An open-label, Phase I/IIa, dose escalating study of 2B3-101 in patients with solid tumors and brain metastases or recurrent malignant glioma.

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Primary Objective:• To assess the safety and tolerability of 2B3-101 when administered intravenously (IV) as single agent in patients with solid tumors and brain metastases or recurrent malignant glioma in order to determine the Maximum Tolerated...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON39207

Source
ToetsingOnline

Brief title
2B3-101-CR-001

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
or recurrent malignant glioma, solid neoplasms, solid tumors and brain metastases

Research involving
Human

Sponsors and support

Primary sponsor: to-BBB technologies B.V.

Source(s) of monetary or material Support: to-BBB technologies B.V.

Intervention

Keyword: 2B3-101, brain metastases, Phase I/IIa, solid tumors or malignant glioma

Outcome measures

Primary outcome

The primary study endpoint includes:

• The incidence rate of DLTs during the DLT observation period (cycle 1) at each 2B3-101 dose level is based on predefined safety parameters and will determine the MTD of 2B3-101 as single agent and in combination with trastuzumab, respectively. These safety parameters are: Adverse drug reactions (ADR) and serious ADRs, changes in hematology and chemistry values, including those associated with hepatic and renal function, and assessment of physical examinations, vital signs and cardiac function (i.e. repeated electrocardiograms). Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used.

Secondary outcome

Secondary endpoints include:

• Pharmacokinetics of 2B3-101 as single agent in plasma; Cmax, Vss, T1/2, AUC, CL;

• Pharmacokinetics of 2B3-101 when combined with trastuzumab in plasma; Cmax, Vss, T1/2, AUC, CL;

• Preliminary efficacy: Antitumor effects of 2B3-101 as single agent and when

combined with trastuzumab according to RECIST 1.1 (solid tumors) and RANO

(malignant gliomas).

Study description

Background summary

The delicate metabolic homeostasis of the central nervous system (CNS) is largely maintained by the blood-brain barrier (BBB). The BBB plays a key role in excluding potentially neurotoxic and exogenous compounds from the brain, while still allowing the penetration and uptake of essential nutrients. Many potentially highly efficacious anticancer drugs are currently not available to treat brain tumors because they do not adequately cross the BBB, and therefore do not reach the brain.

Drug delivery systems are generally used to deliver more drug within a favorable therapeutic window. The most advanced systems in today*s clinical practice utilize liposomal encapsulation of drugs, thereby shielding the body from excess free drug to significantly reduce dose-limiting toxicities. The coating of liposomes with polyethylene glycol (PEG) further ensures a prolonged circulation time in plasma, allowing for a clinically feasible dosing regimen for an intravenous product.

Due to the presence of the BBB, safe and effective drug delivery to brain tumors remains challenging. Even though the BBB is often disrupted in brain tumors, in many cases, the BBB is known to still be in force. This has been shown in smaller (metastatic) brain tumors, as well as in localized (infiltrating) parts of larger (metastatic) tumors. This is of importance especially for liposomal drug delivery systems, since the pore size of contrast-enhancing tumor vasculature was shown to be around 12 nm, which is still significantly smaller than the 100 nm sized liposomes. Nonetheless, moderate efficacy of PEGylated liposomal doxorubicin (Caelyx®) has been shown in patients with brain tumors. These data therefore provide a strong clinical basis for this well-known and very effective anticancer drug formulation to be optimized to improve brain penetration of drug and therefore overall survival of patients with brain tumors.

The most safe and effective way of actively enhancing the delivery of liposomal drugs to the entire brain is by targeting the liposomes to endogenous uptake transport receptors on the brain capillaries that constitute the BBB. Glutathione is an endogenous tri-peptide with antioxidant-like properties in the brain and its active (sodium-dependent) transport receptor is highly expressed on the BBB. To optimally enhance the delivery of liposomal

doxorubicin to the brain, to-BBB technologies B.V. has designed a glutathione (GSH) PEGylated liposomal doxorubicin hydrochloride formulation (2B3-101). Coating of liposomes with PEG ensures the prolonged circulation time in plasma, whilst conjugation of GSH to the tips of the PEG molecules targets the liposomes towards the active GSH transporters on the BBB to enhance the delivery of doxorubicin to the brain.

In preclinical experiments, 2B3-101 showed significant better tumor growth inhibition and survival benefit in rodents with brain tumors as compared to normal PEGylated liposomal doxorubicin. In a systemic breast cancer animal model the tumor suppression was equal between 2B3-101 and Caelyx. Moreover, as compared to Caelyx®, enhanced doxorubicin delivery by 2B3-101 across the BBB was observed, with a favorable pharmacokinetic and safety profile in these animal models. Also, it has been shown that the free concentration of an encapsulated reference compound in the brain increases with increasing percentages of GSH on the surface of the PEG liposomes, further exemplifying the mechanistic effect of enhanced delivery by GSH-modified PEGylated liposomes.

Based on the medical need, and the positive outcome of the preclinical safety and efficacy studies of 2B3-101, clinical studies are warranted to evaluate 2B3-101*s clinical potential in the treatment of brain metastases and recurrent malignant primary brain tumors.

Study objective

Primary Objective:
• To assess the safety and tolerability of 2B3-101 when administered intravenously (IV) as single agent in patients with solid tumors and brain metastases or recurrent malignant glioma in order to determine the Maximum Tolerated Dose (MTD).
• To assess the safety and tolerability of intravenously (IV) administered 2B3-101 in combination with trastuzumab, in patients with HER2+ breast cancer with brain metastases and to determine the Maximum Tolerated Dose (MTD) of this treatment combination

Secondary Objectives:
• To characterize the PK of 2B3-101 after multiple intravenous infusions as single agent and in combination with trastuzumab;
• To evaluate the preliminary efficacy of 2B3-101 as single agent in terms of anti-tumor activity in patients with breast cancer with treated or untreated brain metastases.
• To evaluate the preliminary efficacy of 2B3-101 as single agent in terms of anti-tumor activity in patients with other solid tumors with treated or untreated brain metastases, treated in the dose-escalation phase.
• To evaluate the preliminary antitumor activity of 2B3-101 in combination with trastuzumab in patients with HER2+ breast cancer with treated or untreated

brain metastases.
• To evaluate the preliminary efficacy of 2B3-101 in terms of anti-tumor activity as single agent in patients with small cell lung cancer (SCLC) with treated or untreated brain metastases.
• To evaluate the preliminary efficacy of 2B3-101 in terms of anti-tumor activity as single agent in patients with melanomas with treated or untreated brain metastases.
• To evaluate the preliminary efficacy of 2B3-101 in terms of anti-tumor activity as single agent in patients with recurrent malignant glioma.

Study design

This is a Phase I/IIa, multicenter, open-label, dose-escalation study. The study will be conducted in 6 parts:
• *2B3-101 single agent dose-escalation phase*
• *a 2B3-101 with trastuzumab dose-escalation phase*
• *a Breast cancer brain metastases study arm of the expansion phase*
• *a SCLC brain metastases study arm of the expansion phase*
• *a Melanoma brain metastases study arm of the expansion phase*
• *a Recurrent malignant glioma study arm of the expansion phase*.

2B3-101 single agent dose-escalation phase

In the 2B3-101 single agent dose-escalation phase, patients with solid tumors and brain metastases or with recurrent malignant glioma will be enrolled.

Patients will be assigned to a dose level cohort. - The starting dose will be 5 mg/m2, which is equal to 1/10 of the human equivalent dose of the LD10 of 2B3-101 in rats.

A *3+3* dose-escalation design will be used. The study will investigate sequential cohorts consisting of 3-6 patients to be enrolled and treated at the applicable dose level. Planned dose levels for subsequent cohorts are 10, 20, 30, mg/m2 and steps of 10 mg/m2 thereafter. For more information on the dose escalation design and the increments, please see the dose escalation criteria section.

There will be no intra-patient dose escalation.

Each treatment cycle consists of 21 days.

Patients will receive a single IV dose of 2B3-101 on day 1 of each cycle. In order to minimize the risk of infusion reactions 5% of the total dose of 2B3-101 (in mg) should be infused slowly over the first 30 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes. Blood samples will be taken on day 1, 2, 3, 5, 8 and 11 of cycle 1, on day 1, 8 and 15 of cycle 2, and if applicable on day 1 of

cycle 3 and on day 1 of cycle 4 to assess the PK profile during the first 2-4 cycles.

The dose limiting toxicity (DLT) observation period for each dose level will be cycle 1 (day 1 to day 21).

Patients who do not complete the DLT observation period (cycle 1) for other reasons than a DLT will be replaced.

Once the MTD of 2B3-101 as single agent has been determined, the study will continue to the four arms of the expansion phase

2B3-101 in combination with trastuzumab dose-escalation phase

In the 2B3-101 in combination with trastuzumab dose-escalation phase, only patients with HER2+ breast cancer and brain metastases will be enrolled.

The patients will be assigned to a 2B3-101 dose level cohort. - The starting dose of 2B3-101 will be 40 mg/m2 every 3 weeks. This dose has been selected based upon safety information from patients treated with 2B3-101 at this dose level, as well as upon previous treatment with PEGylated liposomal doxorubicin in combinations trastuzumab (Chia et al 2006).

The dose-escalation will be conducted in steps of 10 mg/m2 up to the MTD level determined for 2B3-101 as single agent, but will not exceed the single agent dose agreed for the expansion phase based on the single agent dose escalation data, i.e. 50 mg/m2. The trastuzumab dose will remain fixed to a loading dose of 8 mg/kg at day 1 and 6 mg/kg every 3 weeks at the subsequent cycles throughout the determination of the MTD. Enrolment of HER2+ patients breast cancer patients in the *2B3-101 in combination with trastuzumab dose-escalation* phase of the study will be allowed in parallel with the determination of the MTD of 2B3-101 as single agent.

A *3+3* dose-escalation design will be used. Thus, the study will investigate sequential cohorts of 3-6 patients, who will be enrolled and treated at the applicable dose levels.

No intra-patient dose-escalation will be allowed.

Each treatment cycle consists of 21 days.

All patients will receive a single IV dose of 2B3-101 on day 1 of each cycle. In order to minimize the risk of infusion reactions 5% of the total dose of 2B3-101 (in mg) should be infused slowly over the first 30 minutes. As long as 2B3-101 is well tolerated, the remaining 95% of the infusion could thereafter be administered over the next 60 min, resulting in a total infusion time of 90 minutes. The infusion of trastuzumab will then follow 30 minutes after the

completion of the 2B3-101 infusion.

Blood samples will be taken on day 1, 2, 3, 5, 8 and 11 of cycle 1, on day 1, 8 and 15 of cycle 2, and if applicable on day 1 of cycle 3 and on day 1 of cycle 4 to assess the PK profile of 2B3-101 during the first 2-4 cycles.

The dose limiting toxicity (DLT) observation period will be cycle 1 (day 1 to day 21) at each individual dose level.

Patients who do not complete the DLT observation period (cycle 1) for other reasons than a DLT will be replaced.

Breast cancer brain metastases study arm of the expansion phase

In the breast cancer brain metastases study-expansion phase, each treatment cycle equally consists of 21 days. On day 1 of each cycle patients will receive a single IV 50 mg/m2 dose of 2B3-101 as single agent, or a dose at the MTD of 2B3-101 in combination with trastuzumab (if different). In order to minimize the risk of infusion reactions 5% of the total dose (in mg) should be infused slowly over the first 30 minutes. As long as 2B3-101 is well tolerated, the remaining 95% of the infusion could thereafter be administered over the next 60 minutes, resulting in a total infusion time of 90 minutes. A trastuzumab infusion will follow 30 minutes after the completion of the 2B3-101 infusion, if applicable.

Blood samples will be taken on day 1, 2, 3, 5, 8 and 11 of cycle 1, on day 1, 8 and 15 of cycle 2, and if applicable on day 1 of cycle 3 and on day 1 of cycle 4 to assess the PK profile during the first 2-4 cycles.

SCLC brain metastases study arm of the expansion phase

In the SCLC brain metastases study arm of the expansion phase, each treatment cycle is equally 21 days long. Patients will receive a single IV 50 mg/m2 dose of 2B3-101 as single agent on day 1 of each cycle. In order to minimize the risk of infusion reactions 5% of the total dose (in mg) should be infused slowly over the first 30 minutes. As long as 2B3-101 is well tolerated, the remaining 95% of the infusion could thereafter be administered over the next 60 minutes, resulting in a total infusion time of 90 minutes.

Blood samples will be taken on day 1, 2, 3, 5, 8 and 11 of cycle 1, on day 1, 8 and 15 of cycle 2, and if applicable on day 1 of cycle 3 and on day 1 of cycle 4 to assess the 2B3-101 PK profile during the first 2-4 cycles.

Melanoma brain metastases study arm of the expansion phase

In the melanoma brain metastases study arm of the expansion phase, each

treatment cycle is equally 21 days long. Patients will receive a single IV 50 mg/m2 dose of 2B3-101 as single agent in the dose escalation phase on day 1 of each cycle. In order to minimize the risk of infusion reactions 5% of the total dose (in mg) should be infused slowly over the first 30 minutes. As long as 2B3-101 is well tolerated, the remaining 95% of the infusion could thereafter be administered over the next 60 minutes, resulting in a total infusion time of 90 minutes.

Blood samples will be taken on day 1, 2, 3, 5, 8 and 11 of cycle 1, on day 1, 8 and 15 of cycle 2, and if applicable on day 1 of cycle 3 and on day 1 of cycle 4 to assess the 2B3-101 PK profile during the first 2-4 cycles.

Recurrent malignant glioma study arm of the expansion phase

In the recurrent malignant glioma study-expansion phase, each treatment cycle is 28 days long. Patients will receive a single IV 60 mg/m2 dose of 2B3-101 on day 1 of each cycle. In order to minimize the risk of infusion reactions 5% of the total dose (in mg) should be infused slowly over the first 30 minutes. As long as 2B3-101 is well tolerated, the remaining 95% of the infusion could thereafter be administered over the next 60 minutes, resulting in a total infusion time of 90 minutes.

Blood samples will be taken on day 1, 2, 3, 5, 8 and 11 of cycle 1, on day 1, 8 and 15 of cycle 2, and if applicable on day 1 of cycle 3 and on day 1 of cycle 4 to assess the 2B3-101 PK profile during the first 2-4 cycles.

For all study phases and patient groups, all patient will stay on treatment until disease progression, unacceptable toxicity, or discontinuation for any other reason.

Intervention

In the 2B3-101 single agent dose-escalation phase, patients eligible for the study will be assigned to a dose level cohort. The starting dose will be 5 mg/m2, which is equal to 1/10 of the human equivalent dose of the LD10 of 2B3-101 in rats. Planned dose levels for subsequent cohorts are 10, 20, 30, mg/m2 and steps of 10 mg/m2 thereafter.

Patients will receive a single IV dose of 2B3-101 on day 1 of each cycle: In order to minimize the risk of infusion reactions 5% of the total 2B3-101 dose (in mg) should be infused slowly over the first 30 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes Each treatment cycle consists of 21 days.

In the 2B3-101 in combination with trastuzumab dose-escalation phase, patients with HER2+ breast cancer and brain metastases will be enrolled.
Patients will be assigned to a 2B3-101 dose level cohort. - The starting dose

of 2B3-101 will be 40 mg/m2 every 3 weeks.

Patients will receive a single IV dose of 2B3-101 on day 1 of each cycle. In order to minimize the risk of infusion reactions 5% of the total dose of 2B3-101 (in mg) should be infused slowly over the first 30 minutes. As long as 2B3-101 is well tolerated, the remaining 95% of the infusion could thereafter be administered over the next 60 min, resulting in a total infusion time of 90 minutes. The infusion of trastuzumab will then follow 30 minutes after the completion of the 2B3-101 infusion.

In the Breast cancer brain metastases study arm of the expansion phase, patients will receive a single 50 mg/m2 IV dose of 2B3-101 at MTD on day 1 of each cycle. In order to minimize the risk of infusion reactions 5% of the total dose (in mg) should be infused slowly over the first 30 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes

In the SCLC brain metastases study arm of the expansion phase, patients will receive a single 50 mg/m2 IV dose of 2B3-101 at MTD on day 1 of each cycle. In order to minimize the risk of infusion reactions 5% of the total dose (in mg) should be infused slowly over the first 30 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes. Each treatment cycle consists of 21 days.

In the Melanoma brain metastases study arm of the expansion phase, patients will receive a single 50 mg/m2 IV dose of 2B3-101 at MTD on day 1 of each cycle. In order to minimize the risk of infusion reactions 5% of the total dose (in mg) should be infused slowly over the first 30 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes. Each treatment cycle consists of 21 days.

In the Recurrent malignant glioma study arm of the expansion phase, patients will receive a single 60 mg/m2 IV dose of 2B3-101 at MTD on day 1 of each cycle. In order to minimize the risk of infusion reactions 5% of the total dose (in mg) should be infused slowly over the first 30 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes. Each treatment cycle consists of 28 days.

For all stages Infusion or hypersensitivity reactions might occur with the first or subsequent doses. Those reactions can be ameliorated by slowing infusion time. In addition, (pre) medication such as hydrocortisone, ranitidine, cimetidine, anti-emetics, and diphenhydramine is allowed according to local institutional guidelines.

Study burden and risks

Due to the presence of the BBB, safe and effective drug delivery to brain

tumors remains challenging. Even though the BBB is often disrupted in brain tumors, in many cases, the BBB is known to still be in force. This has been shown in smaller (metastatic) brain tumors, as well as in localized (infiltrating) parts of larger (metastatic) tumors. This is of importance especially for liposomal drug delivery systems, since the pore size of contrast-enhancing tumor vasculature was shown to be around 12 nm, which is still significantly smaller than the 100 nm sized liposomes. Nonetheless, moderate efficacy of pegylated liposomal doxorubicin (Caelyx®) has been shown in patients with brain tumors. These data therefore provide a strong clinical basis for this well-known and very effective anticancer drug formulation to be optimized to improve brain penetration of drug and therefore overall survival of patients with brain tumors.

The most safe and effective way of actively enhancing the delivery of liposomal drugs to the entire brain is by targeting the liposomes to endogenous uptake transport receptors on the brain capillaries that constitute the BBB. Glutathione is an endogenous tri-peptide with antioxidant-like properties in the brain and its active (sodium-dependent) transport receptor is highly expressed on the BBB. To optimally enhance the delivery of liposomal doxorubicin to the brain, to-BBB technologies B.V. has designed a glutathione (GSH) pegylated liposomal doxorubicin hydrochloride formulation (2B3-101). Coating of liposomes with PEG ensures the prolonged circulation time in plasma, whilst conjugation of GSH to the tips of the PEG molecules targets the liposomes towards the active GSH transporters on the BBB to enhance the delivery of doxorubicin to the brain.

Besides, doxorubicin is a known substrate for drug efflux pumps, also present at the BBB, like P-glycoprotein (P-gp) and breast cancer related protein (BCRP). Targeted liposomal doxorubicin (using conjugated transferrin (Tf) as the targeting ligand directed at the transferrin receptor (TfR)) was shown to increase cytotoxicity in TfR+ drug resistant cells. From these studies it could be concluded that TfR-targeted liposomes loaded with doxorubicin can be more effective in selectively targeting, and reversal of drug resistance. Such an effect could also be hypothesized to occur at the BBB in vivo, where P-gp and BCRP are highly expressed, using our targeted liposomal formulation of doxorubicin, 2B3-101.

In preclinical experiments, 2B3-101 showed significant better tumor growth inhibition and survival benefit in rodents with brain tumors as compared to normal pegylated liposomal doxorubicin. In a systemic breast cancer animal model the tumor suppression was equal between 2B3-101 and Caelyx. Moreover, as compared to Caelyx®, enhanced doxorubicin delivery by 2B3-101 across the BBB was observed, with a favorable pharmacokinetic and safety profile in these animal models. Also, it has been shown that the free concentration of an encapsulated reference compound in the brain increases with increasing percentages of GSH on the surface of the PEG liposomes, further exemplifying the mechanistic effect of enhanced delivery by GSH-modified pegylated

liposomes.

In Europe, Caelyx® is authorized for treatment of the following indications: (1) Treatment of advanced ovarian carcinoma in women who have failed standard first-line therapy (platinum and paclitaxel based chemotherapy), (2) Treatment of patients with AIDS-related Kaposi*s sarcoma with CD4 counts < 200/mm3, (3) Monotherapy in metastatic breast cancer, for patients with an increased cardiac risk, and (4) In combination with bortezomib in multiple myeloma patients with progressive disease who have received at least one other treatment in the past and have already undergone or are unsuitable for a bone marrow transplant.

Breast cancer brain metastases are detected in 10-16% of patients with metastatic breast cancer (MBC). However, in autopsy studies it was found that approximately 30% of these patients have brain metastases (Pestalozzi et al., 2006). The majority of breast cancer patients who develop metastatic brain disease present multiple lesions (78%). Death is attributed to uncontrolled metastatic brain disease in approximately 40% (Wadasadawala et al., 2007). Median survival in untreated patients with CNS involvement is 1 month; in patients administered corticosteroids (to reduce the oedema in the brain due to mass effect), 2 months; and following radiotherapy, 3-6 months. Patients with single CNS lesions and limited systemic disease amenable to surgery or radiotherapy may achieve a median survival in the range of 10-16 months. Corticosteroids, radiotherapy, surgical therapy and radio surgery are all used for the treatment of metastatic brain disease. There are limited data on the use of chemotherapy for brain metastases of breast cancer, even though the systemic cancer is chemo sensitive (Wadasadawala et al., 2007).

Based on the medical need, and the positive outcome of the preclinical safety and efficacy studies of 2B3-101, clinical studies are warranted to evaluate 2B3-101*s clinical potential in the treatment of brain metastases. Specifically, 2B3-101 is intended for the treatment of breast cancer patients with progressive brain metastases following local therapy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria:
1. Age * 18 years.
2. Measurable intracranial disease by MRI.
3. ECOG Performance Status <= 2.
4. Estimated life expectancy of at least 8 weeks.
5. Toxicities incurred as a result of previous anticancer therapy (radiation therapy, chemotherapy, or surgery) must be resolved to <= grade 2 (as defined by CTCAE version 4.0).
6. No evidence of (cortical) cognitive impairment as defined by a Mini-Mental Status Exam (MMSE) score >= 25/30.
7. Written informed consent according to local guidelines.;In addition to the above listed eligibility criteria, the following criteria are applicable:
8. 2B3-101 single agent dose-escalation phase:
Patients with pathologically confirmed diagnosis of advanced, recurrent solid tumors and unequivocal evidence of brain metastases that are refractory to standard therapy or for whom no standard therapy exists or with unequivocal evidence of newly diagnosed untreated brain metastases and controlled extracranial disease, which per the multi-disciplinary team decision do not require immediate radiotherapy, surgery, or standard systemic chemotherapy. Brain metastases may be stable, progressive, symptomatic or asymptomatic brain metastasis/es. Stable or decreasing dosages of steroids (e.g. dexamethasone) for 7 days prior to baseline MRI and/or non-enzyme inducing anti-epileptic drugs are allowed.;Or ;Patients with pathology confirmed diagnosis of advanced, recurrent primary malignant (grade III and IV) glioma that are refractory to standard therapy or for whom no standard

therapy exists. Stable or decreasing dosages of steroids (e.g. dexamethasone) for 7 days prior to baseline MRI and/or non-enzyme inducing anti-epileptic drugs are allowed.;2B3-101 in combination with trastuzumab dose-escalation phase:
Patients with histologically-confirmed HER2-positive (IHC 3+ or fluorescence in situ hybridization [FISH] amplified; by clinical assay on either primary or metastatic tumor) adenocarcinoma of the breast with unequivocal evidence of brain metastases that are refractory to standard therapy or for which no standard therapy exist or with unequivocal evidence of newly diagnosed untreated brain metastases and controlled extracranial disease, which per the multi-disciplinary team decision do not require immediate radiotherapy, surgery, or standard systemic chemotherapy can be included to this escalation phase as well.;Breast cancer brain metastases study arm of the expansion phase:
Patients with pathologically confirmed diagnosis of advanced, recurrent breast cancer with at least one progressive and/or new metastatic brain lesion, that are refractory to standard therapy or for whom no standard therapy exist. Stable or decreasing dosages of steroids (e.g. dexamethasone) for 7 days prior to baseline MRI and/or non-enzyme inducing anti-epileptic drugs are allowed.;Or -;Patients with pathologically confirmed diagnosis of advanced breast cancer with newly diagnosed, untreated, brain metastases and controlled extracranial disease, which per the multi-disciplinary team decision do not require immediate radiotherapy, surgery, or standard systemic chemotherapy.;Once the MTD of 2B3-101 with trastuzumab has been determined, patients with histologically-confirmed HER2-positive (IHC 3+ or fluorescence in situ hybridization [FISH] amplified; by clinical assay on either primary or metastatic tumor) adenocarcinoma of the breast with at least one progressive and/or new metastatic brain lesion, that are refractory to standard therapy or for which no standard therapy exist or with unequivocal evidence of newly diagnosed untreated brain metastases and controlled extracranial disease, which per the multi-disciplinary team decision do not require immediate radiotherapy, surgery, or standard systemic chemotherapy. can be included to this expansion phase as well;SCLC brain metastases study arm of the expansion phase:
Patients with pathologically confirmed diagnosis of advanced, recurrent SCLC with at least one progressive and/or new metastatic brain lesion, that are refractory to standard therapy or for whom no standard therapy exist. Stable or decreasing dosages of steroids (e.g. dexamethasone) for 7 days prior to baseline MRI and/or use of non-enzyme inducing anti-epileptic drugs are allowed.;Or-;Patients with pathologically confirmed diagnosis of advanced SCLC with newly diagnosed, untreated, brain metastases and controlled extracranial disease, which per the multi-disciplinary team decision do not require immediate radiotherapy, surgery, or standard systemic chemotherapy.;Melanoma brain metastases study arm of the expansion phase:
Patients with pathologically confirmed diagnosis of advanced, recurrent melanoma with at least one progressive and/or new metastatic brain lesion, that are refractory to standard therapy or for whom no standard therapy exist. Stable or decreasing dosages of steroids (e.g. dexamethasone) for 7 days prior to baseline MRI and/or use of non-enzyme inducing anti-epileptic drugs are allowed.;Or -;Patients with pathologically confirmed diagnosis of advanced melanoma with newly diagnosed, untreated, brain metastases and controlled extracranial disease, which per the multi-disciplinary team decision do not require immediate radiotherapy, surgery, or standard systemic chemotherapy.;Recurrent malignant glioma study arm of the expansion phase: ;Patients with histologically proven glioma grade IV, which is progressive following first line treatment with surgery or biopsy followed by fractionated

radiotherapy with concurrent temozolomide-containing chemotherapy.;Or;Patients with recurrent histologically confirmed malignant (WHO grade III and IV) glioma or histologically confirmed low-grade (WHO grade II) glioma with radiographic evidence of malignant transformation by MRI, that are refractory to standard therapy, or for whom no standard therapy exists or do not require immediate standard therapy per the multi-disciplinary team decision. ;Patients in both groups should have stable or decreasing dosage of steroids (e.g. dexamethasone) for a minimum of 7 days prior to baseline MRI. Non-enzyme inducing anti-epileptic drugs are allowed

Exclusion criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist:;Prior Treatment:
1. Less than 1 week since the last treatment of lapatinib, dabrafenib, everolimus, capecitabine, anastrazole, letrozole and exemestane; less than 2 weeks since the last treatment of vemurafenib; less than 4 weeks since the last treatment of trametinib, chemotherapy , biological therapy, immunotherapy and systemic radiotherapy (except palliative radiation delivered to <20% of bone marrow), less than 6 weeks for nitrosoureas and mitomycin C and less than 8 weeks since the latest cranial radiotherapy. Previous trastuzumab treatment will be allowed to continue without interruption in patients that are included in either the 2B3-101 in combination with trastuzumab dose-escalation phase or in the breast cancer study-expansion phase once the MTD for the combination has been established.
2. Patients that have received a maximum cumulative dose of free (i.e., non-liposomal) or liposomal doxorubicin > 360mg/m2 or free epirubicin > 600mg/m2 ;Current Treatment:
3. Current or recent (within 30 days of first study treatment) treatment with another investigational drug or participation in another investigational study.;Hematology, coagulation and biochemistry:
4. Inadequate bone marrow function: Absolute Neutrophil Count (ANC): < 1.5 x 109/L, or platelet count < 100 x 109/L or hemoglobin < 6 mmol/L.
5. Inadequate liver function, defined as:
• Serum (total) bilirubin > 1.5 x the ULN for the institution if no liver metastases (> 2 x ULN in patients with liver metastases);
• ASAT or ALAT > 2.5 x ULN if no liver metastases (> 4 x ULN in patients with liver metastases);
• Alkaline phosphatase levels > 2.5 x ULN if no liver metastases (> 5 x ULN in patients with liver metastases, or > 10 x ULN in patients with bone metastases).
6. Inadequate renal function, defined as:
• Serum creatinine > 1.5 x ULN.;Other:
7. Leptomeningeal carcinomatosis as the only site of CNS involvement.
8. Pregnancy or lactation. Serum pregnancy test to be performed in female subjects of childbearing potential (defined as < 2 years after last menstruation and not surgically sterile) within 7 days prior to study treatment start, or within 14 days followed by a confirmatory urine pregnancy test within 7 days prior to study treatment start.
9. For female subjects of childbearing potential (defined as < 2 years after last menstruation

and not surgically sterile) and male subjects who are not surgically sterile or with partners of childbearing potential: absence of effective, non-hormonal means of contraception (intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal gel).
10. Major surgical procedure (including open biopsy, excluding central line IV and portacath) within 28 days prior to the first study treatment, or anticipation of the need for major surgery during the course of the study treatment.
11. Grade 3 or 4 motor, sensory, or cranial neuropathy symptoms (as defined by CTCAE version 4.0).
12. Uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100mm Hg).
13. Clinically significant (i.e. active) cardiovascular disease defined as:
• Stroke within <= 6 months prior to day 1;
• Transient Ischemic Attack (TIA) within <= 6 months prior to day 1;
• Myocardial infarction within <= 6 months prior to day 1;
• Unstable angina;
• New York Heart Association (NYHA) Grade II or greater Congestive Heart Failure (CHF);
• Serious cardiac arrhythmia requiring medication;
• Clinically relevant pathologic findings in ECG.
14. Left Ventricle Ejection Fraction (LVEF) by MUGA or ECHO < 55% for patients receiving 2B3-101 in combination with trastuzumab. ;For patients receiving single agent 2B3-101 treatment. Left Ventricle Ejection Fraction (LVEF) by MUGA or ECHO < 50%
15. Known hypersensitivity to any of the study drug components or excipients (e.g. doxorubicin, PEG or GSH).
16. Evidence of any other medical conditions (such as psychiatric illness, infectious diseases, physical examination or laboratory findings) that may interfere with the planned treatment, affect patient compliance or place the patient at high risk from treatment-related complications.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-08-2011

Enrollment:	45
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Herceptin
Generic name:	Trastuzumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	11-04-2011
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-06-2011
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	07-11-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-11-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	08-03-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	03-07-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	11-07-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	25-07-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	26-07-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	14-01-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	17-01-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	27-02-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-04-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-06-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-08-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-01-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-01-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-09-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-001119-30-NL
ClinicalTrials.gov	NCT01386580
CCMO	NL36053.031.11