NRG ONCOLOGY

RTOG 1119

PHASE II RANDOMIZED STUDY OF WHOLE BRAIN RADIOTHERAPY IN COMBINATION WITH CONCURRENT LAPATINIB IN PATIENTS WITH BRAIN METASTASIS FROM HER2-POSITIVE BREAST CANCER – A COLLABORATIVE STUDY OF NRG Oncology AND KROG

SCHEMA

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<tr>
<th>STRATIFY</th>
<th>Graded Prognostic Assessment (GPA)</th>
<th>RANDOMIZE</th>
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<tr>
<td></td>
<td>Score: 1.5-2 vs. 2.5-3 vs. 3.5-4</td>
<td>Arm A</td>
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<tr>
<td></td>
<td>Use of Non-CNS–Penetrating HER2 Blockade at Study Entry: No vs. Yes: trastuzumab ± pertuzumab</td>
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<td>Previous Stereotactic Radiosurgery (SRS) or Surgical Resection: Yes vs. No</td>
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<td>Arm B</td>
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<td>WBRT: 37.5 Gy in 15 fx for 3 wks</td>
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<td>Versus</td>
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<td>WBRT: 37.5 Gy in 15 fx for 3 wks</td>
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<td>Plus</td>
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<td>Lapatinib: Once daily starting up to 1 day before the first day of WBRT and continuing until 21 days after the final day of WBRT</td>
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See Section 6.0 for details of radiation therapy and Section 7.0 for details of drug therapy.

Patient Population:  (See Section 3.0 for Eligibility) (10/22/2014)
Pathologically (histologically or cytologically) proven diagnosis of invasive HER2-overexpressing breast cancer (3+ staining by immunohistochemistry or HER2 gene amplification by FISH or SISH ≥ 2.0). At least one measurable, unirradiated parenchymal brain lesion (See Section 3.1 for details).

Required Sample Size: 143
3.0 PATIENT SELECTION
NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility (10/22/2014)
For questions concerning eligibility, please contact study data manager

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of invasive breast cancer

3.1.2 HER2 overexpressing breast cancer (3+ staining by immunohistochemistry or HER2 gene amplification by FISH or SISH ≥ 2.0)

3.1.3 At least 1 measurable, unirradiated parenchymal brain metastasis within 21 days prior to study entry. The minimum size as measured on T1-weighted gadolinium-enhanced MRI must be as follows according to the number of brain metastases:
- For a single solitary lesion the size must be ≥10 mm;
- For 2 or more lesions, the size of at least 2 of the lesions must be ≥ 5 mm

Patients may also have the following provided the size requirements above are met:
- Progressive parenchymal brain metastasis following stereotactic radiosurgery for 1-3 brain metastases, with at least 1 new measurable lesion
- Progressive parenchymal brain metastasis following surgical resection of 1-3 brain metastases, with at least 1 measurable brain lesion

3.1.4 History/physical examination within 21 days prior to study entry

3.1.5 Karnofsky performance status ≥ 60 within 21 days prior to study entry

3.1.6 Age ≥ 18

3.1.7 Able to swallow and retain oral medication (Note, for patients unable to swallow tablets, an oral suspension preparation is acceptable, per Section 7.2.10)

3.1.8 Adequate hematologic, renal, hepatic function within 21 days prior to study entry, as defined by the following:
- Absolute neutrophil count (ANC) ≥ 1,200 cells/mm3
- Platelets ≥ 70,000 cells/mm3
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable)
- Creatinine < 1.5 times institutional upper limit of normal
- Bilirubin < 1.5 times institutional upper limit of normal
- AST and ALT ≤ 3.0 times institutional upper limit of normal with or without liver metastasis

3.1.9 Patient must provide study specific informed consent prior to study entry

3.1.10 Women of childbearing potential must have a negative serum pregnancy test within 21 days prior to study entry

3.1.11 Sexually active women of childbearing potential and sexually active men must practice adequate contraception during therapy and for 12 months after protocol treatment completion

3.1.13 Prior lapatinib is allowed as long as the last dose received was > 21 days prior to study entry and provided the patient has not received it at any time after the diagnosis of brain metastasis
3.2 Conditions for Patient Ineligibility (09/02/2014)

3.2.1 Prior WBRT

3.2.2 Prior RT (any site) with concurrent lapatinib defined as 1 or more days on which the patient received both radiation therapy and lapatinib on the same day.

3.2.3 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements

3.2.4 Prior invasive malignancy (except non-melanomatous skin cancer, curatively resected thyroid papillary carcinoma, and invasive and non-invasive cancers related to the breast cancer) unless disease free for a minimum of 3 years

3.2.5 Leptomeningeal disease

3.2.6 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields except patients who have progressed following stereotactic radiosurgery for 1-3 brain metastases, with at least one new lesion

3.2.7 Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months
- Transmural myocardial infarction within the last 6 months
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of study entry
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of study entry
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; hepatic or biliary disease that is acute or currently active or that requires antiviral therapy (with the exception of patients with Gilbert's syndrome, asymptomatic gallstones, liver metastases, or stable chronic liver disease per investigator assessment)
- History of LVEF below institutional normal unless repeated and within institutional normal range within 90 days of study entry

3.2.8 Grade 2 or greater rash of any cause at time of study entry

3.2.9 Grade 2 or greater diarrhea of any cause at time of study entry