Expert consensus recommendations on the daily clinical use of pembrolizumab for early triple-negative breast cancer

Winnie Yeo *, Yolanda HY Chan, Roland CY Leung, Sharon WW Chan, Lorraine CY Chow, William WL Foo, Sara WW Fung, Carol CH Kwok, Stephanie HY Lau, Alex KC Leung, Ting Ying Ng, Janice Tsang, Iris KM Wong, Chun Chung Yau, Marvin HY Yuen, Polly SY Cheung

ABSTRACT

Neoadjuvant chemotherapy is a standard treatment for triple-negative breast cancer (TNBC) at an early stage. Given that pathological complete response is strongly associated with long-term clinical and survival benefits, the selection of appropriate treatment before and after surgery could further optimise treatment outcomes. With the emergence of immunotherapy in breast cancer, more combination treatment options are available, such as pembrolizumab, a programmed death receptor 1 inhibitor, which is approved for the perioperative treatment of stage II and III TNBC. However, the implementation of immunotherapy in perioperative settings for TNBC requires further discussion regarding patient selection and the use of different treatments in conjunction with immunotherapy. The Hong Kong Breast Cancer Foundation convened a multidisciplinary consensus panel consisting of surgeons, clinical oncologists, and medical oncologists to initiate this discussion. A modified Delphi panel was conducted, evaluating seven topics and 45 statements covering the workup and perioperative treatment of early-stage TNBC (eTNBC). The consensus statements provide guidance on determining whether a patient with eTNBC is a suitable candidate for neoadjuvant chemotherapy and immunotherapy.

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[1] **W Yeo *,** MD, FRCP
[2] **YHY Chan,** FRCSEd, FHKAM (Surgery)
[3] **RCY Leung,** MRCP, DABIM
[4] **SWW Chan,** FRACS, FHKAM (Surgery)
[5] **LCY Chow,** FRCSEd, FHKAM (Surgery)
[6] **WWL Foo,** FRCR, FHKAM (Radiology)
[7] **SWW Fung,** FRCSEd, FHKAM (Surgery)
[8] **CCH Kwok,** FRCR, FHKAM (Radiology)
[9] **SHY Lau,** FRCSEd, FHKAM (Surgery)
[10] **AKC Leung,** FRCR, FHKAM (Radiology)
[11] **TY Ng,** FRCR, FHKAM (Radiology)
[12,13] **J Tsang,** FRCP, FHKAM (Medicine)
[14] **IKM Wong,** FRCR, FHKAM (Radiology)
[15] **CC Yau,** FRCP, FHKAM (Radiology)
[16] **MHY Yuen,** FRACS, FHKAM (Surgery)
[17] **PSY Cheung,** FRCS, FRACS

[1] *Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong SAR, China*
[2] *Breast Health Clinic, CUHK Medical Centre, Hong Kong SAR, China*
[3] *Department of Medicine, Queen Mary Hospital, Hong Kong SAR, China*
[4] *Department of Surgery, United Christian Hospital, Hong Kong SAR, China*
[5] *Private Practice, Hong Kong SAR, China*
[6] *Radiotherapy and Oncology Centre, Gleneagles Hospital, Hong Kong SAR, China*
[7] *Department of Surgery, Kwong Wah Hospital, Hong Kong SAR, China*
[8] *Department of Oncology, Princess Margaret Hospital, Hong Kong SAR, China*
[9] *Department of Surgery, Hong Kong Baptist Hospital, Hong Kong SAR, China*
[10] *Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong SAR, China*
[11] *Department of Clinical Oncology, Tuen Mun Hospital, Hong Kong SAR, China*
[12] *Founding Convenor, Hong Kong Breast Oncology Group, Hong Kong SAR, China*
[13] *School of Clinical Medicine, The University of Hong Kong, Hong Kong SAR, China*
[14] *Department of Oncology, United Christian Hospital, Hong Kong SAR, China*
[15] *Comprehensive Oncology Centre, Hong Kong Sanatorium & Hospital, Hong Kong SAR, China*
[16] *Department of Surgery, Pok Oi Hospital, Hong Kong SAR, China*
[17] *Breast Care Centre, Hong Kong Sanatorium & Hospital, Hong Kong SAR, China*

* Corresponding author: winnie@clo.cuhk.edu.hk

Introduction

Triple-negative breast cancer (TNBC), representing 10% to 15% of breast cancer cases, is characterised by the absence of oestrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) amplification or overexpression. It is associated with higher rates of recurrence, metastasis, and worse overall survival (OS) than other subtypes.[1,2] Given its high immune infiltration rate, with over 50% tumour-infiltrating lymphocytes in histological samples,[3,4] TNBC is amenable to immunomodulation through immunotherapy.

Immunotherapies directed against programmed death receptor 1 (PD-1) or programmed death receptor ligand 1 (PD-L1) have shown promising and positive results in patients with metastatic TNBC (mTNBC), based

on the phase III randomised KEYNOTE-355 and IMpassion130 trials.[5-7] Addition of the anti–PD-1 antibody pembrolizumab to chemotherapy significantly improved progression-free survival and OS by 4.1 months and 6.9 months, respectively, in patients with mTNBC whose tumours expressed PD-L1 (combined positive score [CPS] ≥10).[5,6]

The effectiveness of neoadjuvant pembrolizumab in combination with neoadjuvant chemotherapy (NAC) was demonstrated in the KEYNOTE-522[8,9] and NeoImmunoBoost trials.[10] The pathological complete response (pCR) rate significantly increased from 51.2% among patients receiving NAC alone to 64.8% among those receiving pembrolizumab–chemotherapy in the former study, independent of PD-L1 status.[8] Event-free survival (EFS) at 36 months also increased from 76.8% to 84.5%.[9] Although pembrolizumab demonstrated favourable results in the KEYNOTE-522 study, several important questions regarding patient selection, types and schedules of chemotherapy, and treatment plans for patients with residual disease after surgery remain in real-world practice. Therefore, the Hong Kong Breast Cancer Foundation (HKBCF) convened a multidisciplinary consensus to guide the practical use of pembrolizumab locally.

The results of this consensus were partially presented during the Hong Kong Breast Cancer Symposium in November 2023 and in abstract form at the American Society of Clinical Oncology Annual Meeting 2024.[11] Here, we present the full results.

帕博利珠單抗治療早期三陰性乳癌日常臨床應用的專家共識建議

楊明明、陳可恩、梁澄宇、陳穎懷、周芷茵、傅惠霖、馮惠媛、郭子熹、劉曉欣、梁國璋、吳廷英、曾詠恆、黃嘉明、邱振中、袁灝恩、張淑儀

前輔助療法是早期三陰性乳癌的標準治療。由於病理完全緩解與長期臨床及存活益處有密切關聯，因此選擇合適的術前及術後治療可進一步優化治療效果。隨着在乳癌應用免疫療法，更多治療組合應運而生，例如帕博利珠單抗。它是一種免疫檢查點（PD-1）抑制劑，已獲准用於第II及III期三陰性乳癌的圍手術期治療。然而，在三陰性乳癌圍手術期施用免疫療法，仍需就患者篩選及與免疫療法一同使用的其他治療方法展開進一步討論。香港乳癌基金會召集了跨專科共識小組，成員包括外科、臨床腫瘤及內科腫瘤專科醫生，展開相關討論。小組採用經修訂版德爾菲共識法，環繞七個範疇共45個建議進行分析，涵蓋早期三陰性乳癌的診斷及圍手術期治療。這些共識建議為評估早期三陰性乳癌患者是否適合前輔助療法及免疫治療提供指引。

Methods

To explore the perioperative use of immunotherapy and provide expert guidance for routine clinical practice in the treatment of early triple-negative breast cancer (eTNBC), the HKBCF established a consensus panel comprising seven breast surgeons, six clinical oncologists, and three medical oncologists, each with at least 15 years of clinical experience.

A modified Delphi panel was conducted on seven topics encompassing 45 statements, covering the workup for TNBC as well as neoadjuvant and adjuvant treatment for eTNBC. Statements relating to surgery were prepared by breast surgeons, whereas statements concerning non-surgical interventions were developed by oncologists. The statements were generated with reference to established guidelines and clinical trials, after a non-systematic search of databases for literature published in English without time restrictions. The levels of evidence and strength of recommendations were determined using a two-level grading system.[12]

In the first round, votes from 64 practising healthcare professionals in Hong Kong—including surgeons (n=21), clinical oncologists (n=36), and medical oncologists (n=7)—were collected through an online form using a six-point Likert scale: Strongly disagree = 1; Disagree = 2; Slightly disagree = 3; Slightly agree = 4; Agree = 5; Strongly agree = 6. No midpoint or neutral option was provided to encourage definitive responses. Consensus to accept (CTA) was defined as a median score ≥5 with an interquartile range (IQR) ≤1.75. Consensus to reject (CTR) was defined as a median score ≤2 with an IQR ≤1.75. The results, including statements that did not reach consensus, were discussed further by 16 senior panellists, who voted anonymously during a consensus meeting. All panellists were invited to review the manuscript contents to confirm the final statements, as described in later sections. The first- and second-round voting results are summarised in the Table and online supplementary Tables 1 and 2. All voting data were analysed using SPSS (Windows version 28.0; IBM Corp, Armonk [NY], United States) to determine consensus. Recommendations were graded using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system as strong (grade 1) or weak (grade 2); the quality of evidence was classified as high (grade A), moderate (grade B), or low (grade C).[12] This manuscript follows the AGREE (Appraisal of Guidelines Research and Evaluation) reporting guideline.

Consensus statements

Workup for breast cancer

Respondents and panellists agreed that all women with clinical suspicion of breast cancer should be offered mammography, with or without ultrasound, and that imaging should be scored according to

TABLE. Clinical statements in the first-round voting that reached consensus to accept

		Median score	IQR
Topic 1: Workup for breast cancer			
1.	In cases of clinical suspicion of breast cancer, patients should be offered (at minimum) MMG with or without USG.	6	1
2.	All radiologic imaging of unconfirmed cases should be scored according to BI-RADS by a qualified and experienced radiologist.	6	0
3.	All cases with a BI-RADS score of 4 or 5 should undergo pathological assessment for confirmation.	6	1
4.	All cases with histopathological confirmation of breast cancer should be tested for the expression of ER, PR, and HER2 by IHC to aid development of the optimal treatment plan.	6	0
5.	Triple-negative breast cancer is defined as breast cancer lacking expression of ER and PR and without overexpression of HER2, as confirmed by IHC (score 0 or 1+). Equivocal cases with a HER2 IHC 2+ score require a negative result by ISH to be considered triple-negative.	6	0
6.	The uncommon subtype 'ER-low' (ER expression of 1%-9% by IHC) does not formally meet the definition of TNBC but should be treated as TNBC.	5	0
Topic 2: General patient selection for neoadjuvant therapy			
7.	In patients with non-metastatic TNBC (stage II-III and cT1c cN0), the role of NAT lies in downstaging.	5	1
8.	The efficacy of NAT regimens is measured by endpoints used in clinical trials, among which the pCR rate is the standard marker for eTNBC NAT studies.	5	1
9.	Neoadjuvant chemotherapy should be considered the standard and preferred treatment option for stage II to III TNBC, provided the patient's condition allows for NAT.	6	1
10.	Neoadjuvant chemotherapy should be considered in TNBC patients with any cT and cN+ disease, in the absence of contraindications to chemotherapy.	6	1
11.	Neoadjuvant chemotherapy should be considered in TNBC patients with cT2 and cN0 disease, in the absence of contraindications to chemotherapy.	5	1
12†.	Neoadjuvant chemotherapy can be considered in TNBC patients with cT1c and cN0 disease, as per the NCCN Guidelines.	5	0
13.	All eTNBC patients should undergo definitive surgery 3 to 6 weeks after completing the final NAT cycle.	6	1
Topic 3: Neoadjuvant therapy regimens			
14.	Anthracycline-/cyclophosphamide-/taxane-based chemotherapy is considered the standard NAT regimen for stage II to III TNBC patients without contraindications. Other chemotherapy regimens may be considered based on clinical indication or patient preference.	6	1
15.	Carboplatin should be included in the chemotherapy regimen for patients receiving NAT and for stage II to III TNBC patients also receiving taxane-, anthracycline-, and cyclophosphamide-based chemotherapy when pembrolizumab is not administered.	5	0
16.	The KEYNOTE-522 data on the addition of the PD-1 inhibitor pembrolizumab are compelling. Therefore, pembrolizumab should be considered a standard perioperative treatment option adjunct to chemotherapy and RT for stage II to III TNBC patients who are candidates for NAT.	5	1
17†.	The NCCN Guidelines support the administration of NAC in cT1c cN0 patients; however, data remain limited because this group was excluded from the KEYNOTE-522 trial. The KEYNOTE-522 regimen may nevertheless be considered.	5	1
18.	The KEYNOTE-522 trial included eTNBC patients with PD-L1 CPSs of either ≥1 or <1, where CPS reflects PD-L1 expression level. The pCR rate and EFS improved in both CPS ≥1 and CPS <1 subgroups with the addition of pembrolizumab to NAT. Therefore, the decision to prescribe IO as perioperative treatment does not necessarily need to be guided by PD-L1 expression.	5	1
19.	Neoadjuvant RT does not preclude the use of IO.	5	0
Topic 4: Neoadjuvant chemotherapy alternative dosing regimens			
21.	In the KEYNOTE-522 trial, pembrolizumab Q3W was combined with weekly or 3-weekly carboplatin plus weekly paclitaxel for 12 weeks, followed by 3-weekly epirubicin (or doxorubicin) plus cyclophosphamide for another 12 weeks. However, different dosing schedules have been studied in the perioperative setting. The NeoPACT trial showed encouraging EFS and pCR rates by administering pembrolizumab with carboplatin (area under the curve=6) and docetaxel (75 mg/m^2) every 3 weeks for six cycles. Additionally, the phase II NeoImmunoBoost trial, using weekly nab-paclitaxel plus 3-weekly pembrolizumab followed by 3-weekly epirubicin plus cyclophosphamide, demonstrated a reasonably high pCR rate. Based on these findings, different schedules of chemotherapy plus pembrolizumab may be considered according to individual patient needs.	5	0

Abbreviations: AE = adverse event; ALND = axillary lymph node dissection; ASCO = American Society of Clinical Oncology; AT = adjuvant therapy; BCS = breast conserving surgery; BI-RADS = Breast Imaging-Reporting and Data System; *BRCA1/2* = BReast CAncer gene 1/2; cN = clinical nodal stage; CPS = combined positive score; cT = clinical primary tumour stage; eTNBC = early triple-negative breast cancer; EFS = event-free survival; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; IO = immunotherapy; IQR = interquartile range; ISH = in situ hybridisation; LN = lymph node; MMG = mammography; NAC = neoadjuvant chemotherapy; NAT = neoadjuvant therapy; NCCN = National Comprehensive Cancer Network; NHS = National Health Service; PARP = poly (ADP-ribose) polymerase; pCR = pathological complete response; PD-1 = programmed death receptor 1; PD-L1 = programmed death-ligand 1; PR = progesterone receptor; Q3W = once every 3 weeks; RT = radiotherapy; SLN = sentinel lymph node; SLND = sentinel lymph node dissection; TNBC = triple-negative breast cancer; TNM = tumour-node-metastasis; TSH = thyroid-stimulating hormone; USG = ultrasound

* It was assumed that patients were treated with pembrolizumab plus chemotherapy in the neoadjuvant setting

† Statements that were discussed and revoted in the second round

TABLE. (cont'd)

		Median score	IQR
22.	The phase II NeoImmunoBoost trial showed a pCR rate of 73.9% (n=23) in eTNBC patients (stage ≥cT1c) treated with weekly nab-paclitaxel and 3-weekly pembrolizumab for four cycles, followed by 3-weekly epirubicin/cyclophosphamide with pembrolizumab for four cycles. This demonstrated satisfactory efficacy for nab-paclitaxel, indicating that it can be considered an alternative to paclitaxel in the KEYNOTE-522 regimen, based on physician preference and patient tolerability.	5	0
23.	The phase II NeoImmunoBoost trial also included a protocol amendment in which eTNBC patients (stage ≥cT1c) received an additional 200 mg dose of pembrolizumab 3 weeks before starting chemotherapy. In this pre-chemotherapy pembrolizumab-boost cohort, a pCR rate of 59.6% (n=27) was achieved. However, due to the small sample size, the study could not confirm the effect of pembrolizumab in improving pCR rates. Therefore, a single pre-chemotherapy dose of pembrolizumab is not currently supported.	5	0
24†.	The 3-weekly paclitaxel regimen is indicated as an alternative for early breast cancer (unspecified clinical staging) patients, either as NAT or AT, according to the NHS London Cancer Alliance. Therefore, based on patient and disease factors, physicians can choose 3-weekly paclitaxel as an alternative to weekly paclitaxel when administering pembrolizumab to eTNBC patients.	5	0
25.	According to the NeoPACT trial, which recruited stage I to III TNBC patients, the 3-weekly neoadjuvant docetaxel regimen achieved satisfactory pCR and 2-year EFS rates of 60% and 88%, respectively, with good tolerability. Therefore, based on patient and disease factors, physicians can choose 3-weekly docetaxel, in addition to carboplatin, when administering pembrolizumab to eTNBC patients.	5	0
26.	Although the KEYNOTE-522 trial used pembrolizumab administered every 3 weeks, the ASCO 2022 Guideline and the European Medicines Agency recommend either 3-weekly or 6-weekly administration. Based on these data, different pembrolizumab schedules may be considered according to individual patient needs.	5	0
Topic 5: Surgery			
28†.	All eTNBC patients with clinical TNM stage I or stage II disease before NAT, without other contraindications to lumpectomy, should be offered BCS as an option before starting treatment.	5	1
29.	Immunotherapy can help achieve better pCR and should be considered for women who prefer lumpectomy over mastectomy, provided the tumour is not centrally located.	5	1
30.	Early triple-negative breast cancer patients with clinically LN-negative disease at diagnosis who achieve clinical or radiologic complete response after NAT do not need to undergo ALND, provided SLND reveals a negative SLN.	5	1
32.	Early triple-negative breast cancer patients with clinically LN-positive disease at diagnosis and residual disease in the SLN with or without clipped node after NAT should undergo ALND.	5	1
Topic 6: Adjuvant treatment			
33.	Adjuvant capecitabine may be considered for eTNBC patients without pCR after NAC, for a duration of six to eight cycles, with reference to the Asian CREATE-X trial and NCCN Guidelines.	6	1
34.	Based on current data from the KEYNOTE-522 trial, both eTNBC patients achieving a pCR and those not achieving a pCR with NAT can benefit from the addition of pembrolizumab in the adjuvant setting.	5	1
35.	Pembrolizumab should be continued as monotherapy in the adjuvant phase for patients who have achieved pCR after receiving neoadjuvant pembrolizumab–chemotherapy.	5	1
36.	According to a subgroup analysis of the KEYNOTE-522 trial, patients who did not achieve pCR and received pembrolizumab–chemotherapy achieved higher EFS than those in the placebo–chemotherapy group. In clinical practice, if pCR is not achieved after eight cycles of NAT with pembrolizumab, adjuvant pembrolizumab should be continued, weighing the balance between EFS benefit and treatment toxicity.	5	0
37* †.	For eTNBC patients with residual disease after NAT, capecitabine in combination with pembrolizumab may be offered in the adjuvant setting, considering the improved disease-free survival observed among TNBC patients with residual disease who received adjuvant capecitabine versus those who did not, according to the CREATE-X trial.	5	1
38†.	For eTNBC patients with residual disease after NAT with pembrolizumab and a known germline *BRCA1/2* mutation, offering a PARP inhibitor in combination with pembrolizumab in the adjuvant setting should be considered.	5	1
Topic 7: Treatment toxicities			
41.	Physicians should ensure that patients are instructed to seek immediate medical attention upon the onset of AEs, given that AEs associated with chemotherapy and IO may appear similar but have distinct aetiologies. Although immune-related AEs are generally mild, they can be life-threatening.	6	1
42.	Signs and symptoms of hypothyroidism, rash, colitis, pneumonitis, adrenal insufficiency, hepatitis, nephritis, hypophysitis, diabetes mellitus, myalgia, and encephalopathy should always be regarded as potentially immunologically mediated in patients treated with IO.	6	1
43.	Physicians should proactively monitor for thyroid dysfunction in patients treated with IO.	6	1
44.	Testing of total triiodothyronine, free thyroxine, and TSH levels should be performed according to the KEYNOTE-522 trial protocol: prior to NAT plus IO, after the last cycle of the first NAT plus IO phase, after the last cycle of the second NAT plus IO phase before definitive surgery, after definitive surgery, after the last cycle of adjuvant IO, and during long-term follow-up at 3-month intervals for the first 2 years, then at 6-month intervals for years 3 to 5, and annually thereafter until local and/or distant disease progression, recurrence, or death, whichever occurs first.	5	1
45.	The survival benefits of pembrolizumab, as demonstrated in the KEYNOTE-522 trial, outweigh the risks of AEs, which include the potential need for long-term hormone replacement.	5	1

the BI-RADS (Breast Imaging Reporting and Data System) by a qualified and experienced radiologist. The definition of TNBC was also highlighted, referring to breast cancer that lacks expression of ER and PR and does not exhibit overexpression of HER2. Two key statements relating to the histopathology of TNBC are presented below:

Statement 4: All cases with histopathological confirmation of breast cancer should be tested for the expression of oestrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 by immunohistochemistry to aid the development of the optimal treatment plan. (CTA; Recommendation: 1A)

Statement 6: The uncommon subtype 'oestrogen receptors–low' (oestrogen receptor expression of 1%-9% by immunohistochemistry) does not formally meet the definition of triple-negative breast cancer but should be treated as triple-negative breast cancer. (CTA; Recommendation: 2C)

It was agreed that assessment of ER/PR expression and HER2 overexpression in breast cancer is essential to facilitate treatment planning and should be confirmed before treatment initiation. The panel regarded ER-low–positive (1%-9% ER expression) breast cancer as a biologically distinct subgroup for which treatment consensus has not yet been established, due to the uncertain benefit of endocrine therapy.[13] A prospective multicentre registry study of 516 patients conducted between 2011 and 2019 showed that demographic and clinical characteristics, as well as *BRCA1/2* mutation status, were comparable between ER-low breast cancer and TNBC.[14] The respondents therefore believed that breast cancer exhibiting low ER expression on immunohistochemistry should be treated as TNBC.

General patient selection for neoadjuvant therapy

The importance of neoadjuvant therapy (NAT) for downstaging non–metastatic TNBC (non-mTNBC) was generally agreed upon by respondents and panellists. Patients with stage II to III disease or node-negative cases with a primary tumour size between 1 and 2 cm should be considered for NAT. Definitive surgery should be performed within 3 to 6 weeks after completion of the final cycle of NAT. Two key statements relating to NAC use for eTNBC are discussed below:

Statement 9: Neoadjuvant chemotherapy should be considered the standard and preferred treatment option for stage II to III triple-negative breast cancer, provided the patient's condition allows for neoadjuvant therapy. (CTA; Recommendation: 1A)

Statement 12: Neoadjuvant chemotherapy can be considered in triple-negative breast cancer patients with clinical tumour stage 1c (cT1c) and clinical nodal stage 0 (cN0) disease, as per the National Comprehensive Cancer Network Guidelines. (CTA; Recommendation: 1C)

The St Gallen Consensus Conference recommends adding carboplatin to neoadjuvant paclitaxel, followed by anthracyclines and cyclophosphamide, for stage II to III TNBC.[15] The National Comprehensive Cancer Network Guidelines state that preoperative systemic therapy is preferred for TNBC patients at clinical stage ≥cT2 or ≥cN1 and can also be considered for cT1cN0.[16] The American Society of Clinical Oncology recommends offering an anthracycline- and taxane-containing regimen in the neoadjuvant setting for patients with TNBC at clinical stage cT1cN0M0,[17] whereas the European Society for Medical Oncology guidelines suggest NAT for TNBC patients with cT1cN0 disease or greater.[18] After reviewing these guidelines, the panellists agreed on the use of NAT for TNBC patients with a clinical tumour size of 1 to 2 cm and no palpable lymph nodes (LNs).

The panellists also noted that, in clinical practice, establishing a multidisciplinary team comprising surgeons and oncologists is essential when developing a treatment plan, particularly for patients who may be eligible for breast conserving surgery (BCS) after NAT. Patient adherence to treatment plans proposed by a multidisciplinary team is reportedly higher, according to a retrospective study conducted in Europe.[19]

Neoadjuvant therapy regimens

Anthracycline/cyclophosphamide/taxane-based chemotherapy is the standard NAT regimen for stage II to III TNBC.[20] In addition to standard chemotherapy, respondents and panellists agreed that other regimens may be considered as clinically indicated or according to patient preferences. The addition of platinum agents and immune checkpoint inhibitors should also be considered, given the improved EFS observed in stage II or III TNBC patients in recent clinical trials.[9,21] Based on the results of the KEYNOTE-522 trial, respondents and panellists supported the addition of pembrolizumab to NAT for TNBC, regardless of PD-L1 expression level.[8,9] Three key statements concerning the use of pembrolizumab are highlighted below:

Statement 15: Carboplatin should be included in the chemotherapy regimen for patients receiving neoadjuvant therapy and for stage II to III triple-negative breast cancer patients also receiving taxane-, anthracycline-, and cyclophosphamide-based chemotherapy when pembrolizumab is not administered. (CTA; Recommendation: 1C)

Statement 16: The KEYNOTE-522 data on the addition of the programmed death receptor ligand 1 inhibitor pembrolizumab are compelling. Therefore, pembrolizumab should be considered a standard perioperative treatment option adjunct to chemotherapy and radiotherapy for stage II to III triple-negative breast cancer patients who are candidates for neoadjuvant therapy. (CTA; Recommendation: 1B)

Statement 17: The National Comprehensive Cancer Network Guidelines support the administration of neoadjuvant chemotherapy in clinical tumour stage 1c (cT1c) and clinical nodal stage 0 (cN0) patients; however, data remain limited because this group was excluded from the KEYNOTE-522 trial. The KEYNOTE-522 regimen may nevertheless be considered. (Neither CTA nor CTR; Recommendation: 2C)

Respondents and panellists emphasised the importance of adding carboplatin to backbone chemotherapy in the NAT of TNBC. A meta-analysis and systematic review of platinum-based NAT across 11 randomised controlled trials involving 2946 patients suggested that platinum-based chemotherapy was associated with a higher pCR rate (40%) compared with platinum-free chemotherapy (27%).[22] Subgroup analysis showed that taxane plus platinum chemotherapy increased the pCR rate to 44.6% vs 27.8% for platinum-free treatment, supporting the neoadjuvant use of carboplatin plus taxane chemotherapy.[22]

The phase III KEYNOTE-522 trial demonstrated that preoperative pembrolizumab plus chemotherapy achieved a significantly higher pCR rate (64.8% vs 51.2%; P<0.001) than chemotherapy alone in untreated stage II to III TNBC patients.[8] These promising findings were further supported by the trial's 60-month EFS rates, which were 81.3% and 72.3% in the pembrolizumab and control groups, respectively.[23]

Patients with cT1a or cT1bN0 TNBC should not be routinely offered NAT outside clinical trials; guidelines suggest a case-by-case approach to NAT for treating cT1cN0M0 disease.[16] Although combinations of immune checkpoint inhibitors and chemotherapy have been extensively studied in three phase II and III neoadjuvant trials (KEYNOTE-522,[8] IMpassion031,[24] and NeoImmunoBoost[10]), none included cT1cN0 patients. Thus, the panel concluded that there is insufficient evidence to justify extrapolating the addition of immunotherapy to chemotherapy for this patient group.

Panellists were divided on the use of immune checkpoint inhibitors, such as pembrolizumab, in all cT1N0 disease. Some noted that evidence from phase III studies is currently limited, whereas others supported the use of pembrolizumab in cT1N0 disease given its inclusion in the NeoPACT trial.[25] Nonetheless, individualised discussions and multidisciplinary team consultations are encouraged for each case before treatment.

Neoadjuvant chemotherapy alternative dosing regimens

Dosing schedules may influence treatment response, safety outcomes, and patient compliance. Respondents and panellists were open to various dosing regimens combining pembrolizumab with platinum and taxane, followed by anthracyclines.[6,10,25] Dose-dense anthracycline was not considered an alternative to the 3-weekly schedule when neoadjuvant pembrolizumab is administered. Two key statements on 3-weekly and weekly dosage schedules are highlighted below for further discussion:

Statement 24: The 3-weekly paclitaxel regimen is indicated as an alternative for early breast cancer (unspecified clinical staging) patients, either as neoadjuvant therapy or adjuvant therapy, according to the National Health Service London Cancer Alliance. Therefore, based on patient and disease factors, physicians can choose 3-weekly paclitaxel as an alternative to weekly paclitaxel when administering pembrolizumab to early triple-negative breast cancer patients. (Neither CTA nor CTR; Recommendation: 2B)

Statement 25: According to the NeoPACT trial, which recruited stage I to III triple-negative breast cancer patients, the 3-weekly neoadjuvant docetaxel regimen achieved satisfactory pathological complete response and 2-year event-free survival rates of 60% and 88%, respectively, with good tolerability. Therefore, based on patient and disease factors, physicians can choose 3-weekly docetaxel, in addition to carboplatin, when administering pembrolizumab to early triple-negative breast cancer patients. (CTA; Recommendation: 2C)

The National Health Service London Cancer Alliance recommends administering paclitaxel once every 3 weeks (Q3W) for four cycles in early breast cancer.[26] However, the E1199 trial investigated the optimal dosing of docetaxel or paclitaxel after anthracycline plus cyclophosphamide in 4954 patients with axillary LN-positive or high-risk LN-negative breast cancer, including 1025 TNBC patients.[27] Although no difference was observed in the primary comparisons of taxane type (docetaxel vs paclitaxel) or schedule (3-weekly vs weekly), a secondary analysis with a 10-year update reported that weekly paclitaxel produced more favourable survival outcomes than the 3-weekly schedule. In TNBC patients, higher 10-year disease-free survival (DFS) and OS were noted with weekly paclitaxel

(Q1W) compared with Q3W (69% vs 58.7%; hazard ratio [HR]=0.69; P=0.01 and 75.1% vs 65.6%; HR=0.69; P=0.019, respectively), supporting the adjuvant use of weekly paclitaxel.[27] In the recent phase II NeoPACT trial, the neoadjuvant combination of pembrolizumab, carboplatin, and docetaxel Q3W achieved a pCR rate of 58% (95% confidence interval [95% CI]=48%-67%) and a 3-year EFS of 86% for all patients.[25] If validated in a phase III randomised study, this combination may represent a future 3-weekly anthracycline-free chemoimmunotherapy option for TNBC patients.[25]

The efficacy of paclitaxel Q3W remains controversial. Although consensus was not reached, all panellists participating in the discussion preferred weekly paclitaxel (Q1W), considering its long-term data on efficacy, tolerability, and toxicity, as well as its consistency with the KEYNOTE-522 regimen, which utilises weekly paclitaxel in combination with pembrolizumab.[8,9] The panellists did not consider paclitaxel Q3W to be an optimal alternative to weekly regimens but agreed that 3-weekly taxane (docetaxel or paclitaxel) regimens may provide a practical treatment schedule for selected patients.

Surgery

Respondents and panellists agreed that the addition of immunotherapy to chemotherapy improves pCR rates in patients who wish to undergo BCS after NAT. For patients with clinically negative LNs at diagnosis who achieve a complete response after NAT, extensive axillary surgery may be omitted if sentinel LN dissection reveals negative nodes. However, the panellists did not support applying the same approach to patients who had clinically positive LNs at diagnosis.

One statement concerning the option of offering BCS before the initiation of treatment was discussed:

Statement 28: All early triple-negative breast cancer patients with clinical tumour-node-metastasis stage I or stage II disease before neoadjuvant therapy, without other contraindications to lumpectomy, should be offered breast conserving surgery as an option before starting treatment. (Neither CTA nor CTR; Recommendation: 1C)

According to the National Comprehensive Cancer Network Guidelines,[16] early-stage (≤cT1cN0) operable breast cancer patients may undergo upfront BCS or mastectomy with adjuvant systemic therapy where indicated, whereas patients with clinical stage ≥cT2 or ≥cN disease should be treated with NAT. The European Society for Medical Oncology guidelines state that BCS is the preferred local treatment option for most early breast cancer patients, but aggressive phenotypes such as eTNBC should receive NAT first[28]; BCS should only be offered when the response to NAT is satisfactory.[28] The 17th St Gallen International Guidelines also recommend dose-dense anthracycline- and taxane-based NAT for stage II or III eTNBC but do not comment on stage I disease.[29]

The panellists declined to endorse the statement, noting that NAT is a treatment option for eTNBC patients but not a prerequisite for BCS in stage I or II disease. However, it is noteworthy that in-breast recurrences represent 5% to 15% of all recurrence events in early-stage breast cancer under contemporary BCS and RT management.[30,31] Recurrence rates have continued to improve with advances in therapy. In a recent meta-analysis of 14 studies involving 19 819 TNBC patients who underwent BCS (plus radiotherapy) or mastectomy, the pooled odds ratio for locoregional recurrence was 0.64 (95% CI=0.48-0.85; P=0.002), the pooled odds ratio for distant metastasis was 0.70 (95% CI=0.53-0.94; P=0.02), and the pooled HR for all-cause mortality was 0.78 (95% CI=0.69-0.89; P<0.001) among patients who underwent BCS relative to mastectomy.[32] Another retrospective study of 12 761 patients with T1-2N0M0 TNBC also revealed significantly higher 5-year OS (89% vs 84.5%; P<0.001) and breast cancer–specific survival (93% vs 91%; P<0.001) in patients receiving BCS and radiotherapy compared with those undergoing mastectomy alone.[33] Both meta-analyses did not report outcome differences between adjuvant therapy with upfront BCS and NAT followed by BCS in eTNBC. Given these encouraging data, the panellists regarded the statement as unclear but raised no objection to recommending upfront BCS for selected patients with ≤cT1cN0 eTNBC. Risk factors, including age, tumour grade, and disease stage, should be considered when offering this treatment option.

Adjuvant treatment

For patients with residual disease after neoadjuvant pembrolizumab plus chemotherapy, adding capecitabine to adjuvant pembrolizumab was considered acceptable. However, consensus was not reached among panellists regarding the combined use of a poly (ADP-ribose) polymerase inhibitor and pembrolizumab in the adjuvant setting for patients with residual disease and a known germline *BRCA1/2* mutation (*gBRCA1/2m*), due to variations in local testing practices for *gBRCA1/2m*. Discussions of scenarios that may benefit from the adjuvant use of pembrolizumab are summarised in the two statements below:

Statement 34: Based on current data from the KEYNOTE-522 trial, both early triple-negative breast cancer patients achieving a pathological complete response and those not achieving a

pathological complete response with neoadjuvant therapy can benefit from the addition of pembrolizumab in the adjuvant setting. (CTA; Recommendation: 1B)

Statement 37: For early triple-negative breast cancer patients with residual disease after neoadjuvant therapy, capecitabine in combination with pembrolizumab may be offered in the adjuvant setting, considering the improved disease-free survival observed among triple-negative breast cancer patients with residual disease who received adjuvant capecitabine versus those who did not, according to the CREATE-X trial. (CTA; Recommendation: 2B)

According to the KEYNOTE-522 trial, patients receiving perioperative pembrolizumab and NAC demonstrated better EFS than those treated with NAC alone (84.5% vs 76.8%, HR=0.63; 95% CI=0.48-0.82) at a median follow-up of 39.1 months.[9] Further EFS analysis based on pCR outcomes showed that patients who did not achieve pCR also benefited from the KEYNOTE-522 regimen (67.4% vs 56.8%, HR=0.7; 95% CI=0.52-0.95).[9] The panellists agreed that for patients who did not achieve pCR after neoadjuvant pembrolizumab plus chemotherapy, adjuvant pembrolizumab—or pembrolizumab combined with capecitabine—should be administered.

Based on the CREATE-X (Capecitabine for Residual Cancer as Adjuvant Therapy)[34] and EA1131 trials,[35] patients without a pCR after NAT may benefit from adjuvant capecitabine. The phase III CREATE-X study enrolled 910 HER2-negative breast cancer patients with residual disease after NAT containing anthracycline, taxane, or both. Those who received standard treatment with capecitabine demonstrated better long-term survival outcomes than the control (capecitabine-free) group. Among 286 patients with residual TNBC, those receiving adjuvant capecitabine achieved higher DFS (69.8% vs 56.1%; HR=0.58; 95% CI=0.39-0.87) and OS (78.8% vs 70.3%; HR=0.52; 95% CI=0.30-0.90) than those in the control group at 5 years.[34] Another phase III EA1131 study of 410 patients with residual TNBC after NAT also showed better 3-year invasive DFS among those receiving adjuvant capecitabine (49.4%; 95% CI=39.0%-59.0%) than among those receiving adjuvant platinum (42.0%; 95% CI=30.5%-53.1%), although the difference was not statistically significant.[35]

Despite the lack of mature data regarding the adjuvant use of capecitabine in combination with pembrolizumab, the KEYNOTE-522 study demonstrated the additional benefit of perioperative pembrolizumab with NAC without increasing chemotherapy-related adverse effects in the neoadjuvant setting.[8,9] The panellists considered that adding capecitabine to pembrolizumab in patients without pCR after NAT plus pembrolizumab represents a clinically feasible option to improve long-term survival outcomes in cases where residual disease is observed after pembrolizumab-based NAT. They noted that the combination of pembrolizumab and capecitabine has been reported to be safe and tolerable in mTNBC.[36] However, further prospective studies are required to determine the long-term survival and safety benefits, as well as the optimal dosing schedule, in eTNBC. The panellists ultimately reached a consensus to accept this statement, adding that adjuvant capecitabine with pembrolizumab may be considered on a case-by-case basis.

Treatment toxicities

Respondents and panellists reached consensus on all statements relating to treatment toxicities without requiring further discussion in the second round. In summary, for patients receiving immunotherapy plus chemotherapy, clinicians should monitor for potential immunotherapy-related adverse events, which are generally mild in most patients but may be life-threatening in some cases. Thyroid function should be proactively monitored, given that reversible destructive thyroiditis and overt hypothyroidism commonly occur in patients receiving pembrolizumab.[37]

Conclusion

The development of these consensus statements on the management of eTNBC involved a multidisciplinary panel of oncologists and breast surgeons from public, private, and academic institutions, providing a comprehensive overview of clinical practice in Hong Kong. These statements offer guidance to clinicians regarding the general work-up, treatment, and use of immunotherapy for TNBC patients who do not fit the patient profile enrolled in the KEYNOTE-522 study.

Author contributions

Concept or design: PSY Cheung, W Yeo.
Acquisition of data: All authors.
Analysis or interpretation of data: PSY Cheung, W Yeo.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: PSY Cheung, W Yeo, YHY Chan, RCY Leung.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

CC Yau received speaker's honoraria from Novartis and Eli Lilly. AKC Leung is the Second Vice President of the Hong Kong Breast Oncology Group. All other authors have disclosed no conflicts of interest.

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Declaration

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Supplementary material

The supplementary material was provided by the authors and some information may not have been peer reviewed. Accepted supplementary material will be published as submitted by the authors, without any editing or formatting. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by the Hong Kong Academy of Medicine and the Hong Kong Medical Association. The Hong Kong Academy of Medicine and the Hong Kong Medical Association disclaim all liability and responsibility arising from any reliance placed on the content. To view the file, please visit the journal online (https://doi.org/10.12809/hkmj2513054).

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