Cancer Research for the Ozarks

SCHEMA

Patients with TNBC, ≥ 1cm residual invasive breast cancer, or any + LN after neoadjuvant chemotherapy, followed by surgery

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Step 1 Registration

Submit slides to central laboratory for PD-L1 evaluation.
SWOG Statistical Center will notify sites when PD-L1 testing is completed.

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Step 2 Registration

Randomization

Randomization stratification factors will include:

- Nodal Stage: ypN0 vs. ypN+
- Residual tumor size: ≤ 20 mm vs. > 20 mm
- PD-L1: positive vs. negative (blinded to sites)
- Prior post-operative (adjuvant) chemotherapy: yes vs. no

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Arm 1	Arm 2
Observation	MK-3475 (pembrolizumab) IV every 3 weeks for 52 weeks

NOTE: Radiation therapy may be given concurrently on Arm 1 or Arm 2.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at breastquestion@crab.org prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 2 weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14, 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 STEP 1 REGISTRATION

Disease Related Criteria

_____ a. Patients must have histologically confirmed ER-, PR- and HER2-negative (triple-negative, TNBC) with residual invasive breast cancer, as defined by the 2010 and 2013 ASCO CAP guidelines, after completion of neoadjuvant chemotherapy. Residual disease must be ≥ 1 cm in greatest dimension, and/or have positive lymph nodes (ypN+) observed on pathologic exam.

NOTE: IHC-positive isolated tumor cells in the lymph node (N0 [i+]) are not considered node-positive and these patients also must have ≥ 1 cm residual invasive cancer in the breast in order to be eligible.

_____ b. Patients must not have metastatic disease (i.e., must be M0).

_____ c. It is preferred that axillary lymph node sampling is performed after completion of neoadjuvant chemotherapy to allow more accurate assessment of pathologic response. Patients must have a complete axillary lymph node dissection after neoadjuvant chemotherapy in the following situations (exceptions will be granted for patients participating in the Alliance A11202 trial):

- Patients had documented pathologic involvement of the axillary nodes (FNA or core biopsy) before neoadjuvant chemotherapy and had sentinel node biopsy after neoadjuvant chemotherapy with positive sentinel node(s).
- Patient had documented pathologic involvement of the axillary nodes (FNA or core biopsy) before neoadjuvant chemotherapy and had only 1 sentinel lymph node removed after neoadjuvant chemotherapy.

NOTE: Patients who undergo sentinel node biopsy before starting neoadjuvant treatment and do not undergo post neoadjuvant assessment of the axillary nodes or who have negative axillary nodes on post neoadjuvant assessment must have ≥ 1 cm residual invasive cancer in the breast after completion of neoadjuvant chemotherapy.

SWOG Patient No. _____

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5.1 STEP 1 REGISTRATION (contd.)

Specimen Submission Criteria

_____ d. Patients must have a minimum of five, available unstained slides from the residual (post-neoadjuvant) invasive tumor in primary site or lymph node to be submitted within 7 days after registration to determine PD-L1 expression as described in Section 15.1. The tumor tissue must be adequate for PD-L1 testing, which typically requires a minimum of 100 cancer cells per slide.

_____ e. Patients must be offered the opportunity to participate in specimen banking as outlined in Section 15.4.

Prior/Concurrent Therapy Criteria

_____ f. Patients must have had neoadjuvant chemotherapy followed by surgery. The recommended neoadjuvant treatment should include 16-24 weeks of a third generation chemotherapy regimen as recommended by NCCN guidelines for triple negative breast cancer (examples include dose dense AC followed by dose-dense paclitaxel; weekly paclitaxel x 12 followed or preceded by FAC, FEC, AC or dose dense AC; docetaxel either followed or preceded by FEC/FAC or AC. Carboplatin-containing neoadjuvant chemotherapy is also allowed). Patients who cannot complete all planned treatment cycles for any reason are considered high risk and therefore are eligible for the study if they have residual disease. Patients must have resolution of adverse event(s) of the most recent prior chemotherapy to Grade 1 or less, except alopecia and ≤ Grade 2 neuropathy which are allowed.

_____ g. Patients may receive post-operative (adjuvant) chemotherapy for up to 24 weeks of duration (e.g. 8 cycles of capecitabine as in the CREATE-X trial) after completion of surgery at the discretion of the treating physician. Patients must have resolution of adverse event(s) of the most recent prior chemotherapy to Grade 1 or less, except alopecia and ≤ Grade 2 neuropathy which are allowed. Adjuvant chemotherapy, if administered, must have been completed within 35 days prior to screening registration and must be given prior to radiation.

_____ h. Patients must have completed their final breast surgery (rendering them free from disease) with clear resection margins for invasive cancer and DCIS within 90 days prior to screening registration for patients **not receiving post-operative (adjuvant) chemotherapy**, or within 210 days prior to screening registration for patients **who have completed post-operative (adjuvant) chemotherapy**. Positive margins are allowed only if the surgical team of the patient deems further resection impossible.

_____ i. Patients for whom radiation therapy (RT) to the affected breast or chest wall and regional nodal areas is clinically indicated as per NCCN treatment guidelines, should receive RT after randomization when possible, concomitant with MK-3475 (pembrolizumab) if randomized to the experimental arm. However, RT administered prior to registration is also allowed. Patients must specify at the time of screening registration whether or not they will receive RT and the extent of intended RT.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

Prior/Concurrent Therapy Criteria (contd.)

_____ j. Patients must not have had prior immunotherapy with anti-PD-L1, anti-PD-1, anti-CTLA4 or similar drugs. Patients must not be planning to receive any of the prohibited therapies listed in Section 7.3 during the screening or treatment phases of the study.

_____ k. Patients must not be planning to receive concomitantly other biologic therapy, hormonal therapy, other chemotherapy, surgery or other anti-cancer therapy except radiation therapy while receiving treatment on this protocol.

Clinical/Laboratory Criteria

_____ l. Patients must be women or men ≥ 18 years of age.

_____ m. Patients must have Zubrod Performance Status ≤ 2.

_____ n. Patients must not have a history of (non-infectious) pneumonitis that required steroids or evidence of active pneumonitis.

_____ o. Patients must not have an active infection requiring systemic therapy.

_____ p. Patients must not have active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

_____ q. Patients must not have received live vaccines within 30 days prior to registration. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, shingles, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

_____ r. Patients must not have known active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection prior to registration. Patients who have completed curative therapy for HCV are eligible. Patients with known HIV infection are eligible if they meet each of the following 3 criteria:

- CD4 counts ≥ 350 mm^3
- Serum HIV viral load of < 25,000 IU/ml and
- Treated on a stable antiretroviral regimen.

_____ s. No other prior invasive malignancy is allowed except for the following: adequately treated basal (or squamous cell) skin cancer, in situ breast or cervical cancer. Stage I or II invasive cancer treated with a curative intent without evidence of disease recurrence for at least five years.

Regulatory Criteria

_____ t. Patients must be informed of the investigational nature of this study and must sign and give written informed consent for this protocol in accordance with institutional and federal guidelines.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

Regulatory Criteria (cond.)

_____ u. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

5.2 STEP 2 REGISTRATION (Randomization)

An e-mail notification from the SWOG Statistical Center should be received within 10 days of submitting tissue as described in Section 15.1.

The following additional criteria must be met in order for a patient to be considered eligible for registration to the randomized trial. Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at breastquestion@crab.org prior to registration.

_____a. **Patients must not be registered to Step 2 until receiving confirmation from the SWOG Statistical Center that the patient's tissue specimen was adequate for PD-L1 testing. Patients must be registered within 7 days of receiving the e-mail notification confirming submission was evaluable for PD-L1 status.**

_____ b. A serum TSH must be obtained within 28 days prior to Step 2 registration to obtain a baseline value.

_____ c. Patients must have adequate bone marrow function as evidenced by all of the following: ANC ≥ 1,500 microliter (mcL); platelets ≥ 100,000/mcL; Hemoglobin ≥ 9 g/dL. These results must be obtained within 28 days prior to Step 2 registration.

_____ d. Patients must have adequate hepatic function as evidenced by the following: total bilirubin ≤ 1.5 x institutional upper limit of normal (IULN) (except Gilbert's Syndrome, who must have a total bilirubin < 3.0 mg/dL), and SGOT (AST) or SGPT (ALT) and alkaline phosphatase ≤ 2.5 x IULN. These results must be obtained within 28 days prior to Step 2 registration.

_____ e. Patients must have adequate renal function as evidenced by ONE of the following: serum creatinine ≤ IULN OR measured or calculated creatinine clearance ≥ 60 mL/min. This result must have been obtained within 28 days prior to Step 2 registration.

$$\text{Calculated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$$

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

_____ f. Women of childbearing potential must have a negative urine or serum pregnancy test within 28 day prior to registration. Women/men of reproductive potential must have agreed to use an effective contraceptive method for the course of the study through 120 days after the last dose of study medication. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy, bilateral tubal ligation, or vasectomy. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures. Patients must not be pregnant or nursing due to unknown teratogenic side effects.

_____ g. Site must verify that there is no known change in the Step 1 eligibility since initial registration.