

- 7.3 If not already done prior to Step 1 Registration, tumor sample will be submitted to Genomic Health for the Oncotype DX® assay, and will be evaluated for recurrence score (RS). Patients with RS ≤ 25 will undergo discussion of this trial in consultation with their oncologist considering known RS value and number of positive nodes. Patients will then be randomized to one of two arms (Step 2).

Radiation is recommended per institutional and National Comprehensive Cancer Network (NCCN) guidelines (<http://www.nccn.org>) and may be given after chemotherapy and during endocrine therapy. Partial breast irradiation following ASTRO guidelines is allowed (for a copy of the consensus statement, contact communications@astro.org).

- 7.4 **Arm 1 (chemotherapy and endocrine therapy):** All Arm 1 patients will receive a protocol-approved chemotherapy regimen (see below), followed by a protocol-approved endocrine therapy (see below). The approved chemotherapy and endocrine therapy regimens are listed below, though these may be expanded or contracted during the course of the trial as standard of care changes occur.

- a. **Chemotherapy:** All patients will receive a second or third generation chemotherapy. Choice of chemotherapy will depend on patient/physician preference.

Patients must have a normal left ventricular ejection fraction of ≥ 50% if they are scheduled to receive an anthracycline-based regimen as part of their chemotherapy.

1. Second Generation Regimens:

Agents	Schedule	Cycle length
Docetaxel and cyclophosphamide	4-6 cycles	
5-FU, doxorubicin (or epirubicin), and cyclophosphamide*	6 cycles	
Doxorubicin (or epirubicin) and cyclophosphamide (AC/EC) followed by paclitaxel	4 cycles each	q 3 weeks

* includes CAF/CEF with oral cyclophosphamide and FAC/FE(100)C with intravenous cyclophosphamide

2. Third Generation Regimens:

Agents	Schedule	Cycle length
Doxorubicin (or epirubicin) and cyclophosphamide (AC/EC) followed by paclitaxel	4 cycles for AC/EC; 12 cycles for paclitaxel	q 2 weeks or q 3 weeks for AC; weekly for paclitaxel
5-FU, doxorubicin (or epirubicin), and cyclophosphamide followed by docetaxel	4 cycles each	All cycles q 3 weeks
5-FU, doxorubicin (or epirubicin), and cyclophosphamide followed by docetaxel	3 cycles each	
Dose dense doxorubicin and cyclophosphamide followed by dose dense paclitaxel	4 cycles each	All cycles q 2 weeks
Docetaxel, doxorubicin, and cyclophosphamide	6 cycles	
5-FU, doxorubicin (or epirubicin) and cyclophosphamide (FAC) followed by paclitaxel	4 cycles for FAC; 12 cycles for paclitaxel	Weekly for paclitaxel
Paclitaxel followed by 5-FU, doxorubicin (or epirubicin) and cyclophosphamide (FAC)	12 cycles for paclitaxel; 4 cycles for FAC	Weekly for paclitaxel

- b. Endocrine therapy: All patients will receive endocrine therapy. Choice of therapy will depend on menopausal status (see below) and patient/physician preference. Anyone not defined as postmenopausal per institutional standards should be treated as premenopausal. Treatment should be at least 5 years but can be extended. Switching from one therapy to another is allowed.

1. Approved Endocrine Therapy Regimens for **Premenopausal** women:

Treatment	Dose	Treatment duration
Tamoxifen	20 mg daily	5 years
Ovarian suppression or ablation		5 years
Tamoxifen combined with ovarian suppression or ablation	20 mg daily	5 years
Aromatase inhibitor (AI) combined with ovarian suppression or ablation*	Approved dose for AI	5 years
Tamoxifen followed by an aromatase inhibitor (AI)**	20 mg daily for tamoxifen; approved dose for AI	2-3 years each
Tamoxifen followed by an aromatase inhibitor (AI)**	20 mg daily for tamoxifen; approved dose for AI	5 years each

* if the patient cannot tolerate tamoxifen or tamoxifen is contraindicated

** If the patient becomes postmenopausal

2. Approved Endocrine Therapy Regimens for **Postmenopausal** women:

Treatment	Dose	Treatment duration
An aromatase inhibitor	Approved dose	5 years
Tamoxifen*	20 mg daily	5 years
Tamoxifen followed by an aromatase inhibitor	20 mg daily; approved dose	2-3 years each
An aromatase inhibitor followed by tamoxifen	approved dose; 20 mg daily	2-3 years each
Tamoxifen followed by an aromatase inhibitor	20 mg daily; approved dose	5 years each

* if the patient is unsuitable for, cannot tolerate, or refuses an aromatase inhibitor

NOTE: All postmenopausal patients are encouraged to receive an aromatase inhibitor sometime during their course of adjuvant endocrine therapy.

The approved regimens may be expanded or contracted if there is a shift in standard of care during the course of the trial.