multiple brain metastases from NSCLC. (Horton et al., Am J Roentgenol Radium Ther Nucl Med. 1971; 3:334-35). Nearly one half of patients with brain metastases from NSCLC develop progressive neurologic problems, and only 10% to 15% of patients survive more than 1 year after diagnosis of brain metastases. Survival for patients with up to 2 metastatic organ sites may depend on adequate control of brain metastases.

[0007] The management of brain metastases includes both symptomatic and brain-directed therapies. Brain-directed therapies include WBRT, stereotactic radiosurgery (SRS), and neurosurgery as standard of care, either alone or in various combinations, depending on the site, size, and number of brain metastases. None of the currently available treatment modalities has shown a survival advantage against each other in large randomized trials. (Regine et al., Int J Radiat Oncol Biol Phys, 2002; 52(2):333-8). Symptomatic therapy often includes steroid treatment to reduce peri-tumoral edema and anticonvulsants to prevent recurrent seizures. Systemic chemotherapy has limited efficacy in this setting.

[0008] For the majority of patients with brain metastases, WBRT is the standard of care. Nonrandomized studies suggest that WBRT increases the median survival time to 3 to 4 months compared to approximately 1 month without treatment and 2 months with steroids alone. Although the response rate of WBRT for brain metastases patients with NSCLC varies, the rate is typically reported to be in the range of 25% to 30%. (Tsao et al., Cochrane Database Syst Rev. 2006; 3:CD003869).

[0009] Multiple approaches have been used to improve upon the results of WBRT alone, particularly by adding agents suspected of having radio-sensitizing effects in preclinical models. The following radio-sensitizers have been studied in randomized, controlled studies, all failing to benefit in either local brain tumor control or overall survival: lonidamine, metronidazole, misonidazole, motexafin gadolinium, bromodeoxyuridine, and efaproxiral.

[0010] There remains a need for effective methods for the treatment and mitigation of brain metastases and its symptoms. This invention provides methods of treatment that generally address such a need.

BRIEF SUMMARY ~~OF THE INVENTION~~

[0011] The present invention relates to a method for the treatment of brain metastases from non-small cell lung cancer in a subject, comprising administering to the subject an effective amount of 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide

(veliparib or ABT-888), or a pharmaceutically acceptable salt thereof, in combination with whole brain radiation therapy.

[0011a] In one aspect, there is provided a use of an effective amount of 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of brain metastases from non-small cell lung cancer, wherein the medicament is to be administered in combination with an effective amount of whole brain radiation.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] FIG. 1 shows the WBRT Schedule in combination with Veliparib (ABT-888).

[0013] FIG. 2 shows Preliminary Mean Pharmacokinetic Parameters of Veliparib following WBRT in Patients with brain metastases.

[0014] FIG. 3 shows preliminary mean plasma concentration-time profiles following oral administration of veliparib.

[0015] FIG. 4 shows best tumor size percent change from baseline (patients with NSCLC).

[0016] FIG. 5 shows best tumor size percent change from baseline (patients with breast cancer).

[0017] FIG. 6 shows best tumor size percent change from baseline (patients with other types of cancer).

[0018] FIG. 7 shows overall survival for patients with NSCLC (13 events).

[0019] FIG. 8 shows overall survival of responders vs. non-responders (patients with NSCLC).

[0020] FIG. 9 shows overall survival for patients with breast cancer (13 events).

[0021] FIG. 10 shows overall survival of responders vs. non-responders (patients with breast cancer).

[0022] FIG. 11 shows observed vs. expected overall survival for patients with NSCLC (20 events).

[0023] FIG. 12 shows observed vs. expected overall survival for patients with breast cancer (18 events).

DETAILED DESCRIPTION OF THE INVENTION

[0024] Definitions

[0025] The terms "treat", "treating" and "treatment" refer to a method of alleviating or abrogating a disease and/or its attendant symptoms.

WHAT IS CLAIMED IS

1. ~~A method for the treatment of brain metastases from non-small cell lung cancer in a subject, comprising administering to the subject~~ Use of an effective amount of 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of brain metastases from non-small cell lung cancer, wherein the medicament is to be administered in combination with an effective amount of whole brain radiation.

2. The ~~method~~ use of claim 1, wherein the amount of 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide is from about 30 to about 600 mg per day.

3. The ~~method~~ use of claim 1 or 2, wherein the amount of 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide is from about 60 to about 400 mg per day.

4. The ~~method~~ use of any of claims 1-3, wherein the amount of 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide is about 100 mg per day.

5. The ~~method~~ use of any of claims 1-3, wherein the amount of 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide is about 400 mg per day.

6. The ~~method~~ use of any of claims 1-5, wherein the 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide is to be administered twice a day.

7. The ~~method~~ use of any of claims 1-6, wherein the amount of whole brain radiation is a cumulative dose of about 20 Gy to about 40 Gy.

8. The ~~method~~ use of claim 7, wherein the cumulative dose is about 30 Gy.

9. The ~~method~~ use of claim 8, wherein the cumulative dose was delivered in about 3.0 Gy fractions once a day for a total of 10 fractions.

10. The ~~method~~ use of claim 7, wherein the cumulative dose is about 37.5 Gy.

11. The ~~method~~ use of claim 10, wherein the cumulative dose was delivered in about 2.5 Gy fractions once a day for a total of 15 fractions.

12. The ~~method~~ use of claim 7, wherein the cumulative dose is about 35 Gy.

13. The ~~method~~ use of claim 12, wherein the cumulative dose was delivered in about 2.5 Gy fractions once a day for a total of 14 fractions.

14. The ~~method~~ use of any of claims 1-13, wherein the 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide is to be administered before administration of the whole brain radiation therapy.

15. The ~~method~~ use of any of claims 1-13, wherein the 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide is to be administered concurrently with administration of the whole brain radiation therapy.

16. The ~~method~~ use of any of claims 1-13, wherein the 2-[(2R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide is to be administered after administration of the whole brain radiation therapy.