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(54) Titre : NOUVELLE THERAPIE ET MEDICAMENT UTILISANT DES LIGANDS D'INTEGRINE POUR TRAITER UN
CANCER
(54) Title: NEW THERAPY AND MEDICAMENT USING INTEGRIN LIGANDS FOR TREATING CANCER

(57) **Abrégé/Abstract:**

The invention relates to a combination therapy for the treatment of tumors and tumor metastases comprising administration of integrin ligands, preferably integrin antagonists, together with co-therapeutic agents or therapy forms that have synergistic efficacy when administered consecutively with said ligands, such as chemotherapeutic agents and or radiation therapy. The therapy results in a synergistic potential increase of the inhibition effect of each individual therapeutic on tumor cell proliferation, yielding more effective treatment than found by administering an individual component alone, concurrently or not in the dosage regime of the present invention.




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1. (WO2010057596) NEW THERAPY AND MEDICAMENT USING INTEGRIN LIGANDS FOR TREATING CANCER

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Title (EN) NEW THERAPY AND MEDICAMENT USING INTEGRIN LIGANDS FOR TREATING CANCER (FR) NOUVELLE THÉRAPIE ET MÉDICAMENT UTILISANT DES LIGANDS D'INTÉGRINE POUR TRAITER UN CANCER					
Abstract: (EN) The invention relates to a combination therapy for the treatment of tumors and tumor metastases comprising administration of integrin ligands, preferably integrin antagonists, together with co-therapeutic agents or therapy forms that have synergistic efficacy when administered consecutively with said ligands, such as chemotherapeutic agents and or radiation therapy. The therapy results in a synergistic potential increase of the inhibition effect of each individual therapeutic on tumor cell proliferation, yielding more effective treatment than found by administering an individual component alone, concurrently or not in the dosage regime of the present invention. (FR) L'invention concerne une thérapie de combinaison, pour le traitement de tumeurs et de métastases de tumeur, qui comporte l'administration de ligands d'intégrine, de préférence d'antagonistes d'intégrine, conjointement avec des agents co-thérapeutiques ou des formes de thérapie qui ont une efficacité synergique lorsqu'elles sont administrées consécutivement auxdits ligands, tels que des agents chimiothérapeutiques et/ou une radiothérapie. La thérapie conduit à une augmentation du potentiel synergique de l'effet inhibiteur de chaque produit thérapeutique individuel sur la prolifération de cellules tumorales, permettant d'obtenir un traitement plus efficace que celui obtenu par l'administration d'un composant individuel seul, simultanément ou non dans le schéma de posologie de la présente invention.					
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New Therapy and Medicament Using Integrin Ligands for Treating Cancer

Technical Field of the Invention:

5 The invention relates to a specific therapy form for the treatment of tumors (or tumours) and tumor metastases comprising administration of integrin ligands together with cancer cotherapeutic agents or other cancer cotherapeutic therapy forms that have additive or synergistic efficacy when administered together with said integrin ligand, such as chemotherapeutic agents, immunotherapeutics, including antibodies, radioimmunoconjugates and immunocytokines and or radiation therapy, preferably in a timely controlled manner. The therapy will result in a synergistic potential increase of the inhibition effect of each individual therapeutic on tumor cell and tumor endothelial cell proliferation, yielding more effective treatment than found by administering an individual component alone, together or in another therapy regime but the regime of the present invention.

Background of the Invention:

Vascular endothelial cells are known to contain at least three RGD-dependent integrins, including the vitronectin receptors $\alpha_v\beta_3$ or $\alpha_v\beta_5$ as well as the collagen types I and IV receptors $\alpha_v\beta_1$ and $\alpha_2\beta_1$, the laminin receptors $\alpha_6\beta_1$ and $\alpha_3\beta_1$, and the fibronectin receptor $\alpha_5\beta_1$ (Davis *et al.*, 1993, J. Cell. Biochem. 51, 206). The smooth muscle cell is known to contain at least six RGD-dependent integrins, including $\alpha_v\beta_3$ and $\alpha_v\beta_5$.

25 Inhibition of cell adhesion in vitro using monoclonal antibodies immunospecific for various integrin α or β subunits have implicated the vitronectin receptor $\alpha_v\beta_3$ in cell adhesion processes of a variety of cell types including microvascular endothelial cells (Davis *et al.*, 1993, J. Cell. Biol. 51, 206).

30 Integrins are a class of cellular receptors known to bind extracellular matrix proteins, and mediate cell-extracellular matrix and cell-cell interactions, referred generally to as cell adhesion events. The integrin receptors

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constitute a family of proteins with shared structural characteristics of non-covalently associated heterodimeric glycoprotein complexes formed of α and β subunits. The vitronectin receptor, named for its original characteristic of preferential binding to vitronectin, is now known to refer to four different integrins, designated $\alpha_v\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_5$ and $\alpha_v\beta_8$. $\alpha_v\beta_1$ binds fibronectin and vitronectin. $\alpha_v\beta_3$ binds a large variety of ligands, including fibrin, fibrinogen, laminin, thrombospondin, vitronectin and von Willebrand's factor. $\alpha_v\beta_5$ binds vitronectin. It is clear that there are different integrins with different biological functions as well as different integrins and subunits having shared biological specificity and function. One important recognition site in a ligand for many integrins is the Arg-Gly-Asp (RGD) tripeptide sequence. RGD is found in all of the ligands identified above for the vitronectin receptor integrins. The molecular basis of RGD recognition by $\alpha_v\beta_3$ has been identified (Xiong *et al.*, 2001) This RGD recognition site can be mimicked by linear and cyclic (poly)peptides that contain the RGD sequence. Such RGD peptides are known to be inhibitors or antagonists, respectively, of integrin function. It is important to note, however, that depending upon the sequence and structure of the RGD peptide, the specificity of the inhibition can be altered to target specific integrins. Various RGD polypeptides of varying integrin specificity have been described, for example, by Cheresh, *et al.*, 1989, Cell 58, 945, Aumailley *et al.*, 1991, FEBS Letts. 291, 50, and in numerous patent applications and patents (e.g. US patents 4,517,686, 4,578,079, 4,589,881, 4,614,517, 4,661,111, 4,792,525; EP 0770 622).

The generation of new blood vessels, or angiogenesis, plays a key role in the growth of malignant disease and this has generated much interest in developing agents that inhibit angiogenesis.

Nevertheless, although various combination therapies utilizing potential angiogenesis inhibitors are under investigation, in clinical trials and on the market, the outcome of these therapies are not fruitful enough. Therefore, there still exists a need in the art to develop further combinations which can show increased efficacy and reduced side-effects.

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It is known today that tumor vasculature is different from vasculature of healthy tissue. The vasculature is characteristic for the tumor and distinct from the stable, dormant vasculature of healthy tissue. It is often characterized by an increased expression and priming of specific cell adhesion molecules of the alpha-v-integrin series, especially $\alpha_v\beta_3$ and $\alpha_v\beta_5$. When activated these integrins enhance the cellular response to growth factors that drive angiogenesis, for example VEGFA and FGF2: VEGFA was originally termed vascular permeability factor, and it acts via the SRC kinase pathway to increase local vascular permeability. VEGFR2, when activated, increases the activity of $\alpha_v\beta_3$ integrin.

Further, solid tumors depend on an induced and cooped vasculature from the host to develop. This vasculature has unusual molecular properties that distinguish it from the normal host vasculature: it tends to be activated, i.e. progressing through cell cycle under the influence of tumor-derived factors like VEGFs, FGFs and others, and expresses endothelial activation markers like ICAM, VCAM and alpha-v-series Integrins, e.g. $\alpha_v\beta_3$ and $\alpha_v\beta_5$, in a ligand competent state. It has a defective extracellular matrix, and is classically described as leaky. It is notable that tumors often resist therapies systemically applied via the blood stream, due to abnormal nature of tumor vasculature.

The metastatic process is a multistep event and represents the most dreadful aspect of cancer. At the moment of diagnosis, cancers are frequently far advanced in their natural history, and the presence of metastases is a common event. In fact, approximately 30% of patients have detectable metastases at the moment of clinical diagnosis and a further 30% of patients have occult metastases. Metastases can be disseminated and they can infest different organs at the same time, or localize to a specific organ. In the case of localized disease, surgery is the treatment of choice; however recurrence and prognosis depend on many criteria such as: resectability, patient's clinical situation, and number of metastases.

After resection, recurrence is common, suggesting that micrometastatic foci are present at the moment of diagnosis. Systemic chemotherapy is an ideal

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setting but only few patients are cured by it, and in the majority systemic chemotherapy fails. Many physiological barriers and pharmacokinetic parameters contribute to decrease its efficacy.

5 Liver, lungs and lymph nodes are filtration organs and therefore inclined to metastasization. The poor chemosensitivity of metastases, peculiarly those of colorectal origin has forced many researchers to use methods for increasing the time and the concentration of drugs. The need for decreasing or limiting the side effects for this important and delicate organ led to the development
10 of the technique of liver isolation for perfusion of antineoplastic agents. (K. R. Aigner, Isolated liver perfusion. In: Morris DL, McArdle CS, Onik GM, eds. Hepatic Metastases. Oxford: Butterworth Heinemann, 1996. 101-107). Since 1981, modifications and technical improvements have been continuously introduced. Liver metastases may be of different origin and their
15 chemosensitivity may vary according to the histological type and their response in presence of heat.

There still exists a growing need in the art in order to develop new therapeutic strategies for treating cancer, especially metastases systemically. The object of the present invention therefore was to develop such a new
20 strategy. It should be applicable to systemic treatment, and it should lower the dose and/or increase the efficiency of the cancer therapeutical agents to be applied. A further object was to normalize tumor vasculature to increase delivery of systemic therapeutics of tumor, i.e. to reset the tumor vasculature to the functionality of the vasculature of non-tumor tissue.

25 Thus, it is a preferred objective of the instant invention to provide a more effective, better tolerated treatment for cancer patients leading to enhanced progression-free survival (PFS), QOL and/or increased median survival.

30 **Brief description of drawings:**

Fig. 1 shows the results from the rat orthotopic glioblastoma model radiotherapy, cilengitide scheduling experiments. The results are also shown in Table 1.

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Fig. 2 shows the results of a clinical study in glioblastoma (GBM). The results are also shown in Example 3.

5 **Summary of the Invention:**

The present inventions describes for the first time a novel pharmaceutical treatment which is based on the new concept in tumor therapy to administer to an individual in a therapeutically effective amount an integrin ligand prior to the application of a cancer cotherapeutic agent.

10 It was surprisingly found that the tumor vasculature can be functionally normalized by systemically applied integrin ligands as defined below. Such inhibitors of integrin functions, also referred to as integrin ligands in the context of the present invention, increase the amount of cytotoxics and other cancer cotherapeutic agents entering the tumor. In addition, they have been
15 shown to enhance the numbers of leukocytes entering the tumor following systemic immunocytokines therapy, and may directly increase the amounts of antibodies entering the tumor compartment on anti-tumor antibody therapy, or increase access to anti-tumor vaccines.

Although not known today, the possibility exists that this functional
20 normalization of the tumor vasculature may lead to a higher oxygen concentration in the tumor, and allow oxygen dependent therapies like external beam radiotherapy to become more effective.

The "functional normalizing agent" of the present invention is defined here empirically as a reagent targeting alpha-v-integrins within the tumor
25 compartment, that increase the levels of systemic tumor therapeutics or of specific bio-indicators of a systemic therapy within the tumor. The increased local therapeutic overcomes tumor resistance mechanisms, and enhances therapeutic index. For example, the systemic therapeutic might be a classical chemotherapeutic reagent, an immunocytokines, a immunotoxin, or a
30 radioimmunotherapy etc. etc.

In one aspect the present invention relates to a composition comprising as the cotherapeutic agent therapeutically active compounds, preferably selected from the group consisting of cytotoxic agents, chemotherapeutic

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agents and immunotoxic agents, and as the case may be other pharmacologically active compounds which may enhance the efficacy of said agents or reduce the side effects of said agents.

5 Thus, in the same embodiment the present invention relates to pharmaceutical compositions comprising an integrin ligand, preferably any of the $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$ and/or $\alpha_v\beta_8$ integrin receptor ligands, preferably an $\alpha_v\beta_3$, and $\alpha_v\beta_5$ integrin receptor ligand, more preferably an RGD-containing linear or cyclic peptide, even more preferably RGD-containing integrin inhibitors,
10 most preferably the cyclic peptide cyclo-(Arg-Gly-Asp-DPhe-NMe-Val). According to the present invention therapeutically active compositions may also be provided by means of a pharmaceutical kit comprising a package comprising one or more of the said integrin ligands, and one or more cytotoxic and/or chemotherapeutic and/or immunotoxic agents in single
15 packages or in separate containers. The therapy with these combinations may include optionally treatment with radiation with or without a further cotherapeutic agent as defined above.

The invention relates furthermore to a new therapy form comprising the administration of an integrin ligand prior to radiotherapy.

20 In this new therapy form comprising the administration of an integrin ligand prior to radiotherapy, it is a preferred feature that the integrin ligand is administered prior to the further cancer cotherapeutic agent. In this context, according to the present invention, radiation, or, radiotherapy has to be understood as a cancer cotherapeutic agent.

25 Generally, this prior application takes place 1 to 8 hours (h), preferably 1 to 5 h, and more preferably 1 to 3 h before the application of the further cancer cotherapeutic agent. Even more preferably, this prior application takes place 2 to 8 hours (h), preferably 2 to 6 h, and more preferably 2 to 4 h before the
30 application of the further cancer cotherapeutic agent, such as 1 to 2 h, 2 to 3 h, 3 to 6 h, 2 to 5 h or 3 to 7 h before the application of the further cancer therapeutic agent. With respect to the invention, this prior application or

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administration is also referred to as "timed administration" or "timed application".

5 As is shown by the data contained in this application, the effect according to the invention is achieved in non-human animals, especially rats, if this prior application preferably takes place 1 to 8 hours (h), preferably 1 to 5 h, and more preferably 1 to 3 h before the application of the further cancer cotherapeutic agent; and even more preferably this prior application takes
10 place 2 to 8 hours (h), preferably 2 to 6 h, and more preferably 2 to 4 h before the application of the further cancer cotherapeutic agent, such as 1 to 2 h, 2 to 3 h, 3 to 6 h, 2 to 5 h or 3 to 7 h before the application of the further cancer therapeutic agent. With respect to the invention, this prior application or administration is also referred to as "timed administration" or "timed
15 application"

However, the data from experiments with human animals preferably shows that the time of the above/below described and discussed "prior application" can be delayed or multiplied by the factor 1 to 4 and especially 2 to 4. This
20 difference in the response or response time between non-human animals, especially rodents, such as rats, and human animals is known and extensively discussed in the art. While the applicant wishes not to be bound by this theory, he believes that this difference is at least in part caused by the different pharmacokinetic behavior of the different species, which i. a. reflects
25 in different halflives ($t_{1/2}$) in the different kinds of animals. For example, for compounds such as cyclopeptides, the halflives in rats usually are in the range of 10-30 minutes, whereas the halflives in human animals for the same compounds are within 2 to 6 hours and especially 3 to 4 hours.

30 Accordingly, a subject of this application is a method of treatment and/or a method of manufacture as described above/below, wherein the prior application preferably takes place 1 to 32 hours (h), preferably 2 to 32 h, more preferably 2 to 24 h, even more preferably 4 to 24 h, even more

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- preferably 6 to 20 h and especially 6 to 16 h, before the application of the further cancer cotherapeutic agent; or alternatively preferably this prior application takes place 6 to 32 hours (h), preferably 10 to 24 h, and more preferably 12 to 20 h before the application of the further cancer cotherapeutic agent. With respect to the invention, this prior application or administration is also referred to as "timed administration" or "timed application"
- 10 A further subject of this application is a method of treatment and/or a method of manufacture as described above/below, wherein the prior application preferably takes place 18 to 23 h hours (h), preferably 20 to 23 h, more preferably 20 to 22 h before the application of the further cancer cotherapeutic agent; or alternatively preferably this prior application takes
- 15 place 25 to 32 h hours (h), preferably 25 to 30 h, and more preferably 26 to 30 h before the application of the further cancer cotherapeutic agent. With respect to the invention, this prior application or administration is also referred to as "timed administration" or "timed application"
- 20 However, in a more preferred aspect of the instant invention, the timed administration (regardless of whether the patient is a human or nonhuman animal) of the specific integrin ligand takes place 1 to 10 hours (h), preferably 2 to 8 h, more preferably 2 to 6 h, even more preferably 3 to 8 h, even more preferably 3 to 6 h and especially 4 to 8 h prior to the application of the one
- 25 or more cancer cotherapeutic agents, e.g. 1 to 2 h, 1 to 3 h, 1 to 4 h, 2 to 3 h, 2 to 4 h, 2 to 6 h, 2 to 8 h, 2 to 10 h, 3 to 4 h, 3 to 10 h, 4 to 6 h, 4 to 10 h, 5 to 8 or 5 to 10 h. This is especially preferred if the one or more cancer cotherapeutic agents comprise external beam radiation or consist of external beam radiation. With respect to the invention, this prior application or
- 30 administration is also referred to as "timed administration" or "timed application".

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With respect to said timed administration or timed application (of the specific integrin ligand), the hours given for said prior administration or application preferably refer to the beginning or start of the respective administration or application. Accordingly, for example, an administration of the specific integrin ligand starting three hours before the application of the respective cancer cotherapeutic agent is to be regarded as a timed administration or timed application 3 h prior to the application of the one or more cancer cotherapeutic agents according to the invention, even if the specific integrin ligand is administered by i. v. Infusion that takes an hour or two hours to be completed. This definition of prior application/prior administration is in perfect concordance with the understanding of the ones skilled in the art.

If the at least one specific integrin ligand is administered to the patient in a timed administration as described herein, it is preferably timed with respect to the one or more cancer cotherapeutic agents it is combined with. With respect to the timed administration of the specific integrin ligand in combination with two or more cancer cotherapeutic agents, it is preferably timed with respect to the two or more cancer cotherapeutic agents, more preferably timed with respect to at least one of the cancer cotherapeutic agents. If the one or more cancer cotherapeutic agents comprise radiotherapy, especially radiotherapy as described herein, the timed administration preferably refers at least to the radiotherapy.

Especially preferably, the timed administration of the specific integrin ligand refers to radiotherapy as the time-relevant cancer cotherapeutic. Accordingly, in the timed administration, the prior administration of the specific integrin ligand preferably refers to a time prior to the administration of radiotherapy. However, in many cases, it can be advantageous also to administer the one or more further cancer cotherapeutic agents other than radiotherapy within the time window given by the timed administration of the specific integrin ligand and the administration or delivery of the radiotherapy.

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Regarding the timed administration of at least one specific integrin ligand, preferably a specific integrin ligand selected from the group consisting of cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable
5 dervatives, solvates and/or salts thereof, and the cancer cotherapeutic agents temozolomide and radiotherapy, the timed administration of the at least one specific integrin ligand preferably refers to the administration or delivery of the radiotherapy, and more preferably to the administration or delivery of radiotherapy and the administration of the temozolomide.

10

More preferably, the timed administration of the specific integrin ligand refers to the administration of the specific integrin ligand and the radiotherapy, and the additional cancer cotherapeutic agent, for example temozolomide, is preferably administered after the administration of the specific integrin ligand,
15 such as 1 to 2 or 1 to 3 hours after the administration of this specific integrin ligand, but preferably before the administration or delivery of the radiotherapy, preferably at least within one hour before the administration or delivery of the radiotherapy, and more preferably at least 1 hour before radiotherapy, for example 1 to 2 or 1 to 3 h prior to the administration or
20 delivery of the radiotherapy.

If two or more specific integrin ligands are administered in a timed administration as described herein, the timed administration preferably refers at least to one of the specific integrin ligands and more preferably to
25 the two or more specific integrin ligands to be administered in the timed administration as described herein.

It should be understood that the administration of any combination of the present invention can optionally be accompanied by radiation therapy,
30 wherein radiation treatment can preferably be done after the administration of the integrin ligand. The administration of the different agents of the combination therapy according to the invention can optionally also be achieved substantially concurrently or sequentially.

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It is known that tumors elicit alternative routes for their development and growth. If one route is blocked they often have the capability to switch to another route by expressing and using other receptors and signaling pathways. Therefore, the pharmaceutical combinations of the present invention may block several of such possible development strategies of the tumor and provide consequently various therapeutic benefits. The combinations according to the present invention are useful in treating and preventing tumors, tumor-like and neoplasia disorders and tumor metastases, which develop and grow by activation of their relevant hormone receptors which are present on the surface of the tumor cells.

Preferably, the different combined agents of the present invention are administered at a low dose, that is, at a dose lower than has been conventionally used in clinical situations. A benefit of lowering the dose of the compounds, compositions, agents and therapies of the present invention administered to an individual includes a decrease in the incidence of adverse effects associated with higher dosages. For example, by the lowering the dosage of an agent described above and below, a reduction in the frequency and the severity of nausea and vomiting will result when compared to that observed at higher dosages. By lowering the incidence of adverse effects, an improvement in the quality of life of a cancer patient is expected. Further benefits of lowering the incidence of adverse effects include an improvement in patient compliance, a reduction in the number of hospitalizations needed for the treatment of adverse effects, and a reduction in the administration of analgesic agents needed to treat pain associated with the adverse effects. Alternatively, the methods and combination of the present invention can also maximize the therapeutic effect at normal or higher doses. Preferably, the methods and combinations of the present invention can also maximize the therapeutic effect at normal or even lower doses, preferably due to the synergistic effects of the methods and combinations of the present invention.

Tumors, preferably showing an increased expression and priming of specific cell adhesion molecules of the alpha-v-integrin series, especially $\alpha_v\beta_3$

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and $\alpha_v\beta_5$ in their vasculature may be successfully treated by the combinations and therapeutic regimen according to the invention. The combinations within the pharmaceutical treatment according to the invention
5 show an astonishing synergetic effect. In administering the combination of drugs real tumor shrinking and disintegration could be observed during clinical studies while no significant adverse drug reactions were detectable. Preferred aspects of the present invention relate to:

A method for the production of a medicament for the timed and combined
10 use as a combination therapy for the treatment of cancer, the medicament comprising, preferably in two distinct (discrete) application forms,
a) a composition containing at least one specific integrin ligand, and
b) at least one further cancer-cotherapeutic agent different from the at least one specific integrin ligand of a),

15 wherein a) is administered 1 to 8 hours (h), preferably 1 to 5 h, and most preferably 1 to 3 h prior to the application of b).

A preferred method for the production of a medicament for the timed and combined use as a combination therapy for the treatment of cancer, the medicament comprising, preferably in two distinct (discrete) application
20 forms,
c) a composition containing at least one specific integrin ligand, and
d) at least one further cancer-cotherapeutic agent different from the at least one specific integrin ligand of a),

25 wherein a) is administered 1 to 8 hours (h), preferably 2 to 6 h, and most preferably 2 to 4 h prior to the application of b).

Another preferred method for the production of a medicament for the timed and combined use as a combination therapy for the treatment of cancer, the medicament comprising, preferably in two distinct (discrete) application
forms,

30 a) a composition containing at least one specific integrin ligand, and
b) at least one further cancer-cotherapeutic agent different from the at least one specific integrin ligand of a),

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wherein a) is administered 2 to 8 hours (h), preferably 3 to 6 h, and most preferably 3 to 4 h prior to the application of b).

5 A said medicament wherein the at least one integrin ligand is selected from the group consisting of α_v integrin inhibitors, preferably $\alpha_v\beta_3$ inhibitors, most preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal).

A said medicament wherein the at least one cancer-cotherapeutic agent is selected from the group consisting of chemotherapeutical agents, cytotoxic agents, immunotoxic agents and radiotherapy.

10 A preferred said medicament wherein the at least one cancer-cotherapeutic agent is selected from the group consisting of chemotherapeutical agents, cytotoxic agents and immunotoxic agents.

Another preferred said medicament wherein the at least one further cancer-cotherapeutic agent different from the at least one specific integrin ligand of
15 a) is radiotherapy.

A method for the treatment of cancer characterized in treating a subject in need thereof with a therapeutically effective amount of at least one integrin ligand a) and at least one cancer-cotherapeutic agent b) wherein a) is administered 1 to 8 hours (h), preferably 1 to 5 h, and most preferably 1 to 3
20 h prior to the application of b).

A preferred method for the treatment of cancer characterized in treating a subject in need thereof with a therapeutically effective amount of at least one integrin ligand a) and at least one cancer-cotherapeutic agent b) wherein a) is administered 2 to 8 hours (h), preferably 2 to 5 h, and most preferably 2 to
25 4 h prior to the application of b).

Another preferred method for the treatment of cancer characterized in treating a subject in need thereof with a therapeutically effective amount of at least one integrin ligand a) and at least one cancer-cotherapeutic agent b) wherein a) is administered 3 to 8 hours (h), preferably 3 to 5 h, and most
30 preferably 3 to 4 h prior to the application of b).

Another preferred method for the treatment of cancer characterized in treating a subject in need thereof with a therapeutically effective amount of at least one integrin ligand a) and at least one cancer-cotherapeutic agent b)

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wherein a) is administered 4 to 8 hours (h), preferably 4 to 7 h, and most preferably 4 to 6 h prior to the application of b).

5 A said method wherein the at least one integrin ligand is selected from the group consisting of α_v integrin inhibitors, preferably $\alpha_v\beta_3$ inhibitors, most preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal).

A said method wherein the at least one cancer-cotherapeutic agent is selected from the group consisting of chemotherapeutical agents, cytotoxic agents, immunotoxic agents and radiotherapy.

10 A set for the treatment of cancer comprising independent dosage forms of:
a) a therapeutically effective amount of at least one integrin ligand preferably being selected from the group consisting of α_v integrin inhibitors, preferably $\alpha_v\beta_3$ inhibitors, most preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), and
15 b) a therapeutically effective amount of at least one further cancer-cotherapeutic agent different from the integrin ligand of a), selected from the group consisting of chemotherapeutical agents, cytotoxic agents, immunotoxic agents,

20 wherein a) is administered 1 to 8 hours (h), preferably 1 to 5 h, and most preferably 1 to 3 h prior to the application of b).

A set for the treatment of cancer comprising independent dosage forms of:
a) a therapeutically effective amount of at least one integrin ligand preferably being selected from the group consisting of α_v integrin inhibitors, preferably $\alpha_v\beta_3$ inhibitors, most preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), and
25 b) a therapeutically effective amount of at least one further cancer-cotherapeutic agent different from the integrin ligand of a), selected from the group consisting of chemotherapeutical agents, cytotoxic agents, immunotoxic agents,

30 wherein a) is administered 2 to 8 hours (h), preferably 2 to 5 h, and most preferably 2 to 4 h prior to the application of b).

A set for the treatment of cancer comprising independent dosage forms of:

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- 5 a) a therapeutically effective amount of at least one integrin ligand preferably being selected from the group consisting of α_v integrin inhibitors, preferably $\alpha_v\beta_3$ inhibitors, most preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), and
- b) a therapeutically effective amount of at least one further cancer-cotherapeutic agent different from the integrin ligand of a), selected from the group consisting of chemotherapeutical agents, cytotoxic agents, immunotoxic agents,
- 10 wherein a) is administered 3 to 8 hours (h), preferably 3 to 5 h, and most preferably 3 to 4 h prior to the application of b).

A set for the treatment of cancer comprising independent dosage forms of:

- 15 a) a therapeutically effective amount of at least one integrin ligand preferably being selected from the group consisting of α_v integrin inhibitors, preferably $\alpha_v\beta_3$ inhibitors, most preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), and
- b) a therapeutically effective amount of at least one further cancer-cotherapeutic agent different from the integrin ligand of a), selected from the group consisting of chemotherapeutical agents, cytotoxic agents, immunotoxic agents,
- 20 wherein a) is administered 4 to 8 hours (h), preferably 4 to 7 h, and most preferably 4 to 6 h prior to the application of b).

Said set is further characterized in that it will be advantageous to give detailed instructions to and how to use the cancer cotherapeutic agent, e.g. radiotherapy, in connection with the integrin ligand in form of a specific packaging, specific package inserts and similar.

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Therefore, a further preferred aspect of the present invention is a medicament consisting of an integrin ligand as one active ingredient, designed to be applied prior to a further cancer cotherapeutic agent, e.g. radiotherapy, and contained in a container or similar, the container giving in form of writing detailed instructions and/or other technical information on how to use said medicament in combination with radiotherapy, e.g. with respect to the above application schedule.

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A further preferred aspect of the present invention is the use of at least one integrin ligand a) and at least one cancer-cotherapeutic agent b) for the preparation of a medicament for the treatment of cancer, the at least one
5 integrin ligand preferably being selected from the group consisting of α_v integrin inhibitors, preferably $\alpha_v\beta_3$ inhibitors, most preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and the cancer-cotherapeutic agent b) being selected from the group consisting of chemotherapeutical agents, cytotoxic agents and/or immunotoxic agents, wherein a) is administered 1 to 8 hours (h),
10 preferably 1 to 5 h, and most preferably 1 to 3 h prior to the application of b), and a) and b) are provided and/or formulated in(to) discrete application forms.

A said use wherein the organ is liver and the cancer is hepatocellular carcinoma.

15 A preferred aspect of the present invention thus relates to a corresponding pharmaceutical composition, wherein the said integrin ligand is an $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$ or $\alpha_v\beta_8$ integrin inhibitor; a corresponding pharmaceutical composition, wherein said integrin inhibitor is an RGD-containing linear or cyclic peptide; and, as a specific and very preferred aspect, a said pharmaceutical
20 composition, wherein said integrin ligand is cyclo(Arg-Gly-Asp-DPhe-NMeVal), optionally in separate containers or packages, a chemotherapeutic agent selected from any of the compounds of the group: cisplatin, doxorubicin, gemcitabine, temozolomide, docetaxel, paclitaxel, bleomycin; and a corresponding pharmaceutical composition, optionally in separate
25 containers or packages, wherein said integrin inhibitor is an antibody or a functionally intact derivative thereof, comprising a binding site which binds to an epitope of an integrin receptor, preferably selected from the group of antibodies or their bi- or monovalent derivatives (Fab'2)-(Fab'): LM609, Vitaxin, Abegrin, Abciximab (7E3), P1F6, 14D9.F8, CNTO95, humanized,
30 chimeric and de-immunized versions thereof included.

In another aspect of the present invention the chemotherapeutic agent can be melphalan or $\text{TNF}\alpha$, preferably applied in combination.

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It should be understood that all cancer cotherapeutic agents independent from their nature may be used in combination. E.g. one may use cisplatin, doxorubicin, gemcitabine, temozolomide, docetaxel, paclitaxel, bleomycin together with $\text{TNF}\alpha$.

A preferred aspect of the present invention relates to a package for use in cancer therapy comprising at least one integrin ligand, preferably an $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$ or $\alpha_v\beta_8$ integrin receptor inhibiting agent, more preferably an RGD-containing linear or cyclic peptide, especially cyclo(Arg-Gly-Asp-DPhe-NMeVal); optionally further comprising a package comprising a cytotoxic agent.

A further preferred aspect of the present invention relates to a corresponding pharmaceutical kit, wherein said integrin ligand is an antibody or an active derivative thereof, preferably selected from the group of antibodies: LM609, P1F6, and 14D9.F8 as well as Vitaxin, Abegrin, CNTO95, Abciximab.

A preferred aspect of the present invention relates to a specific aspect of the invention, a specific pharmaceutical kit, comprising

(i) a package comprising cyclo(Arg-Gly-Asp-DPhe-NMeVal),

(ii) a package comprising at least one chemotherapeutic agent which is selected from any of the compounds of the group: cisplatin, doxorubicin, gemcitabine, temozolomide, docetaxel, paclitaxel, bleomycin and 5FU, optionally in combination with $\text{TNF}\alpha$, for the treatment of cancer via the application schedule of the present invention.

In a further preferred aspect the kit comprises melphalan and/or $\text{TNF}\alpha$ as cancer cotherapeutic agents.

A further preferred aspect of the present invention relates the use of a pharmaceutical composition or a pharmaceutical kit as defined above, below and in the claims, for the manufacture of a medicament to treat tumors and tumor metastases wherein the integrin ligand a) is administered 1 to 8 hours (h), preferably 1 to 5 h, and most preferably 1 to 3 h prior to the application of the cancer cotherapeutic agent b).

Another further preferred embodiment of the present invention relates the use of a pharmaceutical composition or a pharmaceutical kit as defined

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above, below and in the claims, for the manufacture of a medicament to treat tumors and tumor metastases wherein the integrin ligand a) is administered 2 to 8 hours (h), preferably 2 to 6 h, and most preferably 2 to 4 h prior to the application of the cancer cotherapeutic agent b).

A further preferred aspect of the present invention relates to a pharmaceutical treatment or method for treating tumors or tumor metastases in a patient, the treatment or method comprising administering to said patient a therapeutically effective amount of an agent or agents having

(i) integrin ligand specificity, and

(ii) a cancer cotherapeutic agent

wherein a) is administered 1 to 8 hours (h), preferably 1 to 5 h, and most preferably 1 to 3 h prior to the application of b).

Another further preferred aspect of the present invention relates to a pharmaceutical treatment or method for treating tumors or tumor metastases in a patient, the treatment or method comprising administering to said patient a therapeutically effective amount of an agent or agents having

(i) integrin ligand specificity, and

(ii) a cancer cotherapeutic agent

wherein a) is administered 2 to 8 hours (h), preferably 2 to 6 h, and most preferably 2 to 4 h prior to the application of b).

The cancer cotherapeutic agent optionally is a cytotoxic, preferably chemotherapeutic agent, and said agent (i) is a $\alpha_v\beta_3$, $\alpha_v\beta_5$ or an $\alpha_v\beta_6$ integrin inhibitor or a VEGF receptor blocking agent.

A further preferred aspect of the present invention relates to a corresponding method, wherein said integrin ligand is cyclo(Arg-Gly-Asp-DPhe-NMeVal), and is optionally administered together with a cytotoxic drug selected from the group: cisplatin, doxorubicin, gemcitabine, temozolomide, docetaxel, paclitaxel, bleomycin.

The pharmaceutical treatment using the pharmaceutical compositions and kits according to the invention may be accompanied, concurrently or sequentially, by a radiation therapy.

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The radiation therapy may be the sole cotherapeutic agent to be applied together with the integrin ligand.

5 The pharmaceutical combinations and methods of the present invention provide various benefits. The combinations according to the present invention are useful in treating and preventing tumors, tumor-like and neoplasia disorders. Preferably, the different combined agents of the present invention are administered in combination at a low dose, that is, at a dose lower than has been conventionally used in clinical situations. A benefit
10 of lowering the dose of the compounds, compositions, agents and therapies of the present invention administered to a mammal includes a decrease in the incidence of adverse effects associated with higher dosages. For example, by the lowering the dosage of a chemotherapeutic agent such as methotrexate, doxorubicin, gemcitabine, temozolomide, docetaxel, paclitaxel,
15 bleomycin, cisplatin and/or Melphalan, a reduction in the frequency and the severity of nausea and vomiting will result when compared to that observed at higher dosages. Similar benefits are contemplated for the compounds, compositions, agents and therapies in combination with the integrin antagonists of the present invention. By lowering the incidence of
20 adverse effects, an improvement in the quality of life of a cancer patient is contemplated. Further benefits of lowering the incidence of adverse effects include an improvement in patient compliance, a reduction in the number of hospitalizations needed for the treatment of adverse effects, and a reduction in the administration of analgesic agents needed to treat pain associated with
25 the adverse effects.

Alternatively, the methods and combination of the present invention can also maximize the therapeutic effect at higher doses.

Detailed Description of the Invention

30 If not otherwise pointed out, the terms and phrases used in this invention preferably have the meanings and definitions as given below. Moreover, these definitions and meanings describe the invention in more detail, preferred embodiments and/or aspects included.

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If not otherwise pointed out, the reference to a compound to be used according to the invention preferably includes the reference to the pharmaceutically acceptable derivatives, solvates and salts thereof. If not otherwise pointed out, the reference to the integrin ligands, integrin antagonists, integrin agonists, as well as the reference to the cancer-cotherapeutic agents that are compounds, preferably includes the pharmaceutically acceptable derivatives, solvates and salts thereof. Even more preferably, the reference to the integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) also includes the pharmaceutically acceptable derivatives, solvates and salts thereof, more preferably the pharmaceutically solvates and salts thereof and especially preferably the pharmaceutically acceptable salts thereof, if not indicated otherwise.

By “**combination therapy**” is preferably meant a combination of at least two distinct therapy forms so combined as to form a single therapeutical concept in a timely controlled, consecutive manner.

In a preferred aspect of the present invention this preferably means the combination of an integrin ligand with a further cotherapeutic agent. It is important to note that “**combination therapy**” preferably does not mean a distinct and/or single pharmaceutical composition or medicament. By way of contrast, in a preferred aspect of the present invention the integrin ligand and the further cotherapeutic agent are provided in discrete containers, packages, medicaments, formulations or equivalents. Equally, the combination of integrin ligand therapy with radiation therapy preferably lies within the meaning of “**combination therapy**” of the present invention.

“**Therapy forms**” preferably are any means, uses and/or formulations for treating cancer known in the art. By the term “distinct therapy forms” therefore it is meant that two different means, uses and/or formulations for treating cancer are combined. In the context of the present invention it is preferred that the first to be applied **therapy form** has anti-integrin activity (synonym: integrin ligand), and is applied prior to the second **therapy form**, preferably following the schedule as detailed above.

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The term "**composition comprising radiotherapy**" preferably simply means that subsequent to the integrin ligand radiotherapy is applied. Therefore, the term "**composition comprising radiotherapy**" in the context of the present invention preferably does not apply to a pharmaceutical composition as such, but to a pharmaceutical composition to be used in combination with radiotherapy.

With "**cancer-cotherapeutic agent**" or "**cotherapeutic agent**" preferably a cytotoxic, chemotherapeutical or immunotoxic agent is meant. Equally preferred is radiotherapy.

A "**receptor**" or "**receptor molecule**" is preferably a soluble or membrane bound or membrane associated protein or glycoprotein comprising one or more domains to which a ligand binds to form a receptor-ligand complex. By binding the ligand, which may be an agonist or an antagonist the receptor is activated or inactivated and may initiate or block pathway signaling.

By "**ligand**" or "**receptor ligand**" is preferably meant a natural or synthetic compound which binds a receptor molecule to form a receptor-ligand complex. The term ligand includes agonists, antagonists, and compounds with partial agonist/antagonist activity.

An "**agonist**" or "**receptor agonist**" is preferably a natural or synthetic compound which binds the receptor to form a receptor-agonist complex by activating said receptor and receptor-agonist complex, respectively, initiating a pathway signaling and further biological processes.

By "**antagonist**" or "**receptor antagonist**" is preferably meant a natural or synthetic compound that has a biological effect opposite to that of an agonist. An antagonist binds the receptor and blocks the action of a receptor agonist by competing with the agonist for receptor. An antagonist is defined by its ability to block the actions of an agonist. A receptor antagonist may be also an antibody or an immunotherapeutically effective fragment thereof.

Preferred antagonists according to the present invention are cited and discussed below.

The term "**integrin antagonists / inhibitors**" or "**integrin receptor antagonists / inhibitors**" preferably refers to a natural or synthetic molecule,

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preferably a synthetic molecule, that blocks and inhibit an integrin receptor. In some cases, the term includes antagonists directed to the ligands of said integrin receptors (such as for $\alpha_v\beta_3$: vitronectin, fibrin, fibrinogen, von Willebrand's factor, thrombospondin, laminin; for $\alpha_v\beta_5$: vitronectin; for $\alpha_v\beta_1$: fibronectin and vitronectin; for $\alpha_v\beta_6$: fibronectin). Antagonists directed to the integrin receptors are preferred according to the invention. Integrin (receptor) antagonists may be natural or synthetic peptides, non-peptides, peptidomimetica, immunoglobulins, such as antibodies or functional fragments thereof, or immunoconjugates (fusion proteins). Preferred integrin inhibitors of the invention are directed to receptor of α_v integrins (e.g. $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$ and sub-classes). Preferred integrin inhibitors are α_v antagonists, and in particular $\alpha_v\beta_3$ antagonists. Preferred α_v antagonists according to the invention are RGD peptides, peptidomimetic (non-peptide) antagonists and anti-integrin receptor antibodies such as antibodies blocking α_v receptors.

Exemplary, non-immunological $\alpha_v\beta_3$ antagonists are described in the teachings of US 5,753,230 and US 5,766,591. Preferred antagonists are linear and cyclic RGD-containing peptides. Cyclic peptides are, as a rule, more stable and elicit an enhanced serum half-life. The most preferred integrin antagonist of the invention is, however, cyclo-(Arg-Gly-Asp-DPhe-NMeVal) (EMD 121974, Cilengitide[®], Merck KGaA, Germany; EP 0770 622) which is efficacious in blocking the integrin receptors $\alpha_v\beta_3$, $\alpha_v\beta_1$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_{IIb}\beta_3$, and preferably especially efficacious with respect to integrin receptors $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$. As is clear to the ones skilled in the art, the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) can be also applied in the context of the instant invention in the form of a physiologically functional derivative, physiologically acceptable derivative, a solvate and/or a salt thereof. The same preferably also applies to all other compounds or active ingredients to be used in the context of the present invention.

Suitable peptidyl as well as peptidomimetic (non-peptide) antagonists of the $\alpha_v\beta_3$ / $\alpha_v\beta_5$ / $\alpha_v\beta_6$ integrin receptor have been described both in the scientific

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and patent literature. For example, reference is made to Hoekstra and Poulter, 1998, Curr. Med. Chem. 5, 195; WO 95/32710; WO 95/37655; WO 97/01540; WO 97/37655; WO 97/45137; WO 97/41844; WO 98/08840; WO 98/18460; WO 98/18461; WO 98/25892; WO 98/31359; WO 98/30542; WO 99/15506; WO 99/15507; WO 99/31061; WO 00/06169; EP 0853 084; EP 0854 140; EP 0854 145; US 5,780,426; and US 6,048,861. Patents that disclose benzazepine, as well as related benzodiazepine and benzocycloheptene $\alpha_v\beta_3$ integrin receptor antagonists, which are also suitable for the use in this invention, include WO 96/00574, WO 96/00730, WO 96/06087, WO 96/26190, WO 97/24119, WO 97/24122, WO 97/24124, WO 98/15278, WO 99/05107, WO 99/06049, WO 99/15170, WO 99/15178, WO 97/34865, WO 97/01540, WO 98/30542, WO 99/11626, and WO 99/15508. Other integrin receptor antagonists featuring backbone conformational ring constraints have been described in WO 98/08840; WO 99/30709; WO 99/30713; WO 99/31099; WO 00/09503; US 5,919,792; US 5,925,655; US 5,981,546; and US 6,017,926. In US 6,048,861 and WO 00/72801 a series of nonanoic acid derivatives which are potent $\alpha_v\beta_3$ integrin receptor antagonists were disclosed. Other chemical small molecule integrin antagonists (mostly vitronectin antagonists) are described in WO 00/38665. Other $\alpha_v\beta_3$ receptor antagonists have been shown to be effective in inhibiting angiogenesis. For example, synthetic receptor antagonists such as (S)-10,11-Dihydro-3-[3-(pyridin-2-ylamino)-1-propyloxy]-5H-dibenzo[a,d]cycloheptene-10-acetic acid (known as SB-265123) have been tested in a variety of mammalian model systems. (Keenan *et al.*, 1998, Bioorg. Med. Chem. Lett. 8(22), 3171; Ward *et al.*, 1999, Drug Metab. Dispos. 27(11), 1232). Assays for the identification of integrin antagonists suitable for use as an antagonist are described, e.g. by Smith *et al.*, 1990, J. Biol. Chem. 265, 12267, and in the referenced patent literature. Anti-integrin receptor antibodies are also well known. Suitable anti-integrin (e.g. $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$) monoclonal antibodies can be modified to encompass antigen binding fragments thereof, including F(ab)₂, Fab, and engineered Fv or single-chain antibody. One suitable and preferably used monoclonal

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antibody directed against integrin receptor $\alpha_v\beta_3$ is identified as LM609 (Brooks *et al.*, 1994, Cell 79, 1157; ATCC HB 9537). A potent specific anti- $\alpha_v\beta_5$ antibody, P1F6, is disclosed in WO 97/45447, which is also preferred according to this invention. A further suitable $\alpha_v\beta_6$ selective antibody is MAb 14D9.F8 (WO 99/37683, DSM ACC2331, Merck KGaA, Germany) which is selectively directed to the α_v - chain of integrin receptors. Another suitable anti-integrin antibody is the commercialized Vitroxin®.

The term "**antibody**" or "**immunoglobulin**" herein is preferably used in the broadest sense and specifically covers intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies (e.g. bispecific antibodies) formed from at least two intact antibodies, and antibody fragments, so long as they exhibit the desired biological activity. The term generally includes heteroantibodies which are composed of two or more antibodies or fragments thereof of different binding specificity which are linked together.

Depending on the amino acid sequence of their constant regions, intact antibodies can be assigned to different "**antibody (immunoglobulin) classes**". There are five major classes of intact antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into "subclasses" (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA, and IgA2. The heavy-chain constant domains that correspond to the different classes of antibodies are called α , δ , ϵ , γ and μ respectively. Preferred major class for antibodies according to the invention is IgG, in more detail IgG1 and IgG2.

Antibodies are usually glycoproteins having a molecular weight of about 150,000, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies among the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intra-chain disulfide bridges. Each heavy chain has at one end a variable domain (VH) followed by a number of constant domains. The variable regions comprise hypervariable regions or "**CDR**" regions, which contain the antigen binding site and are responsible for the specificity of the antibody, and the "**FR**" regions, which are important with respect to the

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affinity / avidity of the antibody. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" (e.g. residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the light chain variable domain and 31-35 (H1), 50-65 (H2) and 95-102 (H3) in the heavy chain variable domain; and/or those residues from a "hypervariable loop" (e.g. residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the light chain variable domain and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the heavy chain variable domain; Chothia and Lesk *J. Mol. Biol.* 196:901-917 (1987)). The "**FR**" residues (frame work region) are those variable domain residues other than the hypervariable region residues as herein defined. Each light chain has a variable domain at one end (VL) and a constant domain at its other end. The constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light-chain variable domain is aligned with the variable domain of the heavy chain. Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The "light chains" of antibodies from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

The term "**monoclonal antibody**" as used herein preferably refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations which include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they may be synthesized uncontaminated by other antibodies. Methods for making monoclonal antibodies include the hybridoma method described by Kohler and Milstein (1975, *Nature* 256, 495) and in "Monoclonal Antibody Technology, The

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Production and Characterization of Rodent and Human Hybridomas" (1985, Burdon *et al.*, Eds, Laboratory Techniques in Biochemistry and Molecular Biology, Volume 13, Elsevier Science Publishers, Amsterdam), or may be made by well known recombinant DNA methods (see, e.g., US 4,816,567). Monoclonal antibodies may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.*, *Nature*, 352:624-628 (1991) and Marks *et al.*, *J. Mol. Biol.*, 222:58, 1-597(1991), for example. The term "**chimeric antibody**" preferably means antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (e.g.: US 4,816,567; Morrison *et al.*, *Proc. Nat. Acad. Sci., USA*, 81:6851-6855 (1984)). Methods for making chimeric and humanized antibodies are also known in the art. For example, methods for making chimeric antibodies include those described in patents by Boss (Celltech) and by Cabilly (Genentech) (US 4,816,397; US 4,816,567).

"**Humanized antibodies**" preferably are forms of non-human (e.g., rodent) chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region (CDRs) of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity and capacity. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized

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antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. Methods for making humanized antibodies are described, for example, by Winter (US 5,225,539) and Boss (Celltech, US 4,816,397).

5 **"Antibody fragments"** preferably comprise a portion of an intact antibody, preferably comprising the antigen-binding or variable region thereof. Examples of antibody fragments include Fab, Fab', F(ab')₂, Fv and Fc fragments, diabodies, linear antibodies, single-chain antibody molecules; and multispecific antibodies formed from antibody fragment(s). An "intact"

10 antibody is one which comprises an antigen-binding variable region as well as a light chain constant domain (CL) and heavy chain constant domains, CH1, CH2 and CH3. Preferably, the intact antibody has one or more effector functions. Papain digestion of antibodies produces two identical antigen-binding fragments, called **"Fab"** fragments, each comprising a single antigen-binding site and a CL and a CH1 region, and a residual **"Fc"** fragment, whose name reflects its ability to crystallize readily. The **"Fc"** region of the antibodies comprises, as a rule, a CH2, CH3 and the hinge region of an IgG1 or IgG2 antibody major class. The hinge region is a group of about 15 amino acid residues which combine the CH1 region with the CH2-CH3 region. Pepsin

15 treatment yields an **"F(ab')₂"** fragment that has two antigen-binding sites and is still capable of cross-linking antigen. **"Fv"** is the minimum antibody fragment which contains a complete antigen-recognition and antigen-binding site. This region consists of a dimer of one heavy chain and one light chain variable domain in tight, non-covalent association. It is in this

20 configuration that the three hypervariable regions (CDRs) of each variable domain interact to define an antigen-binding site on the surface of the VH - VL dimer. Collectively, the six hypervariable regions confer antigen-binding specificity to the antibody. However, even a single variable domain

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(or half of an Fv comprising only three hypervariable regions specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site. The **Fab** fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. " **Fab'** " fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known (see e.g. Hermanson, Bioconjugate Techniques, Academic Press, 1996; . US 4,342,566). "**Single-chain Fv**" or "**scFv**" antibody fragments preferably comprise the V_H and V_L domains of antibody, wherein these domains are present in a Single polypeptide chain. Preferably, the Fv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the scFv to form the desired structure for antigen binding. Single-chain FV antibodies are known, for example, from Plückthun (*The Pharmacology of Monoclonal Antibodies*, Vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994)), WO93/16185; US 5,571,894; US 5,587,458; Huston *et al.* (1988, Proc. Natl. Acad. Sci. 85, 5879) or Skerra and Plueckthun (1988, Science 240, 1038). "**Bispecific antibodies**" preferably are single, divalent antibodies (or immunotherapeutically effective fragments thereof) which have two differently specific antigen binding sites. For example the first antigen binding site is directed to an angiogenesis receptor (e.g. integrin or VEGF receptor), whereas the second antigen binding site is directed to an ErbB receptor (e.g. EGFR or Her 2). Bispecific antibodies can be produced by chemical techniques (see e.g., Kranz *et al.* (1981) Proc. Natl. Acad. Sci. USA 78, 5807), by "polydoma" techniques (See US 4,474,893) or by recombinant DNA techniques, which all are known per se. Further methods are described in WO 91/00360, WO 92/05793 and WO 96/04305. Bispecific antibodies can also be prepared from single chain antibodies (see e.g., Huston *et al.* (1988) Proc. Natl. Acad. Sci. 85, 5879; Skerra and Plueckthun (1988) Science 240,

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1038). These are analogues of antibody variable regions produced as a single polypeptide chain. To form the bispecific binding agent, the single chain antibodies may be coupled together chemically or by
5 genetic engineering methods known in the art. It is also possible to produce bispecific antibodies according to this invention by using leucine zipper sequences. The sequences employed are derived from the leucine zipper regions of the transcription factors Fos and Jun (Landschulz *et al.*, 1988, Science 240,1759; for review, see Maniatis and Abel, 1989, Nature 341, 24).
10 Leucine zippers are specific amino acid sequences about 20-40 residues long with leucine typically occurring at every seventh residue. Such zipper sequences form amphipathic α -helices, with the leucine residues lined up on the hydrophobic side for dimer formation. Peptides corresponding to the leucine zippers of the Fos and Jun proteins form heterodimers preferentially
15 (O'Shea *et al.*, 1989, Science 245, 646). Zipper containing bispecific antibodies and methods for making them are also disclosed in WO 92/10209 and WO 93/11162. A bispecific antibody according the invention may be an antibody, directed to VEGF receptor and $\alpha v\beta 3$ receptor as discussed above with respect to the antibodies having single specificity.
20 "**Heteroantibodies**" preferably are two or more antibodies or antibody-binding fragments which are linked together, each of them having a different binding specificity. Heteroantibodies can be prepared by conjugating together two or more antibodies or antibody fragments. Preferred heteroantibodies are comprised of cross-linked Fab/Fab' fragments. A variety of coupling or
25 crosslinking agents can be used to conjugate the antibodies. Examples are protein A, carboimide, N-succinimidyl-S-acetyl-thioacetate (SATA) and N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP) (see e.g., Karpovsky *et al.* (1984) J. EXP. Med. 160,1686; Liu *et al.* (1985) Proc. Natl. Acad. Sci. USA 82, 8648). Other methods include those described by Paulus, Behring Inst. Mitt., No. 78, 118 (1985); Brennan *et al.* (1985) Science 30 Method:81 or
30 Glennie *et al.* (1987) J. Immunol. 139, 2367. Another method uses o-phenylenedimaleimide (oPDM) for coupling three Fab' fragments (WO 91/03493). Multispecific antibodies are in context of this invention also

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suitable and can be prepared, for example according to the teaching of WO 94/13804 and WO 98/50431.

5 The term "**fusion protein**" preferably refers to a natural or synthetic molecule consisting of one or more proteins or peptides or fragments thereof having different specificity which are fused together optionally by a linker molecule. As specific embodiment the term includes fusion constructs, wherein at least one protein or peptide is an immunoglobulin or antibody, respectively or parts thereof ("immunoconjugates").

10 The term "**immunoconjugate**" preferably refers to an antibody or immunoglobulin respectively, or an immunologically effective fragment thereof, which is fused by covalent linkage to a non-immunologically effective molecule. Preferably this fusion partner is a peptide or a protein, which may be glycosylated. Said non-antibody molecule can be linked to the C-terminal
15 of the constant heavy chains of the antibody or to the N-terminals of the variable light and/or heavy chains. The fusion partners can be linked via a linker molecule, which is, as a rule, a 3 – 15 amino acid residues containing peptide. Immunoconjugates according to the invention consist of an immunoglobulin or immunotherapeutically effective fragment thereof, directed
20 to a receptor tyrosine kinase, preferably an ErbB (ErbB1/ErbB2) receptor and an integrin antagonistic peptide, or an angiogenic receptor, preferably an integrin or VEGF receptor and $\text{TNF}\alpha$ or a fusion protein consisting essentially of $\text{TNF}\alpha$ and $\text{IFN}\gamma$ or another suitable cytokine, which is linked with its N-terminal to the C-terminal of said immunoglobulin, preferably the Fc portion
25 thereof. The term includes also corresponding fusion constructs comprising bi- or multi-specific immunoglobulins (antibodies) or fragments thereof.

The term "**functionally intact derivative**" means according to the understanding of this invention preferably a fragment or portion, modification, variant, homologue or a de-immunized form (a modification, wherein
30 epitopes, which are responsible for immune responses, are removed) of a compound, peptide, protein, antibody (immunoglobulin), immunoconjugate, etc., that has principally the same biological and / or therapeutic function as compared with the original compound, peptide, protein, antibody

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(immunoglobulin), immunconjugate, etc. However, the term includes also such derivatives, which elicit a reduced or enhanced efficacy.

5 The term "**cytokine**" is preferably a generic term for proteins released by one cell population which act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; 10 relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor (VEGF); integrin; thrombopoietin (TPO); nerve growth factors such as NGF β ; platelet-growth factor; transforming growth factors (TGFs) such as TGF α and TGF β ; erythropoietin (EPO); interferons such as IFN α , IFN β , and IFN γ ; colony stimulating factors such as M-CSF, GM-CSF and G-CSF; interleukins such as IL-1, IL-1a, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12; and TNF α or TNF β . Preferred 15 cytokines according to the invention are interferons and TNF α .

The term "**cytotoxic agent**" as used herein preferably refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is preferably intended to include radioactive isotopes, 20 chemotherapeutic agents, and toxins such as enzymatically active toxins of bacterial, fungal, plant or animal origin, or fragments thereof. The term may include also members of the cytokine family, preferably IFN γ as well as anti-neoplastic agents having also cytotoxic activity.

25 The term "**chemotherapeutic agent**", "**chemotherapeutical agent**" or "**anti-neoplastic agent**" is regarded according to the understanding of this invention preferably as a member of the class of "cytotoxic agents", as 30 specified above, and includes chemical agents that exert anti-neoplastic effects, i.e., prevent the development, maturation, or spread of neoplastic cells, directly on the tumor cell, e.g., by cytostatic or cytotoxic effects, and not

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indirectly through mechanisms such as biological response modification. Suitable chemotherapeutic agents according to the invention are preferably natural or synthetic chemical compounds, but biological molecules, such as proteins, polypeptides etc. are not expressively excluded. There are large numbers of anti-neoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which could be included in the present invention for treatment of tumors / neoplasia by combination therapy with $\text{TNF}\alpha$ and the anti-angiogenic agents as cited above, optionally with other agents such as EGF receptor antagonists. It should be pointed out that the chemotherapeutic agents can be administered optionally together with above-said drug combination. Examples of chemotherapeutic or agents include alkylating agents, for example, nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action such as nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example, folic acid, purine or pyrimidine antagonists; mitotic inhibitors, for example, vinca alkaloids and derivatives of podophyllotoxin; cytotoxic antibiotics and camptothecin derivatives. Preferred chemotherapeutic agents or chemotherapy include amifostine (ethyol), cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), doxorubicin lipo (doxil), gemcitabine (gemzar), daunorubicin, daunorubicin lipo (daunoxome), procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil (5-FU), vinblastine, vincristine, bleomycin, paclitaxel (taxol), docetaxel (taxotere), aldesleukin, asparaginase, busulfan, carboplatin, cladribine, camptothecin, CPT-11, 10-hydroxy-7-ethyl-camptothecin (SN38), dacarbazine, floxuridine, fludarabine, hydroxyurea, ifosfamide, idarubicin, mesna, interferon alpha, interferon beta, irinotecan, mitoxantrone, topotecan, leuprolide, megestrol, melphalan, mercaptopurine, plicamycin, mitotane, pegaspargase, pentostatin, pipobroman, plicamycin, streptozocin, tamoxifen, teniposide, testolactone, thioguanine, thiotepa, uracil mustard, vinorelbine, chlorambucil and combinations thereof.

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Preferred chemotherapeutic agents according to the invention include cisplatin, gemcitabine, temozolomide, doxorubicin, paclitaxel (taxol) and bleomycin.

- 5 The term “**immunotoxic**” preferably refers to an agent which combines the specificity of a immunomolecule .e.g. an antibody or a functional equivalent thereof with a toxic moiety, e.g. a cytotoxic function as defined above.

- 10 Further examples of cancer cotherapeutic agents and preferably of chemotherapeutical agents, cytotoxic agents, immunomodulating agents and/or immunotoxic agents preferably include antibodies against one or more target, preferably selected from the group consisting of HER, HER2, PDGF, PDGFR, EGF, EGFR, VEGF, VEGFR and/or VEGFR2, wherein said antibodies are preferably selected from Herceptin, Bevacizumab (rhuMAb-VEGF, Avastin®), Cetuximab (Erbix®) and Nimotuzumab, and preferably
15 small molecules or NCEs against one or more of said targets, preferably selected from the group consisting of Sorafenib (Nexavar®), Sunitinib (Sutent®) and ZD6474 (ZACTIMA™).

- 20 In a preferred aspect of the instant invention, the chemotherapeutical agents, cytotoxic agents, immunomodulating agents and/or immunotoxic agents are selected from one or more of the following groups:
- a) alkylating agents,
 - b) antibiotics,
 - 25 c) antimetabolites,
 - d) biologicals and immunomodulators,
 - e) hormones and antagonists thereof,
 - f) mustard gas derivatives,
 - g) alkaloids,
 - 30 h) protein kinase inhibitors.

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In a more preferred aspect of the instant invention, the chemotherapeutical agents, cytotoxic agents, immunomodulating agents and/or immunotoxic agents are selected from one or more of the following groups:

- 5 a) alkylating agents, selected from busulfan, melphalan, carboplatin, cisplatin, cyclophosphamide, dacarbazine, carmustine (BCNU), nimustin (ACNU), lomustine (CCNU), ifosfamide, temozolomide and altretamine,
- b) antibiotics, selected from leomycin, doxorubicin, adriamycin, idarubicin, epirubicin and plicamycin,
- 10 c) antimetabolites, selected from sulfonamides, folic acid antagonists, gemcitabine, 5-fluorouracil (5-FU), leucovorine, leucovorine with 5-FU, 5-FU with calcium folinate, and leucovorin, capecitabine, mercaptopurine, cladribine, pentostatine, methotrexate, raltitrexed, pemetrexed, thioguanine, camptothecin derivatives (topotecan, irinotecan)
- 15 d) biologicals and immunomodulators, selected from interferon $\alpha 2A$, interleukin 2 and levamisole,
- e) hormones and antagonists thereof, selected from flutamide, goserelin, mitotane and tamoxifen,
- f) mustard gas derivatives, selected from melphalan, carmustine and nitrogen
- 20 mustard,
- g) alkaloids, selected from taxanes, docetaxel, paclitaxel, etoposide, vincristine, vinblastine and vinorelbine.

25 Dosings and preferably standard administration schedules for the above given cancer cotherapapeutic agents are known in the art.

The terms "**cancer**" and "**tumor**" preferably refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. By means of the pharmaceutical compositions

30 according of the present invention tumors can be treated such as tumors of the breast, heart, lung, small intestine, colon, spleen, kidney, bladder, head and neck, ovary, prostate, brain, pancreas, skin, bone, bone marrow, blood, thymus, uterus, testicles, cervix, and liver. More specifically the tumor is

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selected from the group consisting of adenoma, angio-sarcoma, astrocytoma, epithelial carcinoma, germinoma, glioblastoma, glioma, hamartoma, hemangioendothelioma, hemangiosarcoma, hematoma, hepato-
 5 blastoma, leukemia, lymphoma, medulloblastoma, melanoma, neuroblastoma, osteosarcoma, retinoblastoma, rhabdomyosarcoma, sarcoma and teratoma.

In detail, the tumor/cancer is selected from the group consisting of acral lentiginous melanoma, actinic keratoses, adenocarcinoma, adenoid cystic
 10 carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, astrocytic tumors, Bartholin gland carcinoma, basal cell carcinoma, bronchial gland carcinomas, capillary, carcinoids, carcinoma, carcinosarcoma, cavernous, cholangio-carcinoma, chondrosarcoma, choroid plexus papilloma/carcinoma, clear cell carcinoma, cystadenoma,
 15 endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, ependymal, epithelioid, Ewing's sarcoma, fibrolamellar, focal nodular hyperplasia, gastrinoma, germ cell tumors, glioblastoma, glucagonoma, hemangioblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic
 20 adenomatosis, hepatocellular carcinoma, insulinoma, intraepithelial neoplasia, intraepithelial squamous cell neoplasia, invasive squamous cell carcinoma, large cell carcinoma, leiomyosarcoma, lentigo maligna melanomas, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, melanoma, meningeal, mesothelial,
 25 metastatic carcinoma, mucoepidermoid carcinoma, neuroblastoma, neuroepithelial adenocarcinoma nodular melanoma, oat cell carcinoma, oligodendroglial, osteosarcoma, pancreatic polypeptide, papillary serous adeno-carcinoma, pineal cell, pituitary tumors, plasmacytoma, pseudo-sarcoma, pulmonary blastoma, renal cell carcinoma, retinoblastoma,
 30 rhabdomyo-sarcoma, sarcoma, serous carcinoma, small cell carcinoma, soft tissue carcinomas, somatostatin-secreting tumor, squamous carcinoma, squamous cell carcinoma, submesothelial, superficial spreading melanoma, undifferentiated carcinoma, uveal melanoma,

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verrucous carcinoma, vipoma, well differentiated carcinoma, and Wilm's tumor. More preferably, the tumor/cancer is selected from the group consisting of intracerebral cancer, head-and-neck cancer, rectal cancer, astrocytoma, preferably astrocytoma grade II, III or IV, glioblastoma, preferably glioblastoma multiforme (GBM), small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), preferably non-small cell lung cancer (NSCLC), metastatic melanoma, metastatic androgen independent prostate cancer (AIPCa), metastatic androgen dependent prostate cancer (ADPCa) and breast cancer. Even more preferably, the tumor/cancer is selected from the group consisting of astrocytoma, preferably astrocytoma grade II, III or IV, glioblastoma, preferably glioblastoma multiforme, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), preferably non-small cell lung cancer (NSCLC), metastatic melanoma, metastatic androgen independent prostate cancer (AIPCa), metastatic androgen dependent prostate cancer (ADPCa). Also more preferably, the tumor/cancer is selected from metastases, preferably brain metastases, of small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), preferably non-small cell lung cancer (NSCLC), metastatic melanoma, metastatic androgen independent prostate cancer (AIPCa), metastatic androgen dependent prostate cancer (ADPCa) and breast cancer.

The "**pharmaceutical compositions**" of the invention can comprise agents that reduce or avoid side effects associated with the combination therapy of the present invention ("adjunctive therapy"), including, but not limited to, those agents, for example, that reduce the toxic effect of anticancer drugs, e.g., bone resorption inhibitors, cardioprotective agents. Said adjunctive agents prevent or reduce the incidence of nausea and vomiting associated with chemotherapy, radiotherapy or operation, or reduce the incidence of infection associated with the administration of myelosuppressive anticancer drugs. Adjunctive agents are well known in the art. The immunotherapeutic agents according to the invention can additionally administered with adjuvants like BCG and immune system stimulators.

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Furthermore, the compositions may include immunotherapeutic agents or chemotherapeutic agents which contain cytotoxic effective radio labeled isotopes, or other cytotoxic agents, such as a cytotoxic peptides (e.g. cytokines) or cytotoxic drugs and the like.

The term "**pharmaceutical kit**" for treating tumors or tumor metastases preferably refers to a package and, as a rule, instructions for using the reagents in methods to treat tumors and tumor metastases. A reagent in a kit of this invention is typically formulated as a therapeutic composition as described herein, and therefore can be in any of a variety of forms suitable for distribution in a kit. Such forms can include a liquid, powder, tablet, suspension and the like formulation for providing the antagonist and/or the fusion protein of the present invention. The reagents may be provided in separate containers suitable for administration separately according to the present methods, or alternatively may be provided combined in a composition in a single container in the package. The package may contain an amount sufficient for one or more dosages of reagents according to the treatment methods described herein. A kit of this invention also contains "instruction for use" of the materials contained in the package.

As used herein, the terms "**pharmaceutically acceptable**" and grammatical variations thereof, as they preferably refer to compositions, carriers, diluents and reagents, are preferably used interchangeably and represent that the materials are capable of administration to or upon a mammal without the production of undesirable physiological effects such as nausea, dizziness, gastric upset and the like. The preparation of a pharmacological composition that contains active ingredients dissolved or dispersed therein is well understood in the art and need not be limited based on formulation. Typically, such compositions are prepared as injectables either as liquid solutions or suspensions, however, solid forms suitable for solution, or suspensions, in liquid prior to use can also be prepared. The preparation can also be emulsified. The active ingredient can be mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient and in amounts suitable for use in the therapeutic methods described herein.

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Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol or the like and combinations thereof. In addition, if desired, the composition can contain minor amounts of auxiliary substances such as wetting or emulsifying agents., pH buffering agents and the like which enhance the effectiveness of the active ingredient. The therapeutic composition of the present invention can include pharmaceutically acceptable salts of the components therein. Pharmaceutically acceptable salts include the acid addition salts (formed with the free amino groups of the polypeptide) that are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, tartaric, mandelic and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine and the like. Particularly preferred is the HCl salt when used in the preparation of cyclic polypeptide α v antagonists. Physiologically tolerable carriers are well known in the art. Exemplary of liquid carriers are sterile aqueous solutions that contain no materials in addition to the active ingredients and water, or contain a buffer such as sodium phosphate at physiological pH value, physiological saline or both, such as phosphate-buffered saline. Still further, aqueous carriers can contain more than one buffer salt, as well as salts such as sodium and potassium chlorides, dextrose, polyethylene glycol and other solutes. Liquid compositions can also contain liquid phases in addition to and to the exclusion of water. Exemplary of such additional liquid phases are glycerin, vegetable oils such as cottonseed oil, and water-oil emulsions. Typically, a therapeutically effective amount of an immunotherapeutic agent in the form of a, for example, antibody or antibody fragment or antibody conjugate is an amount such that when administered in physiologically tolerable composition is sufficient to achieve a plasma concentration of from about 0.01 microgram (μ g) per milliliter (ml) to about 100 μ g/ml, preferably from about 1 μ g/ml to about 5 μ g/ml and usually about 5 μ g/ml. Stated differently the dosage can vary from about 0.1 mg/kg to about 300 mg/kg,

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preferably from about 0.2 mg/kg to about 200 mg/kg, most preferably from about 0.5 mg/kg to about 20 mg/kg, in one or more dose administrations daily for one or several days. Where the immunotherapeutic agent is in the form of a fragment of a monoclonal antibody or a conjugate, the amount can readily be adjusted based on the mass of the fragment / conjugate relative to the mass of the whole antibody. A preferred plasma concentration in molarity is from about 2 micromolar (μM) to about 5 millimolar (mM) and preferably, about 100 μM to 1 mM antibody antagonist. A therapeutically effective amount of an agent according of this invention which is a non-immunotherapeutic peptide or a protein polypeptide (e.g. IFN-alpha), or other similarly-sized small molecule, is typically an amount of polypeptide such that when administered in a physiologically tolerable composition is sufficient to achieve a plasma concentration of from about 0.1 microgram (μg) per milliliter (ml) to about 200 $\mu\text{g}/\text{ml}$, preferably from about 1 $\mu\text{g}/\text{ml}$ to about 150 $\mu\text{g}/\text{ml}$. Based on a polypeptide having a mass of about 500 grams per mole, the preferred plasma concentration in molarity is from about 2 micromolar (μM) to about 5 millimolar (mM) and preferably about 100 μM to 1 mM polypeptide antagonist. The typical dosage of an active agent, which is a preferably a chemical antagonist or a (chemical) chemotherapeutic agent according to the invention (neither an immunotherapeutic agent nor a non-immunotherapeutic peptide/protein) is 10 mg to 1000 mg, preferably about 20 to 200 mg, and more preferably 50 to 100 mg per kilogram body weight per day. The preferred dosage of an active agent, which is a preferably a chemical antagonist or a (chemical) chemotherapeutic agent according to the invention (neither an immunotherapeutic agent nor a non-immunotherapeutic peptide/protein) is 0.5 mg to 3000 mg per patient and day, more preferably 10 to 2500 mg per patient and per day, and especially 50 to 1000 mg per patient and per day, or, per kilogram body weight, preferably about 0.1 to 100 mg/kg, and more preferably 1 mg to 50 mg/kg, preferably per dosage unit and more preferably per day, or, per square meter of the bodysurface, preferably 0.5 mg to 2000 mg/m^2 , more preferably 5 to 1500 mg/m^2 , and

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especially 50 to 1000 mg/m², preferably per dosage unit and more preferably per day.

5 The term **"therapeutically effective"** or **"therapeutically effective amount"** preferably refers to an amount of a drug effective to treat a disease or disorder in a mammal. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and
10 preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy can, for example, be measured by assessing the time to disease
15 progression (TTP) and/or determining the response rate (RR).

As used herein, the term "physiologically functional derivative" preferably refers to any pharmaceutically acceptable derivative of a compound to be used according to the present invention, for example, an ester or an amide,
20 which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the present invention or an active metabolite thereof. Such derivatives are clear to those skilled in the art, without undue experimentation, and with reference to the teaching of Burger's Medicinal Chemistry And Drug Discovery, 5th Edition, Vol 1: Principles and Practice,
25 which is incorporated herein by reference to the extent that it teaches physiologically functional derivatives.

As used herein, the term "solvate" preferably refers to a complex of variable stoichiometry formed by a solute (in this invention, a specific integrin ligand and/or a further cancer cotherapeutic agent (or a salt or physiologically
30 functional derivative thereof)) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically

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acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water. Pharmaceutically acceptable salts of compounds to be used according to the invention and their preparation is known in the art. If the compound itself is not a salt, it can be easily transferred into a salt by addition of a pharmaceutically acceptable acid or of a pharmaceutically acceptable base. Pharmaceutically acceptable acids and bases are known in the art, for example from the literature cited herein.

10

The compounds to be used according to the invention, preferably the specific integrin ligand and/or at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand, can generally be administered to the patient in a form and in a way or manner that is known in the art for the respective compounds or class of compounds, for example as described herein or as described in the literature cited herein.

15

The specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is preferably applied as a pharmaceutically acceptable salt, more preferably the pharmacologically acceptable hydrochloride salt, and especially preferably applied as the inner (or internal) salt, which is the compound cyclo-(Arg-Gly-Asp-DPhe-NMeVal) as such.

20

The molecular weight of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) (as such) is 588.67 g/mol.

25

With regard to the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal), the following kinds of writing the name are preferably to be regarded as equivalent:

30

cyclo-(Arg-Gly-Asp-DPhe-NMeVal) = cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) = cyclo(Arg-Gly-Asp-DPhe-NMeVal) = cyclo(Arg-Gly-Asp-DPhe-NMe-Val) = cRGDfNMeV = c(RGDfNMeV). However, other nomenclatures systems or ways of describing the compound are possible and sometimes used;

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nevertheless they are preferably understood as equivalent or synonymous by the ones skilled in the art.

- 5 The compound cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is also known under the INN (International Non-proprietary Name) Cilengitide.

TMZ is frequently used as the abbreviation for Temozolomide.

- 10 RT or RTX is frequently used as the abbreviation for Radiotherapy.

- 15 Lung cancer remains the leading cause of cancer-related death in men and has increased its incidence in women over the past decades. Non small cell lung cancer (NSCLC) accounts for 80% of cases and small cell lung cancer (SCLC) for the remainder.

- 20 Lung cancer is also the most frequent origin of brain metastases, other common causes being breast cancer, renal cell carcinoma, malignant melanoma, GI tumors and unknown primaries (Schouten et al.). At autopsy, brain metastases may be found in over 50% of lung cancer patients (Hirsch et al. 1983).

- 25 For example, in the palliative setting of NSCLC, when multiple brain metastases are not amenable to surgery or radiosurgery, whole brain radiotherapy is currently the therapeutic standard. A total dose of 30 Gy given in 10 fractions is common practice. However, the median survival of 2 to 6 months only is by no means satisfactory (Kelly et al. 1998, Langer et al.2005).

- 30 A hyperfractionated radiation regimen did not yield any statistically significant advantage in terms of 1-year survival (19 % vs. 16%, Murray et al. 1997). A hypofractionation approach with or without the radiosensitizer misonidazol

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did not raise the median survival beyond 3.9 months either (Kormanicky et al. 1991).

5 In the context of brain metastases from SCLC, whole brain radiotherapy represents the mainstay of palliation, as well (Quan et al. 2004). In these patients, prognosis remains dismal and did not exceed 3.5 months when WBRT was combined with chemotherapy (Postmus et al. 2001). Of note, the benefit of prophylactic cranial irradiation in patients with extensive SCLC was
10 confirmed recently (Slotman et al. 2007).

Thus, there is a high medical need for improved medicaments and/or improved treatment regimens with respect to brain metastases, especially brain metastases of NSCLC and/or SCLC. The instant application describes
15 new and improved medicaments and/or treatment regimens comprising the administration of at least one specific integrin ligand and/or radiotherapy, especially whole brain radiation.

Recent results show that inhibiting integrins, especially $\alpha v\beta 3$ and/or $\alpha v\beta 5$,
20 commonly expressed in various cancerous cells, such as glioblastoma, can significantly decrease the resistance to ionising radiation of otherwise radioresistant cancerous cells and/or can induce an increased sensitivity of cancerous cells towards ionising radiation. Ionising radiation in this respect is preferably external beam radiation and especially fractionated external beam
25 radiation.

Especially with respect to primary brain tumours, such as astrocytoma and glioblastoma multiforme, a significant percentage of the patients will die of a relapse originating in the radiation fields, likely as a result of low tumor
30 sensitivity to radiation caused by an activation of the survival signalling. This increased radiation resistance (thereafter named "radioresistance") is due to the modulation of different biological signal transduction pathways and to a cross-talk between the tumor cells and their microenvironment.

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- Accordingly, specific integrin ligands, especially integrin ligands specific to $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ integrins according to the invention can be successfully applied to improve the efficacy of various cancer cotherapeutic agents and especially the efficacy of radiation therapy. Radiation therapy in this respect is preferably external beam radiation and especially fractionated external beam radiation.
- 5
- 10 Glioblastoma (GBM, Astrocytoma, WHO Grade IV), also named Glioblastomamultiforma or Glioblastoma multiforme, are invasive brain tumors with a poor prognosis, and a median survival irrespective of treatment of around 14-15 months. Generally, locally invasive tumors inevitably relapse, whether treated with surgery, chemotherapy or irradiation. The
- 15 current state of the art regimen ("EORTC protocol", as established by Stupp and coworkers) uses graded RTX accompanied by the cytotoxic agent temozolomide (see especially R.Stupp et al., NEJM 2005). So far, this has extended the life span of patients by some months at best.
- 20 Glioblastoma is highly vascularized, and the angiogenic process is necessary for tumor development. Both the GBM vasculature and the GBMs themselves overexpress the integrin $\alpha_v\beta_3$. This has been shown in vitro to support the survival of GBM cell lines, as well as being a feature of angiogenic endothelia, driven into the cell cycle by tumor derived growth factors like
- 25 VEGF. Inhibition of $\alpha_v\beta_3$ on endothelial cells and isolated glioblastoma cell lines induces cell death, and can activate apoptosis. RTX has also been shown to induce $\alpha_v\beta_3$ expression on endothelial cells. Together these data suggest that $\alpha_v\beta_3$ may support survival of the vascular and tumor compartment of GBM.
- 30 Cilengitide is a cyclic pentapeptide that specifically binds to alpha-v integrins, notably to $\alpha_v\beta_3$, and inhibits their activation by their ligands within the extracellular matrix. Cilengitide preferably induces apoptosis in endothelial and GBM cell cultures.

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5 A phase I clinical study used cilengitide treatment in a dose escalation study on various brain tumors (NABT 9911). In some of the GBM patients in this study, an indication of response was seen. Cilengitide (= cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), in very marked contrast to most cancer therapeutics currently in use has a very innocuous side effect profile, with no known MTD in humans – and is very well tolerated.

10 In addition to the essentially 100% mortality in GBM patients (2-year survival rate about 25%), the morbidity from neurological complications also rapidly degrades the quality of life (QOL).

15 Thus, it is an objective of the instant invention to provide a more effective, and better tolerated treatment for GBM patients leading to enhanced QOL and increased median survival, preferably as well in GBM patients following 1st relapse as in the first line treatment of GBM patients.

20 Thus, a preferred subject of the instant invention is a method of treatment of GBM, comprising Cilengitide administration by i.v. infusion in GBM patients, preferably GBM patients following 1st relapse, more preferably newly diagnosed GBM patients (1st line treatment), preferably until tumor progression, stable disease or healing occurs. In this method of treatment, the Cilengitide is preferably administered at least twice weekly (e.g. q3q4), preferably in an ca. 1 h i.v. infusion, preferably in infusion saline, and
25 preferably either at 500 mg flat dose or 2000 mg flat dose. More preferably in this method of treatment, the Cilengitide is preferably administered five times weekly, preferably on five consecutive days, preferably in a ca. 1h i.v. infusion, preferably in infusion saline, and preferably at about 2000 mg flat dose.

30

Advantageously, MRI and neurological indications of objective tumor response to this method of treatment can be shown in at least 20% of the pathologically confirmed GBM patients under therapy.

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5 This method of treatment can optionally be combined, partially or totally, with administration of one or more cancer cotherapeutic agents, preferably as described herein.

10 Moreover, due to the synergistic, efficacy enhancing properties of the specific integrin ligand Cilengitide with various cancer cotherapeutic agents, the combination of Cilengitide, at least one chemotherapeutic and external beam radiation is a preferred aspect of the instant invention.

15 For example, the standard of treatment of glioblastoma multiforme, associating radiotherapy and temozolomide, has only increased the median survival of resected patients by 2.5 months (12.1 → 14.6 months) compared to radiotherapy alone (Stupp et al., 2005). However, in combination with at least one specific integrin ligand according to the invention, preferably selected from Vitaxin, Abegrin, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more preferably selected from Vitaxin, Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and especially preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), this standard treatment shows significantly improved efficacy with respect to an increased median survival and quality of life. Accordingly, this combination of radiotherapy, temozolomide and at least one specific integrin ligand as described herein, is a preferred aspect of the instant invention.

25 Thus, combinations of at least one specific integrin ligand as described herein and at least one cancer cotherapeutic agent as described herein, can be effectively used to treat intracerebral tumor growth in the brain of a host. Intracerebral tumor growth in the brain of a host according to the invention includes, but is not limited to primary brain tumours, astrocytoma, such as astrocytoma grade I-IV (WHO), and especially glioblastoma multiforme. Intracerebral tumor growth is preferably also including intercerebral metastases of other cancer types, preferably cancer types selected from small cell lung cancer and non-small cell lung cancer, preferably non-small

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cell lung cancer, breast cancer, metastatic melanoma, metastatic androgen independent prostate cancer, metastatic androgen dependent prostate cancer, and more preferably from breast cancer, small cell lung cancer and especially non-small cell lung cancer.

Thus, the instant invention preferably also refers to the use of

- a) (a composition containing) at least one specific integrin ligand, and
- b) at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a)

for the manufacture of a medicament for the treatment of intracerebral tumour growth in the brain of a host, preferably primary brain tumours and especially astrocytoma.

More preferably, the invention also refers to the use of

- a) (a composition containing) at least one specific integrin ligand, and
- b) at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a)

for the manufacture of a medicament for the treatment of intracerebral tumour growth in the brain of a host, preferably primary brain tumours and especially astrocytoma, wherein the at least one specific integrin ligand is selected from Vitaxin, Abegrin, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), preferably selected from Vitaxin, Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val).

More preferably, the invention also refers to the use of

- a) (a composition containing) at least one specific integrin ligand, and
- b) at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a)

for the manufacture of a medicament for the treatment of intracerebral tumour growth in the brain of a host, preferably primary brain tumours and especially astrocytoma wherein the at least one specific integrin ligand is selected from Vitaxin, Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), and

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the at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a) is selected from radiotherapy, preferably external beam radiation, and temozolomide.

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Especially preferably, the invention also refers to the use of (a composition containing) at least one specific integrin ligand, selected from and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val),

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for the manufacture of a medicament for the treatment of intracerebral tumour growth in the brain of a host, preferably primary brain tumours and especially astrocytoma, wherein the medicament is to be used in combination with the two further cancer cotherapeutic agents, temozolomide and radiotherapy, preferably more preferably external beam radiation and especially fractionated external beam radiation. The specific integrin ligand is preferably applied substantially concurrently or sequentially to at least one of the cancer cotherapeutic agents.

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Accordingly, one preferred aspect of the instant invention relates to the use of (a composition containing) at least one specific integrin ligand, comprising cyclo-(Arg-Gly-Asp-DPhe-NMe-Val),

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for the manufacture of a medicament for the treatment of glioblastoma multiforme, wherein the medicament is to be used in combination with the two further cancer cotherapeutic agents, temozolomide and radiotherapy, preferably temozolomide and external beam radiation and especially temozolomide and fractionated external beam radiation. Also in this preferred aspect, at least the specific integrin ligand is preferably applied timed as described herein.

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Especially preferably, the invention also refers to the use of (a composition containing) at least one specific integrin ligand, selected from and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), for the manufacture of a medicament for the treatment of intracerebral tumour growth in the brain of a host, preferably primary brain tumours and

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5 especially astrocytoma, wherein the medicament is to be used in combination with the two further cancer cotherapeutic agents, temozolomide and radiotherapy, preferably more preferably external beam radiation and especially fractionated external beam radiation, wherein at least one of the specific integrin ligands is administered in a timed administration as described herein, preferably 1 to 8 hours (h), preferably 2 to 6 h, and most preferably 2 to 4 h prior to the application of the radiotherapy and/or the temozolomide.

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Even more preferably, the invention also refers to the use of

- a) (a composition containing) at least one specific integrin ligand, and
- b) at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a)

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for the manufacture of a medicament for the treatment glioblastoma, preferably glioblastoma multiforme, wherein the at least one specific integrin ligand is selected from Vitaxin, Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val),

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wherein a) is administered in a timed administration as described herein, preferably 1 to 8 hours (h), preferably 2 to 6 h, and most preferably 2 to 4 h prior to the application of b).

Even more preferably, the invention also refers to the use of

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- a) (a composition containing) at least one specific integrin ligand, and
- b) at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a)

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for the manufacture of a medicament for the treatment glioblastoma, preferably glioblastoma multiforme, wherein the at least one specific integrin ligand is selected from Vitaxin, Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), and the at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a) is selected from radiotherapy, preferably external beam radiation, and chemotherapeutical agents, cytotoxic agents and/or immunotoxic agents, preferably temozolomide,

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wherein a) is administered in a timed administration as described herein, preferably 1 to 8 hours (h), preferably 2 to 6 h, and most preferably 2 to 4 h prior to the application of b).

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Even more preferably, the invention also refers to the use of

a) (a composition containing) at least one specific integrin ligand, and

b) at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a)

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for the manufacture of a medicament for the treatment glioblastoma,

preferably glioblastoma multiforme, in human animals,

wherein the at least one specific integrin ligand is selected from Vitaxin, Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val),

wherein a) is administered 2 to 32 hours (h), preferably 4 to 24h, more

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preferably 6 to 20 h and most preferably 6 to 16 h prior to the application of b).

Even more preferably, the invention also refers to the use of

a) (a composition containing) at least one specific integrin ligand, and

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b) at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a)

for the manufacture of a medicament for the treatment glioblastoma,

preferably glioblastoma multiforme, in human animals,

wherein the at least one specific integrin ligand is selected from Vitaxin,

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Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), and the at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a) is selected from radiotherapy, preferably external beam radiation, and chemotherapeutical agents, cytotoxic agents and/or immunotoxic agents, preferably temozolomide,

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wherein a) is administered 2 to 32 hours (h), preferably 4 to 24h, more preferably 6 to 20 h and most preferably 6 to 16 h prior to the application of b).

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Especially preferably, the invention also refers to the use of
(a composition containing) at least one specific integrin ligand, selected from
cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable
5 derivatives, solvates and salts thereof, and especially cyclo-(Arg-Gly-Asp-
DPhe-NMe-Val), for the manufacture of a medicament for the treatment of
intracerebral tumour growth in the brain of a host, preferably primary brain
tumours and especially astrocytoma, wherein the medicament is to be used
in combination with the two further cancer cotherapeutic agents,
10 temozolomide and radiotherapy, preferably temozolomide and external beam
radiation and especially temozolomide and fractionated external beam
radiation, wherein at least one of the specific integrin ligands is administered
in a timed administration as described herein, preferably 1 to 8 hours (h),
preferably 2 to 6 h, and most preferably 2 to 4 h prior to the application of the
15 radiotherapy and/or the temozolomide.

Especially preferably, the invention also refers to the use of
(a composition containing) at least one specific integrin ligand, selected from
cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and the pharmaceutically acceptable
20 salts thereof, for the manufacture of a medicament for the treatment of
intracerebral tumour growth in the brain of a human animal, preferably
primary brain tumours and especially astrocytoma, wherein the medicament
is to be used in combination with the two further cancer cotherapeutic agents,
temozolomide and radiotherapy, preferably temozolomide and external beam
25 radiation and especially temozolomide and fractionated external beam
radiation, wherein at least one of the specific integrin ligands is administered
2 to 32 hours (h), preferably 4 to 24 h, more preferably 6 to 20 h and most
preferably 6 to 16 h prior to the application of the radiotherapy and/or the
temozolomide.

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Especially preferably, the invention also refers to the use of
(a composition containing) at least one specific integrin ligand, comprising
cyclo-(Arg-Gly-Asp-DPhe-NMe-Val),

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for the manufacture of a medicament for the treatment of glioblastoma multiforme, wherein the medicament is to be used in combination with the two further cancer cotherapeutic agents, temozolomide and radiotherapy, preferably temozolomide and external beam radiation and especially temozolomide and fractionated external beam radiation, wherein at least the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) is administered in a timed administration as described herein, preferably 1 to 24 hours (h), preferably 1 to 20 h, more preferably, 2 to 20 h, more preferably 2 to 16 h, 3 to 16, even more preferably 3 to 12 h and especially 4 to 10 h prior to the application of the radiotherapy and/or the temozolomide.

Especially preferably, the invention also refers to the use of (a composition containing) at least one specific integrin ligand, comprising cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), for the manufacture of a medicament for the treatment of glioblastoma multiforme, wherein the medicament is to be used in combination with the two further cancer cotherapeutic agents, temozolomide and radiotherapy, preferably temozolomide and external beam radiation and especially temozolomide and fractionated external beam radiation, wherein at least the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) is administered in a timed administration as described herein, preferably 1 to 10 hours (h), preferably 2 to 8 h, more preferably 2 to 6 h, even more preferably 3 to 8 h, even more preferably 3 to 6 h and especially 4 to 8 h prior to the application of the radiotherapy and/or the temozolomide.

Recent *in vitro* results show an increase in cell death/deterioration after combination treatment of lung cancer cell lines, such as A549, H157, H322, H460 and/or H1975, with specific integrin ligands, such as Vitaxin, Abegrin, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), and cancer cotherapeutic agents, such as Cisplatin, Oxaliplatin, Vinblastin, Taxol, Gemcitabine, Gleevec, Iressa, and radiotherapy, preferably external beam radiation and/or fractionated external beam radiation. The results suggest that cancer

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cotherapeutic agents, such as radiation, can induce expression of relevant integrins in lung cancer cells, and/or that the specific integrin ligand is acting as an amplifier of efficacy, e.g. as a radio amplifier. Moreover, combined
5 application of at least one specific integrin ligand and at least one cancer cotherapeutic agent, preferably radiation, results in significant cell kill and thus reduced survival curves of the respective treated cells considerably. Accordingly, the combinations appear to effectively induce cell death, likely due to apoptosis and/or mitotic cell death, in endothelial cells and tumour
10 cells, especially in lung cancer cells and especially in non-small cell lung cancer cells. The extent of effect may depend on the degree of target expression, i.e. integrin expression. Thus, combinations of at least one specific integrin ligand as described herein and at least one cancer cotherapeutic agent as described herein, can be effectively used to treat lung
15 cancer, and especially small cell lung cancer, non-small cell lung cancer and/or metastases thereof.

Thus, the instant invention preferably also refers to the use of
a) (a composition containing) at least one specific integrin ligand, and
20 b) at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a)
for the manufacture of a medicament for the treatment lung cancer, preferably non-small cell lung cancer (NSCLC).

25 More preferably, the invention also refers to the use of
a) (a composition containing) at least one specific integrin ligand, and
b) at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a)
for the manufacture of a medicament for the treatment lung cancer,
30 preferably non-small cell lung cancer (NSCLC), wherein the at least one specific integrin ligand is selected from Vitaxin, Abegrin, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), preferably selected from Vitaxin, Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more preferably selected from cyclo-

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(Arg-Gly-Asp-DPhe-NMe-Val) and the pharmaceutically acceptable salts thereof.

- 5 More preferably, the invention also refers to the use of
- a) (a composition containing) at least one specific integrin ligand, and
 - b) at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a)
- for the manufacture of a medicament for the treatment lung cancer,
- 10 preferably non-small cell lung cancer (NSCLC), wherein the at least one specific integrin ligand is selected from Vitaxin, Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), and the at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a) is selected from radiotherapy, preferably external beam radiation, chemotherapeutical agents,
- 15 cytotoxic agents and/or immunotoxic agents, preferably selected from Cisplatin, Oxaliplatin, Vinblastin, Taxol, Gemcitabine, Gleevec and Iressa.

- Even more preferably, the invention also refers to the use of
- a) (a composition containing) at least one specific integrin ligand, and
 - 20 b) at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a)
- for the manufacture of a medicament for the treatment lung cancer, preferably non-small cell lung cancer (NSCLC), wherein the at least one specific integrin ligand is selected from Vitaxin, Abegrin, CNTO95 and cyclo-
- 25 (Arg-Gly-Asp-DPhe-NMe-Val), preferably selected from Vitaxin, Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more preferably selected from cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and the pharmaceutically acceptable salts thereof, wherein a) is administered in a timed administration as described herein, preferably 1 to 8 hours (h), preferably 2 to 6 h, and most preferably 2
- 30 to 4 h prior to the application of b).

Even more preferably, the invention also refers to the use of

- a) (a composition containing) at least one specific integrin ligand, and

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b) at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a)
for the manufacture of a medicament for the treatment lung cancer,
5 preferably non-small cell lung cancer (NSCLC), wherein the at least one specific integrin ligand is selected from Vitaxin, Abegrin, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), preferably selected from Vitaxin, Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more preferably selected from cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and the pharmaceutically acceptable salts
10 thereof, and the at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a) is selected from radiotherapy, preferably external beam radiation, chemotherapeutical agents, cytotoxic agents and/or immunotoxic agents, preferably selected from Cisplatin, Oxaliplatin, Vinblastin, Taxol, Gemcitabine, Gleevec and Iressa,
15 wherein a) is administered in a timed administration as described herein, preferably 1 to 8 hours (h), preferably 2 to 6 h, and most preferably 2 to 4 h prior to the application of b).

Even more preferably, the invention also refers to the use of
20 a) (a composition containing) at least one specific integrin ligand, and
b) at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a)
for the manufacture of a medicament for the treatment lung cancer, preferably non-small cell lung cancer (NSCLC), in human animals,
25 wherein the at least one specific integrin ligand is selected from Vitaxin, Abegrin, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), preferably selected from Vitaxin, Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more preferably selected from and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val),
wherein a) is administered 2 to 32 hours (h), preferably 4 to 24h, more
30 preferably 6 to 20 h and most preferably 6 to 16 h prior to the application of b).

Even more preferably, the invention also refers to the use of

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- a) (a composition containing) at least one specific integrin ligand, and
- b) at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a)

5 for the manufacture of a medicament for the treatment lung cancer, preferably non-small cell lung cancer (NSCLC), in human animals, wherein the at least one specific integrin ligand is selected from Vitaxin, Abegrin, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), preferably selected from Vitaxin, Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more
10 preferably selected from cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and the pharmaceutically acceptable salts thereof, and the at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand of a) is selected from radiotherapy, preferably external beam radiation, chemotherapeutical agents, cytotoxic
15 agents and/or immunotoxic agents, preferably selected from Cisplatin, Oxaliplatin, Vinblastin, Taxol, Gemcitabine, Gleevec and Iressa, wherein a) is administered 2 to 32 hours (h), preferably 4 to 24h, more preferably 6 to 20 h and most preferably 6 to 16 h prior to the application of b).

20 Use of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be used in combination with radiotherapy, preferably external beam radiation, wherein the cyclo-(Arg-
25 Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof is administered 2 to 32 hours (h), preferably 4 to 24h, more preferably 6 to 20 h and most preferably 6 to 16 h prior to the application of radiotherapy. In this regard, the cancer is preferably selected from intracerebral cancer, head-
and-neck cancer, rectal cancer, breast cancer, small cell lung cancer, non-
30 small cell lung cancer and especially from glioblastoma multiforme, breast cancer, small cell lung cancer, non-small cell lung cancer and brain metastases thereof.

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Subject of the instant invention is the use of at least one specific integrin ligand, comprising cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof or consisting of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, for the manufacture of a medicament for the treatment of brain tumours, preferably of primary brain tumours, wherein at least the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof is administered to a patient in an amount of about about 8000 mg per week, about 10000 mg per week or about 12000 mg per week. In one aspect of the instant invention, the medicament is used in the absence of a further cancer cotherapeutic agent. In another aspect of the instant invention, the medicament is combined with one or more further cancer cotherapeutic agents, preferably cancer cotherapeutic agent as described herein. The administration of an amount of about 8000 mg per week and per patient, about 10000 mg per week and per patient or about 12000 mg per week and per patient and especially about 10000 mg per week and per patient is preferred in "unmethylated patients" as defined in this application.

Subject of the instant invention is the use of at least one specific integrin ligand, comprising cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof or consisting of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, for the manufacture of a medicament for the treatment of brain tumours, preferably of primary brain tumours, wherein the medicament is to be used in combination with radiotherapy, preferably external beam radiation, wherein at least the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof is administered to a patient in an amount of about 1000 mg per week, about 4000 mg per week, about 8000 mg per week, about 10000 mg per week or about 12000 mg per week. In one aspect of the instant invention, the medicament is used in the absence of a further cancer cotherapeutic agent. In another aspect of the instant

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invention, the medicament is combined with one or more further cancer cotherapeutic agents, preferably cancer cotherapeutic agent as described herein. The administration of an amount of about 8000 mg per week and per patient, about 10000 mg per week and per patient or about 12000 mg per week and per patient and especially about 10000 mg per week and per patient is preferred in "unmethylated patients" as defined in this application.

Subject of the instant invention is the use of at least one specific integrin ligand, comprising cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof or consisting of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, for the manufacture of a medicament for the treatment of tumours, wherein the medicament is to be used in combination with temozolomide and/or radiotherapy, preferably external beam radiation, wherein at least the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof is administered to a patient in an amount of 800 mg to 7000 mg per week, more preferably in an amount of 8000 mg to 14000 mg per week and even more preferably in an amount of about 10000 mg per week. The administration of an amount of 8000 mg to 14000 mg per week and per patient and especially of about 10000 mg per week and per patient is preferred in "unmethylated patients" as defined in this application. Preferred tumours in this respect are brain tumours, more preferred primary brain tumours as defined herein and especially glioblastoma multiforme.

Preferably, the amount of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), to be administered to a patient per week is administered in about equal amounts of about 500 mg or about 2000 mg for each administration. The amount to be administered to a patient per week is preferably administered in about equal amounts of about 2000 mg per day. This is especially preferred if the amount to be administered to the patient per

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week is 4000 mg and higher and especially preferred if the amount to be administered to the patient is 8000 mg and higher.

- 5 The amount of about 10.000 mg to be administered to a patient per week is preferably administered in about equal amounts of about 2000 mg per day.

- 10 In one aspect, the amount of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is administered to a patient in an amount of about 1000 mg per week, about 1500 mg per week, about 2500 mg per week, about 4000 mg per week or about 6000 mg per week.

- 15 Even more preferably, the amount of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is administered to a patient in an amount of about 8000 mg per week, about 10000 mg per week, about 12000 mg per week or about 14000 mg per week. This is especially preferred for "unmethylated patients" as defined in this application.

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- 25 Preferably, the amount of about 1000 mg of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably of cyclo-(Arg-Gly-Asp-DPhe-NMeVal), per week is administered in a twice weekly administration scheme.

- 30 Preferably, the amount of about 4000 mg of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably of cyclo-(Arg-Gly-Asp-DPhe-NMeVal), per week is administered in a twice weekly administration scheme, preferably in about equal amounts of about 2000 mg each.

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In the twice weekly administration scheme, the administration is preferably done on a day one and then on day three or a day four. Thus, the twice weekly administration scheme is preferably done either in an alternating every third day/every fourth day scheme or an alternating every fourth day/every third day scheme, such as an administration on Mondays and Thursdays (as an example of the 3/4 scheme) or Tuesdays and Fridays (as a further example of the 3/4 scheme), or on Thursdays and Mondays (as an example of the 4/3 scheme) or on Fridays and Tuesdays (as a further example of the 4/3 scheme).

The twice weekly administration scheme, preferably the twice weekly administration scheme as described above, can be applied to the patient once or several times. Preferably, it is applied several times, even more preferably at least three times or at least six times. For example, the twice weekly administration scheme can be applied continuously until healing, stable disease or tumor progression takes place. Typically, the twice weekly administration scheme, preferably the twice weekly administration scheme as described above, is applied 4 to 156 times, such as about 4 times, about 8 times, about 16 times, about 24 times, about 35 times, about 70 times or about 104 times.

The twice weekly administration scheme can be combined partially or totally with radiotherapy, preferably radiotherapy as described herein. Preferably, the twice weekly administration scheme is combined partially with radiotherapy.

Preferably, the amount of about 1500 mg of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably of cyclo-(Arg-Gly-Asp-DPhe-NMeVal), per week is administered in a three times weekly administration scheme, preferably in about equal amounts of about 500 mg each.

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Preferably, the amount of about 6000 mg of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably of cyclo-(Arg-Gly-Asp-DPhe-NMeVal), per week is administered in a three times
5 weekly administration scheme, preferably in about equal amounts of about 2000 mg each.

In the three times weekly administration scheme, the administration is preferably either done on a day one, on a day three or a day four and then on
10 a day 6, or more preferably on a day one, on a day 3 and on a day 5, then followed of two consecutive days off. The latter three times weekly administration scheme, for example, typically starts on a monday, followed by one administration on the following wednesday and one administration on friday, with saturday and sunday off of treatment.

15 The three times weekly administration scheme, preferably the three times weekly administration scheme as described above, can be applied to the patient once or several times. Preferably, it is applied several times, even more preferably at least three times or at least six times. For example, the
20 three times weekly administration scheme can be applied continuously till healing or tumor progression takes place. Typically, the twice weekly administration scheme, preferably the twice weekly administration scheme as described above, is applied 4 to 156 times, such as about 4 times, about 8 times, about 16 times, about 24 times, about 35 times, about 70 times or
25 about 104 times.

The three times weekly administration scheme can be combined partially or totally with radiotherapy, preferably radiotherapy as described herein. Preferably, the three times weekly administration scheme is combined
30 partially with radiotherapy.

Preferably, the amount of about 2500 mg of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably of

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cyclo-(Arg-Gly-Asp-DPhe-NMeVal), per week is administered in a five times weekly administration scheme, preferably in about equal amounts of about 500 mg each. In the five times weekly administration scheme, the administration is preferably done on five consecutive days, preferably followed by 2 days in a row off. This "5 days of consecutive administration followed by 2 consecutive days off" scheme can be repeated once or several times. Preferably, this before described "5 days of consecutive administration followed by 2 consecutive days off" scheme is performed more than once but preferably less than 18 times, more preferably 2 to 12 times, even more preferably 3 to 8 times and especially 4 to 6 times, for example 2 times, 3 times, 4 times, 5 times, 6 times, 8 times or 12 times. Especially preferably, this "5 days of consecutive administration followed by 2 consecutive days off" scheme is applied 6 times.

Preferably, the amount of about 8000 mg of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably of cyclo-(Arg-Gly-Asp-DPhe-NMeVal), per week is administered in a 4 times weekly administration scheme, preferably in about equal amounts of about 2000 mg each. In the four times weekly administration scheme, the administration is preferably either done on four consecutive days, preferably followed by 3 days in a row off, or, on 2 consecutive days, one day off, two more consecutive days and then 2 consecutive days off. This scheme can be repeated once or several times. Preferably, this before described scheme is performed more than once but preferably less than 18 times, more preferably 2 to 12 times, even more preferably 3 to 8 times and especially 4 to 6 times, for example 2 times, 3 times, 4 times, 5 times, 6 times, 8 times or 12 times. Especially preferably, this scheme is applied 6 times.

Preferably, the amount of about 10000 mg of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably of cyclo-(Arg-Gly-Asp-DPhe-NMeVal), per week is administered in a 5 times weekly administration scheme, preferably in about equal amounts of about

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2000 mg each. In the five times weekly administration scheme, the administration is preferably done on five consecutive days, preferably followed by 2 days in a row off. This "5 days of consecutive administration followed by 2 consecutive days off" scheme can be repeated once or several times. Preferably, this before described "5 days of consecutive administration followed by 2 consecutive days off" scheme is performed more than once but preferably less than 18 times, more preferably 2 to 12 times, even more preferably 3 to 8 times and especially 4 to 6 times, for example 2 times, 3 times, 4 times, 5 times, 6 times, 8 times or 12 times. Especially preferably, this "5 days of consecutive administration followed by 2 consecutive days off" scheme is applied 6 times.

Preferably, this "5 days of consecutive administration followed by 2 consecutive days off" scheme is combined with radiotherapy as described herein, preferably radiotherapy as described herein that is applied to the patient in an analog "5 days of consecutive application followed by 2 consecutive days off" scheme that preferably runs in parallel to the other scheme, preferably with the same two days off.

Regarding the herein described weekly administration amounts and/or schemes, the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is preferably administered in a timed administration as described herein, generally 1,5 to 20 hours (h), preferably 2 to 16 h, more preferably 2 to 12 h, even more preferably 2 to 10 h, even more preferably 3 to 10 h and especially 2 to 8 h prior to the application of the radiotherapy. Alternatively, the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof is administered in a timed administration as described herein, preferably 1 to 10 hours (h), preferably 1 to 6, more preferably 2 to 8, even more preferably 3 to 8 h, even more preferably 3 to 6 and especially 4 to 8 h prior to the application of the

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radiotherapy.

According to the invention, the specific integrin ligand cyclo-(Arg-Gly-Asp-
5 DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof,
preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), and optionally the at least one
further cancer cotherapeutic agent different from the at least one specific
integrin ligand, preferably selected from chemotherapeutical agents, cytotoxic
agents and/or immunotoxic agents, more preferably selected from
10 Temozolomide, Cisplatin, Oxaliplatin, Carboplatin, 5-FU, Darcabazine,
Procarbazine, Vinblastin, Vincristine, Irinotecan, Paclitaxel, Docetaxel,
Gemcitabine, Gleevec, Iressa, Tarceva and Nexavar, even more preferably
preferably selected from Temozolomide, Cisplatin, Oxaliplatin, Vinblastin,
Taxol, Gemcitabine, Gleevec and Iressa, and/or selected from the group
15 consisting Herceptin, Bevacizumab (rhuMAb-VEGF, Avastin®), Cetuximab
(Erbix®) and Nimotuzumab, and preferably Sorafenib (Nexavar®), Sunitinib
(Sutent®) and ZD6474 (ZACTIMA™), and radiotherapy, preferably
radiotherapy as described herein, is preferably administered to a patient in
need thereof in a dose/mode of administration/dosing schedule given below:

20 The specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the
pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-
DPhe-NMeVal), is preferably administered at a flat dose of about 500 mg or
about 2000 mg per administration, preferably in a weekly administration
25 scheme selected from a twice weekly administration scheme, three times
weekly administration scheme, four times weekly administration scheme, five
times weekly administration scheme and six times weekly administration
scheme, preferably as described herein, more preferably in the four times
weekly administration scheme as described herein and especially in the six
30 times weekly administration scheme as described herein, which
administration scheme is preferably repeated at least once, more preferably
at least twice, more preferably at least 5 times and even more preferably at
least 35 times. Preferably, it is repeated less than 150 times, more preferably

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less than 100 times, at least if it is administered without a pause, break or gap of at least one week, preferably of at least four weeks. After such a pause, gap or break, the above described administration scheme can be repeated once or several times, if necessary. Accordingly, the afore described administration scheme is preferably applied to the patient for at least 2 weeks, preferably at least 6 weeks, more preferably at least 12 weeks, even more preferably at least 24 weeks, and especially at least 35 weeks, for example for about 4 weeks, for about 6 weeks, for about 35 weeks, for about 36 weeks, for about 72 weeks or for about 120 weeks. In the afore described administration scheme, the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is preferably administered. In the afore described administration scheme, the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is preferably administered by i. v. infusion twice a week, preferably on Day 1 and 4, e. g., Monday and Thursday or Tuesday and Friday), preferably for 35 weeks or at least 35 weeks without a pause. In the afore described administration scheme, the administration can be continued until progression, stable disease or healing occurs. Preferably, the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), begins on Day 1 of each week.

Preferably, the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is combined, partially or totally, preferably partially, with the administration of at least one further cancer cotherapeutic agent different from the at least one specific integrin ligand, wherein the further cancer cotherapeutic agent is preferably as defined herein, more preferably selected from the group consisting of chemotherapeutical agents, cytotoxic agents, immunotoxic agents and/or

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radiotherapy, and especially preferably selected from the group consisting of Temozolomide, Cisplatin, Oxaliplatin, Carboplatin, 5-FU, Darcabazine, Procarbazine, Vinblastin, Vincristine, Irinotecan, Paclitaxel, Docetaxel, Gemcitabine, Gleevec, Iressa, Tarceva and Nexavar, even more preferably preferably selected from Temozolomide, Cisplatin, Oxaliplatin, Vinblastin, Taxol, Gemcitabine, Gleevec and Iressa, and/or selected from the group consisting Herceptin, Bevacizumab (rhuMAb-VEGF, Avastin®), Cetuximab (Erbix®) and Nimotuzumab, and preferably Sorafenib (Nexavar®), Sunitinib (Sutent®) and ZD6474 (ZACTIMA™), and/or radiotherapy.

Preferably, the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is combined, partially or totally, preferably partially, with the administration or delivery of radiotherapy, preferably external beam radiation and especially focal radiotherapy. Preferably, the radiotherapy is administered or delivered on one or more days within one or more weeks in which the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is administered in a weekly administration scheme, preferably a weekly administration scheme as described herein. More preferably, the radiotherapy is administered or delivered on one or more days within one or more weeks in which the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is administered in a twice weekly administration scheme. The radiotherapy, preferably external beam radiation and especially focal radiotherapy, is preferably administered or delivered over a period from 1 to 12 weeks, preferably 2 to 10 weeks, more preferably 3 to 8 weeks and especially 4 to 6 weeks, for example about 3 weeks, about 5 weeks, about 6 weeks, about 7 weeks or about 9 weeks, with an administration or delivery on 1 to 7 days, preferably 2 to 6 days and especially 3 to 5 days, for example, 2 days, 3 days, 5 days or 7 days, per week.

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More preferably, the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is combined, partially or totally, preferably partially, with the administration or delivery of radiotherapy, preferably external beam radiation and especially focal radiotherapy. Preferably, the radiotherapy is administered or delivered on one or more days within one or more weeks in which the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is administered in a 4, 5 or 6 times weekly administration scheme, preferably the 5 times weekly administration scheme as described herein. More preferably, the radiotherapy is administered or delivered on about each day within one or more weeks in which the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is administered in a 4, 5 or 6 times weekly administration scheme. Especially preferably, the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof is administered on each day on which the radiotherapy is administered or delivered to the patient. The radiotherapy, preferably external beam radiation and especially focal radiotherapy, is preferably administered or delivered over a period from 1 to 12 weeks, preferably 2 to 10 weeks, more preferably 3 to 8 weeks and especially 4 to 6 weeks, for example about 3 weeks, about 5 weeks, about 6 weeks, about 7 weeks or about 9 weeks, with an administration or delivery on 1 to 7 days, preferably 2 to 6 days, more preferably 4 to 6 days and especially on 5 days, for example, 2 days, 3 days, 5 days or 7 days, per week.

Thus, the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof is especially preferably administered to the patient on each day on which the radiotherapy is administered or delivered to said patient, preferably both in a five times weekly administration scheme as

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described herein, preferably for 3 to 8 and especially about 6 consecutive weeks.

- 5 Preferably, the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is combined, partially or totally, preferably partially, with the administration or delivery of focal radiotherapy, wherein 40 to 70 Gray (Gy), preferably 50 to 66 Gy, more
10 preferably 55 to 62 Gy, for example about 58 Gy, about 60 Gy or about 65 Gy are administered or delivered to the patient, preferably in fractions of 0.5 to 5 Gy, more preferably 1 to 3 Gy and especially 1.5 to 2.5 Gy, for example about 1.3 Gy, about 1.6 Gy, about 1.8 Gy, about 2.0 Gy or about 2.2 Gy, per per administration or delivery, which is preferably also the amount of
15 radiation per day on which the administration or delivery of the radiation takes place. Accordingly, an administration or delivery of 1.5 to 2.5 Gy and preferably 1.8 to 2.2 Gy per day for 5 days within one week, even more preferably 5 consecutive days within one week, is preferred. The kind of application of focal radiotherapy as described above is preferred in the
20 treatment of primary brain tumors, including astrocytoma, preferably astrocytoma grade III and/or grade IV, and especially GBM.

- Alternatively, the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is combined, partially or
25 totally, preferably partially, with the administration or delivery of focal radiotherapy, wherein 20 to 50 Gray (Gy), preferably 25 to 40 Gy, more preferably 28 to 25 Gy, for example about 28 Gy, about 30 Gy or about 35 Gy are administered or delivered to the patient, preferably in fractions of 0.5
30 to 5 Gy, more preferably 0.8 to 3 Gy and especially 1 to 2.5 Gy, for example about 1.0, about 1.3 Gy, about 1.6 Gy, about 1.8 Gy, about 2.0 Gy, about 2.5 Gy or about 3.0 Gy, per per administration or delivery, which is preferably also the amount of radiation per day on which the administration or delivery

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of the radiation takes place. Accordingly, an administration or delivery of 1.5 to 2.5 Gy and preferably 1.8 to 2.2 Gy per day for 2 or 3 days within one week is preferred. Accordingly, an administration or delivery of 0.7 to 1.3 Gy and preferably 0.9 to 1.2 Gy per day for 3 to 6 days, preferably for 5 days and more preferably 5 consecutive days, within one week, is also preferred. Generally, the administration or delivery of 1.0 to 3.0 Gy, preferably about 1.0, about 2.0 Gy or about 3.0 Gy per day for 2 or 3 days within one week is especially preferred. The kind of application of focal radiotherapy as described above is preferred in the treatment of brain metastases, preferably brain metastases of cancer types selected from the group consisting of small cell lung cancer and non-small cell lung cancer, preferably non-small cell lung cancer, breast cancer, metastatic melanoma, metastatic androgen independent prostate cancer, metastatic androgen dependent prostate cancer.

Typically, both the amounts of about 30 Gy and about 60 Gy are administered or delivered to the patient within about six consecutive weeks.

Depending on the brain cancer type, it can be also advantageous to apply to the patient a certain amount of radiotherapy or radiation in a whole brain radiation setting, more preferably a fractionated whole brain radiation setting. Thus, it can be advantageous to apply to the patient an amount of radiotherapy or radiation in the range 20 to 60 Gy, preferably 20 to 40 Gy, more preferably about 30 Gy, in a whole brain radiation setting. In this setting the amount of radiation applied to the patient is preferably divided (or fractionated) into 5 to 20 applications, preferably consisting of 1 to 6 Gy each, more preferably consisting of 2 to 4 Gy each and especially consisting of about 3 Gy each. In the whole brain radiation setting, it is especially preferred to apply to the patient about 10 separate applications of radiation, preferably consisting of about 3 Gy per application. In the whole brain radiation setting, it is especially preferred to apply the radiation during 1 to 4 consecutive weeks, preferably in a 5 times per week application scheme for the radiation.

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5 A whole brain radiation setting, especially a whole brain radiation setting as described herein, can be advantageous in the treatment of brain metastases, especially brain metastases of cancer types described herein. A whole brain radiation setting, especially a whole brain radiation setting as described herein, can be especially advantageous in the treatment of brain metastases of NSCLC and/or SCLC, preferably NSCLC.

10 In the whole brain radiation setting, the application of the radiation is preferably combined with the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal). In this setting, the administration of the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-
15 DPhe-NMeVal), to the patient is preferably performed on each day or about each day on which the application of the whole brain radiation to the patient takes place.

Accordingly, preferably in this setting, the whole brain radiation (typically 20
20 to 60 Gy in total, preferably 20 to 40 Gy in total, more preferably about 30 Gy in total) is applied to the patient in fractions of 2 to 4 Gy for each single application (i.e. 2 to 4 Gy on each single day that the application of whole brain radiation takes place). In this setting, it is especially preferred to apply to the patient 5 to 20 and more preferably about 10 separate applications of
25 radiation (i.e. to apply the whole brain radiation to the patient on 5 to 20 and more preferably about 10 days), preferably consisting of about 3 Gy per application (i.e. per day). In the whole brain radiation setting, it is especially preferred to apply the radiation to the patient during 1 to 4 consecutive weeks, preferably in a 5 times per week application scheme for the radiation,
30 wherein the radiation consisting of about 2 to 4 Gy and especially of about about 3 Gy per application (i.e. per day) is combined with the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), in an amount of

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about 500 mg, about 1000 mg or about 2000 mg per patient and per day on about each day the application of radiotherapy to the patient takes place.

- 5 Thus, a subject of the instant application is a method of treating brain metastases, preferably brain metastases of lung cancer, more preferably brain metastases of NSCLC and/or SCLC, said method comprising
- a) the application of 2 to 4 Gy of whole brain radiation on 3 to 7 and preferably 4 to 6 days during one week, preferably for two or more
- 10 consecutive weeks and more preferably for 2 to 4 consecutive weeks, and
- b) the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), on about every day on which the application of the whole brain radiation according to step a) takes place, said administration
- 15 preferably consisting of about 500 mg, about 1000 mg or about 2000 mg per day of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), and optionally
- c) the application of one or more further cancer cotherapeutic agents
- 20 (different from the whole brain radiation according to step a) and the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) according to step b).

- Thus, a preferred subject of the instant application is a method of treating brain metastases, preferably brain metastases of lung cancer, more
- 25 preferably brain metastases of NSCLC and/or SCLC, said method comprising
- a) the application of about 3 Gy of whole brain radiation on 5 consecutive during one week, preferably for two or more consecutive weeks and more preferably for 2 consecutive weeks, and
- 30 b) the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), on about every day on which the application of the whole brain radiation according to step a) takes place, said administration

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preferably consisting of about 500 mg, about 1000 mg or about 2000 mg per day of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal),
5 and optionally

c) the application of one or more further cancer cotherapeutic agents (different from the whole brain radiation according to step a) and the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) according to step b).

10 A timed administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), as described herein is also preferred in these methods of treatment. Especially preferred is an administration of the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable
15 salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), to the patient 2 to 5 hours, more preferably about 3 hours, prior to the application of the whole brain radiation. For example, the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), can be administered to the patient in an about one hour i. V.
20 infusion that starts about three hours before the application of the whole brain radiation on the same day.

The further cancer cotherapeutic agent or the further cancer cotherapeutic agents in the two above described methods is/are preferably selected from
25 the cancer cotherapeutic agents described herein and more preferably selected from the group consisting of Temozolomide, Cisplatin, Oxaliplatin, Carboplatin, 5-FU, Darcabazine, Procarbazine, Vinblastin, Vincristine, Irinotecan, Taxol, Paclitaxel, Docetaxel, Gemcitabine, Gleevec, Iressa, Tarceva and Nexavar, Herceptin, Bevacizumab, Cetuximab, Nimotuzumab,
30 Sorafenib, Sunitinib and ZD6474 (ZACTIMA™), and even more preferably selected from Temozolomide, Cisplatin, Oxaliplatin, Vinblastin, Taxol, Gemcitabine, Gleevec and Iressa. Especially preferably the one or more, preferably one or two further cancer cotherapeutic agents are selected from

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the group consisting of Temozolomide, Cisplatin, Oxaliplatin, Carboplatin, Vinblastin, Vincristine, Irinotecan, Taxol, Paclitaxel, Docetaxel, Gemcitabine, Bevacizumab and Cetuximab.

5

The above described regimens or methods of treatment comprising whole brain radiation can optionally be combined with a pre-treatment, post-treatment and/or maintenance treatment, preferably a pre-treatment, post-treatment and/or maintenance treatment as described herein, and especially
10 a pre-treatment, post-treatment and/or maintenance treatment selected from one or more of the below described methods of treatment (A), (B), (C), (D), (E) and (F). Especially preferred in this respect are pre-treatments, post-treatments and/or maintenance treatments that do not comprise radiotherapy.

15

The above described regimens or methods methods of treatment comprising whole brain radiation can also be additional or intermediate treatments, preceded, followed or surrounded by a standard treatment of the respective primary tumour or a standard treatment of the the brain metasases based on
20 the standard treatment of the respective primary tumour.

25

The above described regimens or methods methods of treatment comprising whole brain radiation can preferably also be additional or intermediate treatments, preceded, followed or surrounded by advanced treatment
regimens of the respective primary tumour or by advanced treatment
regimens of the the brain metasases based on said advanced treatment
regimens of the respective primary tumour, wherein said advanced treatment
regimens are selected from the treatment regimens as described in
PCT/EP2008/000328 (WO 2008/087025), and/or described in
30 PCT/EP2008/005831 (WO 2009/010287), the disclosure of which is included herein by reference in their entirety.

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5 The above described regimens or methods of treatment comprising whole brain radiation can preferably also be additional or intermediate treatments, preceded, followed or surrounded by treatment regimens of the respective primary tumour or by treatment regimens of the the brain metasases, said treatment regimens of the respective primary tumour or of the the brain metasases preferably comprising or consisting of one or more, preferably two or more, selected of the following:

- 10 a) the administration of at least one platinum containing chemotherapeutic agent agent, preferably a platinum containing chemotherapeutic agent agent selected from cisplatin, carboplatin and oxaliplatin;
- b) the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal);
- 15 c) the administration of cetuximab;
- d) the administration of one or more chemotherapeutic agents, selected from vinorelbine, etoposide, gemcitabine, vincristine, irinotecan, paclitaxel, docetaxel, pemetrexed, 5-FU and doxorubicine; and/or
- 20 e) the application of radiotherapy, preferably external beam radiation, more preferably standard (external beam) radiotherapy, preferably consisting of 20 to 70 Gray, to the respective tumor and/or the metastases thereof.

25 If two or more of the above treatment options are administered or applied to the patient, they are preferably administered or applied to the patient, substantially concurrently or sequentially, preferably once within one week or more preferably several times within one week, preferably for two or more consecutive weeks.

30 The above described preceding, following or surrounding regimens or methods are preferred with respect to NSCLC, SCLC and/or metatases thereof.

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A preferred subject of the instant invention is a method of treatment (A), being selected from the group consisting the method of treatment (A1), the method of treatment (A2) and method of treatment (A3) as described below:

5

Accordingly, a preferred subject of the instant invention is a method of treatment (A1), comprising per patient within one week

10

a) the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), in a twice weekly administration scheme comprising about 500 mg or about 2000 mg (flat) of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) per administration; and

15

b) the once daily administration or delivery of fractionated focal radiotherapy at 1.5 to 2.5 Gy per fraction, on 2 to 7 days, preferably 3 to 6 days, more preferably 5 days and especially preferably on 5 consecutive days within one week;

20

wherein said treatment is preferably applied to the patient for at least 2 weeks, more preferably for at least 2 consecutive weeks, even more preferably for at least 4 consecutive weeks and especially for 6 or more consecutive weeks, but generally for less than 13 consecutive weeks, preferably less than 11 consecutive weeks and even more preferably less than 9 consecutive weeks, for example an application for 2 consecutive weeks, 4 consecutive weeks, 5 consecutive weeks, 6 consecutive weeks, 7 consecutive weeks or 10 consecutive weeks.

25

With respect to this method, said specific integrin ligand is preferably administered on days on which the fractionated focal radiotherapy is administered or delivered to the patient, more preferably administered in a timed administration as described herein. With respect to this method, said

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specific integrin ligand is preferably administered in a timed administration as described herein, more preferably 1,5 to 20 hours (h), preferably 2 to 16 h, more preferably 2 to 12 h, even more preferably 2 to 10 h, even more

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preferably 3 to 10 h and especially 2 to 8 h prior to the application of the radiotherapy.

- 5 The afore described method of treatment is especially advantageous in the treatment of tumors or cancer as described herein, preferably tumors or cancer selected from the group consisting of primary brain tumours, astrocytoma, preferably astrocytoma grade II, III and/or IV, glioblastoma, preferably glioblastoma multiforme, and brain metastases of other cancer
- 10 types, preferably selected from the group consisting of small cell lung cancer and non-small cell lung cancer, preferably non-small cell lung cancer, breast cancer, metastatic melanoma, metastatic androgen independent prostate cancer, metastatic androgen dependent prostate cancer.
- 15 The afore described method of treatment can optionally be combined with the additional administration of one or more specific integrin ligands as described herein other than cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably specific integrin ligands selected from the group consisting of LM609, Vitaxin, Abegrin, Abciximab,
- 20 P1F6, 14D9.F8 and CNTO95, more preferably Vitaxin, Abegrin, CNTO95 and Abciximab), and/or the additional administration of at least one cancer cotherapeutic agent as described herein other than radiotherapy, preferably at least one cancer cotherapeutic agent selected from the group consisting of
- 25 Temozolomide, Cisplatin, Oxaliplatin, Carboplatin, 5-FU, Darcabazine, Procarbazine, Vinblastin, Vincristine, Irinotecan, Paclitaxel, Docetaxel, Gemcitabine, Gleevec, Iressa, Tarceva and Nexavar, even more preferably preferably selected from Temozolomide, Cisplatin, Oxaliplatin, Vinblastin, Taxol, Gemcitabine, Gleevec and Iressa, and/or selected from the group
- 30 consisting Herceptin, Bevacizumab (rhuMAb-VEGF, Avastin®), Cetuximab (Erbix®) and Nimotuzumab, and preferably Sorafenib (Nexavar®), Sunitinib (Sutent®) and ZD6474 (ZACTIMA™),

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Accordingly, a preferred subject of the instant invention is a method of treatment (A2), comprising per patient within one week

5 a) the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), in a 5 times weekly administration scheme

consisting of about 2000 mg (flat) of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) per administration (i.e. per day) and more preferably

10 consisting of about 2000 mg (flat) of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) administered per day on 5 consecutive days; and

b) the once daily administration or delivery of fractionated focal radiotherapy at 1.5 to 2.5 Gy per fraction, on 2 to 7 days, preferably 3 to 6 days, more preferably 5 days, even more preferably on 5 consecutive days within one
15 week, and preferably on the same days the administration of the specific integrin ligand according to a) takes place;

wherein said treatment is preferably applied to the patient for at least 2 weeks, more preferably for at least 2 consecutive weeks, even more preferably for at least 4 consecutive weeks and especially for 6 or more
20 consecutive weeks, but generally for less than 13 consecutive weeks, preferably less than 11 consecutive weeks and even more preferably less than 9 consecutive weeks, for example an application for 2 consecutive weeks, 4 consecutive weeks, 5 consecutive weeks, 6 consecutive weeks, 7 consecutive weeks or 10 consecutive weeks. Especially preferred are 6
25 consecutive weeks.

Said administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) on 5 consecutive days preferably takes place according to the 5 times weekly administration scheme as described herein.

30

With respect to this method, said specific integrin ligand is preferably administered on days on which the fractionated focal radiotherapy is administered or delivered to the patient, more preferably administered in a

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timed administration as described herein. With respect to this method, said specific integrin ligand is preferably administered in a timed administration as described herein, more preferably 1,5 to 20 hours (h), preferably 2 to 16 h, more preferably 2 to 12 h, even more preferably 2 to 10 h, even more preferably 3 to 10 h and especially 2 to 8 h prior to the application of the radiotherapy.

The afore described method of treatment is especially advantageous in the treatment of tumors or cancer as described herein, preferably tumors or cancer selected from the group consisting of primary brain tumours, astrocytoma, preferably astrocytoma grade II, III and/or IV, glioblastoma, preferably glioblastoma multiforme, and brain metastases of other cancer types, preferably selected from the group consisting of small cell lung cancer and non-small cell lung cancer, preferably non-small cell lung cancer, breast cancer, metastatic melanoma, metastatic androgen independent prostate cancer, metastatic androgen dependent prostate cancer. Especially preferred are astrocytoma grade II, III and/or IV and glioblastoma, preferably glioblastoma multiforme.

This method of treatment (A2) is especially preferred for "unmethylated patients" as defined in this application.

The afore described method of treatment can optionally be combined with the additional administration of one or more specific integrin ligands as described herein other than cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably specific integrin ligands selected from the group consisting of LM609, Vitaxin, Abegrin, Abciximab, P1F6, 14D9.F8 and CNTO95, more preferably Vitaxin, Abegrin, CNTO95 and Abciximab), and/or the additional administration of at least one cancer cotherapeutic agent as described herein other than radiotherapy, preferably at least one cancer cotherapeutic agent selected from the group consisting of

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5 Temozolomide, Cisplatin, Oxaliplatin, Carboplatin, 5-FU, Darcabazine, Procarbazine, Vinblastin, Vincristine, Irinotecan, Paclitaxel, Docetaxel, Gemcitabine, Gleevec, Iressa, Tarceva and Nexavar, even more preferably preferably selected from Temozolomide, Cisplatin, Oxaliplatin, Vinblastin, Taxol, Gemcitabine, Gleevec and Iressa, and/or selected from the group consisting Herceptin, Bevacizumab (rhuMAb-VEGF, Avastin®), Cetuximab (Erbix®) and Nimotuzumab, and preferably Sorafenib (Nexavar®), Sunitinib (Sutent®) and ZD6474 (ZACTIMA™),

10

Accordingly, a preferred subject of the instant invention is a method of treatment (A3), comprising per patient within one week

- 15 a) the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) on 5 consecutive days in an amount of about 2000 mg (flat) per day; and
b) the once daily administration or delivery of fractionated focal radiotherapy at 1.5 to 2.5 Gy per fraction, on the same 5 consecutive days on which the administration of the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) according to a) takes place;

20 wherein said treatment is preferably applied to the patient for at least 2 weeks, more preferably for at least 2 consecutive weeks, even more preferably for at least 4 consecutive weeks and especially for 6 or more consecutive weeks, but generally for less than 13 consecutive weeks, preferably less than 11 consecutive weeks and even more preferably less than 9 consecutive weeks, for example an application for 2 consecutive
25 weeks, 4 consecutive weeks, 5 consecutive weeks, 6 consecutive weeks, 7 consecutive weeks or 10 consecutive weeks. Especially preferred are 6 consecutive weeks.

30 Said administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) on 5 consecutive days preferably takes place according to the 5 times weekly administration scheme as described herein.

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With respect to this method, the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal is administered on the days on which the fractionated focal radiotherapy is administered or delivered to the patient and more preferably administered in a timed administration as described herein. With respect to this method, said specific integrin ligand is preferably administered in a timed administration as described herein, more preferably 1,5 to 20 hours (h), preferably 2 to 16 h, more preferably 2 to 12 h, even more preferably 2 to 10 h, even more preferably 3 to 10 h and especially 2 to 8 h prior to the application of the radiotherapy.

The afore described method of treatment is especially advantageous in the treatment of tumors or cancer as described herein, preferably tumors or cancer selected from the group consisting of primary brain tumours, astrocytoma, preferably astrocytoma grade II, III and/or IV, glioblastoma, preferably glioblastoma multiforme, and brain metastases of other cancer types, preferably selected from the group consisting of small cell lung cancer and non-small cell lung cancer, preferably non-small cell lung cancer, breast cancer, metastatic melanoma, metastatic androgen independent prostate cancer, metastatic androgen dependent prostate cancer. Especially preferred are astrocytoma grade II, III and/or IV and glioblastoma, preferably glioblastoma multiforme.

This method of treatment (A3) is especially preferred for "unmethylated patients" as defined in this application.

Accordingly, a preferred subject of the instant invention is a method of treatment (B), being selected from the group consisting the method of treatment (B1), the method of treatment (B2) and method of treatment (B3) as described below:

Accordingly, a preferred subject of the instant invention is a method of treatment (B1), comprising per patient within one week

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- 5 a) the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), in a twice weekly administration scheme comprising about 500 mg or about 2000 mg (flat) of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) per administration; and
- b) the once daily administration or delivery of fractionated focal radiotherapy at 1.5 to 2.5 Gy per fraction, preferably on 2 to 5 days within one week, more preferably on 5 consecutive days within one week;
- 10 c) the administration of temozolomide on 2 to 7 days, preferably 5 to 7 days, more preferably 5 or 7 days and especially preferably on 5 or 7 consecutive days within one week, preferably in an amount per day of 25 mg/m² to 250 mg/m², more preferably 50 mg/m² to 150 mg/m², even more preferably 65 mg/m² to 100 mg/m², and especially about 75 mg/m²;
- 15 wherein said method of treatment is preferably applied to the patient for at least 2 weeks, more preferably for at least 2 consecutive weeks, even more preferably for at least 4 consecutive weeks and especially for 6 or more consecutive weeks, but generally for less than 13 consecutive weeks, preferably less than 11 consecutive weeks and even more preferably less
- 20 than 9 consecutive weeks, for example it is applied for 2 consecutive weeks, 4 consecutive weeks, 5 consecutive weeks, 6 consecutive weeks, 7 consecutive weeks or 10 consecutive weeks.

25 With respect to this method, said specific integrin ligand is preferably administered on days on which the fractionated focal radiotherapy is administered or delivered to the patient, more preferably administered in a timed administration as described herein. With respect to this method, said specific integrin ligand is more preferably administered in a timed administration as described herein, more preferably 1,5 to 20 hours (h),

30 preferably 2 to 16 h, more preferably 2 to 12 h, even more preferably 2 to 10 h, even more preferably 3 to 10 h and especially 2 to 8 h prior to the application of the radiotherapy. With respect to this method, the temozolomide is preferably administered orally, preferably 15 to 300 minutes,

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more preferably 30 to 180 minutes, even more preferably 45 to 90 minutes and especially about one hour or within one hour before the administration or delivery of the radiotherapy. This administration scheme for cancer
5 cotherapeutic agents other than radiotherapy, preferably temozolomide, is preferably also suitable for the other methods or uses as described herein.

The afore described method of treatment is especially advantageous in the treatment of tumors or cancer as described herein, preferably tumors or
10 cancer selected from the group consisting of primary brain tumours, astrocytoma, preferably astrocytoma grade II, III and/or IV, glioblastoma, preferably glioblastoma multiforme, and brain metastases of other cancer types, preferably selected from the group consisting of small cell lung cancer and non-small cell lung cancer, preferably non-small cell lung cancer, breast
15 cancer, metastatic melanoma, metastatic androgen independent prostate cancer, metastatic androgen dependent prostate cancer.

Accordingly, a preferred subject of the instant invention is a method of treatment (B2), comprising per patient within one week
20 a) the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), in a 5 times weekly administration scheme consisting of about 2000 mg (flat) of cyclo-(Arg-Gly-Asp-DPhe-NMeVal)
25 per administration (i.e. per day) and more preferably consisting of about 2000 mg (flat) of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) administered per day on 5 consecutive days; and
b) the once daily administration or delivery of fractionated focal radiotherapy at 1.5 to 2.5 Gy per fraction, on 2 to 7 days, preferably 3 to 6 days, more
30 preferably 5 days, even more preferably on 5 consecutive days within one week, and preferably on the same days the administration of the specific integrin ligand according to a) takes place;

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- 5 c) the administration of temozolomide on 2 to 7 days, preferably 5 to 7 days, more preferably 5 or 7 days, even more preferably on 5 or 7 consecutive days within one week and especially preferably on the same days the administration of the specific integrin ligand according to a) and/or the delivery of the fractionated focal radiotherapy according to b) takes place, preferably in an amount per day of 25 mg/m^2 to 250 mg/m^2 , more preferably 50 mg/m^2 to 150 mg/m^2 , even more preferably 65 mg/m^2 to 100 mg/m^2 , and especially about 75 mg/m^2 ;
- 10 wherein said method of treatment is preferably applied to the patient for at least 2 weeks, more preferably for at least 2 consecutive weeks, even more preferably for at least 4 consecutive weeks and especially for 6 or more consecutive weeks, but generally for less than 13 consecutive weeks, preferably less than 11 consecutive weeks and even more preferably less
- 15 than 9 consecutive weeks, for example it is applied for 2 consecutive weeks, 4 consecutive weeks, 5 consecutive weeks, 6 consecutive weeks, 7 consecutive weeks or 10 consecutive weeks. Especially preferred are 6 consecutive weeks.
- 20 Said administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) on 5 consecutive days preferably takes place according to the 5 times weekly administration scheme as described herein. The same holds preferably true for the delivery of the radiotherapy and/or the administration of the temozolomide, if temozolomide is administered 5 times a week.
- 25 With respect to this method, said specific integrin ligand is preferably administered on days on which the fractionated focal radiotherapy is administered or delivered to the patient, more preferably administered in a timed administration as described herein. With respect to this method, said
- 30 specific integrin ligand is more preferably administered in a timed administration as described herein, more preferably 1,5 to 20 hours (h), preferably 2 to 16 h, more preferably 2 to 12 h, even more preferably 2 to 10 h, even more preferably 3 to 10 h and especially 2 to 8 h prior to the

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application of the radiotherapy. With respect to this method, the temozolomide is preferably administered orally, preferably 15 to 300 minutes, more preferably 30 to 180 minutes, even more preferably 45 to 90 minutes and especially about one hour or within one hour before the administration or delivery of the radiotherapy. This administration scheme for cancer cotherapeutic agents other than radiotherapy, preferably temozolomide, is preferably also suitable for the other methods or uses as described herein.

The afore described method of treatment is especially advantageous in the treatment of tumors or cancer as described herein, preferably tumors or cancer selected from the group consisting of primary brain tumours, astrocytoma, preferably astrocytoma grade II, III and/or IV, glioblastoma, preferably glioblastoma multiforme, and brain metastases of other cancer types, preferably selected from the group consisting of small cell lung cancer and non-small cell lung cancer, preferably non-small cell lung cancer, breast cancer, metastatic melanoma, metastatic androgen independent prostate cancer, metastatic androgen dependent prostate cancer. Especially preferred are astrocytoma grade II, III and/or IV and glioblastoma, preferably glioblastoma multiforme.

This method of treatment (B2) is especially preferred for "unmethylated patients" as defined in this application.

Accordingly, a preferred subject of the instant invention is a method of treatment (B3), comprising per patient within one week

- a) the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) on 5 consecutive days in an amount of about 2000 mg (flat) per day; and
- b) the once daily administration or delivery of fractionated focal radiotherapy at 1.5 to 2.5 Gy per fraction, on the same 5 consecutive days on which the administration of the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) according to a) takes place;

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c) the administration of temozolomide on 7 consecutive days during the week on which the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) according to a) and/or the delivery of the fractionated focal radiotherapy according to b) takes place, preferably in an amount per day of 25 mg/m² to 250 mg/m², more preferably 50 mg/m² to 150 mg/m², even more preferably 65 mg/m² to 100 mg/m², and especially about 75 mg/m²; wherein said method of treatment is preferably applied to the patient for at least 2 weeks, more preferably for at least 2 consecutive weeks, even more preferably for at least 4 consecutive weeks and especially for 6 or more consecutive weeks, but generally for less than 13 consecutive weeks, preferably less than 11 consecutive weeks and even more preferably less than 9 consecutive weeks, for example it is applied for 2 consecutive weeks, 4 consecutive weeks, 5 consecutive weeks, 6 consecutive weeks, 7 consecutive weeks or 10 consecutive weeks. Especially preferred are 6 consecutive weeks.

Said administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) on 5 consecutive days preferably takes place according to the 5 times weekly administration scheme as described herein. The same holds preferably true for the delivery of the radiotherapy.

With respect to this method, said specific integrin ligand is preferably administered on days on which the fractionated focal radiotherapy is administered or delivered to the patient, more preferably administered in a timed administration as described herein. With respect to this method, said specific integrin ligand is more preferably administered in a timed administration as described herein, more preferably 1,5 to 20 hours (h), preferably 2 to 16 h, more preferably 2 to 12 h, even more preferably 2 to 10 h, even more preferably 3 to 10 h and especially 2 to 8 h prior to the application of the radiotherapy. With respect to this method, the temozolomide is preferably administered orally, preferably 15 to 300 minutes, more preferably 30 to 180 minutes, even more preferably 45 to 90 minutes

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and especially about one hour or within one hour before the administration or delivery of the radiotherapy. This administration scheme for cancer cotherapeutic agents other than radiotherapy, preferably temozolomide, is preferably also suitable for the other methods or uses as described herein.

The afore described method of treatment is especially advantageous in the treatment of tumors or cancer as described herein, preferably tumors or cancer selected from the group consisting of primary brain tumours, astrocytoma, preferably astrocytoma grade II, III and/or IV, glioblastoma, preferably glioblastoma multiforme, and brain metastases of other cancer types, preferably selected from the group consisting of small cell lung cancer and non-small cell lung cancer, preferably non-small cell lung cancer, breast cancer, metastatic melanoma, metastatic androgen independent prostate cancer, metastatic androgen dependent prostate cancer. Especially preferred are astrocytoma grade II, III and/or IV and glioblastoma, preferably glioblastoma multiforme.

This method of treatment (B3) is especially preferred for "unmethylated patients" as defined in this application.

Accordingly, a preferred subject of the instant invention is a method of treatment (C), comprising per patient

a) optionally the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), preferably as a single agent, in a twice weekly administration scheme comprising about 500 mg or about 2000 mg (flat) of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) per administration, wherein the weekly administration scheme is applied to patient for at least one week, preferably 1 to 12 weeks, more preferably 1 to 6 weeks, even more preferably 1 to 3 weeks and especially 1 or 2 weeks; followed by, preferably in the consecutive week(s),

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- b) the administration of temozolomide on 2 to 7 days, preferably 3 to 6 days, more preferably 5 days and especially preferably on 5 consecutive days, within one week, preferably in an amount per day of 50 mg/m² to 350 mg/m², more preferably 75 mg/m² to 250 mg/m², even more preferably 150 mg/m² to 250 mg/m², and especially about 200 mg/m²; preferably combined within said week with the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), in a twice weekly administration scheme comprising about 500 mg or about 2000 mg (flat) of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) per administration, wherein step b) is applied to the patient at least once, preferably 1 to 12 weeks consecutively, more preferably 1 to 6 weeks consecutively, even more preferably 1 to 3 weeks consecutively and especially one week or 2 weeks consecutively; and wherein said specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is preferably administered on days where the temozolomide is also administered; optionally followed by, preferably in the consecutive week(s),
- c) the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), preferably as a single agent, in a twice weekly administration scheme comprising about 500 mg or about 2000 mg (flat) of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) per administration, wherein the weekly administration scheme is applied to patient for at least one week, preferably 1 to 12 weeks, more preferably 2 to 6 weeks, even more preferably 2 to 4 weeks and especially 3 weeks.
- 30

Preferably, said method of treatment is preferably applied to the patient at least once, more preferably at least two times, even more preferably at least four times and especially preferably six or more times, preferably six times,

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5 but generally less than 13 times, preferably less than 9 times, even more preferably less than seven times, for example 3 times, 5 times, 6 times, 7 times or 6 times, preferably in a consecutive row, i.e. without one or more pauses in between the repetition of the method.

10 With respect to this method, said specific integrin ligand is more preferably administered in a timed administration as described herein, more preferably 1,5 to 20 hours (h), preferably 2 to 16 h, more preferably 2 to 12 h, even more preferably 2 to 10 h, even more preferably 3 to 10 h and especially 2 to 8 h prior to the application of the radiotherapy. With respect to this method, the temozolomide is preferably administered orally, preferably in analog manner as described herein for the timed administration of the specific integrin ligand, or preferably within 5 h, preferably within 3 h and especially 15 within 1 h before or after, preferably after, the delivery of the radiotherapy.

The afore described method of treatment (C) is especially advantageous in the treatment of tumors or cancer as described herein, preferably tumors or cancer selected from the group consisting of primary brain tumours, 20 astrocytoma, preferably astrocytoma grade II, III and/or IV, glioblastoma, preferably glioblastoma multiforme, and brain metastases of other cancer types, preferably selected from the group consisting of small cell lung cancer and non-small cell lung cancer, preferably non-small cell lung cancer, breast cancer, metastatic melanoma, metastatic androgen independent prostate cancer, metastatic androgen dependent prostate cancer. 25

Accordingly, a preferred subject of the instant invention is a method of treatment (D), comprising per patient

30 a) within one first week: the administration of temozolomide on 2 to 7 days, preferably 3 to 6 days, more preferably 5 days and especially preferably on 5 consecutive days, preferably in an amount per day of 50 mg/m² to 350 mg/m², more preferably 75 mg/m² to 250 mg/m², even more preferably 150 mg/m² to 250 mg/m², and especially about 200 mg/m²;

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combined within said first week with the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), in a twice weekly administration scheme or a 5 times weekly administration scheme, preferably in a twice weekly administration scheme, said administration scheme comprising about 500 mg or about 2000 mg (flat) of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) per administration, b) and in the directly following weeks 2, 3 and 4: the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), preferably as a single agent, in a twice weekly administration scheme or a 5 times weekly administration scheme, preferably in a twice weekly administration scheme, said administration scheme comprising about 500 mg or about 2000 mg (flat) of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) per administration.

Preferably, said method of treatment (D) is applied to the patient at least once, more preferably at least twice, even more preferably at least four times and especially six or more times, but generally less than 24 times, preferably less than 15 times, more preferably less than 11 times, for example 3 times, 4 times, 5 times, 6 times, 7 times or 12 times. This preferably holds true if treatment (D) is applied to the patient for the given times without a pause, break or gap of at least one week, preferably of at least four weeks. After such a pause, gap or break, the above described administration scheme can be repeated once or several times, if necessary, for example for another 6 times.

With respect to this method, said specific integrin ligand is more preferably administered in a timed administration as described herein, more preferably 1,5 to 20 hours (h), preferably 2 to 16 h, more preferably 2 to 12 h, even more preferably 2 to 10 h, even more preferably 3 to 10 h and especially 2 to 8 h prior to the application of the radiotherapy. With respect to this method,

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the temozolomide is preferably administered orally, preferably With respect to this method, the temozolomide is preferably administered orally, preferably in analog manner as described herein for the timed administration of the
5 specific integrin ligand, or preferably within 5 h, preferably within 3 h and especially within 1 h before or after, preferably after, the delivery of the radiotherapy.

The afore described method of treatment (D) can optionally be combined with
10 one or more weeks of treatment, comprising the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), to a patient, preferably as a single agent, in a twice weekly administration scheme comprising about 500 mg or about 2000 mg (flat) of
15 cyclo-(Arg-Gly-Asp-DPhe-NMeVal) per administration, before, preferably directly before, and/or following, preferably directly following the afore described method of treatment (D). Preferably, the method of treatment (D) is combined with one or more weeks of additional treatment, comprising the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-
20 NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), to a patient, preferably as a single agent, in a twice weekly administration scheme comprising about 500 mg or about 2000 mg (flat) of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) per administration, at least in the week directly prior to the first week of the method of treatment
25 (D), and/or at least one week of said additional treatment (with or without pauses), for example untill progression, stable disease or healing occurs.

The afore described method of treatment (D) is especially advantageous in the treatment of tumors or cancer as described herein, preferably tumors or
30 cancer selected from the group consisting of primary brain tumours, astrocytoma, preferably astrocytoma grade II, III and/or IV, glioblastoma, preferably glioblastoma multiforme, and brain metastases of other cancer types, preferably selected from the group consisting of small cell lung cancer.

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and non-small cell lung cancer, preferably non-small cell lung cancer, breast cancer, metastatic melanoma, metastatic androgen independent prostate cancer, metastatic androgen dependent prostate cancer.

5

A preferred subject of the instant invention is a method of treatment (E), comprising the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), to a patient, preferably as a
10 single agent, in a twice weekly administration scheme comprising about 500 mg or about 2000 mg (flat) of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) per administration, preferably for one week or for at least two consecutive weeks.

If the method of treatment (E) is applied for two or more consecutive weeks,
15 it is preferably applied to the patient at least for four consecutive weeks, more preferably at least for six consecutive weeks, for example until tumor progression, stable disease or healing occurs. Preferably, the method of treatment (E) is combined with one or more of the above/below described methods of treatment (A), (B), (C) and/or (D). If the method of treatment (E)
20 is combined with one or more of the above/below described methods of treatment (A), (B), (C) and/or (D), it is preferably applied in advance or at the end of said methods of treatment (A), (B), (C) and/or (D), or both in advance and at the end of said methods. Preferred combinations including one or more methods of treatment (A), (B), (C) and/or (D) and additionally the
25 method of treatment (E) are given below.

A preferred subject of the instant invention is a method of treatment, wherein two or more of the treatment regimens, administration schemes and/or methods of treatment described herein are combined. A more preferred
30 subject of the instant invention is a method of treatment, comprising two or more of the above/below described methods of treatment (A), (B), (C), (D), (E) and/or (F), preferably including one or more of the preferred options as described with respect to the respective method (A), (B), (C), (D), (E) and/or

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(F). An especially preferred subject of the instant invention is a method of treatment, consisting of three or more of the above/below described methods of treatment (A), (B), (C), (D), (E) and/or (F), preferably including one or more of the preferred options as described with respect to the respective methods (A), (B), (C), (D), (E) and/or (F).

Preferred is a method of treatment (A), preferably a method of treatment (A), selected from the group consisting of (A2) and (A3), wherein said method is applied to the patient for 2 to 8 weeks and especially 6 weeks, preferably without a pause. Preferred in this respect is the method of treatment (A3), wherein said method is applied to the patient for 2 to 8 weeks and especially 6 weeks, preferably without a pause.

Preferred is a method of treatment, comprising or consisting of: the method of treatment (E), wherein said method is applied to the patient for 1 to 4 weeks, preferably without a pause, directly followed by the method of treatment (A), wherein said method is applied to the patient for 2 to 8 weeks and especially 6 weeks, preferably without a pause, optionally directly followed by the method of treatment (E), wherein said method is applied to the patient for at least for weeks, or preferably until progression, stable disease, partial/total response or healing occurs.

25

More preferred is a method of treatment, comprising or consisting of:

- i) optionally the method of treatment (E), wherein said method is applied to the patient for 1 to 4 weeks, preferably without a pause, directly followed by
- ii) the method of treatment (A2) or (A3), wherein said method is applied to the patient for 2 to 8 weeks and especially 6 weeks, preferably without a pause,

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- iii) optionally directly followed by the method of treatment (E), wherein said method is applied to the patient for at least one week, preferably for 2 to 6 weeks and especially for about 4 weeks,
- 5 iv) directly followed by the method of treatment (C) or (D), wherein said method is applied to the patient 2 to 12 times, more preferably 4 to 8 times and especially about 6 times, preferably without a pause,
- v) optionally directly followed by the method of treatment (E), wherein said method is applied to the patient for at least four weeks, or
- 10 preferably until progression, stable disease, partial/total response or healing occurs.

More preferred is a method of treatment, comprising or consisting of:
the method of treatment (E), wherein said method is applied to the patient for
15 1 to 4 weeks, preferably without a pause,
directly followed by
the method of treatment (A2) or (A3), wherein said method is applied to the patient for 2 to 8 weeks and especially 6 weeks, preferably without a pause,
optionally directly followed by
20 the method of treatment (E), wherein said method is applied to the patient for at least for weeks, or preferably until progression, stable disease, partial/total response or healing occurs.

Preferred is a method of treatment, comprising or consisting of:
25 the method of treatment (E), wherein said method is applied to the patient for 1 to 4 weeks without a pause, more preferably about one week,
directly followed by
the method of treatment (B), wherein said method is applied to the patient for 2 to 8 weeks and especially 6 weeks, preferably without a pause,
30 optionally directly followed by
the method of treatment (E), wherein said method is applied to the patient for at least four weeks, or preferably until progression, stable disease, partial/total response or healing occurs.

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More preferred is a method of treatment, comprising or consisting of:
the method of treatment (E), wherein said method is applied to the patient for
5 1 to 4 weeks without a pause, more preferably about one week,
directly followed by
the method of treatment (B2) or (B3), wherein said method is applied to the
patient for 2 to 8 weeks and especially 6 weeks, preferably without a pause,
optionally directly followed by
10 the method of treatment (E), wherein said method is applied to the patient for
at least four weeks, or preferably until progression, stable disease,
partial/total response or healing occurs.

Even more preferred is a method of treatment, comprising or consisting of:

15 i) optionally the method of treatment (E), wherein said method is applied
to the patient for 1 to 4 weeks, preferably without a pause, directly
followed by

ii) the method of treatment (B2) or (B3), wherein said method is applied
to the patient for 2 to 8 weeks and especially 6 weeks, preferably
20 without a pause,

iii) optionally directly followed by the method of treatment (E), wherein
said method is applied to the patient for at least one week, preferably
for 2 to 6 weeks and especially for about 4 weeks,

iv) directly followed by the method of treatment (C) or (D), wherein said
25 method is applied to the patient wherein said method is applied to the
patient 2 to 12 times, more preferably 4 to 8 times and especially
about 6 times, preferably without a pause,

v) optionally directly followed by the method of treatment (E), wherein
said method is applied to the patient for at least four weeks, or
30 preferably until progression, stable disease, partial/total response or
healing occurs.

Preferred is a method of treatment, comprising or consisting of:

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the method of treatment (B), wherein said method is applied to the patient for 2 to 8 weeks and especially 6 weeks, preferably without a pause, directly followed by

5 the method of treatment (D), wherein said method is applied to the patient 2 to 12 times, more preferably 4 to 8 times and especially about 6 times, preferably without a pause.

More preferred is a method of treatment, comprising or consisting of:

10 the method of treatment (B2) or (B3), wherein said method is applied to the patient for 2 to 8 weeks and especially 6 weeks, preferably without a pause, directly followed by

the method of treatment (D), wherein said method is applied to the patient 2 to 12 times, more preferably 4 to 8 times and especially about 6 times,

15 preferably without a pause.

Preferred is a method of treatment, comprising or consisting of:

the method of treatment (B), wherein said method is applied to the patient for 2 to 8 weeks and especially 6 weeks, preferably without a pause,

20 optionally directly followed by

the method of treatment (E), wherein said method is applied to the patient for one or more weeks, preferably one week,

directly followed by

the method of treatment (D), wherein said method is applied to the patient 2

25 to 12 times, more preferably 4 to 8 times and especially about 6 times, preferably without a pause.

More preferred is a method of treatment, comprising or consisting of:

the method of treatment (B2) or (B3), wherein said method is applied to the patient for 2 to 8 weeks and especially 6 weeks, preferably without a pause, optionally directly followed by

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the method of treatment (E), wherein said method is applied to the patient for one or more weeks, preferably one week,

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directly followed by
the method of treatment (D), wherein said method is applied to the patient 2
to 12 times, more preferably 4 to 8 times and especially about 6 times,
5 preferably without a pause.

Preferred is a method of treatment, comprising or consisting of:
the method of treatment (B), wherein said method is applied to the patient for
2 to 8 weeks and especially 6 weeks, preferably without a pause,
10 directly followed by
the method of treatment (E), wherein said method is applied to the patient for
one or more weeks, preferably one week,
directly followed by
the method of treatment (D), wherein said method is applied to the patient 2
15 to 12 times, more preferably 4 to 8 times and especially about 6 times,
preferably without a pause.

More preferred is a method of treatment, comprising or consisting of:
the method of treatment (B2) or (B3), wherein said method is applied to the
20 patient for 2 to 8 weeks and especially 6 weeks, preferably without a pause,
directly followed by
the method of treatment (E), wherein said method is applied to the patient for
one or more weeks, preferably one week,
directly followed by
25 the method of treatment (D), wherein said method is applied to the patient 2
to 12 times, more preferably 4 to 8 times and especially about 6 times,
preferably without a pause.

Preferred is a method of treatment, comprising or consisting of:
30 the method of treatment (E), wherein said method is applied to the patient for
1 to 4 weeks without a pause, more preferably about one week,
directly followed by

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the method of treatment (B), wherein said method is applied to the patient for 2 to 8 weeks and especially 6 weeks, preferably without a pause, optionally directly followed by

5 the method of treatment (E), wherein said method is applied to the patient for one or more weeks, preferably one week, directly followed by

the method of treatment (D), wherein said method is applied to the patient 2 to 12 times, more preferably 4 to 8 times and especially about 6 times, preferably without a pause,

10 optionally directly followed by

the method of treatment (E), wherein said method is applied to the patient for at least 4 weeks, or preferably until progression, stable disease, partial/total response or healing occurs.

15

More preferred is a method of treatment, comprising or consisting of: the method of treatment (E), wherein said method is applied to the patient for 1 to 4 weeks without a pause, more preferably about one week, directly followed by

20 the method of treatment (B2) or (B3), wherein said method is applied to the patient for 2 to 8 weeks and especially 6 weeks, preferably without a pause, optionally directly followed by

the method of treatment (E), wherein said method is applied to the patient for one or more weeks, preferably one week,

25 directly followed by

the method of treatment (D), wherein said method is applied to the patient 2 to 12 times, more preferably 4 to 8 times and especially about 6 times, preferably without a pause,

optionally directly followed by

30 the method of treatment (E), wherein said method is applied to the patient for at least 4 weeks, or preferably until progression, stable disease, partial/total response or healing occurs.

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- Preferred is a method of treatment, comprising or consisting of:
the method of treatment (E), wherein said method is applied to the patient for
1 to 4 weeks without a pause, more preferably about one week,
5 directly followed by
the method of treatment (B), wherein said method is applied to the patient for
2 to 8 weeks and especially 6 weeks, preferably without a pause,
directly followed by
the method of treatment (E), wherein said method is applied to the patient for
10 one or more weeks, preferably one week,
directly followed by
the method of treatment (D), wherein said method is applied to the patient 2
to 12 times, more preferably 4 to 8 times and especially about 6 times,
preferably without a pause,
15 optionally directly followed by
the method of treatment (E), wherein said method is applied to the patient for
at least 4 weeks, or preferably until progression, stable disease, partial/total
response or healing occurs.
- 20 Preferred is a method of treatment, comprising or consisting of:
the method of treatment (E), wherein said method is applied to the patient for
1 to 4 weeks without a pause, more preferably about one week,
directly followed by
the method of treatment (B2) or (B3), wherein said method is applied to the
25 patient for 2 to 8 weeks and especially 6 weeks, preferably without a pause,
directly followed by
the method of treatment (E), wherein said method is applied to the patient for
one or more weeks, preferably one week,
directly followed by
30 the method of treatment (D), wherein said method is applied to the patient 2
to 12 times, more preferably 4 to 8 times and especially about 6 times,
preferably without a pause,
optionally directly followed by

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the method of treatment (E), wherein said method is applied to the patient for at least 4 weeks, or preferably until progression, stable disease, partial/total response or healing occurs.

5

The above given methods that comprise one or more of the methods of treatment selected from (A2), (A3), (B2) and (B3) are especially preferred in the treatment of "unmethyleted patients" as defined according to the instant invention.

10

The above given methods that comprise one or more of the methods of treatment selected from (A2), (A3), (B2) and (B3) can also be advantageous in the treatment of patients of unknown MGMT methylation status.

15

A preferred subject of the instant invention relates to a method or a use according the invention, wherein said specific integrin ligand is preferably administered on days on which the fractionated focal radiotherapy is administered or delivered to the patient, and preferably wherein the administration is a timed administration as described herein.

20

More preferably, the radiotherapy is administered or delivered on one or more days on which the administration of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), also takes place.

25

Even more preferably, cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is administered to the patient on each day on which radiotherapy is administered or delivered to said patient, preferably in an

30

amount of about 2000 mg (flat) per day, preferably calculated as cyclo-(Arg-Gly-Asp-DPhe-NMeVal). Even more preferably, both cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and radiotherapy is

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- administered to the patient on 4 to 6, preferably on 5 or 6 and especially on 5 consecutive days in one week, preferably for two or more consecutive weeks, more preferably for 4 to 8 consecutive weeks and especially about 6
- 5 consecutive weeks. The cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically acceptable salts thereof is preferably administered to the patient in an amount of about 2000 mg (flat) per day, preferably calculated as cyclo-(Arg-Gly-Asp-DPhe-NMeVal).
- 10 This is especially preferred in the treatment of "unmethyleted patients" as defined according to the instant invention, but can also be advantageous in the treatment of patients of unknown MGMT methylation status and/or "methylated patients".
- 15 A preferred subject of the instant invention thus is a method for treating cancer, preferably selected from brain tumours as described herein, wherein:
- a) in week 1, optionally cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered to the patient in a weekly administration scheme as described herein,
- b) in weeks 2 - 7, at least one cancer cotherapeutic agent as described
- 20 herein is applied to the patient, preferably selected from chemotherapeutic agents and radiotherapy as described herein, together with the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) in a weekly administration scheme as described herein,
- c) in weeks 8 – 11, cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered to the
- 25 patient in a weekly administration scheme as described herein,
- d) in weeks 12 – 35, cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered to the patient in a weekly administration scheme as described herein, every fourth week supplemented by the administration of a cancer cotherapeutic agent other than radiotherapy, preferably the chemotherapeutic agent of
- 30 step b), wherein the cancer cotherapeutic agent other than radiotherapy is preferably administered in the weeks 12, 16, 20, 24, 28 and 32.

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- A timed administration as described herein is preferred for cyclo-(Arg-Gly-Asp-DPhe-NMeVal) during weeks 2 – 7. Also preferred is the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) in a 5 times weekly administration scheme, preferably in a 5 times weekly administration scheme consisting of about 10000 mg of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) per patient and per week during weeks 2 – 7. The cancer cotherapeutic agent other than radiotherapy to be applied in steps b) and c) is preferably selected from chemotherapeutic agents, more preferably selected from alkylating agents, even more preferably selected from carboplatin, cisplatin, cyclophosphamide, dacarbazine, carmustine, ifosfamide, lomustine, temozolomide and altretamine, and especially preferably selected from temozolomide and dacarbazine.
- A preferred subject of the instant invention thus is a method for treating cancer, preferably selected from brain tumours as described herein, wherein:
- a) in week 1, optionally cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered to the patient in a weekly administration scheme as described herein,
 - b) in weeks 2 - 7, radiotherapy as described herein, preferably fractionated or a focal radiotherapy as described herein, is applied to the patient, preferably, together with the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) in a weekly administration scheme as described herein, and together with at least one chemotherapeutic agent,
 - c) in weeks 8 – 11, cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered to the patient in a weekly administration scheme as described herein,
 - d) in weeks 12 – 35, cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered to the patient in a weekly administration scheme as described herein, every fourth week supplemented by the administration of the at least one chemotherapeutic agent of step

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b), wherein said chemotherapeutic agent is preferably administered in the weeks 12, 16, 20, 24, 28 and 32.

5 In this method of treatment, the at least one chemotherapeutic agent is preferably selected from alkylating agents, such as carboplatin, cisplatin, cyclophosphamide, dacarbazine, carmustine, ifosfamide, lomustine, temozolomide and altretamine, and more preferably selected from temozolomide and dacarbazine, and or selected from the group consisting of
10 Herceptin, Bevacizumab, Cetuximab, Nimotuzumab, Sorafenib, Sunitinib and ZD6474. A timed administration as described herein is preferred for cyclo-(Arg-Gly-Asp-DPhe-NMeVal) during weeks 2 – 7. Also preferred is the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) in a 5 times weekly administration scheme, preferably in a 5 times weekly administration scheme
15 consisting of about 10000 mg of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) per patient and per week during weeks 2 – 7. The cancer cotherapeutic agent other than radiotherapy to be applied in steps b) and c) is preferably selected from chemotherapeutic agents, more preferably selected from alkylating agents, even more preferably selected from carboplatin, cisplatin,
20 cyclophosphamide, dacarbazine, carmustine, ifosfamide, lomustine, temozolomide and altretamine, and especially preferably selected from temozolomide and dacarbazine.

Accordingly, a preferred subject of the instant invention is a method of
25 treatment (F), being selected from the group consisting of the method of treatment (F1), the method of treatment (F2) and the method of treatment (F2) as described below:

A preferred subject of the instant invention is a method of treatment (F1),
30 comprising or preferably consisting of the following steps or treatments:

- Cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered at a flat dose of about 500 mg or about 2000 mg by i. v. twice a week (preferably on Day 1 and 4, e. g., Monday and Thursday or Tuesday and Friday) for

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35 weeks, preferably without pause. Treatment with cyclo-(Arg-Gly-Asp-DPhe-NMeVal) preferably begins on Day 1 of each week;

- 5 • Additional treatment (1) (Weeks 2 - 7 (max. of 7 weeks)):
Beginning on Day 1 of Week 2, treatment with TMZ and RT will be administered in addition to the cyclo-(Arg-Gly-Asp-DPhe-NMeVal), as follows:
Temomozolomide (TMZ) is administered orally for 6 weeks, at a daily
10 dose of about 75 mg/m^2 (7 days a week),
- 15 Focal radiotherapy (RT) is delivered for 6 weeks, preferably once daily at about 2 Gy per fraction, 5 consecutive days/week, for a total of about 60 Gy. (preferably to be prescribed according to the guidelines of the International Commission on Radiological Units). Adequate immobilization masks can optionally be used to ensure reproducibility. The treatment volume can optionally be determined on the basis of preoperative Gd-MRI of the brain. Treatment volume preferably includes the contrast enhancing lesion as determined by
20 the Gd-MRI, preferably plus plus a 2- to 3-cm margin around that lesion.
- Additional treatment (2) (Weeks 8 - 35)):
Beginning 4 weeks after the end of RT (i.e. in Week 12), concomitant to cilengitide treatment, subjects receive TMZ chemotherapy at a
25 dose of $150 - 200 \text{ mg/m}^2$ daily for 5 days (preferably days 1 to 5 of a given treatment week) every 4 weeks (i.e. Weeks 12, 16, 20, 24, 28 and 32) for up to 6 cycles.

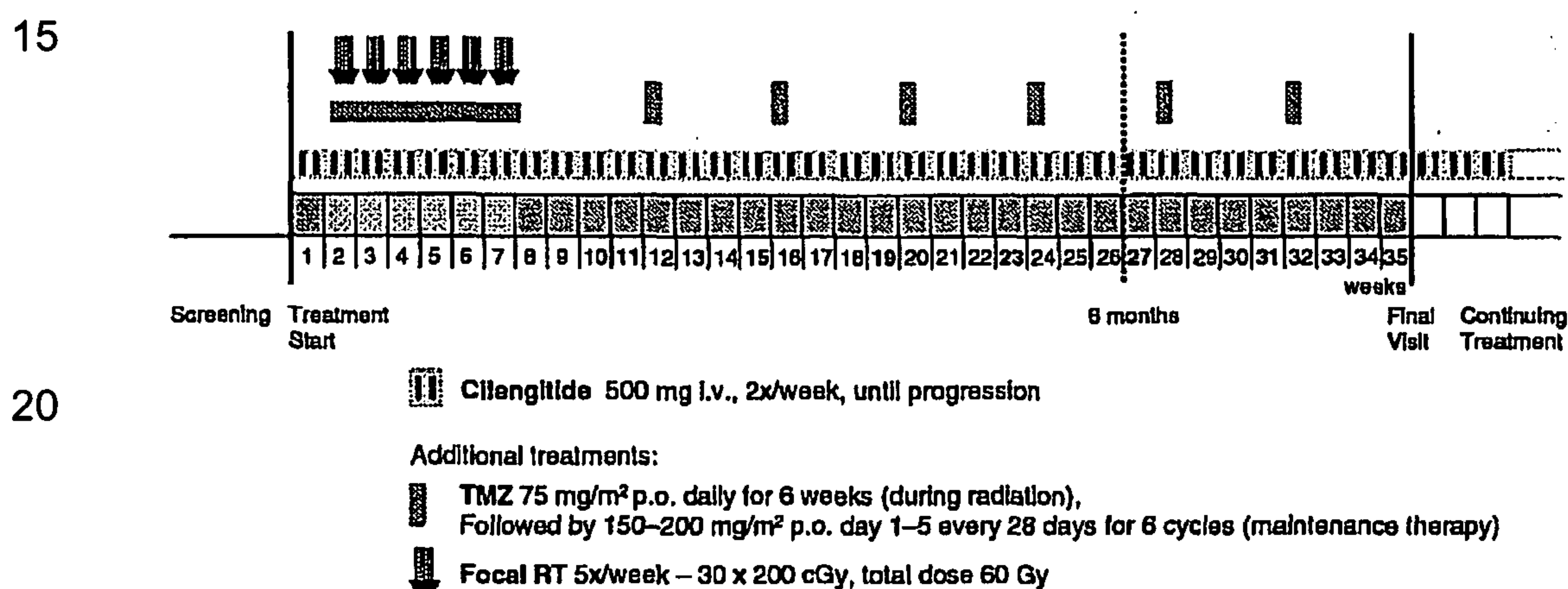
30 In this method of treatment (F1), the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is preferably administered in timed administration as described herein, preferably with respect to the administration of the RT and/or the TMZ; for example, the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered about 3 hours (h) (= start of the about 1 hour infusion) before the delivery of the RT;

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and TMZ is preferably after administration of the cyclo-(Arg-Gly-Asp-DPhe-NMeVal), but preferably before the delivery of the RT, more preferably within two hours before the delivery of the RT, even more preferably within about one hour before the delivery of the RT, and especially about one hour before the delivery of the RT. However, it can optionally also be suitable to administer the TMZ within about one hour after the delivery of the RT.

However, the 35 week schedule of the method of treatment (F) can be terminated or shortened, if unacceptable adverse effects, an early progression, stable disease or healing of the patient occur.

A preferred method of treatment is depicted in the scheme below:



Cilengitide (EMD121 974) and temozolomide with concomitant radiation therapy, followed by cilengitide and temozolomide maintenance therapy in subjects in need thereof, such as subjects with newly diagnosed glioblastoma

An especially preferred subject of the instant invention is a method of treatment (F2), comprising or preferably consisting of the following steps or treatments:

- Optional treatment with Cilengitide as twice weekly i.v. infusion of 2000 mg (flat) per infusion starts 1 week prior to RTX and TMZ treatment (= Week -1), i.e. as single agent. Preferably, the twice

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weekly i.v. infusion of 2000 mg (flat) per infusion takes place on Day 1 and 4, e. g., Monday and Thursday or Tuesday and Friday).

- 5
- During Weeks 1-6, a combination of Cilengitide (about 10000mg (flat) per patient and per week) with RTX and TMZ is applied to the patient:

During Weeks 1-6, patients will receive, during each week, about 2000 mg cilengitide (flat) i.v. 5x/week on days of RTX;

10

During Weeks 1-6, Focal RTX will be delivered for 6 weeks once daily at about 2 Gy per fraction, 5 consecutive days/week for a total of up to about 60 Gy;

15

During Weeks 1-6, TMZ will be administered orally at a daily dose of about 75 mg/m² for 6 weeks (7 days a week) in said combination with RTX and cilengitide.

20

- After the above described 6-week intense treatment, patients will receive about 2000 mg Cilengitide i.v. 2x/week (starting in week 7) in combination with TMZ maintenance treatment for a further 6 cycles (Week 7-34):

25

4 weeks after the end of RTX (i.e. in Week 11), concomitant to Cilengitide treatment, subjects will receive (as said TMZ maintenance treatment) TMZ at a dose of 150-200 mg/m² daily for 5 days (Days 1 to 5 of a given treatment week) every 4 weeks for up to 6 cycles (i.e. Weeks 11, 15, 19, 23, 27 and 31).

30

- After completion of RTX and TMZ standard treatment (i.e. after Week 34), subjects optionally continue receiving 2000 mg cilengitide i.v. 2x/week as maintenance for another 10 months.

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In this method of treatment (F2), the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is preferably administered in timed administration as described herein, preferably with respect to the administration of the RT and/or the TMZ; for example, the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered about 3 or 4 hours (h) (= start of the about 1 hour infusion) before the delivery of the RT; and TMZ is preferably after administration of the cyclo-(Arg-Gly-Asp-DPhe-NMeVal), but preferably before the delivery of the RT, more preferably within two hours before the delivery of the RT, even more preferably within about one hour before the delivery of the RT, and especially about one hour before the delivery of the RT. However, it can optionally also be suitable to administer the TMZ within about one hour after the delivery of the RT.

A preferred subject of the instant invention is a method of treatment (F3), comprising or preferably consisting of the following steps or treatments:

- Cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered at a flat dose about 2000 mg by i. v. 5 times a week (preferably 5 consecutive days a week) for 35 weeks, preferably without pause. Treatment with cyclo-(Arg-Gly-Asp-DPhe-NMeVal) preferably begins on Day 1 of each week;

- Additional treatment (1) (Weeks 2 - 7 (max. of 7 weeks)):
Beginning on Day 1 of Week 2, treatment with TMZ and RT will be administered in addition to the cyclo-(Arg-Gly-Asp-DPhe-NMeVal), as follows:
Temomozolomide (TMZ) is administered orally for 6 weeks, at a daily dose of about 75 mg/m² (7 days a week),

Focal radiotherapy (RT) is delivered for 6 weeks, preferably once daily at about 2 Gy per fraction, 5 consecutive days/week, for a total of about 60 Gy. (preferably to be prescribed according to the guidelines of the International Commission on Radiological Units). Adequate immobilization masks can optionally be used to ensure

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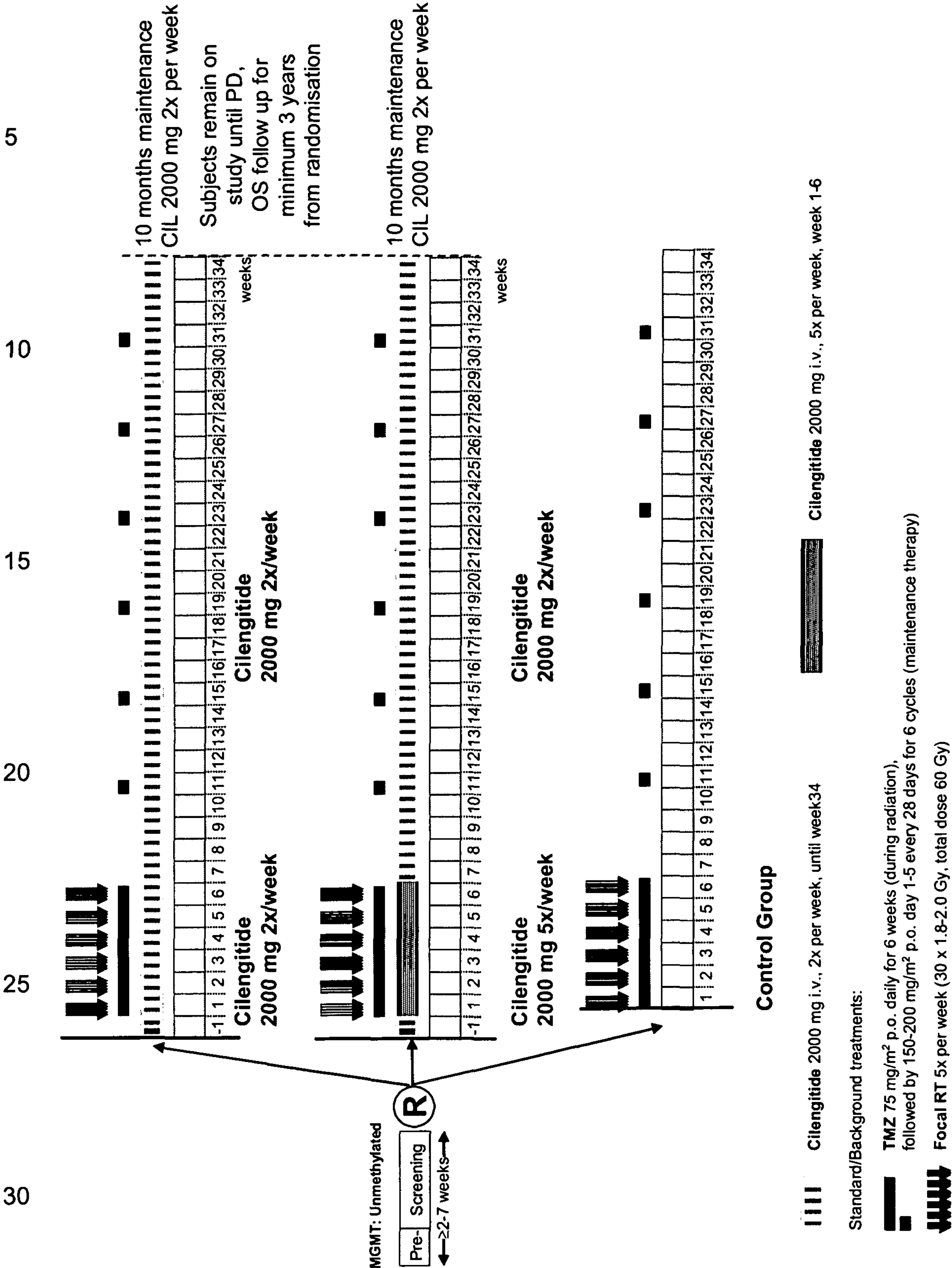
5 reproducibility. The treatment volume can optionally be determined on the basis of preoperative Gd-MRI of the brain. Treatment volume preferably includes the contrast enhancing lesion as determined by the Gd-MRI, preferably plus a 2- to 3-cm margin around that lesion.

- Additional treatment (2) (Weeks 8 - 35):
 - Beginning 4 weeks after the end of RT (i.e. preferably in Week 11 or 12), concomitant to cilengitide treatment, subjects receive TMZ chemotherapy at a dose of 150 - 200 mg/m² daily for 5 days (preferably days 1 to 5 of a given treatment week) every 4 weeks (i.e. Weeks 12, 16, 20, 24, 28 and 32) for up to 6 cycles.

15 In this method of treatment (F3), the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is preferably administered in timed administration as described herein, preferably with respect to the administration of the RT and/or the TMZ; for example, the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered about 3 or 4 hours (h) (= start of the about 1 hour infusion) before the delivery of the RT; and TMZ is preferably after administration of the cyclo-(Arg-Gly-Asp-DPhe-NMeVal), but preferably before the delivery of the RT, more preferably within 20 two hours before the delivery of the RT, even more preferably within about one hour before the delivery of the RT, and especially about one hour before the delivery of the RT. However, it can optionally also be suitable to administer the TMZ within about one hour after the delivery of the RT.

25 Graphical display of preferred embodiments of treatment methods (F), including treatment method (F1) (top scheme) and treatment methods (F2) and/or (F3) (middle scheme), and standard treatment method (bottom scheme) is given on the next page:

30



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The method of treatment (F), including method of treatments (F1); (F2) and/or (F3) are especially advantageous in the treatment of cancer, selected from the group consisting of astrocytoma, more preferably astrocytoma grade II, III and/or IV, and especially consisting
5 of glioblastoma or glioblastoma multiforme;

The above given methods (F2) and (F3) are especially preferred in the treatment of "unmethyleted patients" as defined according to the instant invention.

10

The above given methods (F2) and (F3) can also be advantageous in the treatment of patients of unknown MGMT methylation status.

The methods of treatment as described herein and especially the methods of
15 treatment (A) to (F) as described above, can optionally be followed by a continuing treatment comprising cyclo-(Arg-Gly-Asp-DPhe-NMeVal), preferably a continuing treatment as given below:

Subjects who complete 35 weeks of treatment without progression and
20 preferably for whom continued treatment with cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is considered beneficial, e. g. by the physician, may continue on cyclo-(Arg-Gly-Asp-DPhe-NMeVal) therapy (twice a week about 500 mg or about 2000 mg, i. v.). Accordingly, after the first 35 weeks of therapy, said cyclo-(Arg-Gly-Asp-DPhe-NMeVal) therapy can be continued until
25 progression, stable disease, healing or unacceptable adverse effects occur.

A preferred subject of the of the instant invention relates to methods of treatment as described herein and preferably one or more of the methods of treatment, preferably selected from the group consisting of method of
30 treatment (A), method of treatment (B), method of treatment (C), method of treatment (D), method of treatment (E), method of treatment (F), and combinations thereof, wherein the twice weekly administration scheme regarding cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or the pharmaceutically

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acceptable dervatives, solvates and/or salts thereof, is substituted by a three times weekly administration scheme, preferably a three times weekly administration scheme as described herein, or a five times weekly administration scheme, preferably a five times weekly administration scheme as described herein. This preferred subject can preferably be advantageously applied to patients that do not belong to group of "methylated patients" according to the invention.

10 The criteria for the "methylated patients" are given and discussed in detail below. Preferably, patients do not belong to group of "methylated patients" that can not be shown to have increased DNA methylation status, partial or complete methylation of at least one promotor of at least one MGMT gene and/or or only a Moderate MGMT protein level, or preferably less, in
15 comparison to the MGMT protein level expressed by normal lymphocytes.

An especially preferred subject of the instant invention is the use of a specific integrin ligand as described herein, preferably a specific integrin ligand selected from the group consisting of cyclo-(Arg-Gly-Asp-DPhe-NMeVal), the
20 pharmaceutically acceptable dervatives, solvates and salts thereof, and especially the use of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) for the manufacture of a medicament to be used in the methods of treatment described herein, and especially for the manufacture of a medicament to be used in one or more of the methods of treatment, preferably selected from the group
25 consisting of method of treatment (A), method of treatment (B), method of treatment (C), method of treatment (D), method of treatment (E), method of treatment (F), and combinations thereof.

Another preferred subject of the instant invention relates to a method of
30 treatment of primary brain tumours, comprising administering a specific integrin ligand as described herein, preferably a specific integrin ligand selected from the group consisting of LM609, Vitaxin, Abegrin, Abciximab, P1F6, 14D9.F8, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more

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- preferably Vitaxin, Abegrin, CNTO95, Abciximab and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), even more preferably selected from Vitaxin, Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val),
- 5 and at least one cancer cotherapeutic agent, preferably selected from at least one cancer cotherapeutic agent as described herein, more preferably selected from chemotherapeutic agents as described herein, preferably selected from the group consisting of nitroso urea and nitroso urea
- 10 derivatives, such as ACNU, BCNU and CCNU, vincristine, taxanes, such as paclitaxel and docetaxel, and radiotherapy, preferably fractionated focal radiotherapy as described herein. Preferably, the specific integrin ligand is administered in a timed administration as described herein. If radiotherapy is applied, it is preferably applied as a fractionated focal radiotherapy consisting of about 60 Gy, preferably delivered over a period of six weeks. If the specific
- 15 integrin ligand is cyclo-(Arg-Gly-Asp-DPhe-NMeVal), it is preferably administered to the patient in a dosage and/or a weekly administration scheme as described in the methods of treatment and/or administration schemes described herein.
- 20 Another preferred subject of the instant invention relates to a method of treatment of primary brain tumours, comprising administering a specific integrin ligand as described herein, preferably a specific integrin ligand selected from the group consisting of LM609, Vitaxin, Abegrin, Abciximab, P1F6, 14D9.F8, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more
- 25 preferably Vitaxin, Abegrin, CNTO95, Abciximab and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), even more preferably selected from Vitaxin, Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val),
- and at least one cancer cotherapeutic agent, selected from chemotherapeutic agents as described herein, preferably procarbazine or dacarbazine, and
- 30 radiotherapy, preferably fractionated focal radiotherapy as described herein. More preferably, a combination of at least one chemotherapeutic agent, including dacarbazine or procarbazine, and radiotherapy is applied. Preferably, the specific integrin ligand is administered in a timed

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administration as described herein. The radiotherapy applied is preferably applied as a fractionated focal radiotherapy consisting of about 60 Gy, preferably delivered over a period of six weeks. If the specific integrin ligand is cyclo-(Arg-Gly-Asp-DPhe-NMeVal), it is preferably administered to the patient in a dosage and/or a weekly administration scheme as described in the methods of treatment and/or administration schemes described herein.

Another preferred subject of the instant invention relates to a method of treatment of primary brain tumours, comprising administering a specific integrin ligand as described herein, preferably a specific integrin ligand selected from the group consisting of LM609, Vitaxin, Abegrin, Abciximab, P1F6, 14D9.F8, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more preferably Vitaxin, Abegrin, CNTO95, Abciximab and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), even more preferably selected from Vitaxin, Abegrin and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), and at least one cancer cotherapeutic agent, preferably selected from chemotherapeutic agents as described herein, preferably selected from the group consisting of Herceptin, Bevacizumab (rhuMAb-VEGF, Avastin®), Cetuximab (Erbix®) and Nimotuzumab, and preferably Sorafenib (Nexavar®), Sunitinib (Sutent®) and ZD6474 (ZACTIMA™), optionally combined with radiotherapy, preferably fractionated focal radiotherapy as described herein. Preferably, the specific integrin ligand is administered in a timed administration as described herein. If radiotherapy is applied, it is preferably applied as a fractionated focal radiotherapy consisting of about 60 Gy, preferably delivered over a period of about six weeks. If the specific integrin ligand is cyclo-(Arg-Gly-Asp-DPhe-NMeVal), it is preferably administered to the patient in a dosage and/or a weekly administration scheme as described in the methods of treatment and/or administration schemes described herein.

Another preferred subject of the instant invention relates to a method of treatment of locally advanced lung cancer, comprising administering at least

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one specific integrin ligand, more preferably at least one specific integrin ligand as described herein, even more preferably a specific integrin ligand selected from the group consisting of LM609, Vitaxin, Abegrin, Abciximab, P1F6, 14D9.F8, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more preferably Vitaxin, Abegrin, CNTO95, Abciximab and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), and especially preferably consisting of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, in combination with at least one cancer cotherapeutic agent as described herein, preferably selected from alkylating agents and antimetabolites as described herein, and radiotherapy as described herein. Preferably a combination of at least one alkylating agent and at least one antimetabolites is applied, preferably in combination with radiotherapy, preferably fractionated focal radiotherapy as described herein. Preferably, a combination of the alkylating agent cisplatin with the antimetabolite gemcitabine or a combination of the alkylating agent carboplatin and the antimetabolite paclitaxel is applied, optionally combined with fractionated focal radiotherapy, preferably consisting of about 60 Gy, preferably delivered over a period of about six weeks. Preferably, the specific integrin ligand is administered in a timed administration as described herein. If the specific integrin ligand is cyclo-(Arg-Gly-Asp-DPhe-NMeVal), it is preferably administered to the patient in a dosage and/or a weekly administration scheme as described in the methods of treatment and/or administration schemes described herein.

Another preferred subject of the instant invention relates to a method of treatment of locally advanced head and neck cancer, comprising administering at least one specific integrin ligand, more preferably at least one specific integrin ligand as described herein, even more preferably a specific integrin ligand selected from the group consisting of LM609, Vitaxin, Abegrin, Abciximab, P1F6, 14D9.F8, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more preferably Vitaxin, Abegrin, CNTO95, Abciximab and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), and especially preferably consisting of cyclo-

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(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, in combination with at least one cancer cotherapeutic agent as described herein, preferably selected from alkylating agents, for example

5 cisplatin, antimetabolites, for example 5-FU or combinations comprising 5-FU, alkaloids, for example paclitaxel or docetaxel, and compounds targeted against PDGF, PDGFR, EGFR, VEGF, VEGFR and/or VEGFR2, preferably selected from Bevacizumab (rhuMAb-VEGF, Avastin®), Cetuximab (Erbix®), Nimotuzumab, Sorafenib (Nexavar®), Sunitinib (Sutent®) and

10 ZD6474 (ZACTIMA™), and radiotherapy, preferably fractionated focal radiotherapy as described herein, and combinations thereof.

Preferred is a combination of at least one alkylating agent, preferably comprising cisplatin, and radiotherapy, preferably fractionated focal radiotherapy as described herein. Additionally preferred is a combination of

15 at least one antimetabolite, comprising 5-FU, and radiotherapy, preferably fractionated focal radiotherapy as described herein. Additionally preferred is a combination of at least one alkaloid, comprising paclitaxel or docetaxel, and radiotherapy, preferably fractionated focal radiotherapy as described herein.

Preferred is a combination of at least one alkylating agent, preferably comprising cisplatin, at least one antimetabolite, comprising 5-FU, and

20 radiotherapy, preferably fractionated focal radiotherapy as described herein. Additionally preferred is a combination of at least one compound targeted against PDGF, PDGFR, EGFR, VEGF, VEGFR and/or VEGFR2, preferably selected from Bevacizumab (rhuMAb-VEGF, Avastin®), Cetuximab (Erbix®), Nimotuzumab, Sorafenib (Nexavar®), Sunitinib (Sutent®) and

25 ZD6474 (ZACTIMA™), and radiotherapy, preferably fractionated focal radiotherapy as described herein. The fractionated focal radiotherapy preferably consists of about 60-70 Gy, preferably delivered over a period of about six weeks, about 2 or about 3 Gy per fraction. Preferably, the specific

30 integrin ligand is administered in a timed administration as described herein. If the specific integrin ligand is cyclo-(Arg-Gly-Asp-DPhe-NMeVal), it is preferably administered to the patient in a dosage and/or a weekly

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administration scheme as described in the methods of treatment and/or administration schemes described herein.

- 5 Another preferred subject of the instant invention relates to a method of treatment of locally advanced head and neck cancer, comprising administering at least one specific integrin ligand, more preferably at least one specific integrin ligand as described herein, even more preferably a specific integrin ligand selected from the group consisting of LM609, Vitaxin, 10 Abegrin, Abciximab, P1F6, 14D9.F8, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more preferably Vitaxin, Abegrin, CNTO95, Abciximab and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), and especially preferably consisting of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, in combination with at least one cancer cotherapeutic agent as 15 described herein, preferably three cancer cotherapeutic agents, selected from alkylating agents, for example cisplatin, antimetabolites, for example 5-FU or combinations comprising 5-FU, and alkaloids, for example paclitaxel or docetaxel. In metastatic head and neck cancer, the combinatin of a specific integrin ligand with the cancer cotherapeutics Cisplatin, 5-FU and Taxan, 20 preferably paclitaxel or docetaxel, is especially preferred.

- Another preferred subject of the instant invention relates to a method of treatment of head and neck cancer, preferably locally advanced head and neck cancer, comprising administering at least one specific integrin ligand, 25 more preferably at least one specific integrin ligand as described herein, even more preferably a specific integrin ligand selected from the group consisting of LM609, Vitaxin, Abegrin, Abciximab, P1F6, 14D9.F8, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more preferably Vitaxin, Abegrin, CNTO95, Abciximab and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), and especially 30 preferably consisting of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, in combination with at least one cancer cotherapeutic agent as described herein, selected from compounds targeted against PDGF, PDGFR, EGFR, VEGF, VEGFR and/or VEGFR2,

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preferably selected from Bevacizumab (rhuMAb-VEGF, Avastin®),
Cetuximab (Erbix®), Nimotuzumab, Sorafenib (Nexavar®), Sunitinib
(Sutent®) and ZD6474 (ZACTIMA™), and radiotherapy, preferably
5 fractionated focal radiotherapy as described herein, more preferably 50-70
Gy, in fractions of 1.2 to 2.2 Gy, preferably about 2 Gy, preferably applied on
5 days per week. Especially preferably, a combination of a specific integrin
ligand, at least one targeted compound and radiotherapy as described above
is applied.

10 If fractionated focal radiotherapy is applied with respect to brain metastases,
preferably brain metastases of other cancer types as described herein, it
preferably consists of about 25 to 45 Gy, more preferably 30 to 40 Gy,
preferably delivered in fractions of 1.5 to 3.5, more preferably 1.8 to 3, e. g.
15 about 2 Gy or about 3 Gy, preferably over a period of about three weeks,
preferably 5 days a week.

Another preferred subject of the instant invention relates to a method of
treatment of metastatic malignant melanoma, comprising administering at
20 least one specific integrin ligand, more preferably at least one specific
integrin ligand as described herein, even more preferably at least one
specific integrin ligand selected from the group consisting of LM609, Vitaxin,
Abegrin, Abciximab, P1F6, 14D9.F8, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-
NMe-Val), more preferably Vitaxin, Abegrin, CNTO95, Abciximab and cyclo-
25 (Arg-Gly-Asp-DPhe-NMe-Val), and especially preferably one or two specific
integrin ligands, including cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a
pharmaceutically acceptable salt thereof, in combination with at least one
cancer cotherapeutic agent as described herein, preferably selected from
alkylating agents, for example dacarbazine, and radiotherapy as described
30 herein. Preferably a combination of at least one alkylating agent in
combination with radiotherapy, preferably fractionated focal radiotherapy as
described herein, is applied. Preferably, the specific integrin ligand is
administered in a timed administration as described herein. If the specific

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integrin ligand is cyclo-(Arg-Gly-Asp-DPhe-NMeVal), it is preferably administered to the patient in a dosage and/or a weekly administration scheme as described in the methods of treatment and/or administration schemes described herein.

Another preferred subject of the instant invention relates to a method of treatment of metastatic prostate carcinoma, comprising administering at least one specific integrin ligand, more preferably at least one specific integrin ligand as described herein, even more preferably a specific integrin ligand selected from the group consisting of LM609, Vitaxin, Abegrin, Abciximab, P1F6, 14D9.F8, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more preferably Vitaxin, Abegrin, CNTO95, Abciximab and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), and especially preferably consisting of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, in combination with at least one cancer cotherapeutic agent as described herein, preferably selected from alkaloids, for example docetaxel and paclitaxel, antibiotics, for example doxorubicine and epirubicine, and hormones and antagonists thereof, for example steroids, and preferably radiotherapy as described herein. Preferably, the specific integrin ligand is administered in a timed administration as described herein. If the specific integrin ligand is cyclo-(Arg-Gly-Asp-DPhe-NMeVal), it is preferably administered to the patient in a dosage and/or a weekly administration scheme as described in the methods of treatment and/or administration schemes described herein.

Another preferred subject of the instant invention relates to a method of prophylactic irradiation, preferably prophylactic cranial irradiation or prophylactic mediastinal irradiation, comprising administering at least one specific integrin ligand, more preferably at least one specific integrin ligand as described herein, even more preferably a specific integrin ligand selected from the group consisting of LM609, Vitaxin, Abegrin, Abciximab, P1F6, 14D9.F8, CNTO95 and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), more preferably

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Vitaxin, Abegrin, CNTO95, Abciximab and cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), and especially preferably consisting of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, and
5 radiotherapy, preferably fractionated focal radiotherapy as described herein. The method of prophylactic cranial irradiation is preferably applied with respect to lung cancer, preferably small cell lung cancer, even more preferably small cell lung cancer in complete remission, preferably after chemotherapy and/or surgical procedures. The method of prophylactic
10 mediastinal irradiation is preferably applied with respect to lung cancer, more preferably small cell lung cancer, even more preferably small cell lung cancer in complete remission, preferably after chemotherapy and/or surgical procedures.

15 In all of the above given methods of treatment or methods of prophylactic irradiation, timed administration of the at least one specific integrin ligand is preferred.

A preferred aspect of the instant invention relates to a method for treating
20 brain metastases, preferably brain metastases of lung cancer, more preferably brain metastases of NSCLC and/or SCLC, comprising the application of whole brain radiation and the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal) (= Cilengitide), wherein the
25 whole brain radiation is applied as follows:
the whole brain radiotherapy, preferably at a total dose of about 30 Gy, is given preferably after CT simulation in mask fixation. The target volume is preferably defined to include the whole intracranial contents down to the intervertebral disc between C2 and C3. Special emphasis has preferably to
30 be placed on the inclusion of the cribriform plate and the temporal lobes. Radiation is preferably given with two opposing lateral portals, preferably with about equal weighting. Single doses of about 3 Gy are preferably given on days 1-5 and days 8-12. Radiotherapy should preferably start approximately

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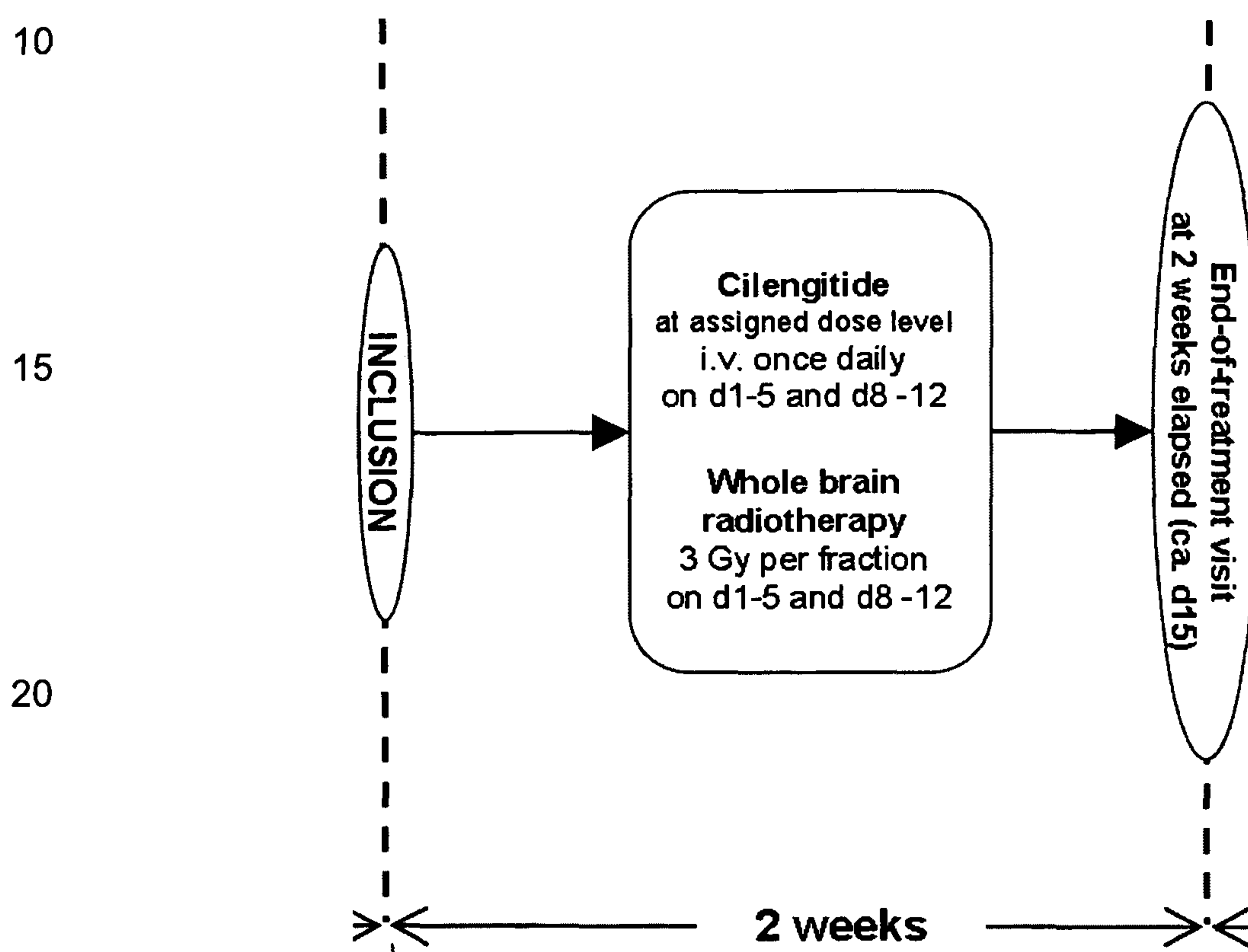
2 hours after the end of cilengitide infusion (i.e. preferably 3 hours after the begin of the Cilengitide infusion). Preferably, each infusion comprises cyclo- (Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal) (= Cilengitide) in an amount of about 500 mg, about 1000 mg or about 2000 mg (flat), preferably about 1000 mg or about 2000 mg (flat).

Another preferred aspect of the instant invention relates to a method for treating brain metastases, preferably brain metastases of lung cancer, more preferably brain metastases of NSCLC and/or SCLC, comprising the application of whole brain radiation and the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), wherein the cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is administered as follows: cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), is administered i.v. once daily on day 1-5 and 8-12 in combination with fractionated whole brain radiation therapy applied to patient on the same day, said fractionated whole brain radiation therapy preferably comprising or more preferably consisting of about 30 Gy, preferably in 10 fractions of about 3 Gy). Preferably, each infusion comprises cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal) (= Cilengitide) in an amount of about 500 mg, about 1000 mg or about 2000 mg (flat), preferably about 1000 mg or about 2000 mg (flat). Said infusion should preferably start approximately 3 hours and should preferably end approximately 2 hours before each application of the fractionated whole brain radiotherapy (i.e. approx. 1 h infusion starting about 3 hours before the application of each fraction of the fractionated whole brain radiotherapy).

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Especially preferably, the characteristics of the above described preferred aspects are combined in one method of treatment.

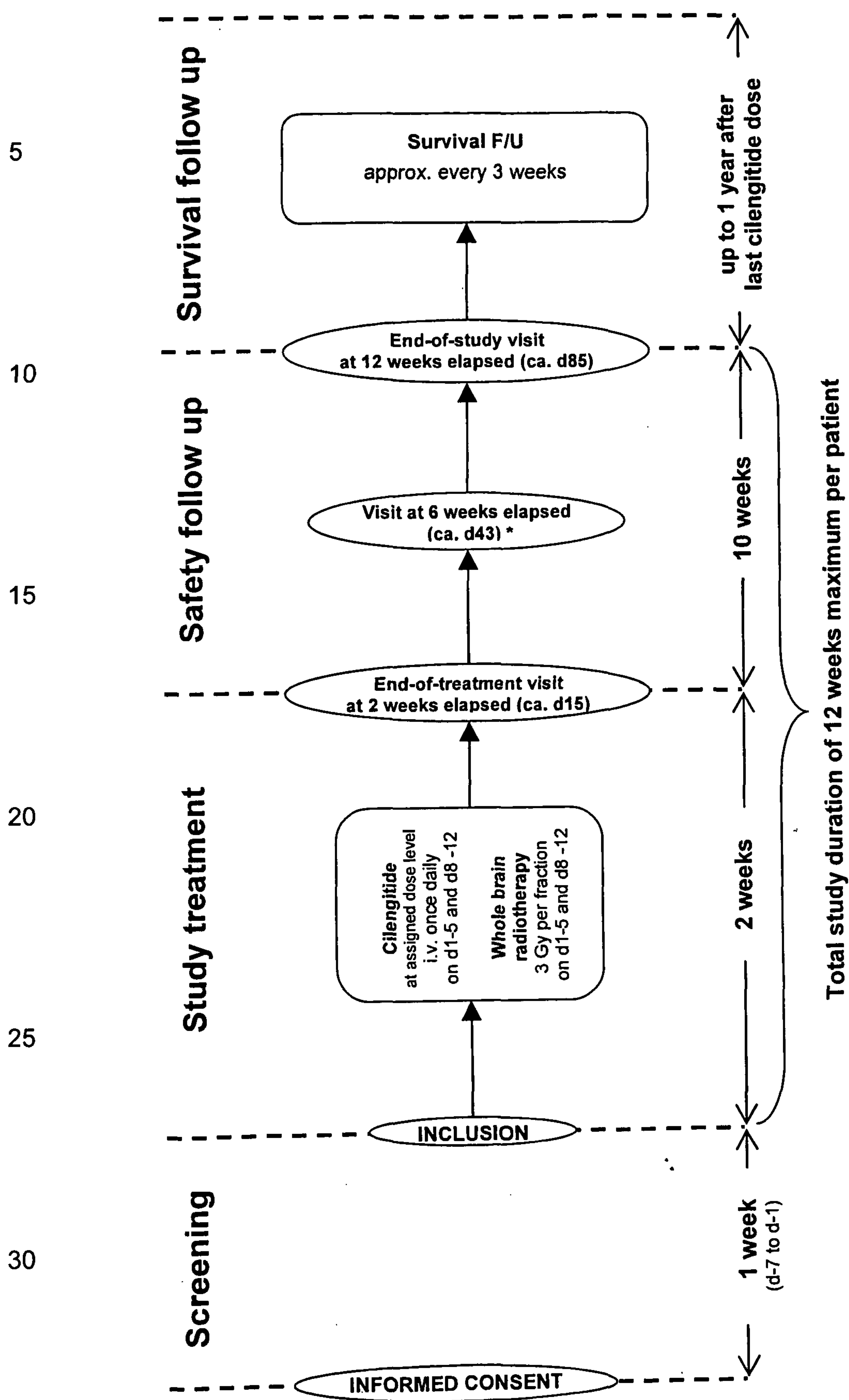
- 5 An example of a method of treatment comprising the application of whole brain radiation and the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal) (= Cilengitide), is depicted in the scheme below:



25

- 30 An example of a study design regarding a method of treatment consisting of the application of whole brain radiation and the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal) (= Cilengitide), is depicted in the scheme below:

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* or at 4 weeks after the last dose of cilengitide, if cilengitide was discontinued early
 ** or at 10 weeks after the last dose of cilengitide, if cilengitide was discontinued early

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Especially preferred subjects of the instant invention are all uses, methods of treatment, medicaments, subjects of the invention, embodiments of the invention and/or methods of production described herein

- 5 i) that comprise the administration of at least one specific integrin ligand in one or more doses so that the weekly dose of the at least one specific integrin ligand contained therein sums up to an amount of 10 to 30 millimoles per patient, preferably for one or more weeks and especially preferably for two or more consecutive weeks; or
- 10 ii) that can be combined with the administration of at least one specific integrin ligand in one or more doses so that the weekly dose of the at least one specific integrin ligand contained therein sums up to an amount of 10 to 30 millimoles per patient, preferably for one or more weeks and especially preferably for two or more consecutive weeks.

15

Even more preferred subjects of the instant invention are all uses, methods of treatment, medicaments, subjects of the invention, embodiments of the invention and/or methods of production described herein

- 20 iii) that comprise the administration of at least one specific integrin ligand, selected from cyclo-(Arg-Gly-Asp-DPhe-NMeVal), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, wherein the at least one specific integrin ligand is to be administered to the patient in one or more doses so that the weekly dose of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) contained therein sums up to an amount
- 25 of 6000 - 14000 mg in total per patient, preferably for one or more weeks and especially preferably for two or more consecutive weeks; or
- 30 iv) that can be combined with the administration of at least one specific integrin ligand, selected from cyclo-(Arg-Gly-Asp-DPhe-NMeVal), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, wherein the at least one specific integrin ligand is to be administered to the patient in one or more doses so that the weekly dose of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) contained therein sums up to an amount

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of 6000 - 14000 mg in total per patient, preferably for one or more weeks and especially preferably for two or more consecutive weeks.

- 5 Even more preferred subjects of the instant invention are all uses, methods of treatment, medicaments, subjects of the invention, embodiments of the invention and/or methods of production described herein
- v) that comprise the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal), the pharmaceutically acceptable derivatives, solvates and/or
- 10 salts thereof, in one or more doses so that the weekly dose of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) contained therein sums up to an amount of about 10000 mg in total per patient, preferably for one or more weeks and especially preferably for two or more consecutive weeks; or
- 15 vi) that can be combined with the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, in one or more doses so that the weekly dose of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) contained therein sums up to an amount of about 10000 mg in total per patient, preferably for one or
- 20 more weeks and especially preferably for two or more consecutive weeks.

- Even more preferred subjects of the instant invention are all uses, methods of treatment, medicaments, subjects of the invention, embodiments of the
- 25 invention and/or methods of production described herein
- vii) that comprise the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), preferably in 5 doses, preferably on 5 consecutive days during one week, each
- 30 dose preferably consisting of about 2000 mg, so that the weekly dose of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) contained therein sums up to an amount of about 10000 mg in total per patient, preferably for one or

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more weeks and especially preferably for two or more consecutive weeks; or

- 5 viii) that can be combined with the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), preferably in 5 doses, preferably on 5 consecutive days during one week, each dose preferably consisting of about 2000 mg, so that the weekly dose of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) contained therein
- 10 sums up to an amount of about 10000 mg in total per patient, preferably for one or more weeks and especially preferably for two or more consecutive weeks.

Even more preferred subjects of the instant invention are all uses, methods

15 of treatment, medicaments, subjects of the invention, embodiments of the invention and/or methods of production described herein

- ix) that comprise the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) in 5 separate doses consisting of about 2000 mg each on 5 consecutive days during one week so that the weekly dose of cyclo-
- 20 (Arg-Gly-Asp-DPhe-NMeVal) contained therein sums up to an amount about 10000 mg in total per patient, and wherein said administration in said weekly dose is repeated for 2 to 12 consecutive weeks, preferably 4 to 8 consecutive weeks and especially about 6 weeks; or
- x) that can be combined with the administration of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) in 5 separate doses consisting of about 2000 mg each
- 25 on 5 consecutive days during one week so that the weekly dose of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) contained therein sums up to an amount about 10000 mg in total per patient, and wherein said administration in said weekly dose is repeated for 2 to 12 consecutive
- 30 weeks, preferably 4 to 8 consecutive weeks and especially about 6 weeks.

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The administration or the administration schemes as described above and especially as described in i) throughout x) above can advantageously be combined with:

- 5 a) the application of radiotherapy to the patient, preferably on one or more days during the one or more weeks in which the above described weekly dose of the at least one specific integrin ligand or cyclo-(Arg-Gly-Asp-DPhe-NMeVal), respectively, is administered to said patient, and/or
- 10 b) the administration of one or more alkylating agents, preferably alkylating agents as described herein and more preferably temozolomide, at least during the one or more weeks in which the above described weekly dose of the at least one specific integrin ligand or preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal),
- 15 respectively, is administered to said patient.

The administration or the administration schemes as described above and especially as described in i) throughout x) above can even more advantageously be combined with:

- 20 c) the application of radiotherapy to the patient on every day on which a dose of about 2000 mg is administered to the patient during the one or more weeks in which the above described weekly dose of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered to said patient, and/or
- 25 d) the administration of temozolomide, preferably on every or about every day during the one or more weeks in which the above described weekly dose of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered to said patient.

30 The administration or the administration schemes as described above and especially as described in i) throughout x) above can even more advantageously be combined with:

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- 5 e) the application of radiotherapy to the patient on every day on which a dose of about 2000 mg is administered to the patient during the one or more weeks in which the above described weekly dose of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered to said patient, and/or
- 10 f) the administration of temozolomide, preferably on 7 days during the one or more weeks in which the above described weekly dose of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered to said patient, i.e. during the one or more weeks in which the above described dose of about 500mg or about 2000 mg cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is administered to said patient four or more times each week, preferably five times during each week.

15 In this respect, the "one or more weeks" preferably are 2 to 12 consecutive weeks, more preferably 4 to 8 consecutive weeks, and especially preferably 6 weeks, during which the above described weekly dose of the at least one specific integrin ligand or cyclo-(Arg-Gly-Asp-DPhe-NMeVal), respectively, is administered to said patient.

20

Also in this respect, the term radiotherapy preferably refers to radiotherapy as defined herein, and more preferably refers to external beam radiation and especially to fractionated external beam radiation.

25 The above described especially preferred and or even more preferred subjects of the instant invention, especially as described in i) throughout x), optionally including one or more of the advantageous combinations as described in a) throughout d), can be additionally combined with pre-treatment regimens, post-treatment regimens and/or maintenance treatment,

30 preferably selected from the treatment regimens described herein, more preferably selected from the treatment regimens described herein but other than those involving the regimens as specified according to one or more of i)

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throughout x) and/or one or more of the optional combinations a) to d) referring to i) throughout x).

- 5 A preferred further aspect of the instant invention relates to the following methods of treatment:

A method of treating cancer comprising administering to the patient within at least one week

- 10 i) at least one alkylating chemotherapeutic agent agent,
ii) at least one further cancer cotherapeutic agent, selected from cetuximab, cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable dervatives, solvates and salts thereof, and radiotherapy.

- 15 A method of treating cancer, selected from the group consisting of intracerebral cancer, head-and-neck cancer, rectal cancer and lung cancer, comprising administering to the patient within at least one week

- i) at least one alkylating chemotherapeutic agent, preferably selected from the group consisting of N-Lost-Derivatives, Nitroso urea derivatives,
20 Oxazaphosphorines, Platin derivatives, Tetrazines, Aziridines, and others, selected from Amsacrine, Estramustinphosphate, Procarbazine and Treosulfane;
and pharmaceutically acceptable dervatives, salts and/or solvates thereof, and

- 25 ii) at least one and preferably at least two further cancer cotherapeutic agents, selected from cetuximab, cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable dervatives, solvates and salts thereof, and radiotherapy.

- 30 In said methods, if not explicitly specified otherwise, the at least one alkylating chemotherapeutic agent is preferably selected from the alkylating chemotherapeutic agents as described herein and more preferably selected from the N-Lost-Derivatives Busulfane and Chlorambucil, the Nitroso urea

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derivatives Nimustine, Carmustine and Lomustine, the Oxazaphosphorines Cyclophosphamide, Ifosfamide and Trofosfamide, Platin derivatives Cisplatin, Carboplatin and Oxaliplatin, the Tetrazines Dacarbazine and Temozolomide, 5 the Aziridine Thiotepa, and others, selected from Amsacrine, Estramustinphosphate, Procarbazine and Treosulfane; and pharmaceutically acceptable dervatives, salts and/or solvates thereof.

10 In said methods, the cancer to be treated is preferably as described herein and more preferably selected from intracerebral cancer, head-and-neck cancer, rectal cancer, small cell lung cancer, non-small cell lung cancer, glioblastoma multiforme, small cell lung cancer, non-small cell lung cancer, breast cancer, metastatic melanoma, metastatic androgen independent prostate cancer, metastatic androgen dependent prostate cancer, and brain 15 metastases thereof. Even more preferably, the cancer to be treated is selected from the group consisting of

- i) intracerebral cancer, more preferably astrocytoma grade II, III or IV, glioblastoma, glioblastoma multiforme (GBM), and brain metastases of other cancers, preferably other cancers selected from lung cancer, 20 especially small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), metastatic melanoma, prostate cancer, especially metastatic androgen independent prostate cancer (AIPCa), metastatic androgen dependent prostate cancer (ADPCa), and breast cancer;
- ii) lung cancer, especially small cell lung cancer (SCLC) and non-small cell 25 lung cancer (NSCLC),
- iii) metastatic melanoma,
- iv) prostate cancer, especially metastatic androgen independent prostate cancer (AIPCa), metastatic androgen dependent prostate cancer (ADPCa),
- 30 v) and breast cancer.

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In said methods, the cancer to be treated it as preferably intracerebral cancer, more preferably astrocytoma grade II, III or IV, and especially preferably glioblastoma or glioblastoma multiforme (GBM).

5

In said methods, the at least one alkylating chemotherapeutic agent is preferably selected from the group consisting of

i) Platin derivatives, more preferably from the Platin derivatives Cisplatin, Carboplatin and Oxaliplatin; and/or

10 ii) Tetrazines, more preferably from the Tetrazines, Dacarbazine and Temozolomide;

and pharmaceutically acceptable dervatives, salts and/or solvates thereof.

In said methods, the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the
15 pharmaceutically acceptable dervatives, solvates and salts thereof is preferably administered to the patient in one or more doses so that the dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of 3 to 30 millimoles per patient within in said week. More preferably, the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable
20 dervatives, solvates and salts thereof is to be administered to the patient in one or more doses so that the dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of 3 to 10 millimoles per patient within said week or to an amount of 10 to 30 millimoles per patient within said week.

25

In said methods, the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable dervatives, solvates and/or salts thereof is preferably administered to the patient in one or more doses so that the dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an
30 amount of 2000 mg to 14000 mg and especially 4000 mg to 10000 mg per patient within in said week. More preferably, the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable dervatives, solvates and/or salts thereof is to be administered to the patient in one or more doses so that the

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dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of about 2000 mg, about 4000 mg, about 6000 mg, about 8000 mg or about 10000 mg per patient within said week. Preferably, each of the one or more doses consists of about 500 mg or about 2000 mg. Preferably, each of said one or more doses is given on a different day within said week, e.g. in a twice weekly administration scheme, a three times weekly administration scheme, a four times weekly administration scheme or a five times weekly administration scheme, preferably as described herein.

10

In said methods, the cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof is preferably administered to the patient in one or more doses so that the dose of the cetuximab contained therein sums up to an amount of 100 mg/m² to 800 mg/m² and especially 200 mg/m² to 500 mg/m² per patient within in said week. More preferably, the cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof is to be administered to the patient in one or more doses so that the dose of the cetuximab contained therein sums up to an amount of about 250 mg/m² or about 400 mg/m² per patient within said week.

20

If a treatment method described herein comprises the administration of cetuximab, wherein the dose to be administered to the patient and week sums up to an amount of about 250 mg/m² or about 400 mg/m², the first dose to be administered to the patient in the very first week of said treatment method preferably is or sums up to about 400 mg/m² per patient in said very first week (loading dose). Preferably, all subsequent doses of cetuximab administered to said patient in the subsequent weeks are or sum up to an amount of about 250 mg/m² in each week of the treatment method wherein cetuximab is administered to the patient. If two or more methods of treatment are combined, said loading dose of about 400 mg/m² per patient and per week is preferably only given in the very first week of the very first treatment method.

30

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In said methods, the amount of each of the at least one alkylating
chemotherapeutic agents administered to the patient within said week is
preferably divided into 2 to 7, preferably 5 to 7 and especially 5, 6 or 7 about
5 equal doses wherein each of the about equal doses is administered to said
patient on a separate day within said week. Preferably, each of said one or
more doses is given on a different day within said week, e.g. in a twice
weekly administration scheme, a three times weekly administration scheme,
a four times weekly administration scheme, a five times weekly
10 administration scheme, a six times weekly administration scheme or a seven
times weekly administration scheme, preferably as described herein. The
seven times weekly administration scheme preferably means that the
respective compound is given on seven consecutive days within one week ,
preferably on each day of a respective week, and more preferably once per
15 day on each day of a respective week.

In said methods, the at least one alkylating chemotherapeutic agent
preferably comprises temozolomide or consists of temozolomide; or a
pharmaceutically acceptable dervative, solvate or salt thereof. The
20 temozolomide, the pharmaceutically acceptable dervatives, solvates and/or
salts thereof is preferably administered to the patient in one or more doses,
preferably three or more doses and especially 5 or more doses, for example
5, 6 or 7 doses, so that the weekly dose of the temozolomide contained
therein sums up to an amount of 300 mg/m² to 800 mg/m² per patient within
25 said week. More preferably, the temozolomide, the pharmaceutically
acceptable dervatives, solvates and/or salts thereof is to be administered to
the patient in one or more doses so that the weekly dose of the
temozolomide contained therein sums up to an amount of 360 mg/m² to 750
mg/m², preferably 550 mg/m² to 700 mg/m², per patient within said week.
30 Preferably, each of said one or more doses is given on a different day within
said week, e.g. in a three times weekly administration scheme, a five times
weekly administration scheme, a six times weekly administration scheme or a
seven times weekly administration scheme, preferably as described herein.

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Preferably, each of said one or more doses consists of about 50 mg/m², about 60 mg/m², about 75 mg/m², about 80 mg/m² or about 100 mg/m².

- 5 Said methods preferably comprise the administration of at least two further cancer cotherapeutic agents, selected from
- i) cetuximab or a pharmaceutically acceptable dervative, solvate or salt thereof, preferably cetuximab,
 - 10 ii) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable dervative, solvate or salt thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), and
 - iii) radiotherapy, preferably external beam radiation.

15 According to the instant invention, radiotherapy is preferably to be regarded as a (further) cancer cotherapeutic agent.

In said methods, the beforehand described administration to the patient within said at least one week is repeated at least once or twice, preferably in consecutive weeks.

20

Thus, especially preferred are methods of treating cancer as described herein and especially as described above, which have a duration of at least one cycle, each cycle preferably consisting of about three weeks (about 21 days) or about four weeks (about 28 days), wherein said cycle preferably

25 comprises one or more weeks during which

- i) at least one alkylating chemotherapeutic agent agent,
 - ii) at least one further cancer cotherapeutic agent, selected from cetuximab, cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable dervatives, solvates and salts thereof, and radiotherapy,
- 30 is administered to the patient. Especially preferably, one or more of the beforehand described preferred embodiments are combined in these methods.

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Thus, a more preferred preferred further aspect of the instant invention relates to the following methods of treating cancer, preferably intracerebral cancer:

5

[1] A method of treating cancer, preferably intracerebral cancer, comprising administering to the patient within at least one week

i) temozolomide or a pharmaceutically acceptable dervative, solvate or salt thereof,

10

ii) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable dervative, solvate or salt thereof, and

iii) cetuximab or pharmaceutically acceptable dervative, solvate or salt thereof,

and optionally

15

iv) radiotherapy.

[2] A method of treating cancer, preferably intracerebral cancer, comprising administering to the patient within at least one week

i) temozolomide or a pharmaceutically acceptable dervative, solvate or salt thereof,

20

ii) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable dervative, solvate or salt thereof, and

iii) cetuximab or pharmaceutically acceptable dervative, solvate or salt thereof,

25

and optionally

iv) radiotherapy.

[3] A method of treating cancer, preferably intracerebral cancer, comprising administering to the patient within at least one week

30

i) temozolomide or a pharmaceutically acceptable dervative, solvate or salt thereof,

ii) at least one further cancer cotherapeutic agent, selected from

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- 5 a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable
 derivative, solvate or salt thereof, and
 b) cetuximab or pharmaceutically acceptable derivative, solvate or salt
 thereof,
and
iii) radiotherapy.

10 [4] A method of treating cancer, preferably intracerebral cancer, comprising 2
to 10 consecutive weeks, preferably 4 to 6 consecutive weeks and especially
about 4 or about 6 consecutive weeks of treatment, wherein each of the
consecutive weeks comprises administering to the patient

- i) temozolomide or a pharmaceutically acceptable derivative, solvate or salt
thereof,
15 ii) at least one further cancer cotherapeutic agent, selected from
 a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable
 derivative, solvate or salt thereof, and
 b) cetuximab or pharmaceutically acceptable derivative, solvate or salt
 thereof,

20 and
iii) radiotherapy.

In this method, the intracerebral cancer is preferably selected from
astrocytoma, especially astrocytoma grade II, III and IV, glioblastoma and
glioblastoma multiforme (GBM). In this method, the temozolomide or a
25 pharmaceutically acceptable derivative, solvate or salt thereof, preferably the
temozolomide, is preferably administered to the patient in 5 or more doses,
for example 5, 6 or 7 doses, more preferably 5, 6 or 7 about equal daily
doses, so that the weekly dose of the temozolomide contained therein sums
up to an amount of 360 mg/m² to 750 mg/m², preferably 550 mg/m² to 700
30 mg/m², per patient within each week. In this method, preferably each of said
5 or more doses is given on a different day within each week, e.g. a five
times weekly administration scheme, a six times weekly administration
scheme or a seven times weekly administration scheme, preferably as

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described herein. In this method, preferably each of said one or more doses of temozolomide consists of about 50 mg/m², about 60 mg/m², about 75 mg/m², about 80 mg/m² or about 100 mg/m², preferably given once daily, more preferably given once daily about every day during said 2 to 10 consecutive weeks and especially during said 4 to 6 consecutive weeks. In this method, the cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof is preferably administered to the patient in one or more doses so that the dose of the cetuximab contained therein sums up to an amount of about 250 mg/m² or about 400 mg/m² per patient within each week. In this method, preferably the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof is administered to the patient in one or more doses so that the dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of about 2000 mg, about 4000 mg, about 6000 mg, about 8000 mg or about 10000 mg per patient within said week. In this method, preferably each of the one or more doses consists of about 500 mg or about 2000 mg of cyclo-(Arg-Gly-Asp-DPhe-NMe-Val). In this method, preferably, each of said one or more doses of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) is given on a different day within said week, e.g. in a twice weekly administration scheme, a three times weekly administration scheme, a four times weekly administration scheme or a five times weekly administration scheme, preferably as described herein. In this method, the radiotherapy is preferably as described herein. In this method, the radiotherapy is more preferably external beam radiation and even more preferably selected from (external beam) whole brain radiation and (external beam) focal radiotherapy of the brain (preferably also referred to as focal radiotherapy). In this method, the external beam radiation preferably consists of 30 to 70 Gy and especially of about 30 Gy or about 60 Gy. In this method, the whole brain radiation preferably consists of about 30 Gy, preferably given in about 10 fractions of about 3 Gy each. In this method, the focal radiotherapy preferably consists of about 60 Gy, preferably given in about 30 fractions of about 2 Gy each.

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[5] A method of treating cancer, preferably intracerebral cancer, said method comprising one or more cycles, preferably 2 to 8 cycles and more preferably 3 or 6 cycles, each cycle preferably consisting of about three weeks (about 21 days) or about four weeks (about 28 days), wherein each cycle preferably comprises 2 or more consecutive weeks, more preferably 2 or 3 consecutive weeks, wherein each of the consecutive weeks comprises administering to the patient

i) temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably administered to the patient in 5 or more about equal doses, preferably 5, 6 or 7 about equal doses, more preferably 5, 6 or 7 about equal daily doses, so that the weekly dose of the temozolomide contained therein sums up to an amount of 360 mg/m^2 to 700 mg/m^2 per patient within each of said consecutive weeks; and

ii) at least one further cancer cotherapeutic agent, selected from

- a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable derivative, solvate or salt thereof, and
- b) cetuximab or pharmaceutically acceptable derivative, solvate or salt thereof.

In this method, the at least one further cancer cotherapeutic agent is preferably administered during each week of said cycle or cycles, preferably as described herein. In this method, the intracerebral cancer is preferably selected from astrocytoma, especially astrocytoma grade II, III and IV, glioblastoma and glioblastoma multiforme (GBM). In this method, the temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably the temozolomide, is preferably administered to the patient in 5 or more doses, for example 5, 6 or 7 doses, more preferably 5, 6 or 7 about equal daily doses, so that the weekly dose of the temozolomide contained therein sums up to an amount of 360 mg/m^2 to 750 mg/m^2 , preferably 550 mg/m^2 to 700 mg/m^2 , per patient within each of said consecutive weeks. In this method, preferably each of said 5 or more doses is given on a different day within each week, e.g. a five times weekly administration scheme, a six times weekly administration scheme or a seven

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times weekly administration scheme, preferably as described herein. In this method, preferably each of said 5 or more doses of temozolomide consists of about 50 mg/m², about 60 mg/m², about 75 mg/m², about 80 mg/m² or about 100 mg/m², preferably given once daily, more preferably given once daily about every day during said 2 to 3 consecutive weeks and especially during said 3 consecutive weeks (about 20 or about 21 consecutive days). In this method, the cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof is preferably administered to the patient in one or more doses so that the dose of the cetuximab contained therein sums up to an amount of about 250 mg/m² or about 400 mg/m² per patient within each of said consecutive weeks. In this method, the cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof is more preferably administered to the patient in one or more doses so that the dose of the cetuximab contained therein sums up to an amount of about 250 mg/m² or about 400 mg/m² per patient within each week of said one or more cycles. In this method, preferably the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof is administered to the patient in one or more doses so that the dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of about 2000 mg, about 4000 mg, about 6000 mg, about 8000 mg or about 10000 mg per patient within said week. In this method, preferably each of the one or more doses consists of about 500 mg or about 2000 mg of cyclo-(Arg-Gly-Asp-DPhe-NMe-Val). In this method, preferably, each of said one or more doses of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) is given on a different day within said week, e.g. in a twice weekly administration scheme, a three times weekly administration scheme, a four times weekly administration scheme or a five times weekly administration scheme, preferably as described herein. This method is preferably not combined with radiotherapy.

Thus, an even more preferred preferred further aspect of the instant invention relates to the following methods of treating cancer, preferably intracerebral cancer:

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[6] A method, wherein the methods according to paragraphs [4] and [5] are combined, preferably sequentially and preferably in the given order.

- 5 [7] A method of treating intracerebral cancer, preferably glioblastoma or glioblastoma multiforme (GBM), comprising 2 to 10 consecutive weeks, preferably 4 to 6 consecutive weeks and especially about 4 or about 6 consecutive weeks of treatment, wherein each of the consecutive weeks comprises administering to the patient
- 10 i) temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof,
- ii) at least one further cancer cotherapeutic agent, selected from
- a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable derivative, solvate or salt thereof, and
- 15 b) cetuximab or pharmaceutically acceptable derivative, solvate or salt thereof,
- and
- iv) external beam radiation, preferably selected from focal radiotherapy and whole brain radiation.
- 20 [8] A method of treating intracerebral cancer, preferably glioblastoma or glioblastoma multiforme (GBM), comprising 2 to 10 consecutive weeks, preferably 4 to 6 consecutive weeks and especially about 4 or about 6 consecutive weeks of treatment, wherein each of the consecutive weeks
- 25 comprises administering to the patient
- i) temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof,
- ii) two further cancer cotherapeutic agents,
- a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable derivative, solvate or salt thereof, and
- 30 b) cetuximab or pharmaceutically acceptable derivative, solvate or salt thereof,
- and optionally

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iv) external beam radiation, preferably selected from focal radiotherapy and whole brain radiation.

- 5 [9] A method of treating intracerebral cancer, preferably glioblastoma or glioblastoma multiforme (GBM), said method comprising two or more cycles, preferably 2 to 8 cycles, and especially 3 or 6 cycles, each cycle preferably consisting of about four weeks (about 28 days), wherein each cycle preferably comprises 2 or 3 consecutive weeks, wherein each of the
- 10 consecutive weeks comprises administering to the patient
- i) temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably administered to the patient in 5 or more about equal doses, preferably 5, 6 or 7 about equal doses, more preferably 5, 6 or 7 about equal daily doses, so that the weekly dose of the temozolomide
- 15 contained therein sums up to an amount of 360 mg/m^2 to 750 mg/m^2 , preferably 550 mg/m^2 to 700 mg/m^2 , per patient within each of said consecutive 2 or 3 consecutive weeks; and
- ii) at least one further cancer cotherapeutic agent, selected from
- a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable
- 20 derivative, solvate or salt thereof, and
- b) cetuximab or a pharmaceutically acceptable derivative, solvate or salt thereof.

During said two or more cycles, preferably no radiotherapy is applied to the patient. During said two or more cycles, the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) (or a pharmaceutically acceptable derivative, solvate or salt thereof)

25 and/or

the cetuximab (or a pharmaceutically acceptable derivative, solvate or salt thereof) is preferably administered to the patient in about each week of said two or more cycles, preferably in a manner as described herein.

30

[10] A method of treating intracerebral cancer, preferably glioblastoma or glioblastoma multiforme (GBM), said method comprising two or more cycles, preferably 2 to 8 cycles, and especially 3 or 6 cycles, each cycle preferably

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consisting of about four weeks (about 28 days), wherein each cycle preferably comprises

- 5 (A) about 2 consecutive weeks or about 3 consecutive weeks, wherein each of the consecutive weeks comprises administering to the patient
- i) temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably administered to the patient in 5 or more about equal doses, preferably 5, 6 or 7 about equal doses, more preferably 5, 6 or 7 about equal daily doses, even more preferably
- 10 6 or 7 about equal daily doses, so that the weekly dose of the temozolomide contained therein sums up to an amount of 360 mg/m² to 750 mg/m², preferably 550 mg/m² to 700 mg/m², per patient within each of said about 2 or about 3 consecutive weeks;

and

- 15 (B) the administration of at least one further cancer cotherapeutic agent during each week of the about four weeks (about 28 days) of said cycle, wherein said at least one further cancer cotherapeutic agent is selected from
- a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable
- 20 derivative, solvate or salt thereof, preferably administered to the patient in one or more about equal doses, preferably 1 to 5 about equal doses, more preferably 2 or 5 about equal daily doses, preferably so that the weekly dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of about 2000 mg,
- 25 about 4000 mg, about 6000 mg, about 8000 mg or about 10000 mg per patient and per week within each week of said cycle, and
- b) cetuximab or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably administered to the patient in one or more about
- 30 equal doses per week, more preferably 1 dose per week, said dose or doses preferably consisting of about 250 mg/m² or about 400 mg/m², preferably so that the weekly dose of the cetuximab contained therein is or sums up to an amount of about 250 mg/m² or

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about 400 mg/m² per patient and per week within each week of said cycle.

- 5 [11] A method, wherein
- a) the methods according to paragraphs [7] and [9] are combined, preferably sequentially and preferably in the given order; or
 - b) the methods according to paragraphs [8] and [9] are combined, preferably sequentially and preferably in the given order.

10

- [12] A method, wherein
- a) the methods according to paragraphs [7] and [10] are combined, preferably sequentially and preferably in the given order; or
 - b) the methods according to paragraphs [8] and [10] are combined, preferably sequentially and preferably in the given order.

15

[13] A method of treating intracerebral cancer, preferably glioblastoma or glioblastoma multiforme (GBM), said method comprising
(A) administering to the patient

- 20 i) temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof,
- ii) at least one further cancer cotherapeutic agent, selected from
- a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable derivative, solvate or salt thereof, and
 - 25 b) cetuximab or pharmaceutically acceptable derivative, solvate or salt thereof,

and

iii) external beam radiation, preferably selected from focal radiotherapy and whole brain radiation

- 30 in each week during weeks 1 to 10, weeks 1 to 6 or weeks 1 to 4;
optionally directly followed by

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0 to 6 weeks, more preferably 3 to 5 weeks and especially about 3 or about 4 weeks wherein only the at least one further cancer cotherapeutic agent, selected from

- 5 a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable dervative, solvate or salt thereof, and
 b) cetuximab or a pharmaceutically acceptable dervative, solvate or salt thereof,

is administered to said patient in about each week of said second cycle;

10 followed by, preferably directly followed by

(B) two or more cycles, preferably 2 to 8 cycles and especially 3 or 6 cycles, each cycle preferably consisting of about four weeks (about 28 days), wherein

- 15 i) each cycle preferably comprises 2 or 3 consecutive weeks, preferably the first 2 or 3 weeks in said cycle, during which temozolomide or a pharmaceutically acceptable dervative, solvate or salt thereof is administered to the patient, preferably in 5 or more about equal doses, more preferably 5, 6 or 7 about equal doses, even more preferably 5, 6 or 7 about equal daily doses, preferably so that the weekly dose of the
20 temozolomide contained therein sums up to an amount of 360 mg/m² to 750 mg/m², preferably 550 mg/m² to 700 mg/m², per patient within each of said consecutive 2 or 3 weeks;

and wherein

- 25 ii) the at least one further cancer cotherapeutic agent, selected from
 a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable dervative, solvate or salt thereof, and
 b) cetuximab or a pharmaceutically acceptable dervative, solvate or salt thereof,

30 is administered to said patient in about each week of said two or more cycles, preferably in a manner as described herein.

During said two or more cycles, preferably no radiotherapy is applied to the patient.

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[14] A method of treating intracerebral cancer, preferably glioblastoma or glioblastoma multiforme (GBM), said method comprising

(A) a first cycle consisting of 2 to 8 weeks, preferably 4 to 6 weeks, more preferably consecutive weeks, and especially about 4 or about 6 consecutive weeks, wherein each week comprises administering to the patient

i) temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof,

ii) at least one further cancer cotherapeutic agent, selected from

a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable derivative, solvate or salt thereof, and

b) cetuximab or pharmaceutically acceptable derivative, solvate or salt thereof,

and

iii) external beam radiation, preferably selected from focal radiotherapy and whole brain radiation; directly followed by

(B) a second cycle consisting of either

i) 1 to 6 and especially 2 to 4 weeks, preferably consecutive weeks, without treating said patient, or

ii) 1 to 6 and especially 2 to 4 weeks, preferably constitutive weeks, wherein only the at least one further cancer cotherapeutic agent, selected from

c) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable derivative, solvate or salt thereof, and

d) cetuximab or a pharmaceutically acceptable derivative, solvate or salt thereof,

is administered to said patient in about each week of said second cycle; directly followed by

(C) two or more cycles, preferably 2 to 8 cycles and especially 3 or 6 cycles, each cycle preferably consisting of about four weeks (about 28 days), wherein

i) temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof is administered to the patient during weeks 1 to 3 of said

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cycles, preferably in 5 or more about equal doses, more preferably 5, 6 or 7 about equal doses per week, even more preferably 5, 6 or 7 about equal daily doses, preferably so that the weekly dose of the temozolomide contained therein sums up to an amount of 360 mg/m² to 750 mg/m², preferably 550 mg/m² to 700 mg/m², per patient within each of said weeks 1 to 3;

and wherein

ii) the at least one further cancer cotherapeutic agent, selected from
 a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable dervative, solvate or salt thereof, and
 b) cetuximab or a pharmaceutically acceptable dervative, solvate or salt thereof,

is administered to said patient in about each week of said two or more cycles, preferably 2 to 8 cycles and especially 3 or 6 cycles, preferably in a manner as described herein; optionally directly followed by

(D) two or more cycles, preferably 3 to 24 cycles and especially 4 to 12 cycles, each cycle preferably consisting of about four weeks (about 28 days), wherein

ii) the at least one further cancer cotherapeutic agent, selected from
 e) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable dervative, solvate or salt thereof, and
 f) cetuximab or a pharmaceutically acceptable dervative, solvate or salt thereof,

is administered to said patient in about each week of said cycles, preferably in a manner as described herein.

Preferably, no radiotherapy is applied or administered to the patient during (C) and (D).

30

[15] A method of treating intracerebral cancer, preferably glioblastoma or glioblastoma multiforme (GBM), comprising the mandatory treatment steps or regimens as described in one or more of the Graphic treatment schemes 1 to

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4 and/or one or more of the Graphic treatment schemes 5 and 6, and especially one or more of the Graphic treatment schemes 1 to 4 and/or one or more of the Graphic treatment schemes 5 and 6 comprising all treatment steps or regiments as described therein.

If a method of treatment described herein comprises two or more cycles, the two or more cycles are preferably constitutive to each other. Thus, two or more cycles in this regard preferably means two or more consecutive cycles.

10

In the method described in the paragraph numbered [13], the further cancer cotherapeutic agent or the combination thereof is preferably the same in both step (A) and (B), e.g.

- if the cancer cotherapeutic agent cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable derivative, solvate or salt thereof, is chosen as the only cancer cotherapeutic agent in step (A), it is preferably also the only cancer cotherapeutic agent in step (B),
- if the cancer cotherapeutic agent cetuximab or a pharmaceutically acceptable derivative, solvate or salt thereof, is chosen as the only cancer cotherapeutic agent in step (A), it is preferably also the only cancer cotherapeutic agent in step (B),
- if a combination of both cancer cotherapeutic agents,
 - (i) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable derivative, solvate or salt thereof, and
 - (ii) cetuximab or a pharmaceutically acceptable derivative, solvate or salt thereof,is chosen as the combined cancer cotherapeutic agents in step (A), the same combination is preferably also used as the cancer cotherapeutic agents in step (B).

30

In the method described in the paragraph numbered [14], the further cancer cotherapeutic agent or the combination thereof is preferably the same in steps (A), (C), (D) and, if applicable, step (B), e.g.

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- if the cancer cotherapeutic agent cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable derivative, solvate or salt thereof, is chosen as the only cancer cotherapeutic agent in step (A), it is preferably also the only cancer cotherapeutic agent in steps C), (D) and, if applicable, step (B),
- if the cancer cotherapeutic agent cetuximab or a pharmaceutically acceptable derivative, solvate or salt thereof, is chosen as the only cancer cotherapeutic agent in step (A), it is preferably also the only cancer cotherapeutic agent in steps C), (D) and, if applicable, step (B),
- if a combination of both cancer cotherapeutic agents,
 - (i) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable derivative, solvate or salt thereof, and
 - (ii) cetuximab or a pharmaceutically acceptable derivative, solvate or salt thereof, is chosen as the combined cancer cotherapeutic agents in step (A), the same combination is preferably also used as the cancer cotherapeutic agents in steps C), (D) and, if applicable, step (B).

In the methods described in the paragraphs numbered [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14] and/or [15], the temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably the temozolomide, is preferably administered to the patient in 5 or more doses, for example 5, 6 or 7 doses, more preferably 5, 6 or 7 about equal daily doses, so that the weekly dose of the temozolomide contained therein sums up to an amount of 360 mg/m² to 750 mg/m², preferably 550 mg/m² to 700 mg/m², per patient within each week. Preferably each of said 5 or more doses is given on a different day within each week, e.g. a five times weekly administration scheme, a six times weekly administration scheme or a seven times weekly administration scheme, preferably as described herein. More preferably each of said 5 or more doses of temozolomide consists of about 50 mg/m², about 60 mg/m², about 75 mg/m², about 80 mg/m² or about 100 mg/m².

In the methods described in the paragraphs numbered [1], [2], [3], [4], [5], [6],

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[7], [8], [9], [10], [11], [12], [13], [14] and/or [15], the cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cetuximab, is preferably administered to the patient in one or more
5 doses so that the dose of the cetuximab contained therein sums up to an amount of about 250 mg/m² or about 400 mg/m² per patient within each week.

In the methods described in the paragraphs numbered [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14] and/or [15], the cyclo-(Arg-Gly-Asp-
10 DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), is administered to the patient in one or more doses so that the dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of about 2000 mg, about 4000 mg, about 6000 mg, about 8000 mg or about 10000 mg per
15 patient within said week. More preferably, each of the one or more doses consists of about 500 mg or about 2000 mg of cyclo-(Arg-Gly-Asp-DPhe-NMe-Val). Even more preferably, each of said one or more doses of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) is given on a different day within said week, e.g. in a twice weekly administration scheme, a three times weekly
20 administration scheme, a four times weekly administration scheme or a five times weekly administration scheme, preferably as described herein.

In the methods described in the paragraphs numbered [1], [2], [3], [4], [7], [8], [13], [14] and/or [15], the radiotherapy is preferably as described herein. More preferably, the radiotherapy is external beam radiation and even more
25 preferably selected from (external beam) whole brain brain radiation and (external beam) focal radiotherapy of the brain (preferably also referred to as focal radiotherapy). Especially preferably, the external beam radiation consists of 20 to 70 Gy and especially of about 30 Gy or about 60 Gy. In this context, the whole brain radiation preferably consists of about 30 Gy,
30 preferably given in about 10 fractions of about 3 Gy each. In this context, the focal radiotherapy preferably consists of about 60 Gy, preferably given in about 30 fractions of about 2 Gy each.

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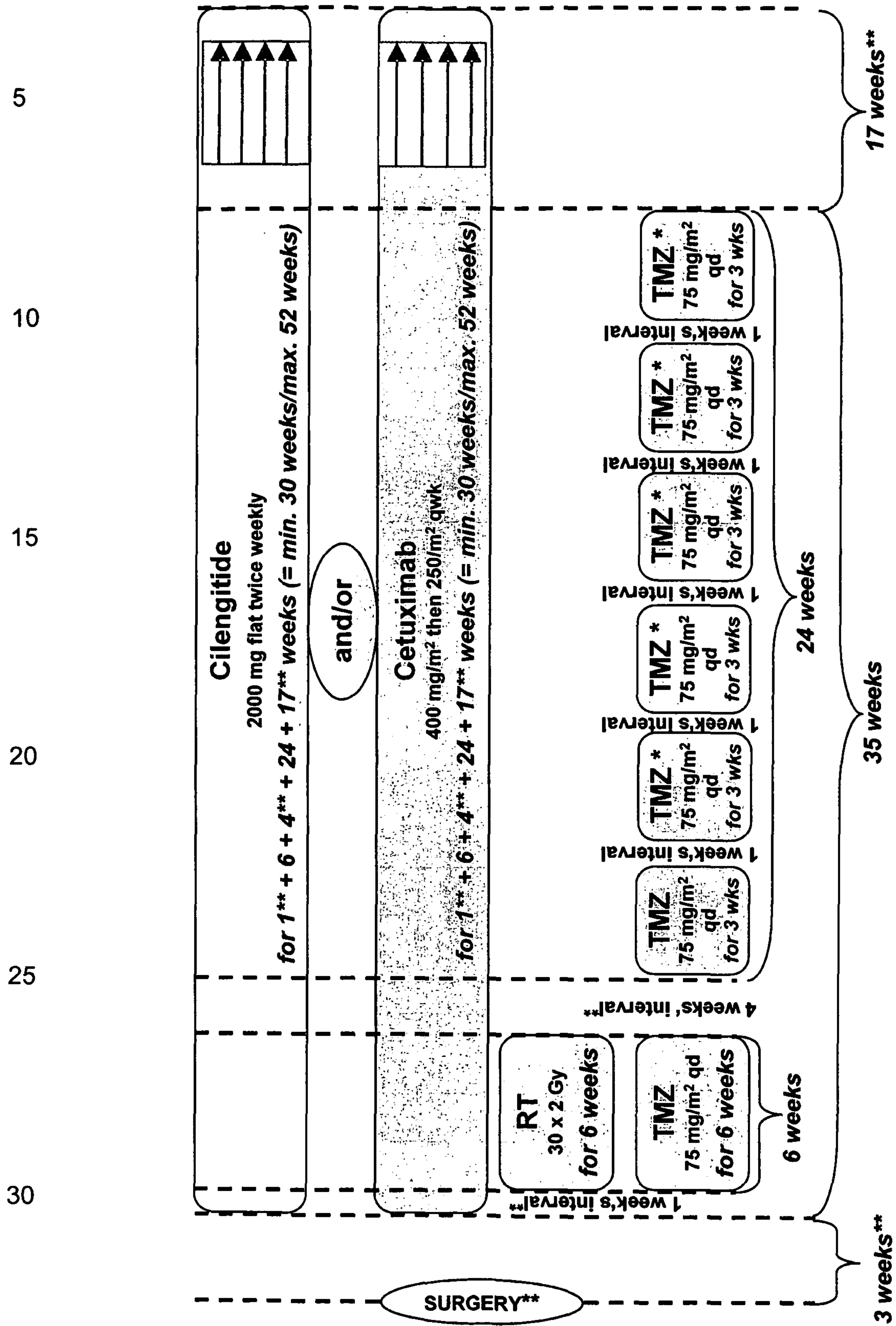
5 The following graphic (Graphic treatment scheme 1) shows a preferred method of treatment which comprises mandatory treatment periods, and preferably optional time periods (e.g. recovery periods, during which preferably no treatment is applied to the patient) and/or optional treatment periods (the latter two marked by two asterisks (**)). During the optional treatment periods preferably only the Cilengitide (i.e. cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the cetuximab is administered to the patient, but preferably no radiotherapy is administered to the patient during said optional treatment periods (see graphic for 1 weeks' interval** and/or 4 weeks' interval**). If this preferred method of treatment according to graphic treatment scheme 1 comprises the "1 weeks' interval**" and cetuximab is administered to the patient, the cetuximab is preferably administered once during said "1 weeks' interval**" in an amount of about 400 mg/m² (this is also referred to as "loading dose"). After the "1 weeks' interval**", the amount of cetuximab that is administered to the patient is preferably about 250 mg/m² per week and more preferably about 250 mg/m² once per week, if applicable. The administration of cetuximab "once per week" is also abbreviated in said graph(s) by "qwk". The administration of temozolomide "once per day" is preferably also abbreviated in said graph(s) by "qd". Preferably, the radiotherapy is only administered to the patient during the mandatory treatment periods and more preferably only where the radiotherapy is explicitly named in said graph.

25 The dosings of the Cetuximab, Cilengitide, Temozolomide and/or Procarbazine (if applicable) given in Graphic treatment schemes 1 to 6 below are preferred embodiments; however, a deviation of plus or minus 20 % and preferably plus or minus 10% of said given dosings is preferably deemed to be in accordance with the instant invention.

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Graphic treatment scheme 1

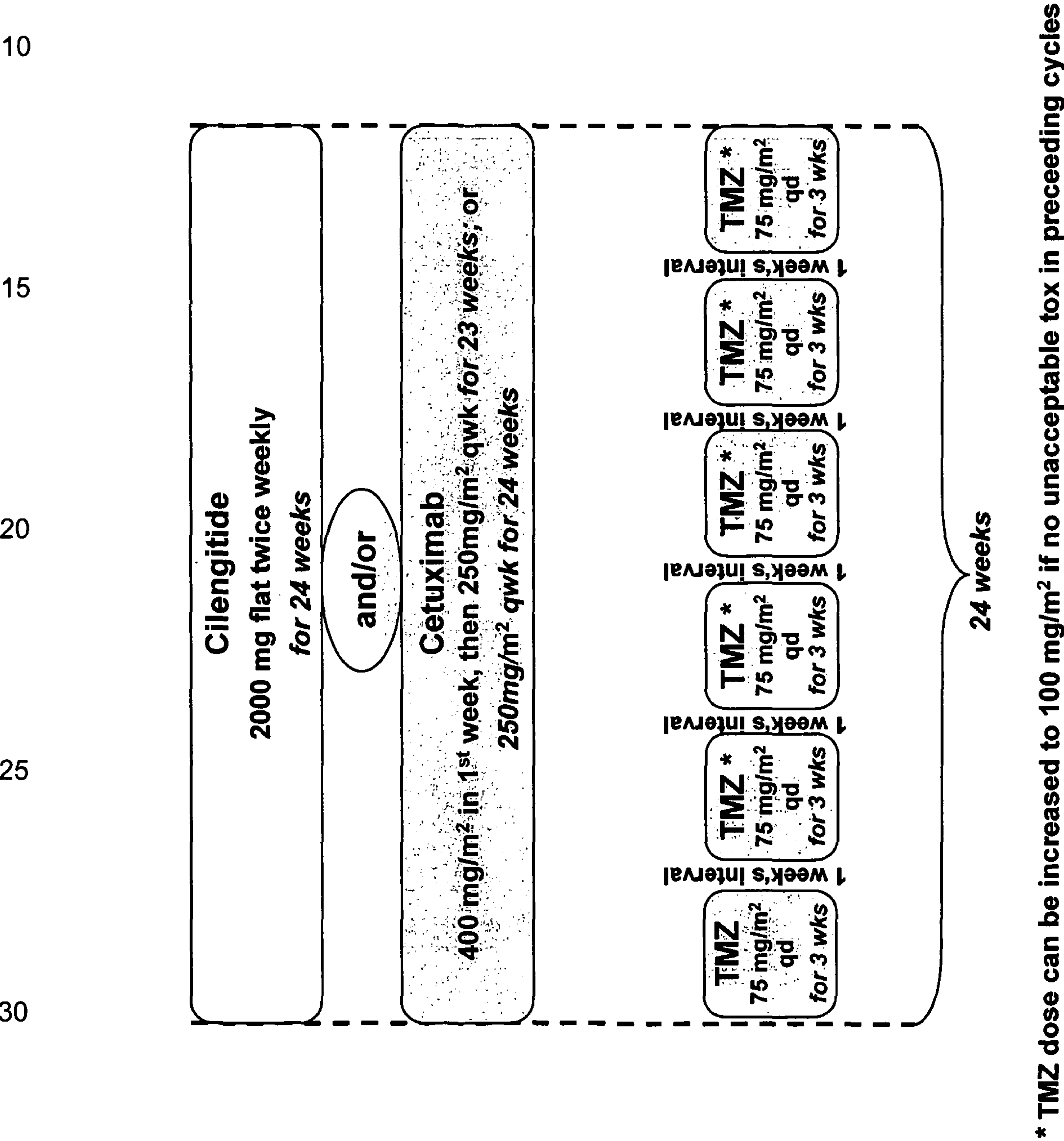


* TMZ dose can be increased to 100 mg/m² if no unacceptable tox in preceeding cycles

** optional time periods or treatment periods

The following graphic (Graphic treatment scheme 2) shows a preferred method of treatment, which preferably does not comprise radiotherapy. The administration of cetuximab "once per week" is also abbreviated in said graph by "qwk". The administration of temozolomide "once per day" is preferably also abbreviated in said graph(s) by "qd".

Graphic treatment scheme 2



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The following graphic (Graphic treatment scheme 3) shows a preferred method of treatment, which preferably does not comprise radiotherapy, but comprises mandatory treatment periods, and preferably also optional treatment periods (the latter marked by two asterisks (**)). During the optional treatment periods preferably only the Cilengitide (i.e. cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the cetuximab is administered to the patient, but preferably no radiotherapy is administered to the patient during said optional treatment periods (see graphic for 17 weeks**). The administration of cetuximab "once per week" is also abbreviated in said graph by "qwk". The administration of temozolomide "once per day" is preferably also abbreviated in said graph(s) by "qd".

15

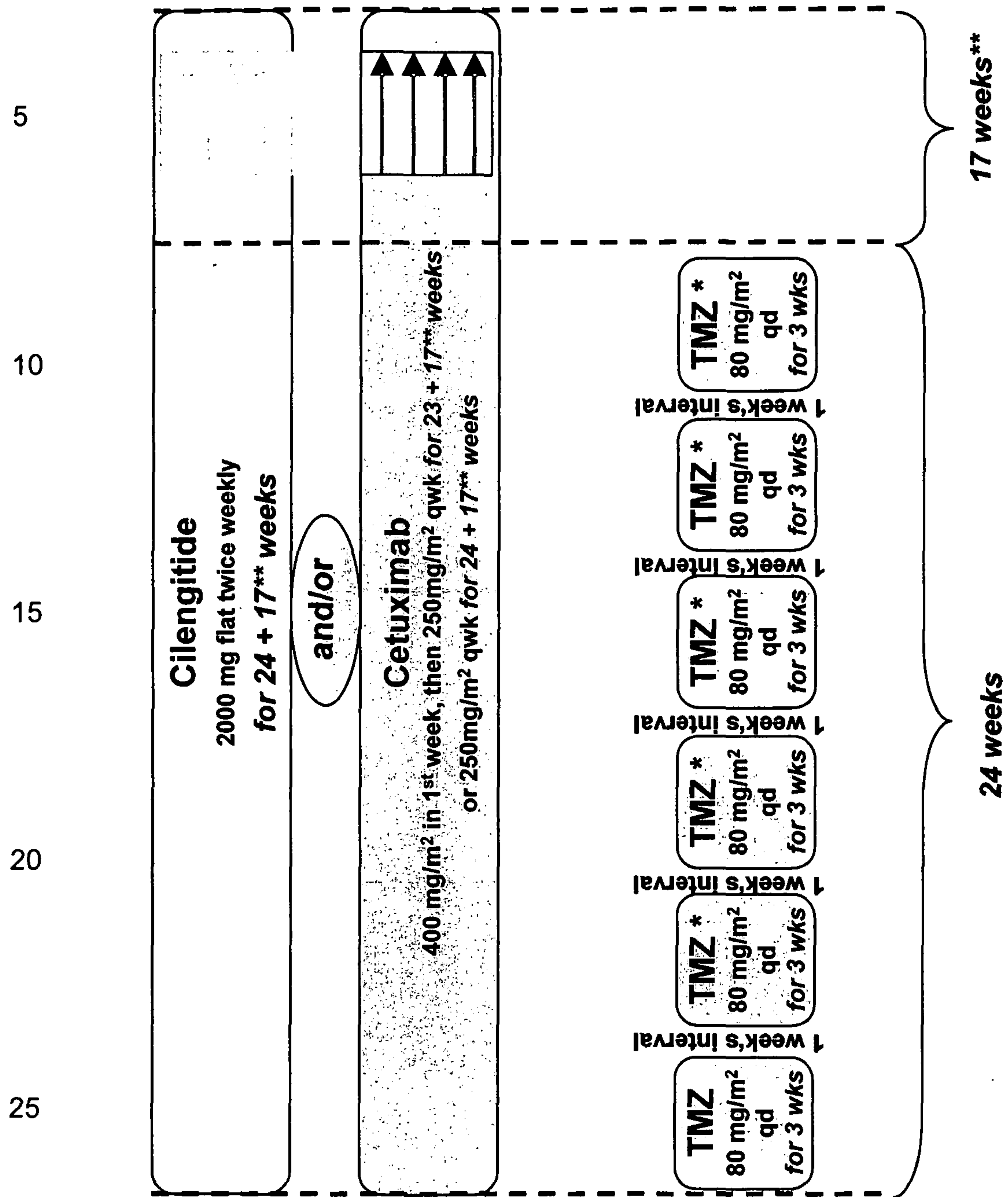
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Graphic treatment scheme 3



* TMZ dose can be increased to 100 mg/m² if no unacceptable tox in preceding cycles

** optional treatment periods

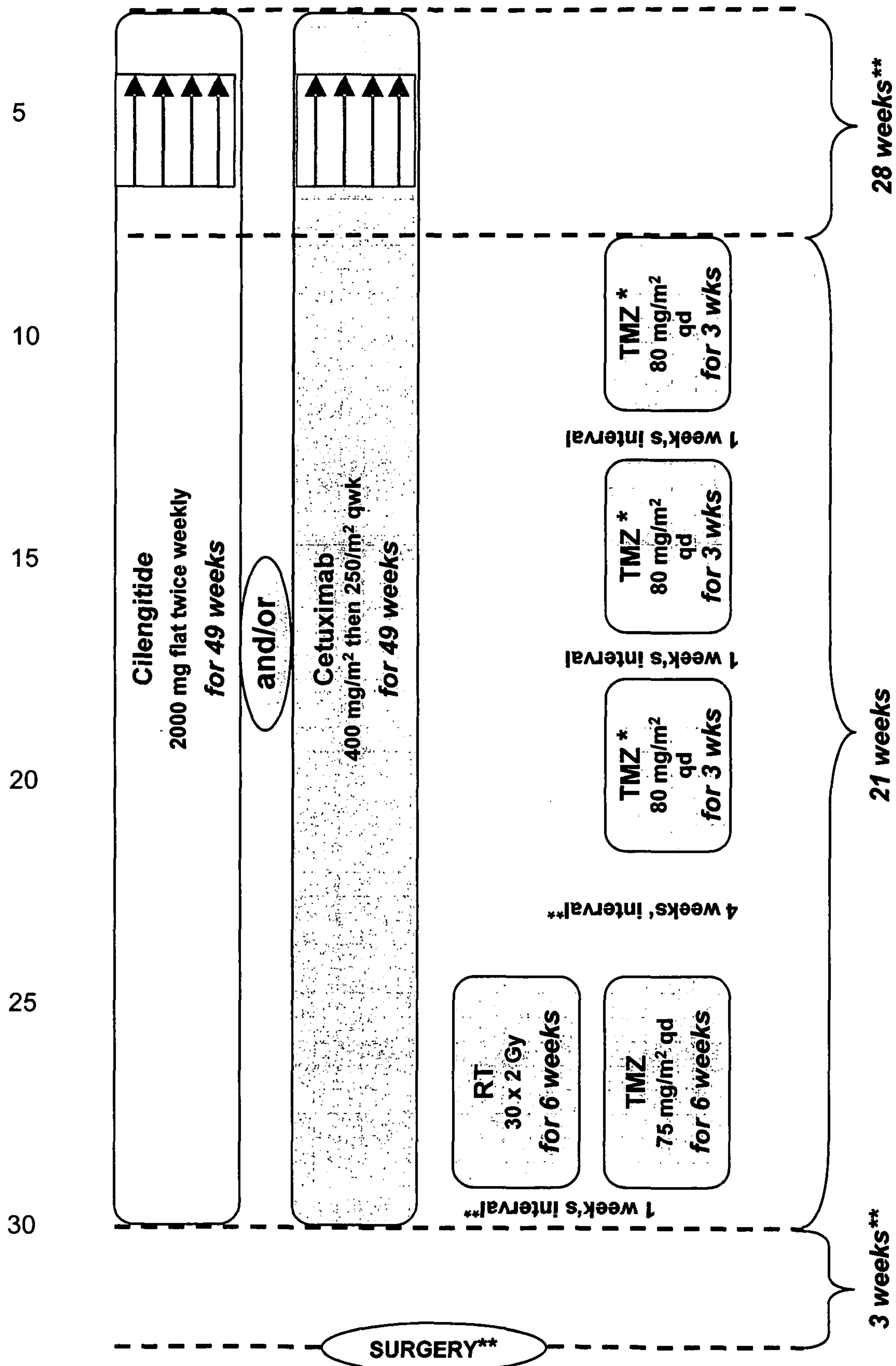
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The following graphic (Graphic treatment scheme 4) shows a preferred method of treatment which comprises mandatory treatment periods, and preferably optional time periods (e.g. recovery periods, during which preferably no treatment is applied to the patient) and/or optional treatment periods (the latter two marked by two asterisks (**)). During the optional treatment periods preferably only the Cilengitide (i.e. cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the cetuximab is administered to the patient, but preferably no radiotherapy is administered to the patient during said optional treatment periods (see graphic for 1 weeks' interval** and/or 4 weeks' interval**). If this preferred method of treatment according to graphic treatment scheme 4 comprises the "1 weeks' interval**" and cetuximab is administered to the patient, the cetuximab is preferably administered once during said "1 weeks' interval**" in an amount of about 400 mg/m² (this is also referred to as "loading dose"). After the "1 weeks' interval**", the amount of cetuximab that is administered to the patient is preferably about 250 mg/m² per week and more preferably about 250 mg/m² once per week, if applicable. The administration of cetuximab "once per week" is also abbreviated in said graph by "qwk". Preferably, the radiotherapy is only administered to the patient during the mandatory treatment periods and more preferably only where the radiotherapy is explicitly named in said graph. The administration of temozolomide "once per day" is preferably also abbreviated in said graph(s) by "qd".

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Graphic treatment scheme 4



*** TMZ dose can be increased to 100 mg/m² if no unacceptable tox in preceding cycles**

**** optional time periods or treatment periods**

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Preferred further aspects of the instant invention preferably relate to:

- 5 Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), for use in the treatment of cancer, preferably intracerebral cancer and even more preferably glioblastoma or glioblastoma multiforme (GBM), in combination with
- 10 i) cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cetuximab,
- ii) temozolomide the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably temozolomide,
- iii) and radiotherapy.
- 15 Cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cetuximab, for use in the treatment of cancer, preferably intracerebral cancer and even more preferably glioblastoma or glioblastoma multiforme (GBM), in combination with
- 20 i) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val),
- ii) temozolomide the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably temozolomide,
- iii) and radiotherapy.
- 25 Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), for use in the treatment of cancer, preferably intracerebral cancer and even more preferably glioblastoma or glioblastoma multiforme
- 30 (GBM), in combination with
- i) cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cetuximab, and

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ii) temozolomide the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably temozolomide, optionally in combination with

5 iii) radiotherapy, preferably external beam radiation, more preferably focal radiotherapy or whole brain radiation.

Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), for use in the treatment of cancer, preferably intracerebral cancer and even more preferably glioblastoma or glioblastoma multiforme (GBM), in combination with

i) temozolomide the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably temozolomide, optionally in combination with

15 ii) cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cetuximab, and/or

iii) the radiotherapy, preferably external beam radiation, more preferably focal radiotherapy or whole brain radiation,

20 wherein in said treatment, the temozolomide the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably temozolomide, is administered to the patient on 6 or 7 days within one week, preferably for one or more weeks, more preferably for about 3 consecutive weeks (about 21 consecutive days) or about 6 consecutive weeks (about 42 consecutive days), and preferably in an amount of 50 to 120 mg/m² per day and per patient, more preferably in an amount of about 75 mg/m², about 80 mg/m² or about 100 mg/m² per day and per patient.

Cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cetuximab, for use in the treatment of cancer, preferably intracerebral cancer and even more preferably glioblastoma or glioblastoma multiforme (GBM), in combination with

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- i) temozolomide the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably temozolomide, optionally in combination with
- 5 ii) Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), and/or
- iii) the radiotherapy, preferably external beam radiation, more preferably focal radiotherapy or whole brain radiation,
- 10 wherein in said treatment, the temozolomide the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably temozolomide, is administered to the patient on 6 or 7 days within one week, preferably for one or more weeks, more preferably for about 3 consecutive weeks (about 21 consecutive days) or about 6 consecutive weeks (about 42 consecutive
- 15 days), and preferably in an amount of 50 to 120 mg/m² per day and per patient, more preferably in an amount of about 75 mg/m², about 80 mg/m² or about 100 mg/m² per day and per patient.

- Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable
- 20 derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), for use in the treatment of cancer, preferably intracerebral cancer and even more preferably glioblastoma or glioblastoma multiforme (GBM), in combination
- i) with temozolomide the pharmaceutically acceptable derivatives, solvates
- 25 and/or salts thereof, preferably temozolomide, and
- ii) with or without radiotherapy,
- wherein said treatment comprises one or more cycles, preferably 2 to 8 cycles and especially 3 or 6 cycles, each cycle preferably consisting of about four weeks (about 28 days), wherein
- 30 a) the temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably the temozolomide, is administered to the patient on 6 or 7 days within one week, preferably on each day within one week, preferably for about 3 consecutive weeks (about 21

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- consecutive days), and preferably in an amount of 50 to 120 mg/m² per day and per patient, more preferably in an amount of about 75 mg/m², about 80 mg/m² or about 100 mg/m² per day and per patient, and
- 5 b) the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), is administered to the patient during each week of said one or more cycles, preferably in one or more
- 10 doses so that the dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of about 2000 mg, about 4000 mg, about 6000 mg, about 8000 mg or about 10000 mg per patient within each week of said cycle.
- 15 Cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cetuximab, for use in the treatment of cancer, preferably intracerebral cancer and even more preferably glioblastoma or glioblastoma multiforme (GBM), in combination
- i) with temozolomide the pharmaceutically acceptable derivatives, solvates
- 20 and/or salts thereof, preferably temozolomide, and
- ii) with or without radiotherapy,
- wherein said treatment comprises one or more cycles, preferably 2 to 8 cycles and especially 3 or 6 cycles, each cycle preferably consisting of about four weeks (about 28 days), wherein
- 25 a) the temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably the temozolomide, is administered to the patient on 6 or 7 days within one week, preferably on each day within one week, preferably for about 3 consecutive weeks (about 21
- 30 consecutive days), and preferably in an amount of 50 to 120 mg/m² per day and per patient, more preferably in an amount of about 75 mg/m², about 80 mg/m² or about 100 mg/m² per day and per patient, and

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b) the cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cetuximab, is administered to the patient during each week of said one or more cycles, preferably in one or more doses so that the dose of the cetuximab contained therein sums up to an amount of 150 to 600 mg/m², preferably 200 to 500 mg/m² and especially about 250 mg/m² or about 450 mg/m² per patient within each week of said cycle.

As used herein, "mg/m²" preferably means milligrams per square meter and especially milligrams per square meter of the body surface of the respective Patient. Thus, amounts or doses given in "mg/m²" preferably mean amounts or doses administered to a patient in milligrams per square meter of the body surface of the respective patient.

Preferably, the above described methods the substances for the use in such treatments and especially the methods described in one or more of the paragraphs numbered [1] to [15] are advantageous for the treatment of "unmethylated" patients, i.e. patients having an normal or decreased DNA methylation status, preferably as described and defined herein.

A preferred further aspect of the instant invention relates to the following methods of treatment:

A method of treating cancer comprising administering to the patient within at least one week

- i) at least one alkylating chemotherapeutic agent agent, comprising procarbazine and/or temozolomide; or the pharmaceutically acceptable derivatives, solvates and salts thereof,
- ii) at least one further cancer cotherapeutic agent, selected from cetuximab, cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and salts thereof, and radiotherapy.

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A method of treating cancer, selected from the group consisting of intracerebral cancer, head-and-neck cancer, rectal cancer and lung cancer, comprising administering to the patient within at least one week

- 5 i) at least two alkylating chemotherapeutic agents, comprising procarbazine and/or temozolomide, optionally in combination with one or more alkylating chemotherapeutic agents, selected from the group consisting of N-Lost-Derivatives, Nitroso urea derivatives, Oxazaphosphorines, Platin derivatives, Tetrazines, Aziridines, and others, selected from Amsacrine,
10 Estramustinphosphate and Treosulfane;
and pharmaceutically acceptable derivatives, salts and/or solvates thereof,
ii) at least one and preferably at least two further cancer cotherapeutic agents, selected from cetuximab, cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and salts thereof, and
15 radiotherapy.

- In said methods, if not explicitly specified otherwise, the at least one alkylating chemotherapeutic agent is preferably selected from the alkylating chemotherapeutic agents as described herein and more preferably selected
20 from the N-Lost-Derivatives Busulfane and Chlorambucil, the Nitroso urea derivatives Nimustine, Carmustine and Lomustine, the Oxazaphosphorines Cyclophosphamide, Ifosfamide and Trofosfamide, Platin derivatives Cisplatin, Carboplatin and Oxaliplatin, the Tetrazines Dacarbazine and Temozolomide, the Aziridine Thiotepa, and others, selected from Amsacrine,
25 Estramustinphosphate Procarbazine and Treosulfane;
and pharmaceutically acceptable derivatives, salts and/or solvates thereof.

- In said methods, the cancer to be treated is preferably as described herein and more preferably selected from intracerebral cancer, head-and-neck
30 cancer, rectal cancer, small cell lung cancer, non-small cell lung cancer, glioblastoma multiforme, small cell lung cancer, non-small cell lung cancer, breast cancer, metastatic melanoma, metastatic androgen independent prostate cancer, metastatic androgen dependent prostate cancer, and brain

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metastases thereof. Even more preferably, the cancer to be treated is selected from the group consisting of

- 5 i) intracerebral cancer, more preferably astrocytoma grade II, III or IV, glioblastoma, glioblastoma multiforme (GBM), and brain metastases of other cancers, preferably other cancers selected from lung cancer, especially small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), metastatic melanoma, prostate cancer, especially metastatic androgen independent prostate cancer (AIPCa), metastatic androgen
10 dependent prostate cancer (ADPCa), and breast cancer;
- ii) lung cancer, especially small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC),
- iii) metastatic melanoma,
- iv) prostate cancer, especially metastatic androgen independent prostate
15 cancer (AIPCa), metastatic androgen dependent prostate cancer (ADPCa),
- v) and breast cancer.

20 In said methods, the cancer to be treated it as preferably intracerebral cancer, more preferably astrocytoma grade II, III or IV, and especially preferably glioblastoma or glioblastoma multiforme (GBM).

In said methods, the at least two alkylating chemotherapeutic agents are preferably selected from the group consisting of

- 25 i) Platin derivatives, more preferably from the Platin derivatives Cisplatin, Carboplatin and Oxaliplatin;
- ii) Tetrazines, more preferably from the Tetrazines, Dacarbazine and Temozolomide; and/or
- iii) Procarbazine;
- 30 and pharmaceutically acceptable dervatives, salts and/or solvates thereof.

In said methods, the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable dervatives, solvates and salts thereof is

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preferably administered to the patient in one or more doses so that the dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of 3 to 30 millimoles per patient within in said week. More preferably, the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable dervatives, solvates and salts thereof is to be administered to the patient in one or more doses so that the dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of 3 to 10 millimoles per patient within said week or to an amount of 10 to 30 millimoles per patient within said week.

In said methods, the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable dervatives, solvates and/or salts thereof is preferably administered to the patient in one or more doses so that the dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of 2000 mg to 14000 mg and especially 4000 mg to 10000 mg per patient within in said week. More preferably, the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable dervatives, solvates and/or salts thereof is to be administered to the patient in one or more doses so that the dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of about 2000 mg, about 4000 mg, about 6000 mg, about 8000 mg or about 10000 mg per patient within said week. Preferably, each of the one or more doses consists of about 500 mg or about 2000 mg. Preferably, each of said one or more doses is given on a different day within said week, e.g. in a twice weekly administration scheme, a three times weekly administration scheme, a four times weekly administration scheme or a five times weekly administration scheme, preferably as described herein.

In said methods, the cetuximab, the pharmaceutically acceptable dervatives, solvates and/or salts thereof is preferably administered to the patient in one or more doses so that the dose of the cetuximab contained therein sums up to an amount of 100 mg/m² to 800 mg/m² and especially 200 mg/m² to 500 mg/m² per patient within in said week. More preferably, the cetuximab, the

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pharmaceutically acceptable derivatives, solvates and/or salts thereof is to be administered to the patient in one or more doses so that the dose of the cetuximab contained therein sums up to an amount of about 250 mg/m² or
5 about 400 mg/m² per patient within said week.

In said methods, the amount of each of the at least one alkylating chemotherapeutic agents administered to the patient within said week is preferably divided into 2 to 7, preferably 5 to 7 and especially 5, 6 or 7 about
10 equal doses wherein each of the about equal doses is administered to said patient on a separate day within said week. Preferably, each of said one or more doses is given on a different day within said week, e.g. in a twice weekly administration scheme, a three times weekly administration scheme, a four times weekly administration scheme, a five times weekly
15 administration scheme, a six times weekly administration scheme or a seven times weekly administration scheme, preferably as described herein.

In said methods, the at least two alkylating chemotherapeutic agents preferably comprise temozolomide and Procarbazine or consist of
20 temozolomide and Procarbazine; or a pharmaceutically acceptable derivative, solvate or salt thereof.

The temozolomide, the pharmaceutically acceptable derivatives, solvates and/or salts thereof is preferably administered to the patient in one or more doses, preferably three or more doses and especially 5 or more doses, for
25 example 5, 6 or 7 doses, so that the weekly dose of the temozolomide contained therein sums up to an amount of 300 mg/m² to 800 mg/m² per patient within said week. More preferably, the temozolomide, the pharmaceutically acceptable derivatives, solvates and/or salts thereof is to be administered to the patient in one or more doses so that the weekly dose of
30 the temozolomide contained therein sums up to an amount of 360 mg/m² to 750 mg/m², preferably 550 mg/m² to 700 mg/m², per patient within said week. Preferably, each of said one or more doses is given on a different day within said week, e.g. in a three times weekly administration scheme, a five times

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weekly administration scheme, a six times weekly administration scheme or a seven times weekly administration scheme, preferably as described herein. Preferably, each of said one or more doses consists of about 50 mg/m²,
5 about 60 mg/m², about 75 mg/m², about 80 mg/m² or about 100 mg/m².

The Procarbazine, the pharmaceutically acceptable derivatives, solvates and/or salts thereof is preferably administered to the patient in one or more doses, preferably three or more doses and especially 5 or more doses, for
10 example 5, 6 or 7 doses, so that the weekly dose of the Procarbazine contained therein sums up to an amount of 200 mg/m² to 800 mg/m² per patient within said week. More preferably, the temozolomide, the pharmaceutically acceptable derivatives, solvates and/or salts thereof is to be administered to the patient in one or more doses so that the weekly dose of
15 the temozolomide contained therein sums up to an amount of 250 mg/m² to 750 mg/m², preferably 300 mg/m² to 700 mg/m², per patient within said week. Preferably, each of said one or more doses is given on a different day within said week, e.g. in a three times weekly administration scheme, a five times weekly administration scheme, a six times weekly administration scheme or a
20 seven times weekly administration scheme, preferably as described herein. Preferably, each of said one or more doses consists of about 40 mg/m², about 50 mg/m², about 75 mg/m², about 80 mg/m² or about 100 mg/m².

Said methods preferably comprise the administration of at least two further
25 cancer cotherapeutic agents, selected from

- i) cetuximab or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably cetuximab,
- ii) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-
30 NMe-Val), and
- iii) radiotherapy, preferably external beam radiation.

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According to the instant invention, radiotherapy is preferably to be regarded as a (further) cancer cotherapeutic agent.

5 In said methods, the beforehand described administration to the patient within said at least one week is repeated at least once or twice, preferably in consecutive weeks.

Thus, especially preferred are methods of treating cancer as described
10 herein and especially as described above, which have a duration of at least one cycle, each cycle preferably consisting of about three weeks (about 21 days) or about four weeks (about 28 days), wherein said cycle preferably comprises one or more weeks during which

i) at least two alkylating chemotherapeutic agents, comprising procarbazine
15 and/or temozolomide

ii) at least one further cancer cotherapeutic agent, selected from cetuximab, cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable
dervatives, solvates and salts thereof, and radiotherapy,
is administered to the patient. Especially preferably, one or more of the
20 beforehand described preferred embodiments are combined in these methods.

Thus, a more preferred preferred further aspect of the instant invention relates to the following methods of treating cancer, preferably intracerebral
25 cancer:

[16] A method of treating cancer, preferably intracerebral cancer, comprising administering to the patient within at least one week

i) temozolomide and procarbazine, or a pharmaceutically acceptable
30 dervative, solvate or salt thereof,

ii) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable
dervative, solvate or salt thereof, and

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iii) cetuximab or pharmaceutically acceptable derivative, solvate or salt thereof,

and optionally

5 iv) radiotherapy.

[17] A method of treating cancer, preferably intracerebral cancer, comprising administering to the patient within at least one week

10 i) temozolomide and procarbazine, or a pharmaceutically acceptable derivative, solvate or salt thereof,

ii) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable derivative, solvate or salt thereof, and

iii) cetuximab or pharmaceutically acceptable derivative, solvate or salt thereof, and

15 iv) radiotherapy.

[18] A method of treating cancer, preferably intracerebral cancer, comprising administering to the patient within at least one week

20 i) temozolomide and procarbazine, or a pharmaceutically acceptable derivative, solvate or salt thereof,

ii) at least one further cancer cotherapeutic agent, selected from

a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable derivative, solvate or salt thereof, and

25 b) cetuximab or pharmaceutically acceptable derivative, solvate or salt thereof,

and

iv) radiotherapy.

30 [19] A method of treating cancer, preferably intracerebral cancer, comprising 2 to 10 consecutive weeks, preferably 4 to 6 consecutive weeks and especially about 4 or about 6 consecutive weeks of treatment, wherein each of the consecutive weeks comprises administering to the patient

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i) temozolomide and procarbazine, or a pharmaceutically acceptable derivative, solvate or salt thereof,

ii) at least one further cancer cotherapeutic agent, selected from

- 5 a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable derivative, solvate or salt thereof, and
- b) cetuximab or pharmaceutically acceptable derivative, solvate or salt thereof,

and

- 10 iv) radiotherapy.

In this method, the intracerebral cancer is preferably selected from astrocytoma, especially astrocytoma grade II, III and IV, glioblastoma and glioblastoma multiforme (GBM). In this method, the temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably the

15 temozolomide, is preferably administered to the patient in 5 or more doses, for example 5, 6 or 7 doses, more preferably 5, 6 or 7 about equal daily doses, so that the weekly dose of the temozolomide contained therein sums up to an amount of 360 mg/m^2 to 750 mg/m^2 , preferably 550 mg/m^2 to 700 mg/m^2 , per patient within each week. In this method, preferably each of said

20 5 or more doses is given on a different day within each week, e.g. a five times weekly administration scheme, a six times weekly administration scheme or a seven times weekly administration scheme, preferably as described herein. In this method, preferably each of said one or more doses of temozolomide consists of about 50 mg/m^2 , about 60 mg/m^2 , about 75 mg/m^2 , about 80 mg/m^2 or about 100 mg/m^2 , preferably given once daily,

25 more preferably given once daily about every day during said 2 to 10 consecutive weeks and especially said 4 to 6 consecutive weeks. In this method, the procarbazine or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably the procarbazine, is preferably

30 administered to the patient in 5 or more doses, for example 5, 6 or 7 doses, more preferably 5, 6 or 7 about equal daily doses, so that the weekly dose of the procarbazine contained therein sums up to an amount of 250 mg/m^2 to 750 mg/m^2 , preferably 300 mg/m^2 to 700 mg/m^2 , per patient within each

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week. In this method, preferably each of said 5 or more doses is given on a different day within each week, e.g. a five times weekly administration scheme, a six times weekly administration scheme or a seven times weekly administration scheme, preferably as described herein. In this method, preferably each of said one or more doses of procarbazine consists of about 40 mg/m², about 50 mg/m², about 60 mg/m², about 80 mg/m² or about 100 mg/m², preferably given once daily, more preferably given once daily about every day during said 2 to 10 consecutive weeks and especially during said 4 to 6 consecutive weeks. In this method, the cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof is preferably administered to the patient in one or more doses so that the dose of the cetuximab contained therein sums up to an amount of about 250 mg/m² or about 400 mg/m² per patient within each week. In this method, preferably the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof is administered to the patient in one or more doses so that the dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of about 2000 mg, about 4000 mg, about 6000 mg, about 8000 mg or about 10000 mg per patient within said week. In this method, preferably each of the one or more doses consists of about 500 mg or about 2000 mg of cyclo-(Arg-Gly-Asp-DPhe-NMe-Val). In this method, preferably, each of said one or more doses of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) is given on a different day within said week, e.g. in a twice weekly administration scheme, a three times weekly administration scheme, a four times weekly administration scheme or a five times weekly administration scheme, preferably as described herein. In this method, the radiotherapy is preferably as described herein. In this method, the radiotherapy is more preferably external beam radiation and even more preferably selected from (external beam) whole brain brain radiation and (external beam) focal radiotherapy of the brain (preferably also referred to as focal radiotherapy). In this method, the external beam radiation preferably consists of 30 to 70 Gy and especially of about 30 Gy or about 60 Gy. In this method, the whole brain radiation preferably consists of about 30 Gy,

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preferably given in about 10 fractions of about 3 Gy each. In this method, the focal radiotherapy preferably consists of about 60 Gy, preferably given in about 30 fractions of about 2 Gy each.

5

[20] A method of treating cancer, preferably intracerebral cancer, said method comprising one or more cycles, preferably 2 to 8 cycles and more preferably 3 or 6 cycles, each cycle preferably consisting of about three weeks (about 21 days) or about four weeks (about 28 days), wherein each
10 cycle preferably comprises 2 or more consecutive weeks, more preferably about 2 or about 3 consecutive weeks, wherein each of the consecutive weeks comprises administering to the patient

i) temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably administered to the patient in 5 or more about equal
15 doses, preferably 5, 6 or 7 about equal doses, more preferably 5, 6 or 7 about equal daily doses, so that the weekly dose of the temozolomide contained therein sums up to an amount of 360 mg/m² to 700 mg/m² per patient within each of said consecutive weeks;

ii) procarbazine or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably administered to the patient in 5 or more about equal
20 doses, preferably 5, 6 or 7 about equal doses, more preferably 5, 6 or 7 about equal daily doses, so that the weekly dose of the procarbazine contained therein sums up to an amount of 300 mg/m² to 700 mg/m² per patient within each of said consecutive weeks; and

25 iii) at least one further cancer cotherapeutic agent, selected from
a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable derivative, solvate or salt thereof, and
b) cetuximab or pharmaceutically acceptable derivative, solvate or salt thereof.

30 In this method, the at least one further cancer cotherapeutic agent is preferably administered during each week of said cycle or cycles, preferably as described herein. In this method, the intracerebral cancer is preferably selected from astrocytoma, especially astrocytoma grade II, III and IV,

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glioblastoma and glioblastoma multiforme (GBM). In this method, the temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably the temozolomide, is preferably administered to the

5 patient in 5 or more doses, for example 5, 6 or 7 doses, more preferably 5, 6 or 7 about equal daily doses, so that the weekly dose of the temozolomide contained therein sums up to an amount of 360 mg/m^2 to 750 mg/m^2 , preferably 550 mg/m^2 to 700 mg/m^2 , per patient within each of said consecutive weeks. In this method, preferably each of said 5 or more doses

10 is given on a different day within each week, e.g. a five times weekly administration scheme, a six times weekly administration scheme or a seven times weekly administration scheme, preferably as described herein. In this method, preferably each of said 5 or more doses of temozolomide consists of about 50 mg/m^2 , about 60 mg/m^2 , about 75 mg/m^2 , about 80 mg/m^2 or about

15 100 mg/m^2 , preferably given once daily, more preferably given once daily about every day during said 2 to 3 consecutive weeks and especially during said 3 consecutive weeks (about 20 or about 21 consecutive days). In this method, the procarbazine or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably the procarbazine, is preferably

20 administered to the patient in 5 or more doses, for example 5, 6 or 7 doses, more preferably 5, 6 or 7 about equal daily doses, so that the weekly dose of the procarbazine contained therein sums up to an amount of 250 mg/m^2 to 750 mg/m^2 , preferably 300 mg/m^2 to 700 mg/m^2 , per patient within each of said consecutive weeks. In this method, preferably each of said 5 or more

25 doses is given on a different day within each week, e.g. a five times weekly administration scheme, a six times weekly administration scheme or a seven times weekly administration scheme, preferably as described herein. In this method, preferably each of said 5 or more doses of temozolomide consists of about 50 mg/m^2 , about 60 mg/m^2 , about 75 mg/m^2 , about 80 mg/m^2 or about

30 100 mg/m^2 , preferably given once daily, more preferably given once daily about every day during said 2 to 3 consecutive weeks and especially during said 3 consecutive weeks (about 20 or about 21 consecutive days). In this method, the cetuximab, the pharmaceutically acceptable derivatives, solvates

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and/or salts thereof is preferably administered to the patient in one or more doses so that the dose of the cetuximab contained therein sums up to an amount of about 250 mg/m² or about 400 mg/m² per patient within each of said consecutive weeks. In this method, the cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof is more preferably administered to the patient in one or more doses so that the dose of the cetuximab contained therein sums up to an amount of about 250 mg/m² or about 400 mg/m² per patient within each week of said one or more cycles. In this method, preferably the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof is administered to the patient in one or more doses so that the dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of about 2000 mg, about 4000 mg, about 6000 mg, about 8000 mg or about 10000 mg per patient within said week. In this method, preferably each of the one or more doses consists of about 500 mg or about 2000 mg of cyclo-(Arg-Gly-Asp-DPhe-NMe-Val). In this method, preferably, each of said one or more doses of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) is given on a different day within said week, e.g. in a twice weekly administration scheme, a three times weekly administration scheme, a four times weekly administration scheme or a five times weekly administration scheme, preferably as described herein. This method is preferably not combined with radiotherapy.

Thus, an even more preferred preferred further aspect of the instant invention relates to the following methods of treating cancer, preferably intracerebral cancer:

[21] A method, wherein the methods according to paragraphs [19] and [20] are combined, preferably sequentially and preferably in the given order.

30

[22] A method of treating intracerebral cancer, preferably glioblastoma or glioblastoma multiforme (GBM), comprising 2 to 10 consecutive weeks, preferably 4 to 6 consecutive weeks and especially about 4 or about 6

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consecutive weeks of treatment, wherein each of the consecutive weeks comprises administering to the patient

i) temozolomide and procarbazine; or a pharmaceutically acceptable

5 derivative, solvate or salt thereof,

ii) at least one further cancer cotherapeutic agent, selected from

a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable
derivative, solvate or salt thereof, and

10 b) cetuximab or pharmaceutically acceptable derivative, solvate or salt
thereof,

and

iii) external beam radiation, preferably selected from focal radiotherapy and whole brain radiation.

15 [23] A method of treating intracerebral cancer, preferably glioblastoma or glioblastoma multiforme (GBM), comprising 2 to 10 consecutive weeks, preferably 4 to 6 consecutive weeks and especially about 4 or about 6 consecutive weeks of treatment, wherein each of the consecutive weeks comprises administering to the patient

20 i) temozolomide and procarbazine; or a pharmaceutically acceptable derivative, solvate or salt thereof,

ii) two further cancer cotherapeutic agents,

a) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable
derivative, solvate or salt thereof, and

25 b) cetuximab or pharmaceutically acceptable derivative, solvate or salt thereof,

and optionally

iii) external beam radiation, preferably selected from focal radiotherapy and whole brain radiation.

30 [24] A method of treating intracerebral cancer, preferably glioblastoma or glioblastoma multiforme (GBM), said method comprising two or more cycles, preferably 2 to 8 cycles, and especially 3 or 6 cycles, each cycle preferably

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consisting of about four weeks (about 28 days), wherein each cycle preferably comprises

- 5 (A) about 2 consecutive weeks or about 3 consecutive weeks, wherein each of the consecutive weeks comprises administering to the patient
- i) temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably administered to the patient in 5 or more about equal doses, preferably 5, 6 or 7 about equal doses, more preferably 5, 6 or 7 about equal daily doses, even more preferably 10 6 or 7 about equal daily doses, so that the weekly dose of the temozolomide contained therein sums up to an amount of 360 mg/m² to 750 mg/m², preferably 550 mg/m² to 700 mg/m², per patient within each of said about 2 or about 3 consecutive weeks;
 - 15 ii) procarbazine or a pharmaceutically acceptable derivative, solvate or salt thereof; preferably administered to the patient in 5 or more about equal doses, preferably 5, 6 or 7 about equal doses, more preferably 5, 6 or 7 about equal daily doses, even more preferably 6 or 7 about equal daily doses, so that the weekly dose of the procarbazine contained therein sums up to an amount of 300 20 mg/m² to 700 mg/m² per patient within each of said about 2 or about 3 consecutive weeks;

and

- (B) the administration of at least one further cancer cotherapeutic agent during each week of the about four weeks (about 28 days) of said cycle, 25 wherein said at least one further cancer cotherapeutic agent is selected from
- c) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably administered to the patient in one or more about equal doses, preferably 1 to 5 about 30 equal doses, more preferably 2 or 5 about equal daily doses, preferably so that the weekly dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of about 2000 mg,

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about 4000 mg, about 6000 mg, about 8000 mg or about 10000 mg per patient and per week within each week of said cycle, and

- 5 d) cetuximab or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably administered to the patient in one or more about equal doses per week, more preferably 1 dose per week, said dose or doses preferably consisting of about 250 mg/m^2 or about 400 mg/m^2 , preferably so that the weekly dose of the cetuximab contained therein is or sums up to an amount of about 250 mg/m^2 or
10 about 400 mg/m^2 per patient and per week within each week of said cycle.

During said two or more cycles, preferably no radiotherapy is applied to the patient. During said two or more cycles, the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) (or a pharmaceutically acceptable derivative, solvate or salt thereof)
15 and/or the cetuximab (or a pharmaceutically acceptable derivative, solvate or salt thereof) is preferably administered to the patient in about each week of said two or more cycles, preferably in a manner as described herein.

[25] A method, wherein the methods according to paragraphs [22] and [24]
20 are combined, preferably sequentially and preferably in the given order.

[26] A method, wherein the methods according to paragraphs [23] and [24] are combined, preferably sequentially and preferably in the given order.

25 [27] A method of treating intracerebral cancer, preferably glioblastoma or glioblastoma multiforme (GBM), said method comprising

(A) administering to the patient

- i) temozolomide and procarbazine; or a pharmaceutically acceptable derivative, solvate or salt thereof,
30 ii) at least one further cancer cotherapeutic agent, selected from
c) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable derivative, solvate or salt thereof, and

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d) cetuximab or pharmaceutically acceptable derivative, solvate or salt thereof,

and

5 iii) external beam radiation, preferably selected from focal radiotherapy and whole brain radiation

in each week during weeks 1 to 10, weeks 1 to 6 or weeks 1 to 4;

optionally directly followed by

0 to 6 weeks, more preferably 3 to 5 weeks and especially about 3 or

10 about 4 weeks wherein only the at least one further cancer cotherapeutic agent, selected from

g) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable derivative, solvate or salt thereof, and

15 h) cetuximab or a pharmaceutically acceptable derivative, solvate or salt thereof,

is administered to said patient in about each week of said second cycle; followed by, preferably directly followed by

(B) two or more cycles, preferably 2 to 8 cycles and especially 3 or 6 cycles, each cycle preferably consisting of about four weeks (about 28 days),

20 wherein

i) each cycle preferably comprises 2 or 3 consecutive weeks, preferably the first 2 or 3 weeks in said cycle, during which temozolomide and procarbazine (or a pharmaceutically acceptable derivative, solvate or salt thereof) is administered to the patient, preferably in 5 or more about equal
25 doses, more preferably 5, 6 or 7 about equal doses; even more preferably 5, 6 or 7 about equal daily doses, preferably so that the weekly dose of the temozolomide contained therein sums up to an amount of 360 mg/m² to 750 mg/m², preferably 550 mg/m² to 700 mg/m², per patient within each of said consecutive 2 or 3 weeks;

30 and wherein

ii) the at least one further cancer cotherapeutic agent, selected from

c) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable derivative, solvate or salt thereof, and

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d) cetuximab or a pharmaceutically acceptable dervative, solvate or salt thereof,

5 is administered to said patient in about each week of said two or more cycles, preferably in a manner as described herein.

During said two or more cycles, preferably no radiotherapy is applied to the patient.

10 [28] A method of treating intracerebral cancer, preferably glioblastoma or glioblastoma multiforme (GBM), said method comprising (A) a first cycle consisting of 2 to 8 and especially 4 to 6 weeks, wherein each week comprises administering to the patient

i) temozolomide and procarbazine; or a pharmaceutically acceptable dervative, solvate or salt thereof,

15 ii) at least one further cancer cotherapeutic agent, selected from

c) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or pharmaceutically acceptable dervative, solvate or salt thereof, and

d) cetuximab or pharmaceutically acceptable dervative, solvate or salt thereof,

20 and

iii) external beam radiation, preferably selected from focal radiotherapy and whole brain radiation; directly followed by

(B) a second cycle consisting of either

i) 1 to 6 and especially 2 to 4 weeks without treating said patient, or

25 ii) 1 to 6 and especially 2 to 4 weeks wherein only the at least one further cancer cotherapeutic agent, selected from

i) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable dervative, solvate or salt thereof, and

30 j) cetuximab or a pharmaceutically acceptable dervative, solvate or salt thereof,

is administered to said patient in about each week of said second cycle; directly followed by

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(C) two or more cycles, preferably 2 to 8 cycles and especially 3 or 6 cycles, each cycle preferably consisting of about four weeks (about 28 days), wherein

- 5 i) temozolomide and procarbazine (or a pharmaceutically acceptable dervative, solvate or salt thereof) is administered to the patient during weeks 1 to 3 of said cycles, preferably in 5 or more about equal doses, more preferably 5, 6 or 7 about equal doses per week, even more preferably 5, 6 or 7 about equal daily doses, preferably so that the weekly
- 10 dose of the temozolomide contained therein sums up to an amount of 360 mg/m² to 750 mg/m², preferably 550 mg/m² to 700 mg/m², per patient within each of said weeks 1 to 3;

and wherein

- ii) the at least one further cancer cotherapeutic agent, selected from
- 15 c) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable dervative, solvate or salt thereof, and
- d) cetuximab or a pharmaceutically acceptable dervative, solvate or salt thereof,

 is administered to said patient in about each week of said two or more

20 cycles, preferably 2 to 8 cycles and especially 3 or 6 cycles, preferably in a manner as described herein; optionally directly followed by

(D) two or more cycles, preferably 3 to 24 cycles and especially 4 to 12 cycles, each cycle preferably consisting of about four weeks (about 28 days), wherein

- 25 ii) the at least one further cancer cotherapeutic agent, selected from
- k) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable dervative, solvate or salt thereof, and
- l) cetuximab or a pharmaceutically acceptable dervative, solvate or salt thereof,

30 is administered to said patient in about each week of said cycles, preferably in a manner as described herein.

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Preferably, no radiotherapy is applied or administered to the patient during (C) and (D).

5 In the method described in the paragraph numbered [27], the further cancer cotherapeutic agent or the combination thereof is preferably the same in both step (A) and (B), e.g.

10 - if the cancer cotherapeutic agent cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable dervative, solvate or salt thereof, is chosen as the only cancer cotherapeutic agent in step (A), it is preferably also the only cancer cotherapeutic agent in step (B),

15 - if the cancer cotherapeutic agent cetuximab or a pharmaceutically acceptable dervative, solvate or salt thereof, is chosen as the only cancer cotherapeutic agent in step (A), it is preferably also the only cancer cotherapeutic agent in step (B),

20 - if a combination of both cancer cotherapeutic agents, (i) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable dervative, solvate or salt thereof, and (ii) cetuximab or a pharmaceutically acceptable dervative, solvate or salt thereof,

is chosen as the combined cancer cotherapeutic agents in step (A), the same combination is preferably also used as the cancer cotherapeutic agents in step (B).

25 In the method described in the paragraph numbered [28], the further cancer cotherapeutic agent or the combination thereof is preferably the same in steps (A), (C), (D) and, if applicable, step (B), e.g.

30 - if the cancer cotherapeutic agent cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable dervative, solvate or salt thereof, is chosen as the only cancer cotherapeutic agent in step (A), it is preferably also the only cancer cotherapeutic agent in steps C), (D) and, if applicable, step (B),

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- if the cancer cotherapeutic agent cetuximab or a pharmaceutically acceptable derivative, solvate or salt thereof, is chosen as the only cancer cotherapeutic agent in step (A), it is preferably also the only cancer cotherapeutic agent in steps C), (D) and, if applicable, step (B),
- if a combination of both cancer cotherapeutic agents,
 - (i) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) or a pharmaceutically acceptable derivative, solvate or salt thereof, and
 - (ii) cetuximab or a pharmaceutically acceptable derivative, solvate or salt thereof,is chosen as the combined cancer cotherapeutic agents in step (A), the same combination is preferably also used as the cancer cotherapeutic agents in steps C), (D) and, if applicable, step (B).

In the methods described in the paragraphs numbered [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27] and/or [28], the temozolomide or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably the temozolomide, is preferably administered to the patient in 5 or more doses, for example 5, 6 or 7 doses, more preferably 5, 6 or 7 about equal daily doses, so that the weekly dose of the temozolomide contained therein sums up to an amount of 360 mg/m² to 750 mg/m², preferably 550 mg/m² to 700 mg/m², per patient within each week. Preferably each of said 5 or more doses is given on a different day within each week, e.g. a five times weekly administration scheme, a six times weekly administration scheme or a seven times weekly administration scheme, preferably as described herein. More preferably each of said 5 or more doses of temozolomide consists of about 50 mg/m², about 60 mg/m², about 75 mg/m², about 80 mg/m² or about 100 mg/m².

In the methods described in the paragraphs numbered [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27] and/or [28], the procarbazine or a pharmaceutically acceptable derivative, solvate or salt thereof, preferably the procarbazine, is preferably administered to the patient in 5 or more doses, for example 5, 6 or 7 doses, more preferably 5, 6 or 7 about equal daily doses,

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so that the weekly dose of the procarbazine contained therein sums up to an amount of 360 mg/m^2 to 750 mg/m^2 , preferably 550 mg/m^2 to 700 mg/m^2 , per patient within each week. Preferably each of said 5 or more doses is given on
5 a different day within each week, e.g. a five times weekly administration scheme, a six times weekly administration scheme or a seven times weekly administration scheme, preferably as described herein. More preferably each of said 5 or more doses of procarbazine consists of about 40 mg/m^2 , about 50 mg/m^2 , about 60 mg/m^2 , about 80 mg/m^2 or about 100 mg/m^2 .

10 In the methods described in the paragraphs numbered [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27] and/or [28], the cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cetuximab, is preferably administered to the patient in one or more doses so that the dose of the cetuximab contained therein sums up to an
15 amount of about 250 mg/m^2 or about 400 mg/m^2 per patient within each week.

In the methods described in the paragraphs numbered [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27] and/or [28], the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or
20 salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), is administered to the patient in one or more doses so that the dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of about 2000 mg, about 4000 mg, about 6000 mg, about 8000 mg or about 10000 mg per patient within said week. More preferably, each of the one or more doses
25 consists of about 500 mg or about 2000 mg of cyclo-(Arg-Gly-Asp-DPhe-NMe-Val). Even more preferably, each of said one or more doses of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) is given on a different day within said week, e.g. in a twice weekly administration scheme, a three times weekly administration scheme, a four times weekly administration scheme or a five
30 times weekly administration scheme, preferably as described herein.

In the methods described in the paragraphs numbered [16], [17], [18], [19], [22], [23], [27] and/or [28], the radiotherapy is preferably as described herein. More preferably, the radiotherapy is external beam radiation and even more

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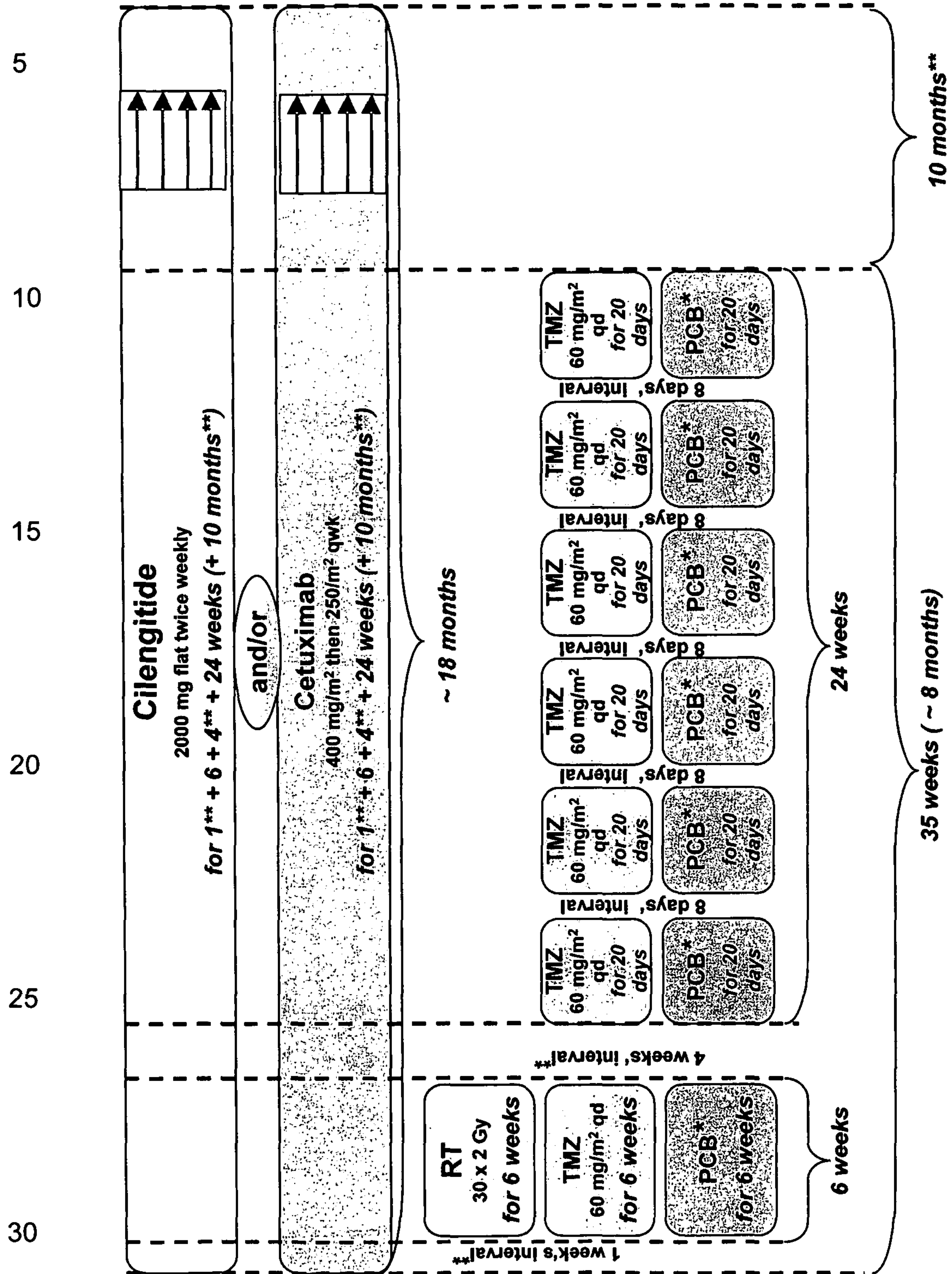
preferably selected from (external beam) whole brain brain radiation and (external beam) focal radiotherapy of the brain (preferably also referred to as focal radiotherapy). Especially preferably, the external beam radiation
5 consists of 20 to 70 Gy and especially of about 30 Gy or about 60 Gy. In this context, the whole brain radiation preferably consists of about 30 Gy, preferably given in about 10 fractions of about 3 Gy each. In this context, the focal radiotherapy preferably consists of about 60 Gy, preferably given in about 30 fractions of about 2 Gy each.

10

The following graphic (Graphic treatment scheme 5) shows a preferred method of treatment which comprises mandatory treatment periods, and preferably optional time periods (e.g. recovery periods, during which preferably no treatment is applied to the patient) and/or optional treatment
15 periods (the latter two marked by two asterisks (**)). During the optional treatment periods preferably only the Cilengitide (i.e. cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the cetuximab is administered to the patient, but preferably no radiotherapy is administered to the patient during said optional treatment periods (see graphic for 1 weeks' interval** and/or 4 weeks' interval**). If this preferred method of treatment according to graphic
20 treatment scheme 5 comprises the "1 weeks' interval**" and cetuximab is administered to the patient, the cetuximab is preferably administered once during said "1 weeks' interval**" in an amount of about 400 mg/m² (this is also referred to as "loading dose"). After the "1 weeks' interval**", the amount
25 of cetuximab that is administered to the patient is preferably about 250 mg/m² per week and more preferably about 250 mg/m² once per week, if applicable. The administration of cetuximab "once per week" is also abbreviated in said graph(s) by "qwk". The administration of temozolomide "once per day" is preferably also abbreviated in said graph(s) by "qd".
30 Preferably, the "once per day" administration also applies to the administration of the procarbazine. Preferably, the radiotherapy is only administered to the patient during the mandatory treatment periods and more preferably only where the radiotherapy is explicitly named in said graph.

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Graphic treatment scheme 5



* Procarbazine dose is 50 mg p.o. or 100 mg p.o.

** optional treatment periods

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The following graphic (Graphic treatment scheme 6) shows a preferred method of treatment which comprises mandatory treatment periods, and preferably optional treatment periods (the latter marked by two asterisks (**)).

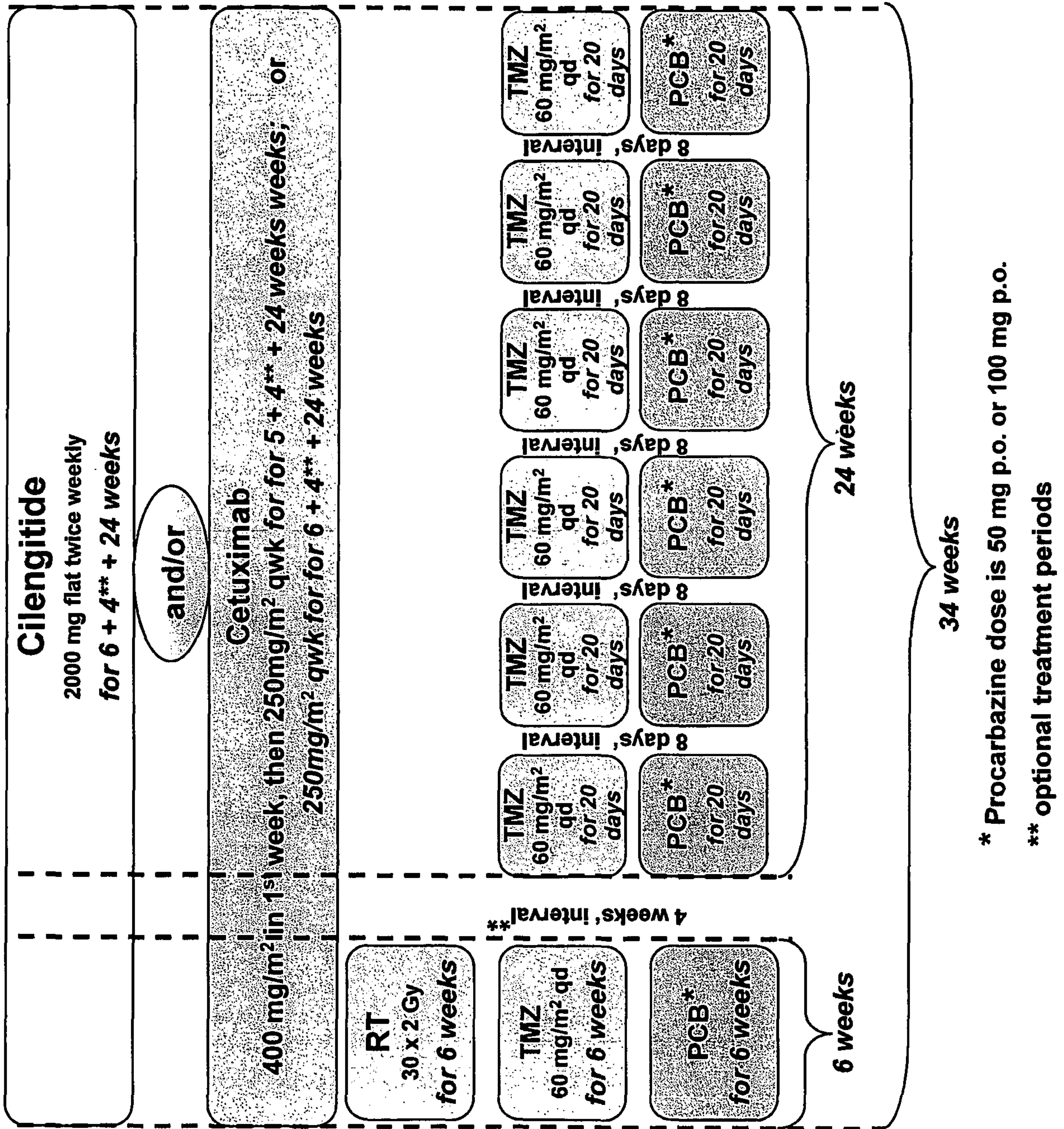
5 During the optional treatment periods preferably only the Cilengitide (i.e. cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) and/or the cetuximab is administered to the patient, but preferably no radiotherapy is administered to the patient during said optional treatment periods (see graphic for "4 weeks' interval"). If
10 cetuximab is administered to the patient, it is preferably administered either once during said first week in an amount of about 400 mg/m^2 (this is also referred to as "loading dose") and then preferably about 250 mg/m^2 per week and more preferably about 250 mg/m^2 once per week during the rest of said method of treatment, or in an amount of about 250 mg/m^2 per week and more preferably about 250 mg/m^2 once per week throughout the whole method of
15 treatment. The administration of cetuximab "once per week" is also abbreviated in said graph(s) by "qwk". The administration of temozolomide "once per day" is preferably also abbreviated in said graph(s) by "qd". Preferably, the "once per day" administration also applies to the administration of the procarbazine. Preferably, the radiotherapy is only
20 administered to the patient during the mandatory treatment periods and more preferably only where the radiotherapy is explicitly named in said graph.

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Graphic treatment scheme 6



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Preferred further aspects of the instant invention preferably relate to:

- 5 Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), for use in the treatment of cancer, preferably intracerebral cancer and even more preferably glioblastoma or glioblastoma multiforme (GBM), in combination with three or more selected from:
- 10 i) cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cetuximab,
- ii) temozolomide, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably temozolomide,
- 15 iii) procarbazine, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably procarbazine,
- and
- iv) radiotherapy.

- Cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cetuximab, for use in the treatment of cancer, preferably
- 20 intracerebral cancer and even more preferably glioblastoma or glioblastoma multiforme (GBM), in combination with three or more selected from:
- i) cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val),
- 25 ii) temozolomide, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably temozolomide,
- iii) procarbazine, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably procarbazine,
- and
- 30 iii) radiotherapy.

Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-

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- DPhe-NMe-Val), for use in the treatment of cancer, preferably intracerebral cancer and even more preferably glioblastoma or glioblastoma multiforme (GBM), in combination with
- 5 i) cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cetuximab,
- ii) temozolomide the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably temozolomide, and
- iii) procarbazine, the pharmaceutically acceptable derivatives, solvates and/or
- 10 salts thereof, preferably procarbazine,
- optionally in combination with
- iii) radiotherapy, preferably external beam radiation, more preferably focal radiotherapy or whole brain radiation.
- 15 Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), for use in the treatment of cancer, preferably intracerebral cancer and even more preferably glioblastoma or glioblastoma multiforme (GBM), in combination with
- 20 i) temozolomide and procabazine (or the pharmaceutically acceptable derivatives, solvates and/or salts thereof), preferably temozolomide and procabazine,
- optionally in combination with
- ii) cetuximab, the pharmaceutically acceptable derivatives, solvates and/or
- 25 salts thereof, preferably cetuximab, and/or
- iii) the radiotherapy, preferably external beam radiation, more preferably focal radiotherapy or whole brain radiation,
- wherein in said treatment, the temozolomide and the procarbazine (or the pharmaceutically acceptable derivatives, solvates and/or salts thereof),
- 30 preferably temozolomide and procabazine, are administered to the patient on 6 or 7 days within one week, preferably for one or more weeks, more preferably for about 3 consecutive weeks (about 20 or about 21 consecutive days) or about 6 consecutive weeks (about 42 consecutive days), preferably

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each independently of one another in an amount of 50 to 120 mg/m² per day and per patient, more preferably in an amount of about 50 mg/m², about 75 mg/m², about 80 mg/m² or about 100 mg/m² per day and per patient.

5

Cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cetuximab, for use in the treatment of cancer, preferably intracerebral cancer and even more preferably glioblastoma or glioblastoma multiforme (GBM), in combination with

10

i) temozolomide and procarbazine (or the pharmaceutically acceptable derivatives, solvates and/or salts thereof), preferably temozolomide and procarbazine,

optionally in combination with

15

ii) Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), and/or

iii) the radiotherapy, preferably external beam radiation, more preferably focal radiotherapy or whole brain radiation,

20

wherein in said treatment, the temozolomide and the procarbazine (or the pharmaceutically acceptable derivatives, solvates and/or salts thereof), preferably temozolomide and procarbazine, is administered to the patient on 6 or 7 days within one week, preferably for one or more weeks, more preferably for about 3 consecutive weeks (about 20 or about 21 consecutive days) or about 6 consecutive weeks (about 42 consecutive days), preferably each independently of one another in an amount of 50 to 120 mg/m² per day and per patient, more preferably in an amount of about 50 mg/m², about 75 mg/m², about 80 mg/m² or about 100 mg/m² per day and per patient.

25

30

Cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), for use in the treatment of cancer, preferably intracerebral cancer and even more preferably glioblastoma or glioblastoma multiforme (GBM), in combination

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i) with temozolomide and with procarbazine, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably temozolomide and procarbazine, and

5 ii) with or without radiotherapy,

wherein said treatment comprises one or more cycles, preferably 2 to 8 cycles and especially 3 or 6 cycles, each cycle preferably consisting of about four weeks (about 28 days), wherein

10 c) the temozolomide and the procarbazine (or a pharmaceutically acceptable derivative, solvate or salt thereof), preferably the temozolomide and the procarbazine, are administered to the patient on 6 or 7 days within one week, preferably on each day within one week, preferably for about 3 consecutive weeks (about 20 or about 21 consecutive days), and preferably each independently of one another
15 in an amount of 50 to 120 mg/m² per day and per patient, more preferably in an amount of about 50 mg/m², about 75 mg/m², about 80 mg/m² or about 100 mg/m² per day and per patient, and

20 d) the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), is administered to the patient during each week of said one or more cycles, preferably in one or more doses so that the dose of the cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) contained therein sums up to an amount of about 2000 mg, about 4000 mg, about 6000 mg, about 8000 mg or about 10000 mg per
25 patient within each week of said cycle.

Cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cetuximab, for use in the treatment of cancer, preferably intracerebral cancer and even more preferably glioblastoma or glioblastoma
30 multiforme (GBM), in combination

i) with temozolomide and procarbazine, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably temozolomide and procarbazine, and

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ii) with or without radiotherapy,

wherein said treatment comprises one or more cycles, preferably 2 to 8 cycles and especially 3 or 6 cycles, each cycle preferably consisting of about four weeks (about 28 days), wherein

- 5 c) the temozolomide and the procarbazine (or a pharmaceutically acceptable derivative, solvate or salt thereof), preferably the temozolomide and the procarbazine, are administered to the patient on 6 or 7 days within one week, preferably on each day within one week, preferably for about 3 consecutive weeks (about 20 or about 21 consecutive days), and preferably each independently of one another in an amount of 50 to 120 mg/m² per day and per patient, more preferably in an amount of about 50 mg/m², about 75 mg/m², about 80 mg/m² or about 100 mg/m² per day and per patient, and
- 10 d) the cetuximab, the pharmaceutically acceptable derivatives, solvates and/or salts thereof, preferably cetuximab, is administered to the patient during each week of said one or more cycles, preferably in one or more doses so that the dose of the cetuximab contained therein sums up to an amount of 150 to 600 mg/m², preferably 200 to 500 mg/m² and especially about 250 mg/m² or about 450 mg/m² per patient within each week of said cycle.
- 15 20

As used herein, "mg/m²" preferably means milligrams per square meter and especially milligrams per square meter of the body surface of the respective Patient. Thus, amounts or doses given in "mg/m²" preferably mean amounts or doses administered to a patient in milligrams per square meter of the body surface of the respective patient.

25

Preferably, the above described methods the substances for the use in such treatments and especially the methods described in one or more of the paragraphs numbered [16] to [28] are advantageous for the treatment of "unmethylated" patients, i.e. patients having an normal or decreased DNA methylation status, preferably as described and defined herein.

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Preferably, the reference to the "administration of at least one specific integrin ligand in one or more doses so that the weekly dose of the at least one specific integrin ligand contained therein sums up to an amount of 10 to 30 millimoles per patient" is intended to mean the "administration of at least one specific integrin ligand in one or more doses during the respective week so that the weekly dose of the at least one specific integrin ligand contained therein sums up to an amount of 10 to 30 millimoles per patient".

10

The same preferably holds true for all equivalent terms within this application. Accordingly, for example the term "in one or more doses so that the weekly dose" is preferably intended to be understood as "in one or more doses during the respective week so that the weekly dose".

15

With respect to the methods of treatment, administered amounts and/or the administration schemes described herein regarding of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) and/or a pharmaceutically acceptable salt thereof, preferably of cyclo-(Arg-Gly-Asp-DPhe-NMeVal), the amounts of (about) 500 mg or (about) 2000 mg to be administered at each administration as well as the amounts of (about) 1000 mg, (about) 1500 mg, (about) 2000 mg, (about) 2500 mg, (about) 4000 mg, (about) 6000 mg, (about) 8000 mg, (about) 10000 mg, (about) 12000 mg and (about) 14000 mg given for the weekly administration schemes are preferably calculated on the compound cyclo-(Arg-Gly-Asp-DPhe-NMeVal) as such (which is also referred to as the inner or internal salt of cyclo-(Arg-Gly-Asp-DPhe-NMeVal). Accordingly, if a different form or derivative, such as the pharmacologically acceptable salts and solvates, of the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMeVal) is to be administered to the patient, it is preferably administered in an amount equimolar to the amounts given above for the compound cyclo-(Arg-Gly-Asp-DPhe-NMeVal) as such.

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The herein described methods, regimen and/or uses are preferably suitable in the treatment of adult patients, more preferably in the treatment of patients having an age of 18 years and older, even more preferably in the treatment of patients having an age of 21 years and older and especially in the treatment of patients having an age of 30 years and older.

The safety and tolerability of cyclo-(Arg-Gly-Asp-DPhe-NMeVal), when administered in rather high doses and as a single agent, was tested in Phase I studies, see Tobey J. MacDonald, Clinton F. Stewart, Mehmet Kocak, Stewart Goldman, Richard G. Ellenbogen, Peter Phillips, Deborah Lafond, Tina Young Poussaint, Mark W. Kieran, James M. Boyett, and Larry E. Kun J in *J Clin Oncol* 26:919-924 (2008), and L. Burt Nabors, Tom Mikkelsen, Steven S. Rosenfeld, Fred Hochberg, Narasimha S. Akella, Joy D. Fisher, Gretchen A. Cloud, Yu Zhang, Kathryn Carson, Sabine M. Wittemer, A. Dimitrios Colevas, and Stuart A. Grossman in *J Clin Oncol* 25:1651-1657 (2007), the entire disclosure of which is incorporated herein by reference.

The specific integrin ligands to be used according to the invention preferably show an advantageously improved effect on patients that are having increased DNA methylation status, are having a partial or complete methylation of at least one promoter of at least one MGMT gene and/or are having an abnormal level of MGMT protein, especially an abnormal low level of MGMT protein. Accordingly, the invention provides medicaments and methods that can be advantageously used to treat patients associated with one or more of the aforementioned effects or defects.

Therefore, subject of the instant invention is the use of a medicament as described herein and/or a method using said medicament for the treatment of patients, wherein the medicament is to be used in the treatment of patients having an increased DNA methylation status, patients showing partial or complete methylation of at least one promoter of at least one MGMT gene and/or patients having an abnormal level of MGMT protein, especially an

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abnormal low level of MGMT protein. Such patients are preferably referred to as "methylated patients" .

5 These subjects are explained and discussed in more detail below:

 Methylation of the DNA-repair gene O⁶-methylguanine-DNA
 methyltransferase (MGMT), more correctly called O⁶-methylguanine-DNA
 methyltransferase repair gene or short MGMT repair gene, causes gene
10 silencing. This epigenetic modification has been associated with a favourable
 prognosis in patients with many different cancer types, such as glioblastoma
 (GBM), who receive alkylating agents, for example, nitrogen mustards,
 ethyleneimine compounds, alkyl sulphonates and other compounds with an
 alkylating action, preferably selected from nitrosoureas, preferably ACNU,
15 BCNU and CCNU, busulfan, melphalan, carboplatin, cisplatin, oxaliplatin,
 cyclophosphamide, dacarbazine, carmustine, ifosfamide and lomustine,
 temozolomide and altretamine, or camptothecin. Accordingly, there is a
 relationship between MGMT promoter methylation and the survival rate and
 sensitivity to alkylating agents, such as temozolomide. The MGMT enzyme
20 removes alkyl groups from the O6 position of guanine, the site of a number of
 chemotherapy-induced DNA alkylations. These chemotherapy induced
 alkylations lead to DNA damage in the tumor cells, including DNA double
 strand breaks and mismatches, which trigger apoptosis and cytotoxicity [5,6].
 The MGMT enzyme repairs DNA damage, thus interfering with the
25 therapeutic effects of chemotherapy alkylating agents [7–10]. Methylation of
 discrete regions of the MGMT promoter CpG island is associated with
 silencing of the gene and diminished DNA-repair enzyme activity [11–13].
 Previous studies have indicated that 30–40% of GBM patients have
 methylated MGMT promoter [1–4].

30

 The MGMT promoter methylation and thus the methylation status of the
 MGMT can be advantageously determined using a 2-stage methylation
 specific PCR analysis on DNA extracted from tumor specimens, such as

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tumour specimens which have been snap frozen at surgery. The Methylation specific PCR analysis can be easily performed according to methods in the art. Preferably it can be performed by the Method by Hegi et al., NEJM, 2005, 352; 997-1003); the following method has been successfully been used in a Phase III trial assessing the methylation status of a subset of the patients (tissue available):

DNA extraction and methylation-specific polymerase chain reaction

Genomic DNA is isolated from one or two paraffin sections of glioblastoma tissue (Ex-Wax DNA Extraction Kit S4530, Chemicon) (proteinase digestion lasted a maximum of six hours). DNA is denatured with sodium hydroxide in a volume of 35 µl and subjected to bisulfite treatment in a volume of 360 µl (4.4 M sodium bisulfite and 20 mM hydroquinone) for five hours at 55°C and then purified (Wizard DNA Clean-Up System A7280, Promega).

Unmethylated cytosine, but not its methylated counterpart, is modified into uracil by the treatment. The methylation-specific polymerase chain reaction (PCR) is performed in a two-step approach. [*Palmisano WA, Divine KK, Saccomanno G, et al. Predicting lung cancer by detecting aberrant promoter methylation in sputum. Cancer Res 2000;60:5954-8.*]

The results can be confirmed in an independent experiment, starting with reisolation of DNA from the tumor. The PCR products are separated on 4 percent agarose gels. The investigators who selected and analyzed the glioblastoma samples are blinded to all clinical information.

Alternatively, it can be performed according to the method described by Donson et al. in Journal Pediatric Blood Cancer, 2006.

According to Donson et al., the MGMT promoter methylation/methylation status of the MGMT can be advantageously determined according to the following procedure:

DNA Extraction and Methylation-Specific Polymerase Chain Reaction

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Genomic DNA is isolated from snap frozen tumor obtained at surgery (COMIRB 95–500) and GBM cell-lines using a DNeasy kit (Qiagen, Valencia, CA). DNA methylation patterns in the CpG island of the MGMT gene are
5 determined by methylation specific PCR. This procedure involves chemical modification of unmethylated, but not methylated cytosines to uracil, followed by a nested, twostage PCR [17]. One microgram of DNA is denatured with sodium hydroxide (final conc. 0.3 M) in a volume of 55 ml and subjected to bisulfite treatment in a volume of 610 ml (3.3 M sodium bisulfite and
10 0.5mMhydroquinone) for 16 hr at 558C and then purified using the Wizard DNA Clean-Up System (Promega, Madison, WI). PCR is performed to amplify a 289-bp fragment of the MGMT gene including a portion of the CpG-rich promoter region. The primers recognize the bisulfite-modified template but do not discriminate between methylated and unmethylated alleles. Primer
15 sequences used in the stage 1 amplification of theMGMTgene are as follows: MGMT-stage 1-Forward, 50-GGATATGTTGGGATAGTT- 30; and MGMT-stage 1-Reverse, 50-CCAAAAACCCCAAACCC- 30. Master Mix (Fermentas, Hanover, MD). The PCR amplification protocol for stage 1 is as follows: 958C for 10 min, then denature at 958C for 30 sec, anneal at 528C for 30 sec,
20 extension at 728C for 30 sec for 40 cycles followed by a 10min final extension.A25-ml volume is used in all of the PCR reactions. The stage-1 PCR products are diluted 50-fold, and 5 ml of this dilution is subjected to a stage-2 PCR in which primers specific to methylated or unmethylated template are used. Primer sequences for the stage 2 PCR for the
25 unmethylated reaction are MGMT-stage 2-Forward, 50-TTTGTGTTTTGATGTTTGTAGGTTTTTGT-30 and MGMT-stage 2-Reverse, 50-AACTCCACACTCTTCCAAAAACAAAACA- 30 and for the methylated reaction MGMT-stage 2-forward 50-TTTCGACGTTCGTAGGTTTTCGC- 30 and MGMT-stage 2-reverse 50-GCACTCTTCCGAAAACGAAACG- 30. The
30 PCR amplification protocol for stage 2 is as follows: 958C for 10 min, then denature at 958C for 15 sec, anneal at 628C for 15 sec, extension at 728C for 15 sec for 40 cycles followed by a 10 min final 728C extension. DNA from normal human lymphocytes treated in vitro with Sssl methyltransferase (New

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England Biolabs, Beverly, MA) is used as positive control for methylated alleles of MGMT and untreated DNA from normal lymphocytes is used as negative control for methylated alleles of MGMT. Each PCR reaction (10 ml) is directly loaded onto 4% agarose gel, stained with ethidium bromide and visualized under UV illumination. Statistical Analysis can be performed with methods known in the art, such as the methods by Kaplan–Meier, correlation and statistical significance analyses, for example using the Prism statistical analysis program (GraphPad Software, Inc., San Diego, CA).

Methylguanine-DNA methyltransferase promoter methylation status analysis is performed on snap frozen tissue of the patients. MGMT methylation status can regularly be determined out the tumors. In a part of the patients, the samples tested for MGMT promoter methylation status proved to be partially methylated (Fig. 3). None of the samples showed complete methylation. The incomplete methylation observed may be due to tumor heterogeneity, infiltrating peripheral blood lymphocytes and/or vasculature. For comparison purposes, it can be determined whether partial methylation of the tumor MGMT promoter can be responsible for this observation by investigating the MGMT promoter methylation status of 6 GBM cell-lines, including cell-line 145 which is established from a patient who is treated with temozolomide and who's snap frozen tumor is also analyzed in the above study. In four out of the six celllines studied, partial methylation of promoter is observed (Fig. 4). The results show that even in pure GBM cell-lines, partial MGMT promoter methylation can exist.

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Fig. 3. shows the Methylation status of the MGMT promoter in GBM biopsy specimens, as determined by a nested methylation-specific PCR assay.

5 DNA from normal peripheral blood lymphocytes (PBL) is used as a control for the unmethylated MGMT promoter (U), enzymatically methylated DNA from PBL (MPBL) served as a positive control for the methylated MGMT promoter (M), and water is used as a negative control for the PCR. A 100-bp marker ladder is loaded to estimate molecular size, as shown on the left

10 scale (L).

Fig. 4. shows the Methylation status of the MGMT promoter in GBM cell-lines, as determined by a nested methylation-specific PCR assay. A 100-bp marker ladder is loaded to estimate molecular size, as shown on the left scale (L).

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The MGMT analysis technique described above has been employed in the majority of recent studies showing MGMT methylation to be a successful

20 predictor of response to alkylating agents [1–3]. This technique has superseded earlier techniques of enzyme activity measurement after it was demonstrated that MGMT methylation was the main cause of loss of MGMT enzymatic activity in GBM.

25 Patients that are tested as patients showing MGMT methylation or that can be tested as patients showing MGMT methylation, preferably using the above described method, an analog method thereof, or any other method which is equally suitable according to the understanding of the ones skilled in the art, are to be regarded as "methylated patients" according to the invention, more

30 preferably as patients having an increased DNA methylation status and/or as patients showing partial or complete methylation of at least one promotor of at least one MGMT gene. They thus belong to the collective of patients that

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can be especially advantageously treated by the methods of treatment or the medicaments according to the invention.

5 However, such techniques, e.g. the method described below, can preferably be used in concordance with the instant invention with respect to the MGMT status.

10 Chemotherapeutic efficacy, the ability of chemotherapy to eradicate tumor cells without causing lethal host toxicity, depends on drug selectivity. One class of anticancer drugs, alkylating agents, cause cell death by binding to DNA which structurally distorts the DNA helical structure preventing DNA transcription and translation. In normal cells, the damaging action of alkylating agents can be repaired by cellular DNA repair enzymes, in
15 particular O⁶-methylguanine-DNA methyltransferase (MGMT) also known as O⁶-alkylguanine-DNA-alkyltransferase (AGAT). The level of MGMT varies in tumor cells, even among tumors of the same type. The gene encoding MGMT is not commonly mutated or deleted. Rather, low levels of MGMT in tumor cells are due to an epigenetic modification; the MGMT promoter region
20 is methylated, thus inhibiting transcription of the MGMT gene and preventing expression of MGMT.

Methylation has been shown by several lines of evidence to play a role in gene expression, cell differentiation, tumorigenesis, X-chromosome inactivation, genomic imprinting and other major biological processes. In
25 eukaryotic cells, methylation of cytosine residues that are immediately 5' to a guanosine, occurs predominantly in cytosine-guanine (CG) poor regions. In contrast, CpG islands remain unmethylated in normal cells, except during X-chromosome inactivation and parental specific imprinting where methylation of 5' regulatory regions can lead to transcriptional repression. Expression of a
30 tumor suppressor gene can also be abolished by de novo DNA methylation of a normally unmethylated CpG.

Hypermethylation of genes encoding DNA repair enzymes can serve as markers for predicting the clinical response to certain cancer treatments.

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Certain chemotherapeutic agents (including alkylating agents for example) inhibit cellular proliferation by cross-linking DNA, resulting in cell death. Treatment efforts with such agents can be thwarted and resistance to such agents develops because DNA repair enzymes remove the cross-linked structures. In view of the deleterious side effects of most chemotherapeutic drugs, and the ineffectiveness of certain drugs for various treatments, it is desirable to predict the clinical response to treatment with chemotherapeutic agents.

U.S. Pat. No. 6,773,897 discloses methods relating to chemotherapeutic treatment of a cell proliferative disorder. In particular, a method is provided for "predicting the clinical response to certain types of chemotherapeutic agents", including specific alkylating agents. The method entails determination and comparison of the methylation state of nucleic acid encoding a DNA repair enzyme from a patient in need of treatment with that of a subject not in need of treatment. Any difference is deemed "predictive" of response. The method, however, offers no suggestion of how to improve clinical outcome for any patient with an unfavorable "prediction".

Temozolomide is an alkylating agent available from Schering Corp. under the trade name of Temodar® in the United States and Temodal® in Europe. Temodar® Capsules for oral administration contain temozolomide, an imidazotetrazine derivative. The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-as-tetrazine-8-carboxamide (see U. S. Pat. No. 5,260,291). The cytotoxicity of temozolomide or metabolite of it, MTIC, is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O⁶ and N⁷ positions of guanine.

Temodar® (temozolomide) Capsules are currently indicated in the United States for the treatment of adult patients with newly diagnosed glioblastoma multiforme as well as refractory anaplastic astrocytoma, i.e. patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine. Temodal® is currently approved in Europe for the treatment of patients with malignant glioma, such as

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glioblastoma multiforme or anaplastic astrocytoma showing recurrence or progression after standard therapy.

5 According to the invention, alternatively to the method described above, the determination of the MGMT gene promoter methylation status can advantageously be done by the following procedures or in an equivalent or analogous manner thereof:

Sample preparation: The clinical samples tested by the MGMT methylation
10 assay preferably should be FFPE tissues. About forty microns of FFPE tumor tissue (equivalent of about 0.5cm x 1.0cm tumor surface, excluding necrosis) is de-paraffinated and DNA is extracted.

DNA extraction: The sample DNA is isolated, preferably by phenol/chloroform extraction.

15 DNA modification: The DNA is modified, preferably using sodium bisulfite.

MSP (methylation specific polymerase chain reaction [PCR]) and detection: methylated MGMT and β -Actin are amplified using methylation specific primers and quantified, preferably using the Amplifluor detection system. These molecules combine the forward primer for the PCR reaction with a
20 fluorescent detector/quencher pair, which fluoresces upon amplification. This signal is compared to the signal generated by known standards to determine the amount of DNA introduced, expressed as copy number. In order to obtain a result independent of sample volume, an independent reference gene, preferably β -Actin, is assessed and quantified in parallel, and the ratio of the
25 two is calculated. This ratio is the value preferably used to determine methylation status by application of a threshold.

Preferably for each tumor, the MGMT status will be determined and tumors will be classified as methylated MGMT gene promoter, or as unmethylated MGMT gene promoter, or optionally as indeterminate (e.g. due to insufficient
30 quality or amount of tumor tissue). Preferably, a ratio value of 8 for MGMT methylation will be applied as a cut-off for subject eligibility, i.e. a ratio value of less than or equal to 8, more preferably less than 8, for MGMT methylation will be preferably regarded as "unmethylated" in the context of

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the instant invention, whereas a ratio value of more than 8, or preferably equal to 8 and more than 8, will preferably be regarded as "unmethylated" in the context of the instant invention.

5

According to the invention, alternatively to the methods described above, the level of methylation of MGMT gene is assessed by determining the level of MGMT protein in a sample obtained from the patient. The level can be classified as being "Very Low", "Low", "Moderate", or "High", preferably as described in more detail below.

10

Assessing whether or not the MGMT gene is methylated can be performed using any method known to one skilled in the art. Techniques useful for detecting methylation of a gene or nucleic acid include, but are not limited to those described by Ahrendt et al., J. Natl. Cancer Inst., 91:332-339 (1999); Belsinky et al., Proc. Natl. Acad. Sci. U.S.A., 95:11891-11896 (1998), Clark et al., Nucleic Acids Res., 22:2990-2997 (1994); Herman et al., Proc Natl Acad Sci U.S.A., 93:9821-9826 (1996); Xiong and Laird, Nucleic Acids Res., 25:2532-2534 (1997); Eads et al., Nuc. Acids. Res., 28:e32 (2002); Cottrell et al., Nucleic Acids Res., 32:1-8 (2004). All references cited herein are incorporated herein by reference.

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Methylation-specific PCR (MSP; Herman et al., Proc. Natl. Acad. Sci. USA, 93(18):9821-9826 (1996); Esteller et al., Cancer Res., 59:793-797 (1999)) see also U.S. Pat. No. 5,786,146, issued Jul. 28, 1998; U.S. Pat. No. 6,017,704, issued Jan. 25, 2000; U.S. Pat. No. 6,200,756, issued Mar. 13, 2001; and U.S. Pat. No. 6,265,171, issued Jul. 24, 2001; U.S. Pat. No. 6,773,897 issued August 10, 2004; the entire contents of each of which is incorporated herein by reference can rapidly assess the methylation status of virtually any group of CpG sites within a CpG island, independent of the use of methylation-sensitive restriction enzymes. This assay entails initial modification of DNA by sodium bisulfite, converting all unmethylated, but not methylated, cytosines to uracil, and subsequent amplification with primers

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specific for methylated versus unmethylated DNA. MSP requires only small quantities of DNA, is sensitive to 0.1% methylated alleles of a given CpG island locus, and can be performed on DNA extracted from paraffin-
5 embedded samples. MSP eliminates the false positive results inherent to previous PCR-based approaches which relied on differential restriction enzyme cleavage to distinguish methylated from unmethylated DNA. This method is very simple and can be used on small amounts of tissue or a few cells.

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An illustrative example of a Western blot assay useful for this aspect of the invention to measure the level of MGMT protein in patient samples is presented in U.S. Pat. No. 5,817,514 by Li et al., the entire disclosure of which is incorporated herein by reference. Li et al. described monoclonal
15 antibodies able to specifically bind either to native human MGMT protein or to human MGMT protein having an active site which is alkylated. An illustrative example of an immunohistochemical technique useful for this aspect of the invention to measure the level of MGMT protein in patient samples is presented in U.S. Pat. No. 5, 407,804, the entire disclosure of which is
20 incorporated herein by reference. Monoclonal antibodies are disclosed which are able to specifically bind to the MGMT protein in single cell preparations (immunohistochemical staining assays) and in cell-extracts (immunoassays).

The use of fluorescent read out coupled with digitization of the cell image is
25 described and allows for quantitative measurement of MGMT levels in patient and control samples, including but not limited to tumor biopsy samples. Useful techniques for measuring the enzymatic activity of MGMT protein include but are not limited to methods described by: Myrnes et al., Carcinogenesis, 5:1061-1 064 (1984); Futscher et al., Cancer Comm., 1: 65-
30 73 (1989); Kreklaw et al., J. Pharmacol. Exper. Ther., 297(2):524-530 (2001); and Nagel et al., Anal. Biochem., 321(1):38-43 (2003), the entire disclosures of which are incorporated herein in their entireties.

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According to one mode of this invention, the level of MGMT protein expressed by cells of the patient is assessed by measurement of the MGMT protein, e.g., by Western blot using an antibody specific to MGMT, see for
5 example, U.S. Pat. No. 5,817,514 (supra) by Li et al. for a description of a Western blot assay to determine MGMT level. The level is compared to that expressed by normal lymphocytes known to express MGMT.

Patient MGMT protein levels are preferably classified as follows: Very Low =
10 0-30% of the MGMT expressed by normal lymphocytes; Low = 31-70% of the MGMT expressed by normal lymphocytes; Moderate = 71-90% and High = 91-300% or higher of the MGMT expressed by normal lymphocytes.

Patients that are tested as patients having Moderate or less MGMT protein
15 levels or that can be tested as patients having Moderate or less MGMT protein levels, preferably using the above described method, an analog method thereof, or any other method which is equally suitable according to the understanding of the ones skilled in the art in the art, are to be regarded as "methylated patients" according to the invention. They thus belong to the
20 collective of patients that can be especially advantageously treated by the methods of treatment or the medicaments according to the invention.

Accordingly, patients that have or can be shown to have Moderate (= 71-90%), preferably (Low = 31-70%) and more preferably Very Low (= 0-30%),
25 of the MGMT expressed by normal lymphocytes are preferably to be regarded as "methylated patients" according to the invention, more preferably as patients having an increased DNA methylation status and/or as patients showing partial or complete methylation of at least one promotor of at least one MGMT gene. They thus belong to the collective of patients that can be
30 especially advantageously treated by the methods of treatment or the medicaments according to the invention.

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Thus, one subject of the invention is a method or a use as described herein, wherein the medicament is to be used in the treatment of patients having an increased DNA methylation status.

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Thus, a further subject of the invention is a method or a use as described herein, wherein the medicament is to be used in the treatment of patients showing partial or complete methylation of at least one promotor of at least one MGMT gene.

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Thus, a further subject of the invention is a method or a use as described herein, wherein the medicament is to be used in the treatment of patients, having a Moderate, preferably a Low and more preferably a Very Low level of MGMT protein, preferably in comparison of the MGMT expressed by normal lymphocytes.

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According to the afore discussed subject, patients that have or can be shown to have at least Low (= 31-70%), preferably at least Moderate (= 71-90%), and especially High (= 91-300% or higher) of the MGMT expressed by normal lymphocytes are preferably to be regarded as "unmethylated patients" according to the invention, more preferably as patients having an normal or less than normal DNA methylation status and/or as patients showing no or incomplete methylation of at least one promotor of at least one MGMT gene. They thus belong to the collective of patients that can be especially advantageously treated by the new methods of treatment or the new medicaments according to this invention.

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MGMT methylation status:

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The MGMT methylation status is determined by a real-time methylation specific PCR (MSP) technique as described by Vlassenbroeck et al (see below). First, genomic DNA is isolated from tumor specimens. The genomic DNA is treated with sodium bisulfite which will convert, by chemical de-amination, unmethylated cytosine bases in the genomic DNA to uracil.

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Methylated cytosine bases will not de-aminates and will remain as cytosine bases. With this converted DNA, PCR probes specific to the methylated MGMT gene sequence are used which take advantage of the bisulfite converted DNA sequences. Real time PCR reactions are monitored and compared to standard curves yielding a quantitative result. In parallel, the beta-actin gene (ACTB) is also quantified and is used to normalize the MGMT assay result by a ratio of mMGMT:ACTB. A sample is considered methylated when the ratio of mMGMT:ACTB equals or exceeds a given threshold, for GBM this has been established as a ratio of 8. This cutoff was established by directly comparing the output of the real-time MSP assay to that of an MSP technique which uses agarose gels to separate the PCR products and is interpreted by visual examination. This assay was chosen as the comparator assay for the establishment of the real-time MSP cutoff as it was used in the landmark NEJM paper (Hegi et al, N Engl J Med. 2005 Mar 10;352(10):997-1003), the disclosure of which is included in its entirety by reference, to show the advantage in progression free survival and overall survival of MGMT methylated GBM patients receiving the alkylation based therapy temozolomide.

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Vlassenbroeck et al:

Vlassenbroeck I, Califice S, Diserens AC, Migliavacca E, Straub J, Di Stefano I, Moreau F, Hamou MF, Renard I, Delorenzi M, Flamion B, DiGuseppi J, Bierau K, Hegi ME. The disclosure of this publication is included into the instant application in its entirety by reference.

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Thus, an especially preferred subject of the invention is a method or a use as described herein, wherein the medicament is to be used in the treatment of patients having a normal or decreased DNA methylation status.

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Thus, an especially preferred subject of the invention is a new method or a new use as described herein, wherein the medicament is to be used in the

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treatment of patients showing no or incomplete methylation of at least one promotor of at least one MGMT gene.

5 Thus, an especially preferred subject of the invention is a method or a use as described herein, wherein the medicament is to be used in the treatment of patients having a Low, more preferably a Moderate and especially a High level of MGMT protein, preferably in comparison of the MGMT expressed by normal lymphocytes.

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Thus, an especially preferred subject of the invention is a method or a use as described herein, wherein the medicament is to be used in the treatment of patients having an normal or decreased DNA methylation status, and wherein said method comprises the administration of one or more

15 alkylating agents, preferably selected from nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action, preferably selected from nitrosoureas, preferably ACNU, BCNU and CCNU, busulfan, melphalan, carboplatin, cisplatin, oxaliplatin, cyclophosphamide, dacarbazine, carmustine, ifosfamide and lomustine,
20 temozolomide and altretamine, or camptothecin.

Thus, an especially preferred subject of the invention is a method or a use as described herein, wherein the medicament is to be used in the treatment of patients showing no or incomplete methylation of at least one promotor of at
25 least one MGMT gene and wherein said method comprises the administration of one or more alkylating agents, preferably selected from nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action, preferably selected from nitrosoureas, preferably ACNU, BCNU and CCNU, busulfan, melphalan, carboplatin,
30 cisplatin, oxaliplatin, cyclophosphamide, dacarbazine, carmustine, ifosfamide and lomustine, temozolomide and altretamine, or camptothecin.

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Thus, an especially preferred subject of the invention is a method or a use as described herein, wherein the medicament is to be used in the treatment of patients, having a Low, more preferably a Moderate and especially a High
5 level of MGMT protein, preferably in comparison of the MGMT expressed by normal lymphocytes, and wherein said method comprises the administration of one or more alkylating agents, preferably selected from, nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other
10 compounds with an alkylating action, preferably selected from nitrosoureas, preferably ACNU, BCNU and CCNU, busulfan, melphalan, carboplatin, cisplatin, oxaliplatin, cyclophosphamide, dacarbazine, carmustine, ifosfamide and lomustine, temozolomide and altretamine, or camptothecin.

In the afore described methods or uses with respect to MGMT, the methods
15 or uses preferably comprise the administration of one or more specific integrin ligands, preferably selected from cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and salts thereof, and especially cyclo-(Arg-Gly-Asp-DPhe-NMe-Val).

20 Methods to assess an increased DNA methylation status and/or showing no or incomplete methylation of at least one promotor of at least one MGMT gene in patients are known in the art. Accordingly, patients to be advantageously treatable by methods or a uses as described herein can readily determined by the ones skilled in the art.

25 Alternatively, patients that are not or that can not be shown to be "methylated patients" as defined herein are preferably regarded to be "unmethylated patients" in the context of this invention.

30 A preferred subject of the instant invention is a method or a use as described herein, wherein the medicament is to be used in the treatment of recurrent cancer, for example in a second line or subsequent treatment setting.

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A more preferred subject of the instant invention is a method or a use as described herein, wherein the medicament is to be used in the treatment of recurrent cancer, for example in a second line or subsequent treatment setting, wherein the cancer is selected from the group consisting of astrocytoma, more preferably astrocytoma grade II, III and/or IV, and especially consisting of glioblastoma or glioblastoma multiforme.

An even more preferred subject of the instant invention is a method or a use as described herein, wherein the medicament is to be used in the treatment of newly diagnosed cancer, preferably in a first line treatment setting.

An especially preferred subject of the instant invention is a method or a use as described herein, wherein the medicament is to be used in the treatment of newly diagnosed cancer, preferably in a first line treatment setting, wherein the cancer is selected from the group consisting of astrocytoma, more preferably astrocytoma grade II, III and/or IV, and especially consisting of glioblastoma or glioblastoma multiforme.

The term "without a pause" as used herein, especially used with respect to treatment regimens or treatment durations, is preferably understood to mean that said treatment regimens or durations are performed or applied in a consecutive order. For example, "2 to 8 weeks and especially 6 weeks, preferably without a pause" is preferably intended to mean "2 to 8 weeks and especially 6 weeks, preferably in a consecutive order".

As used herein, the term "about" with respect to numbers, amounts, dosings, hours, times, timings, durations, and the like, is preferably understood to mean "approximately" with respect to said numbers, amounts, dosings, hours, times, timings, durations, and the like.

If not specified otherwise, amounts administered to a patient given in "mg", such as in 500 mg, 1000 mg, 2000 mg, 4000 mg, 6000 mg, 8000 mg, 10000

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mg, 12000 mg and 14000 mg, are preferably intended to mean the respective amounts to be administered "flat", i.e. as a fixed dose that is not adjusted to the bodyweight and/or body surface of the respective patient.

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Preferably, especially preferred subjects of the instant invention relate to aspects, subjects, uses, methods and/or embodiments, wherein one or more features of two or more of the herein described aspects, subjects, uses, methods and/or embodiments are combined in one subject.

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Examples

5 The following examples are given in order to assist the skilled artisan to better understand the present invention by way of exemplification. The examples are not intended to limit the scope of protection conferred by the claims. The features, properties and advantages exemplified for the compounds, methods and uses defined in the examples may be assigned to other compounds, methods and uses not specifically described and/or
10 defined in the examples, but falling under the scope of what is defined in the claims.

Example 1: Rat orthotopic glioblastoma model radiotherapy, Cilengitide (= cyclo-(Arg-Gly-Asp-DPhe-NMe-Val)) scheduling experiments

15 **NIH *rnu*** nude rats are anaesthetized, restrained, and injected intracerebrally 1 mm retro orbitally, 3mm to the right of the bregma and at a depth of 2.5 mm with 5x10E5 U251 human glioblastoma cells suspended in 10 ul of culture medium, using a #2701 Hamilton syringe fitted with a 26 gauge needle, essentially as previously described (Engelbrechten et al., 1999). After 14 days,
20 cilengitide (4 mg/kg) is given as an intraperitoneal bolus in PBS, at various time (8h, 4h, 2h, 1h) prior to a single treatment with single, collimated, dorsal-ventral beam of 6 MV x-rays, so that 95-100% of the central axis dose of 25 Gy hit the tumor volume (Kim et al., 1999). Each of the 7 subsequent days the animals also received an identical i.p. bolus of cilengitide. The animals
25 are maintained under ad libitum food and drink until they become moribund, or are sampled for tissue analysis (in the t-4 and t-8 h groups, where the animals are healthy past 230 days post tumor injection). A Kaplan-Meier survival curve is calculated and plotted (Fig.1) from the raw data (Table 1). All animals in the RT monotherapy group died by 120 d.

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Reference List:

- 5 Engebraaten,O., Hjortland,G.O., Hirschberg,H., and Fodstad,O. (1999).
Growth of precultured human glioma specimens in nude rat brain. J.
Neurosurg. 90, 125-132.
- Kim,J.H., Khil,M.S., Kolozsvary,A., Gutierrez,J.A., and Brown,S.L. (1999).
Fractionated radiosurgery for 9L gliosarcoma in the rat brain. Int. J. Radiat.
Oncol. Biol. Phys. 45, 1035-1040.

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The Results are given in Table 1 below and Fig. 1:

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Table 1

400,000 U251n Cells Inj.				EMD Survival Study			Days Post Implant
Group	Time Pre-Irradiation	Animal #	Trtmnt	Date of Injection	Date of Radiation	Date of Termination	
5	8 hours	G89-1	Rt	03.03.2005	17.03.2005	(Sick) 6/7/2005	96
	8 hours	G89-2	Rt	03.03.2005	17.03.2005	(Sick) 6/17/2005	106
	8 hours	G89-3	Rt + EMD	03.03.2005	17.03.2005	(Healthy) 11/15/2005	257
	8 hours	G89-4	Rt + EMD	03.03.2005	17.03.2005	(Healthy) 11/15/2005	257
	8 hours	G89-5	Rt + EMD	03.03.2005	17.03.2005	(Alive) 12/15/2005	287
	8 hours	G89-6	Rt + EMD	03.03.2005	17.03.2005	(Alive) 12/15/2005	287
10	4 hours	G90-1	Rt	05.04.2005	19.04.2005	(Sick) 7/20/2005	106
	4 hours	G90-2	Rt	05.04.2005	19.04.2005	(Sick) 7/29/2005	115
	4 hours	G90-3	Rt + EMD	05.04.2005	19.04.2005	(Healthy) 11/29/2005	238
	4 hours	G90-4	Rt + EMD	05.04.2005	19.04.2005	(Healthy) 11/29/2005	238
	4 hours	G90-5	Rt + EMD	05.04.2005	19.04.2005	(Alive) 12/15/2005	254
	4 hours	G90-6	Rt + EMD	05.04.2005	19.04.2005	(Alive) 12/15/2005	254
15	2 hours	G91-1	Rt	12.04.2005	26.04.2005	(Sick) 7/26/2005	105
	2 hours	G91-2	Rt	12.04.2005	26.04.2005	(Sick) 8/12/2005	122
	2 hours	G91-3	Rt + EMD	12.04.2005	26.04.2005	(Sick) 8/10/2005	120
	2 hours	G91-4	Rt + EMD	12.04.2005	26.04.2005	(Sick) 9/6/2005	147
	2 hours	G91-5	Rt + EMD	12.04.2005	26.04.2005	(Sick) 9/21/2005	162
	2 hours	G91-6	Rt + EMD	12.04.2005	26.04.2005	(Sick) 10/25/2005	196
25	1 hour	G92-1	Rt	12.05.2005	26.05.2005	(Sick) 8/26/2005	106
	1 hour	G92-2	Rt	12.05.2005	26.05.2005	(Sick) 9/1/2005	112
	1 hour	G92-3	Rt + EMD	12.05.2005	26.05.2005	(Sick) 9/1/2005	112
	1 hour	G92-4	Rt + EMD	12.05.2005	26.05.2005	(Sick) 9/2/2005	113
	1 hour	G92-5	Rt + EMD	12.05.2005	26.05.2005	(Sick) 9/19/2005	130
	1 hour	G92-6	Rt + EMD	12.05.2005	26.05.2005	(Sick) 9/30/2005	141

Sick = moribund and removed from study

20 Healthy = indicates sampled for tissue at date shown, but alive at this point
 Alive = surviving at time point shown.

Time pre-irradiation = when cilengitide 4 mg/kg is given.

Rt = radiotherapy 25 Gy

25 EMD = cilengitide bolus 4 mg/kg

American date convention in date of termination column, European in date of radiation column

30 **Example 2: Phase IIa Trial of Cilengitide ((= cyclo-(Arg-Gly-Asp-DPhe-NMe-Val))) Single Agent Therapy in Patients with Recurrent Glioblastoma**

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Background: The present phase IIa study was designed to evaluate the safety, toxicity, and clinical activity of the cyclic RGD pentapeptide cilengitide(= cyclo-(Arg-Gly-Asp-DPhe-NMe-Val)), an inhibitor of integrins $\alpha v \beta 3$ and $\alpha v \beta 5$, as a single agent at doses of 500 and 2000 mg in patients (pts) with recurrent glioblastoma (GBM).

Methods: In this multicenter, open-label, randomized, uncontrolled study, pts with GBM and measurable disease that had relapsed after previous therapy with temozolomide and radiotherapy were randomized to receive cilengitide at doses of either 500 mg or 2000 mg i.v., 2x/week, until progression. Histopathology diagnosis and MRI imaging were subject to independent blinded review. The primary endpoint was Progression Free Survival (PFS) at 6 months (mths). Secondary endpoints included response, survival, time to disease progression, safety, tolerability and pharmacokinetics.

Results: Actual accrual; 81 pts (median Karnofsky Performance Status 80%; median age 57 yrs) at 15 sites. 41 pts received 500 mg and 40 pts to receive 2000 mg of i.v. cilengitide 2x/week. No obvious imbalance in prognostic factors was observed. Median infusions;16 [range, 4-179]. Treatment related NCI CTC grade 3 adverse events (AEs) included elevated liver enzymes (at 500 mg), arthralgia/ myalgia (at 500 mg), and weight increase/ edema (at 2000 mg) in 1 patient, respectively. No grade 4 therapy related AEs were reported by the investigators. One CTC grade 2 cerebral hemorrhage was reported, possibly related either to the drug or to the disease. The PFS rate at 6 mths was 16.1% (n=13/81 pts). 10 of these pts (12.3 %, n=4 with 500 mg, n=6 with 2000 mg) received 12 or more cycles of therapy (1 cycle=4 weeks). Six pts (7.4%) were still progression-free and on treatment at the time when this abstract was issued. In the 500 mg arm, median Overall Survival (mOS) was 6.5 mths [95% CI: 5.2-9.3 mths], 12 mth overall survival (OS) rate was 24.4%. In the 2000 mg arm, mOS was 9.9 mths [95% CI, 6.3-15.7 mths], 12 mth OS rate was 37.5%. Although not statistically significant, there was a trend towards better tumor control in pts receiving 2000 mg 2x/week.

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Conclusion: Cilengitide was tolerated well in single agent therapy at two dose levels. Cilengitide demonstrated advantageous single agent activity in recurrent glioblastoma, with long term disease stabilisation in a subset of pts.

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Example 3: Phase I/IIa Trial of Cilengitide (= cyclo-(Arg-Gly-Asp-DPhe-NMe-Val)) and Temozolomide with Concomitant Radiotherapy, Followed by Temozolomide and Cilengitide Maintenance Therapy in Patients With Newly Diagnosed Glioblastoma (GBM).

10

Purpose: To evaluate safety, toxicity, and efficacy of the combination of the cyclic RGD pentapeptide Cilengitide (= cyclo-(Arg-Gly-Asp-DPhe-NMe-Val)), an inhibitor of integrins $\alpha v \beta 3$ and $\alpha v \beta 5$, in addition to standard temozolomide (TMZ) and radiotherapy (RT).

15

Patients and methods: Fifty-two pts (PS 0-1: 92%, 2: 8%; median age 57 yrs) after biopsy (n= 9/17%) or tumor resection (n=43/83%) were treated with standard TMZ/RT (Stupp et al. NEJM 2005). In addition Cilengitide (500 mg i.v., 2x/week) was started one week before TMZ/RT and given throughout for the duration of chemotherapy or until progression. Primary endpoint was progression free survival rate at 6 months (target: 65%). Patients were followed with MRI every 2 months. Histopathologic diagnosis and MRI imaging were independently reviewed, MGMT promotor methylation status was assessed in 45 (86.5%) pts.

20

Results: Forty-six pts (92%) completed RT, $\geq 90\%$ of concomitant TMZ was received by 42 pts and cilengitide by 45 pts. 20 pts (3 ongoing) completed 6 cycles of maintenance TMZ and cilengitide. Observed haematological grade 3 and 4 toxicity was: lymphopenia (28/52, 53.8%), thrombocytopenia (7/52 pt. 13.4%) and neutropenia (5/52, 9.6%). Treatment related non-hematologic grade 3 toxicities were reported for n=3/52 (5.7%) patients: constitutional symptoms (asthenia, fatigue, anorexia, n=3); elevated liver function tests (n=1), deep venous thrombosis and pulmonary embolism (n=1). One patient with a history of sigmoid diverticulosis experienced sigmoid perforation

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(grade 2). In total, 34/52 (65.4% [95% CI, 50.9-78.0%]) of the patients were progression free at 6 months. Pts with O⁶-Methylguanine-DNA methyltransferase (MGMT) gene-promotor methylation in the tumor were more likely to reach 6 months PFS endpoint. In total, 34/52 (65.4% [95% CI, 50.9-78.0%]) of the pts were progression free at 6 months. A major contribution to the overall result was provided by a subgroup of patients (23/52 subjects, with methylated MGMT promoter, silencing the DNA repair enzyme MGMT), which showed a strong increase of the PFS-6 rate compared to historical control (91% vs. 69%). The other major subgroup (22/52, unmethylated MGMT promoter) showed a less relevant difference to the historical control (40.9% vs. 40%), which is likely to be significantly improved by a higher dosing of Cilengitide in comparison to the subgroup with methylated MGMT promoter. Overall the study reached its primary endpoint (PFS-6 = 65.4%)

Conclusion: The study reached its primary endpoint. The combination of the integrin inhibitor RGD peptide Cilengitide and TMZ/RT was well tolerated, PFS at 6 months is very advantageous. MGMT gene promoter methylation provides for even better prognosis.

Example 4: Cilengitide in subjects with newly diagnosed glioblastoma multiforme and unmethylated MGMT gene promoter – a multicenter, open-label Phase II study, investigating two cilengitide regimens in combination with standard treatment (temozolomide with concomitant radiation therapy, followed by temozolomide maintenance therapy).

The study design is as follows:

The expected time for the safety run-in (for an intensified regimen) is about 3-4 months. The planned recruitment period for the randomized part is 18 months, with a follow-up time of at least 21 months.

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5 The overall duration of the study depends on disease progression, unacceptable toxicity, and overall survival time. The study is finished when the last subject received the last dose of study medication (including a safety follow-up of 28 days), and the study objectives are answered, i.e. the final analysis on survival is performed.

Study objectives:

10 **Safety run-in:** To determine the safety and tolerability of a 5-day administration schedule of 2000 mg cilengitide given in combination with RTX and TMZ standard therapy.

15 **Randomized part:** To investigate the overall survival (OS) time in subjects receiving 2 different regimens of 2000 mg cilengitide in combination with RTX and TMZ standard therapy. The secondary objectives of the **randomized part** are:

- To evaluate PFS time.
- To evaluate the safety and tolerability of the combination of cilengitide with standard RTX and TMZ therapy in the overall study population.
- 20 • To evaluate the PK profile of cilengitide when given daily (5 out of 7 days) at 2000 mg in combination with RTX and TMZ on days of RTX.

Detailed study design and plan:

25 This is a multicenter, open-label, controlled, randomized Phase II study with a safety run-in conducted in subjects with newly diagnosed GBM with unmethylated O⁶-methylguanine-DNA methyltransferase (MGMT) gene promoter in the tumor tissue.

30 Due to the lack of previous clinical experience with a 3, 4, or 5 times a week administration of cilengitide as single agent or in combination treatment, a **safety run-in** is conducted to determine the safety and tolerability of the

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intense exposure treatment intended for Group B of the randomized part. In this safety run-in, the regimen is intensified stepwise by cohort (cilengitide i.v. 3, 4, and 5 times a week in addition to RTX and TMZ standard treatment during week 1-6) in a classical 3+3 subjects approach with predefined dose and schedule reduction rules.

After the completion of the safety run-in part, an interim safety report is provided and a schedule for Group B of the randomized part is defined by the SMC according to the SMC charter. This report is provided to the ethics committees and health authorities relevant for the participating centers. Following the successful completion of the safety runin for Group B, the **randomized part** starts, during which all subjects (patients) receive RTX and TMZ standard treatment (RTX and concomitant TMZ during Weeks 1-6, followed by 6 cycles of TMZ). Subjects are randomized to 1 of 3 treatment groups: Subjects in **Group A** receive cilengitide as twice weekly i.v. infusion starting 1 week prior to RTX and TMZ standard treatment, in combination with standard treatment, and as a mandatory maintenance for another 10 months after standard treatment; subjects in **Group B** receive the same regimen as Group A with the exception of an intense cilengitide regimen (determined during the safety run-in) during combination with RTX and TMZ (Weeks 1-6) on days of RTX; subjects in **Group C** receive RTX and TMZ standard treatment alone. A cross-over of subjects of the control group to cilengitide treatment is not allowed.

The treatment duration is 18 months for subjects in the cilengitide groups (safety run-in and Groups A and B of the randomized part), and 8 months for subjects in the control group (Group C). Treatment may stop earlier due to occurrence of progressive disease (PD) or unacceptable toxicity, or withdrawal for any other reason. Subjects in cilengitide groups (safety run-in and Groups A and B of the randomized part) may continue receiving cilengitide after completion of 18 months, until occurrence of PD or unacceptable toxicity, or until withdrawal for any other reason. In case of

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intolerance to TMZ after start of study treatment, subjects in the cilengitide groups may receive at any time cilengitide as monotherapy until occurrence of PD or unacceptable toxicity, or until withdrawal for any other reason.

5

Preferred Indication:

Newly diagnosed Glioblastoma, preferably with unmethylated MGMT gene promoter

Diagnosis: newly diagnosed, histologically proven

10 GBM with proven unmethylated MGMT gene promoter status.

Inclusion criteria:

1. Written informed consent obtained before undergoing any study-related activities.

15 2. Newly diagnosed histologically proven supratentorial GBM (World Health Organization [WHO] Grade IV, including GBM subtypes, e.g. gliosarcoma).

The histological diagnosis must be obtained from a neurosurgical resection of the tumor or by an open biopsy (stereotactic biopsy not allowed).

20 3. Tumor tissue specimens from the GBM surgery or open biopsy (formalin-fixed paraffin-embedded [FFPE] block) must be available for MGMT gene promoter status analysis and central pathology review.

4. Proven unmethylated MGMT gene promoter status (i.e. cut-off ratio <8 by means of applied test to determine MGMT gene promoter status).

Cilengitide administration:

- 25
- i.v infusion over 1 hour
 - Start 4 hours before RTX
 - Flat dose of 2000 mg
 - Twice a week (on Day 1 and on Day 4 [e.g. on Monday and Thursday or on Tuesday and Friday]).
- 30
- In Group B during RTX on each day of RTX (or highest possible frequency based on safety run-in outcome)
 - For 18 month or until disease progression

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Treatment scheme during combined Cilengitide + TMZ + RTX administration:

5 1 h i. v. infusion of Cilengitide, followed, after two hours after the completion of the infusion, by administration of TMZ p.o., followed by an 1h break, followed by the delivery of the RTX.

Administration of radiotherapy:

- 10 • conventionally fractionated regimen
- total dose of 60 Gy
- 30 daily fractions over 6 weeks,
- fraction of 2 Gy once daily (every 24 h $\pm$ 2 h)
- 5 days per week
- 15 • maximum interruption of 72 hours ($\pm$ 2 hours) for weekends or public holiday
- overall RTX treatment for 49 days at maximum

Administration of Temozolomide:

- 20 TMZ administration
 - Oral once a day
 - after cilengitide infusion
 - at least 1 hour before RTX.
- 25 Weeks 1–6 (in combination with RTx):
 - At a daily dose of 75 mg/m²
 - 7 days a week.

Weeks 7-34 (Maintenance treatment):

- 30 – Start 4 weeks ($\pm$ 3 days) after the end of RTX (i.e. in Week 11),
- Starting dose 150 mg/m²/day,
- Single dose escalation to 200 mg/m²/day in subsequent cycles
- 5 consecutive days a week (Days 1-5).

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Randomized part:

Group A: In Group A, 2000 mg cilengitide is administered twice weekly by i.v. infusion throughout the study, starting 1 week prior to RTX and TMZ standard treatment (Week -1), then in combination with standard treatment (Weeks 1-34) and as maintenance for another 10 months after end of standard treatment (after Week 34). The entire treatment is about 18 months.

Group B: In Group B, the treatment regimen is the same as for Group A with the exception that during combination with RTX and TMZ (Weeks 1-6) 2000 mg cilengitide i.v. is given 5 times a week (or another schedule defined in the safety run-in) on days of RTX.

Cilengitide is administered 4 hours (start of 1- hour infusion) before RTX, and TMZ is given orally after completion of the cilengitide infusion and at least 1 hour before RTX. On days without RTX when both cilengitide and TMZ are to be administered, TMZ is administered within 1 hour after completion of the cilengitide infusion. On days without RTX and cilengitide, TMZ is administered in the morning.

Reference therapy: dose/mode of administration/dosing schedule

RTX and TMZ standard therapy during Weeks 1-6 (max. of 7 weeks):

Beginning on Day 1 of Week 1, treatment with TMZ and RTX is administered in addition to cilengitide.

TMZ is administered orally for 6 weeks, at a daily dose of 75 mg/m² (7 days a week).

Focal RTX is delivered for 6 weeks once daily at 2 Gy per fraction, 5 consecutive days/week, for a total of up to 60 Gy. (to be prescribed according to the guidelines of the International Commission on Radiological Units). Adequate immobilization masks are used to ensure reproducibility. The treatment volume is determined on the basis of preoperative Gd-MRI of the brain, including adequate safety margins.

TMZ maintenance treatment during Weeks 7-34:

Beginning 4 weeks after the end of RTX (i.e. in Week 11), concomitant to cilengitide treatment, subjects receive TMZ chemotherapy at a dose of 150-

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200 mg/m² daily for 5 days (Days 1 to 5 of a given treatment week) every 4 weeks (i.e. Weeks 11, 15, 19, 23, 27, and 31) for up to 6 cycles. .

Timing of treatments:

- 5 TMZ is given orally 1 hour before RTX. On days without RTX, TMZ is administered in the morning.

MGMT methylation status:

- 10 The MGMT methylation status is determined by a real-time methylation specific PCR (MSP) technique as described by Vlassenbroeck et al (see below). First, genomic DNA is isolated from tumor specimens. The genomic DNA is treated with sodium bisulfite which will convert, by chemical de-amination, unmethylated cytosine bases in the genomic DNA to uracil. Methylated cytosine bases will not de-amine and will remain as cytosine
- 15 bases. With this converted DNA, PCR probes specific to the methylated MGMT gene sequence are used which take advantage of the bisulfite converted DNA sequences. Real time PCR reactions are monitored and compared to standard curves yielding a quantitative result. In parallel, the beta-actin gene is also quantified and is used to normalize the MGMT assay
- 20 result by a ratio of mMGMT:ACTB. A sample is considered methylated when the ratio of mMGMT:ACTB equals or exceeds a given threshold, for GBM this has been established as a ratio of 8. This cutoff is established by directly comparing the output of the real-time MSP assay to that of an MSP technique which uses agarose gels to separate the PCR products and is
- 25 interpreted by visual examination. This assay is chosen as the comparator assay for the establishment of the real-time MSP cutoff as it was used in the landmark NEJM paper (Hegi et al, N Engl J Med. 2005 Mar 10;352(10):997-1003) to show the advantage in progression free survival and overall survival of MGMT methylated GBM patients receiving the alkylation based therapy
- 30 temozolomide.

Vlassenbroeck et al:

Vlassenbroeck I, Califice S, Diserens AC, Migliavacca E, Straub J, Di

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Stefano I, Moreau F, Hamou MF, Renard I, Delorenzi M, Flamion B, DiGuseppi J, Bierau K, Hegi ME.

Validation of real-time methylation-specific PCR to determine O⁶-

5 methylguanine-DNA methyltransferase gene promoter methylation in glioma. J Mol Diagn. 2008 Jul;10(4):332-7

Example 5: A randomized clinical trial of the effect of radiation therapy plus Temozolomide combined with Cilengitide or Cetuximab on
10 **patients with newly diagnosed MGMT-promoter unmethylated glioblastoma**

Patients shall meet all eligibility criteria for the CENTRIC phase III trial at the exception that no MGMT-promoter methylation can be demonstrated. The
15 treatment backbone in both study arms preferably consists of postoperative radiation therapy with concomitant daily temozolomide, followed by 6 cycles of temozolomide according to a 21 out of 28 days regimen (as in the experimental arm of the RTOG 0525 / EORTC 26052-22053 phase III study). In study arm (A) Cilengitide (at a dose of 2000 mg by iv administration,
20 2x/week) is added to this backbone while in the second study arm (B), Cetuximab is added (at an initial dose of 400 mg/m² administered by intravenous infusion over 2 hours and followed by a weekly dose of 250 mg/m² iv over 1 hours). In both study arms, treatment is administered for 52 consecutive treatment weeks.

25

Radiation therapy and Temozolomide (study arm A and B)

- Beginning on Day 1 of Week 2, treatment with TMZ is initiated concomitantly with RT and TMZ will be administered orally at a daily dose of 75 mg/m² (7 days a week). Focal RT and TMZ will be
30 delivered for 6 weeks, once daily at 2.0 Gy per fraction, 5 consecutive days/week, for a total of up to 60 Gy (preferably prescribed according to the guidelines of the International Commission on Radiological Units). Adequate immobilization masks

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5 is preferably used to ensure reproducibility. The treatment volume is preferably determined on the basis of preoperative Gd-MRI of the brain, including adequate safety margins. TMZ administration is preferably continued on days when RT is interrupted (e.g. during weekends).

- Optional Pneumocystis pneumonia prophylaxis (PCP) is preferably administered during the RT and thereafter in patients with a total lymphocyte count of $< 500/\text{mm}^3$.
- 10 • Beginning 4 weeks after the end of RT, patients receive TMZ chemotherapy daily for 21 days every 28 days for up to 6 cycles. The starting dose for the first cycle is $75 \text{ mg/m}^2/\text{day}$, with a single dose escalation to $100 \text{ mg/m}^2/\text{day}$ in subsequent cycles if no adverse events $>$ grade 2 are noted.
- 15 • Timing of TMZ treatments: TMZ is preferably given orally 1 hour before RT. On days without RT, TMZ is preferably administered on an empty stomach in the morning. On days with Cetuximab or Cilengitide administration, TMZ is preferably given orally 2 hours after completion of the Cetuximab or Cilengitide infusion.

20

Cilengitide (study arm A only)

- Cilengitide is administered at a flat dose of 2000 mg intravenously (i.v.) twice a week (on Day 1 and 4, e.g. Monday and Thursday or Tuesday and Friday) for a total of 52 consecutive weeks. Treatment starts on day 1 of week 1.
- 25 • On days where RT is administered, Cilengitide administration is preferably initiated 4 hours before RT (= start of 1-hour infusion).

Cetuximab (study arm B only)

- 30 • Cetuximab is preferably administered at an initial dose of 400 mg/m^2 administered by intravenous infusion over 2 hours and followed by a weekly dose of 250 mg/m^2 iv over 1 hour for a total of 52 consecutive weeks. Treatment starts on day 1 of week 1.

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- The first administration of Cetuximab is preferably preceded by the administration of an oral antihistaminic and a corticosteroid (e.g. 8 mg of dexamethasone or 32 mg of methylprednisolone or an alternative corticosteroid at an equally potent dose). Corticoid and oral antihistaminic pretreatment before subsequent Cetuximab infusions is recommended.
- On days where RT is administered, Cetuximab administration is preferably initiated 4 hours before RT (= start of 1-hour infusion).

Study arms A and/or B

- The treatment duration in both study arms is preferably 52 weeks (= either Cilengitide or Cetuximab will be administered during a total of 52 consecutive weeks following randomization of the subject).
- Study treatment may stop earlier than planned due to occurrence of progressive disease (PD) or unacceptable AEs, or withdrawal of patient consent or for any other reason when the treating physician or study sponsor considers this to be in the interest of the patient.

Example 6: Clinical study of Cilengitide in combination with concurrent chemotherapy and radiotherapy followed by protracted daily low dose temozolomide (TMZ) and low dose procarbazine (PCB) D1 – 20 in newly diagnosed glioblastoma without methylation of the MGMT promoter gene

Cilengitide 2000 mg flat i.v. twice weekly is administered over a period of 18 months without interruption.

Starting one week after the initiation of Cilengitide, RTX (60 Gy, 2 Gy per fraction) with concurrent daily temozolomide (60 mg/m² p.o.) and daily procarbazine (PCB, 50 mg p.o. if BSA < 1.7; 100 mg p.o. if BSA ≥ 1.7) is given over a period of 6 weeks (RTX Monday to Friday, both TMZ and PCB seven days a week).

After a break of 4 weeks, adjuvant TMZ (50mg/m² p.o. in first cycle, 60 mg/m² p.o. in subsequent cycles) and PCB (50 mg p.o. if BSA < 1.7; 100 mg

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p.o. if BSA ≥ 1.7) are then given daily D1 to 20. This TMZ/PCB cycle is repeated every 28 days over a total period of 6 cycles.

5 Study treatment week by week

Patients will receive study treatment as planned preferably until progression of disease or unacceptable toxicity, or until withdrawal for any other reason.

10

WEEK 1		
Agent	Dose/Route/Schedule	Details
Cilengitide	2000 mg IV twice weekly	Cilengitide thus starts one week before RT/TMZ/PCB.

15

WEEK 2 TO 7 (= 6 weeks)		
Agent/RTX	Dose/Route/Schedule	Details
Cilengitide	2000 mg i.v. twice weekly	
Radiotherapy	RTX is administered in the form of a fractionated focal irradiation at a total dose of 60 Gy (2Gy per fraction, once daily Monday through Friday).	RTX is thus administered over a period of 6 weeks.
TMZ	60 mg/m ² p.o. once daily	TMZ and PCB are given 7 days per week from the first day of RTX until the last day of RTX (stretching over 6 weeks, i.e. 42 days), but for no longer than 49 days.
PCB	<u>Dosage according to BSA:</u> 50 mg p.o. once daily if BSA < 1.7 100 mg p.o. once daily if BSA ≥ 1.7	

25

30

The 1-hour infusion of Cilengitide preferably starts 4 hours before RTX. TMZ and PCB are preferably taken after completion of the Cilengitide infusion and at least 1 hour before RTX. If RTX cannot be administered on the day it was intended, it can be postponed. However, the Cilengitide administration preferably take place regardless of such a postponement or lack of the RTX.

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In such cases, TMZ and PCB is preferably administered within 1 hour after completion of the Cilengitide infusion.

5	WEEK 8 TO 11 (= 4 weeks)		
	Agent	Dose/Route/Schedule	Details
	Cilengitide	2000 mg i.v. twice weekly	During these 4 weeks only Cilengitide is administered.

10	WEEK 12 TO 35 (= 24 weeks)		
	Agent/RTX	Dose/Route/Schedule	Details
	Cilengitide	2000 mg i.v. twice weekly	
15	TMZ	Start at 50mg/m ² p.o. once daily for the first cycle and escalate to 60 mg/m ² p.o. once daily with cycle 2 if there was no grade III or IV toxicity during cycle 1.	TMZ and PCB* are given daily from D1 to D20, followed by a break of 8 days. This is one cycle that will be repeated every 28 days over 6 months (= 6 cycles). This period is referred to as the “ adjuvant treatment phase ”. <i>NB: At the physician's discretion TMZ and PCB can be continued beyond the 6 months.</i>
20	PCB	<u>Dosage according to BSA:</u> 50 mg p.o. once daily if BSA < 1.7 100 mg p.o. once daily if BSA ≥ 1.7	

25 On days where both Cilengitide and TMZ and PCB are to be administered, TMZ and PCB are preferably given within 1 hour after completion of the Cilengitide infusion.

During this treatment phase, in case of intolerance to TMZ and PCB after start of study treatment, subjects in the Cilengitide group preferably shall
30 continue to receive Cilengitide as a monotherapy until occurrence of PD or unacceptable toxicity, or until withdrawal for any other reason.

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WEEK 36 TO 78 (= 10 months)		
Agent	Dose/Route/Schedule	Details
Cilengitide	2000 mg i.v. twice weekly	Cilengitide is thus continued as monotherapy for 10 months; this is referred as "Cilengitide maintenance therapy". Subjects will be offered the opportunity, at the discretion of the investigator, to continue Cilengitide beyond week 78 if they desire; this is referred to as "continuing treatment with Cilengitide".

Patent Claims

- 5 1.) Use of at least one specific integrin ligand for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be administered to the patient in one or more doses so that the weekly dose of the at least one specific integrin ligand contained therein sums up to an amount of 10 to 30 millimoles per patient.
- 10 2.) Use according to claim 1, wherein the amount of 10 to 30 millimoles in total is based on the molar weight of the active principle itself.
- 15 3.) Use according to claim 1 or 2, wherein the medicament is administered to the patient for two or more consecutive weeks.
- 20 4.) Use according to one or more of claims 1, 2 and 3, wherein the at least one integrin ligand is selected from the group consisting of α_v integrin inhibitors, preferably $\alpha_v\beta_3$ inhibitors, most preferably cyclo-(Arg-Gly-Asp-DPhe-NMeVal), and the pharmaceutically acceptable derivatives, solvates and/or salts thereof.
- 25 5.) Use according to one or more of the preceding claims, wherein the medicament is to be used in combination with at least one cancer cotherapeutic agent different from the at least one specific integrin ligand, selected from the group consisting of chemotherapeutical agents, cytotoxic agents, immunotoxic agents and/or radiotherapy.
- 30 6.) Use according to one or more of the claims 1 to 4, wherein in the medicament is to be used in combination with at least one cancer cotherapeutic agent which is different from the at least one specific integrin ligand, and which is selected from the group consisting of chemotherapeutical agents, cytotoxic agents, immunomodulating agents and immunotoxic agents, optionally present in form of

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compositions.

- 5 7.) Use according to one or more of the preceding claims, wherein the at least one further cancer-cotherapeutic agent which is different from the at least one specific integrin ligand comprises or is radiotherapy.
- 10 8.) Use according to one or more of the preceding claims, wherein the at least one further cancer-cotherapeutic agent which is different from the at least one specific integrin ligand comprises or is an alkylating agent.
- 15 9.) Use according to one or more of the preceding claims, wherein the medicament is to be used in the treatment of patients showing no partial or no complete methylation of at least one promotor of at least one MGMT gene.
- 20 10.) Use according to one or more of the preceding claims, wherein the at least one specific integrin ligand is selected from cyclo-(Arg-Gly-Asp-DPhe-NMeVal), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, and wherein the medicament is to be administered to the patient in one or more doses so that the weekly dose of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) contained therein sums up to an amount of 6000 - 14000 mg and especially 8000 -14000 mg in total per patient.
- 25 11.) Use according to one or more of the preceding claims, wherein the alkylating agent is one or more compound selected from the group consisting of busulfan, melphalan, carboplatin, cisplatin, cyclophosphamide, dacarbazine, carmustine (BCNU), nimustin (ACNU), lomustine (CCNU), ifosfamide, temozolomide and altretamine.
- 30 12.) Use according to one or more of the preceding claims, wherein the cancer is selected from the group consisting of intracerebral cancer, head-and-neck cancer, rectal cancer, astrocytoma, preferably

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5 astrocytoma grade II, III or IV, glioblastoma, preferably glioblastoma
multiforme (GBM), small cell lung cancer (SCLC) and non-small cell
lung cancer (NSCLC), preferably non-small cell lung cancer (NSCLC),
metastatic melanoma, metastatic androgen independent prostate
cancer (AIPC_a), metastatic androgen dependent prostate cancer
(ADPC_a) and breast cancer.

10 13.) Use of cyclo-(Arg-Gly-Asp-DPhe-NMeVal) for the manufacture of a
medicament for the treatment of cancer, preferably glioblastoma
multiforme (GBM), optionally in combination with an alkylating agent,
preferably temozolomide, and/or radiotherapy, wherein the medicament
is to be administered to the patient for two or more consecutive weeks
at a weekly dose of 8000-12000 mg, preferably of about 10000 mg.

15 14.) Use according to one or more of the preceeding claims, wherein the at
least one specific integrin ligand is cyclo-(Arg-Gly-Asp-DPhe-NMeVal)
and wherein the weekly dose to be administered to the patient is
divided into daily doses of about 2000 mg each.

20 15.) A method for treating cancer, comprising administering to the patient for
two or more consecutive weeks at least one specific integrin ligand in
an total amount of 10 to 30 millimoles per patient and per week,
optionally in combination with an alkylating agent and/or radiotherapy.

25 16.) A method for treating cancer, comprising administering to the patient for
two or more consecutive weeks cyclo-(Arg-Gly-Asp-DPhe-NMeVal), the
pharmaceutically acceptable dervatives, solvates and/or salts thereof, in
one or more doses of about 2000 mg each so that the weekly dose of
30 cyclo-(Arg-Gly-Asp-DPhe-NMeVal) contained therein sums up to an
amount of 6000 - 14000 mg and especially 8000 - 14000 mg in total per
patient and per week, said method optionally additionally comprising the

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administration of one or more alkylating agents and/or radiotherapy.

5 17.) A method according to one or more of the preceeding claims, wherein the at least one cancer-cotherapeutic agent different from the at least one specific integrin ligand of a) is selected from the group consisting of chemotherapeutical agents, cytotoxic agents, immunotoxic agents and/or radiotherapy.

10 18.) Use of at least one integrin ligand a) and at least one cancer-cotherapeutic agent b) different from said integrin ligand for the treatment of cancer in a subject in need thereof, wherein a) is administered 1 to 8 hours (h), preferably 2 to 6 h, and most preferably 3 to 5 h prior to the application of b).

15 19.) Use of at least one specific integrin ligand, comprising cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable dervatives, solvates and/or salts thereof, for the manufacture of a medicament for the treatment of cancer, wherein the medicament is to be used in
20 combination with radiotherapy, preferably external beam radiation, wherein at least the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable dervatives, solvates and/or salts thereof is administered 1 to 10 hours (h), preferably 1 to 6, more preferably 2 to 8, even more preferably 3 to 8 h, even more preferably 3
25 to 6 and especially 4 to 8 h prior to the application of the radiotherapy.

30 20.) Use of at least one specific integrin ligand, comprising cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable dervatives, solvates and/or salts thereof, for the manufacture of a medicament for the treatment of primary brain tumours, wherein the medicament is to be used in combination with radiotherapy, preferably external beam radiation, wherein at least the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable dervatives,

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solvates and/or salts thereof is administered to a patient in an amount of about 8000 mg per week, of about 10000 mg per week, of about 12000 mg per week or of about 14000 mg per week.

5

21.) Use of at least one specific integrin ligand, comprising cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof, for the manufacture of a medicament for the treatment of tumours, wherein the medicament is to be used in combination with temozolomide and/or radiotherapy, preferably external beam radiation, wherein at least the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof is administered to a patient in an amount of 8000 mg to 12000 mg per week.

15

22.) Use according to one or more of the preceding claims, wherein the amount of about 6000 mg per week is administered in a three times weekly administration scheme, the amount of about 8000 mg per week is administered in a four times weekly administration scheme, the amount of about 10000 mg per week is administered in a five times weekly administration scheme, the amount of about 12000 mg per week is administered in a 6 times weekly administration scheme, and the amount of about 14000 mg per week is administered in a seven times weekly administration scheme.

25

23.) Use according to one or more of the preceding claims, wherein the weekly administration schemes comprise the administration of about 2000 mg cyclo-(Arg-Gly-Asp-DPhe-NMe-Val) per day on the days an administration takes place.

30

24.) Use according to one or more of the preceding claims, wherein at least the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof is

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administered 1,5 to 20 hours (h), preferably 2 to 16 h, more preferably 2 to 12 h, even more preferably 2 to 10 h, even more preferably 3 to 10 h and especially 2 to 8 h prior to the application of the radiotherapy.

5

25.) Use according to one or more of the preceding claims, wherein at least the specific integrin ligand cyclo-(Arg-Gly-Asp-DPhe-NMe-Val), the pharmaceutically acceptable derivatives, solvates and/or salts thereof is administered 1 to 10 hours (h), preferably 1 to 6, more preferably 2 to 8, even more preferably 3 to 8 h, even more preferably 3 to 6 and especially 4 to 8 h prior to the application of the radiotherapy.

10

26.) A method or a use according to one or more of the preceding claims, wherein the cancer is selected from intracerebral cancer, head-and-neck cancer, rectal cancer, small cell lung cancer, non-small cell lung cancer, glioblastoma multiforme, small cell lung cancer, non-small cell lung cancer, breast cancer, metastatic melanoma, metastatic androgen independent prostate cancer, metastatic androgen dependent prostate cancer, and brain metastases thereof.

15

20

27.) A method or a use according to one or more of the preceding claims, wherein at least one cancer cotherapeutic agent other than radiotherapy is applied, preferably selected from chemotherapeutical agents, cytotoxic agents and/or immunotoxic agents, more preferably selected from Temozolomide, Cisplatin, Oxaliplatin, Carboplatin, 5-FU, Darcabazine, Procarbazine, Vinblastin, Vincristine, Irinotecan, Taxol, Paclitaxel, Docetaxel, Gemcitabine, Gleevec, Iressa, Tarceva and Nexavar, Herceptin, Bevacizumab, Cetuximab, Nimotuzumab, Sorafenib, Sunitinib and ZD6474 (ZACTIMA™), and even more preferably selected from Temozolomide, Cisplatin, Oxaliplatin, Vinblastin, Taxol, Gemcitabine, Gleevec and Iressa

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- 28.) A method or a use according to one or more of the preceding claims,
wherein additionally a further cancer cotherapeutic agent is applied,
preferably selected from chemotherapeutical agents, cytotoxic agents
5 and/or immunotoxic agents, more preferably selected from
Temozolomide, Cisplatin, Oxaliplatin, Carboplatin, 5-FU, Darcabazine,
Procarbazine, Vinblastin, Vincristine, Irinotecan, Taxol, Paclitaxel,
Docetaxel, Gemcitabine, Gleevec, Iressa, Tarceva and Nexavar,
Herceptin, Bevacizumab, Cetuximab, Nimotuzumab, Sorafenib,
10 Sunitinib and ZD6474 (ZACTIMA™), and even more preferably
selected from Temozolomide, Cisplatin, Oxaliplatin, Vinblastin, Taxol,
Gemcitabine, Gleevec and Iressa.
- 29.) A method or a use according to one or more of the preceding claims,
15 wherein the medicament is to be used in the treatment of patients
having an normal or decreased DNA methylation status.
- 30.) A method or a use according to one or more of the preceeding claims,
wherein the medicament is to be used in the treatment of patients
20 showing no or incomplete methylation of at least one promotor of at
least one MGMT gene.
- 31.) A method or a use according to one or more of the preceeding claims,
wherein the medicament is to be used in the treatment of patients
25 having MGMT protein level of 71-300% or higher of the MGMT
expressed by normal lymphocytes.
- 32.) A method or a use according to one or more of the preceding claims,
wherein the medicament is to be used in the treatment of newly
30 diagnosed cancer, preferably in a first line treatment setting.

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33.) A method or a use according to one or more of the preceding claims,
wherein the radiotherapy comprises or consists of whole brain radiation,
preferably fractionated whole brain radiation.

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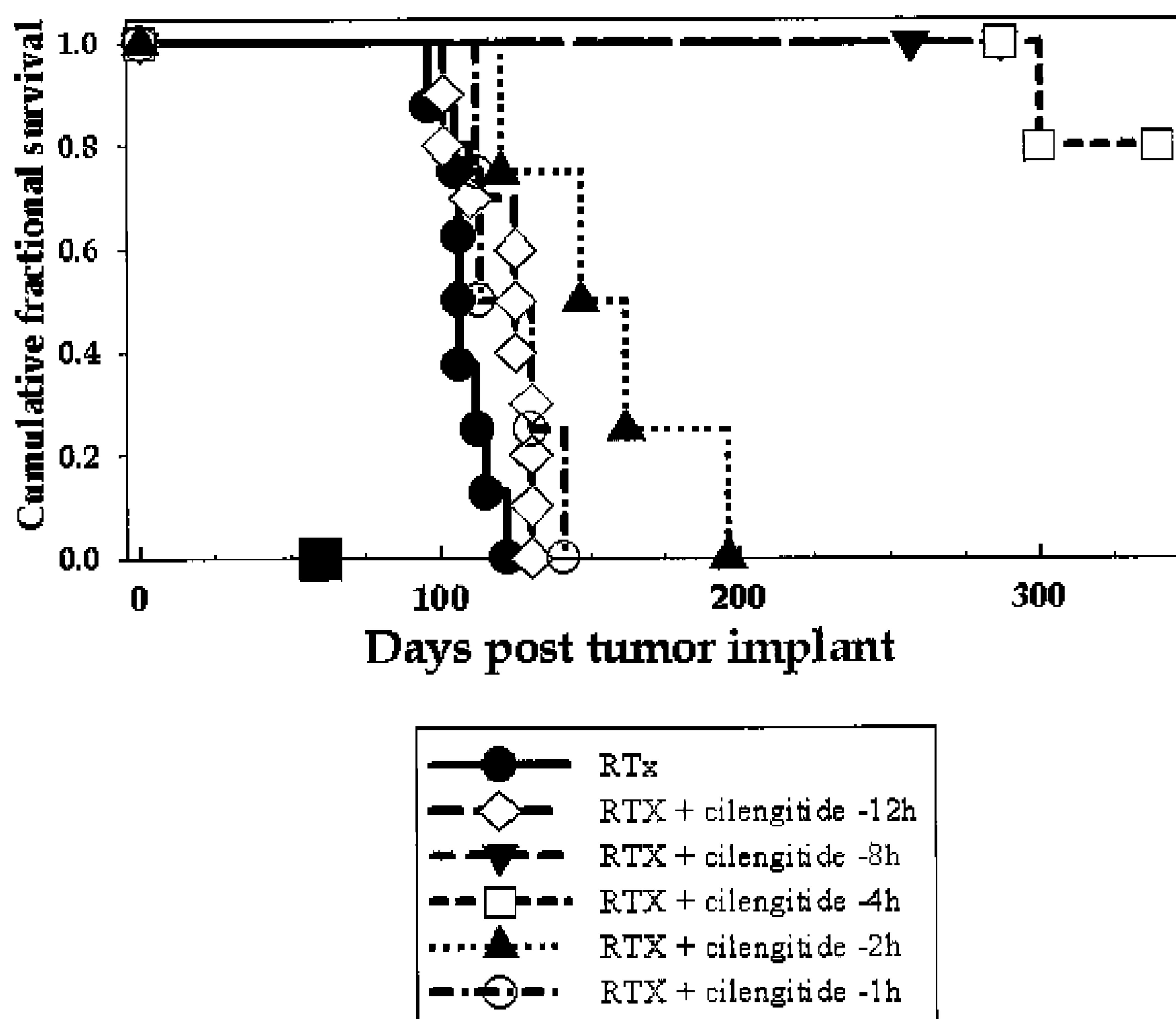
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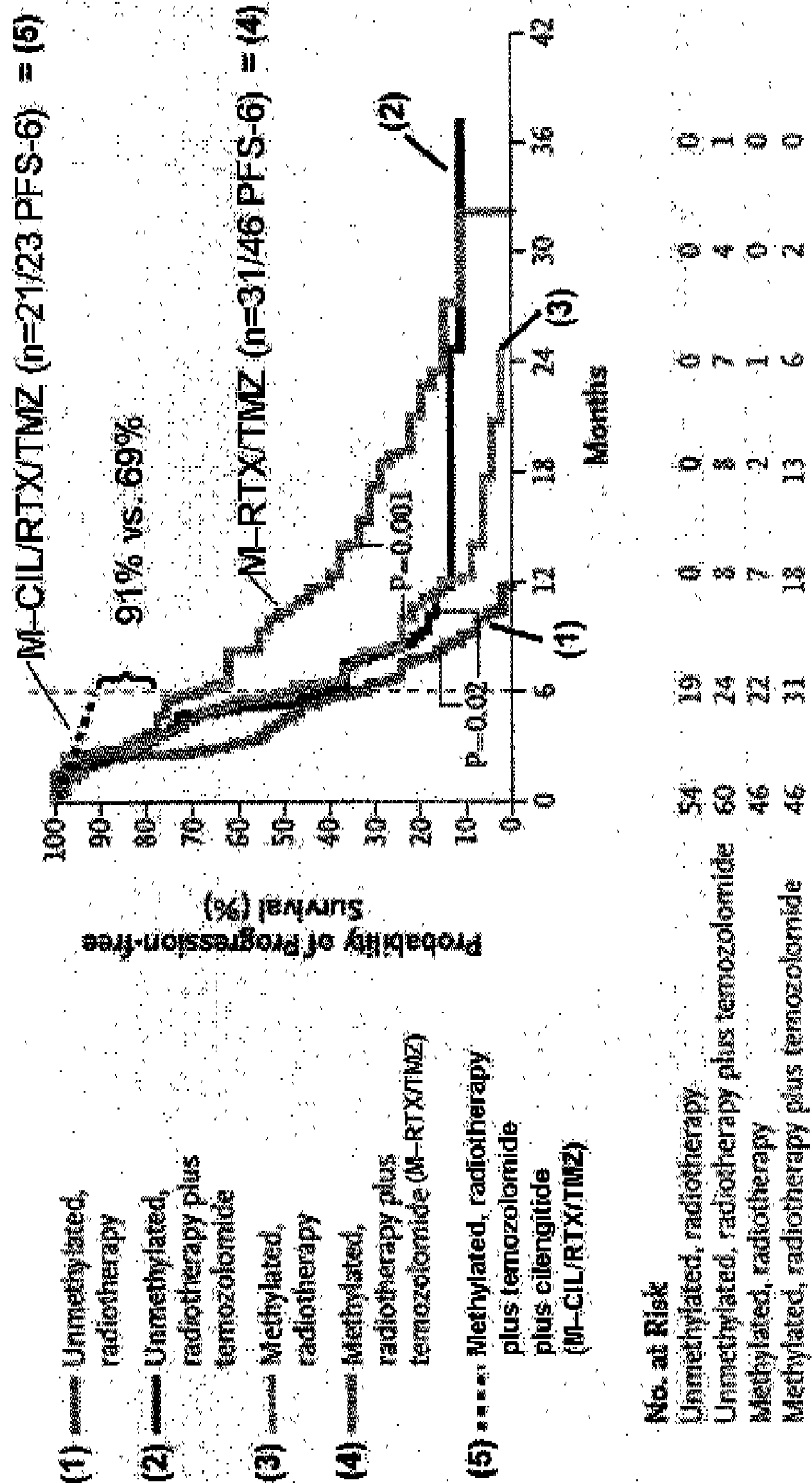
Figure 1

Kaplan Meier survival curves of nude rats bearing orthotopic human glioblastomas U251 derived.

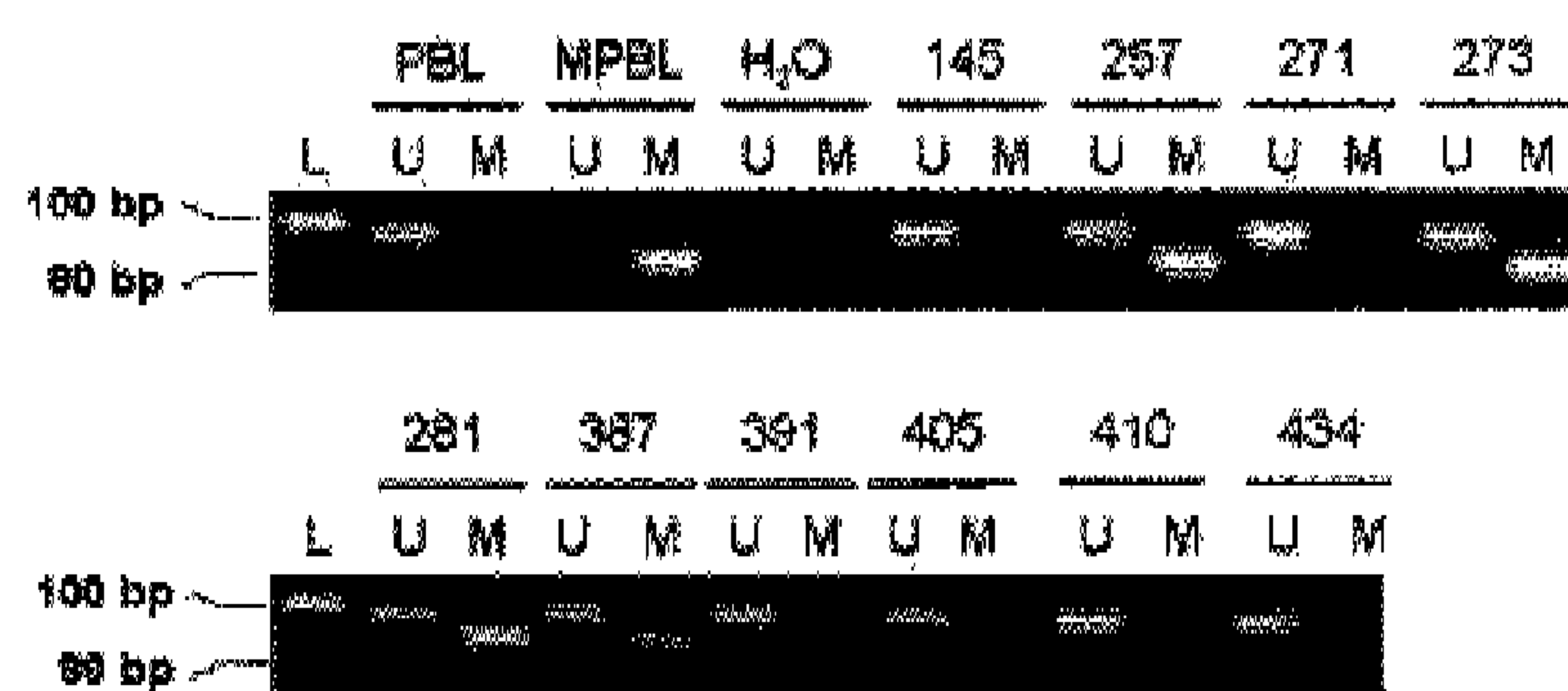


Dark square represents survival of non irradiated animals.

Figure 2



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Figure 3**Figure 4**