

METHODS FOR TREATING GLIOBLASTOMA

FIELD OF THE INVENTION

The present invention relates to methods for treating glioblastoma in a subject in need thereof, wherein a therapeutically effective amount of a radiopharmaceutical compound comprising GRPR antagonist moiety, e.g. [¹⁷⁷Lu]Lu-NeoB, is administered to said subject in combination with radiotherapy and optionally other adjuvant therapies.

BACKGROUND

Glioblastoma (GBM) is the most common and aggressive type of primary brain tumor, with a high mortality rate despite extensive efforts to develop new treatment options.

- 10 The overall age-adjusted incidence of glioblastoma in the United States is 3.22/100.000 persons with a maximum incidence rate between 75 and 79 years of age. It is higher in males and increases with advanced age at diagnosis. Glioblastoma contributes disproportionately to morbidity and mortality, with a 5-year overall relative survival of only 6.8%, which varies by age at diagnosis and by sex (Wen et al 2020, Neuro Oncol; 22(8):1073-1113).
- 15 The survival rate of patients diagnosed with glioblastoma remains low with median overall survival of approximately 15–18 months. glioblastoma has one of the lowest long-term survival rate of malignant brain tumors (Ostrom QT, Cioffi G, Gittleman H, et al (2019) CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. Neuro Oncol; 12(S5):1-10). Once glioblastoma recurs, the median overall survival
- 20 (OS) is estimated to range between 3.5-6 months (Wen PY, Weller M, Lee EQ, et al (2020) Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. Neuro Oncol; 22(8):1073-113).

- The current standard of care (SoC) in newly diagnosed glioblastoma includes the combination of
- 25 the alkylating agent temozolomide with radiotherapy which was approved and has been establish since 2005 based on the results of a large, randomized, phase III trial comparing radiotherapy to radiotherapy with daily temozolomide given concomitantly and followed by temozolomide maintenance alone. The results showed a statistically significant improvement in both progression-free survival (PFS) and overall survival (OS), with a median PFS of 6.9 months in the
- 30 radiotherapy + temozolomide arm vs 5 months in the radiotherapy arm (P<0.001) and a median

OS of 14.6 months vs 12.1 months, respectively ($P < 0.001$) (Stupp et al 2005, N Engl J Med; 352(10):987-96).

Several studies were conducted to improve the standard-of-care regimen using radiotherapy with temozolomide. A phase 3 trial of bevacizumab, a VEGF inhibitor, in newly diagnosed glioblastoma demonstrated improvement of PFS without a corresponding improvement in OS and, on this basis, bevacizumab was not approved for the treatment of patients with newly diagnosed glioblastoma. (Iwamoto et al 2009, Neurology; 73(15):1200-6)

Trials incorporating immunotherapy to the standard-of-care therapy have been conducted in the newly diagnosed setting. Phase 3 clinical trials with nivolumab (NIVO), a PD-1 inhibitor, in newly diagnosed glioblastoma patients with unmethylated MGMT promoter status (CheckMate-498) combined with radiation therapy (Omuro et al 2022, Radiotherapy Combined With Nivolumab or Temozolomide for Newly Diagnosed Glioblastoma With Unmethylated MGMT Promoter: An International Randomized Phase 3 Trial. Neuro Oncol), and in patients with methylated MGMT promoter status (CheckMate-548) (Lim et al 2022, Phase 3 Trial of Chemoradiotherapy With Temozolomide Plus Nivolumab or Placebo for Newly Diagnosed Glioblastoma With Methylated MGMT Promoter. Neuro Oncol) combined with standard-of-care radiotherapy and temozolomide (vs. SoC) both failed to demonstrate improvement in overall survival. CheckMate-498 showed a median OS (mOS) of 13.4 months for patients treated with NIVO+RT and 14.9 months for patients in the temozolomide +RT arm (HR, 1.31; $P = .0037$). Patients with methylated MGMT promoter status who were included in CheckMate-548 showed a mOS of 28.9 months in the NIVO + radiotherapy + temozolomide arm vs. 32.1 months in the placebo+RT+ temozolomide arm, respectively (HR, 1.1).

The use of alternating electric fields (TTFs, tumor treating fields) as an adjunct to temozolomide maintenance in newly diagnosed glioblastoma was approved in US and multiple EU countries based on the results of a Phase 3 trial in which the median OS and PFS were significantly prolonged. Median overall survival was 20.9 months in the TTFields-temozolomide group vs 16.0 months in the temozolomide-alone group (HR, 0.63; $P < .001$) (Stupp et al., JAMA, 2017; 318(23):2306-2316). Despite positive phase 3 results, the use of TTFs remains controversial and they are not widely used in Europe (Lassman et al 2020, Current usage of tumor treating fields for glioblastoma. Neurooncol Adv; 2(1):vdaa069).

Current guidelines continue to recommend treatment of newly diagnosed glioblastoma with RT and concomitant temozolomide followed by temozolomide in maintenance (Nabors et al 2020, J Natl Compr Canc Netw; 18(11):1537-1570; Weller et al 2021, Nat Rev Clin Oncol; 18(3):170-186).

- 5 Hence, there is still a need to provide improved clinical treatments of glioblastoma.

Gastrin-releasing peptide (GRP) is a mammalian bombesin-like peptide that regulates many biological responses mainly in the central and enteric nervous system (Flores et al 2010, Brain Res Bull; 82(1-2):95-8). GRP acts through specific membrane G-protein couple bound receptors (GRPR) which are overexpressed by a variety of cancers including glioma/glioblastoma (Flores et al. 2010, Brain Res Bull; 82(1-2):95-8).

The NeoB peptide is a new generation bombesin analogue which binds to the GRPR with high affinity (half maximal inhibitory concentration (IC₅₀) 1-2 nM, Nock et al *J. Nucl. Med.* 2017; 58(1):75-80) and shows low internalization, consistent with the antagonistic behavior of the peptide. The NeoB peptide contains in its structure a DOTA metal-chelator which allows for radiolabeling with different radionuclides including gallium-68 (for PET imaging), lutetium-177 (for radionuclide therapy) and other relevant radionuclides, which makes the theranostic use of NeoB possible, without affecting receptor affinity, internalization properties or biodistribution. In non-clinical models, [⁶⁸Ga]Ga-NeoB and [¹⁷⁷Lu]-Lu NeoB have shown high affinity to the GRPR which is over-expressed in breast, prostate, gastrointestinal stromal tumors (GIST) and gliomas (including glioblastoma) (Flores et al. 2010, supra, Morgat et al, *J. Nucl. Med.* 2017;58(9):1401-1407), as well as low degree of internalization upon binding to the specific receptor.

The ability of the radiolabeled compound to target the GRPR expressing tumor has been confirmed in in vivo imaging and biodistribution studies in tumor models. [¹⁷⁷Lu]Lu-NeoB is rapidly cleared from the blood, quickly eliminated through the renal system, with no retention in kidneys. Background radioactivity is observed in GRPR-expressing tissues (mostly pancreas), which however decreases over time, consistently with a GRPR antagonist profile. On the contrary, tumor remanence is persistent, with detectable uptake values up to 7 days after injection (Kaloudi A, Lymperis E, Giarika A, Dalm S, Orlandi F, Barbato D, Tedesco M, Maina T, de Jong M, Nock BA. NeoBOMB1, a GRPR-Antagonist for Breast Cancer Theragnostics: First Results of a Preclinical Study with [⁶⁷Ga]NeoBOMB1 in T-47D Cells and Tumor-Bearing Mice. *Molecules.* 2017 Nov 11;22(11):1950. doi: 10.3390/molecules22111950. PMID: 29137110; PMCID: PMC6150197).

SUMMARY

The present disclosure relates to a method for treating glioblastoma in a subject in need thereof by administering to said subject a therapeutically effective amount of a radiopharmaceutical compound in combination with radiotherapy, and optionally, temozolomide, wherein said
5 radiopharmaceutical compound is a compound of formula (I), or pharmaceutically acceptable salts thereof:

C-S-P (I)

wherein:

C is a chelating moiety,

10 P is a GRP receptor antagonist moiety,

S is an optional spacer covalently linking C and P,

and wherein said radiopharmaceutical compound is labelled with a radionuclide M.

The present disclosure is provided in various aspects as outlined in the following:

1. A method of treating glioblastoma in a subject in need thereof, said method comprising
15 administering to said subject a therapeutically effective amount of a radiopharmaceutical compound, in combination with a radiotherapy, wherein said radiopharmaceutical compound is a compound of formula (I), or pharmaceutically acceptable salts thereof:

C-S-P (I)

wherein:

20 C is a chelating moiety,

P is a GRP receptor antagonist moiety,

S is an optional spacer covalently linking C and P,

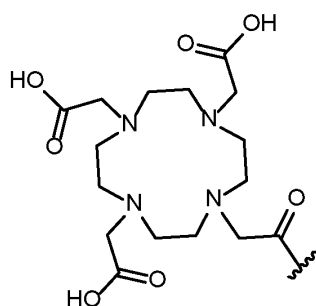
and wherein said radiopharmaceutical compound is labelled with a radionuclide M.

2. The method of embodiment 1, wherein said method further comprises administering a
25 therapeutically effective amount of an alkylating agent.

3. The method of embodiment 2, wherein said alkylating agent is temozolomide.
4. The method of embodiment 2 or 3, wherein said alkylating agent, preferably temozolomide, is administered at an induction phase concomitantly with radiotherapy at a dose of from 50 to 100 mg/m²/day, preferably around 75 mg/m²/day each day, typically for a period from 4 to 8 weeks, preferably 6 weeks.
5. The method of embodiment 4, wherein said alkylating agent, preferably temozolomide, is administered during a maintenance phase following the induction phase, after radiotherapy, at a dose of from 50 to 400 mg/m²/day, preferably from 75 to 300 mg/m²/day, more preferably from 150 to 200 mg/m²/day each day for 5 consecutive days followed by 2 days of rest every 28 days for a period from 20 to 28 weeks, preferably 24 weeks.
6. The method of any one of embodiments 2-5 wherein both radiotherapy and alkylating agent, preferably temozolomide, are initiated the same day, for example from 7 to 10 days after the first administration of the radiopharmaceutical compound.
7. The method of any one of embodiments 2-6, wherein said alkylating agent, preferably temozolomide, is concomitantly administered with the radiotherapy without interruption during an induction phase.
8. The method of any one of embodiments 2-7, wherein said alkylating agent, preferably temozolomide, is daily administered at a first dose during concomitant administration with the radiotherapy, for example for a period of 6 consecutive weeks.
9. The method of any one of embodiments 1-8, wherein said radionuclide M is selected from ⁹⁰Y, ¹³¹I, ¹²¹Sn, ¹⁸⁶Re, ¹⁸⁸Re, ⁶⁴Cu, ⁶⁷Cu, ⁵⁹Fe, ⁸⁹Sr, ¹⁹⁸Au, ²⁰³Hg, ²¹²Pb, ¹⁶⁵Dy, ¹⁰³Ru, ¹⁴⁹Tb, ¹⁶¹Tb, ²¹³Bi, ¹⁶⁶Ho, ¹⁶⁵Er, ¹⁶⁹Er, ¹⁵³Sm, ¹⁷⁷Lu, ²¹³Bi, ²²³Ra, ²²⁵Ac, ²²⁷Ac, ²²⁷Th, ²¹¹At, ⁶⁷Cu, ¹⁸⁶Re, ¹⁸⁸Re, ¹⁶¹Tb, ¹⁷⁵Yb, ¹⁰⁵Rh, ¹⁶⁶Dy, ¹⁹⁹Au, ⁴⁴Sc, ¹⁴⁹Pm, ¹⁵¹Pm, ¹⁴²Pr, ¹⁴³Pr, ⁷⁶As, ¹¹¹Ag and ⁴⁷Sc.
10. The method of embodiment 9, wherein M is ¹⁷⁷Lu.
11. The method of any one of embodiments 1-10, wherein C is obtained by grafting to S or P, a chelating agent selected from 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) (tetraxetan), trizoxetan, 1,4,7,10-tetraazacyclododecane,1(glutaric acid)-4,7,10-triacetic acid (DOTAGA), diethylenetriaminepentaacetic acid (DTPA), nitrilotriacetic acid (NTA), ethylenediaminetetraacetic acid (EDTA), 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid

(DO3A), triethylenetetramine (TETA), 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), NOTAGA, 1-(1,3-carboxypropyl)-4,7-carboxymethyl-1,4,7-triazacyclononane (NODAGA), NODASA, NODAPA, and 1,4-bis(carboxymethyl)-6-[bis(carboxymethyl)]amino-6-methylperhydro-1,4-diazepine (AAZTA, e.g. AAZTA5).

- 5 12. The method of embodiment 11, wherein C is of the following formula,

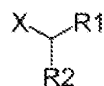


13. The method of any one of embodiments 1-12, wherein P is of the general formula

DPhe-Gln-Trp-Ala-Val-Gly-His-Z

wherein Z is selected from Leu-ψ(CH₂N)-Pro-NH₂ and NH-CH(CH₂-CH(CH₃)₂)₂

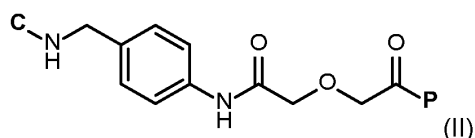
- 10 or Z is



wherein X is NH (amide) and R2 is (CH₂-CH(CH₃)₂) and R1 is the same as R2 or (CH₂N)-Pro-NH₂.

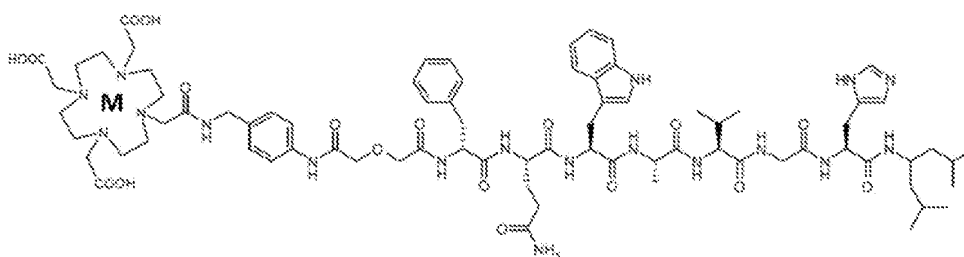
14. The method of embodiment 13, wherein P is DPhe-Gln-Trp-Ala-Val-Gly-His-NH-CH(CH₂-CH(CH₃)₂)₂.

- 15 15. The method of any one of embodiments 1-14, wherein the compound of Formula (I) is the following compound of Formula (II)



wherein C and P are as defined in any one of Claims 1 and 11-14, and wherein the chelating moiety C is complexed with a radionuclide M.

16. The method of any one of embodiments 1-15, wherein the radiopharmaceutical compound is M-NeoB of the following formula (III).



(III),

or pharmaceutically acceptable salts thereof,

- 10 wherein M is a radionuclide, preferably M is ^{177}Lu .

17. The method of any one of embodiments 1-16, wherein said radiopharmaceutical compound is administered 1 to 10 times per treatment, preferably 4 to 10 times per treatment, more preferably 6 to 8 times per treatment.

18. The method of embodiment 17, wherein treatment with said radiopharmaceutical compound comprises an administration interval of 2 weeks, or 3 weeks, or 4 weeks, or 5 weeks or even 6 weeks, preferably 3 or 4 weeks, more preferably every 4 weeks.

19. The method of any one of embodiments 1-18, wherein said radiopharmaceutical compound is administered to the subject in multiple treatments, preferably 2-3 treatments, with a pause of 2-12 months between treatments.

20. The method of any one of embodiments 1-19, wherein said radiopharmaceutical compound is administered at each administration at a dose ranging from 0.925 GBq (25mCi) to 29.6GBq (800 mCi), preferably from 1.48 GBq (40 mCi) to 18.5 GBq (500mCi), preferably from 1.85 GBq

(50mCi) to 14.8 GBq (400mCi), more preferably from 3.7 GBq (100mCi) to 11.1 GBq(300mCi), even more preferably of about 3.7 GBq (100mCi), about 5.55 GBq (150mCi), about 7.4 GBq (200mCi), about 9.25GBq (250mCi), or about 11.1 GBq(300mCi).

21. The method of any one of embodiments 1-20, wherein said radiotherapy comprises irradiating
5 said subject at a total dose of from 40 – 80 Gy, for example 60 Gy.

22. The method of any one of embodiments 1-21, wherein said radiotherapy is conducted at a dose from 1Gy to 4Gy/day, preferably around 2Gy/day, during a period from 3 to 7 days, preferably around 5 days per week during a period from 4 to 8 weeks, preferably for 6 weeks.

23. The method of any one of embodiments 1-22, wherein said radiotherapy is initiated 7-10 days
10 after the first administration of said radiopharmaceutical compound.

24. The method of any one of embodiments 1-23, wherein said subject is newly diagnosed with glioblastoma.

25. The method of any one of embodiments 1-24, wherein said subject has been selected from subjects with positive methylated O-6-methylguanine-DNA methyltransferase promoter status.

15 26. The method of any one of embodiments 1-25, wherein said radiotherapy is whole-brain irradiation.

27. The method of any one of embodiments 1-26, wherein said subject has been selected by SPECT/CT or PET/CT or SPECT/MRI, PET/MRI imaging with the same radiopharmaceutical compound as defined for the treatment, but with an alternate radionuclide or contrast agent
20 suitable for imaging, preferably 68-Gallium, 67-Gallium or 64-Copper, more preferably 68-Gallium, based on detection of said radionuclide in the imaging scan at the tumor region, prior to any surgery, for example, two weeks prior to start of said treatment.

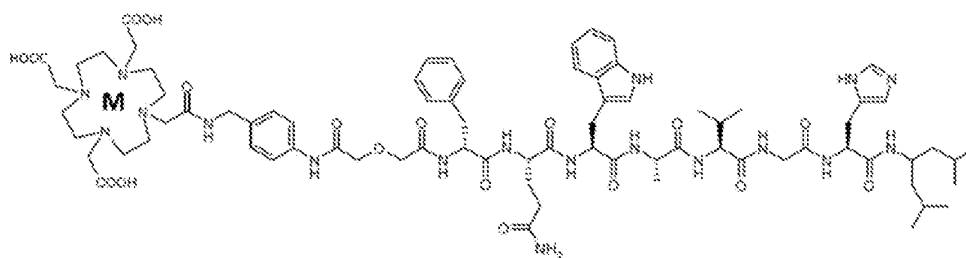
28. The method of embodiment 27, wherein said subject is selected from subjects showing presence of alternate radionuclide or contrast agent enhancement, for example gadolinium
25 enhancement, in a PET/MRI scan at the tumor region, prior to any surgery.

29. The method of any one of embodiments 1-28, wherein said subject is newly diagnosed with glioblastoma and has a positive methylated O-6-methylguanine-DNA methyltransferase promoter status, wherein said radiopharmaceutical compound is administered to said subject in combination with radiotherapy and an alkylating agent, preferably temozolomide, wherein a first

dose of said radiopharmaceutical compound is administered preferably 7 to 10 days prior to initiation of radiotherapy.

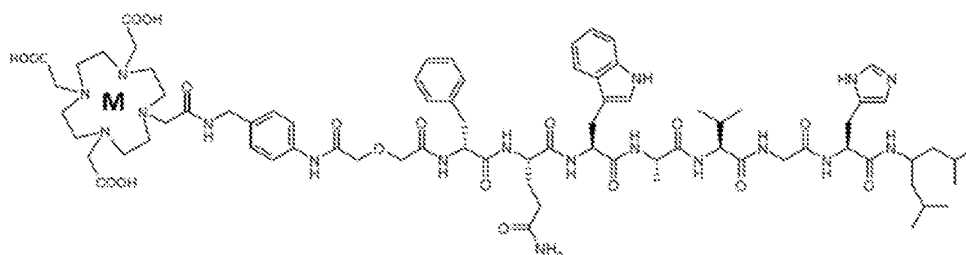
30. The method of any one of embodiments 1-28, wherein said subject is newly diagnosed with glioblastoma and has a negative methylated O-6-methylguanine-DNA methyltransferase promoter status, wherein said radiopharmaceutical compound is administered at least 6 times to said subject in combination with radiotherapy and further in combination with temozolomide, and wherein the administration interval between two administrations of said radiopharmaceutical compound is 4 weeks, and, wherein a first dose of said radiopharmaceutical compound is administered preferably 7 to 10 days prior to initiation of radiotherapy and temozolomide.

10 31. The method of embodiment 29 or 30, wherein said radiopharmaceutical compound is M-NeoB
of the following formula:



wherein M is ^{177}Lu .

32. The method of any one of embodiments 1-30, wherein said radiopharmaceutical compound
15 is M-NeoB of the following formula:



wherein M is ^{177}Lu , and said radiopharmaceutical compound is administered by intravenous infusion at a concentration of 370MBq/mL.

33. A radiopharmaceutical compound for use in a method for treating glioblastoma in a subject in

need thereof, said method comprising administering to said subject a therapeutically effective amount of a radiopharmaceutical compound, in combination with a radiotherapy, wherein said radiopharmaceutical compound is a compound of formula (I), or pharmaceutically acceptable salts thereof:

5 C-S-P (I)

wherein:

C is a chelating moiety,

P is a GRP receptor antagonist moiety,

S is an optional spacer covalently linking C and P,

10 and wherein said radiopharmaceutical compound is labelled with a radionuclide M.

34. The radiopharmaceutical compound for use of embodiment 33, wherein said method further comprises administering a therapeutically effective amount of an alkylating agent.

35. The radiopharmaceutical compound for use of embodiment 34, wherein said alkylating agent is temozolomide.

15 36. The radiopharmaceutical compound for use of embodiment 34 or 35, wherein said alkylating agent, preferably temozolomide, is administered at an induction phase at a dose of from 50 to 100 mg/m²/day, preferably around 75 mg/m²/day each day, typically for a period from 4 to 8 weeks, preferably 6 weeks.

20 37. The radiopharmaceutical compound for use of embodiment 36, wherein said alkylating agent, preferably temozolomide, is administered during a maintenance phase following the induction phase at a dose of from 50 to 400 mg/m²/day, preferably from 75 to 300 mg/m²/day, more preferably from 150 to 200 mg/m²/day each day for 5 consecutive days followed by 2 days of rest every 28 days for a period from 20 to 28 weeks, preferably 24 weeks.

25 38. The radiopharmaceutical compound for use of any one of embodiments 34-37 wherein both radiotherapy and alkylating agent, preferably temozolomide, are initiated the same day, for example from 7 to 10 days after the first administration of the radiopharmaceutical compound.

39. The radiopharmaceutical compound for use of any one of embodiments 34-38, wherein said

alkylating agent, preferably temozolomide, is concomitantly administered with the radiotherapy without interruption during an induction phase.

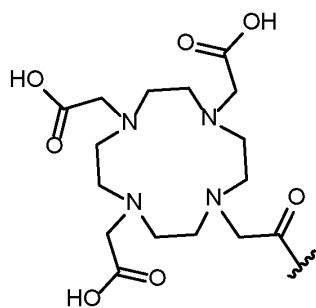
40. The radiopharmaceutical compound for use of any one of embodiments 34-39, wherein said alkylating agent, preferably temozolomide, is daily administered at a first dose during concomitant administration with the radiotherapy, for example for a period of 6 consecutive weeks.

41. The radiopharmaceutical compound for use of any one of embodiments 33-40, wherein said radionuclide M is selected from ^{90}Y , ^{131}I , ^{121}Sn , ^{186}Re , ^{188}Re , ^{64}Cu , ^{67}Cu , ^{59}Fe , ^{89}Sr , ^{198}Au , ^{203}Hg , ^{212}Pb , ^{165}Dy , ^{103}Ru , ^{149}Tb , ^{161}Tb , ^{213}Bi , ^{166}Ho , ^{165}Er , ^{169}Er , ^{153}Sm , ^{177}Lu , ^{213}Bi , ^{223}Ra , ^{225}Ac , ^{227}Ac , ^{227}Th , ^{211}At , ^{67}Cu , ^{186}Re , ^{188}Re , ^{161}Tb , ^{175}Yb , ^{105}Rh , ^{166}Dy , ^{199}Au , ^{44}Sc , ^{149}Pm , ^{151}Pm , ^{142}Pr , ^{143}Pr , ^{76}As , ^{111}Ag and ^{47}Sc .

42. The radiopharmaceutical compound for use of embodiment 41, wherein M is ^{177}Lu .

43. The radiopharmaceutical compound for use of any one of embodiments 33-42, wherein C is obtained by grafting to S or P, a chelating agent selected from 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) (tetraxetan), trizoxetan, 1,4,7,10-tetraazacyclododecane-1(glutaric acid)-4,7,10-triacetic acid (DOTAGA), diethylenetriaminepentaacetic acid (DTPA), nitrilotriacetic acid (NTA), ethylenediaminetetraacetic acid (EDTA), 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (DO3A), triethylenetetramine (TETA), 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), NOTAGA, 1-(1,3-carboxypropyl)-4,7-carboxymethyl-1,4,7-triazacyclononane (NODAGA), NODASA, NODAPA, and 1,4-bis(carboxymethyl)-6-[bis(carboxymethyl)]amino-6-methylperhydro-1,4-diazepine (AAZTA, e.g. AAZTA5).

44. The radiopharmaceutical compound for use of embodiment 43, wherein C is of the following formula:

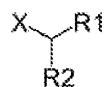


45. The radiopharmaceutical compound for use of any one of embodiments 33-44, wherein P is of the general formula

DPhe-Gln-Trp-Ala-Val-Gly-His-Z

wherein Z is selected from Leu- ψ (CH₂N)-Pro-NH₂ and NH-CH(CH₂-CH(CH₃)₂)₂

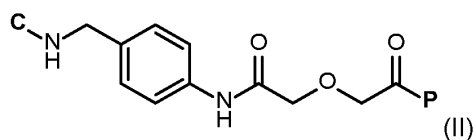
5 or Z is



wherein X is NH (amide) and R2 is (CH₂-CH(CH₃)₂) and R1 is the same as R2 or (CH₂N)-Pro-NH₂.

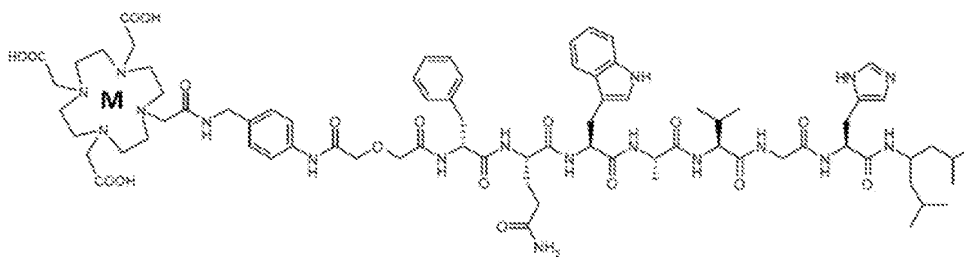
46. The radiopharmaceutical compound for use of embodiment 45, wherein P is DPhe-Gln-Trp-Ala-Val-Gly-His-NH-CH(CH₂-CH(CH₃)₂)₂.

10 47. The radiopharmaceutical compound for use of any one of embodiments 33-46, wherein the compound of Formula (I) is the following compound of Formula (II)



15 wherein C and P are as defined in Claim 1, and wherein the chelating moiety C is complexed with a radionuclide M.

48. The radiopharmaceutical compound for use of any one of embodiments 33-47, wherein the radiopharmaceutical compound is M-NeoB of the following formula (III).



(III),

or pharmaceutically acceptable salts thereof,

wherein M is radionuclide, preferably M is ^{177}Lu .

49. The radiopharmaceutical compound for use of any one of embodiments 33-48, wherein said
5 radiopharmaceutical compound is administered 1 to 10 times per treatment, preferably 4 to 10
times per treatment, more preferably 6 to 8 times per treatment.

50. The radiopharmaceutical compound for use of embodiment 49, wherein treatment with said
radiopharmaceutical compound comprises an administration interval of 2 weeks, or 3 weeks, or
4 weeks, or 5 weeks or even 6 weeks, preferably 3 or 4 weeks, more preferably every 4 weeks.

10 51. The radiopharmaceutical compound for use of any one of embodiments 33-50, wherein said
radiopharmaceutical compound is administered to the subject in multiple treatments, preferably
2-3 treatments, with a pause of 2-12 months between treatments.

52. The radiopharmaceutical compound for use of any one of embodiments 33-51, wherein said
radiopharmaceutical compound is administered at each administration at a dose ranging from
15 0.925 GBq (25mCi) to 29.6GBq (800 mCi), preferably from 1.48 GBq (40 mCi) to 18.5 GBq
(500mCi), preferably from 1.85 GBq (50mCi) to 14.8 GBq (400mCi), more preferably from 3.7
GBq (100mCi) to 11.1 GBq(300mCi), even more preferably of about 3.7 GBq (100mCi), about
5.55 GBq (150mCi), about 7.4 GBq (200mCi), about 9.25GBq (250mCi), or about 11.1
GBq(300mCi).

20 53. The radiopharmaceutical compound for use of any one of embodiments 33-52, wherein said
radiotherapy comprises irradiating said subject at a total dose of from 40 – 80 Gy, for example 60
Gy.

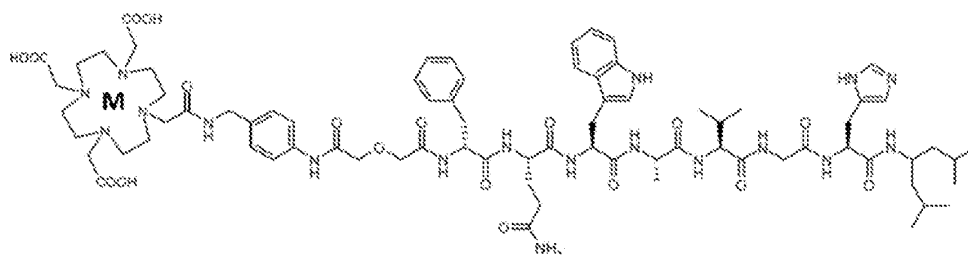
54. The radiopharmaceutical compound for use of any one of embodiments 33-53, wherein said
radiotherapy is conducted at a dose from 1Gy to 4Gy/day, preferably around 2Gy/day, during a
25 period from 3 to 7 days, preferably around 5 days per week during a period from 4 to 8 weeks,
preferably for 6 weeks.

55. The radiopharmaceutical compound for use of any one of embodiments 33-54, wherein said
radiotherapy is initiated 7-10 days after the first administration of said radiopharmaceutical
compound.

56. The radiopharmaceutical compound for use of any one of embodiments 33-55, wherein said subject is newly diagnosed with glioblastoma.
57. The radiopharmaceutical compound for use of any one of embodiments 33-56, wherein said subject has been selected from subjects with positive methylated O-6-methylguanine-DNA methyltransferase promoter status.
58. The radiopharmaceutical compound for use of any one of embodiments 33-57, wherein said radiotherapy is whole-brain irradiation.
59. The radiopharmaceutical compound for use of any one of embodiments 33-58, wherein said subject has been selected by SPECT/CT or PET/CT or SPECT/MRI, PET/MRI imaging with the same radiopharmaceutical compound as defined for the treatment, but with an alternate radionuclide or contrast agent suitable for imaging, preferably 68-Gallium, 67-Gallium or 64-Copper, more preferably 68-Gallium, based on detection of said radionuclide in the imaging scan at the tumor region, prior to any surgery, for example, two weeks prior to start of said treatment.
60. The radiopharmaceutical compound for use of embodiment 59, wherein said subject is selected from subjects showing presence of alternate radionuclide or contrast agent enhancement, for example gadolinium enhancement, in a PET/MRI scan at the tumor region, prior to any surgery.
61. The radiopharmaceutical compound for use of any one of embodiments 33-60, wherein said subject is newly diagnosed with glioblastoma and has a positive methylated O-6-methylguanine-DNA methyltransferase promoter status, wherein said radiopharmaceutical compound is administered to said subject in combination with radiotherapy and an alkylating agent, preferably temozolomide, wherein a first dose of said radiopharmaceutical compound is administered preferably 7 to 10 days prior to initiation of radiotherapy.
62. The radiopharmaceutical compound for use of any one of embodiments 33-60, wherein said subject is newly diagnosed with glioblastoma and has a negative methylated O-6-methylguanine-DNA methyltransferase promoter status, wherein said radiopharmaceutical compound is administered at least 6 times to said subject in combination with radiotherapy and further in combination with temozolomide, and wherein the administration interval between two administrations of said radiopharmaceutical compound is 4 weeks, and, wherein a first dose of said radiopharmaceutical compound is administered preferably 7 to 10 days prior to initiation of

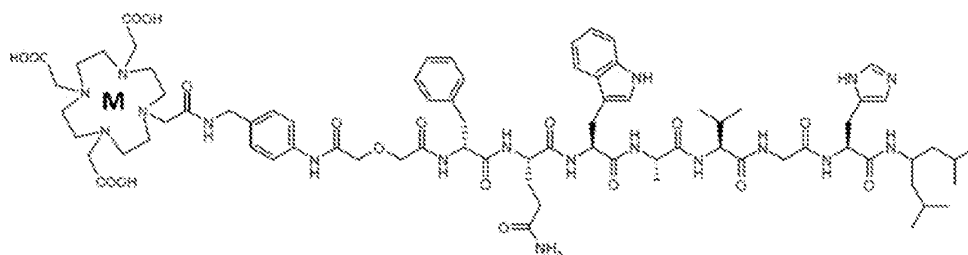
radiotherapy and temozolomide.

63. The radiopharmaceutical compound for use of embodiment 61 or 62, wherein said radiopharmaceutical compound is M-NeoB of the following formula:



5 wherein M is ^{177}Lu .

64. The radiopharmaceutical compound for use of any one of embodiments 1-62, wherein said radiopharmaceutical compound is M-NeoB of the following formula:



10 wherein M is ^{177}Lu , and said radiopharmaceutical compound is administered by intravenous infusion at a concentration of 370MBq/mL.

65. Use of a radiopharmaceutical compound in the manufacture of a medicament for use in a method for treating glioblastoma in a subject in need thereof, said method comprising administering a therapeutically effective amount of said radiopharmaceutical compound to said subject in combination with a radiotherapy, wherein said radiopharmaceutical compound is a compound of formula (I), or pharmaceutically acceptable salts thereof:

C-S-P (I)

wherein:

C is a chelating moiety,

P is a GRP receptor antagonist moiety,

S is an optional spacer covalently linking C and P,

and wherein said radiopharmaceutical compound is labelled with a radionuclide M.

66. The use of embodiment 65, wherein said method further comprises administering a therapeutically effective amount of an alkylating agent.

67. The use of embodiment 66, wherein said alkylating agent is temozolomide.

68. The use of embodiment 66 or 67, wherein said alkylating agent, preferably temozolomide, is administered at an induction phase at a dose of from 50 to 100 mg/m²/day, preferably around 75 mg/m²/day each day, typically for a period from 4 to 8 weeks, preferably 6 weeks.

69. The use of embodiment 68, wherein said alkylating agent, preferably temozolomide, is administered during a maintenance phase following the induction phase at a dose of from 50 to 400 mg/m²/day, preferably from 75 to 300 mg/m²/day, more preferably from 150 to 200 mg/m²/day each day for 5 consecutive days followed by 2 days of rest every 28 days for a period from 20 to 28 weeks, preferably 24 weeks.

70. The use of any one of embodiments 66-69 wherein both radiotherapy and alkylating agent, preferably temozolomide, are initiated the same day, for example from 7 to 10 days after the first administration of the radiopharmaceutical compound.

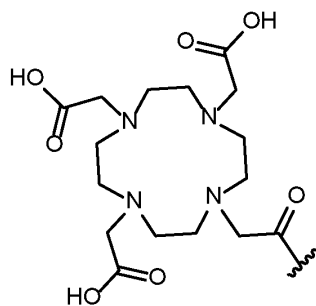
71. The use of any one of embodiments 66-70, wherein said alkylating agent, preferably temozolomide, is concomitantly administered with the radiotherapy without interruption during an induction phase.

72. The use of any one of embodiments 66-71, wherein said alkylating agent, preferably temozolomide, is daily administered at a first dose during concomitant administration with the radiotherapy, for example for a period of 6 consecutive weeks.

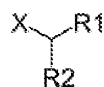
73. The use of any one of embodiments 65-72, wherein said radionuclide M is selected from ⁹⁰Y, ¹³¹I, ¹²¹Sn, ¹⁸⁶Re, ¹⁸⁸Re, ⁶⁴Cu, ⁶⁷Cu, ⁵⁹Fe, ⁸⁹Sr, ¹⁹⁸Au, ²⁰³Hg, ²¹²Pb, ¹⁶⁵Dy, ¹⁰³Ru, ¹⁴⁹Tb, ¹⁶¹Tb, ²¹³Bi, ¹⁶⁶Ho, ¹⁶⁵Er, ¹⁶⁹Er, ¹⁵³Sm, ¹⁷⁷Lu, ²¹³Bi, ²²³Ra, ²²⁵Ac, ²²⁷Ac, ²²⁷Th, ²¹¹At, ⁶⁷Cu, ¹⁸⁶Re, ¹⁸⁸Re, ¹⁶¹Tb, ¹⁷⁵Yb, ¹⁰⁵Rh, ¹⁶⁶Dy, ¹⁹⁹Au, ⁴⁴Sc, ¹⁴⁹Pm, ¹⁵¹Pm, ¹⁴²Pr, ¹⁴³Pr, ⁷⁶As, ¹¹¹Ag and ⁴⁷Sc.

74. The use of embodiment 73, wherein M is ¹⁷⁷Lu.

75. The use of any one of embodiments 65-73, wherein C is obtained by grafting to S or P, a chelating agent selected from 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) (tetraxetan), trizoxetan, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTAGA), diethylenetriaminepentaacetic acid (DTPA), nitrilotriacetic acid (NTA),
 5 ethylenediaminetetraacetic acid (EDTA), 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (DO3A), triethylenetetramine (TETA), 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), NOTAGA, 1-(1,3-carboxypropyl)-4,7-carboxymethyl-1,4,7-triazacyclononane (NODAGA), NODASA, NODAPA, and 1,4-bis(carboxymethyl)-6-[bis(carboxymethyl)]amino-6-methylperhydro-1,4-diazepine (AAZTA, e.g. AAZTA5).
- 10 76. The use of embodiment 75, wherein C is of the following formula,



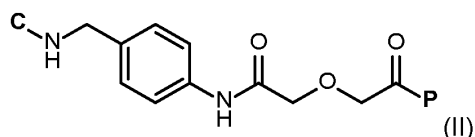
77. The use of any one of embodiments 65-76, wherein P is of the general formula
 DPhe-Gln-Trp-Ala-Val-Gly-His-Z
 wherein Z is selected from Leu-ψ(CH₂N)-Pro-NH₂ and NH-CH(CH₂-CH(CH₃)₂)₂
 15 or Z is



wherein X is NH (amide) and R2 is (CH₂-CH(CH₃)₂) and R1 is the same as R2 or (CH₂N)-Pro-NH₂.

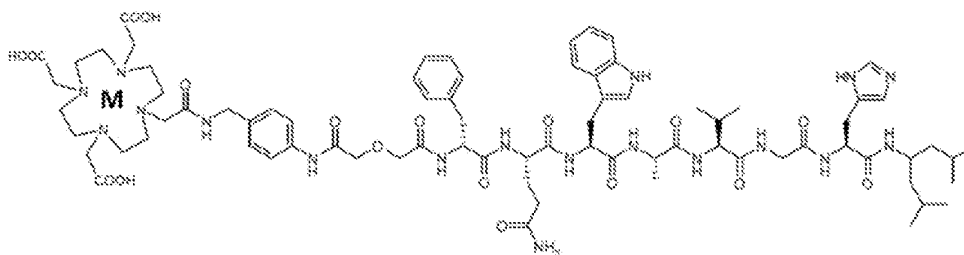
78. The use of embodiment 77, wherein P is DPhe-Gln-Trp-Ala-Val-Gly-His-NH-CH(CH₂-CH(CH₃)₂)₂.

79. The use of any one of embodiments 65-78, wherein the compound of Formula (I) is the following compound of Formula (II)



5 wherein C and P are as defined in any one of Claims 65 and 75-78, and wherein the chelating moiety C is complexed to a radionuclide M.

80. The use of any one of embodiments 65-79, wherein the radiopharmaceutical is M-NeoB of the following formula (III).



10

(III),

or pharmaceutically acceptable salts thereof,

wherein M is radionuclide, preferably M is ^{177}Lu .

81. The use of any one of embodiments 65-80, wherein said radiopharmaceutical compound is administered 1 to 10 times per treatment, preferably 4 to 10 times per treatment, more preferably 6 to 8 times per treatment.

82. The use of embodiment 81, wherein treatment with said radiopharmaceutical compound comprises an administration interval of 2 weeks, or 3 weeks, or 4 weeks, or 5 weeks or even 6 weeks, preferably 3 or 4 weeks, more preferably every 4 weeks.

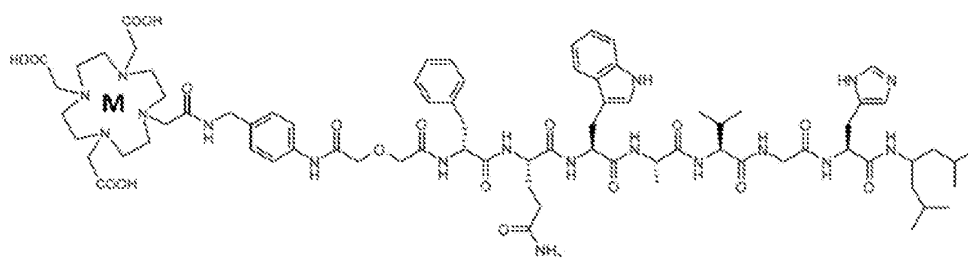
83. The use of any one of embodiments 65-82, wherein said radiopharmaceutical compound is administered to the subject in multiple treatments, preferably 2-3 treatments, with a pause of 2-12 months between treatments.

84. The use of any one of embodiments 65-83, wherein said radiopharmaceutical compound is administered at each administration at a dose ranging from 0.925 GBq (25mCi) to 29.6GBq (800 mCi), preferably from 1.48 GBq (40 mCi) to 18.5 GBq (500mCi), preferably from 1.85 GBq (50mCi) to 14.8 GBq (400mCi), more preferably from 3.7 GBq (100mCi) to 11.1 GBq(300mCi),
5 even more preferably of about 3.7 GBq (100mCi), about 5.55 GBq (150mCi), about 7.4 GBq (200mCi), about 9.25GBq (250mCi), or about 11.1 GBq(300mCi).
85. The use of any one of embodiments 65-84, wherein said radiotherapy comprises irradiating said subject at a total dose of from 40 – 80 Gy, for example 60 Gy.
86. The use of any one of embodiments 65-85, wherein said radiotherapy is conducted at a
10 dose from 1Gy to 4Gy/day, preferably around 2Gy/day, during a period from 3 to 7 days, preferably around 5 days per week during a period from 4 to 8 weeks, preferably for 6 weeks.
87. The use of any one of embodiments 65-86, wherein said radiotherapy is initiated 7-10 days after the first administration of said radiopharmaceutical compound.
88. The use of any one of embodiments 65-87, wherein said subject is newly diagnosed with
15 glioblastoma.
89. The use of any one of embodiments 65-88, wherein said subject has been selected from subjects with positive methylated O-6-methylguanine-DNA methyltransferase promoter status.
90. The use of any one of embodiments 65-89, wherein said radiotherapy is whole-brain irradiation.
- 20 91. The use of any one of embodiments 65-90, wherein said subject has been selected by SPECT/CT or PET/CT or SPECT/MRI, PET/MRI imaging with the same radiopharmaceutical compound as defined for the treatment, but with an alternate radionuclide or contrast agent suitable for imaging, preferably 68-Gallium, 67-Gallium or 64-Copper, more preferably 68-Gallium, based on detection of said radionuclide in the imaging scan at the tumor region, prior to
25 any surgery, for example, two weeks prior to start of said treatment.
92. The use of embodiment 91, wherein said subject is selected from subjects showing presence of alternate radionuclide or contrast agent enhancement, for example gadolinium enhancement, in a PET/MRI scan at the tumor region, prior to any surgery.
93. The use of any one of embodiments 65-92, wherein said subject is newly diagnosed with

glioblastoma and has a positive methylated O-6-methylguanine-DNA methyltransferase promoter status, wherein said radiopharmaceutical compound is administered to said subject in combination with radiotherapy and an alkylating agent, preferably temozolomide, wherein a first dose of said radiopharmaceutical compound is administered preferably 7 to 10 days prior to initiation of radiotherapy.

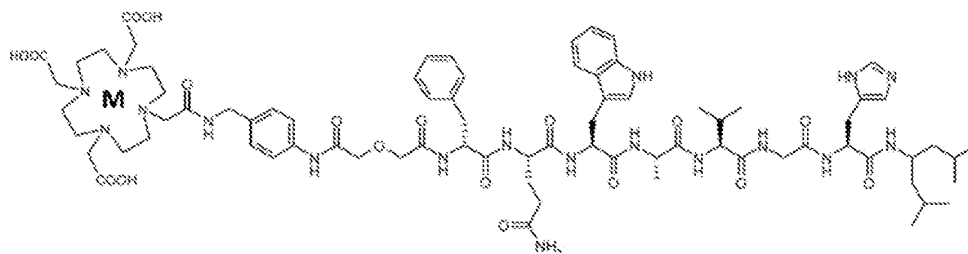
94. The use of any one of embodiments 65-92, wherein said subject is newly diagnosed with glioblastoma and has a negative methylated O-6-methylguanine-DNA methyltransferase promoter status, wherein said radiopharmaceutical compound is administered at least 6 times to said subject in combination with radiotherapy and further in combination with temozolomide, and wherein the administration interval between two administrations of said radiopharmaceutical compound is 4 weeks, and, wherein a first dose of said radiopharmaceutical compound is administered preferably 7 to 10 days prior to initiation of radiotherapy and temozolomide.

95. The use of embodiment 93 or 94, wherein said radiopharmaceutical compound is M-NeoB of the following formula:



wherein M is ^{177}Lu .

96. The use of any one of embodiments 1-94, wherein said radiopharmaceutical compound is M-NeoB of the following formula:



wherein M is ^{177}Lu , and said radiopharmaceutical compound is administered by intravenous infusion at a concentration of 370MBq/mL.

According to one aspect of the disclosure, the combination of radiopharmaceutical radiotherapy, and optionally in combination with other treatments, such as an alkylating agent, e.g. temozolomide, in the method of treatment of the disclosure has been found to be at least additive or preferably synergistic.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 represents the proposed treatment scheme of the clinical study.

10 DETAILED DESCRIPTION

The present disclosure relates to a method for treating glioblastoma in a subject in need thereof by administering a therapeutically efficient amount of a radiopharmaceutical compound to said subject in combination with radiotherapy, and optionally, an alkylating agent, preferably temozolomide.

15 General Definitions

The use of the articles “a”, “an”, and “the” in both the description and claims are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms “comprising”, “having”, “being of”, “including”, and “containing” are to be construed as open terms (i.e., meaning “including but not limited to”) unless otherwise noted.

20 Additionally, whenever “comprising” or another open-ended term is used in an embodiment, it is to be understood that the same embodiment can be more narrowly claimed using the intermediate term “consisting essentially of” or the closed term “consisting of”.

The term “about” or “ca.” has herein the meaning that the following value may vary for $\pm 20\%$, preferably $\pm 10\%$, more preferably $\pm 5\%$, even more preferably $\pm 2\%$, even more preferably $\pm 1\%$.

25 The term “treating” or “treatment” as used herein comprises a treatment relieving, reducing or alleviating at least one symptom in a subject or effecting a delay of progression of a disease. For example, treatment can be the diminishment of one or several symptoms of a disorder or complete eradication of a disorder, such as cancer. Within the meaning of the present disclosure, the term “treat” also denotes to arrest, delay the onset (i.e., the period prior to clinical

manifestation of a disease) and/or reduce the risk of developing or worsening a disease. As used herein in the context the disclosed combination therapy, the term "treatment" encompasses the administration of the radiopharmaceutical compound, optionally in combination with radiotherapy and/or the alkylating agent. Such treatment may comprises one or more administrations of the radiopharmaceutical compound over a determined period.

As used herein "glioblastoma" refers to an aggressive brain tumor belonging to Grade IV astrocytoma brain tumor. The term glioblastoma also includes its variants gliosarcoma, giant cell glioblastoma and small cell glioblastoma. Because cells in this tumor vary in size and shape, i.e. they are pleomorphic, glioblastoma is also called glioblastoma multiforme (GBM).

As used herein the term "radiopharmaceutical" or "radiopharmaceutical compound" refers to a pharmaceutical compound which is labelled with a radionuclide element, typically of metallic nature. Such radiopharmaceutical compound has binding affinity to a specific marker on target cells, for example, a receptor or a tumor antigen, and therefore includes a target ligand (or target binding moiety). Radiopharmaceutical compounds are useful as contrast agents in imaging techniques, such as PET scan or MRI scan, or as therapeutics in nuclear medicine, also known as radioligand therapy (RLT), or PRRT (peptide receptor radionuclide therapy).

Consistent with the International System of Units, "MBq" is the abbreviation for the unit of radioactivity "megabecquerel."

As used herein, "PET" stands for positron-emission tomography.

As used herein, "SPECT" stands for single-photon emission computed tomography.

As used herein, "MRI" stands for magnetic resonance imaging.

As used herein, "CT" stands for computed tomography.

The terms "tumor" and "cancer" are used interchangeably herein, e.g., both terms encompass solid and liquid, e.g., diffuse or circulating, tumors. As used herein, the term "cancer" or "tumor" includes premalignant, as well as malignant cancers and tumors and benign cancers. The term "cancer" as used herein includes primary malignant cells or tumors (e.g., those whose cells have not migrated to sites in the subject's body other than the site of the original malignancy or tumor) and secondary malignant cells or tumors (e.g., those arising from metastasis, the migration of

malignant cells or tumor cells to secondary sites that are different from the site of the original tumor).

As used herein, the phrase "therapeutically effective amount" of a compound refer to an amount of the compound that will elicit a desired therapeutic response in at least a sub-population of subjects, for example, ameliorate the symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, at a reasonable benefit/risk ratio applicable to any medical treatment.

The term "subject" or "patient" as used herein is intended to include animals, which are capable of suffering from or afflicted with a cancer or any disorder involving, directly or indirectly, a cancer.

Examples of subjects include mammals, e.g., humans, apes, monkeys, dogs, cows, horses, pigs, sheep, goats, cats, mice, rabbits, rats, and transgenic non-human animals. In an embodiment, the subject is a human, e.g., a human suffering from, at risk of suffering from, or potentially capable of suffering from cancers.

"Combination therapy" refers to either a therapy comprising administration of a fixed combination in one dosage unit form, or therapies where a radiopharmaceutical compound as disclosed herein and a combination partner, e.g. another drug as explained below, such as an alkylating agent, and/or a radiotherapy, may be administered concurrently or separately, i.e. separately within time intervals, especially where these time intervals allow that the combination partners and/or combination radiotherapies show a cooperative effect with the radiopharmaceutical compound, e.g. synergistic effect. The single components may be packaged in a kit or separately. One or both of the components (e.g., powders or liquids) may be reconstituted or diluted to a desired dose prior to administration.

The terms "co-administration" or "combined administration" or the like as utilized herein are also meant to encompass administration of the selected combination partners, e.g. the radiopharmaceutical compound and the alkylating agent, to a single subject in need thereof (e.g. a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

In the chemical formulae, the wavy line  represents the attachment point of the moiety.

The radiopharmaceutical compound for use in the combination therapy of the disclosure

The radiopharmaceutical compound for use in the methods of the disclosure is a compound of formula (I), or pharmaceutically acceptable salts thereof:

C-S-P (I)

wherein :

5 C is a chelating moiety;

S is an optional spacer covalently linking C and P;

P is a GRP receptor binding moiety covalently linked to C, either directly, or indirectly via S,

wherein said compound is labelled with a radionuclide M.

M is selected among the radioactive isotopes useful in nuclear medicine. Examples of such
10 radioactive isotopes include without limitation ^{90}Y , ^{131}I , ^{121}Sn , ^{186}Re , ^{188}Re , ^{64}Cu , ^{67}Cu , ^{59}Fe , ^{89}Sr , ^{198}Au , ^{203}Hg , ^{212}Pb , ^{165}Dy , ^{103}Ru , ^{149}Tb , ^{161}Tb , ^{213}Bi , ^{166}Ho , ^{165}Er , ^{169}Er , ^{153}Sm , ^{177}Lu , ^{213}Bi , ^{223}Ra , ^{225}Ac , ^{227}Ac , ^{227}Th , ^{211}At , ^{67}Cu , ^{186}Re , ^{188}Re , ^{161}Tb , ^{175}Yb , ^{105}Rh , ^{166}Dy , ^{199}Au , ^{44}Sc , ^{149}Pm , ^{151}Pm , ^{142}Pr , ^{143}Pr , ^{76}As , ^{111}Ag and ^{47}Sc . Preferably, M is ^{177}Lu .

In specific embodiments, M is complexed to the chelating moiety.

15 Preferred GRP receptor binding compounds are GRP receptor antagonist compounds. Examples of GRP receptor antagonist compounds includes RM2, SB3, RM26, BAY-864367, CB-TE2A-AE06, or Pro-BOMB1.

In preferred embodiments, P is a GRP receptor antagonist moiety of the general formula :

Xaa1-Xaa2—Xaa3—Xaa4 —Xaa5—Xaa6—Xaa7—Z; wherein

20 Xaa1 is not present or is selected from the group consisting of amino acid residues Asn, Thr, Phe, 3- (2-thienyl) alanine (Thi), 4-chlorophenylalanine (Cpa) , α -naphthylalanine (α -Nal) , β -naphthylalanine (β -Nal) , 1,2,3,4-tetrahydronorharman-3-carboxylic acid (Tpi), Tyr, 3-iodo-tyrosine (o-I-Tyr) , Trp and pentafluorophenylalanine (5-F-Phe) (all as L- or D-isomers) ; preferably D-Phe,

25 Xaa2 is Gln, Asn or His; preferably Gln,

Xaa3 is Trp or 1, 2, 3, 4-tetrahydronorharman-3-carboxylic acid (Tpi); preferably Trp,

Xaa4 is Ala, Ser or Val; preferably Ala,

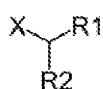
Xaa5 is Val, Ser or Thr; preferably Val,

Xaa6 is Gly, sarcosine (Sar), D-Ala, or β -Ala; preferably Gly,

Xaa7 is His or (3-methyl)histidine (3-Me)His; preferably His,

Z is selected from -NHOH, -NHNH₂, -NH-alkyl, -N(alkyl)₂, and -O-alkyl

5 or Z is



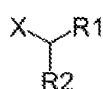
wherein X is NH (amide) or O (ester) and R1 and R2 are the same or different and selected from a proton, an optionally substituted alkyl, an optionally substituted alkyl ether, an aryl, an aryl ether or an alkyl-, halogen, hydroxyl, hydroxyalkyl, amine, amino, amido, or amide substituted aryl or

10 heteroaryl group.

According to an embodiment, P is DPhe-Gln-Trp-Ala-Val-Gly-His-Z; wherein Z is defined as above.

According to an embodiment, P is DPhe-Gln-Trp-Ala-Val-Gly-His-Z wherein Z is selected from Leu- ψ (CH₂N)-Pro-NH₂ and NH-CH(CH₂-CH(CH₃)₂)₂

15 or Z is



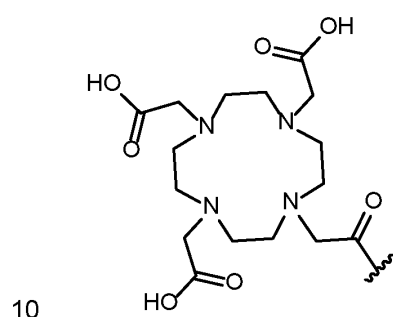
wherein X is NH (amide) and R2 is CH(CH₂-CH(CH₃)₂) and R1 is the same as R2 or different (CH₂N)-Pro-NH₂.

As used herein, the term "chelating moiety" refers to an organic moiety comprising functional
20 groups that are able to form non-covalent bonds with the radionuclide M and, thereby, form stable radionuclide complex.

The chelating moiety in the context of the present disclosure may be obtained by grafting one chelating agent to S or P, said chelating agent being selected among the following list: 1,4,7,10-

tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) (tetraxetan), trizoxetan, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTAGA), diethylenetriaminepentaacetic acid (DTPA), nitrilotriacetic acid (NTA), ethylenediaminetetraacetic acid (EDTA), 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (DO3A), triethylenetetramine (TETA), 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), NOTAGA, 1-(1,3-carboxypropyl)-4,7-carboxymethyl-1,4,7-triazacyclononane (NODAGA), NODASA, NODAPA, and 1,4-bis(carboxymethyl)-6-[bis(carboxymethyl)]amino-6-methylperhydro-1,4-diazepine (AAZTA, e.g. AAZTA5).

In specific embodiments, the chelating moiety C is of the following formula,



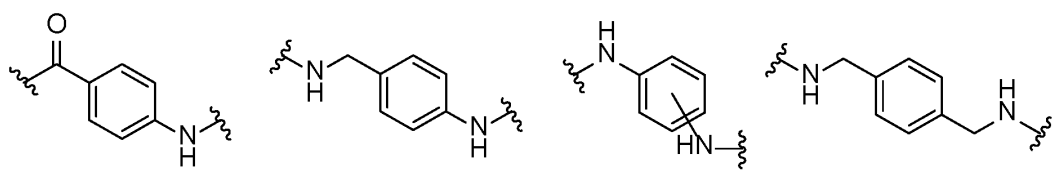
wherein the wavy bond represents the point of attachment of the chelating agent to the spacer S, or to the GRP receptor antagonist P.

Such chelating moiety are either directly linked to the GRP receptor antagonist moiety or connected via a linker molecule or also referred herein as the spacer S. The linking bond(s) is (are) either covalent or non-covalent bond(s) between GRP receptor antagonist (and the spacer) and the chelating moiety, preferably the bond(s) is (are) covalent.

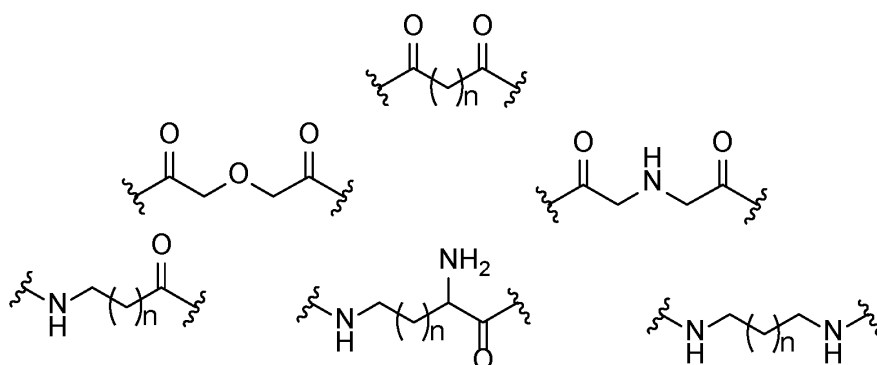
The chelating moiety C is typically bonded to the N-terminal end of the above disclosed peptide derivatives formulae, such as DPhe-Gln-Trp-Ala-Val-Gly-His-Z, optionally via the spacer S.

In specific embodiments, the spacer S is selected from the group consisting of:

20 a) aryl containing residues of any the formulae:

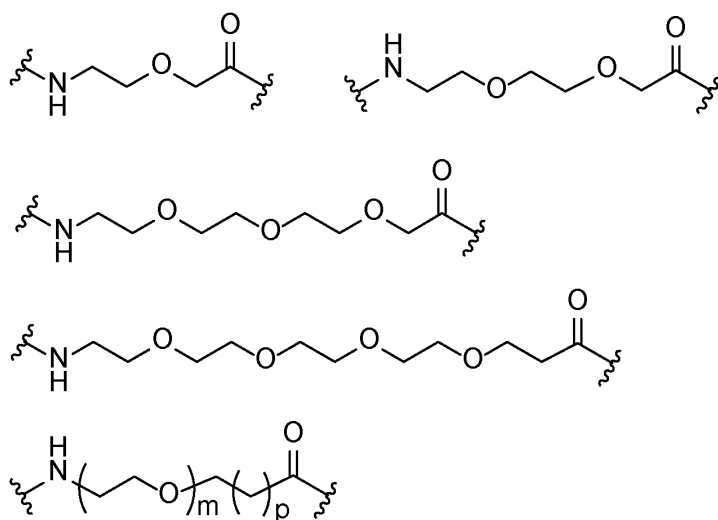


b) dicarboxylic acids, ω -aminocarboxylic acids, ω -diaminocarboxylic acids or diamines derivatives of any of the following formulae:



5 wherein each n represents independently an integer from 0 to 12, for example $n = 0, 1, 2, 3$ or 4 ;

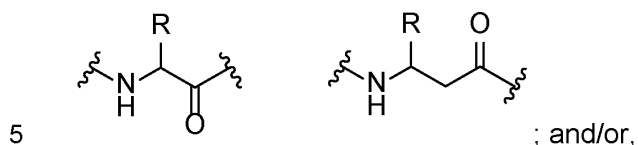
c) PEG spacers of various chain lengths, in particular PEG spacers selected from any the following formulae:



wherein m is an integer from 1 to 36, for example m = 1, 2, 3 or 4, and

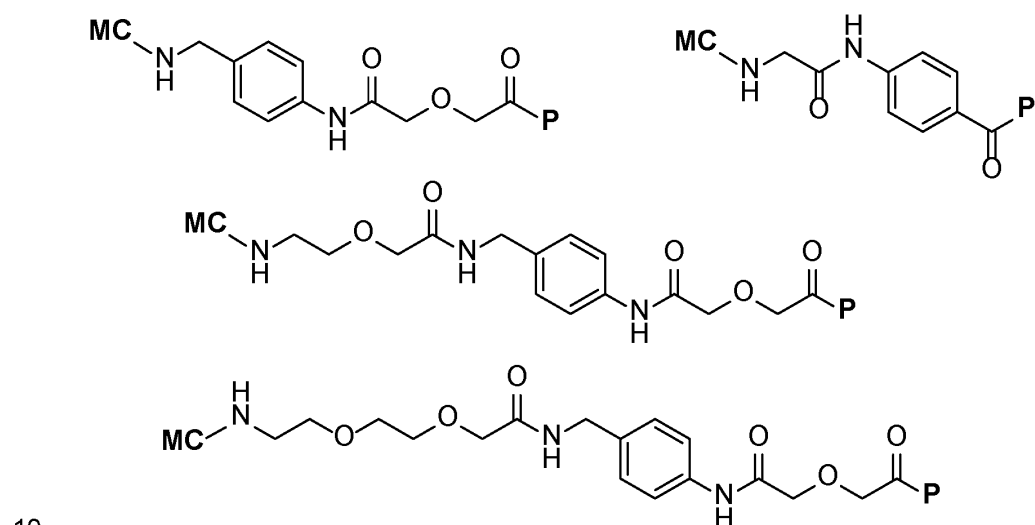
p is an integer from 0 to 5, for example p = 0 or 1;

d) β -amino acid residues, single or in homologous chains of various chain lengths or heterologous chains of various chain lengths, in particular:



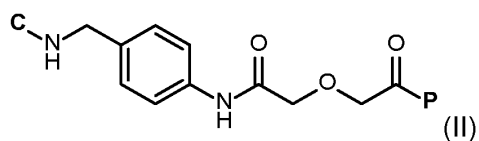
e) any combinations of one or more of a, b, c and/or d.

According to preferred embodiments, the radiopharmaceutical compound for use in the treatment methods of the disclosure is selected from the group consisting of the radiolabelled compounds of the following formulae:



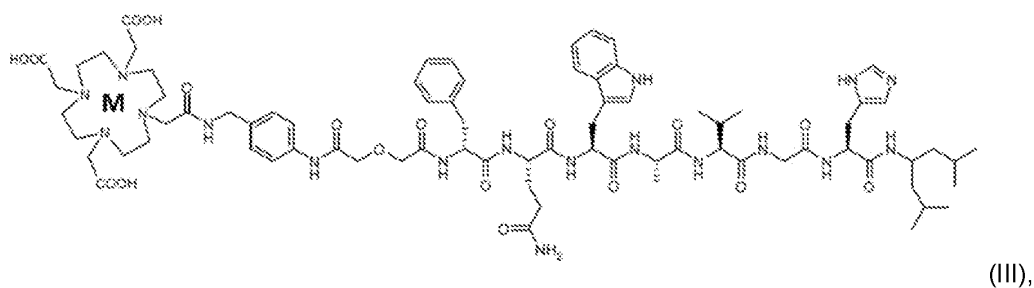
wherein C and P are as defined above, and M is a radioactive isotope complexed to the chelating moiety, preferably M is selected from ^{177}Lu .

Preferably, the radiopharmaceutical compound for use according to the disclosure is the following compound of Formula (II)



wherein C and P are as defined above, and C is complexed to a radionuclide M.

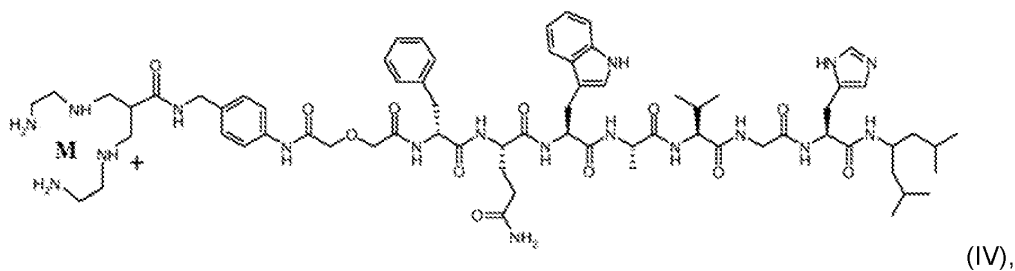
According to a particularly preferred embodiment, the radiopharmaceutical compound for use in the treatment methods is M-NeoB of formula (III):



wherein M is as defined above, preferably M is ^{177}Lu .

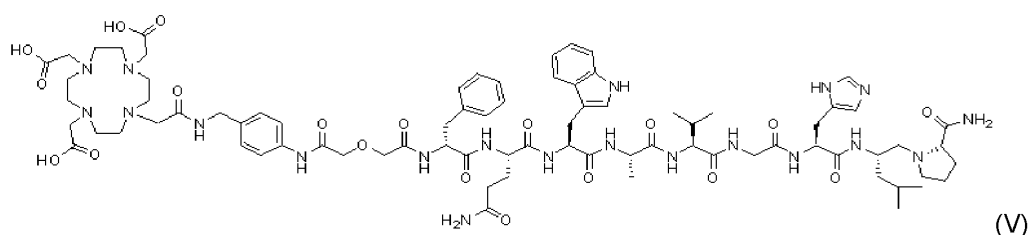
The radiopharmaceutical compound [^{177}Lu]Lu-NeoB refers to the compound of formula (III) wherein M is ^{177}Lu .

According to an embodiment, the radiopharmaceutical compound is the radiolabeled NeoB2 of formula (IV):



wherein M is as defined above, preferably ^{177}Lu .

According to another specific embodiment, the radiopharmaceutical compound for use according to the disclosure is a compound of formula (I) is ProBOMB1 of the following formula (V):



which is radiolabelled with M, preferably ^{177}Lu .

Many embodiments of the disclosure encompass combination therapy preferably with [^{177}Lu]Lu-NeoB as the radiopharmaceutical compound.

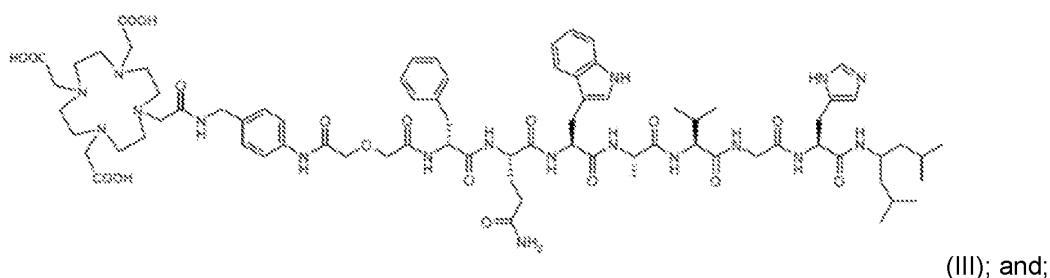
- 5 The radiopharmaceutical compound is for use in treating glioblastoma in a subject in need thereof wherein a therapeutically effective amount of said radiopharmaceutical compound is administered to said subject.

The single components or their precursor, typically non-labelled NeoB, may be packaged in a kit or separately. One or both of the components (e.g., powders or liquids) may be reconstituted or
10 diluted to a desired dose prior to administration.

In specific embodiments, the radiopharmaceutical compound for use in the disclosed combination therapy may be formulated as previously described, for example in WO2021/052960

Typically, the combination therapy comprises administering a pharmaceutical composition consisting of:

- 15 (a) a complex formed by
(ai) radionuclide ^{177}Lu (Lutetium (^{177}Lu), and
(aia) NeoB of formula (III):



- (b) gentisic acid or salts thereof and ascorbic acid or salts thereof;
20 (c) optionally, Macrogol 15 Hydroxystearate ;

- (d) acetate buffer;
- (e) water for injection, and
- (f) at least one other pharmaceutically acceptable excipient, for example a sequestering agent, such as DTPA.

5 Synthesis of the compounds of formula (I), (II), (III), (IV) and (V)

The compounds of formula (I), (II), (III), (IV) and (V) can be synthesized using the methods disclosed in the reference *"Positron Emission Tomography Imaging of the Gastrin-Releasing Peptide Receptor with a Novel Bombesin Analogue"* ACS Omega 2019, 4, 1470–1478.

Further information on the synthesis of compound of formula (V) may be found in
10 WO2021/0608051.

Radiotherapy as used in the combination therapy

In an embodiment, the method of treating glioblastoma in a subject in need thereof includes a step of irradiating the subject with an efficient dose of ionizing radiations, i.e. radiotherapy.

As used herein, the term "radiotherapy" is used for the treatment of diseases of oncological nature
15 with irradiation corresponding to ionizing radiation. Ionizing radiation deposits energy that injures or destroys cells in the area being treated (the target tissue) by damaging their genetic material, making it impossible for these cells to continue to grow.

In specific embodiment, the method of the disclosure comprises exposing the tumor to be treated to an efficient dose of ionizing radiations, wherein said ionizing radiations are photons, e.g. X-rays. Depending on the amount of energy they possess, the rays can be used to destroy cancer
20 cells on the surface of or deeper in the body. The higher the energy of the X-ray beam, the deeper the X-rays can go into the target tissue. Linear accelerators and betatrons produce X-rays of increasingly greater energy. The use of machines to focus radiation (such as X-rays) on a cancer site is called external beam radiotherapy.

25 In an alternative embodiment of the method of treatment according to the disclosure, gamma rays are used. Gamma rays are produced spontaneously as certain elements (such as radium, uranium, and cobalt 60) release radiation as they decompose, or decay.

Ionizing radiations are typically of 2keV to 25000 keV, in particular of 2 keV to 6000 keV (i.e. 6 MeV) or of 2 keV to 1500 keV (such as cobalt 60 source).

A person of ordinary skill in the radiotherapy art knows how to determine an appropriate dosing and application schedule, depending on the nature of the disease and the constitution of the patient. In particular, the person knows how to assess dose-limiting toxicity (DLT) and how to determine the maximum tolerated dose (MTD) accordingly.

- 5 The amount of radiation used in radiation therapy is measured in gray (Gy), and varies depending on the type and stage of cancer being treated. For curative cases, the typical total dose for a solid tumor ranges from 20 to 120 Gy. Many other factors are considered by radiation oncologists when selecting a dose, including whether the patient is receiving chemotherapy, patient co-morbidities, whether radiation therapy is being administered before or after surgery, and the degree of success
10 of surgery.

The total dose is typically fractionated (spread out over time). Amount and schedules (planning and delivery of ionizing radiations, fraction dose, fraction delivery schema, total dose alone or in combination with other anti-cancer agents etc) is defined for any disease/anatomical site/disease stage patient setting/age and constitutes the standard of care for any specific situation.

- 15 A typical conventional fractionation schedule for adults for the methods of the present disclosure may be 1 to 4 Gy per day, preferably around 2Gy/day during a period from 3 to 7 days, preferably around 5 days per week during a period from 4 to 8 weeks, preferably 6 weeks. In specific embodiments, said radiotherapy consists of exposing the subject to a total dose of ionizing radiations from 50 and 70 Gy, for example 60 Gy.

- 20 In other specific embodiments, the subject is exposed to a dose of ionizing radiations per fraction of about 2 to 12 Gy, and the total dose is administered preferably in a maximum of 6 fractions. In another words, said radiotherapy is conducted for 5 consecutive days followed by 2 days of rest for 6 consecutive weeks.

- 25 Preferably, the subject will be exposed to the standard of care to treat patients with glioblastoma, in combination with temozolomide. Such clinical standard comprises subjecting the subject to a dose of 2 Gy/day for 5 days, followed by 2 days of rest, for 6 consecutive weeks with a total dose of 60 Gy.

In specific embodiment where the subject is suffering from glioblastoma, the radiation therapy applied of the herein disclosed methods is a whole-brain radiotherapy (WBRT).

- 30 Alkylating agent as used in the combination therapy

The method of treating glioblastoma in a subject in need thereof optionally includes a step of administering the radiopharmaceutical compound to said subject in combination with radiotherapy and with a therapeutically effective amount of an alkylating agent, preferably temozolomide.

Alkylating agents are divided into different classes, including:

- 5 1. Nitrogen mustards: such as mechlorethamine (nitrogen mustard), chlorambucil, cyclophosphamide (Cytosan®), ifosfamide, and melphalan;
2. Nitrosoureas: such as streptozocin, carmustine (BCNU), and lomustine;
3. Alkyl sulfonates: busulfan;
4. Triazines: dacarbazine (DTIC) and temozolomide (Temodar®); and
- 10 5. Ethylenimines: thiotepa and altretamine (hexamethylmelamine).

As used herein, “temozolomide” refers to a triazines alkylating agent and more specifically compound of formula 3,4-Dihydro-3-methyl-4-oxoimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide and pharmaceutically acceptable salts thereof (CAS number of 85622-93-1). Alkylating agents directly damage DNA (the genetic material in each cell) to keep the cell from reproducing. These
15 drugs work in all phases of the cell cycle and are used to treat many different cancers, including glioblastoma, leukemia, lymphoma, Hodgkin disease, multiple myeloma, and sarcoma, as well as cancers of the lung, breast, and ovary.

In an embodiment, said alkylating agent, preferably temozolomide, is administered at an induction phase at a dose of from 50 to 100 mg/m²/day, preferably around 75 mg/m²/day each day for a
20 period from 4 to 8 weeks, preferably 6 weeks.

As used herein, “induction phase” refers to the period in which said alkylating agent, preferably temozolomide, is administered to the subject concomitantly with the radiotherapy. The induction phase may have a duration of up to 11 weeks, for example from week 1 day 1 to end of week 11 day 7.

25 Treatment of glioblastoma with temozolomide concomitantly with radiotherapy is standard of care and temozolomide may be administered according to the prescribed information for the combination therapy according to the present disclosure.

In an embodiment, both radiotherapy and alkylating agent, preferably temozolomide, are initiated

the same day. In certain aspect the alkylating agent, preferably temozolomide, is concomitantly daily administered with the radiotherapy without interruption. In a more specific embodiment, both radiotherapy and alkylating agent, preferably temozolomide, are initiated the same day, from 7 to 10 days after the first administration of the radiopharmaceutical compound.

- 5 For example, temozolomide is first administered at week 2 until end of week 7, with a dosage of 75mg/m²/day from first to last day of the radiotherapy (external beam radiation therapy).

In certain embodiment, said alkylating agent, preferably temozolomide, is daily administered at a first dosing regimen during the concomitant administration with the radiotherapy (induction phase), for example for a period of 6 weeks, and at a second dosing regimen during a
10 maintenance phase, following the concomitant administration with the radiotherapy for example, for a period up to 24 weeks.

As used herein, "maintenance phase" refers to the period starting after the induction phase or the concomitant administration with the radiotherapy, with an increased dose as compared to dose at the induction phase, for example at week 12 day 1 with a duration of up to 25 weeks.

- 15 In specific embodiments, in this maintenance phase, said alkylating agent, preferably temozolomide, may be administered, at a dose of from 50 to 400 mg/m²/day, preferably from 75 to 300 mg/m²/day, more preferably from 150 to 200 mg/m²/day each day for 5 consecutive days followed by 2 days of rest every 28 days for a period from 20 to 28 weeks, preferably 24 weeks.

In specific embodiment, during the maintenance treatment period, an intra-patient dose
20 escalation with temozolomide treatment will occur. For the same patient, the dosage of temozolomide is 150 mg/m² for 5 days in week 12, and 200 mg/m² for 5 days each in week 16, 20, 24, 28 and 32, if 150 mg/m² temozolomide treatment is well tolerated. More generally, one can follow the approved prescribing information.

The combination therapy

- 25 In a specific embodiment, the method of treating glioblastoma in a subject in need thereof comprises administering to said subject a therapeutically effective amount of a radiopharmaceutical compound as described above, preferably [¹⁷⁷Lu]Lu-NeoB, in combination with a radiotherapy.

In another embodiment, the present disclosure is directed to methods of treating glioblastoma in

a subject in need thereof comprising administering to said subject a therapeutically effective amount of said radiopharmaceutical compound as described above, preferably [¹⁷⁷Lu]Lu-NeoB, in combination with radiotherapy, and further in combination, with a therapeutically effective amount of an alkylating agent, preferably temozolomide.

- 5 The disclosure also relates to the use of radiopharmaceutical compound in the preparation of a drug for use in treating glioblastoma in a subject in need thereof wherein a therapeutically effective amount of said radiopharmaceutical compound, e.g. [¹⁷⁷Lu]Lu-NeoB, is administered to said subject in combination, simultaneously, separately or sequentially, with radiotherapy, and optionally, with a therapeutically effective amount of an alkylating agent, preferably temozolomide.
- 10 In various embodiments of the disclosure, the combination therapy comprises jointly (i) administering to a subject in need thereof therapeutically effective amounts of a pharmaceutical composition comprising a radiopharmaceutical compound (e.g. [¹⁷⁷Lu]Lu-NeoB); and (ii) irradiating the subject with a therapeutically effective dose of ionizing radiations, and, (iii) administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical
- 15 composition comprising an alkylating agent, preferably temozolomide.

As used herein, the term “jointly” means that the therapeutic agents and ionizing radiations may be given separately within time intervals (e.g. in a chronologically staggered manner, especially a sequence-specific manner in such time intervals) to show a (preferably synergistic) interaction (i.e. joint therapeutic effect).

- 20 In various embodiments of the disclosure, a combined administration where the radiopharmaceutical compound (e.g. ¹⁷⁷Lu-NeoB) and the radiotherapy is administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative, e.g. synergistic, effect.

- In an embodiment, the radiopharmaceutical compound, e.g., [¹⁷⁷Lu]Lu-NeoB, is administered 1 to
- 25 20 days, preferably 3 to 15 days, more preferably 7 to 10 days, prior to initiation of radiotherapy.

Administration of the radiopharmaceutical compound may comprise an administration interval of 2 weeks, or 3 weeks, or 4 weeks, or 5 weeks or even 6 weeks, preferably 3 or 4 weeks, more preferably every 4 weeks.

- In specific embodiments, said radiopharmaceutical compound, e.g. [¹⁷⁷Lu]Lu-NeoB is
- 30 administered at least 6 times to said subject in combination with radiotherapy and further in

combination with temozolomide, and wherein the administration interval between two administrations of said radiopharmaceutical compound is 4 weeks, and, wherein a first dose of said radiopharmaceutical compound is administered preferably 7 to 10 days prior to initiation of radiotherapy and temozolomide.

- 5 In specific embodiments, said radiopharmaceutical compound, e.g., [¹⁷⁷Lu]Lu-NeoB, is administered at each administration at a dose ranging from 0.925 GBq (25mCi) to 29.6GBq (800 mCi), preferably from 1.48 GBq (40 mCi) to 18.5 GBq (500mCi), preferably from 1.85 GBq (50mCi) to 14.8 GBq (400mCi), more preferably from 3.7 GBq (100mCi) to 11.1 GBq(300mCi), even more preferably of about 3.7 GBq (100mCi), about 5.55 GBq (150mCi), about 7.4 GBq
10 (200mCi), about 9.25GBq (250mCi), or about 11.1 GBq(300mCi), for example ranging from about 5.55 GBq (150mCi) and about 9.25GBq (250 mCi).

- In specific embodiments, said radiopharmaceutical compound, e.g., [¹⁷⁷Lu]Lu-NeoB, is administered 1 to 10 times per treatment, preferably 4 to 10 times per treatment, more preferably 6 to 8 times per treatment. For example, said radiopharmaceutical compound, e.g., [¹⁷⁷Lu]Lu-
15 NeoB, is administered 6 to 10 times, every 4 weeks, preferably at a dose ranging from 5.55 GBq (150mCi) and 9.25GBq (250 mCi).

A particularly preferred treatment scheme for the combination therapy is shown in Figure 1.

- Advantageously, in specific embodiments, the combined effect of the radiopharmaceutical compound (e.g., [¹⁷⁷Lu]Lu-NeoB) treatment and radiotherapy, and optionally the alkylating agent
20 such as temozolomide, increases the overall survival in subjects to at least 10%, 20%, 30%, 40%, or at least 50% as compared to single radiotherapy or the combined therapy of radiotherapy and the alkylating agent, such as temozolomide

- “Overall survival” (OS) is defined herein as the time from date of first dose to date of death due to any cause in participants of a clinical study, for example as disclosed in Example 1. If a participant
25 is not known to have died, then overall survival is censored at the latest date the participant was known to be alive (on or before the cut-off date). The OS distribution will be estimated using the Kaplan-Meier method.

- In specific embodiments, the combined effect of the radiopharmaceutical compound (e.g., [¹⁷⁷Lu]Lu-NeoB), treatment and radiotherapy, and optionally the alkylating agent such as
30 temozolomide, also increases the progression-free survival to at least 10%, 20%, 30%, 40%, or

at least 50% as compared to single radiotherapy or the combined therapy of radiotherapy and the alkylating agent, such as temozolomide.

The term "Progression-free survival" (PFS), as used herein, is defined as the time from the date of first dose to the date of confirmed progression according to modified RANO or death due to any cause. If no PFS event is observed, PFS is censored at the date of the last adequate tumor assessment prior to data cut-off date and start of new anti-neoplastic therapy, whichever comes first. PFS distribution is estimated using the Kaplan-Meier method.

In certain aspects, the administration of the composition comprising the radiopharmaceutical compound (e.g., [¹⁷⁷Lu]Lu-NeoB) to a subject eligible for said treatment can inhibit, delay, and/or reduce tumor growth in the subject. In certain aspects, the growth of the tumor is delayed by at least 50%, 60%, 70% or 80% in comparison to an untreated control subject. In certain aspects, the growth of the tumor is delayed by at least 80% in comparison to an untreated control subject. In certain aspects, the growth of the tumor is delayed by at least 50%, 60%, 70% or 80% in comparison to the predicted growth of the tumor without the treatment. In certain aspects, the growth of the tumor is delayed by at least 80% in comparison to the predicted growth of the tumor without the treatment. Assessment of the volume of the tumor in glioblastoma may be determined by using the modified Response Assessment in Neuro-Oncology (mRANO) criteria, employing for example international brain tumor imaging protocol allowing both dimensional and volumetric measurements of enhancing tumor in clinical trials. For further details refer to the mRANO criteria (Ellingson BM, Wen PY, Cloughesy TF. Modified Criteria for Radiographic Response Assessment in Glioblastoma Clinical Trials. *Neurotherapeutics*. 2017 Apr;14(2):307-320. doi: 10.1007/s13311-016-0507-6. PMID: 28108885; PMCID: PMC5398984).

In certain aspects, the administration of the composition comprising the radiopharmaceutical compound (e.g., [¹⁷⁷Lu]Lu-NeoB) to a subject eligible for said treatment can increase the length of survival of the subject. In certain aspects, the increase in survival is in comparison to an untreated control subject or control subject with standard of care treatment, such as a combination of radiotherapy and temozolomide for patients newly diagnosed with glioblastoma. In certain aspects, the increase in survival is in comparison to the predicted length of survival of the subject with the standard of care treatment. In certain aspects, the length of survival is increased by at least 3 times, 4 times, or 5 times the length in comparison to an untreated control subject or a control subject with standard of care treatment, such as a combination of radiotherapy and temozolomide for patients newly diagnosed with glioblastoma. In certain aspects, the length of

- survival is increased by at least one week, two weeks, one month, two months, three months, six months, one year, two years, or three years in comparison to control subject with standard of care treatment, such as a combination of radiotherapy and temozolomide for patients newly diagnosed with glioblastoma. In certain aspects, the length of survival is increased by at least one month,
- 5 two months, or three months in comparison to the predicted length of survival of the subject with the standard of care treatment, such as a combination of radiotherapy and temozolomide for patients newly diagnosed with glioblastoma.

Methods for selecting a subject for the combination treatment

In certain embodiments of the disclosure, said glioblastoma is GRPR positive disease.

- 10 In specific embodiments, the subject is selected for the treatment by SPECT/CT or PET/CT or SPECT/MRI, PET/MRI imaging with the same compound as defined for the treatment but wherein M is an alternate radiometal or contrast agent suitable for imaging i.e. imaging radiopharmaceutical compound, based on detection of said radionuclide in the imaging scan at the tumor region, post-surgery.
- 15 Typical radiometal suitable for use as contrast agent in imaging include the following: ^{111}In , $^{133\text{m}}\text{In}$, $^{99\text{m}}\text{Tc}$, $^{94\text{m}}\text{Tc}$, ^{67}Ga , ^{66}Ga , ^{68}Ga , ^{52}Fe , ^{72}As , ^{97}Ru , ^{203}Pb , ^{62}Cu , ^{64}Cu , ^{61}Cu , ^{177}Lu , ^{86}Y , ^{51}Cr , $^{52\text{m}}\text{Mn}$, ^{157}Gd , ^{169}Yb , ^{172}Tm , $^{117\text{m}}\text{Sn}$, ^{123}I , ^{124}I , ^{125}I , ^{18}F , Al^{18}F , ^{152}Tb , ^{155}Tb , ^{82}Rb , ^{89}Zr , ^{43}Sc , ^{44}Sc .

According to a preferred embodiment, the radiometal suitable for imaging is ^{67}Ga , ^{68}Ga or ^{64}Cu , preferably ^{68}Ga .

- 20 In an embodiment, the subject is selected by evaluating the ^{68}Ga -NeoB uptake by PET/CT or PET/MRI scan at the tumor region, e.g. whole brain.

In specific embodiments, said subject eligible for the combination therapy is selected from subjects showing presence of alternate radionuclide or contrast agent enhancement, for example gadolinium enhancement, in a PET/MRI scan at the tumor region, post-surgery.

- 25 Typically, PET scan with the radiopharmaceutical compound labelled with a suitable radiometal for imaging, e.g. [^{68}Ga]Ga-NeoB, may be performed at least 3 days prior the first administration of said radiopharmaceutical compound for the combination treatment.

Thus, the disclosure also relates to methods for determining whether a human subject having glioblastoma can be selected for the combination therapy as disclosed herein, said method comprising the steps of:

1. administering an efficient amount of an imaging radiopharmaceutical compound as a contrast agent for imaging the uptake of said radiopharmaceutical compound,
2. acquiring an image scan by PET/MRI or PET/CT of said patient, and
3. comparing with a control image scan.

The objective of the above selection method is to select the patient with GRPR-positive tumors, i.e. which patients are better responders to the combination therapy of the present disclosure. GRPR-positive tumors may be advantageously detected by evaluating the uptake of a imaging radiopharmaceutical compound by PET/MRI or PET/CT imaging after injection of said imaging radiopharmaceutical compound as contrast agent.

As used herein, a good responder is a patient selected from a patient population which shows statistically better response to a treatment as compared to a randomized patient population (i.e. which has not been selected by the selection step of the present method), and/or which shows less side effects to a treatment as compared to a randomized patient population (i.e. which has not been selected by the selection step of the present method).

In certain aspect, the [^{68}Ga]Ga-NeoB is provided in a kit. The kit may consist of 2 sterile vials as single dose product:

Vial 1: NeoB (active ingredient), 50 μg , powder for solution for injection, to be reconstituted with a solution of gallium-68 chloride ($^{68}\text{GaCl}_3$) in HCl eluted from a $^{68}\text{Ge}/^{68}\text{Ga}$ generator;

Vial 2: Reaction buffer. Vial 2 is to be added to the reconstituted Vial 1.

Examples of such kits are disclosed in WO2021053040.

The volume of [^{68}Ga]Ga-NeoB solution for injection, corresponding to the radioactive dose to be administered, is calculated according to the estimated time of injection, on the basis of the current activity provided by the generator and of physical decay of the radionuclide (half-life = 68 min).

In an embodiment, the selection of subject is performed from 10 to 18 days, preferably around 14 days prior to the first administration of the radiopharmaceutical compound.

In certain embodiment, said imaging radiopharmaceutical is administered at a single intravenous dose from 150 and 250 MBq (4.1-6.8 mCi).

Images of subject's body are then acquired by PET/MRI or PET/CT imaging and the images are compared with a control image to identify whether the lesions identified by conventional imaging, for example by MRI, CT, SPECT or PET, are also identified by said imaging radiopharmaceutical compound uptake, i.e. [⁶⁸Ga]Ga-NeoB uptake. Typically, PET/MRI or PET/CT imaging is performed from 30 to 120 minutes, preferably from 60 to 90 minutes after the intravenous administration of said imaging radiopharmaceutical compound to the subject.

In a specific embodiment of the method, a subject is selected for the combination therapy of the disclosure fulfils the following condition: at least 10%, preferably more than 20%, preferably more than 30%, preferably more than 40%, preferably more than 50%, preferably more than 60%, preferably more than 70%, preferably more than 80% of the lesions as detected by conventional imaging in said subject, for example by MRI, CT, SPECT or PET, are also identified by the imaging radiopharmaceutical compound uptake, e.g. [⁶⁸Ga]Ga-NeoB uptake, as determined by PET/MRI or PET/CT imaging in said subject.

In specific embodiment, the term "lesion" refers to measurable tumor lesions according to Modified RANO criteria as defined in *Ellingson BM, Wen PY, Cloughesy TF. Modified Criteria for Radiographic Response Assessment in Glioblastoma Clinical Trials. Neurotherapeutics. 2017 Apr;14(2):307-320. doi: 10.1007/s13311-016-0507-6. PMID: 28108885; PMCID: PMC5398984.*

Pathologic conditions, including brain tumors such as glioblastoma, and chemical or physical stimuli such as surgery, radiotherapy or some chemotherapy agents, could increase the blood brain barrier (BBB) permeability, disrupting its integrity (Chen et al, *Front. Pharmacol.* 2019; 10:86; Deeken and Löscher, *Clin. Cancer Res.*, 2007;13(6):1663-74). Accordingly, in certain aspect, said subject is selected among the subjects which are newly diagnosed with glioblastoma and which exhibit blood brain barrier (BBB) disruption as determined for example by conventional gadolinium contrast enhancement by magnetic resonance imaging (MRI).

In certain aspect, said subject is newly diagnosed with glioblastoma or suffers from recurrent glioblastoma.

Methylation of O6-methylguanine-DNA methyltransferase (MGMT) promoter has been studied extensively as a predictive and prognostic biomarker in glioblastoma. Methylation of MGMT

promoter leads to loss of MGMT protein expression, which reduces the DNA repair activity of glioma cells and subsequently leads to sensitivity to alkylating agents such as TMZ (Hegi et al 2005, N Engl J Med; 352(10):997-1003, Nabors et al 2020, J Natl Compr Canc Netw; 18(11):1537-1570). Interestingly, MGMT promoter methylation has also been shown to associate
5 with improved outcome to radiotherapy in glioblastoma, in the absence of adjuvant alkylating chemotherapy (Rivera et al 2010, Neuro Oncol; 12(2):116-21).

Accordingly, in specific embodiments, the subject is further selected by evaluating its methylated O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status. Typically, subjects receiving alkylating agent, preferably temozolomide, with the combination
10 therapy as disclosed herein, may be advantageously selected from subjects with positive MGMT promoter status. Methods for determining the MGMT promoter status in the subject are for example disclosed in Mansouri, Alireza et al. ("MGMT promoter methylation status testing to guide therapy for glioblastoma: refining the approach based on emerging evidence and current challenges." *Neuro-oncology* vol. 21,2 (2019): 167-178. doi:10.1093/neuonc/noy132)

15

In certain aspects, in these selected subjects with methylated MGMT promoter, the radiopharmaceutical compound, e.g., [¹⁷⁷Lu]Lu-NeoB, may be administered in combination with concomitant radiotherapy and alkylating agent, preferably temozolomide, during an induction phase, followed by administration of the radiopharmaceutical compound in combination with
20 alkylating agent, preferably temozolomide, during a maintenance phase.

For example, in specific embodiments, said subject is newly diagnosed with glioblastoma and has a positive methylated O-6-methylguanine-DNA methyltransferase promoter status, and said radiopharmaceutical compound, preferably [¹⁷⁷Lu]Lu-NeoB, is administered to said subject in combination with radiotherapy and an alkylating agent, preferably temozolomide, .

25 in specific embodiments, said subject is newly diagnosed with glioblastoma and has a positive methylated O-6-methylguanine-DNA methyltransferase promoter status, wherein said radiopharmaceutical compound is administered at least 6 times to said subject in combination with radiotherapy and further in combination with temozolomide, and wherein the administration interval between two administrations of said radiopharmaceutical compound is 4 weeks, and,
30 wherein a first dose of said radiopharmaceutical compound is administered preferably 7 to 10 days prior to initiation of radiotherapy and temozolomide.

in specific embodiments, said subject is newly diagnosed with glioblastoma and has a positive methylated O-6-methylguanine-DNA methyltransferase promoter status, wherein said radiopharmaceutical compound is administered at least 6 times to said subject in combination with radiotherapy and further in combination with temozolomide, and wherein the administration
5 interval between two administrations of said radiopharmaceutical compound is 4 weeks, and, wherein a first dose of said radiopharmaceutical compound is administered preferably 7 to 10 days prior to initiation of radiotherapy and temozolomide, and

wherein said alkylating agent, preferably temozolomide, is daily administered at a first dosing regimen during the concomitant administration with the radiotherapy (induction phase), for
10 example for a period of 6 weeks, and at a second dosing regimen during a maintenance phase, following the concomitant administration with the radiotherapy for example, for a period up to 24 weeks.

Preferably, during the maintenance treatment period, temozolomide is administered the week before the administration of the radiopharmaceutical compound, typically [¹⁷⁷Lu]Lu-NeoB.
15 Suitable dosage regimen for alkylating agents, and temozolomide in particular, during the induction and maintenance phases are disclosed for example in the previous section related to the alkylating agent for use in the combination therapy.

Hereinafter, further aspects of the combination therapy of the present disclosure are described in more details and specifically with reference to examples, which however are not intended to limit
20 the present invention.

EXAMPLES

Example 1: Clinical study for treating glioblastoma subjects

Provided herein is a protocol example describing a Phase Ib Dose Finding Study Assessing Safety and Activity of [¹⁷⁷Lu]Lu-NeoB in Combination with Radiotherapy and Temozolomide in
25 Subjects with Newly Diagnosed Glioblastoma with MGMT methylated or unmethylated promoter status

Synopsis

Brief title	A Phase 1b dose finding study assessing safety and activity of [¹⁷⁷ Lu]Lu-NeoB in combination with radiotherapy and temozolomide in subjects with newly diagnosed glioblastoma with MGMT methylated or unmethylated promoter status
Sponsor and Clinical Phase	Novartis, Phase Ib
Study type	Interventional
Purpose	This study aims to investigate different doses of [¹⁷⁷ Lu]Lu-NeoB in combination with radiotherapy (RT) and temozolomide (TMZ) in participants with newly diagnosed glioblastoma (GBM) with methylated or unmethylated promoter to assess the safety and efficacy of [¹⁷⁷ Lu]Lu-NeoB in combination with the SoC to identify the recommended dose and to also explore the safety of the PET imaging agent [⁶⁸ Ga]Ga-NeoB and characterize its uptake in the tumor area.
Primary Objective(s)	Dose Escalation Phase: To identify the recommended dose (RD) of [¹⁷⁷Lu]Lu-NeoB in combination with RT and TMZ in participants with newly diagnosed GBM Dose Expansion Phase: To further characterize the safety and tolerability of the [¹⁷⁷Lu]Lu-NeoB RD in combination with RT and TMZ in participants with newly diagnosed GBM
Secondary Objectives	In Dose Escalation: to characterize the safety and tolerability of [¹⁷⁷Lu]Lu-NeoB in combination with RT and TMZ In Dose Escalation and Dose Expansion: to characterize the PK and biodistribution (dosimetry) of [¹⁷⁷Lu]Lu-NeoB in combination with RT and TMZ In the Dose Expansion to assess the preliminary antitumor activity of [¹⁷⁷Lu]Lu-NeoB in combination with RT and TMZ in patients treated at the RD

	In the Dose Escalation and Dose Expansion to evaluate the safety and tolerability of [⁶⁸ Ga]Ga-NeoB
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Trial Design:

1.

Single arm, Phase Ib, multi-center, dose finding study with an expansion phase
2.

newly diagnosed Glioblastoma
3.

open-label
- 5

4. assignment to dose escalation and expansion cohorts
5. review groups: dose escalation committee and study steering committee

Brief Summary:

Glioblastoma (GBM) is the most common and aggressive type of primary brain tumor, with a high mortality rate. The current standard of care (SoC) in newly diagnosed GBM includes the combination of the alkylating agent Temozolomide (TMZ) with Radiotherapy (RT). The hypothesis of this study is to improve the outcome for patients by combining the current standard of care with the radioligand therapy [¹⁷⁷Lu]Lu-NeoB. Patients enrolled into this trial will be treated for up to 32 weeks with the standard regimen TMZ and RT, combined with [¹⁷⁷Lu]Lu-NeoB every 4 weeks. In exceptional cases, where patients tolerate and benefit from [¹⁷⁷Lu]Lu-NeoB, they can receive up to 10 dose administrations, resulting in a treatment duration of up to 37 weeks. During this period, regular safety and efficacy assessments are planned on a weekly basis. The primary objective of this trial is to estimate the recommended dose of [¹⁷⁷Lu]Lu-NeoB in combination with TMZ and RT in participants with newly diagnosed GBM and to characterize the safety and tolerability of this treatment. For this reason, patients will be enrolled and treated in cohorts with increasing dose levels and the totality of available data will be used to define the recommended dose. In an expansion cohort, additional patients will be treated to further characterize the safety and tolerability, as well as to collect preliminary efficacy data from this cohort. Contrast enhanced MRI assessments are recommended to be repeated every 8 weeks and patient reported outcomes (PRO) questionnaires will be used to assess the effect of the study treatment on patient reported symptoms and tolerability. Following treatment, all patients will be followed for up to 5 additional years for safety, progression of disease and survival.

Study Treatment and Treatment Form:

In this study, the term "investigational drug" refers to [⁶⁸Ga]Ga-NeoB as radioligand imaging compound, used to explore GRPR expression and to [¹⁷⁷Lu]Lu-NeoB, used as radioligand therapy. The term "study treatment" refers to the combination of [¹⁷⁷Lu]Lu-NeoB, temozolomide (TMZ) and radiotherapy (RT).

- 5 Study Duration: During the follow-up period of 60 months (from the last dose of study treatment), participants will be monitored for safety (for 8 weeks post last dose of [¹⁷⁷Lu]Lu-NeoB and 4 weeks post last dose of TMZ), for efficacy with contrast-enhanced MRI every 8 weeks until confirmed disease progression. Follow-up for survival will monitored every 12 weeks thereafter.

- 10 **Treatment Duration:** [¹⁷⁷Lu]Lu-NeoB will be given every 4 weeks for up to 6 administrations starting at Week 1 Day 1. In exceptional cases, where participants tolerate and benefit from [¹⁷⁷Lu]Lu-NeoB, they could receive up to 4 additional doses.

- 15 **Treatment of interest:** The term "investigational drug" refers to [⁶⁸Ga]Ga-NeoB as radioligand imaging compound, used to explore GRPR expression and to [¹⁷⁷Lu]Lu-NeoB, used as radioligand therapy. The term "study treatment" refers to the combination of [¹⁷⁷Lu]Lu-NeoB, radiotherapy (RT) and Temozolomide (TMS).

Number of Participants: Approximately 42 participants will be enrolled with a maximum of 21 participants in the dose escalation phase and approximately 15 participants in the dose expansion phase.

Key Inclusion criteria:

- 20 1. Signed informed consent must be obtained prior to participation in the study
2. Histologically confirmed Glioblastoma according to WHO classification established following either a surgical resection or biopsy
3. Adequate bone marrow and organ function as defined by the following laboratory values obtained within ≤ 14 days prior to receiving the study treatment
25 4. Presence of gadolinium enhancement at the tumor region in the pre-surgery MRI
5. Karnofsky performance status ≥ 60%

Key Exclusion criteria

6. Additional, concurrent, or active therapy for Glioblastoma outside of the present study

7. Administration of a radiopharmaceutical with therapeutic intent within a period corresponding to 10 half-lives of the radionuclide used prior to injection of [⁶⁸Ga]Ga-NeoB
8. History or current diagnosis of impaired cardiac function
- 5 9. History of another active malignancy in the previous 3 years prior to study entry
10. Known hypersensitivity to any of the study treatments, their excipients or dacarbazine

Treatment Groups:

- [¹⁷⁷Lu]Lu-NeoB will be given every 4 weeks for up to 6 administrations starting at Week 1 Day 1. Participants who tolerate and benefit from [¹⁷⁷Lu]Lu-NeoB may receive up to 10 doses. TMZ and
- 10 RT administration will begin 7 to 10 days after the first administration of [¹⁷⁷Lu]Lu-NeoB.

TMZ will be administered orally at a dose of 75 mg/m²/day during the concomitant period with RT, as per the approved prescribing information. RT will be delivered at a dose of 2 Gy/day, 5 days per week (followed by 2 resting days) for 6 consecutive weeks.

Example 2: Rationale for the study

15 Nonclinical Biodistribution and Drug Metabolism and Pharmacokinetics

- The biodistribution of [¹⁷⁷Lu]Lu-NeoB has been evaluated in vivo in healthy mice and in tumor-bearing models. NeoB is rapidly cleared from the blood, eliminated through the renal system with no retention in the body. Background radioactivity, observed in GRPR-expressing tissues (mostly pancreas), decreases over time, as expected for an antagonist. On the contrary, tumor uptake
- 20 remains high at all time points evaluated, yielding to increased tumor/background ratios.

- Pathologic conditions, including brain tumors (i.e. Glioblastoma) and chemical or physical stimuli such as surgery, RT, some chemotherapy agents, could increase the blood brain barrier (BBB) permeability, disrupting its integrity (Chen et al 2019 supra, Deeken and Löscher 2007 supra). In brain tumors, the BBB dysfunction is detected on conventional gadolinium contrast- enhanced
- 25 magnetic resonance imaging (MRI) (Sarkaria et al, *Neuro. Oncol.*, 2018 Jan 22;20(2):184-191). In this study, participants showing contrast enhancement with MRI will be selected to ensure that BBB is disrupted and [¹⁷⁷Lu]Lu-NeoB, the investigational agent could permeate through. In addition, [¹⁷⁷Lu]Lu-NeoB will be administered concomitantly to chemoradiation.

- [¹⁷⁷Lu]Lu-NeoB induces cellular damage mainly through free radical formation in GRPR-positive
- 30 tumor and neighboring cells.

Based on the results of *in vitro* drug-drug interaction (DDI) studies, [¹⁷⁷Lu]Lu-NeoB is not considered to have a potential for CYP- or transporter-mediated drug-drug interactions.

Toxicology

Non-clinical studies were conducted with the non-radioactive surrogate [¹⁷⁵Lu]Lu-NeoB formulation and support the absence of pharmacological activity of the NeoB peptide. No adverse effects have been observed in the safety pharmacology studies. Similarly, no signs of toxicity have been reported after either the acute or repeated administrations of [¹⁷⁵Lu]Lu-NeoB confirming the safety of the non-radioactive molecule.

Clinical Experience with [¹⁷⁷Lu]Lu-NeoB

NeoRay (EUDRACT no. 2018-004727-37) is an ongoing phase I/IIa, open-label, multi-center study, to evaluate the safety, tolerability, whole-body distribution, radiation dosimetry and anti-tumor activity of [¹⁷⁷Lu]Lu-NeoB administered in patients with advanced solid tumors known to overexpress GRPR.

In the NeoRay study, as of October 11th 2022, [¹⁷⁷Lu]Lu-NeoB has been administered to 11 patients. Patients included in the first cohort received a first dose (Cycle 1) of [¹⁷⁷Lu]Lu-NeoB of 1.85 GBq (50 millicurie (mCi)). An intra-patient dose escalation to 150 mCi [¹⁷⁷Lu]Lu-NeoB was implemented from Cycle 2 onwards, based on clinical dosimetry in Cycle 1. Each treatment cycle has a duration of 6 weeks.

Dose Level 1 (50 mCi in cycle 1 and 150 mCi in subsequent cycles) has been assessed in 3 patients affected by breast, prostate and GIST cancer, respectively. Two patients received 2 cycles and 1 patient received 6 cycles. Overall treatment was well tolerated with no dose limiting toxicities (DLTs) or SAEs reported.

Dose Level 2 evaluated 300 mCi per cycle and has enrolled 4 patients, 2 with prostate cancer and 2 with GIST. Two patients have received 1 cycle, 1 patient received 2 cycles and 1 patient received 3 cycles. Two out of the 4 enrolled patients experienced DLTs (anemia grade 3 in both patients and encephalopathy grade 3 in one). All these events have resolved. One of the anemia grade 3 events occurred in a prostate cancer patient with extensive bone metastasis and ongoing grade 2 anemia at screening (for which the subject also received red cell transfusion before starting treatment); the patient developed grade 3 anemia at day 36 after infusion and later grade 4 thrombocytopenia while in progressive disease; the patient discontinued treatment, anemia

temporarily improved to grade 2 with supportive treatment while grade 4 thrombocytopenia was ongoing at the time of death, which occurred due to progressive disease. Two DLTs were recorded for a patient affected by GIST (grade 3 anemia and grade 3 encephalopathy) with onset within one week from treatment administration of the first treatment dose. The patient had
5 extensive pelvic bone metastasis, and grade 1 anemia at baseline. The patient was noted to have left sided facial paresis and altered mental changes concomitantly with grade 2 vomiting and grade 3 hyponatremia; brain MRI ruled out stroke and brain metastases. Three days later, the patient also developed seizures. The patient was undergoing treatment with very high doses of diazepam that were interrupted a few days after [¹⁷⁷Lu]Lu-NeoB infusion, raising the suspicion of
10 withdrawal syndrome as a confounding factor. No other significant toxicities were reported, patient only received one [¹⁷⁷Lu]Lu-NeoB infusion.

With the observed incidence of DLTs at dose level 2, a dose de-escalation to 250 mCi (dose level 3) was decided in alignment with the protocol. Dose level 3 was evaluated in 4 patients (2 affected by GIST, 1 by prostate cancer and 1 by glioblastoma). The glioblastoma patient received
15 3 cycles, one of the GIST patients received 2 cycles and both patients discontinued per disease progression while the other 2 patients (GIST and prostate cancer) have received 2 cycles each and treatment is still ongoing. Overall treatment was very well tolerated with the majority of the reported AEs being mild/moderate, with no DLTs and no SAEs reported.

Across the dose levels assessed, two prolonged disease stabilizations were observed:
20 approximately one year in a GIST patient and five months in a patient with prostate cancer .

Out of the 11 treated patients in the study, 3 patients completed treatment, 2 patients discontinued due to AE, 3 discontinued due to progressive disease (PD), 1 patient decided to stop treatment, and 2 patients are ongoing.

Preliminary blood-radioactivity PK of [¹⁷⁷Lu]Lu-NeoB from NeoRay showed a quick elimination
25 from systemic circulation with a geometric mean elimination half-life of ~60-80 hours and an average effective half-life of ~48 hours. Radio-HPLC data shows sign of metabolism in systemic circulation and urine (likely pharmacologic inactive metabolites unable to bind to the receptor) however cumulative excretion of activity indicates that radioactivity is primarily (≥80% on average) excreted via the kidneys within 24-48 hours.

Preliminary dosimetry results demonstrate favorable biodistribution with low uptake in organs
30 considered to be at risk due to GRPR-expression, such as the pancreas, or due to RLT, such as

the red marrow, and the route of excretion, such as the kidneys. Dose normalized mean absorbed doses (rounded to 2 significant digits) across all investigated dose levels in Gy/GBq ($\pm$ SD, n=10) were 0.11 ± 0.059 (kidneys), 0.019 ± 0.0066 (red marrow), 0.063 ± 0.038 (pancreas), 0.011 ± 0.0034 (testes, n=7), 0.021 ± 0.0077 (ovaries, n=3) and 0.72 ± 0.94 (all tumor lesions, n=18), respectively.

Given the safety and biodistribution profile at 250 mCi, a re-escalation to 300 mCi was decided as per protocol. The study is ongoing and recruiting patients to receive the dose level of 300 mCi per cycle.

Study update as of June 7, 2023

As of Jun 7th, 2023, [¹⁷⁷Lu]Lu-NeoB has been administered to 17 patients as per Table 1. Patients included in the first cohort received a first dose (Cycle 1) of [¹⁷⁷Lu]Lu-NeoB of 50 mCi (1.85 GBq). In Dose level (DL) 1, an intra-patient dose escalation to 150 mCi [¹⁷⁷Lu]Lu-NeoB was implemented based on clinical dosimetry in Cycle 1.

Table 1. Patients enrolled across cohorts in NeoRay

	Dose Level 1 (50 and 150mCi)	Dose Level 2 (300 mCi)	Dose Level 3 (250mCi)
N patients enrolled	3	5	9
Tumor type	1 Breast cancer 1 Prostate cancer 1 GIST	2 Prostate cancer 2 GIST 1 Glioblastoma	2 Prostate cancer 6 GIST 1 Glioblastoma
N cycles completed	2 for 2 patients 6 for 1 patient	1 for 3 patients 2 for 1 patient 3 for 1 patient	3 in 3 patients 2 in 5 patients 1 in 1 patient

Cut-off date 07-Jun-2023

DL1 (50 mCi in cycle 1 and 150 mCi in subsequent cycles) did not lead to any significant toxicity (no Serious Adverse Events (SAE)). The patient with breast cancer enrolled in this cohort was a 54-year old woman with a stage IV HR+/HER2+ invasive ductal carcinoma with multiple bone metastasis first diagnosed on May-2018. The patient received prior mastectomy, radiotherapy, and multiple lines of therapies (including palbociclib + ET, trastuzumab, pertuzumab, fulvestrant, capecitabine, and everolimus + exemestane) prior to enrolling in the study. The patient discontinued study treatment after 2 administrations of [¹⁷⁷Lu]Lu-NeoB due to disease progression.

- In the second cohort of patients receiving dose level 2 (300 mCi) two out of the 4 enrolled patients experienced dose limiting toxicities (DLTs) (anemia grade 3 in both patients and encephalopathy grade 3 in one). All these events have resolved.
- With the observed incidence of DLTs at dose level 2, a dose de-escalation to 250 mCi (dose level 3) was decided in alignment with the protocol.
- Dose level 3 evaluated 250 mCi in 4 patients initially and treatment was overall well tolerated with the majority of the reported AEs being mild/moderate, with no DLTs and no SAEs reported. Given the overall favorable safety profile of DL 3, a dose re-escalation to 300 mCi for cohort 4 was decided. Only one patient with GBM was enrolled and developed moderate (grade 2) nausea, severe (grade 3) vomiting 5 days after the first dose of study treatment and 'neurological decline' (grade 3) (preferred term: nervous system disorder) leading to hospitalization the following day. All the events were considered serious and probably related to [¹⁷⁷Lu]Lu-NeoB by the investigator. Neurological decline has met the definition of DLT. Twelve days after the first dose of the study treatment, a new event of grade 2 nausea and grade 3 vomiting developed while the AE of nervous system disorder worsened to grade 4. While the events of nausea and vomiting rapidly resolved the day after, the event of nervous system disorder further worsened to grade 4 despite the increase of the dexamethasone therapy, led to treatment discontinuation and was ongoing at the time of patient's death due to active euthanasia. Considering that the very first patient treated in this new cohort at 300 mCi experienced a DLT (neurological decline) and taking into account the other 2 patients who experienced DLTs (anemia and encephalopathy) in the prior cohort at 300 mCi (DL 2), the dose was de-escalated as per protocol to 250 mCi (DL 3) and cohort 5 was opened for enrollment. As of Jun 7th, 2023, in cohort 5 with 250 mCi dose (DL 3) a total of 5 patients were enrolled of which 4 were with GIST and 1 patient with prostate cancer indications. None of the patients in cohort 5 experienced any DLT or SAE. Reported AEs were mild or moderate in severity. Laboratory abnormalities of $\geq$ grade 2 were non clinically significant.
- Across the dose levels assessed, two prolonged disease stabilization were observed in cohort 1 (50 mCi and 150 mCi) (approximately one year in a GIST patient and five months in a prostate cancer patient).
- Out of the 17 treated patients in the study, 4 patients completed treatment, 2 patients discontinued due to AEs, 7 discontinued due to PD, 3 patients discontinued due to investigator/patient decision, and 1 patient is ongoing.

- Preliminary blood-radioactivity pharmacokinetics of [^{177}Lu]Lu-NeoB from NeoRay showed a quick elimination from systemic circulation with a geometric mean elimination half-life of ~55-80 h and an average effective half-life of ~44 h. Radio-HPLC data shows metabolites in systemic circulation and urine (likely pharmacologically inactive metabolites unable to bind to the receptor) and cumulative excretion of activity indicates that radioactivity is still primarily ($\geq 80\%$ on average) excreted via the kidneys within 24-48 hours. Metabolites will be investigated in plasma.
- Preliminary dosimetry results demonstrate favorable biodistribution with low uptake in organs considered to be at risk due to GRPR-expression, such as the pancreas, or due to RLT, such as the red marrow, and the route of excretion, such as the kidneys. Dose normalized observed mean absorbed doses (rounded to 2 significant digits) from all cohorts in Gy/GBq ($\pm$ SD, $n=13$) were 0.10 ± 0.056 (kidneys), 0.018 ± 0.0076 (red marrow), 0.056 ± 0.038 (pancreas), 0.011 ± 0.0041 (testes, $n=10$), 0.021 ± 0.0094 (ovaries, $n=3$) and 0.53 ± 0.84 (all tumor lesions, $n=28$), respectively.
- Given the overall favorable safety profile of DL 3, a dose re-escalation to 300 mCi for cohort 4 was decided. Only one patient with GBM was enrolled and developed moderate (grade 2) nausea, severe (grade 3) vomiting 5 days after the first dose of study treatment and 'neurological decline' (grade 3) (PT: nervous system disorder) leading to hospitalization the following day. All the events were considered serious and probably related to [^{177}Lu]Lu-NeoB by the investigator. Neurological decline has met the definition of DLT. Considering that the very first patient treated in this new cohort at 300 mCi experienced a DLT (neurological decline) and taking into account the other 2 patients who experienced DLTs (anemia and encephalopathy) in the prior cohort at 300 mCi (DL 2), the dose was de-escalated as per protocol to 250 mCi (DL 3). As of 29-Jan-2023, recruitment of patients in cohort 5 at 250 mCi was ongoing with 2 additional patients affected by GIST (for a total of 6) having received 1 cycle of [^{177}Lu]Lu-NeoB at this DL and no DLT been reported.
- The generated Phase I dosimetry data displayed a favorable [^{177}Lu]Lu-NeoB organ dosimetry profile with large safety margin compared to EBRT thresholds even at high cumulative activities. Consequently, based on the observed safety and tolerability data in the tested dose levels, the MTD was determined to be 250 mCi every 6 weeks. Novartis with the participating investigators declared Recommended Phase II Dose (RP2D) as 250 mCi and would be further tested in Phase IIa part of the FIH study CAAA603A12101.

Clinical Experience with [⁶⁸Ga]Ga-NeoB

[⁶⁸Ga]Ga-NeoB has shown a favorable technical and diagnostic performance to identify GRPR-expressing malignancies, both in preclinical and in clinical studies, with a good image quality that allows an easy interpretation. [⁶⁸Ga]Ga-NeoB PET agent has been assessed in two completed clinical trials and is currently assessed in one ongoing trial:

A Phase I/IIa clinical trial (MITIGATE; EudraCT Number 2016-002053-38) aimed at evaluating the safety, biodistribution, dosimetry and preliminary diagnostic performance of [⁶⁸Ga]Ga-NeoB in patients with advanced tyrosine-kinase inhibitors-pretreated GIST. [⁶⁸Ga]Ga-NeoB was very well tolerated in all 9 participants, with no adverse events related to [⁶⁸Ga]Ga-NeoB reported. Radiation exposure was low, due to a rapid renal and blood clearance. Biodistribution showed a high [⁶⁸Ga]Ga-NeoB uptake in the pancreas, followed by the kidneys and the liver. A fast, visually moderate-to-high tumor-specific uptake in GRPR expressing lesions was identified.

A Phase II clinical trial (NeoFIND; EudraCT Number 2017-003432-37), evaluated the preliminary diagnostic performance of [⁶⁸Ga]Ga-NeoB in 19 patients with breast (n=5), prostate (n=5), colorectal (n=5), non-small cell (n=3) and small cell (n=1) lung cancers. The safety profile of [⁶⁸Ga]Ga-NeoB was confirmed in this study. Results indicated a variable [⁶⁸Ga]Ga-NeoB uptake in tumor lesions, with the highest number of lesions showing a visually moderate-to-high uptake in breast cancer patients.

[⁶⁸Ga]Ga-NeoB is currently used in the ongoing Phase I/IIa NeoRay study (EudraCT Number 2018-004727-37) as an imaging agent to select patients for the treatment with [¹⁷⁷Lu]Lu-NeoB. As of October 11th 2022, 41 patients received [⁶⁸Ga]Ga-NeoB and no safety concerns related to [⁶⁸Ga]Ga-NeoB have been reported, with an administered dose of 150-250 MBq.

In this study, [⁶⁸Ga]Ga-NeoB will be explored as a positron emission tomography (PET) agent for imaging of the tumor area before treatment with [¹⁷⁷Lu]Lu-NeoB and at disease progression.

Rationale for targeting GRPR in Glioblastoma

The presence of GRPR has been confirmed in various glioma cell lines (Sharif et al., *Mol. Cell Endocrinol.*, 1997;130:119-130; Farias CB et al., *Oncology*, 2008; 75(1-2):27-31). An immunohistochemistry (IHC) staining study evaluated GRPR expression in gliomas of different WHO grades as well as in normal human brain (34 samples from patients with glioma of which 24 were glioblastoma multiforme, and 9 samples of normal brain tissues from nine autopsies were

selected). GRPR was detected in 100% of the gliomas in the samples analyzed. High GRPR expression was also observed in tumor endothelial cells. GRPR was not detected in glial cells in normal brain tissue samples; 10–50% of neuronal cells showed GRPR expression with varying intensity (Flores et al., 2010, Brain Res Bull; 82(1-2):95-8).

- 5 Dynamic PET imaging studies with a [⁶⁸Ga]Ga-bombesin analog, the [⁶⁸Ga]Ga-BZH3, were performed in patients with highly suspected recurrent gliomas. All 3 WHO grade IV astrocytomas demonstrated an increased [⁶⁸Ga]Ga-BZH3 uptake visually (Dimitrakopoulou-Strauss et al., *Clin. Nucl. Med.*, 2011 Feb;36(2):101-8). Another imaging study assessed the level of receptor expression in glioma patients with a GRPR-targeting, ⁶⁸Ga-labeled bombesin (BBN) peptide derivative PET tracer, NOTA-Aca-BBN (denoted as [⁶⁸Ga]Ga-BBN). Twelve patients with glioma
10 diagnosed by contrast-enhanced MRI underwent PET/CT after [⁶⁸Ga]Ga-BBN injection. Within one week, the tumor was surgically removed and IHC staining of tumor samples against GRPR was performed and correlated with the PET/CT results. In twelve glioma patients (glioblastoma multiforme n=2), all MRI-identified lesions showed high signal intensity on [⁶⁸Ga]Ga-BBN PET/CT.
15 With normal brain tissue as background, tumor-to-background ratios were 24.0 ± 8.85 and 13.4 ± 4.54 based on SUVmax and SUVmean, respectively. The IHC staining confirmed a positive correlation between SUV and GRPR expression level ($r_2 = 0.71$, $P < 0.001$). No significant difference in SUV was found between lesions of different WHO grades (Zhang et al., *J. Nucl. Med.*, 2018 Jun;59(6):922-928).
- 20 In summary, GRPR is shown to be highly expressed by IHC staining in glioblastoma multiforme samples. In addition, imaging studies using ⁶⁸Ga-labeled BBN analogs showed strong uptake in high grade glioma patients including GBM. For a radiosensitive tumor like glioblastoma, radiation delivered via targeting a specific receptor overexpressed in glioblastoma cancer cells like GRPR in combination with the current SoC (RT and TMZ) could improve treatment outcomes for subjects
25 with newly diagnosed glioblastoma and thus warrants further investigation. The ultimate treatment goal for this patient population is prolongation of survival but current therapeutic alternatives offer limited benefit.

In some embodiments, the combination of GRPR radiopharmaceutical of the present disclosure with radiation and optionally other agents provides a synergistic effect for treatment of
30 glioblastoma.

Justification for dose

The starting dose for the dose escalation phase will be 100mCi (3.7 GBq) of [¹⁷⁷Lu]Lu-NeoB every 4 weeks (Q4W). Based on the data from NeoRay 50 mCi (Cycle 1) + 150 mCi [¹⁷⁷Lu]Lu-NeoB Q6W was well tolerated as monotherapy with no DLTs and no G3/4 adverse events. Absorbed radiation dose in key organs (kidney, pancreas, red marrow, testes, ovaries) were low indicating
5 that the risk of radiation related toxicities from singular administrations is low.

GBM is an aggressive and fast-growing tumor with high mortality and low long term survival rates, with rapid progression of the disease (i.e., less than 7 months in newly diagnosed patients). Therefore, [¹⁷⁷Lu]Lu-NeoB will be administered with a shorter interval of Q4W, compared to the Q6W schedule in the NeoRay first in human study. The shorter interval will enable administration
10 of sufficient cycles of radioligand therapy to reach a potentially effective cumulative dose in an appropriate timeframe.

While contribution of frequency to the safety has not been fully investigated yet for [¹⁷⁷Lu]Lu-NeoB safety review of blood laboratory parameters over time after [¹⁷⁷Lu]Lu-NeoB administration showed that there is no trend for decrease or deterioration of hematological parameters. As such
15 there is no necessity to grant a certain recovery period between administrations and no data is available that would suggest that a higher frequency of administration would aggravate the safety of a single administration, especially since [¹⁷⁷Lu]Lu-NeoB related radioactivity is cleared rapidly from the body. Hence, Q4W is considered to be an acceptable administration frequency for [¹⁷⁷Lu]Lu-NeoB.

20 Based on the above information and given that [¹⁷⁷Lu]Lu-NeoB is going to be combined with RT and TMZ and the frequency of administration is reduced to Q4W days as compared to Q6W in monotherapy (NeoRay study), the study will start with a dose of 100 mCi.

Six administrations of [¹⁷⁷Lu]Lu-NeoB every 4 weeks are given in this study. Based on the currently available dosimetry data from the three investigated dose levels in the FIH study (150
25 mCi, 250 mCi and 300 mCi) the mean cumulative absorbed dose in kidney, pancreas, red marrow, testes and ovaries are significantly below external beam radiation therapy (EBRT) thresholds. Margins for 6 cycles of 11.1 GBq (300 mCi) [¹⁷⁷Lu]Lu-NeoB the highest investigated radiation dose thus far were ~9-10-fold for the pancreas (40 Gy EBRT threshold; ICRP 118 et al 2012), ~1.6-fold margin for the red marrow (2 Gy EBRT threshold; Howard et al 2017), a 1.3-2-
30 fold margin for testis and ovaries (1 Gy and 3 Gy EBRT thresholds; De Felice et al, 2019; Husseinzadeh et al, 1994; Chambers SK), and a 3-fold margin for the kidneys (23 Gy EBRT

threshold; Emami et al 1991, Emami 2013, ICRP 2012). Calculations are based on the mean absorbed doses referenced in Section 2.2 and above mentioned EBRT thresholds. Margins are proportionally higher for the lower starting dose.

5 The application of these EBRT limits to RLT is, however, likely too conservative due to the intrinsic differences between external beam radiation and radionuclide therapy. This includes different dose rates and fractionation schemes, an inhomogeneous absorbed dose distribution and potentially different radiobiological mechanisms of cytotoxicity resulting in varying biological effects (Wessels et al 2008, J Nucl Med; 49(11):1884-99; Bergsma et al 2016 Eur J Nucl Med Mol Imaging; 43(3):453-63; Bergsma et al 2016, Eur J Nucl Med Mol Imaging; 43(10):1802-11).
10 In fact, there is growing evidence that a biologically effective dose (BED) of ~40 Gy is safe for the kidneys with ¹⁷⁷Lu labelled RLTs, with a conversion factor of 1.09 to convert absorbed dose to BED with (Bodei, 2008, Eur J Nucl Med Mol Imaging; 35(10):1847-56; Schäfer 2022, Extensive ¹⁷⁷Lu-PSMA Radioligand Therapy Can Lead to Radiation Nephropathy with a Renal Thrombotic Microangiopathy-like Picture. Eur Urol). Hence, even if with more than 6 cycles, there may be
15 minimal concern for radiation-induced toxicities, as organs may be able to tolerate higher radiation dose.

Based on the evidence above, there is margin to administer more than 6 cycles. Thus, up to 4 additional administrations beyond the planned 6 administrations of [¹⁷⁷Lu]Lu-NeoB may be considered in this study based on an individual benefit-risk assessment performed by the treating
20 physician and in agreement with the study participant; based on treatment tolerability, clinical benefit and the participant's willingness to continue on [¹⁷⁷Lu]Lu-NeoB and in agreement with the Sponsor.

In order to proceed with each of the additional 4 administrations of [¹⁷⁷Lu]Lu-NeoB beyond 6 doses, The investigator should determine if:

- 25
- The participant shows evidence of disease stabilization or response (i.e. assessed either radiologically or clinically),
 - The participant does not show any sign or symptoms of clinical deterioration
 - The participant has shown good tolerance to the [¹⁷⁷Lu]Lu-NeoB treatment, no recorded SAEs related to [¹⁷⁷Lu]Lu-NeoB that were not resolved before the next [¹⁷⁷Lu]Lu-NeoB
30 dose and that led to treatment interruption.

If the patient meets all of the criteria above and agrees to continue with further treatment with [¹⁷⁷Lu]Lu-NeoB, the Investigator may administer a maximum of 4 additional administrations (i.e. maximum total of 10 administrations) of [¹⁷⁷Lu]Lu-NeoB, upon agreement with the Sponsor.

Study Treatments

- 5 In this clinical study, the term "investigational drug" refers to [⁶⁸Ga]Ga-NeoB as radioligand imaging compound, used to explore GRPR expression and to [¹⁷⁷Lu]Lu-NeoB, used as radioligand therapy.

The term "study treatment" refers to the combination of [¹⁷⁷Lu]Lu-NeoB, temozolomide (TMZ) and radiotherapy (RT).

Investigational /Control Drugs (Name/Strength)	Pharmaceutical Dosage Form	Route of Administration
[¹⁷⁷ Lu]Lu-NeoB 370MBq/mL (10 mCi/mL)	Radiopharmaceutical solution for infusion	Intravenous use
[⁶⁸ Ga]Ga-NeoB(50 ug)	Either provided as Kit for the radiopharmaceutical preparation of [⁶⁸ Ga]Ga-NeoB or as ready to use radiopharmaceutical solution for injection	Intravenous use
Temozolomide (TMZ)	Capsules/ lyophilized powder in single-dose vial for reconstitution*.	Oral use/ Intravenous use

10 [¹⁷⁷Lu]Lu-NeoB

[¹⁷⁷Lu]Lu-NeoB is a sterile radiopharmaceutical supplied as a ready-to-use solution for infusion containing [¹⁷⁷Lu]Lu-NeoB with a volumetric activity of 370 Megabecquerel (MBq)/mL at reference date and time (calibration time (tc). Starting dose level of [¹⁷⁷Lu]Lu-NeoB is 100 mCi.

[¹⁷⁷Lu]Lu-NeoB will be given every 4 weeks for up to 6 administrations starting at Week 1 Day 1 .

- 15 In exceptional cases, where patients tolerate and benefit from [¹⁷⁷Lu]Lu-NeoB, they can receive up to 10 doses, additional details are outlined in Section 4.3. No intra-patient dose escalation is allowed for [¹⁷⁷Lu]Lu-NeoB.

TMZ and RT administration will begin 7 to 10 days after the first administration of [¹⁷⁷Lu]Lu-NeoB.

TMZ will be administered orally at a dose of 75 mg/m²/day during the concomitant period with RT, as per the approved prescribing information

RT will be delivered at a dose of 2 Gy/day, 5 days per week (followed by 2 resting days) for 6 consecutive weeks with a total dose of 60 Gy (without interruption).

- 5 During the maintenance treatment period, an intra-patient dose escalation with TMZ treatment will occur. For the same patient, the dosage of TMZ is 150 mg/m² for 5 days in week 12, and 200 mg/m² for 5 days each in week 16, 20, 24, 28 and 32, if 150 mg/m² TMZ treatment is well tolerated. For additional details, please refer to the approved prescribing information.

[⁶⁸Ga]Ga-NeoB

- 10 The kit for radiopharmaceutical preparation of [⁶⁸Ga]Ga-NeoB contains 50 micrograms of NeoB. In this study [⁶⁸Ga]Ga-NeoB will be used as imaging agent for PET/CT or PET/MRI.

After radiolabeling with Ga-68, [⁶⁸Ga]Ga-NeoB will be used for positron emission tomography (PET) for localization of GRPR-positive tumors.

- 15 [⁶⁸Ga]Ga-NeoB will be administered as a single intravenous (i.v.) dose with an activity from 150 and 250 MBq (4.1-6.8 mCi).

After reconstitution, [⁶⁸Ga]Ga-NeoB will be administered by slow intravenous injection. Images should be acquired at 120 ± 30 min after the intravenous administration.

Eligibility screening

- 20 Participants will be evaluated against study inclusion and exclusion criteria and safety assessments. Repeated laboratory evaluation is allowed if an out of normal range value is observed in the screening laboratory results. If the repeated laboratory results fall into the lab normal range, that will be used for enrollment eligibility test.

- 25 During the screening period, images and findings of Gadolinium-enhanced MRI performed during the regular work-up pre-surgery, are required for eligibility assessment, and will be collected in the clinical database. In addition the findings of the post-surgery MRI will be also collected.

During the screening period, a [⁶⁸Ga]Ga-NeoB PET/CT (or PET/MRI) must be performed in the time interval starting 2 weeks after the surgery/biopsy and at least 3 days prior to the

administration of the investigational drug [^{177}Lu]Lu-NeoB. The [^{68}Ga]Ga-NeoB PET/CT will not be used for assessment of eligibility but for exploratory purposes.

[^{68}Ga]Ga-NeoB PET scan

5 A [^{68}Ga]Ga-NeoB PET/CT or PET/MRI will be performed at baseline, at least 2 weeks after the surgery/biopsy of the tumor lesion and at least 3 days prior to the first dose of [^{177}Lu]Lu-NeoB. In the event of disease progression, a PET/CT or PET/MRI will be performed to assess GRPR expression in the tumor.

10 The PET/CT or PET/MRI will be a brain-dedicated acquisition performed 120 ± 30 minutes after the injection of 150-250 MBq (4.1-6.8 mCi) of the radiotracer. PET scans will be read locally, by the same local radiologist/nuclear medicine physician throughout the study when possible..

[^{68}Ga]Ga-NeoB uptake in the tumor area (guided by findings of the post-surgery MRI at baseline, and by those of the MRI confirming disease progression for the PET scan acquired at Progressive Disease). will be assessed both visually and semi quantitatively. The visual assessment will record the pattern (focal or diffuse, homogeneous or heterogeneous) and the degree of uptake
15 (mild, moderate or high). The semiquantitative evaluation will include SUVmax, SUVmean and uptake-to-background ratio (UBR). Background activity will be considered as the uptake within a region of healthy brain parenchyma (e.g., the contralateral brain hemisphere if preserved).

Claims

1. A method of treating glioblastoma in a subject in need thereof, said method comprising administering to said subject a therapeutically effective amount of a radiopharmaceutical compound in combination with a radiotherapy, wherein said radiopharmaceutical compound is a
5 compound of formula (I), or pharmaceutically acceptable salts thereof:

C-S-P (I)

wherein:

C is a chelating moiety,

P is a GRP receptor antagonist moiety,

- 10 S is an optional spacer covalently linking C and P,

and wherein said radiopharmaceutical compound is labelled with a radionuclide M.

2. The method of Claim 1, wherein said method further comprises administering a therapeutically effective amount of an alkylating agent.

3. The method of Claim 2, wherein said alkylating agent is temozolomide.

- 15 4. The method of Claim 2 or 3, wherein said alkylating agent, preferably temozolomide, is administered at an induction phase concomitantly with radiotherapy at a dose of from 50 to 100 mg/m²/day, preferably around 75 mg/m²/day each day, typically for a period from 4 to 8 weeks, preferably 6 weeks.

- 20 5. The method of Claim 4, wherein said alkylating agent, preferably temozolomide, is administered during a maintenance phase following the induction phase, after radiotherapy, at a dose of from 50 to 400 mg/m²/day, preferably from 75 to 300 mg/m²/day, more preferably from 150 to 200 mg/m²/day each day for 5 consecutive days followed by 2 days of rest every 28 days for a period from 20 to 28 weeks, preferably 24 weeks.

- 25 6. The method of any one of Claims 2-5 wherein both radiotherapy and alkylating agent, preferably temozolomide, are initiated the same day, for example from 7 to 10 days after the first administration of the radiopharmaceutical compound.

7. The method of any one of Claims 2-6, wherein said alkylating agent, preferably

temozolomide, is concomittantly administered with the radiotherapy without interruption during an induction phase.

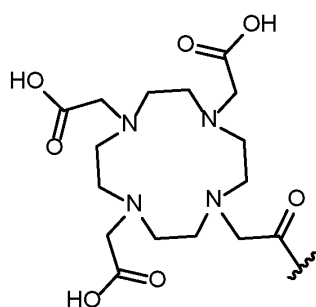
8. The method of any one of Claims 2-7, wherein said alkylating agent, preferably temozolomide, is daily administered at a first dose during concomitant administration with the radiotherapy, for example for a period of 6 consecutive weeks.

9. The method of any one of Claims 1-8, wherein said radionuclide M is selected from ^{90}Y , ^{131}I , ^{121}Sn , ^{186}Re , ^{188}Re , ^{64}Cu , ^{67}Cu , ^{59}Fe , ^{89}Sr , ^{198}Au , ^{203}Hg , ^{212}Pb , ^{165}Dy , ^{103}Ru , ^{149}Tb , ^{161}Tb , ^{213}Bi , ^{166}Ho , ^{165}Er , ^{169}Er , ^{153}Sm , ^{177}Lu , ^{213}Bi , ^{223}Ra , ^{225}Ac , ^{227}Ac , ^{227}Th , ^{211}At , ^{67}Cu , ^{186}Re , ^{188}Re , ^{161}Tb , ^{175}Yb , ^{105}Rh , ^{166}Dy , ^{199}Au , ^{44}Sc , ^{149}Pm , ^{151}Pm , ^{142}Pr , ^{143}Pr , ^{76}As , ^{111}Ag and ^{47}Sc .

10. The method of Claim 9, wherein M is ^{177}Lu .

11. The method of any one of Claims 1-10, wherein C is obtained by grafting to S or P, a chelating agent selected from 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) (tetraxetan), trizoxetan, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTAGA), diethylenetriaminepentaacetic acid (DTPA), nitrilotriacetic acid (NTA), ethylenediaminetetraacetic acid (EDTA), 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid (DO3A), triethylenetetramine (TETA), 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), NOTAGA, 1-(1,3-carboxypropyl)-4,7-carboxymethyl-1,4,7-triazacyclononane (NODAGA), NODASA, NODAPA, and 1,4-bis(carboxymethyl)-6-[bis(carboxymethyl)]amino-6-methylperhydro-1,4-diazepine (AAZTA, e.g. AAZTA5).

12. The method of Claim 11, wherein C is of the following formula,

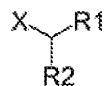


13. The method of any one of Claims 1-12, wherein P is of the general formula

D⁺Phe-Gln-Trp-Ala-Val-Gly-His-Z

wherein Z is selected from Leu- ψ (CH₂N)-Pro-NH₂ and NH-CH(CH₂-CH(CH₃)₂)₂

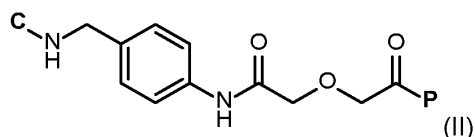
or Z is



wherein X is NH (amide) and R2 is (CH₂-CH(CH₃)₂) and R1 is the same as R2 or (CH₂N)-Pro-NH₂.

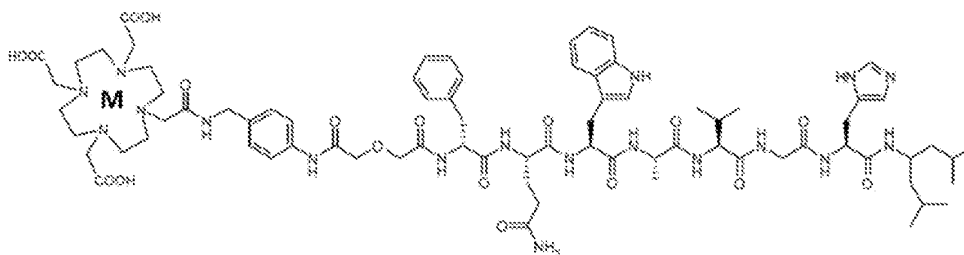
14. The method of Claim 13, wherein P is DPhe-Gln-Trp-Ala-Val-Gly-His-NH-CH(CH₂-CH(CH₃)₂)₂.

15. The method of any one of Claims 1-14, wherein the compound of Formula (I) is the following compound of Formula (II)



wherein C and P are as defined in any one of Claims 1 and 11-14, and wherein the chelating moiety C is complexed with a radionuclide M.

16. The method of any one of Claims 1-15, wherein the radiopharmaceutical compound is M-NeoB of the following formula (III).



(III),

or pharmaceutically acceptable salts thereof,

wherein M is a radionuclide, preferably M is ¹⁷⁷Lu.

17. The method of any one of Claims 1-16, wherein said radiopharmaceutical compound is administered 1 to 10 times per treatment, preferably 4 to 10 times per treatment, more preferably 6 to 8 times per treatment.
18. The method of Claim 17, wherein treatment with said radiopharmaceutical compound comprises an administration interval of 2 weeks, or 3 weeks, or 4 weeks, or 5 weeks or even 6 weeks, preferably 3 or 4 weeks, more preferably every 4 weeks.
19. The method of any one of Claims 1-18, wherein said radiopharmaceutical compound is administered to the subject in multiple treatments, preferably 2-3 treatments, with a pause of 2-12 months between treatments.
20. The method of any one of Claims 1-19, wherein said radiopharmaceutical compound is administered at each administration at a dose ranging from 0.925 GBq (25mCi) to 29.6GBq (800 mCi), preferably from 1.48 GBq (40 mCi) to 18.5 GBq (500mCi), preferably from 1.85 GBq (50mCi) to 14.8 GBq (400mCi), more preferably from 3.7 GBq (100mCi) to 11.1 GBq(300mCi), even more preferably of about 3.7 GBq (100mCi), about 5.55 GBq (150mCi), about 7.4 GBq (200mCi), about 9.25GBq (250mCi), or about 11.1 GBq(300mCi).
21. The method of any one of Claims 1-20, wherein said radiotherapy comprises irradiating said subject at a total dose of from 40 – 80 Gy, for example 60 Gy.
22. The method of any one of Claims 1-21, wherein said radiotherapy is conducted at a dose from 1Gy to 4Gy/day, preferably around 2Gy/day, during a period from 3 to 7 days, preferably around 5 days per week during a period from 4 to 8 weeks, preferably for 6 weeks.
23. The method of any one of Claims 1-22, wherein said radiotherapy is initiated 7-10 days after the first administration of said radiopharmaceutical compound.
24. The method of any one of Claims 1-23, wherein said subject is newly diagnosed with glioblastoma.
25. The method of any one of Claims 1-24, wherein said subject has been selected from subjects with positive methylated O-6-methylguanine-DNA methyltransferase promoter status.
26. The method of any one of Claims 1-25, wherein said radiotherapy is whole-brain irradiation.
27. The method of any one of Claims 1-26, wherein said subject has been selected by

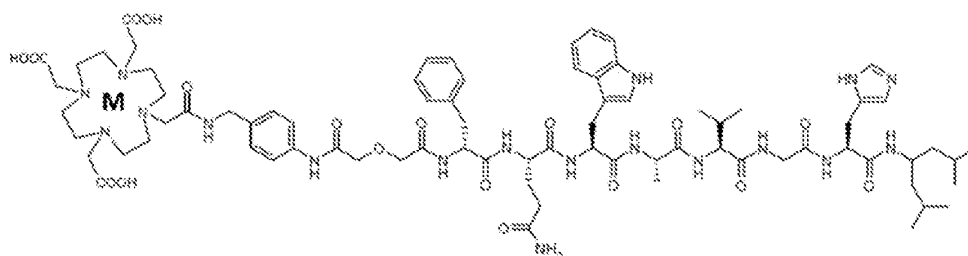
SPECT/CT or PET/CT or SPECT/MRI, PET/MRI imaging with the same radiopharmaceutical compound as defined for the treatment, but with an alternate radionuclide or contrast agent suitable for imaging, preferably 68-Gallium, 67-Gallium or 64-Copper, more preferably 68-Gallium, based on detection of said radionuclide in the imaging scan at the tumor region, prior to any surgery, for example, two weeks prior to start of said treatment.

28. The method of Claim 27, wherein said subject is selected from subjects showing presence of alternate radionuclide or contrast agent enhancement, for example gadolinium enhancement, in a PET/MRI scan at the tumor region, prior to any surgery.

29. The method of any one of Claims 1-28, wherein said subject is newly diagnosed with glioblastoma and has a positive methylated O-6-methylguanine-DNA methyltransferase promoter status, wherein said radiopharmaceutical compound is administered to said subject in combination with radiotherapy and an alkylating agent, preferably temozolomide, wherein a first dose of said radiopharmaceutical compound is administered preferably 7 to 10 days prior to initiation of radiotherapy.

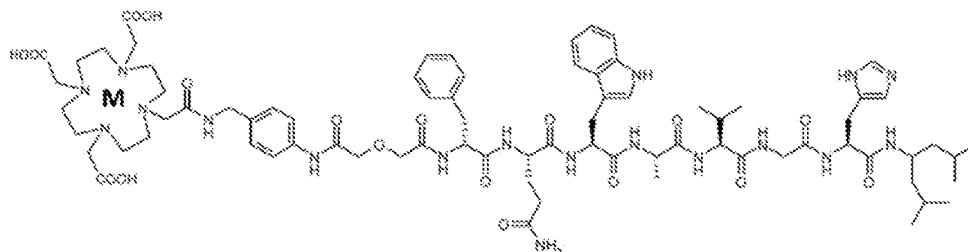
30. The method of any one of Claims 1-28, wherein said subject is newly diagnosed with glioblastoma and has a negative methylated O-6-methylguanine-DNA methyltransferase promoter status, wherein said radiopharmaceutical compound is administered at least 6 times to said subject in combination with radiotherapy and further in combination with temozolomide, and wherein the administration interval between two administrations of said radiopharmaceutical compound is 4 weeks, and, wherein a first dose of said radiopharmaceutical compound is administered preferably 7 to 10 days prior to initiation of radiotherapy and temozolomide.

31. The method of Claim 29 or 30, wherein said radiopharmaceutical compound is M-NeoB of the following formula:



wherein M is ^{177}Lu .

32. The method of any one of Claims 1-30, wherein said radiopharmaceutical compound is M-NeoB of the following formula:



wherein M is ^{177}Lu , and said radiopharmaceutical compound is administered by intravenous
5 infusion at a concentration of 370MBq/mL.