Philippine Society of Medical Oncology (PSMO) Consensus Recommendations for the Management of Breast Cancer in the Coronavirus Disease 2019 (COVID-19) Era

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I. Background and Context

The coronavirus disease (COVID-19) pandemic continues to affect the global healthcare system causing overwhelming challenges to both physicians and patients. The Philippines has been affected greatly by the outbreak since the first reported case on January 30, 2020 and is consistently among the highest in Southeast Asia in terms of the total number of cases and mortality rate.[1-2] Elderly patients and those with comorbidities and immunocompromised states, e.g. cancer patients, remain to be highly vulnerable. If afflicted with the disease, they mostly encounter life-threatening consequences of this pandemic.[3] Cancer patients are said to be more susceptible to infections and have poorer prognosis compared to healthy individuals due to systemic immunosuppression secondary to oncologic treatments and the malignancy itself.[4]

Breast cancer is the leading cause of cancer in the Philippines and comprises a huge percentage of oncologic hospital admissions.[5] Its treatment is complex, and outcomes are essentially based on timing. Given the current situation, the management of breast cancer is facing unique challenges; hence, there is a clamor to modify old guidelines and adapt new protocols to lessen exposure risk and preserve resources without compromising the overall well-being of these patients.

II. Rationale

Since flattening the curve has always been a continuous struggle especially in our country, the COVID-19 pandemic situation might take longer than expected; hence, local consensus recommendations should be urgently employed in managing breast cancer patients. These local recommendations are composed of modified guidelines on prioritizing, screening, diagnosis, treatment, and surveillance of breast cancer patients not suspected to have COVID-19-related illness in the face of a global crisis. However, a major limitation is the lack of prospective experiences to provide sufficient evidence at present.

III. Objective

These recommendations aim to provide local guidance on the management of breast cancer patients **not suspected** to have COVID-19-related illness or have negative real-time reverse transcription polymerase chain reaction (rRT-PCR) test results for COVID-19.

IV. Target Users

These recommendations are intended for the use of medical oncologists taking care of breast cancer patients in the Philippines.

V. Methods

Clinical questions and dilemmas applicable to the local setting were gathered. Literature was reviewed and a draft statement for each clinical question was made indicating the level of evidence, if applicable, and the corresponding strength of recommendation. Recommendations were tailored to the local Philippine setting. The strength of recommendation was determined based on an online voting process among the training institution consultants. They were asked to vote on a scale of A to E, where A=accept completely, B=accept with some reservation, C=accept with major reservations, D=reject with some reservation and E=reject completely. A consensus was considered to have been achieved when 80% voted to accept completely (A) or accept with some reservation (B) a specific recommendation. A recommendation was considered to have

been rejected when >80% rejected completely (E) or rejected with some reservation (D). Recommendations were then presented to the PSMO Guidelines Committee. After presentation, the manuscript was revised and finalized.

VI. Related Guidelines

This guideline primarily localizes to the Philippine setting the recommendations by the European Society of Medical Oncology (ESMO) as published in *ESMO management and treatment adapted recommendations in the COVID-19 era: breast cancer* by De Azambuja E, et al.[6]

For the surgical management of breast cancer, recommendations primarily came from the local guidelines published by the Philippine Society of Breast Surgeons (PSBS) in collaboration with the Philippine Society of General Surgeons (PSGS) last May 4, 2020.[14]

VII. Grading of Evidence and Strength of Recommendation

To rate the level of evidence and strength of recommendations of each statement, the ESMO grading consensus system was adopted (Table 1).[7] Levels of evidence have been assigned to evidence-based recommendations where appropriate.

Table 1. Grading of the level of clinical evidence and strength of recommendation for clinical practice according to the ESMO consensus guidelines.

	Level of evidence
I	≥ 1 large well-conducted randomized controlled trial or meta-analyses of such trials
II	Randomized controlled trials with a suspicion of bias or meta-analyses of such trials
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, and expert opinions
	Strength of recommendation
A	Strongly recommended
B	Generally recommended
C	Optional
D	Generally not recommended
E	Never recommended

VIII. General Recommendations

A. Overall Guiding Statements

In the light of insufficient evidence on oncology practice during COVID-19 times, the following are made, guiding across the following recommendations, hereof:

1. Best practice is still "early detection, diagnosis, and treatment promise the best outcomes for patients with breast cancer" – in non-COVID-19 and COVID-19 times. [Strength B]
2. Cancer patients must be empowered to take care of themselves (e.g. wear facial mask, keep social distancing, practice proper hand hygiene, observe cough etiquette, and keep away from COVID-19 identified areas) while in the health facility and the community. [Strength A]
3. Hospital and clinics must keep cancer patients away from COVID-19 designated areas of the hospital. [Strength B]
4. During hospital visits, if there is adequate personnel, there should be at least a double screening process at the hospital prior to the entry of cancer patients to the designated clinic area - 1st before hospital entry and 2nd before cancer clinic entrance, and triage to cancer clinic or as indicated, diverted to COVID-19 designated areas for management. Patients should be screened for symptoms, temperature, and recent travel history. [Strength B]
5. As much as possible, health workers assigned in cancer clinics and wards of the hospital must be COVID-19 free and must not be rotated to COVID-19 designated patient rooms or wards in the hospital to avoid cross-contamination. Health workers must wear the appropriate personal protective equipment (PPE) as prescribed by the hospital. [Strength B]

B. Prioritization

Q: In general, how should breast cancer patients be prioritized during the COVID-19 pandemic?

A: The tiered approach of ESMO for cancer patients during the COVID-19 pandemic is designed across three levels of priorities, namely: tier 1 (high priority), 2 (medium priority) and 3 (low priority) as follows [Strength B]:

- High Priority: Patient's condition is immediately life threatening, clinically unstable, and/or the magnitude of benefit qualifies the intervention as high priority (e.g. significant overall survival [OS] gain and/or substantial improvement in quality of life [QoL])
- Medium Priority: Patient's situation is non-critical but delay beyond 6 weeks could potentially impact overall outcome and/or the magnitude of benefit qualifies for intermediate priority
- Low Priority: Patient's condition is stable enough that services can be delayed for the duration of the COVID-19 pandemic and/or the intervention is non-priority based on the magnitude of benefit (e.g. no survival gain with no change nor reduced QoL)[6]

C. Screening for COVID-19

Q: Among patients with breast cancer, is it necessary to screen for COVID-19 before treatment?

A: All patients and their companions should be screened for symptoms relating to SARS-COV-2.[8-11] Due to the different contexts of various countries and areas within the countries, it is recommended that testing be accorded to local guidelines and present directives. Should tests be available and allowed, SARS-COV-2 testing should be done before surgery or any invasive procedure, and before initiating immunosuppressive therapies regardless of symptoms.[10-11] [Strength B]

rRT-PCR test must be performed before patients start the cancer-related procedure:

- If with negative result:
  - May undergo anti-cancer drug therapy
  - May undergo radiotherapy
  - May undergo elective breast cancer surgery
  - May undergo invasive screening/diagnostic procedure (e.g., endoscopy, biopsy)
- If with positive result:
  - Asymptomatic – defer anti-cancer treatment until infectious disease (IDS) clearance, quarantine
  - Symptomatic – defer anti-cancer treatment until IDS clearance; hospitalize with IDS as primary management team/medical oncology will only continue management once IDS cleared
  - If needs emergency anti-cancer treatment and with good prognosis with high probability of good treatment response scenario – may continue anti-cancer treatment with IDS co-management, observing COVID-19 precautions always
- For repeated anti-cancer procedures within at most <1-6 weeks apart (e.g., chemotherapy cycles/radiotherapy daily sessions/blood transfusion/BMA/intrathecal infusion, etc.) – repeat rRT-PCR test will be done only if the patient develops new COVID-19-like symptoms or has been exposed inadvertently to COVID-19 areas
- Best to do the rT-PCR test on an outpatient basis prior to hospital admission of the cancer patient for anti-cancer treatments needing admission. Hospitals usually triage admitted patients with pending rRT-PCR testing orders as COVID suspects and so houses them in semi-COVID-19 rooms/wards – this would inadvertently expose the vulnerable cancer patient to a possible hot zone. Test results turn-around time is usually 24-48 hours, depending on the testing facility.

Q: Among patients with breast cancer, what is the best screening test for COVID-19?

A: Recommendations regarding screening will depend on the availability of tests in the health facility as well as local and institutional guidelines.[9-11] At present, only rRT-PCR assays can be used to confirm COVID-19 infection using nasopharyngeal, oropharyngeal swabs, or other bodily fluids. Should another test (e.g. rapid antigen tests) be used as initial screening, this should be confirmed with an rRT-PCR.[12] [Strength B]

D. Outpatient Visits

Q: Among patients with breast cancer, who should be prioritized for outpatient visits?

A: With the discretion of the attending physician, patients can be prioritized into High, Medium, and Low priority for outpatient visits.[6] [Strength B]

- High Priority
  - Those with post-operative unstable conditions (e.g. hematoma or infection)
  - Breast cancer diagnosis during pregnancy
  - Patients with suspected or recently established diagnosis of invasive breast cancer
  - Patients in the active phase of treatment
  - Patients with serious adverse events from treatment
  - Patients with development of new lesions/symptoms upon cancer surveillance
- Medium Priority
  - Post-operative visits in patients with no complications
  - Diagnosed cancer patients at high risk of relapse during cancer surveillance
- Low Priority
  - Follow-up for patients without breast cancer but at high risk of breast cancer development (e.g. BRCA mutation carriers)
  - Patients in between negative cancer screening schedules

E. Telemedicine

Q: Among patients with breast cancer, who can be attended to via telemedicine?

A: If local resources allow (access to technology and internet), the following patients can be attended to via telemedicine: on-treatment patients with new symptoms or side effects (depending on severity of symptoms or side effects and burden of progression), established patients with no new issues, survivorship follow-up, and psychological support visits. Safety monitoring of patients on oral chemotherapy or endocrine therapy plus biological agents may be intensified.[6] [Strength B]

IX. Specific Recommendations

A. Diagnosis and Staging

Q: Among patients presenting with a breast mass, who should be prioritized for a biopsy?

A: Patients with a breast mass highly suspicious for a malignancy or who have already undergone imaging with highly suspicious findings for malignancy (e.g. BIRADS 4/5 on mammography) should be promptly referred for tissue diagnosis (High Priority).[6] Biopsies for lower suspicion lesions (BIRADS 3) may be

postponed. If negative rRT-PCR test result is already available and breast imaging results can be released on the same day of the procedure, biopsies for suspicious lesions should be done on the same day of the breast imaging procedure to minimize hospital visits. However, if there is really a need to postpone a biopsy (e.g. patient is still for rRT-PCR testing or awaiting breast imaging results) – keep this within 6-8 weeks.[13] [Strength B]

Q: Among patients with a breast mass needing biopsy, what are the recommendations?

A: Core needle biopsy is recommended as the initial biopsy procedure for diagnosis and testing for estrogen receptor (ER)/progesterone receptor (PR)/human epidermal growth factor receptor 2 (HER2) should be requested on all patients confirmed to have invasive cancer and ER/PR for patients confirmed to have non-invasive cancer (DCIS). Biopsies for suspicious lesions that can be done on the same day of consultation is encouraged to minimize exposure to both the patient and staff.[14] [Strength B]

Q: Among patients presenting with discordant biopsy results, should a repeat biopsy be done?

A: Establishing the presence of malignancy is required. Though discordant biopsies are uncommon, these patients would be categorized as Medium or Low Priority depending on the level of suspicion.[13] If there is a high clinical index of suspicion of a malignancy and the biopsy says otherwise, or the intent of treatment is curative, then a re-biopsy should be prioritized. [Strength B]

Q: Among patients with symptomatic metastatic relapse, should a repeat biopsy of the metastatic site be done?

A: For patients with symptomatic metastatic relapse, whenever the treatment can be lifesaving or can significantly modify the quality of life, obtaining a histopathological diagnosis cannot be deferred.[6] However, in circumstances where there is limited capacity to access biopsy services, emphasis should be on supportive care to alleviate symptoms (Medium to High Priority, depending on severity of symptoms and urgency of care). [Strength B]

Q: Among patients with breast conditions, who should be prioritized for breast focused imaging?

A: Urgent situations needing immediate breast focused imaging include patients with severe breast abscess formation or a serious postoperative complication (High Priority). Further diagnostic imaging for an abnormal mammogram (BIRADS 4-5) or for suspicious breast symptoms, and breast MRI for disease extent evaluation or pre-chemotherapy assessment may be delayed but not indefinitely until the end of the pandemic (Medium Priority). BIRADS 3 patients returning for short-term follow-up diagnostic mammogram and/or ultrasound and routine breast exam should be postponed until the COVID-19 pandemic is over (Low Priority). If a malignant condition is unlikely, the diagnostic procedure should be postponed.[13] [Strength B]

Q: Among patients with early stage invasive breast cancer, can initial metastatic work-up be delayed?

A: Initial metastatic work-up in early stage invasive breast cancer can be delayed but not beyond 6 weeks (Medium Priority).[6] [Strength B]

Q: Among patients diagnosed with metastatic breast cancer, should routine restaging imaging tests be done?

A: Patients without signs or symptoms of tumor progression may defer routine restaging scans (Low Priority).[13] [Strength B]

B. Treatment: Early and Locally Advanced Breast Cancer

a. Surgery

Q: Among patients with early/locally advanced breast cancer needing surgery, what is the necessary preoperative workup?

A: Once a patient is scheduled for surgery, a thorough preoperative workup and screening is necessary to protect the facility and all health care workers. These include checking for exposure history and COVID-19 related signs and symptoms, physical examination (i.e. RR >30/min, O2 sat < 92% at room air, rales). Chest x-ray (consider chest CT scan for preoperative cancer patients) and COVID-19 rRT-PCR testing should be done according to each institution's protocol.[14] [Strength B]

Q: For patients diagnosed with early/locally advanced breast cancer, should surgery be done without postponement?

A: Primary surgery of low-risk early breast cancer can safely be postponed for up to 12 weeks (but preferably within 6-8 weeks) (Low Priority) guided by molecular profiling (if available) and experts' opinion. If very aggressive tumor biology is present in histopathology, neoadjuvant chemotherapy may be considered prior to the surgery. For luminal-like breast cancers, using appropriate preoperative endocrine treatment can be an option.[6] [Strength B]

Q: Among patients with early/locally advanced breast cancer, which cases should be considered priority for surgery?

A: Cases that should be done as soon as feasible (Medium-High Priority) include:

- Neoadjuvant patients finishing treatment
- Clinical Stage T2 or N1 ER/PR-positive/HER2-negative tumors
- Triple negative or HER2-positive patients
- Discordant biopsies likely to be malignant
- Excision of malignant recurrence
- Incision and drainage of breast abscess
- Evacuation of a hematoma
- Revision of an ischemic mastectomy flap
- Revascularization/revision of an autologous tissue flap (reconstruction should not be done urgently and should be done after the pandemic)[14,15]

Breast conserving surgery is encouraged whenever possible. Defer definitive mastectomy and/or reconstruction until after the COVID-19 pandemic resolves provided radiation oncology services are available.[14,15] [Strength B]

Q: Among patients with early/locally advanced breast cancer, which cases can be deferred during the pandemic?

A: Cases that can be deferred during the pandemic (Low Priority) include: [Strength B]

- Excision of benign lesions-fibroadenomas, nodules, etc.
- Duct excisions
- Discordant biopsies likely to be benign
- High risk lesions-atypia, papillomas, etc.
- Prophylactic surgery for cancer and noncancer cases
- Delayed SNB for cancer identified on excisional biopsy
- cTisN0 lesions
- Re-excision surgery
- Tumors responding to neoadjuvant hormonal treatment
- Clinical stage T1N0 ER-positive/PR-positive/HER2-negative tumors (hormonal therapy can be given instead)
- Inflammatory and locally advanced breast cancers (neoadjuvant chemotherapy can be given first instead) [15]

Q: Among patients with early/locally advanced breast cancer, what are the limitations likely to be experienced during the pandemic that can affect surgical treatment?

A: Factors that can affect surgical treatment during the pandemic include: [Strength B]

- Increasing number of admitted COVID-19 patients within the hospital
- Limited ICU beds and ventilator capacity
- OR supplies/PPEs limited during the pandemic
- Healthcare personnel become limited - staffing issues
- COVID-19 trajectory within hospital is rapidly escalating
- Hospital resources are mostly routed towards COVID-19 related needs [15]

Q: For patients with locally advanced breast cancer who have undergone neoadjuvant treatment, should surgery be done after completion of the neoadjuvant chemotherapy?

A: Patients who have completed neoadjuvant chemotherapy or, those who are progressing during such treatments, should receive curative surgery with no postponement (Medium-High Priority). However, if scheduling of the surgery cannot be facilitated, adding another cycle of neoadjuvant therapy in patients responding well to therapy may be considered.[6] [Strength B]

Q: Among breast cancer patients with early/locally advanced breast cancer, what is the acceptable delay in surgery after neoadjuvant chemotherapy?

A: Surgical management is needed within 4-8 weeks among patients who completed neoadjuvant chemotherapy and opted to have upfront surgery rather

than further systemic therapy and patients with progressive disease during neoadjuvant chemotherapy or hormonal therapy.[14] [Strength B]

b. Radiotherapy

Q: Among patients with early/locally advanced breast cancer who are for radiation therapy (RT), what are the considerations in RT planning?

A: For early/locally advanced breast cancer patients for RT, these general guidelines should be considered when planning their radiation treatment:

- Hospital visits should be kept to the absolute minimum.
- Reduce the complexity of RT planning/treatment whenever possible to ease pressure on the limited medical workforce.
- Decreasing the duration of RT treatment is encouraged.[16] [Strength B]

Q: Among patients with early/locally advanced breast cancer who are for RT, who should be prioritized?

A: Adjuvant RT for high-risk patients (e.g., inflammatory breast cancer, node-positive or high-risk biology) should be scheduled as High Priority, respecting the highest standards of quality for RT when proposing alternative (shorter) radiation regimens. Adjuvant RT for low-risk/intermediate-risk patients with breast cancer (e.g. aged <65 years and stage I/II luminal cancer, ER-positive regardless of nodal status or positive margins) are considered Medium Priority for RT.[6] [Strength B]

Q: Among patients with early/locally advanced breast cancer who are for RT, which cases would warrant omission of RT?

A: Omit RT for patients 65 years and over (or younger with relevant comorbidities) with invasive breast cancer that are up to 30 mm with clear margins, grade 1-2, ER-positive, HER2-negative and node negative who are planned for treatment with endocrine therapy.[16] Starting adjuvant endocrine therapy is recommended while postponing radiation therapy.[6] Trials investigating safe omission of RT can be considered if they do not impact on patients visits and resources are available. Centers may also consider omitting RT for ductal carcinoma in-situ (DCIS) depending on individual risk and benefit.[16] [Strength B]

Q: Among patients with early/locally advanced breast cancer undergoing RT, can RT regimens be shortened?

A: Use of hypofractionated regimens should be considered to reduce hospital visits. Accelerated partial breast irradiation should be proposed for low-risk patients, when indicated and technically feasible. Shorter treatment courses should be favored, including single dose intraoperative electron radiation therapy or up to 5 fractions of preferably external beam radiation therapy and not brachytherapy as this implicates a second intervention and more frequent hospital visits.[6] [Strength B]

Q: Among patients with early/locally advanced breast cancer patients needing RT, what RT regimens can be followed?

A: Deliver RT in 5 fractions only for all patients requiring RT with node negative tumors that do not require a boost. Options include 28-30Gy in once weekly fractions over 5 weeks or 26Gy in 5 daily fractions over 1 week. Boost RT should be omitted to reduce fractions and/or complexity in most patients unless they are 40 years old and under, or over 40 years with significant risk factors for local relapse. Moderate hypofractionation should be used for all breast/chest wall and nodal RT, e.g. 40Gy in 15 fractions over 3 weeks.[16] [Strength B]

Q: Among patients with early/locally advanced breast cancer, what is the acceptable time for delay in the initiation of RT after chemotherapy?

A: The initiation of RT with an interval longer than 8 weeks was associated with an increase in local recurrence rates at 5 years.[17] There is no significant decrease in disease-specific survival in patients with early breast cancer who get delayed for adjuvant RT, but there is a significant decrease in disease-specific survival among those with locally advanced cancer and a delay of 60 days or more before starting RT.[18] When systemic chemotherapy is being given, RT may be delayed to complete the systemic chemotherapy since there is no impact on overall survival when chemotherapy is administered first. Adjuvant RT should be administered within 7 months of surgery.[19,20] [Level V; Strength B]

Q: Given the current pandemic setting and with the community quarantine in effect making travel difficult, what other options can be explored for patients with early/locally advanced breast cancer in lieu of RT?

A: Several options can be explored for breast cancer patients needing RT: [Strength B]

- Referral to a radiation oncology facility that is near the residence of the patient for easier access.
- For patients who cannot travel or have no access to a radiation oncology facility, and they are ER/PR positive, hormonal therapy can be offered while postponing RT.
- For patients who cannot travel or have no access to a radiation oncology facility, and they are HER2 positive, trastuzumab therapy can be offered while postponing RT.
- For patients who cannot travel or have no access to a radiation oncology facility, and is diagnosed with triple negative breast cancer, adjuvant capecitabine can be considered while postponing RT.[6]

c. Systemic Treatment

Q: Among patients with early/locally advanced breast cancer, when is the best time to initiate (neo)adjuvant chemotherapy?

A: Neoadjuvant treatment should start within 2-4 weeks of diagnosis and staging. Adjuvant treatment should start within 3-6 weeks after surgery.[21] [Strength B]

Q: Among patients with early/locally advanced breast cancer, what subset of patients should be given high priority in giving (neo)adjuvant chemotherapy?

A: For patients necessitating neoadjuvant/adjuvant treatment, the following are considered high priority: [Strength B]

- TNBC patients
- Chemotherapy in combination with targeted therapy for HER2-positive breast cancer patients
- Neoadjuvant and adjuvant endocrine therapy +/- chemotherapy for high-risk ER-positive/HER2-negative breast cancer as defined by current guidelines
- Completion of neoadjuvant chemotherapy that has already been initiated
- Continuation of adjuvant capecitabine treatment in high-risk TNBC patients, and T-DM1 in high-risk HER2-positive breast cancer patients (in the post-neoadjuvant setting)
- Continuation of treatment in the context of a clinical trial, provided patient benefits outweigh risks, with possible adaptation of procedures without affecting patient safety and study conduct. [6]

Q: Among patients with early/locally advanced breast cancer receiving chemotherapy, how can dosing schedules be modified during the COVID-19 pandemic?

A: Chemotherapy schedules may be modified to reduce visits to the hospital (e.g. 2-weekly (dose-dense) or 3-weekly regimens should be preferred). For example, there was no significant difference between giving weekly versus 3-weekly docetaxel in terms of quality of life, clinical response, and pathologic response among early breast cancer patients on neoadjuvant chemotherapy *(see Appendix A)*.[22] However, in patients above the age of 65 years, the number of visits should be balanced with the substantially better tolerability of weekly paclitaxel when compared to 3-weekly docetaxel.[22] [Level I] Dose-dense regimens allow for the shortest duration of treatment *(see Appendix B)*,[6,10,23] but must be balanced with the higher risk of immunosuppression [Level I; Strength B].

Q: Among patients with early/locally advanced breast cancer who will undergo systemic treatment, how can we decrease the significant risk of immunosuppression during systemic chemotherapy?

A: When utilizing chemotherapy regimens with intermediate/high risk of immunosuppression, such as anthracyclines, 3-weekly docetaxel or 3-weekly platinum, patients should receive G-CSF and prophylactic antibiotics for the prevention of febrile neutropenia should be considered. Dexamethasone use should be limited, as appropriate, to reduce immunosuppression.[6,10] [Strength B]

Q: Among HER2-positive early/locally advanced breast cancer who are low-risk or elderly patients with cardiovascular or other comorbidities, how long can we discontinue treatment with anti-HER2 therapy?

A: Anti-HER2 therapy may reasonably be discontinued after 6 months instead of 12 months of treatment according to data from a prospective randomized trial *(see Appendix C)*.[6,24-26] [Level I; Strength B]

Q: Among patients with early/locally advanced breast cancer receiving anti-HER2 therapy, what is the allowable delay of treatment?

A: Ongoing adjuvant trastuzumab alone may be postponed by 6-8 weeks in patients at high risk of complicated COVID-19 infection.[6] [Strength B]

Q: Among patients with early/locally advanced breast cancer on adjuvant trastuzumab therapy, what is the preferred route of administration?

A: Trastuzumab subcutaneous formulation is preferred and, when resources allow it, home administration can be used *(see Appendix D)*. [6,27,28] [Level I; Strength B]

d. Endocrine Therapy

Q: Among patients with early hormone-positive breast cancer, who are the best candidates for neoadjuvant endocrine treatment?

A: For postmenopausal women with stage I cancers, with low-intermediate grade tumors, low Ki-67 proliferation index, high ER/PR expression, and lobular breast cancers, endocrine therapy may be started first while surgery can be delayed. [6,29] If given, this treatment should be continued for a minimum of 4-8 months.[30] [Level V] If available and can be done, for patients with low-risk genomic signatures/score, endocrine therapy is preferred alone.[6] [Strength B]

Q: Among patients with early/locally advanced hormone-positive breast cancer who received neoadjuvant chemotherapy, can endocrine therapy be used after completing chemotherapy if surgery cannot be immediately facilitated?

A: Sequential use of neoadjuvant endocrine therapy may be considered for post-menopausal women whose surgery will be delayed for > 4 months.[30] [Level V; Strength B]

Q: Among patients with early/locally advanced breast cancer on luteinizing hormone-releasing hormone (LHRH) analogue, what is the recommendation on the dosing of administration?

A: LHRH analogue administration should follow the usual international guidelines since no additional risk is foreseen from these agents. LHRH analogue may be given with long acting, every 3 months dosing, to reduce patient visits or alternatively, home administration of LHRH analogue by the patient or visiting nurse may be considered and is the preferred recommendation. However, in very young women and/or women taking an aromatase inhibitor, the risk of inadequate ovarian suppression with the 3-monthly administration can be a concern.[6,10] [Strength B]

Q: Among patients with early/locally advanced breast cancer, what is the role of adding oral targeted agents to endocrine therapy?

A: The addition of oral targeted agents (e.g. CDK4/6, mTOR, or PIK3CA inhibitors), if locally available, to endocrine therapy may be delayed in first-line

treatment, or in situations where endocrine therapy alone is providing or is likely to provide effective tumor control.[13] [Strength B]

C. Treatment: Metastatic Breast Cancer

a. Systemic Treatment

Q: Among patients receiving chemotherapy for metastatic breast disease, what are the recommendations regarding dosing schedule?

A: Chemotherapy schedules is the same as in early and locally advanced breast cancer. It may be modified to reduce visits to the hospital. Dose-dense regimens allow for the shortest duration of treatment,[6] but must be balanced with the higher risk of immunosuppression. [Strength B]

Q: Among patients receiving chemotherapy for metastatic breast disease, what is the recommended route of chemotherapy during the pandemic?

A: Oral therapy is recommended to reduce hospital visits. Oral chemotherapy with capecitabine and vinorelbine, if locally available, is preferred *(see Appendix E, F)*.[6,21,31,32] [Level I; Strength B]

Q: Among patients with metastatic breast cancer, what chemotherapy regimens/agents are preferred?

A: Early line chemotherapy, endocrine therapy, targeted agents, or immune checkpoint inhibitors likely to improve outcomes in metastatic disease (high priority for trastuzumab/pertuzumab plus chemotherapy) may be initiated. Consider giving CDK 4/6 inhibitors in ER-positive/HER2-negative breast cancer, and chemotherapy plus atezolizumab in PD-L1-positive TNBC.[6,10] [Strength B]

Q: Among patients with metastatic breast cancer, should treatment under clinical trials be continued?

A: If possible, continuation of treatment in the context of a clinical trial is recommended, provided benefits outweighs risk.[6] [Strength B]

Q: Among patients with metastatic breast disease receiving anti-HER2 therapy, how can dosing schedules be modified?

A: Trastuzumab, pertuzumab, and related antibody-drug conjugates for HER2-positive tumors may be given at less frequent dosing intervals, as necessary. Patients with HER2-positive breast cancer with >2 years duration of tumor control and minimal disease burden with trastuzumab-based regimens may consider interrupting maintenance therapy. Monitoring for progression every 3-6 months via telemedicine is recommended. Trastuzumab and pertuzumab for metastatic HER2-positive breast cancer may reasonably be administered at longer intervals (e.g. 4 weeks).[13,33] [Level IV; Strength B]

Q: Among patients with metastatic breast cancer, can mTOR inhibitor, PI3KCA inhibitor, or CDK 4/6 inhibitor be added to endocrine therapy?

A: During this pandemic, the decision to add mTOR, PIK3CA, or CDK 4/6 inhibitors, if locally available, to endocrine therapy should take into account the burden of metastatic disease, the pace of disease progression, the possibility of using these agents later in the course of the disease, and the availability of other treatment options. The addition of oral targeted agents (CDK 4/6, mTOR, or PIK3CA inhibitors), if locally available, to endocrine therapy may be delayed in the first-line setting, or in situations where endocrine therapy alone is providing or is likely to provide effective tumor control.[10,34-36] [Level V; Strength A]

Q: Among patient with PD-L1-positive metastatic triple negative breast cancer (TNBC), can immunotherapy therapy be started?

A: For patients with advanced-metastatic PD-L1-positive TNBC, first line treatment can be defined based on biomarkers, according to local practice and resource availability. Immunotherapy can be considered.[37,38] [Level V] Risks associated with immunotherapy with COVID-19 progression have not been clearly described but close monitoring for patients with specific symptoms is recommended.[6] [Strength B]

b. Endocrine Therapy

Q: Among patients with hormone-positive/HER2-negative metastatic breast cancer, what is the preferred choice of treatment?

A: Endocrine-based therapy is the preferred choice for most patients with hormone-positive/HER2-negative metastatic breast cancer not in visceral crisis and should follow the usual international guidelines.[6,10] [Strength A]

Q: Among patients with metastatic breast cancer, should endocrine treatment be continued?

A: Endocrine treatments (e.g. tamoxifen, aromatase inhibitors, luteinizing hormone releasing hormone (LHRH) agonists) are safe and can be continued.[6] [Strength B]

Q: Among patients with metastatic breast disease on LHRH analogue, what is the recommendation on the dosing of administration?

A: LHRH analogue administration should follow the usual international guidelines since no additional risk is foreseen from these agents. LHRH analogue may be given with long acting, every 3 months dosing, to reduce patient visits. Monthly home administration of LHRH analogue by the patient or visiting nurse is preferred.[6,10] [Strength A]

c. Surgery and Radiotherapy for Palliation

Q: Among patients with metastatic breast cancer, what indications may justify emergency breast surgery?

A: Indications warranting emergency breast surgery include breast abscess in a septic patient and expanding hematoma in a hemodynamically unstable patient as assessed by the surgeon (High Priority).[6] [Strength B]

Q: Among patients with metastatic breast cancer, what indications may justify immediate RT?

A: Emergency palliative RT is justified when there is bleeding/painful inoperable locoregional disease, symptomatic metastatic disease such as acute spinal cord compression, and symptomatic brain metastasis not improving with steroidal medication, and any urgent irradiation with an expected impact in survival or a modifying effect on the risk of disabling sequelae and/or quality of life (High Priority). Use of hypofractionated regimen is recommended.[6] [Strength B]

D. Supportive and Palliative Care

a. Granulocyte Colony Stimulating Factor (G-CSF)

Q: Among patients with breast cancer undergoing chemotherapy, what is the recommended protocol for the use of G-CSF?

A: Patients receiving chemotherapy should receive appropriate supportive care to reduce side effects; in particular, G-CSF should be used to minimize neutropenia, and can be considered for regimens with <20% chance of febrile neutropenia not usually offered G-CSF.[13] [Strength B]

Q: Among patients who have no access or cannot afford G-CSF/pegylated G-CSF, should dose reduction be considered to reduce occurrence of neutropenia?

A: Dose reductions and dose interruptions should be considered, whenever the anticipated side effects are significant.[10] [Strength B]

b. Bone Support Therapy

Q: Among breast cancer patients with bone metastasis, what is the recommended protocol for the use of bone modulating agents?

A: The use of bone modulating agents should be discussed on a case-by-case basis, depending on the burden of bone disease and the presence of symptoms. When there is no evidence of hypercalcemia or gross pain, or in patients who are otherwise not in need for in-hospital treatment, consider deferring treatment or increasing the interval of administration of bone modulating agents to every 3 months. Moreover, administration of subcutaneous denosumab can be performed at home if resources allow it.[6,10,13] [Strength A]

c. Blood Transfusion

Q: Among patients with breast cancer, how should care for patients at risk for or experiencing cancer-related anemia be affected by the COVID-19 pandemic?

A: For patients with symptomatic anemia, transfusion should be provided in accordance with usual practice. The American Society of Hematology recommends not transfusing more than the minimum number of red blood cell units needed to relieve symptoms of anemia or to return a patient to a safe hemoglobin range (7-8 g/dL in stable, non-cardiac inpatients). In terms of prophylaxis, consider giving erythropoietin-stimulating agents when serious and/or symptomatic anemia is anticipated, and the agents are deemed to be safe.[39] [Strength A]

d. Pain Control

Q: Among patients with breast cancer, how should pain be managed during the COVID-19 pandemic?

A: Adequate supply of analgesics and other medications for symptom control must be ensured and proactive monitoring of symptoms via telemedicine should likewise be done.[40] [Strength A]

e. Patient Education

Q: Among patients with breast cancer, how should we educate patients regarding their disease and treatment during the COVID-19 pandemic?

A: Patient education may be done through providing patient information via handouts, signs, web-based communication, and a dedicated phone line for questions and triage.[13] [Strength A]

f. End of Life Care

Q: Among patients with breast cancer, how should end-of-life care be provided during the COVID-19 pandemic?

A: Due to the additional risk associated with COVID-19, proactive advance care planning is vital especially for cancer patients. Discussions regarding end-of-life care, including advance directives, should be done. Mental health issues should likewise be addressed. If there is rapid progression of disease, with need for urgent symptom control, consult with palliative care specialists should be readily available.[41,42] [Strength A]

g. Vaccination

Q: Among patients with breast cancer, what are the recommendations for vaccination during the COVID-19 pandemic?

A: Scheduled vaccination visits should be postponed except when:

- A hospital visit must be scheduled for some other purpose and vaccination can be done during the same visit with no additional risk
- The clinician together with the patient believe that there is a compelling indication to receive the vaccination based on the assessment that the potential benefit outweighs the risk of exposure to the coronavirus.[43] [Strength A]

h. Psychological Care

Q: Among patients with breast cancer, what are the recommendations in managing psychological concerns (e.g. having to deal with delays in cancer management, fear of the risk of infection, anxiety, isolation, etc.) during the COVID-19 pandemic?

A: Psychological concerns of patients with breast cancer during the COVID-19 pandemic should be addressed through telemedicine. Psychological status, issues, and possible contributing factors should be monitored throughout the duration of treatment. Validated tools like the *Hospital Anxiety and Depression Scale (HADS*) can be used to monitor the levels of anxiety and depression as to provide adequate recommendation, referral, and treatment for the patient, if needed.[10] [Strength A]

E. Surveillance and Follow-up

Q: Among patients with breast cancer, how can surveillance/follow-up be done during the COVID-19 pandemic?

A: Patients for follow-up, including those who are at high risk of relapse, or for survivorship follow-up are considered low priority for outpatient visits. Telemedicine (via e-mail or phone) or a postponement of appointment to a later date is recommended.[6] [Strength A]

F. Screening

Q: Among asymptomatic patients, how can screening for breast cancer be done during the COVID-19 pandemic?

A: All screening examinations for breast cancer in asymptomatic patients, including mammography, ultrasound, and MRI should be temporarily postponed by a few weeks or months, or until the post-COVID-19 period.[6,13,14] [Strength B]

G. Multidisciplinary Meetings and Clinic

Q: How should we conduct multidisciplinary team (MDT) meetings and clinics for breast cancer patients during the COVID-19 pandemic?

A: MDT discussions for the treatment of breast cancer should continue during the pandemic. The recommended setup for this kind of meeting is an online meeting. A coordinator, designated by the team, will be the overall in-charge of the conduct of the meeting. The tasks of the coordinator are as follows but not limited to: 1) setting up the online platform for the meeting; 2) arranging the schedule of the meeting; and 3) checking or troubleshooting the internet connectivity of the attendees prior to the agreed date and time. The MDT discussions will be recorded and transcribed then relayed to the patient concerned via telemedicine.[13,44] Multidisciplinary clinics should follow recommendations on the prioritization of patients for outpatient visits. [Strength A]

H. Pregnant Patients with Breast Cancer

Q: Among pregnant patients with breast cancer, what are the recommendations in management during the COVID-19 pandemic?

A: Pregnant patients with breast cancer should be given High Priority for outpatient clinic consults. Those necessitating surgical intervention as decided by the multidisciplinary board of the institution, if any, should also be given High Priority where surgery should be done within 2 weeks.[6,10] [Strength B]

X. Acknowledgments

We would like to thank the PSMO Guidelines Committee for spearheading this project.

XI. Conflicts of Interest

The authors and developers of this consensus recommendations declare no conflicts of interest.

XII. References

1. World Health Organization. Coronavirus disease 2019 (COVID-19) in the Philippines. https://www.who.int/philippines/emergencies/covid-19-in-the-philippines. Publication date unavailable. Updated May 9, 2020. Accessed May 23, 2020.
2. Center for Strategic & International Studies. Southeast Asia COVID-19 tracker. https://www.csis.org/programs/southeast-asia-program/southeast-asia-covid-19-tracker-0. Publication date unavailable. Updated May 15 ,2020. Accessed May 23, 2020.
3. Centers for Disease Control and Prevention. People who are at higher risk for severe illness. https://www.cdc.gov/coronavirus/2019-ncov/specific-groups/high-risk-complications.html. Publication date unavailable. Updated May 14, 2020. Accessed May 23, 2020.
4. Landman A, Feetham L, Stuckey D. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol.* 2020;21:335−337. doi:10.1016/S1470-2045(20)30096-6.
5. Philippine Cancer Society. 2015 Philippine cancer facts and estimates. http://www.philcancer.org.ph/wp-content/uploads/2017/07/2015-PCS-Ca-Facts-Estimates_CAN090516.pdf. Published 2015. Accessed May 23, 2020.
6. de Azambuja E, Trapani D, Loibl S, et al. ESMO management and treatment adapted recommendations in the COVID-19 era: breast cancer. *ESMO Open.* 2020;5: e000793. doi:10.1136/esmoopen-2020-000793.
7. European Society of Medical Oncology. Standard operating procedures (SOPs) for authors and templates for ESMO clinical practice guidelines (CPGs) and ESMO-MCBS scores. https://www.esmo.org/content/download/77789/1426712/1. Published May 2020. Accessed May 24, 2020.
8. Al-Shamsi HO, Alhazzani W, Alhuraiji A, et al. A practical approach to the management of cancer patients during the novel coronavirus disease 2019 (COVID-19) pandemic: an international collaborative group. *Oncologist.* 2019;1–10. doi:10.1634/theoncologist.2020-0213.
9. Cinar P, Kubal T, Freifeld A, et al. Safety at the time of the COVID-19 pandemic: how to keep our oncology patients and healthcare workers safe. *J Natl Comp Cance Ne.* 2020;18(5):1–6. doi:10.6004/jnccn.2020.7572.

10. Curigliano G, Cardoso MJ, Poortmans P, et al. Recommendations for triage, prioritization and treatment of breast cancer patients during the COVID-19 pandemic. *Breast J*. 2020;52:8–16. doi:10.1016/j.breast.2020.04.006.
11. Viale G, Licata L, Sica L, et al. Personalized risk-benefit ratio adaptation of breast cancer care at the epicentre of COVID-19 outbreak. *Oncologist*. 2020;0316. doi:10.1634/theoncologist.2020-0316.
12. Philippine Society of Microbiology and Infectious Diseases. Interim guidelines on the clinical management of adult patients with suspected or confirmed COVID-19 infection version 2.1. https://www.psmid.org/cpg-for-covid-19-ver-2-1-as-of-march-31-2020. Published March 31, 2020. Accessed May 23, 2020.
13. Dietz JR, Moran MS, Isakoff SJ, et al. Recommendations for prioritization, treatment and triage of breast cancer patients during the COVID-19 pandemic: the COVID-19 pandemic breast cancer consortium. *Breast Cancer Res Tr.* 2020;181(3):487–497. doi:10.1007/s10549-020-05644-z.
14. The Philippine Society of Breast Surgeons (PSBS) in collaboration with the Philippine Society of General Surgeons (PSGS). Guidelines on the prioritization of management of breast diseases during the COVID pandemic. Published May 4, 2020.
15. American College of Surgeons. COVID 19: elective case triage guidelines for surgical care: breast cancer surgery. https://www.facs.org/covid-19/clinical-guidance/elective-case/breast-cancer. Published March 24, 2020. Accessed May 23, 2020.
16. Coles CE, Aristei C. Boersma L, et al. International guidelines on radiation therapy for breast cancer during the COVID-19 pandemic. *Clin Oncol*. 2020;32(5):279-281. doi: 10.1016/j.clon.2020.03.006.
17. Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. J Clin Oncol. 2003;21(3):555-563. doi:10.1200/JCO.2003.04.171
18. Flores-Balcázar CH, Flores-Luna L, Villarreal-Garza C, Mota-García A, Bargalló-Rocha E. Impact of Delayed Adjuvant Radiotherapy in the Survival of Women with Breast Cancer. Cureus. 2018;10(7):1-14. doi:10.7759/cureus.3071
19. Tsoutsou PG, Koukourakis MI, Azria D, Belkacémi Y. Optimal timing for adjuvant radiation therapy in breast cancer. A comprehensive review and perspectives. Crit Rev Oncol Hematol. 2009;71(2):102-116. doi:10.1016/j.critrevonc.2008.09.002
20. Abbas H, Elyamany A, Salem M, Salem A, Binziad S, Gamal B. The optimal sequence of radiotherapy and chemotherapy in adjuvant treatment of breast cancer. Int Arch Med. 2011;4(1):1-7. doi:10.1186/1755-7682-4-35
21. Cardoso F, et al. Early Breast Cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-Up. *Clinical Practice Guidelines: an ESMO Product, ESMO,* 2019. www.esmo.org/guidelines/breast-cancer. Accessed May 22, 2020.
22. Walker L, Eremin J, et al. Effect on quality of life, anti-cancer responses, breast conserving surgery and survival with neoadjuvant docetaxel: a randomised study of sequential weekly versus three-weekly docetaxel following neoadjuvant doxorubicin and cyclophosphamide in women with primary breast cancer. *BMC Cancer* 2011; 11: 179. doi: 10.1186/1471-2407-11-179.
23. Zhou W, Chen S, et al. Survival Benefit of Pure Dose-Dense Chemotherapy in Breast Cancer: A Meta-analysis of Randomized Controlled Trials. *World Journal of Surgical Oncology* 2018; 16:144. doi: 10.1186/s12957-018-1424-4.
24. Earl H, Hiller L, et al. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. *Lancet* 2019 Jun; 393 (10191): 2599-2612. doi: 10.1016/S0140-6736(19)30650-6.

25. Pivot X, Romieu G, et al. 6 months versus 12 months of adjuvant trastuzumab in early breast cancer (PHARE): final analysis of a multicentre, open-label, phase 3 randomised trial. *Lancet* 2019 Jun; 393: 2591-98. doi: 10.1016/S0140-6736(19)30653-1.
26. Pivot X, Romieu G, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet* 2013 Jul; 8; 741-748. doi: 10.1016/S1470-2045(13)70225-0.
27. Jackisch C, Stroyakovskiy D, et al. Subcutaneous vs Intravenous Trastuzumab for Patients with ERBB2-Positive Early Breast Cancer. *JAMA Oncology* 2019 May; 5(5): e190339. doi: 10.1001/jamaoncol.2019.0339.
28. Cocquyt V, Martinez-Mena C, et al. Safety and Tolerability of at home administration of trastuzumab (Herceptin) subcutaneous for the treatment of patients with HER2-positive early breast cancer. *Cancer Res* 2017; 77. doi: 10.1158/1538-7445.SABCS16-P4-21-17.
29. Colleoni M, Bagnardi V, Rotmensz N et al. Increasing steroid hormone receptors expression defines breast cancer subtypes nonresponsive to preoperative chemotherapy. Breast Cancer Res Treat. 2009;116:359–369.
30. Colleoni M, Montagna E. Neoadjuvant therapy for ER-positive breast cancers. *Ann Oncol* (Supplement 10) 2012, doi:10.1093/annonc/mds305.
31. Bergen E, Berghoff A, et al. Taxanes Plus Trastuzumab Compared to Oral Vinorelbine Plus Trastuzumab in HER2-Overexpressing Metastatic Breast Cancer. *Breast Care (Basel).* 2014 Oct. 9(5): 344-348. doi: 10.1159/000368330.
32. Yin W, Pei G, et al. Efficacy and safety of capecitabine-based first-line chemotherapy in advanced or metastatic breast cancer: a meta-analysis of randomised controlled trials. *Oncotarget* 2015 Sep. 6(36): 39365-39372. doi: 10.18632/oncotarget.5460.
33. Moilanen T, Mustanoja S, Karihtala P, Koivunen JP. Retrospective analysis of HER2 therapy interruption in patients responding to the treatment in metastatic HER2+ breast cancer. *ESMO Open.* 2017; 2(3):e000202.
34. Royce M, Osman D. Everolimus in the treatment of metastatic breast cancer. *Breast Cancer: Basic and Clinical Research* 2015; 9: 73-79. doi: 10.4137/BCBCR.S29268.
35. Spring L, Bardia A, Modi S. Targeting the cyclin D-cyclin-dependent kinase (CDK) 4/6-retinoblastoma pathway with selective CDK 4/6 inhibitors in hormone receptor-positive breast cancer: rationale, current status, and future directions. *Discov Med* 2016 Jan. 21 (113): 65-74.
36. Brandao M, Caparica R, et al. Biomarkers of response and resistance to PI3K inhibitors in estrogen receptor-positive breast cancer patients and combination therapies involving PI3K inhibitors. *Annals of Oncology* 2019 Dec; 30 (10):x27-x42. doi: 10.1093/annonc/mdz280.
37. Marra A, Viale G, Curigliano G. Recent advances in triple negative breast cancer: the immunotherapy era. *BMC Medicine.* 2020; 17:90. doi: 10.1186/s12916-019-1326-5.
38. Li Z, Qiu Y, et al. Immunotherapeutic Interventions of triple negative breast cancer. *Journal of Translational Medicine* 2018; 16:147. doi: 10.1186/s12967-018-1514-7.
39. American Society of Clinical Oncology. COVID-19 patient care information. https://www.asco.org/asco-coronavirus-information/care-individuals-cancer-during-covid-19. Published May 19, 2020. Accessed May 22, 2020.
40. European Society of Medical Oncology. Supportive care strategies during the COVID-19 pandemic. https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/supportive-care-in-the-covid-19-era. Published April 16, 2020. Accessed May 25, 2020.
41. European Society of Medical Oncology. Introduction to the ESMO COVID-19 palliative care pathways. https://www.esmo.org/covid-19-and-cancer/covid-19-full-coverage/covid-19-useful-resources/covid-19-palliative-care-pathways. Published April 16, 2020. Accessed May 22, 2020.

42. Uzzo RG, Kutikov A, Geynisman DM, et al. Coronavirus disease 2019 (COVID-19): cancer care during the pandemic. https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-cancer-care-during-the-pandemic. Publication date unknown. Updated May 21, 2020. Accessed Mar 22, 2020.
43. Centers for Disease Control and Prevention. Immunization schedules: schedule changes & guidance. https://www.cdc.gov/vaccines/schedules/hcp/schedule-changes.html. Publication date unavailable. Updated April 14, 2020. Accessed May 28, 2020.
44. Salari A, Shirkhoda M. COVID-19 pandemic & head and neck cancer patients management: the role of virtual multidisciplinary team meetings. *Oral Oncology*. 2020;105:104693. doi:10.1016/j.oraloncology.2020.104693.

XIII. Appendices

Though the findings of the following studies are helpful in the management of breast cancer patients, the readers should exercise caution in generalizing and applying the results for specific patients particularly for studies with small sample sizes or those associated with conflicting reports.

APPENDIX A

STUDY TITLE: Effects on quality of life, anti-cancer responses, breast conserving surgery and survival with neoadjuvant docetaxel: a randomised study of sequential weekly versus three-weekly docetaxel following neoadjuvant doxorubicin and cyclophosphamide in women with primary breast cancer

DATE PUBLISHED: 2011

P	N = 89 Women (ages 18-70) with unilateral/ bilateral large (≥ 3cm) or LABCs (T3, T4, TxN2), no distant metastases, WHO performance status of < 2; no history of abnormal cardiac function, adequate hematological, renal and hepatic function and were not pregnant
I	N = 45 Weekly group: given twelve further cycles of docetaxel, 33 mg/m^2 as one-hour intravenous infusions at weekly intervals with a two-week break between cycle 6 and 7
C	N = 44 3-weekly group: received four further cycles of docetaxel at a dose of 100 mg/m^2, as one-hour intravenous infusions every 3 weeks
O	**Median follow-up:** 71.5 months **Quality of life** • No significant differences in Trial Outcome Index (TOI) scores between the weekly and 3-weekly groups (p = 0.86) **Clinical Response** • Weekly group: ORR 93% (p= 0.37) • 3-weekly group: ORR 90% (p = 0.37) **Pathological Response** • No significant difference in the pCR rate between groups (20% in the weekly and 27% in the 3-weekly groups, p = 0.43) • Using multivariate logistic regression analysis, none of the variables (age, clinical nodal status, and clinical tumour size) were statistically significant predictors of a pCR **Toxicity** • A higher percentage of patients in the 3-weekly groups experienced asthenia, neuropathy, peripheral oedema, and nail problems; the reverse was true for epiphora (Table 5). No death-related toxicity occurred during treatment.
M	Prospective cohort study

CLINICAL BOTTOM LINE: There was no significant difference between giving weekly vs 3-weekly docetaxel in terms of quality of life, clinical response, and pathologic response among early breast cancer patients on neoadjuvant chemotherapy. The favorable toxicity profile of weekly docetaxel may be used for certain groups of patients (particularly older patients or those with poor performance status).

CITATION: Walker L, Eremin J, et al. Effect on quality of life, anti-cancer responses, breast conserving surgery and survival with neoadjuvant docetaxel: a randomised study of sequential weekly versus three-weekly docetaxel following neoadjuvant doxorubicin and cyclophosphamide in women with primary breast cancer. *BMC Cancer* 2011; 11: 179. doi: 10.1186/1471-2407-11-179.

APPENDIX B

STUDY TITLE: Survival benefit of pure dose-dense chemotherapy in breast cancer: a meta-analysis of randomized controlled trials

DATE PUBLISHED: 2018

P	N = 7 studies based on 5 phase III RCTs comparing pure dose-dense chemotherapy with conventional therapy with total of 9851 patients • Four studies (3 trials): based on anthracycline • Three studies (2 trials): based on anthracycline and taxane
I	Dose-dense arm: Delivering drugs over shorter interval with the same cycle and dosage of the conventional schedule
C	Conventional arm: Same cycle and dosage of conventional schedule
O	**OS: 9731 patients** • OS benefit of dose-dense chemotherapy was less impressive (HR 0.86; 95% CI 0.73–1.02, p =0.08) • Significant OS benefit was observed in node-positive patients (HR = 0.77; 95% CI 0.66–0.90; p = 0.001). **DFS: 5340 patients** • Dose-dense chemotherapy obtained better DFS than those treated with the conventional schedule (HR 0.83, 95% CI 0.75-0.91, p = 0.0001) **Grade 3-5 Toxicities** • The incidences of grade 3 to 5 neutropenia (OR = 0.14; 95% CI 0.09–0.24; p < 0.0001), leukopenia (OR = 0.39; 95% CI 0.28–0.55; p < 0.0001), and neuropathy (OR = 0.72; 95% CI 0.54–0.97; p = 0.03) were significantly lower in the dose-dense arm than those in the conventional arm. • Pooled analyses demonstrated that dose-dense chemotherapy significantly increased the incidences of grade 3 to 5 anemia (OR = 4.08; 95% CI 0.67–9.99; p=0.002), pain (OR = 1.67; 95% CI 1.24–2.55; p = 0.0007), and transaminase elevation (OR = 3.71; 95% CI 1.50–9.17; p=0.005) compared with the conventional regimen. • No significant differences in thrombocytopenia, asthenia, diarrhea, stomatitis, nausea/vomiting, and infection between the two arms.
M	Meta-analysis of Randomized Controlled Trials

CLINICAL BOTTOM LINE: Dose-dense chemotherapy leads to better prognosis; these findings suggest that it may be a potentially preferred treatment for breast cancer patients, particularly for women with lymph node involvement.

CITATION: Zhou W, Chen S, et al. Survival Benefit of Pure Dose-Dense Chemotherapy in Breast Cancer: A Meta-analysis of Randomized Controlled Trials. *World Journal of Surgical Oncology* 2018; 16:144. doi: 10.1186/s12957-018-1424-4.

APPENDIX C

STUDY TITLE: 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial

DATE PUBLISHED: June 6, 2019

P	N = 4089 eligible patients, aged 18 years or older, had a histological diagnosis of invasive early breast cancer with overexpression of HER2 receptor
I	N = 2044 6 months (experimental 9 cycles) of trastuzumab intravenously (loading dose of 8mg/kg followed by maintenance doses of 6mg/kg) or subcutaneously (600mg) every 3 weeks
C	N = 2045 12 months (standard 18 cycles) of trastuzumab intravenously (loading dose of 8mg/kg followed by maintenance doses of 6mg/kg) or subcutaneously (600mg) every 3 weeks
O	Median follow-up: 5.4 years (IQR 3.6-6.7) DFS • 6-month group: 265/2043 (13%) • 12-month group: 247/2045 (12%) 4-year DFS • 6-month group: 89.4% (95% CI 87.9-90.7) • 12-month group: 89.8% (95% CI 88.3-91.1) • HR for relapse or death with 6 months compared with 12 months trastuzumab was 1.07 (90% CI 0.93-1.24, non-inferiority p= 0.011) OS • 6-month group: 93.8% (95% CI 92.6-94.9) • 12-month group: 94.8% (95% CI 93.7-95.8) • HR 1.14 (90% CI 0.95-1.37, non-inferiority p = 0.0010) Severe adverse events • 6-month group: 373/1939 patients (19%), p=0.0002 o Stopping because of cardiotoxicity: 61/1939 (3%), p< 0.0001 • 12-month group: :459/ 1894 patients (24%), p= 0.0002 o Stopping because of cardiotoxicity: 146/1894 (8%), p< 0.0001
M	Open-label, randomized phase 3 non-inferiority trial

CLINICAL BOTTOM LINE: 6-month trastuzumab treatment is non-inferior to 12-month treatment in patients with HER2-positive early breast cancer, with less cardiotoxicity and fewer severe adverse events.

CITATION: Earl H, Hiller L, et al. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. *Lancet* 2019 Jun; 393 (10191): 2599-2612. doi: 10.1016/S0140-6736(19)30650-6.

APPENDIX D

STUDY TITLE: Subcutaneous vs Intravenous Trastuzumab for Patients with ERBB2-Positive Early Breast Cancer: Final Analysis of the HannaH Phase 3 Randomized Clinical Trial

DATE PUBLISHED: May 2019

P	N = 596 patients with ERBB2-positive early breast cancer (October 19, 2009 to December 1, 2010)
I	N = 294 Fixed-dose subcutaneous trastuzumab, 600mg every 3 weeks in the neoadjuvant setting + additional 10 cycles in the adjuvant setting
C	N = 297 Intravenous trastuzumab (loading dose of 8mg/kg followed by maintenance doses of 6mg/kg) in the neoadjuvant setting + additional 10 cycles in the adjuvant setting
O	Six-year event-free survival rates • 65% in both study groups; hazard ratio, 0.98; 95% CI, 0.74-1.29 Overall survival rates • 84% in both study groups; hazard ratio, 0.94; 95% CI, 0.61-1.45 Long-term Safety • Overall rates of AEs (290 of 297 [97.6%] vs 282 of 298 [94.6%]), grade 3 or higher AEs (158 of 297 [53.2%] vs 160 of 298 [53.7%]), and serious AEs (65 of 297 [21.9%] vs 45 of 298 [15.1%]) were comparable between the subcutaneous and intravenous trastuzumab treatment groups. • Incidence of cardiac AEs was low and was similar for patients treated with subcutaneous trastuzumab and patients treated with intravenous trastuzumab (44 of 297 [14.8%] vs 42 of 298 [14.1%]), even for patients in the lowest body-weight quartile (<59 kg).
M	Open-label, prospective, multicenter, randomized, phase 3 noninferiority clinical trial

CLINICAL BOTTOM LINE: This final analysis of the HannaH trial further confirms the comparable efficacy and safety of subcutaneous and intravenous trastuzumab and highlights the suitability of subcutaneous trastuzumab as an alternative route of administration for patients with ERBB2-positive early breast cancer.

CITATION: Jackisch C, Stroyakovskiy D, et al. Subcutaneous vs Intravenous Trastuzumab for Patients with ERBB2-Positive Early Breast Cancer. *JAMA Oncology* 2019 May; 5(5): e190339. doi: 10.1001/jamaoncol.2019.0339.

APPENDIX E

STUDY TITLE: Taxanes Plus Trastuzumab Compared to Oral Vinorelbine Plus Trastuzumab in HER2-Overexpressing Metastatic Breast Cancer

DATE PUBLISHED: October 2014

<table>
<tr><td>P</td><td>Patients with HER2-positive metastatic breast cancer treated with trastuzumab-based first-line chemo-immunotherapy from 2000 until 2010 (n=76)</td></tr>
<tr><td>I</td><td>N = 40
Oral Vinorelbine (OV) (60mg/m^2 on days 1 and 8 of a 3-week cycle)
+
Trastuzumab (4mg/kg body weight loading dose followed by 2mg/kg body weight weekly thereafter; or 8mg/kg body weight loading dose followed by 6mg/kg body weight every 3 weeks thereafter)</td></tr>
<tr><td>C</td><td>N = 36
Taxanes (Docetaxel 75-100mg/m^2 once every 3 weeks; docetaxel 35mg/m^2 weekly; paclitaxel 90mg/m^2 weekly for 3 weeks followed by 1 week of rest; or paclitaxel 175mg/m^2 once every 3 weeks)
+
Trastuzumab (4mg/kg body weight loading dose followed by 2mg/kg body weight weekly thereafter; or 8mg/kg body weight loading dose followed by 6mg/kg body weight every 3 weeks thereafter)</td></tr>
<tr><td>O</td><td>Median follow-up: 47.5 months

Primary outcome: PFS
• Taxanes + Trastuzumab: 7 months (95% CI, 5.4-8.6)
• OV + Trastuzumab: 9 months (95% CI, 7.23-10.77; log-rank test; non-significant)

Secondary outcome:
• OS
o Taxanes + Trastuzumab: 49 months (95% CI, 38.24 – 59.76)
o OV + Trastuzumab: 59 months (95% CI, 41.17 – 76.83; log-rank test; p = 0.033)
• RR

<table><tr><td></td><td>Taxane + Trastuzumab</td><td>OV + Trastuzumab</td></tr><tr><td>Complete response</td><td>2.8% (0.00-0.08)</td><td>15% (0.04-0.26)</td></tr><tr><td>Partial response</td><td>58.3% (0.42-0.74)</td><td>47.5% (0.32-0.63)</td></tr><tr><td>Stable disease</td><td>16.7% (0.05-0.29)</td><td>17.5% (0.06-0.29)</td></tr><tr><td>Progressive disease</td><td>22.2% (0.09-0.36)</td><td>12.5% (0.02-0.23)</td></tr></table>
• Incidence of brain metastases (BM)
o 36/76 (47.4%) patients were diagnosed with symptomatic BM during their course of disease.
• Brain metastases-free survival (BMFS)
o BMFS was longer in patients receiving OV + Trastuzumab as compared to patients receiving taxanes + Trastuzumab as first-line therapy (69 months vs 51 months; p = 0.032)</td></tr>
<tr><td>M</td><td>Retrospective Analysis</td></tr>
</table>

CLINICAL BOTTOM LINE: OV plus trastuzumab yielded similar results in terms of PFS and RR and was superior in terms of OS and BMFS compared to taxanes plus trastuzumab therapy. These results add to the growing body of evidence that vinorelbine is a viable alternative to taxanes in HER2-positive metastatic breast cancer.

CITATION: Bergen E, Berghoff A, et al. Taxanes Plus Trastuzumab Compared to Oral Vinorelbine Plus Trastuzumab in HER2-Overexpressing Metastatic Breast Cancer. *Breast Care (Basel).* 2014 Oct. 9(5): 344-348. doi: 10.1159/000368330.

APPENDIX F

STUDY TITLE: Efficacy and Safety of Capecitabine-Based First-line chemotherapy in Advanced or Metastatic Breast Cancer: A Meta-Analysis of Randomised Controlled Trials

DATE PUBLISHED: September 30, 2015

P	N = 9 RCTs of capecitabine monotherapy or combined treatment as first-line therapy for advanced or metastatic breast cancer with 1798 patients
I and C	• 6 RCT: Capecitabine combination therapy • 3 RCT: Capecitabine monotherapy versus other chemotherapy
O	**PFS** • Capecitabine-based chemotherapy was associated with significantly longer PFS when compared to capecitabine-free chemotherapy as first-line treatment for advanced or metastatic breast cancer (HR 0.77, 95% CI: 0.69 – 0.87, p = < 0.0001) **OS** • No significant difference in OS between capecitabine-based chemotherapy and capecitabine-free chemotherapy (HR 0.88, 95% CI 0.77 – 1.00, p = 0.056). **ORR** • Significant improvement with capecitabine-based chemotherapy compared with capecitabine-free chemotherapy (RR 1.14, 95% CI: 1.03-1.26, p= 0.013) **Grades 3-4 drug related adverse events** • Incidences of neutropenia and neutropenic fever were fewer with capecitabine-based chemotherapy (RR 0.59, 95% CI 0.39-0.89, p = 0.012 compared with capecitabine-free chemotherapy (RR 0.50, 95% CI 0.35-0.70, 0 < 0.0001). • Incidences of anemia and thrombocytopenia were not significantly different between the two groups. • More grade 3-4 vomiting, diarrhea, and hand-foot syndrome occurred in the capecitabine-based chemotherapy group (RR 4.47, 95% CI 2.21-9.03, p < 0.0001; RR 2.86, 95% CI 1.75 – 4.68, p = 0.0001; RR 12.4, 95% CI 3.6-42.8, p < 0.0001, respectively). • No significant differences in nausea, fatigue, cardiotoxicity or mucositis/ stomatitis between the two arms.
M	Meta-analysis

CLINICAL BOTTOM LINE: Capecitabine-based chemotherapy significantly improves ORR and PFS in patients with advanced breast cancer but has no demonstrable impact on OS. Capecitabine-based regimens are suitable as first-line treatment for patients with advanced breast cancer.

CITATION: Yin W, Pei G, et al. Efficacy and safety of capecitabine-based first-line chemotherapy in advanced or metastatic breast cancer: a meta-analysis of randomised controlled trials. *Oncotarget* 2015 Sep. 6(36): 39365-39372. doi: 10.18632/oncotarget.5460.