

METHODS FOR TREATING BREAST CANCER

FIELD OF THE INVENTION

The present invention relates to methods for treating breast cancer in a subject in need thereof, wherein a therapeutically effective amount of a radiopharmaceutical compound comprising GRPR
5 binding moiety, e.g. [¹⁷⁷Lu]Lu-NeoB, is administered to said subject in combination with a CDK4/6 inhibitor and an endocrine treatment.

BACKGROUND

Breast cancer is the most common cancer and the leading cause of cancer death for women worldwide. The global incidence is 85.8 to 91.6 cases per 100,000, whereas mortality rates range
10 from 17.4 to 20.1 deaths per 100,000 (DeSantis et al. Breast cancer statistics, 2015: Convergence of incidence rates between black and white women. CA Cancer J Clin; 66(1):31-42 ; Hashim et al. The global decrease in cancer mortality: trends and disparities. Ann Oncol; 27(5):926-33 ; Torre et al. Global Cancer Incidence and Mortality Rates and Trends--An Update. Cancer Epidemiol Biomarkers Prev; 25(1):16-27; Heer et al. The incidence
15 of breast cancer in Canada 1971-2015: trends in screening-eligible and young-onset age groups. Can J Public Health; 111(5):787-793).

Despite progress in new treatment methods, there is still a need to provide improved clinical treatments of breast cancer.

SUMMARY

20 The present disclosure relates to a method for treating breast cancer in a subject in need thereof by administering to said subject a therapeutically effective amount of a radiopharmaceutical compound in combination with a CDK4/6 inhibitor, e.g. ribociclib, and, with an endocrine treatment, e.g. fulvestrant, wherein said radiopharmaceutical compound is a compound of formula
(I), or pharmaceutically acceptable salts thereof:

25 C-S-P (I)

wherein:

C is a chelating moiety,

P is a GRP receptor binding 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 breast cancer in a subject in need thereof, said method comprising
5 administering to said subject a therapeutically effective amount of a radiopharmaceutical compound, in combination with a CDK4/6 inhibitor and an endocrine treatment, wherein said radiopharmaceutical compound is a compound of formula (I), or pharmaceutically acceptable salts thereof:

C-S-P (I)

- 10 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.

- 15 2. The method of embodiment 1, wherein said CDK4/6 inhibitor is selected from the group consisting of ribociclib, palbociclib, and abemaciclib.

3. The method of embodiment 2, wherein said CDK4/6 inhibitor is ribociclib.

4. The method of any one of embodiments 1-3, wherein said endocrine therapy comprises administering a therapeutically effective amount of a selective estrogen receptor modulator, a
20 non-steroidal aromatase inhibitor, a steroidal aromatase inhibitor, or a selective ER degrader.

5. The method of any one of embodiments 1-4, wherein said endocrine treatment comprises administering a therapeutically effective amount of a selective ER degrader.

6. The method of embodiment 5, wherein said selective ER degrader is fulvestrant.

7. The method of embodiment 5 or 6, wherein a therapeutically effective amount of said
25 selective ER degrader is administered once every 14 to 56 days, for example 28 days, for example starting the same day as the administration of said radiopharmaceutical compound, and is

administered for at least as long as the radiopharmaceutical is administered, and optionally administration of ER degrader continues until disease progression.

8. The method of any one of embodiments 1-7, wherein said CDK4/6 inhibitor is ribociclib and said endocrine treatment comprises administering a therapeutically effective amount of fulvestrant.

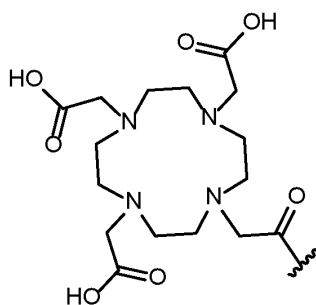
9. The method of embodiment 8, wherein said CDK4/6 inhibitor, preferably ribociclib, is concomitantly administered with fulvestrant.

10. The method of any one of embodiments 1-9, wherein 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 .

11. The method of any one of embodiments 1-10, wherein M is ^{177}Lu .

12. The method of any one of embodiments 1-11, wherein C is obtained by linking 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).

13. The method of embodiment 12, wherein C is of the following formula,

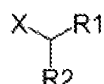


14. The method of any one of embodiments 1-13, wherein said peptide P is of the general formula



wherein Z is selected from Leu- $\psi(\text{CH}_2\text{N})$ -Pro-NH₂ and NH-CH(CH₂-CH(CH₃)₂)₂

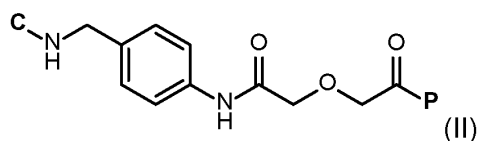
5 or Z is



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

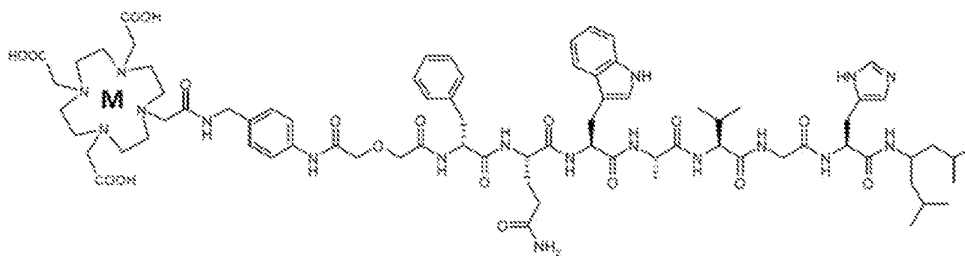
15. The method of embodiment 14, wherein P is DPhe-Gln-Trp-Ala-Val-Gly-His-NH-CH(CH₂-CH(CH₃)₂)₂.

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



wherein C and P are as defined in Claim 1.

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



(III),

20 or pharmaceutically acceptable salts thereof,
wherein M is radionuclide, for example M is ¹⁷⁷Lu.

18. The method of any one of embodiments 1-17, wherein said radiopharmaceutical compound

is administered 3 to 12 times, 4 to 10 times, 4 to 8 times, 6 times, or 10 times.

19. The method of embodiment 18, wherein said radiopharmaceutical compound comprises an administration interval of 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 3 or 4 weeks, or 4 weeks.

20. The method of any one of embodiments 1-19, wherein said radiopharmaceutical compound
5 is administered at a dose ranging from 0.925 GBq (25mCi) to 29.6GBq (800 mCi), from 1.48 GBq (40 mCi) to 18.5 GBq (500mCi), from 1.85 GBq (50mCi) to 14.8 GBq (400mCi), from 3.7 GBq (100mCi) to 11.1 GBq(300mCi), 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 CDK4/6 inhibitor, e.g. ribociclib,
10 is administered orally at a daily dose of 400 to 800 mg, e.g. about 600 mg, e.g. from one to 6 cycles of a period of 15 to 28 days, each cycle including e.g. 21 days of daily administration followed by a period of 7 days off treatment.

22. The method of embodiment 21, wherein said radiopharmaceutical compound is ¹⁷⁷Lu-NeoB and is administered intravenously every 28 days, for 3-12 cycles, for example 6 cycles, at
15 a dose ranging from 3.7 GBq (100mCi) to 11.1 GBq(300mCi), or from 3.7 GBq (100mCi) to 9.25 GBq(250mCi), e.g. 250 mCi, e.g. 150 mCi, in combination with ribociclib administered orally at a daily dose of 600 mg, for 15 to 21 days per cycle.

23. The method of any one of embodiments 1-22, wherein said endocrine therapy, e.g. fulvestrant, is administered via intramuscular administration, at a dose of 250 to 700 mg, for
20 example using a long-acting formulation.

24. The method of any one of embodiments 1-23, wherein said subject has ER positive, HER-2 negative (ER+/HER2-) and GRPR-positive (GRPR+) breast cancer.

25. The method of any one of embodiments 1-24, wherein said subject has been selected from subjects experiencing early relapse after neoadjuvant or adjuvant prior endocrine treatment, or
25 experiencing progression on prior endocrine treatment optionally in combination with a prior CDK4/6 inhibitor.

26. The method of any one of embodiments 1-25, wherein said subject is a post-menopausal woman with advanced metastatic breast cancer.

27. The method of any one of embodiments 1-26, wherein said subject is a pre-menopausal or

peri-menopausal woman with advanced metastatic breast cancer.

28. The method of any one of claims 1-27, wherein said subject has been selected from subjects experiencing early relapse after neoadjuvant or adjuvant prior endocrine treatment.

29. The method of any one of claims 1-27, wherein said subject has been selected from subjects
5 experiencing progression on prior endocrine treatment optionally in combination with a prior CDK4/6 inhibitor.

30. The method of embodiment 29, wherein said prior CDK4/6 inhibitor is selected from the group consisting of ribociclib, palbociclib, and abemaciclib, e.g., ribociclib.

31. The method of any one of embodiments 25-30, wherein said prior endocrine treatment
10 comprises administering a therapeutically effective amount of a selective estrogen receptor modulator, a non-steroidal aromatase inhibitor, a steroidal aromatase inhibitor, or a selective ER degrader. 32. The method of any one of embodiments 1-31, wherein said endocrine therapy further comprises concomitantly administering a synthetic analog of gonadotropin releasing hormone, for example goserelin, for example via subcutaneous administration, e.g. every 28 days
15 at a dose of about 3.6mg.

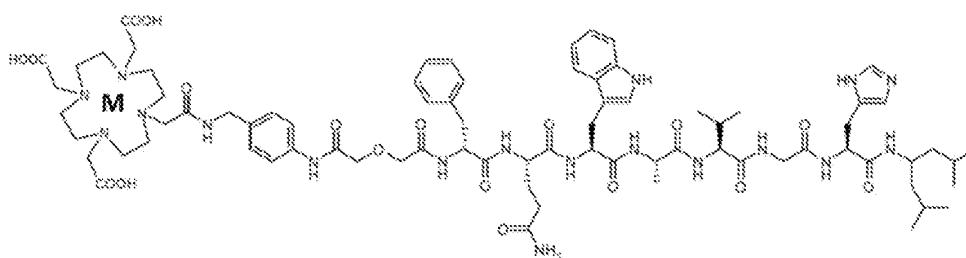
33. The method of any one of embodiments 1-32, wherein said subject has been selected by SPECT/CT or PET/CT or SPECT/MRI, PET/MRI imaging with the same radiopharmaceutical compound as defined for the treatment, but with a alternate radionuclide suitable for imaging, for example 68-Gallium, 67-Gallium or 64-Copper, e.g. 68-Gallium, based on detection of said
20 alternate radionuclide in the imaging scan at the tumor region, prior to any surgery, for example, two weeks prior to start of said treatment.

34. The method of embodiment 33, wherein said subject is selected among subjects showing presence of radiometal enhancement, for example gadolinium enhancement, in a PET/MRI scan at the tumor region, prior to any surgery.

25 35. The method of any one of embodiments 1-34, wherein said subject has ER positive, HER-2 negative (ER+/HER2-) and GRPR-positive (GRPR+) breast cancer and is experiencing early relapse from neoadjuvant or adjuvant therapy, wherein said radiopharmaceutical compound is administered to said subject in combination with ribociclib and fulvestrant, wherein a first dose of said radiopharmaceutical compound is administered the same day as the first dose of ribociclib.

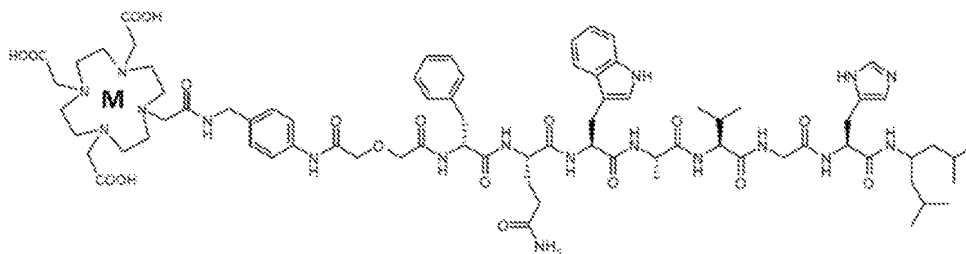
36. The method of embodiment 35, wherein ribociclib is administered orally at a daily dose of about 600 mg, for example in cycles of a period of 28 days, each cycle for example including 21 days of administration followed by a period of 7 days off treatment, wherein the radiopharmaceutical compound is administered for 4-10 cycles, and ribociclib is administered
 5 for at least as long as the radiopharmaceutical is administered, and optionally administration of said CDK4/6 inhibitor continues until disease progression.

37. The method of embodiment 35 or 36, wherein said radiopharmaceutical compound is M-NeoB of the following formula:



10 wherein M is 177-Lu.

38. The method of any one of embodiments 1-37, wherein said radiopharmaceutical compound is M-NeoB of the following formula:



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

39. A radiopharmaceutical compound for use in a method of treating breast cancer 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 CDK4/6 inhibitor and an endocrine treatment, 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,

5 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.

40. The radiopharmaceutical compound for use of embodiment 39, wherein said CDK4/6 inhibitor is selected from the group consisting of ribociclib, palbociclib, and abemaciclib.

10 41. The radiopharmaceutical compound for use of embodiment 40, wherein said CDK4/6 inhibitor is ribociclib.

42. The radiopharmaceutical compound for use of embodiments 39-41, wherein said endocrine treatment comprises administering a therapeutically effective amount of a selective estrogen receptor modulator, a non-steroidal aromatase inhibitor, a steroidal aromatase inhibitor, or a
15 selective ER degrader.

43. The radiopharmaceutical compound for use of embodiments 39-42, wherein said endocrine treatment comprises administering a therapeutically effective amount of a selective ER degrader.

44. The radiopharmaceutical compound for use of embodiment 43, wherein said selective ER degrader is fulvestrant.

20 45. The radiopharmaceutical compound for use of embodiment 43 or 44, wherein a therapeutically effective amount of said selective ER degrader is administered once every 14 to 56 days, for example 28 days, for example starting the same day as the administration of said radiopharmaceutical compound, and is administered for at least as long as the radiopharmaceutical is administered, and optionally administration of ER degrader continues until
25 disease progression..

46. The radiopharmaceutical compound for use of embodiments 39-45, wherein said CDK4/6 inhibitor is ribociclib and said endocrine treatment comprises administering a therapeutically

effective amount of fulvestrant.

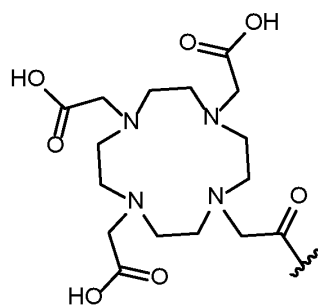
47. The radiopharmaceutical compound for use of embodiment 46, wherein said CDK4/6 inhibitor, preferably ribociclib, is concomitantly administered with fulvestrant.

48. The radiopharmaceutical compound for use of embodiments 39-47, wherein 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.

49. The radiopharmaceutical compound for use of embodiments 38-47, wherein M is ¹⁷⁷Lu.

50. The radiopharmaceutical compound for use of embodiments 39-49, wherein C is obtained by linking 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-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) chelating moiety.

51. The radiopharmaceutical compound for use of embodiment 50, wherein C is of the following formula,

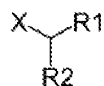


52. The radiopharmaceutical compound for use of embodiments 39-51, wherein said peptide P is of the general formula



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

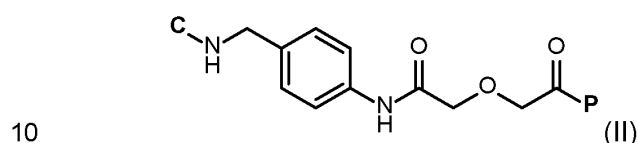
or Z is



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

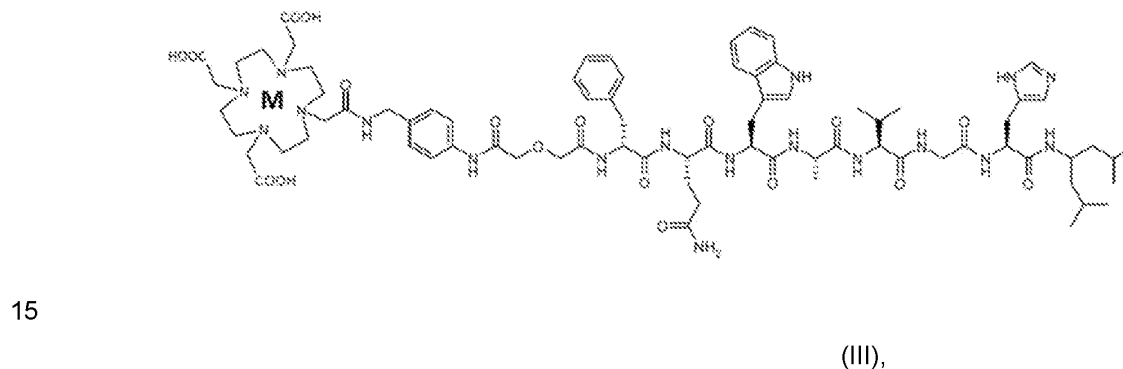
5 53. The radiopharmaceutical compound for use of embodiment 52, wherein P is DPhe-Gln-Trp-Ala-Val-Gly-His-NH-CH(CH₂-CH(CH₃)₂)₂.

54. The radiopharmaceutical compound for use of any one of embodiments 39-53, wherein the compound of Formula (I) is a compound of Formula (II)



wherein C and P are as defined in Claim 1.

55. The radiopharmaceutical compound for use of any one of embodiments 39-54, wherein the radiopharmaceutical compound is M-NeoB of the following formula (III)



or pharmaceutically acceptable salts thereof,

wherein M is radionuclide, for example M is ¹⁷⁷Lu.

20 56. The radiopharmaceutical compound for use of any one of embodiments 39-55, wherein said radiopharmaceutical compound is administered 3 to 12 times, 4 to 10 times, 4 to 8 times, 6 times, or 10 times.

57. The radiopharmaceutical compound for use of embodiment 56, wherein said radiopharmaceutical compound comprises an administration interval of 2 weeks, 3 weeks, 4

weeks, 5 weeks, 6 weeks, y 3 or 4 weeks, or 4 weeks.

58. The radiopharmaceutical compound for use of any one of embodiments 39-57, wherein said radiopharmaceutical compound is administered at a dose ranging from 0.925 GBq (25mCi) to 29.6GBq (800 mCi), from 1.48 GBq (40 mCi) to 18.5 GBq (500mCi), from 1.85 GBq (50mCi) to 14.8 GBq (400mCi), from 3.7 GBq (100mCi) to 11.1 GBq(300mCi), about 3.7 GBq (100mCi),
5 about 5.55 GBq (150mCi), about 7.4 GBq (200mCi, about 9.25GBq (250mCi), or about 11.1 GBq (300mCi).

59. The radiopharmaceutical compound for use of any one of embodiments 39-58, wherein said CDK4/6 inhibitor, e.g. ribociclib, is administered orally at a daily dose of 400 to 800 mg, e.g. about
10 600 mg, e.g. from one to 6 cycles of a period of 15 to 28 days, each cycle including e.g. 21 days of daily administration followed by a period of 7 days off treatment.

60. The radiopharmaceutical compound for use of embodiment 59, wherein said radiopharmaceutical compound is [¹⁷⁷Lu]Lu-NeoB and is administered intravenously every 28 days, for 3-12 cycles, for example 6 cycles, at a dose ranging from 3.7 GBq (100mCi) to 11.1
15 GBq(300mCi), or from 3.7 GBq (100mCi) to 9.25 GBq(250mCi), e.g. 250 mCi, e.g. 150 mCi, in combination with ribociclib administered orally at a daily dose of 600 mg, for 15 to 21 days per cycle.

61. The radiopharmaceutical compound for use of any one of embodiments 39-60, wherein said endocrine therapy, e.g. fulvestrant, is administered via intramuscular administration, at a dose of
20 250 to 700 mg, for example using a long-acting formulation.

62. The radiopharmaceutical compound for use of any one of embodiments 39-61, wherein said subject has ER positive, HER-2 negative (ER+/HER2-) and GRPR-positive (GRPR+) breast cancer.

63. The radiopharmaceutical compound for use of any one of embodiments 39-62, wherein said
25 subject has been selected from subjects experiencing early relapse after neoadjuvant or adjuvant prior endocrine treatment, or experiencing progression on prior endocrine treatment optionally in combination with a prior CDK4/6 inhibitor.

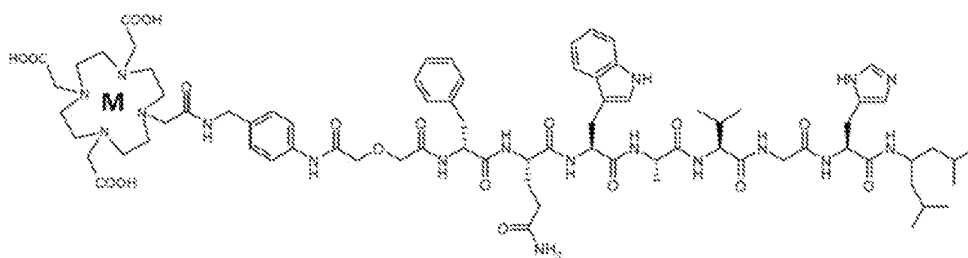
64. The radiopharmaceutical compound for use of any one of embodiments 39-63, wherein said subject is a post-menopausal woman with advanced metastatic breast cancer.

65. The radiopharmaceutical compound for use of any one of embodiments 39-63, wherein said subject is a pre-menopausal or peri-menopausal woman with advanced metastatic breast cancer.
66. The method of any one of embodiments 39-65, wherein said subject has been selected from subjects experiencing early relapse after neoadjuvant or adjuvant prior endocrine treatment.
- 5 67. The method of any one of embodiments 39-65, wherein said subject has been selected from subjects experiencing progression on prior endocrine treatment optionally in combination with a prior CDK4/6 inhibitor
68. The method of embodiment 67, wherein said prior CDK4/6 inhibitor is selected from the group consisting of ribociclib, palbociclib, and abemaciclib, e.g., ribociclib.
- 10 69. The method of any one of embodiments 63-68, wherein said prior endocrine treatment comprises administering a therapeutically effective amount of a selective estrogen receptor modulator, a non-steroidal aromatase inhibitor, a steroidal aromatase inhibitor, or a selective ER degrader.
- 15 70. The radiopharmaceutical compound for use of any one of embodiments 1-69, wherein said endocrine therapy further comprises concomitantly administering a synthetic analog of gonadotropin releasing hormone, for example goserelin, e.g. via subcutaneous administration, every 28 days at a dose of about 3.6mg.
- 20 71. The radiopharmaceutical compound for use of any one of embodiments 39-70, 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 a alternate radionuclide suitable for imaging, e.g. 68-Gallium, 67-Gallium or 64-Copper, e.g. 68-Gallium, based on detection of said alternate radionuclide in the imaging scan at the tumor region, prior to any surgery, for example, two weeks prior to start of said treatment.
- 25 72. The radiopharmaceutical compound for use of embodiment 71, wherein said subject is selected among subjects showing presence of radiometal enhancement, for example gadolinium enhancement, in a PET/MRI scan at the tumor region, prior to any surgery.
73. The radiopharmaceutical compound for use of any one of embodiments 39-72, wherein said subject has ER positive, HER-2 negative (ER+/HER2-) and GRPR-positive (GRPR+) breast cancer experiencing early relapse from neoadjuvant or adjuvant therapy, wherein said

radiopharmaceutical compound is administered to said subject in combination with ribociclib and fulvestrant, wherein a first dose of said radiopharmaceutical compound is administered the same day as the first dose of ribociclib.

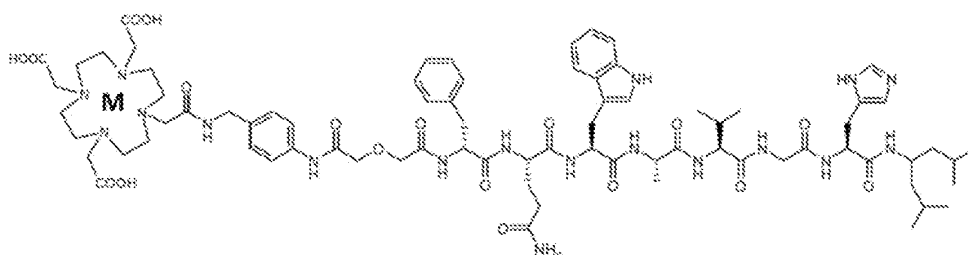
74. The radiopharmaceutical compound for use of embodiment 73, wherein ribociclib is administered orally at a daily dose of about 600 mg, for example in cycles of a period of 28 days, each cycle for example including 21 days of administration followed by a period of 7 days off treatment, wherein the radiopharmaceutical compound is administered for 4-10 cycles, and ribociclib is administered for at least as long as the radiopharmaceutical is administered, and optionally administration of said CDK4/6 inhibitor continues until disease progression.

10 75. The radiopharmaceutical compound for use of embodiment 73 or 74, wherein said radiopharmaceutical compound is M-NeoB of the following formula:



wherein M is ^{177}Lu .

76. The radiopharmaceutical compound for use of any one of embodiments 39-735 wherein said
15 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 .

77. Use of a radiopharmaceutical compound in the manufacture of a medicament for use in a

method of treating breast cancer 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 CDK4/6 inhibitor and an endocrine treatment, 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,

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

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

78. The use of embodiment 77, wherein said CDK4/6 inhibitor is selected from the group consisting of ribociclib, palbociclib, and abemaciclib.

79. The use of embodiment 78, wherein said CDK4/6 inhibitor is ribociclib.

15 80. The use of embodiments 77-79, wherein said endocrine treatment comprises administering a therapeutically effective amount of a selective estrogen receptor modulator, a non-steroidal aromatase inhibitor, a steroidal aromatase inhibitor, or a selective ER degrader.

81. The use of embodiments 77-80, wherein said endocrine treatment comprises administering a therapeutically effective amount of a selective ER degrader.

20 82. The use of embodiment 81, wherein said selective ER degrader is fulvestrant.

83. The use of embodiment 81 or 82, wherein a therapeutically effective amount of said selective ER degrader is administered once every 14 to 56 days, for example 28 days, for example starting the same day as the administration of said radiopharmaceutical compound, and is administered for at least as long as the radiopharmaceutical is administered, and optionally administration of ER degrader continues until disease progression.

84. The use of embodiments 77-83, wherein said CDK4/6 inhibitor is ribociclib and said endocrine treatment comprises administering a therapeutically effective amount of fulvestrant.

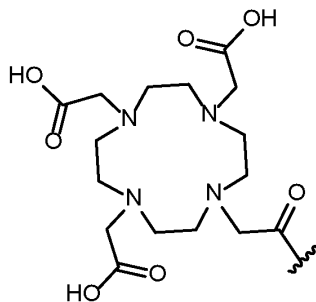
85. The use of embodiment 84, wherein said CDK4/6 inhibitor, preferably ribociclib, is concomittantly administered with fulvestrant.

86. The use of embodiments 77-85, wherein 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 ,
5 ^{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 .

87. The use of embodiments 77-86, wherein M is ^{177}Lu .

88. The use of embodiments 77-87, wherein C is obtained by linking to S or P a chelating agent selected from 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) (tetraxetan),
10 trizoxetan, 1,4,7,10-tetraazacyclododeceane,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-
15 bis(carboxymethyl)-6-[bis(carboxymethyl)]amino-6-methylperhydro-1,4-diazepine (AAZTA, e.g. AAZTA5).

89. The use of embodiment 88 wherein C is of the following formula,

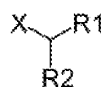


90. The use of embodiments 77-89, wherein said peptide P is of the general formula

20 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

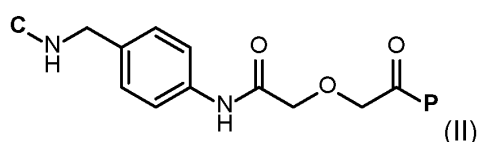
or Z is



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

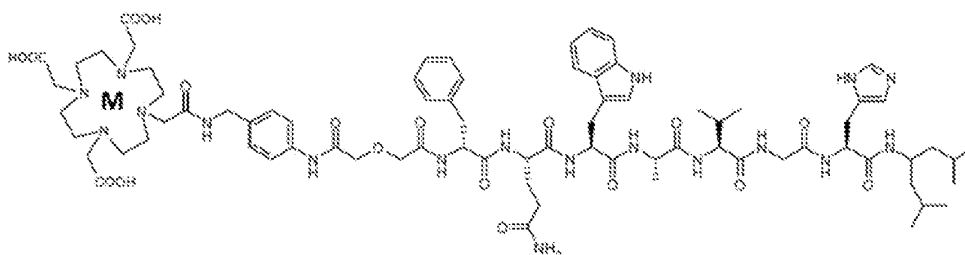
91. The use of embodiment 90, wherein P is DPhe-Gln-Trp-Ala-Val-Gly-His-NH-CH(CH₂-CH(CH₃)₂)₂.

- 5 92. The use of any one of embodiments 77-91, wherein the compound of Formula (I) is a compound of Formula (II)



wherein C and P are as defined in Claim 1.

- 10 93. The use of any one of embodiments 77-92, wherein the radiopharmaceutical compound is M-NeoB of the following formula (III)



(III),

- 15 or pharmaceutically acceptable salts thereof,
wherein M is radionuclide, for example M is ¹⁷⁷Lu.

94. The use of any one of embodiments 77-93, wherein said radiopharmaceutical compound is administered 3 to 12 times, 4 to 10 times, 4 to 8 times, 6 times, or 10 times.

95. The use of embodiment 94, wherein said radiopharmaceutical compound comprises an
20 administration interval of 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 3 or 4 weeks, or 4 weeks.

96. The use of any one of embodiments 77-95, wherein said radiopharmaceutical compound is administered at a dose ranging from 0.925 GBq (25mCi) to 29.6GBq (800 mCi), from 1.48 GBq

(40 mCi) to 18.5 GBq (500mCi), preferably from 1.85 GBq (50mCi) to 14.8 GBq (400mCi), from 3.7 GBq (100mCi) to 11.1 GBq(300mCi), 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).

97. The use of any one of embodiments 77-96, wherein said CDK4/6 inhibitor, e.g. ribociclib, is administered orally at a daily dose of 400 to 800 mg, e.g. about 600 mg, e.g. from one to 6 cycles of a period of 15 to 28 days, each cycle including e.g. 21 days of daily administration followed by a period of 7 days off treatment.

98. The use of embodiment 97, wherein said radiopharmaceutical compound is [¹⁷⁷Lu]Lu-NeoB and is administered intravenously every 28 days, for 3-12 cycles, for example 6 cycles, at a dose ranging from 3.7 GBq (100mCi) to 11.1 GBq(300mCi), or from 3.7 GBq (100mCi) to 9.25 GBq(250mCi), e.g. 250 mCi, e.g. 150 mCi, in combination with ribociclib administered orally at a daily dose of 600 mg, for 15 to 21 days per cycle.

99. The use of embodiments 77-98, wherein said endocrine therapy, preferably fulvestrant, is administered via intramuscular administration, at a dose of 250 to 700 mg, for example using a long-acting formulation.

100. The use of any one of embodiments 77-99, wherein said subject has ER positive, HER-2 negative (ER+/HER2-) and GRPR-positive (GRPR+) breast cancer.

101. The use of any one of embodiments 77-100, wherein said subject has been selected from subjects experiencing early relapse after neoadjuvant or adjuvant prior endocrine treatment, or experiencing progression on prior endocrine treatment optionally in combination with a prior CDK4/6 inhibitor.

102. The use of any one of embodiments 77-101, wherein said subject is a post-menopausal woman with advanced metastatic breast cancer.

103. The use of any one of embodiments 77-101, wherein said subject is a pre-menopausal or peri-menopausal woman with advanced metastatic breast cancer.

104. The method of any one of embodiments 77-103, wherein said subject has been selected from subjects experiencing early relapse after neoadjuvant or adjuvant prior endocrine treatment.

105. The method of any one of embodiments 77-104, wherein said subject has been selected from subjects experiencing progression on prior endocrine treatment optionally in combination

with a prior CDK4/6 inhibitor.

106. The method of embodiment 105, wherein said prior CDK4/6 inhibitor is selected from the group consisting of ribociclib, palbociclib, and abemaciclib, e.g., ribociclib.

107. The method of any one of embodiments 107-106, wherein said prior endocrine treatment
5 comprises administering a therapeutically effective amount of a selective estrogen receptor modulator, a non-steroidal aromatase inhibitor, a steroidal aromatase inhibitor, or a selective ER degrader. 108. The use of any one of embodiments 77-107, wherein said endocrine therapy further comprises concomitantly administering a synthetic analog of gonadotropin releasing hormone, for example goserelin, e.g. via subcutaneous administration, every 28 days at a dose
10 of about 3.6mg.

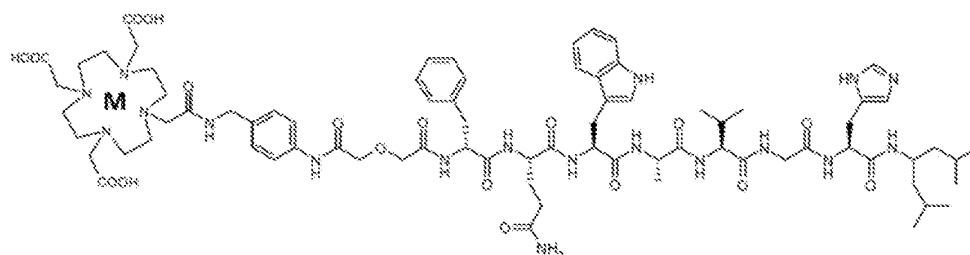
109. The use of any one of embodiments 77-108, wherein said subject has been selected by SPECT/CT or PET/CT or SPECT/MRI, PET/MRI imaging with the same radiopharmaceutical compound as defined for the treatment, but with a radiometal suitable for imaging, e.g. 68-Gallium, 67-Gallium or 64-Copper, e.g. 68-Gallium, based on detection of said radiometal in the
15 imaging scan at the tumor region, prior to any surgery, for example, two weeks prior to start of said treatment.

110. The use of embodiment 109, wherein said subject is selected among subjects showing presence of radiometal enhancement, for example gadolinium enhancement, in a PET/MRI scan at the tumor region, prior to any surgery.

20 111. The use of any one of embodiments 77-110, wherein said subject has ER positive, HER-2 negative (ER+/HER2-) and GRPR-positive (GRPR+) breast cancer experiencing early relapse from neoadjuvant or adjuvant therapy, wherein said radiopharmaceutical compound is administered to said subject in combination with ribociclib and fulvestrant, wherein a first dose of said radiopharmaceutical compound is administered the same day as the first dose of ribociclib.

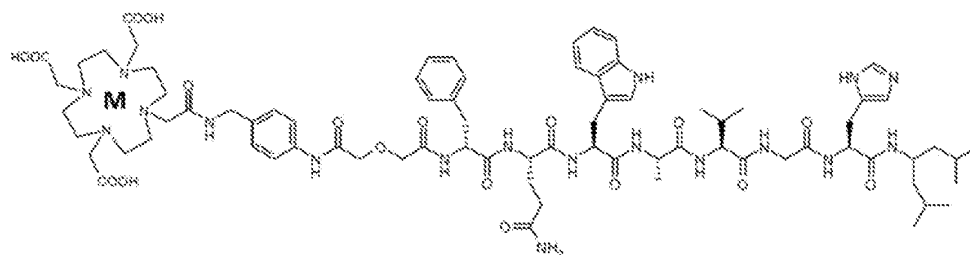
25 112. The use of embodiment 111, wherein ribociclib is administered orally at a daily dose of about 600 mg, for example in cycles of a period of 28 days, each cycle for example including 21 days of administration followed by a period of 7 days off treatment, wherein the radiopharmaceutical compound is administered for 4-10 cycles, and ribociclib is administered for at least as long as the radiopharmaceutical is administered, and optionally administration of said CDK4/6 inhibitor
30 continues until disease progression.

113. The use of embodiment 111 or 112, wherein said radiopharmaceutical compound is M-NeoB of the following formula:



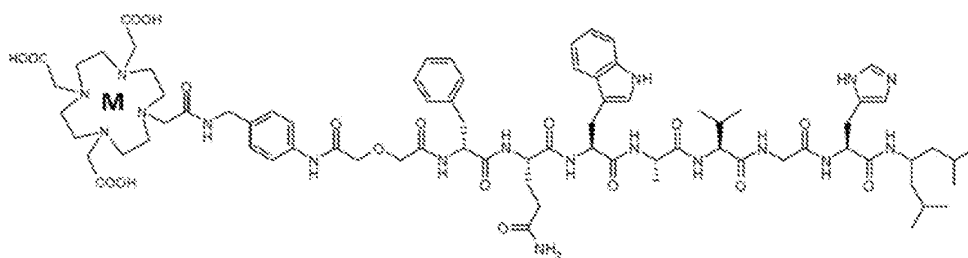
wherein M is 177-Lu.

- 5 114. The use of any one of embodiments 77-113, 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.

- 10 In some embodiments, provided is a method of use, a use, or a use in the manufacture of a medicament, of a radiopharmaceutical compound for treating breast cancer in a subject in need thereof, said method, use, or use in the manufacture of a medicament, comprising administering to said subject a therapeutically effective amount of a radiopharmaceutical compound, in combination with a CDK4/6 inhibitor and an endocrine treatment, wherein said
15 radiopharmaceutical compound is M-NeoB of the following formula:



wherein M is ^{177}Lu ;

said subject has ER positive, HER-2 negative (ER+/HER2-) and GRPR-positive (GRPR+) breast cancer; and

- 5 said subject has been selected from subjects experiencing early relapse after neoadjuvant or
adjuvant prior endocrine treatment, or experiencing progression on prior endocrine treatment
optionally in combination with a prior CDK4/6 inhibitor

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 represents the treatment scheme of the dose escalation part of the clinical study.

- 10 Fig. 2 represents the treatment scheme of the dose expansion part of the clinical study .

Fig. 3 represents a decision tree for the escalation or backfill part of the clinical study

DETAILED DESCRIPTION

The present disclosure relates to a method for treating breast cancer in a subject in need thereof by administering a therapeutically effective amount of a radiopharmaceutical compound to said
15 subject in combination with a CDK4/6 inhibitor, and an endocrine treatment.

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/breast cancer (Flores et al. 2010, Brain Res Bull; 82(1-2):95-8).

The NeoB compound 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 compound 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.
- 10 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
- 15 radioactivity is persistent, with detectable uptake values up to 7 days after injection.

Given that ER is a major oncogenic driver in ER+ breast cancers, the treatment can incorporate endocrine treatment (ET) which targets the ER either through direct inhibition by selective estrogen receptor modulators (SERMs), estrogen deprivation with selective non steroidal aromatase inhibitors (NSAIs) and steroidal aromatase inhibitors (SAIs) or promotion of ER

20 degradation via selective ER-degraders (SERDs).

In the past few years, the advent of CDK4/6i (palbociclib, abemaciclib and ribociclib) combined with ET has dramatically improved progress free survival (PFS), and quality of life compared to ET alone, and delayed the emergence of endocrine resistance in the treatment of advanced/metastatic HR+/HER2-breast cancer (Chen et al (2019) Latest Overview of the Cyclin-Dependent Kinases 4/6 Inhibitors in Breast Cancer: The Past, the Present and the Future. *J Cancer*; 10(26):6608-6617; (2020) 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol*; 31(12):1623-1649).

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CDK4/6i can be combined with fulvestrant in 1st line in those patients relapsed on adjuvant AI therapy, or within 12 months of stopping adjuvant AI (Gennari et al 2021, NCCN Guideline Breast Cancer Version 4.2022). Updated results from the Monarch-2 (Sledge et al (2020) The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-

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Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. JAMA Oncol; 6(1):116-124)

General Definitions

- 5 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. 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 $\pm 1\%$.

- 15 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 a CDK4/6 inhibitor and/or the endocrine treatment. Such treatment may comprises one or more administrations of the radiopharmaceutical compound over a determined period.

- 25 As used herein “breast cancer” refers to the most common cancer and the leading cause of cancer death for women worldwide. The term breast cancer also includes its subtypes based on the presence or absence of the ER and progesterone receptor (PgR), and the expression and amplification of HER2: HR-positive (HR+; ER+, PgR+ and HER2-), HER2-positive (HER2+) and triple-negative (TN; ER-, PR- and HER2-).

- 30 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).

As used herein "prior endocrine treatment" refers to an endocrine treatment as defined herein which precedes the treatment with the radiopharmaceutical compound. Methods using "endocrine treatment" which is not "prior," refer to use of endocrine treatment in combination with the radiopharmaceutical compound. The compounds used in the "prior endocrine treatment" may be the same or different from the compounds used in the endocrine treatment in combination with the radiopharmaceutical compound.

In some embodiments, said subject has been selected from subjects experiencing early relapse after previous endocrine therapy in combination with a CDK4/6 inhibitor. In some embodiments, the CDK4/6 inhibitor is palbociclib, ribociclib or abemaciclib.

As used herein "early relapse" refers to relapse during neoadjuvant or adjuvant endocrine therapy or within 12 months after completion of neoadjuvant or adjuvant endocrine therapy. "Relapse" in the case of a cancer refers to a return to progressive disease after a period of static or regressive disease. Progressive disease can be measured in ways that would be appropriate for the cancer in question, for example, increase in the number or size of tumors or cancerous lesions.

In some embodiments, "endocrine therapy" comprises administering a therapeutically effective amount of a selective estrogen receptor modulator, a non-steroidal aromatase inhibitor, a steroidal aromatase inhibitor, or a selective ER degrader. In some embodiments, said endocrine therapy comprises administering a therapeutically effective amount of a selective ER degrader. In some embodiments, endocrine therapy comprises administering a therapeutically effective amount of fulvestrant or an aromatase inhibitor.

"Neoadjuvant therapy" is therapy given before another therapy. "Adjuvant therapy" is therapy given after another therapy. For example, if an aromatase inhibitor is given to a breast cancer patient before surgical removal of a breast cancer tumor, the aromatase inhibitor is being administered as neoadjuvant therapy to the surgery. As a further example, if an aromatase inhibitor is given to a breast cancer patient after surgical removal of a breast cancer tumor, the aromatase inhibitor is being administered as adjuvant therapy to the surgery.

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.

5 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).

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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.

20

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 non6WO 2021/171261 PCT/IB2021/051643 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.

25

"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 CDK4/6 inhibitor,

and/or an endocrine therapy, 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
 5 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 CDK4/6 inhibitor, to a single subject in need thereof (e.g.
 10 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

15 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 :

C is a chelating moiety;

20 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 radioactive isotopes include without limitation ^{90}Y , ^{131}I , ^{121}Sn , ^{186}Re , ^{188}Re , ^{64}Cu , ^{67}Cu , ^{59}Fe , ^{89}Sr ,
 25 ^{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.

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 :

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

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

- 10 D-Phe,

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,

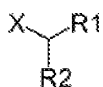
Xaa5 is Val, Ser or Thr; preferably Val,

- 15 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

or Z is

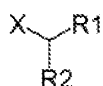


- 20 wherein X is NH (amide) or O (ester) and R1 and R2 are the same or different and selected from a proton, an optionally substituted alkyl, an optionally substituted alkyl ether, an aryl, an aryl ether or an alkyl-, halogen, hydroxyl, hydroxyalkyl, amine, amino, amido, or amide substituted aryl or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

5 or Z is

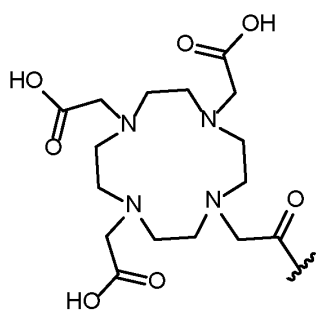


wherein X is NH (amide) and R2 is CH(CH₂-CH(CH₃)₂) and R1 is the same as R2 or different (CH₂N)-Pro-NH₂.

10 As used herein, the term “chelating moiety” refers to an organic moiety comprising functional groups that are able to form non-covalent bonds with the radionuclide M and, thereby, form a 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 may be selected among the following list (which is not limitative): 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) (tetraxetan),
 15 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-
 20 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,



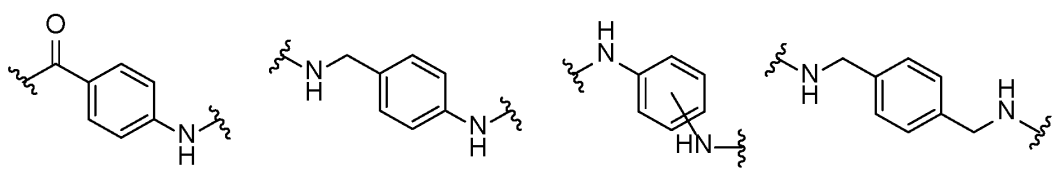
wherein the wavy bond represents the point of attachment of the chelating agent to the spacer S, or to the GRP receptor antagonist P.

- 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) from GRP receptor antagonist (and the spacer) and the chelating moiety, preferably the bond(s) is (are) covalent.

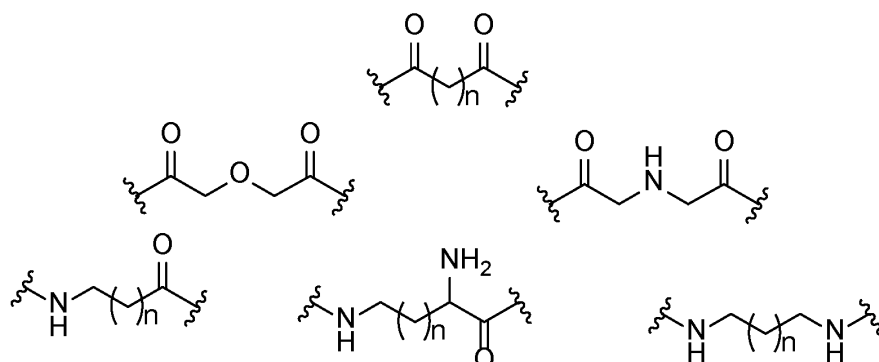
The chelating moiety C is typically bonded to the N-terminal end of the above disclosed peptide derivatives formulae, such as DPhe-Gln-Trp-Ala-Val-Gly-His-Z, optionally via the spacer S.

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

a) aryl containing residues of any the formulae:

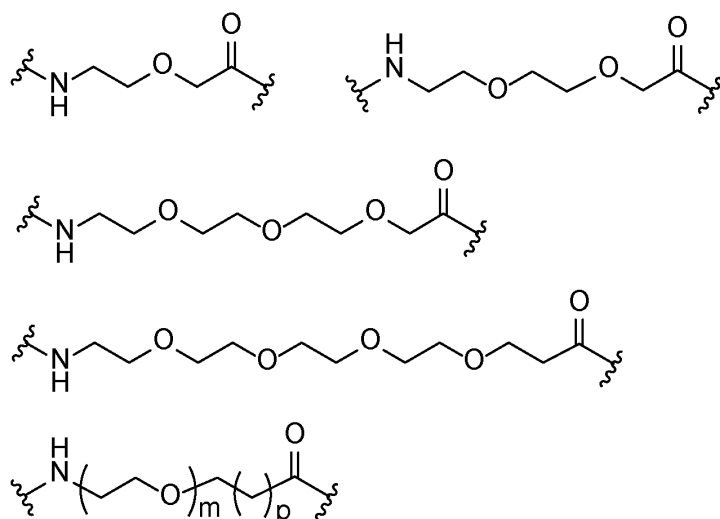


b) dicarboxylic acids, ω -aminocarboxylic acids, ω -diaminocarboxylic acids or diamines derivatives of any of the following formulae:



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:

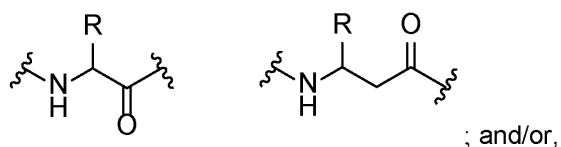


5

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

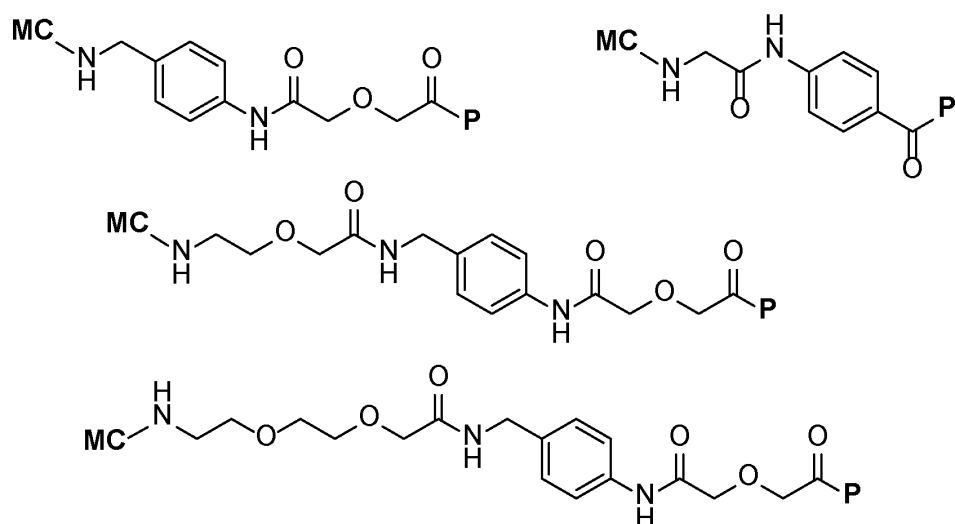
p is an integer from 0 to 5, for example $p = 0$ or 1 ;

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



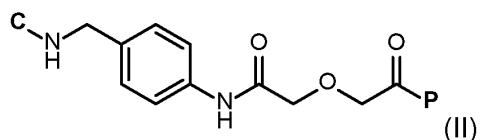
e) any combinations of one or more of a, b, c and/or d.

In some 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:



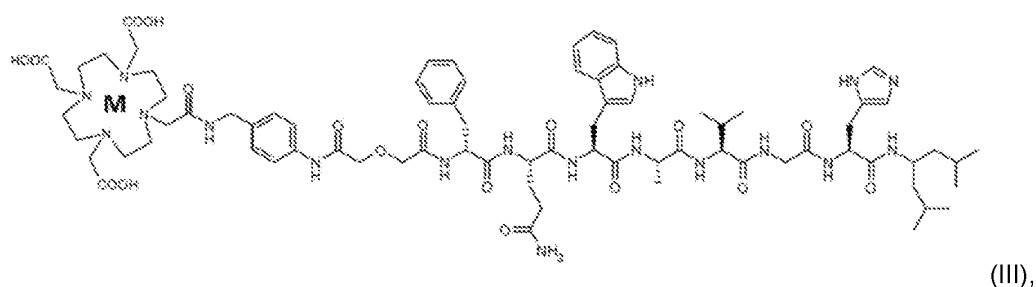
wherein C and P are as defined above, and M is a radioactive isotope complexed to the chelating moiety, in some embodiments M is selected from ^{177}Lu .

In some embodiments, 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.

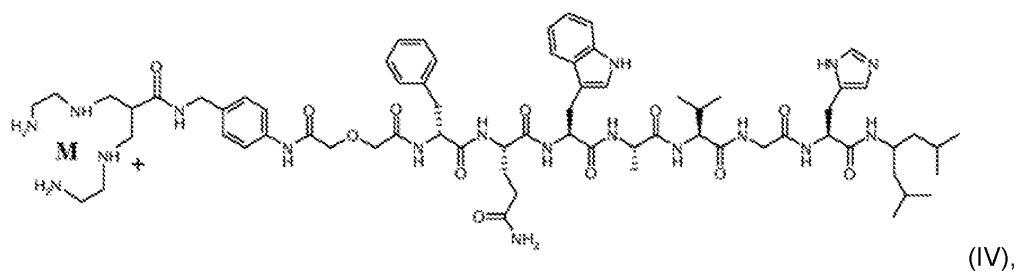
In some embodiments, the radiopharmaceutical compound for use in the treatment methods is M-NeoB of formula (III):



wherein M is as defined above, in some embodiments M is ^{177}Lu .

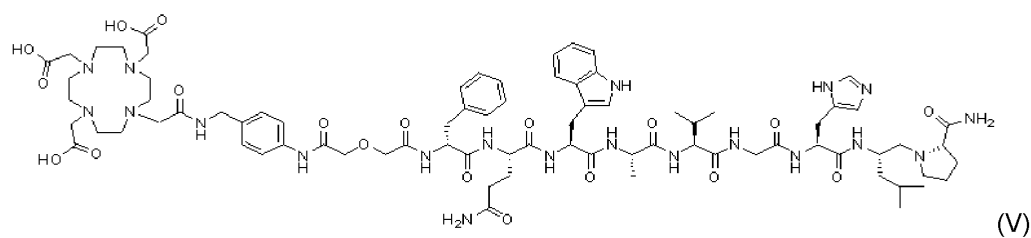
The radiopharmaceutical compound $[^{177}\text{Lu}]\text{Lu-NeoB}$ refers to the compound of formula (III) wherein M is ^{177}Lu .

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



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

- 10 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, in some embodiments M is ^{177}Lu .

Some embodiments of the disclosure encompass combination therapy with $[^{177}\text{Lu}]\text{Lu-NeoB}$ as the radiopharmaceutical compound.

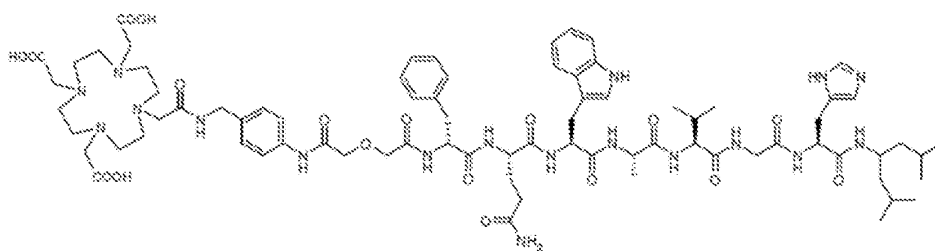
The radiopharmaceutical compound is for use in treating breast cancer in a subject in need thereof wherein a therapeutically effective amount of said radiopharmaceutical compound is administered to said subject.

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 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

In some embodiments, the combination therapy comprises administering a pharmaceutical composition consisting of:

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



(III); and;

- (b) gentisic acid or salts thereof and ascorbic acid or salts thereof;
- (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.

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 WO2021/0608051.

CDK4/6 inhibitor as used in the combination therapy

5 The method of treating breast cancer in a subject in need thereof includes a step of administering the radiopharmaceutical compound to said subject in combination with a CDK4/6 inhibitor, e.g. ribociclib, and an endocrine treatment, e.g. fulvestrant.

As used herein, the term "CDK4/6 inhibitor" refers to cyclin-dependent kinase 4/6 inhibitor and is used for the treatment of diseases of oncological nature by affecting cell cycle progression and leading to cell apoptosis. Indeed, the CDK4/6 proteins are found both in healthy cells and cancer
10 cells and control how quickly cells grow and divide. In breast cancer, these proteins can become overactive and cause the cells to grow and divide uncontrollably. CDK4/6 inhibitors interrupt these proteins in order to slow or even stop the cancer cells from growing

In some embodiments, the method of the disclosure comprises exposing the tumor to be treated to a therapeutically effective amount of CDK4/6 inhibitor. CDK4/6 inhibitor may be selected from
15 the group consisting of ribociclib (Kisqali), palbociclib (Ibrance), and abemaciclib (Verzenio). Preferably CDK4/6 inhibitor is ribociclib.

As used herein, "ribociclib" refers to a cyclin-dependent kinase 4/6 inhibitor and more specifically to a compound of formula: 7-cyclopentyl-N,N-dimethyl-2-[(5-piperazin-1-ylpyridin-2-yl)amino]pyrrolo[2,3-d]pyrimidine-6-carboxamide and pharmaceutically acceptable salts thereof
20 (CAS number of 1211441-98-3).

In an embodiment, said CDK4/6 inhibitor, preferably ribociclib, is administered orally at a daily therapeutically effective amount from 400 to 800 mg, preferably from 500 to 700 mg, more preferably from 550 to 650 mg, and even more preferably about 600 mg.

In an embodiment, said CDK4/6 inhibitor, e.g. ribociclib, is administered orally at a daily dose of
25 about 600 mg, e.g. from one to 6 cycles of a period of 15 to 28 days, each cycle including e.g. 21 days of daily administration followed by a period of 7 days off treatment.

In some embodiments, said CDK4/6 inhibitor, e.g. ribociclib, is administered orally at a daily dose of about 600 mg, e.g. from one to 6 cycles of a period of 28 days, each cycle including e.g. 21

days of administration followed by a period of 7 days off treatment, wherein the radiopharmaceutical compound is administered for 3-12cycles.

Endocrine treatment as used in the combination therapy

5 The method of treating breast cancer in a subject in need thereof includes a step of administering the radiopharmaceutical compound to said subject in combination with a CDK4/6 inhibitor and with a therapeutically effective amount of an endocrine treatment, e.g. fulvestrant.

As used herein, the term "endocrine treatment", "hormonal therapy", "hormone treatment" or "hormone therapy" refers to treatment that slows or stops the growth of hormone-sensitive tumors by blocking the body's ability to produce hormones or by interfering with effects of hormones on
10 breast cancer cells.

Several strategies are used to treat hormone-sensitive breast cancer, including:

1. Blocking ovarian function which may be done surgically or by treatment with radiation or by treatment with gonadotropin-releasing hormone (GnRH) agonists, which are also known as luteinizing hormone-releasing hormone (LHRH) agonists. Examples of ovarian
15 suppression drugs are leuprolide (Lupron) or a synthetic analog of gonadotropin releasing hormone such as gosereline (Zoladex);
2. Blocking estrogen production which may be done by treatment with steroidal or non-steroidal aromatase inhibitors such as asatrozole (Arimidex), letrozole (Femara) or exemestane (Aromasin);
- 20 3. Blocking estrogen's effects which may be done by treatment with selective estrogen receptor modulators (SERMs) such as tamoxifen (Nolvadex) and toremifene (Fareston), or with selective ER degrader such as fulvestrant (Faslodex).

In some embodiments, said endocrine treatment comprises administering a therapeutically effective amount of a selective estrogen receptor modulator, a non-steroidal aromatase inhibitor,
25 a steroidal aromatase inhibitor, or a selective ER degrader. in some embodiments, said endocrine treatment comprises administering a therapeutically effective amount of a selective ER degrader.

In some embodiments, said selective ER degrader is fulvestrant.

As used herein, "fulvestrant" refers to a steroidal antiestrogen and more specifically compound of formula (7R,8R,9S,13S,14S,17S)-13-methyl-7-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)nonyl]-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthrene-3,17-diol and pharmaceutically acceptable salts thereof (CAS number of 129453-61-8).

5 In some embodiments, said selective ER degrader, e.g. fulvestrant, is administered once every 14 to 56 days, for example 28 days, for example starting the same day as the administration of said radiopharmaceutical compound, and is administered for at least as long as the radiopharmaceutical is administered, and optionally administration of ER degrader continues until disease progression.

10 In an embodiment, said endocrine treatment, e.g. said selective ER degrader, e.g. fulvestrant, is administered concomitantly with said CDK4/6 inhibitor, e.g. ribociclib.

In an embodiment, said endocrine treatment, e.g. fulvestrant, is administered via intramuscular administration, at a dose from 250 to 700 mg, for example using a long-acting formulation.

15 In some embodiments, both CDK4/6 inhibitor and endocrine treatment, e.g. fulvestrant, are initiated the same day. In some embodiments the CDK4/6 inhibitor, e.g. ribociclib, is concomitantly administered with the endocrine treatment, e.g. fulvestrant.

In some embodiments, said endocrine therapy further comprises concomitantly administering a synthetic analog of gonadotropin releasing hormone, for example goserelin, e.g. via subcutaneous administration, every 28 days at a dose of about 3.6mg. In some embodiments, the CDK4/6 inhibitor, e.g. ribociclib, the endocrine treatment, e.g. fulvestrant, and the synthetic analog of gonadotropin releasing hormone, e.g. goserelin, are initiated the same day. In some
20 embodiments, said synthetic analog of gonadotropin releasing hormone, for example goserelin, is administered once every 28 days, preferably starting the same day as the administration of said radiopharmaceutical compound, and is administered for at least as long as the
25 radiopharmaceutical is administered, and optionally administration of ER degrader continues until disease progression.

The combination therapy

In some embodiments, the method of treating breast cancer in a subject in need thereof comprises administering to said subject a therapeutically effective amount of a
30 radiopharmaceutical compound as described above, preferably [¹⁷⁷Lu]Lu-NeoB, in combination

with a CDK4/6 inhibitor and an endocrine treatment.

In some embodiments, the present disclosure is directed to methods of treating breast cancer 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 a CDK4/6 inhibitor, e.g. ribociclib, and further in combination with a therapeutically effective amount of an endocrine treatment, e.g. fulvestrant.

The disclosure also relates to the use of radiopharmaceutical compound in the preparation of a drug for use in treating breast cancer 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 a CDK4/6 inhibitor, e.g. ribociclib, and, with a therapeutically effective amount of an endocrine treatment, e.g. fulvestrant.

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) administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a CDK4/6 inhibitor, e.g. ribociclib, and, (iii) administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising an endocrine treatment, e.g. fulvestrant.

As used herein, the term “jointly” means that the therapeutic agents 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).

In various embodiments of the disclosure, a combined administration where the radiopharmaceutical compound (e.g. ¹⁷⁷Lu-NeoB) and the CDK4/6 inhibitor 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 some embodiments, the radiopharmaceutical compound, e.g., [¹⁷⁷Lu]Lu-NeoB, is administered the same day as the CDK4/6 inhibitor.

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

In some embodiments, said radiopharmaceutical compound, e.g., [¹⁷⁷Lu]Lu-NeoB is administered at least 6 times to said subject in combination with CDK4/6 inhibitor and further in combination with an endocrine treatment, 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 the same day as said CDK4/6 inhibitor, e.g. ribociclib and said endocrine treatment, e.g. fulvestrant.

In some 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), from 1.48 GBq (40 mCi) to 18.5 GBq (500mCi), from 1.85 GBq (50mCi) to 14.8 GBq (400mCi), from 3.7 GBq (100mCi) to 11.1 GBq(300mCi), 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), for example ranging from about 3.7 GBq (100mCi) to about 7.4 GBq (200 mCi).

In some embodiments, said radiopharmaceutical compound, e.g., [¹⁷⁷Lu]Lu-NeoB, is administered intravenously every 28 days, for 3-12cycles, e.g. 4-10 cycles, for example 6 cycles. For example, said radiopharmaceutical compound, e.g., [¹⁷⁷Lu]Lu-NeoB, is administered for 3-12 cycles, e.g. 4-10 cycles, for example 6 cycles, every 4 weeks, for example at a dose ranging from 3.7 GBq (100mCi) to 11.1 GBq(300mCi), e.g. 150 mCi, in combination with said CDK4/6 inhibitor, e.g. ribociclib, administered orally at a daily dose of 400 to 800 mg, e.g. about 600 mg, for 15 to 21 days per cycle and in combination with said endocrine treatment, e.g. fulvestrant, administered via intramuscular administration once every 14 or 28 days, for 4-6 cycles, at a dose of 250 to 700 mg, for example using a long-acting formulation.

An embodiment of a treatment scheme for the combination therapy is shown in Figure 1.

In some embodiments, said endocrine therapy further comprises concomitantly administering a synthetic analog of gonadotropin releasing hormone, for example goserelin, typically via subcutaneous administration, once every 28 days at a dose of about 3.6mg. In some embodiments, the CDK4/6 inhibitor, e.g. ribociclib, the endocrine treatment, e.g. fulvestrant, and the synthetic analog of gonadotropin releasing hormone, e.g. goserelin, are initiated the same day. In some embodiments, said synthetic analog of gonadotropin releasing hormone, for example goserelin, is administered once every 28 days, for example starting the same day as the

administration of said radiopharmaceutical compound, for 4 to 10 cycles, or for at least as long as the radiopharmaceutical is administered, and optionally administration of the synthetic analog of gonadotropin releasing hormone continues until disease progression. In some embodiments, said radiopharmaceutical compound, e.g., [¹⁷⁷Lu]Lu-NeoB, is administered intravenously every 28 days, for 3-12 cycles, for example 4-10 cycles, for example 6 cycles. For example, said radiopharmaceutical compound, e.g., [¹⁷⁷Lu]Lu-NeoB, is administered for 3-12 cycles, for example 4-10 cycles, for example 6 cycles, every 4 weeks, for example at a dose ranging from 3.7 GBq (100mCi) to 11.1 GBq(300mCi), e.g. 150 mCi, in combination with said CDK4/6 inhibitor, preferably ribociclib administered orally at a daily dose of 600 mg, for 15 to 21 days per cycle and in combination with said endocrine treatment, e.g. fulvestrant, administered via intramuscular administration once every 14 or 28 days, for at least as long as the radiopharmaceutical is administered, and optionally administration of the endocrine treatment continues until disease progression, at a dose of 250 to 700 mg, for example using a long-acting formulation, and further comprising said synthetic analog of gonadotropin releasing hormone, e.g. goserelin, administered once every 28 days, at a dose of about 3.6mg, for at least as long as the radiopharmaceutical is administered, and optionally administration of the synthetic analog of gonadotropin releasing hormone continues until disease progression.

A second embodiment of a treatment scheme for the combination therapy is shown in Figure 2.

In some embodiments, the combined effect of the radiopharmaceutical compound (e.g., [¹⁷⁷Lu]Lu-NeoB) treatment and said CDK4/6 inhibitor, e.g. ribociclib, and the endocrine treatment, e.g. fulvestrant and/or goserelin, increases the overall survival in subjects to at least 10%, 20%, 30%, 40%, or at least 50% as compared to single CDK4/6 inhibitor, e.g. ribociclib or the combined therapy of CDK4/6 inhibitor, e.g. ribociclib, and the endocrine treatment, e.g. fulvestrant and/or gosereline.

“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 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 some embodiments, the combined effect of the radiopharmaceutical compound (e.g., [¹⁷⁷Lu]Lu-NeoB), treatment and CDK4/6 inhibitor, and the endocrine treatment, also increases the

progression-free survival to at least 10%, 20%, 30%, 40%, or at least 50% as compared to single CDK4/6 inhibitor, e.g. ribociclib or the combined therapy of CDK4/6 inhibitor, e.g. ribociclib, and the endocrine treatment, e.g. fulvestrant and/or goserelin.

5 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.

10 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
15 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 breast cancer may be determined by using the RECIST criteria for tumor responses (Therasse P, Arbuck SG, Eisenhauer EA, et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European
20 Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst; 92(3):205-16) and the revised RECIST 1.1 guidelines (Eisenhauer EA, Therasse P, Bogaerts J, et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer; 45(2):228-47.).

25 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 CDK4/6 inhibitor, e.g. ribociclib and the endocrine treatment, e.g. fulvestrant and/or gosereline
30 for patients newly diagnosed with breast cancer. 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 of CDK4/6 inhibitor, e.g. ribociclib and the endocrine treatment, e.g. fulvestrant and/or gosereline for patients newly diagnosed with breast cancer. 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 ith standard of care treatment, such as a combination of CDK4/6 inhibitor, e.g. ribociclib and the endocrine treatment, e.g. fulvestrant and/or goserelin for patients newly diagnosed with breast cancer. In certain aspects, the length of survival is increased by at least one month, 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 CDK4/6 inhibitor, e.g. ribociclib and the endocrine treatment, e.g. fulvestrant and/or gosereline for patients newly diagnosed with breast cancer.

In some embodiments, the combined therapeutic effect of the radiopharmaceutical, ER degrader and endocrine treatment shows synergy.

15 **Methods for selecting a subject for the combination treatment**

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

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 a alternate radionuclide suitable for imaging i.e. imaging radiopharmaceutical compound, based on detection of said radionuclide in the imaging scan at the tumor region, post-surgery.

Typical alternate radionuclide 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 .

In some embodiments, the radionuclide suitable for imaging is ^{67}Ga , ^{68}Ga or ^{64}Cu , preferably ^{68}Ga .

In some embodiments, the subject is selected by evaluating the ^{68}Ga uptake by PET/CT or PET/MRI scan at the tumor region, e.g. breast region.

In some embodiments, said subject eligible for the combination therapy is selected from subjects showing presence of radionuclide enhancement, for example gadolinium enhancement, in a

PET/MRI scan at the tumor region, post-surgery.

In some embodiments, PET scan with the radiopharmaceutical compound labelled with a suitable radiometal for imaging, e.g. [⁶⁸Ga]Ga-NeoB, may be performed from 42 days to 1 day prior the first administration of said radiopharmaceutical compound for the combination treatment.

5 Thus, the disclosure also relates to methods for determining whether a human subject having breast cancer 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,
- 10 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
15 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
20 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 [⁶⁸Ga]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
25 a solution of gallium-68 chloride (⁶⁸GaCl₃) in HCl eluted from a ⁶⁸Ge/⁶⁸Ga 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 some embodiments, the selection of subject is performed from 10 to 18 days, preferably around
5 14 days prior to the first administration of the radiopharmaceutical compound.

In some embodiments, 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,
10 for example by MRI, CT, SPECT or PET, are also identified by said imaging radiopharmaceutical compound uptake, i.e. [^{68}Ga]Ga-NeoB uptake. In some embodiments, PET/MRI or PET/CT imaging is performed from 30 to 120 minutes, e.g. from 60 to 90 minutes after the intravenous administration of said imaging radiopharmaceutical compound to the subject.

In some embodiments of the method, a subject is selected for the combination therapy of the
15 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. [^{68}Ga]Ga-NeoB uptake, as determined by PET/MRI
20 or PET/CT imaging in said subject.

In some embodiments, the term "lesion" refers to measurable tumor lesions according to RECIST 1.1 criteria as defined above.

In some embodiments, said subject is newly diagnosed with breast cancer or suffers from recurrent breast cancer.

25 As used herein "recurrent" refers to patients who have relapsed after at least one treatment.

In some embodiments, said subject has ER positive, HER-2 negative (ER+/HER2-) and GRPR-positive (GRPR+) breast cancer.

In some embodiments, said subject has been selected from subjects experiencing early relapse after neoadjuvant or adjuvant endocrine therapy.

As used herein “early relapse” refers to relapse during neoadjuvant or adjuvant endocrine therapy or within 12 months after completion of neoadjuvant or adjuvant endocrine therapy.

As used herein “neoadjuvant endocrine therapy” refers to aromatase inhibitors, e.g. letrozole.

5 In some embodiments, said subject is a post-menopausal woman with advanced metastatic breast cancer.

10 In some embodiments, said subject is a pre-menopausal or peri-menopausal woman with advanced metastatic breast cancer. In such specific embodiment, the endocrine treatment may further comprise concomitantly administering a synthetic analog of gonadotropin releasing hormone, for example goserelin, typically via subcutaneous administration, every 28 days at a dose of about 3.6mg.

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 the present invention.

EXAMPLES

15 **Example 1: Clinical study I for treating breast cancer 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 ribociclib and fulvestrant in subjects with ER-positive, HER-2 negative and GRPR-positive breast cancer experiencing early relapse from (neo)adjuvant endocrine therapy.

20 **Synopsis**

Brief title	Phase Ib Dose Finding Study Assessing Safety and Activity of [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant in subjects with ER-positive, HER-2 negative and GRPR-positive breast cancer experiencing early relapse from (neo)adjuvant endocrine therapy
Sponsor and Clinical Phase	Novartis, Phase Ib
Study type	Interventional

Purpose	This study aims to investigate different doses of [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant in postmenopausal women with estrogen receptor (ER) positive (ER+), human epidermal growth factor receptor-2 (HER2) negative (HER2-) and gastrin releasing peptide receptor (GRPR) positive (GRPR+) breast cancer who have relapsed during or within 12 months from completion of (neo)adjuvant endocrine therapy (ET) in the escalation part. Additionally, to characterize the safety and tolerability of [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant in postmenopausal women and in combination with ribociclib, fulvestrant and goserelin in pre/peri-menopausal women in the expansion part.
Primary Objective(s)	Dose Escalation Phase: To estimate the RD of [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant in post-menopausal participants Dose Expansion Phase: To characterize the safety and tolerability of [177Lu]Lu-NeoB RD in combination with ribociclib and fulvestrant in post-menopausal participants and in combination with ribociclib, fulvestrant and goserelin in pre/peri-menopausal participants.
Secondary Objectives	In Dose Escalation: 1. To characterize the safety and tolerability of [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant in post-menopausal participants. 2. To assess the preliminary antitumor activity of [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant in post-menopausal participants. In the Dose Expansion 1. To assess the preliminary antitumor activity of [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant in post-menopausal and in combination with ribociclib, fulvestrant and goserelin in pre/peri-menopausal participants. In the Dose Escalation and Dose Expansion 1. To characterize the pharmacokinetics (PK) and biodistribution (dosimetry) of [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant in post-menopausal participants and in combination with ribociclib, fulvestrant and goserelin in pre/peri-menopausal participants

	2. To evaluate the safety and tolerability of [68Ga]Ga-NeoB in all participants who have received [68Ga]Ga-NeoB at screening
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Trial Design:

This is a phase Ib, single arm, multicenter, open label, dose finding study of [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant in adult female participants with ER+/HER2-, GRPR+, advanced/metastatic breast cancer who have relapsed during or within 12 months from completion of prior (neo)adjuvant ET. The study comprises of a dose escalation part, followed by a dose expansion part. The dose expansion part will also include pre/perimenopausal women who will receive [177Lu]Lu-NeoB in combination with ribociclib, fulvestrant and goserelin.

Brief Summary:

Metastatic breast cancer (MBC) is an incurable disease with a 5 year OS rate of approximately 22% (National Cancer Institute 2021). In the past few years, the addition of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (CDK4/6i) to ET has dramatically improved the prognosis of patients with hormone receptor positive (HR+)/HER2-, advanced/metastatic breast cancer but the OS benefit remains limited in the subset of patients who relapse during or within 12 months from completion of (neo)adjuvant therapy (early relapsed) versus those with de novo disease or relapse >12 months from completion of (neo)adjuvant ET (38.8 vs 67.6 months, respectively (Novartis unpublished data, Neven et al 2022). These patients represent an unmet medical need for which novel therapies are needed.

The addition of [177Lu]Lu-NeoB, a radionuclide therapy, targeting the GRPR which is overexpressed in breast cancer cells, to the currently recommended and approved combination of ET and CD4/6i is expected to be a safe and efficacious treatment option as first line treatment of HR+/HER2- MBC patients early relapsed after a (neo)adjuvant ET.

The purpose of this phase 1b, single arm, multicenter, open label, dose finding study is to estimate the RD of [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant in adult female participants with ER+, HER2-, GRPR+, advanced or metastatic breast cancer who have relapsed during or within 12 months from completion of prior (neo)adjuvant ET (escalation part). Additionally this study aims to characterize the safety and tolerability of [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant in post-menopausal participants and in combination with ribociclib, fulvestrant and goserelin in pre/peri-menopausal participants (expansion part).

The study comprises of a dose escalation part, followed by a dose expansion part. The dose escalation part will estimate the RD of [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant; four provisional dose levels are planned to be tested: 100mCi (initial dose), 150mCi, 200 mCi and 250mCi in cohorts of 3 to 6 participants. After inclusion of each cohort of 3 to 6 participants, the incidence rate of DLTs will be compared to the pre-defined toxicity rate boundaries to decide whether the next cohort will receive a lower, higher or same dose or whether the trial will be terminated. The expansion part will assess the safety, tolerability and anti-tumor activity of the RD dose of [177Lu]Lu-NeoB, as established in the dose escalation part, in combination with ribociclib and fulvestrant in both post menopausal and pre-/peri-menopausal participants (who will additionally receive goserelin). A total of 15 participants will be enrolled in the expansion part.

During screening, study participants will receive the investigational imaging agent [68Ga]Ga-NeoB. An additional administration of the [68Ga]Ga-NeoB will be performed within 2-8 weeks from the last administration of [177Lu]Lu-NeoB for a PET/CT or PET/MRI.

Study treatment will include [177Lu]Lu-NeoB on day 1 of each 28-day cycle (± 3 days) for 6 cycles, ribociclib (once daily; days 1 to 21 in a 28-day cycle) and fulvestrant (C1D1, C1D15, C2D1 and every 28 days thereafter) until disease progression. Pre- and perimenopausal participants in the expansion part will additionally receive goserelin on day 1 of every cycle.

During the treatment period participants will be required to attend a site visit approximately every 28 days, on the first day of each cycle (as well as on C1D2, C1D3, C1D8, C1D15, C2D15, C3D3 and C5D3), to undergo study treatment administration, dosimetry and safety assessments. Tumor assessments are performed every 8 weeks until month 18, every 12 weeks until month 36 and as clinically indicated thereafter, until disease progression. After study treatment discontinuation, participants will be followed up for safety for 8 weeks after their last study treatment administration. Beyond the initial 8 weeks of safety follow-up, all participants will be followed up every 12 weeks until month 36 and every 24 weeks thereafter until month 60, as per the Section 1.3, SoA, for a total of 5-years from the participant's enrollment in the study, or until death, lost to follow-up, or WoC.

The end of study is defined as the date of the last visit, scheduled procedure or follow up (or date of death, WoC or lost to follow up, whichever occurs first) of the last participant in the study

globally, as shown in Section 1.3 SoA, or at 5 years from the date of the last participant enrolled, whichever occurs earlier.

Treatment of interest

This study includes [68Ga]Ga-NeoB as an imaging agent, and [177Lu]Lu-NeoB, ribociclib, fulvestrant, as well as goserelin (in the expansion part for pre/peri-menopausal women only), as study treatments.

The NeoB peptide is a new generation bombesin (BN) analogue, a GRPR-antagonist with superior pharmacokinetic and toxicological properties when compared to agonist analogues, which binds to the GRPR with high affinity and shows low internalization, consistent with antagonistic behaviour (Nock et al 2017). Its structure contains a DOTA metal-chelator which allows for radiolabeling with different radionuclides including gallium-68 (for positron emission tomography (PET) imaging), and lutetium-177 (for radionuclide therapy) without affecting receptor affinity, internalization properties, or biodistribution.

[68Ga]Ga-NeoB will be used as imaging agent and is intended as a selection tool for [177Lu]Lu-NeoB treatment in patients with tumors overexpressing GRPR, including subjects affected by breast cancer (Flores et al 2010, Morgat et al 2017). [68Ga]Ga-NeoB has shown favorable technical and diagnostic performance to identify GRPR-expressing malignancies, both in preclinical and in clinical studies, with good image quality that allows easy interpretation.

[177Lu]Lu-NeoB has shown high affinity to the GRPR and its ability 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, being consistent with a GRPR antagonist profile. On the contrary, tumor remanence is persistent, with detectable uptake values up to 7 days after injection. These characteristics make [177Lu]-Lu NeoB an ideal candidate for peptide receptor radionuclide therapy (PRRT). [177Lu]Lu-NeoB is currently being evaluated as single agent 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 who have no therapeutic available options. Data show that [177Lu]Lu-NeoB has shown a good tolerability and safety profile and a favorable biodistribution with low uptake in organs

considered to be at risk due to GRPR-expression, such as the pancreas, or due to radioligand therapy (RLT), such as the red marrow, and the route of excretion, such as the kidneys.

In this study, participants will receive [¹⁷⁷Lu]Lu-NeoB in combination with ribociclib and fulvestrant (and goserelin, where applicable, in the expansion part only).

5 Number of Participants:

Up to 27 participants will be enrolled to the study dose escalation part: 4 cohorts of 3-6 participants for 4 dose levels; an additional 3-6 participants, up to a total of 9 participants may be enrolled at a specific dose level. Once the RD has been estimated, approximately 15 participants will be enrolled in the dose expansion part.

10 Key Inclusion criteria:

- Adult female ≥ 18 years of age at the time of informed consent
 - Participant is post-menopausal at the time of starting study treatment (escalation part).
 - Participant is pre-/peri or post-menopausal at the time of starting study treatment (expansion part).
- 5
- Histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive with ER >10% (regardless of PgR expression) breast cancer by local laboratory testing (based on the most recently analyzed tissue sample)
- 10
- HER2 negative breast cancer defined as a negative in situ hybridization test or an immunohistochemistry (IHC) status of 0, 1+ or 2+. If IHC is 2+, a negative in situ hybridization (e.g. FISH, CISH, or SISH) test is required by local laboratory testing (based on the most recently analyzed tissue sample)
- 15
- Disease relapse during (neo)adjuvant ET or ≤ 12 months from completion of (neo)adjuvant ET (which may have included a CDK4/6 inhibitor)
 - Advanced [loco regionally recurrent not amenable to curative therapy (e.g. surgery and/or RT)] or metastatic disease
- 20
- Measurable disease, i.e., at least one measurable lesion as per RECIST 1.1. (a lesion at a previously irradiated site may only be counted as a target lesion if there is a clear sign of progression since the irradiation) OR if only lytic bone lesions are present, at least one lesion must have a soft tissue component that can be evaluated by CT or MRI and meets the definition of measurability as per RECIST criteria 1.1 (participants with only one predominantly lytic bone lesion that has been previously irradiated are eligible if there is documented evidence of disease progression of the bone lesion after irradiation).
- 25
- Participant has at least one target lesion (RECIST 1.1, based on the baseline stand alone Computed Tomography (CT)/Magnetic Resonance Imaging (MRI) with [68Ga]Ga-NeoB uptake at PET/CT or PET/MRI. The same identified measurable lesion shows [68Ga]Ga-NeoB uptake on PET/CT or PET/MRI based on the Visual Scoring Scale
- Adequate bone marrow and organ function
 - Standard 12-lead ECG values defined as the mean of the triplicate ECGs and assessed by the central laboratory
- 30
- QT interval corrected by Fridericia's formula (QTcF) interval at screening < 450 msec
 - Mean resting heart rate 50-90 bpm (determined from the ECG)
 - Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

Key Exclusion criteria

- Prior treatment in the advanced/metastatic setting
- Symptomatic visceral disease or any disease burden that makes the participant ineligible for ribociclib plus endocrine treatment per the Investigator's best judgment
- Presence of CNS involvement unless meeting BOTH of the following criteria: 1) At least 4
5 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment. 2) Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme inducing anti-epileptic medications for brain metastases.
- Currently receiving warfarin or other Coumadin derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin, or fondaparinux is
10 allowed
- Diagnosis of inflammatory breast cancer at screening
- Child Pugh score B or C
- History or current diagnosis of impaired cardiac function, clinically significant cardiac disease or ECG abnormalities indicating significant risk of safety for participants
- 15 • Known or expected hypersensitivity to any of the study drugs or any of their excipients
- Prior administration of a radiopharmaceutical unless 10 or more half-lives have elapsed before injection of [68Ga]Ga-NeoB
- Participant has received extended-field RT $\leq$ 4 weeks or limited field RT $\leq$ 2 weeks prior to start of treatment and has not recovered to grade 1 or better from related side effects of such
20 therapy (with the exception of alopecia or other toxicities not considered a safety risk for the participant at Investigator's discretion) and/or prior EBRT to more than 25% of the bone marrow.
- Patient is currently receiving or has received systemic corticosteroids $\leq$ 2 weeks prior to starting study treatment, or who have not fully recovered from side effects of such treatment. Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g.,
25 for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular)
- Participant has a history of or ongoing acute pancreatitis within 1 year of screening

- Participant is currently receiving any of the following substances and cannot be discontinued 7 days prior to starting study treatment:
- Concomitant medications, herbal supplements, and/or fruits (e.g., grapefruit, pummelos, star fruit, Seville oranges) and their juices that are strong inducers or inhibitors of cytochrome P450 3A4 (CYP3A4/5),
- Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5
- Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause TdP that cannot be discontinued or replaced by safe alternative medication (e.g., within 5 half-lives or 7 days prior to starting study treatment)

Treatment Groups:

- The screening period of 42 days is followed by the treatment period until disease progression, discontinuation of study treatment due to any other reason such as unacceptable toxicity, symptomatic deterioration, withdrawal of consent (WoC), lost to follow up, Investigator decision or death, whichever occurs first. The post treatment follow up period comprises the safety follow up period for 8 weeks after treatment discontinuation and the long term follow up for up to 5 years from the date of the participant's enrollment.
- During screening, each participant will receive [68Ga]Ga-NeoB for PET/CT or PET/MRI imaging. [68Ga]Ga-NeoB will be administered as a single intravenous dose of an activity within a range of 150-250 MBq (4.1-6.8 mCi).
- In the dose escalation part, each participant in a particular cohort will receive [177Lu]Lu-NeoB at a starting dose of 3.7 GBq (100 mCi) +/- 10% (intravenous infusion, every 28 days for 6 cycles) in combination with ribociclib (tablet, 600 mg daily for 21 consecutive days followed by 7 days off treatment) and fulvestrant (intramuscular injection, 500 mg on day 1, of a 28-day cycle plus an additional single dose to be administered on D15 of cycle 1). Four dose levels of [177Lu]Lu-NeoB are planned to be explored during the escalation part (100, 150, 200 or 250 mCi) in order to estimate the RD.
- In the expansion part, each participant will receive [177Lu]Lu-NeoB at the RD (intravenous infusion, RD, every 28 days for 6 cycles) in combination with ribociclib (tablet, 600 mg daily for 21

consecutive days followed by 7 days off treatment) and fulvestrant (intramuscular injection, 500 mg on day 1, of a 28-day cycle plus an additional single dose to be administered on D15 of cycle 1). Additionally, pre-/peri-menopausal women will receive goserelin (3.6 mg on day 1 of a 28-day cycle)

- 5 • If the starting dose of [177Lu]Lu-NeoB in the escalation part is not tolerated there will be no lower dose tested and the study will be terminated
- Within 2-8 weeks from the last administration of [177Lu]Lu-NeoB, an additional administration of the investigational imaging agent [68Ga]Ga-NeoB will be performed to assess the difference between baseline [68Ga]Ga-NeoB PET scan and after the administration of the
- 10 last dose of [177Lu]Lu-NeoB.

Example 2: Clinical study II for treating breast cancer subjects, updates to protocol of clinical study I from Example 1

Changes from Example 1:

Change in the study design

- 15 The study design has been updated from the ‘dose escalation followed by a dose expansion part’ to dose escalation and parallel backfilling at lower and previously cleared dose levels. The dose expansion part has been removed. The purpose of this design change is to allow robust and efficient data generation in all tested dose levels, which will facilitate determination of the recommended dose for future studies and inform future dose optimization based on totality of data.

20 **Key Changes in Eligibility criteria**

- Patients with HR+, HER2- advanced breast cancer who progressed on first line treatment (ET + CDK4/6 inhibitor) for advanced disease will be allowed in the study. Patients in the post-CDK4/6i setting are with a challenging clinical scenario, as they may have more aggressive disease as compared to patients in an endocrine only failure setting. Furthermore, the choice
- 25 of subsequent therapies is challenging and often based on clinical experience as no guidelines identifying the optimal therapeutic sequence are available, highlighting the unmet medical need for novel therapies in this population.
- Male patients will be allowed in the study.

- Female participants will be allowed regardless of their menopausal status throughout the study in order to harmonize the patient population across all dose levels.
- The threshold of uptake of [⁶⁸Ga]Ga-NeoB to select participants for treatment with [¹⁷⁷Lu]Lu-NeoB has been updated following the updated study design. While two different thresholds based on a visual uptake scoring scale were previously applied to each part of the study (dose escalation and dose expansion), only the set of criteria requiring higher uptake has been selected with the current design. The required score corresponds to the one that was previously set for the escalation part of the study and is based on the purpose of enriching a more homogeneous population with the aim to maximize efficacy.
- Introduced new exclusion criteria pertaining to use of NEP inhibitors at the time of study entry. This is due to the potential risk of drug-drug interaction between [¹⁷⁷Lu]Lu-NeoB and neprilysin (NEP) inhibitors.

Other Changes

- Clinical experience with [¹⁷⁷Lu]Lu-NeoB has been updated with the most recent data supporting determination of RP2D in the ongoing first in human study CAAA603A12101 (NeoRay).
- Statistical considerations have been updated according to the new study design, including endpoints definitions, and sample size. The diagnosed set, used for [⁶⁸Ga]Ga-NeoB related analyses has been split into two analysis sets: [⁶⁸Ga]Ga-NeoB Safety Analysis Set and [⁶⁸Ga]Ga-NeoB Evaluable Set.
- Update of the biomarker strategy to allow paired pre- and post-treatment tumor biopsy collection when medically feasible. In addition, a new assessment for [⁶⁸Ga]Ga-NeoB has been added to check the relationship of GRPR expression in tissue biopsies taken at C3D1 with uptake of [⁶⁸Ga]Ga-NeoB in PET at C2D15.
- Time lapse between the last administered dose of [¹⁷⁷Lu]Lu-NeoB and the subsequent PET scan has been changed from 2-8 weeks to 4-8 weeks, following HA feedback.
- Information and specification on concomitant use and potential DDI with NEP-inhibitors (e.g. Entresto, racecadotril) has been added.

- In Section 7.5 (Criteria for stopping or pausing the study), the number of participants triggering a coordinated safety review has been updated given that all participants will undergo DLT evaluation (according to the new study design). In addition, clarification was added on process for HA notification and restart of recruitment based on local regulations, as
5 per HA feedback.
- The additional exploratory assessments of ‘Clinical Outcome Assessments (COAs)’ (Section 8.5) are removed since, in the new design there will no longer be a dedicated expansion part with one single recommended dose for expansion. Instead, the backfill part will inform on the preliminary benefit risk assessment of the different doses. This type of clinical outcome
10 assessments will be implemented in future development steps on the program level.

Title:

A phase Ib dose finding study assessing safety and activity of [¹⁷⁷Lu]Lu-NeoB in combination with ribociclib and fulvestrant in participants with ER+, HER2- and GRPR+ advanced breast
15 cancer who have relapsed early from (neo)adjuvant endocrine therapy or who have progressed on endocrine therapy in combination with a CDK4/6 inhibitor.

Purpose:

To estimate the recommended dose (RD) of [¹⁷⁷Lu]Lu-NeoB in combination with ribociclib and
20 fulvestrant in participants with estrogen receptor (ER) positive (ER+), human epidermal growth factor receptor-2 (HER2) negative (HER2-) and gastrin releasing peptide receptor (GRPR) positive (GRPR+) advanced breast cancer experiencing early relapse from (neo)adjuvant endocrine therapy or who have progressed on endocrine therapy in combination with a CDK4/6 inhibitor for advanced disease.

25 Trial Design:

This is a phase Ib, single arm, multicenter, open label, dose finding study of [¹⁷⁷Lu]Lu-NeoB in combination with ribociclib and fulvestrant (+/- goserelin) in adult female and male participants

with ER+/HER2-, GRPR+, advanced breast cancer experiencing early relapse from (neo)adjuvant endocrine therapy or who have progressed on endocrine therapy in combination with a CDK4/6 inhibitor for advanced disease. The study comprises a dose escalation part and a concurrent backfill part. The backfill part will allow enrollment to a previously cleared dose level (during escalation part) in order to obtain additional safety and tolerability data.

The study comprises a dose escalation part and a concurrent backfill part. The backfill part will allow enrollment to a previously cleared dose level (during escalation part) in order to obtain additional safety, tolerability as well as preliminary efficacy data. Four provisional dose levels are planned to be tested: 100 millicurie (mCi) (initial dose), 150mCi, 200 mCi and 250mCi in cohorts of 3 to 6 participants. After inclusion of each cohort of 3 to 6 participants, the incidence rate of DLTs will be compared to the pre-defined toxicity rate boundaries to decide whether the next cohort will receive a lower, higher or same dose or whether the trial will be terminated. During the backfill part, the cumulative incidence rate of DLTs will also be compared to the pre-defined toxicity rate boundaries to determine if escalation should be restarted from a lower dose level.

During screening, study participants will receive the investigational imaging agent [⁶⁸Ga]Ga-NeoB. An additional administration of the [⁶⁸Ga]Ga-NeoB will be performed within 4-8 weeks from the last administration of [¹⁷⁷Lu]Lu-NeoB for a positron emission tomography (PET)/computed tomography (CT) or PET/magnetic resonance imaging (MRI). Study treatment will include [¹⁷⁷Lu]Lu-NeoB on day 1 of each 28-day cycle (+≤3 days) for 6 cycles, ribociclib (once daily; days 1 to 21 in a 28-day cycle) and fulvestrant (C1D1, C1D15, C2D1 and every 28 days thereafter) until disease progression. Pre- and perimenopausal participants will additionally receive goserelin on day 1 of every cycle.

During the treatment period participants will be required to attend a site visit approximately every 28 days, on the first day of each cycle (as well as on C1D2, C1D3, C1D8, C1D15, C2D15, C3D3 and C5D3), to undergo study treatment administration, dosimetry and safety assessments. Tumor assessments are performed every 8 weeks until month 18, every 12 weeks until month 36 and as clinically indicated thereafter, until disease progression. After study treatment discontinuation, participants will be followed up for safety for 8 weeks after their last study treatment administration. Beyond the initial 8 weeks of safety follow-up, all participants will be followed up every 12 weeks until month 36 and every 24 weeks thereafter until month 60, i.e., for a total of 5

years from the participant's enrollment in the study, or until death, lost to follow-up, or withdrawal of consent (WoC), whichever occurs first.

The end of study is defined as the date of the last visit, scheduled procedure or follow up (or date of death, WoC or lost to follow up, whichever occurs first) of the last participant in the study globally, or at 5 years from the date of the last participant enrolled, whichever occurs earlier.

Treatment Phase

The study comprises a dose escalation part and a concurrent backfill part. The backfill part will allow enrollment to a previously cleared dose level (during escalation part) in order to obtain additional safety, tolerability as well as preliminary efficacy data. Four provisional dose levels are planned to be tested: 100 millicurie (mCi) (initial dose), 150mCi, 200 mCi and 250mCi in cohorts of 3 to 6 participants. After inclusion of each cohort of 3 to 6 participants, the incidence rate of DLTs will be compared to the pre-defined toxicity rate boundaries to decide whether the next cohort will receive a lower, higher or same dose or whether the trial will be terminated. During the backfill part, the cumulative incidence rate of DLTs will also be compared to the pre-defined toxicity rate boundaries to determine if escalation should be restarted from a lower dose level.

During screening, study participants will receive the investigational imaging agent [⁶⁸Ga]Ga-NeoB. An additional administration of the [⁶⁸Ga]Ga-NeoB will be performed within 4-8 weeks from the last administration of [¹⁷⁷Lu]Lu-NeoB for a positron emission tomography (PET)/computed tomography (CT) or PET/magnetic resonance imaging (MRI). Study treatment will include [¹⁷⁷Lu]Lu-NeoB on day 1 of each 28-day cycle (+≤3 days) for 6 cycles, ribociclib (once daily; days 1 to 21 in a 28-day cycle) and fulvestrant (C1D1, C1D15, C2D1 and every 28 days thereafter) until disease progression. Pre- and perimenopausal participants will additionally receive goserelin on day 1 of every cycle.

During the treatment period participants will be required to attend a site visit approximately every 28 days, on the first day of each cycle (as well as on C1D2, C1D3, C1D8, C1D15, C2D15, C3D3 and C5D3), to undergo study treatment administration, dosimetry and safety assessments. Tumor assessments are performed every 8 weeks until month 18, every 12 weeks until month 36 and as clinically indicated thereafter, until disease progression. After study treatment discontinuation, participants will be followed up for safety for 8 weeks after their last study treatment

administration. Beyond the initial 8 weeks of safety follow-up, all participants will be followed up every 12 weeks until month 36 and every 24 weeks thereafter until month 60, as per the Section 1.3, Schedule of Activities (SoA), i.e., for a total of 5 years from the participant's enrollment in the study, or until death, lost to follow-up, or withdrawal of consent (WoC),
5 whichever occurs first.

The end of study is defined as the date of the last visit, scheduled procedure or follow up (or date of death, WoC or lost to follow up, whichever occurs first) of the last participant in the study globally, as shown in Section 1.3 SoA, or at 5 years from the date of the last participant enrolled, whichever occurs earlier.

10 **Number of Participants**

Up to approximately 48 participants are expected to be treated at 4 dose levels. Cohorts of 3 to 6 evaluable participants will be enrolled in the dose-escalation part. Additional participants will be backfilled in each dose level up to a total of approximately 12 participants (including the participants enrolled during escalation part in that dose level).

Key Inclusion criteria

- Adult female or male ≥ 18 years of age at the time of informed consent
- Histologically and/or cytologically confirmed diagnosis of estrogen-receptor positive with ER >10% (regardless of progesterone receptor (PgR) expression) breast cancer by local
5 laboratory testing (based on the most recently analyzed tissue sample)

- HER2 negative breast cancer defined as a negative in situ hybridization test or an immunohistochemistry (IHC) status of 0, 1+ or 2+. If IHC is 2+, a negative in situ hybridization (e.g. fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH), or silver in situ hybridization (SISH)) test is required by local
10 laboratory testing (based on the most recently analyzed tissue sample)

Participant has advanced (loco regionally recurrent not amenable to curative therapy (e.g. surgery and/or radiotherapy) or metastatic) breast cancer

Participants may be:

- a. relapsed with documented evidence of relapse on or within 12 months from
15 completion of (neo)adjuvant endocrine therapy (+/- CDK4/6 inhibitor) with no treatment for advanced disease **OR**
- b. relapsed with documented evidence of relapse more than 12 months from completion of (neo)adjuvant endocrine therapy and then subsequently progressed with documented evidence of progression after one line of endocrine therapy
20 (except fulvestrant) (+/- CDK4/6 inhibitor) for advanced disease **OR**
- c. advanced breast cancer at diagnosis that progressed with documented evidence of progression after one line of endocrine therapy (except fulvestrant) (+/- CDK4/6 inhibitor)

Note: Participant who relapsed with documented evidence of relapse on/or within 12 months
25 from completion of (neo)adjuvant endocrine therapy and then subsequently progressed with documented evidence of progression after one line of endocrine therapy (with either an antiestrogen or an aromatase inhibitor) for advanced disease will NOT be included in the study. At least one target lesion (i.e., a measurable lesion as per RECIST 1.1) in the baseline stand-alone CT or MRI, showing [^{68}Ga]Ga-NeoB uptake on PET/CT or PET/MRI scoring 2
30 or above, based on the Visual Scoring Scale (see Section 8.5.2).

- Adequate bone marrow and organ function.
- Standard 12-lead ECG values defined as the mean of the triplicate ECGs and assessed locally:
 - QT interval corrected by Fridericia's formula (QTcF) interval at screening < 450 msec
- 5 • Mean resting heart rate 50-90 bpm (determined from the ECG)
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

Key Exclusion criteria

- More than one line of prior treatment in the advanced/metastatic setting. Participant shouldn't have received prior fulvestrant treatment.
- 10 • Documented evidence of prior ribociclib dose reduction due to safety reasons either in adjuvant setting or for advanced disease.
- Relapse or disease progression within 6 months of receiving a CDK4/6 inhibitor therapy either in adjuvant setting or for advanced disease. Symptomatic visceral disease or any disease burden that makes the participant ineligible for ribociclib plus endocrine treatment
- 15 per the Investigator's best judgment.
- Presence of central nervous system (CNS) involvement unless meeting BOTH of the following criteria: 1) At least 4 weeks from prior therapy completion (including radiation and/or surgery) to starting the study treatment. 2) Clinically stable CNS tumor at the time of screening and not receiving steroids and/or enzyme inducing anti-epileptic medications for
- 20 brain metastases.
- Currently receiving warfarin or other Coumadin derived anti-coagulant, for treatment, prophylaxis or otherwise. Therapy with heparin, low molecular weight heparin, or fondaparinux is allowed.
- Diagnosis of inflammatory breast cancer at screening
- 25 • Child Pugh score B or C
- History or current diagnosis of impaired cardiac function, clinically significant cardiac disease or ECG abnormalities indicating significant risk of safety for participants.
- Known or expected hypersensitivity to any of the study drugs or any of their excipients.

- Prior administration of a radiopharmaceutical unless 10 or more half-lives have elapsed before injection of [⁶⁸Ga]Ga-NeoB or [¹⁷⁷Lu]Lu-NeoB
- Participant has received extended-field RT ≤ 4 weeks or limited field RT ≤ 2 weeks prior to start of treatment and has not recovered to grade 1 or better from related side effects of such therapy (with the exception of alopecia or other toxicities not considered a safety risk for the participant at Investigator's discretion) and/or prior external beam radiation therapy (EBRT) to more than 25% of the bone marrow.
- Participant is currently receiving or has received systemic corticosteroids ≤ 2 weeks prior to starting study treatment, or who have not fully recovered from side effects of such treatment.
Note: The following uses of corticosteroids are permitted: single doses, topical applications (e.g., for rash), inhaled sprays (e.g., for obstructive airways diseases), eye drops or local injections (e.g., intra-articular)
- Participant has a history of or ongoing acute pancreatitis within 1 year of screening.
- Participant is currently receiving any of the following substances and cannot be discontinued 7 days prior to starting study treatment:
 - Concomitant medications, herbal supplements, and/or fruits (e.g., grapefruit, pummelos, star fruit, Seville oranges) and their juices that are strong inducers or inhibitors of cytochrome P450 (CYP) 3A4
 - Medications that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5
 - Concomitant medication(s) with a known risk to prolong the QT interval and/or known to cause Torsades de Pointes (TdP) that cannot be discontinued or replaced by safe alternative medication (e.g., within 5 half-lives or 7 days prior to starting study treatment)
- Participant is currently receiving NEP inhibitors (e.g. Entresto®, racecadotril) and images for dosimetry assessments cannot be acquired for this participant.

Backfill part

- Once a dose level is declared safe during the dose escalation part, additional participants will be allowed to backfill that previously cleared dose level (during dose escalation part) to obtain additional data. Participants enrolled in the backfill part will also be evaluated for dose limiting toxicity. Any new DLT observed for a given dose level in a backfill participant will trigger the review of the cumulative DLT rate for the considered dose level vs. the BOIN defined boundaries. If the BOIN suggests de-escalation or staying on that dose level, then the participating investigators and the Sponsor will meet and agree on the next dose to be tested. The recommended dose (RD) will be determined considering all available data from the escalation and backfill part. Only one escalation cohort and one backfill cohort can be open to recruitment in parallel. Participant's allocation either in the escalation cohort or in the backfill cohorts will be guided by the following principles and decision tree (Fig. 3).
- Priority will be always given to the escalation cohort.
 - If more than one dose levels are declared safe (during escalation part), backfilling will be allowed to the lowest dose level open to enrolment until that dose level has reached the maximum required number of participants. Thereafter, backfilling will be allowed to the next safe dose level.

See [Fig. 3](#) for the decision tree for participants allocation in escalation cohort or backfill part.

Example 3: Rationale for the study**Nonclinical Biodistribution and DMPK**

- 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, GIST and gliomas (including glioblastoma) (Flores et al 2010, Morgat et al 2017).
- The ability of the radiolabeled peptide to target the GRPR expressing tumor has been confirmed in in vivo imaging and biodistribution studies in healthy mice and tumor models. [177Lu]Lu-NeoB is rapidly cleared from the blood, quickly eliminated through the renal system, with no retention in kidneys. Indeed, at 4 hours after injection, the uptake remains relatively high only in GRPR-expressing tissues (mostly pancreas), which however decreases over time, consistent with

a GRPR antagonist profile. On the contrary, tumor remanence is persistent, with detectable uptake values up to 7 days after injection. These characteristics make [177Lu]-Lu NeoB an ideal candidate for PRRT. For more information refer to the [177Lu]Lu-NeoB Investigator's Brochure (IB).

- 5 [177Lu]Lu-NeoB induces cellular damage mainly through free radical formation in GRPR-positive 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 DDI.

- 10 Preclinical cardiac safety studies, conducted in vivo, indicate a negligible risk of an electrophysiological effect by [177Lu]Lu-NeoB. No significant effects were observed on cardiac electrophysiological function or hemodynamics as measured by telemetry in conscious minipigs with a 55-85-fold margin to the NeoB administered peptide mass dose of 200-300 µg. As [177Lu]Lu-NeoB was also shown to be metabolized, the concentration of parent is projected to be even lower. In addition, [177Lu]Lu-NeoB showed a very low radiation uptake in the heart.
- 15 Therefore, the overall cardiac risk can be considered to be very low.

Toxicology

- Non-clinical studies were conducted with the non-radioactive surrogate [175Lu]Lu-NeoB formulation, and support the NeoB peptide safety for administration in patients. No adverse effects have been observed in the safety pharmacology studies. Similarly, no signs of toxicity have been
- 20 reported after either 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
- 25 overexpress GRPR.

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 (50mCi). An intra-

patient dose escalation to 150 mCi [¹⁷⁷Lu]Lu-NeoB was implemented from cycle 2 onwards, based on clinical dosimetry in cycle 1.

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. Two patients received 2 cycles and 1 patient received 6 cycles. Overall treatment was well tolerated with no 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 (PD); 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 PD. The other two DLTs (grade 3 anemia and grade 3 encephalopathy) were recorded for a patient affected by GIST, with an onset within one week from administration of the first treatment dose. The patient had 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 on treatment with very high doses of diazepam interrupted a few days after [¹⁷⁷Lu]Lu-NeoB infusion, raising the suspicion of withdrawal syndrome as a confounding factor. No other significant toxicity were reported.

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 3 cycles of [¹⁷⁷Lu]Lu-NeoB and one of the GIST patients received 2 cycles. Both patients discontinued due to disease progression while the other 2 patients (GIST and prostate cancer) have received 2 cycles each and treatment is still ongoing. Overall treatment was 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: approximately one year in a GIST patient and five months in a prostate cancer patient.

Out of the 11 treated patients in the study, three patients completed treatment, two patients discontinued due to AE, three discontinued due to PD, one patient decided to stop treatment, and
5 two patient is ongoing.

Preliminary blood-radioactivity PK of [¹⁷⁷Lu]Lu-NeoB from NeoRay showed a quick elimination from systemic circulation with a geometric elimination half-life of ~60-80 hours and an average effective half-life of ~48 hours. Radio-high performance liquid chromatography (HPLC) data
10 shows metabolization in systemic circulation and urine (likely pharmacologic inactive metabolites unable to bind to the receptor) but cumulative excretion of activity indicates that radioactivity is still primarily (≥80% on average) excreted via the kidneys within 24-48 hours. The enzymes involved in the metabolism of [¹⁷⁷Lu]Lu-NeoB are presently unknown.

Preliminary dosimetry results demonstrate favorable biodistribution with low uptake in organs
15 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 (± 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),
20 respectively.

Given the safety and biodistribution profile at 250 mCi, a re-escalation to 300 mCi was decided as per the NeoRay study protocol.

As of 07Jun2023, 17 patients received [¹⁷⁷Lu]Lu-NeoB treatment in 5 cohorts and across 3 dose levels in study CAAA603A12101.

25 *Table 1 Patients enrolled across cohorts in study CAAA603A12101*

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

	Dose Level 1 (50 and 150 mCi)	Dose Level 2 (300 mCi)	Dose Level 3 (250 mCi)
	1 GIST	1 Glioblastoma	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 2 patients 2 in 6 patients 1 in 1 patient
Cut-off date 07-Jun-2023			

Subsequently, based on the overall favorable safety profile of Dose Level 3, a dose re-escalation to 300 mCi was decided in alignment with the protocol. Considering that some patients treated at 300 mCi dose experienced a DLT, the dose was de-escalated as per protocol to 250 mCi (DL 3) in cohort 5.

- 5 In Cohort 5, as of 07-Jun-2023, five (5) patients received [¹⁷⁷Lu]Lu-NeoB at 250 mCi dose (Dose Level 3). None of these 5 patients experienced any DLTs or SAEs. The majority of the reported AEs were mild or moderate in severity. Laboratory abnormalities of $\geq$ grade 2 were non clinically significant.

- 10 The generated Phase I dosimetry data displayed a favorable [¹⁷⁷Lu]Lu-NeoB organ dosimetry profile with large safety margin compared to EBRT thresholds even at high cumulative activities. Consequently, based on totality of data including dosimetry, the observed safety (including DLT data) and tolerability data in the tested dose levels, Novartis with the participating investigators declared RP2D as 250 mCi. This dose will be further tested in Phase IIa part of the study.

15 Background on [⁶⁸Ga]Ga-NeoB

- [⁶⁸Ga]Ga-NeoB will be used in the study; it is used for PET and is intended as a selection tool for [¹⁷⁷Lu]Lu-NeoB treatment in patients with tumors overexpressing GRPR, including MBC patients. [⁶⁸Ga]Ga-NeoB has shown favorable technical and diagnostic performance to identify GRPR-expressing malignancies, both in preclinical and in clinical studies, with good image quality that allows easy interpretation. Its diagnostic performance has been assessed in two completed clinical trials:

- MITIGATE (EudraCT Number 2016-002053-38), a Phase I/IIa clinical trial evaluated the safety, biodistribution, dosimetry and preliminary diagnostic performance of [⁶⁸Ga]Ga-NeoB in subjects with advanced, tyrosine-kinase-inhibitor-pretreated GIST. [⁶⁸Ga]Ga-NeoB was well tolerated in all 9 participants, with a good safety profile (administered radioactivity dose 127-214 MBq). 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.

- NeoFIND (EudraCT Number 2017-0003432-37), as mentioned in Section 2.2.3 a Phase II clinical trial, evaluated the preliminary diagnostic performance of [68Ga]Ga-NeoB in 19 subjects 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.

Background on ribociclib

Ribociclib is an orally bioavailable and highly selective small molecule inhibitor of the CDK4/cyclin-D1 and CDK6/cyclin-D3 enzyme complexes with IC50's of 0.01 and 0.039 μ M in biochemical assays, respectively.

- Following oral administration, time to reach maximal plasma concentrations (T_{max}) occurred from 1 to 4 h, while binding to human plasma protein was 70% in vitro. Elimination of ribociclib is dominated by oxidative metabolism mainly via CYP3A4 with a minor contribution by flavin-containing monooxygenase 3. The elimination of ribociclib may be affected by co-administered drugs that inhibit or induce CYP3A4 (KISQALI® US prescribing information).
- Ribociclib is indicated for the treatment of adult patients with HR+/HER2- advanced/metastatic breast cancer at a dose of 600mg p.o. daily (per US prescribing information), in combination with:
- an AI as initial endocrine-based therapy; or
 - fulvestrant as initial endocrine-based therapy or following disease progression on ET in postmenopausal women or in men.
- Ribociclib has been studied in combination with ET (letrozole or fulvestrant) in 2 randomized studies (Monaleesa-2 and -3, respectively) in post menopausal women with HR+/HER2- advanced/metastatic breast cancer, and has persistently shown significant survival benefit versus the matched placebo arm.

In Monaleesa-2, ribociclib combined with letrozole at a median follow-up of 79.7 months shows a median OS of 63.9 vs 51.4 months of the matched placebo arm (HR, 0.76; 95% CI, 0.63-0.93; P=.004) with an estimated 6-year OS rate of 44.2% for ribociclib + letrozole versus 32.0% for letrozole alone (Hortobagyi et al 2022).

- 5 In Monaleesa-3, ribociclib combined with fulvestrant at a median follow-up of 70.8 months, shows a median OS of 67.6 versus 51.8 months (HR 0.67; 95% CI, 0.50-0.90) of the matched placebo arm with a 5-year OS of 56.5 for ribociclib+ fulvestrant versus 42.1 months for fulvestrant alone in the 1st line metastatic setting (Neven et al 2022).

- 10 Ribociclib has also been studied in another phase 3, randomized study, enrolling only pre/perimenopausal women with HR+/HER2- advanced/metastatic breast cancer (Monaleesa-7), in combination with ET (the LHRH analog goserelin and either an NSAI or tamoxifen) and has also showed significantly longer OS than ET alone (70.2% versus 46%) at 42 months (Im et al 2019).

- 15 Based on the above results, ribociclib remains the only CDK4/6i therapy with statistically significant OS benefit across 3 phase 3 trials regardless of endocrine partner, line of therapy and menopausal status.

Clinical safety of ribociclib

- 20 The most common side effects (reported at a frequency $\geq 20\%$) in the Monaleesa-3 study, in the combination arm (ribociclib + fulvestrant) were neutropenia, infections, leukopenia, cough, nausea, diarrhea, vomiting, constipation, pruritus, and rash. Most AEs were of mild or moderate severity. The most common Grade 3/4 adverse reactions (reported at a frequency $\geq 5\%$) were neutropenia, leukopenia, infections, and abnormal liver function tests (LFT). Neutropenia was generally uncomplicated, no incidence of Torsades de Pointes (TdP) were observed. AE-related treatment discontinuations were rare, further supporting the manageable safety profile of ribociclib-based combinations. AEs leading to treatment discontinuation of fulvestrant plus
- 25 ribociclib (as compared to fulvestrant plus placebo) were alanine transaminase (ALT) increased (5% vs. 0%), AST increased (3% vs. 0.6%), and vomiting (1% vs. 0%) (KISQALI® US prescribing information).

For additional information on ribociclib and management of ribociclib related adverse events refer to local prescribing information.

- 30 **Background on fulvestrant**

Fulvestrant is an ER downregulator with no known agonist effects (Addo et al 2002). It binds, blocks and degrades the ER, completely inhibiting ER signaling. As a result, there is less chance of the ER being activated by alternative pathways that are believed to cause resistance (e.g. growth factor-mediated mechanisms) (Nicholson et al 2007).

- 5 Fulvestrant is slowly absorbed after administration of 500 mg intramuscularly (long-acting formulation). After intramuscular administration, the exposure is approximately dose proportional in the dose range of 50 to 500 mg. Maximum plasma concentrations are reached after about 5 days. Steady-state is achieved within the first month of dosing, if an additional dose is given 2 weeks after the initial dose. At steady-state there is more than a 2-fold difference between mean
10 C_{max} and C_{min}. Fulvestrant is subject to extensive and rapid distribution and is eliminated mainly by metabolism. The major route of excretion is via the feces with less than 1% being excreted in the urine. It has a high clearance, suggesting that it is a drug with high extraction ratio. The terminal half-life after intramuscular administration is governed by the absorption rate and was estimated to be 40-50 days. Increased exposure to fulvestrant was observed in patients with
15 moderate hepatic impairment (Child-Pugh class B). It has not been administered to patients with severe hepatic impairment (Child-Pugh class C) (FASLODEX® prescribing information). Therefore, patients with Child-Pugh class B and C will not be enrolled in this study.

- Fulvestrant is a first in class endocrine agent that was approved for the treatment of postmenopausal women with HR+ advanced/metastatic breast cancer who have failed on prior
20 anti-estrogen therapy based on data from the CONFIRM study (Di Leo et al 2010, Di Leo et al 2014). Additional randomized studies (Mehta et al 2012, Ellis et al 2015) have shown superiority of fulvestrant as a first-line therapy compared to or in association with anastrozole. Fulvestrant in combination with a CDK4/6i is the recommended therapy in subjects who relapsed on adjuvant ET, or within 12 months of stopping adjuvant therapy (Gennari et al 2021).

25 **Clinical safety of fulvestrant**

- Fulvestrant has a manageable safety profile; the most common clinically significant adverse reactions occurring in ≥5% of patients in monotherapy are the following: injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea and constipation. Increased hepatic
30 enzymes (ALT, aspartate transaminase (AST), alkaline phosphatase (ALP)) occurred in >15% of patients treated with fulvestrant and were not dose-dependent.

Fulvestrant needs to be used with caution in subjects with bleeding diatheses, thrombocytopenia, or anticoagulant use (FASLODEX® prescribing information).

Background on goserelin

5 Goserelin will be used in combination with [177Lu]Lu-NeoB, ribociclib and fulvestrant in the expansion part of the study in pre/peri-menopausal women only.

10 Goserelin is a synthetic decapeptide analog of gonadotropin releasing hormone indicated for prostatic carcinoma, endometriosis, endometrial thinning, and advanced breast cancer. Goserelin is administered subcutaneously every 28 days at a dose of 3.6 mg. Following subcutaneous administration of goserelin (3.6 mg for 2 months), Tmax was 12-15 days post-dose in males and 8-22 days post-dose in females. The metabolism of goserelin is not CYP-mediated; rather it is metabolized by hydrolysis of C-terminal amino acids. More than 90% of a radiolabeled dose is excreted in the urine, with approximately 20% of the dose in urine accounted for by unchanged goserelin (Zoladex® US prescribing information).

Clinical safety of goserelin

15 Goserelin has been associated with different types of ET in the treatment of HR+/HER2- pre/peri-menopausal patients and has shown a manageable and well tolerated safety profile (Jakesz 2006, Kim et al 2018).

20 In the Paloma-3 study, goserelin was used for the treatment of pre/peri-menopausal women in association with palbociclib and fulvestrant, and the safety profile of the triple combination was not different from the combination of palbociclib and fulvestrant (Turner et al 2018). Goserelin was also associated to ribociclib and tamoxifen or AI in the Monaleesa-7 study without showing any new safety signal (Im et al 2019).

25 AEs occurring in >20% of women treated with goserelin for breast cancer, dysfunctional uterine bleeding and endometriosis include hot flushes, headache, sweating, acne, emotional lability, depression, decreased libido, vaginitis, breast atrophy, seborrhea and peripheral edema (as per US prescribing information).

For additional information on goserelin and management of goserelin related adverse events refer to the local prescribing information

Screening

The study informed consent form (ICF) must be signed and dated before any study specific screening procedures are performed, except for evaluations performed as part of standard of care.

5 During the screening period of up to 42 days, participant eligibility will be determined according to the protocol's pre-defined inclusion and exclusion criteria. All screening assessments should be performed according to the SoA. Each participant will receive an administration of [68Ga]Ga-NeoB during screening to confirm eligibility for treatment with [177Lu]Lu-NeoB. A safety follow-up phone call will occur at 3 (+/-1) days after [68Ga]Ga-NeoB administration for all participants.

Participants who meet all eligibility criteria at screening can be enrolled in the study.

10 **Treatment period**

1- Dose escalation part

15 The dose escalation part as described in Figure 1 will estimate the RD of [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant. The BOIN approach (Yuan et al 2015, Yuan et al 2016) will be used to determine the requirement of dose escalation or de-escalation. After inclusion of each cohort of 3 to 6 participants, the incidence rate of DLTs will be compared to the pre-defined toxicity rate boundaries to decide whether the next cohort will receive a lower, higher or same dose or whether the trial will be terminated.

20 The initial dose of [177Lu]Lu-NeoB will be 100 mCi (every 28 days for 6 cycles) in combination with ribociclib (600 mg daily for 21 consecutive days followed by 7 days off treatment) and fulvestrant (500 mg on day 1, of a 28-day cycle plus an additional single dose to be administered on D15 of cycle 1). Provisional dose levels have been established within the protocol to guide dose selection. [177Lu]Lu-NeoB may be continued until completion of 6 cycles (or beyond up to a maximum of 10 cycles, as per Investigator's decision), based on risk-benefit and if the participant is tolerating the treatment and displaying benefit, upon agreement with the Sponsor.

25 Participants will continue treatment with ribociclib and fulvestrant until disease progression (per Investigator's assessment according to RECIST 1.1) or until discontinuation of study treatment due to any other reason such as unacceptable toxicity, symptomatic deterioration, WoC, lost to follow up, Investigator decision or death, whichever occurs first. Participants will then enter the post treatment follow up period regardless of the reasons for treatment discontinuation, where

30 applicable.

Dose escalation/de-escalation decisions will be made by the Investigators and the Sponsor at the end of the DLT reporting period of the last participant in each dose cohort and will be guided by DLT rate, biodistribution (dosimetry) data of [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant from evaluable participants, all AEs of CTCAE grade > 2 reported during the DLT reporting period and the cumulative safety data collected in previously treated participants possibly including other dose levels.

2- Dose expansion part

The dose expansion part as described in Figure 2 will assess the RD dose of [177Lu]Lu-NeoB (every 28 days for 6 cycles), as established in the dose escalation part, in combination with ribociclib (600 mg daily for 21 consecutive days followed by 7 days off treatment) and fulvestrant (500 mg on day 1 of a 28-day cycle plus an additional single dose to be administered on D15 of cycle 1) in post menopausal participants. Pre/peri-menopausal participants will be included in the expansion part and will also receive goserelin (3.6 mg on day 1 of a 28-day cycle) in addition to the above mentioned treatment. [177Lu]Lu-NeoB may be continued until completion of 6 cycles (or beyond up to a maximum of 10 cycles, as per Investigator's decision), based on risk-benefit and if the participant is tolerating the treatment and displaying benefit, upon agreement with the Sponsor. Participants will continue study treatment with ribociclib, fulvestrant and goserelin (pre/peri-menopausal women only) until disease progression (per Investigator's assessment according to RECIST 1.1) or until discontinuation of study treatment due to any other reason such as unacceptable toxicity, symptomatic deterioration, WoC, lost to follow up, Investigator's decision or death, whichever occurs first. Participants will then enter the post treatment follow up period regardless of the reasons for treatment discontinuation, where applicable.

A total of 15 participants will be enrolled in the expansion part to further assess the safety, tolerability and anti tumor activity of the RD of [177Lu]Lu-NeoB. Approximately 1/3 of the cohort will be comprised of pre/peri-menopausal participants.

Scientific rationale for study design

This is a phase Ib, single arm, dose finding study of [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant (and goserelin for pre/peri-menopausal women in the expansion part) in adult female participants with HR+/HER2-, GRPR+, advanced/metastatic breast cancer, relapsing during or within 12 months from completing (neo)adjuvant ET.

Patients with early relapse from adjuvant therapy represent a subset of patients with poorer prognosis in need of better therapies. Given the recommended treatment for HR+/HER2-advanced/metastatic breast cancer in premenopausal and postmenopausal women is generally similar (Azim and Partridge 2014, Gennari et al 2021, NCCN Guideline Breast Cancer Version 4.2022) with the exception of the above mentioned addition of LHRH in pre/perimenopausal women (Rugo et al 2016, Bardia and Hurvitz 2018), in the expansion phase this study will enroll both premenopausal and postmenopausal participants. Although no difference in safety profile is anticipated, due to the lack of data for this treatment combination, the study will start with a more conservative approach and investigate the three treatments ([¹⁷⁷Lu]Lu-NeoB, ribociclib, fulvestrant) in the escalation part in postmenopausal women, before adding goserelin for pre/perimenopausal women in the expansion part.

The evidence of high expression of GRPR in breast cancer, the possibility to select patients with a specific threshold of GRPR using [⁶⁸Ga]Ga-NeoB as imaging agent, the synergic effect of ribociclib with RLT, make the addition of [¹⁷⁷Lu]Lu-NeoB a possible effective therapy aiming at improving the prognosis of this patient population.

The study comprises of a dose escalation part, followed by a dose expansion part.

The dose escalation part is assessing 4 provisional dose levels using a BOIN design. The BOIN design was selected as it does not require a fixed cohort size and allows for decision making at any time during the trial by comparing the observed DLT rate at the current dose with the escalation and de-escalation boundaries. Another feature of the BOIN design is that the sample size is determined to achieve the desirable probability of correctly estimating the RD (Yuan et al 2016). Furthermore, considering the small number of dose levels to be tested, the BOIN design is more suitable than more complex model-based designs.

An expansion part was added in order to further characterize the safety, tolerability and preliminary antitumor activity of [¹⁷⁷Lu]Lu-NeoB at the RD. This does not preclude the need for further dose optimization in future studies.

Justification for dose

Rationale for Dose Selection and frequency of administration of [¹⁷⁷Lu]Lu-NeoB

The starting dose for the dose escalation part will be 100 mCi (3.7 GBq) of [¹⁷⁷Lu]Lu-NeoB every 28 days.

Based on the data from the NeoRay study (data cut off 15-JUN-2022), the starting dose of 50 mCi (cycle 1) + 150 mCi (cycle 2 onwards) of [177Lu]Lu-NeoB administered every 42 days was well tolerated as monotherapy with no DLTs or Grade 3/4 adverse events experienced in this cohort. Absorbed radiation dose in key organs (kidney, pancreas, red marrow, testes, ovaries) was low, indicating that the risk of radiation related toxicities from singular administrations is low.

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. Based on the data generated thus far, 28-day schedule is proposed for the administration frequency for [177Lu]Lu-NeoB and the dose will be gradually assessed as part of the dose finding scheme. In addition, the 4 week schedule would serve to accommodate the 4 week cycle of ribociclib and fulvestrant, and to enable a concurrent administration with the other 2 therapies.

Based on the above information and given that [177Lu]Lu-NeoB is going to be combined with ribociclib and fulvestrant and the frequency of administration is reduced to 28 days (from the 42-day cycle as the single agent in NeoRay), the study will start at a dose of 100 mCi.

Six administrations of [177Lu]Lu-NeoB every 4 weeks are given in this study. Based on the available dosimetry data from the three investigated dose levels in the FIH study (150 mCi, 250 mCi and 300 mCi) the mean cumulative absorbed dose in kidney, pancreas, red marrow, testes and ovaries are significantly below 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; Stewart et al 2012), ~1.6-fold margin for the red marrow (2 Gy EBRT threshold; Howard et al 2017), a 1.3-2-fold margin for testis and ovaries (1 Gy and 3 Gy EBRT thresholds; Chambers et al 1991, De Felice et al 2019), and a 3-fold margin for the kidneys (23 Gy EBRT threshold; Emami et al 1991, Stewart et al 2012).

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, Bergsma et al 2016a, Bergsma et al 2016b). In fact, there is growing evidence that a biologically effective dose (BED) of ~40 Gy is safe for the kidneys with Lu-177 labelled RLTs, with a conversion factor of 1.09 to convert absorbed dose to BED with 177Lu-based RLTs (Bodei et al 2008, Schäfer et al 2022). Hence, even if with more than 6 cycles, there

may be 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.

In order to proceed with each of the additional 4 administrations of [177Lu]Lu-NeoB, the Investigator should determine if:

- The participant shows evidence of disease stabilization or response (i.e. assessed either radiologically or clinically),
- 10 • 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 NeoB dose and that led to treatment interruption.

If the participant 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. up to a maximum total of 10 administrations) of [177Lu]Lu-NeoB, upon agreement with the Sponsor.

Rationale for dose selection of ribociclib

Ribociclib will be administered at the recommended starting dose of 600 mg p.o. (three 200 mg tablets), taken once daily with or without food for 21 consecutive days followed by 7 days off. Dose interruption, reduction, and/or discontinuation may be required based on individual safety and tolerability.

Rationale for dose selection of fulvestrant

Fulvestrant will be administered at the approved dose of 500 mg intramuscularly into the buttocks (gluteal area) slowly (1 -2 minutes per injection) as two 5 mL injections, one in each buttock, on days 1, 15, 29, and once monthly thereafter. A dose of 250 mg is recommended in patients with moderate hepatic impairment to be administered intramuscularly into the buttock (gluteal area) slowly (1 -2 minutes) as one 5 mL injection on days 1, 15, 29, and once monthly thereafter.

Rationale for dose selection of goserelin (applicable only for pre/peri-menopausal women in the expansion part)

Goserelin will be administered subcutaneously at the approved dose of 3.6 mg on day 1 of a 28-day cycle.

5 Study Treatments

In this study, the term "investigational drug" refers to the radioligand imaging compound [68Ga]Ga-NeoB, used for participant selection during screening and for PET imaging after the last dose of [177Lu]Lu-NeoB to assess treatment-induced changes in the PET scan pattern, and to [177Lu]Lu-NeoB, used for RLT. The term "study treatment" refers to the combination of [177Lu]Lu-NeoB, ribociclib, and fulvestrant (+/- goserelin, as applicable, in the expansion part only).

Participants will receive [177Lu]Lu-NeoB in combination with ribociclib and fulvestrant, in the dose escalation and the dose expansion parts of the study. Goserelin administration is only applicable for pre/peri-menopausal participants, in the dose expansion part.

The [177Lu]Lu-NeoB and the kit for the radiopharmaceutical preparation of [68Ga]Ga-NeoB will be provided centrally by Novartis. Ribociclib, fulvestrant and goserelin will be provided locally by the study site, by the Novartis subsidiary or designee, as commercially available, or centrally by Novartis, in each participating country according to local practices and regulations.

All dosages prescribed and dispensed to the participant and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

Details on requirements for storage, management and administration of study treatment, instructions for participant numbering, prescribing and dispensing are outlined in the accompanying Pharmacy Manual.

Investigational and control drugs

Investigational/ Control drugs (Name/Strength)	Pharmaceutical Dosage Form	Route of Administration
[⁶⁸ Ga]Ga-NeoB (50µg)	Either provided as Kit for the radiopharmaceutical	Intravenous

	preparation of [⁶⁸ Ga]Ga-NeoB or as ready to use radiopharmaceutical solution for injection	
[¹⁷⁷ Lu]Lu-NeoB 370 MBq/mL (10 mCi/mL)	Radiopharmaceutical solution for infusion	Intravenous
Ribociclib	Tablet	Oral use
Fulvestrant	Solution for injection	Intramuscular use
Goserelin ¹	Implant	Sub-cutaneous use

¹ for pre- and perimenopausal women in the expansion part only.

[⁶⁸Ga]Ga-NeoB

In this study, after radiolabeling with Ga-68, [⁶⁸Ga]Ga-NeoB serves as a radioactive imaging compound to be used for PET for localization of GRPR positive lesions.

- 5 [⁶⁸Ga]Ga-NeoB will be administered as a single intravenous dose of an activity within a range of 150-250 MBq (4.1-6.8 mCi).

[¹⁷⁷Lu]Lu-NeoB

Study participants will receive a dose of 3.7 GBq (100 mCi) +/- 10% of [¹⁷⁷Lu]Lu-NeoB which will be administered once every 28 days (1 cycle) for 6 cycles.

10 Dose and treatment schedule (escalation part)

Study treatment	Dose	Frequency
[⁶⁸ Ga]Ga-NeoB	4.1-6.8 mCi	Once at screening and after the last dose of [¹⁷⁷ Lu]Lu-NeoB
[¹⁷⁷ Lu]Lu-NeoB	100, 150, 200 or 250 mCi depending on the cohort	D1 of a 28-day cycle
Ribociclib	600 mg	Once daily; days 1 to 21 in a 28-day cycle
Fulvestrant	500 mg	C1D1, C1D15, C2D1 and every 28 days (Cx D1) thereafter

Dose and treatment schedule (expansion part)

Study treatment	Dose	Frequency
[⁶⁸ Ga]Ga-NeoB	4.1-6.8 mCi	Once at screening and after the last dose of [¹⁷⁷ Lu]Lu-NeoB

[¹⁷⁷ Lu]Lu-NeoB	RD	D1 of a 28-day cycle
Ribociclib	600 mg	Once daily; days 1 to 21 in a 28-day cycle
Fulvestrant	500 mg	C1D1, C1D15, C2D1 and every 28 days (Cx D1) thereafter
For pre/peri-menopausal women Goserelin	3.6mg	D1 of a 28-day cycle

The dose escalation part will start with an initial dose of 100 mCi of [¹⁷⁷Lu]Lu-NeoB given on day 1 (+≤3 days) every 28 days for 6 cycles, in combination with ribociclib (600 mg daily for 21 consecutive days followed by 7 days off treatment) and fulvestrant (500 mg on day 1 of a 28-day cycle). On cycle 1, a single additional dose of fulvestrant will be administered on D15 (C1D15).

- 5 The first infusion of [¹⁷⁷Lu]Lu-NeoB for each evaluated dose level will be followed by the DLT period, defined as a total of 28 days/4 weeks.

The dose expansion part will assess the RD dose of [¹⁷⁷Lu]Lu-NeoB (on day 1 (+≤3 days) every 28 days for 6 cycles), as established in the dose escalation part, in combination with ribociclib (600 mg daily for 21 consecutive days followed by 7 days off treatment) and fulvestrant (500 mg on day 1 of a 28-day cycle and a single additional dose of fulvestrant on D15 (C1D15)) in post, pre/peri-menopausal participants. Pre/peri-menopausal participants will also receive goserelin (3.6 mg) on day 1 of every 28-day cycle.

Ribociclib, fulvestrant and goserelin (where applicable) will be administered on the same day and preferably prior to [¹⁷⁷Lu]Lu-NeoB.

15 Eligibility screening

Informed consent must be obtained before any study specific procedures are performed, except for evaluations performed as part of standard of care. After signing the study ICF, all screening assessments will be done within 42 days prior to study enrollment.

- 20 During the screening period, imaging with [68Ga]Ga-NeoB should be performed as soon as possible in order not to delay participant enrollment. All participants receiving [68Ga]Ga-NeoB will be followed for safety before being discharged from the imaging unit at screening and with a dedicated call 3 +/- 1 days after administration to assess occurrence of AEs.

Only participants who meet all eligibility criteria at screening can be enrolled in the study. The screening period must be shortened as much as possible. Participant enrollment and ordering of [177Lu]Lu-NeoB must be performed immediately after all eligibility criteria are verified and the participant is confirmed to be eligible and at least 14 days before the planned administration of [177Lu]Lu-NeoB.

Once a participant has been identified for screening, they will be registered in the IRT system. Following registering in the IRT for screening, participant eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

[68Ga]Ga-NeoB Imaging

[68Ga]Ga-NeoB PET scan as an inclusion criterion

[68Ga]Ga-NeoB PET/CT or PET/MRI must be acquired at 120±30 minutes after the intravenous injection of 4.1-6.8 mCi (150-250 MBq) of the radiotracer, scanning from the top of the head to proximal-mid thigh (torso with head included), with arms raised whenever possible.

PET/CT or PET/MRI will be read locally. [68Ga]Ga-NeoB uptake in tumor lesions must be graded in the PET/CT or PET/MRI using a visual scale, according to the following Table.

[68Ga]Ga-NeoB visual uptake scoring scale

Score	Reference organs	Uptake intensity
0	< spleen	Negative
1	≥ spleen but ≤ liver	Mild
2	> liver but < pancreas	Moderate
3	≥ pancreas	High

Eligible participants must have at least one target lesion (according to RECIST 1.1 criteria) detected on the baseline stand-alone CT or MRI with [68Ga]Ga-NeoB uptake at PET/CT or PET/MRI scoring 1 or above for participants in the escalation part, and scoring 2 or above for those in the expansion part. The required score is based on the purpose of [68Ga]Ga-NeoB uptake in each part of the study: in the escalation part, with the objective of identifying lesions, a mild uptake (score 1) is acceptable; however, in the expansion part, to enrich the population and thus get a preliminary notion of efficacy, a higher uptake (moderate, score 2) is required.

[68Ga]Ga-NeoB PET scan after the last dose of [177Lu]Lu-NeoB

For participants in the expansion part, a [68Ga]Ga-NeoB PET/CT or PET/MRI will be performed from two and eight weeks after administering the last dose of [177Lu]Lu-NeoB. The injected [68Ga]Ga-NeoB radioactivity dose and the acquisition characteristics of this PET scan should be the same used in the baseline PET/CT or PET/MRI.

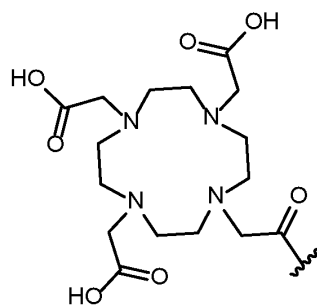
- 5 This PET scan will assess the change in the number of target lesions (visual evaluation) and the change in semiquantitative parameters [SUVmax, SUVmean and TBR], compared to the baseline PET/CT or PET/MRI.

- 10 TBR is defined as the ratio between the SUVmax of a tumoral lesion and the SUVmean of a healthy tissue (Rogasch et al 2015). For the TBR calculation, background activity will be considered as the uptake of [68Ga]Ga-NeoB within a spherical volume of interest (VOI) of about 3 cm diameter (Wahl et al 2009). In each PET scan, two TBR values will be retrieved: one taking the spleen as background activity and the other one taking the liver.

Claims

1. A method of treating breast cancer 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 CDK4/6 inhibitor, e.g. ribociclib, and with an endocrine treatment, e.g. fulvestrant, 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,
10 S is an optional spacer covalently linking C and P,
P is a GRP receptor antagonist moiety,
and wherein said radiopharmaceutical compound is labelled with a radionuclide M.
2. The method of claim 1, wherein said CDK4/6 inhibitor is selected from the group consisting of ribociclib, palbociclib, and abemaciclib.
- 15 3. The method of claim 2, wherein said CDK4/6 inhibitor is ribociclib.
4. The method of any one of claims 1-3, wherein said endocrine treatment comprises administering a therapeutically effective amount of a selective estrogen receptor modulator, a non-steroidal aromatase inhibitor, a steroidal aromatase inhibitor, or a selective ER degrader.
- 20 5. The method of any one of claims 1-4, wherein said endocrine therapy comprises administering a therapeutically effective amount of a selective ER degrader.
6. The method of claim 5, wherein said selective ER degrader is fulvestrant.
7. The method of claim 5 or 6, wherein a therapeutically effective amount of said selective ER degrader is administered once every 14 to 56 days, e.g., 28 days, e.g. starting the same day as the administration of said radiopharmaceutical compound, and is administered for at least as long as the radiopharmaceutical is administered, and optionally administration of ER degrader continues until disease progression.
- 25 8. The method of any one of claims 1-7, wherein said CDK4/6 inhibitor is ribociclib and said endocrine treatment comprises administering a therapeutically effective amount of fulvestrant.

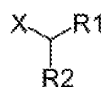
9. The method of claim 8, wherein said CDK4/6 inhibitor, preferably ribociclib, is concomitantly administered with fulvestrant.
10. The method of any one of claims 1-9, wherein M is selected from ^{90}Y , ^{131}I , ^{121}Sn , ^{186}Re , ^{188}Re , ^{64}Cu , ^{67}Cu , ^{59}Fe , ^{89}Sr , ^{198}Au , ^{203}Hg , ^{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 .
11. The method of any one of claims 1-10, wherein M is ^{177}Lu .
12. The method of any one of claims 1-11, wherein C is obtained by linking 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).
13. The method of claim 12, wherein C is of the following formula,



14. The method of any one of claims 1-13, wherein P is of the general formula
- 20 DPhe-Gln-Trp-Ala-Val-Gly-His-Z

wherein Z is selected from Leu- $\psi(\text{CH}_2\text{N})$ -Pro-NH₂ and NH-CH(CH₂-CH(CH₃)₂)₂

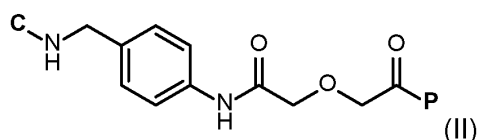
or Z is



wherein X is NH (amide) and R2 is $(\text{CH}_2\text{-CH}(\text{CH}_3)_2)$ and R1 is the same as R2 or $(\text{CH}_2\text{N})\text{-Pro-NH}_2$.

15. The method of claim 14, wherein P is DPhe-Gln-Trp-Ala-Val-Gly-His-NH-CH $(\text{CH}_2\text{-CH}(\text{CH}_3)_2)$.

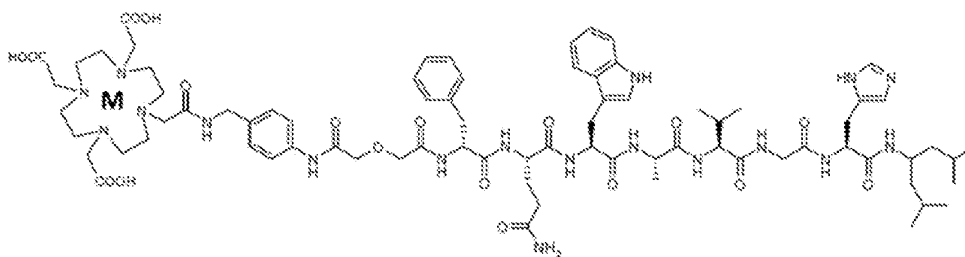
- 5 16. The method of any one of claims 1-15, wherein the compound of Formula (I) is a compound of Formula (II)



wherein C and P are as defined in any one of Claim 1 and 12-15, and wherein the chelating moiety

- 10 C is complexed with a radionuclide M.

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



- 15 (III),

or pharmaceutically acceptable salts thereof,

wherein M is a radionuclide, for example M is ^{177}Lu .

18. The method of any one of claims 1-17, wherein said radiopharmaceutical compound is administered 3 to 12 times, 4 to 10 times, 4 to 8 times, 6 times, or 10 times.

- 20 19. The method of claim 18, wherein said radiopharmaceutical compound comprises an administration interval of 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 3 or 4 weeks, or 4 weeks.

20. The method of any one of Claims 1-19, wherein said radiopharmaceutical compound is administered at a dose ranging from 0.925 GBq (25mCi) to 29.6GBq (800 mCi), from 1.48 GBq (40 mCi) to 18.5 GBq (500mCi), from 1.85 GBq (50mCi) to 14.8 GBq (400mCi), from 3.7 GBq (100mCi) to 11.1 GBq(300mCi), 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 CDK4/6 inhibitor, e.g. ribociclib, is administered orally at a daily dose of 400 to 800 mg, e.g. 600 mg, e.g. in cycles of a period of 15 to 28 days, each cycle including e.g. 21 days of daily administration followed by a period of 7 days off treatment, and is administered for at least as long as the radiopharmaceutical is administered, and optionally administration of said CDK4/6 inhibitor continues until disease progression.

22. The method of claim 21, wherein said radiopharmaceutical compound is [¹⁷⁷Lu]Lu-NeoB and is administered intravenously every 28 days, for 3 to 12 cycles, for example 6 cycles, at a dose ranging from 3.7 GBq (100mCi) to 11.1 GBq(300mCi), or from 3.7 GBq (100mCi) to 9.25 GBq(250mCi), e.g. 250 mCi, e.g. 150 mCi, in combination with ribociclib administered orally at a daily dose of 600 mg, for 15 to 21 days per cycle.

23. The method of any one of claims 1-22, wherein said endocrine therapy, preferably fulvestrant, is administered via intramuscular administration, at a dose of 250 to 700 mg, for example using a long-acting formulation.

24. The method of any one of claims 1-23, wherein said subject has ER positive, HER-2 negative (ER+/HER2-) and GRPR-positive (GRPR+) breast cancer.

25. The method of any one of claims 1-24, wherein said subject has been selected from subjects experiencing early relapse after neoadjuvant or adjuvant prior endocrine treatment, or experiencing progression on prior endocrine treatment optionally in combination with a prior CDK4/6 inhibitor

26. The method of any one of Claims 1-25, wherein said subject is a post-menopausal woman with advanced metastatic breast cancer.

27. The method of any one of Claims 1-26, wherein said subject is a pre-menopausal or peri-menopausal woman with advanced metastatic breast cancer.

28. The method of any one of claims 1-27, wherein said subject has been selected from subjects

experiencing early relapse after neoadjuvant or adjuvant prior endocrine treatment.

29. The method of any one of claims 1-27, wherein said subject has been selected from subjects experiencing progression on prior endocrine treatment optionally in combination with a prior CDK4/6 inhibitor.

- 5 30. The method of claim 29, wherein said prior CDK4/6 inhibitor is selected from the group consisting of ribociclib, palbociclib, and abemaciclib, e.g., ribociclib.

31. The method of any one of claims 25-30, wherein said prior endocrine treatment comprises administering a therapeutically effective amount of a selective estrogen receptor modulator, a non-steroidal aromatase inhibitor, a steroidal aromatase inhibitor, or a selective ER degrader.

- 10 32. The method of any one of claims 1-31, wherein said endocrine treatment further comprises concomitantly administering a synthetic analog of gonadotropin releasing hormone, for example goserelin, for example via subcutaneous administration, e.g. every 28 days at a dose of about 3.6mg.

- 15 33. The method of any one of claims 1-32, 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 suitable for imaging, for example 68-Gallium, 67-Gallium or 64-Copper, e.g. 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.

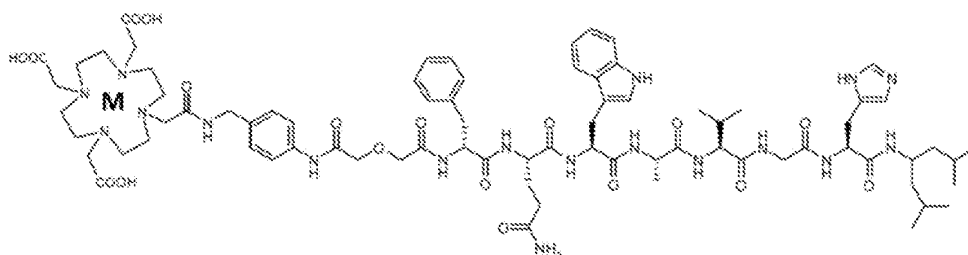
- 20 34. The method of Claim 33, wherein said subject is selected among subjects showing presence of alternate radionuclide enhancement, for example gadolinium enhancement, in a PET/MRI scan at the tumor region, prior to any surgery.

- 25 35. The method of any one of claims 1-34, wherein said subject has ER positive, HER-2 negative (ER+/HER2-) and GRPR-positive (GRPR+) breast cancer and is experiencing early relapse from neoadjuvant or adjuvant therapy, wherein said radiopharmaceutical compound is administered to said subject in combination with ribociclib and fulvestrant, wherein a first dose of said radiopharmaceutical compound is administered the same day as the first dose of ribociclib.

36. The method of claim 35, wherein ribociclib is administered orally at a daily dose of about 600 mg, for example in cycles of a period of 28 days, each cycle for example including 21 days of

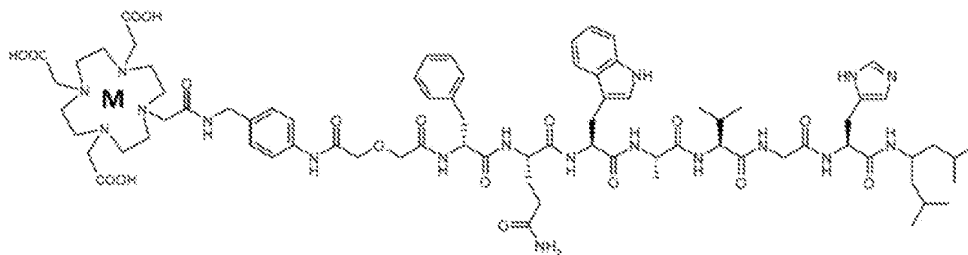
administration followed by a period of 7 days off treatment, wherein the radiopharmaceutical compound is administered for 4-10 cycles, and ribociclib is administered for at least as long as the radiopharmaceutical is administered, and optionally administration of said CDK4/6 inhibitor continues until disease progression.

- 5 37. The method of Claim 35 or 36, wherein said radiopharmaceutical compound is M-NeoB of the following formula:



wherein M is ^{177}Lu .

38. The method of any one of claims 1-37, wherein said radiopharmaceutical compound is M-
10 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 .