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Clinical Oncology Congress
هفدهمین کنگره سالیانه کلینیکال انکولوژی
2-4 Febuary 2023
Olympic hotel, Tehran, IRAN

Evidence-Based practice in HR+/HER2- Advanced/Metastatic Breast Cancer

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Mashhad University of Medical Sciences,

Mashhad, Iran

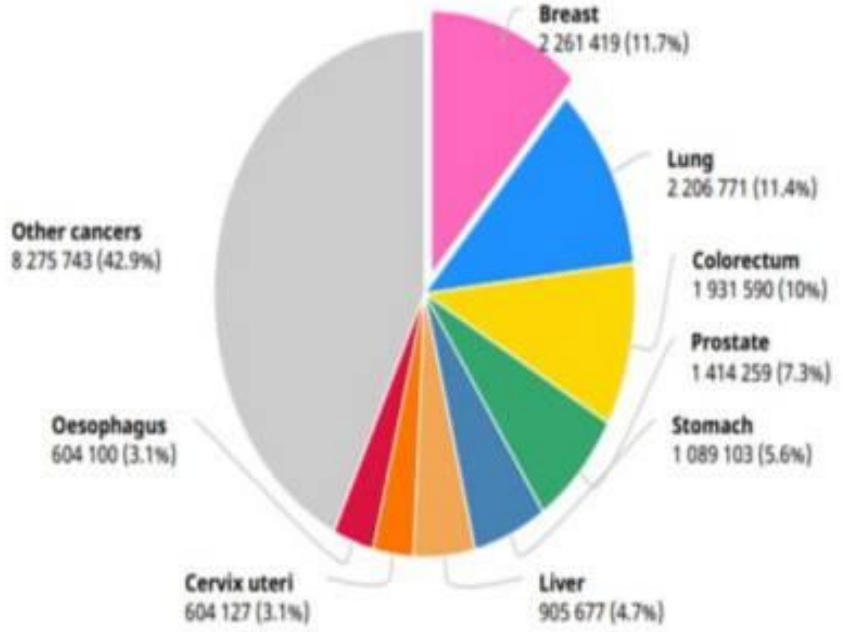
International Agency for Research on Cancer
World Health Organization

Breast

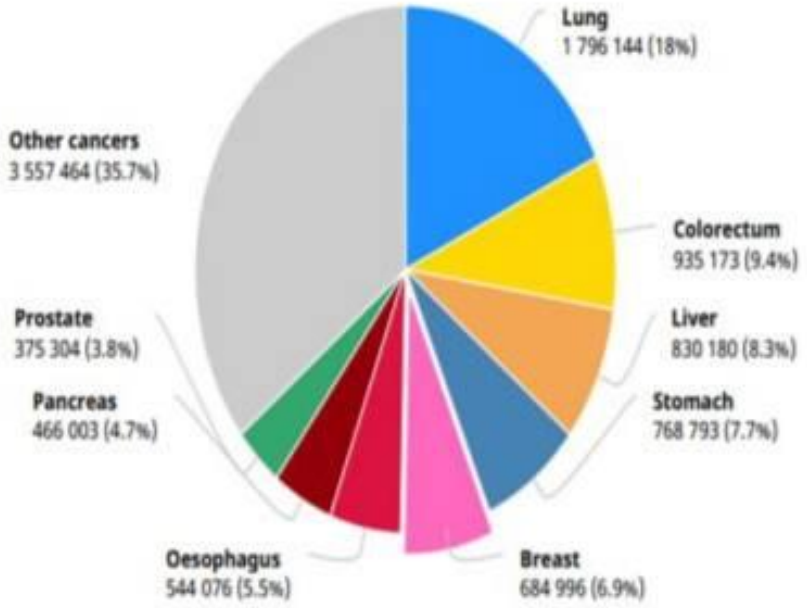
Source: Globocan 2020

GCO

Number of new cases in 2020, both sexes, all ages



Number of deaths in 2020, both sexes, all ages



a clinically heterogenous group of tumors with different prognoses and responses to treatment

JAMA Network | Open

Original Investigation | Oncology

Clinicopathological Characteristics and Breast Cancer–Specific Survival of Patients With Single Hormone Receptor–Positive Breast Cancer

Yunhai Li, PhD; Dejuan Yang, PhD; Xuedong Yin, PhD; Xiang Zhang, PhD; Jiefeng Huang, MD; Yusheng Wu, MD; Mengxue Wang, MD; Zhiying Yi, MD; Hongyuan Li, PhD; Hongzhong Li, PhD; Guosheng Ren, MD

Nearly 65- 70% are estrogen receptor-positive (ER^+)
(Andreas D. Hartkopf et al., 2020)
(Fabi A, et al. 2022)

ER+ breast cancer, while considered a more treatable and better prognosis subtype of breast cancer, is associated with a consistent annual relapse rate that persists beyond ten years after diagnosis.
(Jonathan T. Lei et al., 2019).

HR+/HER2- Advanced/Metastatic Breast Cancer

The ABC Global Charter, is
to double the survival among patients with advanced breast cancer by 2025.

“This is starting to happen especially in HR+ subtype of advanced breast cancer.”

Dr. Cardoso said.

(ABC Sixth International Consensus)

Historical Timeline of Therapies for HR+ Advanced Breast Cancer

Endocrine therapy is one of the most effective treatment options for ER-positive breast cancer.

ER POSITIVE / HER-2 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**

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Breast Cancer

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SYSTEMIC TREATMENT OF RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE: ER- AND/OR PR-P

Visceral crisis[m]

Progression
See BINV-22

According to
visceral cr
laboratory s
visceral met

breast cancer
symptoms,
presence of
ndication for

No visceral crisis
and
No prior
endocrine
therapy within 1 y

F. Cardoso et al.

Section I. ABC definitions

Guideline statement	LoE/GoR	Consensus
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 >1.5× ULN in the absence of Gilbert's syndrome or biliary tract obstruction. ***Lung visceral crisis***: rapidly increasing dyspnoea at rest, not alleviated by drainage of pleural effusion.	Expert opinion/n/a	97%

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SYSTEMIC THERAPY REGIMENS FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

HR-Positive and HER2-Negative with Visceral Crisis or Endocrine Refractory		
Setting	**Subtype/Biomarker**	**Regimen**
First Line	No germline *BRCA1/2* mutation[b]	Systemic chemotherapy see BINV-Q (5)
	Germline *BRCA1/2* mutation[b]	PARPi (olaparib, talazoparib)[c] (Category 1, preferred)
Second Line	HER2 IHC 1+ or 2+/ISH negative[d]	Fam-trastuzumab deruxtecan-nxki[e] (Category 1, preferred)
	Not a candidate for fam-trastuzumab deruxtecan- nxki	Sacituzumab govitecan[f] (Category 1, preferred)
		Systemic chemotherapy see BINV-Q (5)
Third Line and beyond	Any	Systemic chemotherapy see BINV-Q (5)
	Biomarker positive (ie, MSI-H, NTRK, RET, TMB-H)	Targeted agents see BINV-Q (6)

b Assess for germline BRCA1/2 mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy.

c PARPi can be considered for a later line for those with BRCA1/2 mutation, however available evidence suggests it is more effective if used earlier.

d See Principles of HER2 Testing (BINV-A).

e Maybe considered in a later line for HER2 IHC 1+ or 2+/ISH negative, if not used in second–line.

f Sacituzumab govitecan-hziy may be used for adult patients with HR-positive, HER2-negative metastatic/locally advanced unresectable breast cancer after prior treatment including endocrine therapy, a CDK4/6 inhibitor, and at least two lines of chemotherapy, one of which was a taxane, and at least one of which was in the metastatic setting. It may be considered for later line if not used as second line therapy.

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Systemic Chemotherapy for HR-Positive or -Negative and HER2-Negative[a,s,t,u]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Anthracyclines ▸ Doxorubicin ▸ Liposomal doxorubicin • Taxanes ▸ Paclitaxel	• Cyclophosphamide • Docetaxel • Albumin-bound paclitaxel • Epirubicin • Ixabepilone	• AC (doxorubicin/cyclophosphamide) • EC (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/ methotrexate/fluorouracil) • Docetaxel/capecitabine

Conclusions

METEORA-II trial showed VEX significantly improved TTF compared with P.
VEX metronomic oral treatment should be considered as a first-line CT regimen for pts with ER+/HER2- MBC that require CT.

216MO - A randomized phase II trial of metronomic oral vinorelbine plus cyclophosphamide and capecitabine (VEX) vs weekly paclitaxel (P) as first- or second-line treatment in patients (pts) with ER+/HER2- metastatic breast cancer (MBC): The METEORA-II trial (IBCSG 54-16)

Date
10 Sep 2022

Presenters
Elisabetta Munzone

Session
Mini Oral session: Breast cancer, metastatic

Citation
Annals of Oncology (2022) 33 (suppl_7): S88-S121. 10.1016/annonc/annonc1040

Resources

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ow we treat patie....pdf

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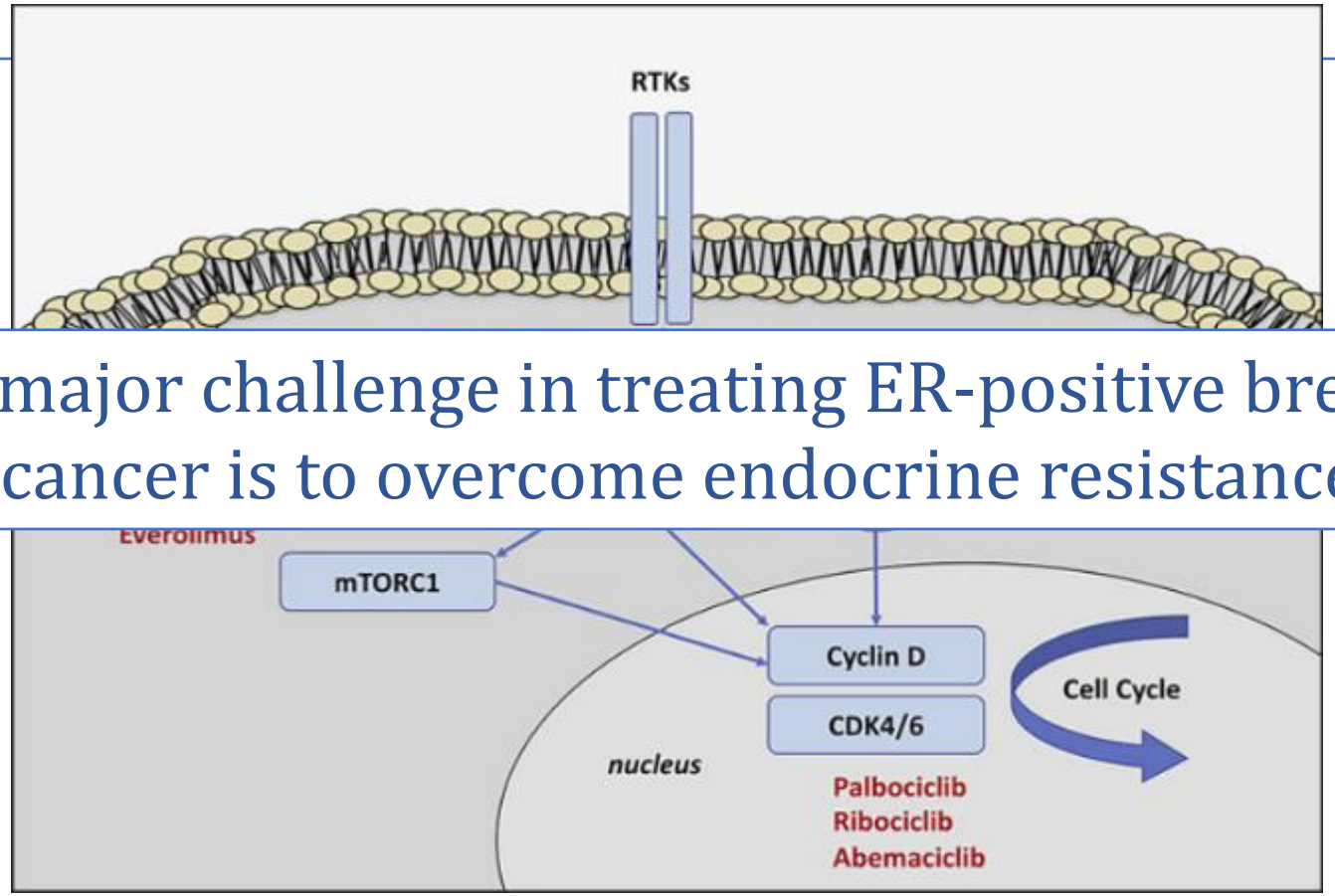
ER POSITIVE / HER-2 NEGATIVE MBC

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**

50% of HR+MBCs don't benefit from ET due to Hormone resistance in breast cancer



A major challenge in treating ER-positive breast cancer is to overcome endocrine resistance.

Miranda F, Prazeres H, Mendes F, Martins D, Schmitt F. Resistance to endocrine therapy in HR + and/or HER2 + breast cancer: the most promising predictive biomarkers. Mol Biol Rep. 2022 Jan;49(1):717-733. doi: 10.1007/s11033-021-06863-3. Epub 2021 Nov 5. PMID: 34739691.

Unchanged statement

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 ABC, while on ET

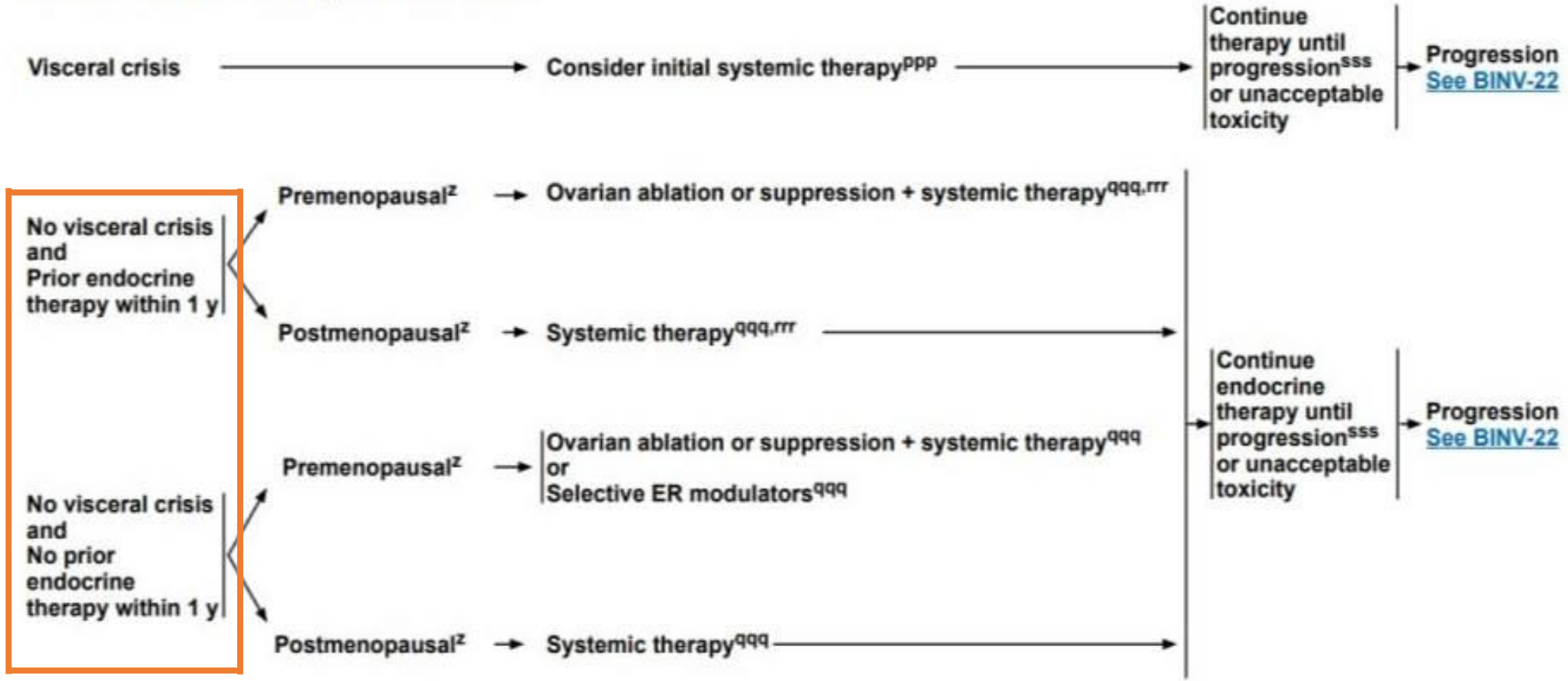
SECONDARY (ACQUIRED) ENDOCRINE RESISTANCE is defined as:

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 ABC, while on ET

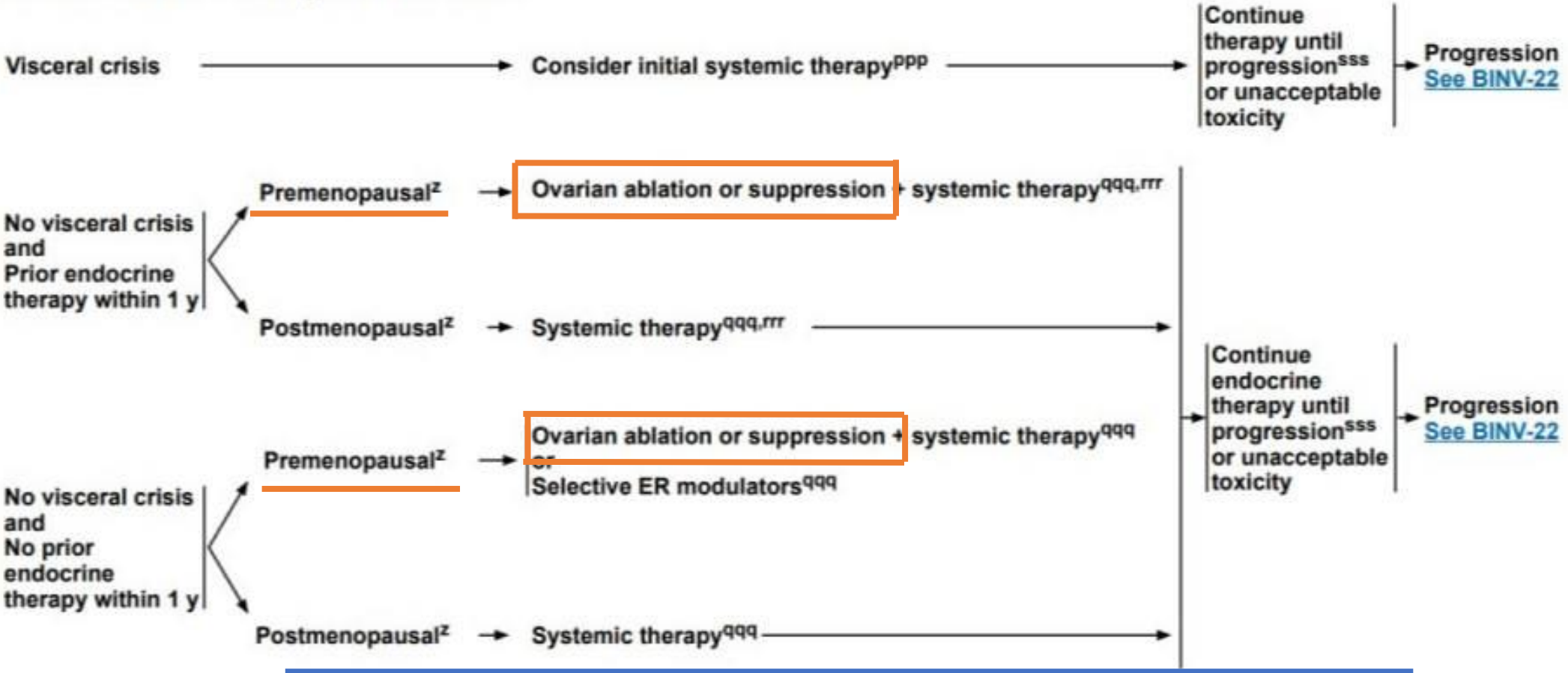
(LoE: Expert opinion/NA) (67%)

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

SYSTEMIC TREATMENT OF RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE: ER- AND/OR PR-POSITIVE; HER2-NEGATIVE[d]



SYSTEMIC TREATMENT OF RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE: ER- AND/OR PR-POSITIVE; HER2-NEGATIVE[d]



Many trials in ER+ ABC have not included pre-menopausal women. (ABC5)

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%)

DEFINITION OF MENOPAUSE

- Menopause is the permanent cessation of menses and includes a profound and permanent decrease in ovarian estrogen synthesis.
- Determination of menopausal status may be required to guide selection of endocrine therapy for breast cancer.
- Menopause is usually a clinical diagnosis made after ≥12 months of amenorrhea. Natural menopause is experienced between ages 42–58 years.
- Breast cancer treatments may affect ovarian function and menses.
  - In those who are pre-menopausal at the beginning of chemotherapy and who develop chemotherapy-induced amenorrhea, ovarian function may still be intact despite amenorrhea or may resume over time. The likelihood of ovarian function resuming after chemotherapy is higher among those aged <40 years.
  - Tamoxifen may cause amenorrhea without inducing menopause in pre-menopausal individuals.
  - Ovarian function suppression induces amenorrhea and reduces ovarian estrogen synthesis without causing permanent menopause.
- Twelve months of amenorrhea alone is insufficient to diagnose menopause with chemotherapy-induced amenorrhea or with tamoxifen ± ovarian suppression. Follicle-stimulating hormone (FSH) and estradiol levels are used to support the diagnosis of menopause; however, clear criteria to guide interpretation of FSH and estradiol in this population is lacking.
  - Tamoxifen may alter FSH levels, limiting its utility in determination of menopausal status.
  - FSH and estradiol should be repeated serially to ensure menopausal status in breast cancer patients with chemotherapy-induced amenorrhea.
- Evidence-based criteria for the diagno
  utilized a variety of definitions of men
  the following:
  - Prior bilateral oophorectomy
  - Age ≥60
  - Age <60
    and estr
  - Age <60
    assessn
  - Age <60
- Menopau

Evidence-based criteria for the diagnosis of menopause in patients with breast cancer are lacking.

- Evidence-based criteria for the diagnosis of menopause in patients with breast cancer are lacking. Clinical trials in breast cancer have utilized a variety of definitions of menopause. Reasonable criteria for determining menopause in patients with breast cancer include any of the following:
  - Prior bilate
  - Age ≥60 ye
  - Age <60 wi
    and estradi
  - Age <60 ye
    assessmen
  - Age <60 ye
- Menopausal

Age <60 with amenorrhea for ≥12 months in the absence of prior chemotherapy, receipt of tamoxifen, toremifene, or ovarian suppression
and
estradiol and FSH in the post-menopausal range

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

BINV-O

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

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)

As all endocrine interventions for premenopausal patients with endocrine-responsive ABC require indefinite OFS, choosing one method over the other requires balance of patient's wish for potentially preserving fertility, compliance with frequent injections over a long period of time, risk of inadequate estrogen level suppression and cost.

HR+/HER2- MBC: First-line Treatment

No head-to-head trials comparing CDK4/6 inhibitors

Phase III Trial	PALOMA-2[1,2]	MONALEESA-2[3,4]	MONARCH-3[5,6]	MONALEESA-3[†7-9]	MONALEESA-7*[10-12]
CDK4/6i	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Ribociclib
Endocrine partner	Letrozole	Letrozole	Letrozole or anastrozole	Fulvestrant	Tamoxifen, letrozole, or anastrozole
Patients, N	666	668	493	365	672
Patient population	Postmenopausal	Postmenopausal	Postmenopausal	Postmenopausal	Pre/perimenopausal
mOS, mo	–	–	–	NR vs 40.0	NR vs 40.9
▪ Hazard ratio	–	–	–	0.724; *P* = .00455	0.712; *P* = .00973
mPFS, mo	27.6 vs 14.5	25.3 vs 16.0	28.18 vs 14.76	33.6 vs 19.2	23.8 vs 13.0
▪ Hazard ratio	0.563	0.568	0.54	0.55[‡]	0.55
ORR, %	55.3 vs 44.4	52.7 vs 37.1	59 vs 44	40.9 vs 28.7[†]	41 vs 30

*First-line ET; up to 1 previous CT line permitted in advanced setting (14% had received CT). †Includes first and second line. ‡Descriptive analysis.

1. Finn. NEJM. 2016;375:1925. 2. Rugo. Breast Cancer Res Treat. 2019;174:719. 3. Hortobagyi. NEJM. 2016;375:1738. 4. Hortobagyi. Ann Oncol. 2018;29:1541. 5. Goetz. JCO. 2017;35:3638. 6. Johnston. NPJ Breast Cancer. 2019;5:5. 7. Slamon. JCO. 2018;36:2465. 8. Slamon. NEJM. 2020;382:514. 9. Slamon. ESMO 2019. Abstr LBA7_PR. 10. Tripathy. Lancet Oncol. 2018;19:904. 11. Hurvitz. ASCO 2019. Abstr LBA1008. 12. Im. NEJM. 2019;381:307

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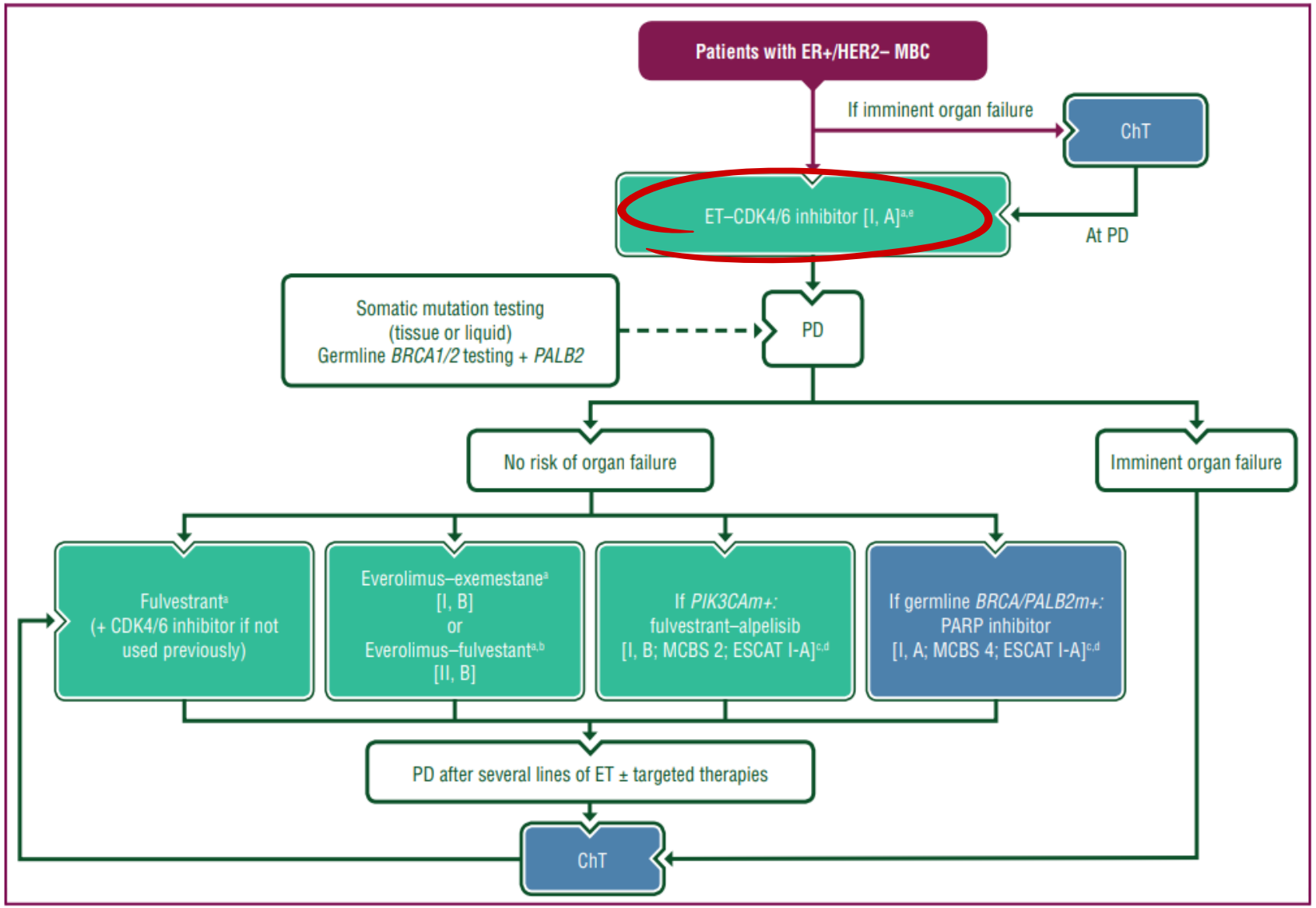

Figure 2. Treatment of ER-positive/HER2-negative MBC.

Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy.

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4 and 6; ChT, chemotherapy; EMA, European Medicines Agency; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESR1, estrogen receptor 1; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; m, mutation; MBC, metastatic breast cancer; MCBS, ESMO-Magnitude of Clinical Benefit Scale; OFS, ovarian function suppression; *PALB2, partner and localiser of BRCA2*; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; *PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha*.

[a] OFS if the patient is premenopausal.

HR+/HER2- MBC: First-line Treatment

- Preferred regimens
  - CDK4/6i + NSAI* (anastrozole or letrozole)
  - CDK4/6i + fulvestrant*
- FDA-approved CDK4/6i
  - Palbociclib
  - Ribociclib
  - Abemaciclib

No head-to-head trials comparing CDK4/6 inhibitors

- Factors influencing selection of CDK4/6i
  - Long-term survival data
  - Menopause status
  - Toxicity profile
  - Organ function
  - Drug interactions

Matutino. Curr Oncol. 2018;25:S131. Rugo. JCO. 2016;34:3069. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V2.2022. © National Comprehensive Cancer Network, Inc 2022. All rights reserved. Accessed March 18, 2022.

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HR+/HER2- MBC: First-line Treatment

No head-to-head trials comparing CDK4/6 inhibitors

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Endocrine partner	Letrozole	Letrozole	Letrozole or anastrozole	Fulvestrant	Tamoxifen, letrozole, or anastrozole
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Patient population	Postmenopausal	Postmenopausal	Postmenopausal	Postmenopausal	Pre/perimenopausal
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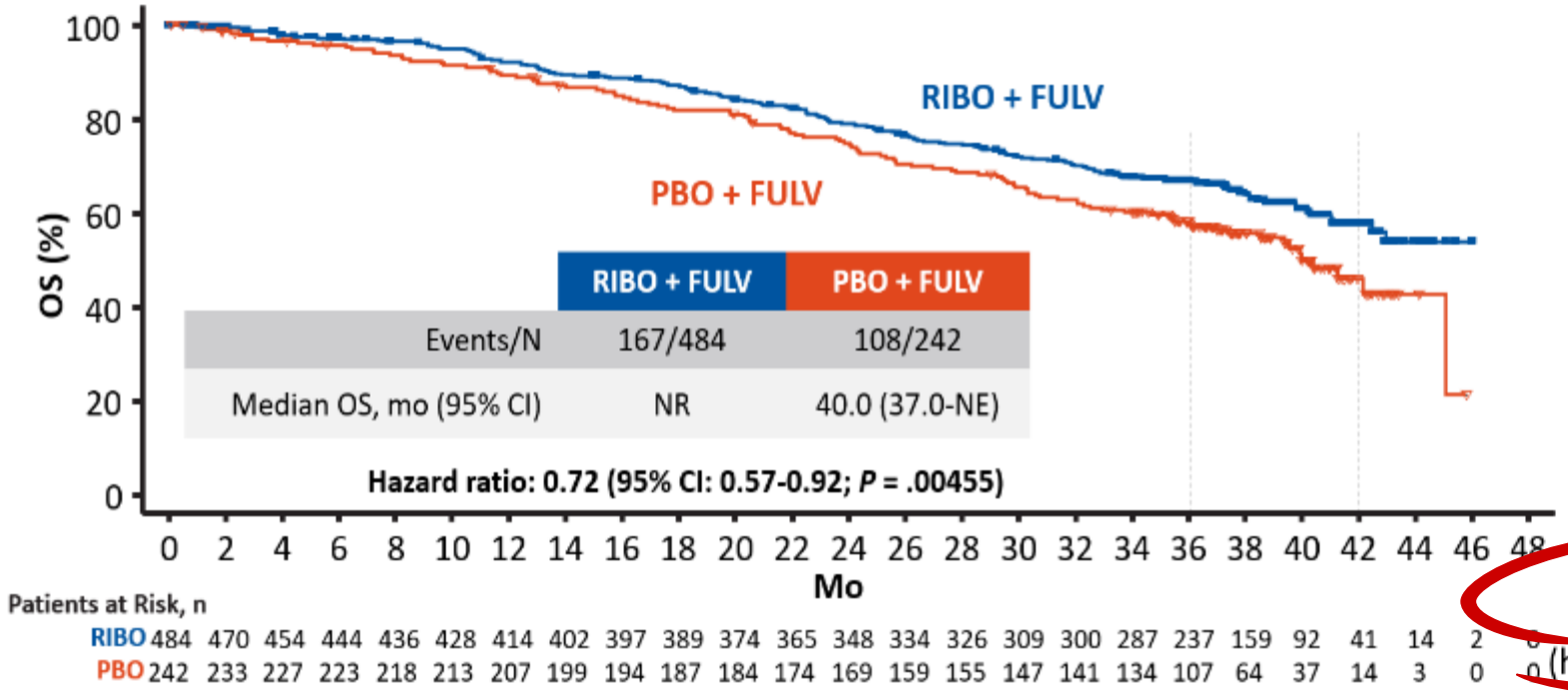
MONALEESA-3: Ribociclib + FULV as First- or Second-line Tx for HR+/HER2- ABC and Postmenopausal

- Reduction in relative risk of death with ribociclib: 28%



Original Analyses
(Median follow-up: 39.4 mo)

KM Est, %	RIBO + FULV	PBO + FULV
36 mo	67.0	58.2
42 mo	57.8	45.9

Updated Analyses
(Median follow-up: 56.3 mo)

KM Est, %	RIBO + FULV	PBO + FULV
48 mo	54.0	45.0
60 mo	46.0	31.0

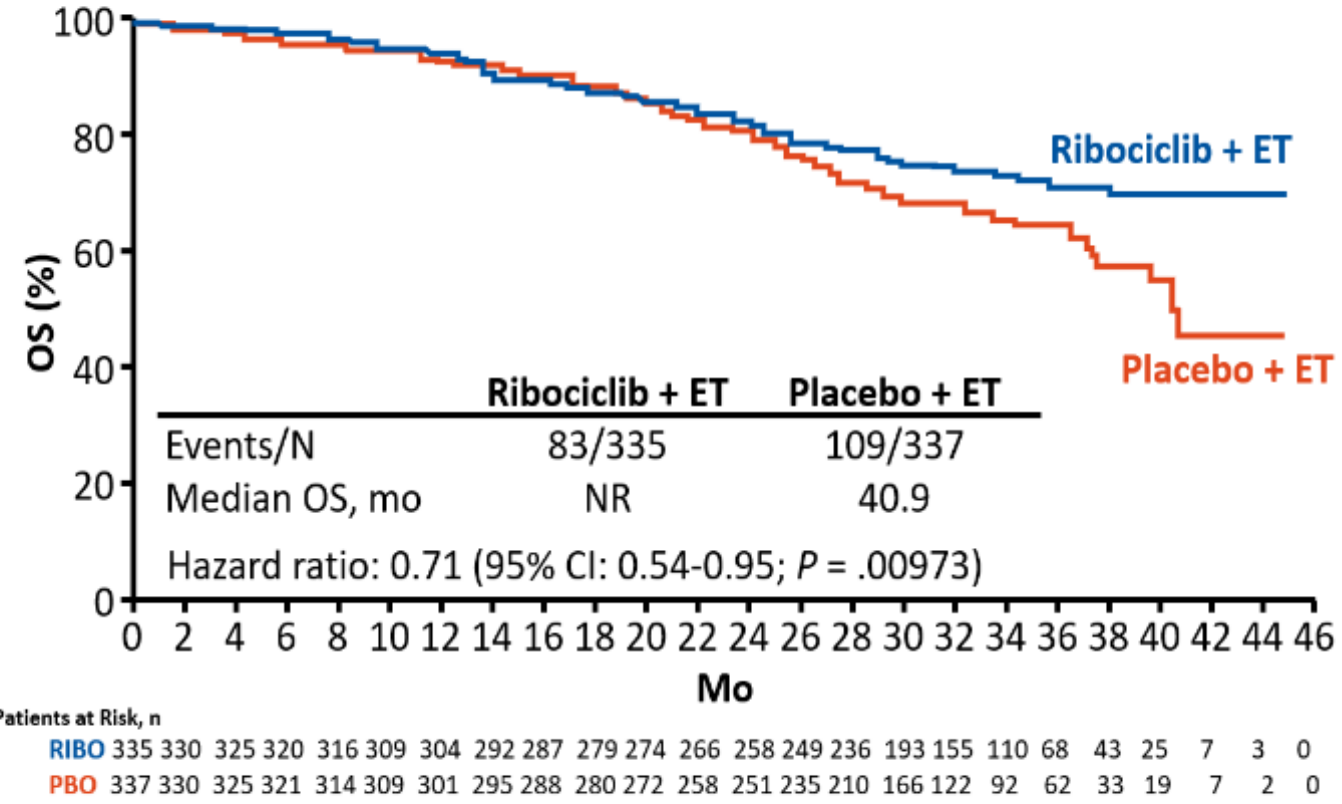
Median OS 53.7 mo vs
41.5 mo with ribociclib vs placebo
(hazard ratio: 0.73; 95% CI 0.59-0.90)

Slamon. NEJM. 2020;382:514.; Slamon. Ann Oncol. 2021;32:1015.

Slide credit: ProCE.com and clinicaloptions.com

MONALEESA-7: Ribociclib + ET as First-line Tx of HR+/HER2- ABC and Pre/Perimenopausal

- 29% relative reduction in risk of death with ribociclib



Original Analyses
(Median follow-up: 34.6 mo)

KM Est, %	RIBO + ET	PBO + ET
36 mo	71.9	64.9
42 mo	70.2	46.0

Updated Analyses
(Median follow-up: 53.5 mo)

KM Est, %	RIBO + ET	PBO + ET
48 mo	60.0	50.0
54 mo	53.0	44.0

Median OS 58.7 mo vs
48.0 mo with ribociclib vs placebo
(hazard ratio: 0.76; 95% CI 0.61-0.96)

Im. NEJM. 2019;381:307. Lu. Clin Cancer Res. 2022;28:851.

Slide credit: ProCE.com and clinicaloptions.com

Clinical Trial > Clin Cancer Res. 2022 Mar 1;28(5):851-859. doi: 10.1158/1078-0432.CCR-21-3032.

Updated Overall Survival of Ribociclib plus Endocrine Therapy versus Endocrine Therapy Alone in Pre- and Perimenopausal Patients with HR+/HER2- Advanced Breast Cancer in MONALEESA-7: A Phase III Randomized Clinical Trial

Yen-Shen Lu [# 1], Seock-Ah Im [# 2], Marco Colleoni [3], Fabio Franke [4], Aditya Bardia [5], Fatima Cardoso [6], Nadia Harbeck [7], Sara Hurvitz [8], Louis Chow [9], Joohyuk Sohn [10], Keun Seok Lee [11], Saul Campos-Gomez [12], Rafael Villanueva Vazquez [13], Kyung Hae Jung [14], K Govind Babu [15], Paul Wheatley-Price [16], Michelino De Laurentiis [17], Young-Hyuck Im [18], Sherko Kuemmel [19 20], Nagi El-Saghir [21], Ruth O'Regan [22], Claudia Gasch [23], Nadia Solovieff [24], Craig Wang [25], Yongyu Wang [26], Arunava Chakravartty [26], Yan Ji [26], Debu Tripathy [27]

Affiliations + expand

PMID: 34965945 PMCID: PMC9377723 DOI: 10.1158/1078-0432.CCR-21-3032

Free PMC article

Clinical Trial > Clin Cancer Res. 2022 Mar 1;28(5):851-859. doi: 10.1158/1078-0432.CCR-21-3032.

Updated Overall Survival of Ribociclib plus Endocrine Therapy versus Endocrine Therapy Alone in Pre- and Perimenopausal Patients with HR+/HER2- Advanced Breast Cancer in MONALEESA-7: A Phase III

Conclusions:

Ribociclib plus ET continued to show significantly longer OS than ET alone in pre-/perimenopausal patients, including patients aged less than 40 years, with HR=/HER2 ABC with 53.5 months of median follow-up (ClinicalTrials.gov, NCT02278120).

PMID: 34965945 PMCID: PMC9377723 DOI: 10.1158/1078-0432.CCR-21-3032
Free PMC article

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Invasive Breast Cancer

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SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

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)[b]
- Selective ER down-regulator (fulvestrant, category 1)[c] + non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[c]
- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)[b]

Preferred Regimens

Second- and Subsequent-Line Therapy

- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[d,e]
- For *PIK3CA*-mutated tumors, see additional targeted therapy options (see BINV-R)[e,f]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[e,g]

Other Recommended Regimens

First- and Subsequent-Line Therapy

- Selective ER down-regulator
  - Fulvestrant[c]
- Non-steroidal aromatase inhibitor
  - Anastrozole
  - Letrozole
- Selective estrogen receptors modulator
  - Tamoxifen
- Steroidal aromatase inactivator
  - Exemestane

Useful in Certain Circumstances[f]

Subsequent-Line Therapy

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

HER2-Positive and Postmenopausal[i,j,k] or Premenopausal Receiving Ovarian Ablation or Suppression

- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

[a] Baseline assessment of bone density recommended for patients receiving an aromatase inhibitor who are at risk of osteoporosis (eg, age >65, family history, chronic steroids).

[b] In phase 3 randomized controlled trials, ribociclib + endocrine therapy has shown overall survival benefit in the first-line setting.

[c] A single study (S0226) in patients with HR-positive breast cancer and no prior chemotherapy, biological therapy, or endocrine therapy for metastatic disease demonstrated that the addition of fulvestrant to anastrozole resulted in prolongation of time to progression and overall survival. Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. Two studies with similar design (FACT and SOFEA) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole.

[d] In phase 3 randomized controlled trials, fulvestrant in combination with a CDK4/6 inhibitor (abemaciclib, palbociclib, and ribociclib) has shown overall survival benefit in the second-line setting.

[e] If there is disease progression while on a CDK4/6 inhibitor, there are limited data to support the use of another CKD4/6 inhibitor. If there is progression while on a PI3K inhibitor, there are limited data to support another line of therapy with a PIK3CA-containing regimen. If there is disease progression while on an everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.

[f] See Additional Targeted Therapies and Associated Biomarker Testing for Recurrent or Stage IV (M1) Disease (BINV-R).

[g] A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal aromatase inhibitor).

[h] Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting.

[i] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

[j] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine or fam-trastuzumab deruxtecan-nxki.

[k] If treatment was initiated with chemotherapy and trastuzumab + pertuzumab, and the chemotherapy was stopped, endocrine therapy may be added to trastuzumab + pertuzumab.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

BINV-P

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE[a]

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

Preferred Regimens

First-Line Therapy

- Aromatase inhibitor + CDK4/6 inhibitor[b]
  - Aromatase inhibitor + ribociclib (category 1)[c]
  - Aromatase inhibitor + abemaciclib
  - Aromatase inhibitor + palbociclib
- Fulvestrant[d] + CDK4/6 inhibitor[b]
  - Fulvestrant + ribociclib (category 1)[e]
  - Fulvestrant + abemaciclib (category 1)[e]
  - Fulvestrant + palbociclib

Second- and Subsequent-Line Therapy

- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) if CKD4/6 inhibitor not previously used (category 1)[f,g]
- For *PIK3CA*-mutated tumors, see additional targeted therapy options, see BINV-Q (6)[h]
- Everolimus + endocrine therapy (exemestane, fulvestrant, tamoxifen)[i,j]

Other Recommended Regimens

First- and Subsequent-Line Therapy

- Selective ER down-regulator
  - Fulvestrant[k]
- Selective ER down-regulator (fulvestrant, category 1) + non-steroidal aromatase inhibitor (anastrozole, letrozole) (category 1)[k]
- Non-steroidal aromatase inhibitor
  - Anastrozole
  - Letrozole
- Selective ER modulator
  - Tamoxifen
- Steroidal aromatase inactivator
  - Exemestane

Useful in Certain Circumstances

Subsequent-Line Therapy

- Megestrol acetate
- Estradiol
- Abemaciclib[l]
- Addtional targeted therapy options, see BINV-Q (6)

[f] If there is disease progression while on a CDK4/6 inhibitor, there are limited data to support the use of another CKD4/6 inhibitor. If there is progression while on a PI3K inhibitor, there are limited data to support another line of therapy with a PIK3CA-containing regimen. If there is disease progression while on an everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.

Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine or fam-trastuzumab deruxtecan-nxki.

[k] If treatment was initiated with chemotherapy and trastuzumab + pertuzumab, and the chemotherapy was stopped, endocrine therapy may be added to trastuzumab + pertuzumab.

Note: All recommendations are category 2A unless otherwise indicated.
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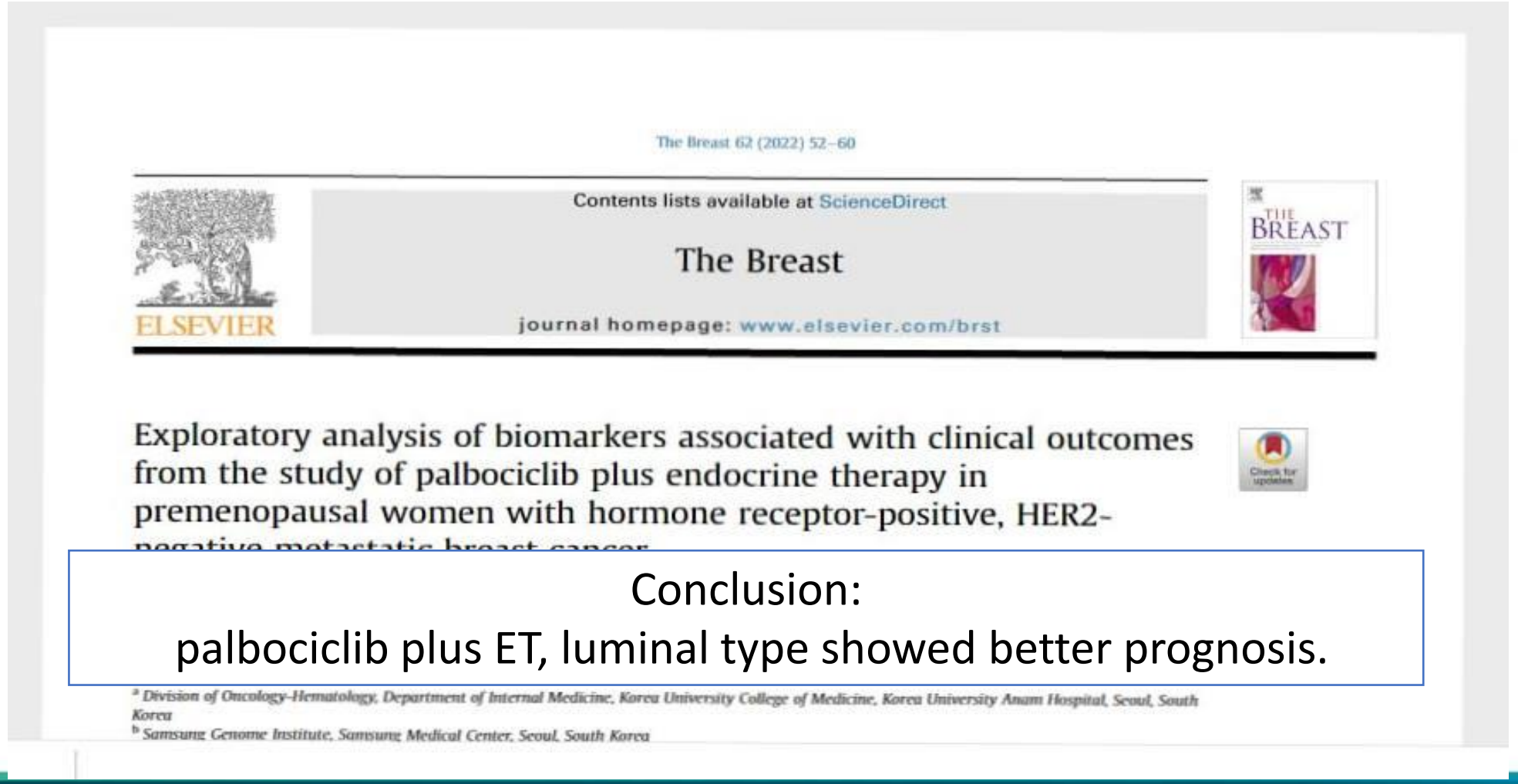
Key AEs With CDK4/6 Inhibitors: Monitoring and Prevention

Diarrhea	Hepatobiliary Toxicity	QT Prolongation	Neutropenia	VTE	ILD/ Pneumonitis
Abemaciclib Palbociclib Ribociclib	Abemaciclib Ribociclib	Ribociclib	Abemaciclib Palbociclib Ribociclib	Abemaciclib	Abemaciclib Palbociclib Ribociclib
Antidiarrheal therapy Increase oral hydration Notify healthcare provider	LFTs before starting tx, Q2W x 2 mo, then: ▪ *Abemaciclib,* as indicated ▪ *Ribociclib,* at start of cycle x 4 cycles	ECG before cycle 1, Day 14 of cycle 1, start of cycle 2, then as indicated Electrolytes at start of cycle x 6 cycles, then as indicated	CBC before starting treatment, then: ▪ *Abemaciclib,* Q2W x 2 mo, QM x 2 mo, then as indicated ▪ *Palbociclib,* Days 1 and 15 of cycles 1-2, then as indicated ▪ *Ribociclib,* Q2W x 2 cycles, start of next 4 cycles, then as indicated	Monitor for signs and symptoms of thrombosis or pulmonary embolism	Monitor for pulmonary symptoms indicative of ILD or pneumonitis (eg, hypoxia, cough, dyspnea)

Abemaciclib PI. Palbociclib PI. Ribociclib PI.

Slide credit: ProCE.com and clinicaloptions.com

ET + CDK4/6i or Chemo for Metastatic Premenopausal Women?
Phase II Young-PEARL Trial (KCSG-BR 15-10, NCT02592746)



The Breast 62 (2022) 52–60

Contents lists available at ScienceDirect

The Breast

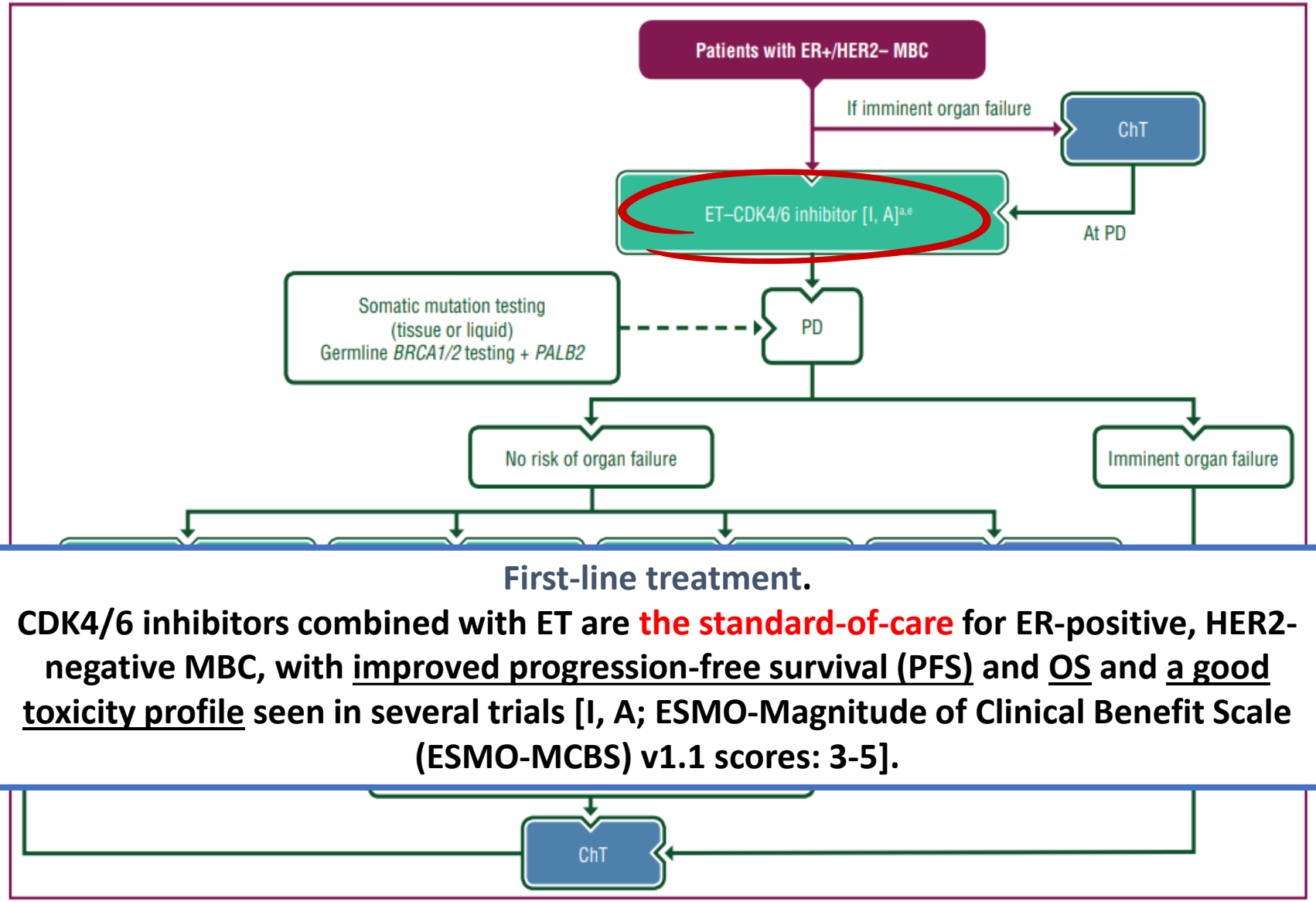
journal homepage: www.elsevier.com/brst

Exploratory analysis of biomarkers associated with clinical outcomes from the study of palbociclib plus endocrine therapy in premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer

Conclusion:
palbociclib plus ET, luminal type showed better prognosis.

[a] Division of Oncology-Hematology, Department of Internal Medicine, Korea University College of Medicine, Korea University Anam Hospital, Seoul, South Korea
[b] Samsung Genome Institute, Samsung Medical Center, Seoul, South Korea

50% in each arm treated in first-line metastatic setting



First-line treatment.

CDK4/6 inhibitors combined with ET are the standard-of-care for ER-positive, HER2-negative MBC, with improved progression-free survival (PFS) and OS and a good toxicity profile seen in several trials [I, A; ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 scores: 3-5].

Figure 2. Treatment of ER-positive/HER2-negative MBC.

Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy.

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4 and 6; ChT, chemotherapy; EMA, European Medicines Agency; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESR1, estrogen receptor 1; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; m, mutation; MBC, metastatic breast cancer; MCBS, ESMO-Magnitude of Clinical Benefit Scale; OFS, ovarian function suppression; *PALB2, partner and localiser of BRCA2*; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; *PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha*.

[a] OFS if the patient is premenopausal.

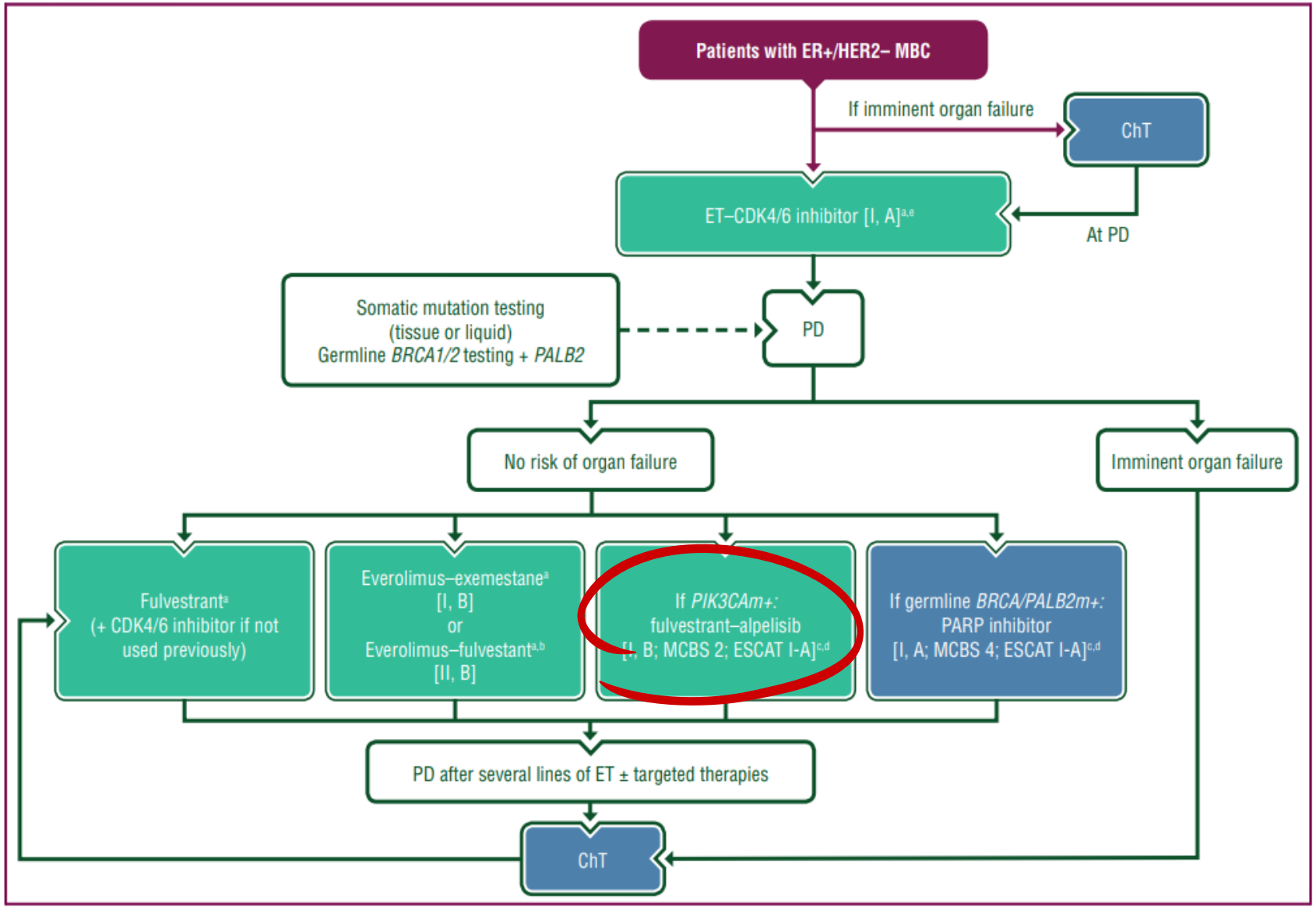
HR+/HER2- MBC: Beyond First-line Treatment

- Most patients with HR+/HER2- MBC will develop resistance to first-line CDK4/6i + ET
- **Endocrine resistance (ESMO guidelines)**
  - **Primary:** PD within first 6 mo of first-line ET for MBC, while on ET
  - **Secondary:** PD 6 mo after starting ET for MBC, while on ET

- Addtional targeted therapies and associated biomarker testing
  - ✓Alpelisib for *PIK3CA*m
  - ✓PARP inhibitors (olaparib or talazoparib) for g*BRCA1/2*m
  - ✓Everolimus (no biomarker testing required)

 3. Mayer. Clin Cancer Res. 2017;23:26. 4. Loi. PNAS. 2010;107:10208. 5. Stemke-Hale. Cancer Res. 2008;68:6084.

Slide credit: ProCE.com and clinicaloptions.com



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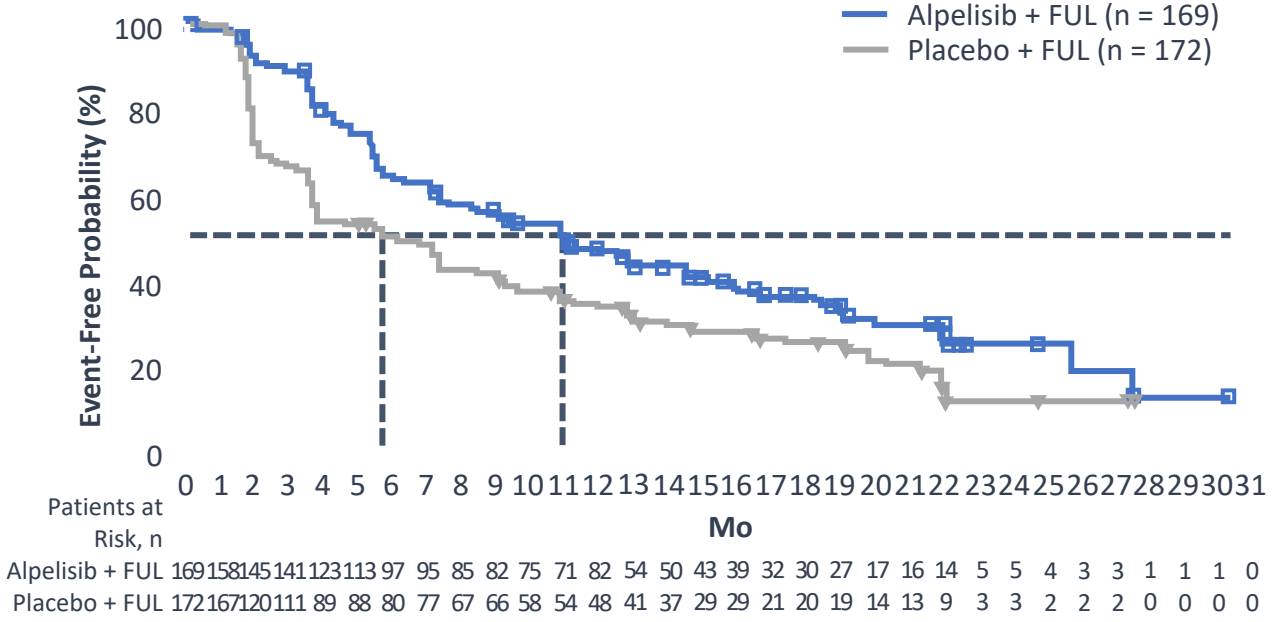
[a] OFS if the patient is premenopausal.

SOLAR-1: PFS and OS Results in *PIK3CA*-mut After perior AI

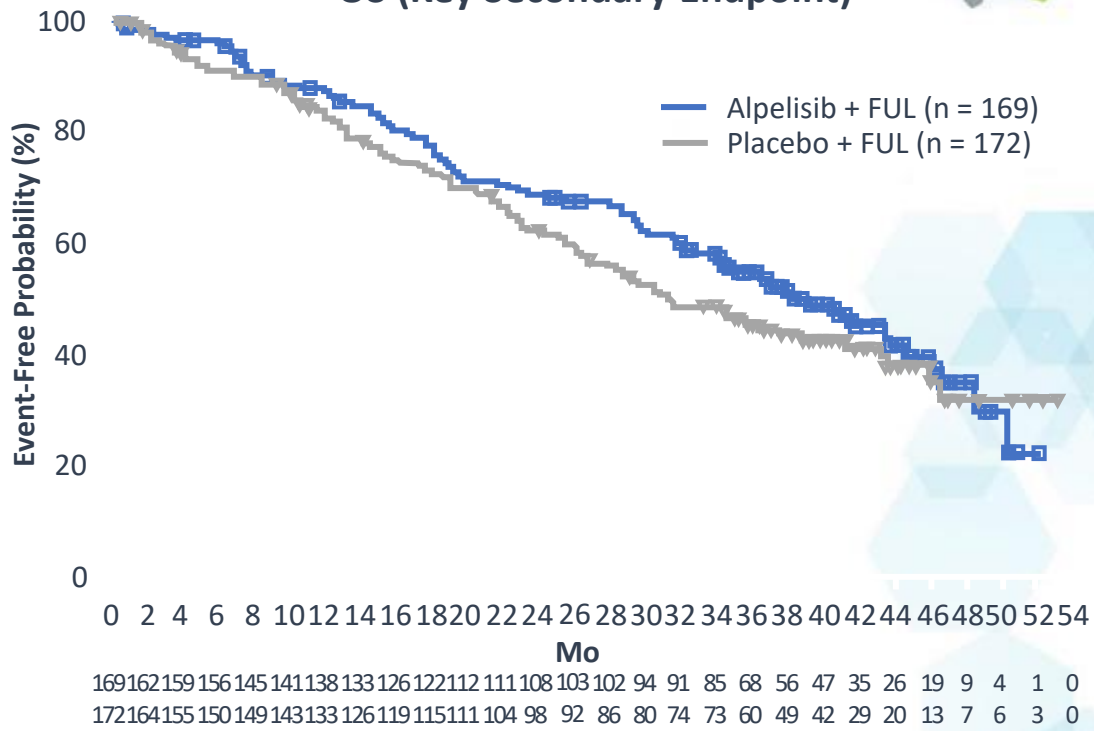
Only 6% of patients with prior CDK4/6i exposure

PFS (Primary Endpoint)



Median PFS 11.0 vs 5.7 months
HR 0.65 (0.50–0.85)
P = .00065

OS (Key Secondary Endpoint)



Median OS 39.3 vs 31.4 months
HR 0.86 (0.64–1.15)
P = .15

Slide credit: clinicaloptions.com

Table 1. BYLieve patient cohorts and treatment assignments

Cohort	Immediate prior therapy	Study treatment

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Breast Cancer

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ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING FOR RECURRENT UNRESECTABLE (LOCAL OR REGIONAL) OR STAGE IV (M1) DISEASE

Biomarkers Associated with FDA-Approved Therapies

Breast Cancer Subtype	Biomarker	Detection	FDA-Approved Agents	NCCN Category of Evidence	NCCN Category of Preference
HR-positive/ HER2-negative[v]	*PIK3CA* activating mutation	PCR (blood or tissue block if blood negative)	Alpelisib + fulvestrant[w]	Category 1	Preferred second- or subsequent-line therapy
Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[x] Entrectinib[x]	Category 2A	Useful in certain circumstances
Any	MSI-H/dMMR	IHC, NGS, PCR (tissue block)	Pembrolizumab[y,z] Dostarlimab-gxly[aa]	Category 2A	
Any	TMB-H (≥10 mut/mb)	NGS	Pembrolizumab[y,z]	Category 2A	
Any	*RET*-fusion	NGS	Selpercatinib[bb]	Category 2A	

Alpelisib Monitoring Requirements

All Patients[1]

Verify pregnancy status in women of reproductive potential prior to initiating alpelisib

Consider an antihistamine when initiating alpelisib

- Prophylactic antihistamines administered prior to rash onset on SOLAR-1 decreased incidence and severity of rash

Assess FPG and A1C before initiating treatment with alpelisib

- Optimize blood glucose before initiating alpelisib
- Consider prophylactic metformin

Plan for glucose monitoring after treatment initiation

Monitor fasting glucose:

- At least weekly during the first 2 wks
- Then at least every 4 wks and as clinically indicated

Monitor A1C:

- Every 3 mo and as clinically indicated

Hyperglycemia Monitoring Schedule[1,2]

Additional monitoring as clinically indicated

Prediabetic/Diabetic Patients*[1]

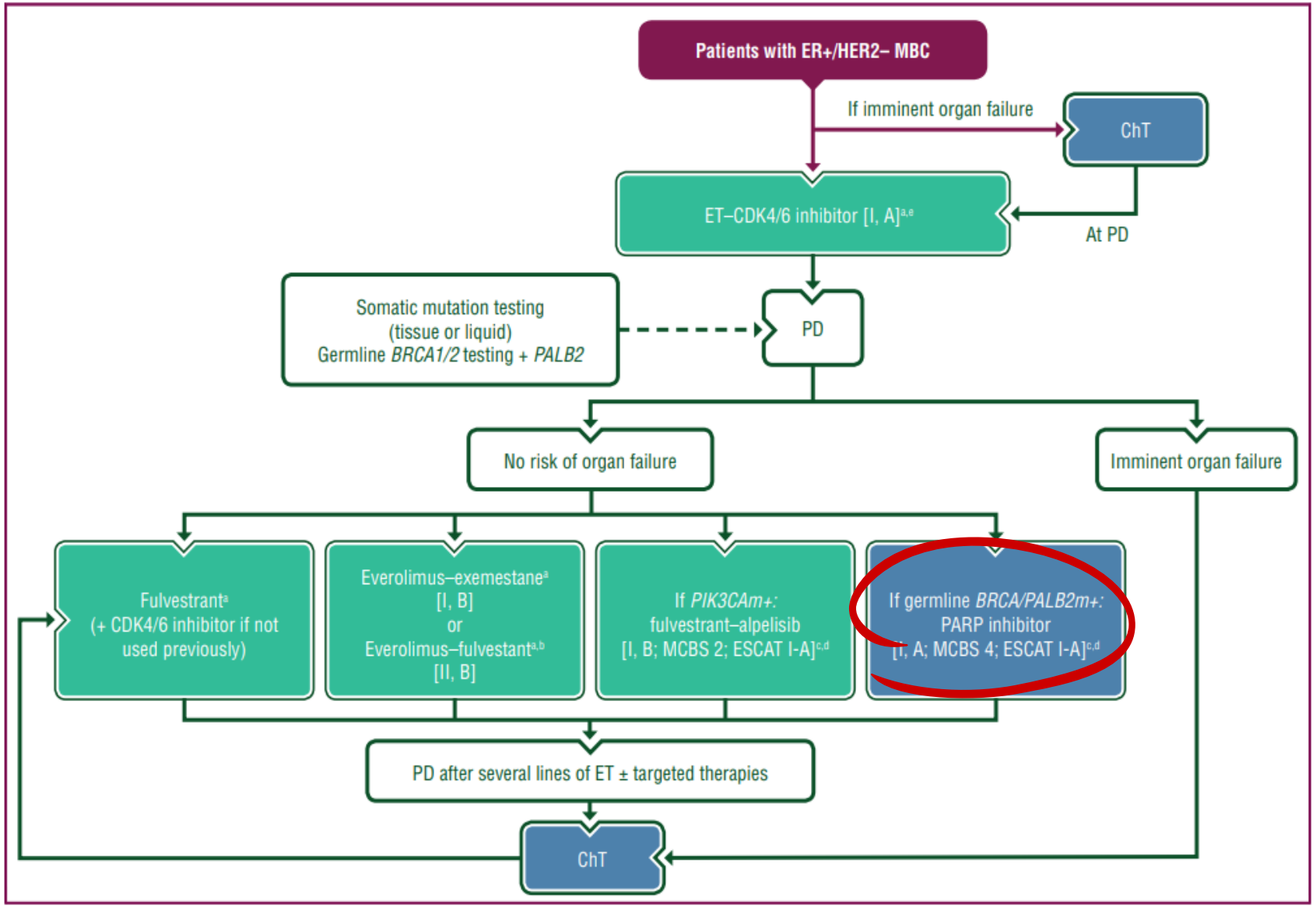
Closely monitor glucose, may require intensified antihyperglycemic treatment

Counsel patients on lifestyle changes related to exercise and dietary intake, as appropriate

*SOLAR-1 excluded patients with type 1 diabetes or uncontrolled type 2 diabetes. At baseline in alpelisib arm, 56% of patients were prediabetic (FPG 5.6 to <7.0 mmol/L and A1C 5.7% to <6.5%) and 4% were diabetic (FPG ≥7.0 mmol/L or A1C ≥6.5%).[2,3]

1. Alpelisib PI. 2. Rugo. Ann Oncol. 2020;31:1001. 3. André. NEJM. 2019;380:1929.

Slide credit: ProCE.com and clinicaloptions.com



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[a] OFS if the patient is premenopausal.

PARP Inhibitor Phase III Trials in *BRCA1/2*-Positive, HER2- MBC

Trial	N	Prior Therapy	Stratification	Intervention	Median PFS, Mo Hazard Ratio (95% CI)
OlympiAD[1]	302	Anthracycline and taxane; ≤2 prior lines of CT* for MBC; If HR+, not suitable for ET or PD on ≥1 ET	HR status; prior CT for MBC; prior platinum tx	**Olaparib**† 300 mg PO BID (n = 205) vs **CT**‡ (n = 97)	**7.0 vs 4.2** 0.58 (0.43-0.80) *P* <.001
EMBRACA[2]	431	Anthracycline and/or taxane; ≤3 previous lines of CT§ for ABC	HR status, prior CT; history of CNS mets	**Talazoparib** 1 mg PO QD (n = 287) vs **CT**# (n = 144)	**8.6 vs 5.6** 0.54 (0.41-0.71) *P* <.001

*If platinum-based tx, patient could not have experienced PD on tx in advanced setting or ≥12 mo since (neo)adjuvant tx. †Tablet. ‡Physician's choice of: capecitabine 2500 mg/m^2 PO Days 1-14; vinorelbine 30 mg/m^2 IV Days 1/8; or eribulin 1.4 mg/m^2 IV Days 1/8 (21-day cycles). § Previous platinum-based therapy for EBC permitted if DFI ≥6 mo. #Physician's choice of: capecitabine 1250 mg/m^2 PO BID Days 1-14; eribulin 1.4 mg/m^2 IV Days 1/8; gemcitabine 1250 mg/m^2 IV Days 1/8; or vinorelbine 30 mg/m^2 IV Days 1/8/15 (21-day cycles)

1. Robson. NEJM. 2017;377:523. 2. Litton. NEJM. 2018;379:753.

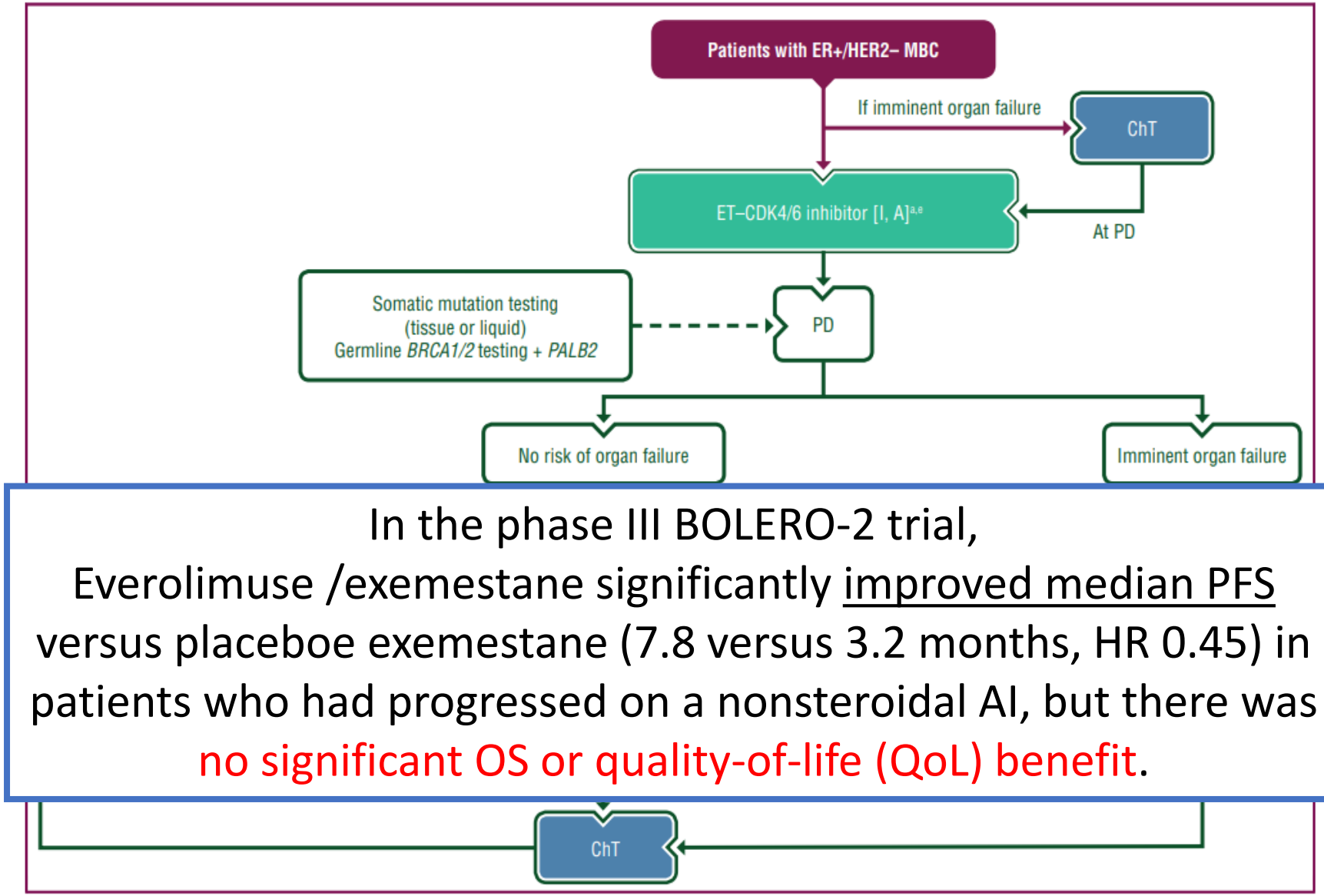
Practical Management Strategies: PARPi Adverse Events

	Olaparib	Talazoparib
Anemia*	Hb <8 g/dL and/or requiring transfusion for symptomatic relief: ▪ Monitor closely ▪ Recurrent: Dose reduce to avoid multiple transfusions	Hb <8 g/dL: ▪ Hold until Hb ≥9 g/dL ▪ Resume at a reduced dose
Neutropenia	ANC <500 lasting ≥5-7 days or associated with fever: ▪ Hold until recovery of infection and granulocytes ▪ Resume at a reduced dose	ANC <1000: ▪ Hold until ANC ≥1500 ▪ Resume at a reduced dose
Thrombocytopenia	Persistent or significant bleeding despite dose reduction: ▪ Discontinue olaparib	PLT <50,000: ▪ Hold until PLT ≥75,000 ▪ Resume at reduced dose
Gastrointestinal	▪ Moderate emetogenicity; 5-HT3 receptor antagonists (eg, ondansetron) recommended as prophylaxis ▪ Persistent nausea requiring daily antiemetics and/or resulting in >5% weight loss: Consider dose reduction	
Secondary MDS/AML (rare)	▪ Incidence: olaparib 1.5%; talazoparib <1% ▪ If prolonged hematologic toxicity occurs (>grade 1 for >4 weeks), further evaluation is warranted†	
Pneumonitis‡ (rare)	▪ Interrupt treatment and evaluate promptly for new or worsening respiratory symptoms (eg, cough, dyspnea, fever, wheezing), or radiographic abnormalities ▪ Permanently discontinue olaparib if pneumonitis confirmed	

*Most frequently AE reported with PARPi; †Including bone marrow and cytogenetic evaluation; ‡Olaparib only

Tew. J Clin Oncol. 20202;38:3468. Olaparib PI. Talazoparib PI.

Slide credit: ProCE.com and clinicaloptions.com



In the phase III BOLERO-2 trial,
Everolimuse /exemestane significantly improved median PFS versus placeboe exemestane (7.8 versus 3.2 months, HR 0.45) in patients who had progressed on a nonsteroidal AI, but there was no significant OS or quality-of-life (QoL) benefit.

Figure 2. Treatment of ER-positive/HER2-negative MBC.

Purple: general categories or stratification; turquoise: combination of treatments or other systemic treatments; white: other aspects of management; blue: systemic anticancer therapy.

AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4 and 6; ChT, chemotherapy; EMA, European Medicines Agency; ER, estrogen receptor; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESR1, estrogen receptor 1; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; m, mutation; MBC, metastatic breast cancer; MCBS, ESMO-Magnitude of Clinical Benefit Scale; OFS, ovarian function suppression; *PALB2, partner and localiser of BRCA2*; PARP, poly (ADP-ribose) polymerase; PD, progressive disease; *PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha*.

[a] OFS if the patient is premenopausal.

HR+/HER2- MBC: Beyond Third-line Treatment

- For patients with endocrine-sensitive tumours, continuation of ET with agents not previously received in the metastatic setting may represent an option [III, B].
- Patients with tumours that are endocrine resistant should be considered for ChT [V, B].
- Sequential single-agent ChT is generally preferred over combination strategies. In patients where a rapid response is needed due to imminent organ failure, combination ChT is preferred [II, A].
- Available drugs for single-agent ChT include anthracyclines, taxanes, capecitabine, eribulin, vinorelbine, platinums and other agents. Rechallenge with anthracyclines or taxanes is feasible in patients with a DFI 12 months. If available, the use of liposomal anthracyclines or protein-bound paclitaxel may be considered for the rechallenge [II, B].
- The combination of a taxane or capecitabine with bevacizumab, if available, is an option for the first line of ChT [I, C; ESMO-MCBS v1.1 score: 2].
- If capecitabine is used, patients should undergo germline variant testing for the lack of enzyme, DPD, before starting treatment. ChT should generally be continued until PD or intolerable toxicity (except for anthracyclines where the cumulative limit needs to be taken into account) [II, B].
- The optimal sequence of therapy in MBC has not been established. Available options should be discussed with the patient [I, A].

https://doi.org/10.1016/j.annonc.2021.09.019

EMERALD: Elacestrant vs SoC in HR+/HER2- MBC

- 477 men and postmenopausal women with ER+/HER2- MBC who progressed after 1-2 lines of ET(1 line with a CDK4/6 inhibitor); ≤1 line of chemo for advanced disease
- Randomized to elacestrant 400 mg PO daily vs SoC
  - SoC: investigator's choice of fulvestrant, anastrozole, letrozole, exemestane
- Coprimary endpoints: PFS in all patients, PFS in patients with *mESR1* (BICR)
- Prespecified subgroups generally showed a consistent trend toward improved PFS with elacestrant vs SoC

	All Patents		Patients With *mESR1*	
	Elacestrant (n = 239)	SoC (n = 238)	Elacestrant (n = 115)	SoC (n = 113)
Median PFS, mo	2.79	1.91	3.78	1.87
▪ HR (95% CI)	0.697 (0.552-0.880)		0.546 (0.387-0.768)	
▪ *P* value	.0018		.0005	

	Elacestrant (n = 239)	FULV (n = 165)	Elacestrant (n = 115)	FULV (n = 83)
Median PFS, mo	2.79	1.94	3.78	1.87
▪ HR (95% CI)	0.684 (0.521-0.897)		0.504 (0.341-0.741)	
▪ *P* value	.0049		.0005	

- Although data are not yet mature, trend toward improved OS observed with elacestrant vs SoC among all patients and patients with *mESR1*

Bardia. SABCS 2021. Abstr GS2-02.

Slide credit: ProCE.com and clinicaloptions.com

FDA Approves Elacestrant for ER-Positive, HER2-Negative, *ESR1*-Mutated Advanced or Metastatic Breast Cancer

By The ASCO Post Staff

A statistically significant difference in progression-free survival was observed in the intention-to-treat (ITT) population and in the subgroup of patients with *ESR1* mutations.
In the 228 (48%) patients with *ESR1* mutations, median progression-free survival was 3.8 months (95% CI confidence interval [CI] = 2.2–7.3) in the elacestrant arm and 1.9 months (95% CI = 1.9–2.1) in the fulvestrant or aromatase inhibitor arm (hazard ratio [HR] = 0.55, 95% CI = 0.39–0.77, two-sided *P*-value = .0005).

Patients were randomly assigned 1:1 to receive elacestrant at 345 mg orally once daily (n = 239) or investigator's choice of endocrine therapy (n = 239), which included fulvestrant (n = 166) or an aromatase inhibitor (n = 73). Random assignment was stratified by *ESR1* mutation status (detected vs not detected), prior treatme…he
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The recommended elacestrant dose is 345 mg taken orally with food once daily until disease progression or unacceptable toxicity.

In the 228 (48%) patients with *ESR1* mutations, median progression-free survival was 3.8 months (95% CI confidence interval [CI] = 2.2–7.3) in the elacestrant arm and 1.9 months (95% CI = 1.9–2.1) in the fulvestrant or aromatase inhibitor arm (hazard ratio [HR] = 0.55, 95% CI = 0.39–0.77, two-sided *P*-value = .0005).
An exploratory analysis of progression-free survival in the 250 (52%) patients without *ESR1* mutations showed a hazard ratio of 0.86 (95% CI = 0.63–1.19), indicating that the improvement in the ITT population was primarily attributed to the results seen in the *ESR1*-mutated population.
The most common adverse events (≥ 10%), including laboratory abnormalities, were musculoskeletal pain, nausea, increased cholesterol, increased aspartate aminotransferase, increased triglycerides, fatigue, decreased hemoglobin, vomiting, increased alanine transaminase, decreased sodium, increased creatinine, decreased appetite, diarrhea, headache, constipation, abdominal pain, hot flush, and dyspepsia.
The recommended elacestrant dose is 345 mg taken orally with food once daily until disease progression or unacceptable toxicity.
This review used the Assessment Aid, a voluntary submission from the applicant to facilitate the FDA's assessment. This application was granted Priority Review and Fast Track designation.

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Any	*NTRK* fusion	FISH, NGS, PCR (tissue block)	Larotrectinib[x] Entrectinib[x]	Category 2A	Useful in certain circumstances
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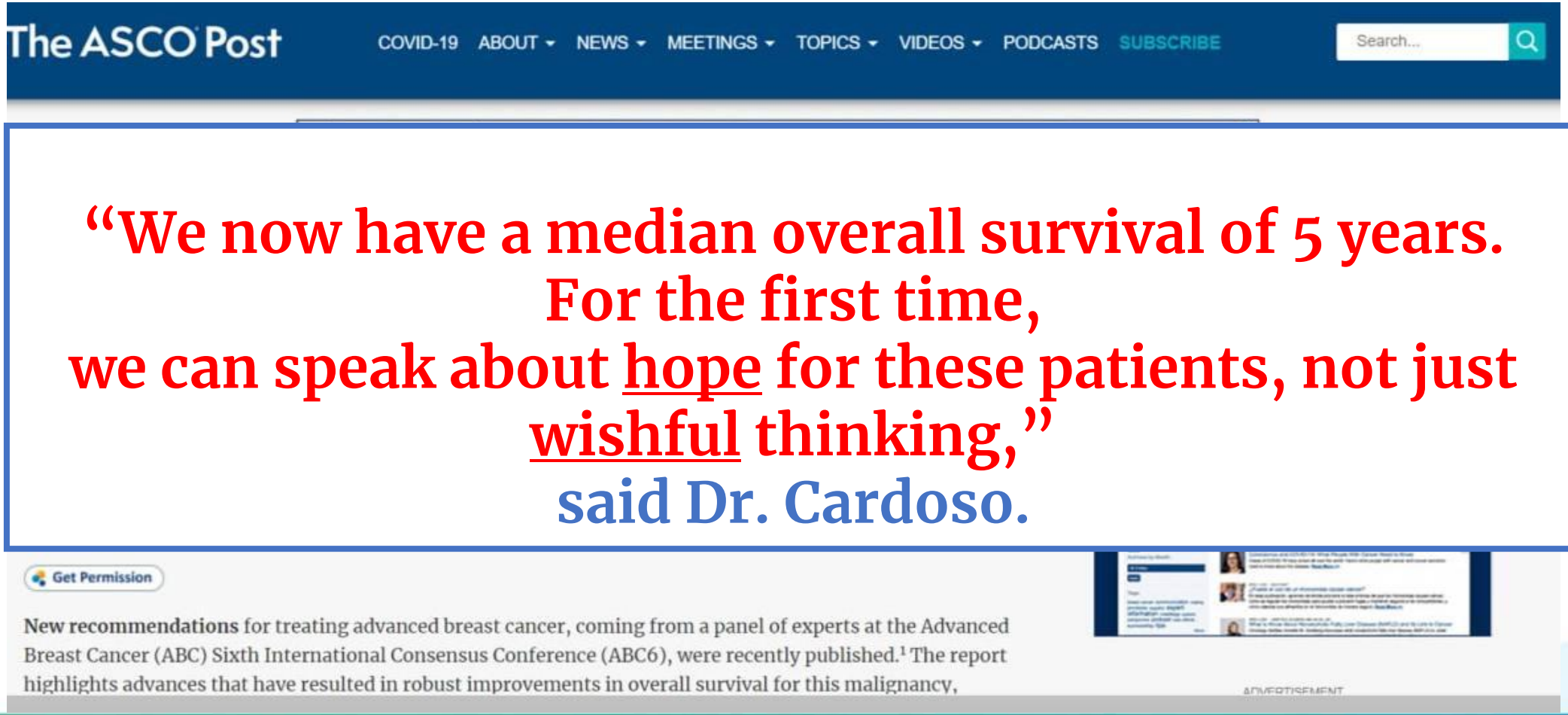
Any	TMB-H (≥10 mut/mb)	NGS	Pembrolizumab[y,z]	Category 2A	
Any	*RET*-fusion	NGS	Selpercatinib[bb]	Category 2A	

Key Points to Consider:

- Pembrolizumab (MSI-H/dMMR) (TMB-H)
- Larotrectinib/entrectinib (*NTRK* fusions)
- Antibody–drug conjugates:
  - **Trastuzumab deruxtecan** might be FDA approved for HER2-low metastatic breast cancer in patients with no more than 2 lines of chemotherapy
  - **Sacituzumab govitecan** demonstrated statistically significant efficacy compared to standard chemotherapy in endocrine refractory MBC who have received 2-4 lines of chemotherapy

Take home massage



"We now have a median overall survival of 5 years.
For the first time,
we can speak about <u>hope</u> for these patients, not just <u>wishful</u> thinking,"
said Dr. Cardoso.