台灣乳房醫學會
TAIWAN BREAST CANCER SOCIETY

2021 HER2 Early Breast Cancer Neoadjuvant Consensus

主編　台灣乳房醫學會

PREFACE

近一年多來，無論在HER2陽性早期乳癌或轉移性乳癌，許多新的藥物如tucatinib, neratinib, T-Dxd, trastuzumab duocarmazine等皆有新進展。其中neratinib在去年下半年正式在台灣核准HER2陽性早期乳癌的適應症，2021 ST. Gallen 國際乳癌大會中也有最新的專家意見更新。故於今年與國內眾多乳癌治療專家召開專家會議討論，並達成共識。此版本以2020年版為基礎更新最新臨床實證 (第19-22頁)。

共同促進醫學之進步發展為吾人終生努力職志，學會期盼透過不定期更新乳癌治療共識，提高臨床實證率及治療品質，誠摯期待各界先進能不吝指教、提供新知，協助病人得到更精準的治療，共同為台灣乳癌治療盡最大心力。

台灣乳房醫學會 理事長
曾令民 于 2021 年 07月

特別感謝以下專家（依姓氏筆畫排列、職稱省略概以醫師稱謂）

于承平、王明暘、王惠暢、王甄、沈士哲、杜世興、李國鼎、林季宏、林柏翰、洪志強、俞志誠、侯明鋒、洪朝明、郭文宏、馬旭、陳守棟、陳芳銘、陳訓徹、陳達人、許志怡、張金堅、許居誠、張振祥、許桓銘、莊捷翰、張獻崑、張源清、張耀仁、曾令民、黃其晟、黃俊升、葉大成、葉顯堂、趙大中、趙祖怡、廖國秀、鄭翠芬、劉自嘉、劉良智、蔡宜芳、蔡青樺、劉建良、劉美瑾、劉峻宇、盧彥伸、沈陳石銘、戴明燊、鍾為邦、饒坤銘、歐陽賦等諸位醫師。

CONTENT

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

A. CLINICAL BENEFIT AND INDICATION OF NEOADJUVANT

2020 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Neoadjuvant therapy is the preferred schedule for patients with HER2+ high risk breast cancer (≧ T2 or N+).	I	A	[1], [2]
2. Pertuzumab in combination with trastuzumab and chemotherapy is recommended for patients in neoadjuvant setting.	I	A	[3]
3. Consider using neoadjuvant platform to tethering regimens based on "clinical" and/or pathologic response to therapy	III	C	[4], [5]

References

1. Sara A, et al. Hurvitz. 2019 ASCO Annual Meeting.
2. Prat A, et al. SABCS 2016.
3. Llombart-Cussac A, et al. Lancet Oncol 2017
4. Harbeck N, et al. J Clin Oncol 2017 35:3046-3054.
5. Metzger O, et al. ASCO, 2019, abstract 502

B. RECOMMENDATION FOR EVALUATION OF AXILLARY LYMPH NODE BEFORE AND AFTER NEOADJUVANT THERAPY

2020 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. No benefit of Pre-Neoadjuvant chemotherapy Sentinel Lymph Node Dissection except for drug application	II	B	[1]
2. In a patient clinically node positive at presentation who downstages after neoadjuvant chemotherapy, the Panel considered that sentinel node biopsy was appropriate, but that in this situation axillary lymph node dissection was required if even one sentinel node were positive.	I	B	[2]
3. False negative rates however remain high unless 3 or more sentinel nodes are examined.	II	B	[2]
4. High false negative rate in 2nd Sentinel Lymph Node Dissection	I	B	[3]
5. Data from the SENTINA Trial do not support the use of repeat SNB after NST due to an unacceptably low sentinel node identification rate and an exceedingly high false negative rate if neoadjuvant SNB showed positive result.	II	B	[3]
6. Among patients shown to be node-positive prior to neoadjuvant systemic therapy, SLNB has a >10% false-negative rate when performed after neoadjuvant systemic therapy. This rate can be improved by marking biopsied lymph nodes to document their removal, using dual tracer, and by removing more than 2 sentinel nodes.	II	B	[4]
7. Several clinical trials have evaluated the feasibility of SNB after NST in patients with T1-3, N1-3 disease at baseline. Currently, NCCN guidelines support use of the SNB procedure after NST among previously node-positive patients converted to clinically node-negative. Acceptable SN false negative rates may be obtained when dual tracers (i.e., blue dye and radioisotope) are used for SN mapping, a minimum of three SN are removed, and when specimen radiography of the SN confirms removal of the original biopsy-positive axillary node. Under such circumstances, SNB-negative patients may avoid ALND whereas SNB-positive patients should undergo ALND.	II	B	[3], [5], [6], [7], [8]

2020 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
8. Identification of the originally biopsied node may be facilitated by wire-guided or ultrasound-guided dissection. There may be a role for emerging nodal localization techniques, e.g., tattoo ink-guided or radioactive seed localization. A specimen radiograph of the resected node(s) should be obtained of the resected node(s) to document removal of any radio-opaque marker placed within a biopsy-positive node.	III	C	[9], [10]

References

1. Guidelines of the AGO Breast Committee: Diagnosis and Treatment of Patients with early and advanced Breast Cancer. Guidelines Breast Version 2020.1.
2. ST Gallen Guidelines 2019
3. Thorsten Kuehn, et al. Lancet Oncology Vol 14, No. 7, p 609-618, 2013
4. Eleftherios P Mamounas, et al. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2005 Apr 20;23(12):2694-702.
5. Judy C. Boughey, et al. Sentinel Lymph Node Surgery After Neoadjuvant Chemotherapy in Patients With Node-Positive Breast Cancer: The ACOSOG Z1071 (Alliance) Clinical Trial. JAMA. 2013;310(14):1455-1461.
6. NSABP B-51/RTOG 1304. ClinicalTrials.gov Identifier: NCT01872975
7. Alliance A112020. ClinicalTrials.gov Identifier: NCT01901094
8. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Breast Cancer. 2019.V3
9. Nicole Choy, et al. Initial results with preoperative tattooing of biopsied axillary lymph nodes and correlation to sentinel lymph nodes in breast cancer patients. Ann Surg Oncol. 2015 Feb;22(2):377-82.
10. Sergi Vidal-Sicart, et al. Pre- and intra-operative imaging techniques for sentinel node localization in breast cancer. Imaging Med. 2013; 5(3), 275–291

A. CURRENT THERAPY FOR EARLY BREAST CANCER CHEMOTHERAPY & TARGET THERAPY

2020 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. The regimens recommended in adjuvant setting can be considered in neoadjuvant setting.	I	A	[1], [2]
2. Similar to that in adjuvant setting (with duration at least 18 weeks, recommend complete all neoadjuvant chemotherapy if tolerable and no evidence of progression)	I	A	[3]
3. Patients who fit the main characteristics (not eligibility) of APT trial may consider surgery first followed by standard adjuvant treatment.	II	B	[4], [5]
4. For HER2+ disease, trastuzumab (plus pertuzumab neoadjuvant at high risk) - Sequential A/T-based regimen with concurrent T+ anti-HER2 therapy. - Anthracycline-free, platinum-containing regimen - Anthracycline-free, taxane-containing regimen.	I	A	[3]

References

1. Slamon D, et al. SABCS 2015. Abstract S5-04.
2. Andreas Schneeweiss, et al. Eur J Cancer. 2018 Jan;89:27-35.
3. AGO Guidelines Breast Cancer. Version 2019.1
4. Sara M. Tolaney, et al. 2019. J Clin Oncol 37:1868-1875.
5. NCCN Guidelines Breast Cancer. Version 5.2020

B. ROLE OF APPROVED NEW (SC) FORMULATION OF HER2 TARGETED AGENTS

2020 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Comparable efficacy and safety of subcutaneous and intravenous trastuzumab highlights the suitability of subcutaneous trastuzumab as an alternative route of administration for patients with ERBB2-positive early breast cancer.	I	A	[1]

References

1. Christian Jackisch, et al. Subcutaneous vs Intravenous Trastuzumab for Patients With ERBB2-Positive Early Breast Cancer Final Analysis of the HannaH Phase 3 Randomized Clinical Trial: JAMA Oncol. 2019;5(5):e190339

C. NEOADJUVANT CONSIDERATION IN CASE OF NO EARLY RESPONSE

2020 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Multiple imaging modalities may enhance the diagnostic accuracy of (no) early response.	II	B	[1],[2]
2. Neoadjuvant therapy allows individualization of therapy according to mid-course treatment effect.	II	B	[1],[2],[4],[5]
3. In case of no change in mid-term evaluation, completion of neoadjuvant therapy with original regimen or with non cross-resistant regimen is reasonable.	II	B	[1],[2],[3] also based on opinions from CY Liu and CS Huang
4. In case of progressive but without systemic metastatic disease and under adequate NACT, stop current therapy and proceed with surgery, RT, or non cross-resistant NACT is recommended. The appropriate action for most PD patients is to cease current treatment and proceed immediately to surgery and/or radiotherapy. In addition, alternative medical treatment as a clinical trial should be considered.	III	C	[1],[2],[6-8]
5. The full course of NAC should be completed unless there is evidence of disease progress.	III	C	[8-10]

References

1. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, Zackrisson S, Senkus E; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Ann Oncol. 2019 Aug 1;30(8):1194-1220. doi: 10.1093/annonc/mdz173.

2. Guidelines of the AGO Breast Committee: Diagnosis and Treatment of Patients with early and advanced Breast Cancer. Guidelines Breast Version 2019.1.Url://www.ago-online.de/

3. A randomized, 3-arm, neoadjuvant, phase 2 study comparing docetaxel + carboplatin + trast uzumab + pertuzumab (TCbHP), TCbHP followed by trastuzumab emtansine and pertuzumab (T-DM1+P), and T-DM1+P in HER2-positive primary breast cancer. Masuda N, Ohtani S, Takano T, Inoue K, Suzuki E, Nakamura R, Bando H, Ito Y, Ishida K, Yamanaka T, Kuroi K, Yasojima H, Kasai H, Takasuka T, Sakurai T, Kataoka TR, Morita S, Ohno S, Toi M. Breast Cancer Res Treat. 2020 Feb;180(1):135-146. doi: 10.1007/s10549-020-05524-6. Epub 2020 Jan 17. PMID: 31953696

4. Factors predicting relapse in early breast cancer patients with a pathological complete response after neoadjuvant therapy- Results of a pooled analysis based on the GBG meta-database. Huober J et al. SABCS 2018 Abstract P2-08-01.

5. Risk of Recurrence and Death in Patients with Early HER2-Positive Breast Cancer Who Achieve a Pathological Complete Response after Different Types of HER2-Targeted Therapy: A Pooled Analysis. Sandra M. Swain SM et al. SABCS 2019 Abstract P1-18-01.

6. Neoadjuvant Therapy in Early Breast Cancer: Treatment Considerations and Common Debates in Practice. Cain H, Macpherson IR, Beresford M, Pinder SE, Pong J, Dixon JM. Clin Oncol (R Coll Radiol). 2017 Oct;29(10):642-652

7. Impact of progression during neoadjuvant chemotherapy on surgical management of breast cancer. Caudle AS, Gonzalez-Angulo AM, Hunt KK, Pusztai L, Kuerer HM, Mittendorf EA, Hortobagyi GN, Meric-Bernstam F. Ann Surg Oncol. 2011 Apr;18(4):932-8.

8. Predictors of tumor progression during neoadjuvant chemotherapy in breast cancer. Caudle AS, Gonzalez-Angulo AM, Hunt KK, Liu P, Pusztai L, Symmans WF, Kuerer HM, Mittendorf EA, Hortobagyi GN, Meric-Bernstam F. J Clin Oncol. 2010 Apr 10;28(11):1821-8.

A. MANAGEMENT OF PRIMARY TUMOR

2020 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Resection into new margin is the goal of neoadjuvant therapy. The resection extent should be limited to residual lesions with reasonable safety margin. If no detectable lesion remains, the resection extent may be limited to the tissue in the immediate vicinity of the biopsy site marker.	II	A	[1]
2. It is recommended to place a clip or tattooing in the primary tumor after biopsy.	III	B	[1], [2]
3. It is recommended to remove all suspicious microcalcifications after neoadjuvant therapy.	II	B	[1],[3]
4. Obtaining an image (mammography and/or ultrasound) for resected specimen is recommended.	III	B	[1]
5. Placing multiple clips around the resection cavity is helpful for future radiotherapy planning.	III	C	[1]
6. For patients whose negative margin were achieved after breast conserving surgery, but having large amount of tumor or scatter lesions presented in proximity to the margin, the decision for re-excision should be individualized and discussed in a multidisciplinary setting to determine if wider margins are needed.	III	B	[1]

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1. Holmes, D., Colfry, A., Czerniecki, B. et al. Performance and Practice Guideline for the Use of Neoadjuvant Systemic Therapy in the Management of Breast Cancer. Ann Surg Oncol (2015) 22: 3184

2. Dash N, Chafin SH, Johnson RR, Contractor FM. Usefulness of tissue marker clips in patients undergoing neoadjuvant chemotherapy for breast cancer. AJR Am J Roentgenol. 1999;173(4):911-917. doi:10.2214/ajr.173.4.10511147

3. Weiss A, Lee KC, Romero Y, et al. Calcifications on mammography do not correlate with tumor size after neoadjuvant chemotherapy. Ann Surg Oncol. 2014;21:3310–6.

B. BREAST CONSTRUCTION AFTER NEOADJUVANT THERAPY

2020 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Neoadjuvant therapy does not increase the complication rate after breast reconstruction.	II	B	[1]
2. Delay timing or insufficient dosage of radiotherapy may increased the risk of recurrence. Patients with clinical node positive or locally advanced stage whose post-mastectomy R/T was planed, delayed reconstruction may be considered for avoid complication.	II	B	[2],[3], [4]
3. It should be caution if radiotherapy is planned after breast reconstruction due to increased complication rate. Autologous reconstruction had a lower complication rate than implant after radiotherapy.	II	B	[3],[5]
4. If nipple sparing mastectomy was planned, it should be careful evaluation of tumor to nipple distance by image before operation and standard retroareolar biopsy should be performed.	II	B	[6],[7]
5. Breast reconstruction is oncologic safe to perform in the setting of neoadjuvant therapy.	II	B	[8],[9]

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1. Ann Surg Oncol. 2019 Sep;26(9):2768-2772. doi: 10.1245/s10434-019-07418-4.
2. Anticancer Res. 2014 Nov;34(11):6677-83
3. Int J Radiat Oncol Biol Phys. 2016 Mar 1;94(3):493-502. doi: 10.1016
4. Int J Radiat Oncol Biol Phys. 2012 Mar 15;82(4):e587-93. doi: 10.1016
5. J Surg Oncol. 2017 Dec;116(7):797-802. doi: 10.1002
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8. Clin Breast Cancer. 2019 Oct;19(5):377-382. doi: 10.1016/j.clbc.2019.04.011.
9. Breast J. 2019 May;25(3):528-530. doi: 10.1111/tbj.13277

C. SYSTEMIC ADJUVANT ACCORDING TO PCR AND BASELINE RISK-STRATIFICATION

2020 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. T-DM1 for 14 cycles as the adjuvant treatment is a better option than trastuzumab if pCR is not achieved after HER2-directed neoadjuvant treatments.	I	A	[1]
2. In those pCR population, trastuzumab (to complete 12 months) as the adjuvant treatment is the standard of care and adding pertuzumab may be the other option.	II	B	[2],[3]
3. Pertuzumab together with trastuzumab (to complete 12 months) as the adjuvant treatment offers better outcomes than trastuzumab alone in the high risk population (esp. N+) but its efficacy in non-pCR population is unknown.	II	C	[4]
4. Neratinib can be a single agent, for the extended adjuvant treatment of adult patients with early stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy.	I	A	[5],[6], [7]
5. Extended 1-year adjuvant neratinib should be an option in HR+/HER2+ and high-risk patients (such as ≥ 4 positive LN) after receiving trastuzumab/pertuzumab as (neo)adjuvant therapy regimens, with or without adjuvant T-DM1 therapy.	III	B	[8], [9], [10]

References

1. Gunter von Minckwitz, et al., Trastuzumab Emtansine for Residual InvasiveHER2-Positive Breast Cancer, N Engl J Med 2019; 380:617-628
2. Gianni Luca, et al., 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial, Lancet Oncol 2016; 17: 791–800
3. Sara A. Hurvitz, et al., Neoadjuvant Trastuzumab Emtansine and Pertuzumab in Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: Three-Year Outcomes From the Phase III KRISTINE Study, J Clin Oncol 37:2206-2216
4. Gunter von Minckwitz, et al., Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer, N Engl J Med 2017; 377:122-131
5. Chan A, et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology, 2016, 17(3), pp.367-377.
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7. Chan A, et al. Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial. Clinical Breast Cancer, 2021, 21(1), pp.80-91.e7.
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9. Untch M, et al. Treatment of Patients with Early Breast Cancer: Evidence, Controversies, Consensus: German Expert Opinions on the 17th International St. Gallen Consensus Conference. Geburtshilfe Frauenheilkd. 2021 Jun;81(6):637-653. doi: 10.1055/a-1483-2782. Epub 2021 May 19. PMID: 34168378; PMCID: PMC8216767.
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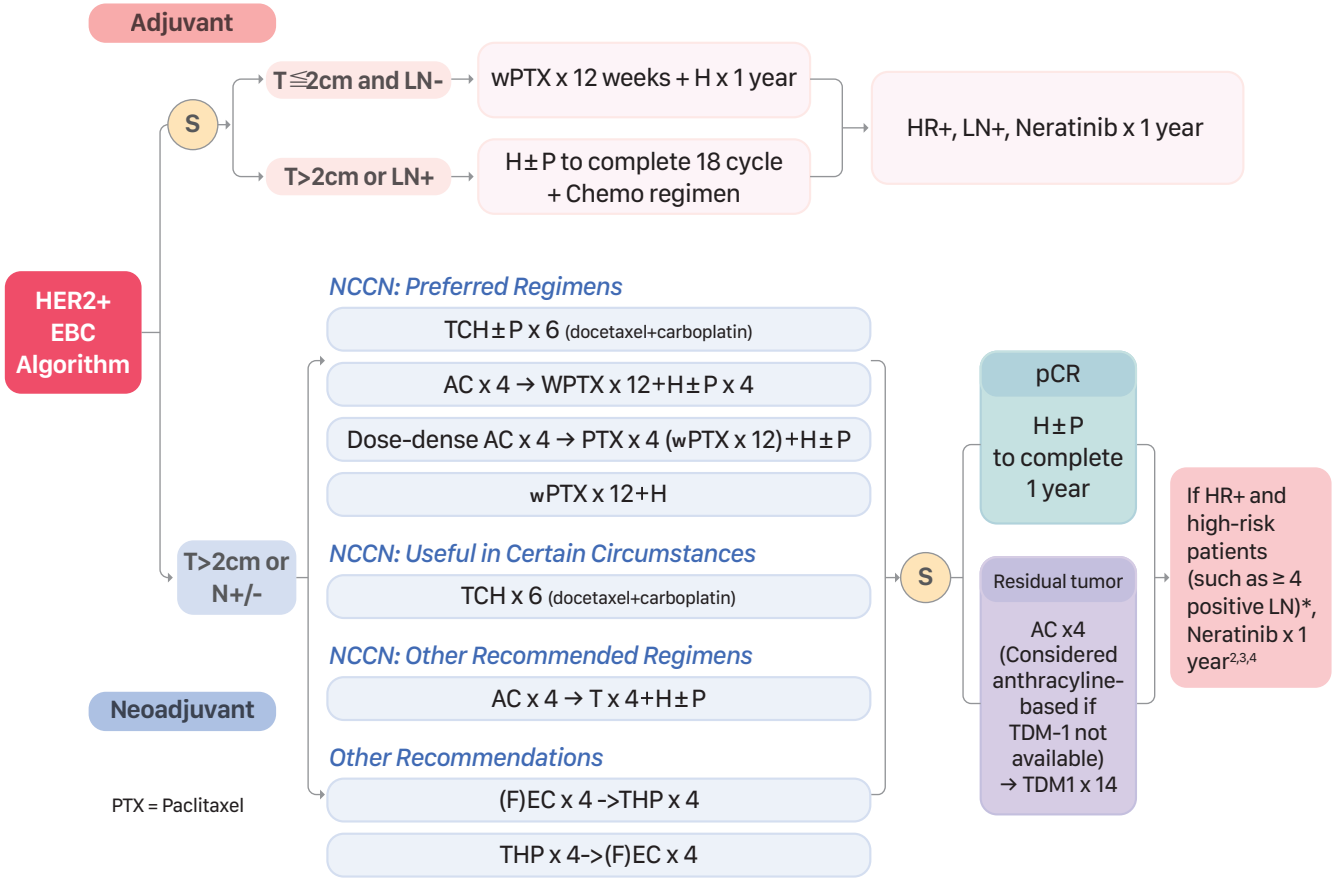
ALGORITHM ESTABLISHMENT IN HER2+ EBC



NCCN Guidelines. Breast Cancer 2020 v6.

*2021 ST. GALLEN Panel Voting

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