ABC-NZ

2nd New Zealand Consensus Guidelines for Advanced Breast Cancer (ABC-NZ2)

October 2022

Contents

Abbreviations guide:

TNBC = triple negative breast cancer
QoL = quality of life
CT = chemotherapy
ET = endocrine therapy
RT = radiation therapy

Introduction

Personal note from the chair of the Breast SIG

It is my true honour and pleasure to present this new set of clinical guidelines for the treatment of advanced breast cancer (ABC). These guidelines have been developed by the Breast Special Interest Group (Breast SIG), a group of passionate practitioners - doctors and nurses - specialising in the diagnosis and treatment of breast cancer, with the assistance of Breast Cancer Foundation NZ (BCFNZ). Our expert panel, including several patient advocates, produced these guidelines to be a framework for everyone involved in the management of ABC. They provide an evidence-based summary of what New Zealand clinicians consider is best practice to manage ABC, a complex disease requiring specialist care, if we are to help our patients live as long as possible with the best possible quality of life.

We want our patients to be informed about the expected standard of care when they are diagnosed with and treated for ABC, and want them to receive the best care, regardless of their ethnicity and their location of residence within New Zealand. We want all healthcare providers to be familiar with the expected standard of care that should be delivered to our patients. We want government health organisations to be up to date with what should be available and funded for New Zealand patients with ABC. As the standard of care evolves, these guidelines are a living document which will be updated every two years.

Dr Marion Kuper-Hommel
Chair of the Breast SIG and Specialist Medical Oncologist

Background

Consensus guidelines offer opinions or recommendations on management of a specific condition and are meant to encourage safe, high-quality, evidence-based patient care. While they constitute the general opinion of a group of experts, they are not necessarily a unanimous view of those experts (a percentage of agreement is published for each statement). The guidelines are not rules for clinicians to follow; rather, they are a snapshot of what their peers consider to be best practice.

The ABC-NZ guidelines are adapted for Aotearoa New Zealand from the international ABC guidelines in consultation with ABC Global Alliance chair Dr Fatima Cardoso. The voting panel was made up of New Zealand breast cancer experts including medical oncologists, radiation oncologists, breast surgeons, ABC clinical nurse specialists, GP/breast physician, patient advocates.

In September 2022, the ABC-NZ2 guidelines were reviewed by the Breast SIG at the Breast Cancer InSIGhts meeting.

Our vision

To provide the best care to all patients in NZ with ABC, with equity of access, regardless of their ethnicity and their location of residence within NZ.

Our mission

For these guidelines to be endorsed and implemented by all stakeholders involved in management of ABC.

Important information about medicines

- If a **medicine is funded by Pharmac**, it is available for use in the public system. If a **medicine is not Pharmac-funded**, patients will need to pay for the medicine and usually for its administration in a private oncology clinic.
- For **medicines that are not Pharmac-funded but are approved by Medsafe**, patients with health insurance may be able to claim some of these costs against their policies. Medsafe approves medicines for specific uses, but they can also be used off-label for different conditions. **Medicines that are neither Pharmac-funded nor Medsafe-approved** may still be prescribed to patients by clinicians under section 29 of the Medicines Act.
- These guidelines include **medicines that may not be Medsafe-approved or Pharmac-funded** but can still be accessed privately. Including them is important as it also acknowledges international standards of care, and where we expect New Zealand to head in the future.
- The terms "Medsafe-approved" and "Pharmac-funded" in these guidelines refer to indications in advanced breast cancer.
  For example, a drug that is Medsafe-approved in renal cancer, but not for ABC, will be described as "not Medsafe-approved". For Pharmac-funded drugs, clinicians should check the specific eligibility critieria.
- The **ESMO Magnitude of Clinical Benefit Scale (MCBS)** is reported for newer medicines in these guidelines. This score indicates the overall efficacy of the medicine as reported in clinical trials, and can be a useful tool for clinicians and patients in treatment decision-making. However, it is important to note that these scores may be too general to apply to individual patients, for example where a subgroup may have reported better or worse trial outcomes than the overall MCBS score suggests, or where a low MCBS score results from lack of phase 3 trial evidence.

Section I. ABC Definitions

Guideline statement	LoE / GoR	NZ Consensus
Visceral crisis is defined as severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease. Visceral crisis is not the mere presence of visceral metastases but implies important ORGAN COMPROMISE leading to a clinical indication for the most rapidly efficacious therapy. Examples: • *Liver visceral crisis:* rapidly increasing bilirubin >1.5x ULN, in the absence of Gilbert's Syndrome or biliary tract obstruction • *Lung visceral crisis:* rapidly increasing dyspnea at rest, not alleviated by drainage of pleural effusion	Expert opinion/ n/a	100%
Endocrine therapy (ET) naïve population: not known if there is sensitivity or resistance to endocrine therapy (ET) since ET never used. **Primary endocrine resistance** is defined as: relapse while on the first 2 years of adjuvant ET, or progressive disease (PD) within first 6 months of 1st line ET for ABC, while on ET. **Secondary (acquired) endocrine resistance** is defined as: all other clinical situations.	Expert opinion/ n/a	100%
Patients with multiple chronic conditions (MCCs) are defined as patients with additional comorbidities (cardiovascular, impaired renal or liver function, autoimmune disease), which may decrease tolerance to treatment and impact outcomes and the incidence of toxicities. This limits the ability to extrapolate existing data and make evidence-based recommendations for care.	Expert opinion/ n/a	100%

Adequate ovarian function suppression (OFS) for premenopausal patients with ABC can be obtained through bilateral oophorectomy, continuous use of LHRH agonists or ovarian function ablation (OFA) through pelvic radiotherapy (the latter is not always effective and therefore is the least preferred option).	I/A	100%
If a LHRH agonist is used in this age group, it should usually be given on a q4w basis to optimise OFS.	II/B	89%
Efficacy of OFS must be initially confirmed analytically through serial evaluations of serum estradiol, even in the presence of amenorrhea, especially if an AI is administered. As all endocrine interventions for premenopausal patients with endocrine-responsive ABC require indefinite OFS, choosing one method over the other requires balance of patient's wish for potentially preserving fertility, compliance with frequent injections over a long period of time, risk of inadequate estrogen level suppression, and cost.	Expert opinion/B	Yes 32% No 47% Abstain 21%
Maintenance therapy, in the context of ABC Guidelines, refers to the continuation of anti-HER2 therapy and/or endocrine therapy after discontinuation of chemotherapy.	Expert opinion/ n/a	100%
Complementary and integrative medicine (CIM) represents the use of complementary treatments side by side with conventional approaches in a proper therapeutic environment	Expert opinion/ n/a	100%

Section II. General guidelines

Guideline statement	LoE / GoR	NZ Consensus
The management of ABC is complex and, therefore, involvement of all appropriate specialties in a multidisciplinary team (including but not restricted to medical, radiation, surgical oncologists, imaging experts, pathologists, gynaecologists, psycho-oncologists, social workers, nurses and palliative care specialists), is crucial.	Expert opinion/A	100%
From the time of diagnosis of ABC, patients should be offered appropriate psychosocial care, supportive care, and symptom-related interventions as a routine part of their care. The approach must be personalised to meet the needs of the individual patient.	Expert opinion/A	100%
Following a thorough assessment and confirmation of ABC, the potential treatment goals of care should be discussed. Patients should be told that ABC is incurable but treatable, and that some patients can live with ABC for extended periods of time (many years in some circumstances). This conversation should be conducted in accessible language, respecting patient privacy and cultural differences, and whenever possible, written information should be provided.	Expert opinion/A	100%
Doctors should ensure that patients are involved, as far as possible, in understanding the nature of their problems, the range of possible solutions, and the likely benefits, risks and costs, to assist them in making informed choices.	Expert opinion/NA	100%
All ABC patients should be offered comprehensive, culturally sensitive, up-to-date and easy to understand information about their disease and its management. Doctors should provide adequate information to their patients about their assessment and treatment options, which are considered standard of care, even if these options are not readily available in NZ.	Expert opinion/NA	100%

Patients (and their families, caregivers or support network, if the patient agrees) should be invited to participate in the decision-making process at all times. When possible, patients should be encouraged to be accompanied by persons who can support them and share treatment decisions (e.g. family members, caregivers, support network).	Expert opinion/A	100%
Every ABC patient must have access to optimal cancer treatment and supportive care according to the highest standards of patient centred care, as defined by: • Open communication between patients and their cancer care teams as a primary goal. • Educating patients about treatment options and supportive care, through development and dissemination of evidence-based information in a clear, culturally appropriate form. • Encouraging patients to be proactive in their care and to share decision-making with their healthcare providers. • Empowering patients to develop the capability of improving their own quality of life within their cancer experience. • Always taking into account patient preferences, values and needs as essential to optimal cancer care. • Patients should have easy access to well-designed clinical studies, since these are crucial for further improvement in the management of ABC.	Expert opinion/A	100%
Every ABC patient should:		
• Have access to the most up-to-date, effective and best tolerated treatments at specialised Cancer Centres.	Expert opinion/A	95%
• Be treated by a practitioner experienced in the management of ABC and the potential side effects of treatment and who has regular access to a multidisciplinary breast cancer specialist team.	I/A	100%
• Survivorship issues and palliative care should be addressed and offered at an early stage. Referral to palliative care does not preclude continuation of active treatment.	Expert opinion/A	100%
• Quality Assurance Programmes undertaken in specialised Cancer Centres should specifically include treatment and support of ABC patients. A Quality Assurance Programme covering the entire breast cancer pathway from screening and diagnosis to treatment, rehabilitation, follow up and palliative care including services and support for ABC patients and their caregivers, should be implemented by specialised Cancer Centres.	Expert opinion/B	100%

ABC strategies, care and treatment protocols should recognise and acknowledge the principles and obligations underpinned by Te Tiriti o Waitangi (The Treaty of Waitangi). This includes assisting wāhine Māori to access relevant services and support, and where possible incorporating a "by Māori, for Māori" approach to help address ethnic inequities, consulting with iwi and Māori to meet their needs. Health providers should look to restore mauri, enhance mana and recognise and respect the role of whānau.	Expert opinion	100%

General Statements: QoL

Guideline statement	LoE / GoR	NZ Consensus
Strong consideration should be given to the use of validated PROMs (patient-reported outcome measures) for patients to record the symptoms of disease and side effects of treatment experienced as a regular part of clinical care. These PROMs should be simple and user-friendly to facilitate their use in clinical practice and thought needs to be given to the easiest collection platform e.g. tablets or smartphones. Systematic monitoring would facilitate communication between patients and their treatment teams by better characterising the toxicities of all anticancer therapies. This would permit early intervention of supportive care services enhancing QoL.	I/C	100%

General Statements: Clinical Trials

Guideline statement	LoE / GoR	NZ Consensus
After appropriate informed consent, inclusion of patients in well-designed, prospective, independent trials must be a priority, whenever such trials are available, and the patient is willing to participate.	Expert opinion/A	100%
The ABC community strongly calls for clinical trials addressing important unanswered clinical questions in this setting, and not just for regulatory purposes. Clinical trials should continue to be performed, even after approval of a new treatment, to provide real world data on its performance, efficacy and toxicity.	Expert opinion/A	100%
Maximum tolerated dose vs. minimal effective dose When using chemotherapy in the palliative setting, the optimal dose level and the best schedule for treatment should be individualised for every patient. This should be based on what is the most effective and best tolerated dose, which, in most cases, is the minimal effective dose and not the maximum.	Expert opinion/NA	100%

General Statements: Affordability/Cost Effectiveness

Guideline statement	LoE / GoR	NZ Consensus
The medical community is aware of the problems raised by the cost of ABC treatment. Balanced decisions should be made in all instances; patients' wellbeing, length of life and preferences should always guide decisions.	Expert opinion/A	100%
Biosimilars The ABC community strongly supports the use of appropriately developed and validated biosimilars both for treatment of breast cancer (e.g. trastuzumab) and for supportive care. To be used, the biosimilar must be approved after passing the stringent development and validation processes required by Medsafe, EMA or FDA or other similarly strict authority. *For use in NZ public practice the biosimilar needs to be Medsafe-approved and Pharmac-funded.* *One trastuzumab biosimilar is Medsafe-approved (but not Pharmac-funded) as of September 2022.*	I/A	100%

General Statements: Survivorship issues

Guideline statement	LoE / GoR	NZ Consensus
As survival is improving in many patients with ABC, consideration of **survivorship issues** should be part of the routine care of these patients. Health professionals should therefore be ready to change and adapt treatment strategies to disease status, treatment adverse effects and QoL, patients' priorities and life plans. Attention to chronic needs for home and family care, job and social requirements, should be incorporated in the treatment planning and periodically updated.	Expert opinion/A	100%
ABC patients who desire to work or need to **work** for financial reasons should have the opportunity to do so, with due consideration to safety, and with needed and reasonable flexibility in their working schedules to accommodate continuous treatment and hospital visits.	Expert opinion/A	100%
The impact of the anticancer therapies on fertility should be discussed with all women with ABC of childbearing age and their partners, before the start of treatment. The discussion must also include appropriate information about the prognosis of the disease and the potential consequences of pregnancy (e.g. stopping ongoing treatment).	Expert opinion/B	100%
The panel recommends that routine breast imaging is not undertaken in patients with ABC, even with long-standing, stable disease or complete remission.		84%
Breast imaging could be considered when there is a suspicion of loco-regional progression.	I/A	100%

The wellbeing of all informal and formal caregivers of patients with ABC is frequently ignored and their pivotal role in supporting patients underestimated and undervalued. They, too, often need appropriate psychological and practical support. Working carers require protection from discrimination in the workplace (current and future). With the patient's agreement, culturally sensitive, up-to-date, and easy to understand information about their loved one's disease and its management throughout the whole trajectory from diagnosis to end-of-life should be provided by the healthcare team and needs to be congruent with that given to patients. Identification of formal and informal carers' needs and referral to appropriate resources should be available for all patients with ABC. For working carers, entitlement to continued employment and requests for reasonable adjustments, such as flexible working, to accommodate their caring responsibilities should be addressed.	Expert opinion/A	100%

General Statements: Other

Guideline statement	LoE / GoR	NZ Consensus
Specialised oncology nurses (if possible specialised breast nurses) should be part of the multidisciplinary team managing ABC patients. This role may be played by a physician assistant, MOSS or another trained and specialised health care practitioner.	Expert opinion/A	100%
The use of **telemedicine in oncology** to help management of patients with ABC living in remote places is an important option to consider when geographic distances are a problem and provided that issues of connectivity and the need for physical examination are solved.	Expert opinion/B	100%

Section III. Assessment and treatment general guidelines

Guideline statement	LoE / GoR	NZ Consensus
Minimal **staging workup for ABC** includes a history and physical examination, haematology and biochemistry tests, and imaging of chest, abdomen, pelvis and bones.	II/A	100%
Preferred staging modality is CT imaging of chest, abdomen and pelvis. A bone scan is only done for confirmation if CT imaging shows suspicious bone lesions.	Expert opinion	89%
For staging of non-special type (NST) invasive breast cancers, PET-CT, if available, is preferred instead of and not in addition to CT-scans and bone scan. For staging of non-special type (NST) invasive breast cancers, PET-CT, if available, is preferred instead of and not in addition to CT-scans and bone scan. Note: PET-CT should be used for specific indications, to characterise/clarify equivocal findings (and this is usually based on CT findings). Small bone and liver lesions might be missed on PET-CT. Low grade and lobular cancers and small <1 cm metastasisses have relatively high false negative rates on FDG-PET.	II/B	53%
CT-scans and bone scans are preferred for invasive lobular breast cancers.		83%
Brain imaging should *not* be routinely performed in asymptomatic patients. This approach is applicable to all patients with ABC including those with HER2+ and/or triple negative ABC.	II/D	95%
The clinical value of **tumour markers** is not well established for diagnosis or follow-up after adjuvant therapy, but their use (if elevated) as an aid to evaluate response to treatment, particularly in patients with non-measurable metastatic disease, is reasonable. A change in tumour markers alone should not be used to initiate a change in treatment.	II/C	100%

Evaluation of response to therapy should generally occur every 2 to 4 months for ET or after 3 to 4 cycles for CT, depending on the dynamics of the disease, the location and extent of metastatic involvement, and type of treatment. In certain patients, such as those with indolent disease, less frequent monitoring is acceptable. Additional testing should be performed in a timely manner, irrespective of the planned intervals, if PD is suspected or new symptoms appear. Thorough history and physical examination must always be performed.	Expert opinion/B	95%

Biopsy of Metastatic Lesion(s)

Guideline statement	LoE / GoR	NZ Consensus
A biopsy (preferably providing histology or cytology) of a metastatic lesion should be performed, if possible, to confirm diagnosis particularly when metastasis is diagnosed for the first time.	I/B	95%
Biological markers (especially ER, PR and HER2) should be reassessed at least once in the metastatic setting, if clinically feasible. Depending on the metastatic site (e.g. bone tissue), technical considerations need to be discussed with the pathologist.	I/B	100%
The value of PR in the metastatic setting is limited and reserved only for confirmation of triple negative status. In the very rare cases of ER-/HER2-/PR+ ABC, approved therapies for triple negative ABC can be used. Depending on the metastatic site (e.g. bone tissue), technical considerations need to be discussed with the pathologist and the interventional radiologist. The quality of IHC assessments is crucial to ensure adequate treatment decisions.	Expert opinion/B	80%

If the results of ER and HER2 in the metastatic lesion differ from the primary tumour, it is currently unknown which result should be used for treatment-decision making. Since a clinical trial addressing this issue is difficult to undertake, we recommend considering the use of endocrine therapy or anti-HER2 therapy, respectively, when ER or HER2 are positive in at least one biopsy, regardless of timing. When reporting HER2 status of a metastatic lesion, the IHC or FISH score should be reported (not just a positive or negative status).	Expert opinion/B	85%
For tumours with confirmed triple negative histology in the primary tumour, if the results of any receptor status in the metastatic lesion differ, it is currently unknown which result should be used for treatment decision making. Since a clinical trial addressing this issue is difficult to undertake, the use of therapies specifically approved for triple negative, ER+/HER2 negative or HER2+ ABC should be discussed on a case-by-case basis. When reporting HER2 status of a metastatic lesion, the IHC or FISH score should be reported (not just a positive or negative status).	Expert opinion/B	100%

Locoregional Treatment General Guidelines

Guideline statement	LoE / GoR	NZ Consensus
To date, the **removal of the primary tumour in patients with *de novo stage 4 breast cancer*** has not been associated with prolongation of survival, with the possible exception of the subset of patients with bone-only disease. However, it can be considered in selected patients, particularly for local control or to improve quality of life or both, always taking into account the patient's preferences.	I/C	100%
Of note, some studies suggest that surgery is only valuable if performed with the same attention to detail (e.g. complete removal of the disease) as in patients with early stage disease.	II/B	100%

Oligo-metastatic disease - Definition Oligo-metastatic disease is defined as low volume metastatic disease with limited number and size of metastatic lesions (up to 5 and not necessarily in the same organ), potentially amenable for local treatment, aimed at achieving a complete remission status. The definition of oligo-metastatic disease is highly dependent on the imaging method used. Trials are necessary to compare different imaging techniques specifically in breast cancer and to evaluate the exact benefit of local treatments.	Expert opinion/NA	100%
Oligo-metastatic disease - Management An important subset of patients with ABC achieve long term remission and survival. These may have oligo-metastatic disease amenable to local therapy or low volume disease very sensitive to systemic therapy. A multimodality approach including locoregional treatments with "potentially curative" intent can be considered in these selected patients, but they should be seen as the exceptions and long-term cure can never be promised. Systemic therapy should be the 1st treatment initiated and decision about possible locoregional treatments should be taken based on disease response.	Expert opinion/B	95%
Oligo-metastatic disease in contralateral axilla Contralateral axillary nodal metastasis (in the absence of contralateral primary) as initial diagnosis of recurrent disease is considered stage 4 metastatic breast cancer. However, after prior local therapy to ipsilateral axilla for early breast cancer, subsequent metachronous contralateral axillary nodal metastasis, either alone or concurrent with an in-breast ipsilateral recurrence, could be considered and treated as a regional metastasis (due to altered lymphatic drainage), and has the potential for long survival or cure with a multidisciplinary approach.	Expert opinion/NA	95%

Systemic Treatment General Guidelines

Guideline statement	LoE / GoR	NZ Consensus
Systemic treatment choice should take at least these factors into account: • HR & HER2 status & germline BRCA status • Patient's preference • Need for a rapid disease/symptom control • Previous therapies and their toxicities, disease-free interval • Tumour burden (defined as number and site of metastases) • Biological age, performance status, co-morbidities (including organ dysfunctions), • Menopausal status (for ET) • Socio-economic and psychological factors • Available therapies • PIK3CA in HR+ and PD-L1 in TNBC, if targeted therapies are accessible.	Expert opinion/A	100%
The **age** of the patient should not be the sole reason to withhold effective therapy (in elderly patients) nor to over-treat (in young patients). Age alone should not determine the intensity of treatment.	I/E	100%

Chemotherapy General Guidelines

Guideline statement	LoE / GoR	NZ Consensus
Both combination and sequential single agent CT are reasonable options. Based on the available data, we recommend **sequential monotherapy** as the preferred choice for ABC. Combination CT should be reserved for patients with rapid clinical progression, life-threatening visceral metastases or the need for rapid symptom and/or disease control.	I/A	95%
If given in the adjuvant setting, a taxane can be re-used as 1st line therapy, particularly if there has been at least one year of disease-free survival.	I/B	95%
Metronomic chemotherapy is a treatment option for patients not requiring rapid tumour response. Available options are low dose oral cyclophosphamide and methotrexate, capecitabine and vinorelbine. Randomised trials are needed and underway to accurately compare metronomic CT with standard dosing regimens.	I/B	95%
Duration of each regimen and number of regimens should be tailored to each individual patient.	Expert opinion/A	100%
Usually each regimen (except anthracyclines) should be given until progression of disease or unacceptable toxicity. What is considered unacceptable should be defined together with the patient.	I/B	89%

HER2- ABC

Guideline statement	LoE / GoR	NZ Consensus
For patients with HER2-negative ABC for whom chemotherapy is appropriate, and in the absence of medical contraindications or patient concerns, single agent chemotherapy from the available options would usually be preferred as first line CT. The decision should be individualised and take into account different toxicity profiles, previous exposure, patient preferences and breast cancer subtype. Available options include anthracyclines, taxanes, capecitabine, vinorelbine or gemcitabine.	I/A	67%
In patients with taxane-naive and anthracycline-resistant ABC or with anthracycline maximum cumulative dose or toxicity (i.e. cardiac) who are being considered for further CT, single agent chemotherapy would usually be considered the treatment of choice. A taxane would be an option; other options include capecitabine, vinorelbine or gemcitabine. The decision should be individualized and take into account different toxicity profiles, previous exposure, patient preferences and breast cancer subtype.	I/A	75%
In patients pre-treated (in the adjuvant and/or metastatic setting) with an anthracycline and a taxane, single agent capecitabine, vinorelbine or gemcitabine are the preferred choices. Additional choices include platinum agents, a different taxane, liposomal anthracyclines or eribulin. The decision should be individualised and take into account different toxicity profiles, previous exposure, patient preferences, and country availability. *Liposomal anthracyclines, albumin-bound taxane and eribulin are Medsafe-approved but not Pharmac-funded (as of September 2022).*	I/A	89%
If given in the adjuvant setting, provided that maximum cumulative dose has not been achieved and that there are no cardiac contra-indications, anthracyclines can be re-used in ABC, particularly if there has been at least one year of disease-free survival.	I/B	85%

Section IV. ER-positive/HER2-negative (luminal-like) ABC

Guideline statement	LoE / GoR	NZ Consensus
Endocrine therapy is the preferred option for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis, for pre- and perimenopausal women with OFS/OFA, men (preferably with an LHRH agonist) and postmenopausal women.	I/A	100%
Many trials in ER+ ABC have not included ***pre-menopausal*** women. Despite this, young women with ER+ ABC should have adequate ovarian function suppression or ablation (OFS/OFA) and then be treated in the same way as post-menopausal women, with endocrine therapies with and without targeted therapies.	Expert opinion/A	100%
Future trials exploring new endocrine-based strategies should be designed to allow for enrolment of both pre- and post-menopausal women, and men.	Expert opinion/A	100%
For pre-menopausal women, for whom endocrine therapy was decided, ovarian suppression/ablation combined with additional endocrine-based therapy is the preferred choice.	I/A	89%
Ovarian ablation by laparoscopic bilateral oophorectomy ensures definitive estrogen suppression and contraception, avoids potential initial tumour flare with LHRH agonist, and may increase eligibility for clinical trials. Patients should be informed on the options of OFS/OFA and decision should be made on a case-by-case basis.	Expert opinion/C	90%
Single agent tamoxifen is the only available endocrine option for pre-menopausal women who decline ovarian suppression or ablation (OFS/OFA) but the panel believes it is a less effective option.	I/D	95%

The preferred 1st line endocrine agent depends on type and duration of adjuvant ET as well as time elapsed from the end of adjuvant ET; it can be an aromatase inhibitor (AI), tamoxifen or fulvestrant for pre- and perimenopausal women with OFS/OFA, men (preferably with a LHRH agonist if AI or fulvestrant is used) and postmenopausal women.	I/A	100%
A CDK4/6 inhibitor combined with endocrine therapy is the standard of care for patients with ER+/HER2 -ABC, since it very substantially increases OS, as well as PFS and either maintains or improves QoL. The CDK4/6 inhibitor can be combined with an AI or with fulvestrant, in de novo or recurrent ABC, in 1st or 2nd line, and in cases of primary or secondary resistance (as defined per ABC guidelines). This recommendation applies to post-menopausal women, to pre- and perimenopausal women in combination with an LHRH agonist, and to men preferably in combination with a LHRH agonist. *Currently there are three CDK4/6 inhibitors available: palbociclib, ribociclib and abemaciclib.* *All three are Medsafe-approved; only palbociclib is Pharmac-funded.*	I/A	100%
There are no data supporting the use of a combination of CDK4/6 inhibitor and ET as maintenance therapy after chemotherapy.	NA/D	42% Yes 21% No 37% Abstain
The addition of the mTOR inhibitor everolimus to an aromatase inhibitor (AI) is a valid option for some patients previously exposed to or naïve of (in case CDK4/6i are not available) endocrine therapy, since it significantly prolongs PFS, albeit without evidence of significant OS benefit. Tamoxifen or fulvestrant can also be combined with everolimus. Adequate prevention with steroid mouthwashes, close monitoring and proactive treatment of adverse events is needed, particularly in older patients treated with everolimus, due to the increased incidence of toxic deaths reported in the Bolero-2 trial. *Everolimus is not Pharmac-funded (as of September 2022), and not Medsafe-approved for advanced breast cancer.* * for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women. ESMO-MCBS: 2	Expert opinion/C I/B	100%

At present, no validated predictive biomarkers other than hormone receptor status exist to identify patients who will/ will not benefit from the addition of a CDK4/6 inhibitor or an mTOR inhibitor to endocrine therapy and none of the studied biomarkers is ready for use in clinical practice. Research efforts must continue.	I/E	100%
The optimal sequence of endocrine-based therapy is uncertain. It depends on which agents were previously used in (neo)-adjuvant settings, duration of response to those agents, burden of disease, patient's preference and availability. Available options for 1st line include AI/Tamoxifen+LHRH agonist (in pre-/perimenopausal) + CDK4/6 inhibitor. For 2nd line: AI/tamoxifen/fulvestrant + CDK4/6 inhibitor (only if not used in 1st line) or + everolimus, fulvestrant + alpelisib (for PIK3CA mutant), AI, tamoxifen, fulvestrant. * for pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women.	I/A	95%
Options for treatment of ER+ disease beyond second line include single agents not previously used (non-steroidal and steroidal AI, tamoxifen, fulvestrant, megesterol acetate, low dose estrogen).	II/B	89%
Challenging a patient with an agent on which the disease previously progressed, after an initial response, is occasionally considered, but there are no robust data to support this approach.	Expert opinion/B	100%
Concomitant CT + ET has not shown a survival benefit and should not be performed outside a clinical trial.	II/D	100%
Endocrine treatment after CT (maintenance ET) to maintain benefit is a reasonable option, though it has not been properly assessed in randomised trials.	III/B	100%

ER positive / HER2 negative ABC: Alpelisib Aleplisib with fulvestrant is a treatment option for patients with PIK3CA-mutant tumours (in exons 9 or 20), previously exposed to an AI and with appropriate HbA1C levels, since it provided about 5 months benefit in median PFS, without statistically significant OS benefit. The decision to give alpelisib should take into consideration the inclusion/exclusion criteria in the Solar-1 study (i.e: pre-existing diabetes & baseline HbA1c), as well as the toxicity profile of alpelisib. *Alpelisib or other PI3K inhibitors are not Pharmac-funded (as of September 2022), but is Medsafe-approved (as of 18/08/2020)* MCBS: 3 For pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women.	I/A	100%
ER positive / HER2 negative ABC: Alpelisib Few patients previously treated with a CDK4/6i were included in the Solar-1. However, a non-randomized cohort study (ByLieve) seems to indicate that alpelisib retains its efficacy if used after a CDK4/6i. In view of the magnitude of OS benefit seen with ET + CDK4/6i, this approach is considered the standard of care for 1st line therapy and ET (fulvestrant or AI) + alpelisib should be reserved for the 2nd line setting in cases of PIK3CA-mutant tumours. *Alpelisib or other PI3K inhibitors are not Pharmac-funded (as of September 2022) but is Medsafe-approved.* ESMO-MCBS: 3 For pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women.	I/B	95%
ER positive / HER2 negative ABC: Alpelisib Patients receiving alpelisib in combination with endocrine therapy for PIK3CA mutated ABC should be instructed to take non-sedating antihistamines daily to prevent rash at start of therapy. Antihistamines can be discontinued after 4 weeks, as the risk for rash is primarily in the first 2 weeks of therapy. *Alpelisib or other PI3K inhibitors are not Pharmac-funded (as of September 2022) but is Medsafe-approved.*	I/B	100%

ER positive / HER2 negative ABC	I/A	100%

Trials comparing the different combinations of endocrine + targeted agents with single agent CT, in the 1st and later lines settings, are ongoing and some have been reported.

In the PEARL trial, despite several trial limitations, ET + palbociclib versus capecitabine yielded similar efficacy, while toxicity profiles were different, in favour of ET + palbociclib. In Young-PEARL, for premenopausal women, ET + palbociclib was superior to capecitabine in terms of PFS.

In view of the substantial survival benefit seen with ET + CDK4/6 inhibitors in 1st line, never seen before with chemotherapy, this combination should be considered the standard of care for 1st line therapy of ER+/HER2 negative ABC.

For pre and peri with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women.

Section V. HER2-positive ABC

Guideline statement	LoE / GoR	NZ Consensus
Anti-HER2 therapy should be offered early (as 1st line) to all patients with HER2+ ABC, except in the presence of contra-indications to the use of such therapy.	I/A	95%
The optimal duration of anti-HER2 therapy for ABC (i.e. when to stop these agents) is currently unknown.	Expert opinion/C	100%
In patients achieving a complete remission, the optimal duration of maintenance anti-HER2 therapy is unknown and needs to be balanced against treatment toxicity, logistical burden and cost. Stopping anti-HER2 therapy, after several years of sustained complete remission, may be considered in some patients, particularly if treatment re-challenge is available in case of progression.	Expert opinion/C	100%
*New Zealand funding criteria do not allow for the HER2 targeted therapies trastuzumab and pertuzumab to be continued when the disease progresses on treatment. *An exception to this rule is for patients who develop brain metastases on trastuzumab +/- pertuzumab, while their extracerebral disease is still well controlled. * Trastuzumab and pertuzumab are large molecules that normally don't cross the blood-brain barrier. * In this scenario, when local therapy could be offered to treat the brain metastases, these HER2 targeted therapies could be continued to control the extracerebral metastatic disease.		100%

ER + / HER2+ ABC For patients with ER+/HER2+ ABC, for whom CT + anti-HER2 therapy was chosen as 1st line therapy and provided a benefit, it is reasonable to use ET + anti-HER2 therapy as maintenance therapy, after stopping CT, although this strategy has not been studied in randomised trials. Duration of maintenance therapy should be until progression, unacceptable toxicity or patient request, and needs to be evaluated in clinical trials. There are no data to decide between single agent anti-HER2 or dual blockade, to combine with maintenance ET after stopping CT, in ER+/HER2+ ABC. Note: In Cleopatra, maintenance was done with dual blockade alone (without ET)	NA/A	100%
The standard 1st line therapy for patients previously untreated with anti-HER2 therapy is the combination of CT + trastuzumab and pertuzumab, because it has proven to be superior to CT + trastuzumab in terms of OS in this population.	I/A	100%
HER2-positive ABC CT agents to combine with a dual blockade of trastuzumab + pertuzumab are docetaxel or paclitaxel. Also possible are vinorelbine, nab-paclitaxel and capecitabine. *Nab-paclitaxel is Medsafe-approved but not Pharmac-funded (as of September 2022). Trastuzumab and pertuzumab are Pharmac-funded.*	I/A I/B II/A, II/B II/A	89%
HER2-positive ABC Regarding the CT component of HER2-positive ABC treatment: When pertuzumab is not given, 1st line regimens for HER2+ ABC can include trastuzumab combined with vinorelbine* or a taxane. Differences in toxicity between these regimens should be considered and discussed with the patient in making a final decision. Other CT agents can be administered with trastuzumab but are not as well studied and are not preferred. * Single agent vinorelbine in association with anti-HER2 therapy has shown superior or equal efficacy compared to taxanes and has a better tolerability.	I/A	100%

HER2-positive ABC: 1st line For patients previously treated (in the (neo)adjuvant setting) with anti-HER2 therapy, the combination of CT + trastuzumab and pertuzumab is the preferred option for 1st line therapy. Few (N=88; 10%) of patients in Cleopatra trial received prior trastuzumab in (neo-) adjuvant setting and all with trastuzumab-free interval > 12 months. *Pertuzumab is Pharmac funded.* ESMO-MCBS: 4	I/A	100%
HER2-positive ABC: 2nd line and beyond Trastuzumab deruxtecan (T-Dxd) showed substantial PFS (HR: 0.28, absolute benefit not yet reached) and an initial trend for OS benefit when compared to T-DM1, in pretreated patients with HER2+ ABC. About 50% of patients received the treatment as 1st or 2nd line and the other 50% in later lines. Where approved, trastuzumab deruxtecan (T-Dxd) is the preferred treatment option in the 2nd line setting, after exposure to trastuzumab and pertuzumab (DESTINY-03 trial). Pulmonary toxicity (ILD*/Pneumonitis) is rare but can be fatal and requires active surveillance and proper management. Nausea and vomiting require adequate prophylaxis. If not used in the 2nd line setting, trastuzumab deruxtecan (T-Dxd) is the preferred treatment option in later lines of therapy, including in heavily pretreated patients with HER2+ ABC (median lines of therapy: 6). *Trastuzumab-deruxtecan is not Medsafe-approved or Pharmac-funded (as of September 2022).* ESMO-MCBS: pending	I/A	95%

HER2-positive ABC: 2nd line and beyond For patients without access to or with contra-indications for T-Dxd, T-DM1 remains the preferred 2nd line therapy, since it has proven superior efficacy (in terms of OS) relative to other HER2-based therapies in the 2nd line (vs. lapatinib + capecitabine) and beyond (vs. treatment of physician's choice). *Trastuzumab-emtansine (T-DM1) is Pharmac-funded after progression on trastuzumab+/- pertuzumab in 1st line. Lapatinib is Medsafe-approved but not Pharmac-funded (as of September 2022) as a second line therapy after progression on trastuzumab.* ESMO-MCBS: 3	I/A	95%
HER2-positive ABC: 2nd line and beyond Dual blockade with tucatinib + trastuzumab + capecitabine showed a benefit in median PFS (2 months) and median OS (4 months), over trastuzumab + capecitabine, in patients previously treated with trastuzumab, pertuzumab and T-DM1, including patients with stable or active brain metastases. Toxicity needs education and early intervention (i.e. diarrhoea). Where approved, it is a treatment option in this setting. *Tucatinib is not Pharmac-funded (as of September 2022) or Medsafe-approved.* *Trastuzumab is not Pharmac-funded (as of September 2022) for continuation beyond progression.* ESMO-MCBS: 3	I/A	95%
HER2-positive ABC For later lines of therapy, trastuzumab can be administered with several CT agents, including but not limited to, vinorelbine (if not given in 1st line), taxanes (if not given in 1st line), capecitabine, liposomal anthracyclines, platinum, gemcitabine, or metronomic CM. *Trastuzumab is not Pharmac-funded (as of September 2022) for continuation beyond progression.* *Liposomal anthracyclines are Medsafe-approved but not Pharmac-funded (as of September 2022).* The decision should be individualized and take into account different toxicity profiles, previous exposure, patient preferences, and country availability.	II/A	84%

Section VI. Triple Negative ABC

Guideline statement	LoE / GoR	NZ Consensus
In triple negative ABC patients (regardless of BRCA status), previously treated with anthracyclines with or without taxanes in the (neo)adjuvant setting, carboplatin demonstrated comparable efficacy and a more favorable toxicity profile, compared to docetaxel, and is therefore an important treatment option.	I/A	100%
For non-BRCA-associated triple negative ABC, there are no data supporting different or specific CT recommendations, besides platinum. Therefore, all CT recommendations for HER2 negative disease also apply for triple negative ABC.	I/A	100%
Immunotherapy for triple negative ABC Checkpoint inhibitors + chemotherapy (pembrolizumab + taxane or carboplatin/gemcitabine) is the preferred treatment option for 1st line therapy for most patients with PD-L1+* triple negative ABC, either de novo or diagnosed at least 6 months from (neo)adjuvant chemotherapy. *Pembrolizumab is Medsafe-approved but not Pharmac-funded (as of September 2022) for triple negative ABC.* *Nab-paclitaxel is Medsafe-approved but not Pharmac-funded (as of September 2022).* * CPS score ≥10	I/A	100%
Immunotherapy for triple negative ABC Atezolizumab in combination with nab-paclitaxel may be an option for 1st line therapy of patients with PD-L1+* triple negative ABC. *Atezoluzimab is Medsafe-approved but not Pharmac-funded (as of September 2022).* *Nab-paclitaxel is Medsafe-approved but not Pharmac-funded (as of September 2022).* * PD-L1 score ≥1% (SP142 PD-L1 IHC). ESMO-MCBS:3	II/B	85%

Checkpoint inhibitor monotherapy in later lines for triple negative ABC is not recommended, due to low response rates.	I/E	84%
Immunotherapy for other ABC subtypes Several ongoing trials are evaluating the role of this type of treatment in other ABC subtypes (non-TNBC) and, for the moment, it is not recommended outside clinical trials. * For PD-L1 testing, see Precision Medicine Statements.	NA/E	100%
Sacituzumab govitecan for triple negative ABC Sacituzumab govitecan is the preferred treatment option for patients with triple negative ABC, treated with ≥ 2 lines (at least one of them in the metastatic setting), since it demonstrated a 5.5 months benefit in OS and a 4 months benefit in PFS. Education, prophylaxis and early management of side effects, in particular diarrhea and nausea/vomiting, are important. *Sacituzumab govitecan is not Pharmac-funded or Medsafe-approved (as of September 2022).* ESMO-MCBS: 4	I/A	90%

Section VII. Hereditary ABC

Guideline statement	LoE / GoR	NZ Consensus
For ABC patients, results from germline genetic testing have therapeutic implications and testing should therefore be performed as early as possible. Appropriate counselling should be provided, to patients and their families, if a pathogenic germline mutation is found.	I/A	89%
At present only germline mutations in BRCA 1/2 have proven clinical utility and therapeutic impact.	I/A	79%
Testing for other additional moderate-to high-penetrance genes may be considered, if deemed appropriate by the geneticist/genetic counsellor, in particular because they may have implications for family members. However, it must be clarified to the patient that at present, a mutation in another moderate-high penetrance gene has no direct clinical implications for the patients themselves, in the setting of ABC.	Expert opinion/C	84%
In patients with gBRCA-associated triple negative or endocrine-resistant HER2- ABC, previously treated with an anthracycline +/- a taxane (in adjuvant and/or metastatic setting), a platinum regimen is the preferred chemotherapy option, if not previously administered. All other chemotherapy recommendations are similar to those for sporadic ABC.	I/A	84%
Hereditary ABC - PARP Inhibitors For patients with a gBRCA mutation single agent PARP inhibitor (olaparib or talazoparib) is one of the preferred treatment options for those with basal-like ABC, since they are associated with a PFS benefit, improvement in QoL and a favorable toxicity profile. *Olaparib and talazoparib are not Pharmac-funded (as of September 2022), both are Medsafe-approved for treatment of germline BRCA-mutated HER2 negative ABC.*	I/A	100%

Hereditary ABC - PARP Inhibitors Data from a small phase 2 trial demonstrated a benefit from olaparib for individuals with a somatic BRCA1/2 mutation or a germline PALB2 mutation. It is acceptable to offer this treatment to these patients, acknowledging the limitation of data, since it is unlikely that large trials will be run. *Olaparib is not Pharmac-funded (as of September 2022), but is Medsafe-approved for treatment of germline BRCA-mutated HER2 negative ABC after prior treatment with chemotherapy.*	II/B	95%
Hereditary ABC - PARP Inhibitors It is unknown how single agent olaparib or talazoparib compare with platinum compounds in this setting, as well as to the optimal use with platinum (combined or sequential), and their efficacy in tumours progressing after platinum. *Olaparib and talazoparib are not Pharmac-funded (as of September 2022), but both are Medsafe-approved.*	II/B	95%
Hereditary ABC - PARP Inhibitors In ER+ gBRCA-associated ABC, the optimal sequence between PARPi and ET+ CDK4/6i was not formally tested. However, given the OS benefit seen with CDK4/6i, the panel considers them the standard of care for 1st line therapy and recommends their use before a PARPi.	Expert opinion/A	90%
Hereditary ABC - PARP Inhibitors In triple negative PD-L1+ and gBRCA-associated ABC, the optimal sequence between PARPi and CT + immune-checkpoint inhibitors was not formally tested. However, given the OS benefit seen with immunotherapy, the panel considers it the preferred option for 1st line therapy, for the majority of the patients. More research is needed to answer questions related to treatment sequencing and other disease subtypes, i.e., HER2+ disease in the context of BRCA1/2 mutations. *Immune checkpoint inhibitors are Medsafe-approved but not Pharmac-funded (as of September 2022) for treatment of ABC.* *PARPi are Medsafe-approved but not Pharmac-funded (as of September 2022) for treatment of gBRCA- associated ABC.*	Expert opinion/B	89%

Hereditary ABC - PARP Inhibitors BROCADE3 was the first phase 3 trial testing a PARP inhibitor (veliparib) in gBRCA ABC that included platinum. Initial presentation of results showed a small benefit in PFS (1.9 ms). However, durable PFS at 3 years was seen in a significant minority (1/4 patients) during veliparib maintenance, which could provide patients lacking other maintenance treatment options, with chemotherapy-free time. Mature OS data are needed before this regimen can be recommended for routine clinical practice. *Veliparib is not Medsafe-approved or Pharmac-funded (as of September 2022).*	I/D	90%

Section VIII. Precision Medicine

Guideline statement	LoE / GoR	NZ Consensus
Multigene panels, such as those obtained using next generation sequencing (NGS) or other technology on tumour DNA have not yet proven beneficial in clinical trials for ABC, their impact on outcome remains undefined and should not be used in routine clinical practice.	I/D	
For patients who are suitable to participate in clinical trials of novel therapies and readily able/motivated to attend a centre with relevant clinical trials, NGS testing may be used in the context of prospective molecular triage programs to select patients for therapeutic trials.		83%
Specific tests (as distinguished from broad mutation profiles) are useful and discussed in separate statements; others may play a role in the future as the medicines they are linked with, achieve regulatory approval.		
NGS is not publicly funded in NZ.		
In patients with advanced/recurrent TNBC, TILs should be quantified (using light microscopy from a recent metastatic biopsy or from their primary).	I/B	63%
In patients with advanced/recurrent TNBC, PD-L1 status (assays SP142 Ventana assay >1% or more) should be assessed as well.	I/B	78%
Combined positive score (CPS) ≥10) as pre-existing immune response is associated with higher benefit from checkpoint blockade with CT.		
Circulating tumour DNA (ctDNA) assessment is not recommended for demonstration of disease progression at this stage.	I/D	100%
Circulating tumour DNA (ctDNA) assessment is an option for the detection of PIK3CA mutations, for selection of patients eligible for alpelisib.	II/A	100%

PIK3CA mutation status If treatment with PI3K inhibitor alpelisib is accessible, patients should be tested for PIK3CA mutation (in exon 9 and 20) in a tissue (metastasis or primary) and/or by ctDNA testing in blood. Patients who do not have an available archival tissue sample and have an uninformative result using the liquid biopsy test could consider undergoing a tumour biopsy for PIK3CA mutation testing. *Testing for PIK3CA mutation is available in NZ but is not publicly funded in NZ.*	I/B	100%
ESR1 mutation status Where ESR1 mutation status is available, in the presence of an ESR1 mutation, treatment with an aromatase inhibitor is not the optimal strategy. Acquired ESR1 mutations occur commonly in case of disease progression under treatment with an AI +/- a targeted agent (i.e. CDK4/6 inhibitor). For the next line of therapy, a non-AI-based option may therefore be a better option.	II/B	90%
ESR1 mutation status Treatment should not be changed based on ESR1 mutation status alone and confirmation of disease progression is mandatory. Availability of ESR1 mutation status is not mandatory for the adequate management of ER+/HER2 negative ABC.	II/D	90%
PD-L1 status for ABC PD-L1 status should be tested in cases of 1st line triple negative ABC, if treatment with immune checkpoint inhibitors is accessible available, preferably in a metastatic tumour sample. *PD-L1 testing for TN ABC is not publicly funded in NZ.* *Immune-checkpoint inhibitors are not Pharmac-funded (as of September 2022) for PD-L1 pos TN ABC.*	I/A	100%

PD-L1 status for ABC PD-L1 status is the companion test for the use of the combination of pembrolizumab and CT, as 1st line therapy for triple negative ABC, using PD-L1 IHC with a Combined Positive Score or CPS ≥ 10 (CPS score: number of PD-L1 staining cells (tumour cells, lymphocytes, macrophages) divided by the total number of viable tumour cells, multiplied by 100). *PD-L1 testing for TN ABC is not publicly funded in NZ.*	I/A	100%
PD-L1 status for ABC PD-L1 status is the companion test for the use of the combination of atezolizumab and nab-paclitaxel, as 1st line therapy for triple negative ABC, using IHC with the SP142 antibody (Ventana), and a cut-off of 1% of positive staining on immune cells.	I/A	90%
Patients with low (1-10%) ER positive (and PR positive), HER2 negative ABC should not be considered for endocrine therapy exclusively. Patients with low (1-10%) ER positive (and PR positive), HER2 negative ABC can be considered as patients with triple negative ABC for clinical trials.	III/B	100%

Section IX. Specific sites of metastases: Bone/Brain/Liver/Pleural Effusion/Chest Wall Recurrences

Guideline statement	LoE / GoR	NZ Consensus
Bone metastases: Radiological assessments are required in patients with persistent and localised pain due to bone metastases to determine whether there are impending or actual pathological fractures. If a fracture of a long bone or vertebrae is likely or has occurred, an orthopaedic assessment is required as the treatment of choice may be surgical stabilisation which is generally followed by radiotherapy. In the absence of a clear fracture risk, radiotherapy is the treatment of choice.	I/A	100%
For palliative radiation of an uncomplicated* symptomatic bone metastasis, a single 8 Gy fraction is recommended. *Uncomplicated is no impending fracture or no spinal canal involvement and without significant neuropathic involvement.		74%
Neurological symptoms and signs which suggest the possibility of spinal cord compression must be investigated as a matter of urgency. This requires a full radiological assessment of the potentially affected area as well as adjacent areas of the spine. MRI is the method of choice. An emergency surgical opinion (neurosurgical or orthopaedic) may be required for surgical decompression. If no decompression/stabilisation is feasible and indicated, emergency radiotherapy is the treatment of choice and vertebroplasty is also an option.	I/B	100%
Bone metastases Regarding the use of bone targeted agents (bisphosphonate, denosumab), the ABC panel endorses the ESMO Guidelines related to this subject. *Denosumab is not Pharmac-funded (as of September 2022) and not Medsafe-approved.*	I/A	100%

Brain metastases Patients with a single or a small number of potentially resectable brain metastases should be treated with surgery or radiosurgery. Radiosurgery is also an option for some unresectable brain metastases.	I/B	95%
If surgery/radiosurgery is performed it may be followed by whole brain radiotherapy but this should be discussed in detail with the patient, balancing the longer duration of intracranial disease control and the risk of neurocognitive effects.	I/C	89%
HER2-positive ABC and brain metastases Because patients with HER2+ ABC and brain metastases can live for several years, consideration of long-term toxicity is important and less toxic local therapy options (e.g. stereotactic radiotherapy) should be preferred to whole brain radiotherapy, when available and appropriate (e.g. in the setting of a limited number of brain metastases).	I/A	100%
In patients with HER2 positive ABC who develop brain metastases with stable extracranial disease, systemic therapy should not be changed.	I/D	84%
HER2-positive ABC & brain metastases For patients with HER2 positive ABC where brain metastases are the only site of recurrence and for whom stereotactic radiotherapy is feasible and accessible, the addition of chemotherapy to local therapy is not known to alter the course of the disease and is not recommended.	I/D	100%
HER2-positive ABC & brain metastases Patients who received localized treatments for brain metastases from HER2-positive ABC and who have well-controlled systemic disease, should continue anti-HER2 therapy. It is recommended to re-start the anti-HER2 therapy (trastuzumab) if this had been stopped.	II/B	95%

HER2-positive ABC & brain metastases A possible alternative is the usage of tucatinib + trastuzumab + capecitabine, although this option may also be reserved for progression of the disease after local therapy. *Tucatinib is not Medsafe-approved or Pharmac-funded (as of September 2022).* *Trastuzumab is not Pharmac-funded (as of September 2022) to be continued beyond progression.*	I/A	100%
HER2-positive ABC & brain metastases TDM-1 has also shown activity against active brain metastases in one prospective single arm study (KAMILLA) and is therefore a treatment option.	II/A	95%
HER2-positive ABC & brain metastases For patients with HER2 positive ABC with progressive brain metastases as the predominant site of disease burden and no local therapy option available, treatment with tucatinib + trastuzumab + capecitabine is the best available option. *Tucatinib is not Medsafe-approved or Pharmac-funded (as of September 2022).* *Trastuzumab is not Pharmac-funded (as of September 2022) to be continued beyond progression.*	I/A	86%
If this treatment is not accessible and/or if no further relevant local therapy options are available, a change in systemic therapy is a reasonable option.	II/B	100%

Brain metastases		
Radio-necrosis after stereotactic radiotherapy for brain metastases is an uncommon complication that may occur especially with longer survival and follow-up, and in particular in cases of re-irradiation.		
Differential diagnosis with tumour progression is often difficult.		
A course of high-dose steroids is the first treatment of choice for symptomatic patients. Surgery may also be considered.	III/B	76%
Where a steroid-sparing option is essential and/or other options have failed, bevacizumab may be used to decrease the surrounding oedema, usually at a dose of 7.5 mg/kg every 2 weeks, for a median of four cycles. Prospective randomized trials are needed to validate further this option.	III/B	
Bevacizumab is not Pharmac-funded (as of September 2022) and is not Medsafe-approved.		
Malignant pleural effusions	III/B	89%
Use of an intrapleural catheter and consideration of pleurodesis with intrapleural administration of talc or drugs (e.g. bleomycin, biological response modifiers) after successful thoracocentesis when the lung is fully expanded (not useful in case of a trapped lung or extensive pleural thickening), can be helpful to reduce the likelihood of rapid re-accumulation of pleural fluid.		
Systemic therapy to treat the underlying malignant pleural disease should be considered.	III/A	95%
Chest wall or regional (nodal) recurrences	Expert opinion/A	100%
Due to the high risk of concomitant distant metastases, patients with chest wall or regional (nodal) recurrence should undergo full restaging, including assessment of chest, abdomen and bone.		

Chest wall and regional recurrences should be treated with surgical excision when feasible with limited risk of morbidity.	II/A	100%
Locoregional radiotherapy is indicated for patients not previously irradiated.	II/A	
For patients previously irradiated, re-irradiation of all or part of the chest wall may be considered in selected cases.	Expert opinion/C	
In addition to local therapy (surgery and/or RT), in the absence of distant metastases, the use of systemic therapy (CT, ET and/or anti-HER2 therapy) should be considered.	I/B	100%
Chemotherapy after first local or regional recurrence improves long term outcomes in ER negative disease and can be used.	I/B	100%
Endocrine therapy in this setting improves long term outcomes for ER positive disease and should be used.	I/B	95%
The choice of systemic treatment depends on tumour biology, previous treatments, length of disease free interval, and patient-related factors (co-morbidities, preferences, etc).	Expert opinion/A	100%
Chest wall and regional (nodal) recurrences In patients with disease not amenable to radical local treatment, the choice of palliative systemic therapy should be made according to principles previously defined for metastatic disease. These patients may still be considered for palliative local therapy.	Expert opinion/B	100%

Section X. Specific populations

Guideline statement	LoE / GoR	NZ Consensus
Male patients with ABC should be offered genetic counselling and testing.	II/A	100%
For ER positive Male ABC, which represents the majority of the cases, ET is the preferred option, unless there is visceral crisis or rapidly progressive disease needing a fast response.	III/A	100%
For ER positive Male ABC tamoxifen is the preferred option.	IV/B	95%
For male patients with ABC who need to receive an aromatase inhibitor (AI), a concomitant LHRH agonist or orchidectomy is the preferred option.	IV/B	89%
Male patients with ER+ ABC should be treated with the same options as female patients, including access to targeted agents such as CDK4/6, mTOR and PIK3CA inhibitors. *mTORi and PIK3CAi are not Pharmac-funded (as of September 2022), mTORi are not Medsafe-approved but a PIK3CAi is.*	II/A	95%

Section XI. Supportive and Palliative Care

Guideline statement	NZ Consensus
Supportive care allowing safer and more tolerable delivery of appropriate treatments should always be part of the treatment plan.	87%
Introduction of expert palliative care early in the ABC journey, for effective control of symptoms such as pain, should be a priority.	93%
Access to effective pain treatment is necessary for all patients in need of pain relief.	100%
Optimally, discussions about patient preferences at the end of life should begin early in the course of metastatic disease. However, when active treatment no longer is able to control widespread and life-threatening disease, and the toxicities of remaining options outweigh the benefits, physicians and other members of the healthcare team should initiate discussions with the patient (and whānau/family members/friends, if the patient agrees) about end-of-life care.	93%
Cancer-related fatigue is frequently experienced by patients with ABC, exerts a deleterious impact on QoL and limits physical, functional, psychological and social wellbeing. The aetiology of this fatigue is complex, therefore effective management needs to be multidimensional. It is important to assess cancer-related fatigue using appropriate patient-reported outcome (PRO) measures before implementing various non-pharmacological (such as exercise) and if needed pharmacological interventions.	87%
Management of dyspnea: Treatable causes like pleural effusion, pulmonary emboli, cardiac insufficiency, anemia, drug toxicity must be ruled out. Patient support is essential. Oxygen is of no use in non-hypoxic patients. Opioids are the drugs of choice in the palliation of dyspnea.	93%
Benzodiazepines can be used in patients experiencing anxiety.	93%

	LoE / GoR	
Steroids can be effective in dyspnea caused by lymphangitis carcinomatosis, radiation or drug-induced pneumonitis, superior vena cava syndrome, an inflammatory component, or in (cancer-induced) obstruction of the airways (in which case laser/stent is to be considered).		93%
Management of cancer and treatment-related cognitive impairment (CRCI), aka "Onco-brain" Cognitive dysfunction associated with cancer diagnosis and treatment has been increasingly reported by breast cancer patients, in the early and advanced settings, who did not have localised treatment to the brain nor other cognitive disorders. Poor performance in neuropsychological tests and of structural changes in brain imaging (i.e. volume reduction in grey matter, less connectivity and activation) are findings of this effect. However self reports of cognitive dysfunction are more prevalent than objective findings, probably due to the multidimensionality of this complaint. Imaging studies should only be used to rule out CNS disease. The exact mechanisms of CRCI are not clear, probably multifactorial and is frequently associated with other cancer related symptoms such as fatigue, anxiety, depression, pain, distress and sleep disorders.	III/NA	98%
Management of cancer and treatment-related cognitive impairment (CRCI), aka "Onco-brain" Routine assessment of clinical symptoms of cognitive dysfunction and awareness/education.	II/A	91%
Routine physical activity is recommended (weekly: 150–300 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity activity) in view of its association with neurogenesis in brain areas related to memory.	II/A	89%
Management of cancer and treatment-related cognitive impairment (CRCI), aka "Onco-brain" Screening for potential reversible factors and corrective measures when possible. [Such factors include: medications and their side effects, emotional distress, depression/anxiety, symptom burden (specially pain, fatigue and sleep disturbance), comorbidities, use of alcohol and other agents that may alter cognition, new-onset vitamin deficiencies and endocrinopathies (eg, TSH, B12)].	II/A	91%
If important impact on self-reported QoL: Refer to neuropsychological assessment and cognitive rehabilitation	III/A	96%

Relevant drug interactions Special attention should be given to potential interactions between targeted agents and common medications for comorbidities, due to the risk of interference with efficacy and/or safety. Examples: • Tamoxifen and ribociclib – increased risk of QTC prolongation • PPI and ribociclib/palbociclib/abemaciclib – decreased efficacy due to shared metabolism • Corticosteroids and checkpoint inhibitors – possible decreased efficacy due to competing mechanisms of action (i.e. immunosuppression) • Antibiotics and checkpoint inhibitors – decreased efficacy due to possible interference with microbiota	100%
Alternative therapies (i.e. therapies used instead of scientifically evidence based medicines) are not recommended in any phase or stage of cancer treatment.	100%
Complementary and integrative medicine: Some complementary therapies have the potential to reduce disease symptom burden and/or side effects of anticancer therapies, and therefore improve the QoL of ABC patients.	100%
Integrative medicine brings conventional and complementary approaches together in a coordinated way. It emphasises a holistic, patient-focused approach to health care and wellness – often including mental, emotional, functional, spiritual, social, and community. It aims for well-coordinated care between different providers and institutions.	80%
Evidence suggests beneficial effects of the following methods, which can therefore be used: Physical exercise/sport (equivalent to 3–5 hrs of moderate walking per week) improves QoL, cardio-respiratory fitness, physical performance and fatigue, and it may also improve DFS and OS; MBSR (Mindfulness-based stress reduction) programs, hypnosis and yoga may improve QoL and fatigue, and help reduce anxiety, distress and some side effects of anti-cancer therapies; Acupuncture may help against CT-induced nausea and vomiting, fatigue and hot flashes.	100%

The following methods of alternative medicine are **not recommended** in ABC since available evidence shows no effect at best, or even association with worse outcome: Antioxidant supplements; Drugs outside the approved indication (e.g. methadone); Herbs including Chinese herbal medicine; Orthomolecular substances (selenium, zinc, etc.); Oxygen and ozone therapy; Proteolytic enzymes, thymic peptides; Phytoestrogens (soy-food, isoflavones); High-dose vitamins (vitamin C, D, E, carotenoids, etc.); L-carnitine, laetrile.	87%
In 2018, the American Society of Clinical Oncology (ASCO) Expert Panel endorsed the Society of Integrative Oncology guideline on the use of integrative therapies during and after breast cancer treatment. The panel deemed the guideline to be clear, thorough, and based on the most relevant scientific evidence, and endorsed it with added discussion points. Key recommendations include the following: Music therapy, meditation, stress management, and yoga are recommended for anxiety/stress reduction.; Meditation, relaxation, yoga, massage, and music therapy are recommended for depression/mood disorders.; Meditation and yoga are recommended to improve quality of life.; Acupressure and acupuncture are recommended for reducing chemotherapy-induced nausea and vomiting.; Acetyl-L-carnitine is not recommended to prevent chemotherapy-induced peripheral neuropathy because of a possibility of harm.; No strong evidence supports the use of ingested dietary supplements to manage breast cancer treatment–related adverse effects. Clinicians should consider referring ABC patients to the guidelines. Additional information is available at: www.asco.org/supportive-care-guidelines	93%
Breast cancer centres/units/departments should be aware that the majority of their patients would like to be informed about complementary and integrative medicine and that many of them are using it. Physicians should actively ask for information about its use, in view of the potential deleterious interactions with specific anti-cancer therapies.	100%
Clinicians should consider providing patients with a list of registered local practitioners of complementary therapies that have the potential to reduce disease symptom burden and/or side effects of anticancer therapies. Such professionals could include NZASA-registered acupuncturists, MNZ-registered massage therapists, CEPNZ-registered exercise physiologists.	80%

Levels of Evidence Grading System

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity.
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity.
III	Prospective cohort studies.
IV	Retrospective cohort studies or case–control studies.
V	Studies without control group, case reports, experts' opinions.

Levels of Evidence Grading System

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended.
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended.
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional.
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended.
E	Strong evidence against efficacy or for adverse outcome, never recommended.