from patients with advanced breast cancer who have progressed on endocrine therapies, largely aromatase inhibitors (Li S, et al. Cell Rep (2013); 4(6): 1116-1130 ; Merenbakh-Lamin K, et al. Cancer Res (2013); 73(23): 6856-6864 ; Robinson DR, et al. Nat Genet (2013); 45(12): 1446-1451 ; Toy W, et al. Nat Genet (2013); 45(12): 1439-1445 ; Jeselsohn R, et al. Clin Cancer Res (2014); 20: 1757-1767). These ligand-binding domain (LBD) mutations confer high basal activity of the apo-receptor rendering them ligand-independent and thus active in the setting of low estradiol. There is a tremendous need for therapies that target ER signaling with robust activity in the setting of progressive disease post AI or tamoxifen treatment including the subset of patients harboring ESR1 mutant tumors.

ARN-810 (GDC-0810, Seragon Pharmaceuticals, Genentech Inc.) is a potent small molecule, nonsteroidal, selective ER modulator that antagonizes the effects of estrogens and induces ER degradation via proteasome. ARN-810 is in clinical trials as an orally-delivered therapy to treat advanced metastatic ER-α positive (ER+) breast cancer.

Non-steroidal, Selective Estrogen Receptor Degraders (SERD) have been described (WO 2011/156518; US 8703810; WO 2012/037411; WO 2012/037410; US 8299112; US 8455534; WO 2013/090829; WO 2013/142266; WO 2014/151899; WO 2013/090836; WO 2014/025138; WO 2014/205136).

SUMMARY ~~OF THE INVENTION~~

Described herein, in certain embodiments, are methods for treating a hormone resistant-estrogen receptor (ER) positive breast cancer in a patient characterized as having a mutation in the *ESR1* gene, comprising administering an estrogen receptor modulator (ERM). In some embodiments, the estrogen receptor modulator is a Selective Estrogen Receptor Degrader (SERD). In some embodiments, the estrogen receptor modulator is a selective estrogen receptor modulator (SERM). In some embodiments, the estrogen receptor modulator is a compound having the structure of Formula (A), (B), (C) or (D). In some embodiments, the compound having the structure of Formula (A) is a compound having the structure of Formula (A-1). In some embodiments, the compound having the structure of Formula (C) is a compound having the structure of Formula (C-1). In some embodiments, the compound having the structure of Formula (D) is a compound having the structure of Formula (D-1), (D-2), (D-3), (D-4), (D-5), or (D-6). In some embodiments, the mutation in the *ESR1* gene results in an ER polypeptide having an amino acid substitution at a position selected from among amino acids positions 6, 118, 269, 311, 341, 350, 380, 392, 394, 433, 463, 503, 534, 535, 536, 537, 538 and 555 of SEQ ID NO:2.

17, 4-18, 4-19, 4-20, 4-21, 4-22, 4-23, 4-24, 4-25, 4-26, 4-27, 4-28, 4-29, 4-30, 4-31, 4-32, 4-33, 4-34; 4-35, 4-36, 4-37, 4-38, 4-39, 4-40, 4-41, 4-42, 4-43, 4-44 and 4-45.

In some embodiments, the estrogen receptor modulator is 4-23.

In some embodiments, the estrogen receptor modulator is 1-3 or 4-23.

In some embodiments, the estrogen receptor modulator is (E)-3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid or (S)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol.

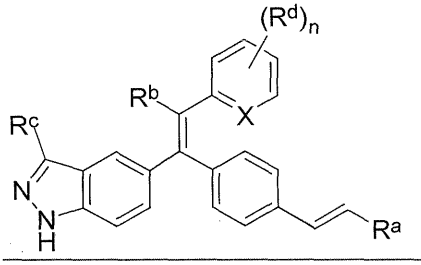
In some embodiments, the estrogen receptor modulator is (E)-3-(4-((E)-2-(2-chloro-4-fluorophenyl)-1-(1H-indazol-5-yl)but-1-en-1-yl)phenyl)acrylic acid.

In some embodiments, the estrogen receptor modulator is (S)-2-(4-(2-(3-(fluoromethyl)azetidin-1-yl)ethoxy)phenyl)-3-(3-hydroxyphenyl)-4-methyl-2H-chromen-6-ol.

In one aspect, there is provided an estrogen receptor modulator compound of Formula (A), (B), (C), or (D) for use in the treatment of an ER-related disease or condition

wherein the a patient has a mutation in the *ESR1* gene;

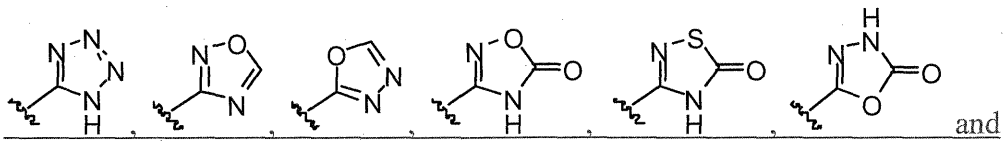
wherein the compound of Formula (A) has the structure:



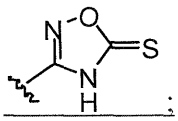
Formula (A)

where,

R^a is $-CO_2H$ or a 5-membered heterocycle selected from the group consisting of



and



;

R^b is C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

R^c is H or F;

each R^d is independently selected from H, halogen, -CN, $-OR^e$, $-NHR^e$, $-NR^eR^f$, $-SR^e$, $-S(=O)R^f$, $-S(=O)_2R^f$, C_1-C_6alkyl, and C_1-C_6fluoroalkyl;

each R^e is independently selected from H, -C(=O)R^f, -C(=O)OR^f, -C(=O)NHR^f, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

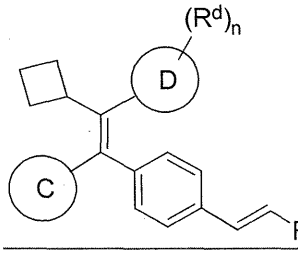
each R^f is independently selected from C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

X is CH or N; and

n is 0, 1, or 2,

or a pharmaceutically acceptable salt, or solvate thereof;

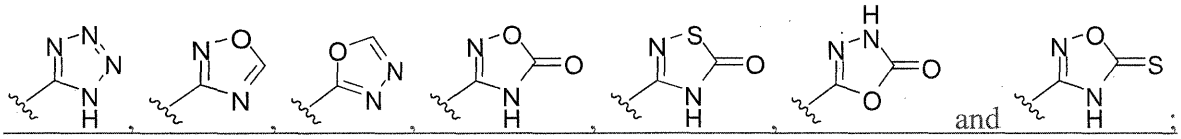
wherein the compound of Formula (B) has the structure:



Formula (B),

where,

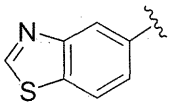
R^a is $-CO_2H$ or a 5-membered heterocycle selected from the group consisting of



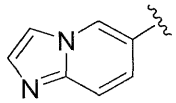
and

;

ring C is



or



;

ring D is phenyl or thienyl;

each R^d is independently selected from H, halogen, -CN, -OR^e, -NHR^e, -N$R^e R^f$, -SR^e, -S(=O)R^f, -S(=O)$_2R^f$, C_1-C_6 alkyl, and C_1-C_6 fluoroalkyl;

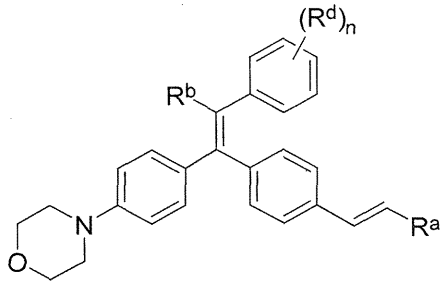
each R^e is independently selected from H, -C(=O)R^f, -C(=O)OR^f, -C(=O)NHR^f, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

each R^f is independently selected from C_1-C_6alkyl, C_1-C_6fluoroalkyl, C_3-C_6cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

n is 0, 1, or 2,

or a pharmaceutically acceptable salt, or solvate thereof;

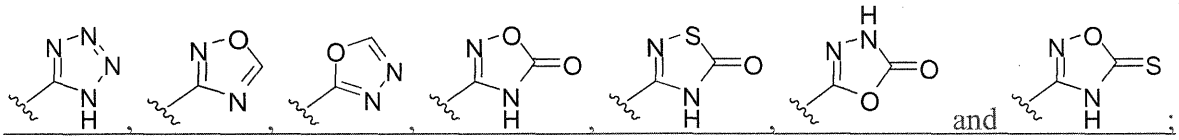
wherein the compound of Formula (C) has the structure:



Formula (C),

where,

R^a is $-CO_2H$ or a 5-membered heterocycle selected from the group consisting of



and

;

R^b is C_1-C_6 alkyl or C_3-C_6 cycloalkyl;

each R^d is independently selected from H, halogen, -CN, $-OR^e$, $-NHR^e$, $-NR^eR^f$, $-SR^e$, $-S(=O)R^f$, $-S(=O)_2R^f$, C_1-C_6alkyl, and C_1-C_6 fluoroalkyl;

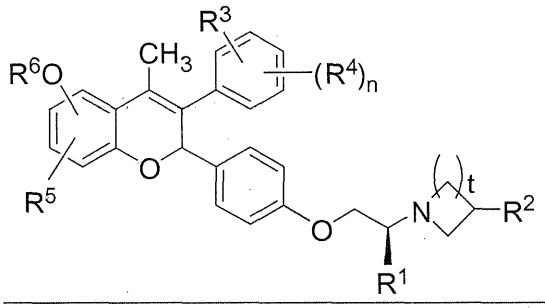
each R^e is independently selected from H, $-C(=O)R^f$, $-C(=O)OR^f$, $-C(=O)NHR^f$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

each R^f is independently selected from C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl; and

n is 0, 1, or 2,

or a pharmaceutically acceptable salt, or solvate thereof; and

wherein the compound of Formula (D) has the structure:



Formula (D)

where,

R^1 is H, C_1-C_4 alkyl, or C_1-C_4 fluoroalkyl;

R^2 is H, F, C_1-C_4 alkyl or C_1-C_4 fluoroalkyl;

R^3 is H, halogen, -CN, $-OR^6$, $-NHR^6$, $-NR^6R^7$, $-SR^6$, $-S(=O)R^7$, $-S(=O)_2R^7$, C_1-C_4alkyl, or C_1-C_4 fluoroalkyl;

each R^4 is independently selected from H, halogen, -CN, -OH, C_1-C_6 alkyl, C_1-C_4 fluoroalkyl, C_1-C_4 fluoroalkoxy, and C_1-C_4 alkoxy;

each R^5 is H, F, Cl, -OH, $-CH_3$, $-CF_3$, or $-OCH_3$;

each R^6 is independently selected from H, $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NHR^7$, C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, C_3-C_6 cycloalkyl, substituted or unsubstituted C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

each R^7 is independently selected from C_1-C_6 alkyl, C_1-C_6 fluoroalkyl, substituted or unsubstituted C_3-C_6 cycloalkyl, substituted or unsubstituted monocyclic C_2-C_6 heterocycloalkyl, substituted or unsubstituted phenyl, and substituted or unsubstituted monocyclic heteroaryl;

n is 0, 1, or 2; and

t is 1 or 2,

or a pharmaceutically acceptable salt, or solvate thereof.

In some embodiments, the ER-related disease or condition is cancer. In some embodiments, the cancer is a breast cancer. In some embodiments, the breast cancer is a metastatic breast cancer. In some embodiments, the breast cancer is a hormone resistant breast cancer. In some embodiments, the breast cancer is an estrogen receptor positive breast cancer. In some embodiments, the breast cancer is a HER2 positive breast cancer. In some embodiments, the breast cancer is a HER2 negative breast cancer. In some embodiments, the breast cancer is resistant to treatment with an aromatase inhibitor. In some embodiments, the mutation in the *ESR1* gene is a somatic mutation. In some embodiments, the patient expresses a wild-type ER and a mutant ER. In some embodiments, the patient expresses a homodimer of two mutant ER-α polypeptides. In some embodiments, the patient expresses a heterodimer of one wild-type ER-α polypeptide and one mutant ER-α polypeptide or a heterodimer of one

wild-type ER-β polypeptide and one mutant ER-α polypeptide. In some embodiments, the patient has a tumor. In some embodiments, a plurality of cells of the tumor express the mutant ER. In some embodiments, the patient is pre-menopausal or post-menopausal. In some embodiments, the patient has failed one or more anti-cancer therapies. In some embodiments, the patient has received a chemotherapeutic agent, a biological therapy, a cancer vaccine, an angiogenesis inhibitor, hormone therapy, radiation therapy, surgery, or any combination thereof. In some embodiments, the biological therapy is a peptide, a cytokine, an antibody, a therapeutic virus, a therapeutic bacterium, gene therapy, siRNA, adoptive T-cell transfer, or any combination thereof. In some embodiments, the patient has received an aromatase inhibitor, a selective estrogen receptor modulator (SERM), a selective estrogen degrader (SERD), a phosphoinositide 3-kinase (PI3K)/mTOR pathway inhibitor, a CDK 4/6 inhibitor, a HER-2 inhibitor, an EGFR inhibitor, a

nucleic acid sample. In some embodiments, the method further comprises amplifying a nucleic molecule comprising the mutation from the nucleic acid sample. In some embodiments, amplification is by polymerase chain reaction (PCR) or digital PCR. In some embodiments, PCR amplification comprises using a pair of oligonucleotide primers that flank the region comprising the mutation. In some embodiments, the methods comprise contacting the nucleic acid with a sequence specific nucleic acid probe, wherein the sequence specific nucleic acid probe that binds to the nucleic acid having the mutation and does not bind to the wild-type nucleic acid. In some embodiments, the sample comprises nucleic acid from one or more tumor cells. In some embodiments, the tumor cell is taken from a tumor biopsy sample, a blood sample, a serum sample, a lymph sample, or a bone marrow aspirate. In some embodiments, the tumor cell is a circulating tumor cell. In some embodiments, the sample comprises circulating tumor DNA (ctDNA).

Described herein, in ~~certain embodiments~~another aspect, are kits comprising one or more reagents for the detection of a mutation in *ESR1* and an estrogen receptor modulator compound of Formula (A), (B), (C), or (D) as defined herein. In some embodiments, the kits comprise one or more primers or probes for the detection of a mutation in *ESR1*. In some embodiments, the ESR1 mutation results in a substitution, insertion or deletion of one or more amino acids in the ER polypeptide. In some embodiments, the ESR1 mutation results in an amino acid substitution the N-terminal domain, the DNA binding domain, the hinge region or the ligand binding domain of the estrogen receptor. In some embodiments, the ESR1 mutation results in an amino acid substitution in the ligand binding domain of the estrogen receptor. In some embodiments, the amino acid substitution is at amino acid position 6, 118, 269, 311, 341, 350, 380, 392, 394, 433, 463, 503, 534, 535, 536, 537, 538 and 555 of SEQ ID NO:2. In some embodiments, the amino acid substitution is selected from among H6Y, S118P, R269C, T311M, S341L, A350E, E380Q, V392I, R394H, S433P, S463P, R503W, V534E, P535H, L536R, L536P, L536Q, Y537N, Y537C, Y537S, D538G, and R555C. In some embodiments, the amino acid substitution is selected from among Y537N, Y537C, Y537S, and D538G.

In some embodiments, the estrogen receptor modulator of Formula (A), (B), (C), (D) is administered orally to a patient. In some embodiments, the estrogen receptor modulator of Formula (A), (B), (C), (D) is administered daily. In some embodiments, the estrogen receptor modulator of Formula (A), (B), (C), (D) is administered on a continuous daily dosing schedule.

In some embodiments, the estrogen receptor modulator of Formula (A), (B), (C), (D) is administered at about 5 mg per day to about 1000 mg per day. In some embodiments, the

therapeutically effective amount of an estrogen receptor modulator of Formula (A), (B), (C), (D) is about 10 mg per day to about 100 mg per day.

In some embodiments, the estrogen receptor modulator of Formula (A), (B), (C), (D) is administered once a day or multiple times a day. In some embodiments, the estrogen receptor modulator of Formula (A), (B), (C), (D) is administered once a day, twice a day, three times a day, or four times a day.

In another aspect, there is provided a pharmaceutical composition comprising an estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition as defined herein and one or more pharmaceutically acceptable excipients.

In another aspect, there is provided use of an estrogen receptor modulator compound as defined herein for the preparation of medicaments for use in the treatment of an ER-related disease or condition.

Other objects, features and advantages of the methods, uses and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

Breast cancer is the most common form of cancer and the leading cause of cancer death in women worldwide. Approximately 80% of all breast cancers express and are dependent on the estrogen receptor (ER) for tumor growth and progression. Other cancers also are thought to be dependent on ER-α signaling for growth and survival, such as, for example, ovarian and endometrial cancers.

Estrogen receptor alpha (ER-α) and estrogen receptor beta (ER-β) are steroid hormone receptors, which are members of the large nuclear receptor superfamily. Nuclear receptors share a common modular structure, which minimally includes a DNA binding domain (DBD) and a ligand binding domain (LBD). Steroid hormone receptors are soluble, intracellular proteins that act as ligand-regulated transcription factors. Vertebrates contain five closely related steroid hormone receptors (estrogen receptor, androgen receptor, progesterone receptor, glucocorticoid receptor, mineralcorticoid receptor), which regulate a wide spectrum of

reproductive, metabolic and developmental activities. The activities of ER are controlled by the binding of endogenous estrogens, including 17β-estradiol and estrones.

The ER-α gene is located on 6q25.1 and encodes a 595 AA protein. The ER- β gene resides on chromosome 14q23.3 and produces a 530 AA protein. However, due to alternative splicing and translation start sites, each of these genes can give rise to multiple isoforms. In addition to the DNA binding domain (called C domain) and ligand binding domain (E domain) these receptors contain an N-terminal (A/B) domain, a hinge (D) domain that links the C and E

47. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 37 wherein the sample comprises nucleic acid from one or more tumor cells.

48. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 47 wherein the tumor cell is taken from a tumor biopsy sample, a blood sample, a serum sample, a lymph sample, or a bone marrow aspirate.

49. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 48 wherein the tumor cell is a circulating tumor cell.

50. The estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to claim 49 wherein the sample comprises circulating tumor DNA (ctDNA).

51. A kit comprising one or more reagents for the detection of a mutation in *ESR1* and an estrogen receptor modulator compound of Formula (A), (B), (C), or (D) according to claim 1.

52. A pharmaceutical composition comprising an estrogen receptor modulator compound for use in the treatment of an ER-related disease or condition according to any of claims 1 to 50 and one or more pharmaceutically acceptable excipients.

53. The use of an estrogen receptor modulator compound according to any of claims 1 to 50 for the preparation of medicaments for use in the treatment of an ER-related disease or condition.

~~54. The use of an estrogen receptor modulator compound according to any of claims 1 to 50 for the treatment of an ER-related disease or condition.~~

~~55. A method for treating an ER-related disease or condition in a patient comprising administering an estrogen receptor modulator compound according to any of claims 1 to 34 to a patient.~~

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