Alliance A071701: Genomically-Guided Treatment Trial in Brain Metastases

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TAP TO RETURN TO KIOSK MENU

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

NCI National Clinical Trials Network
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Rationale

Central nervous system (CNS) disease leads to devastating complications for patients, with profound consequences for quality of life, clinical trial opportunities, and duration of life [1,2, 3-5]. The most common primary histologies that metastasize to the brain are lung, breast and melanoma. Approximately 30% of lung cancer patients will have CNS disease at time of diagnosis and an estimated 50% will eventually develop brain metastases [6]. Up to 30% of patients with advanced breast cancer and 50% of patients with advanced melanoma will develop brain metastases [7, 8]. Effective treatments for brain metastases are limited. Radiation therapy (RT) has historically been the mainstay of treatment, albeit with only a limited survival benefit and risk of cognitive impairment following therapy [9-12]. In the precision medicine era, some tyrosine kinase inhibitors (TKIs) have demonstrated good treatment efficacy for patients whose tumors harbor selected mutations or rearrangements, but this does not reflect the majority of patients [8].

Furthermore, even patients with targetable mutations in genes such as HER2 and EGFR have high rates of progression in the CNS after initial control of their systemic disease [13, 14]. Targeted or chemotherapeutic agents that cross the blood-brain barrier (BBB) are also used in these patients, but patients inevitably progress in the brain [15]. Furthermore, although immunotherapy is rapidly becoming standard of care in patients with metastatic lung cancer, melanoma and other cancers, the majority of patients treated with immunotherapy progress in the CNS [5, 16]. Novel targets are clearly needed. The total annual cost of caring for patients with metastatic CNS disease exceeds $10 billion in the US alone, yet only about 5% of all cancer research funding is specifically devoted to the study of metastatic disease [17]. Overall, CNS metastases represent a dreaded and frequent complication for cancer patients and their families: there is an urgent need for more focused efforts to develop improved therapeutic options.

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Objective

Primary

- To determine the activity of a CDK inhibitor in patients with progressive brain metastases derived from lung cancer, breast cancer, and other cancers harboring actionable genetic alterations associated with sensitivity to CDK inhibitors as measured by response rate (Response Assessment in Neuro-Oncology [RANO] criteria).
- To determine the activity of a PI3K inhibitor in patients with progressive brain metastases derived from lung cancer, breast cancer, and other cancers harboring actionable genetic alterations in the PI3K pathway as measured by response rate (RANO criteria).
- To determine the activity of an NTRK/ROS1 inhibitor in patients with progressive brain metastases derived from lung cancer harboring actionable NTRK/ROS1 gene fusions as measured by response rate (RANO criteria).

Secondary

- To evaluate the systemic response by Response Evaluation Criteria in Solid Tumors (RECIST) criteria in each of the cohorts determined by treatment and primary cancer type.
- To evaluate the clinical benefit rate (complete response [CR] + partial response [PR] + stable disease [SD]) by Brain Metastases (BM)-RANO for central nervous system (CNS) in each of the cohorts determined by treatment and primary cancer type.
- To evaluate the clinical benefit rate (CR + PR + SD) by RECIST for extracranial disease in each of the cohorts determined by treatment and primary cancer type.
- To evaluate the duration of response by BM-RANO in each of the cohorts determined by treatment and primary cancer type.
- To evaluate the duration of response by RECIST in each of the cohorts determined by treatment and primary cancer type.
- To evaluate the progression-free survival for intracranial disease in each of the cohorts determined by treatment and primary cancer type.
- To evaluate the progression-free survival for extracranial disease in each of the cohorts determined by treatment and primary cancer type.
- To evaluate the site of first progression (CNS versus [vs] non-CNS) in each of the cohorts determined by treatment and primary cancer type.
- To evaluate the overall survival in each of the cohorts determined by treatment and primary cancer type.
- To evaluate the toxicity profile of agents in patients with brain metastases in each of the cohorts determined by treatment and primary cancer type.

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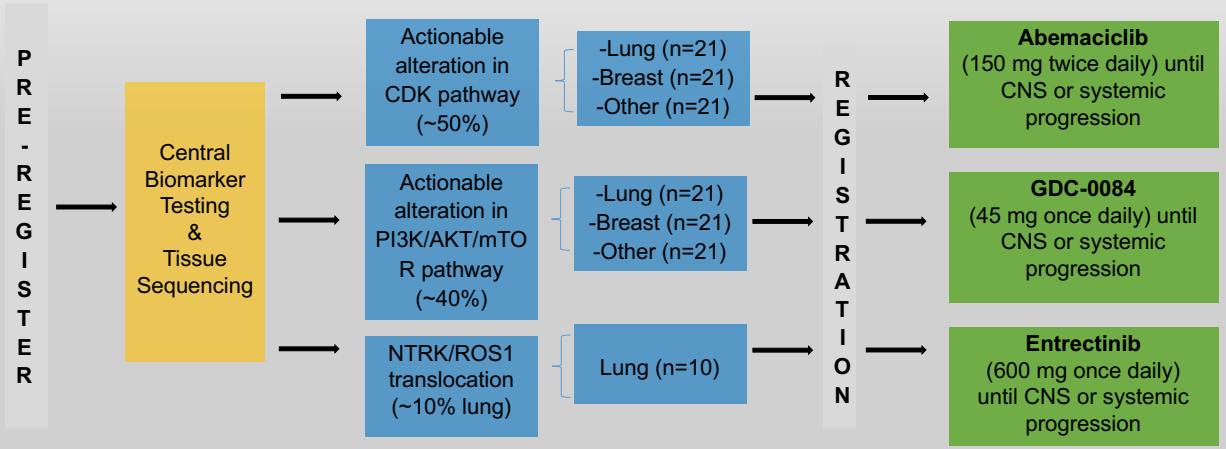
Study Schema



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Each cycle is 28 days. Treatment is to continue until CNS or systemic progression or unacceptable adverse event. Patients will be followed for 5 years from registration or until death, whichever comes first.

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

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Treatment Plan

Arm I (CDK gene mutation)
- Patients receive abemaciclib PO BID on days 1-28. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.

Arm II (PI3K gene mutation)
- Patients receive PI3K inhibitor GDC-0084 PO QD on days 1-28. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.

Arm III (NTRK/ROS1 gene mutation)
- Patients receive entrectinib PO QD on days 1-28. Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity.

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Key Eligibility Criteria

Key Pre-Registration Eligibility Criteria

- Tissue available for biomarker testing

Key Registration Eligibility Criteria

- Histologically confirmed metastatic disease to the brain from any solid tumor defined by one of the following:
  - Untreated measurable lesions in patients who have received surgery and/or stereotactic radiosurgery (SRS) to one or more other lesions
  - Residual or progressive lesions after surgery if asymptomatic.
  - Prior whole-brain radiotherapy (WBRT) and/or SRS and then lesions progressed or new lesions
  - Not previously been treated with cranial radiation (e.g. WBRT or SRS) are eligible, but such patients must be asymptomatic or neurologically stable from their CNS metastases.
- Measurable CNS disease (>10 mm)
- Ability to obtain MRIs
- No surgery within 2 weeks prior to or after registration.
- No chemotherapy within 14 days prior to registration.
  - For melanoma, progression after immunotherapy or for BRAF positive melanoma, BRAF/MEK inhibitors
  - For lung cancer, failed EGFR therapies.
  - For HER2-positive breast cancer received prior HER-2 directed therapy in the metastatic setting
  - For triple negative breast cancer (TNBC), at least one chemotherapy in the metastatic settingFor ER/PR+ breast cancer, at least one endocrine therapy in the metastatic setting
  - Breast cancer patients who have received ribociclib or palbociclib are eligible as long as there is documentation of CDK4 pathway alteration on a biopsy at the point of progression post-ribociclib or palbociclib.

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