2019 HR+ Metastatic Breast Cancer Consensus

主編

台灣乳房醫學會

BREAST CANCER SOCIETY OF TAIWAN

序

隨著醫學進展，近年來乳癌患者存活率已大幅提高，乳癌治療牽涉的範圍甚廣，仍舊有許多需要克服的地方，但在一些重要議題上，隨著許多臨床試驗結果的發表，國際間已經漸漸產生共識，學會秉持加強乳房疾病之醫療、教學及研究之宗旨精神，特參照國際準則並因應國內狀況，制定全國性的治療共識，給予乳癌領域相關醫生遵循參考，是本人擔任理事長任內的重要目標，循此，在秘書長曾令民醫師策劃籌辦下，2017年學會已順利舉辦了Neoadjuvant Leading Opinion Symposium並形成早期乳癌的術前輔助治療共識。現今晚期賀爾蒙陽性乳癌患者，因著標靶藥物加入有了新的突破性發展，國內醫師對於晚期荷爾蒙受體陽性乳癌患者的治療策略共識，亦是亟需討論制定的。據此，在本人及曾秘書長的努力下，再次匯聚了臨床專家之意見，以晚期荷爾蒙受體陽性病人的危險評估處置為出發點，至第一及第二線用藥的選擇，無論是賀爾蒙療法、化學療法的使用時機，更將新的標靶藥物加入臨床應用的討論範疇，此為本人任內第二個共識。接下來將建立老年乳癌治療共識，期望為台灣乳癌治療建立一套完整醫療流程。

現今乳癌治療在國際間已有許多實證，本手冊內容是彙整國內專家們豐碩之臨床經驗與研究成果，經由台灣乳房醫學會第七屆理監事會議通過，希望能夠提供臨床醫師重要參考。最後特別感謝以下專家提供寶貴意見

理事長：沈陳石銘

秘書長：曾令民

歷屆理事長：張金堅、劉自嘉、侯明鋒、陳訓徹、俞志誠、黃俊升

理監事及委員：杜世興、張宏泰、張振祥、陳守棟、鄭翠芬、歐陽賦、于承平
王　甄、張獻崑、許居誠、許桓銘、郭文宏、陳達人、楊圳隆
葉大成、葉名煝、葉顯堂、趙祖怡、劉建良、饒坤銘、陳芳銘
趙大中、沈士哲、洪朝明、張源清、盧彥伸、謝家明、王明暘
莊捷翰、郭耀隆、黃其晟、廖國秀、劉良智、劉峻宇、羅　喬
李國鼎

及以下專家：王惠暢醫師、邱昌芳醫師、高偉堯醫師、陳鵬宇醫師、蔡青樺醫師
戴明燊醫師

甚盼能藉此拋磚引玉，有更多的精研發展以造福乳癌患者。

本治療共識謹做為參考，因每人狀況不同，而由各醫師選擇最適當之處置方式，不作為醫療訴訟用

Contents

HR+ risk evaluation and management

01 Factors to consider when selecting treatment options for hormone receptor–positive metastatic breast cancer patients

Patient	• Age • Menopausal status • Comorbidities • Performance status	• Expectations and preferences • Toxicities to previous treatments • Adherence, compliance
Tumor	• Histological subtype • Expression intensity of hormone receptors • HER2 overexpression/ amplification	• Intrinsic subtype • Predictive biomarkers
Disease	• Site of metastasis • Tumor burden • Symptomatic and/ or need for rapid response • Previous endocrine treatment (ET)	• Disease–free interval on adjuvant setting • Response to previous ET • Duration of disease control to previous ET
Agent	• Mechanism of action • Expected toxicities • Pharmacological interactions • Availability	• Cost • Route of administration • Efficacy • Concomitant Medication
Other issues	• Availability of clinical research • Existing guidelines • Financial hardship • Social support	

02 Treatment principles for risk of deterioration of tumor characteristics

- Every ABC patient must have access to optimal cancer treatment and supportive care according to the highest standards of patient–centred care. (ABC4: LoE/GoR: Expert opinion/A)

- Differing therapies shall be provided to patients of varying tumor characteristics and risks of disease progression. (BCST, LoE: Expert Opinion)

03 “Overall survival” vs drug selection

- As survival is improving in many patients with ABC, consideration of survivorship issues should be part of the routine care of these patients. (ABC4: LoE/GoR: Expert opinion/A)

- Overall survival rate is a long–term goal in clinical treatments. However, care regarding the patient‘s disease progression, personal needs, and willingness to receive treatment must be taken during the treatment process. (BCST, LoE: Expert Opinion)

- In addition to assessing alleviation of the disease, extended disease free survival , and absence of drug side effects on the patient, as well as improve–ment to the patient's quality of life are all crucial therapeutic indicators to the clinical efficacy of a drug. (BCST, LoE: Expert Opinion)

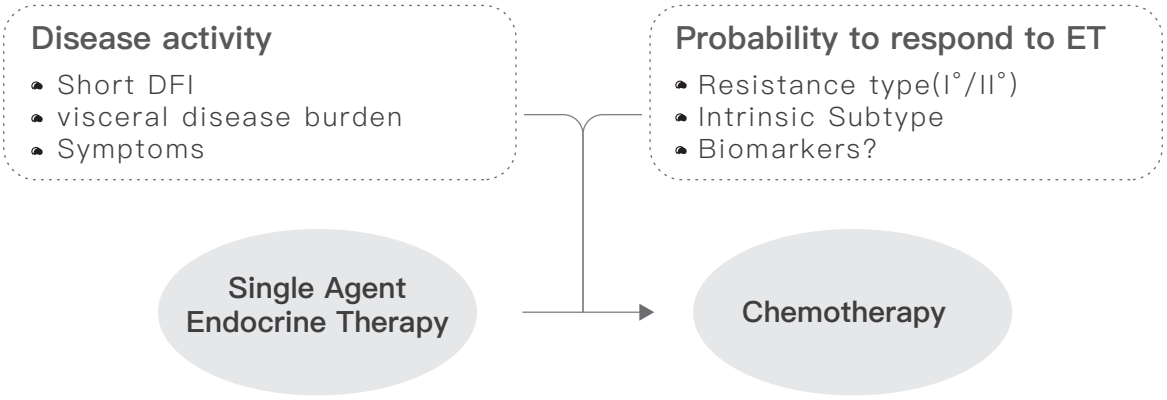
Selection of first–line treatment for post menopausal hormone receptor–positive metastatic breast cancer

01 Endpoint

1. In 2016, the European Society for Medical Oncology (ESMO) advised selecting first–line treatment drugs according to various disease progression risks for the patient

- **Low risk of disease progression:**
  Prefer endocrine therapy alone, or endocrine therapy + CDK4/6i
- **Medium risk of disease progression:**
  Prefer endocrine therapy + CDK4/6i, or endocrine therapy alone or chemotherapy
- **High risk of disease progression:**
  Prefer chemotherapy, or endocrine therapy + CDK4/6i

First line therapy: ET alone or ET + CDK4/6 or Chemotherapy



CDK4/6 inhibitors + Endocrine Therapy

Low Risk	Intermediate Risk	High Risk
Single agent ET* (ET + CDK4/6)	ET + CDK4/6 (Single agent ET) (Chemo)	Chemo ET + CDK4/6

Visceral/non–visceral?
* ESR1 Mutation and choice of ET

Courtesy Peter Schmid, ESMO 2016, Discussant

2. Treatment choice should take into account at least these factors: 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, available therapies in the patient's country and patient's preferences. (ABC4: LoE/GoR: Expert opinion/A)

3. Clinically, various disease progression risks must be used as a basis for designing personalized treatments for the patient.

Indicators for assessing disease progression risks include

Tumor	ER%, PR%, HER–2 status
Patient	Age, Menopausal status, Comorbidities, Organ function, Patient preference (Socio–economic, psychologic factors.)
Disease	Disease free interval (DFI), Visceral disease burden, Symptom
RxHistory	Response to prior Rx

(BCST, LoE: Expert Opinion)

02 First–line standard treatment principles of fulvestrant monotherapy or endocrine Therapy + CDK4/6i combination therapy for post menopausal hormone receptor–positive metastatic breast cancer

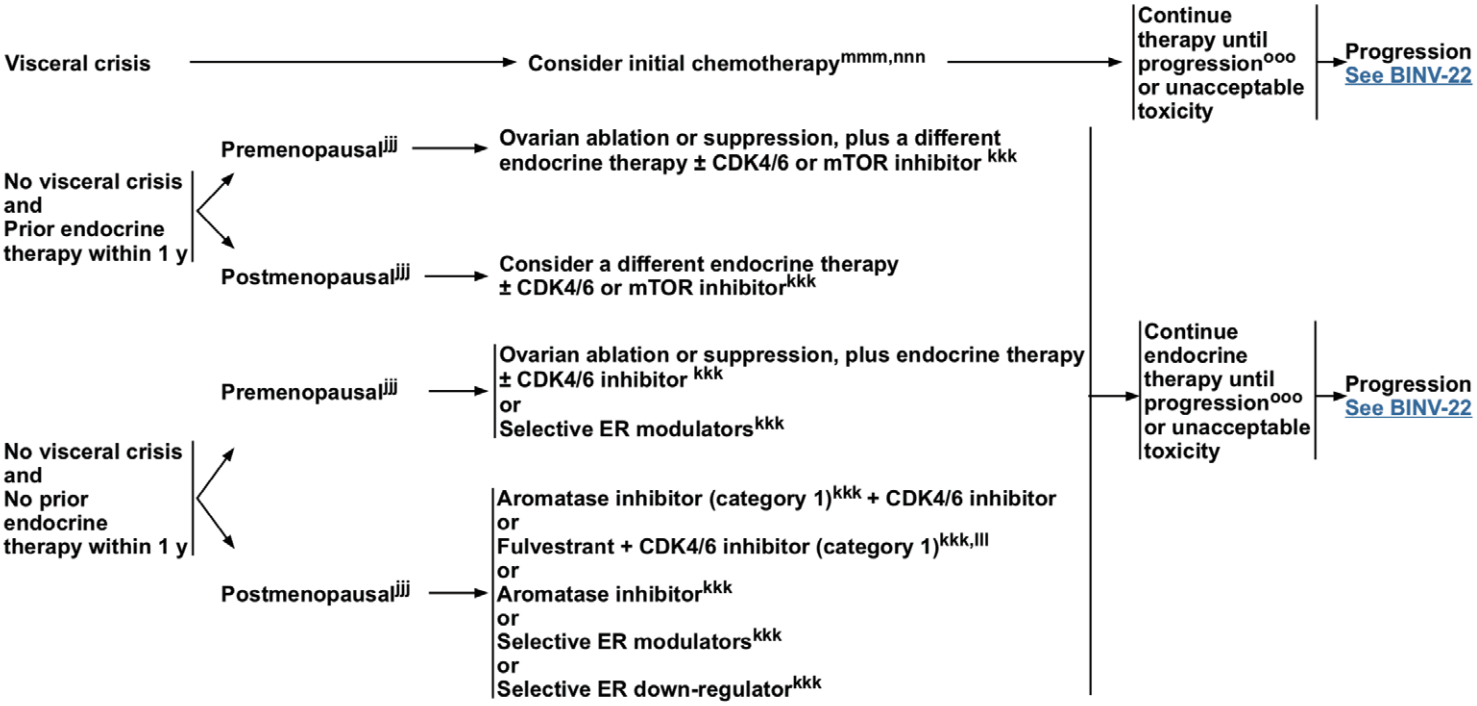
- ET is the preferred option for HR–positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance (ABC4: LoE/GoR: I/A)

- The addition of a CDK 4/6 inhibitor to an AI, in patients naïve or pre–exposed to ET, provided a significant improvement in median PFS (10 months), with an acceptable toxicity profile, and is, therefore, one of the preferred treatment options for pre– and peri–menopausal women with OFS/OFA, men (preferably with LHRH agonist) and post–menopausal women. (ABC–4, LoE: 1A)

- According to the 2019 NCCN Guideline, it is recommended that the first–line standard treatment for post menopausal hormone receptor–positive metastatic breast cancer be aromatase Inhibitor, selective ER modulators, selective ER down–regulator, CDK4/6 inhibitor + aromatase inhibitor or CDK4/6 inhibitor + fulvestrant.

NCCN Guidelines 1.2019 Invasive Cancer

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



- d See Principles of HER2 Testing (BINV–A).
- jjj See Definition of Menopause (BINV–O).
- kkk See Systemic Therapy for ER– and/or PR–Positive Recurrent or Stage IV (M1) lll Disease (BINV–P).
- lll Fulvestrant has been combined with CDK4/6 inhibitors (palbociclib, ribociclib) in the first–line setting in two randomized trials.
- mmm See Chemotherapy Regimens for Recurrent or Stage IV (M1) Disease nnn (BINV–Q).
- nnn Consider PARP–inhibitor monotherapy as an option for patients with HER2– ooo negative tumors and germline BRCA1/2 mutations.
- ooo See Principles of Monitoring Metastatic Disease (BINV–R).

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

- For post menopausal hormone receptor–positive metastatic breast cancer patients, it is recommended for the first–line standard treatment to adopt monotherapy (i.e., tamoxifen, aromatase inhibitor, or fulvestrant) or a combination therapy (i.e., endocrine therapy + CDK4/6i).
  (BCST, LoE: Expert Opinion)

- If the patient is receiving adjuvant therapy and the disease condition deteriorates during the letrozole or anastrazole treatment process, a monotherapy using tamoxifen, another AI, or fulvestrant is recommended; a combination therapy can consist in everolimus+ exemestane or fulvestrant＋CDK4/6i

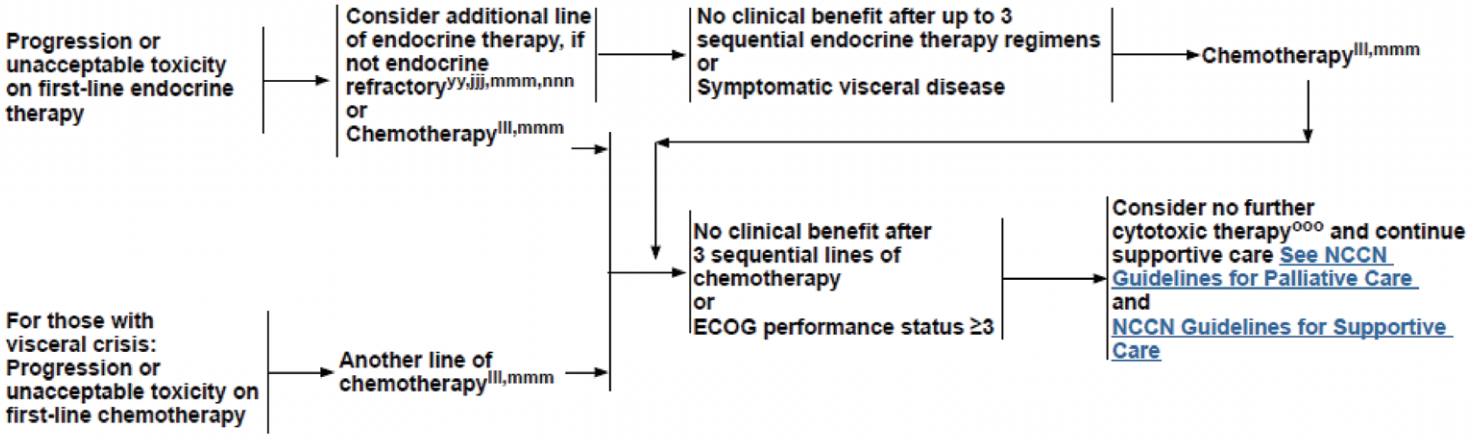
- For post menopausal hormone receptor–positive (non–visceral) metastatic breast cancer patients, the Fulvestrant monotherapy is clinically favorable.
  (BCST, LoE: Expert Opinion)

03 Consideration of first-line drug use affecting last-line drug response in post menopausal hormone receptor-positive metastatic breast cancer

- Based on the urgency of the patient's condition, select the therapy with the most suitable intensity. (BCST, LoE: Expert Opinion)
- According to the 2019 NCCN Guideline, it is recommended that post menopausal hormone receptor-positive metastatic breast cancer patients receive at least 3 sequential lines of endocrine therapy regimens.

NCCN Guidelines 1.2019 Invasive Cancer

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE : ER AND/OR POSITIVE; HER2 NEGATIVE[c]



- d See Principles of HER2 Testing (BINV-A).
- v See Special Considerations for Breast Cancer in Men (BINV-J).
- zz False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).
- kkk See Systemic Therapy for ER- and/or PR-Positive Recurrent or Stage IV (M1) Disease (BINV-P).
- mmm See Chemotherapy Regimens for Recurrent or Stage IV (M1) Disease (BINV-Q).
- nnn Consider PARP-inhibitor monotherapy as an option for patients with HER2- negative tumors and germline BRCA1/2 mutations.
- ooo See Principles of Monitoring Metastatic Disease (BINV-R).
- ppp If there is disease progression while on CDK4/6 inhibitor therapy, there are no data to support an additional line of therapy with another CDK4/6-containing regimen. Likewise, if there is disease progression while on a everolimus- containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.
- qqq The potential side effects of additional chemotherapy may outweigh any clinical benefit in a patient who has a compromised performance status. Patient preference must be taken into account.

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

- Patients treated with fulvestrant in the first-line setting retained sensitivity to subsequent endocrine treatment. (Reference: Breast Cancer Res Treat. 2012 Nov;136(2):503-11.)

- Fulvestrant can down-regulate the estrogen receptor expression based on its unique mechanism of action. If fulvestrant is used in first-line treatment and subsequently administered with other endocrine therapy treatment drugs, clinical therapeutic effects can still be achieved.

Setting/ study	Experimental Arm	Comparator Arm	Key Outcomes	Comments
First-line				
FIRST	FUL500	ANA	FUL superior to ANA	75%pts w/o prior ET
Second-line				
CONFIRM	FUL500	FUL250	FUL500 superior to FUL 250	Longer PFS in FUL 250 arm vs EFFECT; possibly because of more pts in first-line setting and less frequent tumor assessments

AI, Aromatase inhibitor; ANA, anastrozole; ET, endocrine therapy; EXE, exemestane; FUL, fulvestrant; NSAI,nonsteroidal aromatase inhibitor; pts, patients; TAM, tamoxifen; w/o, without

Faslodex without affecting the sensitivity to further endocrine agent

- In terms of response to subsequent (i.e. second–line) endocrine therapy, there does not appear to be a difference between initial (i.e. first–line) antiestrogen therapy with tamoxifen or fulvestrant. In other words, fulvestrant is no more likely than tamoxifen in induce hormone insensitivity.

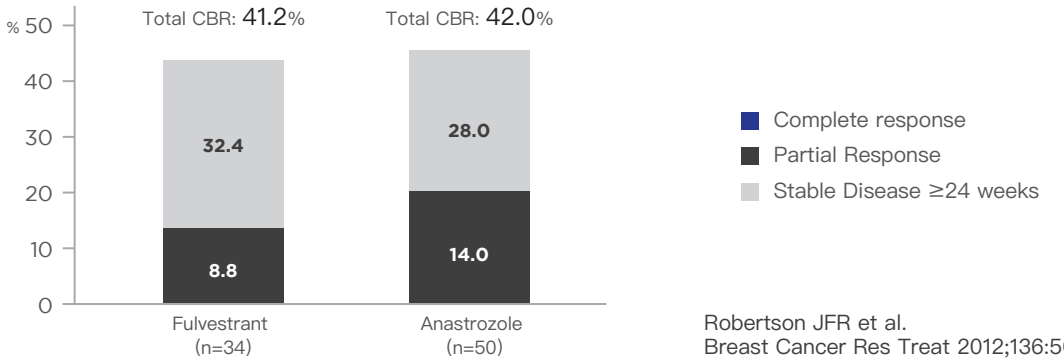
(Breast Cancer Research and Treatment (2005) 92: 169—174)

- Patients treated with fulvestrant in the first–line setting retained sensitivity to subsequent endocrine treatment (Breast Cancer Res Treat (2012) 136:503—511)

Post–progression therapies after Faslodex 1L result from FIRST study

The FIRST study (fulvestrant 500mg)

Of 133 patients receiving subsequent systemic therapy, 84 received endocrine therapy



Robertson JFR et al.
Breast Cancer Res Treat 2012;136:503–11

- response to subsequent therapies (systemic chemotherapy or endocrine therapy) has previously been shown to be similar between the treatment groups, demonstrating that patients with disease progression on fulvestrant retain sensitivity to subsequent treatments

(2015 NOV 10;33(32):3781–7)

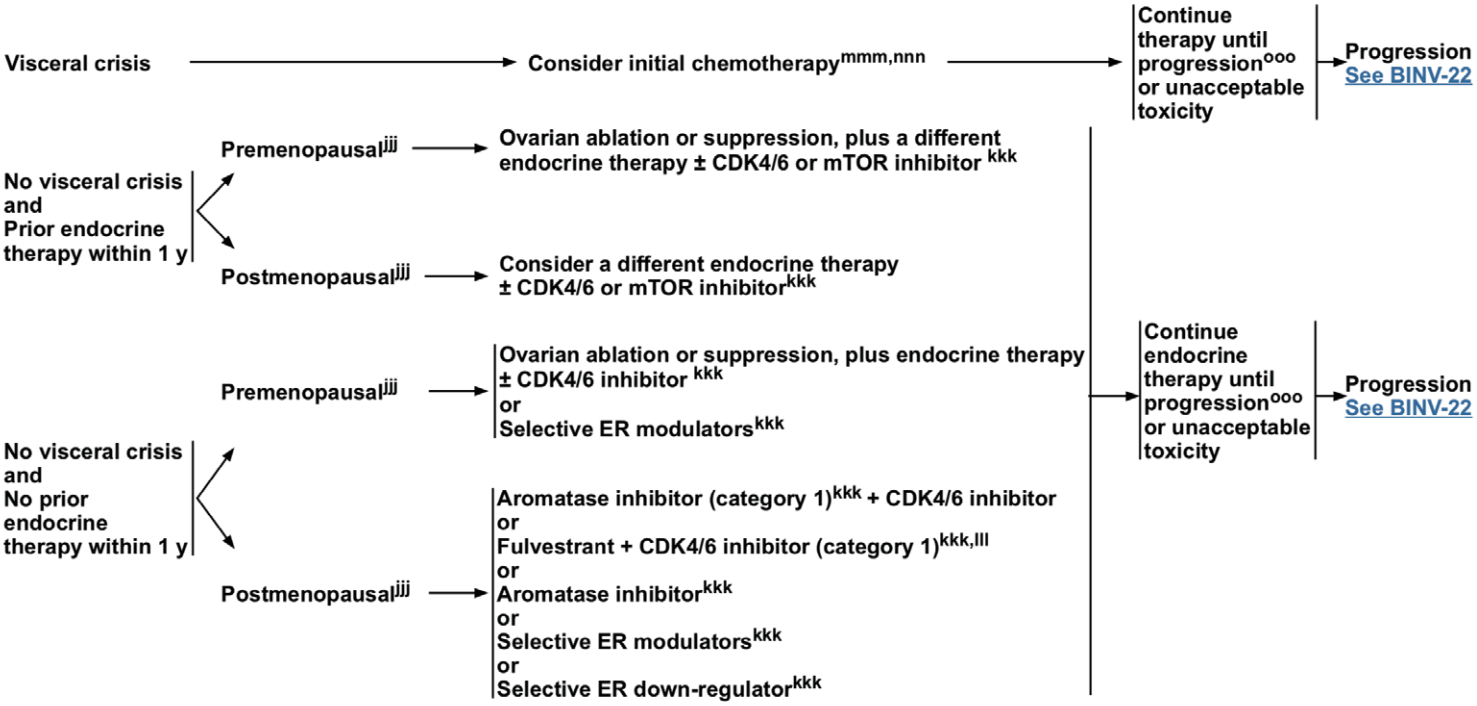
Selection of second–line treatment for post menopausal hormone receptor–positive metastatic breast cancer

01 Drug guideline

- The optimal sequence of endocrine–based therapy is uncertain. It depends on which agents were previously used [in the (neo)adjuvant or advanced settings], the burden of the disease, patients' preference, costs and availability. Available options [for pre– and peri–menopausal women with OFS/OFA, men (preferably with LHRH agonist) and post–menopausal women] include AI, tamoxifen, fulvestrant, AI/fulvestrant + CDK 4/6 inhibitor, AI/tamoxifen/fulvestrant + everolimus. In later lines, also megestrol acetate and oestradiol, as well as repetition of previously used agents, may be used. (ABC4: LoE/GoR: I/A)
- The addition of a CDK 4/6 inhibitor to fulvestrant, in patients previously exposed to ET, provided significant improvement in median PFS (6—7 months) as well as improvement in QoL, and is one of the preferred treatment options, if a CDK 4/6 inhibitor was not previously used, for pre– and peri–menopausal women with OFS /OFA and postmenopausal women and men. OS results are awaited.(ABC4: LoE/ GoR: I/A)
- According to the 2019 NCCN Guideline, it is recommended that the second–line standard therapy for post menopausal hormone receptor–positive metastatic breast cancer patients to be endocrine therapy alone, endocrine therapy + CDK4/6i, or endocrine therapy + mTOR inhibitor
- Previously received therapies must be considered when selecting second–line treatment for post menopausal hormone receptor–positive metastatic breast cancer patients. Aromatase inhibitor, fulvestrant, or tamoxifen can be selected for monotherapy and fulvestrant + CDK4/6i or mTORi + steroid aromatase inhibitor can be selected for combination therapy. (BCST, LoE: Expert Opinion)

NCCN Guidelines 1.2019 Invasive Cancer

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



- d See Principles of HER2 Testing (BINV–A).
- jjj See Definition of Menopause (BINV–O).
- kkk See Systemic Therapy for ER– and/or PR–Positive Recurrent or Stage IV (M1) lll Disease (BINV–P).
- lll Fulvestrant has been combined with CDK4/6 inhibitors (palbociclib, ribociclib) in the first–line setting in two randomized trials.
- mmm See Chemotherapy Regimens for Recurrent or Stage IV (M1) Disease nnn (BINV–Q).
- nnn Consider PARP–inhibitor monotherapy as an option for patients with HER2– ooo negative tumors and germline BRCA1/2 mutations.
- ooo See Principles of Monitoring Metastatic Disease (BINV–R).

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

Novel agents for post menopausal hormone receptor–positive metastatic breast cancer

01 Treatment positioning of mTOR inhibitor in late stage breast cancer therapy

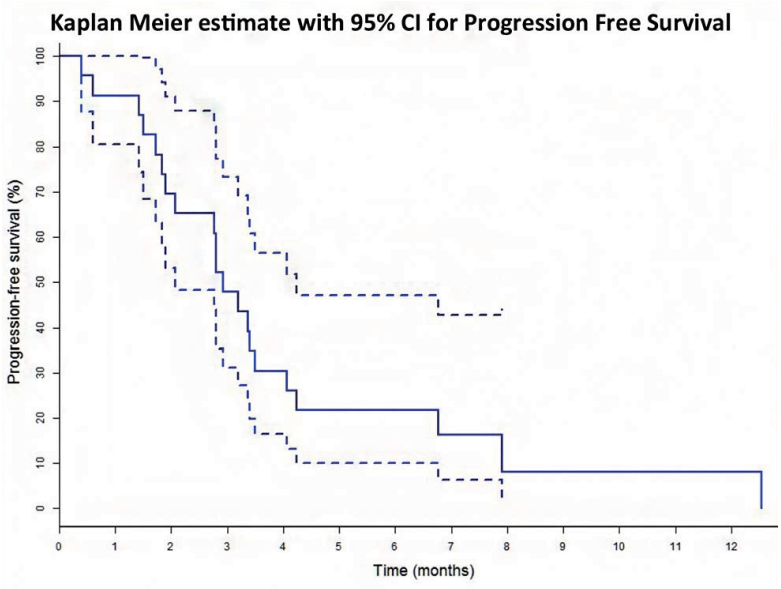
- 2017 American Society of Clinical Oncology (ASCO)

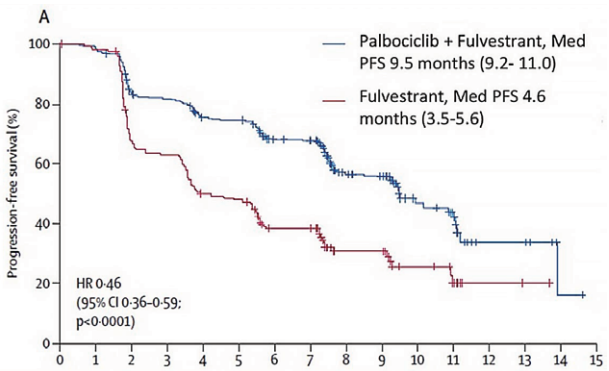
Outcome of Palbociclib Based Therapy in Hormone Recptor Positive Metastatic Breast Cancer Patients After Treatment With Everolimus

Ajay Dhakal, Christina Matthews, Fan Zhang, Ellis G Levine, Stephen B Edge,Kilian E Salerno, Tracy O'Connor, Amy P Early, Thaer Khoury, Kazuzki Takabe, Jessica S Young, Mateusz Opyrchal
Roswell Park Canaer Institute, Buffalo, NY

Conclusion

Outcomes with palbociclib in HR+ everolimus treated MBCP were worse when compared to the palbociclib cohort of PALOMA 3 trial. Treatment with everolimus may lead to resistance to CDK inhibition. Further studies including more patients are necessary to confirm these findings. The data would provide further evidence to allow best sequencing of therapies in HR+ metastatic breast cancer patients.





Progression Free Survival(PFS) with 95% CI of Study Cohort(Left) showing Median PFS 2.9(2.0–4.2) months while Palbociclib cohort from PALOMA 3 (above, blue) 9.5(9.2–11.0) months.

Variables	Study Cohort		Palbociclib Cohort of PALOMA 3		p value
Population	23		347		
Complete response	0	(0%)	0	(0%)	
Partial Response	0	(0%)	66	(19%)	
Stable disease	5	(21.7%)	213	(61%)	
Progressive disease	18	(78.2%)	58	(17%)	
Objective tumor response	0	(0%)	66	(19%)	0.02*
Clinical Benefit#	4	(17.4%)	231	(67%)	0.00*

* Fisher's Exact test #CR, PR or SD of at least 24 weeks

- With palbociclib combinations, median PFS was short, and ORR and CBR were poor in our cohort, thus suggesting that palbociclib–based therapy is associated with limited clinical outcomes among heavily pretreated, everolimus–exposed HR+ MBCs, and supports the current practice of using palbociclib–based therapy before everolimus in this sequence. (Reference: Clin Breast Cancer. 2018 Apr 28. pii: S1526–8209(17)30805–4.)

- However, according to PALOMA 3 's subgroup analysis, it imply that patient who has refractory to prior mTORi+AI has poor mPFS. Therefore, they imply that we had better use CDK4/6i before mTORi.

02 After menopause, HR + late stage or MBC patients are patient groups for which using the CDK4/6i treatment is suitable

- Precautionary clinical monitoring items when using CDK 4/6 inhibitors
  - CBC
  - Monitor ECG
  - Monitor electrolytes
  - Monitor liver toxicity, etc.

CDK4/6 Inhibitor	Neutropenia	Hepatobiliary Toxicity	QTc Prolongation	
	CBC With Differential	LFTs (AST, ALT, Total Bilirubin)	Serum Electrolytes (K, Ca, Mg, Phos)	ECG
Palbociclib	• Baseline • Every 2 wks for 2 mos • Monthly for 4 mos • Then every 3 mos*	NA	NA	NA
Ribociclib	• Baseline • Every 2 wks for 2 mos • Monthly for 4 mos	• Baseline • Every 2 wks for 2 mos • Monthly for 4 mos	• Baseline • Monthly for 6 mos	• Baseline • Day 14 of cycle 1 • Day 1 of cycle 2
Abemaciclib	• Baseline • Every 2 wks for 2 mos • Monthly for 2 mos	• Baseline • Every 2 wks for 2 mos • Monthly for 2 mos	NA	NA

* If no grade 1 or 2 neutropenia within first 6 mos. In general, continue monitoring as clinically indicated.

* For abemaciclib: monitor for signs/symptoms of thrombosis, pulmonary embolism; instruct patients to start supportive care, contact HCP at first indication of diarrhea

Monitoring in the First 6 cycles

	Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Clinically indicated
	Day 1	Day 14	Day 1	Day 14					
PALBOCICLIB	CBC	CBC	CBC	CBC	CBC	CBC	CBC	CBC*	CBC
	–	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	–	–
	–	–	–	–	–	–	–	–	–

	Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Clinically indicated
	Day 1	Day 14	Day 1	Day 14					
RIBOCICLIB	CBC	CBC	CBC	CBC	CBC	CBC	CBC	CBC	CBC
	EOG	EOG	EOG	–	–	–	–	–	EOG
	SE	–	SE	SE	SE	SE	SE	SE	SE
	LFT	LFT	LFT	LFT	LFT	LFT	LFT	LFT	LFT

	Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Clinically indicated
	Day 1	Day 14	Day 1	Day 14					
ABEMACICLIB	CBC	CBC	CBC	CBC	CBC	CBC	–	–	CBC
	LFT	LFT	LFT	LFT	LFT	LFT	–	–	LFT
	Additional warning and precaution to be taken with respect to diarrhea management on first sign of loose stools with antidiarrhoeal treatment, and Monitoring for signs and symptoms of thrombosis and pulmonary embolism Monitoring for serum creatinine levels								

* For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, monitor complete blood counts for subsequent cycles every 3 months, prior to the beginning of a cycle and as clinically indicated.

Toxicity differences between agents: Grade 3/4

	Palbociclib	Ribociclib	Abemaciclib
Neutropenia	V V V	V V V	V
Anemia	V V	V V	V V
Thrombocytopenia	V		
Fatigue	V	V	V
Diarrhea	V	V	V V
Nausea			V
QTc prolongation		V	

- Presented By Angela DeMichele at 2018 ASCO Annual Meeting

Safety Profile Correction/Update

G3/4 neutropenia

- PALOMA 2 (palbociclib): 66.5%
- MONALEESA 2 (ribociclib): 62%
- MONARCH 3 (abemaciclib): 21.1%

Abemaciclib G3/4 neutropenia is 1/3 of palbociclib/ribociclib based on updated study results

Management guide for neutropenia

	Palbociclib	Ribociclib	Abemaciclib
CTCAE grading	Dosage adjustment methods		
Grade 1 or grade 2: (ANC 1000 mm^3 –< LLM)	No need to adjust dosage	No need to adjust dosage	No dose modification required
Grade 3[a]: (ANC 500 – <1000 mm^3)	**Day 1 of cycle** Suspend administration and repeat complete blood count (CBC) monitoring within 1 week. If grading returned to ≤Grade 2, use identical dosage to start the next treatment cycle **Day 14 of the first two cycles** Continue using identical dosage of palbociclib to complete treatment for the cycle. Repeat CBC monitoring on Day 21. If the recovery time of Grade 3 neutropenia is too long (≥ 1 week) or a relapse of Grade 3 neutropenia occurs, a reduction of dosage shall be considered in subsequent cycles	If grading recovered to ≤Grade 2 from time of interruption, use identical dosage level to restart the treatment cycle. If Grade 3 toxicity recurs, please interrupt dosage until recovery, and then reduce one dosage level to restart treatment.	Grade 3: suspend dose until AE resolves to Grade ≤2. No dose reduction required. Grade 3 recurrent: suspend dose until toxicity resolves to ≤Grade 2. Resume at next lower dose.
Grade 3 neutropenia accompanied by fever	Interrupt dosage until recovery to ≤ Grade 2, and reduce one dosage level to restart the treatment cycle	Interrupt dosage until recovery to ≤Grade 2, and reduce one dosage level to restart the treatment cycle	
Grade 4[a]: (ANC < 500/mm^3)	Interrupt dosage until recovery to ≤ Grade 2, and reduce one dosage level to restart the treatment cycle	Interrupt dosage until recovery to ≤Grade 2, and reduce one dosage level to restart the treatment cycle.	Suspend dose until toxicity resolves to ≤Grade 2. Resume at next lower dose