

OPTIMICE-PCR: DE-ESCALATION OF THERAPY IN EARLY-STAGE TNBC PATIENTS WHO ACHIEVE PCR AFTER NEOADJUVANT CHEMOTHERAPY WITH CHECKPOINT INHIBITOR THERAPY

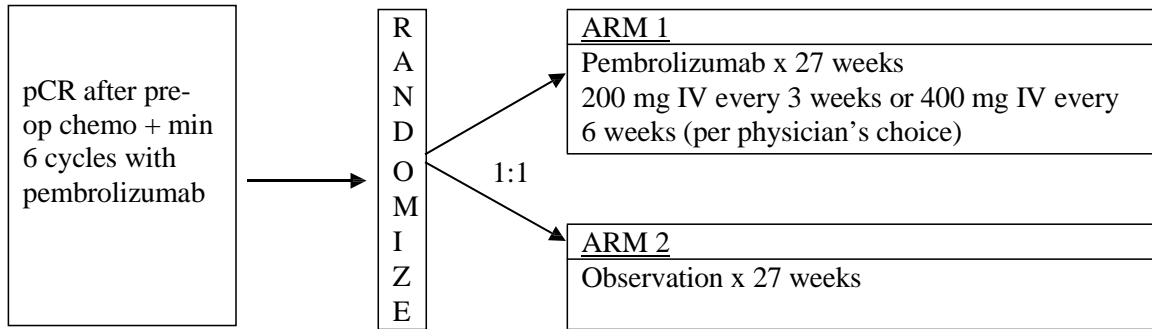
Eligibility Criteria (see [Section 3.0](#))

- Age \geq 18 years
- ECOG Performance Status 0-2
- History of stage T1cN1-2 or T2-4N0-2 breast cancer per AJCC 8th edition
- Patients must have no residual invasive disease in the breast or lymph nodes after the completion of neoadjuvant therapy
- ER and PR \leq 10%; HER2-negative by ASCO/CAP guidelines (IHC and FISH)
- If invasive disease was present in both breasts, participation in the study is permitted as long as the eligibility criteria are met for both tumors/breasts.
- Patients must have received neoadjuvant chemotherapy in combination with pembrolizumab for a minimum of 6 cycles. All systemic chemotherapy and ICI therapy should have been completed preoperatively.
- An interval of no more than 12 weeks between the completion date of the final surgery and the date of randomization. See [Section 3.2.4.2](#).
- Use of investigational anti-cancer agents must be discontinued at time of registration.
- If breast-conserving surgery was performed but patient will not be receiving breast radiation, the patient is not eligible.
- Adequate excision per [Section 3.2.4.4](#)
- Not pregnant and not nursing
- Patients must be willing to provide tumor tissue from diagnostic core biopsy. If inadequate tumor tissue is available, patients are still eligible to participate in the trial.
- No stage IV (metastatic) breast cancer
- Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
- No history of any prior (ipsi- or contralateral) invasive breast cancer. Prior DCIS is allowed.
- No evidence of recurrent disease following preoperative therapy and surgery.
- No known active liver disease, e.g. due to HBV, HCV, autoimmune hepatic disorders, or sclerosing cholangitis
- Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.
- HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months prior to registration are eligible for this trial.
- No history of intolerance, including Grade 3 or 4 infusion reaction or hypersensitivity to pembrolizumab or murine proteins or any components of the product. See [Section 3.2.8.8](#).
- No medical conditions that require chronic systemic steroids ($>$ 10 mg prednisone daily or equivalent) or any other form of immunosuppressive medications and has required such therapy in the last two years. See [Section 3.2.8.9](#).
- Patients who are unable or unwilling to comply with the requirements of the protocol per investigator assessment are not eligible.

Required Initial Laboratory Values

ANC	\geq 1000/mm ³
Platelet count:	\geq 100,000/mm ³
eGFR:	\geq 15 mL/min/1.73m ²
Total bilirubin:	\leq 1.5 x ULN*
AST/ALT:	\leq 3 x ULN

*Patients with Gilbert's disease with a total bilirubin \leq 2.5 x ULN and direct bilirubin within normal limits are permitted.

Schema

Treatment or observation is to continue for 27 weeks or until unacceptable adverse event. Patients will be followed for 5 years after registration or recurrence. Thereafter, patients will be followed annually (+/- 3 months) for overall survival for a total of 10 years after registration.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

If the Group credited for enrollment is a non-Alliance Group, then other requirements from the credited Group may apply.

Until institutions receive a formal notice from the Alliance regarding termination to patient follow-up, institutions must not close this trial with the IRB of record for the study. Please contact the Alliance Regulatory team at regulatory@alliancenctn.org with any questions.

3.1 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.2 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study and for four months following the last dose of study treatment due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom). Breastfeeding should also be discontinued during study treatment and for four months following the last dose of study treatment.

3.3 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.1 Age \geq 18 years**

___ **3.2.2 ECOG Performance Status 0-2**

___ **3.2.3 Triple Negative Breast Cancer**

___ **3.2.3.1** Patients with a history of stage T1cN1-2 or T2-4N0-2 breast cancer according to the primary tumor-regional lymph node anatomic staging criteria of the American Joint Committee on Cancer (AJCC), 8th edition as determined by the investigator in radiologic assessment, clinical assessment or both.

___ **3.2.3.2** Patients must have no residual invasive disease in the breast or lymph nodes after the completion of neoadjuvant therapy. Residual DCIS is allowed. Isolated tumor cells are considered node-negative.

___ **3.2.3.3** ER and PR \leq 10%; HER2-negative by ASCO/CAP guidelines (IHC and FISH)

___ **3.2.3.4** If invasive disease was present in both breasts, participation in the study is permitted as long as the eligibility criteria are met for both tumors/breasts.

3.2.4 Prior Treatment

___3.2.4.1 Patients must have received neoadjuvant chemotherapy in combination with pembrolizumab for a minimum of 6 cycles. All systemic chemotherapy must have been completed preoperatively.

___3.2.4.2 An interval of no more than 12 weeks between the completion date of the final surgery and the date of randomization.

Note: Adjuvant radiation can be given on study. If given, it is encouraged to be given concurrently with pembrolizumab, per investigator discretion. Treatment with adjuvant pembrolizumab is strongly discouraged prior to participation in this trial, but if administered (e.g., if patients are awaiting pathology results), pembrolizumab may be administered for up to 6 weeks post-surgery and must be completed prior to registration.

___3.2.4.3 Use of investigational anti-cancer agents must be discontinued at time of registration.

___3.2.4.4 Adequate excision: Surgical removal of all clinically evident disease in the breast and lymph nodes as follows:

___Breast surgery: Total mastectomy or breast-conserving surgery with histologically negative margins, including no ink on tumor for DCIS, at the time of excision.

___ For patients who undergo breast-conserving surgery, the margins of the resected specimen must be histologically free of ductal carcinoma in-situ (DCIS) as determined by the local pathologist. If pathologic examination demonstrates DCIS at the line of resection, additional operative procedures may be performed to obtain clear margins. If DCIS is still present at the resected margin after re-excision(s), the patient must undergo total mastectomy to be eligible. Patients with margins positive for classic lobular carcinoma in situ (LCIS) are eligible without additional resection.

___Lymph node surgery:

___ For a patient with clinically N0 disease, a sentinel lymph node biopsy should have been performed at time of surgical evaluation, and if pathologically node positive, the patient is no longer eligible. Isolated tumor cells are considered node-negative.

___ For a patient with clinically N1 disease at diagnosis (with positive results from a fine-needle aspiration, core biopsy, or sentinel node biopsy performed prior to preoperative therapy) additional surgical evaluation of the axilla following preoperative therapy is required.

- If they become cN0 (no palpable adenopathy), then a sentinel lymph node biopsy could have been performed at time of surgery (axillary dissection would also be permitted); if the sentinel lymph node biopsy is positive, the patient is no longer eligible

___ If sentinel node biopsy performed before preoperative therapy was negative, no additional surgical evaluation of the axilla is required after preoperative therapy. If sentinel node biopsy performed before preoperative therapy was positive, an ALND is required after preoperative therapy.

___ If the only sentinel node identified by isotope scan is in the internal mammary chain, surgical evaluation of the axilla is still required.

___ If sentinel node evaluation after preoperative therapy is negative, no further additional surgical evaluation of the axilla is required.

___ Axillary dissection without sentinel node evaluation is permitted as the initial or sole axillary evaluation after preoperative therapy.

___ **3.2.4.5** If breast-conserving surgery was performed but patient will not be receiving breast radiation, the patient is not eligible.

___ **3.2.5 Not pregnant and not nursing**, because this study involves an agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

Therefore, for women of childbearing potential only, a negative serum or urine pregnancy test done ≤ 7 days prior to randomization is required.

___ **3.2.6 Adequate hepatic, renal and bone marrow function.**

Required Initial Laboratory Values:

Absolute Neutrophil Count (ANC)	$\geq 1,000/\text{mm}^3$
Platelet Count	$\geq 100,000/\text{mm}^3$
Estimated glomerular filtration rate (eGFR)	$\geq 15 \text{ mL}/\text{min}/1.73\text{m}^2$
Total Bilirubin	$\leq 1.5 \times$ upper limit of normal (ULN)*
AST(SGOT) / ALT(SGPT)	$\leq 3 \times$ institutional ULN

*Patients with Gilbert's disease with a total bilirubin $\leq 2.5 \times$ ULN and direct bilirubin within normal limits are permitted.

___ **3.2.7** Patients must be willing to provide tumor tissue from the diagnostic core biopsy. If inadequate tumor tissue is available, patients are still eligible to participate in the trial.

___ **3.2.8 Comorbid conditions**

___ **3.2.8.1** No stage IV (metastatic) breast cancer

___ **3.2.8.2** Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

___ **3.2.8.3** No history of any prior (ipsi- or contralateral) invasive breast cancer. Prior DCIS is allowed.

___ **3.2.8.4** No evidence of recurrent disease following preoperative therapy and surgery.

___ **3.2.8.5** No known active liver disease, e.g. due to HBV, HCV, autoimmune hepatic disorders, or sclerosing cholangitis

___ **3.2.8.6** Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

___ **3.2.8.7** HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months prior to registration are eligible for this trial.

3.2.8.8 No history of intolerance, including Grade 3 or 4 infusion reaction or hypersensitivity to pembrolizumab or murine proteins or any components of the product.

Note: Prior immune-related adverse events (irAEs) are allowed if they resolved and the patient tolerated subsequent therapy without requiring chronic steroids for the irAE.

 3.2.8.9 No medical conditions that require chronic systemic steroids (>10 mg prednisone daily or equivalent) or any other form of immunosuppressive medications and has required such therapy in the last two years. Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic therapy

 3.2.8.10 Patients who are unable or unwilling to comply with the requirements of the protocol per investigator assessment are not eligible.
