

METHODS FOR TREATING CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to US Provisional Patent Application No. 63/627,853
5 filed on February 1, 2024 and US Provisional Patent Application No. 63/642,999 filed on May 6,
2024. The contents of these applications are hereby incorporated by reference in their entireties.

TECHNICAL FIELD

This application relates to the use of FAP-targeting radiotherapeutic agents for the
10 treatment of cancer, including in combination with chemotherapies.

BACKGROUND

Fibroblast activation protein (FAP) is a cell surface protein that is highly expressed on the
surface of cancer-associated fibroblasts (CAFs) present in the tumor microenvironment of most
15 epithelial cancers, whereas limited expression of FAP is observed in normal tissues. In some
cancers of mesenchymal origin, notably sarcoma and mesothelioma, FAP expression has also
been observed on the tumor cells themselves. Given the restricted expression profile, FAP is a
promising target for radionuclide imaging and therapeutic agents in the treatment of cancer,
particularly for solid tumors.

20 Pancreatic cancer, in particular, is difficult to treat due to the harsh tumor
microenvironment, making chemotherapeutic drug delivery challenging. The tumor
microenvironment is rich in stromal cells that are high in FAP expression and there is some
suggestion that pancreatic adenocarcinoma cells themselves may also express FAP. FAP has
been implicated in cancer progression, immunosuppression and treatment resistance.
25 Unfortunately, FAP expression in pancreatic ductal adenocarcinoma (PDAC) also correlates with
poor survival and reiterates the significant need for more therapeutic options in this patient
population (Cheng, C-s et al. (2022) Front. Oncol; 12:969731). Thus, PDAC is a good target for
FAP directed therapy.

Lung cancer is the second most common cancer in men and women and the leading cause
30 of cancer related deaths worldwide (Thandra K C, et al. (2021) Contemp Oncol (Pozn); 25 (1):

45-52). These patients are diagnosed with advanced disease with a 5-year survival rate of about 18% (Yanagawa N, et al. (2022) Thorac Cancer; 13:2377–2384).

NSCLC is known to have a tumor microenvironment (TME) with CAFs having high FAP expression. In a recent study, 54.1% of patients with NSCLC (N=126) were found to have high FAP expression as defined by intensity of IHC staining and percentage of FAP-positive cells (Zhao Y, et al. (2023) J Can Res Clin Onc; 149:3469-3483). FAP expression on lung cancer cells and in the CAFs of the tumor microenvironment has also correlated with worse survival outcomes and less response to immunotherapy (Yanagawa et al. 2022, Zhao et al. 2023).

FAP-expressing NSCLC tumors can also be readily identified through imaging. PET scans using ⁶⁸Ga-FAPI as a tracer demonstrate high uptake by primary lung tumors and metastases allowing for visualization and measurement of FAP expressing disease (Borgonje PE, et al. (2022) Cancers; 14:5566). NSCLC is also a good target for FAP directed therapy.

Despite recent advances in NSCLC there is a high unmet need in this disease. Once patients progress on first line chemoimmunotherapy, there are a handful of drug options including docetaxel +/- ramucirumab, pemetrexed, gemcitabine or nab-paclitaxel (National Comprehensive Cancer Network (NCCN) (2023). NCCN Clinical Practice Guideline in Oncology. Non-Small Cell Lung Cancer Version 3.2023; National Comprehensive Cancer Network). Based on two studies, docetaxel has become a preferred 2L option for patients with NSCLC (Shepherd FA, et al. (2000) J Clin Oncol; 18:2095-2103; Fossella F, et al. (2000) J Clin Oncol; 18:2354-2362; Weiss JM, Stinchcombe TE (2013) The Oncologist; 18:947-953). However, median OS in these two studies with docetaxel 75 mg/m² every 3 weeks given 2L was 7.5 months and 5.7 months, respectively (ORR 5.8% mDOR 26.1 weeks (Shepherd FA, et al. 2000); ORR 6.7% mDOR 9.1 months (Fossella F, et al. 2000). In general, docetaxel is poorly tolerated and has significant toxicities (Weiss JM, et al. 2013). To improve efficacy, new therapies are needed for patients that progress on first line therapy.

Breast cancer (BC) is the most commonly diagnosed malignancy and leading cause of cancer related death in women worldwide. Despite clinical advances, BC mortality rates have increased in the last decades indicating an urgent need for innovative treatments (Lukasiewicz S, et al. (2021) Cancers; 13:4287).

Patients with BC may receive combinations of endocrine therapy and cyclin-dependent kinase 4 and 6 inhibitors in the 1 L setting, if hormone receptor positive, HER2 directed therapy

in the setting of HER2 positive disease or cytotoxic therapy if hormone receptor negative and HER2 negative. Beyond second and third line therapy, regardless of subtype, treatment has limited response rates and durability. In the Destiny-04 trial, participants with hormone receptor positive disease, who had a median of 3 prior lines of therapy, had a median progression-free survival (PFS) of 5.4 months (mOS 17.5 months ORR 16.3% and DOR 6.8 months) with physician's choice of therapy (Modi S, et al. (2022) N Engl J Med; 387:9-20). In the TROPiCS-02 trial, median PFS was 4.0 months, OS was 11.2 months, ORR 14% and mDOR 5.6 months with physician's choice of therapy in this hormone receptor positive population with a median of three lines of prior therapy (Rugo HS, et al. (2023) Lancet; 10411:1423-1433). Sacituzumab in patients with relapsed, refractory hormone receptor negative, HER2 negative BC also had a PFS of 4.8 months in comparison to investigator's choice of cytotoxic chemotherapy (mOS 11.8 months, ORR 31% mDOR 6.3 months, Bardia A, et al. (2021) N Engl J Med; 384(16):1529-1541). Lastly, in a recent trial of patients with HER2 positive disease who had been heavily pretreated with anti-HER2 therapy, tucatinib showed a median PFS of 7.8 months versus placebo (mOS 21.9 months ORR 40.6%, Murthy RK, et al. (2020) N Engl J Med; 382(7):597-609).

Breast cancer also has a strong FAP signal. A review of available data regarding FAP in the BC literature shows evidence that FAP based imaging may provide superior for diagnostic information in comparison to traditional [¹⁸F]-FDG PET (Zhao Y, et al. (2023) J Can Res Clin Onc; 149:3469-83). Furthermore, a recent imaging trial has correlated [⁶⁸Ga]Ga-FAPi-46 PET uptake with FAP tissue expression by IHC (Mona CE, et al. (2022) J Nucl Med; 63:1021-1026). Breast Cancer is, therefore, also a good target for FAP directed therapy.

In sum, FAP overexpression in multiple tumor types both in the tumor cells and surrounding stroma make it a valuable target for directed treatment. Utilizing RLT while targeting FAP represents a unique therapeutic opportunity for the treatment of cancer, including, for example, PDAC, NSCLC, and BC, for which there is a high need for new therapeutic options which are both efficacious and safe.

SUMMARY

Provided herein are methods for treating cancer comprising administering a FAP-targeting radiotherapeutic agent.

In an aspect, provided herein is a method for treating a FAP-expressing cancer (e.g., a solid tumor) in a subject in need thereof comprising administering to a subject in need thereof a FAP-targeting radiotherapeutic agent, wherein the FAP-targeting radiotherapeutic agent is administered as a single daily dose once about every four weeks $\pm$ three days or about every 6 weeks $\pm$ three days to achieve a cumulative dose of about 40 to about 60 GBq.

In an aspect, provided herein is a method for treating pancreatic ductal adenocarcinoma (PDAC) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

- (a) a fibroblast activation protein (FAP)-targeting radiotherapeutic agent; and
- (b) chemotherapy comprising at least one, two, three, or four agents selected from 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin.

In an aspect, provided herein is a method for treating non-small cell lung cancer (NSCLC) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

- (A) a fibroblast activation protein (FAP)-targeting radiotherapeutic agent; and
- (B) a taxane (e.g., paclitaxel, nab-paclitaxel, or docetaxel).

In an aspect, provided herein is a method for treating non-small cell lung cancer (NSCLC) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

- (A) a fibroblast activation protein (FAP)-targeting radiotherapeutic agent; and
- (B) nab-paclitaxel.

In an aspect, provided herein is a method for treating pancreatic ductal adenocarcinoma (PDAC) in a subject in need thereof comprising administering to a subject in need thereof a FAP-targeting radiotherapeutic agent, wherein the FAP-targeting radiotherapeutic agent is administered as a single daily dose once every four weeks $\pm$ three days or every 6 weeks $\pm$ three days to achieve a cumulative dose of about 40 to about 60 GBq.

In another aspect, provided herein is a method for treating non-small cell lung cancer (NSCLC) in a subject in need thereof comprising administering to a subject in need thereof a FAP-targeting radiotherapeutic agent, wherein the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days or every 6 weeks $\pm$ three days to achieve a cumulative dose of about 40 to 60 GBq.

In another aspect, provided herein is a method for treating breast cancer in a subject in need thereof comprising administering to a subject in need thereof a FAP-targeting radiotherapeutic agent, wherein the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days or every 6 weeks $\pm$ three days to achieve a cumulative dose of about 40 to 60 GBq.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates a schema of the Phase 1 study described in Example 2.

FIG. 2 illustrates a schema of the Phase 2 monotherapy study described in Example 2.

FIG. 3 illustrates a schema of the Phase 2 combination therapy studies described in Example 2.

DETAILED DESCRIPTION

Provided herein are methods of treating cancer comprising administering a FAP-targeting radiotherapeutic agent to a subject in need thereof.

FAP-targeting radiopharmaceuticals

As used herein, “FAP-targeting” means that a compound exhibits affinity to fibroblast activation protein (FAP). Techniques for measuring FAP affinity for FAP are known in the art and readily available to one of skill in the art to identify a compound as having affinity for FAP. For example, the dissociation constant (K_D) for certain FAP-targeting radiopharmaceuticals disclosed herein can be measured according to the surface plasmon resonance assays disclosed in WO2021/005125A1 and US Publication No. 2022/0273831A1 or in Zboralski et al. (Eur. J. Nuc. Med., 2022, 49:3651-3667), each of which is incorporated by reference in its entirety.

In certain embodiments, the FAP-targeting radiopharmaceuticals disclosed herein exhibit a dissociation constant (K_D) for human FAP of about 100 nM or less as measured by the surface plasmon resonance assays disclosed in WO2021/005125A1 and US Publication No. 2022/0273831A1 or in Zboralski et al. (Eur. J. Nuc. Med., 2022, 49:3651-3667).

In certain embodiments, the FAP-targeting radiopharmaceuticals disclosed herein exhibit a dissociation constant (K_D) for human FAP of about 10 nM or less as measured by the surface

plasmon resonance assays disclosed in in WO2021/005125A1 and US Publication No. 2022/0273831A1 or in Zboralski et al. (Eur. J. Nuc. Med., 2022, 49:3651-3667).

In certain embodiments, the FAP-targeting radiopharmaceuticals disclosed herein exhibit a dissociation constant (K_D) for human FAP of about 5 nM or less as measured by the surface plasmon resonance assays disclosed in in WO2021/005125A1 and US Publication No. 2022/0273831A1 or in Zboralski et al. (Eur. J. Nuc. Med., 2022, 49:3651-3667).

The FAP-targeting radiopharmaceutical agents contemplated for use in the methods disclosed herein may also exhibit selectivity for FAP (or limited off-target activity) over, e.g., DPP4 and/or PREP (see the method disclosed for FAP-2286 in Zboralski et al. (Eur. J. Nuc. Med., 2022, 49:3651-3667)).

FAP-targeting radiopharmaceutical agents are known. Such FAP-targeting radiopharmaceutical agents comprise at least one FAP-targeting moiety and a radionuclide. FAP-targeting radiopharmaceutical agents can further comprise one or more chelating agents. FAP-targeting radiopharmaceutical agents can further comprise one or more linkers that, e.g., connect the at least one FAP-targeting moiety with the radionuclide or when present, a chelator.

In an embodiment, the FAP-targeting radiopharmaceutical agent comprises:

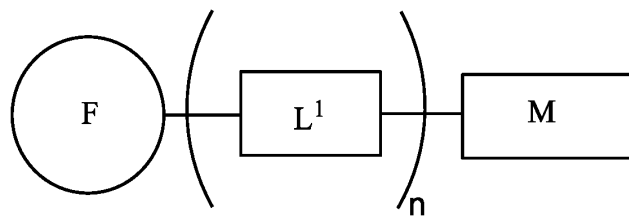
i) a FAP-targeting moiety; and

ii) at least one radionuclide or at least one chelator labeled with a radionuclide,

wherein the FAP-targeting moiety is conjugated to the at least one radionuclide or the at

least one chelator labeled with a radionuclide through a bond or through a linker.

In certain embodiments, the radiopharmaceutical has a structure:

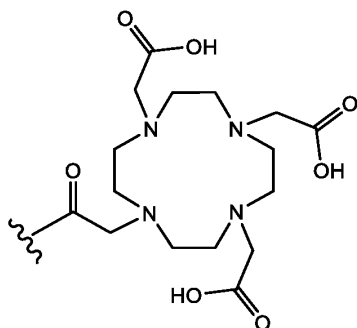


or a pharmaceutically acceptable salt or solvate thereof,

wherein F is a FAP-targeting moiety; M is a radionuclide or a chelator labeled with a radionuclide; L^1 is a linker adapted to form a chemical bond between P and M; and n is 0 or 1.

In some embodiments, M is a DOTA (2,2',2'',2'''-(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid) residue or derivative thereof labeled with a radionuclide.

In some embodiments, M is



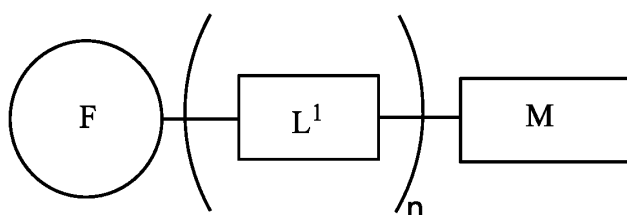
, which is labeled with a radionuclide.

When the chelator is labeled, chelated, or complexed to a radionuclide, it can be said that the chelator is radiolabeled.

- 5 FAP-targeting radiopharmaceutical agents (radiotherapeutic and radioimaging agents) that can be used in methods of the present disclosure include those disclosed and characterized in WO2021/005125 and US Publication No. 2022/0273831; WO2021/005131 and US Publication No. 2022/0315554; WO2022/148851; and WO2022/148843, each of which is incorporated by reference in its entirety. FAP-targeting radiopharmaceutical agents (radiotherapeutic and
- 10 radioimaging agents) that can be used in methods of the present disclosure include those disclosed and characterized in WO2021/195198 and US Publication No. 2022/0370647, which is incorporated by reference in its entirety.

FAP-targeting radiotherapeutic agents

- 15 In certain embodiments, the FAP-targeting radiotherapeutic agent has the structure:



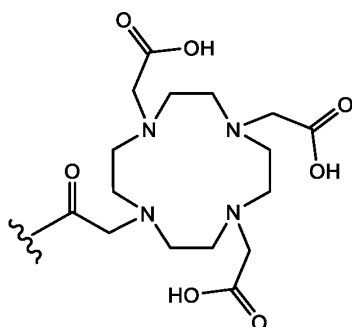
or a pharmaceutically acceptable salt or solvate thereof,

- wherein F is a FAP-targeting moiety; M is a therapeutic radionuclide or a chelator labeled with a therapeutic radionuclide; L¹ is a linker adapted to form a chemical bond between F and M;
- 20 and n is 0 or 1.

In some embodiments, the therapeutic radionuclide is selected from ^{47}Sc , ^{67}Cu , ^{90}Y , ^{131}I , ^{153}Sm , ^{161}Tb , ^{169}Er , or ^{177}Lu . In some embodiments, the therapeutic radionuclide is ^{177}Lu .

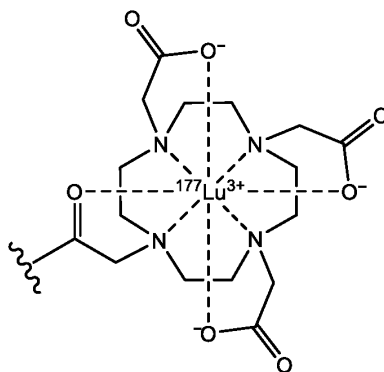
In some embodiments, M comprises DOTA (2,2',2'',2'''-(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid) or is a DOTA residue or derivative thereof labeled with a therapeutic radionuclide.

In some embodiments, M is



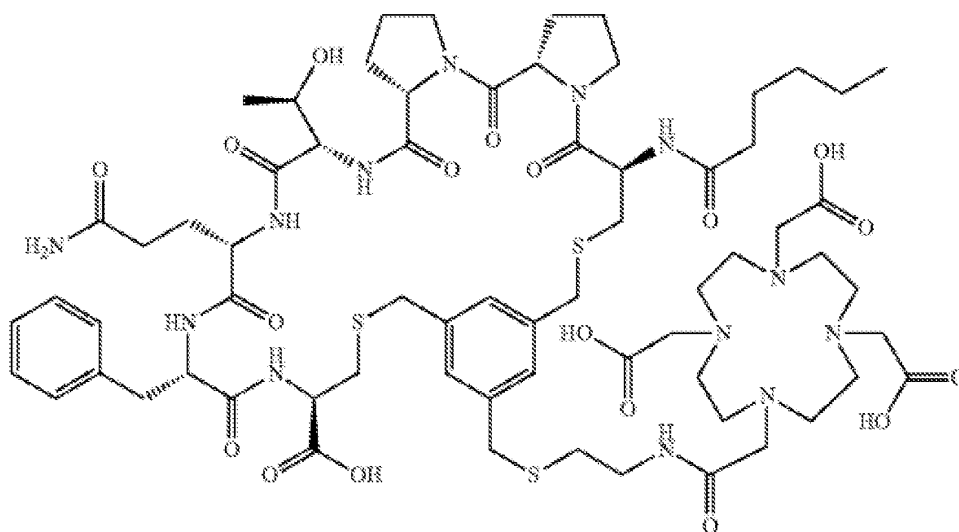
, which is labeled with a therapeutic radionuclide.

In some embodiments, M is



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In an embodiment of any of the methods disclosed herein, the FAP-targeting radiotherapeutic agent is Compound (I):



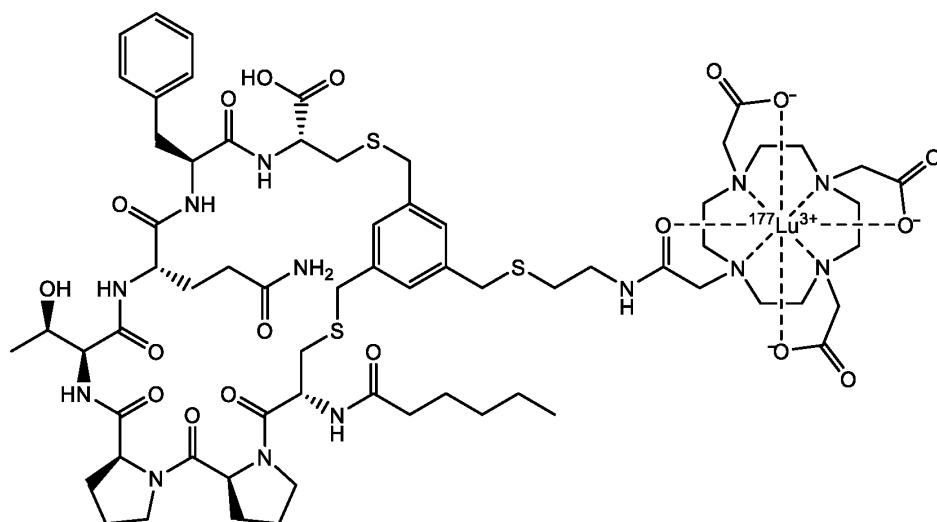
(I),

or a pharmaceutically acceptable salt or solvate thereof, which is radiolabeled with a therapeutic radionuclide, e.g., ^{177}Lu .

Compound (I) can also be referred to as FAP-2286. When radiolabeled with ^{177}Lu ,

5 Compound (I) can be referred to as [^{177}Lu]Lu-FAP-2286.

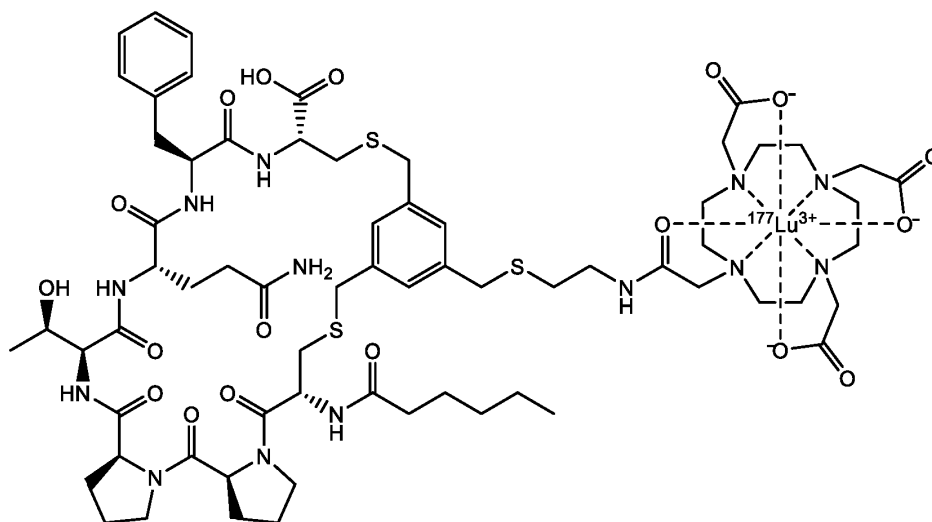
In some embodiments of any of the methods disclosed herein, the FAP-targeting radiotherapeutic agent is



, or a

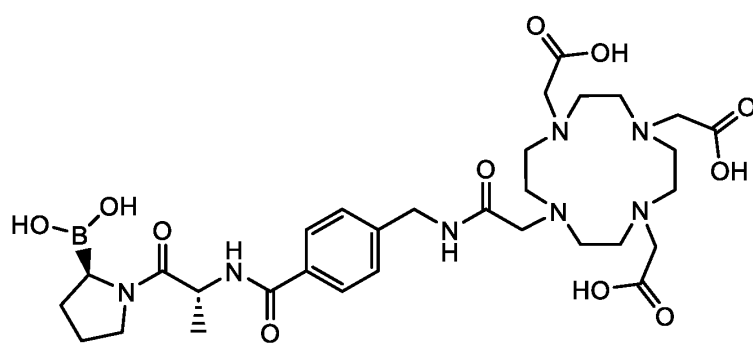
pharmaceutically acceptable salt or solvate thereof (i.e., [¹⁷⁷Lu]Lu-FAP-2286 or a pharmaceutically acceptable salt or solvate thereof).

In some embodiments of any of the methods disclosed herein, the FAP-targeting radiotherapeutic agent is



In some embodiments, the FAP-targeting radiotherapeutic agent is selected from any of PNT6555, CAM-FAP (e.g., [²²⁵Ac]Ac- or [¹³¹I]I-CAM-FAP), OncoFAP, 3BP-3940, RPS-309, NM-05, and FAP-46 when radiolabeled with a therapeutic radionuclide. In some embodiments, the therapeutic radionuclide is ¹⁷⁷Lu.

In an embodiment of any of the methods disclosed herein, the FAP-targeting radiotherapeutic agent is Compound (II):



(II), or a

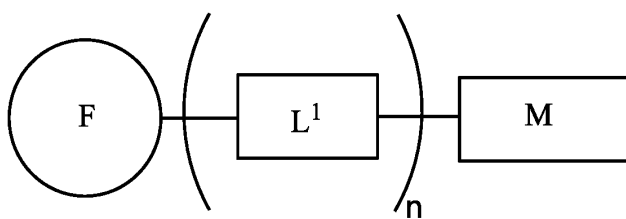
pharmaceutically acceptable salt or solvate thereof, which is radiolabeled with a therapeutic radionuclide, e.g., ^{177}Lu .

Compound (II) can also be referred to as PNT6555 and is disclosed in WO2021/195198. When radiolabeled with ^{177}Lu , Compound (II) can be referred to as [^{177}Lu]-PNT6555 (see, Bodei, L. et al., *JCO* **41**, TPS3161(2023)). [^{177}Lu]-PNT6555 is also disclosed in Poplawski et al. (J. Nucl. Med 2024; 65:100-108).

- 5 In some embodiments, the FAP-targeting radiotherapeutic agent is ^{177}Lu -OncoFAP-DOTAGA (Philogen).

FAP-targeting radioimaging agents

In certain embodiments, the FAP-targeting radioimaging agent has the structure:



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or a pharmaceutically acceptable salt or solvate thereof,

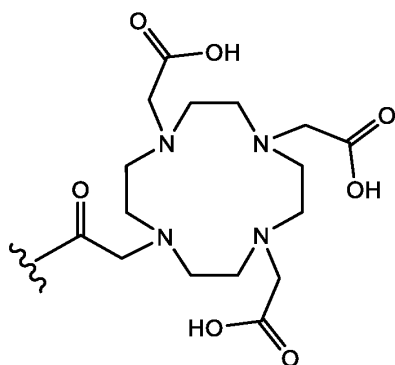
wherein F is a FAP-targeting moiety; M is a diagnostic radionuclide or a chelator labeled with a diagnostic radionuclide; L^1 is a linker adapted to form a chemical bond between F and M; and n is 0 or 1.

In some embodiments, the diagnostic radionuclide is selected from ^{68}Ga , ^{64}Cu , and ^{18}F

In some embodiments, M comprises a chelator suitable for chelating Al^{18}F , e.g., NOTA (where NOTA is 2,2',2''-(1,4,7-triazonane-1,4,7-triyl)triacetic acid).

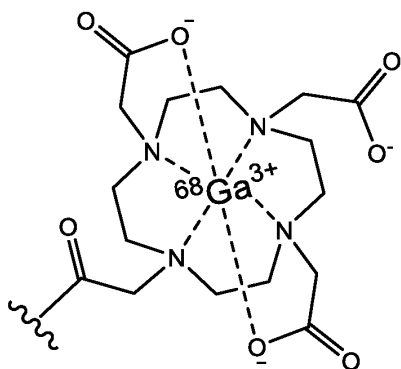
- 15 In some embodiments, M comprises DOTA (2,2',2'',2'''-(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid) or is a DOTA residue or derivative thereof labeled with diagnostic radionuclide.

In some embodiments, M is



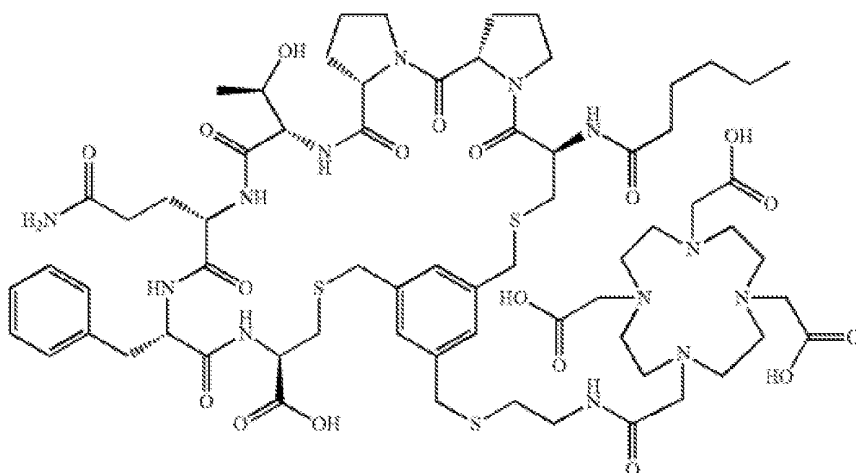
, which is labeled with a diagnostic radionuclide.

In some embodiments, M is



- 5 FAP-targeting radioimaging agents that can be used in methods of the present disclosure include those disclosed in WO2021/005125A1 and US Publication No. 2022/0273831A1.

In an embodiment of any of the methods disclosed herein, the FAP-targeting radioimaging agent is Compound (I):

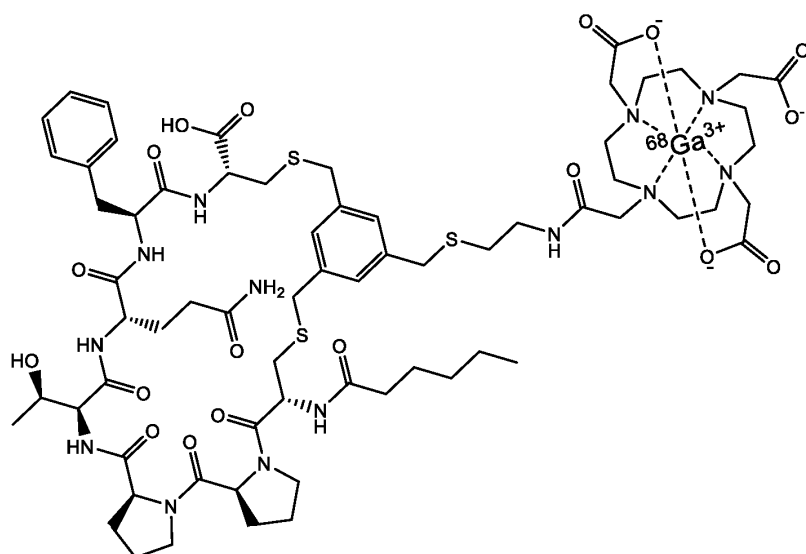


(I), or a

pharmaceutically acceptable salt or solvate thereof, which is radiolabeled with ^{68}Ga .

When Compound (I) is radiolabeled with ^{68}Ga , it can also be referred to as [^{68}Ga]Ga-FAP-2286.

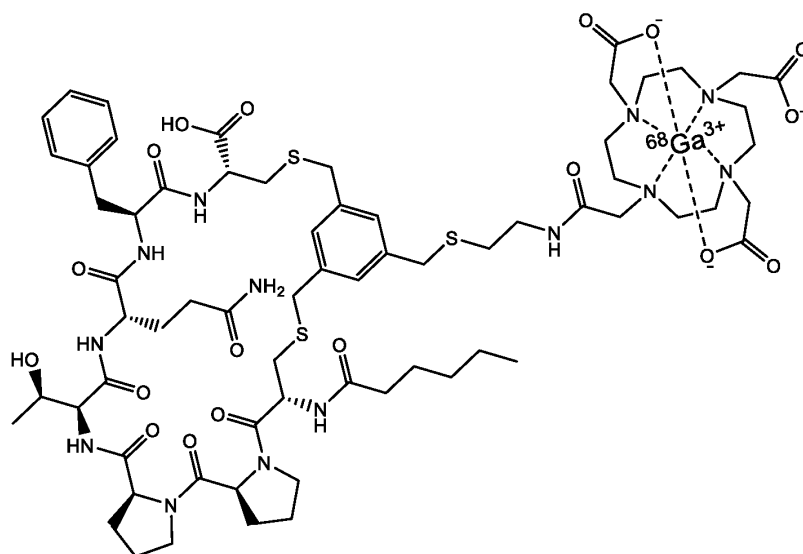
- 5 In some embodiments of any of the methods disclosed herein, the FAP-targeting radioimaging agent is:



, or a pharmaceutically

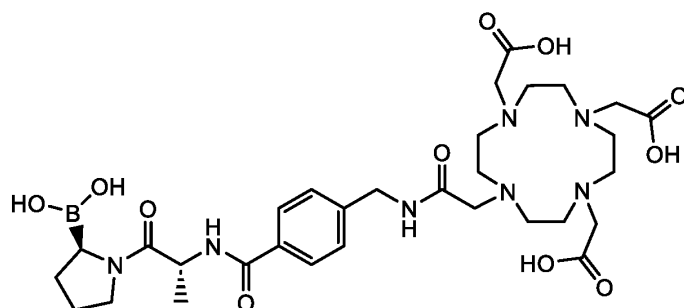
acceptable salt or solvate thereof.

- 10 In some embodiments of any of the methods disclosed herein the FAP-targeting radioimaging agent is:



In some embodiments, the FAP-targeting radioimaging agent is selected from ^{18}F -FAPI-74, $[^{68}\text{Ga}]\text{Ga}$ -FAPI-46, FL-L3- $^{99\text{m}}\text{Tc}$, $[^{68}\text{Ga}]\text{Ga}$ -MHLL1, $[^{68}\text{Ga}]\text{Ga}$ -DOTA.SA.FAPi, $[^{68}\text{Ga}]\text{Ga}$ -RPS-309, $[^{68}\text{Ga}]\text{Ga}$ -FAPI-02, $[^{68}\text{Ga}]\text{Ga}$ -FAPI-04, $[^{68}\text{Ga}]\text{Ga}$ -FAPI-21, $^{99\text{m}}\text{Tc}$ -FAPI-34, $[^{18}\text{F}]\text{FGlc}$ -FAPI, $[^{18}\text{F}]\text{AlF}$ NOTA-FAPI-04, $[^{68}\text{Ga}]\text{Ga}$ -PNT6555, radiolabeled-CAM-FAP, $[^{68}\text{Ga}]\text{Ga}$ -OncoFAP or $[^{68}\text{Ga}]\text{Ga}$ -OncoFAP-DOTAGA (Philogen), $[^{68}\text{Ga}]\text{Ga}$ -3BP-3940, ^{68}Ga -RPS-309, and ^{64}Cu -RTX-1363S. In some embodiments, the FAP-targeting radioimaging agent is $[^{68}\text{Ga}]\text{Ga}$ -FAPI-46.

In an embodiment of any of the methods disclosed herein, the FAP-targeting radioimaging agent is Compound (II):



(II), or a pharmaceutically

acceptable salt or solvate thereof, which is radiolabeled with a diagnostic radionuclide, e.g.,

^{68}Ga .

Methods for treating cancer

Disclosed herein are methods for treating cancer comprising administering a FAP-targeting radiotherapeutic agent. The methods disclosed herein provide for greater efficacy than current standard of care treatment for cancer with an acceptable safety profile.

5 As used herein, “treating” or “treatment” is the means for obtaining beneficial or desired results in a subject, i.e., clinical results. These results may include one or more of (a) reducing the extent of the disease, stabilizing the disease; (b) decreasing or lessening the symptoms resulting from the disease; (c) preventing or delaying spread of the disease (e.g., preventing or delaying metastases); (d) preventing or delaying recurrence of the disease; (e) ameliorating the
10 disease state, providing a remission (partial or total) of the disease, decreasing the dose of one or more other therapeutic agents for treating the disease in the subject; (f) increasing the quality of life of the subject; and/or (g) prolonging survival whether overall or progression-free.

In various embodiments, the methods described herein are directed to treating cancer. In certain embodiments, the cancer is a solid tumor. In certain embodiments, the cancer or solid
15 tumor expresses FAP (i.e., the cancer is a FAP-expressing cancer). In some embodiments, the cancer is a solid tumor selected from appendiceal, breast, colorectal, desmoplastic small round cell tumor, gallbladder, head and neck, lung, peritoneal mesothelioma, pancreatic, prostate, rectal, solitary fibrous tumor, sarcoma (such as soft tissue sarcoma), and uterus/endometrial (specifically uterine leiomyosarcoma) solid tumors. In certain embodiments, the solid tumor is
20 selected from breast, colorectal, head and neck, lung, and pancreatic solid tumors. In some embodiments, the cancer is pancreatic cancer, lung cancer, or breast cancer. In a particular embodiment, the cancer is pancreatic ductal adenocarcinoma (PDAC). In another particular embodiment, the cancer is non-small cell lung cancer (NSCLC). In another particular embodiment, the cancer is breast cancer (BC).

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Solid Tumors

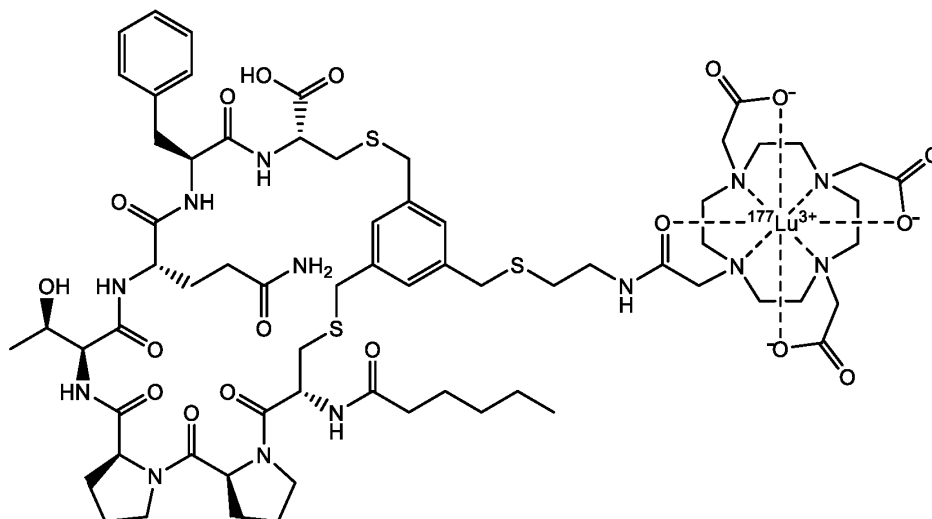
In an aspect, provided herein is a method for treating cancer in a subject in need thereof comprising administering to the subject a FAP-targeting radiotherapeutic agent, wherein the FAP-targeting radiotherapeutic agent is administered intravenously as a single dose once every
30 28 ± 3 days to achieve a cumulative dose of about 40 to about 60 GBq, wherein the cancer is a FAP-expressing solid tumor.

In another aspect, provided herein is a method for treating cancer in a subject in need thereof comprising administering to the subject a FAP-targeting radiotherapeutic agent, wherein the FAP-targeting radiotherapeutic agent is administered intravenously as a single dose once every 28 ± 3 days to achieve a cumulative dose of about 40 to about 60 GBq, wherein the cancer is a FAP-expressing solid tumor and wherein the single dose is about 3.7 GBq, about 5.6 GBq, about 7.4 GBq, or about 9.3 GBq.

In an aspect, provided herein is a method for treating cancer in a subject in need thereof comprising administering to the subject a FAP-targeting radiotherapeutic agent comprising ^{177}Lu , wherein the FAP-targeting radiotherapeutic agent is administered intravenously as a single dose once every 28 ± 3 days to achieve a cumulative dose of about 40 to about 60 GBq, wherein the cancer is a FAP-expressing solid tumor.

In another aspect, provided herein is a method for treating cancer in a subject in need thereof comprising administering to the subject a FAP-targeting radiotherapeutic agent comprising ^{177}Lu , wherein the FAP-targeting radiotherapeutic agent is administered intravenously as a single dose once every 28 ± 3 days to achieve a cumulative dose of about 40 to about 60 GBq, wherein the cancer is a FAP-expressing solid tumor and wherein the single dose is about 3.7 GBq, about 5.6 GBq, about 7.4 GBq, or about 9.3 GBq.

In an aspect, provided herein is a method for treating cancer in a subject in need thereof comprising administering to the subject a FAP-targeting radiotherapeutic agent which is



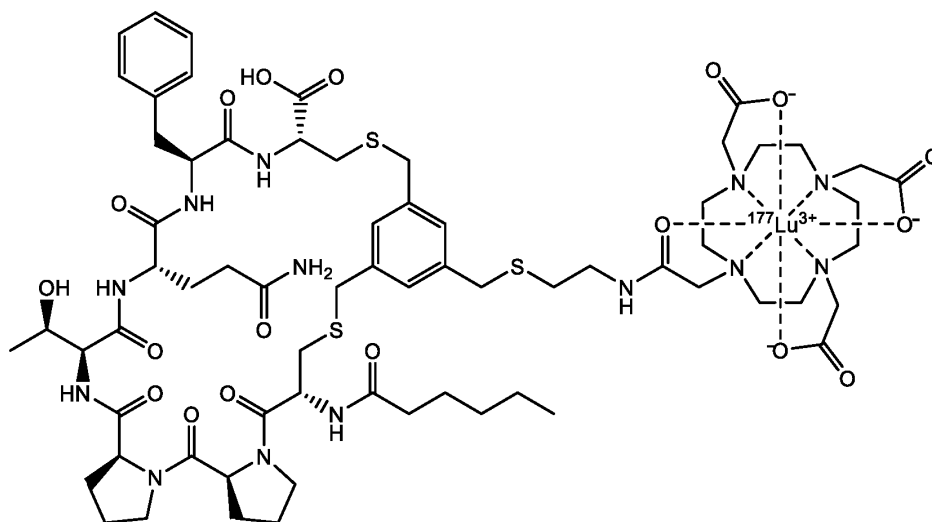
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, or

a pharmaceutically acceptable salt or solvate thereof, wherein the FAP-targeting radiotherapeutic

agent is administered intravenously as a single dose once every 28 ± 3 days to achieve a cumulative dose of about 40 to about 60 GBq, wherein the cancer is a FAP-expressing solid tumor.

In another aspect, provided herein is a method for treating cancer in a subject in need thereof comprising administering to the subject a FAP-targeting radiotherapeutic agent which is



, or

a pharmaceutically acceptable salt or solvate thereof, wherein the FAP-targeting radiotherapeutic agent is administered intravenously as a single dose once every 28 ± 3 days to achieve a cumulative dose of about 40 to about 60 GBq, wherein the cancer is a FAP-expressing solid tumor and wherein the single dose is about 3.7 GBq, about 5.6 GBq, about 7.4 GBq, or about 9.3 GBq.

In an embodiment, the single dose of the FAP-targeting radiotherapeutic agent is about 9.3 GBq.

In an embodiment, the cumulative dose of the FAP-targeting radiotherapeutic agent is about 55.5 GBq.

In certain embodiments, the methods disclosed herein further comprises administering to the subject a therapeutically effective amount of a chemotherapy.

In certain embodiments, the chemotherapy comprises a taxane. In certain embodiments, the taxane is paclitaxel, nab-paclitaxel, docetaxel, or cabazitaxel. In certain embodiments, the taxane is paclitaxel, nab-paclitaxel, or docetaxel.

In certain embodiments, the chemotherapy comprises nab-paclitaxel, FOLFIRINOX, mFOLFIRINOX, or NALIRIFOX.

In certain embodiments, the chemotherapy comprises nab-paclitaxel, FOLFIRINOX, or mFOLFIRINOX.

5 In certain embodiments, the solid tumor is selected from appendiceal, breast, colorectal, desmoplastic small round cell tumor, gallbladder, head and neck, lung, peritoneal mesothelioma, pancreatic, prostate, rectal, solitary fibrous tumor, sarcoma (e.g., soft tissue sarcoma), and uterus/endometrial (specifically uterine leiomyosarcoma) solid tumors. In certain embodiments, the solid tumor is selected from breast, colorectal, head and neck, lung, and pancreatic solid
10 tumors.

In an aspect, provided herein is a FAP-targeting radiotherapeutic agent for use in the treatment of a FAP-expressing solid tumor (i.e., for use in any of the methods of treating a FAP-expressing solid tumor disclosed herein), wherein the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days or every 6 weeks $\pm$ three days
15 to achieve a cumulative dose of about 40 GBq to about 60 GBq.

Pancreatic Cancer

Provided herein are methods for treating pancreatic cancer comprising administering a FAP-targeting radiotherapeutic agent to a subject in need thereof. With clear FAP expression in
20 PDAC, this is an excellent therapeutic target for novel therapy. A FAP-targeting radiotherapeutic (such as, e.g., [^{177}Lu]Lu-FAP-2286) may allow delivery of targeted radiation directly to the tumor bed. Through the expression of FAP on CAFs, FAP-targeting radiotherapeutic agent (e.g., [^{177}Lu]Lu-FAP-2286) can lead to destruction of the tumor stroma via direct radiation damage. In addition, tumor cells in proximity to the FAP positive target cells may also see their demise
25 through radiation effect causing DNA damage leading to cell death. Thus, administration of a FAP-targeting radiotherapeutic agent (such as, e.g., [^{177}Lu]Lu-FAP-2286) alone and at an appropriate dose may lead to improved tumor control.

Monotherapy for the Treatment of Pancreatic Ductal Adenocarcinoma (PDAC)

30 Provided herein is a method for treating pancreatic ductal adenocarcinoma (PDAC) in a subject in need thereof comprising administering to a subject in need thereof a FAP-targeting

radiotherapeutic agent, wherein the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days or every 6 weeks $\pm$ three days to achieve a cumulative dose of about 40 to about 60 GBq.

In an embodiment, the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days.

In an embodiment, the single dose of the FAP-targeting radiotherapeutic agent is from about 3 GBq to about 10 GBq.

In an embodiment, the single dose of the FAP-targeting radiotherapeutic agent is about 3.7 GBq, about 5.6 GBq, about 7.4 GBq, or about 9.3 GBq.

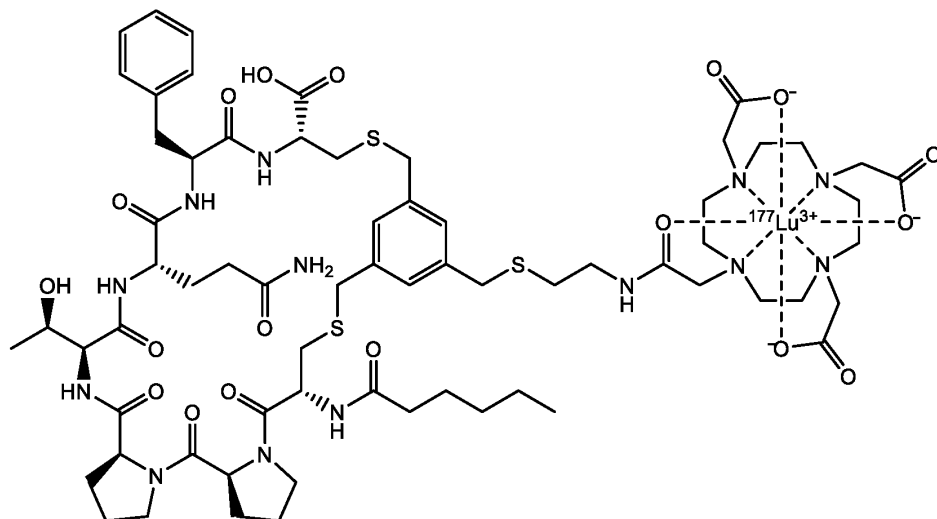
In an embodiment, the single dose of the FAP-targeting radiotherapeutic agent is about 9.3 GBq.

In an embodiment, the cumulative dose of the FAP-targeting radiotherapeutic agent is about 55.5 GBq.

In some embodiments, the FAP-targeting radiotherapeutic agent comprises ^{47}Sc , ^{67}Cu , ^{90}Y , ^{131}I , ^{153}Sm , ^{161}Tb , ^{169}Er , or ^{177}Lu .

In an embodiment, the FAP-targeting radiotherapeutic agent comprises ^{177}Lu .

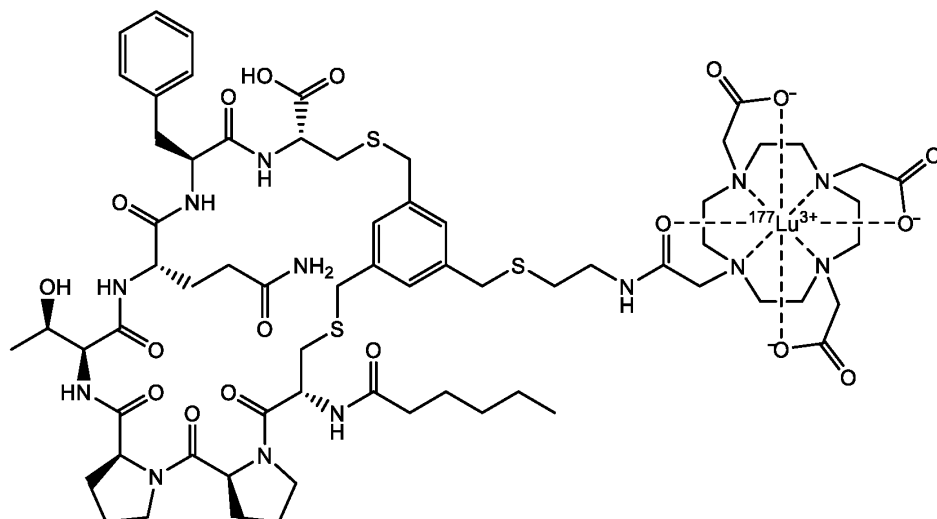
In an embodiment, the FAP-targeting radiotherapeutic agent is



, or a

pharmaceutically acceptable salt or solvate thereof.

In an embodiment, the FAP-targeting radiotherapeutic agent is



In an embodiment, the PDAC is FAP-expressing.

In an embodiment, the PDAC is metastatic.

5 In an embodiment, the PDAC is not an endocrine or neuroendocrine tumor.

In an embodiment, the subject has received at least one prior therapy for the treatment of PDAC, wherein each of the at least one prior therapy is other than a therapy comprising a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.

10 In an embodiment, the subject has progressed after at least one, but no more than two, prior chemotherapy regimens for locally advanced unresectable or metastatic PDAC.

In an embodiment, the subject has received at least two prior therapies for the treatment of PDAC, wherein each of the prior therapies is other than a therapy comprising a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.

15 In an aspect, provided herein is a FAP-targeting radiotherapeutic agent for use in the treatment of pancreatic ductal adenocarcinoma (PDAC) (i.e., for use in any of the methods of treating PDAC disclosed herein), wherein the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days or every 6 weeks $\pm$ three days to achieve a cumulative dose of about 40 to about 60 GBq.

20 In an aspect, provided herein is a FAP-targeting radiotherapeutic agent for use in the treatment of pancreatic ductal adenocarcinoma (PDAC) (i.e., for use in any of the methods of treating PDAC disclosed herein), wherein the FAP-targeting radiotherapeutic agent is

administered as a single dose once every four weeks $\pm$ three days to achieve a cumulative dose of about 40 to about 60 GBq, and wherein the single dose of the FAP-targeting radiotherapeutic agent is about 3.7 GBq, about 5.6 GBq, about 7.4 GBq, or about 9.3 GBq.

5 Combination Therapy for the Treatment of Pancreatic Ductal Adenocarcinoma (PDAC)

Furthermore, targeting directly the tumor microenvironment by the administration of a FAP-targeting radiotherapeutic agent (e.g., [^{177}Lu]Lu-FAP-2286), chemotherapy may have the opportunity for improved delivery to the tumor cells and lead to additional cytotoxic destruction. By combining chemotherapy with a FAP-targeting radiotherapeutic agent (e.g., [^{177}Lu]Lu-FAP-
10 2286), there is a potential for a multimodal approach to tumor destruction.

Chemotherapy given with a FAP-targeting radiotherapeutic (e.g., [^{177}Lu]Lu-FAP-2286) may therefore show improved efficacy over and above each treatment as monotherapy.

FOLFIRINOX is a commonly used first line regimen for metastatic PDAC in participants with good performance status (Conroy T, et al. (2011) The New England Journal of Medicine; 15 364(19):1817-1825). mFOLFIRINOX was developed to decrease the incidence and severity of cytopenias and GI toxicity. In a study of participants with both localized and metastatic PDAC, mFOLFIRINOX has demonstrated a more favorable safety profile while not compromising efficacy (Mahaseth H, et al. (2013) Pancreas; 42(8):1311-1315). Additional studies have shown an improved safety profile with mFOLFIRINOX (Stein SM, et al. (2016) Br J Cancer; 20 114(7):737-743). Therefore, mFOLFIRINOX every two weeks may be a suitable chemotherapy partner with a FAP-targeting radiotherapeutic agent (e.g., [^{177}Lu]Lu-FAP-2286) every 4 weeks (28 days) in participants with 1L PDAC. Other variations on FOLFIRINOX, such as NALIRIFOX, may also be suitable chemotherapy partner with a FAP-targeting radiotherapeutic agent (e.g., [^{177}Lu]Lu-FAP-2286) (see, e.g., Wainberg Z, et al. (2023) Lancet; 402: 1272-1281).

25 A FAP-targeting radiotherapeutic (e.g., [^{177}Lu]Lu-FAP-2286) in combination with mFOLFIRINOX (or a variation thereof, such as NALIRIFOX) in patients with PDAC may further demonstrate improved tumor response in comparison to chemotherapy alone. The FAP-targeting radiotherapeutic may cause direct cell death to FAP-positive cells in the tumor microenvironment as well as surrounding cells through “cross-fire” radiation effect. In addition, 30 modulation of the tumor microenvironment may improve the cytotoxic drug delivery to the tumor cells creating synergy with cytotoxic chemotherapy. Lastly, 5-FU based chemotherapy

may sensitize the tumor to the effects of radiation. Therefore, FAP-targeting radiotherapeutic agents (such as, e.g., [^{177}Lu]Lu-FAP-2286) in combination with mFOLFIRINOX is a promising combination approach for tumor destruction. mFOLFIRINOX comprises (modified) leucovorin calcium (folinic acid), fluorouracil, irinotecan, and oxaliplatin. NALIRIFOX comprises

5 liposomal irinotecan, oxaliplatin, 5-fluorouracil, and leucovorin.

Accordingly, in an aspect, provided herein is a method for treating pancreatic ductal adenocarcinoma (PDAC) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

- (a) a fibroblast activation protein (FAP)-targeting radiotherapeutic agent; and
- 10 (b) chemotherapy comprising one, two, three, or four agents selected from 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin. Any of the agents in part (b) may be in a pharmaceutically acceptable salt form. For example, recitation of leucovorin includes its pharmaceutically acceptable salts, e.g., leucovorin calcium. When an amount of the agent is specified, the amount corresponds to the active agent in its free acid or base form.

- 15 In some embodiments, the FAP-targeting radiotherapeutic agent comprises ^{47}Sc , ^{67}Cu , ^{90}Y , ^{131}I , ^{153}Sm , ^{161}Tb , ^{169}Er , or ^{177}Lu .

In some embodiments, the FAP-targeting radiotherapeutic agent comprises ^{177}Lu .

In some embodiments, the FAP-targeting radiotherapeutic agent is [^{177}Lu]Lu-FAP-2286 or a pharmaceutically acceptable salt or solvate thereof.

- 20 In some embodiments, the FAP-targeting radiotherapeutic agent is [^{177}Lu]Lu-FAP-2286.

In some embodiments, the chemotherapy comprises 5-FU, leucovorin, and irinotecan.

In some embodiments, the chemotherapy comprises 5-FU, leucovorin, and oxaliplatin.

- In some embodiments, the chemotherapy comprises 5-FU, leucovorin, irinotecan, and oxaliplatin. In some embodiments, the chemotherapy comprises 5-FU, leucovorin calcium,
- 25 irinotecan, and oxaliplatin.

In some embodiments, the chemotherapy comprises liposomal irinotecan.

In some embodiments, the chemotherapy is administered to the subject prior to administration of the FAP-targeting radiotherapeutic agent.

- In some embodiments, the chemotherapy is administered to the subject in one to two
- 30 cycles prior to the administration of the FAP-targeting radiotherapeutic agent.

In some embodiments, the chemotherapy is administered on a 14-day cycle.

In some embodiments, the chemotherapy is administered on a 14-day cycle, wherein:

- i. oxaliplatin is administered on the first day of the 14-day cycle;
- ii. leucovorin is administered on the first day of the 14-day cycle;
- iii. irinotecan is administered on the first day of the 14-day cycle; and
- 5 iv. 5-fluorouracil is administered on the first and second day of the 14-day cycle
(e.g., the 5-FU is administered as a continuous IV infusion over 46 hours).

In some embodiments, the oxaliplatin is administered intravenously at a dose from about 60 mg/m² to about 100 mg/m².

10 In some embodiments, the oxaliplatin is administered intravenously at a dose of about 85 mg/m².

In some embodiments, the leucovorin is administered intravenously at a dose from about 50 mg/m² to about 500 mg/m².

In some embodiments, the leucovorin is administered intravenously at a dose from about 300 mg/m² to about 500 mg/m².

15 In some embodiments, the leucovorin is administered intravenously at a dose of about 400 mg/m².

In some embodiments, the irinotecan is administered intravenously at a dose from about 100 mg/m² to about 200 mg/m².

20 In some embodiments, the irinotecan is administered intravenously at a dose of about 150 mg/m².

In some embodiments, the 5-fluorouracil is administered intravenously at a dose from about 1000 mg/m² to about 3000 mg/m².

In some embodiments, the 5-fluorouracil is administered intravenously at a dose of about 2400 mg/m².

25 In some embodiments, the FAP-targeting radiotherapeutic agent is administered intravenously as a single dose once every three weeks $\pm$ three days, four weeks $\pm$ three days, five weeks $\pm$ three days, or six weeks $\pm$ three days.

In some embodiments, the FAP-targeting radiotherapeutic agent is administered intravenously as a single dose once every four weeks $\pm$ three days.

30 In some embodiments, the single dose of the FAP-targeting radiotherapeutic agent is from about 3 GBq to about 10 GBq.

In some embodiments, the single dose of the FAP-targeting radiotherapeutic agent is about 3.7 GBq, about 5.6 GBq, about 7.4 GBq, or about 9.3 GBq.

In some embodiments, the FAP-targeting radiotherapeutic agent is administered to the subject as a single dose once every four weeks $\pm$ three days for a length of time to achieve a
5 cumulative dose of about 55.5 GBq.

In some embodiments, the FAP-targeting radiotherapeutic agent is administered on any one of the first day, second day, third day, fourth day, or fifth day of each 14-day chemotherapy cycle.

In some embodiments, the PDAC is FAP-expressing.

10 In some embodiments, the PDAC is metastatic.

In an embodiment, the PDAC is not an endocrine or neuroendocrine tumor.

In some embodiments, the subject has not received any prior systemic therapy for metastatic PDAC (i.e., the method is a 1L therapy for metastatic PDAC or the method is for a subject newly diagnosed with metastatic PDAC).

15 In another aspect, provided herein is a pharmaceutical combination comprising a therapeutically effective amount of:

(a) a fibroblast activation protein (FAP)-targeting radiotherapeutic agent; and

(b) chemotherapy comprising at least one, two, three, or four agents selected from 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin

20 for use in any of the methods for treating pancreatic ductal adenocarcinoma (PDAC) disclosed herein.

In another aspect, provided herein is a fibroblast activation protein (FAP)-targeting radiotherapeutic agent for use in the treatment of pancreatic ductal adenocarcinoma (PDAC) (i.e., for use in any of the methods disclosed herein) wherein the treatment further comprises
25 administration of a chemotherapy comprising at least one, two, three, or four agents selected from 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin.

In another aspect, provided herein is a chemotherapy comprising at least one, two, three, or four agents selected from 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin for use in the treatment of pancreatic ductal adenocarcinoma (PDAC) (i.e., for use in any of the methods
30 disclosed herein) wherein the treatment further comprises administration of a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.

Non-Small Cell Lung Cancer (NSCLC)

Provided herein are methods for treating non-small cell lung cancer comprising administering a FAP-targeting radiotherapeutic agent to a subject in need thereof.

5

Monotherapy for the Treatment of Non-Small Cell Lung Cancer (NSCLC)

Provided herein is a method for treating non-small cell lung cancer (NSCLC) in a subject in need thereof comprising administering to a subject in need thereof a FAP-targeting radiotherapeutic agent, wherein the FAP-targeting radiotherapeutic agent is administered as a
10 single dose once every four weeks $\pm$ three days or every 6 weeks $\pm$ three days to achieve a cumulative dose of about 40 to 60 GBq.

In some embodiments, the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days.

In some embodiments, the single dose of the FAP-targeting radiotherapeutic agent is
15 from about 3 GBq to about 10 GBq.

In some embodiments, the single dose of the FAP-targeting radiotherapeutic agent is about 3.7 GBq, about 5.6 GBq, about 7.4 GBq, or about 9.3 GBq.

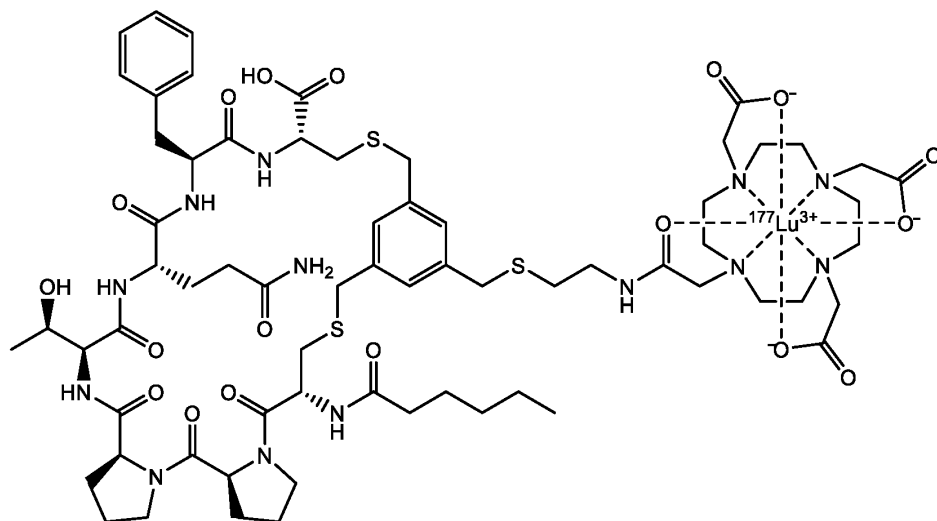
In some embodiments, the single dose of the FAP-targeting radiotherapeutic agent is about 9.3 GBq.

20 In some embodiments, the cumulative dose of the FAP-targeting radiotherapeutic agent is about 55.5 GBq.

In some embodiments, the FAP-targeting radiotherapeutic agent comprises ^{47}Sc , ^{67}Cu , ^{90}Y , ^{131}I , ^{153}Sm , ^{161}Tb , ^{169}Er , or ^{177}Lu .

In some embodiments, the FAP-targeting radiotherapeutic agent comprises ^{177}Lu .

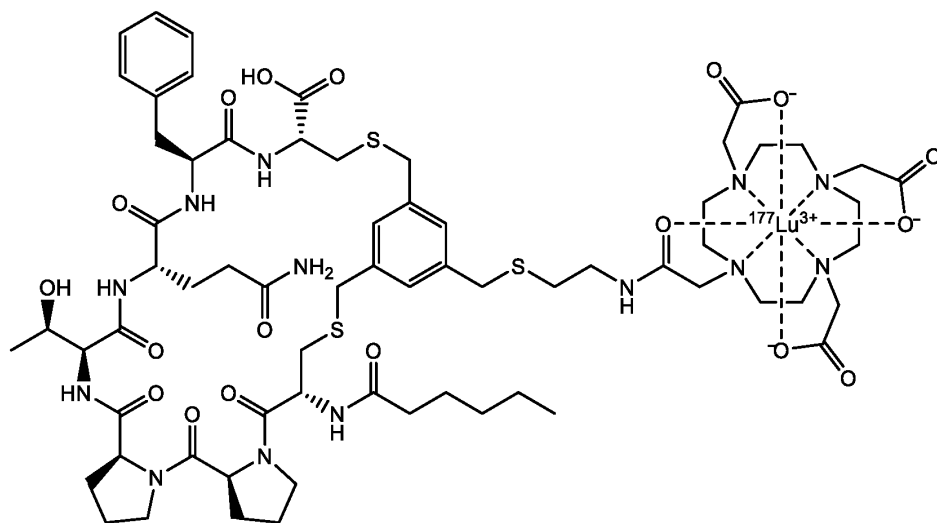
In some embodiments, the FAP-targeting radiotherapeutic agent is



, or a

pharmaceutically acceptable salt or solvate thereof.

In some embodiments, the FAP-targeting radiotherapeutic agent is



5

In some embodiments, the NSCLC is FAP-expressing.

In some embodiments, the NSCLC is metastatic.

In some embodiments, the NSCLC is characterized as adenocarcinoma or squamous.

In some embodiments, the NSCLC is not characterized as endocrine, neuroendocrine, or

10 small cell.

In some embodiments, the subject has received at least one prior therapy for the treatment of NSCLC, wherein each of the at least one prior therapy is other than a therapy comprising a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.

5 In some embodiments, the subject has received at least two prior therapies for the treatment of NSCLC, wherein each of the two prior therapies is other than a therapy comprising a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.

In an embodiment, the subject has progressed after at least one, but no more than two, prior chemotherapy and/or immunotherapy regimens the treatment of the NSCLC.

10 In an embodiment, the subject has received prior adjuvant or neoadjuvant platinum-doublet chemotherapy and a prior immune checkpoint inhibitor regimen.

In an embodiment, the subject has received prior treatment comprising adjuvant or neoadjuvant platinum-doublet chemotherapy and an immune checkpoint inhibitor regimen and developed recurrent or metastatic disease during or within 12 months of said prior treatment comprising adjuvant or neoadjuvant platinum-doublet chemotherapy and an immune checkpoint
15 inhibitor.

In an embodiment, the subject has recurrent NSCLC more than 12 months after prior adjuvant or neoadjuvant platinum-based chemotherapy, wherein the subject also subsequently progressed during or after a prior platinum doublet regimen and a prior immune checkpoint inhibitor regimen.

20 In an embodiment, the subject has progressed after receiving prior platinum-based chemotherapy for advanced or metastatic NSCLC and a prior immune checkpoint inhibitor regimen; wherein the prior platinum-based chemotherapy and the prior immune checkpoint inhibitor regimen were administered concurrently (together, in the same line of treatment) or sequentially (two different lines of treatment).

25 In an aspect, provided herein is a FAP-targeting radiotherapeutic agent for use in the treatment of non-small cell lung cancer (NSCLC) (i.e., for use in any of the methods of treating NSCLC disclosed herein), wherein the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days or every 6 weeks $\pm$ three days to achieve a cumulative dose of about 40 to about 60 GBq.

30 In an aspect, provided herein is a FAP-targeting radiotherapeutic agent for use in the treatment of non-small cell lung cancer (NSCLC) in a subject in need thereof (i.e., for use in any

of the methods of treating NSCLC disclosed herein), wherein the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days to achieve a cumulative dose of about 40 to about 60 GBq and wherein the single dose of the FAP-targeting radiotherapeutic agent is about 3.7 GBq, about 5.6 GBq, about 7.4 GBq, or about 9.3 GBq.

5

Combination Therapy for the Treatment of Non-Small Cell Lung Cancer

In an aspect, provided herein is a method for treating non-small cell lung cancer (NSCLC) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

- 10 (A) a fibroblast activation protein (FAP)-targeting radiotherapeutic agent; and
(B) a taxane.

In some embodiments, the taxane is paclitaxel, nab-paclitaxel, or docetaxel.

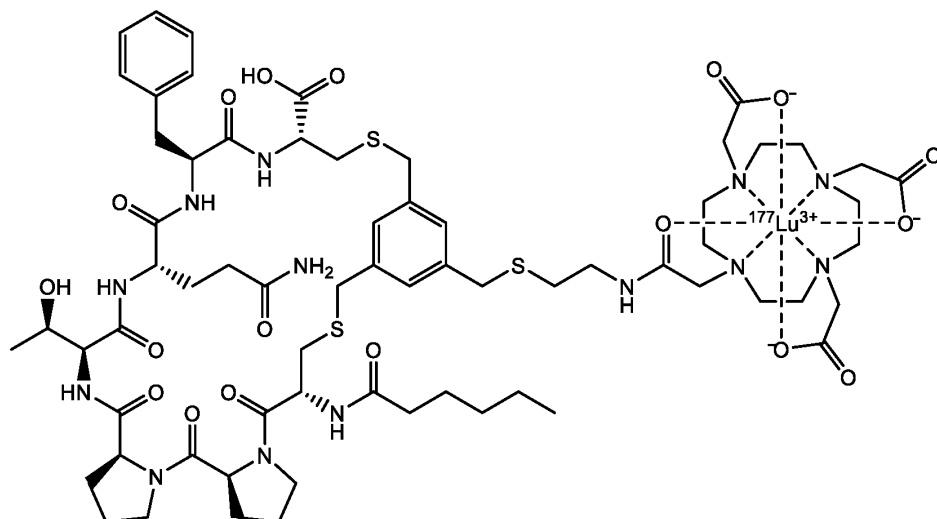
- In an aspect, provided herein is a method for treating non-small cell lung cancer (NSCLC) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

- (A) a fibroblast activation protein (FAP)-targeting radiotherapeutic agent; and
(B) nab-paclitaxel.

In some embodiments, the FAP-targeting radiotherapeutic agent comprises ^{47}Sc , ^{67}Cu , ^{90}Y , ^{131}I , ^{153}Sm , ^{161}Tb , ^{169}Er , or ^{177}Lu .

- 20 In some embodiments, the FAP-targeting radiotherapeutic agent comprises ^{177}Lu .

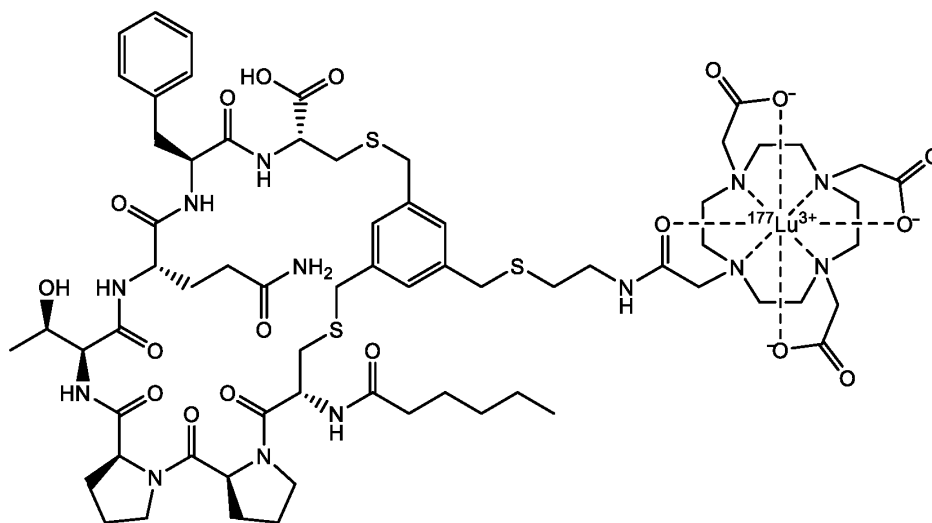
In some embodiments, the FAP-targeting radiotherapeutic agent is



, or a

pharmaceutically acceptable salt or solvate thereof.

In some embodiments, the FAP-targeting radiotherapeutic agent is



5

In some embodiments, the subject has previously received at least one prior therapy for the treatment of NSCLC, wherein each of the at least one prior therapy is other than a therapy comprising a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.

In some embodiments, the subject has previously received at least two prior therapies for the treatment of NSCLC, wherein each of the prior therapies is other than a therapy comprising a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.

5 In an embodiment, the subject has progressed after at least one, but no more than two prior systemic regimens for the treatment of the NSCLC.

In an embodiment, the subject has progressed after at least one, but no more than two prior chemotherapy and/or immunotherapy regimens for the treatment of the NSCLC.

In an embodiment, the subject has received prior adjuvant or neoadjuvant platinum-doublet chemotherapy and an immune checkpoint inhibitor.

10 In an embodiment, the subject has received prior treatment comprising adjuvant or neoadjuvant platinum-doublet chemotherapy and an immune checkpoint inhibitor and developed recurrent or metastatic disease during or within 12 months of said prior treatment comprising adjuvant or neoadjuvant platinum-doublet chemotherapy and an immune checkpoint inhibitor.

15 In an embodiment, the subject has recurrent NSCLC more than 12 months after prior adjuvant or neoadjuvant platinum-based chemotherapy, wherein the subject also subsequently progressed during or after a prior platinum doublet regimen and an immune checkpoint inhibitor.

20 In an embodiment, the subject has progressed after receiving prior platinum-based chemotherapy for advanced or metastatic NSCLC and an immune checkpoint inhibitor; wherein the prior platinum-based chemotherapy and the immune checkpoint inhibitor were administered concurrently (together, in the same line of treatment) or sequentially (two different lines of treatment).

In an embodiment, the subject has not received prior taxane therapy (i.e., a prior taxane regimen) either as a monotherapy or as a combination.

25 In some embodiments, the nab-paclitaxel is administered to the subject prior to administration of the FAP-targeting radiotherapeutic agent.

In some embodiments, the nab-paclitaxel is administered to the subject in one to two cycles prior to the administration of the FAP-targeting radiotherapeutic agent.

In some embodiments, the nab-paclitaxel is administered once in a nab-paclitaxel seven-day cycle.

30 In some embodiments, the nab-paclitaxel is administered on the first day in the nab-paclitaxel seven-day cycle (i.e., the nab-paclitaxel is administered once a week, or weekly).

In some embodiments, the nab-paclitaxel is administered intravenously at a dose from about 50 mg/m² to about 150 mg/m².

In some embodiments, the nab-paclitaxel is administered intravenously at a dose of about 100 mg/m².

5 In some embodiments, the FAP-targeting radiotherapeutic agent is administered on any one of the first day, the second day, the third day, the fourth day, or the fifth day of the nab-paclitaxel seven-day cycle.

 In some embodiments, the FAP-targeting radiotherapeutic agent is administered intravenously as a single dose once every three weeks ± three days, four weeks ± three days, five
10 weeks ± three days, or six weeks ± three days.

 In some embodiments, the FAP-targeting radiotherapeutic agent is administered intravenously as a single dose once every four weeks ± three days.

 In some embodiments, the single dose of the FAP-targeting radiotherapeutic agent is from about 3 GBq to about 10 GBq.

15 In some embodiments, the single dose of the FAP-targeting radiotherapeutic agent is about 3.7 GBq, about 5.6 GBq, about 7.4 GBq, or about 9.3 GBq.

 In some embodiments, the FAP-targeting radiotherapeutic agent is administered to the subject once every four weeks ± three days for a length of time to achieve a cumulative dose of about 55.5 GBq.

20 In some embodiments, the NSCLC is FAP-expressing.

 In some embodiments, the NSCLC is metastatic.

 In another aspect, provided herein is a pharmaceutical combination comprising a therapeutically effective amount of:

 (A) a fibroblast activation protein (FAP)-targeting radiotherapeutic agent; and
25 (B) nab-paclitaxel

 for use in any of the methods for treating non-small cell lung cancer (NSCLC) disclosed herein.

 In another aspect, provided herein is a fibroblast activation protein (FAP)-targeting radiotherapeutic agent for use in the treatment of non-small cell lung cancer (NSCLC) (i.e., for
30 use in any of the methods disclosed herein) wherein the treatment further comprises administration of a chemotherapy comprising nab-paclitaxel.

In another aspect, provided herein is a chemotherapy comprising nab-paclitaxel for use in the treatment of non-small cell lung cancer (NSCLC) (i.e., for use in any of the methods disclosed herein) wherein the treatment further comprises administration of a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.

5

Breast Cancer

Provided herein are methods for treating breast cancer comprising administering a FAP-targeting radiotherapeutic agent to a subject in need thereof.

In an aspect, provided herein is a method for treating breast cancer in a subject in need thereof comprising administering to a subject in need thereof a FAP-targeting radiotherapeutic agent, wherein the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days or every 6 weeks $\pm$ three days to achieve a cumulative dose of about 40 to 60 GBq.

In some embodiments, the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days.

In some embodiments, the single dose of the FAP-targeting radiotherapeutic agent is from about 3 GBq to about 10 GBq.

In some embodiments, the single dose of the FAP-targeting radiotherapeutic agent is about 3.7 GBq, about 5.6 GBq, about 7.4 GBq, or about 9.3 GBq.

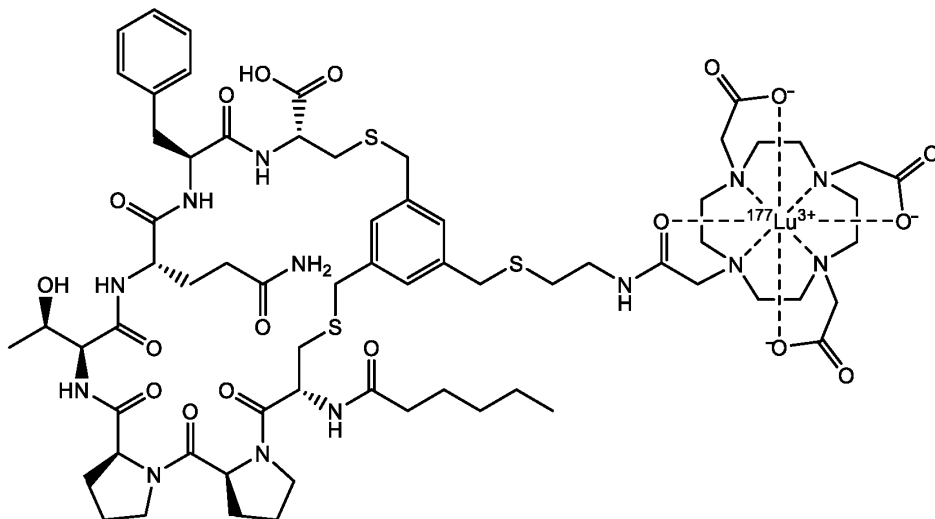
In some embodiments, the single dose of the FAP-targeting radiotherapeutic agent is about 9.3 GBq.

In some embodiments, the cumulative dose of the FAP-targeting radiotherapeutic agent is about 55.5 GBq.

In some embodiments, the FAP-targeting radiotherapeutic agent comprises ^{47}Sc , ^{67}Cu , ^{90}Y , ^{131}I , ^{153}Sm , ^{161}Tb , ^{169}Er , or ^{177}Lu .

In some embodiments, the FAP-targeting radiotherapeutic agent comprises ^{177}Lu .

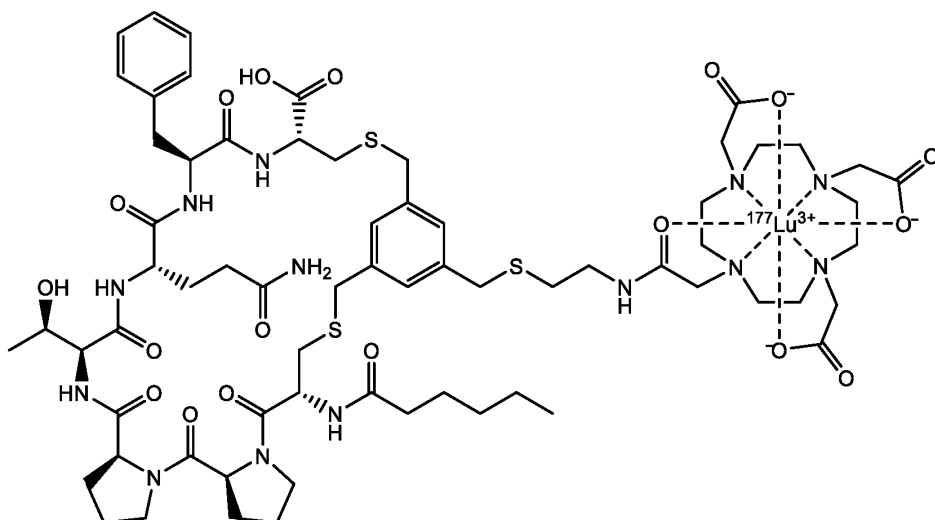
In some embodiments, the FAP-targeting radiotherapeutic agent is



, or a

pharmaceutically acceptable salt or solvate thereof.

In some embodiments, the FAP-targeting radiotherapeutic agent is



5

In some embodiments, the breast cancer is FAP-expressing.

In some embodiments, the breast cancer is metastatic.

In some embodiments, the breast cancer is HR positive HER2 negative and the subject has progressed on at least one prior line of hormone-based therapy (either alone or in

combination) and at least one, but not more than two prior lines of chemotherapy (including cytotoxic, targeted and/or anti-drug conjugate therapies).

In some embodiments, the breast cancer is HER2 positive and the subject has progressed on at least two prior lines of HER2 targeted therapy.

5 In some embodiments the breast cancer is triple negative breast cancer (TNBC) and the subject has progressed on at least two prior lines of cytotoxic chemotherapy (including cytotoxic, anti-drug conjugate, targeted therapies, and/or immune-oncology (I-O) therapies).

In some embodiments, the subject has received at least one prior therapy for the treatment of breast cancer, wherein each of the at least one prior therapy is other than a therapy comprising
10 a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.

In some embodiments, the subject has received at least two prior therapies for the treatment of breast cancer, wherein each of the two prior therapies is other than a therapy comprising a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.

In an aspect, provided herein is a FAP-targeting radiotherapeutic agent for use in the
15 treatment of breast cancer (i.e., for use in any of the methods of treating breast cancer disclosed herein), wherein the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days or every 6 weeks $\pm$ three days to achieve a cumulative dose of about 40 to about 60 GBq.

In an aspect, provided herein is a FAP-targeting radiotherapeutic agent for use in the
20 treatment of breast cancer (i.e., for use in any of the methods of treating breast cancer disclosed herein), wherein the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days to achieve a cumulative dose of about 40 to about 60 GBq and wherein the single dose of the FAP-targeting radiotherapeutic agent is about 3.7 GBq, about 5.6 GBq, about 7.4 GBq, or about 9.3 GBq.

25

Fap-Expression and Subject Selection

In certain embodiments, the cancers to be treated by the methods disclosed herein express FAP (which is also referred to as “FAP-expressing”). For a cancer to express FAP or be a FAP-expressing cancer means that any of the cancer cells, the extracellular matrix (ECM), or the
30 cancer-associated fibroblasts (CAFs) express FAP.

FAP-expressing solid tumors can be imaged by positron emission tomography (PET) scanning after administration of a FAP-targeting radioimaging agent. In certain embodiments, the subject is selected for treatment by any of the methods described herein through a diagnostic process comprising administering a FAP-targeting radioimaging agent to the subject and then
5 imaging the subject by positron emission tomography (PET) scanning.

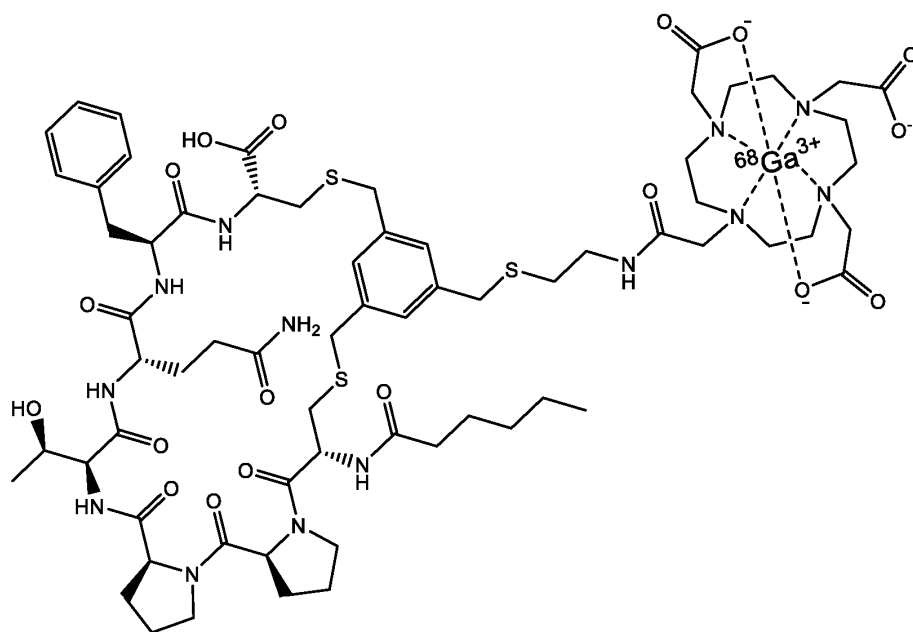
In certain embodiments, the subject has a cancer suitable for treatment by any of the methods disclosed herein if a target lesion has positive uptake, defined as having ≥ 1.5 times higher SUVmax (maximum standardized uptake value) compared with the SUVmean (mean standardized uptake value) of the mediastinal blood pool that is not attributable to other
10 etiologies of tracer distribution.

In certain embodiments, the subject has a cancer suitable for treatment by any of the methods disclosed herein if a target lesion has positive uptake, defined as FAP-targeting radioimaging agent uptake in at least 50% of the target lesions with an SUVmax ≥ 8 (wherein SUVmax is maximum standardized uptake value), and the remaining target lesions with uptake
15 above the surrounding background.

Accordingly, in some embodiments of any of the methods disclosed herein, the method further comprises administering a FAP-targeting radioimaging agent prior to administration of the FAP-targeting radiotherapeutic agent.

In some embodiments, the FAP-targeting radioimaging agent comprises ^{68}Ga or ^{18}F .

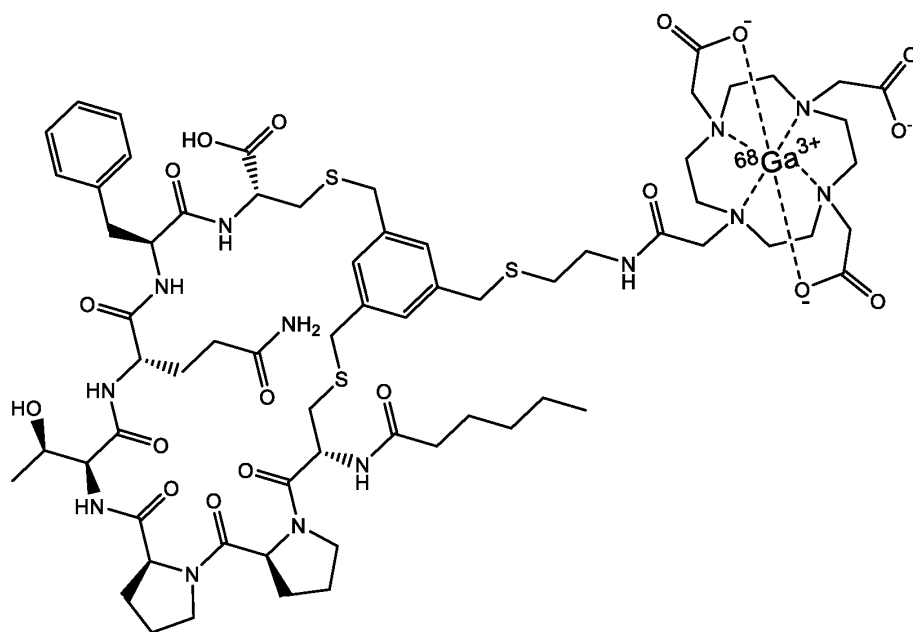
20 In some embodiments, the FAP-targeting radioimaging agent is:



, or a

pharmaceutically acceptable salt or solvate thereof.

In some embodiments, the FAP-targeting radioimaging agent is:



Dosing, Scheduling, and Administration

The methods described herein include administration of a therapeutically effective amount, (which can also be referred to as “a therapeutically effective dose”), of a FAP-targeting radiotherapeutic agent alone or in combination with one or more chemotherapeutic agents.

5 A therapeutically effective amount is an amount that is 1) effective to ameliorate a symptom of the disease (e.g., a cancer as described herein); 2) arrest or reduce cancer cell proliferation or expansion; and/or 3) reduce cancer cells, tumor size, and/or tumor burden.

A therapeutically effective amount may also be an amount that achieves an anti-tumor effect. An “anti-tumor effect” or “anti-tumor activity” may be achieved by administration of a
10 therapeutically effective amount of a FAP-targeting radiotherapeutic agent alone or in combination with one or more chemotherapeutic agents. An anti-tumor effect (or anti-tumor activity) refers to a biological effect that can present as a decrease in tumor volume, a decrease in the number of tumor cells, a decrease in tumor cell proliferation, a decrease in the number of metastases, an increase in overall or progression-free survival, an increase in life expectancy, or
15 amelioration of various physiological symptoms associated with the tumor.

In some embodiments of any of the methods disclosed herein, the anti-tumor activity will exceed an ORR (objective response rate) of about 10% or more, of about 15% or more, more of about 20% or more, of about 25% or more, of about 30% or more, of about 35% or more, of about 40% or more, or about 45% or more, of about 50% or more, of about 55% or more, of
20 about 60% or more, of about 65% or more, of about 70% or more, or of about 75% or more. It is understood to one of skill in the art that that the ORR cannot exceed 100%.

A therapeutically effective dose of the FAP-targeting radiotherapeutic agent will also be determined by the particular radionuclide, and whether said radionuclide is a β -emitter (can also be referred to in the art as a beta-minus emitter) (e.g., ^{32}P , ^{47}Sc , ^{67}Cu , ^{89}Sr , ^{90}Y , ^{131}I , ^{153}Sm , ^{161}Tb ,
25 ^{166}Ho , ^{169}Er , ^{177}Lu , ^{188}Re , and ^{212}Pb) or an α -emitter (e.g., ^{211}As , ^{212}Pb , ^{212}Bi , ^{223}Ra , ^{225}Ac , or ^{227}Th). In some embodiments of the methods provided herein, the FAP-targeting radiotherapeutic comprises ^{177}Lu , a beta-minus emitting radionuclide.

In some embodiments, the total dose (over the course of a treatment regimen, also referred to herein as a “cumulative dose”) of the FAP-targeting radiotherapeutic radiolabeled
30 with a β -emitter such as, e.g., ^{177}Lu , is from about 1 GBq to about 200 GBq. In some embodiments, the FAP-targeting radioligand comprising a β -emitter is administered to achieve a

cumulative dose of from about 40 to about 100 GBq of radiation. In some embodiments, the FAP-targeting radioligand comprising a β -emitter is administered to achieve a cumulative dose of from about 40 to about 60 GBq of radiation. In some embodiments, the FAP-targeting radioligand comprising a β -emitter is administered to achieve a cumulative dose of about 55.5 GBq. As used herein (and throughout the disclosure), the term “about” can mean $\pm 10\%$. Accordingly, in some embodiments, the FAP-targeting radioligand comprising a β -emitter is administered to achieve a cumulative dose of $55.5 \text{ GBq} \pm 10\%$.

In some embodiments, the FAP-targeting radioligand comprising the β -emitter is administered in a single dose (once within a 24-hour period) to deliver from about 1 to about 20 GBq of radiation. In some embodiments, the FAP-targeting radiotherapeutic agent comprising the β -emitter is administered in a single dose (once within a 24-hour period) to deliver from about 3 to about 15 GBq of radiation. In some embodiments, the FAP-targeting radiotherapeutic agent comprising the β -emitter is administered in a single dose (once within a 24-hour period, followed by a period of FAP-targeting radiotherapeutic agent dose free days, e.g., 28 ± 3 days) to deliver from about 3 to about 10 GBq of radiation. In some embodiments, the FAP-targeting radiotherapeutic agent comprising the β -emitter is administered at a single dose of about 3.7 GBq, about 5.6 GBq, about 7.4 GBq, or about 9.3 GBq. In some embodiments, the FAP-targeting radiotherapeutic agent comprising the β -emitter is administered at a single dose of $3.7 \text{ GBq} \pm 10\%$, $5.6 \text{ GBq} \pm 10\%$, $7.4 \text{ GBq} \pm 10\%$, or $9.3 \text{ GBq} \pm 10\%$.

In some embodiments, the FAP-targeting radiotherapeutic agent is administered as a single dose once about every 2 weeks to 10 weeks. In some embodiments, the FAP-targeting radiotherapeutic agent is administered as a single dose once about every 2 weeks to 6 weeks. In some embodiments, FAP-targeting radiotherapeutic agent is administered as a single dose once about every 3 weeks. In some embodiments, FAP-targeting radiotherapeutic agent is administered as a single dose once about every 4 weeks. In some embodiments, the FAP-targeting radiotherapeutic agent is administered as a single dose once about every 5 weeks. In some embodiments, the FAP-targeting radiotherapeutic agent is administered as a single dose once about every 6 weeks. In some embodiments, the FAP-targeting radiotherapeutic agent is administered as a single dose once every 6 weeks with a window of minus one day and plus 7 days (i.e., about every 41-49 days).

In some embodiments, FAP-targeting radiotherapeutic agent is administered as a single dose once every three weeks $\pm$ three days (i.e., 21 ± 3 days). In some embodiments, FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days (i.e., 28 ± 3 days). In some embodiments, the FAP-targeting radiotherapeutic agent is administered as a single dose once every five weeks $\pm$ three days (i.e., 35 ± 3 days). In some embodiments, the FAP-targeting radiotherapeutic agent is administered as a single dose once every six weeks $\pm$ three days (i.e., 42 ± 3 days). In some embodiments, the FAP-targeting radiotherapeutic agent is administered as a single dose once every six weeks with a window of minus one day and plus 7 days (i.e., once every 41-49 days).

In some embodiments of the methods provided herein, when the FAP-targeting radiotherapeutic agent is combined with a chemotherapeutic agent, the combination exhibits synergy. The terms “synergy”, “synergism”, “synergistic” each refer to a measured effect of compounds administered in combination where the measured effect is greater than the sum of the individual effects of each of the agents were said agents administered alone (i.e., as a single agent).

In some embodiments, administration of the FAP-targeting radiotherapeutic agent and a chemotherapeutic agent allows for lower doses of the chemotherapeutic agents as compared to administration of the chemotherapeutic agent as a single agent for the treatment of the same cancer or tumor type.

In some embodiments of any of the methods disclosed herein, the FAP-targeting pharmaceutical (whether a FAP-targeting radiotherapeutic agent or FAP-targeting radioimaging agent) is administered to the subject intravenously (IV administration).

Kits

Also described herein are kits comprising one or more unitary doses of the active agents, e.g., a FAP-targeting radiotherapeutic agent or the components for on-site production of the FAP-targeting radiotherapeutic agent. The kit may further include one or more further chemotherapeutic agents (e.g., FOLFIRINOX/mFOLFIRINOX/NALIRIFOX components and/or nab-paclitaxel). The kit may further include a FAP-targeting radioimaging agent or the components for on-site production of the FAP-targeting radioimaging agent. Kits may also

include a label indicating the intended use of the contents of the kit, as well as instructions for the use of the kit components.

Medical Use Formats

- 5 Any aspect or embodiment herein formulated as method of treatment aspect or embodiment may be likewise formulated into other medical use formats.

Incorporation by Reference

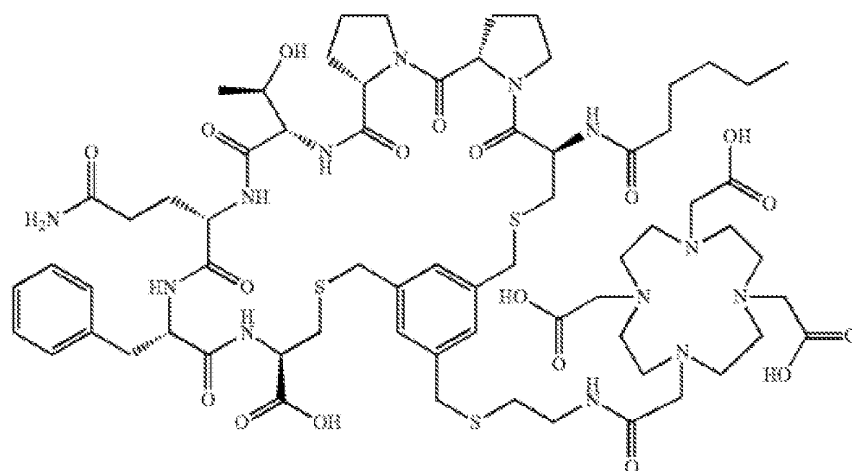
- 10 All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entireties for all purposes.

EXAMPLES

The disclosure is further illustrated by the following examples, which are not to be construed as limiting this disclosure in scope or spirit. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same or similar results.

Example 1: Preparation of a FAP-targeting Radiotherapeutic Agent and a FAP-targeting Radioimaging Agent

Synthesis of FAP-targeting compounds are described in PCT Publication No. WO2021/005125A1 and US Publication No. 2022/0273831A1, each of which is hereby incorporated by reference in its entirety. Specifically, synthesis and characterization of Compound I:



(Compound I)

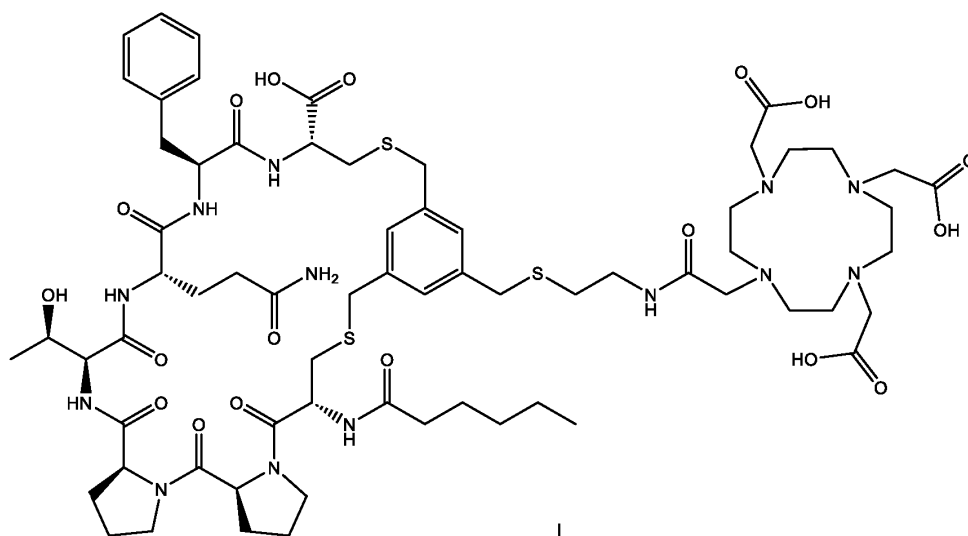
is described in Example 2 of PCT Publication No. WO2021/005125A1 and US Publication No. 2022/0273831A1. Methods of labeling Compound I with radioisotopes are provided in Example 11 of PCT Publication No. WO2021/005125A1 and US Publication No. 2022/0273831A1.

¹⁷⁷Lu-Compound I for injection is manufactured through the complexation of ¹⁷⁷Lu(III) to Compound I followed immediately by formulation and filtration through a 0.22 μm membrane into a pre-sterilized vial. For the complexation step, the following process is used. To a solution of ¹⁷⁷LuCl₃ is added radiolabeling buffer (comprising, e.g., ~74 mg/mL Sodium Acetate; ~18

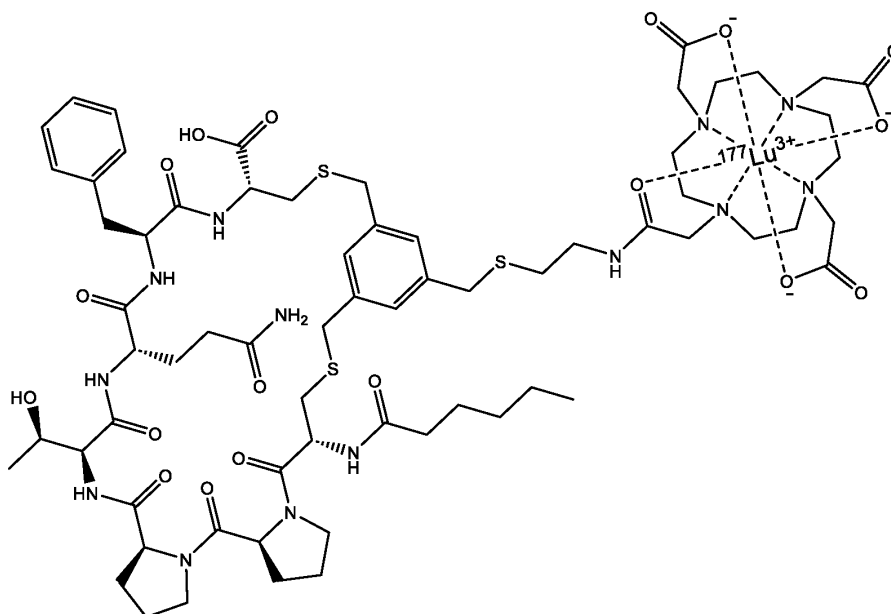
mg/mL Ascorbic Acid; ~25 mg/mL N-Acetyl-L-cysteine) such that 100 μ L of buffer is added for each 1 GBq of activity. To the $^{177}\text{LuCl}_3$ solution is added the precursor (Compound I, ~310 μ g) dissolved in sterile water for injection (SWFI, 0.3 mL). The mixture is heated to $90 \pm 5^\circ\text{C}$ for 10 ± 1 minute while mixing. The reaction mixture is diluted with formulation buffer such that the

5 final volume of formulated product is approx. 22 mL. The formulation buffer comprises ~0.2 mg/mL DTPA, ~100 mg/mL Ascorbic Acid, ~40 mg/mL N-Acetyl-L-cysteine, ~33 mg/mL sodium hydroxide, ~44 mg/mL ethanol in SWFI.

A reaction scheme for the complexation of Compound I with ^{177}Lu is found below:



[^{177}Lu] LuCl_3 , NaOAc,
Ascorbic Acid, NAC
~10 min, $90 \pm 5^\circ \text{C}$

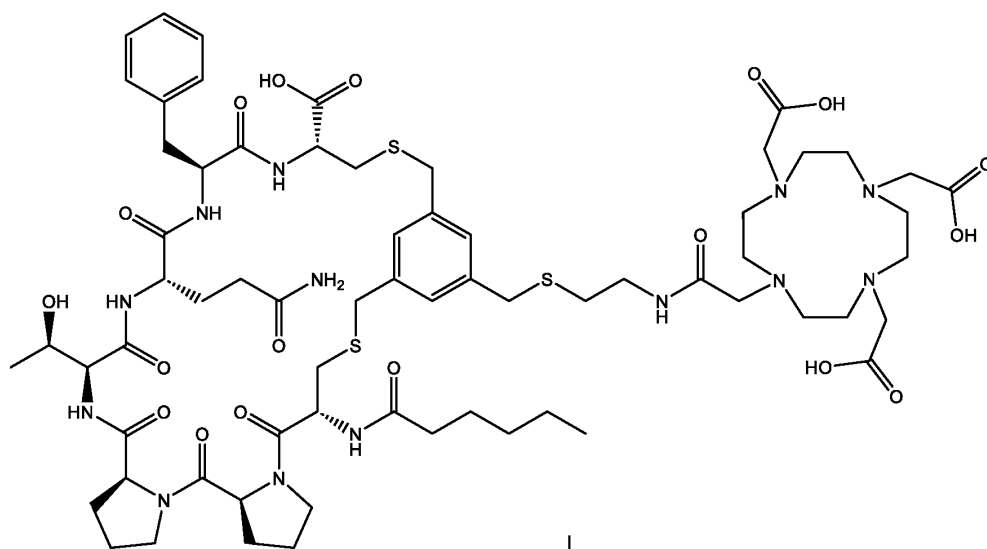


NAC is N-Acetyl-L-cysteine

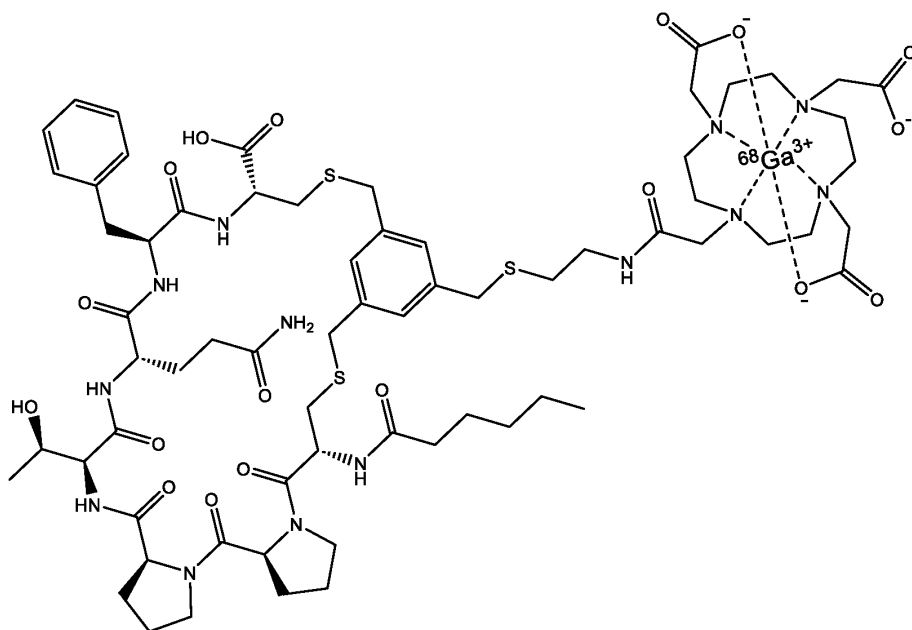
⁶⁸Ga-Compound I for injection is manufactured according to the following process. GMP grade [⁶⁸Ga]gallium chloride is produced on-site through a ⁶⁸Ge/⁶⁸Ga Generator. [⁶⁸Ga]gallium chloride is eluted with 0.1M hydrochloric acid. The radiolabeling vial is charged with the eluted

5 [⁶⁸Ga]gallium chloride, the reaction mixture containing Compound 1 (41±4 µg net peptide) in ultra-high purity (UHP) water (50 ± 5 µL), 1M Ammonium Acetate (0.8 mL), and 0.125 M Sodium Ascorbate (0.2 mL). The reaction mixture is heated to 95°C for 10 minutes. Heating is discontinued and the reaction mixture is allowed to cool for 5 minutes. This mixture is transferred to an ISO-5 environment. Environmental monitoring is initiated, and the solution is

10 sent through a sterile 0.22 micron membrane filter into the final product collection, pre-assembled sterile vial.



[^{68}Ga] GaCl_3 , NH_4OAc ,
Sodium Ascorbate
10 min, 95° C



Example 2: Phase 1/2, Multicenter, Open-label, Non-randomized Study to Investigate Safety and Tolerability, Pharmacokinetics, Dosimetry, and Preliminary Activity of a FAP-targeting radiopharmaceutical [¹⁷⁷Lu]Lu-FAP2286 in Participants with an Advanced Solid Tumor

5 Phase 1 of this study is designed to evaluate the safety and establish the recommended intravenous (IV) Phase 2 dose (RP2D) for [¹⁷⁷Lu]LuFAP2286 monotherapy in participants with FAPexpressing solid tumors. Phase 2 is designed to evaluate the safety and efficacy of [¹⁷⁷Lu]LuFAP2286 as monotherapy in participants with pancreatic ductal adenocarcinoma (PDAC), non-small cell lung cancer (NSCLC), and breast cancer (BC) and in combination with
10 chemotherapy in participants with untreated PDAC or relapsed NSCLC. Participants in both Phase 1 and 2 have been and will be selected for treatment with [¹⁷⁷Lu]LuFAP2286 based on [⁶⁸Ga]GaFAP2286 imaging for determining tumor FAP expression.

Objectives and Endpoints: Table 1 presents the study objectives and end points.

Table 1. Study Objectives and Endpoints	
Phase 1	
Primary Objective	Primary Endpoints
To evaluate the safety and tolerability of [¹⁷⁷ Lu]Lu-FAP-2286 and determine the RP2D	DLTs, AEs, SAEs, and clinical laboratory abnormalities
Secondary Objectives	Secondary Endpoints
To measure the radiation dosimetry of [¹⁷⁷ Lu]Lu-FAP-2286	Absorbed dose (Gy) estimated in organs and tumor lesions
To determine tumor uptake using [⁶⁸ Ga]Ga-FAP-2286	Maximum standardized uptake value (SUVmax) in tumor lesions
To evaluate tumor uptake of [⁶⁸ Ga]Ga-FAP-2286 as compared to FDG	Comparison of SUVmax in tumor lesions
To evaluate the PK of [¹⁷⁷ Lu]Lu-FAP-2286	Concentration of [¹⁷⁷ Lu]Lu-FAP-2286 in blood over time and derived PK parameters (Cmax, Tmax, AUC, CL, Vd, and t1/2)
To evaluate preliminary efficacy of [¹⁷⁷ Lu]Lu-FAP-2286 in advanced solid tumors	Investigator-assessed objective response by RECIST v 1.1
Phase 2	
Primary Objective	Primary Endpoint
To evaluate objective response rate (ORR) (Phase 2 dose expansion)	Investigator-assessed ORR per RECIST v1.1

To evaluate the safety and tolerability of [¹⁷⁷ Lu]Lu-FAP-2286 and determine the RP2D in combination with mFOLFIRINOX in PDAC and the RP2D in combination with nab-paclitaxel in NSCLC (Phase 2 dose escalation for combination therapy)	DLTs, AEs, SAEs and clinical laboratory abnormalities
Secondary Objectives	Secondary Endpoints
To evaluate DOR (Phase 2 dose expansion)	DOR per RECIST v1.1, as assessed by investigator
To evaluate disease control rate (Phase 2 dose expansion)	Confirmed PR or CR, or SD of at least 12 weeks
To evaluate PFS (Phase 2 dose expansion)	Disease progression according to RECIST v1.1, as assessed by investigator, or death due to any cause
To further evaluate the safety of [¹⁷⁷ Lu]Lu-FAP-2286 at the RP2D for monotherapy, the RP2D in combination with mFOLFIRINOX in PDAC and the RP2D in combination with nab-paclitaxel in NSCLC (Phase 2 dose expansion)	AEs, SAEs, and clinical laboratory abnormalities
To evaluate the safety and tolerability of [⁶⁸ Ga]Ga-FAP-2286	AEs and SAEs

Study Design

- This is a Phase 1/2, open-label study. The focus of Phase 1 will be to evaluate safety and determine the RP2D of [¹⁷⁷Lu]Lu-FAP-2286 monotherapy in participants with an advanced or metastatic solid tumor expressing FAP who have relapsed following prior treatment. In Phase 1,
- 5 dose escalation strategies are designed to identify the maximum tolerated dose (MTD) and RP2D. Phase 2 will establish a RP2D in combination with mFOLFIRINOX, a RP2D in combination with nab-paclitaxel and further evaluate the safety and efficacy of [¹⁷⁷Lu]Lu-FAP-2286 in both monotherapy and in combination with chemotherapy. Participants in the monotherapy groups will receive [¹⁷⁷Lu]Lu-FAP-2286 at the RP2D established in Phase 1.
- 10 The combination groups with chemotherapy will start with an escalation phase for [¹⁷⁷Lu]Lu-FAP-2286 at 100 mCi, followed by an expansion phase at the dose determined in the escalation part. Thus, the combination groups are not dependent on the RP2D from Phase 1.

Both Phase 1 and Phase 2 will consist of Screening, Treatment, and LTFU Periods. Participants must meet all entry criteria in order to be enrolled in the study. Participants enrolled

in Phase 1 will undergo PET imaging with [¹⁸F]fluoro-D-glucose (FDG) at any time during screening prior to Cycle 1 Day 1 (C1D1). Following enrollment, all participants in Phase 1, who have not had prior PET/CT imaging with [⁶⁸Ga]Ga-FAP-2286 within the previous 3 months, and all participants in Phase 2 will have a PET/CT scan with [⁶⁸Ga]Ga-FAP-2286. Participants in

5 Phase 1 and 2 eligible for [¹⁷⁷Lu]Lu-FAP-2286 treatment will have uptake of [⁶⁸Ga]Ga-FAP-2286 on PET/CT scan as described in Criteria for Continuation to [¹⁷⁷Lu]Lu-FAP-2286 Therapy in order to initiate treatment with [¹⁷⁷Lu]Lu-FAP-2286. Participants who do not have FAP-positive tumors based on [⁶⁸Ga]Ga-FAP-2286 imaging according to the above mentioned criteria will discontinue from the study.

Table 2. Criteria for Continuation to [¹⁷⁷ Lu]Lu-FAP-2286 Therapy:	
•	Participants considered eligible for treatment with [¹⁷⁷ Lu]Lu-FAP-2286 will fulfill all eligibility criteria and present [⁶⁸ Ga]Ga-FAP-2286 uptake on PET/CT in all target lesions, as assessed by the investigator and according to the specific criteria for each phase of the study. Target lesions are defined based on stand-alone CT or MRI.
•	For Phase 1, positive uptake is defined as having ≥ 1.5 times higher SUVmax compared with the SUVmean of the mediastinal blood pool that is not attributable to other etiologies of tracer distribution.
•	For Phase 2, positive uptake is defined as [⁶⁸ Ga]Ga-FAP uptake in at least 50% of the target lesions with an SUVmax ≥ 8, and the remaining target lesions with uptake above the surrounding background
•	Participants will not be eligible for treatment with [¹⁷⁷ Lu]Lu-FAP-2286 if the [⁶⁸ Ga]Ga-FAP-2286 PET identifies non-tumor uptake in tissues or organs that, in the opinion of the investigator, increases the risk associated with [¹⁷⁷ Lu]Lu-FAP-2286 treatment. This may include, but may not be limited to, fibrotic processes involving the liver or lung, for example.
•	Participants who obtain [⁶⁸ Ga]Ga-FAP-2286 imaging and do not meet entry criteria to continue [¹⁷⁷ Lu]Lu-FAP-2286 treatment phase, will discontinue from the study.

10

Phase 1

Phase 1 will enroll participants with an advanced or metastatic solid tumor who have relapsed following prior treatment. Once enrolled, participants who have disease with positive uptake of [⁶⁸Ga]Ga-FAP-2286 on PET/CT scan, as defined in the Criteria for Continuation

15 (Table 2) to [¹⁷⁷Lu]Lu-FAP-2286 Therapy, will begin treatment with [¹⁷⁷Lu]Lu-FAP-2286. Participants will receive up to 6 doses of [¹⁷⁷Lu]Lu-FAP-2286 administered at 6-week intervals; this interval may be modified (with a protocol amendment and justification) based on emerging data.

Dose Escalation

The Phase 1 Dose Escalation and determination of the MTD (maximum tolerated dose) will be based on a Bayesian optimal interval (BOIN) design. There will be an estimated 4 dose escalation cohorts, with a minimum of 3 evaluable participants and a maximum of 12 evaluable participants enrolled in each cohort. To be evaluable for DLT (dose-limiting toxicity) assessment, a participant must have received the first dose of [¹⁷⁷Lu]Lu-FAP-2286 and completed Cycle 1 or experienced a DLT prior to completion of Cycle 1. An additional participant may be enrolled in a cohort if a participant withdraws from treatment or the study during the first 6 weeks (42 days) due to a reason other than a DLT and is not evaluable.

DLTs will be assessed by the investigator based on National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0) or higher toxicity grade and possible relationship to [¹⁷⁷Lu]Lu-FAP-2286 treatment.

A Dose Cohort Review Committee (DCRC) will review safety and dosimetry data when at least 3 evaluable participants complete the first cycle of treatment with [¹⁷⁷Lu]Lu-FAP-2286, and agree to either escalate to the next dose level, expand the current dose level, or reduce to a lower or intermediate dose level. The DCRC will not recommend dose escalation above the dose level recommended per the BOIN design. These steps will be repeated until the maximum sample size is reached, or until the number of participants treated at a given dose level reaches n=12, or the study is stopped for safety or other reasons. The DCRC may also decide to modify the total number of doses allowed for participants in the current and/or previous cohorts based on available clinical, safety, and dosimetry data. Any changes to the maximum number of doses will be made by protocol amendment and will include a justification for the change.

After the dose escalation part is completed with a maximum sample size of 30 DLT evaluable participants, or a maximum of 12 DLT-evaluable participants at a given dose level, the MTD will be estimated based on the BOIN design. The single-dose MTD is defined as the administered dose level at which $\leq 30\%$ of participants experience a DLT during the 6 weeks (42 days) after administration of the first dose of [¹⁷⁷Lu]Lu-FAP-2286. A multiple-dose MTD will be determined based on the evaluation of cumulative treatment received at any dose level. The RP2D will not exceed the MTD identified in Phase 1.

Phase 2

During Phase 2, there will be five groups all investigating [^{177}Lu]LuFAP-2286 every 4 weeks. Phase 2 will evaluate the efficacy of [^{177}Lu]Lu-FAP-2286 as monotherapy in participants with PDAC, NSCLC, and BC, as well as in combination with chemotherapy in participants with PDAC and NSCLC. The PDAC combination group will investigate [^{177}Lu]Lu-FAP-2286 every 4 weeks in combination with mFOLFIRINOX (1L metastatic). The NSCLC combination group will investigate [^{177}Lu]Lu-FAP-2286 every 4 weeks with weekly nab-paclitaxel in patients with relapsed disease.

Phase 2 participants will undergo screening assessments, [^{68}Ga]Ga-FAP-2286 imaging for continuation to [^{177}Lu]Lu-FAP-2286, and as applicable, treatment with [^{177}Lu]Lu-FAP-2286, an EOT (end of treatment) visit, and enter safety follow-up and LTFU (long-term follow-up). Efficacy, safety, and tolerability will be evaluated continuously for all participants enrolled in the study.

Up to 192 participants will be enrolled in the Phase 2 dose escalation and expansion groups. Participants in the combination group dose escalation who receive the recommended dose will contribute to the expansion analysis for that combination group. Participants will only be enrolled into one distinct part of the study (i.e., Phase 1 Dose Escalation or Phase 2) and will not transition from one part to another. The schemas for the Phase 1 and Phase 2 are shown in FIG. 1, FIG. 2, and FIG. 3.

Imaging Dosimetry

Phase 1:

All participants will have SPECT/CT scans at four time points, including scans on Day 1, Day 2, Day 3, and Day 8 of each cycle. The windows for the post-infusion SPECT/CT time points are: 4 hours (± 2 hours); 24 hours (± 4 hours), 48 hours (± 4 hours); and 168 hours (± 8 hours). All SPECT/CT scans should encompass 2 or more contiguous bed positions, such that all target lesions and both kidneys are imaged at each time point.

Phase 2:

Phase 2 dosimetry will be acquired in selected participants in each group. In monotherapy groups, quantitative dosimetry will be acquired in approximately 10 participants enrolled per

disease indication (PDAC, NSCLC, and BC). In the PDAC + mFOLFIRINOX and the NSCLC + nab-paclitaxel combination groups, at least 3 participants per dose level will require SPECT/CT imaging assessments for quantitative dosimetry during the dose escalation part. Approximately 10 participants in the subsequent expansion parts at the recommended dose of each combination group will also require SPECT/CT imaging assessments for quantitative dosimetry. To further reduce the burden for participants who had to undergo full 4-time point dosimetry imaging at every cycle during the Phase 1 part, dosimetry will only be acquired in Cycle 1, 3 and 5 in the Phase 2.

10 **Dose Levels in Phase 1:**

 The starting radioactive dose of [¹⁷⁷Lu]Lu-FAP-2286 and the preliminary dose levels are defined in **Table 3**. The starting dose is 3.70 GBq (100 mCi), with escalation in 1.85 GBq (50 mCi) increments for a total of 4 dose levels to potentially be evaluated. The maximum radioactive dose to be administered is 9.25 GBq (250 mCi). The planned schedule of administration is every 6 weeks (window of – 1 to + 7 days) for up to 6 total doses.

 Dosimetry, clinical, and safety evaluations will be performed after the first dose of [¹⁷⁷Lu]Lu-FAP-2286. Intermediate dose levels, adjustments to total number of doses, or alteration of the dosing interval may be evaluated following a protocol amendment, which will include a justification for the change.

Table 3. Dose Levels in Phase 1

Dose Level	Radioactive Dose
–1	1.85 GBq (50 mCi) ± 10%
1 (Starting dose)	3.7 GBq (100 mCi) ± 10%
2	5.55 GBq (150 mCi) ± 10%
3	7.4 GBq (200 mCi) ± 10%
4 (Maximum dose)	9.25 GBq (250 mCi) ± 10%

20

Screening Period

 All participants will undergo screening assessments including disease assessments by CT or MRI per RECIST v1.1 criteria prior to administration of [⁶⁸Ga]Ga-FAP-2286. Each participant must provide informed consent and agree to provide an archival tumor tissue sample, if available, and blood samples for potential biomarker assessment.

25

In Phase 1, all participants will also undergo FDG-PET imaging prior to administration of [¹⁷⁷Lu]Lu-FAP-2286.

[⁶⁸Ga]Ga-FAP-2286 Imaging for Continuation to [¹⁷⁷Lu]Lu-FAP-2286 Therapy

- 5 Participants meeting entry criteria will be enrolled. In Phase 1, participants who have not had prior PET/CT imaging with [⁶⁸Ga]Ga-FAP-2286 in the previous 3 months will undergo PET imaging with [⁶⁸Ga]Ga-FAP-2286 prior to initiating treatment with [¹⁷⁷Lu]Lu-FAP-2286.

Treatment Period

- 10 At the beginning of the Phase 1 part, [¹⁷⁷Lu]Lu-FAP-2286 will be initially administered every 6 weeks (window of – 1 day to + 7 days) up to a maximum of 6 doses.

- All participants will be monitored for safety throughout the treatment phase. In addition, all participants will be assessed for disease status per RECIST v1.1 every 6 weeks (42 days). Participants will receive [¹⁷⁷Lu]Lu-FAP-2286 until the maximum doses allowed (e.g., up to 6)
- 15 are administered, confirmed radiographic disease progression assessed by investigator based on RECIST v1.1 criteria, unequivocal clinical disease progression, unacceptable toxicity or inability to tolerate further treatment, loss to follow-up, or withdrawal of consent.

End of Treatment Visit

- 20 Upon treatment discontinuation, regardless of reason (with the exception of participant withdrawal of consent from the study or death), participants will have an EOT Visit. Note that participants who withdraw consent from treatment only will have an EOT Visit and enter the LTFU Period.

- The EOT Visit for each participant will occur 6 to 8 weeks after the last dose of
- 25 [¹⁷⁷Lu]Lu-FAP-2286, or within 1 week after the decision to discontinue treatment for any reason other than participant withdrawal of consent from the study or death, including withdrawal of consent for treatment, withholding the last dose of [¹⁷⁷Lu]Lu-FAP-2286, or not being eligible for continuation to [¹⁷⁷Lu]Lu-FAP-2286 therapy following administration of [⁶⁸Ga]Ga-FAP-2286. Participants who are assessed as not having FAP-positive tumors based on [⁶⁸Ga]Ga-FAP-2286
- 30 imaging and/or who do not continue to meet entry criteria are not eligible for [¹⁷⁷Lu]Lu-FAP-2286 treatment; these participants will discontinue from the study and will not

proceed to the treatment phase or LTFU, but will have safety assessments performed at the EOT Visit.

Long-term Follow-up Period

- 5 Upon completion of the EOT Visit, participants will enter the LTFU Period (with the exception of participant withdrawal of consent from the study, death, or not being eligible for continuation to [¹⁷⁷Lu]Lu-FAP-2286 therapy). LTFU includes safety, disease, and survival assessments, as applicable.
- 10 • Safety assessments will be performed for all participants in LTFU. Assessments, including hematology, clinical chemistry, and urinalysis, will occur every 12 weeks ($\pm$ 1 week) for 2 years, then every 6 months until 5 years.
 - 15 • Disease assessments will be performed for all participants in LTFU who complete the EOT for a reason other than radiographic disease progression. Participants should continue to have tumor scans performed until radiographic disease progression as assessed by the investigator, death, loss to follow-up, withdrawal from study, study closure, or initiation of subsequent anticancer treatment. Tumor assessments should be performed every 12 weeks ($\pm$ 1 week) for 2 years, then every 6 months until 5 years.
 - 20 • Survival assessments will be performed for all participants in LTFU. Participants will be followed and information collected for subsequent treatments and survival every 12 weeks ($\pm$ 1 week) from the EOT Visit until death, loss to follow-up, withdrawal of consent from study, or closure of the study. Follow-up can be performed via the telephone or other method of communication and can be completed to coincide with scheduled tumor and/or safety assessments.
 - 25 • SAEs considered related to study treatment are to be reported during the LTFU Period.

Determination and Expansion of the RP2D

- The RP2D will be selected based on overall safety, tolerability, dosimetry, PK, and efficacy data, and may or may not be the same as the MTD identified in the dose escalation design. The RP2D will not exceed the MTD identified in Phase 1. For example, if the MTD is
- 30 not reached, if exposure at the designated MTD is much higher than the level believed to be

required for efficacy, or if subsequent treatments provide additional insight on the safety profile, then the RP2D may be different, although not higher, than the MTD.

Dose levels in Phase 2

5 **Monotherapy Expansion Group:**

Participants diagnosed with PDAC, NSCLC and BC will receive [¹⁷⁷Lu]Lu-FAP-2286 every 4 weeks (28 days) in expansion at the RP2D declared in Phase 1. There will be a safety assessment after the first 10 participants are treated, regardless of study indication.

PDAC combination with mFOLFIRINOX:

10 Participants diagnosed with PDAC in the combination group will receive [¹⁷⁷Lu]Lu-FAP-2286 every 4 weeks (28 days) (in combination with mFOLFIRINOX). The starting dose (dose level 1 in the escalation) of [¹⁷⁷Lu]Lu-FAP-2286 will be 100 mCi with 3 additional dose levels for escalation (**Table 4**). This starting dose is not dependent on the RP2D from Phase 1.

Table 4. Dose levels in PDAC combinations with mFOLFIRINOX

Dose Level	Radioactive Dose
1 (Starting dose)	3.70 GBq (100 mCi) ± 10%
2	5.55 GBq (150 mCi) ± 10%
3	7.40 GBq (200 mCi) ± 10%
4 (Maximum dose)	9.25 GBq (250 mCi) ± 10%

15 mFOLFIRINOX will be administered on Day 1 of each 14 day cycle.

Participants may begin chemotherapy prior to [¹⁷⁷Lu]Lu-FAP-2286. [¹⁷⁷Lu]Lu-FAP-2286 must be received by the completion of the second cycle of mFOLFIRINOX. [¹⁷⁷Lu]Lu-FAP-2286 must be initiated on Day 1 (or up to and including Day 5) of Cycle 1 or 2 and then continue every 4 weeks (window ±3 days).

20 Once a dose is determined in escalation, the PDAC combination group will move to dose expansion at the determined dose level.

NSCLC combination with nab-paclitaxel

Participants diagnosed with NSCLC will receive [¹⁷⁷Lu]Lu-FAP-2286 every 4 weeks (28 days) in combination nab-paclitaxel. The starting dose (dose level 1 in escalation) of [¹⁷⁷Lu]Lu-FAP-2286 will be 100 mCi with 3 additional dose levels for escalation (**Table 5**). This starting dose is not dependent on the RP2D from Phase 1.

Table 5. Dose levels in NSCLC combinations with nab-paclitaxel

Dose Level	Radioactive Dose
1 (Starting dose)	3.70 GBq (100 mCi) $\pm$ 10%
2	5.55 GBq (150 mCi) $\pm$ 10%
3	7.40 GBq (200 mCi) $\pm$ 10%
4 (Maximum dose)	9.25 GBq (250 mCi) $\pm$ 10%

Nab-paclitaxel will be administered weekly.

Participants may begin chemotherapy prior to [¹⁷⁷Lu]Lu-FAP-2286. [¹⁷⁷Lu]Lu-FAP-2286 may be administered on Day 1 (or up to and including Day 5) after chemotherapy. [¹⁷⁷Lu]Lu-FAP-2286 may be initiated at any time during the first week and up to and including Week 3 of weekly nab-paclitaxel. [¹⁷⁷Lu]Lu-FAP-2286 will be continued every 4 weeks (window $\pm$ 3 days).

Once a dose is determined in escalation, the NSCLC combination group will move to dose expansion at the determined dose level.

For each participant, a number of administrations up to the ECD (estimated cumulative dose) of 55.5 GBq of [¹⁷⁷Lu]Lu-FAP-2286 are planned. Consecutive cohorts of 3 to 9 participants will be treated during the dose escalation for a total of up to approximately 27 participants in each escalation group: PDAC combination and NSCLC combination.

Dose escalation process for combination groups

Dose escalation decisions will be made by Investigators and study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all CTCAE Grade $\geq$ 2 toxicity data during the DLT observation period, available PK, and dosimetry data. The DLT period for the PDAC and NSCLC combination groups will be 4 weeks (28 days) from the first administration of [¹⁷⁷Lu]Lu-FAP-2286. For the combination groups, two full administrations of mFOLFIRINOX and at least 3-4 administrations of nab-paclitaxel will occur during this four week DLT period which is deemed sufficient to observe any trends in occurrence or severity of AEs. In addition, the [¹⁷⁷Lu]Lu-FAP-2286 dosing interval is every 4 weeks for Phase 2, so the DLT period was adapted to suit the administration of [¹⁷⁷Lu]Lu-FAP-2286 and chemotherapy in combination. The recommended dose for the next cohort of participants will be guided by the BOIN design. The initial dose of [¹⁷⁷Lu]Lu-FAP-2286 will be 100 mCi every 4 weeks (28 days) in the PDAC and NSCLC combination groups with provisional dose levels established to guide the dose selection.

The MTD is the highest drug dose that is not expected to cause DLT in more than 30% of the treated participants during the DLT evaluation period. For the purpose of dose escalation

decision, each cohort will consist of 3 to 6 evaluable participants treated at the considered dose level.

A participant is considered evaluable for the dose escalation/de-escalation decision if he/she received at least 90% of the planned dose of [¹⁷⁷Lu]Lu-FAP-2286, 75% of the chemotherapy dose and have completed the DLT observation period.

Consecutive cohorts of 3 to 6 participants will be treated. The BOIN design uses the following rules, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation.

- If the observed DLT rate at the current dose is $\leq 23.6\%$, escalate the dose to the next higher dose level;
- If the observed DLT rate at the current dose is $> 35.9\%$, de-escalate the dose top the next lower dose level;
- Otherwise, stay at the current dose.

For the purpose of overdose control, dose j and higher levels will be eliminated from further examination if $\Pr(p_j > 0.30 \mid \text{data}) > 0.95$ and at least 3 evaluable participants for DLT have been treated at dose level j , where p_j is the true DLT rate of dose level j . When the lowest dose is eliminated, the study must be stopped for safety.

Determination of expansion in Phase 2

Monotherapy and combination groups will enroll in expansion (Table 6).

Table 6. Disease indication expansion group

Disease indication expansion group	N
PDAC monotherapy	28
NSCLC monotherapy	40
BC monotherapy	20
PDAC combination with mFOLFIRINOX	30
NSCLC combination with nab-paclitaxel	20

End of treatment

Upon study treatment completion or earlier discontinuation, all participants will undergo an EOT follow-up visit within 28 days from last study treatment administration and subsequently enter the post-treatment safety follow-up and LTFU period unless they have died, are lost to follow-up or have withdrawn consent.

Post treatment safety follow-up

After discontinuation of study treatment for any reason, all participants will have a safety follow-up visit 42 days (± 7 days) after their last study treatment administration, except in case
5 of death, loss to follow-up or withdrawal of consent.

Inclusion Criteria

Eligible participants must meet the following inclusion criteria. The criteria below apply to participants enrolling into Phase 1 and Phase 2, unless otherwise specified.

- 10 1. Have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved ICF prior to any study-specific evaluation.
2. Be ≥ 18 years of age at the time the ICF is signed.
3. Have consented to submission of fresh or archival tumor tissue, if available.
- 15 4. Have adequate organ function confirmed by the following laboratory values obtained within the Screening Period prior to administration of [^{68}Ga]Ga-FAP-2286 and prior to first cycle of chemotherapy in the combination groups:
 - a. Bone Marrow Function (independent of transfusion or growth factor support within 21 days prior to planned first administration of [^{177}Lu]Lu-FAP-2286):
 - 20 i. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/\text{L}$;
 - ii. Platelets $> 100 \times 10^9/\text{L}$; and
 - iii. Hemoglobin $\geq 9 \text{ g/dL}$.
 - b. Hepatic Function:
 - i. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 3 \times$ institutional upper limit of normal (ULN); if liver metastases, then $\leq 5 \times$ the institutional ULN;
 - 25 ii. Serum Bilirubin $\leq 1.5 \times$ institutional ULN or if known Gilbert's syndrome then $\leq 3 \times$ institutional ULN;
 - iii. Serum albumin $\geq 30 \text{ g/L}$ (3 g/dL); and
 - iv. INR $\leq 1.5 \times$ ULN and activated partial thromboplastin time (aPTT) $\leq 1.5 \times$ ULN. This applies to participants who are not receiving therapeutic anticoagulation; participants
30 receiving therapeutic anticoagulation should be on a stable dose.
 - c. Renal Function:

- i. $\text{eGFR} \geq 60$ mL/min using the Cockcroft-Gault formula.
- 5. Eastern Oncology Group (ECOG) performance status of 0 or 1.
- 6. Life expectancy ≥ 6 months.
- 7. Have measurable disease per RECIST v1.1 meeting the following criteria:
- 5 a. At least 1 lesion of ≥ 10 mm in the longest diameter for a non-lymph node or ≥ 15 mm in the short-axis diameter for a lymph node that is serially measurable according to RECIST v1.1 using conventional CT and/or MRI.
 - i. Lesions that have had external beam radiotherapy or loco-regional therapies such as radiofrequency ablation must show subsequent evidence of substantial
 - 10 size increase to be deemed a target lesion.

For Phase 1 only:

- 8. Have a histologically and/or cytologically confirmed advanced/metastatic solid tumor not amenable to treatment with curative intent.
- 15 a. Tumor must be refractory to or have progressed following prior treatment and have no satisfactory alternative treatment options.

For Phase 2 only:

- 9. Have cytologically or histologically and radiologically confirmed recurrent, or metastatic
- 20 disease as outlined below:
 - a. Pancreatic Cancer monotherapy group:
 - i. Pancreatic ductal adenocarcinoma (ductal adenocarcinoma and related subtypes eligible; endocrine and neuroendocrine tumors excluded)
 - ii. Participants must have progressed after at least 1, but no more than two prior
 - 25 chemotherapy regimens for locally advanced unresectable or metastatic disease.
 - b. Pancreatic Cancer combination group (with mFOLFIRINOX)
 - i. Pancreatic ductal adenocarcinoma (ductal adenocarcinoma and related subtypes eligible; endocrine and neuroendocrine tumors excluded);
 - 30 ii. Participants have not received prior systemic therapy for metastatic disease.
 - c. Non-small cell lung cancer monotherapy group

- i. Non-small cell lung cancer (adenocarcinoma and squamous eligible; endocrine, neuroendocrine and small cell tumors are excluded)
 - ii. Participants must have progressed after at least 1 but not more than 2 prior systemic regimens including chemotherapy and immunotherapy, if eligible.
 - 5 iii. Participants who have received adjuvant or neoadjuvant platinum-doublet chemotherapy (after surgery and/or radiation therapy) and an immune checkpoint inhibitor and developed recurrent or metastatic disease while on or within 12 months of completing therapy are eligible.
 - 10 iv. Participants with recurrent disease > 12 months after adjuvant or neoadjuvant platinum-based chemotherapy, who also subsequently progressed during or after a platinum-doublet regimen and an immune checkpoint (given either together or sequentially to treat the recurrence), are eligible.
 - 15 v. Participants must have received platinum-based chemotherapy for advanced or metastatic disease and immune checkpoint inhibitor either together (in the same line of treatment) or sequentially (two different lines of treatment) and then progressed.
- d. Non-small cell lung cancer combination group
 - 20 i. Non-small cell lung cancer (adenocarcinoma and squamous eligible; endocrine, neuroendocrine and small cell tumors are excluded)
 - ii. Participants must have progressed after at least 1 but not more than 2 prior systemic regimens including chemotherapy and immunotherapy, if eligible.
 - 25 iii. Participants who have received adjuvant or neoadjuvant platinum-doublet chemotherapy (after surgery and/or radiation therapy) and an immune checkpoint inhibitor and developed recurrent or metastatic disease while on or within 12 months of completing therapy are eligible.
 - 30 iv. Participants with recurrent disease > 12 months after adjuvant or neoadjuvant platinum-based chemotherapy, who also subsequently progressed during or after a platinum-doublet regimen and an immune checkpoint (given either together or sequentially to treat the recurrence), are eligible.

- v. Participants must not have received prior taxane therapy either as monotherapy or in combination.
- e. Breast cancer monotherapy group
- i. HR positive HER2 negative
- 5 • Participant has a histologically and/or cytologically documented diagnosis of HR positive HER2 negative metastatic breast cancer (based on the most recently analyzed tissue sample tested by a local laboratory).
- Participants must have progressed on at least one line of hormone-based therapy (either alone or in combination) and at least one, but not more than two lines of
- 10 chemotherapy (including cytotoxic, targeted and/or anti-drug conjugate therapies) for metastatic disease.
- ii. HER2 positive
- Participant has a histologically and/or cytologically documented diagnosis of HER2 positive metastatic breast cancer (based on the most recently analyzed tissue sample
- 15 tested by a local laboratory).
- Participant must have progressed on at least two lines of HER2 targeted therapy for metastatic disease.
- iii. Triple negative breast cancer (TNBC)
- Participant has a histologically and/or cytologically documented diagnosis of TNBC (based
- 20 on the most recently analyzed tissue sample tested by a local laboratory).
- Participants must have progressed on at least two lines of cytotoxic chemotherapy (including cytotoxic, anti-drug conjugate, targeted therapies and/or IO) for metastatic disease.

General principles for prior anticancer treatment:

- 25 • Prior chemoradiotherapy is permitted and will be counted as a chemotherapy regimen (unless low-dose cytotoxics are utilized purely for radiosensitization), provided measurable disease is evaluable outside of the radiotherapy field(s) or, if within a previously irradiated field, has shown substantial increase in size to qualify as a target lesion and the participant developed progressive disease within 6 months of last treatment.
- 30 • Any change of agents within the same regimen (e.g., switch from paclitaxel to nab-paclitaxel due to intolerability) will still be considered 1 chemotherapy regimen.

Criteria for Continuation to [¹⁷⁷Lu]Lu-FAP-2286 Therapy

Participants considered eligible for treatment with [¹⁷⁷Lu]Lu-FAP-2286 will fulfill all eligibility criteria and present [⁶⁸Ga]Ga-FAP-2286 uptake on PET/CT scan, as assessed by the investigator according to the specific criteria for each phase of the study. Target lesions are defined based on stand-alone CT or MRI.

For Phase 1:

Positive uptake is defined as ≥ 1.5 times higher SUVmax compared with the SUVmean of the mediastinal blood pool that is not attributable to other etiologies of tracer distribution in all target lesions.

For Phase 2:

In Phase 2, positive uptake is defined as a [⁶⁸Ga]Ga-FAP uptake at PET/CT with an SUVmax ≥ 8 in at least 50% of the target lesions, and above the surrounding background in the remaining target lesions.

Participants will not be eligible for treatment with [¹⁷⁷Lu]Lu-FAP-2286 if the [⁶⁸Ga]Ga-FAP-2286 PET identifies non-tumor uptake in tissues or organs that, in the opinion of the investigator, increases the risk associated with [¹⁷⁷Lu]Lu-FAP-2286 treatment. This may include, but may not be limited to, fibrotic processes involving the liver or lung, for example.

Participants who obtain [⁶⁸Ga]Ga-FAP-2286 imaging and do not meet entry criteria to continue to the [¹⁷⁷Lu]Lu-FAP-2286 treatment phase, will discontinue from the study.

Exclusion Criteria

Participants who meet any of the following criteria will be excluded from the study. The criteria below apply to participants enrolling in Phase 1 or Phase 2.

1. Active malignancy except for the specific cancer under investigation in this study, i.e., participant known to have potentially fatal cancer present for which he/she may be (but not necessarily) currently receiving treatment, with the following exceptions:
 - a. History of second malignancy that has been successfully treated, with no evidence of active cancer for 3 years prior to enrollment;

- b. Surgically cured low-risk tumors, such as early-stage cervical or endometrial cancer, any cancer in situ, or non-melanoma skin cancers; and
 - c. Prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen.
- 5 2. Symptomatic and/or untreated CNS metastases or leptomeningeal disease or with primary tumor of CNS origin.
- a. Participants with asymptomatic, previously treated CNS metastases are eligible provided they have been clinically stable for at least 4 weeks and have completed RT > 2 weeks prior to treatment. Participants may be on corticosteroids if on a stable dose equivalent to
- 10 prednisone 10 mg daily or less.
3. Received anticancer treatment with chemotherapy, antibody therapy or other immunotherapy, gene therapy, vaccine therapy, angiogenesis inhibitors, or experimental drugs ≤ 14 days prior (≤ 28 days prior in case of checkpoint inhibitor therapy and other antibody therapies) to administration of [^{177}Lu]Lu-FAP-2286.
- 15 4. Received prior radiopharmaceutical therapy (eg, radium 223 ^{223}Ra -dichloride, [^{177}Lu]Lu-DOTA-TATE, [^{177}Lu]Lu-prostate-specific membrane antigen (PSMA)-617, actinium 225 [^{225}Ac]Ac-PSMA-617, etc.) or prior EBRT to more than 25% of the bone marrow or received any prior EBRT directly to kidney, or received any EBRT within 2 weeks prior to the administration of [^{177}Lu]Lu-FAP-2286.
- 20 • Prior administration of a radiopharmaceutical unless 10 or more half-lives have elapsed before injection/infusion of [^{68}Ga]Ga-FAP-2286 or [^{177}Lu]Lu-FAP-2286.
5. Ongoing adverse effects from anticancer treatment NCI-CTCAE v5.0 (or higher) Grade 1, with the exception for alopecia and vitiligo.
6. Impaired cardiac function or clinically significant cardiac diseases, including any of the
- 25 following:
- a. Clinically significant and/or uncontrolled cardiac disease such as congestive heart failure requiring treatment (New York Heart Association > Class 2), uncontrolled hypertension, clinically significant arrhythmia, or congenital prolonged QT syndrome;
 - b. Corrected QT interval (Fridericia's formula) > 450 msec for males or > 470 msec for
- 30 females at Screening; or

- c. Acute coronary syndrome or acute myocardial infarction ≤ 6 months prior to the administration of [^{177}Lu]Lu-FAP-2286.
- 7. Active severe urinary incontinence, severe voiding dysfunction, or urinary obstruction requiring an indwelling/condom catheter that, in the judgment of the investigator, could prevent adhering to radiation safety instructions.
- 8. Severe chronic or active HIV infection:
 - a. Participants on effective antiretroviral therapy with undetectable viral load within 6 months prior to the first dose of [^{177}Lu]Lu-FAP-2286 are eligible.
- 9. Non-study-related minor surgical procedure ≤ 5 days, or major surgical procedure ≤ 21 days, prior to administration of [^{177}Lu]Lu-FAP-2286; in all cases, the participant must be sufficiently recovered and stable before treatment administration.
- 10. The following are exclusion criteria, as applicable:
 - a. Female participants of childbearing potential:
 - i. Refusal to use a highly effective method of contraception or to practice true abstinence during treatment and for 6 months following the last dose of investigational product.
 - ii. Pregnant, suspected pregnancy, or breast feeding.
 - iii. Planning on getting pregnant during treatment and for 6 months following the last dose of investigational product.
 - b. Male participants with female partners of childbearing potential:
 - i. Refusal to use a highly effective method of contraception or to practice true abstinence during treatment and for 6 months following the last dose of investigational product.
 - c. All male participants:
 - i. Refusal to use condoms during sex.
 - ii. Planning to make semen donations during treatment and for 6 months following the last dose of investigational product.
- 11. Significant weight loss ($> 10\%$ of body weight within 28 days prior to providing informed consent for this study).

12. Presence of any other condition that may increase the risk associated with study participation or interfere with the interpretation of study results, and, in the opinion of the investigator, would make the participant inappropriate for entry into the study.
13. Inability to complete the needed investigational and standard imaging examinations due to any reason (e.g., severe claustrophobia, inability to lie still for the entire imaging time).
14. Participants with known hypersensitivity to the active agent or excipients.
15. Severe chronic or active infections (including active tuberculosis, HBV, or HCV infection) requiring systemic antibacterial, antifungal or antiviral therapy within 2 weeks before enrollment.

10 **Standard of care chemotherapy**

The combination groups will receive SOC chemotherapy with [¹⁷⁷Lu]Lu-FAP-2286. The regimen of mFOLFIRINOX is considered a standard of care in 1L PDAC. Participants in the PDAC combination group will be treated with mFOLFIRINOX every 2 weeks until disease progression. mFOLFIRINOX and supportive medications should be administered as per local guidelines and prescribing information. Primary prophylaxis with Granulocyte colony stimulating factor (G-CSF) is allowed.

Table 7. mFOLFIRINOX administration protocol

Drug	Dose and route	Administration	Timepoints
Oxaliplatin	85 mg/m ² IV	Administer over 2 hours	Day 1 of each 14-day cycle
Leucovorin	400 mg/m ² IV	Administer over 2 hours	Day 1 of each 14-day cycle
Irinotecan	150 mg/m ² IV	Administer over 90 minutes	Day 1 of each 14-day cycle
Fluorouracil (5FU)	2400 mg/m ² IV	Administer as continuous IV infusion over 46 hours	Day 1 of each 14-day cycle

20 Similarly, nab-paclitaxel is considered a standard of care in 2L + NSCLC. Participants in the NSCLC combination group will be treated with nab-paclitaxel 100 mg/m² administered over 30 minutes via intravenous infusion weekly until progression. Primary prophylaxis with G-CSF is allowed.

Table 8. Nab-paclitaxel administration protocol

Drug	Dose and route	Administration	Timepoints
Nab-paclitaxel	100 mg/m ² IV	Administer over 30 minutes	weekly

Table 9. Treatment groups

Treatment group	Treatment type	Treatment description
PDAC monotherapy	Investigational drug	Dose expansion: [¹⁷⁷ Lu]Lu-FAP-2286 at the RP2D on Day 1 of each 28-day cycle, for a max of 6 cycles.
PDAC combination	Investigational drug and SOC chemotherapy	Dose escalation: Starting dose of 100mCi (with up to 3 additional dose levels for escalation) [¹⁷⁷ Lu]Lu-FAP-2286 administration is synchronized to day 1 of a chemotherapy cycle. [¹⁷⁷ Lu]Lu-FAP-2286 must be given any day 1-5 of chemotherapy. [¹⁷⁷ Lu]Lu-FAP-2286 to be administered every 28-days, with a number of administrations up to ECD of 55.5 GBq. mFOLFIRINOX on Day 1 of each 14-day cycle (see Table 7). Dose expansion: [¹⁷⁷ Lu]Lu-FAP-2286 at the RP2D synchronized to day 1 of a chemotherapy cycle. [¹⁷⁷ Lu]Lu-FAP-2286 must be given any day 1-5 of chemotherapy. [¹⁷⁷ Lu]Lu-FAP-2286 to be administered every 28 days, with a number of administrations up to the ECD of 55.5 GBq. mFOLFIRINOX on Day 1 of each 14-day cycle (see Table 7).
BC monotherapy	Investigational drug	Dose expansion: [¹⁷⁷ Lu]Lu-FAP-2286 at the RP2D on Day 1 of each 28-day cycle, for a max of 6 cycles.
NSCLC monotherapy	Investigational drug	Dose expansion: [¹⁷⁷ Lu]Lu-FAP-2286 at the RP2D on Day 1 of each 28-day cycle, for a max of 6 cycles.
NSCLC combination	Investigational drug and SOC chemotherapy	Dose escalation: Starting dose of 100mCi (with 3 additional dose levels for escalation) [¹⁷⁷ Lu]Lu-FAP-2286 synchronized to Day 1 of chemotherapy. [¹⁷⁷ Lu]Lu-FAP-2286 must be given any day 1-5 of chemotherapy. [¹⁷⁷ Lu]Lu-FAP-2286 to be administered every 28-days,

Treatment group	Treatment type	Treatment description
		with a number of administrations up to ECD of 55.5 GBq. Nab-paclitaxel on Day 1 of each week. Dose expansion: [¹⁷⁷ Lu]Lu-FAP-2286 synchronized to day 1 of chemotherapy. [¹⁷⁷ Lu]Lu-FAP-2286 must be given any day 1-5 of chemotherapy. [¹⁷⁷ Lu]Lu-FAP-2286 to be administered every 28 days, with a number of administrations up to ECD of 55.5 GBq. Nab-paclitaxel to be administered weekly.

Efficacy Evaluations

Disease/Tumor Assessments

CT/MRI imaging assessments for RECIST v1.1 will be performed at screening/baseline within 28 days of start of treatment (Day -28 to Day -1 prior to Cycle 1 Day 1 for monotherapy groups and within 28 days from the start of the chemotherapy for the combination groups). Any imaging assessments already completed during the regular work-up of the participant within 28 days prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after the start of study treatment cannot be considered baseline images for response assessment.

Target and non-target lesions will be evaluated for evidence of radiographic response based on RECIST v1.1 criteria.

During the Treatment Phase until radiographic disease progression, death, lost to follow-up or withdrawal of consent/opposition to use of data/biological samples, study closure or initiation of subsequent anticancer treatment, tumor assessment scans will be performed. Tumor imaging assessments should be scheduled using the date of first [¹⁷⁷Lu]Lu-FAP-2286 treatment for monotherapy groups and using the first day of chemotherapy for combination groups and continued every 6 weeks (42 days). This schedule should be respected regardless of whether study treatment is temporarily withheld, or unscheduled assessments performed unless progressive disease is assessed on imaging.

For participants who complete EOT and enter LTFU for a reason other than radiographic disease progression, tumor scans should be performed every 6 weeks ($\pm$ 1 week) for 1 year, then every 12 weeks until 2 years, then every 6 months until 5 years.

EOT scans do not need to be repeated if on-treatment scans are collected within the last 6 weeks (42 days) and are not required if disease progression has already been demonstrated radiographically. For participants who complete EOT and enter LTFU, tumor assessment measurements will be performed relative to first treatment until disease progression by RECIST v1.1 as assessed by the investigator, loss to follow-up, withdrawal from study, initiation of subsequent anticancer treatment, death, or study closure.

For any participant who discontinues from study treatment for a reason other than radiographic disease progression or death, a scan should be performed at treatment discontinuation unless a scan has been performed within the previous ≥ 6 weeks.

Disease/tumor assessments will comprise clinical examination and appropriate imaging techniques per RECIST v1.1 (ie, CT scans of the chest, abdomen, and pelvis with appropriate slice thickness); other assessments (MRI, X-ray, PET, bone scan, and color photography) may also be performed as clinically indicated. MRI may be used in place of CT scans for assessment of target lesions if requested by local authorities. All sites of disease should be followed, and the same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. If a participant has known brain metastases, this disease should be evaluated at each required assessment time. Tumor markers should be collected as clinically indicated, concurrent with disease assessments, and assessed locally.

Table 10. Imaging assessment collection plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement)	Mandated	Mandated, every 6 weeks (+/- 7 days) for 1 year and every 12 weeks until 2 years, then every 6 months until 5 years, until documented disease progression, death, lost to follow-up or withdrawal of consent/opposition to use of data/biological samples, study

Procedure	Screening/Baseline	During Treatment/Follow-up
		closure or initiation of subsequent anticancer treatment
Brain CT or MRI	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Whole body bone scan	If clinically indicated	If clinically indicated
Localized bone CT, MRI, or x-ray	For any lesions identified on the whole body bone scan that are not visible on the chest, abdomen, and pelvis CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Color photography (with scale/ruler)	For any skin lesions present	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
CT or MRI of other metastatic sites (e.g., neck)	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis

The local investigator's assessment will be used for the tumor response and treatment decision making using RECIST v1.1. Disease progression will only be determined by RECIST v1.1.

- A quantitative analysis of [¹⁷⁷Lu]Lu-FAP-2286 SPECT/CT scans will be used to
- 5 calculate dosimetry for selected organs and regions of interest, including tumor. The resulting dosimetry data will be generated by a central reviewer. Tumor dosimetry data may be compared with tumor response data from disease/tumor assessments.

PET imaging with [⁶⁸Ga]Ga-FAP-2286

The [⁶⁸Ga]Ga-FAP-2286 PET allows assessment of the target molecule (FAP) on the surface of CAFs present in the tumor microenvironment, to which [¹⁷⁷Lu]Lu-FAP-2286 will subsequently bind, and to evaluate the intensity of such expression. In the current study, a baseline PET/CT will be performed to select participants for treatment with [¹⁷⁷Lu]Lu-FAP-2286.

[⁶⁸Ga]Ga-FAP-2286 PET/CT as an eligibility criterion

In the current study, [⁶⁸Ga]Ga-FAP-2286 PET positivity is an eligibility criterion for treatment with [¹⁷⁷Lu]Lu-FAP-2286, both in Phase 1 and Phase 2. Specific eligibility criteria related to [⁶⁸Ga]Ga-FAP-2286 uptake apply to each phase, as assessed by each site investigator.

For Phase 1

Participants will be considered eligible for treatment with [¹⁷⁷Lu]Lu-FAP-2286 if they have uptake of [⁶⁸Ga]Ga-FAP-2286 on PET/CT in all target lesions with SUV_{max} ≥ 1.5 times higher than the SUV_{mean} of the mediastinal blood pool, that is not attributable to other etiologies of tracer distribution.

For Phase 2

Eligible participants are required to have at least 50% of the target lesions with SUV_{max} ≥ 8, and the remaining target lesions with uptake above the surrounding background.

Image quality of PET scans

As part of the technical performance assessments of [⁶⁸Ga]Ga-FAP-2286, the image quality of baseline PET scan acquired in the Phase 2 part of the study will be determined. A qualitative scoring scale will be used to assess all PET scans acquired in the Phase 2 (Delpassand ES, et al. (2020). J Nucl Med;61(6):890-896). Image quality will be assessed by local readers.

Table 11. [⁶⁸Ga]Ga-FAP-2286 visual image quality scoring scale

Score	Quality of the PET image
0	Inadequate: images look grainy, with poor delineation of lesions

- 1 Questionable: images are clear, but lesion delineation is suboptimal and small lesions (<1 cm) are hard to assess
- 2 Acceptable: images are clear, and large and small lesion delineation is possible

[⁶⁸Ga]Ga-FAP-2286 PET/CT after the last administered dose of [¹⁷⁷Lu]Lu-FAP-2286

- Participants in Phase 2 will undergo a second PET/CT with [⁶⁸Ga]Ga-FAP-2286 after the last administered dose of [¹⁷⁷Lu]Lu-FAP-2286 (4-8 weeks after the administration). This PET/CT will assess the change in the number of lesions (visual evaluation) and in semiquantitative parameters (SUVmax, SUVmean and TBRs) of all measurable lesions, compared to the baseline PET/CT. In case of participants not receiving [¹⁷⁷Lu]Lu-FAP-2286, this second PET/CT will not be performed.
- The injected [⁶⁸Ga]Ga-FAP-2286 radioactivity dose and the acquisition characteristics in this second PET/CT should be the same as those used at baseline. The 6-9 participants included in the [⁶⁸Ga]Ga-FAP-2286 radioactivity and time to scan optimization subset, will receive a radioactivity dose of [⁶⁸Ga]Ga-FAP-2286 in the same dose range as administered at baseline which provided adequate image quality. If data analysis of the baseline PET is not available at the time they need to undergo the PET/CT after the last administered dose of [¹⁷⁷Lu]Lu-FAP-2286 (and thus the optimal acquisition timeframe has not yet been defined), the second PET/CT will be acquired at 60±10 min, as this is the timeframe at which most participants in Phase 1 were scanned and which has shown good performance in terms of visual identification of tumoral lesions and low background activity.
- This objective will be assessed by central review. The results will not be used to define efficacy, but to support evidence of treatment effect in addition to conventional response criteria.

Efficacy Analyses

- Efficacy analyses will be conducted using the [¹⁷⁷Lu]Lu-FAP-2286 Efficacy Set.
- Analyses for efficacy endpoints below will be performed separately for each group. For combination only participants receiving the dose selected for expansion will contribute to the efficacy summaries.

Objective Response

The primary efficacy endpoint for Phase 2 and secondary endpoint for Phase 1 of objective response is defined as a best confirmed response of CR (complete response) or PR (partial response) by RECIST v1.1 as assessed by the investigator. A confirmed CR or PR is a response that is maintained and documented on a subsequent tumor assessment no less than 28 days after the initial response. For Phase 2, ORR (objective response rate) defined as the frequency and percentage of participants with a best confirmed response of CR or PR will be analyzed.

10 Statistical model, hypothesis and method of analysis

The primary objective of the Phase 2 part of the study is to assess the anti-tumor activity of the following treatment arms:

- [¹⁷⁷Lu]Lu-FAP-2286 monotherapy in participants with PDAC in second or third line of therapy
- 15 • [¹⁷⁷Lu]Lu-FAP-2286 monotherapy in participants with NSCLC in second or third line of therapy
- [¹⁷⁷Lu]Lu-FAP-2286 monotherapy in participants with BC in third or later lines of therapy
- [¹⁷⁷Lu]Lu-FAP-2286 + mFOLFIRINOX in participants with PDAC in first line of therapy
- [¹⁷⁷Lu]Lu-FAP-2286 + nab-paclitaxel in participants with NSCLC in second or third line of therapy
- 20

as measured by ORR per investigator's assessment according to RECIST v1.1. ORR based on RECIST v1.1 will be calculated based on the [¹⁷⁷Lu]Lu-FAP-2286 Efficacy Set.

Anti-tumor activity will be assessed against the following benchmarks: 10% ORR for PDAC 2/3L monotherapy groups (Hua J, Shi S, Liang D, et al. (2018) OncoTargets and Therapy; 11: 4591–4608; Cherri S et al. (2021) World J Gastroenterol; 27(17): 1847-1863) and NSCLC 2/3L (Garon EB et al. (2014) Lancet; 384:665-673; Borghaei H et al. (2015) N Engl J Med; 373(17):1627-1639; Herbst RS et al. (2016) Lancet; 387:1540-1550; Rittmeyer A et al. (2017) Lancet; 389:255-265), 15% ORR for the BC 2/3L monotherapy group (Modi S et al. (2022) N Engl J Med; 387:9-20; Rugo HS et al. (2023) Lancet; S0140-6736(23)01245-X) and 30% ORR for the 1L PDAC combination with FOLFIRINOX group (Conroy T et al. (2011) The New England Journal of Medicine; 364(19):1817-1825) and 10% ORR for the 2/3L NSCLC

combination with nab-paclitaxel group (Auclin E et al. (2023) Lung Cancer; 178:116–122; Moliner L, et al. (2023). ESMO Open; 8(2):1-3. //doi.org/10.1016/j.esmoop.2023.100879).

The binary endpoint of ORR will be modelled with binomial distribution and analyzed via Bayesian approach. The posterior distribution of ORR will be derived from the prior
5 distribution and all available data from the subjects included in the [¹⁷⁷Lu]Lu-FAP-2286 Efficacy Set. A neutral prior, Beta (1/3, 1/3) will be used for ORR in each group (Kerman J (2011) Electronic J of Stats; 5:1450-1470).

Additionally, ORR will be summarized by group along with the two-sided exact binomial 95% confidence interval (Clopper CJ and Pearson (1934) Biometrical;26:404-413). Waterfall
10 graphs, which display the best percentage change from baseline in the sum of diameters of all target lesions for each subject with measurable disease at baseline, will be used to depict the anti-tumor activity of each group.

Response Evaluation Criteria in Solid Tumors Criteria – RECIST v1.1

The RECIST Version 1.1 guidelines are described in: Eisenhauer EA, et al. (2009) New
15 response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European Journal of Cancer;45(2):228-47; and at //eortc.be/Recist/Default.htm. A short summary is given below.

Measurable Disease:

Tumor lesions: measurable lesions are defined as those that can be accurately measured
20 in at least 1 dimension (longest diameter to be recorded) with the following:

- A minimum size of 10 mm by CT scan (CT scan thickness no greater than 5 mm);
- A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable); or
- A minimum size of 20 mm by chest X-ray.

25 All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will
30 be measured and followed.

Nonmeasurable Disease:

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable include
5 leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Bone Lesions

Bone lesions, cystic lesions, and lesions previously treated with local therapy require
10 particular comment. Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be
15 considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are nonmeasurable.

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be
20 considered as malignant lesions (neither measurable nor nonmeasurable) because they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same participant, these are preferred as target lesions.

Lesions with Prior Local Treatment

Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions

30 All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and

measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Nontarget Lesions

RECIST criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion.

Guidelines for Evaluation of Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Table 12. Evaluation of Target Lesions

Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
Partial Response	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

Table 13. Evaluation of Nontarget Lesions

Complete Response	Disappearance of all nontarget lesions and normalization of tumor marker level.
Stable Disease/Incomplete Response	Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of 1 or more new lesions and/or unequivocal progression of existing nontarget lesions.

If tumor markers are initially above the institutional ULN, they must normalize for a participant to be considered a complete responder.

Evaluation of Best Overall Response

- 5 The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 14. Evaluation of Best Overall Response

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = Complete response

NE = Not evaluable

PD = Progressive disease

PR = Partial response

SD = Stable disease

10

Participants with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

15

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) prior to confirming the complete response status.

20 Confirmatory Measurement/Duration of Response

Confirmation

If an initial CR or PR is noted, confirmatory scans should be performed at least 4 weeks (28 days) after response was first documented.

Duration of Overall Response

5 The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

10 Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Treatment Groups

15 Phase 2: Following the completion of the Phase 1 part of the study, the RP2D of [¹⁷⁷Lu]Lu-FAP-2286 monotherapy administered every 6 weeks for up to 6 cycles will be established.

The Phase 2 part of the study seeks to evaluate the safety and efficacy of [¹⁷⁷Lu]Lu-FAP-2286 every 4 weeks in monotherapy or combination across five treatment groups.

20 Monotherapy groups: These three treatment groups are dependent on the RP2D declared in the Phase 1 part of the study.

- Participants with FAP-expressing metastatic (2/3L) pancreatic ductal adenocarcinoma (PDAC) treated with [¹⁷⁷Lu]Lu-FAP-2286 monotherapy at RP2D every 4 weeks
- 25 • Participants with FAP-expressing metastatic (2/3L) non-small cell lung cancer (NSCLC) treated with [¹⁷⁷Lu]Lu-FAP-2286 monotherapy at RP2D every 4 weeks
- Participants with FAP-expressing metastatic (3L+) breast cancer (BC) treated with [¹⁷⁷Lu]Lu-FAP-2286 monotherapy at RP2D every 4 weeks

30 Combination groups: These two treatment groups will be initiated with a dose escalation starting with [¹⁷⁷Lu]Lu-FAP-2286 at 100 mCi (dose level 1) every 4 weeks. Therefore, the combination groups are not dependent on the RP2D declared in the Phase 1 part of the study.

- Participants with FAP-expressing metastatic (1L) PDAC treated with [^{177}Lu]Lu-FAP-2286 every 4 weeks in combination with modified FOLFIRINOX (dose escalation starting at 100 mCi followed by dose expansion at selected dose)
- Participants with FAP-expressing metastatic (2/3L) NSCLC treated with [^{177}Lu]Lu-FAP-2286 every 4 weeks in combination with nab-paclitaxel (dose escalation starting at 100 mCi followed by dose expansion at selected dose)

Gallium-68 FAP-based imaging has demonstrated the ability to detect tumoral lesions in PDAC, NSCLC and BC. Within these tumor types, ^{68}Ga -FAP-2286 imaging has shown notable uptake with similar SUV in primary and metastatic lesions (Kratohwil C., et al. J Nucl Med; 60(6):801-805). Assuming [^{68}Ga]Ga-FAP-2286 imaging uptake is predictive of response to [^{177}Lu]Lu-FAP-2286 therapy, these specific therapeutic indications were chosen for the Phase 2 study design in lieu of the originally planned cohorts, including the basket cohort.

Phase 2 dosing interval

The Phase 1 study part investigated administration of [^{177}Lu]Lu-FAP-2286 every 6 weeks, while the Phase 2 will investigate the administration of [^{177}Lu]Lu-FAP-2286 every 4 weeks. The Phase 1 participant population consisted of participants with advanced malignancies in a heavily pretreated population. The disease progression in these participants often occurs within weeks and thus many participants in Phase 1 received only one cycle of treatment and discontinued from the study due to progressive disease. Since the safety of [^{177}Lu]Lu-FAP-2286 as determined in the 26 participants treated in the Phase 1 part is manageable and has not shown any concerning trend in terms of an increased frequency of cytopenias or other adverse events, the dosing interval in Phase 2 will be every 4 weeks to improve the chance to administer an effective cumulative dose.

Example 3. Phase I Dosing Results

34 participants were imaged with [^{68}Ga]Ga-FAP-2286 and 27^a participants were treated with [^{177}Lu]Lu FAP 2286 across 4 dose levels ranging from 100 mCi – 250 mCi under the Phase 1 Protocol described in Example 2 (See also NCT04939610). The most common treatment-emergent adverse events (TEAEs) of any causality occurring in $\geq 20\%$ of participants include fatigue (n=7, 25.9%), abdominal pain (n=6, 22.2%) and anemia (n=6, 22.2%). TEAEs reported

to be treatment related in $\geq 10\%$ of participants include fatigue (n=3, 11.1%) and anemia (n=4, 14.8%). No cardiac related events were reported to date.

Full dosimetry of [^{177}Lu]Lu-FAP-2286 was evaluated, for each patient after every cycle (hybrid method (4 whole body-planar images + 1 SPECT/CT) or quantitative SPECT/CT (4 SPECT/CT images)). Based on the dosimetry data in cycle 1 per dosage level, overall and cumulatively (dose of 55.5 GBq, equivalent to 6 administrations of 250 mCi (9.25 GBq)), favorable biodistribution was observed.

Overall, [^{177}Lu]Lu-FAP-2286 was well tolerated in heavily pretreated patients with a low incidence of DLTs and Grade ≥ 3 AEs observed, supporting the commencement of phase 2.

Given the safety profile and dosimetry data, [^{177}Lu]Lu-FAP-2286 monotherapy of 250 mCi (9.25 GBq) has been determined to be the recommended phase 2 dose (RP2D) over the tested doses. Further, since there are known benefits of cumulative radiation and the potential for radiosensitization of the tumor when chemotherapy is given concurrently with radiation, an every 4-week administration interval of [^{177}Lu]Lu-FAP-2286 will be explored in Phase 2. With respect to the safety profile of [^{177}Lu]Lu-FAP-2286 and absence of cumulative hematologic toxicity in Phase 1 as well as the opportunity to deliver more timely therapy directly to the tumor and in the context of chemotherapy, an increased administration frequency is supported.

^a The 27 participants treated with [^{177}Lu]Lu-FAP-2286 had solid tumors of the following type: appendiceal, colorectal, desmoplastic small round cell tumor, gallbladder, head and neck, peritoneal mesothelioma, pancreatic, prostate, rectal, solitary fibrous tumor, soft tissue sarcoma, and uterus/endometrial (specifically uterine leiomyosarcoma).

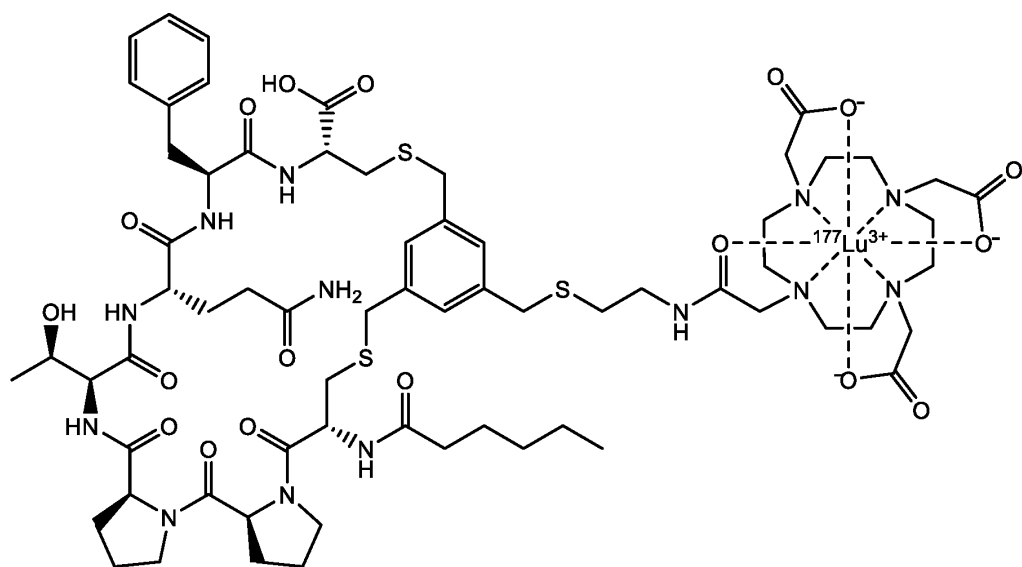
CLAIMS

1. A method for treating pancreatic ductal adenocarcinoma (PDAC) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:

- (a) a fibroblast activation protein (FAP)-targeting radiotherapeutic agent; and
- (b) chemotherapy comprising one, two, three, or four agents selected from 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin.

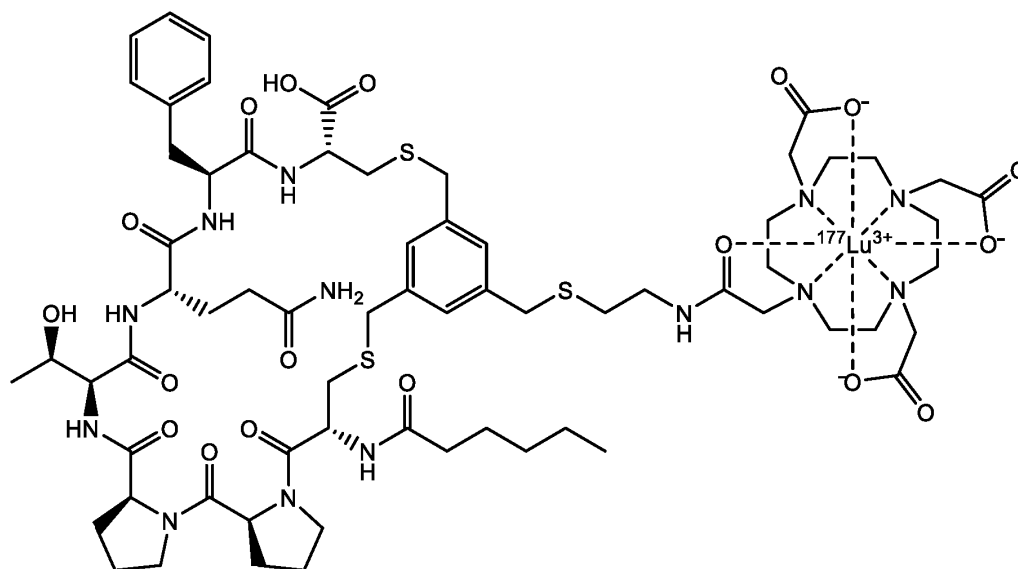
2. The method of claim 1, wherein the FAP-targeting radiotherapeutic agent comprises ^{177}Lu .

3. The method of claim 1 or 2, wherein the FAP-targeting radiotherapeutic agent is



a pharmaceutically acceptable salt or solvate thereof.

4. The method of any one of claims 1-3, wherein the FAP-targeting radiotherapeutic agent is

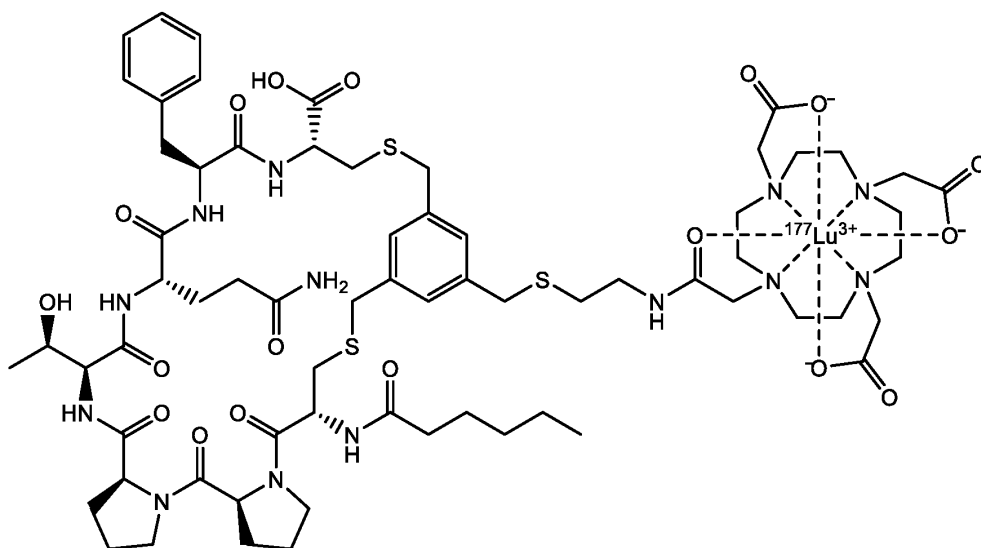


5. The method of any one of claims 1-4, wherein the chemotherapy comprises 5-FU, leucovorin, and irinotecan.
6. The method of any one of claims 1-4, wherein the chemotherapy comprises 5-FU, leucovorin, and oxaliplatin.
7. The method of any one of claims 1-4, wherein the chemotherapy comprises 5-FU, leucovorin, irinotecan, and oxaliplatin.
8. The method of any one of claims 1-6, wherein chemotherapy is administered to the subject prior to administration of the FAP-targeting radiotherapeutic agent.
9. The method of any one of claims 1-8, wherein the chemotherapy is administered to the subject in one to two cycles prior to the administration of the FAP-targeting radiotherapeutic agent.
10. The method of any one of claims 1-9, wherein the chemotherapy is administered on a 14-day cycle.

11. The method of claim 10, wherein the chemotherapy is administered on a 14-day cycle, wherein:
- i. oxaliplatin is administered on the first day of the 14-day cycle;
 - ii. leucovorin is administered on the first day of the 14-day cycle;
 - iii. irinotecan is administered on the first day of the 14-day cycle; and
 - iv. 5-fluorouracil is administered on the first and second day of the 14-day cycle.
12. The method of claim 11, wherein the oxaliplatin is administered intravenously at a dose from about 60 mg/m² to about 100 mg/m².
13. The method of claim 11 or 12, wherein the oxaliplatin is administered intravenously at a dose of about 85 mg/m².
14. The method of any one of claims 11-13, wherein the leucovorin is administered intravenously at a dose from about 300 mg/m² to about 500 mg/m².
15. The method of any one of claims 11-14, wherein the leucovorin is administered intravenously at a dose of about 400 mg/m².
16. The method of any one of claims 11-15, wherein the irinotecan is administered intravenously at a dose from about 100 mg/m² to about 200 mg/m². mg/m².
17. The method of any one of claims 11-16, wherein the irinotecan is administered intravenously at a dose of about 150 mg/m².
18. The method of any one of claims 11-17, wherein the 5-fluorouracil is administered intravenously at a dose from about 1000 mg/m² to about 3000 mg/m².
19. The method of claim 11-18, wherein the 5-fluorouracil is administered intravenously at a dose of about 2400 mg/m².

20. The method of any one of claims 1-19, wherein the FAP-targeting radiotherapeutic agent is administered intravenously as a single dose once every three weeks $\pm$ three days, four weeks $\pm$ three days, five weeks $\pm$ three days, or six weeks $\pm$ three days.
21. The method of any one of claims 1-20, wherein the FAP-targeting radiotherapeutic agent is administered intravenously as a single dose once every four weeks $\pm$ three days.
22. The method of claim 20 or 21, wherein the single dose of the FAP-targeting radiotherapeutic agent is from about 3 GBq to about 10 GBq.
23. The method of any one of claims 20-22, wherein the single dose of the FAP-targeting radiotherapeutic agent is about 3.7 GBq, about 5.6 GBq, about 7.4 GBq, or about 9.3 GBq.
24. The method of any one of claims 1-23, wherein the FAP-targeting radiotherapeutic agent is administered to the subject as a single dose once every four weeks $\pm$ three days for a length of time to achieve a cumulative dose of about 55.5 GBq.
25. The method of any one of claims 10-24, wherein the FAP-targeting radiotherapeutic agent is administered on any one of the first day, second day, third day, fourth day, or fifth day of each 14-day chemotherapy cycle.
26. The method of any one of claims 1-25, wherein the PDAC is FAP-expressing.
27. The method of any one of claims 1-26, wherein the PDAC is metastatic.
28. A method for treating non-small cell lung cancer (NSCLC) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of:
- (A) a fibroblast activation protein (FAP)-targeting radiotherapeutic agent; and
 - (B) nab-paclitaxel.

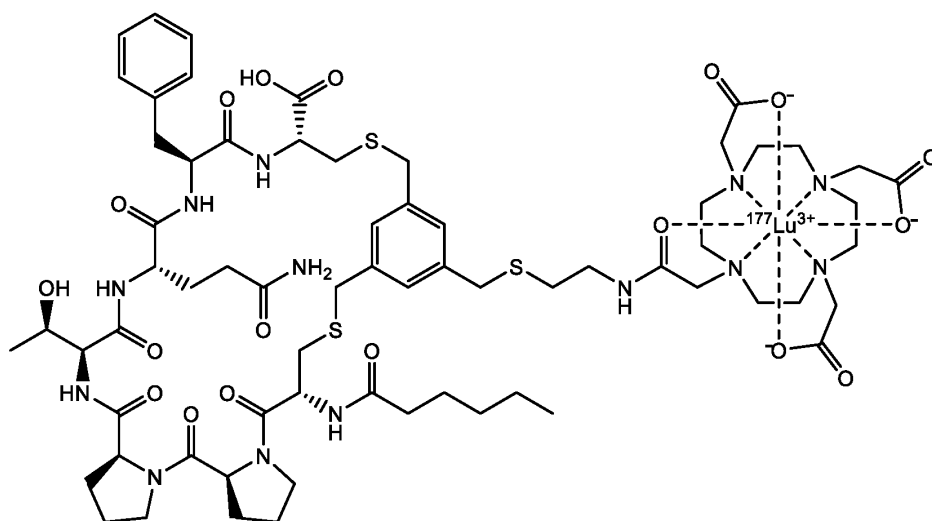
29. The method of claim 28, wherein the FAP-targeting radiotherapeutic agent comprises ^{177}Lu .
30. The method of claim 28 or 29, wherein the FAP-targeting radiotherapeutic agent is



, or a

pharmaceutically acceptable salt or solvate thereof.

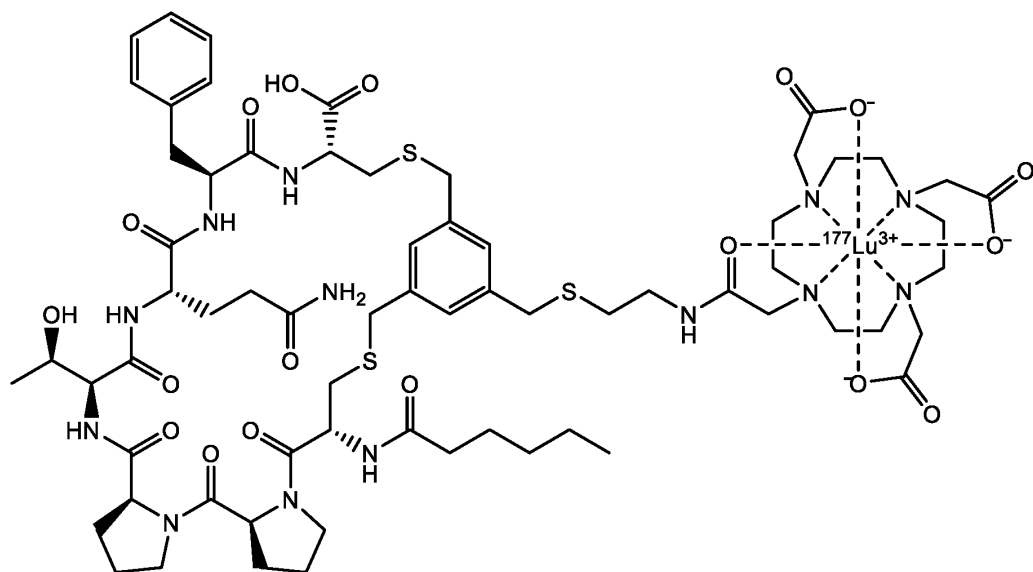
31. The method of any one of claims 28-30, wherein the FAP-targeting radiotherapeutic agent is



32. The method of any one of claims 28-31, wherein the subject has previously received at least one prior therapy for the treatment of NSCLC, wherein each of the at least one prior therapy is other than a therapy comprising a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.
33. The method of any one of claims 28-32, wherein the subject has previously received at least two prior therapies for the treatment of NSCLC, wherein each of the prior therapies is other than a therapy comprising a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.
34. The method of any one of claims 28-33, wherein nab-paclitaxel is administered to the subject prior to administration of the FAP-targeting radiotherapeutic agent.
35. The method of any one of claims 28-34, wherein the nab-paclitaxel is administered to the subject in one to two cycles prior to the administration of the FAP-targeting radiotherapeutic agent.
36. The method of any one of claims 28-35, wherein the nab-paclitaxel is administered once in a nab-paclitaxel seven-day cycle.
37. The method of claim 36, wherein the nab-paclitaxel is administered on the first day in the nab-paclitaxel seven-day cycle.
38. The method of any one of claims 28-37, wherein the nab-paclitaxel is administered intravenously at a dose from about 50 mg/m² to about 150 mg/m².
39. The method of any one of claims 28-38, wherein the nab-paclitaxel is administered intravenously at a dose of about 100 mg/m².

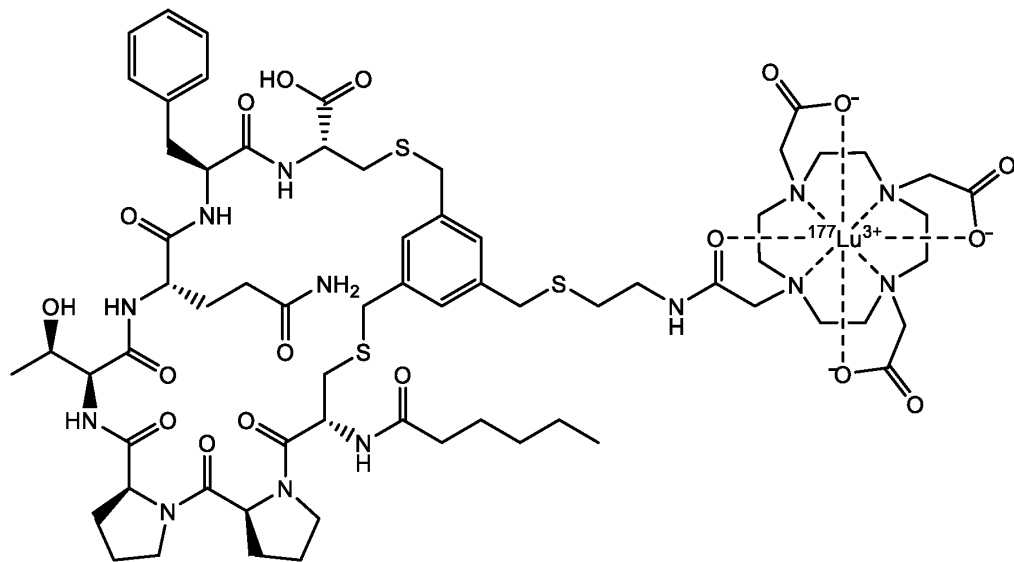
40. The method of any one of claims 36-39, wherein the FAP-targeting radiotherapeutic agent is administered on any one of the first day, the second day, the third day, the fourth day, or the fifth day of the nab-paclitaxel seven-day cycle.
41. The method of any one of claims 28-40, wherein the FAP-targeting radiotherapeutic agent is administered intravenously as a single dose once every three weeks $\pm$ three days, four weeks $\pm$ three days, five weeks $\pm$ three days, or six weeks $\pm$ three days.
42. The method of any one of claims 28-41, wherein the FAP-targeting radiotherapeutic agent is administered intravenously as a single dose once every four weeks $\pm$ three days.
43. The method of claim 41 or 42, wherein the single dose is from about 3 GBq to about 10 GBq.
44. The method of any one of claims 41-43, wherein the single dose is about 3.7 GBq, about 5.6 GBq, about 7.4 GBq, or about 9.3 GBq.
45. The method of any one of claims 28-44, wherein the FAP-targeting radiotherapeutic agent is administered to the subject once every four weeks $\pm$ three days for a length of time to achieve a cumulative dose of about 55.5 GBq.
46. The method of any one of claims 28-45, wherein the NSCLC is FAP-expressing.
47. The method of any one of claims 28-46, wherein the NSCLC is metastatic.
48. A method for treating pancreatic ductal adenocarcinoma (PDAC) in a subject in need thereof comprising administering to a subject a FAP-targeting radiotherapeutic agent, wherein the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days to achieve a cumulative dose of about 40 to about 60 GBq.

49. A method for treating non-small cell lung cancer (NSCLC) in a subject in need thereof comprising administering to the subject a FAP-targeting radiotherapeutic agent, wherein the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days to achieve a cumulative dose of about 40 to about 60 GBq.
50. A method for treating breast cancer in a subject in need thereof comprising administering to the subject a FAP-targeting radiotherapeutic agent, wherein the FAP-targeting radiotherapeutic agent is administered as a single dose once every four weeks $\pm$ three days to achieve a cumulative dose of about 40 to about 60 GBq.
51. The method of any one of claims 48-50, wherein the single dose is from about 3 GBq to about 10 GBq.
52. The method of claim any one of claims 48-51, wherein the single dose is about 3.7 GBq, about 5.6 GBq, about 7.4 GBq, or about 9.3 GBq.
53. The method of any one of claims 48-52, wherein the single dose is about 9.3 GBq.
54. The method of any one of claims 48-53, wherein the cumulative dose is about 55.5 GBq.
55. The method of any one of claims 48-54, wherein the FAP-targeting radiotherapeutic agent comprises ^{177}Lu .
56. The method of any one of claims 48-55, wherein the FAP-targeting radiotherapeutic agent is



or a pharmaceutically acceptable salt or solvate thereof.

57. The method of any one of claims 48-56, wherein the FAP-targeting radiotherapeutic agent is

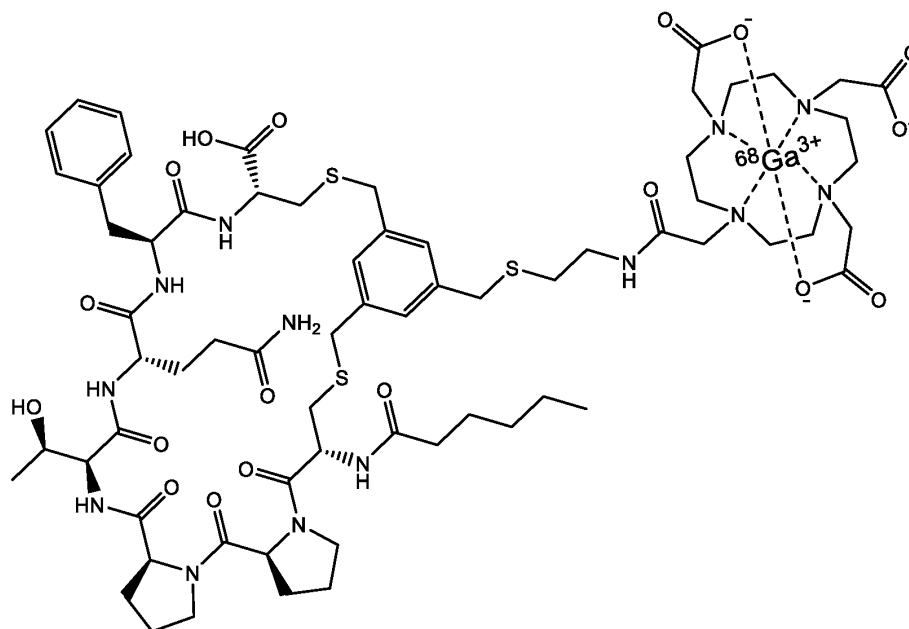


58. The method of any one of claims 48 and 51-57, wherein the PDAC is FAP-expressing.

59. The method of any one of claims 48 and 51-58, wherein the PDAC is metastatic.
60. The method of any one of claims 48 and 51-59, wherein the subject has received at least one prior therapy for the treatment of PDAC, wherein each of the at least one prior therapy is other than a therapy comprising a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.
61. The method of any one of claims 48 and 51-60, wherein the subject has received at least two prior therapies for the treatment of PDAC, wherein each of the prior therapies is other than a therapy comprising a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.
62. The method of any one of claims 49 and 51-57, wherein the NSCLC is FAP-expressing.
63. The method of any one of claims 49, 51-57, and 62 wherein the NSCLC is metastatic.
64. The method of any one of claims 49, 51-57, 62, and 63 wherein the subject has received at least one prior therapy for the treatment of NSCLC, wherein each of the at least one prior therapy is other than a therapy comprising a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.
65. The method of any one of claims 49, 51-57, and 62-64, wherein the subject has received at least two prior therapies for the treatment of NSCLC, wherein each of the two prior therapies is other than a therapy comprising a fibroblast activation protein (FAP)-targeting radiotherapeutic agent.
66. The method of any one of claims 50-57, wherein the breast cancer is FAP-expressing.
67. The method of any one of claims 50-57 and 66, wherein the breast cancer is metastatic.

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73. The method of any one of claims 70-72, wherein the FAP-targeting radioimaging agent is;



74. A method for treating cancer in a subject in need thereof comprising administering to the subject a FAP-targeting radiotherapeutic agent comprising ^{177}Lu , wherein the FAP-targeting radiotherapeutic agent is administered intravenously as a daily dose once every 28 ± 3 days to achieve a cumulative dose of about 40 to about 60 GBq, wherein the cancer is a FAP-expressing solid tumor.

75. The method of claim 74, wherein the method further comprises administering to the subject a therapeutically effective amount of a chemotherapy.

76. The method of claim 75, wherein the chemotherapy comprises nab-paclitaxel, FOLFIRINOX, or mFOLFIRINOX.