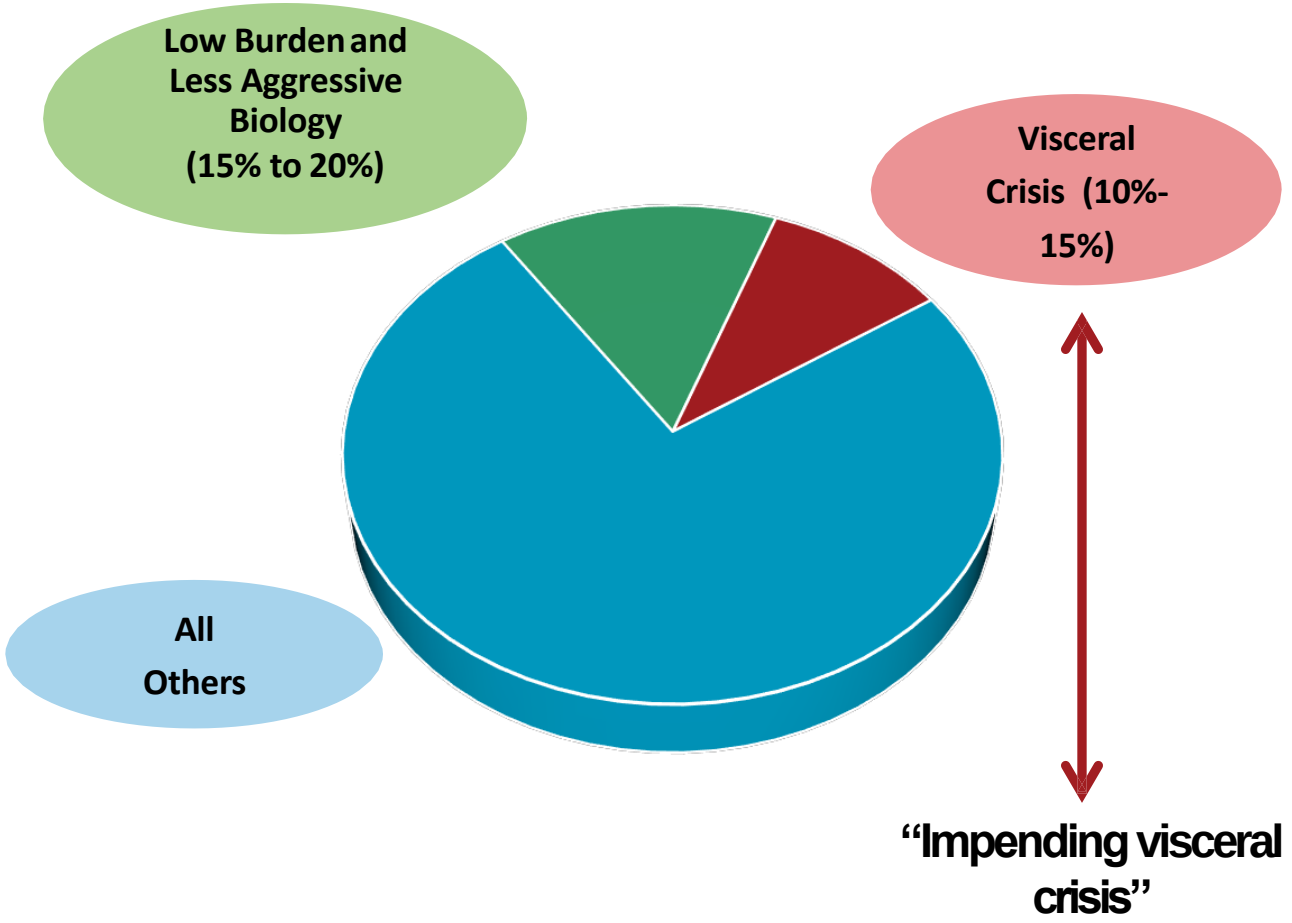
PD ≥ 6 months after initiating ET for MBC, while on ET

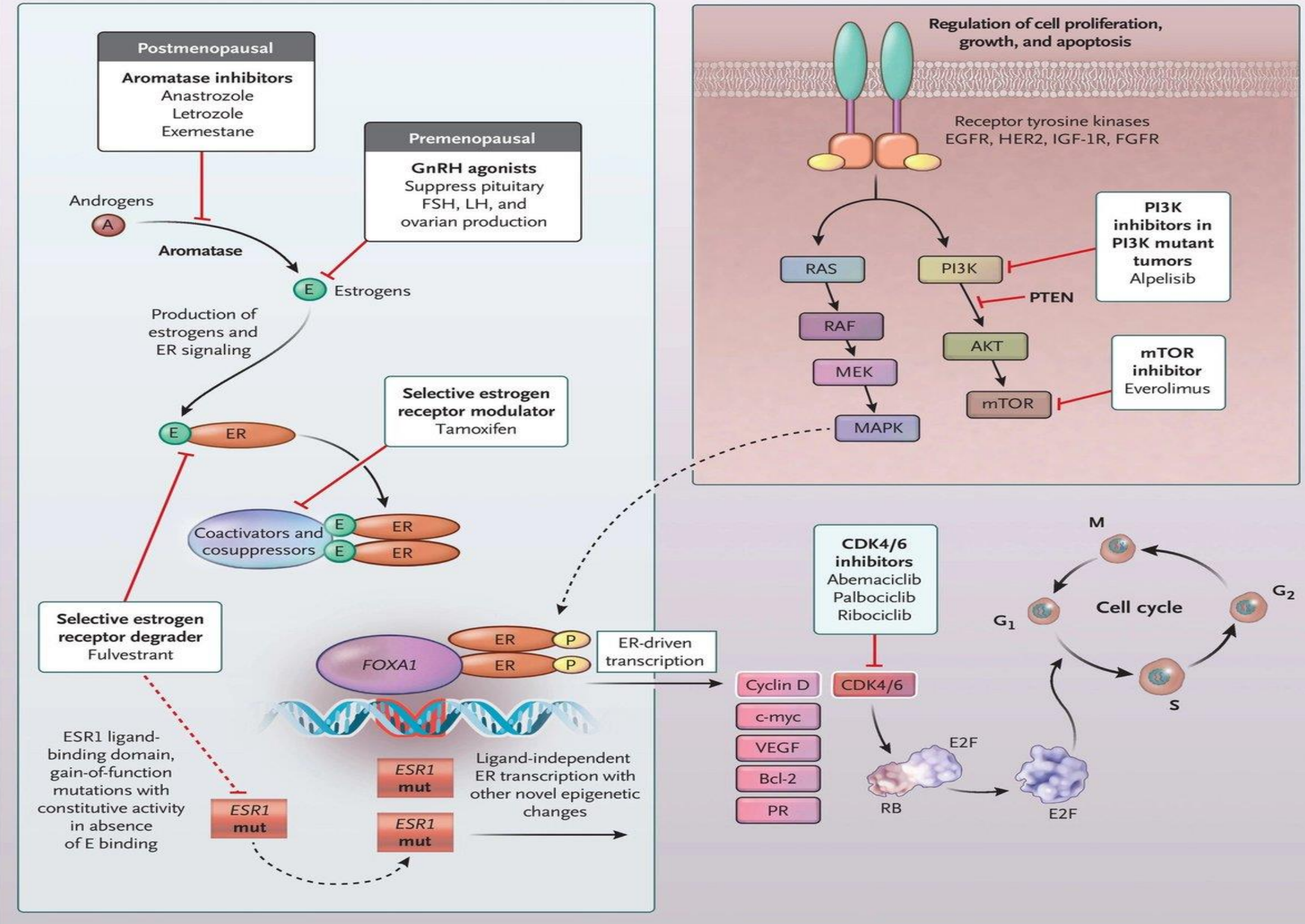
(LoE: Expert opinion/NA) (67%)

Note: resistance is a continuum and these definitions help mainly clinical trials and not necessarily clinical practice

Clinical Heterogeneity of Luminal Tumours

Implications for therapeutic decisions




Postmenopausal
Aromatase inhibitors
Anastrozole
Letrozole
Exemestane
Premenopausal
GnRH agonists
Suppress pituitary FSH, LH, and ovarian production
Androgens
A
Aromatase
E
Estrogens
Production of estrogens and ER signaling
E
ER
Selective estrogen receptor modulator
Tamoxifen
Coactivators and cosuppressors
E
ER
E
ER
Selective estrogen receptor degrader
Fulvestrant
FOXA1
ER
P
ER
P
ER-driven transcription
ESR1 ligand-binding domain, gain-of-function mutations with constitutive activity in absence of E binding
ESR1 mut
ESR1 mut
Ligand-independent ER transcription with other novel epigenetic changes
Regulation of cell proliferation, growth, and apoptosis
Receptor tyrosine kinases
EGFR, HER2, IGF-1R, FGFR
RAS
RAF
MEK
MAPK
PI3K
PTEN
AKT
mTOR
PI3K inhibitors in PI3K mutant tumors
Alpelisib
mTOR inhibitor
Everolimus
CDK4/6 inhibitors
Abemaciclib
Palbociclib
Ribociclib
Cyclin D
CDK4/6
c-myc
VEGF
Bcl-2
PR
RB
E2F
E2F
M
G1
G2
S
Cell cycle

ER POSITIVE / HER-2 NEGATIVE MBC

Many trials in ER+ ABC have not included pre-menopausal women.
Despite this, we recommend that young women with ER+ ABC should have adequate ovarian suppression or ablation (OFS/OFA) and then be treated in the same way as post-menopausal women with endocrine agents with or without targeted therapies.
(LoE/GoR: Expert Opinion/A) (95%)

Future trials exploring new endocrine-based strategies should be designed to allow for enrollment of both pre- and post-menopausal women, and men.

(LoE/GoR: Expert Opinion/A) (92%)

ADEQUATE OVARIAN FUNCTION SUPPRESSION (OFS) IN THE CONTEXT OF MBC

Adequate OFS for ABC premenopausal patients can be obtained through bilateral ovariectomy, continuous use of LHRH agonists or ovarian function ablation through pelvic radiotherapy (this latter is not always effective and therefore is the least preferred option). (LoE/GoR: I/A) (85%)
If a LHRH agonist is used in this age group, it should usually be given on a q4w basis to optimize OFS. (LoE/GoR: II/B) (85%)

Efficacy of OFS must be initially confirmed analytically through serial evaluations of serum estradiol, even in the presence of amenorrhea, especially if an AI is administered. (LoE/GoR: Expert Opinion/B)

ER POSITIVE / HER2 NEGATIVE MBC

Endocrine-based therapy is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis.

(LoE/GoR: I/A) (93%)

* for pre and peri- with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women

VISCERAL CRISIS is defined as **severe organ dysfunction** as assessed by signs and symptoms, laboratory studies, and rapid progression of disease.

Visceral crisis is not the mere presence of visceral metastases but implies **important ORGAN compromise** leading to a clinical indication for the most rapidly efficacious therapy.

Examples:
Liver visceral crisis: rapidly increasing bilirubin >1.5x ULN, in the absence of Gilbert's Syndrome or biliary tract obstruction
Lung visceral crisis: rapidly increasing dyspnea at rest, not alleviated by drainage of pleural effusion

(LoE: Expert opinion/NA) (97%)

ESTIMATION OF % OF PATIENTS: 10 to 15%

ER POSITIVE / HER2 NEGATIVE MBC

The preferred 1st line endocrine agent *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.

(LoE/GoR: I/A) (84%)

*** for pre and peri- with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women**

ER POSITIVE / HER2 NEGATIVE MBC CDK4/6 INHIBITORS

A CDK4/6 inhibitor combined with endocrine therapy is the standard of care for patients with ER+/HER-2 neg ABC, since it achieves substantial PFS benefit, significantly increases OS and either maintains or improves QoL.

The CDK4/6 inhibitor *can be combined with an AI or with Fulvestrant*, *in de novo or recurrent ABC*, in *1st or 2nd line*, and in cases of *primary or secondary resistance* (as defined per ABC guidelines).

This recommendation applies to post-menopausal women, to premenopausal women in combination with an LHRH agonist, and to men preferably in combination with an LHRH agonist.

(LoE/GoR : I/A) (97%)

ER POSITIVE / HER2 NEGATIVE MBC
CDK4/6 INHIBITORS

It remains unclear if CDK4/6 inhibitors should be preferably administered in the 1st line or in the 2nd line setting. However, the majority of panelists preferred giving a CDK4/6 inhibitor in the 1st line setting for the majority of their patients.

(LoE/GoR : Expert Opinion/NA) (100%)

ER POSITIVE / HER-2 NEGATIVE MBC CDK4/6 INHIBITORS

The ESMO-MCBS scores for the use of a CDK4/6 inhibitor combined with endocrine therapy for ABC patients vary according to the setting and drug.
They are the following, with the current available data and FU:

- **PALBOCICLIB + AI 1st line: Efficacy score: 3 (PFS); No improved QoL; MCBS = 3**
- **ABEMACICLIB + AI 1st line: Efficacy score: 3 (PFS); No QoL reported; MCBS = 3**
- **RIBOCICLIB + AI 1st line Post-menopausal: Efficacy score: 3 (PFS); No improved QoL; MCBS: 3**
- **RIBOCICLIB + ET 1st line Pre-menopausal: Efficacy score: 4 (PFS&OS); Improved QoL; MCBS: 5**
- **PALBOCICLIB + Fulvestrant 2nd line: Efficacy score: 3 (PFS&OS); Improved QoL; MCBS: 4**
- **RIBOCICLIB + Fulvestrant (1st , 2nd line): Efficacy score: 4 (PFS&OS); No improvement in QoL; MCBS = 4**
- **ABEMACICLIB + Fulvestrant 2nd line: Efficacy score: 4 (PFS&OS); No QoL reported; MCBS = 4**

(LoE/GoR : I/A) (100%)

Of note, the three CDK4/6 inhibitors have not been compared head-to-head within a clinical trial.

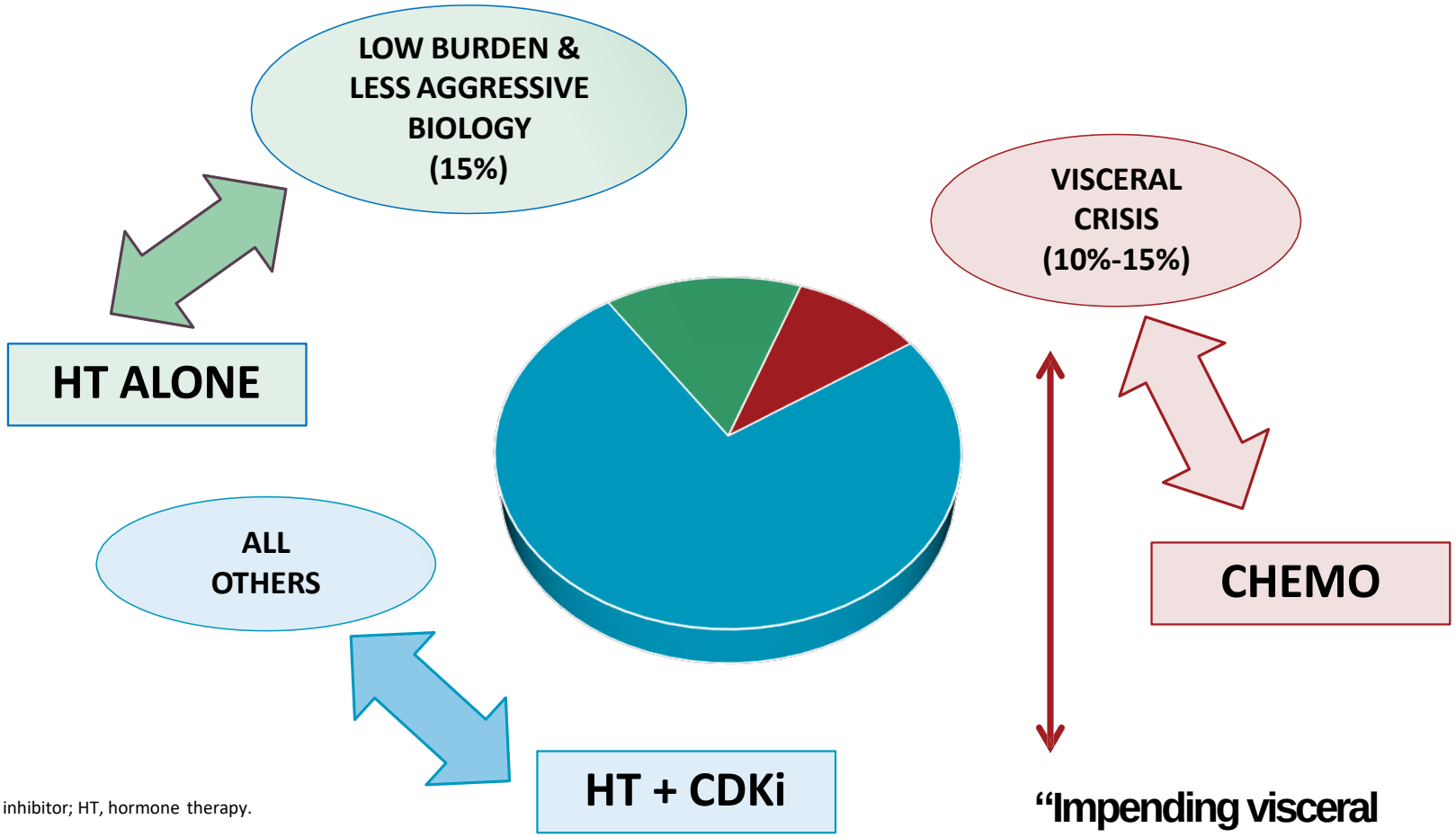
ER POSITIVE / HER-2 NEGATIVE MBC

Trials comparing the different combinations of endocrine + targeted agents with single agent CT are ongoing.
Initial results from phase 2 & 3 randomized trials seem to indicate that combinations of endocrine + targeted agents are at least equivalent to single agent CT, in terms of efficacy, and compare favorably in terms of safety.

(LoE/GoR : II/B)

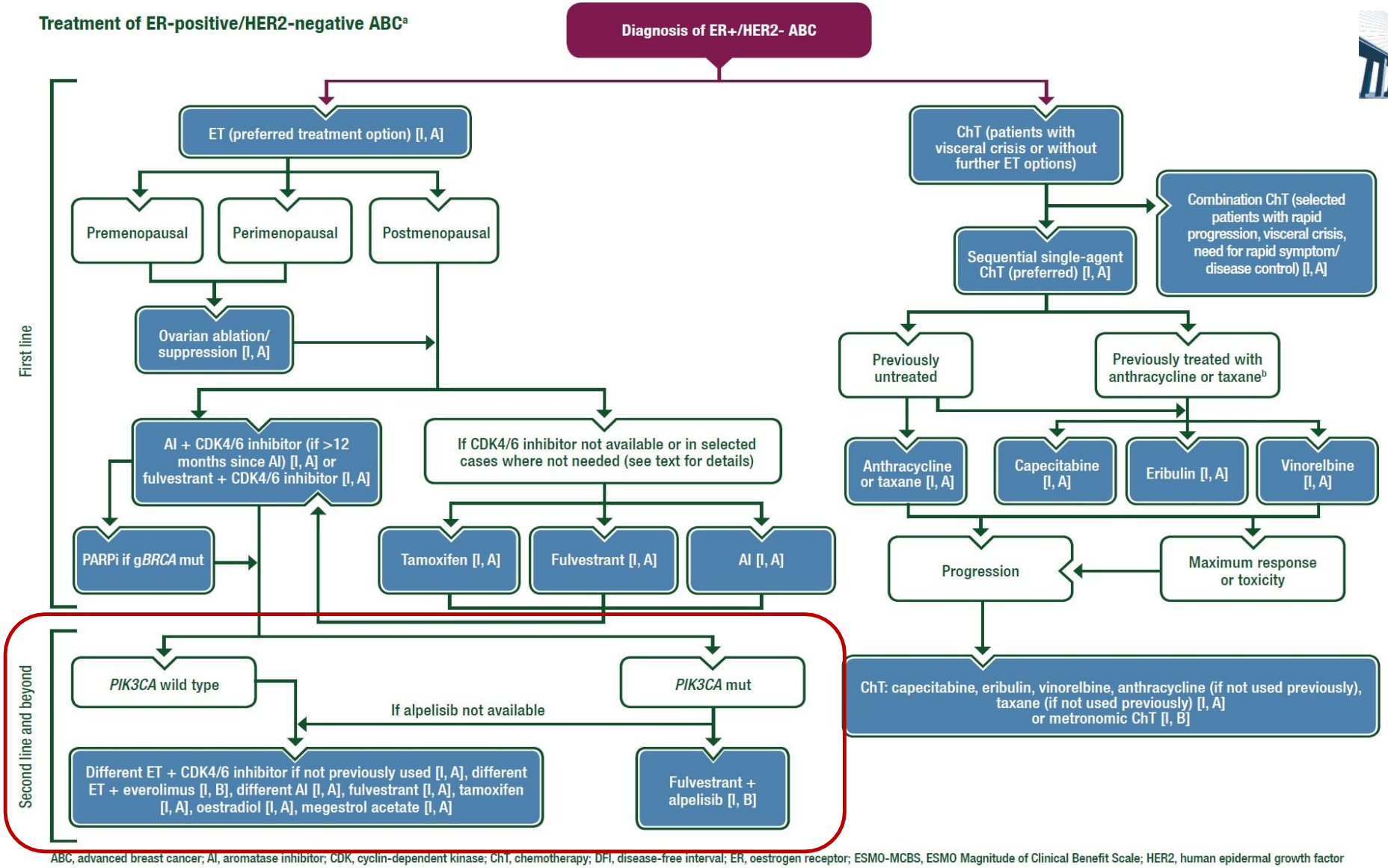
*** for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women**

SUMMARY OF 1ST LINE MANAGEMENT OF ER+/HER2 NEG ABC



CDKi, cyclin-dependent kinase inhibitor; HT, hormone therapy.

Treatment of ER-positive/HER2-negative ABC[a]



ABC, advanced breast cancer; AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ChT, chemotherapy; DFI, disease-free interval; ER, oestrogen receptor; ESMO-MCBS, ESMO Magnitude of Clinical Benefit Scale; HER2, human epidermal growth factor receptor 2; PARPi, poly-adenosine diphosphate ribose polymerase inhibitor; *PIK3CA*, phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha.

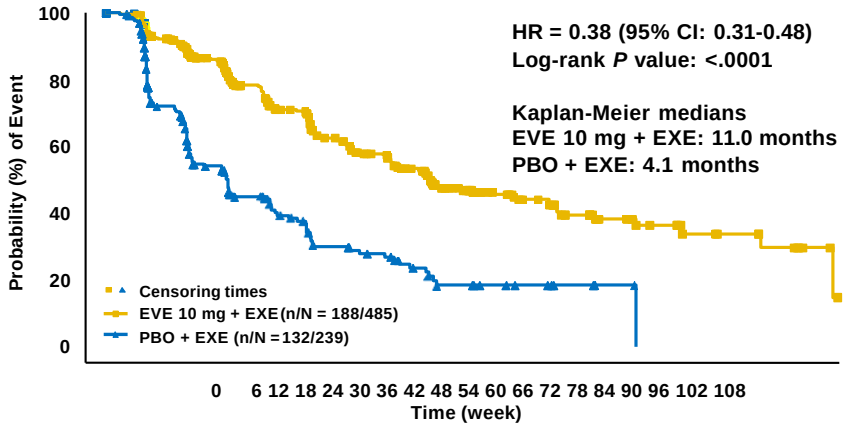
[a] For ESMO-MCBS scores, please refer to the manuscript and https://www.esmo.org/Guidelines/ESMO-MCBS.

[b] Rechallenge with a taxane or anthracycline is possible if cumulative dose not reached and DFI ≥12 months.

Cardoso F, et al. Ann Oncol. 2020

BOLERO-2 (18-ms FU): PFS Central

BOLERO-2



Number of patients still at risk

EVE 10 mg + EXE	485	427	359	292	239	211	166	140	108	77	62			48	32	21	18	11	10	5	0
PBO + EXE		239	179	114	76	56	39	31	27	16	13	9	6	4	1	0	0	0	0	0	

Piccart M, et al. ASCO 2012. Abstract 559.

4 months "absolute benefit" in OS

BUT

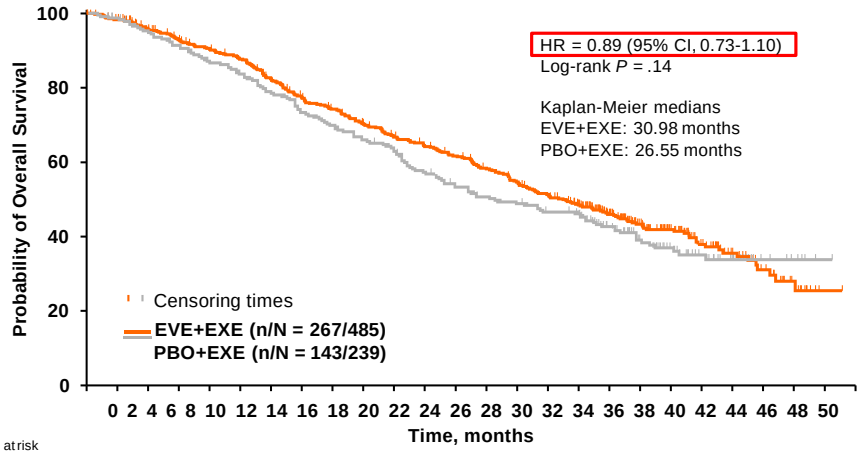
NOT STATISTICAL SIGNIFICANT

BOLERO-2

Everolimus + AI

4.6 to 6.9 ms benefit PFS

BOLERO-2 (39-mo): Final OS Analysis



No. at risk

EVE+EXE	485	471	448	429	414	399	373	347	330	311	292	279	266	248	232	216	196	154	118	91	58	39	23	11	1	0
PBO+EXE	239	232	220	211	201	194	182	170	162	153	145	130	120	113	109	102	98	77	56	41	28	18	8	5	1	0

- At 39 months median follow-up, 410 deaths had occurred (data cutoff date: 03 October 2013): 55% deaths (n = 267) in the EVE+EXE arm vs 60% deaths (n = 143) in the PBO+EXE arm

Piccart M, et al, EBCC 2014,LBA

ER POSITIVE / HER-2 NEGATIVE MBC

The addition of everolimus to an AI is a valid option for some patients previously exposed to or naïve of (in case CDK4/6i are not available) endocrine therapy, since it significantly prolongs PFS, albeit without evidence of OS benefit.
The decision to treat must take into account the toxicities associated with this combination, lack of statistically significant OS benefit, cost and availability.
(LoE/GoR : I/B) (88%)

Tamoxifen or fulvestrant can also be combined with everolimus.
(LoE/GoR : II/B) (80%)

*** for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women**

Management of MUCOSITIS/STOMATITIS

Steroid mouthwash should be used for prevention of stomatitis induced by mTOR inhibitors (suggested schedule: 0.5mg/5ml dexamethasone, 10 ml to swish x 2 minutes then spit out qid). (LoE/GoR: I/B) (100%)

Early intervention is recommended. (LoE/GoR: Expert opinion/A) (100%).
For > Grade 2 stomatitis, delaying treatment until the toxicity resolves and considering lowering the dose of the targeted agent are also recommended. (LoE/GoR: Expert opinion/A) (100%).
Mild toothpaste and gentle hygiene are recommended for the treatment of stomatitis. (LoE/GoR: Expert opinion/B) (100%).
Consider adding steroid dental paste to treat developing ulcerations. (LoE/GoR: Expert opinion/B) (100%).

ER POSITIVE / HER-2 NEGATIVE MBC

The optimal sequence of endocrine-based therapy is uncertain.
It depends on which agents were previously used (in the (neo)adjuvant or advanced settings), duration of response to those agents, burden of the disease, patients' preference and availability.

Available options for 1st and 2nd line include *AI/fulvestrant + CDK4/6 inhibitor, AI/tamoxifen/fulvestrant + everolimus, fulvestrant + alpelisib (for PIK3CA mut), AI, tamoxifen, fulvestrant.*

(LoE/GoR : Expert Opinion) (100%)

*** for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women**

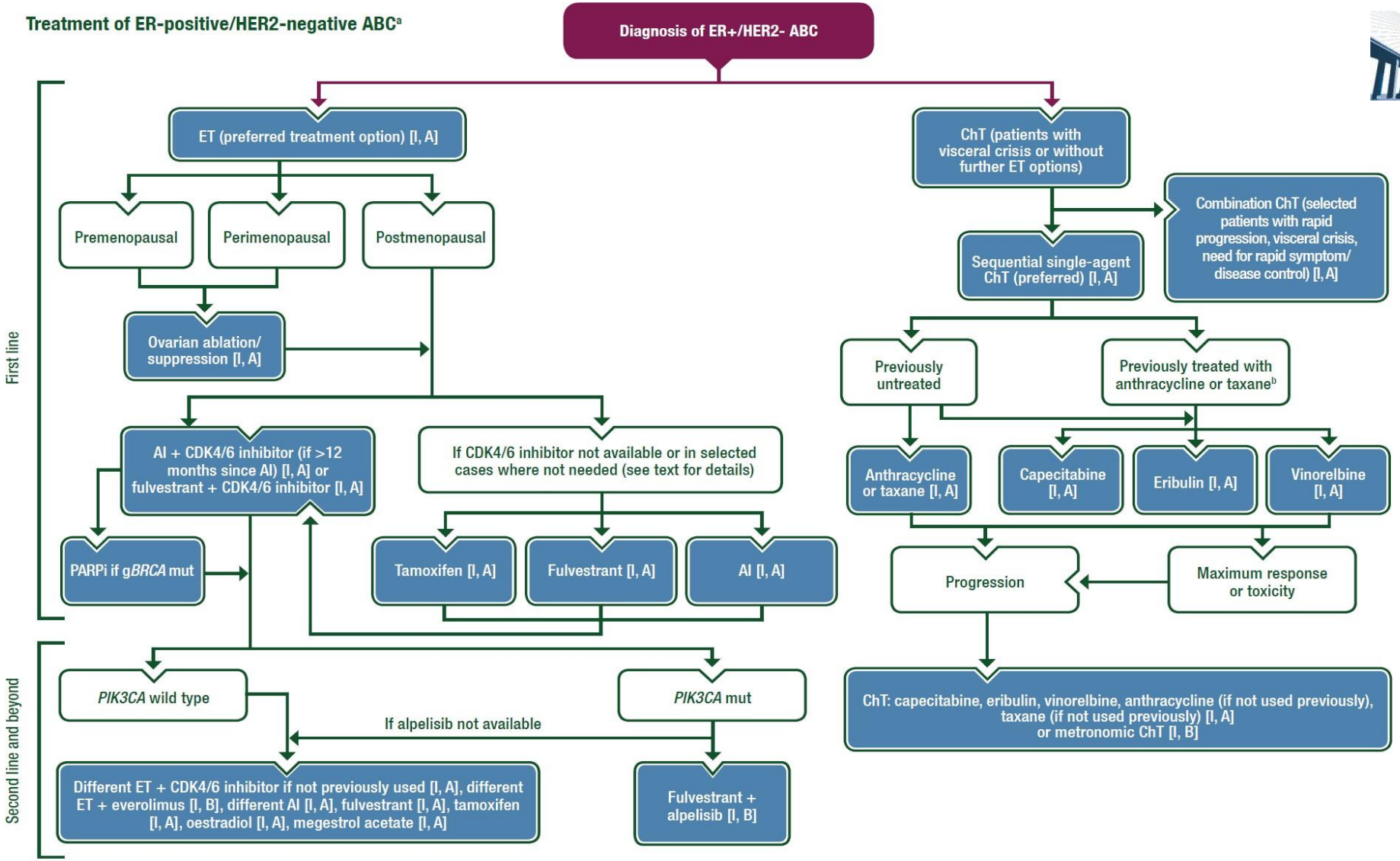
ER POSITIVE / HER-2 NEGATIVE MBC

Options for treatment of ER positive disease beyond second line include *single agents not previously used (NSAI, SAI, tamoxifen, fulvestrant, megesterol acetate, low dose estrogen). Single agent abemaciclib* is also a potential option.
Challenging a patient with an agent on which the disease previously progressed, after an initial response, is occasionally considered, but there are no robust data to support this approach.

(LoE/GoR : II/B) (98%)

*** for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women**

Treatment of ER-positive/HER2-negative ABC[a]



ABC, advanced breast cancer; AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ChT, chemotherapy; DFI, disease-free interval; ER, oestrogen receptor; ESMO-MCBS, ESMO Magnitude of Clinical Benefit Scale; HER2, human epidermal growth factor receptor 2; PARPi, poly-adenosine diphosphate ribose polymerase inhibitor; *PIK3CA*, phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha.

[a] For ESMO-MCBS scores, please refer to the manuscript and https://www.esmo.org/Guidelines/ESMO-MCBS.

[b] Rechallenge with a taxane or anthracycline is possible if cumulative dose not reached and DFI ≥12 months.

Cardoso F, et al. Ann Oncol. 2020

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

Preferred Regimens

First-Line Therapy

- Aromatase inhibitor + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)
- Selective ER down-regulator (fulvestrant, category 1)[b] ± non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[b]
- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Selective estrogen receptors modulator (tamoxifen or toremifene)
- Steroidal aromatase inactivator (exemestane)

Preferred Regimens

Second- and Subsequent-Line Therapy

- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[c]
- For *PIK3CA*-mutated tumors, see additional targeted therapy options (see BINV-R)[c,d]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[c,f]
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator (exemestane)
- Selective ER down-regulator (fulvestrant)
- Selective estrogen receptors modulator (tamoxifen or toremifene)

Useful in Certain Circumstances[d]

- Megestrol acetate
- Estradiol
- Abemaciclib[c,e]

THANK YOU