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(71) Applicants: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, 4056 Basel (CH). **ARTIOS PHARMA LIMITED** [GB/GB]; Babraham Hall, Babraham Research Campus, Cambridge, Cambridgeshire CB22 3AT (GB).

(72) Inventors: **HINDUPUR, Sravanth Kumar**; c/o Novartis Pharma AG, Lichtstrasse 34, 4056 Basel (CH). **PINTO DO COUTO E SILVA, Joana**; c/o Novartis Pharma AG, Lichtstrasse 35, 4056 Basel (CH). **BARYS, Louise**; c/o Novartis Pharma AG, Lichtstrasse 35, 4056 Basel (CH). **REBER, Josefine Astrid**; c/o Novartis Pharma AG, Lichtstrasse 35, 4056 Basel (CH). **RESCHKE, Markus**; c/o Novartis Pharma AG, Lichtstrasse 35, 4056 Basel (CH). **SCHMELZLE, Tobias**; c/o Novartis AG, Lichtstrasse 35, 4056 Basel (CH). **CORTES-CROS, Marta**; c/o Novartis Pharma AG, Lichtstrasse 35, 4056 Basel (CH). **RANZANI, Marco**; c/o Artios Pharma Limited, Babraham Hall, Babraham Research Campus, Cambridge, Cambridgeshire CB22 3AT (GB). **ROBINSON, Helen Marie Ruth**; c/o Artios Pharma Limited, Babraham Hall, Babraham Research Campus, Cambrdige, Cambridgeshire CB22 3AT (GB). **SMITH, Graeme Cameron Murray**; c/o Artios Pharma Limited, Babraham Hall, Babraham Research Campus, Cambrdige, Cambridgeshire CB22 3AT (GB).

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(54) **Title:** COMBINATION THERAPIES WITH DNA DAMAGE RESPONSE INHIBITORS AND [^{177}LU]LU-PSMA-617

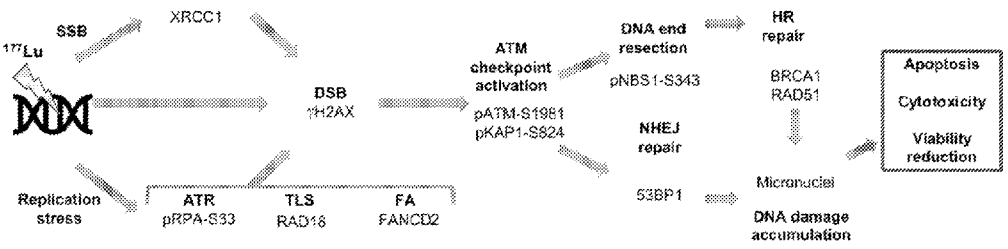

FIG. 7

(57) **Abstract:** Described herein are combination therapies featuring [^{177}Lu]Lu-PSMA-617 and a DNA Damage Response inhibitor (DDRi), and their use in treating cancers, such as, e.g., PSMA-expressing cancers.

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COMBINATION THERAPIES WITH DNA DAMAGE RESPONSE INHIBITORS AND [^{177}Lu]Lu-PSMA-617

CROSS-REFERENCE TO RELATED APPLICATIONS

This Application claims the benefit of U.S. Provisional Application No. 63/575,373, filed April 5, 2024, the entire contents of which are incorporated by reference herein.

FIELD

This disclosure relates to combination therapies featuring a radiopharmaceutical targeting prostate specific membrane antigen (PSMA) and a DNA Damage Response inhibitor (DDRi), and their use in increasing treatment efficacy for cancers, such as, *e.g.*, PSMA-expressing cancers.

BACKGROUND

Prostate cancer (PC) is a leading cause of cancer-related death among men around the world, with an estimated 1.4 million new cases and 375,000 deaths in 2020 (Wang et al. 2022, Prostate Cancer Incidence and Mortality: Global Status and Temporal Trends in 89 Countries From 2000 to 2019. Frontiers in Public Health). The tumors of 10-20% of prostate cancer patients become refractory to androgen-deprivation therapy by pharmaceutical or surgical castration, and progress as metastatic castration-resistant prostate cancer (mCRPC) (Juzeniene et al. 2021, Preclinical and Clinical Status of PSMA-Targeted Alpha Therapy for Metastatic Castration-Resistant Prostate Cancer, Cancers).

During the past decade, new therapeutic options such as antihormonal therapies, poly(ADP-ribose) polymerase (PARP) inhibitors, radiopharmaceuticals, immunotherapies, and chemotherapies have been approved for mCRPC patients. Despite these developments, mCRPC remains incurable, which may be explained, in part, by the inter- and intra-patient heterogeneity of the disease. Thus, there is an urgent need for personalized, highly effective targeted therapies for mCRPC patients.

Targeted radioligand therapy (RLT) offers the possibility to treat cancer lesions in a specific and tumor-selective manner by exploiting cell surface receptors that are mainly expressed in malignant cells, such as, *e.g.*, prostate specific membrane antigen (PSMA). Systemically administered RLT is concentrated at target sites and surrounding cells through radioligand binding. Targeted RLTs bind with high affinity to biomarker-expressing, ligand-expressing, and/or receptor-expressing lesions, delivering DNA strand-breaking radiation. PSMA is an attractive target for prostate cancer therapy because, while it is highly expressed in cancerous cells, including mCRPC cells, it has much lower expression in normal tissues. Accordingly, PSMA has the potential to be a viable target for RLT with minimized radioactivity-

related side effects. Pluvicto® ([^{177}Lu]Lu-PSMA-617) is one example of an FDA-approved PSMA-based RLT drug for the treatment of PSMA-positive metastatic castration-resistant prostate cancer (mCRPC).

Despite the clinical success of targeted RLT, there are opportunities for improving aspects of therapeutic efficacy, such as enhancing the duration or extent of the response for a wider population of patients.

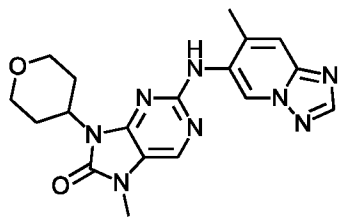
SUMMARY

In one aspect, the present disclosure provides a method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi).

In certain embodiments, the DDRi can be selected from the group consisting of Ataxia-Telangiectasia Mutated (ATM) inhibitors, Ataxia Telangiectasia and Rad3-related (ATR) inhibitors, Poly (ADP-ribose) Polymerase (PARP) inhibitors, DNA-dependent Protein Kinase (DNA-PK) inhibitors, WEE1 protein kinase family inhibitors, Checkpoint Kinase (CHK) inhibitors, DNA polymerase theta (Polθ) inhibitors, RAD51 recombinase (RAD51) inhibitors, Ubiquitin-Specific Protease 1 (USP1) inhibitors, Polo-Like serine/threonine Kinase 1 (PLK1) inhibitors, Aurora kinase inhibitors, mutant p53 reactivators, Poly(ADP-ribose) Glycohydrolase (PARG) inhibitors, Werner Syndrome protein (WRN) inhibitors, and combinations thereof. Optionally, the DDRi is not olaparib.

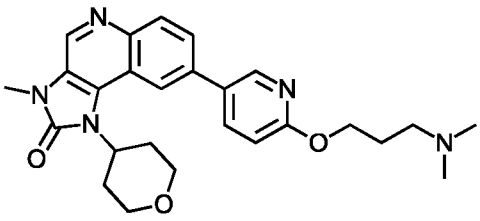
In certain embodiments, the DDRi can be selected from the group consisting of ATM inhibitors, ATR inhibitors, PARP inhibitors, DNA-PK inhibitors, WEE1 protein kinase family inhibitors, CHK1 inhibitors, and Polθ inhibitors. Optionally, the PARP inhibitor is not olaparib.

In certain embodiments, the DDRi can include at least one DNA-PK inhibitor listed in TABLE **4**, at least one of XRD-0394, SN-39536, BY101298, XZP-6877 and IMP-11, or a pharmaceutically acceptable salt thereof. In some cases, the at least one DNA-PK inhibitor can include:



(7-Methyl-2-[(7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino]-9-(oxan-4-yl)purin-8-one (AZD7648)), or a pharmaceutically acceptable salt thereof.

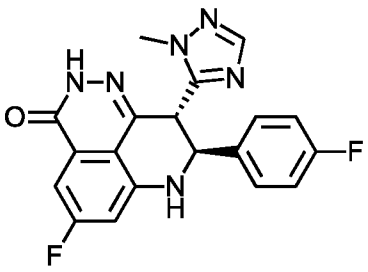
In certain embodiments, the DDRi can include at least one ATM inhibitor listed in TABLE **1**, at least one of XRD-0394 and SX-RDS1, or a pharmaceutically acceptable salt thereof. In some cases, the at least one ATM inhibitor can include:



(8-[6-[3-(dimethylamino)propoxy]pyridin-3-yl]-3-methyl-1-(oxan-4-yl)imidazo[4,5-c]quinolin-2-one (AZD0156)), or pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one ATR inhibitor listed in TABLE **2**, at least one of LF0397, IMP-9064, ART0380, SC0245, and ATRN-119, or a pharmaceutically acceptable salt thereof. In some cases, the at least one ATR inhibitor can include ART0380, or a pharmaceutically acceptable salt thereof.

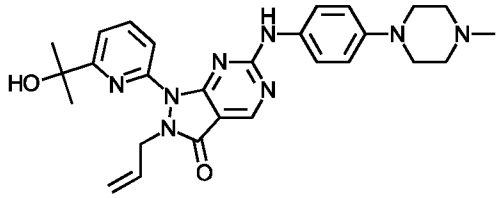
In certain embodiments, the DDRi can include at least one PARP inhibitor listed in TABLE **3**, or a pharmaceutically acceptable salt thereof. Optionally the PARP inhibitor is not olaparib. In some cases, the at least one PARP inhibitor can include:



((11*S*,12*R*)-7-fluoro-11-(4-fluorophenyl)-12-(2-methyl-1,2,4-triazol-3-yl)-2,3,10-triazatricyclo[7.3.1.$0^{5,13}$]trideca-1,5(13),6,8-tetraen-4-one (talazoparib)), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one WEE1 protein kinase family inhibitor selected from the group consisting of Wee1-like protein kinase inhibitors (WEE1) and Protein Kinase, Membrane Associated Tyrosine/Threonine 1 (PKMYT1) inhibitors.

In certain embodiments, the DDRi can include at least one WEE1 inhibitor listed in TABLE **5**, at least one of SC0191, SY-4835, and IMP7068, or a pharmaceutically acceptable salt thereof. In some cases, the at least one WEE1 inhibitor can include:

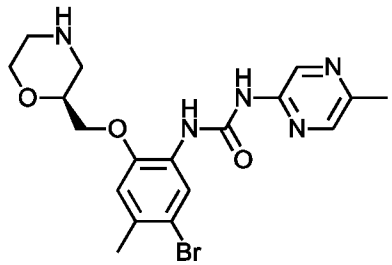


(1-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]-6-[4-(4-methylpiperazin-1-yl)anilino]-2-prop-2-enylpyrazolo[3,4-d]pyrimidin-3-one (Adavosertib or MK-1775), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one PKMYT1 inhibitor listed in TABLE **6**, ACR-2316, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one CHK inhibitor selected from the group consisting of CHK1 selective inhibitors, CHK2 selective inhibitors, and CHK1/2 dual inhibitors.

In certain embodiments, the DDRi can include at least one CHK1 selective inhibitor listed in TABLE **7**, VER250840, or a pharmaceutically acceptable salt thereof. In some cases, the at least one CHK1 selective inhibitor can include:

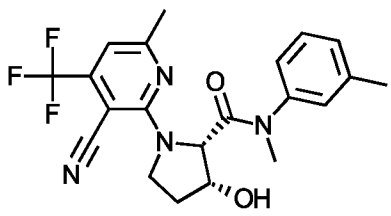


(1-[5-bromo-4-methyl-2-[[(2*S*)-morpholin-2-yl]methoxy]phenyl]-3-(5-methylpyrazin-2-yl)urea (Rabusertib or LY2603618), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one CHK2 selective inhibitor listed in TABLE **8**, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one CHK1/2 dual inhibitor listed in TABLE **9**, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one Polθ inhibitor listed in TABLE **10**, at least one of ART4215, ART6043, RP-3467, and GSK101 (GSK4524101/IDE705), or a pharmaceutically acceptable salt thereof. In some cases, the at least one Polθ inhibitor can include:



((2*S*,3*R*)-1-[3-cyano-6-

methyl-4-(trifluoromethyl)pyridin-2-yl]-3-hydroxy-*N*-methyl-N-(3-methylphenyl)pyrrolidine-2-carboxamide (ART558), ART6043, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one RAD51 inhibitor listed in TABLE **11**, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one USP1 inhibitor listed in TABLE **12**, at least one of TNG348, HSK39775, FT-3171 (Debio 0432), and ISM3091, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one PLK1 inhibitor listed in TABLE **13**, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one Aurora kinase inhibitor selected from the group consisting of Aurora A inhibitors and Aurora B inhibitors listed in TABLE **14**, WJ05129, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one PARG inhibitor listed in TABLE **16**, IDE161, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one WRN inhibitor listed in TABLE **17**, RO7589831, HRO761, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one mutant p53 reactivator listed in TABLE **15**, PC14586, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi and [^{177}Lu]Lu-PSMA-617 can be administered via the same route of administration.

In certain embodiments, the DDRi and [^{177}Lu]Lu-PSMA-617 are formulated in the same dosage form.

In certain embodiments, the DDRi and [^{177}Lu]Lu-PSMA-617 can be formulated as separate dosage forms.

In certain embodiments, the DDRi can be administered via a different route than [^{177}Lu]Lu-PSMA-617.

In certain embodiments, the DDRi can be administered within 24 hours of [^{177}Lu]Lu-PSMA-617 administration.

In certain embodiments, the therapeutically effective amount of the DDRi can be administered over a course of about, or at least about, 5 days.

In certain embodiments, the DDRi can be administered within 20 hours of [^{177}Lu]Lu-PSMA-617 administration.

In certain embodiments, the DDRi can be administered within 4 hours of [^{177}Lu]Lu-PSMA-617 administration.

In certain embodiments, the DDRi can be administered in one or more doses for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration.

In certain embodiments, the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617, the DDRi, or both, is lower than the amount required for a monotherapy response. In some cases, the monotherapy response can be an objective response rate (ORR), disease control rate (DCR), progression free survival (PFS), duration of response (DOR), overall survival (OS), complete response (CR), partial response (PR), PSA response rate, radiographic response rate, change from baseline in blood and tumor tissue microenvironment pharmacodynamic (PD) biomarkers, or a combination thereof. In some cases, the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617, the DDRi, or both is at least about 10% to about 50% lower than the amount required for the monotherapy response. In some cases, the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 is about 10%, 15%, 20%, 25%, 30% 35%, 40%, 45% or about 50% lower than the amount of [^{177}Lu]Lu-PSMA-617 required for the monotherapy response.

In some cases, the therapeutically effective amount of the DDRi is about 10%, 15%, 20%, 25%, 30% 35%, 40%, 45% or about 50% lower than the amount of the DDRi required for the monotherapy response.

In certain embodiments, an anti-cancer response produced by practicing the method is synergized as compared to a method of administering the [^{177}Lu]Lu-PSMA-617 or the DDRi as monotherapy.

In certain embodiments, the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 is a dose of from about 10 MBq to about 10 GBq, about 100 MBq to about 10 GBq, about 1 GBq to about 10 GBq, about 3 GBq to about 10 GBq, about 5 GBq to about 9 GBq, about 6 GBq to about 8 GBq. or about 7.4 GBq.

In certain embodiments, the PSMA-expressing cancer is PSMA-positive prostate cancer, optionally PSMA-positive metastatic castration-resistant prostate cancer (mCRPC), optionally PSMA-positive metastatic hormone-sensitive prostate cancer (mHSPC), optionally PSMA-positive oligometastatic prostate cancer (OMPC), optionally PSMA-positive cancer in the biochemical recurrence (BCR) setting, optionally PSMA-positive caner in the high-risk BCR setting.

In another aspect, the present disclosure provides a combination comprising [^{177}Lu]Lu-PSMA-617 and a DDRi for use in treating a PSMA-expressing cancer, wherein the DDRi is selected from the group consisting of Ataxia-Telangiectasia Mutated (ATM) inhibitors, Ataxia Telangiectasia and Rad3-related (ATR) inhibitors, Poly (ADP-ribose) Polymerase (PARP) inhibitors, DNA-dependent Protein Kinase (DNA-PK) inhibitors, WEE1 protein kinase family inhibitors, Checkpoint Kinase (CHK) inhibitors, DNA Polymerase theta (Polθ) inhibitors, RAD51 recombinase (RAD51) inhibitors, Ubiquitin-Specific Protease 1 (USP1) inhibitors, Polo-Like serine/threonine Kinase 1 (PLK1) inhibitors, Aurora kinase inhibitors, mutant p53

reactivators, Poly(ADP-ribose) Glycohydrolase (PARG) inhibitors, and Werner Syndrome protein (WRN) inhibitors, and combinations thereof. Optionally the DDRi is not olaparib.

In certain embodiments, the combination can have an enhanced therapeutic index as compared with a [^{177}Lu]Lu-PSMA-617 monotherapy or a DDRi monotherapy. In some cases, the therapeutic index of the combination is at least about 10% to about 50% wider than the therapeutic index of the [^{177}Lu]Lu-PSMA-617 monotherapy or the DDRi monotherapy.

In certain embodiments, the DDRi can include at least one DNA-PK inhibitor listed in TABLE **4**, at least one of XRD-0394, SN-39536, BY101298, XZP-6877 and IMP-11, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one ATM inhibitor listed in TABLE **1**, at least one of XRD-0394 and SX-RDS1, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one ATR inhibitor listed in TABLE **2**, at least one of LF0397, IMP-9064, SC0245, and ATRN-119, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one PARP inhibitor listed in TABLE **3**, or a pharmaceutically acceptable salt thereof. Optionally the PARP inhibitor is not olaparib.

In certain embodiments, the DDRi can include at least one WEE1 protein kinase family inhibitor selected from the group consisting of Wee1-like protein kinase inhibitors (WEE1) and Protein Kinase, Membrane Associated Tyrosine/Threonine 1 (PKMYT1) inhibitors.

In certain embodiments, the DDRi can include at least one WEE1 inhibitor listed in TABLE **5**, at least one of SC0191, SY-4835, and IMP7068, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one PKMYT1 inhibitor listed in TABLE **6**, ACR-2316, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one CHK inhibitor selected from the group consisting of CHK1 selective inhibitors, CHK2 selective inhibitors, and CHK1/2 dual inhibitors.

In certain embodiments, the DDRi can include at least one CHK1 selective inhibitor listed in TABLE **7**, VER250840, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one CHK2 selective inhibitor listed in TABLE **8**, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one CHK1/2 dual inhibitor listed in TABLE **9**, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one Polθ inhibitor listed in TABLE **10,** at least one of ART4215, ART6043, RP-3467, and GSK101 (GSK4524101/IDE705) or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one RAD51 inhibitor listed in TABLE **11**, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one USP1 inhibitor listed in TABLE **12**, at least one of TNG348, HSK39775, FT-3171 (Debio 0432), and ISM3091, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one PLK1 inhibitor listed in TABLE **13**, or a pharmaceutically acceptable salt thereof.

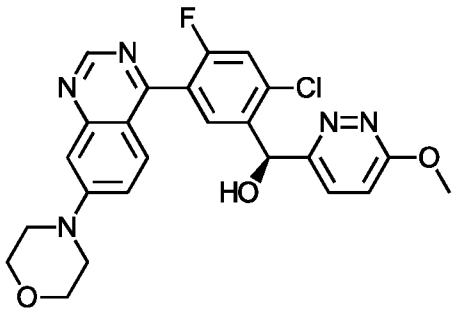
In certain embodiments, the DDRi can include at least one Aurora kinase inhibitor selected from the group consisting of Aurora A inhibitors and Aurora B inhibitors listed in TABLE **14**, WJ05129, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one PARG inhibitor listed in TABLE **16**, IDE161, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi can include at least one WRN inhibitor listed in TABLE **17**, RO7589831, HRO761, or a pharmaceutically acceptable salt thereof.

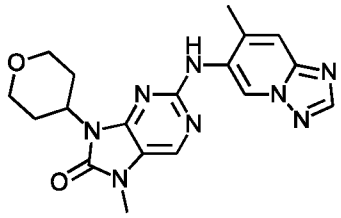
In certain embodiments, the DDRi can include at least one mutant p53 reactivator listed in TABLE **15**, PC14586, or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure provides a method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:

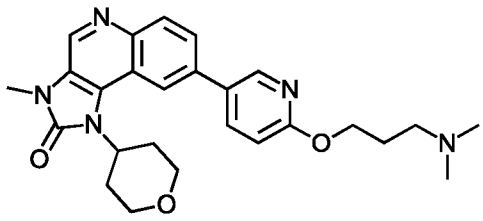


((S)-[2-chloro-4-fluoro-5-(7-morpholin-4-ylquinazolin-4-yl)phenyl]-(6-methoxypyridazin-3-yl)methanol (M3814)), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi. In some cases, the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 is a dose of about 10 MBq to 10 GBq, such as about 100 MBq to about 10 GBq, about 1 GBq to about 10 GBq, about 3 GBq to about 10 GBq, about 5

GBq to about 9 GBq, about 6 GBq to about 8 GBq. or about 7.4 GBq, and the therapeutically effective amount of the DDRi is a dose of about 1 to 1000 mg/kg, about 10 to 900 mg/kg, about 15 to 800 mg/kg, about 20 to 700 mg/kg, about 25 to 600 mg/kg, about 30 mg to 500 mg/kg, about 35 to 400 mg/kg, about 40 to 300 mg/kg, about 45 to 200 mg/kg, about 50 to 100 mg/kg, optionally about 100 mg/kg, administered twice daily for about 5 days, or about 50 mg, about 100 mg, about 150 mg, or about 250 mg, and the initial dose of the DDRi is administered less than 1 hour prior to [^{177}Lu]Lu-PSMA-617 administration.

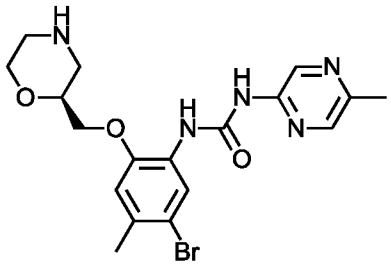
In another aspect, the present disclosure provides a method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is  ((7-Methyl-2-[(7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino]-9-(oxan-4-yl)purin-8-one (AZD7648)), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi. In some cases, the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 is a dose of from about 10 mBq to 10 GBq, such as from about 100 MBq to about 10 GBq, about 1 GBq to about 10 GBq, about 3 GBq to about 10 GBq, about 5 GBq to about 9 GBq, or about 6 GBq to about 8 GBq, and optionally about 7.4 GBq, and the therapeutically effective amount of the DDRi is a dose of from about 1 to 1000 mg/kg, about 10 to 900 mg/kg, about 15 to 800 mg/kg, about 20 to 700 mg/kg, about 25 to 600 mg/kg, about 30 mg to 500 mg/kg, about 35 to 400 mg/kg, about 40 to 300 mg/kg, about 45 to 200 mg/kg, or about 50 to 100 mg/kg, optionally about 100 mg/kg, administered once daily for about 5 days, and the initial dose of the DDRi is administered less than 1 hour prior to [^{177}Lu]Lu-PSMA-617 administration.

In another aspect, the present disclosure provides a method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:



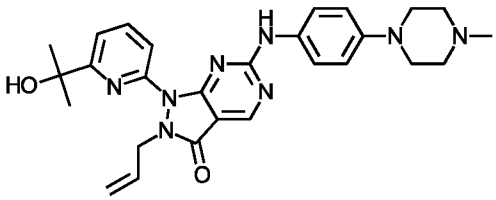
(8-[6-[3-(dimethylamino)propoxy]pyridin-3-yl]-3-methyl-1-(oxan-4-yl)imidazo[4,5-c]quinolin-2-one (AZD0156)), or pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

In another aspect, the present disclosure provides a method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:



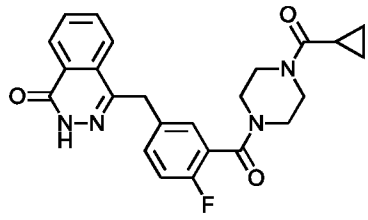
(1-[5-bromo-4-methyl-2-[[(2S)-morpholin-2-yl]methoxy]phenyl]-3-(5-methylpyrazin-2-yl)urea (LY2603618, Rabusertib)) or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is improved or synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

In another aspect, the present disclosure provides a method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:



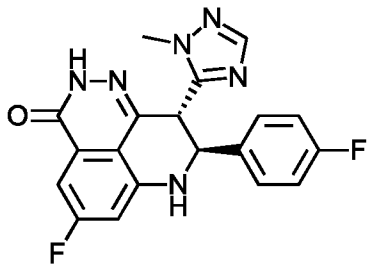
(1-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]-6-[4-(4-methylpiperazin-1-yl)anilino]-2-prop-2-enylpyrazolo[3,4-d]pyrimidin-3-one (Adavosertib or MK-1775), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is improved or synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

In another aspect, the present disclosure provides a method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA



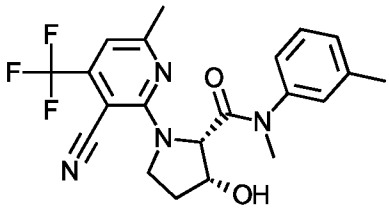
Damage Response inhibitor (DDRi), wherein the DDRi is: 4-[[3-[4-(cyclopropanecarbonyl)piperazine-1-carbonyl]-4-fluorophenyl]methyl]-2*H*-phthalazin-1-one (olaparib), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi, optionally wherein the DDRi is administered within 24 hours of administration of [^{177}Lu]Lu-PSMA-617 and/or the DDRi is administered within 24 hours of administration and over a course of at least 48 hours.

In another aspect, the present disclosure provides a method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:



((11S,12R)-7-fluoro-11-(4-fluorophenyl)-12-(2-methyl-1,2,4-triazol-3-yl)-2,3,10-triazatricyclo[7.3.1.0^{5,13}]trideca-1,5(13),6,8-tetraen-4-one (talazoparib), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

In another aspect, the present disclosure provides a method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:



((2*S*,3*R*)-1-[3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl]-3-hydroxy-*N*-methyl-N-(3-methylphenyl)pyrrolidine-2-carboxamide (ART558), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

In another aspect, the present disclosure provides a method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is ART6043, or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

In another aspect, the present disclosure provides a method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is ART0380 or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts the time course for γH2AX and 53BP1 induction in DLD-1 cells with 2.5 MBq/ml 177Lu-DOTA.

FIG. 2 depicts induction of DDR markers in DLD-1 cells treated with increasing activities of 177Lu-DOTA.

FIG. 3 depicts quantification of the induction of representative DDR markers in LNCaP cells treated for 4h with 177Lu-PSMA-617.

FIGs. 4A-B depict results of viability assays showing induced sensitization to 177Lu-DOTA and 177Lu-PSMA-617 with loss of PRKDC. (A) HCT-116 (PSMA negative) and (B) DU-145 PSMA high (engineered to express high levels of PSMA) were treated with 177Lu-DOTA for 8 days, or 177Lu-PSMA-617 for 24 h, respectively. Viability as measured after 8 days incubation. X-axis represents the activity of 177Lu-DOTA (A) or 177Lu-PSMA-617 (B) (in

MBq/mL), y-axis represents relative viability normalized for vehicle. Solid lines represent cells expressing PRKDC, while dashed lines indicate cells with knockout of PRKDC.

FIG. 5 depicts viability curves from 8-day viability assay in a panel of cell lines treated continuously with 177Lu-DOTA (EC_{50} values provided in TABLE **23**).

FIGs. 6A-C depict the time-course analysis of DU145 PSMA high cells treated with increasing activities of 177Lu-PSMA-617 for 24h. (A) Analysis of the percentage of confluency. (B) Cytotoxicity and (C) apoptosis analysis, using the Cytotox or the Caspase 3/7 dye, respectively. Assay run with IncuCyte**.**

FIG. 7 shows a graphical representation of the 177Lu mode of action.

FIGs. 8A-C depict results from viability assays in isogenic models of (A) homologous recombination (HR) deficiency; (B) non-homologous end joining (NHEJ) deficiency, or (C) combination of a DNA-PK inhibitor (AZD7648) with 177Lu-DOTA.

FIGs. 9A-D depict results of genetic screening to identify radioligand therapy sensitizers. (A) is an illustration of the experimental outline; (B, C, D) provide representative volcano plots of the sensitizers identified by CRISPR/Cas9 KO screen in 3 cell lines.

FIGs. 10A-B depict the results of continuous treatment with the indicated compounds in the presence (dashed line) or absence (solid line) of 177Lu-DOTA for 8 days, after which viability was measured in the indicated cells (A) PARP, ATM, CHK1 and WEE1 inhibitors and (B) Polθ and ATR inhibitors. The x-axis represents the concentration of each compound and the y-axis represents the relative viability normalized either for vehicle (solid line) or for 177Lu-DOTA alone (dashed line).

FIGs. 11A-F depict the results of the combination of DNA-PK inhibitor, AZD7648 and 177Lu-DOTA in a panel of cancer cell lines. The cell lines were treated with 177Lu-DOTA alone (solid line) or in combination with 1μM of DNA-PK inhibitor (dashed lines) for 8 days until the viability assay endpoint readout. X axis represents the activity of 177Lu-DOTA (in MBq/mL), Y axis the relative viability normalized for vehicle.

FIGs. 12A-D depict the results of the combination of 177Lu-PSMA-617 with indicated DDRi in PSMA-expressing cell lines. (A, B, and C) LNCaP cells were treated with 177Lu-PSMA-617 alone (solid lines) for 24h alone or in combination with an ATR inhibitor and Polθ inhibitors (dashed lines) for 8 days, until the viability assay endpoint readout, and PSMA-expressing DU 145 engineered cells (D) were treated with 177Lu-PSMA-617 alone (solid lines) for 24h or in combination with ATM inhibitor (dashed lines) for 8 days, until the viability assay endpoint readout. The x-axis represents the concentration of 177Lu-PSMA-617 in MBq/ml, while the y-axis represents the relative viability normalized for the vehicle.

FIGs. 13A-G depict results of the combination of DNA-PK inhibitor, AZD7648, and 177Lu-PSMA-617 in cell lines expressing PSMA. DU-145 (A) and PC-3 (D) PSMA negative

cells were engineered to express low (B, E) or high (C, F) levels of PSMA. LNCaP FGC cells (G) express high endogenous levels of PSMA. Cells were treated with 177Lu-PSMA-617 alone (solid lines) or in combination with DNA-PK inhibitor (dashed lines). X-axis represents the activity of 177Lu-PSMA-617 (in MBq/mL), y-axis the relative viability normalized for vehicle (solid line) or DNA-PK inhibitor alone (dashed line). The cells were exposed for 4 h to 177Lu-PSMA-617 and for 8 days to the DNA-PK inhibitor.

FIGs. 14A-F depict results of viability assays showing that the DNA-PK inhibitor, AZD7648, synergizes with 177Lu-PSMA-617 when administered before or concomitantly with 177Lu-PSMA-617. Viability assays were conducted in DU145 PSMA high (A-E) with different schedules of DNA-PK inhibitor administration (as outlined in (F): (A) -24h addition of DNA-PK inhibitor, (B) -1h addition of DNA-PK inhibitor, (C) 0h addition of DNA-PK inhibitor, (D) 4h addition of DNA-PK inhibitor, and (E) 24h addition of DNA-PK inhibitor).

FIGs. 15A-F depict results of viability assays showing that maximal synergy between DNA-PK inhibitor, AZD7648, and 177Lu-PSMA-617 is achieved with a prolonged inhibition DDR. Viability assays were conducted in DU145 PSMA high (A-E) with different schedules of DNA-PK inhibitor administration (as outlined in (F): (A) 4h removal of DNA-PK inhibitor, (B) 16h removal of DNA-PK inhibitor, (C) 24h removal of DNA-PK inhibitor, (D) 48h removal of DNA-PK inhibitor, and (E) continuous DNA-PK inhibitor treatment.

FIG. 16 depicts the normalized quantification of γ-H2AX foci immunofluorescence (top panel) or 53BP1 foci immunofluorescence (bottom panel). Statistical analysis by one-way Anova with Dunnett's post-hoc test (stars over the bar) or 2 tailed T-test (the star above the bracket) comparing the combination with predicted additivity. Solid bars indicate 24h timepoint, dashed bars indicate 96h timepoint.

FIG. 17A-C depict the accumulation of DDR markers and cell cycle alterations: (A) Time-course of γH2AX foci induction in PC-3 MP9 cells treated with 177Lu-PSMA-617 alone (solid bars) or in combination with DNA-PKi (1μM AZD7648 – dashed bars). Induction of micronuclei (B) or cell cycle alterations (C) in DU 145 PSMA high treated for 4h with 177Lu-PSMA-617 alone or in combination with DNA-PKi (1μM AZD7648). Statistical analysis by one-way Anova with Dunnett's post-test vs vehicle treatment at matched timepoint.

FIGs. 18A-B depict the effect of the combination of Polθ inhibitor, ART6043, with 177Lu-PSMA-617 *in vivo*. (A) Body weight over time (mean ± SEM). (B) Survival curves of the 4 experimental groups. Mice were terminated when tumor volumes reached over 1500 mm^3. Statistics by Log-Rank test.

FIG. 19 depicts the biodistribution of [^{177}Lu]Lu-PSMA-617 alone or in combination with two DDRi compounds of the present disclosure in PC3 FOLH1 MP9 PSMA high tumors at 4h and 24h (p.i.).

FIGs. 20A-D depict the experimental protocol and effect of [^{177}Lu]Lu-PSMA-617 alone or in combination with two DDRi of the present disclosure in PC3 FOLH1 MP9 PSMA tumor bearing female nude mice: (A) is a schematic representation of the protocol; (B) and (C) show the effect of [^{177}Lu]Lu-PSMA-617 alone or in combination with a DDRi (AZD7648); and (D) show the effect of [^{177}Lu]Lu-PSMA-617 alone or in combination with a DDRi (M3814).

DETAILED DESCRIPTION

PSMA is a transmembrane glycoprotein of about 100 kDA with folate hydrolase, carboxypeptidase, and internalization activities that exhibits low expression in normal prostate tissue, kidneys, duodenum, salivary and lacrimal glands, brain, and intestines. Increased PSMA expression is significantly associated with the degree of differentiation and progression of mCRPC. Accordingly, PSMA-targeting ligands may selectively accumulate in malignant cells, allowing development opportunities for imaging and treating mCRPC. The systemic administration of PSMA-targeted RLT allows the simultaneous treatment of wide-spread bone and extraskeletal metastases, thereby limiting radiotoxicity to healthy tissues.

Radioligand therapy (RLT) is emerging as a safe and effective targeted approach for treating several types of cancers. Pluvicto® ([^{177}Lu]Lu-PSMA-617) is one examples of an FDA-approved ^{177}Lu-based RLT drug for the treatment of PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). Despite the clinical success of ^{177}Lu-RLT, a subset of patients do not achieve a complete, durable response. Thus, there is an opportunity for improving patient therapy.

In an aspect, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi).

In an aspect, the present disclosure provides combinations of [177Lu]Lu-PSMA-617 and a DNA Damage Response inhibitor (DDRi) for use in the treatment of a PSMA-expressing cancer. The treatment can include administering the DDRi within 24 hours of [^{177}Lu]Lu-PSMA-617 administration, administering the DDRi in one or more doses for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration, and/or administering the DDRi over a course of about or at least about 5 days.

The therapeutically effective amount of [^{177}Lu]Lu-PSMA-617, the DDRi, or both in the combination can be lower than the amount required for a monotherapy response for [^{177}Lu]Lu-PSMA-617 and/or the DDRi. The amount required can be based upon the amount of ^{177}Lu]Lu-PSMA-617 and/or the DDRi alone that achieves a predetermined objective response rate (ORR), disease control rate (DCR), progression free survival (PFS), duration of response

(DOR), overall survival (OS), complete response (CR), partial response (PR), PSA response rate, radiographic response rate, change from baseline in blood and tumor tissue microenvironment pharmacodynamic (PD) biomarkers, or a combination thereof, or an improvement one or more of these responses as compared to the monotherapy response.

Combinations of [177Lu]Lu-PSMA-617 and a DNA Damage Response inhibitor (DDRi) for use in the treatment of a PSMA-expressing cancer can have a wider therapeutic index for use in the treatment of a PSMA-expressing cancer than [177Lu]Lu-PSMA-617 monotherapy and/or DDRi monotherapy.

Use of the combination can provide a synergistic effect in the treatment of the PSMA-expressing cancer. For example, one or more anti-cancer effects of the DDRi can be synergized by combination with [^{177}Lu]Lu-PSMA-617 or one or more anti-cancer effects of [^{177}Lu]Lu-PSMA-617 can be synergized by combination with the DDRi.

The details of the disclosure are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, illustrative methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

Definitions

Unless specific definitions are provided, the nomenclature used in connection with, and the procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art. Standard techniques may be used for chemical synthesis, and chemical analysis. Certain such techniques and procedures may be found for example in “Remington's Pharmaceutical Sciences,” Mack Publishing Co., Easton, Pa., 21st edition, 2005, which is hereby incorporated by reference for any purpose. Where permitted, all patents, applications, published applications and other publications and other data referred to throughout in the disclosure are incorporated by reference herein in their entirety.

The term “radiopharmaceutical” is used herein to refer to pharmaceutical compounds, *e.g.*, peptides, oligonucleotides, small molecules, and antibodies, that are radiolabeled with a radionuclide. A radiopharmaceutical may be a radioligand. In some embodiments,

radiopharmaceutical refers to [^{177}Lu]Lu-PSMA-617, i.e., ^{177}Lu-Labeled PSMA-617. In other embodiments, radiopharmaceutical refers to a radiolabeled compound known in the art.

As used herein, the term "target binding organic moiety" refers to an organic moiety which has specific binding affinity to a target protein, typically a cell surface receptor or cellular protein. In specific embodiments, said target binding receptor moiety is an organic moiety which has specific binding affinity to prostate specific membrane antigen (PSMA).

As used herein, the term "chelating moiety" refers to an organic moiety comprising functional groups that form non-covalent bonds with a radionuclide during the reacting step of the method and, thereby, form a stable radionuclide complex. The chelating moiety in the context of the present invention may be or may comprise 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), which is directly linked to the target binding organic moiety via covalent bonding.

The term "radiolabeled" (or "chelated," or "complexed") as used herein means that a non-radioactive compound is labeled with a radioisotope. Radiolabeling can be achieved, *e.g.*, via chelation or complexation of a chelator with an appropriate radionuclide. Radiolabeling can also refer to chemically substituting one group on a compound for a radionuclide, such as, *e.g.*, in the case of ^{18}F.

Furthermore, it is intended that within the scope of the present invention, any element, in particular when mentioned in relation to a compound of the disclosure, shall comprise all isotopes and isotopic mixtures of said element, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. For example, a reference to hydrogen includes within its scope ^{1}H, ^{2}H (*i.e.*, deuterium or D), and ^{3}H (*i.e.*, tritium or T). In some embodiments, the compounds described herein include a ^{2}H (*i.e.*, deuterium) isotope. By way of example, the group denoted -$C_{(1\text{-}6)}$alkyl includes not only -CH_3, but also CD_3; not only CH_2CH_3, but also CD_2CD_3, *etc.* Similarly, references to carbon and oxygen include within their scope respectively ^{12}C, ^{13}C and ^{14}C and ^{15}O and ^{16}O and ^{17}O and ^{18}O. The isotopes may be radioactive or non-radioactive. Radiolabelled compounds of the disclosure may include a radioactive isotope selected from the group comprising ^{3}H, ^{11}C, ^{18}F, ^{35}S, ^{122}I, ^{123}I, ^{125}I, ^{131}I, ^{75}Br, ^{76}Br, ^{77}Br and ^{82}Br. In some embodiments, the radioactive isotope is selected from the group of ^{3}H, ^{11}C and ^{18}F.

As used herein, the term "reaction solution" refers to a solution comprising ions of a radionuclide, a target binding organic molecule which is suitable for chelating the radionuclide ions, and one or more stabilizers against radiolytic degradation. The target binding organic molecule comprises a target binding organic moiety linked directly or indirectly to a chelating moiety.

As used herein, the term “stabilizer against radiolytic degradation” refers to a stabilizing agent which protects organic molecules against radiolytic degradation, e.g. when a gamma ray emitted from the radionuclide is cleaving a bond between the atoms of an organic molecules and radicals are forms, those radicals are then scavenged by the stabilizer which avoids the radicals undergo any other chemical reactions which might lead to undesired, potentially ineffective or even toxic molecules. Therefore, those stabilizers are also referred to as “free radical scavengers” or in short “radical scavengers”. Other alternative terms for those stabilizers are “radiation stability enhancers”, “radiolytic stabilizers”, or simply “quenchers”.

As used herein, “sequestering agent” refers to a chelating agent suitable to complex free radionuclide metal ions in the formulation (which are not complexed with the radiolabeled peptide).

As used herein, the term “mother solution” refers to a solution which is obtained when the aforesaid reaction solution has finished reacting forming radionuclide complexes, has been processed as described further below (if applicable) and has been mixed and diluted with water for injection (WFI) (if applicable).

As used herein, the term “dispensing solution” refers to a solution which is obtained when the aforesaid mother solution has been additionally mixed with a dilution solution. The dispensing solution comprises all the components and an activity that is suitable for patient administration. The dispensing solution is the solution that is dispensed into multiple patient doses (vials), which are destined for subsequent administration to a patient without further material change.

The term “DNA Damage Response inhibitor” or “DDRi” as used herein refers to a compound capable of blocking cellular surveillance and signaling network that responds to DNA damage and maintains the stability of the genome by one or more of: (1) sensing and identifying DNA damage; (2) recruiting repair machinery; (3) halting the cell cycle to provide an opportunity for repair; (4) activating programmed cell death or deactivating cellular replication; and (5) repairing DNA damage. Exemplary DDRi compounds include, but are not limited to, Ataxia-Telangiectasia Mutated (ATM) inhibitors, Ataxia Telangiectasia and Rad3-related (ATR) inhibitors, Poly (ADP-ribose) Polymerase (PARP) inhibitors, DNA-dependent Protein Kinase (DNA-PK) inhibitors, WEE1 protein kinase family inhibitors, Checkpoint Kinase (CHK) inhibitors, DNA polymerase theta (Polθ) inhibitors, RAD51 recombinase (RAD51) inhibitors, Ubiquitin-Specific Protease 1 (USP1) inhibitors, Polo-Like serine/threonine Kinase 1 (PLK1) inhibitors, Aurora kinase inhibitors, mutant p53 reactivators, Poly(ADP-ribose) Glycohydrolase (PARG) inhibitors, and Werner Syndrome protein (WRN) inhibitors.

The phrase “pharmaceutically acceptable” as employed herein refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of

sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, the term "treat," "treatment," or "treating" means decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disorder or disease.

As used herein, the term "prevent" or "prevention" means no disorder or disease development if none had occurred, or no further disorder or disease development if there had already been development of the disorder or disease. Also considered is the ability of one to prevent some or all of the symptoms associated with the disorder or disease.

As used herein, the term "synergistic effect" refers to the action of two therapeutic agents such as, for example, [^{177}Lu]Lu-PSMA-617 and a DDRi, producing an effect, which is greater than the simple addition of the effects of each compound administered as a monotherapy. A synergistic effect can be calculated, for example, using suitable methods such as the Sigmoid-Emax equation (Holford, N. H. G. and Scheiner, L. B., Clin. Pharmacokinet. 6: 429-453 (1981)), the equation of Loewe additivity (Loewe, S. and Muischnek, H., Arch. Exp. Pathol Pharmacol. 114: 313-326 (1926)) and the median-effect equation (Chou, T. C. and Talalay, P., Adv. Enzyme Regul. 22: 27-55 (1984)).

The terms "administer," "administering," and "administration" refer to the giving of a compound disclosed herein, or another indicated compound, to a patient by any appropriate route. In particular, the compounds disclosed herein may be administered by oral or parenteral route, such as via a parenteral route by injection or infusion, wherein the injection or infusion may be made intravenously, intramuscularly, intra-arterially, subcutaneously, intra-dermally, intraperitoneally, etc. Depending on the administration route, the compounds of the present disclosure can be administered in a pharmaceutical composition that further comprises appropriate constituents, such as carriers, solvents, and excipients generally known in the art.

The term "pharmaceutical composition" is defined herein to refer to a mixture (*e.g.*, a solution or an emulsion) containing at least one active ingredient or therapeutic agent to be administered to a subject, *e.g.*, a human, in order to prevent or treat a particular disease or condition affecting the subject.

As used herein, the term "carrier" or "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences,

18th Ed. Mack Printing Company, 1990, pp. 1289-1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous, intradermal and intraarticular injection and infusion.

Unless otherwise specified, conventional definitions of terms control and conventional stable atom valences are presumed and achieved in all formulas and groups.

As used herein, the term "about" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which it is used. As used herein when referring to a measurable value such as an amount, a temporal duration, and the like, the term "about" is meant to encompass variations of ±10%, including ±5%, ±1%, and ±0.1% from the specified value, as such variations are appropriate to perform the disclosed methods, and when a numerical value or range is preceded by "about", the "about" indicates a deviation of the value or range by ± 20%, ± 10%, or ± 5%, unless a specific deviation is described. In some contexts, the deviation indicated by "about" can be ± 2% or ± 1%.

The articles "a" and "an" are used in this disclosure to refer to one or more than one (*e.g.,* to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

Compounds

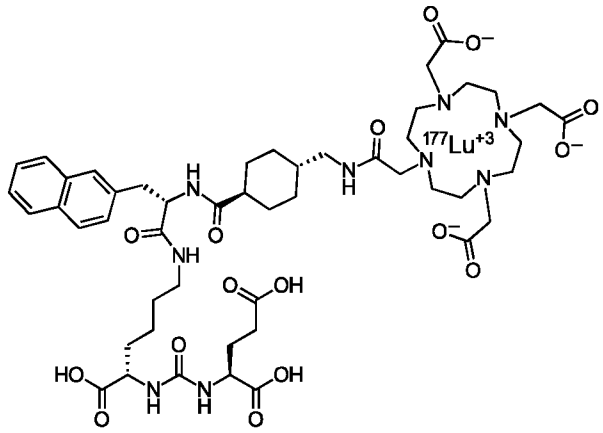
The present disclosure provides therapeutic combinations for the treatment or prevention of PSMA-expressing cancers including [177Lu]Lu-PSMA-617 and a DNA Damage Response inhibitor (DDRi).

[^{177}Lu]Lu-PSMA-617

[^{177}Lu]Lu-PSMA-617 is available under the drug product name PLUVICTO ([INN] lutetium (^{177}Lu) vipivotide tetraxetan). Methods to produce [^{177}Lu]Lu-PSMA-617 are described in WO2023/148680 A1, published on 10 August 2023, and following the methods as disclosed in WO 2020/089379 A1, published on 7 May 2020, US 2020/131224 A1, published on 30 April 2020, US 2021/0316019 A1, published on 14 October 2021, US 2022/0041649 A1, published on 10 February 2022. The content of those patent application publications are incorporated herein by reference in their entireties.

Throughout the entire present disclosure, [^{177}Lu]Lu-PSMA-617 may be also referred to as Lutetium (^{177}Lu) vipivotide tetraxetan, Lutetium (^{177}Lu) vipivotide tetraxetan [INN] or Lutetium Lu 177 vipivotide teraxetan [USAN], PLUVICTO, or 2- [4-[2-[[4-[[(2 S)-1-[[(5 S)-5-carboxy-5-[[(1 S)- 1,3-dicarboxy-propyl]car ɔ]pentyl]amino]-3-naphthalen-2-y1-1-

oxopropan-2-yl] carbamoyl] cyclohexyl]methylamino]-2-oxoethy1]-4,7,10-tris(carboxylatomethyl)-1,4,7,10-tetraza cyclododec-1-yl]acetate; lutetium-177(3+). The molecular mass is 1216.06 g/mol and the molecular formula is $C_{49}H_{68}{}^{177}LuN_9O_{16}$. The chemical structure for [^{177}Lu]Lu-PSMA-617 is shown below:

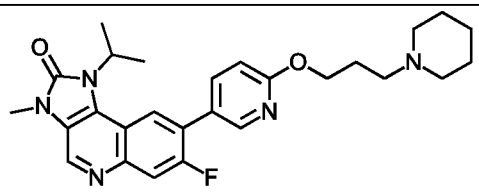
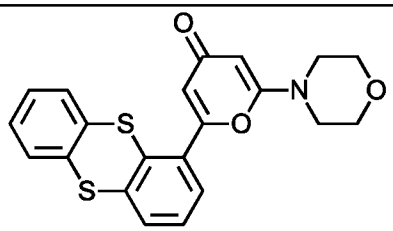


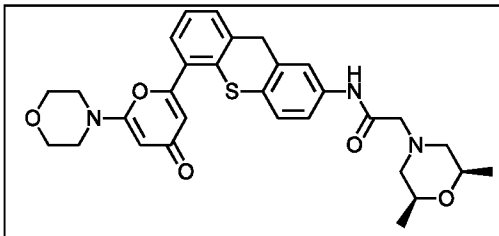
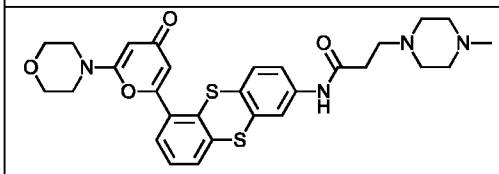
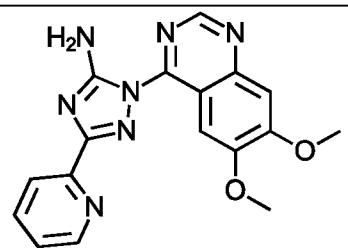
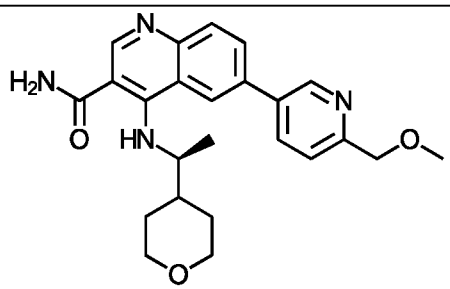
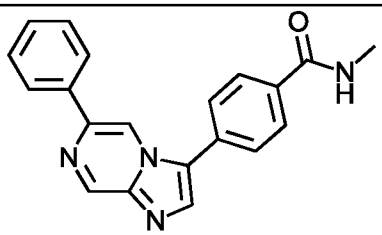
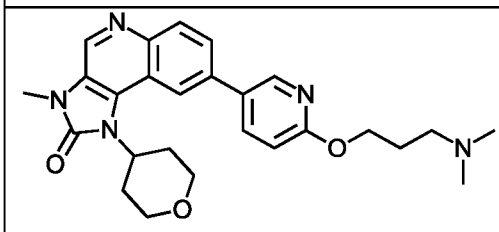
Methods of making and using [^{177}Lu]Lu-PSMA-617 can also be found, for example, in the Examples of the instant application, see, *e.g.*, Examples 1-3.

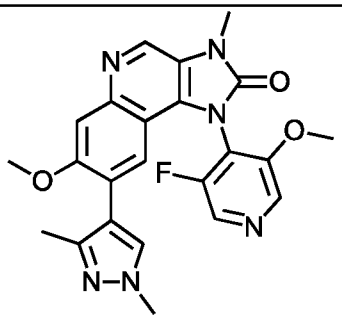
DDRi

In certain embodiments, the DDRi of the therapeutic combination is selected from the group of Ataxia-Telangiectasia Mutated (ATM) inhibitors listed in TABLE **1**, or a pharmaceutically acceptable salt thereof:

TABLE 1: Ataxia-Telangiectasia Mutated (ATM) inhibitors (ATMi)

ATMi CHEMICAL STRUCTURE	IUPAC NAME	ALTERNATIVE NAME(S)
	7-fluoro-3-methyl-8-[6-(3-piperidin-1-ylpropoxy)pyridin-3-yl]-1-propan-2-ylimidazo[4,5-c]quinolin-2-one	AZD1390 developed by AstraZeneca
	2-morpholin-4-yl-6-thianthren-1-ylpyran-4-one	KU-55933 developed by KuDOS Pharmaceuticals Ltd.

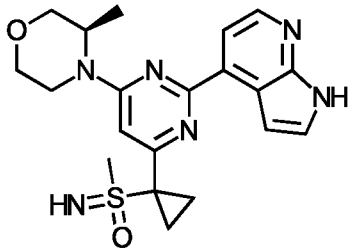
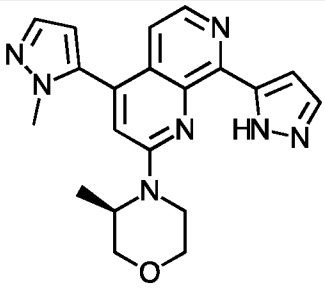
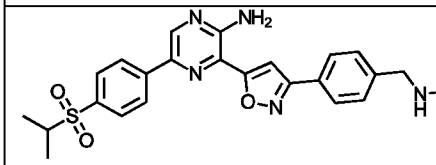
	2-[(2*S*,6*R*)-2,6-dimethylmorpholin-4-yl]-*N*-[5-(6-morpholin-4-yl-4-oxopyran-2-yl)-9*H*-thioxanthen-2-yl]acetamide	KU-60019 developed by KuDOS Pharmaceuticals Ltd.
	3-(4-methylpiperazin-1-yl)-N-[6-(6-morpholin-4-yl-4-oxopyran-2-yl)thianthren-2-yl]propanamide	KU-59403 developed by KuDOS Pharmaceuticals Ltd.
	2-(6,7-dimethoxyquinazolin-4-yl)-5-pyridin-2-yl-1,2,4-triazol-3-amine	CP-466722, developed by Pfizer
	6-[6-(methoxymethyl)pyridin-3-yl]-4-[[(1S)-1-(oxan-4-yl)ethyl]amino]quinoline-3-carboxamide	AZ31 developed by AstraZeneca
	N-methyl-4-(6-phenylimidazo[1,2-a]pyrazin-3-yl)benzamide	AZ32 developed by AstraZeneca
	8-[6-[3-(dimethylamino)propoxy]pyridin-3-yl]-3-methyl-1-(oxan-4-yl)imidazo[4,5-c]quinolin-2-one	AZD0156 developed by AstraZeneca

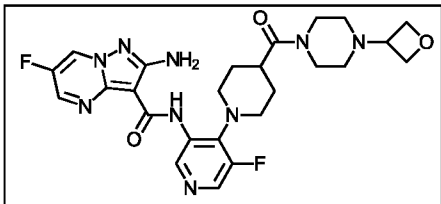
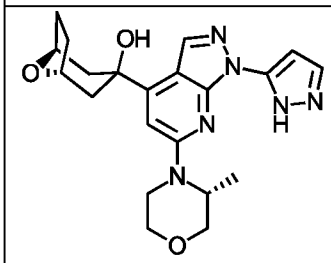
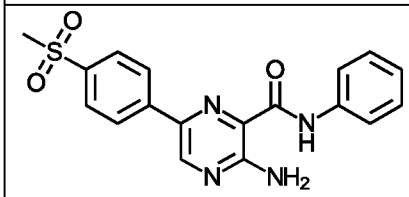
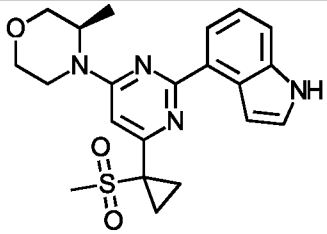
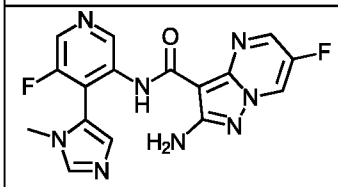
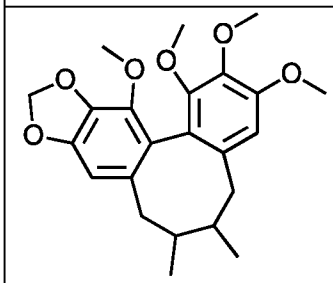
	8-(1,3-dimethylpyrazol-4-yl)-1-(3-fluoro-5-methoxypyridin-4-yl)-7-methoxy-3-methylimidazo[4,5-c]quinolin-2-one	Lartesertib (M4076) developed by Merck

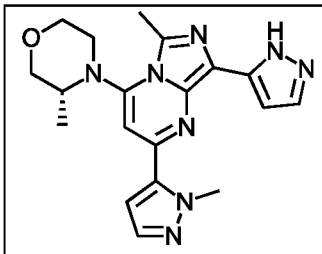
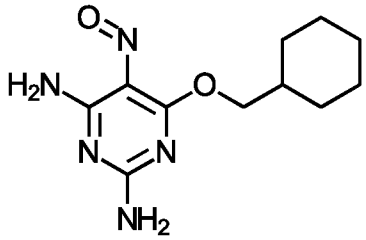
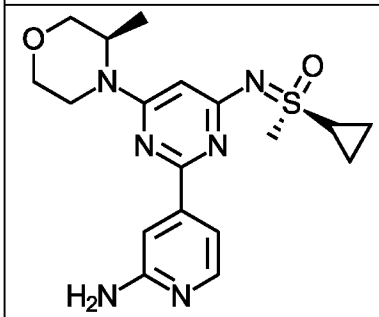
In addition to the ATM inhibitors listed above, the group of ATM inhibitors can include one or more of XRD-0394 under development by XRad Therapeutics Inc, and SX-RDS1 initially developed by Serometrix LLC, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi is selected from the group of Ataxia Telangiectasia and Rad3-related (ATR) inhibitors listed in TABLE **2**, or a pharmaceutically acceptable salt thereof:

TABLE 2: Ataxia Telangiectasia and Rad3-related inhibitors (ATRi)

ATRi CHEMICAL STRUCTURE	IUPAC NAME	ALTERNATIVE NAME(S)
	imino-methyl-[1-[6-[(3R)-3-methylmorpholin-4-yl]-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)pyrimidin-4-yl]cyclopropyl]-oxo-λ6-sulfane	ceralasertib (AZD6738) developed by AstraZeneca
	(3R)-3-methyl-4-[4-(2-methylpyrazol-3-yl)-8-(1H-pyrazol-5-yl)-1,7-naphthyridin-2-yl]morpholine	elimusertib (BAY-1895344) developed by Bayer
	3-[3-[4-(methylaminomethyl)phenyl]-1,2-oxazol-5-yl]-5-(4-propan-2-ylsulfonylphenyl)pyrazin-2-amine	berzosertib (M6620, VX-970, VE-822) under development by Merck

	2-amino-6-fluoro-N-[5-fluoro-4-[4-[4-(oxetan-3-yl)piperazine-1-carbonyl]piperidin-1-yl]pyridin-3-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide	gartisertib (M4344, VX-803) under development by Merck
	(1*R*,5*S*)-3-[6-[(3*R*)-3-methylmorpholin-4-yl]-1-(1*H*-pyrazol-5-yl)pyrazolo[3,4-b]pyridin-4-yl]-8-oxabicyclo[3.2.1]octan-3-ol	Camonsertib (RP-3500) developed by Roche Pharma AG
	3-amino-6-(4-methylsulfonylphenyl)-*N*-phenylpyrazine-2-carboxamide	VE-821 developed by Vertex Pharmaceuticals
	(3R)-4-[2-(1H-indol-4-yl)-6-(1-methylsulfonylcyclopropyl)pyrimidin-4-yl]-3-methylmorpholine	AZ20 developed by AstraZeneca
	2-amino-6-fluoro-N-[5-fluoro-4-(3-methylimidazol-4-yl)pyridin-3-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide	tuvusertib (M1774) developed by Merck
	3,4,5,19-tetramethoxy-9,10-dimethyl-15,17-dioxatetracyclo[10.7.0.0^{2,7}.0^{14,18}]nonadeca-1(19),2,4,6,12,14(18)-hexaene	Schisandrin B (Sch B) isolated from *Schisandrae fructus*

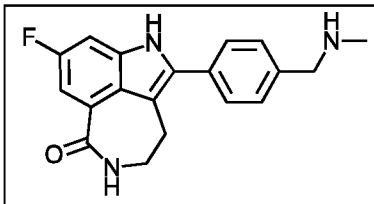
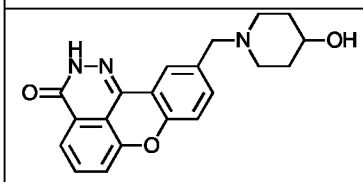
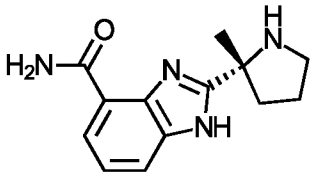
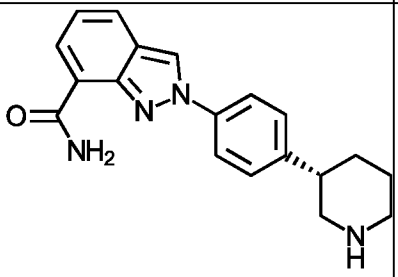
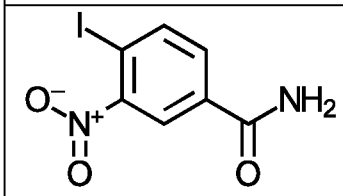
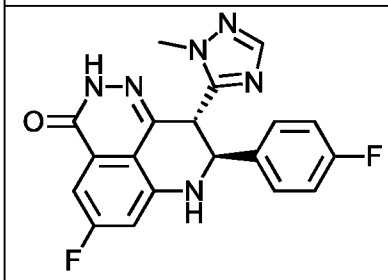
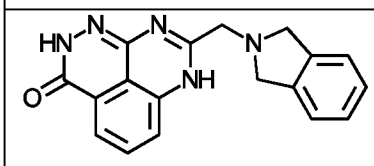
	(3*R*)-3-methyl-4-[6-methyl-2-(2-methylpyrazol-3-yl)-8-(1*H*-pyrazol-5-yl)imidazo[1,5-a]pyrimidin-4-yl]morpholine	ATR-IN-15 developed by Jiangsu Hengrui Medicine Co.
	6-(cyclohexylmethoxy)-5-nitrosopyrimidine-2,4-diamine	NU6027 developed by Newcastle University
	(S)-((2-(2-aminopyridin-4-yl)-6-((R)-3-methyl-morpholino)pyrimidin-4-yl)imino)(cyclopropyl)(methyl)-λ^6 -sulfanone	ART0380 developed by Artios Pharma Ltd

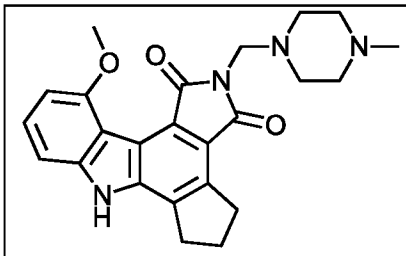
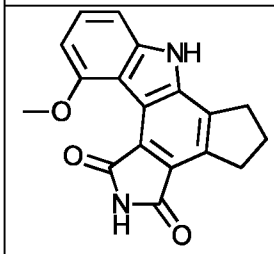
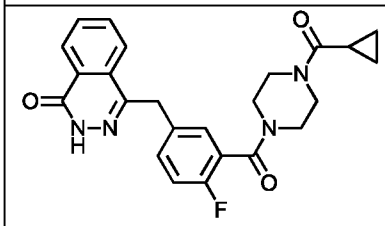
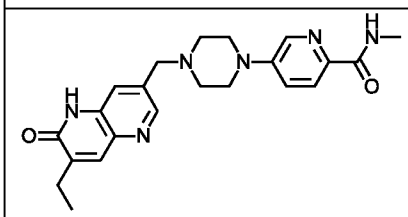
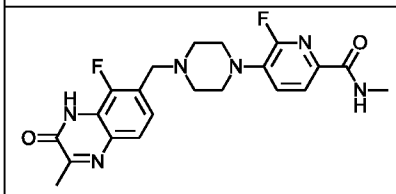
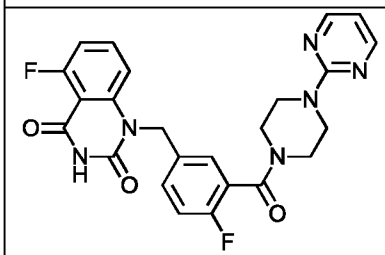
In addition to the ATR inhibitors listed above, the group of ATR inhibitors can include one or more of LF0397 under development by Shenzhen Lingfang Biomedical Technology Co., Ltd., IMP-9064 under development by IMPACT Therapeutics, Inc., SC0245 under development by Shijiazhuang Zhikang Hongren New Drug Development Co., Ltd., and ATRN-119 under development by Aprea Therapeutics, or a pharmaceutically acceptable salt thereof.

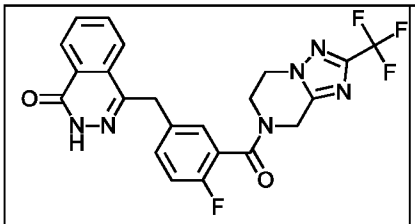
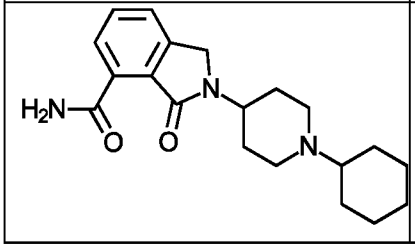
In certain embodiments, the DDRi is selected from the group of Poly (ADP-ribose) Polymerase (PARP) inhibitors listed in TABLE **3**, or a pharmaceutically acceptable salt thereof:

TABLE 3: Poly (ADP-ribose) Polymerase inhibitors (PARPi)

PARPi CHEMICAL STRUCTURE	IUPAC NAME	ALTERNATIVE NAME(S)

	6-fluoro-2-[4-(methylaminomethyl)phenyl]-3,10-diazatricyclo[6.4.1.0^{4,13}]trideca-1,4,6,8(13)-tetraen-9-one	rucaparib (PF-01367338), developed by Pharma& GmbH
	4-[(4-hydroxypiperidin-1-yl)methyl]-8-oxa-15,16-diazatetracyclo[7.7.1.0^{2,7}.0^{13,17}]heptadeca-1(16),2(7),3,5,9,11,13(17)-heptaen-14-one	E7016, developed by Eisai Inc.
	2-[(2*R*)-2-methylpyrrolidin-2-yl]-1*H*-benzimidazole-4-carboxamide	veliparib (ABT-888), developed by AbbVie
	2-[4-[(3*S*)-piperidin-3-yl]phenyl]indazole-7-carboxamide	niraparib (ZL-2306), developed by GSK
	4-iodo-3-nitrobenzamide	iniparib (BSI-201), developed by Sanofi
	(11*S*,12*R*)-7-fluoro-11-(4-fluorophenyl)-12-(2-methyl-1,2,4-triazol-3-yl)-2,3,10-triazatricyclo[7.3.1.0^{5,13}]trideca-1,5(13),6,8-tetraen-4-one,	talazoparib (BMN 673), developed by Pfizer
	11-(1,3-dihydroisoindol-2-ylmethyl)-2,3,10,12-tetrazatricyclo[7.3.1.0^{5,13}]trideca-1,5(13),6,8,11-pentaen-4-one	stenoparib (2X-121, E7449), developed by Allarity Therapeutics, Inc.

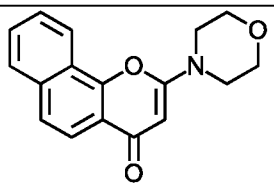
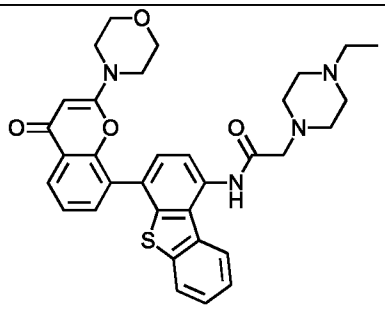
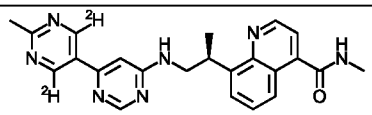
	14-methoxy-9-[(4-methylpiperazin-1-yl)methyl]-9,19-diazapentacyclo[10.7.0.0^{2,6}.07,11.0^{13,18}]nonadeca-1(12),2(6),7(11),13(18),14,16-hexaene-8,10-dione	CEP-9722, developed by Cephalon
	14-methoxy-9,19-diazapentacyclo[10.7.0.0^{2,6}.07,11.0^{13,18}]nonadeca-1(12),2(6),7(11),13(18),14,16-hexaene-8,10-dione	CEP-8983 (CK-102) (the Active Moiety of CEP-9722)
	4-[[3-[4-(cyclopropanecarbonyl)piperazine-1-carbonyl]-4-fluorophenyl]methyl]-2*H*-phthalazin-1-one	olaparib (KU-0059436, AZD2281) developed by KuDOS Pharmaceuticals
	5-[4-[(7-ethyl-6-oxo-5*H*-1,5-naphthyridin-3-yl)methyl]piperazin-1-yl]-*N*-methylpyridine-2-carboxamide	saruparib (AZD5305), developed by AstraZeneca
	6-fluoro-5-[4-[(5-fluoro-2-methyl-3-oxo-4*H*-quinoxalin-6-yl)methyl]piperazin-1-yl]-*N*-methylpyridine-2-carboxamide	AZD9574, developed by AstraZeneca
	5-fluoro-1-[[4-fluoro-3-(4-pyrimidin-2-ylpiperazine-1-carbonyl)phenyl]methyl]quinazoline-2,4-dione	Senaparib (IMP4297), developed by IMPACT Therapeutics, Inc.

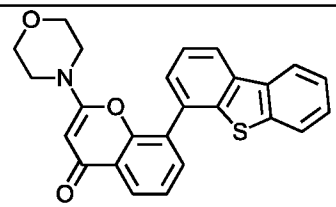
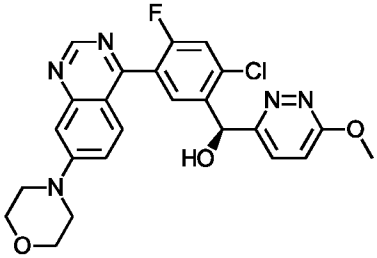
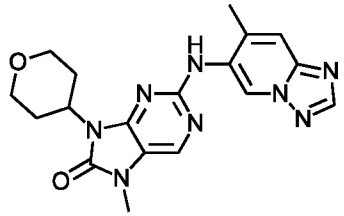
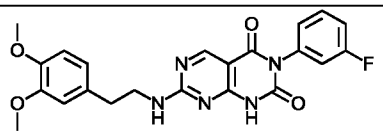
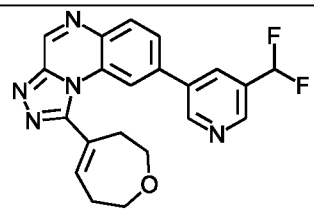
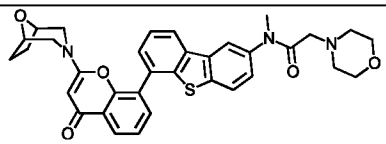
	4-[[4-fluoro-3-[2-(trifluoromethyl)-6,8-dihydro-5*H*-[1,2,4]triazolo[1,5-a]pyrazine-7-carbonyl]phenyl]methyl]-2*H*-phthalazin-1-one	fluzoparib (SHR-3162), developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd.
	2-(1-cyclohexylpiperidin-4-yl)-3-oxoisoindoline-4-carboxamide	NMS-293, developed by Nerviano Medical Sciences

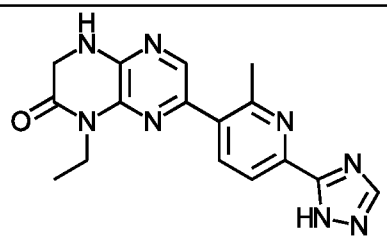
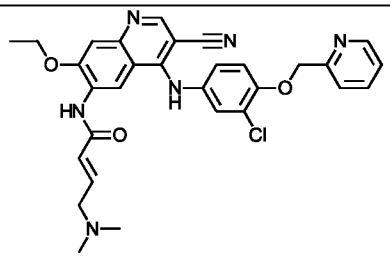
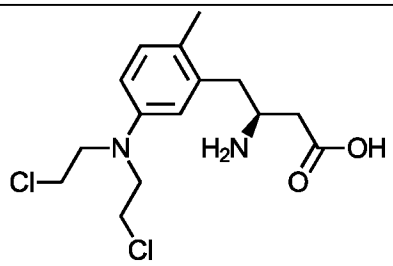
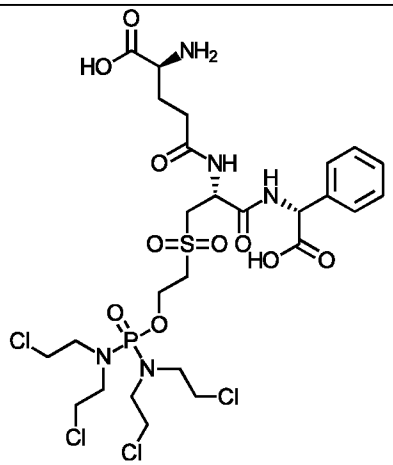
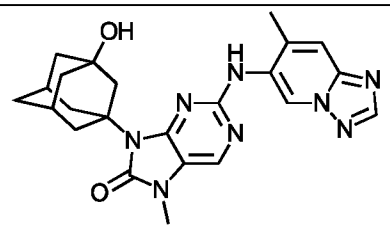
In certain embodiments, the DDRi is not olaparib. In certain embodiments, the DDRi is not a Poly (ADP-ribose) polymerase (PARP) inhibitor.

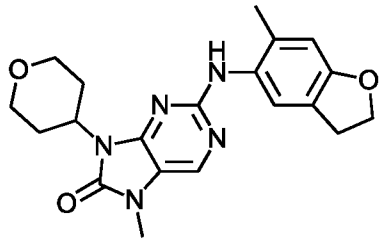
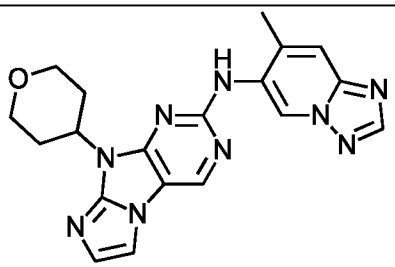
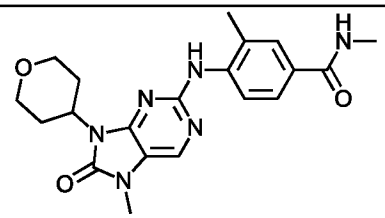
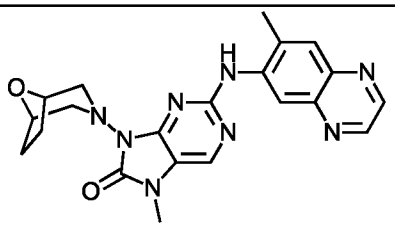
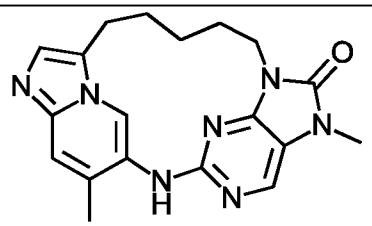
In certain embodiments, the DDRi is selected from the group of DNA-dependent Protein Kinase (DNA-PK) inhibitors listed in TABLE **4**, or a pharmaceutically acceptable salt thereof:

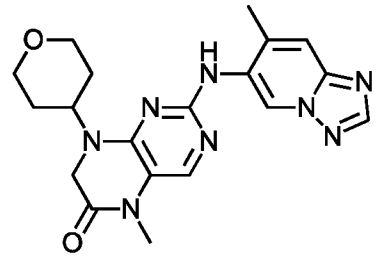
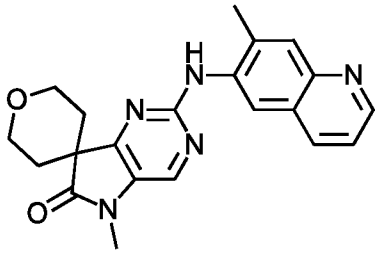
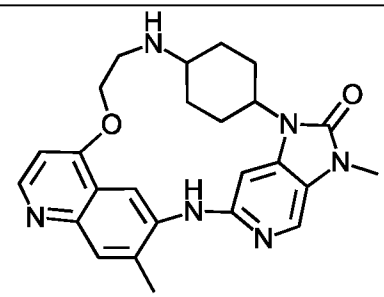
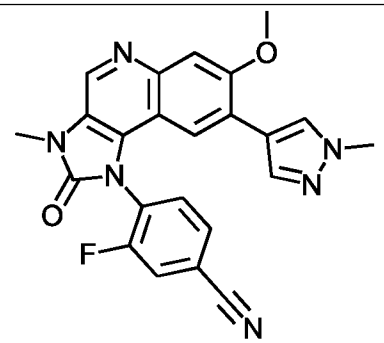
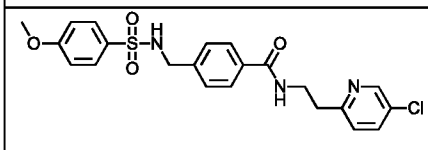
TABLE 4: DNA-dependent Protein Kinase inhibitors (DNA-PKi)

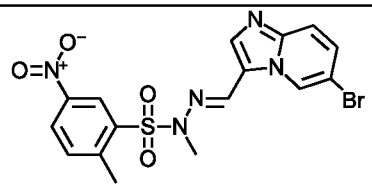
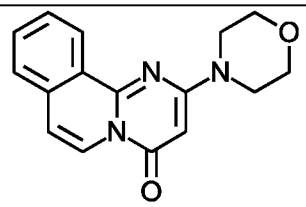
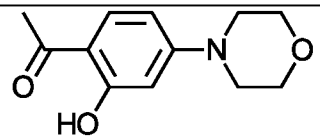
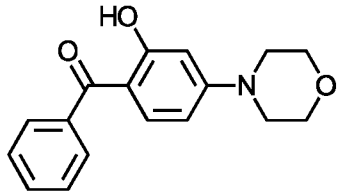
DNA-PKi CHEMICAL STRUCTURE	IUPAC NAME	ALTERNATIVE NAME(S)
	2-morpholin-4-ylbenzo[h]chromen-4-one	NU7026 developed by KuDOS Pharmaceuticals
	2-(4-ethylpiperazin-1-yl)-*N*-[4-(2-morpholin-4-yl-4-oxochromen-8-yl)dibenzothiophen-1-yl]acetamide	KU-0060648 developed by KuDOS Pharmaceuticals
	8-[(2*S*)-1-[[6-(4,6-dideuterio-2-methylpyrimidin-5-yl)pyrimidin-4-yl]amino]propan-2-yl]-*N*-methylquinoline-4-carboxamide	VX-984 (M9831) developed by Merck

	8-dibenzothiophen-4-yl-2-morpholin-4-ylchromen-4-one	NU7441 (KU-57788) developed by KuDOS Pharmaceuticals
	(*S*)-[2-chloro-4-fluoro-5-(7-morpholin-4-ylquinazolin-4-yl)phenyl]-(6-methoxypyridazin-3-yl)methanol	Nedisertib (peposertib or M3814) developed by Merck
	7-Methyl-2-[(7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino]-9-(oxan-4-yl)purin-8-one	AZD7648 developed by AstraZeneca
	2-[2-(3,4-dimethoxyphenyl)ethylamino]-6-(3-fluorophenyl)-8*H*-pyrimido[4,5-d]pyrimidine-5,7-dione	Compound L (STL127705) developed by University of Arizona Cancer Center
	8-[5-(difluoromethyl)pyridin-3-yl]-1-(2,3,6,7-tetrahydrooxepin-4-yl)-[1,2,4]triazolo[4,3-a]quinoxaline	BAY-8400 developed by Bayer
	*N*-methyl-2-morpholin-4-yl-*N*-[6-[2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-4-oxochromen-8-yl]dibenzothiophen-2-yl]acetamide	NU5455 developed by KuDOS Pharmaceuticals

	5-ethyl-3-[2-methyl-6-(1*H*-1,2,4-triazol-5-yl)pyridin-3-yl]-7,8-dihydropyrazino[2,3-b]pyrazin-6-one	CC-115 developed by Celgene Corporation
	(*E*)-*N*-[4-[3-chloro-4-(pyridin-2-ylmethoxy)anilino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide	Neratinib developed by Puma Biotechnology
	(3*S*)-3-amino-4-[5-[bis(2-chloroethyl)amino]-2-methylphenyl]butanoic acid	QBS10072S developed by Quadriga Biosciences, Inc.
	(2S)-2-amino-5-[[(2R)-3-[2-[bis[bis(2-chloroethyl)amino]phosphoryloxy]ethylsulfonyl]-1-[[(R)-carboxy(phenyl)methyl]amino]-1-oxopropan-2-yl]amino]-5-oxopentanoic acid	Canfosfamide (TLK-286, TER286) developed by Telik, Inc. (MabVax Therapeutics, Inc.)
	9-(3-hydroxy-1-adamantyl)-7-methyl-2-[(7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino]purin-8-one	DNA-PK-IN-1 developed by CHENGDU BAIYU PHARMACEUTICAL CO LTD

	7-methyl-2-[(6-methyl-2,3-dihydro-1-benzofuran-5-yl)amino]-9-(oxan-4-yl)purin-8-one	DNA-PK-IN-2 developed by CHENGDU BAIYU PHARMACEUTICAL CO LTD
	*N*-(7-Methyl[1,2,4]triazolo[1,5-a]pyridin-6-yl)-9-(tetrahydro-2H-pyran-4-yl)-9H-imidazo[2,1-f]purin-2-amine	DNA-PK-IN-3 developed by CHENGDU BAIYU PHARMACEUTICAL CO LTD
	*N*,3-dimethyl-4-[[7-methyl-9-(oxan-4-yl)-8-oxopurin-2-yl]amino]benzamide	DNA-PK-IN-4 developed by CHENGDU BAIYU PHARMACEUTICAL CO LTD
	7-methyl-2-[(7-methylquinoxalin-6-yl)amino]-9-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)purin-8-one	DNA-PK-IN-5 developed by CHENGDU BAIYU PHARMACEUTICAL CO LTD
	7,20-dimethyl-2,4,7,9,17,22,24-heptazapentacyclo[13.5.2.2^{3,6}.0^{5,9}.0^{18,22}]tetracosa-1(21),3(24),4,6(23),15,17,19-heptaen-8-one	DNA-PK-IN-6 developed by CHENGDU BAIYU PHARMACEUTICAL CO LTD

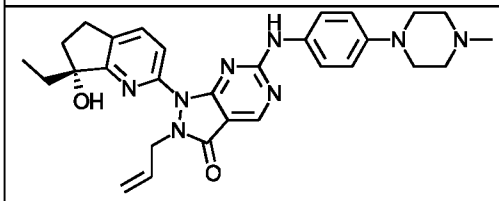
	5-methyl-2-[(7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino]-8-(oxan-4-yl)-7*H*-pteridin-6-one	DNA-PK-IN-8 developed by CHENGDU BAIYU PHARMACEUTICAL CO LTD
	5'-methyl-2'-[(7-methylquinolin-6-yl)amino]spiro[oxane-4,7'-pyrrolo[3,2-d]pyrimidine]-6'-one	DNA-PK-IN-9 developed by CHENGDU BAIYU PHARMACEUTICAL CO LTD
	7,24-dimethyl-17-oxa-2,7,9,14,21,30-hexazahexacyclo[16.6.2.2^{3,6}.2^{10,13}.0^{5,9}.0^{22,26}]triaconta-1(25),3(30),4,6(29),18(26),19,21,23-octaen-8-one	DNA-PK-IN-10 developed by CHENGDU BAIYU PHARMACEUTICAL CO LTD
	3-fluoro-4-[7-methoxy-3-methyl-8-(1-methylpyrazol-4-yl)-2-oxoimidazo[4,5-c]quinolin-1-yl]benzonitrile	DNA-PK-IN-11 (M3541) under development by Merck
	*N*-[2-(5-chloropyridin-2-yl)ethyl]-4-[[(4-methoxyphenyl)sulfonylamino]methyl]benzamide	YU238259 developed by Yale University

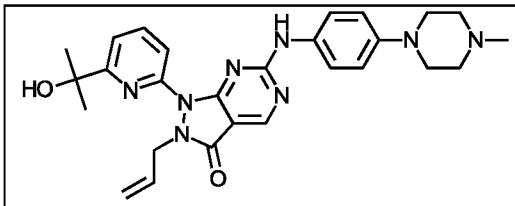
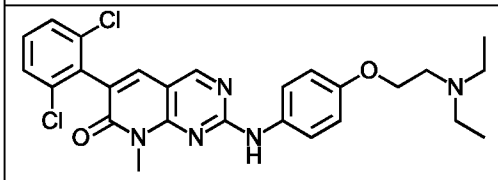
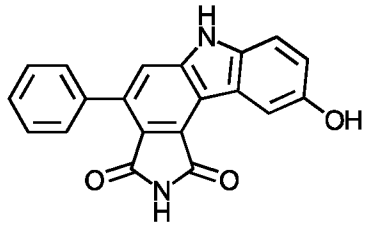
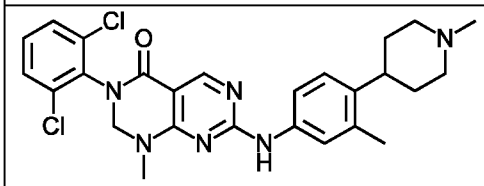
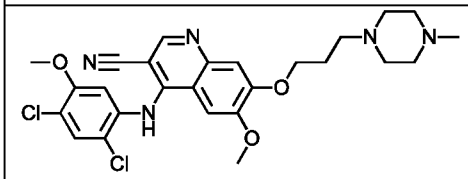
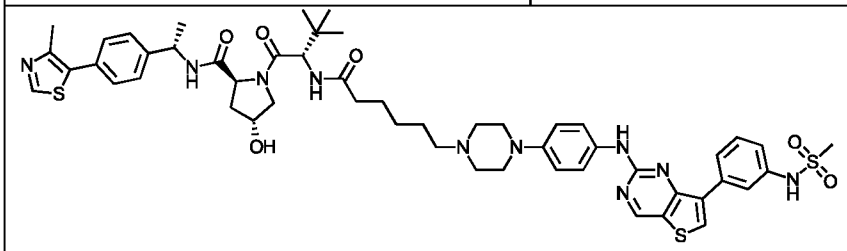
	*N*-[(*E*)-(6-bromoimidazo[1,2-a]pyridin-3-yl)methylideneamino]-*N*,2-dimethyl-5-nitrobenzenesulfonamide	PIK-75 developed by Georgetown University
	2-morpholino-4H-pyrimido[2,1-a]isoquinolin-4-one	Compound 401 developed by Stony Brook University
	1-(2-hydroxy-4-morpholin-4-ylphenyl)ethanone	IC 86621 developed by Eli Lilly and Company
	(2-hydroxy-4-morpholin-4-ylphenyl)-phenylmethanone	AMA-37 developed by Calbiochem

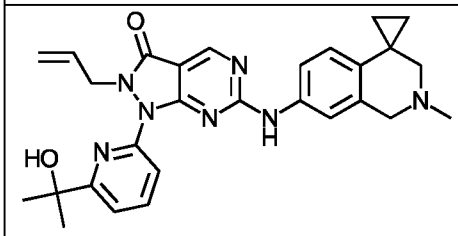
In addition to the DNA-PK inhibitors above, the group of DNA-PK inhibitors can include one or more of XRD-0394 under development by XRad Therapeutics Inc, SN-39536 developed by Auckland Uniservices Limited, BY101298 developed by Chengdu Baiyu Pharmaceutical Co., XZP-6877 developed by Xuanzhu Biopharm, and IMP-11 under development by IMPACT Therapeutics Inc., or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi is selected from the group of WEE1 protein kinase family inhibitors listed in TABLE **5**, or a pharmaceutically acceptable salt thereof:

TABLE 5: WEE1 protein kinase family inhibitors (WEE1i)

WEE1i CHEMICAL STRUCTURE	IUPAC NAME	ALTERNATIVE NAME(S)
	1-[(7*R*)-7-ethyl-7-hydroxy-5,6-dihydrocyclopenta[b]pyridin-2-yl]-6-[4-(4-methylpiperazin-1-yl)anilino]-2-prop-2-enylpyrazolo[3,4-d]pyrimidin-3-one	Azenosertib, developed by Zentalis Pharmaceuticals

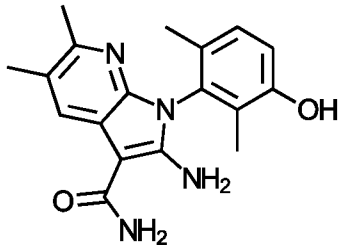
	1-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]-6-[4-(4-methylpiperazin-1-yl)anilino]-2-prop-2-enylpyrazolo[3,4-d]pyrimidin-3-one	Adavosertib (AZD1775, MK-1775), developed by AstraZeneca
	6-(2,6-dichlorophenyl)-2-[4-[2-(diethylamino)ethoxy]anilino]-8-methylpyrido[2,3-d]pyrimidin-7-one	PD0166285, developed by Parke-Davis Pharmaceutical Research
	9-hydroxy-4-phenyl-6*H*-pyrrolo[3,4-c]carbazole-1,3-dione	PD 407824, developed by Parke-Davis Pharmaceutical Research
	6-(2,6-dichlorophenyl)-8-methyl-2-[3-methyl-4-(1-methylpiperidin-4-yl)anilino]-7*H*-pyrimido[4,5-d]pyrimidin-5-one	WEE1-IN-5 (Debio-0123) under development by Debiopharm International SA
	4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile	Bosutinib under development by Pfizer
		
	(2*S*,4*R*)-4-hydroxy-1-[(2*S*)-2-[6-[4-[4-[[7-[3-(methanesulfonamido)phenyl]thieno[3,2-d]pyrimidin-2-yl]amino]phenyl]piperazin-1-yl]hexanoylamino]-3,3-	RSS0680 developed by Korea University

	dimethylbutanoyl]-*N*-[(1*S*)-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]pyrrolidine-2-carboxamide	
	1-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]-6-[(2-methylspiro[1,3-dihydroisoquinoline-4,1'-cyclopropane]-7-yl)amino]-2-prop-2-enylpyrazolo[3,4-d]pyrimidin-3-one	WEE1-IN-3 (ZN-c3) under development by Zentalis Pharmaceuticals

In addition to the WEE1 inhibitors above, the group of WEE1 inhibitors can include one or more of SC0191 under development by Biocity Biopharmaceutics, IMP7068, developed by Impact Therapeutics, Inc, and SY-4835, developed by Shouyao holdings, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi is selected from the group of PKMYT1 inhibitors listed in TABLE **6**:

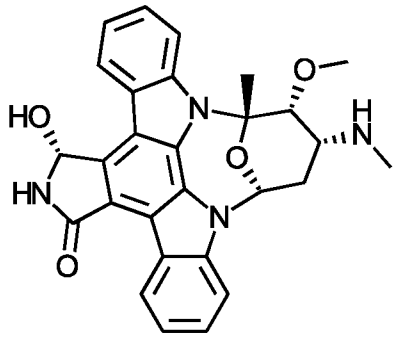
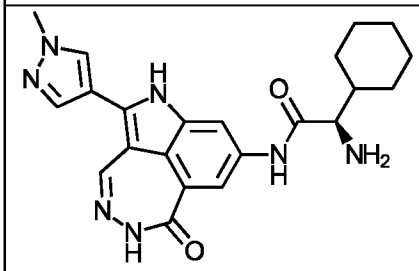
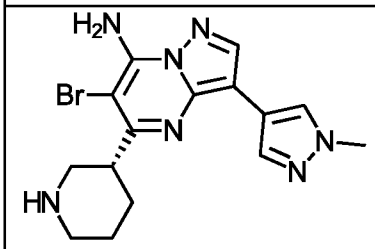
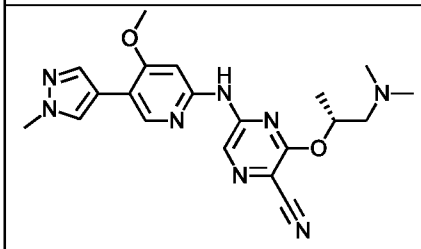
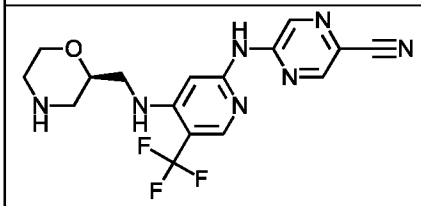
TABLE 6: PKMYT1 inhibitors (PKMYT1i)

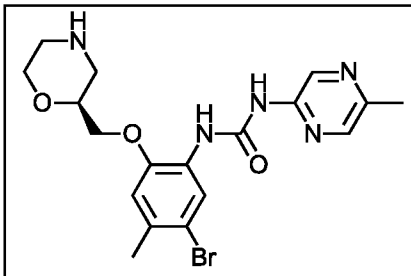
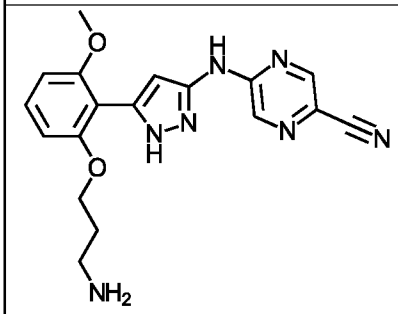
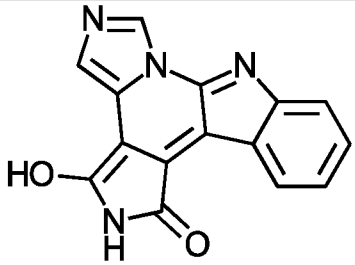
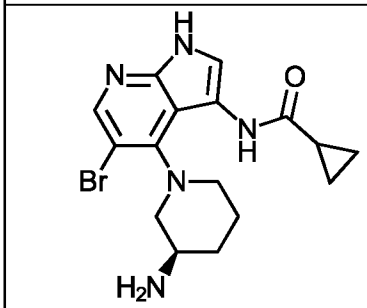
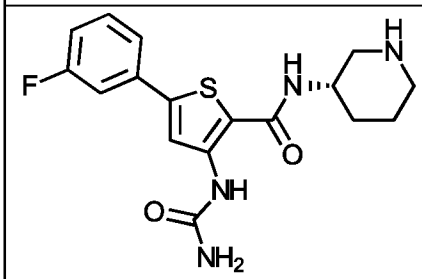
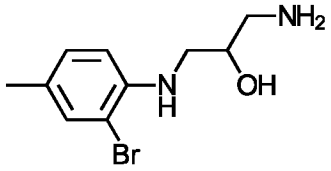
PKMYT1i CHEMICAL STRUCTURE	IUPAC NAME	ALTERNATIVE NAME(S)
	2-amino-1-(3-hydroxy-2,6-dimethylphenyl)-5,6-dimethylpyrrolo[2,3-b]pyridine-3-carboxamide	Lunresertib (RP-6306), under development by Repare Therapeutics

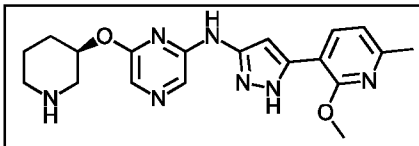
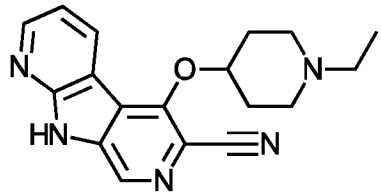
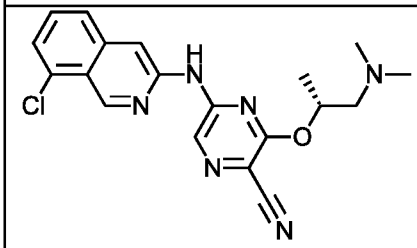
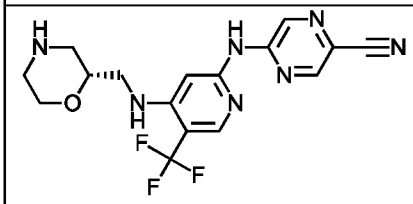
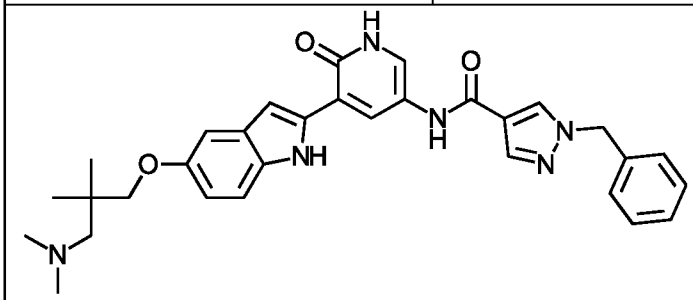
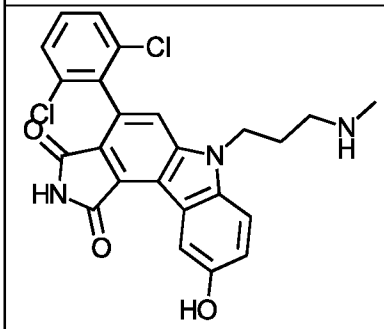
In addition to lunresrtib, the group of PKMYT1 inhibitors can include ACR-2316, developed by Acrivon Therapeutics, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi is a Checkpoint Kinase (CHK) inhibitor. In certain embodiments, the CHK inhibitor is selected from the group of CHK1 selective inhibitors, a CHK2 selective inhibitor, or a CHK1/2 inhibitor. In certain embodiments, the DDRi is selected from the group of CHK1 selective inhibitors listed in TABLE **7**, or a pharmaceutically acceptable salt thereof:

TABLE 7: CHK1 inhibitors (CHK1i)

CHK1i CHEMICAL STRUCTURE	IUPAC NAME	ALTERNATIVE NAME(S)
	(2S,3R,4R,6R,18R)-18-hydroxy-3-methoxy-2-methyl-4-(methylamino)-29-oxa-1,7,17-triazaoctacyclo[12.12.2.12,6.07,28.08,13.015,19.020,27.021,26]nonacosa-8,10,12,14,19,21,23,25,27-nonaen-16-one	7-Hydroxy-staurosporine (UNC-01) under development by the National Cancer Institute (NCI)
	(2*R*)-2-amino-2-cyclohexyl-*N*-[2-(1-methylpyrazol-4-yl)-9-oxo-3,10,11-triazatricyclo[6.4.1.0^{4,13}]trideca-1,4,6,8(13),11-pentaen-6-yl]acetamide	PF477736 developed by Pfizer
	6-bromo-3-(1-methylpyrazol-4-yl)-5-[(3*R*)-piperidin-3-yl]pyrazolo[1,5-a]pyrimidin-7-amine	MK8776/SCH900776 under development by National Cancer Institute (NCI) and Merck
	3-[(2*R*)-1-(dimethylamino)propan-2-yl]oxy-5-[[4-methoxy-5-(1-methylpyrazol-4-yl)pyridin-2-yl]amino]pyrazine-2-carbonitrile	CCT244747 developed by The Institute of Cancer Research
	5-[[4-[[(2*R*)-morpholin-2-yl]methylamino]-5-(trifluoromethyl)pyridin-2-yl]amino]pyrazine-2-carbonitrile	CCT245737 (SRA737, PNT-737) under development by Sierra Oncology LLC

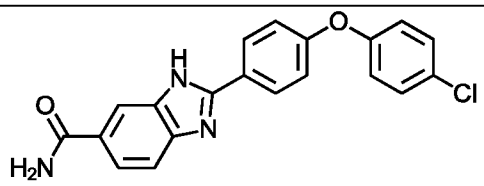
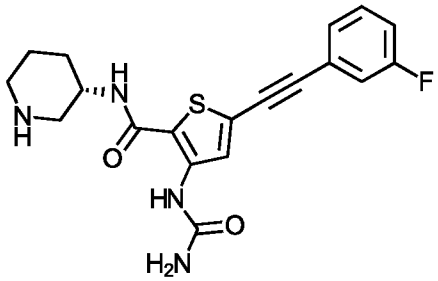
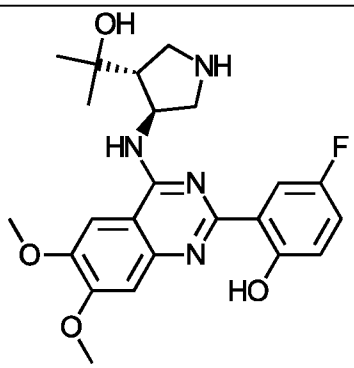
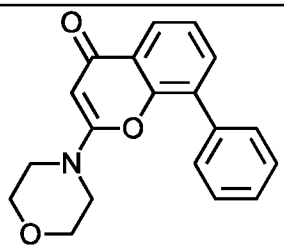
	1-[5-bromo-4-methyl-2-[[(2*S*)-morpholin-2-yl]methoxy]phenyl]-3-(5-methylpyrazin-2-yl)urea	Rabusertib (LY2603618) developed by Eli Lilly and Company
	5-[[5-[2-(3-aminopropoxy)-6-methoxyphenyl]-1*H*-pyrazol-3-yl]amino]pyrazine-2-carbonitrile	Prexasertib (LY2606368) developed by Eli Lilly and Company
	8-hydroxy-2,4,9,19-tetrazapentacyclo[10.7.0.0^{2,6}.0^{7,11}.0^{13,18}]nonadeca-1(19),3,5,7,11,13,15,17-octaen-10-one	AB-IsoG (Isogranulatimide) developed by Alethia Biotherapeutics
	*N*-[4-[(3*R*)-3-aminopiperidin-1-yl]-5-bromo-1*H*-pyrrolo[2,3-b]pyridin-3-yl]cyclopropanecarboxamide	GDC-0575 (ARRY575) developed by Genentech
	3-(carbamoylamino)-5-(3-fluorophenyl)-*N*-[(3*S*)-piperidin-3-yl]thiophene-2-carboxamide	AZD7762 developed by AstraZeneca
	1-Amino-3-[(2-bromo-4-methylphenyl)amino]-2-propanol	CBP-93872 developed by Chugai Pharmaceutical Co. Ltd.

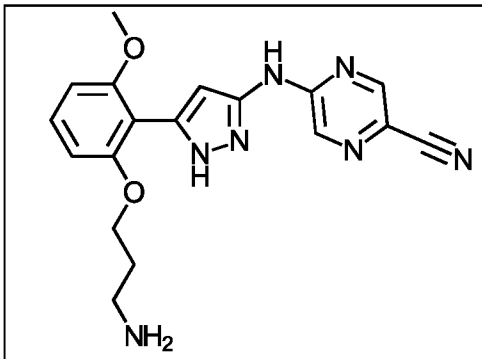
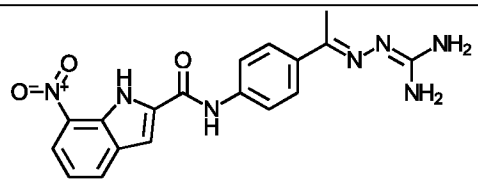
	*N*-[5-(2-methoxy-6-methylpyridin-3-yl)-1*H*-pyrazol-3-yl]-6-[(3*R*)-piperidin-3-yl]oxypyrazin-2-amine	ESP01 (LY2880070) under development by Esperas Pharma
	3-(1-ethylpiperidin-4-yl)oxy-5,8,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2,4,6,10,12-hexaene-4-carbonitrile	GDC0425 developed by Genentech, Inc.
	5-[(8-chloroisoquinolin-3-yl)amino]-3-[(2*R*)-1-(dimethylamino)propan-2-yl]oxypyrazine-2-carbonitrile	SAR020106 developed by Sareum Ltd.
	5-[[4-[[(2*R*)-morpholin-2-yl]methylamino]-5-(trifluoromethyl)pyridin-2-yl]amino]pyrazine-2-carbonitrile	SRA737 developed by Sierra Oncology LLC
		
	1-benzyl-*N*-[5-[5-[3-(dimethylamino)-2,2-dimethylpropoxy]-1*H*-indol-2-yl]-6-oxo-1*H*-pyridin-3-yl]pyrazole-4-carboxamide	V158411 developed by Vernalis Research
	4-(2,6-dichlorophenyl)-9-hydroxy-6-[3-(methylamino)propyl]pyrrolo[3,4-c]carbazole-1,3-dione	PD-321852 developed by Pfizer

In addition to the CHK1 selective inhibitors listed above, the group of CHK1 selective inhibitors can include VER250840 under development by Cumulus Oncology, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi is selected from the group of CHK2 selective inhibitors in TABLE **8**, or a pharmaceutically acceptable salt thereof:

TABLE 8: CHK2 selective inhibitors (CHK2i)

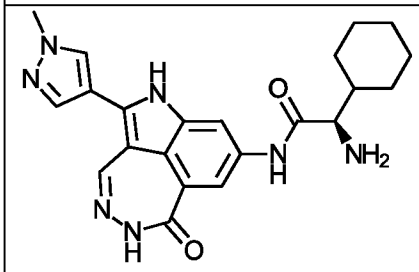
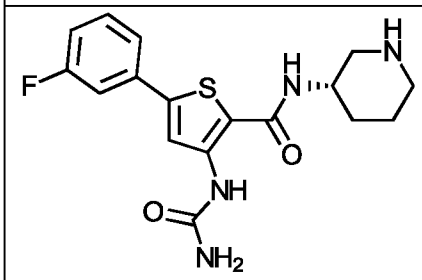
CHK2i CHEMICAL STRUCTURES	IUPAC NAME	ALTERNATIVE NAME(S)
	2-[4-(4-chlorophenoxy)phenyl]-3*H*-benzimidazole-5-carboxamide	BML-277 developed by Johnson & Johnson Pharmaceutical Research and Development
	3-(carbamoylamino)-5-[2-(3-fluorophenyl)ethynyl]-*N*-[(3*S*)-piperidin-3-yl]thiophene-2-carboxamide	PHI-101 developed by Pharos iBio Co., Ltd.
	4-fluoro-2-[4-[[(3*S*,4*R*)-4-(2-hydroxypropan-2-yl)pyrrolidin-3-yl]amino]-6,7-dimethoxyquinazolin-2-yl]phenol	CCT241533 developed by Cancer Research UK Centre for Cancer Therapeutics
	2-morpholin-4-yl-8-phenylchromen-4-one	LY294002 developed by Eli Lilly and Company

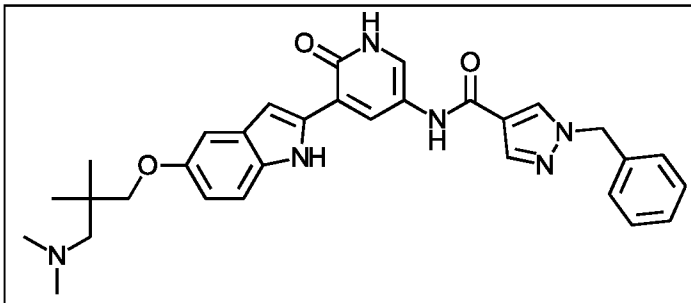
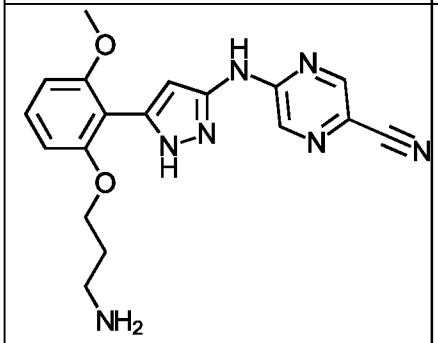
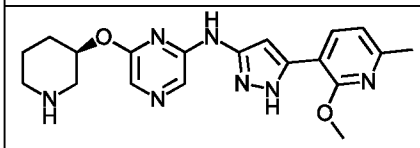
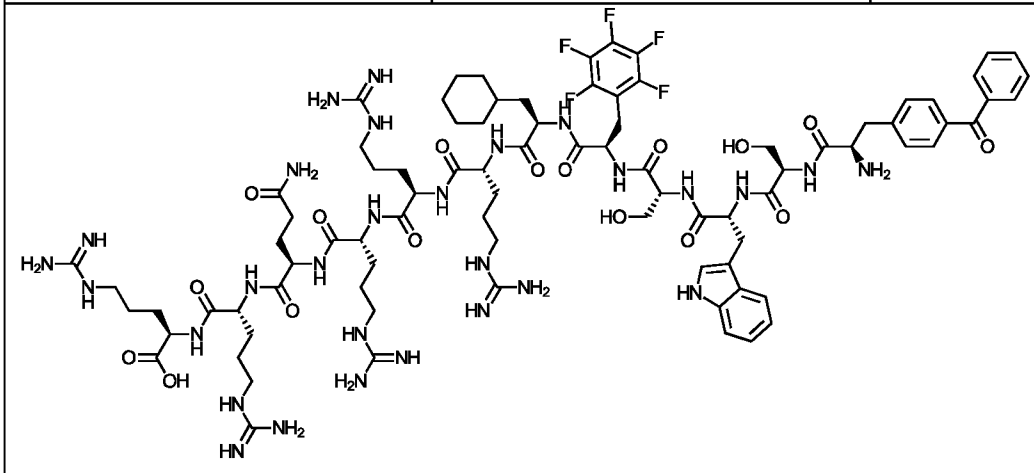
	5-[[5-[2-(3-aminopropoxy)-6-methoxyphenyl]-1*H*-pyrazol-3-yl]amino]pyrazine-2-carbonitrile	prexasertib (LY2606368) developed by Eli Lilly and Company
	*N*-[4-[(E)-*N*-(diaminomethylideneamino)-*C*-methylcarbonimidoyl]phenyl]-7-nitro-1*H*-indole-2-carboxamide	PV1019 (NSC 744039) developed by Provid Pharmaceuticals

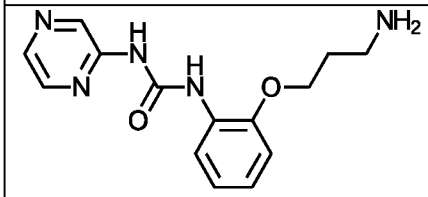
In certain embodiments, the DDRi is selected from the group of CHK1/2 inhibitors in TABLE **9**, or a pharmaceutically acceptable salt thereof:

5

TABLE 9: CHK1/2 inhibitors (CHK1/2i)

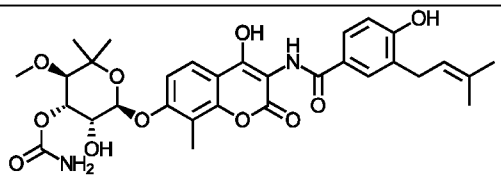
CHK1/2i CHEMICAL STRUCTURES	IUPAC NAME	ALTERNATIVE NAME(S)
	(2*R*)-2-amino-2-cyclohexyl-*N*-[2-(1-methylpyrazol-4-yl)-9-oxo-3,10,11-triazatricyclo[6.4.1.0^{4,13}]trideca-1,4,6,8(13),11-pentaen-6-yl]acetamide	PF477736 developed by Pfizer
	3-(carbamoylamino)-5-(3-fluorophenyl)-*N*-[(3*S*)-piperidin-3-yl]thiophene-2-carboxamide	AZD7762 developed by AstraZeneca

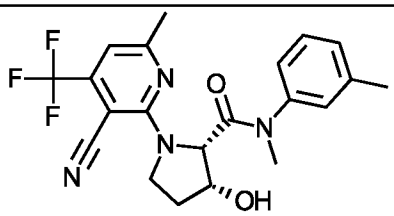
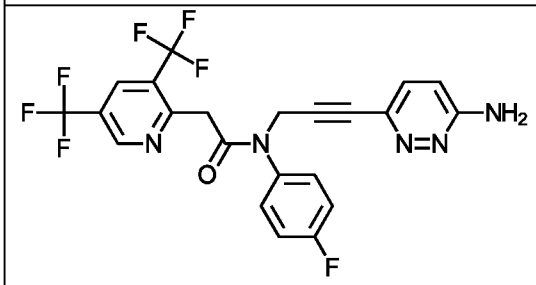
		
	1-benzyl-*N*-[5-[5-[3-(dimethylamino)-2,2-dimethylpropoxy]-1*H*-indol-2-yl]-6-oxo-1*H*-pyridin-3-yl]pyrazole-4-carboxamide	V158411 developed by Vernalis Research
	5-[[5-[2-(3-aminopropoxy)-6-methoxyphenyl]-1*H*-pyrazol-3-yl]amino]pyrazine-2-carbonitrile	prexasertib (LY2606368) developed by Eli Lilly and Company
	*N*-[5-(2-methoxy-6-methylpyridin-3-yl)-1*H*-pyrazol-3-yl]-6-[(3*R*)-piperidin-3-yl]oxypyrazin-2-amine	ESP01 (LY2880070) under development by Esperas Pharma
		

	(2*R*)-2-[[(2*R*)-2-[[(2*R*)-5-amino-2-[[(2*R*)-2-[[(2*R*)-2-[[(2*R*)-2-[[(2*R*)-2-[[(2*R*)-2-[[(2*R*)-2-[[(2*R*)-2-[[(2*R*)-2-amino-3-(4-benzoylphenyl)propanoyl]amino]-3-hydroxypropanoyl]amino]-3-(1*H*-indol-3-yl)propanoyl]amino]-3-hydroxypropanoyl]amino]-3-(2,3,4,5,6-pentafluorophenyl)propanoyl]amino]-3-cyclohexylpropanoyl]amino]-5-carbamimidamidopentanoyl]amino]-5-carbamimidamidopentanoyl]amino]-5-carbamimidamidopentanoyl]amino]-5-oxopentanoyl]amino]-5-carbamimidamidopentanoyl]amino]-5-carbamimidamidopentanoic acid	CBP501 developed by CanBas Co. Ltd.
	1-[2-(3-aminopropoxy)phenyl]-3-pyrazin-2-ylurea	XL844 developed by Exelixis

In certain embodiments, the DDRi is selected from the group of DNA polymerase theta (Polθ) inhibitors listed in TABLE **10**, or a pharmaceutically acceptable salt thereof:

TABLE 10: DNA polymerase theta (Polθ) inhibitors (Polθi)

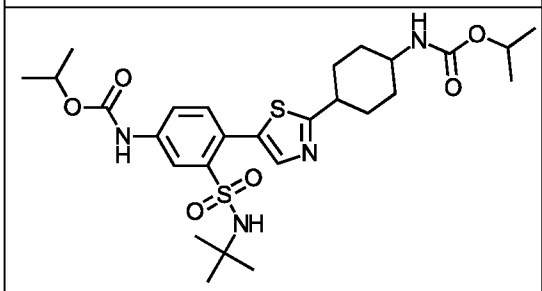
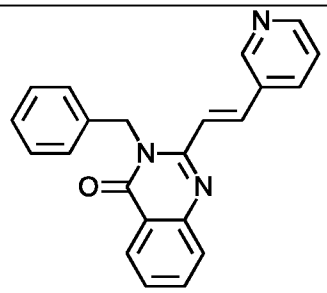
Polθi CHEMICAL STRUCTURES	**IUPAC NAME**	**ALTERNATIVE NAME(S)**
	[(3*R*,4*S*,5*R*,6*R*)-5-hydroxy-6-[4-hydroxy-3-[[4-hydroxy-3-(3-methylbut-2-enyl)benzoyl]amino]-8-methyl-2-oxochromen-7-yl]oxy-3-methoxy-2,2-dimethyloxan-4-yl] carbamate	Novobiocin (NVB), under development by the National Cancer Institute

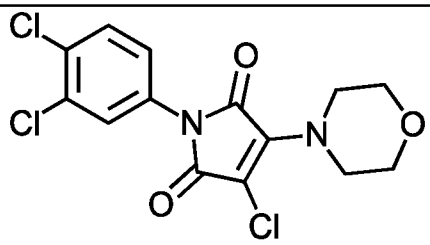
	(2*S*,3*R*)-1-[3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl]-3-hydroxy-*N*-methyl-N-(3-methylphenyl)pyrrolidine-2-carboxamide	ART558 developed by Artios Pharma
	*N*-[3-(6-aminopyridazin-3-yl)prop-2-ynyl]-2-[3,5-bis(trifluoromethyl)pyridin-2-yl]-*N*-(4-fluorophenyl)acetamide	RP-6685 developed by Repare Therapeutics

In addition to the Polθ inhibitors above, the group of Polθ inhibitors can include one or more of ART4215, ART6043, both developed by Artios Pharma, RP-3467, developed by Repare Therapeutics, and GSK101 (GSK4524101/IDE705) developed by Ideaya Biosciences, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi is selected from the group of RAD51 recombinase (RAD51) inhibitors listed in TABLE **11**, or a pharmaceutically acceptable salt thereof:

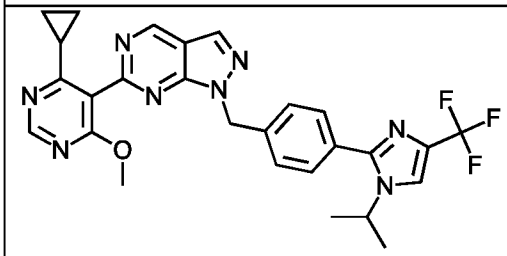
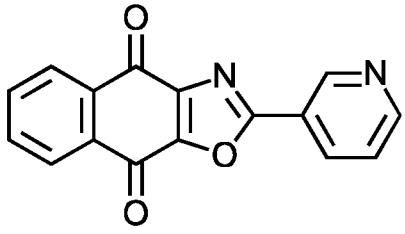
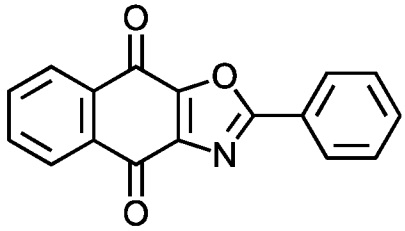
TABLE 11: RAD51 inhibitors (RAD51i)

RAD51i CHEMICAL STRUCTURES	IUPAC NAME	ALTERNATIVE NAME(S)
	propan-2-yl *N*-[3-(*tert*-butylsulfamoyl)-4-[2-[4-(propan-2-yloxycarbonylamino)cyclohexyl]-1,3-thiazol-5-yl]phenyl]carbamate	CYT0851 developed by Cyteir Therapeutics, Inc.
	3-benzyl-2-[(*E*)-2-pyridin-3-ylethenyl]quinazolin-4-one	B02 developed by Drexel University.

	3-chloro-1-(3,4-dichlorophenyl)-4-morpholin-4-ylpyrrole-2,5-dione	RI-1 developed by University of Chicago

In certain embodiments, the DDRi is selected from the group of Ubiquitin-Specific Protease 1 (USP1) inhibitors listed in TABLE **12**, or a pharmaceutically acceptable salt thereof:

TABLE 12: USP1 inhibitors

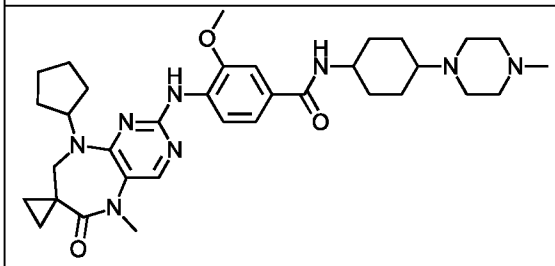
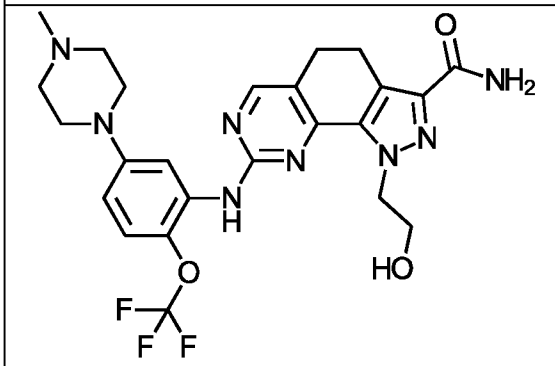
USP1i CHEMICAL STRUCTURES	IUPAC NAME	ALTERNATIVE NAME(S)
	6-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-1-[[4-[1-propan-2-yl-4-(trifluoromethyl)imidazol-2-yl]phenyl]methyl]pyrazolo[3,4-d]pyrimidine	KSQ4279 developed by KSQ Therapeutics and under development by Hoffmann-La Roche
	2-pyridin-3-ylbenzo[f][1,3]benzoxazole-4,9-dione	SJB3-019A developed by Dana-Farber Cancer Institute
	2-phenylbenzo[f][1,3]benzoxazole-4,9-dione	SJB2-043 developed by Dana-Farber Cancer Institute

In addition to the USP1 inhibitors listed above, the group of USP1 inhibitors can include one or more of TNG348 developed by Tango Therapeutics, Inc., and ISM3091 (XL309) under

development by Exelixis, HSK39775, developed by Haisco Pharmaceutical, FT-3171 (Debio 0432) developed by Forma Therapeutics, or a pharmaceutically acceptable salt thereof:

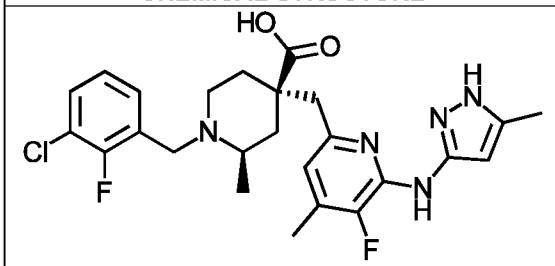
In certain embodiments, the DDRi is selected from the group of Polo-Like serine/threonine Kinase 1 (PLK1) inhibitors listed in TABLE **13**, or a pharmaceutically acceptable salts thereof:

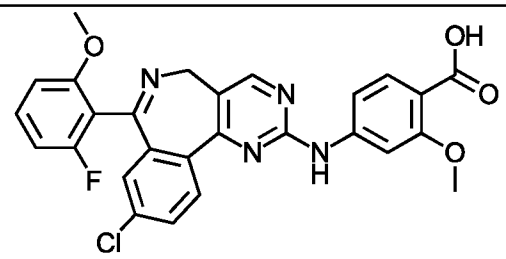
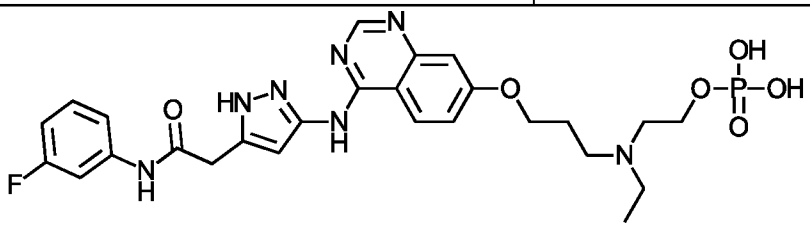
TABLE 13: PLK1 inhibitors (PLK1i)

PLK1i CHEMICAL STRUCTURES	IUPAC NAME	ALTERNATIVE NAME(S)
	4-[(9-cyclopentyl-5-methyl-6-oxospiro[8H-pyrimido[4,5-b][1,4]diazepine-7,1'-cyclopropane]-2-yl)amino]-3-methoxy-*N*-[4-(4-methylpiperazin-1-yl)cyclohexyl]benzamide	Plogosertib developed by Cyclacel Pharmaceuticals, Inc.
	1-(2-hydroxyethyl)-8-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)anilino]-4,5-dihydropyrazolo[4,3-h]quinazoline-3-carboxamide	Onvansertib developed by Cardiff Oncology

In certain embodiments, the DDRi is selected from the group of Aurora kinase inhibitors. In certain embodiments, the DDRi is selected from the group of Aurora A and Aurora B inhibitors listed in TABLE **14**, or a pharmaceutically acceptable salt thereof:

TABLE 14: Aurora A and Aurora B inhibitors

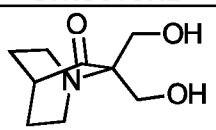
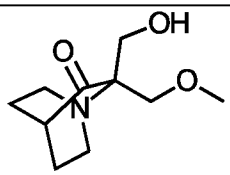
Aurora A and Aurora B inhibitors CHEMICAL STRUCTURE	IUPAC NAME	ALTERNATIVE NAME(S)
	(2*R*,4*R*)-1-[(3-chloro-2-fluorophenyl)methyl]-4-[[5-fluoro-4-methyl-6-[(5-methyl-1*H*-pyrazol-3-yl)amino]pyridin-2-yl]methyl]-2-methylpiperidine-4-carboxylic acid	JAB-2485 developed by Jacobio Pharmaceuticals Co., Ltd.

	4-[[9-chloro-7-(2-fluoro-6-methoxyphenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino]-2-methoxybenzoic acid	Alisertib (MLN8237) developed by Millennium Pharmaceuticals, Inc. and under development by Takeda Pharmaceuticals
		
	2-[ethyl-[3-[4-[[5-[2-(3-fluoroanilino)-2-oxoethyl]-1*H*-pyrazol-3-yl]amino]quinazolin-7-yl]oxypropyl]amino]ethyl dihydrogen phosphate	Barasertib (AZD1152) developed by AstraZeneca

In addition to the Aurora kinase inhibitors listed above, the group of Aurora A and Aurora B inhibitors can include WJ05129 developed by Suzhou Junjing BioSciences Co., Ltd., or a pharmaceutically acceptable salt thereof:

In certain embodiments, the DDRi is selected from the group of mutant p53 re-activators listed in TABLE **15**, or a pharmaceutically acceptable salt thereof:

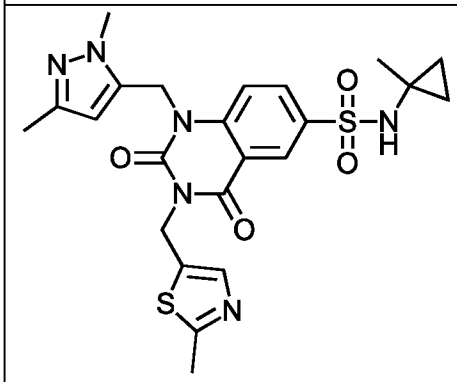
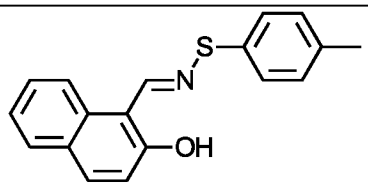
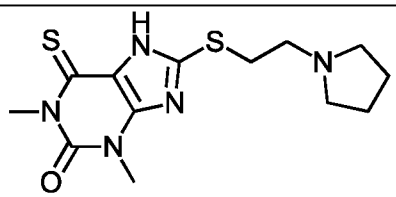
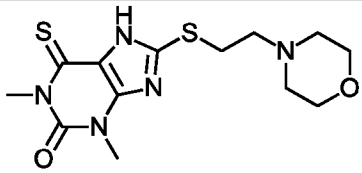
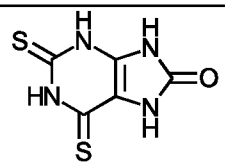
TABLE 15: Mutant p53 re-activators

MUTANT p53 RE-ACTIVATORS CHEMICAL STRUCTURE	IUPAC NAME	ALTERNATIVE NAME(S)
	2,2-bis(hydroxymethyl)-1-azabicyclo[2.2.2]octan-3-one	PRIMA-1 (NSC-281668) developed by the Karolinska Institutet
	2-(hydroxymethyl)-2-(methoxymethyl)-1-azabicyclo[2.2.2]octan-3-one	APR246 (PRIMA-1^{MET}) developed by Aprea Therapeutics

In addition to the mutant p53 re-activators listed above, the group of mutant p53 re-activators can include PC14586 developed by PMV Pharmaceuticals, Inc., or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi is selected from the group of Poly(ADP-ribose) Glycohydrolase (PARG) inhibitors listed in TABLE **16**, or a pharmaceutically acceptable salt thereof:

TABLE 16: PARG inhibitors (PARGi)

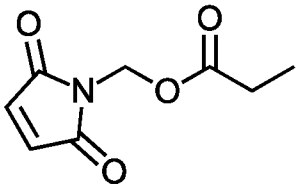
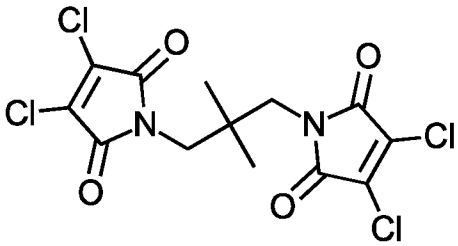
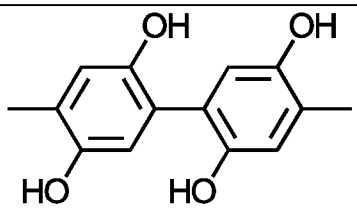
PARGi CHEMICAL STRUCTURE	IUPAC NAME	ALTERNATIVE NAME(S)
	1-[(2,5-dimethylpyrazol-3-yl)methyl]-N-(1-methylcyclopropyl)-3-[(2-methyl-1,3-thiazol-5-yl)methyl]-2,4-dioxoquinazoline-6-sulfonamide	PDD00017273 developed by Cancer Research UK
	1-[(E)-(4-methylphenyl)sulfanyliminomethyl] naphthalen-2-ol	COH34 developed by City of Hope
	1,3-dimethyl-8-(2-pyrrolidin-1-ylethylsulfanyl)-6-sulfanylidene-7*H*-purin-2-one	JA2-4 (NSC99657) developed by the National Cancer Institute
	1,3-dimethyl-8-(2-morpholin-4-ylethylsulfanyl)-6-sulfanylidene-7*H*-purin-2-one	JA2131 (NSC98003) developed by the National Cancer Institute
	2,6-bis(sulfanylidene)-7,9-dihydro-3H-purin-8-one	JA2-3 (NSC29192) developed by

		the National Cancer Institute

In addition to the PARG inhibitors listed above, the group of PARG inhibitors can include IDE161 developed by IDEAYA Biosciences, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DDRi is selected from the group of Werner Syndrome protein (WRN) inhibitors listed in TABLE **17**, or a pharmaceutically acceptable salt thereof:

TABLE 17: WRN inhibitors

WRNi CHEMICAL STRUCTURE	IUPAC NAME	ALTERNATIVE NAME(S)
	(2,5-dioxopyrrol-1-yl)methyl propanoate	NSC 19630 developed by the National Cancer Institute
	3,4-dichloro-1-[3-(3,4-dichloro-2,5-dioxopyrrol-1-yl)-2,2-dimethylpropyl]pyrrole-2,5-dione	NSC 617145 developed by the National Cancer Institute
	2-(2,5-dihydroxy-4-methylphenyl)-5-methylbenzene-1,4-diol	NSC 2805 developed by the National Cancer Institute

In addition to the WRN inhibitors listed above, the group of WRN inhibitors can include: RO7589831, developed by Hoffmann-La Roche, and HRO761, developed by Novartis.

Methods of Treatment

The present disclosure provides methods of treating or preventing a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi). The [177Lu]Lu-

PSMA-617 and the DDRi can be as previously described. In certain embodiments, the DDRi is not olaparib.

In the present methods, the amount of [177Lu]Lu-PSMA-617 administered and the amount of DDRi administered comprise quantities that are jointly therapeutically effective against a PSMA-expressing cancer. The amount of [177Lu]Lu-PSMA-617 administered and the amount of DDRi administered can be administered in a single formulation or unit dosage form, administered concurrently, but optionally separately, or administered sequentially by any suitable route. In certain embodiments, the DDRi can be administered via a different route than [^{177}Lu]Lu-PSMA-617.

In certain embodiments, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DDRi selected from the group as previously described. In certain embodiments, the DDRi is selected from the group consisting of Ataxia-Telangiectasia Mutated (ATM) inhibitors, Ataxia Telangiectasia and Rad3-related (ATR) inhibitors, Poly (ADP-ribose) Polymerase (PARP) inhibitors, DNA-dependent Protein Kinase (DNA-PK) inhibitors, WEE1 protein kinase family inhibitors, Checkpoint Kinase (CHK) inhibitors, DNA polymerase theta (Polθ) inhibitors, RAD51 recombinase (RAD51) inhibitors, Ubiquitin-Specific Protease 1 (USP1) inhibitors, Polo-Like serine/threonine Kinase 1 (PLK1) inhibitors, Aurora kinase inhibitors, mutant p53 reactivators, Poly(ADP-ribose) Glycohydrolase (PARG) inhibitors, Werner Syndrome protein (WRN) inhibitors, and combinations thereof. In certain embodiments, the PARP inhibitor is not olaparib.

Typically, the amount of a radiopharmaceutical, *e.g.*, [177Lu]Lu-PSMA-617, to be administered to a subject in need thereof, is based on the amount of radiation that will be administered to the subject. The amount of radiation may be reflected as a unitary dose (in MBq) or as an amount of radiation per kg bodyweight (in kBq/kg). When referring to a radioactivity-related value, e.g. 7.4 GBq (200 mCi) of radioactivity, the amount can refer to the radioactivity at the date and time of administration.

In the present methods, [177Lu]Lu-PSMA-617 can be administered in a unitary dose of from about 3 GBq to about 10 GBq, such as, for example, about 3 GBq, about 4 GBq, about 5 GBq, about 6 GBq, about 7 GBq, about 8 GBq, about 9 GBq, or about 10 GBq. In certain embodiments, amount of [177Lu]Lu-PSMA-617 administered in combination with the DDRi can be reduced as compared to a monotherapy method without a reduction in therapeutic efficacy. In certain embodiments, [177Lu]Lu-PSMA-617 can be administered in a unitary dose of from about 6 GBq to about 8 GBq. In certain embodiments, [177Lu]Lu-PSMA-617 can be administered in combination with the DDRi in a unitary dose of about 7.4 GBq, such as 7.4

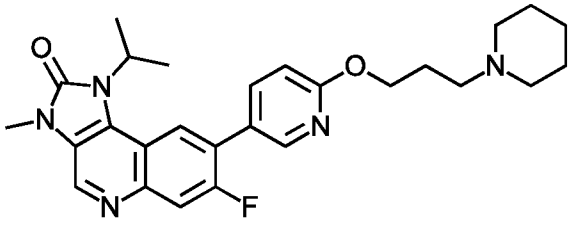
GBq (+/- 10%), while achieving one or more improvements in therapeutic efficacy as compared with [177Lu]Lu-PSMA-617 monotherapy.

Typically, the amount of a DDRi to be administered to a subject in need thereof is based on factors such as the severity of the PSMA-expressing cancer, the characteristics of the subject being treated, *e.g.*, the particular animal or human subject treated, age, weight, and health, frequency of treatments, the route of administration, the severity of side effects of the one or more DDRi compounds and/or the amount of 177Lu]Lu-PSMA-617 being administered. In certain embodiments, the therapeutically effective amount can be the maximal dose or dosing protocol that avoids significant side effects or toxic effects, an occurrence of unacceptable toxicity. In certain embodiments, the therapeutically effective amount is the minimal dose that provides an improvement in the extent of response, slowing the symptomatic progression of the cancer, or symptoms thereof, duration of response, progression-free survival, Prostate-Specific Antigen (PSA) level, Alkaline Phosphatase (ALP) level, Lactate Dehydrogenase (LDH) level, pain Intensity, Functional Assessment of Cancer Therapy (FACT) score, health-related quality of life, number of hospitalizations, duration of hospitalization, and/or improvement in overall survival, or an improvement in another clinical measure or parameter. The improvement of a clinical measure or parameter can be by at least 1%, at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, where 100% is defined as the clinical measure or parameter shown by a healthy subject.

In certain embodiments, amount of a DDRi administered in combination with [177Lu]Lu-PSMA-617 can be reduced as compared to a monotherapy method without a reduction in therapeutic efficacy. In certain embodiments, the amount of the DDRi is a synergistically effective amount. The improvement of a clinical measure or parameter can be by at least 100%, at least 105%, at least 110%, at least 115%, at least 120%, at least 125%, at least 130%, at least 135%, at least 140%, at least 145%, at least 150%, at least 155%, at least 160%, at least 165%, at least 170%, at least 175%, at least 180%, at least 185%, at least 190%, at least 195%, at least 200%, at least 205%, at least 210%, at least 215%, at least 220%, at least 225%, at least 230%, at least 235%, where 240% or at least 250%, where 100% can be defined as the clinical measure or parameter observed after DDRi monotherapy or [177Lu]Lu-PSMA-617 monotherapy.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the ATM inhibitors listed in TABLE **1**, XRD-0394 and SX-RDS1, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the ATM inhibitor is:



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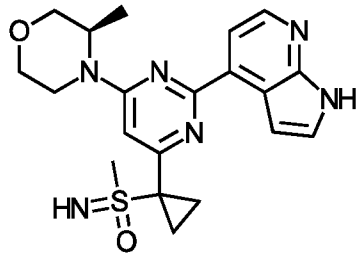
7-fluoro-3-methyl-8-[6-(3-piperidin-1-ylpropoxy)pyridin-3-yl]-1-propan-2-ylimidazo[4,5-c]quinolin-2-one (AZD1390) and the amount administered can be about 10 mg, 40 mg, or 80 mg.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the ATR inhibitors listed in TABLE **2**, LF0397, IMP-9064, SC0245, and ATRN-119, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the ATR inhibitor is:



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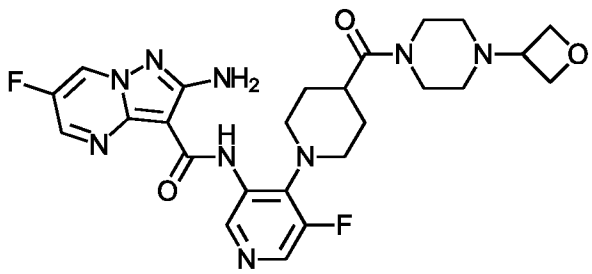
imino-methyl-[1-[6-[(3R)-3-methylmorpholin-4-yl]-2-(1H-pyrrolo[2,3-b]pyridin-4-yl)pyrimidin-4-yl]cyclopropyl]-oxo-λ^6-sulfane (ceralasertib (AZD6738)), and the amount administered can be about 160 mg.

In certain embodiments, the ATR inhibitor is:



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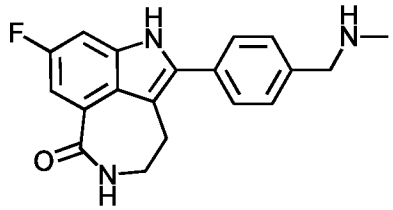
2-amino-6-fluoro-N-[5-fluoro-4-[4-[4-(oxetan-3-yl)piperazine-1-carbonyl]piperidin-1-yl]pyridin-3-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide, gartisertib (M4344, VX-803) and the amount administered can be about 10 mg, 20 mg, or 40 mg.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the PARP inhibitors listed in TABLE **3**, or a pharmaceutically acceptable salt thereof. In certain embodiments, the PARP does not include olaparib.

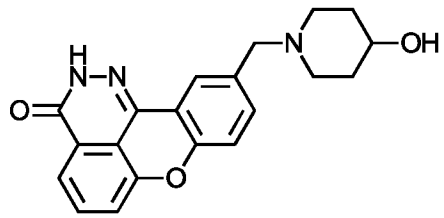
In certain embodiments, the PARP inhibitor is:



,

6-fluoro-2-[4-(methylaminomethyl)phenyl]-3,10-diazatricyclo[6.4.1.$0^{4,13}$]trideca-1,4,6,8(13)-tetraen-9-one rucaparib (PF-01367338) and the amount administered can be about 600 mg.

In certain embodiments, the PARP inhibitor is:



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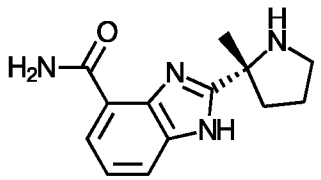
4-[(4-hydroxypiperidin-1-yl)methyl]-8-oxa-15,16-diazatetracyclo[7.7.1.^{2,7}.$0^{13,17}$]heptadeca-1(16),2(7),3,5,9,11,13(17)-heptaen-14-one (E7016) and the amount administered can be about 320-mg.

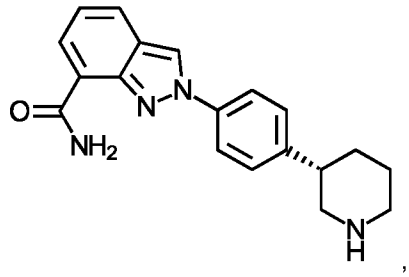
In certain embodiments, the PARP inhibitor is:



,

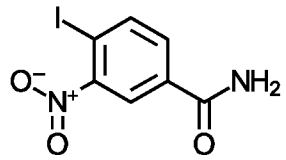
2-[(2*R*)-2-methylpyrrolidin-2-yl]-1*H*-benzimidazole-4-carboxamide (veliparib (ABT-888)) and the amount administered can be about 40, 80, and 120 mg.

In certain embodiments, the PARP inhibitor is:



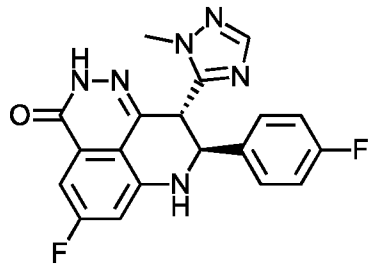
2-[4-[(3S)-piperidin-3-yl]phenyl]indazole-7-carboxamide (niraparib (ZL-2306)) and the amount administered can be about 300 mg once a day.

In certain embodiments, the PARP inhibitor is:



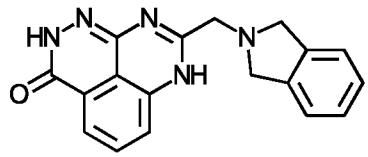
4-iodo-3-nitrobenzamide iniparib (BSI-201) and the amount administered can be about 5.6 mg/kg.

In certain embodiments, the PARP inhibitor is:



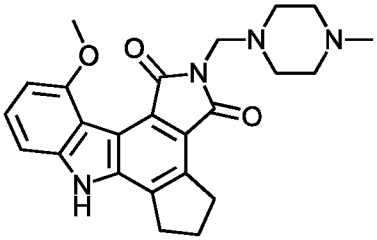
(11S,12R)-7-fluoro-11-(4-fluorophenyl)-12-(2-methyl-1,2,4-triazol-3-yl)-2,3,10-triazatricyclo[7.3.1.$0^{5,13}$]trideca-1,5(13),6,8-tetraen-4-one (talazoparib (BMN 673)) and the amount administered can be about 0.5 or 1 mg.

In certain embodiments, the PARP inhibitor is:



11-(1,3-dihydroisoindol-2-ylmethyl)-2,3,10,12-tetrazatricyclo[7.3.1.05,13]trideca-1,5(13),6,8,11-pentaen-4-one (stenoparib (2X-121/E7449)) and the amount administered can be about 100 mg.

In certain embodiments, the PARP inhibitor is:



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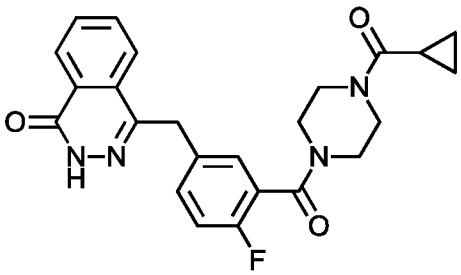
14-methoxy-9-[(4-methylpiperazin-1-yl)methyl]-9,19-diazapentacyclo[10.7.0.0^{2,6}.0^{7,11}.0^{13,18}]nonadeca-1(12),2(6),7(11),13(18),14,16-hexaene-8,10-dione (CEP-9722) and the amount administered can be about 150 mg.

In certain embodiments, the PARP inhibitor is:



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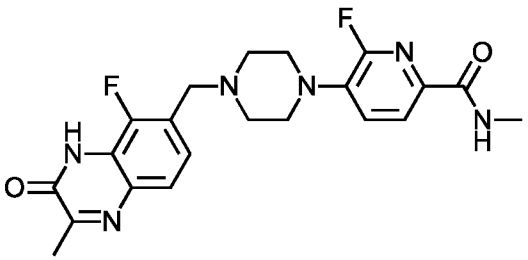
4-[[3-[4-(cyclopropanecarbonyl)piperazine-1-carbonyl]-4-fluorophenyl]methyl]-2H-phthalazin-1- (olaparib (KU-0059436, AZD2281) and the amount administered can be about 300 mg.

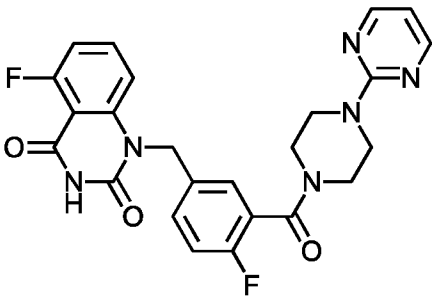
In certain embodiments, the PARP inhibitor is:



,

6-fluoro-5-[4-[(5-fluoro-2-methyl-3-oxo-4H-quinoxalin-6-yl)methyl]piperazin-1-yl]-N-methylpyridine-2-carboxamide (AZD9574) and the amount administered can be about 440 µg.

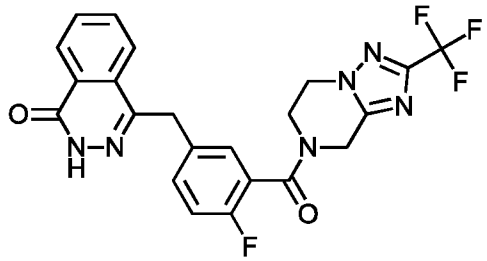
In certain embodiments, the PARP inhibitor is:



,

5-fluoro-1-[[4-fluoro-3-(4-pyrimidin-2-ylpiperazine-1-carbonyl)phenyl]methyl]quinazoline-2,4-dione (Senaparib (IMP4297)) and the amount administered can be about 100 mg.

In certain embodiments, the PARP inhibitor is:



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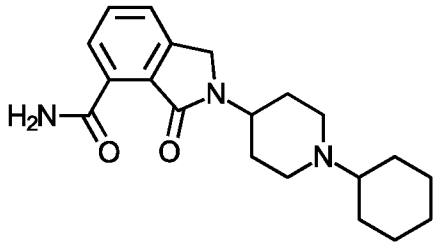
4-[[4-fluoro-3-[2-(trifluoromethyl)-6,8-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrazine-7-carbonyl]phenyl]methyl]-2H-phthalazin-1-one (fluzoparib (SHR-3162)) and the amount administered can be about 100 or 150 mg.

In certain embodiments, the PARP inhibitor is:



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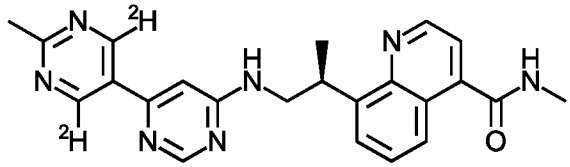
2-(1-cyclohexylpiperidin-4-yl)-3-oxoisoindoline-4-carboxamide (NMS-293) and the amount administered can be about 100 mg.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the DNA-PK inhibitors listed in TABLE **4**, XRD-0394, SN-39536, XZP-6877, and IMP-11, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the DNA-PK inhibitor is:



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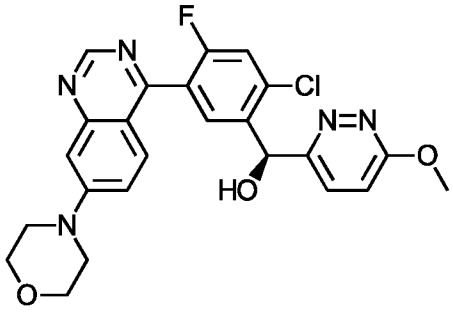
8-[(2S)-1-[[6-(4,6-dideuterio-2-methylpyrimidin-5-yl)pyrimidin-4-yl]amino]propan-2-yl]-N-methylquinoline-4-carboxamide (VX-984 (M9831)) and the amount administered can be about 120 mg, 240 mg, 480 mg, or 720 mg.

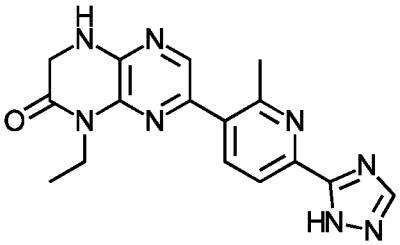
In certain embodiments, the DNA-PK inhibitor is:



,

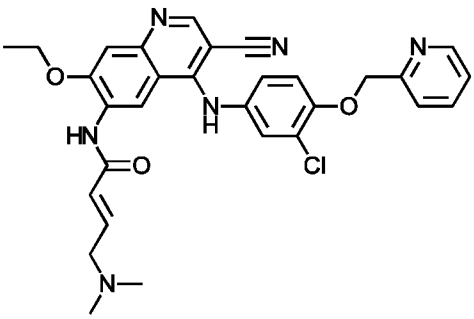
(S)-[2-chloro-4-fluoro-5-(7-morpholin-4-ylquinazolin-4-yl)phenyl]-(6-methoxypyridazin-3-yl)methanol (nedisertib/peposertib (M3814)) and the amount administered can be about 50 mg, 100 mg, 150 mg, or 250 mg.

In certain embodiments, the DNA-PK inhibitor is



5-ethyl-3-[2-methyl-6-(1H-1,2,4-triazol-5-yl)pyridin-3-yl]-7,8-dihydropyrazino[2,3-b]pyrazin-6-one (CC-115) and the amount administered can be about 7.5 or 10 mg.

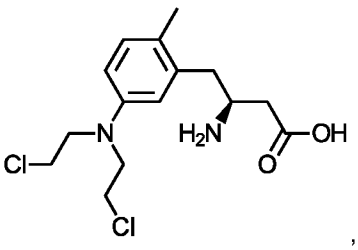
In certain embodiments, the DNA-PK inhibitor is:



,

(E)-N-[4-[3-chloro-4-(pyridin-2-ylmethoxy)anilino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide (neratinib) and the amount administered can be about 240 mg.

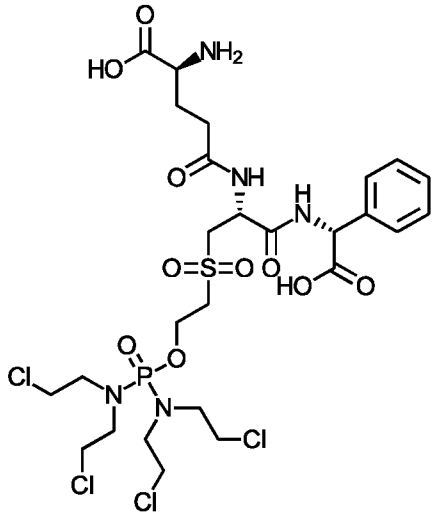
In certain embodiments, the DNA-PK inhibitor is:



,

(3*S*)-3-amino-4-[5-[bis(2-chloroethyl)amino]-2-methylphenyl]butanoic acid (QBS10072S) and the amount administered can be about 12mg/m^2 injection.

In certain embodiments, the DNA-PK inhibitor is:



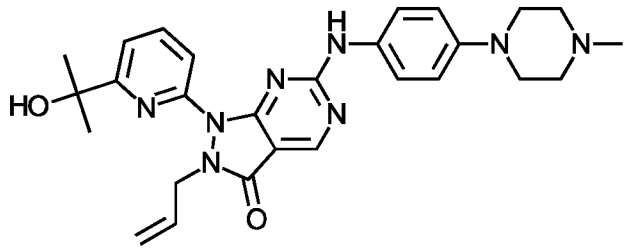
,

(2S)-2-amino-5-[[(2R)-3-[2-[bis[bis(2-chloroethyl)amino]phosphoryloxy]ethylsulfonyl]-1-[[(R)-carboxy(phenyl)methyl]amino]-1-oxopropan-2-yl]amino]-5-oxopentanoic acid (Canfosfamide (TLK-286, TER286)) and the amount administered can be about 1000 mg/m^2.

In certain embodiments, the DNA-PK inhibitor is XRD-0394 from XRad Therapeutics Inc. and the amount administered can be about 40 mg, 80, mg, or 160 mg.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the WEE1 inhibitors listed in TABLE **5**, SC0191, SY-4835, and IMP7068, or a pharmaceutically acceptable salt thereof.

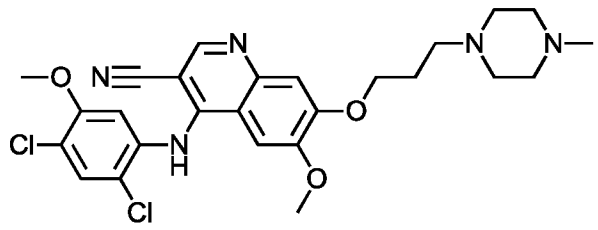
In certain embodiments the WEE1 inhibitor is:



,

1-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]-6-[4-(4-methylpiperazin-1-yl)anilino]-2-prop-2-enylpyrazolo[3,4-d]pyrimidin-3-one (adavosertib (AZD1775, MK-1775)) and the amount administered can be about 300 mg.

In certain embodiments the WEE1 inhibitor is:



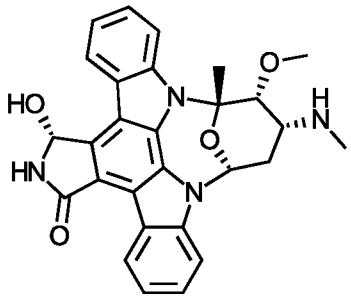
,

4-(2,4-dichloro-5-methoxyanilino)-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile (bosutinib) and the amount administered can be about 400 mg.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the PKMYT1 inhibitors listed in TABLE **6** and ACR-2316, or a pharmaceutically acceptable salt thereof.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the CHK1 selective inhibitors listed in TABLE **7** and VER250840, or a pharmaceutically acceptable salt thereof.

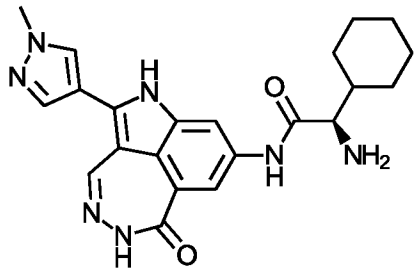
In certain embodiments the CHK1 selective inhibitor is:



,

(2S,3R,4R,6R,18R)-18-hydroxy-3-methoxy-2-methyl-4-(methylamino)-29-oxa-1,7,17-triazaoctacyclo [12.12.2.1^{2,6}.0^{7,28}.0^{8,13}.0^{15,19}.0^{20,27}.0^{21,26}]nonacosa-8,10,12,14,19,21,23,25,27-nonaen-16-one (7-Hydroxystaurosporine (UNC-01)) and the amount administered can be about 68 or 135 mg/m^2.

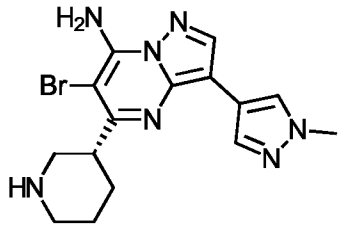
In certain embodiments the CHK1 selective inhibitor is:



,

(2R)-2-amino-2-cyclohexyl-N-[2-(1-methylpyrazol-4-yl)-9-oxo-3,10,11-triazatricyclo[6.4.1.$0^{4,13}$]trideca-1,4,6,8(13),11-pentaen-6-yl]acetamide (PF477736) and the amount administered can be from about 750 to 1250 mg/m^2.

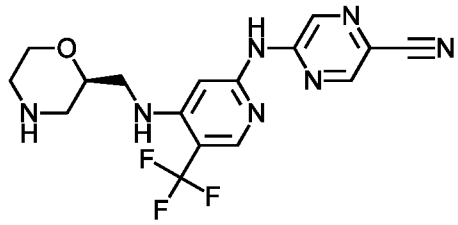
In certain embodiments the CHK1 selective inhibitor is:



,

6-bromo-3-(1-methylpyrazol-4-yl)-5-[(3R)-piperidin-3-yl]pyrazolo[1,5-a]pyrimidin-7-amine (MK8776/SCH900776) and the amount administered can be from about 10, 20, 40 or 56 mg/m^2.

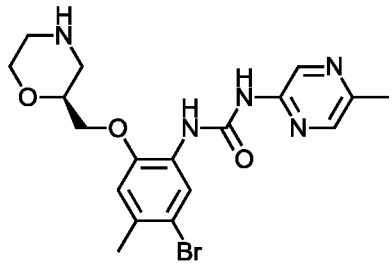
In certain embodiments the CHK1 selective inhibitor is:



,

5-[[4-[[(2R)-morpholin-2-yl]methylamino]-5-(trifluoromethyl)pyridin-2-yl]amino]pyrazine-2-carbonitrile (CCT245737 (SRA737, PNT-737)) and the amount administered can be about 500 mg.

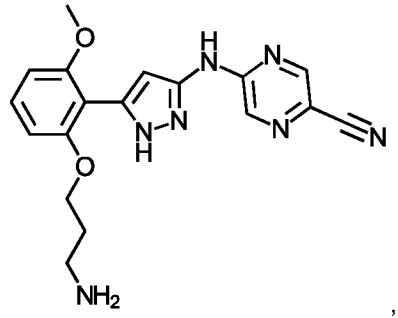
In certain embodiments the CHK1 selective inhibitor is:



,

1-[5-bromo-4-methyl-2-[[(2S)-morpholin-2-yl]methoxy]phenyl]-3-(5-methylpyrazin-2-yl)urea (LY2603618, Rabusertib) and the amount administered can be about 230-275 mg.

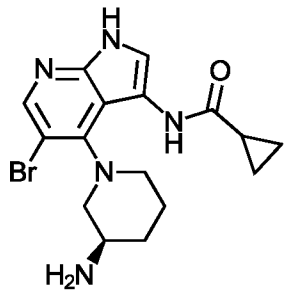
In certain embodiments the CHK1 selective inhibitor is:



,

5-[[5-[2-(3-aminopropoxy)-6-methoxyphenyl]-1*H*-pyrazol-3-yl]amino]pyrazine-2-carbonitrile (prexasertib (LY2606368)) and the amount administered can be about 105, 150, or 170 mg/m^2.

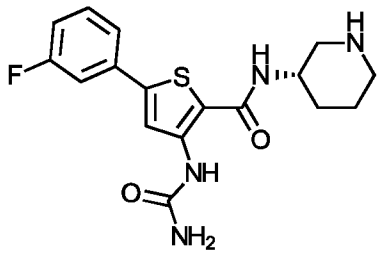
In certain embodiments the CHK1 selective inhibitor is:



,

N-[4-[(3R)-3-aminopiperidin-1-yl]-5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl]cyclopropanecarboxamide (ARRY575, GDC-0575) and the amount administered can be about 45 or 80 mg.

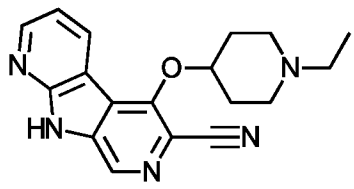
In certain embodiments the CHK1 selective inhibitor is:



,

3-(carbamoylamino)-5-(3-fluorophenyl)-N-[(3S)-piperidin-3-yl]thiophene-2-carboxamide (AZD7762) and the amount administered can be about 6, 9, 14, 21, 30, 32, or 40 mg.

In certain embodiments, the CHK1 selective inhibitor is:

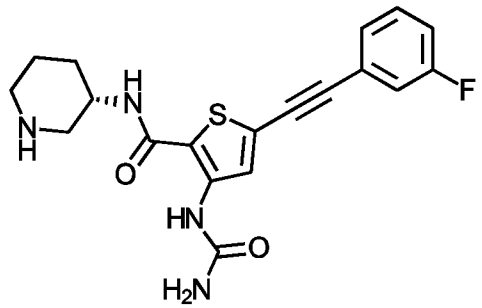


,

3-(1-ethylpiperidin-4-yl)oxy-5,8,10-triazatricyclo[7.4.0.0^{2,7}]trideca-1(9),2,4,6,10,12-hexaene-4-carbonitrile (GDC0425) and the amount administered can be about 60-80 mg.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the CHK2 selective inhibitors listed in TABLE **8**, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the CHK2 selective inhibitor is:

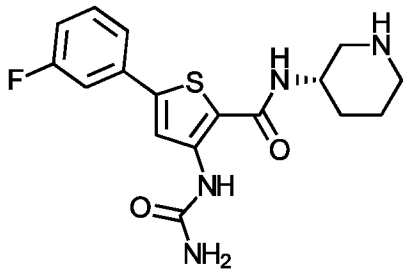


,

3-(carbamoylamino)-5-[2-(3-fluorophenyl)ethynyl]-N-[(3S)-piperidin-3-yl]thiophene-2-carboxamide (PHI-101) and the amount administered can be about 40, 80, 120, 160, 200, or 240 mg.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the dual CHK1/2 inhibitors listed in TABLE **9**, or a pharmaceutically acceptable salt thereof.

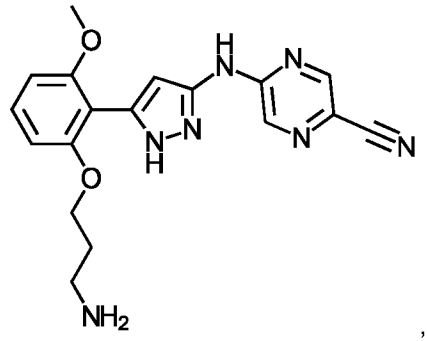
In certain embodiments, the dual CHK1/2 inhibitor is:



,

3-(carbamoylamino)-5-(3-fluorophenyl)-N-[(3S)-piperidin-3-yl]thiophene-2-carboxamide (AZD7762) and the amount administered can be about 6, 9, 14, 21, 30, 32, or 40 mg.

In certain embodiments, the dual CHK1/2 inhibitor is:



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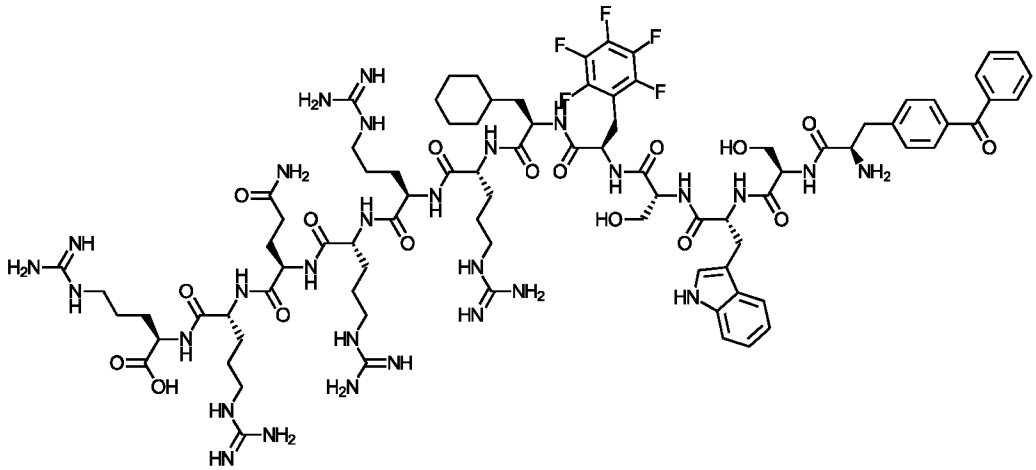
5-[[5-[2-(3-aminopropoxy)-6-methoxyphenyl]-1*H*-pyrazol-3-yl]amino]pyrazine-2-carbonitrile (prexasertib (LY2606368)) and the amount administered can be about 105, 150, or 170 mg/m^2.

In certain embodiments, the dual CHK1/2 inhibitor is:



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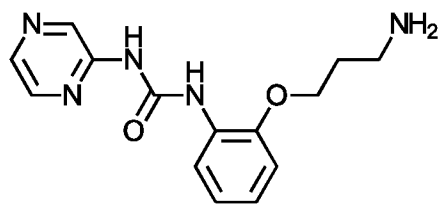
(2R)-2-[[(2R)-2-[[(2R)-5-amino-2-[[(2R)-2-[[(2R)-2-[[(2R)-2-[[(2R)-2-[[(2R)-2-[[(2R)-2-[[(2R)-2-[[(2R)-2-[[(2R)-2-amino-3-(4-benzoylphenyl)propanoyl]amino]-3-hydroxypropanoyl]amino]-3-(1H-indol-3-yl)propanoyl]amino]-3-hydroxypropanoyl]amino]-3-(2,3,4,5,6-pentafluorophenyl)propanoyl]amino]-3-cyclohexylpropanoyl]amino]-5-carbamimidamidopentanoyl]amino]-5-carbamimidamidopentanoyl]amino]-5-carbamimidamidopentanoyl]amino]-5-oxopentanoyl]amino]-5-carbamimidamidopentanoyl]amino]-5-carbamimidamidopentanoic acid (CBP501) and the amount administered can be about 16 or 25 mg/m^2.

In certain embodiments, the dual CHK1/2 inhibitor is:



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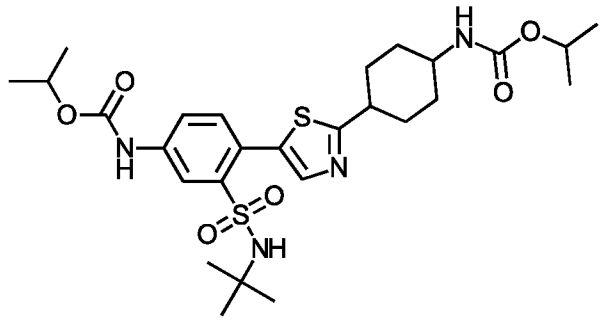
1-[2-(3-aminopropoxy)phenyl]-3-pyrazin-2-ylurea (XL844) and the amount administered can be about 5, 25, or 100 mg.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the Polθ inhibitors listed in TABLE **10**, ART4215, ART6043, RP-3467, and GSK101 (GSK4524101/IDE705), or a pharmaceutically acceptable salt thereof.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the RAD51 inhibitors listed in TABLE **11**, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the RAD51 inhibitor is:



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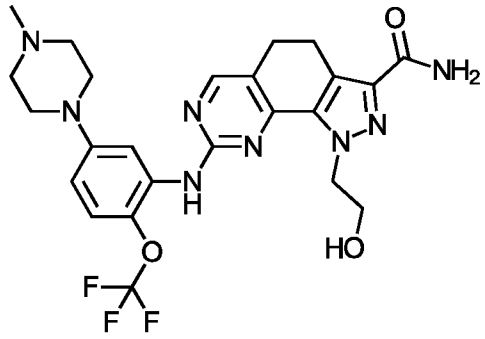
propan-2-yl *N*-[3-(*tert*-butylsulfamoyl)-4-[2-[4-(propan-2-yloxycarbonylamino)cyclohexyl]-1,3-thiazol-5-yl]phenyl]carbamate (CYT0851) and the amount administered can be about 300 or 400 mg.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the USP1 inhibitors listed in TABLE **12**, TNG348, HSK39775, FT-3171 (Debio 0432), and ISM3091 (XL309), or a pharmaceutically acceptable salt thereof.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the PLK1 inhibitors TABLE **13**, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the PLK1 inhibitor is:



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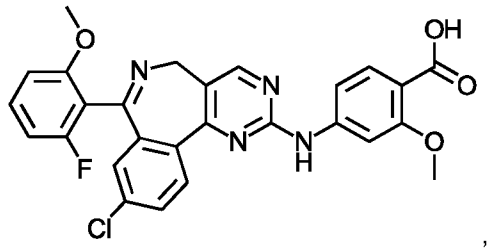
1-(2-hydroxyethyl)-8-[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy)anilino]-4,5-dihydropyrazolo[4,3-h]quinazoline-3-carboxamide (onvansertib) and the amount administered can be about 12, 15 or 18 mg/m^2.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the Aurora kinase inhibitors listed in TABLE **14** and WJ05129, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the Aurora kinase inhibitors is the Aurora kinase A inhibitor WJ05129 and the amount administered can be about 1.25, 2.5, 5, 7.5, or 10 mg.

In certain embodiments, the Aurora kinase inhibitor is the Aurora kinase A inhibitor:



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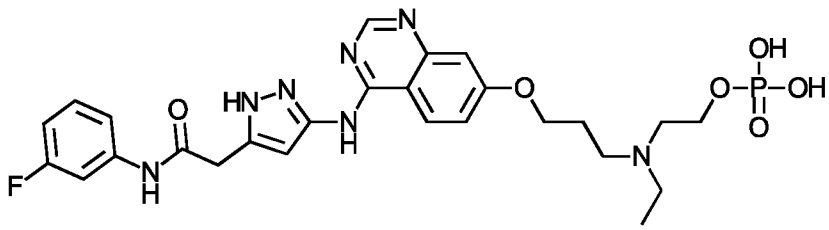
4-[[9-chloro-7-(2- fluoro-6-methoxyphenyl)-5H-pyrimido[5,4-d][2]benzazepin-2-yl]amino]-2-methoxybenzoic acid (Alisertib (MLN8237)) and the amount administered can be about 50 mg.

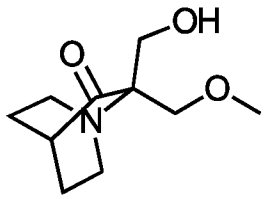
In certain embodiments, the Aurora kinase inhibitor is the Aurora Kinase B inhibitor:



2-[ethyl-[3-[4-[[5-[2-(3-fluoroanilino)-2-oxoethyl]-1H-pyrazol-3-yl]amino]quinazolin-7-yl]oxypropyl]amino]ethyl dihydrogen phosphate (Barasertib (AZD1152)) and the amount administered can be about 200 mg.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the mutant p53 re-activators listed in TABLE **15** and PC14586, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the mutant p53 re-activator is:



2-(hydroxymethyl)-2-(methoxymethyl)-1-azabicyclo[2.2.2]octan-3-one (APR246) and the amount administered can be about 60 mg/kg.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the PARG inhibitors listed in TABLE **16** and IDE161, or a pharmaceutically acceptable salt thereof.

In particular, the present disclosure provides methods of treating a PSMA-expressing cancer in a subject in need thereof, wherein the method comprises administering to the subject a therapeutically effective amount of [177Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of one or more of the WRN inhibitors listed in TABLE **17**, RO7589831 and HRO761, or a pharmaceutically acceptable salt thereof.

In one or more of the above embodiments, the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617, the DDRi, or both, is lower than the amount required for a monotherapy response of objective response rate (ORR), disease control rate (DCR), progression free survival (PFS), duration of response (DOR), overall survival (OS), complete response (CR), partial response (PR), PSA response rate, radiographic response rate, change from baseline in blood and tumor tissue microenvironment pharmacodynamic (PD) biomarkers, or a combination thereof. For example, the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617, the DDRi, or both can be at least about 10% lower to about 50% lower than the amount required for the monotherapy response.

In certain embodiments, the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 can be about 10%, 15%, 20%, 25%, 30% 35% 40% 45% or about 50% lower than the amount

of [^{177}Lu]Lu-PSMA-617 required for an objective response rate (ORR), disease control rate (DCR), progression free survival (PFS), duration of response (DOR), overall survival (OS), complete response (CR), partial response (PR), PSA response rate, radiographic response rate, change from baseline in blood and tumor tissue microenvironment pharmacodynamic (PD) biomarkers, or a combination thereof observed with [^{177}Lu]Lu-PSMA-617 monotherapy.

In certain embodiments, the therapeutically effective amount of the DDRi can be about 10%, 15%, 20%, 25%, 30% 35%, 40%, 45% or about 50% lower than the amount of the DDRi required for an objective response rate (ORR), disease control rate (DCR), progression free survival (PFS), duration of response (DOR), overall survival (OS), complete response (CR), partial response (PR), PSA response rate, radiographic response rate, change from baseline in blood and tumor tissue microenvironment pharmacodynamic (PD) biomarkers, or a combination thereof observed with DDRi monotherapy.

In certain embodiments, practicing a method as described above produces a synergistic response in the subject, such as a synergistic anti-cancer response, as compared to a method of administering the [^{177}Lu]Lu-PSMA-617 or the DDRi as monotherapy.

In certain embodiments, practicing a method as described above widens the therapeutic index of administering the [^{177}Lu]Lu-PSMA-617 or the DDRi as monotherapy. For example, practicing a method as described above can widen the therapeutic index of [^{177}Lu]Lu-PSMA-617 monotherapy or DDRi monotherapy by at least about 10% to about 50%.

As is common with radiation therapy, in order to deliver the total dose of radiation required to eradicate the PSMA-expressing cancer, the method may include administering [177Lu]Lu-PSMA-617, about every 4 to 8 weeks for a number of cycles. In the present methods, the therapeutically effective amount of [177Lu]Lu-PSMA-617, *e.g.*, about 3 GBq to about 10 GBq as described above, can be administered to the subject about every 4 to 8 weeks, such as about every 4 to 6 weeks, about every 6 to 8 weeks, about every 4 to 5 weeks, about every 5 to 8 weeks, about every 4 to 7 weeks, about every 5 to 6 weeks, about every 5 to 7 weeks, and about every 6 to 7 weeks.

In certain embodiments, the number of weeks and/or number of cycles of [177Lu]Lu-PSMA-617 administration in the present methods can be reduced as compared to [177Lu]Lu-PSMA-617 monotherapy without a reduction in therapeutic efficacy. In certain embodiments, the number of weeks and/or number of cycles of [177Lu]Lu-PSMA-617 administration required to achieve desired clinical measure or parameter can be reduced as compared to [177Lu]Lu-PSMA-617 monotherapy. In some embodiments, the therapeutically effective amount of [177Lu]Lu-PSMA-617, *e.g.*, about 3 GBq to about 10 GBq as described above, can be administered to the subject about every 4 weeks, about every 5 weeks, about every 6 weeks, about every 7 weeks, or about every 8 weeks.

In some embodiments, the therapeutically effective amount of [177Lu]Lu-PSMA-617, *e.g.*, about 3 GBq to about 10 GBq as described above, can be administered to the subject can be administered for a duration as described above for 4 to 6 cycles. For example, the therapeutically effective amount of [177Lu]Lu-PSMA-617 can be administered about every 4 to 8 weeks for 4 cycles, for 5 cycles, or for 6 cycles.

In some embodiments, the therapeutically effective amount of [177Lu]Lu-PSMA-617 can be administered about every 4 to 6 weeks for 4 to 6 cycles, about every 6 to 8 weeks for 4 to 6 cycles, about every 6 to 8 weeks for 4 cycles, about every 6 to 8 weeks for 5 cycles, about every 6 to 8 weeks for 6 cycles, about every 4 to 5 weeks for 4 to 6 cycles, about every 4 to 7 weeks for 4 to 6 cycles, about every 5 to 8 weeks for 4 to 6 cycles, about every 5 to 6 weeks for 4 to 6 cycles, about every 5 to 7 weeks for 4 to 6 cycles, about every 6 to 7 weeks for 4 to 6 cycles, about every 4 weeks for 4 to 6 cycles, about every 5 weeks for 4 to 6 cycles, about every 6 weeks for 4 to 6 cycles, about every 7 weeks for 4 to 6 cycles, about every 8 weeks for 4 to 6 cycles, about every 4 weeks for 4 cycles, about every 4 weeks for 6 cycles, about every 6 weeks for 4 cycles, about every 6 weeks for 6 cycles, about every 8 weeks for 4 cycles, or about every 8 weeks for 6 cycles.

In some embodiments, the therapeutically effective amount of [177Lu]Lu-PSMA-617 can be administered about every 5 weeks for 4 cycles, about every 5 weeks for 6 cycles, about every 7 weeks for 4 cycles, about every 7 weeks for 6 cycles, about every 4 weeks for 5 cycles about every 6 weeks for 5 cycles, about every 8 weeks for 5 cycles, about every 5 weeks for 5 cycles, or about every 7 weeks for 5 cycles.

Duration or frequency of administering the therapeutically effective amount of the DDRi can vary depending on the compound used, the subject being treated and the particular PSMA-expressing cancer being treated. In certain embodiments, the duration or frequency can be the maximal duration or frequency protocol that avoids significant side effects or toxic effects or an occurrence of unacceptable toxicity. In certain embodiments, the duration or frequency is the minimal duration or frequency that provides an improvement in the clinical measure or parameter, as described above, or the minimal duration or frequency for a synergistic effect.

In certain embodiments, the therapeutically effective amount of the DDRi is administered in one or more doses within 24 hours of [^{177}Lu]Lu-PSMA-617 administration, within 22 hours of [^{177}Lu]Lu-PSMA-617 administration, within 20 hours of [^{177}Lu]Lu-PSMA-617 administration, within 18 hours of [^{177}Lu]Lu-PSMA-617 administration, within 16 hours of [^{177}Lu]Lu-PSMA-617 administration, within 14 hours of [^{177}Lu]Lu-PSMA-617 administration, within 12 hours of [^{177}Lu]Lu-PSMA-617 administration, within 10 hours of [^{177}Lu]Lu-PSMA-617 administration, within 8 hours of [^{177}Lu]Lu-PSMA-617 administration, within 6 hours of

[^{177}Lu]Lu-PSMA-617 administration, within 4 hours of [^{177}Lu]Lu-PSMA-617 administration, within 3 hours of [^{177}Lu]Lu-PSMA-617 administration, within 2 hours of [^{177}Lu]Lu-PSMA-617 administration, within 1 hour of [^{177}Lu]Lu-PSMA-617 administration, or within 30 minutes of [^{177}Lu]Lu-PSMA-617 administration. In certain embodiments, the therapeutically effective amount of the DDRi is administered in one or more doses and the therapetucially effective amount of [^{177}Lu]Lu-PSMA-617 is administered in one or more doses concurrently (optionally in separate dosage forms)

In certain embodiments, the therapeutically effective amount of the DDRi is administered in one or more doses for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 20 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 24 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 28 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 32 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 36 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 40 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 44 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 48 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 52 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 56 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 60 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 64 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 68 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 72 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 76 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 80 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 84 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 88 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 92 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 98 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 102 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 106 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 110 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 114 hours after [^{177}Lu]Lu-PSMA-617 administration, for at least 118 hours after [^{177}Lu]Lu-PSMA-617 administration, or for at least 122 hours after [^{177}Lu]Lu-PSMA-617 administration. In certain embodiments, the therapeutically effective amount of the DDRi is administered in one or more doses over a course of about, or at least about, 5 days.

The range encompassed by “at least about 5 days” can include at least about 1, 2, 3, or 4 weeks, at least about 1, 2, 3, 4, 5, or 6 months. In some cases, at least about 5 days can be 4 to 8 weeks, for one or more cycles. The cycles can occur with the same periodicity as a 177Lu]Lu-PSMA-617 cycle, or can occur at different intervals of therapy.

Administration for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration or over a course of about, or at least about, 5 days can occur at regular intervals (*e.g.*, q.d., b.i.d., t.i.d., or on alternating days), on specific days of a [^{177}Lu]Lu-PSMA-617 cycle, or continuously.

In certain embodiments, the DDRi is administered within 24 hours of [^{177}Lu]Lu-PSMA-617 administration and for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration (*e.g.*, over a course of about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration, or any time interval between 16 hours and about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration. In certain embodiments, the DDRi is administered within 22 hours of [^{177}Lu]Lu-PSMA-617 administration and for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration (*e.g.*, over a course of about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration, or any time interval between 16 hours and about 5 days after [^{177}Lu]Lu-PSMA-617 administration. In certain embodiments, the DDRi is administered within 20 hours of [^{177}Lu]Lu-PSMA-617 administration and for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration (*e.g.*, over a course of about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration, or any time interval between 16 hours and about 5 days after [^{177}Lu]Lu-PSMA-617 administration. In certain embodiments, the DDRi is administered within 18 hours of [^{177}Lu]Lu-PSMA-617 administration and for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration (*e.g.*, over a course of about 5 days after [^{177}Lu]Lu-PSMA-617 administration, or any time interval between 16 hours and about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration. In certain embodiments, the DDRi is administered within 16 hours of [^{177}Lu]Lu-PSMA-617 administration and for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration (e.g., over a course of about 5 days after [^{177}Lu]Lu-PSMA-617 administration, or any time interval between 16 hours and about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration. In certain embodiments, the DDRi is administered within 14 hours of [^{177}Lu]Lu-PSMA-617 administration and for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration (*e.g.*, over a course of about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration, or any time interval between 16 hours and about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration. In certain embodiments, the DDRi is administered within 12 hours of [^{177}Lu]Lu-PSMA-617 administration and for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration (*e.g.*, over a course of about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration, or any time interval between 16 hours and about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration. In certain embodiments, the DDRi is administered within 10 hours of [^{177}Lu]Lu-PSMA-617 administration and for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration (*e.g.*, over a course of about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration, or any time interval between 16 hours and about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration. In certain embodiments, the DDRi is administered within 8 hours of [^{177}Lu]Lu-PSMA-617 administration and for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration (*e.g.*, over a course of about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration, or any time interval between

16 hours and about 5 days after [^{177}Lu]Lu-PSMA-617 administration. In certain embodiments, the DDRi is administered within 6 hours of [^{177}Lu]Lu-PSMA-617 administration and for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration (*e.g.*, over a course of about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration, or any time interval between 16 hours and about 5 days after [^{177}Lu]Lu-PSMA-617 administration. In certain embodiments, the DDRi is administered within 4 hours of [^{177}Lu]Lu-PSMA-617 administration and for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration (*e.g.*, over a course of about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration, or any time interval between 16 hours and about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration. In certain embodiments, the DDRi is administered within 2 hours of [^{177}Lu]Lu-PSMA-617 administration and for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration (*e.g.*, over a course of about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration, or any time interval between 16 hours and about 5 days after [^{177}Lu]Lu-PSMA-617 administration. In certain embodiments, the DDRi is administered within 1 hour of [^{177}Lu]Lu-PSMA-617 administration and for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration (*e.g.*, over a course of about, or at least about, 5 days after [^{177}Lu]Lu-PSMA-617 administration, or any time interval between 16 hours and about 5 days after [^{177}Lu]Lu-PSMA-617 administration.

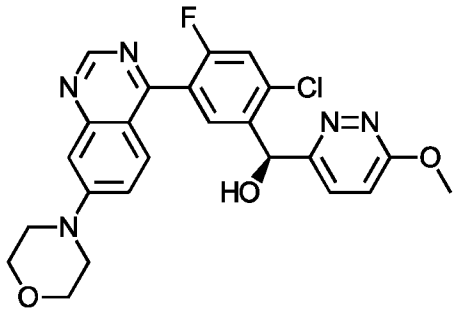
In certain embodiments, at least one dose of the DDRi is administered concurrently (optionally separately) with [^{177}Lu]Lu-PSMA-617 administration and one or more additional doses of the DDRi is administered for at least 16 hours after the concurrent administration (*e.g.*, over a course of about, or at least about, 5 days after the concurrent administration, or any time interval between 16 hours and about, or at least about, 5 days after the concurrent administration.

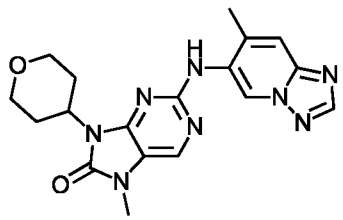
In the methods described herein, the PSMA-expressing cancer can be any cancer that exhibits high PSMA expression compared to corresponding healthy cells or tissues. For example, in various prostate cancers and salivary gland cancers, the level of PSMA expression of the malignant cells is markedly increased compared to that of healthy cells. In certain embodiments, the PSMA-expressing cancer is PSMA-positive cancer in the biochemical recurrence (BCR) setting, such as PSMA-positive cancer in the high-risk BCR setting.

In one or more embodiments of the methods described herein, the PSMA-expressing cancer is prostate cancer. In some embodiments, the prostate cancer is PSMA-positive oligometastatic prostate cancer (OMPC). In some embodiments, when the PSMA-expressing cancer is prostate cancer, then the prostate cancer is metastatic prostate cancer. In certain embodiments, the metastatic prostate cancer is metastatic castration-resistant prostate

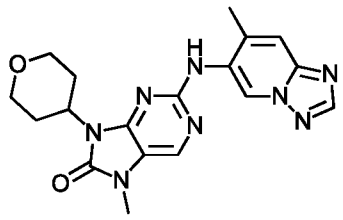
cancer (mCRPC). In certain embodiments, the metastatic prostate cancer is PSMA-positive metastatic hormone-sensitive prostate cancer (mHSPC).

Particular Embodiments of the Methods of Treatment

In particular, provided herein are methods of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:  ((S)-[2-chloro-4-fluoro-5-(7-morpholin-4-ylquinazolin-4-yl)phenyl]-(6-methoxypyridazin-3-yl)methanol (M3814), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi. The therapeutically effective amount of the DDRi can be a dose of from about 1 to 1000 mg/kg, about 10 to 900 mg/kg, about 15 to 800 mg/kg, about 20 to 700 mg/kg, about 25 to 600 mg/kg, about 30 mg to 500 mg/kg, about 35 to 400 mg/kg, about 40 to 300 mg/kg, about 45 to 200 mg/kg, or about 50 to 100 mg/kg, optionally about 100 mg/kg, administered twice daily for about, or at least about, 5 days, or about 50 mg, about 100 mg, about 150 mg, or about 250 mg daily.

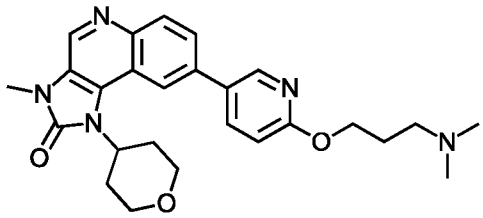
In an embodiment, provided herein are methods of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is  ((7-Methyl-2-[(7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino]-9-(oxan-4-yl)purin-8-one (AZD7648)), or a pharmaceutically acceptable salt thereof. In an embodiment, the prostate cancer is prostate-specific membrane antigen–positive metastatic castration-resistant prostate cancer (PSMA-positive mCRPC).

In particular, provided herein are methods of treating PSMA-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is



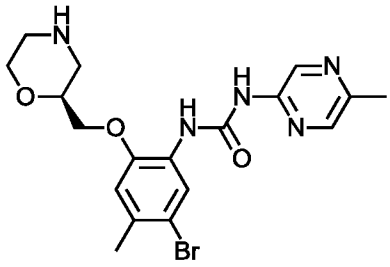
((7-Methyl-2-[(7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino]-9-(oxan-4-yl)purin-8-one (AZD7648)), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi. The therapeutically effective amount of the DDRi can be a dose of from about 1 to 1000 mg/kg, about 10 to 900 mg/kg, about 15 to 800 mg/kg, about 20 to 700 mg/kg, about 25 to 600 mg/kg, about 30 mg to 500 mg/kg, about 35 to 400 mg/kg, about 40 to 300 mg/kg, about 45 to 200 mg/kg, or about 50 to 100 mg/kg, optionally about 100 mg/kg, administered once daily.

In particular, provided herein are methods of treating PSMA-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:



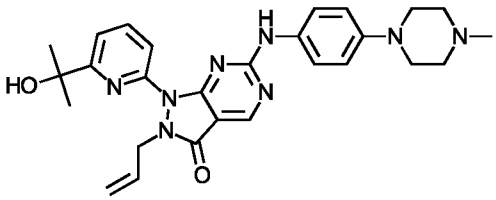
(8-[6-[3-(dimethylamino)propoxy]pyridin-3-yl]-3-methyl-1-(oxan-4-yl)imidazo[4,5-c]quinolin-2-one (AZD0156)), or pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

In particular, provided herein are methods of treating PSMA-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:



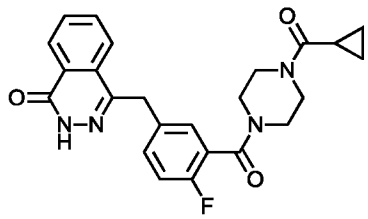
,1-[5-bromo-4-methyl-2-[[(2S)-morpholin-2-yl]methoxy]phenyl]-3-(5-methylpyrazin-2-yl)urea (LY2603618, Rabusertib) or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is improved or synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

In particular, provided herein are methods of treating PSMA-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:



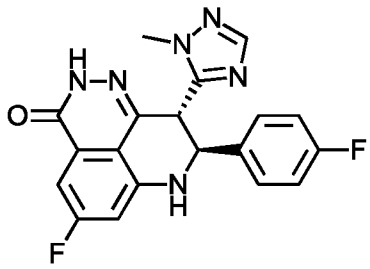
(1-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]-6-[4-(4-methylpiperazin-1-yl)anilino]-2-prop-2-enylpyrazolo[3,4-d]pyrimidin-3-one (Adavosertib or MK-1775), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is improved or synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

In particular, provided herein are methods of treating PSMA-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:



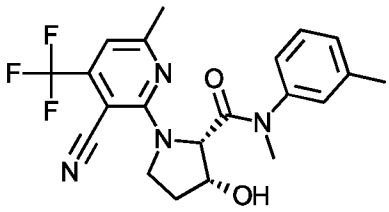
4-[[3-[4-(cyclopropanecarbonyl)piperazine-1-carbonyl]-4-fluorophenyl]methyl]-2*H*-phthalazin-1-one (olaparib), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi, optionally wherein the DDRi is administered within 24 hours of administration of [^{177}Lu]Lu-PSMA-617 and/or the DDRi is administered within 24 hours of administration and over the course of at least 48 hours.

In particular, provided herein are methods of treating PSMA-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:



((11S,12R)-7-fluoro-11-(4-fluorophenyl)-12-(2-methyl-1,2,4-triazol-3-yl)-2,3,10-triazatricyclo[7.3.1.0^{5,13}]trideca-1,5(13),6,8-tetraen-4-one (talazoparib), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

In particular, provided herein are methods of treating PSMA-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:

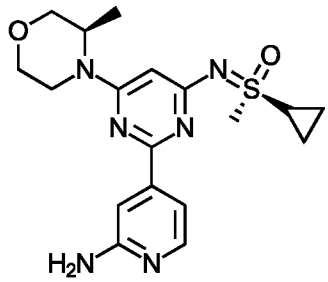


((2*S*,3*R*)-1-[3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl]-3-hydroxy-*N*-methyl-N-(3-methylphenyl)pyrrolidine-2-carboxamide (ART558), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

In an embodiment, provided herein are methods of treating prostate cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is ART6043, or a pharmaceutically acceptable salt thereof. In an embodiment, the prostate cancer is prostate-specific membrane antigen–positive metastatic castration-resistant prostate cancer (PSMA-positive mCRPC).In particular, provided herein are methods of treating PSMA-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the

DDRi is ART6043, or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is improved or synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi. The improvement can include an extended response (*e.g.*, extended survival) as compared to the monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi. The therapeutically effective amount of the DDRi can be about 100 mg/kg. The DDRi can be administered daily for least about 5 days (*e.g.*, at least about 20 days).

In particular, provided herein are methods of treating PSMA-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is



((S)-((2-(2-aminopyridin-4-yl)-6-((R)-3-methylmorpholino)pyrimidin-4-yl)imino)(cyclopropyl)(methyl)-λ^6 -sulfanone (ART0380)), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

In any of the particular embodiments described above, the PSMA-expressing cancer can be prostate cancer (*e.g.*, metastatic prostate cancer or metastatic castration-resistant prostate cancer (mCRPC) optionally PSMA-positive metastatic hormone-sensitive prostate cancer (mHSPC), optionally PSMA-positive oligometastatic prostate cancer (OMPC)) and/or PSMA-positive cancer in the biochemical recurrence (BCR) setting, optionally PSMA-positive cancer in the high-risk BCR setting, the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 can be a dose of from about 10 MBq to 10 GBq, such as from about 0.1 GBq to 10 GBq, from about 1 GBq to 10 GBq, from about 3 GBq to 10 GBq, from about 5 GBq to about 9 GBq, or from about 6 GBq to about 8 GBq (optionally about 7.4 GBq), the DDRi can be administered for about, or at least about, 5 days, and/or the initial dose of the DDRi can be administered less than 1 hour prior to [^{177}Lu]Lu-PSMA-617 administration.

Pharmaceutical Compositions

Also provided herein are pharmaceutical compositions for use in the methods described above comprising [^{177}Lu]Lu-PSMA-617 and/or a DDRi and a pharmaceutically acceptable carrier, diluent, or excipient. In certain embodiments, [^{177}Lu]Lu-PSMA-617 and/or

a DDRi are not formulated together, and can be supplied separately, *e.g.*, as separate pharmaceutical compositions.

The amount of [^{177}Lu]Lu-PSMA-617 and/or DDRi that may be combined with pharmaceutically acceptable carrier, diluent, or excipient to produce a single dosage form will vary depending upon the individual subject and the particular mode of administration. In some embodiments the unit dosage forms containing the combination of [^{177}Lu]Lu-PSMA-617 and DDRi as described above will contain the amounts of each compound in the combination that are administered when the compounds are administered alone, or the amount of [^{177}Lu]Lu-PSMA-617 and/or DDRi can be less than the amount of each compound when the compounds are administered alone, or the amount of [^{177}Lu]Lu-PSMA-617 and/or DDRi can be greater than the amount of each compound when the compounds are administered alone. The pharmaceutically acceptable carrier, diluent or excipient may be a solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type.

The pharmaceutical compositions may be administered parenterally. Accordingly, in certain embodiments, the compositions are formulated for delivery by any of these routes of administration. A pharmaceutical composition may be formulated for and administered by parenteral administration. In particular, a pharmaceutical composition of the present disclosure may be formulated for and administered by intravenous administration.

In certain embodiments, pharmaceutical compositions for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders, for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, β-cyclodextrin, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. These compositions may also contain additives such as preservatives, wetting agents, emulsifying agents, chelating agents, buffering agents, and dispersing agents.

In some embodiments, the pharmaceutical composition comprises a chelating agent to sequester internally deposited radionuclides. Any chelating agent known in the art that complexes to alpha-emitting radionuclides may be included in pharmaceutical compositions described herein. In various embodiments, the pharmaceutical composition comprises DTPA. Additional exemplary chelating agents that may be included in pharmaceutical compositions of the present disclosure are described in Holik, et al. “The Chemical Scaffold of Theranostic

Radiopharmaceuticals: Radionuclide, Bifunctional Chelator, and Pharmacokinetics Modifying Linker." Molecules 27,10 (2022): 3062 and Kostelnik, Thomas I., and Chris Orvig. "Radioactive main group and rare earth metals for imaging and therapy." Chemical reviews 119.2 (2018): 902-956, both of which are incorporated herein by reference in their entireties.

Pharmaceutical compositions can further include a stabilizer, such as, for example, a free radical scavenger or radiation stability enhancer, in order to prevent autoradiolysis of the radioligand. Stabilizer(s) present in the solutions of the present disclosure can be selected from gentisic acid (2,5-dihydroxybenzoic acid) or salts thereof, ascorbic acid (L-ascorbic acid, vitamin C) or salts thereof (e.g. sodium ascorbate), methionine, histidine, melatonine, ethanol, and Se-methionine. In some cases, the stabilizer(s) can include gentisic acid or salts thereof, and not ethanol. Suitable stabilizers for inclusion in the disclosed pharmaceutical compositions include, but are not limited to, 2,5-dihydroxybenzoic acid or salts thereof, ascorbic acid or salts thereof, gentisic acid or salts thereof, methionine, histidine, melatonine, N-acetylmethionine, ethanol, an amino acid infusion solution, or any combination thereof. In some embodiments, the pharmaceutical composition includes a gentisic acid stabilizer. In some embodiments, the pharmaceutical composition includes an ascorbic acid stabilizer. In some embodiments, the pharmaceutical composition include stabilizer including gentisic acid and ascorbic acid.

In some embodiments, the pharmaceutical composition comprises one or more buffering agents to maintain a pH of about 3 to 5. Suitable buffering agents include, but are not limited to acetate, citrate, Tris, lactate, and tartrate, and the acid forms thereof.

In some embodiments, the [^{177}Lu]Lu-PSMA-617 pharmaceutical composition is an aqueous pharmaceutical solution.

In a specific embodiment the present disclosure provides the following aqueous solution:

(A) [^{177}Lu]Lu-PSMA-617 in an activity in the range from 800 to 1200 MBq/ml, 900 to 1100 MBq/ml, 950 to 1050 MBq/ml, or about 1000 MBq/mL (27 mCi/mL);

(B + C) a buffer to provide a pH in the range of 4.5 to 7.0;

(D) gentisic acid or a salt thereof in a concentration in the range from 0.3 to 1.0, 0.3 to 0.5, 0.31 to 0.47 mg/mL, 0.35 to 0.43 mg/mL, 0.37 to 0.41, or about 0.39 mg/mL with regard to the free acid;

(E) ascorbic acid or a salt thereof, such as the sodium salt thereof, in a concentration in the range from 20 to 52.5 mg/mL, 47.5 to 52.5 mg/mL, 48 to 52 mg/mL, or about 50 mg/mL with regard to the sodium salt;

(F) pentetic acid or a salt thereof in a concentration in the range from 0.08 to 0.12 mg/mL, 0.09 to 0.11 mg/mL, 0.095 to 0.105 mg/mL, or about 0.1 mg/mL with regard to the free acid.

In a specific embodiment the present disclosure provides the following aqueous solution:

(A) [^{177}Lu]Lu-PSMA-617 in an activity in the range from 800 to 1200 MBq/ml, 900 to 1100 MBq/ml, 950 to 1050 MBq/ml, or about 1000 MBq/mL (27 mCi/mL);

(B) acetic acid in a concentration in the range from 0.24 to 0.36 mg/mL, 0.27 to 0.33 g/mL, 0.285 to 0.315 mg/mL, or about 0.3 mg/mL;

(C) an acetate salt, such as the sodium salt thereof, in the concentration in the range from 0.33 to 0.49 mg/mL, 0.37 to 0.45 mg/mL, 0.39 to 0.43 mg/mL, or about 0.41 mg/mL with regard to the sodium salt;

(D) gentisic acid or a salt thereof in a concentration in the range from 0.3 to 1.0, 0.3 to 0.5, 0.31 to 0.47 mg/mL, 0.35 to 0.43 mg/mL, 0.37 to 0.41, or about 0.39 mg/mL with regard to the free acid;

(E) ascorbic acid or a salt thereof, *e.g.*, the sodium salt thereof, in a concentration in the range from 20 to 52.5 mg/mL, 47.5 to 52.5 mg/mL, 48 to 52 mg/mL, or about 50 mg/mL with regard to the sodium salt;

(F) pentetic acid or a salt thereof in a concentration in the range from 0.08 to 0.12 mg/mL, 0.09 to 0.11 mg/mL, 0.095 to 0.105 mg/mL, or about 0.1 mg/mL with regard to the free acid.

In certain embodiments, the aqueous solution comprises, contains, or consists of about [^{177}Lu]Lu-PSMA-617 (about 1,000 MBq/mL, about 27 mCi/mL), acetic acid (about 0.30 mg/mL), sodium acetate (about 0.41 mg/mL), gentisic acid (about 0.39 mg/mL), sodium ascorbate (about 50.0 mg/mL), pentetic acid (about 0.10 mg/mL), and water for injection (e.g. q.s. to 1 mL) with the pH range of the solution being from about 4.5 to about 7.0. The term “about” here means ±10% for all ingredients, or ±10% for the radioactive ingredient and ±5% for the non-radioactive ingredients.

In certain embodiments, any one of the aqueous solutions of the embodiments above can have a radiochemical purity (RCP, determined by HPLC) that is maintained at ≥ 95% for at least 120 hours when stored at 30°C or below. Accordingly, the shelf-life of the aqueous solutions of the present disclosure is about 120 hours or about 5 days, and in some cases, from the date and time of calibration, with storage conditions of below 30°C (86°F), without freezing.

In certain embodiments, any one of the aqueous solutions of the embodiments above can include not more than 5% (w/w) ethanol or not more than 1% ethanol. In some cases, the solution is substantially free of ethanol.

In certain embodiments, any one of the aqueous solutions of the embodiments above can include a total peptide content of from 10 to 20 microgram/mL, 13 to 17 microgram/mL, 14 to 16 microgram/mL, or 15 microgram/mL.

In certain embodiments, any one of the aqueous solutions of the embodiments above can be provided as a sterile, preservative-free, clear, colorless to slightly yellow solution. In certain embodiments, the aqueous solution is provided as ready-to-use solution.

The present disclosure further provides an individual patient dose unit containing a volume of any one of the aqueous solutions as described in any one of the embodiments above. In certain embodiments, the individual patient dose unit volume is about 7.5 to about 12.5 mL of any one of the aqueous solutions as described in any one of the embodiments above.

The patient dose unit can be in the form of a vial, e.g. a single-dose vial, e.g. a colorless borosilicate (type I) glass vial, e.g. of about 30 mL size, e.g. closed with a bromobutyl rubber stopper (stopper with silicate filler and inorganic coloring system) and a seal, such as an aluminum seal, or in the form of a pre-filled syringe or cartridge, e.g. a cartridge that can be loaded into a device for infusion/injection, e.g. a cartridge for a syringe or an infusion system. The aqueous solutions of the present disclosure can be dispensed in a vial and then transferred into a syringe.

The dose unit can be provided in a lead shielded container. The lead shielded container can be placed in a plastic sealed container. The dose unit can be shipped in a Type A packaging system (according to the corresponding regulations of the International Air Transport Association (IATA) and International Carriage of Dangerous Good by Road (ADR)). The Type A packaging can be designed to meet the radiological protection requirements.

The aqueous solutions of any of the embodiments above can be injected intravenously (IV, by bolus injection or infusion) or intraarterially, or intratumorally. The aqueous solutions of any of the embodiments above can be administered to the patient by slow intravenous push within approximately 1 to 10 minutes (either with a syringe pump or infusion pump or manually), e.g. via an intravenous catheter that is pre-filled with e.g. 0.9% sterile sodium chloride solution.

The aqueous solutions of any of the embodiments above can be administered at a dosage/dose described above, and for any duration or number of cycles described above. In certain embodiments, the dosage/dose is about 7.4 (±10%) GBq (200 (±10%) mCi) every about 6 weeks for up to about 6 doses. The dose can be temporarily interrupted (*e.g.*, by extending the dosing interval from every about 6 weeks up to every about 7, 8, 9, or 10 weeks), or the dose may be reduced or increased, *e.g.*, by about 20% to about 5.9 (±10%) GBq (160 (±10%) mCi).

Processes for Manufacturing [177Lu]Lu-PSMA-617

The Lutetium-177 for the embodiments of the present disclosure can be prepared using two different sources of stable isotopes (either lutetium-176 or ytterbium-176). Lutetium-177 is accessible via (n,γ) reaction. There are two methods of ^{177}Lu production in a nuclear reactor. One method comprises irradiation of ^{176}Lu, leading to the direct formation of ^{177}Lu. However, this method leads to concomitant formation of the metastable ^{177m}Lu isotope and other lutetium isotopes. Due to difficulties and challenges of separating the isotopes a composition comprising ^{177}Lu and ^{177m}Lu and others may be used. Such a composition comprising ^{177}Lu and related isotopes is called carrier-added ^{177}Lu source or ^{177}Lu (C.A.) source.

The second method involves beta decay of the short-lived radioisotope ^{177}Yb (half-life of 1.9 hours), which is produced by neutron capture of enriched ^{176}Yb (> 99%) target. The low thermal neutron cross section of the ^{176}Yb (n,γ) ^{177} Yb reaction (2.1 barn), however, results in a production of only very small amounts of the desired ^{177}Lu in comparison with the total mass of the target. However, separation of ^{177}Lu from ^{176}Yb is feasible leading to a composition comprising only the ^{177}Lu isotope. Such compositions provide non-carrier-added ^{177}Lu, in short ^{177}Lu (N.C.A.).

The radionuclide can be lutetium-177 (^{177}Lu) in the form of ^{177}Lu(III) ions. For example, the radionuclide ions may originate from $^{177}LuCl_3$ in HCl solution. The reaction solution may comprise the ^{177}Lu(III) ions in a volumetric activity of at least 17 GBq/ml, 18 GBq/ml, 19 GBq/ml, 20 GBq/mL, 25 GBq/mL, 28 GBq/mL, or at least 30 GBq/mL. The upper limits for radionuclide can be 30, 40, or 50 GBq/mL.

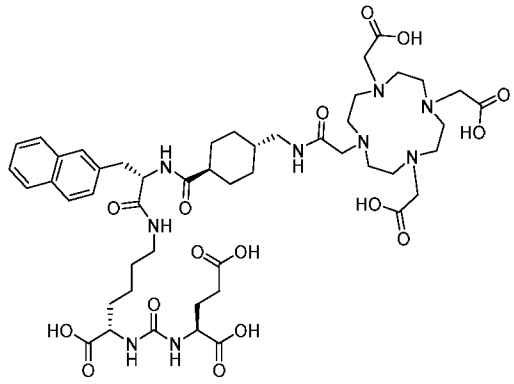
The present disclosure provides a process for manufacturing a radionuclide complex by way of a reaction, *e.g.*, comprising ^{177}Lu(III) ions (radionuclide) and PSMA-617 (the target binding organic molecule). The reaction is also called radiolabeling.

In certain embodiments, a radiopharmaceutical solution comprising [^{177}Lu]Lu-PSMA-617 can be manufactured according to the following process, which affords the solutions and the container, respectively, the process including the steps of:

(1) providing a reaction solution comprising:

a. ^{177}Lu(III) ions in a volumetric activity of at least 17 GBq/mL,

b. a target binding organic molecule comprising an organic moiety which has binding affinity to prostate specific membrane antigen and a chelating moiety for chelating Lu(III) ions (i.e., a compound according to formula (I)



(I), and

c. one or more stabilizers against radiolytic degradation; and

(2) reacting the target binding organic molecule with ^{177}Lu(III) ions at below atmospheric pressure, optionally in the presence of an inert gas, to obtain a radionuclide complex in a single container for radiolabeling.

The reaction solution can include the target binding organic molecule in molar excess to the ^{177}Lu(III) ions, even when the ^{177}Lu(III) ions originate from a non-carrier-added (N.C.A.) ^{177}Lu(III) ion source (i.e., at a molar ratio >1). The molar ratio between the target binding organic molecule and the ^{177}Lu(III) ions can be at least 1.2, or between 1.5 and 3.5.

The reaction solution can include the target binding organic molecule in molar excess to the group of all Lu(III) ions including ^{177}Lu(III) ions, ^{176}Lu(III) ions, ^{175}Lu(III), and metastable ^{177}mLu(III) ions, which are present in the composition that provides the ^{177}Lu(III) ions at the volumetric activity given above for use in the instant reaction solution, when carrier-added (C.A.) ^{177}Lu(III) is used as a source of ^{177}Lu(III) ions. The molar ratio between the target binding organic molecule and the group of all Lu(III) ions including ^{177}Lu(III) ions, ^{176}Lu(III) ions, ^{175}Lu(III), and metastable ^{177m}Lu(III) ions can be at least 1.2, or between 1.5 and 3.5.

The reaction solution can include a pharmaceutically acceptable buffer to provide a pH in the range of 2 to 8, which is suitable for the reaction between the ^{177}Lu(III) ions and the target binding organic molecule. In some cases, the pharmaceutically acceptable buffer provides a pH in the range of 4 to 6.

The pharmaceutically acceptable buffer can include an acetate buffer, citrate buffer or a phosphate buffer. An acetate buffer can include acetic acid and sodium acetate. A citrate buffer can include a citrate and HCl and/or citric acid. A phosphate buffer can include sodium dihydrogen phosphate and disodium hydrogen phosphate.

In some embodiments, step (1) can include mixing the stabilizer against radiolytic degradation with the ^{177}Lu(III) ions prior to addition of the target binding organic molecule. The

individual components of the reaction solution can be mixed under ambient atmosphere and ambient pressure.

In some embodiments, step (1) can include mixing the individual components described herein at below atmospheric pressure to form the reaction solution. A pressure below atmospheric pressure can be within a pressure range that is suitable to remove gaseous components from a container up to removing gaseous components from a solution, but minimizes or avoids substantial evaporation of the solvent (water). The pressure can be at least 150 mbar, 200 mbar, 250 mbar or 300 mbar below atmospheric pressure. The pressure can be up to 400 mbar, 500 mbar, 650 mbar or 700 mbar below atmospheric pressure. The pressure can be at least about 250 mbar and up to 500 mbar below atmospheric pressure.

In some embodiments, step (1) can include degassing solutions of the individual components described herein by letting an inert gas bubble through the solutions or purging the headspace above the individual solutions by an inert gas and then mixing the individual solutions under an inert gas atmosphere.

In some embodiments, step (1) can include degassing solutions of the individual components by letting an inert gas bubble through the solutions or purging the headspace above the individual solutions using an inert gas and then mixing the individual solutions at below atmospheric pressure to form the reaction solution. Below atmospheric pressure can include a pressure as described above.

Mixing at below atmospheric pressure and/or degassing reduces the concentration of oxygen in the reaction solution, thereby reducing radiolytic degradation.

In some embodiments, step (1) can include providing the reaction solution in a container, such as one single container. Providing the reaction solution in a container can include applying a pressure below atmospheric pressure as described above prior to the above step of mixing.

In step (1), the reaction solution can have an activity of at least 5 Ci, such as from about 5 to 20 Ci, about 5 to 15 Ci, about 5 to 12 Ci, about 5.4 to 12 Ci, about 7 to 12 Ci, or about 8 to 12 Ci.

In step (2) the target binding organic molecule and the ^{177}Lu(III) ions, which are comprised in the reaction solution, are reacted with each other at below atmospheric pressure to obtain a radionuclide complex composed of the target binding organic molecule and the ^{177}Lu(III) ions in a single container for radiolabeling. Below atmospheric pressure includes applying a pressure as described above under step (1). Carrying out the reaction at below atmospheric pressure reduces radiolytic degradation. Step (2) can include carrying out the reaction in one single container.

In step (2) the single container for radiolabeling can include an oxygen concentration lower than 7 mg/L or 6 mg/L, or 5 mg/L, or 4 mg/L, or 3 mg/L, or 2 mg/L or 1 mg/L (all values at 25°C). Oxygen can be substantially absent in the single container. A low oxygen concentration in the single container reduces radiolytic degradation. Due to a low oxygen concentration, a volumetric activity of at least 17 GBq/ml, at least 18 GBq/ml, at least 19 GBq/ml, at least 20 GBq/ml, at least 25 GBq/mL, or at least 30 GBq/mL ^{177}Lu(III) ions can be included in the single container. Upper limits for volumetric activity of ^{177}Lu(III) ions can be 20, 25, 30, 40, or 50 GBq/mL.

In step (2) a molar excess of the target binding organic molecule over the ^{177}Lu(III) ions as described above is reacted, to ensure high radiochemical labelling yields. In certain embodiments, the process does not require or include any purification steps to remove free (i.e., non-chelated) ^{177}Lu(III) ions. For example, a Solid-phase extraction (SPE) purification step with tC18 sorbent cartridge can be used to remove free (non-chelated)^{177}Lu(III) ions, however, use of this sorbent cartridge may require the elution of the product with ethanol, which can be undesired (A. Mathur et al., Cancer Biother. Radiopharm. 2017, 32, 266-273). The use of a tC18 sorbent cartridge can also result in removal of stabilizers, which then need to be added again (S. Maus et al., Int. J. Diagnostic imaging, 2014, 1, 5-12).

In step (2), the step of reacting the target binding organic molecule with the ^{177}Lu(III) ions at below atmospheric pressure to obtain the radionuclide complex can be carried out over 2 to 15 minutes, 4 to 10 minutes, or 5 min ± 0.5 min.

In step (2), the step of reacting the target binding organic molecule with the ^{177}Lu(III) ions at below atmospheric pressure to obtain the radionuclide complex can be carried out at 80 to 100°C, 90 to 98°C, or 94°C ± 4 °C. Generally, temperatures lower than 90 °C do not ensure quantitative labelling yields.

In step (2), the radionuclide complex can be obtained in a solution with a volume within 15 to 19 ml.

The process for manufacturing a [^{177}Lu]Lu-PSMA-617 solution can further include a step of:

(3) recovering the radionuclide complex, which is formed in step (2) to obtain a mother solution.

The mother solution can be used for and is suitable for preparing a dispensing solution, which can be is dispensed into multiple patient doses (vials) destined for subsequent administration to a patient without further material change. In certain embodiments, the mother solution comprises ^{177}Lu(III) ions in a volumetric activity of at least 10 GBq/mL, a [^{177}Lu]Lu-PSMA-617 radionuclide complex, one or more stabilizers against radiolytic degradation, and an oxygen concentration lower than 50 mg/L. The mother solution can include the ^{177}Lu(III)

ions in a volumetric activity of at least 10 GBq/ml, at least 11 GBq/ml, at least 12 GBq/ml, at least 13 GBq/ml, at least 15 GBq/ml, or at least 16 GBq/ml.

The one or more stabilizers against radiolytic degradation and their specifics can be those described above with respect to the reaction solution. The one or more stabilizers can include gentisic acid or its salts and in concentration ranges as described above with respect to the reaction solution. In specific embodiments, the reaction solution and mother solution do not include ascorbic acid, for example, they include gentisic acid as stabilizer agent but not ascorbic acid. In specific embodiments, the reaction solution and mother solution do not include ethanol as stabilizing agent. In specific embodiments, the reaction solution and mother solution do not include either of ascorbic acid and ethanol as stabilizers.

The oxygen concentration can be lower than 20 mg/L, lower than 10 mg/L, lower than 7 mg/L, lower than 5 mg/L, lower than 4 mg/L, lower than 3 mg/L, lower than 2, or lower than 1 mg/L (all values at 25°C). In some cases, the mother solution is substantially free of oxygen.

The mother solution can further include a nitrogen concentration of up to 20 ml/L at 25°C or an argon concentration of up to 60 ml/L at 25°C. The presence of an inert gas like nitrogen or argon in the mother solution is a consequence of the steps leading up to the formation of the mother solution as part of the process described further below. The concentration of inert gas in the mother solution can reduce radiolytic degradation of the components of the mother solution. The mother solution can include a nitrogen concentration in a range of 3 to 20 ml/L 25°C, or 5 to 15 ml/L or 10 to 15 ml/L at 25°C.

Alternatively, the mother solution can include a nitrogen concentration in a range of 3 to 20 mg/L 25°C, 5 to 15 ml/L, or 10 to 15 mg/L at 25°C. Alternatively, the mother solution may comprise an argon concentration of 3 to 60 mg/L at 25°C, or 10 to 50 mg/L or 20 to 40 mg/L at 25°C.

Methods for determining oxygen, nitrogen, and/or argon concentrations and content in aqueous solutions or in the gas phase are well known and have been described in the literature and encyclopedias (see, e.g. Determination of Argon in Air and Water, J. Lasa et al., Chem. Anal. (Warsaw), 47, 839 (2002), H. H. Willard et al., Instrumental methods of analysis, 6th ed. D. Van Norstrand, New York, 1981, pages 910-912; M. L. Hitchman, Measurement of dissolved oxygen, John Wiley & Sons, New York 1978; Ullmann's Encyclopedia of Industrial Chemistry; S. Uchiyama, Analysis of Dissolved Argon, Oxygen, and Nitrogen in Solutions, Shimadzu Corporation publication, July 2021).

The description of ascorbic acid or salts thereof and ethanol, the target binding organic molecule, the molar excess of the target binding organic molecule over Lu(III) ions, the pH, and pharmaceutically acceptable buffer above with respect to the reaction solution apply equally to the mother solution. In a specific embodiment, the mother solution can include the

radionuclide complex ^{177}Lu PSMA-617 in a volumetric activity of 10 to 30, 10 to 25, 15 to 25, 17 to 25, 17 to 20, or 18 to 19 GBq/ml.

Step (3) can include recovering the radionuclide complex at below atmospheric pressure, wherein the pressure range is as given above. Step (3) can include recovering the radionuclide complex under an inert gas atmosphere. In certain embodiments, the step of recovering the radionuclide complex can be achieved under an inert gas atmosphere.

The inert gas atmosphere can be provided by nitrogen or argon. In step (3) the mother solution can include a nitrogen concentration of up to 20 ml/L at 25°C or an argon concentration of up to 60 ml/L at 25°C due to the purging with nitrogen and argon, respectively. The mother solution can include a nitrogen concentration in a range of 3 to 20 ml/L 25°C, or 5 to 15°C or 10 to 15 ml/L at 25°C. The mother solution can include an argon concentration of 3 to 60 ml/L at 25°C, or 10 to 50 ml/L or 20 to 40 ml/L at 25°C.

In certain embodiments, step (3) of recovering the radionuclide complex can include purging the mother solution container with an inert gas before and during introducing or transferring the mother solution into the mother solution container. Purging the mother solution container with an inert gas before and during introducing or transferring of the mother solution into the mother solution container reduces radiolytic degradation of the components comprised in the mother solution container.

In certain embodiments, step (3) of recovering the radionuclide complex can include purging the mother solution container with an inert gas at a pressure of at least 250 mbar above atmospheric pressure before and during introducing or transferring the mother solution into the mother solution container. The above atmospheric pressure can be at least 300 mbar, 350 mbar, or 400 mbar and up to 450 mbar or 500 mbar.

The transfer from the single container of step (2) into the mother solution container of step (3) can be performed under a pressure above atmospheric pressure or by way of syringes. In step (3) recovering the radionuclide complex can include using water-for-injection (WFI) for rinsing. For example, WFI can be added to the single container of step (2) after completion of the reaction and the solution formed in the single container is introduced or transferred into the mother solution container as described above. This ensures complete (or almost complete) transfer of the solution comprising the radionuclide complex, while maintaining a relatively high volumetric activity concentration.

In step (3) the final volume of mother solution can be between 20 to 23 ml.

The process comprising steps (1), (2) and (3), described above, provides a technical advantage of maximizing volumetric activity while keeping radiolytic degradation at a minimum. The process affords a number of patient doses per given time unit via large-scale

synthesis to meet the globally growing need for radiochemicals used in radiotherapy and radiodiagnosis.

In certain embodiments, step (3) can include introducing or transferring the mother solution into a single container affording a mother solution container. The mother solution container can be used for collecting solutions formed in a radiolabeling reaction, such as after completion of a radiolabeling reaction. The mother solution container can include the mother solution described above. The mother solution container can further include a headspace gas volume above the mother solution.

In certain embodiments, the mother solution container for collecting solutions formed in a radiolabeling reaction contains: a mother solution comprising ^{177}Lu(III) ions in a volumetric activity of at least 10 GBq/mL, a radionuclide complex formed by a target binding organic molecule comprising a target binding organic moiety linked to a chelating moiety and the ^{177}Lu(III) ions, and one or more stabilizers against radiolytic degradation, and also a headspace gas volume above the mother solution, wherein said headspace gas volume contains not more than 10 vol% oxygen.

The headspace gas volume can contain less than 10 vol%, less than 7 vol%, less than 5 vol%, or less than 3 vol% oxygen. The headspace gas volume can contain substantially 0 vol% oxygen. A low volume percentage of oxygen in the headspace gas volume can reduce radiolytic degradation of the components of the mother solution.

The mother solution container can include the mother solution described above, and as such, all features and embodiments described above under the mother solution can also be applied to the mother solution container.

In an embodiment the process can further include the steps of:

(4) diluting the mother solution of step (3) with a dilution solution to obtain a dispensing solution at a defined volumetric activity, and

(5) dispensing the dispensing solution into individual patient dose units.

A dilution solution can include a stabilizer against radiolytic degradation, a sequestering agent, and optionally an isotonic agent. The stabilizer against radiolytic degradation can be selected from among the stabilizers described above. In certain embodiments, the stabilizer is selected from ascorbic acid and salts thereof, di-ethylene-triamine-penta-acetic acid (DTPA, also called pentetic acid), or a combination thereof.

The optional isotonic agent can be a salt selected from sodium, potassium, calcium or magnesium chloride, or monosodium or disodium phosphate, and the like or mixtures of such salts. In certain embodiments, the isotonic agent can be sodium chloride.

In certain embodiments, the dilution solution includes ascorbic acid or salts thereof, DTPA, and optionally NaCl.

The dilution solution can include ethanol in concentrations described above. For example, the dilution solution can be substantially free of ethanol.

Performing steps (4) and (5) affords individual patient doses which are destined for subsequent administration to a patient without further material change. The individual patient doses can include a volumetric activity required for therapeutic or diagnostic purposes. The defined volumetric activity of the dispensing solution can be adjusted to provide individual patient dose units having a volumetric activity of 1000 MBq/mL ± 5% for [^{177}Lu]Lu-PSMA-617.

The process of the present disclosure can be advantageously used for the synthesis of [^{177}Lu]Lu-PSMA-617, especially for production of a mother solution which is used for the production of [^{177}Lu]Lu-PSMA-617 individual patient doses (ready-to-use).

In another specific embodiment of the process the dispensing solution obtained in above step (4) comprises:

(A) [^{177}Lu]Lu-PSMA-617 in an activity in the range from 800 to 1200 MBq/ml, 900 to 1100 MBq/ml, 950 to 1050 MBq/ml, or about 1000 MBq/mL (27 mCi/mL);

(B) acetic acid in a concentration in the range from 0.24 to 0.36 mg/mL, 0.27 to 0.33 mg/mL, 0.285 to 0.315 mg/mL, or about 0.3 mg/mL;

(C) an acetate salt, such as the sodium salt thereof, in a concentration in the range from 0.33 to 0.49 mg/mL, 0.37 to 0.45 mg/mL, 0.39 to 0.43 mg/mL, or about 0.41 mg/mL with regard to the sodium salt;

(D) gentisic acid or a salt thereof in a concentration in the range from 0.3 to 1.0 mg/mL, 0.3 to 0.5 mg/mL, 0.31 to 0.47 mg/mL, 0.35 to 0.43 mg/mL, 0.37 to 0.41, or about 0.39 mg/mL with regard to the free acid;

(E) ascorbic acid or a salt thereof in a concentration in the range from 20 to 52.5 mg/mL, 47.5 to 52.5 mg/mL, 48 to 52 mg/mL, or about 50 mg/mL with regard to the sodium salt;

(F) pentetic acid or a salt thereof in a concentration in the range from 0.08 to 0.12 mg/mL, 0.09 to 0.11 mg/mL, 0.095 to 0.105 mg/mL, or about 0.1 mg/mL with regard to the free acid.

The process described above can be implemented in a sealed device (*e.g.*, a synthesis module) comprising an inlet for inert gas, and an adaptor for applying reduced pressure the device are connectable. Also, containers comprising the reactants described above and water-for-injection (WFI) are provided and connected to the device. Moreover, containers suitable to receive the reaction solution and the mother solution are provided and connected to the device. All connections to the device are equipped with valves, so that directed transfer of solutions to and from containers is possible, effected by the application of reduced pressure or pressure of an inert gas, depending on the individual step. Additionally or alternatively,

transfers can be effected by the use of syringes connectable to containers and the device via adaptors. All pieces of equipment are made of materials compatible with the reagents used in the process.

The process described above can be advantageously automated and implemented in a synthesis module employing a single use kit cassette, such as the kit cassettes used for the preparation of fluorine-18 labeled radiopharmaceuticals. An example kit cassette can include a reaction vial (reactor) and connections for incoming and outgoing fluids, spikes for connecting reagent vials, and, optionally, solid phase cartridges. For example, a single use kit cassette can be installed on the front of a synthesis module which contains a fluid pathway (tubing), a reactor vial and sealed reagent vials. The disposable cassette components can be made of materials specifically chosen to be compatible with the reagents used in the process. In particular, the components can be designed to minimize potential leaching from surfaces in contact with the fluids of the process while maintaining mechanical performance and integrity of the cassette. The process can be fully automated and implemented within a computer assisted system.

In specific embodiments, the synthesis module can include a first needle positioned for inserting in the top of a first vial containing the radioactive ^{177}Lu(III) solution, a second needle positioned for inserting in the top of a vial containing a solution comprising the target binding organic moiety linked to a chelating agent, a bag with water-for-injection for rinsing steps, the solution comprising one or more stabilizers against radiolytic degradation, and one or more additional needles positioned for inserting in the top of respective one or more additional vials (e.g. mother solution container) or tubing for transfer from the synthesis module to a dispensing isolator.

The disclosure is further illustrated by the following examples and synthesis schemes, 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. The compounds of the Examples have demonstrated efficacy in the treatment of prostate cancer, and in particular, metastatic resistance prostate cancer (mCRPC).

EXAMPLES

Example 1: Formulation with [177Lu]Lu-PSMA-617

[177Lu]Lu-PSMA-617 was synthesized as described in WO 2023/148680, to produce the radioactive Drug Substance as a sterile, aqueous concentrated solution (so-called Mother Solution).

Synthesis steps were performed in an automated self-contained closed-system synthesis module, which was remotely controlled by GMP compliant software with automated monitoring and recording of the process parameters. Drug Substance synthesis at 200 GBq or 400 GBq scale was carried out using MinAio (Trasis) kit cassette.

Step 1: $^{177}LuCl_3$ in HCl 0.05 N was transferred into the reactor by a vacuum pump.

Step 2: Reaction buffer was drawn by a syringe and transferred into the $^{177}LuCl_3$ vial.

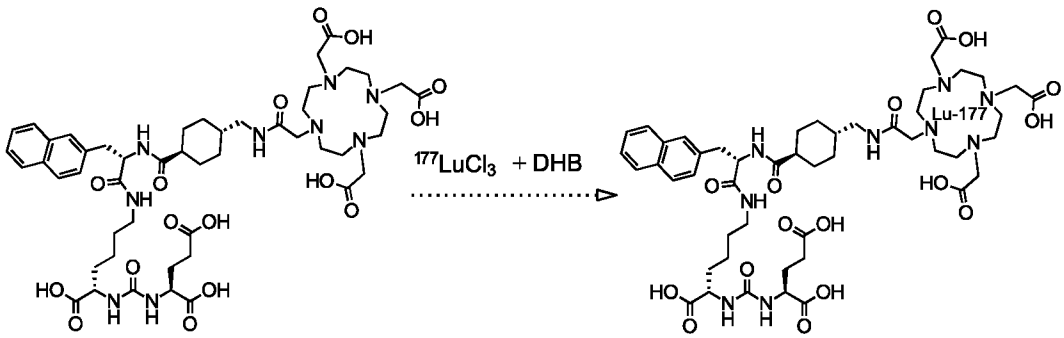
Step 3: The reaction buffer was transferred into the reactor by the vacuum pump.

Step 4: Water-for-injection (WFI) was drawn by the syringe and transferred into the $^{177}LuCl_3$ vial.

Step 5: The WFI was transferred into the reactor by the vacuum pump.

Step 6: The PSMA-617 compound was transferred into the reactor by the vacuum pump.

Step 7: The reaction mixture was left to react for 5 ± 0.5 minutes at 94°C (± 4°C), whereby ^{177}Lu is chelated into the DOTA moiety of the PSMA-617 peptide. In the reaction mixture, DOTA-PSMA is present in a molar excess with respect to the ^{177}Lu to ensure acceptable radiochemical labeling yields. Nitrogen pressure in the mother solution container was higher than 250 mbar at start and end of labelling reaction. The chemical reaction for producing the Drug Substance [^{177}Lu]Lu-PSMA-617 is illustrated in the scheme below:



Step 8: The [177Lu]Lu-PSMA-617 drug substance was transferred into intermediate mother vial, located inside the dispensing isolator.

Step 9: The WFI was drawn by the syringe, transferred into the reactor, and then transferred into the intermediate mother vial, twice.

Drug Product formulation, sterilization filtration and dispensing were carried out in a Grade A Dispensing Isolator.

Step 10: The [177Lu]Lu-PSMA-617 drug substance solution was sterilized by a 0.20 µm filter into the intermediate mother Product Vial.

Step 11: Filtered diluent solution is added to achieve a 1000 MBq/mL volumetric activity at calibration time (Tc). The dilution solution was prepared by dissolving the appropriate amounts of sodium ascorbate and pentetic acid (DTPA) in WFI.

Step 12: [177Lu]Lu-PSMA-617 solution for injection was sterilized by a 0.20 µm filter and dispensed aseptically into an open Drug Product Vial, which was sealed by crimping.

TABLE 18: PSMA-617 Experimental information

Batch size (validated with ± 20%)	**200 GBq, 5.4 Ci**	**400 GBq, 10.8 Ci.**
$^{177}LuCl_3$ solution	200 GBq in 2 mL	400 GBq in 4 mL
Reaction buffer solution: Gentisic acid (DHB): 157.5 mg Acetic acid: 120.2 mg Sodium acetate: 164.0 mg Water WFI: ad 4 mL	4.0 mL, but only used 2.0 mL	4.0 mL
PSMA-617 solution (in WFI)	3 mg in 3.0 mL	6 mg in 6.0 mL
Total volume at radiolabeling	7-10.5 mL	14-15.5 mL
RADIOLABELING REACTION		
Rinsed 2-3 x with 2-3 mL WFI	~8 mL	~6 mL
MOTHER SOLUTION		
Specification for mother solution	≥ 120.0 GBq in ≥ 16.0 mL	≥ 240.0 GBq in ≥ 16.0 mL

Holding time for handling the mother solution: 60 mins

Typical yield of the process: 92-95%

The theoretical batch formula of the bulk drug product [177Lu]Lu-PSMA-617 solution is described in TABLE **19**. Independently of the size of the batch of drug product, the ratios of acetic acid, sodium acetated, gentisic acid, sodium ascorbate, pentetic acid, and WFI are maintained.

TABLE 19: Batch formulation for [177Lu]Lu-PSMA-617 solution for injections/infusions

Component	**Amount per 200 GBq batch size (5.4 Ci)**	**Amount per 400 GBq batch size (10.8 Ci)**
[^{177}Lu]Lu-PSMA-617	1000 MBq/mL ± 5 % at Tc	
Acetic acid	60.1 mg	120.2 mg
Sodium Acetate	82.0 mg	164.0 mg
Gentisic acid	78.8 mg	157.5 mg
Sodium Ascorbate	10.0 mg	20.0 mg
Pentetic acid (DTPA)	20.0 mg	40.0 mg

Water for injection(s)	Up to 200 mL	Up to 400 mL

Tc: Calibration time; DTPA: Diethylenetriaminepentaacetic acid

A batch size can contain 1-40 customer vials according to the batch size.

TABLE 20: Composition of the drug product [177Lu]Lu-PSMA-617 solution for injection/infusion per mL of solution

Component	**Amount (per mL)[3]**	**Function**
[^{177}Lu]Lu-PSMA-617	1000 MBq/mL ± 5 % (Tc)	Drug substance
Acetic acid	0.30 mg	pH adjuster
Sodium Acetate	0.41 mg	pH adjuster
Gentisic acid	0.39 mg	Radiation stability enhancer
Sodium Ascorbate	50.0 mg	Radiation stability enhancer
Pentetic acid (DTPA)	0.10 mg	Sequestering agent
Water for injection(s)	q.s. to 1 mL[2]	Solvent

Tc: calibration time = end of production; 2: includes all water, also the small amounts of water that may be left over from the sterilization process; 3: calculated and rounded values.

As consequence of the natural decay of the radionuclide, the total radioactive and the radio-concentration (volumetric activity) of the drug product change over time. The composition of the drug product per single dose taking as reference the minimum (7.5 mL) and the maximum (12.5 mL) filling content is described in TABLE **21**.

TABLE 21: Drug product per single dose

Component	**Amount per 7.5 mL (minimum volume)**	**Amount per 12.5 mL (maximum volume)**	**Function**
[^{177}Lu]Lu-PSMA-617	1000 MBq/mL ± 5 % (Tc)		Drug substance
Acetic acid	2.25 mg	3.75 mg	pH adjuster
Sodium Acetate	3.08 mg	5.13 mg	pH adjuster
Gentisic acid	2.93 mg	4.88 mg	Radiation stability enhancer
Sodium Ascorbate	375.0 mg	625.0 mg	Radiation stability enhancer
Pentetic acid (DTPA)	0.75 mg	1.25 mg	Sequestering agent
Water for injection(s)	q.s. to 7.5 mL[2]	q.s. to 12.5 mL[2]	Solvent

Tc: calibration time = end of production; 2: includes all water, also the small amounts of water that may be left over from the sterilization process.

Example 2: [^{177}Lu]Lu-PSMA-617 mechanism of action and cellular responses

Radioligand therapy (RLT) is emerging as a safe and effective targeted approach for treating several types of cancers. Pluvicto® ([^{177}Lu]Lu-PSMA-617) is one examples of an FDA-approved ^{177}Lu-based RLT drug for the treatment of PSMA-positive metastatic castration-resistant prostate cancer (mCRPC). Despite the clinical success of ^{177}Lu-RLT, a subset of patients do not achieve a complete, durable response. Elucidating the cellular responses to RLT and its mechanism of action can reveal potential opportunities for the improvement of therapy and outcome for patients.

The following example describes the phenotypes and responses of multiple ^{177}Lu-RLT-treated cell lines. The results of the methods described below show: (1) Time-dependent and dose-dependent induction of DNA Damage Response (DDR) biomarkers by 177Lu, especially those indicative of double-strand break (DSB) repair by either non-homologous end-joining (NHEJ) or homologous recombination (HR) (FIGs. **1-3**); (2) Induced sensitization to 177Lu with loss of the PRKDC gene or inhibitor of DNA-PKcs (i.e., NHEJ core factors such as the catalytic subunit of DNA-PK (PRKDC)) (FIG. **4A-B**) (3) Reduced viability in a panel of cell lines treated with 177Lu (FIG. **5** and TABLE **23**), (4) 177Lu-PSMA-RLT induced apoptosis and cell death (FIGs. **6A-C**); (5) the 177Lu mode of action (FIG. **7**), suggesting that DSB are the most cytotoxic form of ^{177}Lu-RLT-induced DNA damage; (6) DDR deficiency (i.e., isogenic models of homologous recombination (HR)m non-homologous end joining (NHEJ) deficiency, or DNA-PK inhibition) sensitizes cells to 177Lu (FIG. **8A-C**); (7) identification of Radioligand therapy sensitizers by genetic screenings (FIG. **9A-D**), which found PRKDC as a hit; (8) 177Lu-DOTA synergizes with DDRi (*e.g.*, PARP, ATM, CHK1 and WEE1 inhibitors (FIG. **10A**) and Polθ and ATR inhibitors (FIG. **10B**)), which may also sensitize to ^{177}Lu-RLT; DNA-PK inhibitor (AZD7648) synergizes with 177Lu-DOTA in a panel of cancer cell lines (FIG. **11A-F**); (9) 177Lu-PSMA-617 synergizes with Polθ, ATR and ATM inhibitors in PSMA-expressing cell lines (FIGs. **12A-D**); and (10) DNA-PK inhibitor (AZD7648) synergizes with 177Lu-PSMA-617 in cell lines expressing PSMA (FIGs. **13A-G**).

In addition, the results show that DNA-PK inhibitor, AZD7648, synergizes with 177Lu-PSMA-617 when administered before or concomitantly with 177Lu-PSMA-617 whilst addition 24h after 177Lu-PSMA-617 treatment did not lead to synergy (FIGs. **14A-F**) and maximal synergy between DNA-PK inhibitor, AZD7648, and 177Lu-PSMA-617 is achieved with a prolonged inhibition of DNA-PK (FIGs. **15A-F**), in DU145 PSMA high cells (as shown in FIGs. **13A-G**) with different schedules of DNA-PK inhibitor administration (outlined in FIGs. **14F** and **15F**), and that combination treatment of DNA-PK inhibitor AZD7648 with 177Lu-PSMA-617 induces increased accumulation of DDR markers (FIG. **16**)

Furthermore, ^{177}Lu-RLT-treatment leads to cell-cycle alterations, accumulation of micronuclei and cell death (FIGs. **17A-C**). Taken together, these studies provide better

understanding of the cellular responses to ^{177}Lu-RLT and pinpoints NHEJ as a critical pathway promoting survival to this treatment, and underlying the combination therapies of the present disclosure.

Materials and Methods

1. Cell lines and cell viability assays

Cells were cultured under normal growth conditions (37°C, 5% CO_2), and passaged at 80% confluency. Details of the cell line and the seeding density used for viability assay are listed in TABLE **22**.

TABLE 22: Viability assay cell lines and the seeding density

Cell line	Source	Tissue	Media	Seeding density/well
DU-145 empty vector	engineered by Novartis	Prostate	EMEM + 10% FBS + 1% Pen/Strep	250
DU145 PSMA low	engineered by Novartis	Prostate	EMEM + 10% FBS + 1% Pen/Strep	250
DU145 PSMA high	engineered by Novartis	Prostate	EMEM + 10% FBS + 1% Pen/Strep	250
DU 145	ATCC	Prostate	EMEM + 10% FBS + 1% Pen/Strep	250
PC-3 empty vector	engineered by Novartis	Prostate	Ham's F-12K (Kaighn's) + 10% FBS + 1% Pen/Strep	300
PC-3 PSMA low	engineered by Novartis	Prostate	Ham's F-12K (Kaighn's) + 10% FBS + 1% Pen/Strep	300
PC-3 PSMA high	engineered by Novartis	Prostate	Ham's F-12K (Kaighn's) + 10% FBS + 1% Pen/Strep	300
PC-3 MP9	engineered by Novartis	Prostate	Ham's F-12K (Kaighn's) + 10% FBS + 1% Pen/Strep	300
PC-3	ATCC	Prostate	Ham's F-12K (Kaighn's) + 10% FBS + 1% Pen/Strep	300
LNCaP clone FGC	ATCC	Prostate	RPMI + 10% FBS + 1% Pen/Strep	6000
DLD-1	Horizon	Colorectal	RPMI + 10% FBS + 1% Pen/Strep	100
DLD-1 BRCA2-/-	Horizon	Colorectal	RPMI + 10% FBS + 1% Pen/Strep	600
HCT 116	ATCC	Colorectal	McCoy's 5A + 10% FBS + 1% Pen/Strep	100

NCI-H460	ATCC	Lung	RPMI + 10% FBS + 1% Pen/Strep	100

TABLE 23: EC_{50} values from 8-day viability assay in a panel of cell lines treated continuously with 177Lu-DOTA for curves in FIG. **5**

Cell Line	EC_{50} (MBq/mL)
DLD-1	3.004
SUM149PT	2.948
Calu-6	1.842
LncaP	1.803
PC-3	1.767
UWB1.289	1.186
22Rv1	1.106
NCI-H460	0.817
HCT 116	0.7852
MR-32	0.1187

Viability assays were performed as previously described (P G Pilie *et al.*, Clin Cancer Res. 2024 Feb 28). Briefly, cells in exponential growth phase were seeded in 96-well plates (VWR, Cat no. 734-1660) in 100 µL of media at the density indicated above. The day after seeding, cells were treated with dilutions of [^{177}Lu]Lu-PSMA-617 and/or DDR inhibitor AZD7648 or matched vehicle, for a final volume of 150 µL. For scheduling regimen, the media with compound was washed out at selected time-points and replaced with new media containing the matched concentration of required compound, depending on the experimental protocol. After 8 days of treatment, 50 µL of Cell Titre Glow (Promega, G7570) was added to each well, incubated according to manufacturer protocols and read with GloMax microplate reader (Promega). The viability readout was normalized for vehicle control (or single agent control, for combinations). GraphPad Prism was used to generate viability curve and EC_{50} with "log(inhibitor) vs response — Variable slope (four parameters)" fit, with top and bottom constraints set respectively at 1 and 0. Each data point was generated in technical triplicate. Average and standard error mean are shown on the viability curve graphs for each data point. Details of the DNA damage response inhibitors used for the assays are summarized in TABLE **24**.

TABLE 24: DNA damage response inhibitors tested

Inhibitor	Target	Source	Cat Number
AZD7648	DNA-PK	Med[illegible] ss	HY-111783

AZD0156	ATM	Selleckchem	S8375
LY2603618	CHK1	Selleckchem	S2626
MK1775	WEE1	Selleckchem	S1525
Olaparib	PARP	Selleckchem	S1060
Talazoparib	PARP	MedChemExpress	HY-16106
ART558	PolΘ	Artios proprietary compound	
ART6043	PolΘ	Artios proprietary compound	
ART0380	ATR	Artios proprietary compound	

2. Immunofluorescence for DNA damage response biomarkers and cell cycle analysis

The day before treatment cells were seeded in technical quadruplicate in 96-well plate (Perkin Elmer, 6055300) at the seeding densities indicated below.

TABLE 25: Immunofluorescence seeding densities

Cell line	Media	Seeding density/well for 1-24h	Seeding density/well for 96h
DU145 PSMA high	EMEM + 10% FBS + 1% Pen/Strep + 1% Na-Pyruvate +1% stable glutamine	12000	1500
PC-3 MP9	Ham's F-12K + 10% FBS + 1% Pen/Strep	32000	5000

The day after seeding, cells were treated with serial dilution of the indicated compounds ([^{177}Lu]Lu-PSMA-617, AZD7648 or combination). After 4 h of incubation, the media with the compounds was washed out and replaced with fresh media containing the matched concentration of the required compound, depending on the experimental protocol. At the experimental endpoint, cells were fixed with 4% paraformaldehyde in PBS (Santa Cruz Biotechnology, sc-281692) for 10 minutes, blocked for 1 h in blocking buffer (0.5% Triton™ X-100 /0.5% BSA/PBS) and incubated overnight at 4°C with the primary antibodies diluted in blocking buffer (dilutions indicated in TABLE **26**). (The non-ionic surfactant sold under the trade name Triton™ X-100 is 2-[4-(2,4,4-trimethylpentan-2-yl)phenoxy]ethanol).

TABLE 26: Primary Antibodies

Antibody target	Source	Catalogue code	Species	Dilution
γ-H2AX	Millipore	05-636	Mouse	1:2000
53BP1	Bethyl	A300-272A	Rabbit	1:2000

The day after, the excess of primary antibodies was washed with 0.1% Triton™ X-100/PBS and the samples were incubated for 1 h at room temperature with the matched secondary antibodies and DAPI diluted in blocking buffer (dilutions used detailed below).

TABLE 27: Secondary Antibodies

Reagent	Supplier	Catalogue code	Dilution
Goat anti-mouse Alexa Fluor 488 secondary antibody	Invitrogen	A11001	1:2000
Goat anti-rabbit Alexa Fluor 647 secondary antibody	Invitrogen	A21245	1:2000
DAPI	ThermoFisher	62248	1:10000

The excess of antibody was washed with 0.1% Triton™ X-100/PBS and the samples were kept in PBS for imaging. Imaging was performed with an Operetta CLS High-Content Analysis System using a 20X objective in air. The obtained images were analyzed using the Harmony 4.9 software to determine the percentage of cells displaying at least 5 or 10 DDR foci, depending on the marker. The values obtained were normalized for the average induction in the vehicle-treated samples to obtain the fold change of induction. The predicted additivity was calculated multiplying the single agent inductions. One-way ANOVA followed by Dunnett's post-hoc test was used to assess the significance of the induction with any of the single agent or combination against the vehicle-treated samples, while a 2-tailed t test was used to assess the significance of the induction observed with the combination against the predicted additivity.

For cell cycle analysis, the Click-iT EdU Imaging kit with Alexa Fluor 647 (Fisher Scientific, C10340) was used. The cells were incubated with 10 μM EdU to label actively replicating cells for 30 minutes before fixation with 4% PFA/PBS. The Click-iT reaction to detect EdU was performed following the manufacturer's protocol and the DNA was subsequentially stained with DAPI. After imaging of the samples using the same settings described above, the intensity of EdU and DAPI staining were calculated using the Harmony 4.9 software and plotted to obtain the cell cycle profiles of the samples.

Example 3: *In vivo* efficacy of the combination of [^{177}Lu]Lu-PSMA-617 and DDRi

The combination of both the 177Lu-RLT and Polθ inhibitor (ART6043) is well-tolerated and effective *in vivo*, significantly extending the survival of tumor bearing mice (LNCaP xenografts, results outlined in **FIGs. 18A-B**).

The combination of both the 177Lu-RLT and DNA-PK inhibitor does not affect the biodistribution of 177Lu-RLT. Biodistribution of [^{177}Lu]Lu-PSMA-617 alone or in combination with DDRi AZD7648 or Peposertib (M3814) in PC3 FOLH1 MP9 PSMA high tumors was evaluated at 4h and 24h. Results are shown in TABLE **27** and Fig. **19**.

TABLE 28: Biodistribution Study

Tissue	4h

	[^{177}Lu]Lu-PSMA-617	[^{177}Lu]Lu-PSMA-617 + AZD7648	[^{177}Lu]Lu-PSMA-617 + M3814
Blood	0.02±0.00	0.02±0.00	0.01±0.00
Kidney	3.94±0.19	4.21±0.89	2.02±0.41
Liver	0.11±0.07	0.04±0.00	0.03±0.00
Tumor	9.30±1.52	8.64±0.07	7.90±1.00
	24h		
	[^{177}Lu]Lu-PSMA-617	**[^{177}Lu]Lu-PSMA-617 + AZD7648**	**[^{177}Lu]Lu-PSMA-617 + M3814**
Blood	0.00±0.00	0.98±0.98	0.00±0.00
Kidney	0.30±0.08	0.28±0.05	0.27±0.01
Liver	0.01±0.01	0.02±0.00	0.02±0.00
Tumor	6.11±1.63	7.46±0.39	5.65±0.38

The combination of both the 177Lu-RLT and DNA-PK inhibitor provides a beneficial tumor growth inhibition *in vivo*. The effect of [^{177}Lu]Lu-PSMA-617 alone or in combination with AZD7648 or M3814 in PC3 FOLH1 MP9 PSMA tumor bearing female nude mice was evaluated. Results are shown in FIGs. **20A-D**.

Material and Methods

TABLE 29: Abbreviations used

bid	two times per day
Crl:NU(NCr)-Foxn1nu	athymic nude mice
EDTA	Ethylenediaminetetraacetic acid
FCS	fetal calf serum
FOLH1	folate hydrolase 1
h	hour
HBSS	Hanks' balanced salt solution
i.v.	intravenous
kg	kilogram
MBq	mega-becquerel
mL	milliliter
Na	sodium
pH	potential hydrogen
p.i.	Past injection
p.o.	per os
PSMA	prostate-specific membrane antigen
qd	every day
PBS	Phosphate-buffered saline
PC3	cell line initiated from a bone metastasis of a grade IV prostatic adenocarcinoma from a 62-year-old, White, male
SEM	standard error of the mean
%ID/g	% injected c n of tissue

µL	microliter

1. Animals and maintenance conditions:

Experiments were performed in female nude Crl:NU(NCr)-Foxn1nu-Homozygous mice (Charles River, Germany). Animals were 14 weeks of age at time of application of the compound. Animals were housed under optimized hygienic conditions in type XJ cages (max. 5 animals per cage) with free access to food and water and a 12-hour light-dark cycle. They were allowed to adapt for at least 7 days before the experiment was started.

2. Cell line and cell culture:

PC3 FOLH1 MP9 PSMA high cells were grown in 500mL F-12K Nutrient Mixture Kaighn's Modification Medium (Gibco, 21127-022, 500mL) + 50mL FCS (Bio Concept, 2-01F30-I) and incubated at 37°C in a 5% CO_2 humidified atmosphere. Cells were harvested with trypsin-EDTA, re-suspended in culture medium (with additives) and counted with a NucleoCounter® NC-200TM system. Finally, cells were centrifuged and suspended in ice-cold Hanks' balanced salt solution (HBSS) and Matrigel® Matrix (Corning,354234) (1:1).

3. Establishment of tumor xenografts in vivo:

PC3 FOLH1 MP9 PSMA tumors were established by subcutaneous injection of $5x10^6$ cells in 200 µL HBSS (Sigma #H8264): Matrigel® Matrix (Corning, 354234) (50%:50%) into the right flank of nude mice.

4. Compound formulation and animal treatment:

AZD7648 was prepared for dosing as homogenous suspensions in 0.5% MC + 0.1 % polysorbate 80 (Tween 80™). M3814 was prepared for dosing as homogenous suspensions in 0.5% Methocel™ + 0.25% polysorbate 20 (Tween 20™) in 300 mM Na-Citrate Buffer, pH 2.5. Fresh suspensions were prepared once every 7 days and stored at RT.

For the biodistribution AZD7648 and M3814 were administered orally 10 minutes before the i.v. injection of 4 MBq [^{177}Lu]Lu-PSMA-617 (0.1 nmol).

For the efficacy study AZD7648 was administered orally at a volume of 10mL/kg, qd for 5 days and M3814 was administered orally at a volume of 10mL/kg, bid for 5 days. [^{177}Lu]Lu-PSMA-617 was prepared in PBS and was administered i.v. at a volume of 100uL with a total activity of 10 MBq (0.1 nmol per single injection). Vehicle control was administered once with 100uL PBS i.v.

5. Statistical analysis:

Absolute values of the radioactive uptake in the tissue and the values for the tumor growth to make the statistical comparison between groups (2way ANOVA followed Dunnett's multiple comparison test). The significant level was set at $p < 0.05$. All statistical calculations were carried out using GraphPad Prism 10.1.2 (324). For the efficacy study the last date of the vehicle control group was uses to assess the significance.

6. Evaluation of biodistribution:

The biodistribution study was performed when tumors were approximately 200 mm^3 in volume. Tumor volumes were measured with calipers and determined according to the formula: length x $diameter^2$ x $\pi/6$. Values are mean ± SEM. Mice were randomized into groups of three, and freshly prepared test articles were injected through the lateral tail vein or gavage in a volume of 10mL/kg. Four h and 24 h post radioactive-agent dose administration, mice were euthanized, and organs (blood, liver, spleen, kidneys, and tumor) were collected, weighed and placed inside counting vials. Each tissue sample was counted for the activities of radioelement using a gamma-counter. Samples of the injectate were used as decay correction standards. Final bar graphs are expressed as % injected dose per gram of tissue.

7. Evaluation of antitumor activity:

Efficacy treatments were initiated when the mean tumor volumes were approx. 210 mm^3 (26 days post tumor cells injection) in mice. Values are mean ± SEM; sample size, (n=8 mice per group).

Tumor volumes were measured with calipers and determined according to the formula: length x $diameter^2$ x $\pi/6$. Carry forward was applied to the mean graph when animals were taken down and mean tumor graph was stopped when less than four animals remained in each group. Body weights and tumor volumes were recorded two to three times a week.

8. *In vivo* efficacy study in LNCaP FGC xenograft with [^{177}Lu]Lu-PSMA-617 combined with Polθ inhibitor ART6043.

Male NMRI nude mice bearing subcutaneous LNCaP FGC tumors (see cell line in TABLE **22** above) were treated with either vehicle (PO, BID), ART6043 (PO, 100 mg/kg BID), a single dose of 10 MBq ^{177}Lu-PSMA-617 (i.v.) or a combination of 10 MBq [^{177}Lu]Lu-PSMA-617 (i.v.) + ART6043 (PO, 100 mg/kg BID). Six mice were included in each experimental group. Mice were dosed for a further 20 days with vehicle or ART6043. Mice were terminated when tumor volume reached over 1500 mm^3 and the timepoint of termination was used for survival analysis. Body weight and tumor volume were measured twice a week. All drug treatments were well tolerated. Combination of ART6043 + ^{177}Lu-PSMA-617 treatment

significantly increased survival as compared to ^{177}Lu-PSMA-617 alone. Median survival for the combination group increased to 47 days as compared to 31 days for ^{177}Lu-PSMA-617 group (FIG. **18A-B**). These results indicate that the combination of Polθ inhibitor, ART6043, with ^{177}Lu-PSMA-617 is well tolerated and increases survival *in vivo*.

CLAIMS

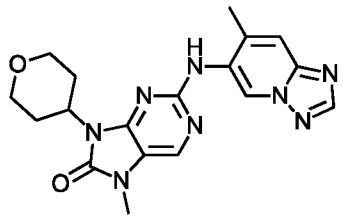
1. A method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi).

2. The method of claim 1, wherein the DDRi is selected from the group consisting of Ataxia-Telangiectasia Mutated (ATM) inhibitors, Ataxia Telangiectasia and Rad3-related (ATR) inhibitors, Poly (ADP-ribose) Polymerase (PARP) inhibitors, DNA-dependent Protein Kinase (DNA-PK) inhibitors, WEE1 protein kinase family inhibitors, Checkpoint Kinase (CHK) family inhibitors, DNA polymerase theta (Polθ) inhibitors, RAD51 recombinase (RAD51) inhibitors, Ubiquitin-Specific Protease 1 (USP1) inhibitors, Polo-Like serine/threonine Kinase 1 (PLK1) inhibitors, Aurora kinase inhibitors, mutant p53 reactivators, Poly(ADP-ribose) Glycohydrolase (PARG) inhibitors, Werner Syndrome protein (WRN) inhibitors, and combinations thereof, optionally wherein the DDRi is not olaparib.

3. The method of claim 1 or 2, wherein the DDRi is selected from the group consisting of Ataxia-Telangiectasia Mutated (ATM) inhibitors, Ataxia Telangiectasia and Rad3-related (ATR) inhibitors, Poly (ADP-ribose) Polymerase (PARP) inhibitors, DNA-dependent Protein Kinase (DNA-PK) inhibitors, WEE1 protein kinase family inhibitors, Checkpoint Kinase (CHK1) inhibitors, and DNA polymerase theta (Polθ) inhibitors, optionally wherein the DDRi is not olaparib.

4. The method of any one of claims 1-3, wherein the DDRi includes at least one DNA-PK inhibitor listed in TABLE 4, at least one of XRD-0394, SN-39536, BY101298, XZP-6877 and IMP-11, or a pharmaceutically acceptable salt thereof.

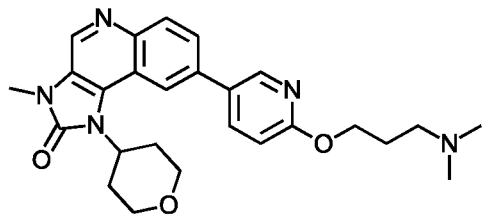
5. The method of claim 4, wherein the at least one DNA-PK inhibitor includes:



(7-Methyl-2-[(7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino]-9-(oxan-4-yl)purin-8-one (AZD7648)), or a pharmaceutically acceptable salt thereof.

6. The method of any one of claims 1-5, wherein the DDRi includes at least one ATM inhibitor listed in TABLE 1, at least one of XRD-0394 and SX-RDS1, or a pharmaceutically acceptable salt thereof.

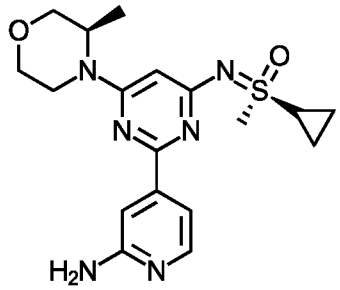
7. The method of claim 6, wherein the at least one ATM inhibitor includes:



(8-[6-[3-(dimethylamino)propoxy]pyridin-3-yl]-3-methyl-1-(oxan-4-yl)imidazo[4,5-c]quinolin-2-one (AZD0156)), or pharmaceutically acceptable salt thereof.

8. The method of any one of claims 1-7, wherein the DDRi includes at least one ATR inhibitor listed in TABLE 2, at least one of LF0397, IMP-9064, SC0245, and ATRN-119, or a pharmaceutically acceptable salt thereof.

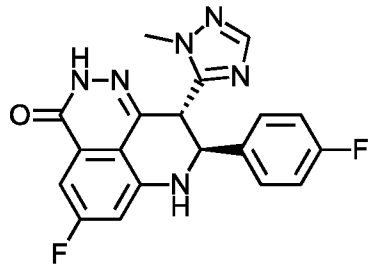
9. The method of claim 8, wherein the at least one ATR inhibitor includes



((S)-((2-(2-aminopyridin-4-yl)-6-((R)-3-methylmorpholino)pyrimidin-4-yl)imino)(cyclopropyl)(methyl)-λ^6 -sulfanone (ART0380)), or a pharmaceutically acceptable salt thereof.

10. The method of any one of claims 1-8, wherein the DDRi includes at least one PARP inhibitor listed in TABLE 3, or a pharmaceutically acceptable salt thereof, optionally wherein the PARP inhibitor is not olaparib.

11. The method of claim 10, wherein the at least one PARP inhibitor includes:

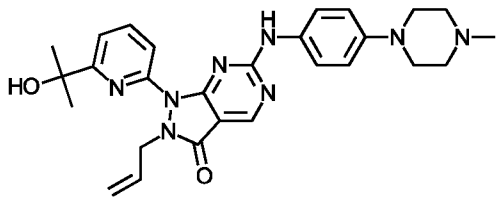


((11*S*,12*R*)-7-fluoro-11-(4-fluorophenyl)-12-(2-methyl-1,2,4-triazol-3-yl)-2,3,10-triazatricyclo[7.3.1.$0^{5,13}$]trideca-1,5(13),6,8-tetraen-4-one (talazoparib)), or a pharmaceutically acceptable salt thereof.

12. The method of any one of claims 1-11, wherein the DDRi includes at least one WEE1 protein kinase family inhibitor selected from the group consisting of Wee1-like protein kinase (WEE1) inhibitors and Protein Kinase, Membrane Associated Tyrosine/Threonine 1 (PKMYT1) inhibitors.

13. The method of claim 12, wherein the DDRi includes at least one WEE1 inhibitor listed in TABLE 5, at least one of SC0191, SY-4835, and IMP7068, or a pharmaceutically acceptable salt thereof.

14. The method of claim 13, wherein the at least one WEE1 inhibitor includes:



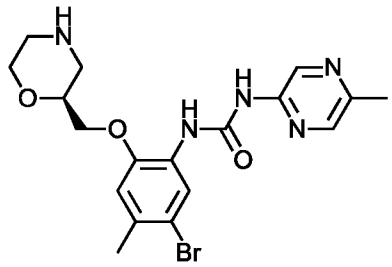
(1-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]-6-[4-(4-methylpiperazin-1-yl)anilino]-2-prop-2-enylpyrazolo[3,4-d]pyrimidin-3-one (Adavosertib or MK-1775), or a pharmaceutically acceptable salt thereof.

15. The method of claim 12, wherein the DDRi includes at least one PKMYT1 inhibitor listed in TABLE 6, ACR-2316, or a pharmaceutically acceptable salt thereof.

16. The method of any one of claims 1-15, wherein the DDRi includes at least one CHK family inhibitor selected from the group consisting of CHK1 selective inhibitors, CHK2 selective inhibitors, and CHK1/2 dual inhibitors.

17. The method of claim 16, wherein the DDRi includes at least one CHK1 selective inhibitor listed in TABLE 7, VER250840, or a pharmaceutically acceptable salt thereof.

18. The method of claim 17, wherein the at least one CHK1 selective inhibitor includes:



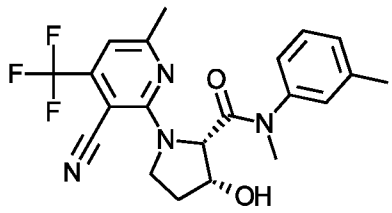
(1-[5-bromo-4-methyl-2-[[(2*S*)-morpholin-2-yl]methoxy]phenyl]-3-(5-methylpyrazin-2-yl)urea (Rabusertib or LY2603618), or a pharmaceutically acceptable salt thereof.

19. The method of claim 16, wherein the DDRi includes at least one CHK2 selective inhibitor listed in TABLE 8, or a pharmaceutically acceptable salt thereof.

20. The method of claim 16, wherein the DDRi includes at least one CHK1/2 dual inhibitor listed in TABLE 9, or a pharmaceutically acceptable salt thereof.

21. The method of any one of claims 1-20, wherein the DDRi includes at least one Polθ inhibitor listed in TABLE 10, at least one of ART4215, ART6043, RP-3467, and GSK101 (GSK4524101/IDE705), or a pharmaceutically acceptable salt thereof.

22. The method of claim 21, wherein the at least one Polθ inhibitor includes:



((2*S*,3*R*)-1-[3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl]-3-hydroxy-*N*-methyl-N-(3-methylphenyl)pyrrolidine-2-carboxamide (ART558), ART6043, or a pharmaceutically acceptable salt thereof.

23. The method of any one of claims 1-22, the DDRi includes at least one RAD51 inhibitor listed in TABLE 11, or a pharmaceutically acceptable salt thereof.

24. The method of any one of claims 1-23, the DDRi includes at least one USP1 inhibitor listed in TABLE 12, at least one of TNG348, HSK39775, FT-3171 (Debio 0432), and ISM3091, or a pharmaceutically acceptable salt thereof.

25. The method of any one of claims 1-24, wherein the DDRi includes at least one PLK1 inhibitor listed in TABLE 13, or a pharmaceutically acceptable salt thereof.

26. The method of any one of claims 1-25, wherein the DDRi includes at least one Aurora kinase inhibitor selected from the group consisting of Aurora A inhibitors and Aurora B inhibitors listed in TABLE 14, WJ05129, or a pharmaceutically acceptable salt thereof.

27. The method of any one of claims 1-26, wherein the DDRi includes at least one PARG inhibitor listed in TABLE 16, IDE161, or a pharmaceutically acceptable salt thereof.

28. The method of any one of claims 1-27, wherein the DDRi includes at least one WRN inhibitor listed in TABLE 17, RO7589831, HRO761, or a pharmaceutically acceptable salt thereof.

29. The method of any one of claims 1-28, wherein the DDRi includes at least one mutant p53 reactivator listed in TABLE 15, PC14586, or a pharmaceutically acceptable salt thereof.

30. The method of any one of claims 1-29, wherein the DDRi and [^{177}Lu]Lu-PSMA-617 are administered via the same route of administration.

31. The method of any one of claims 1-30, wherein the DDRi and [^{177}Lu]Lu-PSMA-617 are in separate dosage forms.

32. The method of any one of claims 1-31, wherein the DDRi and [^{177}Lu]Lu-PSMA-617 are in the same dosage form.

33. The method of any one of claims 1-32, wherein the DDRi is administered via a different route than [^{177}Lu]Lu-PSMA-617.

34. The method of any one of claims 1-33, wherein the DDRi is administered within 24 hours of [^{177}Lu]Lu-PSMA-617 administration.

35. The method of any one of claims 1-34, wherein the therapeutically effective amount of the DDRi is administered over a course of about, or at least about, 5 days.

36. The method of any one of claims 1-35, wherein the DDRi is administered within 20 hours of [^{177}Lu]Lu-PSMA-617 administration.

37. The method of any one of claims 1-36, wherein the DDRi is administered within 4 hours of [^{177}Lu]Lu-PSMA-617 administration.

38. The method of any one of claims 1-37, wherein the DDRi is administered in one or more doses for at least 16 hours after [^{177}Lu]Lu-PSMA-617 administration.

39. The method of any one of claims 1-38, wherein the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617, the DDRi, or both, is lower than the amount required for a monotherapy response.

40. The method of claim 39, wherein the monotherapy response is selected from the group consisting of objective response rate (ORR), disease control rate (DCR), progression free survival (PFS), duration of response (DOR), overall survival (OS), complete response (CR), partial response (PR), PSA response rate, radiographic response rate, change from baseline in blood and tumor tissue microenvironment pharmacodynamic (PD) biomarkers, or a combination thereof.

41. The method of claim 39 or 40, wherein the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617, the DDRi, or both is at least about 10% to about 50% lower than the amount required for the monotherapy response.

42. The method of any one of claims 39-41, wherein the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 is about 10%, 15%, 20%, 25%, 30% 35%, 40%, 45% or about 50% lower than the amount of [^{177}Lu]Lu-PSMA-617 required for the monotherapy response.

43. The method of any one of claims 39-42, wherein the therapeutically effective amount of the DDRi is about 10%, 15%, 20%, 25%, 30% 35%, 40%, 45% or about 50% lower than the amount of the DDRi required for the monotherapy response.

44. The method of any one of claims 1-43, whereby an anti-cancer response is synergized as compared to a method of administering the [^{177}Lu]Lu-PSMA-617 or the DDRi as monotherapy.

45. The method of any one of claims 1-44, wherein the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 is a dose of from about 3 GBq to about 10 GBq.

46. The method of any one of claims 1-45, wherein the PSMA-expressing cancer is PSMA-positive prostate cancer, optionally PSMA-positive metastatic castration-resistant prostate cancer (mCRPC), optionally PSMA-positive metastatic hormone-sensitive prostate cancer (mHSPC), optionally PSMA-positive oligometastatic prostate cancer (OMPC), optionally PSMA-positive cancer in the biochemical recurrence (BCR) setting, optionally PSMA-positive caner in the high-risk BCR setting.

47. A combination comprising [^{177}Lu]Lu-PSMA-617 and a DDRi for use in treating a Prostate Specific Membrane Antigen (PSMA)-expressing cancer, wherein the DDRi is

selected from the group consisting of Ataxia-Telangiectasia Mutated (ATM) inhibitors, Ataxia Telangiectasia and Rad3-related (ATR) inhibitors, Poly (ADP-ribose) Polymerase (PARP) inhibitors, DNA-dependent Protein Kinase (DNA-PK) inhibitors, WEE1 protein kinase family inhibitors, Checkpoint Kinase (CHK) inhibitors, DNA Polymerase theta (Polθ) inhibitors, RAD51 recombinase (RAD51) inhibitors, Ubiquitin-Specific Protease 1 (USP1) inhibitors, Polo-Like serine/threonine Kinase 1 (PLK1) inhibitors, Aurora kinase inhibitors, mutant p53 reactivators, Poly(ADP-ribose) Glycohydrolase (PARG) inhibitors, and Werner Syndrome protein (WRN) inhibitors, and combinations thereof, optionally wherein the DDRi is not olaparib.

48. The combination of claim 47, having an enhanced therapeutic index as compared with a [^{177}Lu]Lu-PSMA-617 monotherapy or a DDRi monotherapy.

49. The combination of claim 48, wherein the therapeutic index of the combination is at least about 10% to about 50% wider than the therapeutic index of the [^{177}Lu]Lu-PSMA-617 monotherapy or the DDRi monotherapy.

50. The combination of any one of claims 47-49, wherein the DDRi includes at least one DNA-PK inhibitor listed in TABLE 4, at least one of XRD-0394, SN-39536, BY101298, XZP-6877 and IMP-11, or a pharmaceutically acceptable salt thereof.

51. The combination of any one of claims 47-50, wherein the DDRi includes at least one ATM inhibitor listed in TABLE 1, at least one of XRD-0394 and SX-RDS1, or a pharmaceutically acceptable salt thereof.

52. The combination of any one of claims 47-51, wherein the DDRi includes at least one ATR inhibitor listed in TABLE 2, at least one of LF0397, IMP-9064, SC0245, and ATRN-119, or a pharmaceutically acceptable salt thereof.

53. The combination of any one of claims 47-52, wherein the DDRi includes at least one PARP inhibitor listed in TABLE 3, or a pharmaceutically acceptable salt thereof, optionally wherein the PARP inhibitor is not olaparib.

54. The combination of any one of claims 47-53, wherein the DDRi includes at least one WEE1 protein kinase family inhibitor selected from the group consisting of Wee1-like protein kinase (WEE1) inhibitors and Protein Kinase, Membrane Associated Tyrosine/Threonine 1 (PKMYT1) inhibitors.

55. The combination of claim 54, wherein the DDRi includes at least one WEE1 inhibitor listed in TABLE 5, at least one of SC0191, SY-4835, and IMP7068, or a pharmaceutically acceptable salt thereof.

56. The combination of claim 54, wherein the DDRi includes at least one PKMYT1 inhibitor listed in TABLE 6, ACR-2316, or a pharmaceutically acceptable salt thereof.

57. The combination of any one of claims 47-56, wherein the DDRi includes at least one CHK inhibitor selected from the group consisting of CHK1 selective inhibitors, CHK2 selective inhibitors, and CHK1/2 dual inhibitors.

58. The combination of claim 57, wherein the DDRi includes at least one CHK1 selective inhibitor listed in TABLE 7, VER250840, or a pharmaceutically acceptable salt thereof.

59. The combination of claim 57, wherein the DDRi includes at least one CHK2 selective inhibitor listed in TABLE 8, or a pharmaceutically acceptable salt thereof.

60. The combination of claim 57, wherein the DDRi includes at least one CHK1/2 dual inhibitor listed in TABLE 9, or a pharmaceutically acceptable salt thereof.

61. The combination of any one of claims 47-60, wherein the DDRi includes at least one Polθ inhibitor listed in TABLE 10, at least one of ART4215, ART6043, RP-3467, and GSK101 (GSK4524101/IDE705), or a pharmaceutically acceptable salt thereof.

62. The combination of any one of claims 47-61, the DDRi includes at least one RAD51 inhibitor listed in TABLE 11, or a pharmaceutically acceptable salt thereof.

63. The combination of any one of claims 47-62, the DDRi includes at least one USP1 inhibitor listed in TABLE 12, at least one of TNG348, HSK39775, FT-3171 (Debio 0432), and ISM3091, or a pharmaceutically acceptable salt thereof.

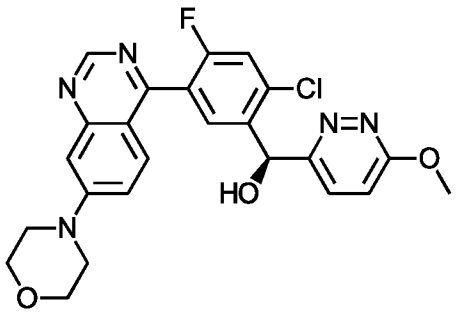
64. The combination of any one of claims 47-63, wherein the DDRi includes at least one PLK1 inhibitor listed in TABLE 13, or a pharmaceutically acceptable salt thereof.

65. The combination of any one of claims 47-64, wherein the DDRi includes at least one Aurora kinase inhibitor selected from the group consisting of Aurora A inhibitors and Aurora B inhibitors listed in TABLE 14, WJ05129, or a pharmaceutically acceptable salt thereof.

66. The combination of any one of claims 47-65, wherein the DDRi includes at least one PARG inhibitor listed in TABLE 16, IDE161, or a pharmaceutically acceptable salt thereof.

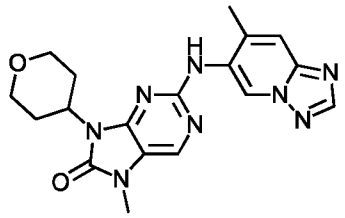
67. The combination of any one of claims 47-66, wherein the DDRi includes at least one WRN inhibitor listed in TABLE 17, RO7589831, HRO761, or a pharmaceutically acceptable salt thereof.

68. The combination of any one of claims 47-67, wherein the DDRi includes at least one mutant p53 reactivator listed in TABLE 15, PC14586, or a pharmaceutically acceptable salt thereof.

69. A method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:  ((S)-[2-chloro-4-fluoro-5-(7-morpholin-4-ylquinazolin-4-yl)phenyl]-(6-methoxypyridazin-3-yl)methanol (M3814)), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

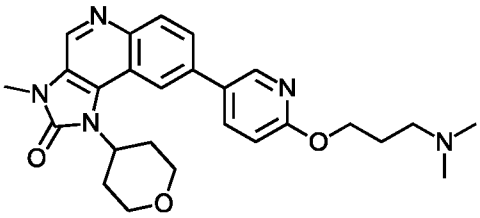
70. The method of claim 69, wherein the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 is a dose of from about 10 MBq to 10 GBq, optionally from about 100 MBq to about 10 GBq, about 1 GBq to about 10 GBq, about 3 GBq to about 10 GBq, about 5 GBq to about 9 GBq, about 6 GBq to about 8 GBq, optionally about 7.4 GBq, and the therapeutically effective amount of the DDRi is a dose of from about 1 to 1000 mg/kg, optionally about 100 m/kg, administered twice daily for about, or at least about, 5 days, or about 50 mg, about 100 mg, about 150 mg, or about 250 mg, and wherein the initial dose of the DDRi is administered less than 1 hour prior to [^{177}Lu]Lu-PSMA-617 administration.

71. A method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the

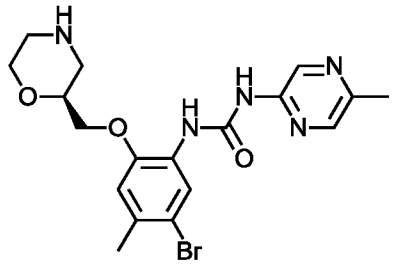
DDRi is  ((7-Methyl-2-[(7-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)amino]-9-(oxan-4-yl)purin-8-one (AZD7648)), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

72. The method of claim 71, wherein the therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 is a dose of from about 10 MBq to 10 GBq, optionally from about 100 MBq to about 10 GBq, about 1 GBq to about 10 GBq, about 3 GBq to about 10 GBq, about 5 GBq to about 9 GBq, or about 6 GBq to about 8 GBq, optionally about 7.4 GBq, and the therapeutically effective amount of the DDRi is a dose of from about 1 to 1000 mg/kg, optionally about 100 mg/kg about 100 mg/kg administered once daily for about, or at least about, 5 days, and the initial dose of the DDRi is administered less than 1 hour prior to [^{177}Lu]Lu-PSMA-617 administration.

73. A method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:

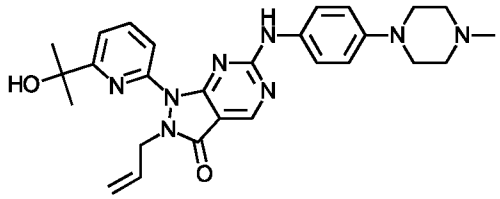
 (8-[6-[3-(dimethylamino)propoxy]pyridin-3-yl]-3-methyl-1-(oxan-4-yl)imidazo[4,5-c]quinolin-2-one (AZD0156)), or pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

74. A method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:



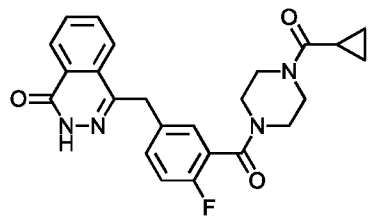
(1-[5-bromo-4-methyl-2-[[(2S)-morpholin-2-yl]methoxy]phenyl]-3-(5-methylpyrazin-2-yl)urea (LY2603618, Rabusertib)) or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is improved or synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

75. A method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:



(1-[6-(2-hydroxypropan-2-yl)pyridin-2-yl]-6-[4-(4-methylpiperazin-1-yl)anilino]-2-prop-2-enylpyrazolo[3,4-d]pyrimidin-3-one (Adavosertib or MK-1775), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is improved or synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

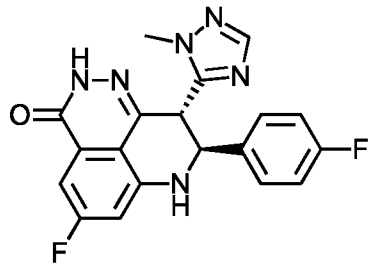
76. A method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:



4-[[3-[4-(cyclopropanecarbonyl)piperazine-1-carbonyl]-4-fluorophenyl]methyl]-2*H*-phthalazin-1-one (olaparib), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a

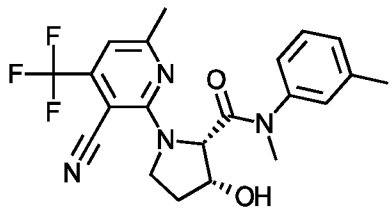
monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi, optionally wherein the DDRi is administered within 24 hours of administration of [^{177}Lu]Lu-PSMA-617 and/or the DDRi is administered within 24 hours of administration and over a course of at least 48 hours.

77. A method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:



((11S,12R)-7-fluoro-11-(4-fluorophenyl)-12-(2-methyl-1,2,4-triazol-3-yl)-2,3,10-triazatricyclo[7.3.1.0^{5,13}]trideca-1,5(13),6,8-tetraen-4-one (talazoparib), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

78. A method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is:

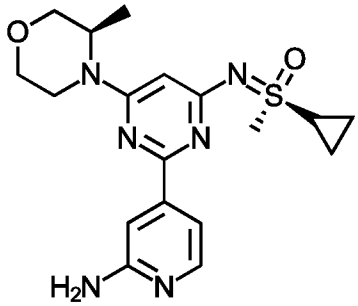


((2*S*,3*R*)-1-[3-cyano-6-methyl-4-(trifluoromethyl)pyridin-2-yl]-3-hydroxy-*N*-methyl-N-(3-methylphenyl)pyrrolidine-2-carboxamide (ART558), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

79. A method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a

therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the DDRi is ART6043, or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

80. A method of treating a prostate specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of [^{177}Lu]Lu-PSMA-617 and administering to the subject a therapeutically effective amount of a DNA Damage Response inhibitor (DDRi), wherein the



DDRi is ((S)-((2-(2-aminopyridin-4-yl)-6-((R)-3-methyl-morpholino)pyrimidin-4-yl)imino)(cyclopropyl)(methyl)-λ^6 -sulfanone (ART0380)), or a pharmaceutically acceptable salt thereof, whereby an anti-cancer response is synergized as compared to a monotherapy response with [^{177}Lu]Lu-PSMA-617 or the DDRi.

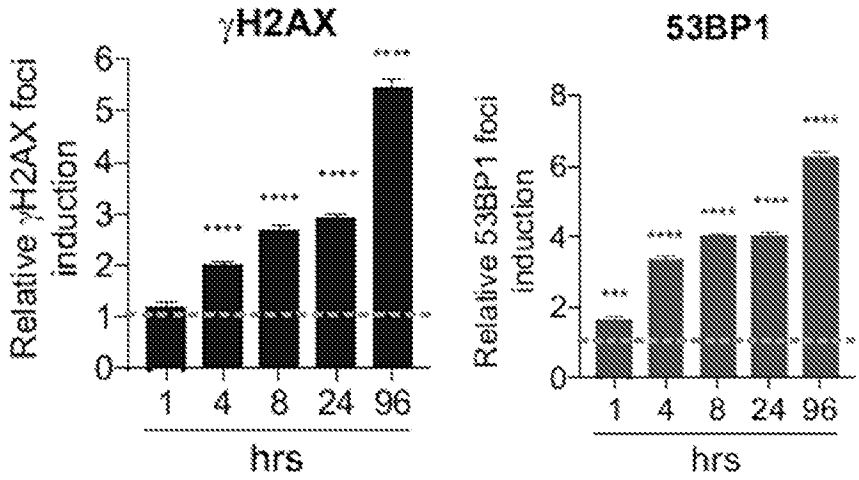

γH2AX
Relative γH2AX foci induction
0
1
2
3
4
5
6
1 4 8 24 96
hrs
53BP1
Relative 53BP1 foci induction
0
2
4
6
8
1 4 8 24 96
hrs

FIG. 1

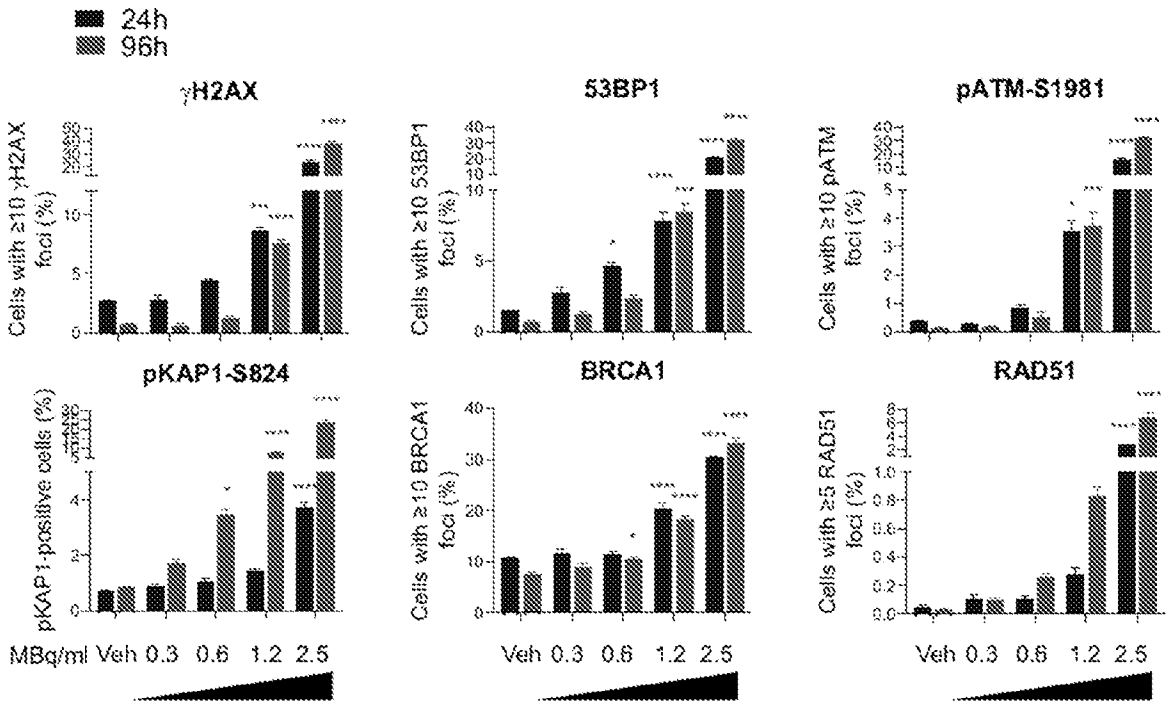

24h
96h
γH2AX
53BP1
pATM-S1981
pKAP1-S824
BRCA1
RAD51
Cells with ≥10 γH2AX foci (%)
Cells with ≥10 53BP1 foci (%)
Cells with ≥10 pATM foci (%)
pKAP1-positive cells (%)
Cells with ≥10 BRCA1 foci (%)
Cells with ≥5 RAD51 foci (%)
MBq/ml Veh 0.3 0.6 1.2 2.5
Veh 0.3 0.6 1.2 2.5
Veh 0.3 0.6 1.2 2.5

FIG. 2

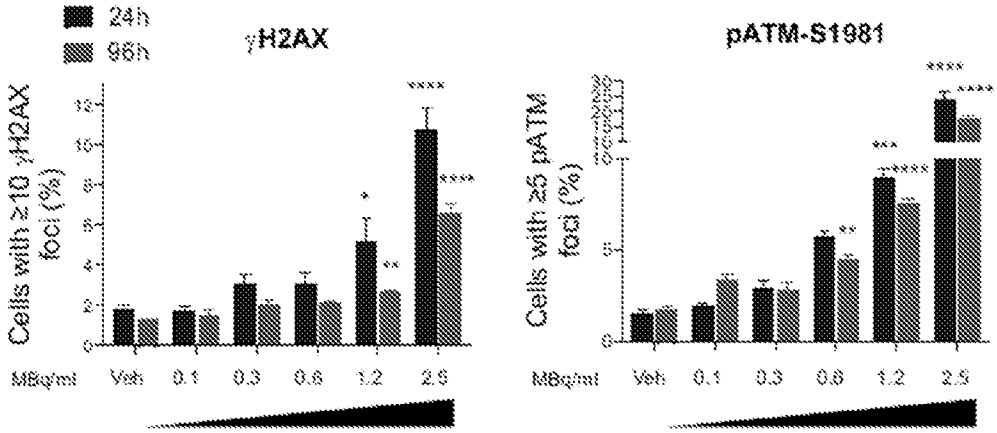


FIG. 3

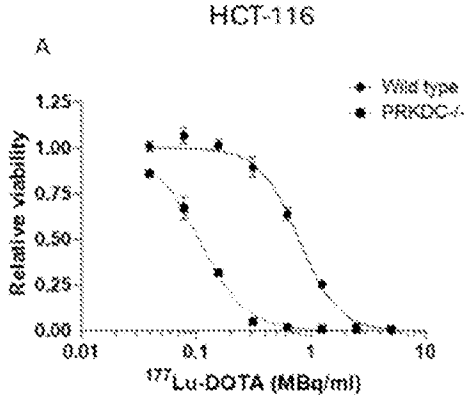


FIG. 4A

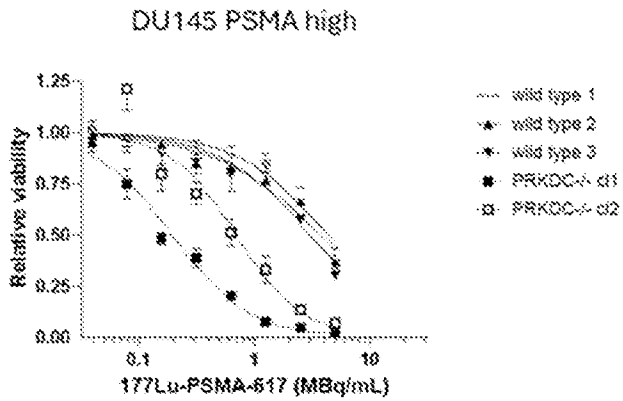


FIG. 4B

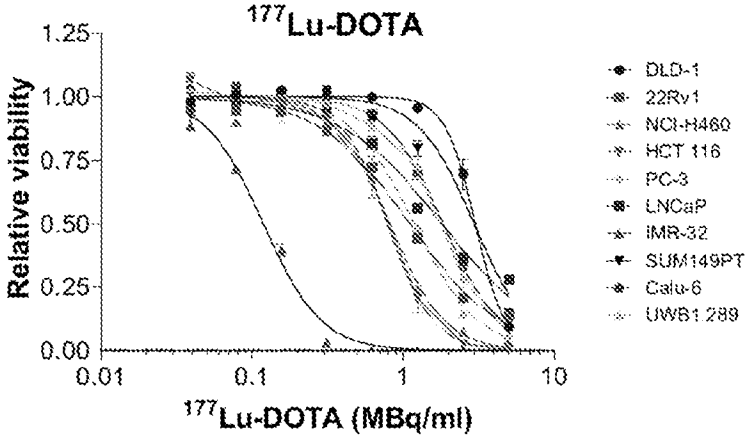

177Lu-DOTA
Relative viability
1.25
1.00
0.75
0.50
0.25
0.00
0.01
0.1
1
10
177Lu-DOTA (MBq/ml)
DLD-1
22Rv1
NCI-H460
HCT 116
PC-3
LNCaP
IMR-32
SUM149PT
Calu-6
UWB1.289

FIG. 5

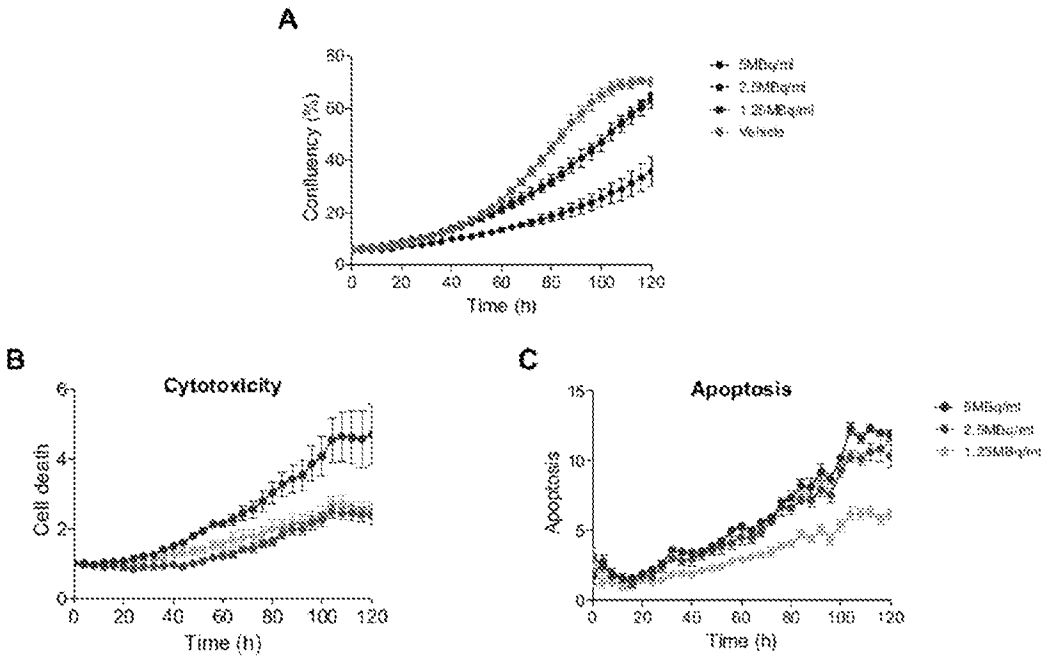

A
Confluency (%)
Time (h)
B
Cytotoxicity
Cell death
Time (h)
C
Apoptosis
Apoptosis
Time (h)

FIG. 6A-C

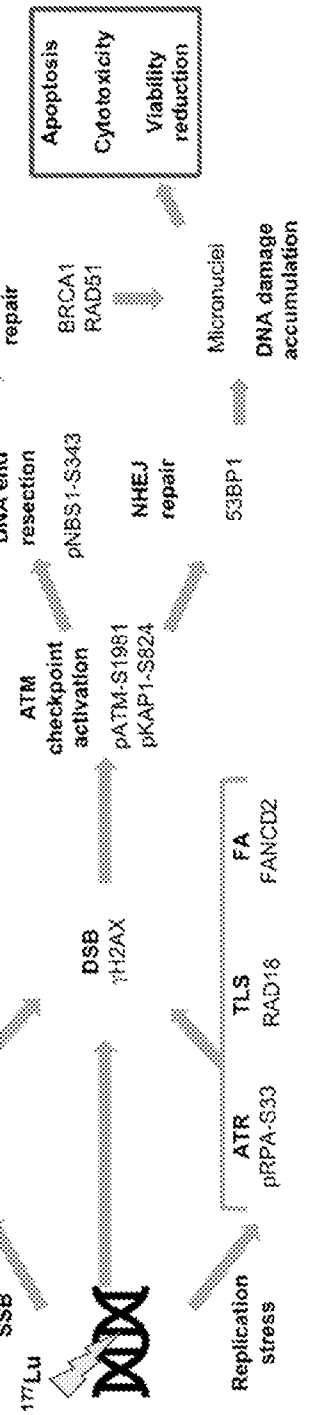
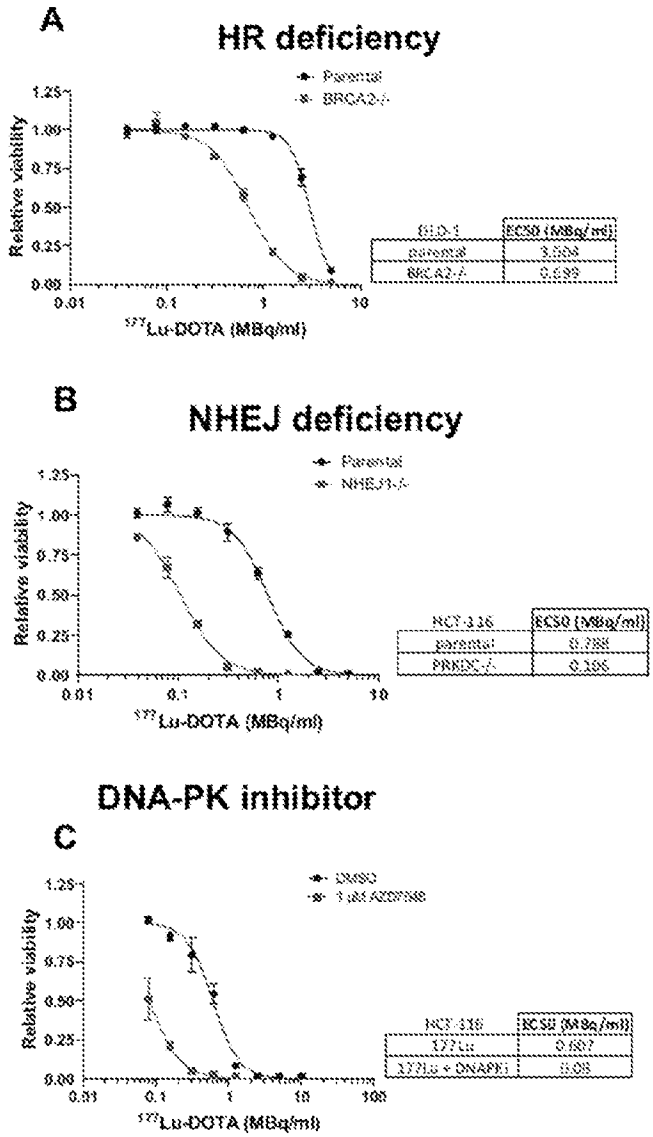

177Lu
SSB
XRCC1
DSB
γH2AX
Replication stress
ATR
pRPA-S33
TLS
RAD18
FA
FANCD2
ATM checkpoint activation
pATM-S1981
pKAP1-S824
DNA end resection
pNBS1-S343
NHEJ repair
53BP1
HR repair
BRCA1
RAD51
Micronuclei
DNA damage accumulation
Apoptosis
Cytotoxicity
Viability reduction

FIG. 7


A
HR deficiency
Parental
BRCA2-/-
Relative viability
1.25
1.00
0.75
0.50
0.25
0.00
0.01
0.1
1
10
177Lu-DOTA (MBq/ml)
B
NHEJ deficiency
Parental
NHEJ1-/-
Relative viability
177Lu-DOTA (MBq/ml)
C
DNA-PK inhibitor
DMSO
1 µM AZD7648
Relative viability
177Lu-DOTA (MBq/ml)

FIGs. 8A-C

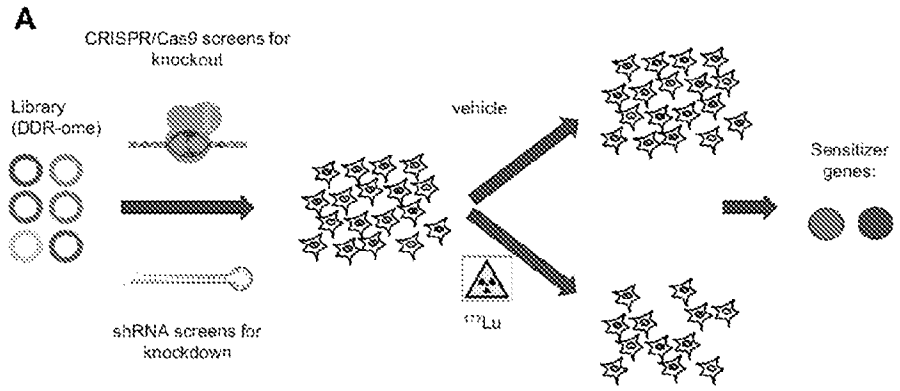


FIG. 9A

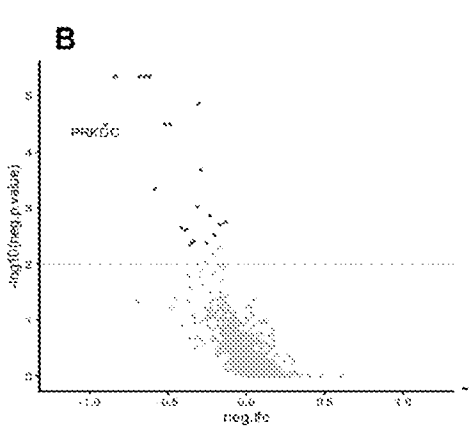


FIG. 9B

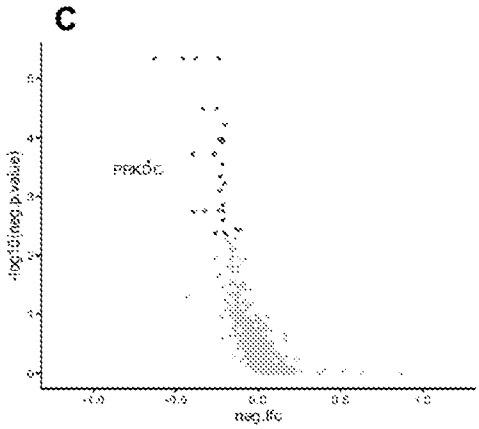


FIG. 9C

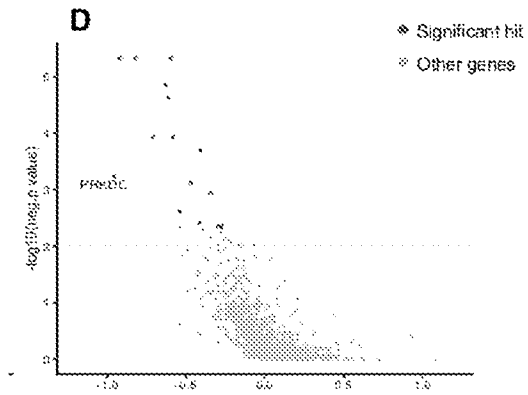


FIG. 9D

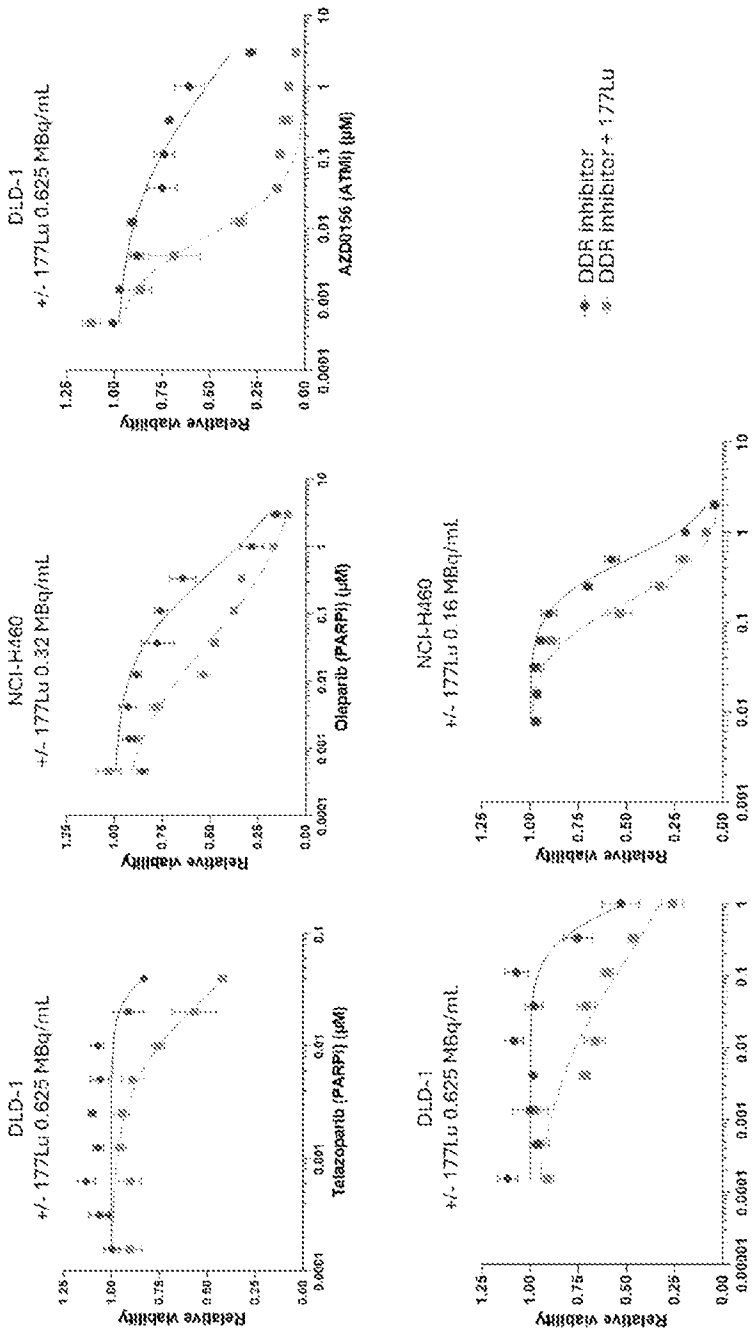

DLD-1
+/- 177Lu 0.625 MBq/mL
Relative viability
Talazoparib (PARPi) (μM)
NCI-H460
+/- 177Lu 0.32 MBq/mL
Olaparib (PARPi) (μM)
DLD-1
+/- 177Lu 0.625 MBq/mL
AZD0156 (ATMi) (μM)
DLD-1
+/- 177Lu 0.625 MBq/mL
LY2603618 (CHK1i) (μM)
NCI-H460
+/- 177Lu 0.16 MBq/mL
MK1775 (WEE1i) (μM)
DDR inhibitor
DDR inhibitor + 177Lu

FIG. 10A

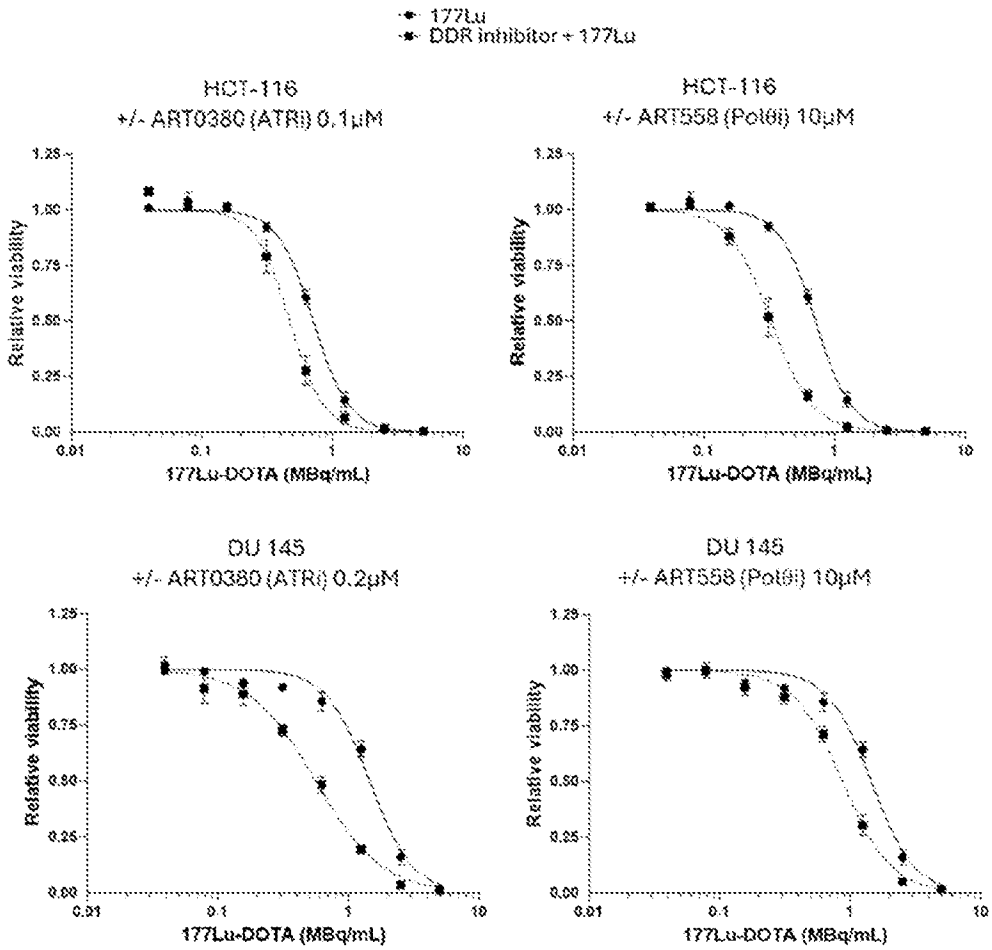

177Lu
DDR inhibitor + 177Lu
HCT-116
+/- ART0380 (ATRi) 0.1µM
HCT-116
+/- ART558 (Polθi) 10µM
DU 145
+/- ART0380 (ATRi) 0.2µM
DU 145
+/- ART558 (Polθi) 10µM
Relative viability
177Lu-DOTA (MBq/mL)

FIG. 10B

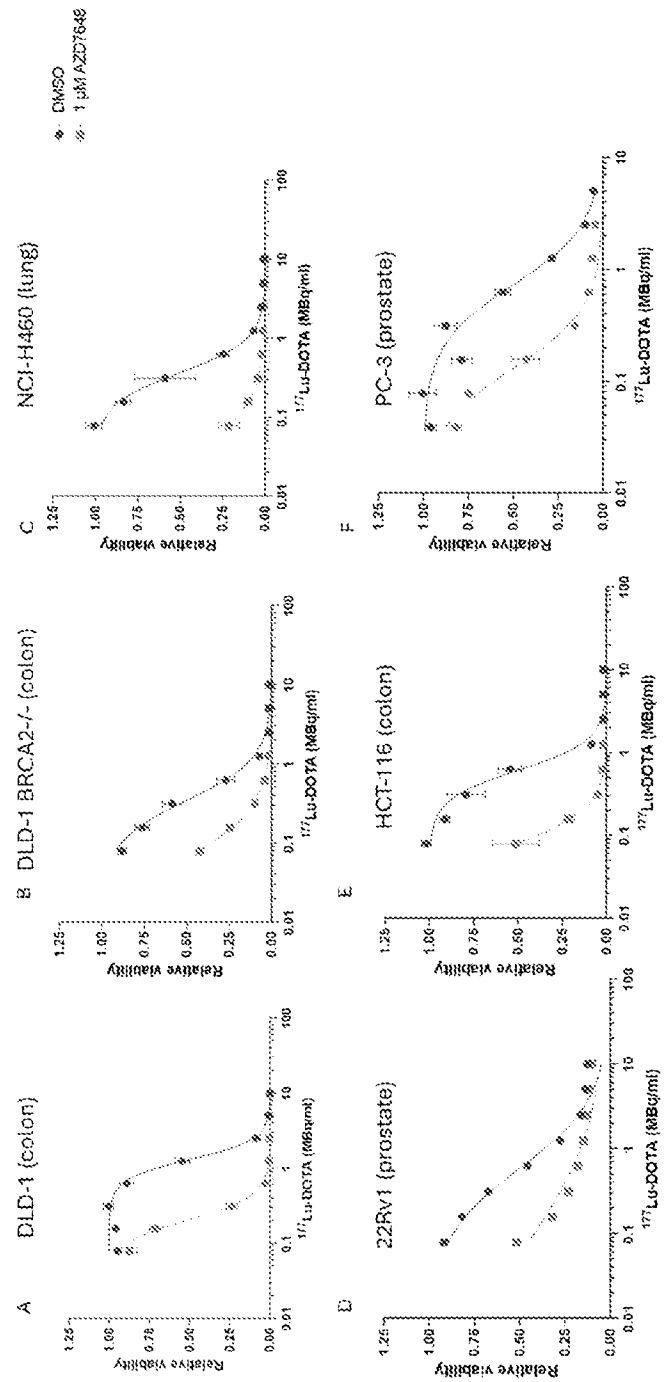
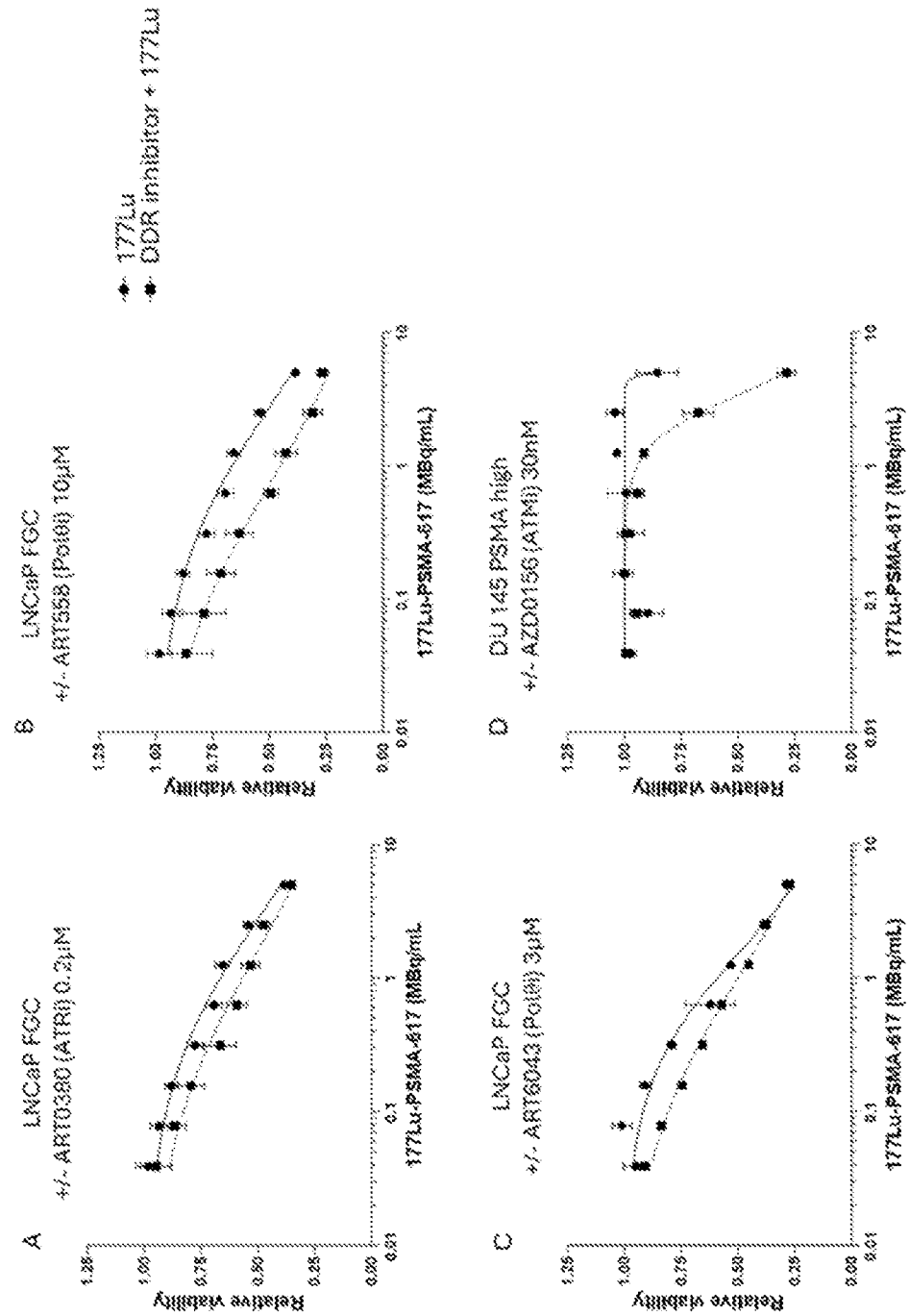
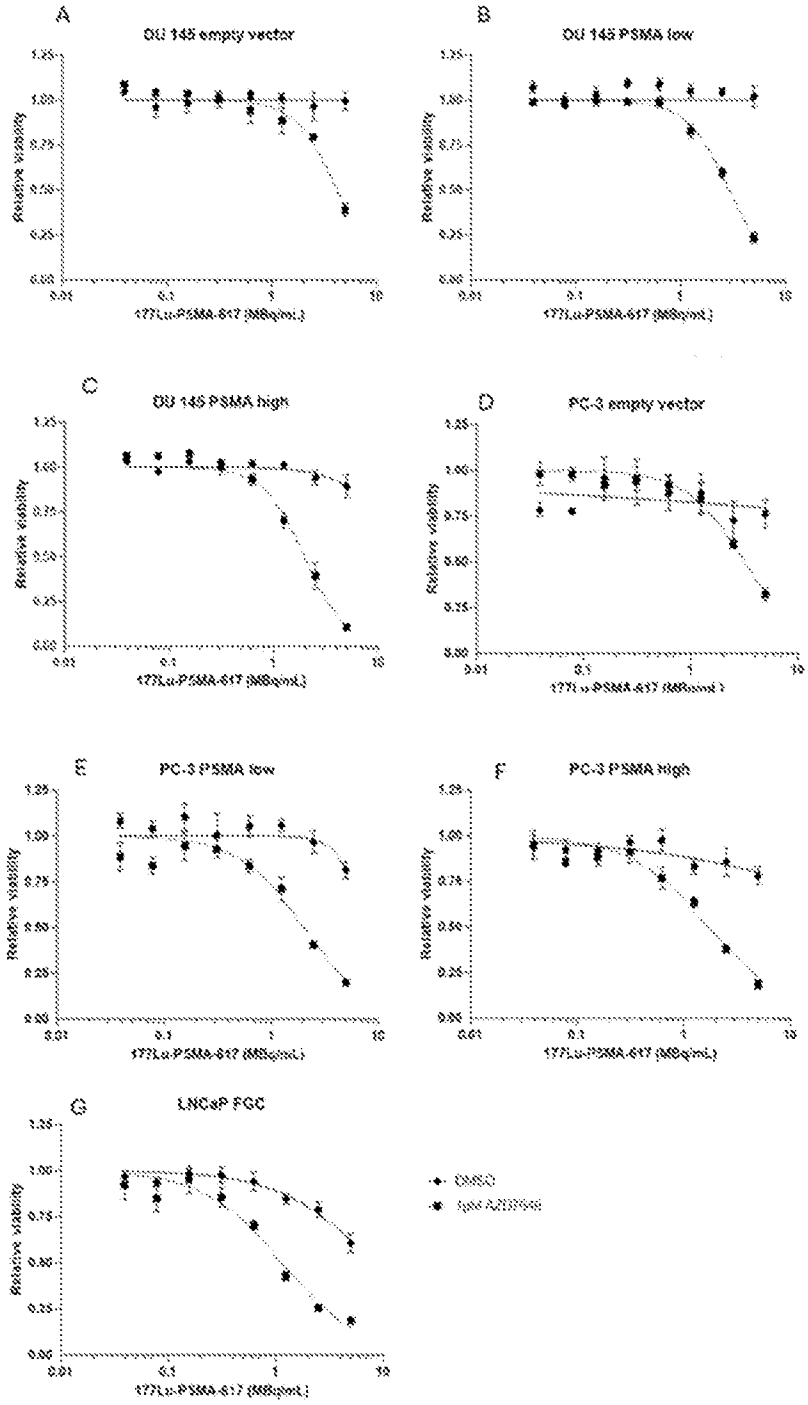

A
DLD-1 (colon)
B
DLD-1 BRCA2-/- (colon)
C
NCI-H460 (lung)
D
22Rv1 (prostate)
E
HCT-116 (colon)
F
PC-3 (prostate)
DMSO
1 µM AZD7648
Relative viability
^{177}Lu-DOTA (MBq/ml)

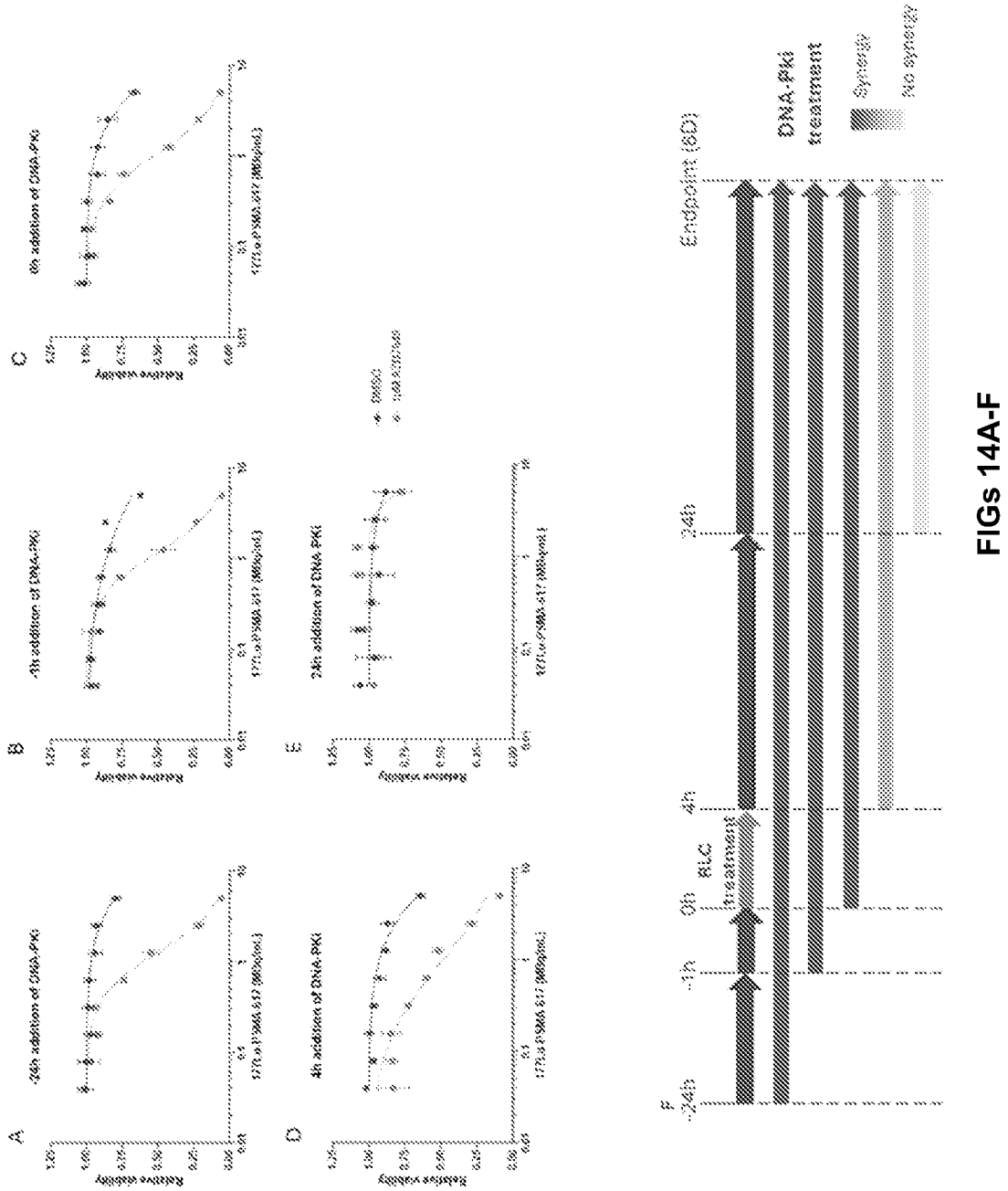
FIG. 11A-F


A
LNCaP FGC
+/- ART0380 (ATRi) 0.2µM
B
LNCaP FGC
+/- ART558 (Polθi) 10µM
C
LNCaP FGC
+/- ART6043 (Polθi) 3µM
D
DU 145 PSMA high
+/- AZD0156 (ATMi) 30nM
Relative viability
177Lu-PSMA-617 (MBq/mL)
177Lu
DDR inhibitor + 177Lu

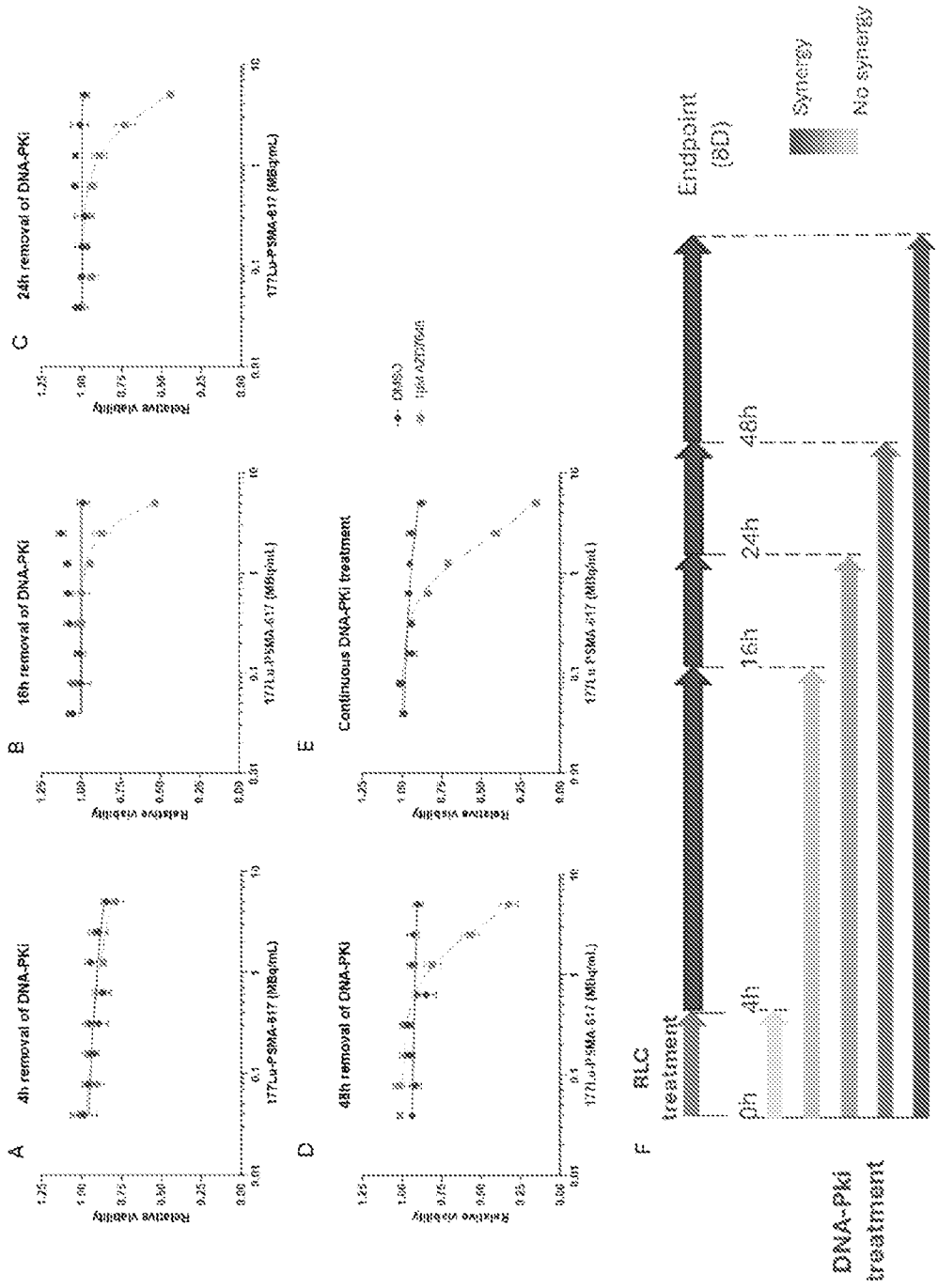
FIGs. 12A-D


A
OU 145 empty vector
B
OU 145 PSMA low
C
OU 145 PSMA high
D
PC-3 empty vector
E
PC-3 PSMA low
F
PC-3 PSMA high
G
LNCaP FGC
Relative viability
177Lu-PSMA-617 (MBq/mL)

FIGs. 13A-G


A
B
C
D
E
F
-24h
-1h
0h
RLC treatment
4h
24h
Endpoint (6D)
DNA-PKi treatment
Synergy
No synergy

FIGs 14A-F


A
4h removal of DNA-PKi
B
16h removal of DNA-PKi
C
24h removal of DNA-PKi
D
48h removal of DNA-PKi
E
Continuous DNA-PKi treatment
DMSO
Relative viability
177Lu-PSMA-617 (MBq/mL)
F
RLC treatment
DNA-PKi treatment
0h
4h
16h
24h
48h
Endpoint (6D)
Synergy
No synergy

FIGs. 15A-F

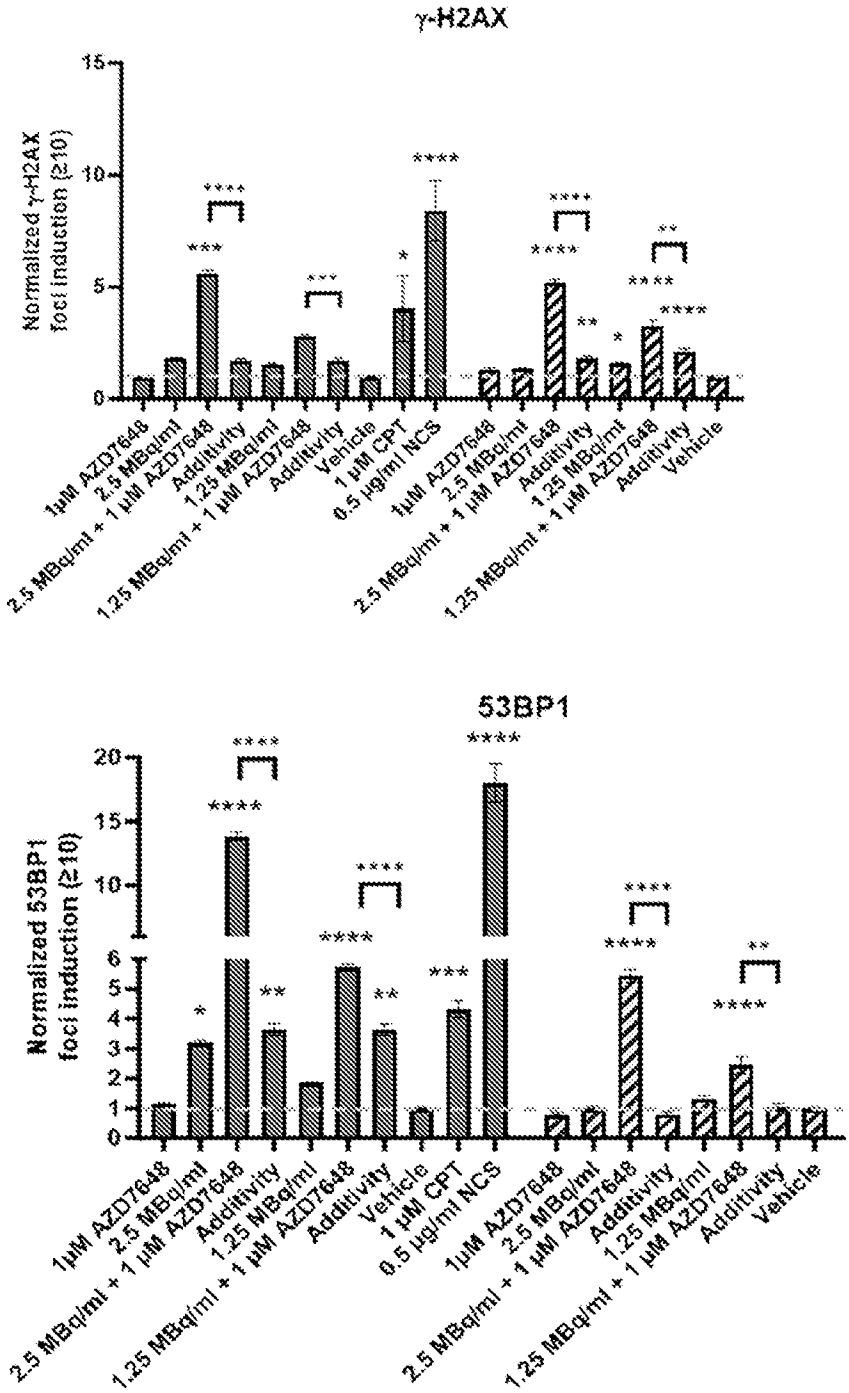

γ-H2AX
Normalized γ-H2AX foci induction (≥10)
1µM AZD7648
2.5 MBq/ml
2.5 MBq/ml + 1 µM AZD7648
Additivity
1.25 MBq/ml
1.25 MBq/ml + 1 µM AZD7648
Additivity
Vehicle
1 µM CPT
0.5 µg/ml NCS
1µM AZD7648
2.5 MBq/ml
2.5 MBq/ml + 1 µM AZD7648
Additivity
1.25 MBq/ml
1.25 MBq/ml + 1 µM AZD7648
Additivity
Vehicle
53BP1
Normalized 53BP1 foci induction (≥10)
1µM AZD7648
2.5 MBq/ml
2.5 MBq/ml + 1 µM AZD7648
Additivity
1.25 MBq/ml
1.25 MBq/ml + 1 µM AZD7648
Additivity
Vehicle
1 µM CPT
0.5 µg/ml NCS
1µM AZD7648
2.5 MBq/ml
2.5 MBq/ml + 1 µM AZD7648
Additivity
1.25 MBq/ml
1.25 MBq/ml + 1 µM AZD7648
Additivity
Vehicle

FIG. 16

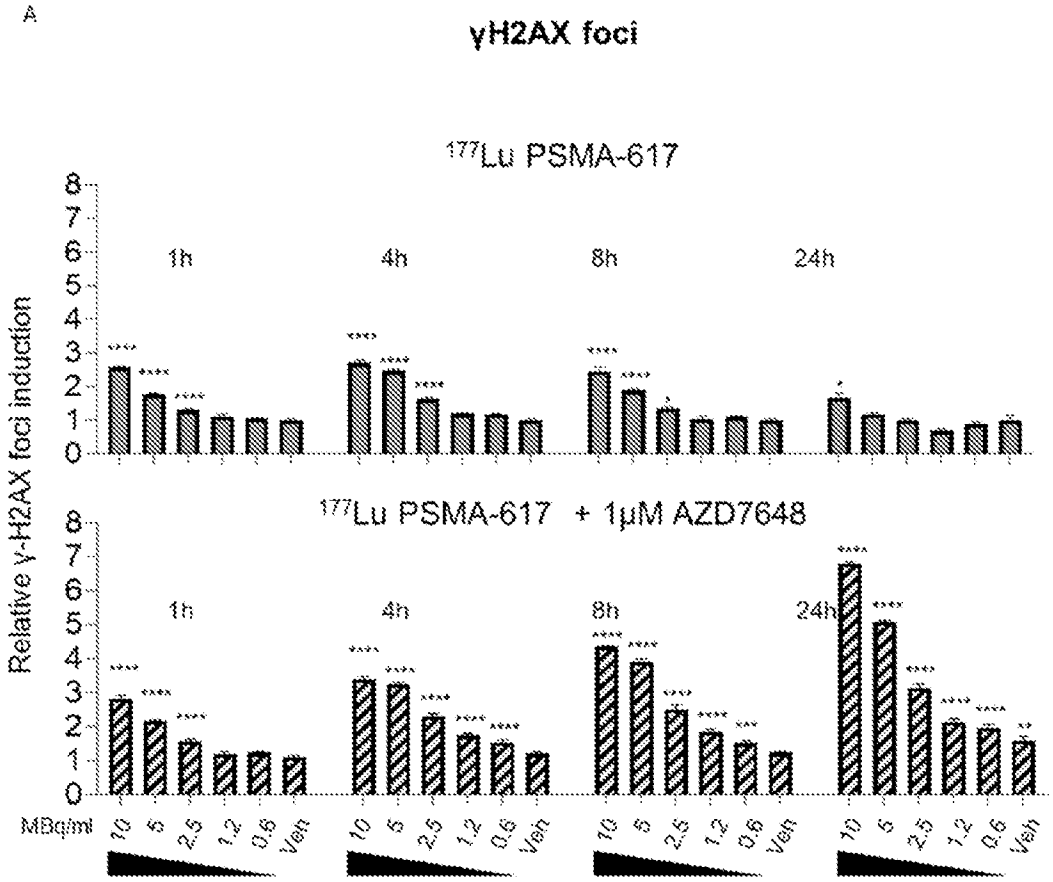

A
γH2AX foci
177Lu PSMA-617
177Lu PSMA-617 + 1μM AZD7648
Relative γ-H2AX foci induction
1h
4h
8h
24h
MBq/ml
10
5
2.5
1.2
0.6
Veh

FIG. 17A

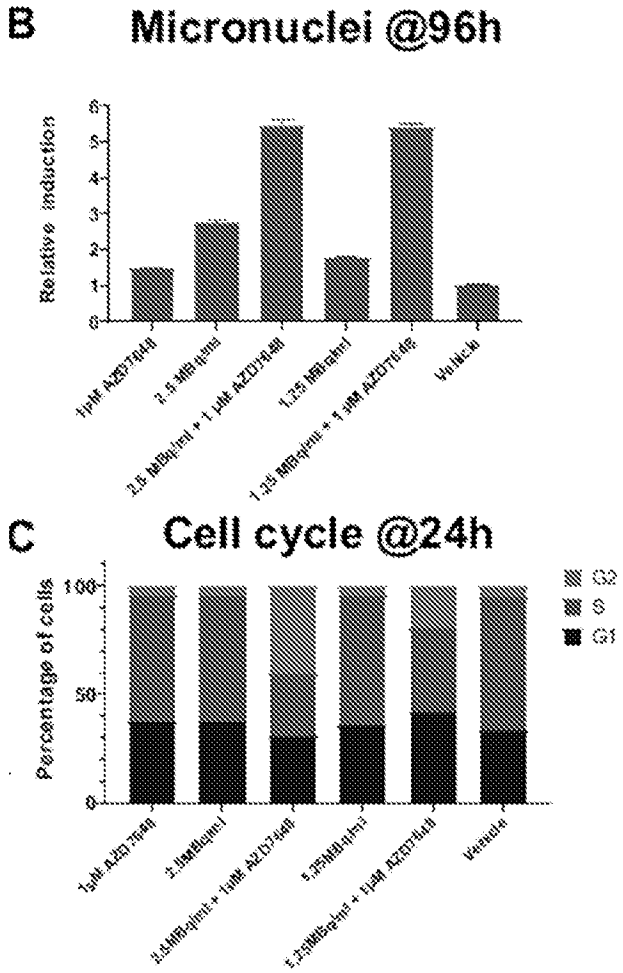
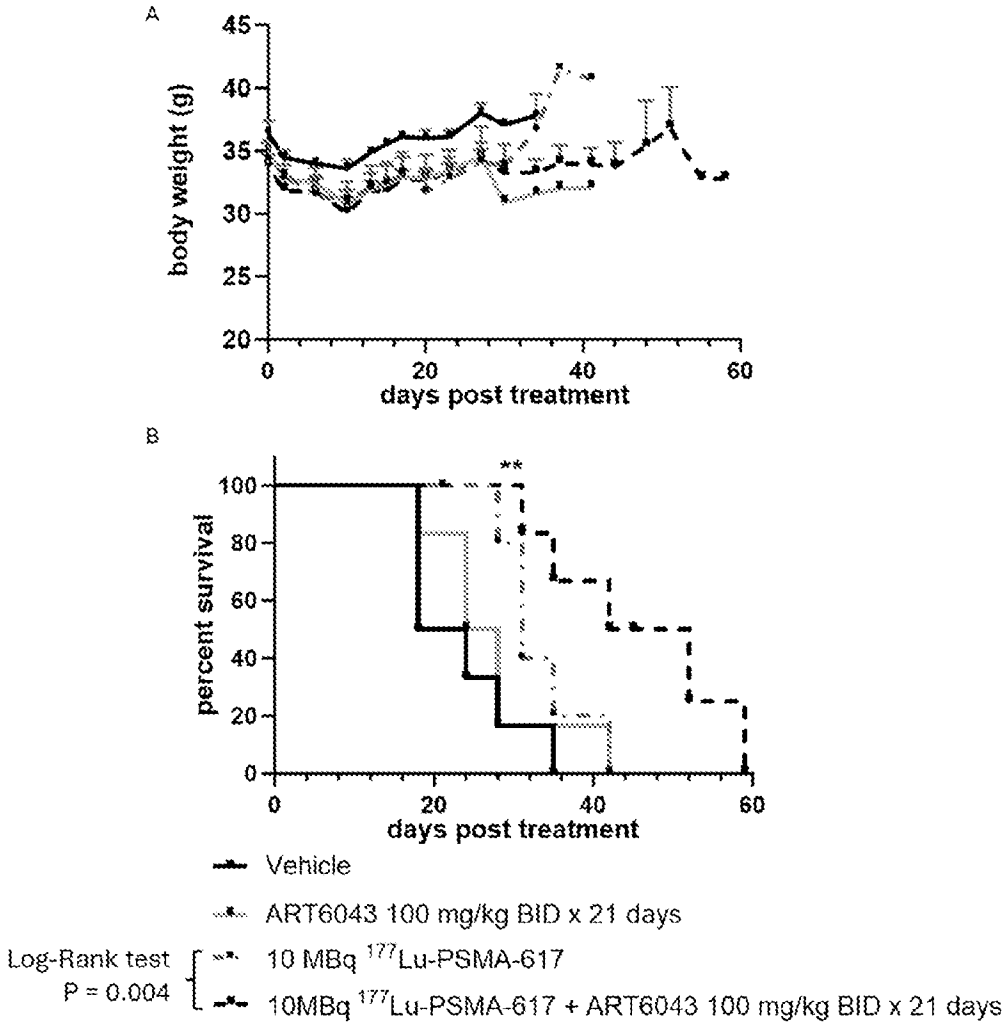

B
Micronuclei @96h
Relative induction
0
1
2
3
4
5
6
1µM AZD7648
2.5 MB/µmL
2.5 MB/µmL + 1 µM AZD7648
1.25 MB/µmL
1.25 MB/µmL + 1 µM AZD7648
Vehicle
C
Cell cycle @24h
Percentage of cells
0
50
100
G2
S
G1
1µM AZD7648
2.5MB/µmL
2.5MB/µmL + 1µM AZD7648
1.25MB/µmL
1.25MB/µmL + 1µM AZD7648
Vehicle

FIG. 17B-C


A
body weight (g)
45
40
35
30
25
20
0
20
40
60
days post treatment
B
percent survival
100
80
60
40
20
0
**
0
20
40
60
days post treatment
Vehicle
ART6043 100 mg/kg BID x 21 days
Log-Rank test
P = 0.004
10 MBq 177Lu-PSMA-617
10MBq 177Lu-PSMA-617 + ART6043 100 mg/kg BID x 21 days

FIGs. 18A-B

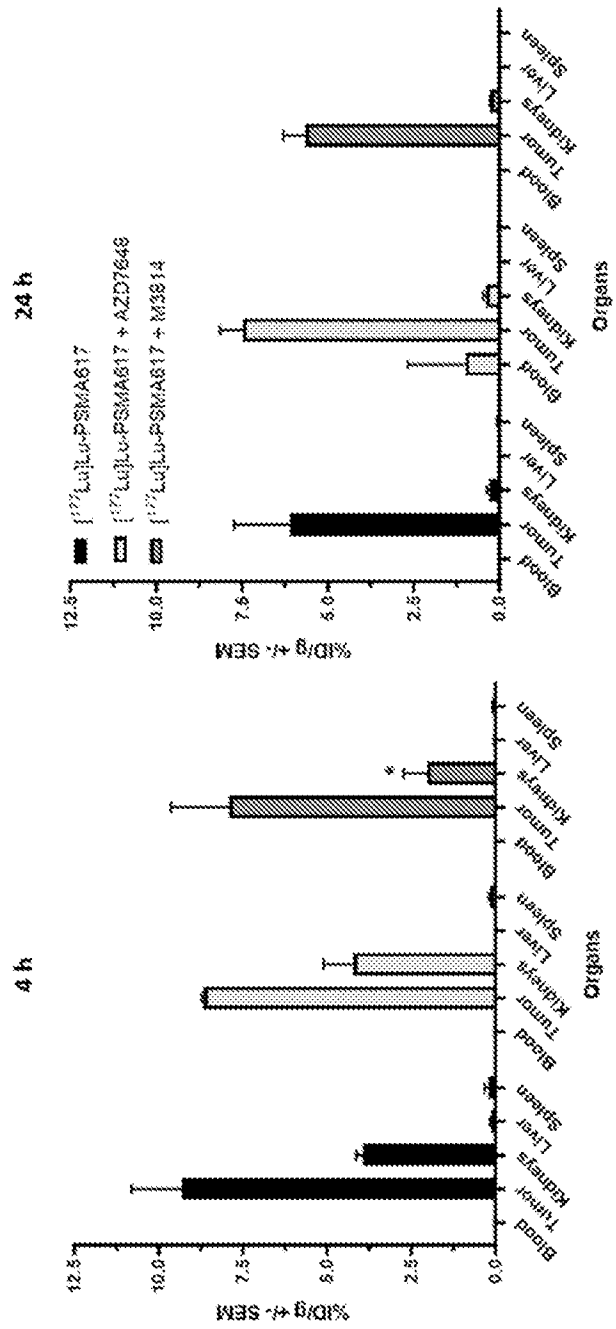

24 h
4 h
%ID/g +/- SEM
Organs
Blood
Tumor
Kidneys
Liver
Spleen
12.5
10.0
7.5
5.0
2.5
0.0
*

FIG. 19

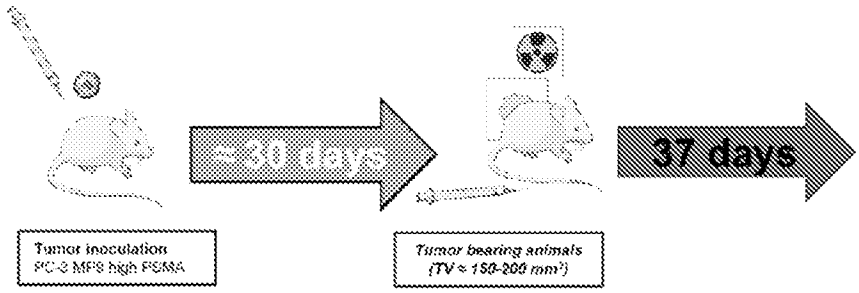


FIG. 20A

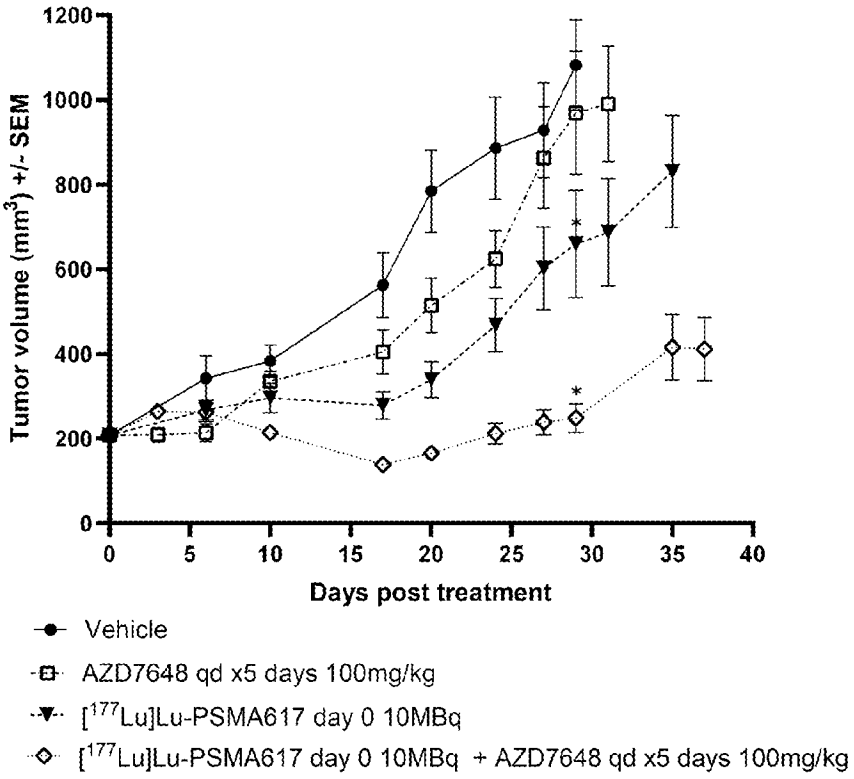


FIG. 20B

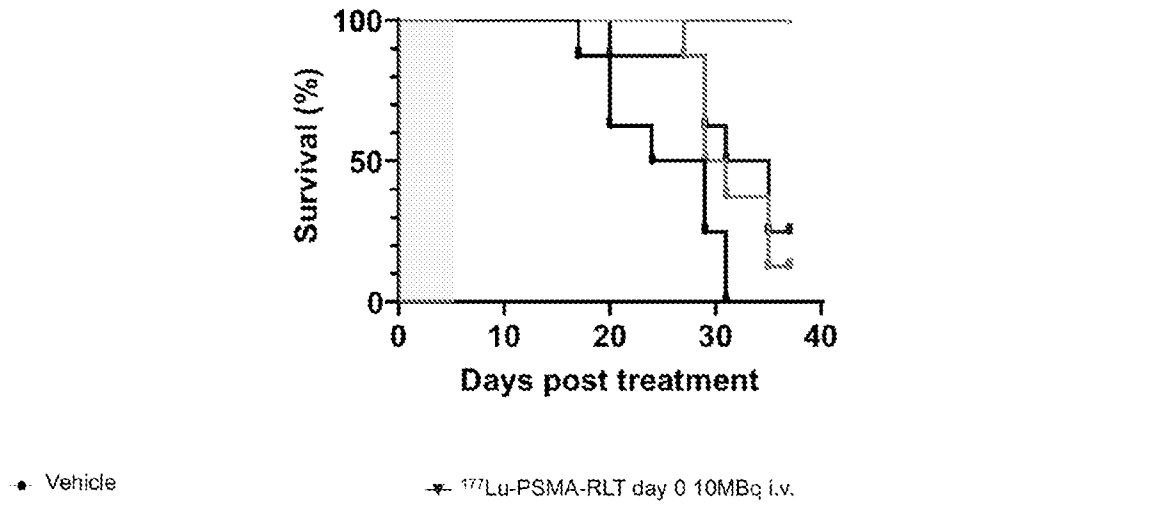


FIG. 20C

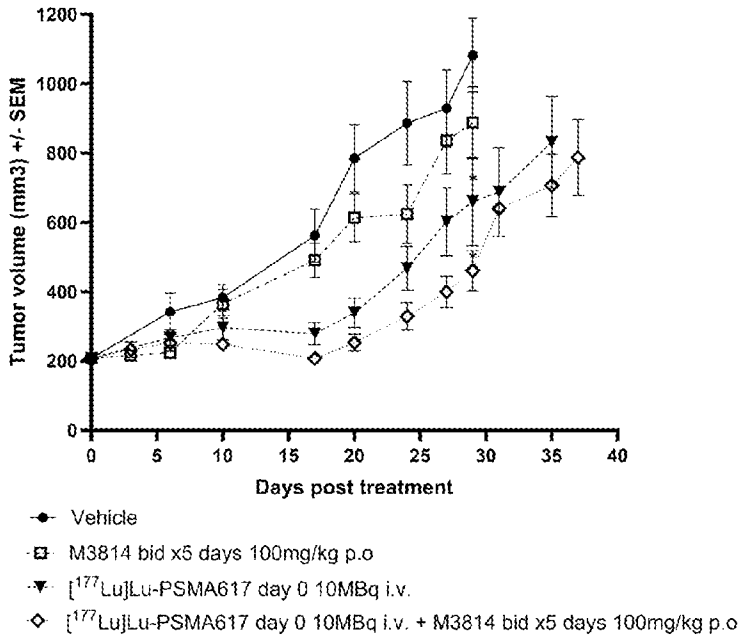


FIG. 20D