2023 HR-POSITIVE METASTATIC BREAST CANCER 共識會議

2023 HR(+) mBC Consensus Symposium

主編 _____ 台灣乳房醫學會

台灣乳房醫學會
TAIWAN BREAST CANCER SOCIETY

Preface

乳癌至今仍居高台灣女性癌症發生率第一名，隨著醫學知識和技術的不斷演進，我們期望能夠提供更有效的方法和更全面的照護。然而，由於臨床醫事人員能夠使用的工具日益增多，且病人需求與背景多元化，治療方式的選擇變得更加複雜。

為了整合更多關於荷爾蒙受體陽性的轉移性乳癌治療的參考資訊，因此在 2023 年 5 月學會邀請多位專家成立共識會議工作小組，進行共識會議籌備，擬定 HR+ MBC 治療的重要議題，包含 HR+ risk evaluation and biomarker testing、Selection of first-line treatment、Selection of second-line treatment、Treatment options other than endocrine-based approaches 等議題，本人衷心感謝工作小組的辛勞付出。

本會於 2023 年 11 月 19 日舉辦「2023 HR+ MBC Consensus」，與眾多專家學者們共同討論，會後彙整專家建議，經台灣乳房醫學會第九屆理監事審議通過，期望本次共識會議手冊能夠成為臨床醫師治療時的參考依據。

透過這份共識的制定和實施，我們期望在臨床實踐中引領方向，促進更高水平的乳癌治療，並進一步改善患者的生存率和生活品質。同時，我們也能夠加強醫療專業人員之間的溝通和協調，提升整體醫療水平，為台灣的乳房疾病治療作出更大的貢獻。

最後，我代表台灣乳房醫學會衷心感謝各位醫療專業人士的參與和支持，期待這份共識的實施能夠為病人和乳房疾病治療帶來更多的福祉和價值。

台灣乳房醫學會 理事長

陳守棟 于 2024 年 1 月

特別感謝以下專家提供寶貴建議（依姓氏筆畫排列、職稱省略概以醫師稱謂）

于承平、王明暘、朱崧肇、吳建廷、李忠良、李國鼎、沈陳石銘、林季宏、林金瑤、俞志誠、洪志杰、洪志強、洪朝明、洪進昇、張金堅、張振祥、張源清、張獻崑、張端瑩、張耀仁、郭文宏、郭玟伶、陳守棟、陳怡君、陳芳銘、陳訓徹、陳偉武、陳達人、曾令民、曾彥敦、黃其晟、黃俊升、葉顯堂、廖國秀、趙大中、趙祖怡、劉良智、劉峻宇、蔡青樺、鄭翠芬、盧彥伸、賴峻毅、戴明燊、鍾奇峰、鍾為邦、饒坤銘等諸位醫師。

本治療共識僅做為參考，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

Strength of the Recommendation and Quality of Evidence

Strength	Recommendation
A	Strong recommendation for use
B	Moderate recommendation for use
C	Marginal recommendation for use
D	Recommendation against use

Quality	Evidence
I	Evidence from at least 1 properly designed randomized, controlled trial
II	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

1. AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ 2012; 182: E839–E842
2. Grading quality of evidence and strength of recommendations in clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations. Allergy 2011; 66:8
3. Annals of Hematology (2018) 97:1271–1282

The Principle of Voting for Strength of Recommendation

Strength	Recommendation
A	Strong recommendation for use
B	Moderate recommendation for use
C	Marginal recommendation for use
D	Recommendation against use

For the “Strength of Recommendation A and B”, a majority panel vote of at least 85% is required.

For the “Strength of Recommendation C”, a panel vote of at least 50% (but less than 85%) is required.

For recommendations where there is strong panel disagreement regardless of the quality of the evidence, “Strength of Recommendation D” requires a panel vote of at least 25%.

1. NCCN giudelines. Development and Update of Guidelines.

HR+ Risk Evaluation and Biomarker Testing (I)

—— 長庚醫院 / 郭玟伶 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
Single hormone receptor–positive (ER–/PR+ and ER+/PR–) metastatic breast cancer is associated with worse OS than double hormone receptor–positive metastatic breast cancer.	II	A	1, 4, 5
Histological type (lobular vs. ductal) is inconsistently associated with worse OS and PFS.	II	B	1
High Ki67 in primary tumor or metastatic site is associated with worse OS and PFS.	II	B	1, 7
Disease–free interval[a] < 2 years is associated with worse OS and PFS.	II	A	1, 6, 11
De novo metastasis is associated with better OS compared with relapsed disease.[b]	II	A	1, 6, 8
Oligometastasis is associated with better OS and PFS.	II	A	1, 6, 12

a. Disease–free interval or recurrence–free interval is often defined as the date of surgery for early breast cancer to the date of first recurrence.

b. Late recurrence with disease free interval > 5 years has similar survival outcome with de novo metastasis[6].

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
Bone metastasis is associated with better outcome.[c]	II	A	1, 6
Endocrine resistance[d] is associated with poor PFS and OS. **Primary endocrine resistance** is defined as a relapse within 2 years of adjuvant endocrine treatment or disease progression during the first 6 months of first–line endocrine therapy for advanced or metastatic breast cancer (MBC). **Secondary endocrine resistance** is defined in early breast cancer as a relapse that occurs after at least 2 years of endocrine therapy and during or within the first year of completing adjuvant endocrine therapy. In advanced breast cancer or MBC, secondary resistance is defined as disease progression after more than 6 months of endocrine therapy.	III	A	12, 13

c. Liver metastasis in HR+ HER2– breast cancer has poor outcome[13].

d. With more modern or advanced endocrine–based treatment approaches, endocrine resistance might be better defined more by the nature of the resistance and the availability of precision medicine tools to address it, but less by the relapse or progression–free interval[15].

◎ Reference

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2. Endocrine–Based Treatments in Clinically–Relevant Subgroups of Hormone Receptor–Positive/HER2–Negative Metastatic Breast Cancer: Systematic Review and Meta–Analysis. Francesco Schettini , Mario Giuliano, Fabiola Giudici , Benedetta Conte , Pietro De Placido , Sergio Venturini , Carla Rognoni , Angelo Di Leo , Mariavittoria Locci , Guy Jerusalem , Lucia Del Mastro , Fabio Puglisi , PierFranco Conte , Michelino De Laurentiis , Lajos Pusztai , Mothaffar F Rimawi , Rachel Schiff , Grazia Arpino , Sabino De Placido , Aleix Prat, Daniele GeneraliCancers (Basel) . 2021 Mar 22;13(6):1458. DOI: 10.3390/cancers13061458.
3. Is progression–free survival a more relevant endpoint than overall survival in first–line HR+/HER2 — metastatic breast cancer? Anna Forsythe , David Chandiwana , Janina Barth , Marroon Thabane , Johan Baeck , Anastasiya Shor , Gabriel Tremblay Cancer Management and Research 2018:10 1015—1025. DOI: 10.2147/CMAR.S162714.
4. Prognostic factors for stage IV hormone receptor–positive primary metastatic breast cancer. Akiko Kawano 1 , Chikako Shimizu, Kenji Hashimoto, Takayuki Kinoshita, Hitoshi Tsuda, Hirofumi Fujii, Yasuhiro Fujiwara Breast Cancer . 2013 Apr;20(2):145–51. DOI: 10.1007/s12282–011–0320–3. Epub 2011 Dec 3.
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HR+ Risk Evaluation and Biomarker Testing (II)

—— 臺北榮總 / 賴峻毅 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
Mutations in somatic PIK3CA, and in germline pathogenomic BRCA1/2 mutations are associated with improved treatment outcome[a] to relevant targeted therapies.[b]	I	A	1–3
PIK3CA liquid biopsy (Mutation hotspots by PCR or next generation sequencing) is an acceptable alternative when genomic testing in tumor samples is not accessible.[c]	I	A	1
In HR(+) mBC with low HER2 expression[d], HER2 status (1–2, 0) is predictive of trastuzumab deruxtecan treatment efficacy.	I	A	4–5
ESR1 mutation in either tumor and/or circulating tumor DNA has both predictive and prognostic indicator values.	II	B	6–7
Determination of TROP2 expression status is not required for decision of TROP2 antibody drug conjugates use (such as Sacituzumab Govitecan)[e]	II	B	8

a. PIK3CA inhibitors and PARP inhibitors currently have not demonstrated overall survival benefit in metastatic HR(+) breast cancer trials

b. Somatic BRCA1/2 and germline PALB2 has also demonstrated efficacy in smaller, noncontrolled studies

c. Global and Taiwanese studies have shown that the majority (70–80) of PIK3CA mutations occur within the following hotspots: H1047R , E545K , E542K , N345K, H1047L.

d. Trastuzumab deruxtecan has shown PFS and OS benefit in low HER2 mBC. Low HER2 status is defined as HER2 IHC 1+ or IHC 2+ and ISH–negative

e. Subgroup analysis from TROPICS–02 trial suggest better efficacy of Sacituzumab govitecan in tumors with higher TROP2 expression

◎ Reference

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Selection of First-Line Treatment (I)

—— 臺中榮總 / 洪志強 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
CDK4/6 inhibitors combined with ET are advised for first line treatment of HR–positive, HER2–negative MBC, including those with clinically aggressive disease,[a] regardless of primary or secondary resistance of ET.[b] In the case of premenopausal patients, ovarian function suppression is recommended.	I	A	1–6
For patients who did not relapse on an aromatase inhibitor (AI), or did not recurrence within 12 months of stopping adjuvant AI, a CDK4/6 inhibitor in combination with an AI is advised. Otherwise, fulvestrant combined with a CDK4/6 inhibitor is considered.	I	A	7–8
Delayed combination of CDK4/6 inhibitor to second line treatment is acceptable.[c]	I	B	9–10
Biopsy of metastatic sites should be considered for treatment adjustment if no risk of major complication.	II	A	11
If recurrence develops at least one year after the completion of adjuvant CDK 4/6 inhibitor treatment, the re–introduction of a CDK 4/6 inhibitor could be considered.	III	B	12

a. Definition of aggressive ABC: symptomatic visceral metastases, rapid disease progression or impending visceral compromise, marked non–visceral–disease but with total bilirubin <1.5 ULN.

b. Ribociclib and Abemaciclib have shown OS benefit in phase 3 randomized controlled trial.

c. ET alone is acceptable for patients with comorbidities or a poor performance status. Palbociclib may be safer for older patients.

◎ Reference

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Selection of First-Line Treatment (II)

—— 臺大醫院 / 陳怡君 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
ET with CDK 4/6 inhibitor is standard of care in 1st line therapy for the majority of ER+/ HER2– advanced breast cancer patients, including those with clinically aggressive disease. #Definition of aggressive ABC: symptomatic visceral metastases, rapid disease progression or impending visceral compromise, marked non–visceral–disease but with total bilirubin <1.5 ULN.	I	A	1
ET with CDK 4/6 inhibitor may be considered after surgical resection or radiotherapy for clinically stable CNS metastasis.	II	B	2
ET with CDK4/6 inhibitor is effective both in luminal A and luminal B subgroups.* *The subgroups refer to PAM50 defined intrinsic subtypes, rather than clinicopathologic subtypes.	II	B	3

◎ Reference

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Selection of Second-Line Treatment (I)

—— 台中慈濟 / 林金瑤 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
Fulvestrant in combination with a CDK 4/6 inhibitor may be offered to patients who experienced disease progression during prior treatment with endocrine therapy.	I	A	1–5
Alpelisib plus fulvestrant is a treatment option for patients with PIK3CA–mutated metastatic breast cancer who have progressed on endocrine therapy with or without a CDK4/6 inhibitor.	I	B	6–8
Everolimus plus any other endocrine therapy is an option for patients who have progressed on endocrine therapy with or without a CDK4/6 inhibitor.	I–II	B	9–13
CDK4/6 inhibitor combined with switching endocrine therapy is the treatment option for HR+, HER2– metastatic breast cancer after CDK4/6 inhibitor progression with endocrine therapy.[a]	II	B	14

a. There was a significant PFS benefit for patients who switched ET and received ribociclib compared with placebo after previous CDK4/6i and different ET.

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Selection of Second-Line Treatment (II)

—— 大同醫院 / 李忠良 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
Selective estrogen receptor degrader (SERD,such as Elacestrant, Fulvestrant) is an option for patients with ER–positive, HER2–negative, ESR1–mutated metastatic breast cancer progressing after at least one line of endocrine therapy.	I	A	1
Capivasertib plus fulvestrant is a treatment choice for one or more PIK3CA/AKT1/PTEN alterations metastatic breast cancer after at least one line of endocrine therapy.[a]	I	A	2
Tucidinostat (a HDAC inhibitor) plus exemestane could be used for patients with ER–positive HER2–negative metastatic breast cancer who have received at least one line of endocrine therapy in early of metastatic setting.	II**	A	3

a. In CAPItello–291 trial, this treatment also showed the efficacy of non–AKT pathway alternations group.

** Only in Asia, not global trial

◎ Reference

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Treatment Options Other Than Endocrine-Based Approaches (I)

—— 成大醫院 / 鍾為邦 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
PARP inhibitors could be used for patients bearing deleterious germline BRCA1/2 mutations who fail or are not suitable for endocrine therapies and have received at least one line of chemotherapy either in early or metastatic setting.	I	A	1, 2
Trastuzumab deruxtecan could be used for patients with HR+/HER2−low (HER2 IHC 1+ or HER2 IHC 2+ with negative FISH) metastatic breast cancer who fail endocrine therapies and ≥ 1 line of chemotherapy.[a]	I	A	3
Sacituzumab govitecan could be used for patients with HR+/HER2− metastatic breast cancer who fail endocrine therapies and ≥ 2 lines of chemotherapy.[b]	I	A	4, 5
Abemaciclib as monotherapy could be considered for patients with HR+/HER2− metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.[c]	II	A	6

a. DESTINY−Breast04 trial did not enroll patients who received more than two lines of chemotherapy.
b. TROPiCS−02 trial did not enroll patients who received more than four lines of chemotherapy.
c. The dosage of Abemaciclib used in MONARCH 1 trial was 200mg twice a day, which caused notable diarrhea.

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Treatment Options Other Than Endocrine-Based Approaches (II)

—— 臺大醫院 / 陳偉武 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
Chemotherapy is an option for patients with clinically aggressive metastatic breast cancer or evidence of endocrine resistance.[a]	I	A	1
The optimal sequence of chemotherapeutic agents has not been established.[b]	II	A	2, 3
Metronomic chemotherapy is an option for patients with advanced hormone–receptor positive disease.[c,d]	I	B	4, 5

a. Please refer to previous points about the definition endocrine resistance

b. Anthracyclines (including liposomal doxorubicin) and taxanes (paclitaxel, docetaxel, nab–paclitaxel), vinorelbine, capecitabine, cisplatin/carboplatin, gemcitabine, eribulin, and ixabepilone could be considered as options for MBC patients when chemotherapy is considered.

c. Metronomic chemotherapy treatment refers to the chronic administration of low doses of chemotherapeutic agent(s). The availability of NHI coverage makes metronomic chemotherapy a reasonable alternative.

d. Metronomic chemotherapy regimens that have been validated in prospective clinical trials includes single agent oral vinorelbine and capecitabine or combinations such as oral methotrexate plus oral cyclophosphamide, oral vinorelbine plus capecitabine, oral cyclophosphamide plus capecitabine, and triple combination of oral vinorelbine, oral cyclophosphamide, and capecitabine.

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Note

Note

2023 HR-POSITIVE METASTATIC BREAST CANCER 共識會議

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