first-line therapy in advanced non-small cell lung cancer. Clin Cancer Res, 2008 Mar 1;14(5):1464-9.] These studies have largely excluded patients with active brain metastasis. *Ibid.* This exclusion is done on the general view that existing brain metastases will not respond to treatment and, thus, morbidity and symptoms due to these metastases would mask the effects of the test treatment on the primary tumor. [Carden CP, et al., Eligibility of patients with brain metastases for phase I trials: time for a rethink? *The Lancet Oncology*, Vol 9, Issue 10, Pages 1012-1017, October 2008 doi:10.1016/S1470-2045(08)70257-2.] This standard clinical trial design strategy serves to emphasize the general expectation that therapies effective against primary tumors and even non-brain metastasis tumors will fail to effect brain metastasis tumors.

Summary

In one aspect, there is provided the use of Macitentan in the manufacture of a medicament for the prevention or treatment of brain metastases in combination with a cytotoxic chemotherapy agent selected from paclitaxel, temozolomide and a mixture of paclitaxel and temozolomide, with radiotherapy or with both radiotherapy and a cytotoxic chemotherapy agent selected from paclitaxel, temozolomide and a mixture of paclitaxel and temozolomide.

Brief Description of the Drawings

FIGURE 1: *In vitro* culture of MDA-MB-231 breast cancer cells (T) and murine astrocytes (A) were evaluated by scanning electron microscopy. Direct contact between the astrocytes (extending pods-feet) and tumor cells is evident;

FIGURE 2: The astrocyte-metastatic cancer cell co-cultures showed dye transfer between co-cultured cells;

FIGURE 3: Culturing of human MDA-MB-231 breast cancer cells or human PC14Br4 lung cancer cells with astrocytes (but not 3T3 fibroblasts) reduced the relative apoptotic index (increased resistance) of tumor cells incubated for 72 hours with paclitaxel (5 ng/ml) by 58.3 + 8.9% (mean ± S.D., $P<0.01$) and 61.8 ± 6.7% (mean ± S.D., $P<0.05$), respectively (the apoptotic index was compared by the Student's *t* test);

FIGURE 4: Human lung cancer PC14Br4 cells were cultured alone or with astrocytes (direct cell to cell contact) in medium containing P-glycoprotein-associated Adriamycin (200 ng/ml), paclitaxel (5 ng/ml), vinblastine (3 ng/ml), vincristine (8 ng/ml), and P-glycoprotein-dissociated 5-FU (500 ng/ml) or cisplatinum (2.4 μg/ml);

FIGURE 5: Astrocyte-mediated protection of brain metastasis cells from cytotoxic chemotherapy-induced cell death does not last longer than 72 hours after direct astrocyte-brain metastasis cell contact is lost;

FIGURE 6: Gene transcription profiling conditions distinguished between murine and human mRNA;

FIGURE 7: In the MDA-MB-231 cells, 1069 genes, and in the PC14Br4 cells, 594 genes were differentially expressed. A two-gene list comparison revealed increased expression of