AR+ BREAST CANCER TREATMENT METHODS

PRIORITY CLAIM

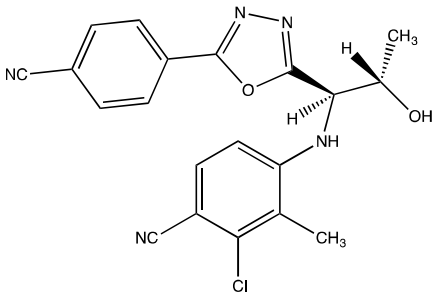
This application claims priority to U.S. Provisional Application No. 62/353,350, filed June 22, 2016, U.S. Provisional Application No. 62/377,497, filed August 19, 2016, and U.S. Provisional Application No. 62/461,546, filed February 21, 2017, all of which are incorporated herein by reference in their entirety, including drawings.

BACKGROUND

The relationship between androgens and breast cancer has been recognized for some time. In the past, androgen therapy has been used for treating breast cancer in women with mixed success. As breast cancer rapidly evolves to develop resistance to antiestrogen hormonal treatments, there is an urgent need to develop new treatment of breast cancer.

SUMMARY

In one aspect, the disclosure relates to use of a compound which is RAD140 (Compound III):



RAD 140 (Compound III)

a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof in the manufacture of a medicament for treating AR+/ER+ breast cancer.

In one example, the disclosure relates to methods for treating a subject (e.g., human) with breast cancer expressing the androgen receptor (AR+ breast cancer) through the administration of one or more AR agonist(s). In certain examples, the AR agonist is a selective androgen receptor modulator (SARM). In some examples, the breast cancers are positive for both the androgen receptor and the estrogen receptor (AR+/ER+). In certain examples of the methods disclosed herein, the breast cancers are positive for AR, ER and progesterone receptor (AR+/ER+/PR+). In certain examples, the breast cancers expressing AR do not test positive for Her2 ($Her2^-$). In certain examples, the breast cancers comprise one or more mutations in the ER as disclosed herein. In certain examples, the one or more ER mutations affect the ability of the ligand binding domain of the ER to bind ligands having affinity to non-mutated ER (wild-type ER). In certain examples, the breast cancers initially

positive for ER may lose tumor expression of ER. In certain examples, the subject is a premenopausal or postmenopausal woman. In certain examples, the SARM used for treating breast cancer is used in combination with a cell cyclin inhibitor and in some examples, the cell cyclin inhibitor is an inhibitor of CDK4 and/or CDK6 (CDK4/6 inhibitor). In certain examples, the SARM is used in combination with an mTOR inhibitor. In certain examples, the mTOR inhibitor is an inhibitor of mTOR2 and/or mTOR3. In some instances, the SARM is given by oral administration. In some examples, the cell cyclin inhibitor and/or mTOR inhibitor is given by oral administration. In certain examples the SARM and mTOR inhibitor or SARM and CDK4/6 inhibitor are combined together in a kit. In some examples, the SARM and mTOR inhibitor or SARM and CDK4/6 inhibitor are co-formulated.

In certain examples, the SARM is steroidal or non-steroidal and in certain examples the SARM is non-steroidal. In some examples, the SARM of this disclosure is selected from the group consisting of enobosarm, BMS-564929, LGD-4033, AC-262,356, JNJ-28330835, S-40503, LY-2452473 and GSK-2881078. In certain examples of the methods disclosed herein, the SARMs used according to the methods of this disclosure are described by the genus of compounds represented by Formula I and Formula IV as disclosed herein.

In some examples of the methods disclosed herein, the cell cyclin inhibitor is a CDK4/CDK6 inhibitor selected from the group consisting of palbociclib, ribociclib, trilaciclib and abemaciclib. In certain examples, the CDK4/CDK6 inhibitor is a compounds that inhibits both CDK4 and CDK6 with an IC_{50}<250 nM or <100 nM or <50nM. In certain examples of the methods disclosed herein, the mTOR inhibitor (TORC1 and/or TORC2) is selected from the group consisting of sirolimus, temsirolimus, everolimus, ridafarolimus, and MLN0128. In certain examples, the methods of treating breast cancer using a combination of a SARM together with a PARP inhibitor and in some examples the PARP inhibitor is talazoparib, veliparib, niraparib, beigene290, E7449, KX01, ABT767, CK102, JPI289, KX02, IMP4297, SC10914, NT125, PJ34, VPI289, ANG-3186 are disclosed. In certain examples, the methods of treating breast cancer using a combination of a SARM together with a BCL2 inhibitor are described and in some examples the BCL-2 inhibitor is venetoclax, navitoclax, ABT737, G3139 or S55746. In certain examples, the methods of treating breast cancer using a combination of a SARM together with an MCL1 inhibitor are described and in some examples the MCL-1 inhibitor is 7-(5-((4-(4-(N,N-Dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1H-pyrazol-4-yl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1H-indole-2-carboxylic Acid, S63845, omacataxine, seliciclib, UMI-77,

AT101, sabutoclax, TW-37. In particular examples, the methods of treating breast cancer using a combination of a SARM together with a PI3K inhibitor

In some examples of the methods disclosed herein, the breast cancer is treatment naïve. In some examples, the breast cancer has not yet been treated with any endocrinological therapies. In certain examples of the methods disclosed herein, the breast cancer is resistant to at least one prior therapy. In some examples the prior treatment for which resistance has developed is an antiestrogen therapy, e.g., at least one of an aromatase inhibitor, a selective estrogen receptor modulator (SERM) or a selective estrogen receptor degrader (SERD). In certain examples, the subject (e.g., woman) is postmenopausal and has progressed on prior endocrine therapy, including, without limitation, SERDs (e.g., fulvestrant, RAD1901, AZD9496); SERMs (e.g., tamoxifen, toremifene), aromatase inhibitors, and combinations thereof. In some examples, the subject (e.g.woman) has metastatic breast cancer but has not yet been treated. In some examples, the subject (e.g.woman) has metastatic breast and has progressed after prior endocronological therapy. In some examples, the subject (e.g.woman) has metastatic breast and has progressed after treatment with a mTOR inhibitor, or a CDK4/6 inhibitor, or a PIK3 inhibitor.

Certain examples provide a method of treating breast cancer comprising the steps of measuring a baseline level of *ZBTB16* mRNA expression or protein expression in an ER+/AR+ breast cancer subject, treating with an AR agonist or selective androgen receptor modulator as described herein, measuring the level of *ZBTB16* (encoding protein PLZF) after the treatment, and if the *ZBTB16* level after treatment has increased, continuing the treatment with the AR agonist or selective androgen receptor modulator. In certain examples, the subject is a woman, e.g., premenopausal or postmenopausal woman.

Also provided herein in some examples Isa diagnostic kit containing reagents for measuring the mRNA or protein expression of *ZBTB16*.

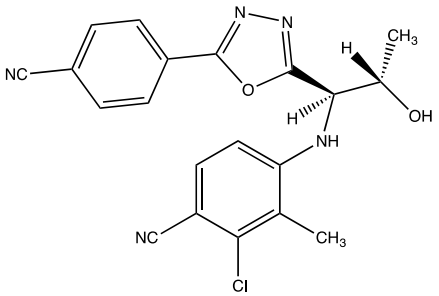
Provided herein is a method of identifying a subject who is likely to be responsive to the AR agonist therapy disclosed herein, comprising the steps of measuring a baseline level of *ZBTB16* mRNA expression or protein expression, treating with an AR agonist (e.g., SARM) for a period of time comprising at least one administration, measuring the *ZBTB16* mRNA expression level after the AR agonist therapy, and identifying the subject to be likely responsive to the AR agonist therapy if an increase in *ZBTB16* mRNA expression has occurred. In some examples, the expression cut off to determine responsiveness is at least a x2 fold increase, a x4 fold increase; an x8 fold increase, a x10 fold increase; a x25 fold increase; a x50 fold increase or a >1x100 fold increase.

In certain examples, a method of treating a woman with breast cancer is provided wherein said woman expresses one or mutations in the estrogen receptor, for example, a mutation of ERα gene (ESR1). Such mutations can include fusion proteins where part of the estrogen receptor has been fused to part or all of another protein. In some examples, a method of treating a woman with breast cancer is provided wherein said woman is first evaluated for one or more of said mutations and/or fusions and if she tests positive for the one or more mutations and/or fusions, she is treated with an AR agonist, for example a SARM, either as a monotherapy or with one or more additional chemotherapeutics as described herein. In some examples, the subject expresses a mutated PI3K.

CLAIMS

What is claimed is:

1. Use of a compound which is RAD140 (Compound III):



RAD 140 (Compound III)

a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof in the manufacture of a medicament for treating AR+/ER+ breast cancer.

2. The use according to claim 1 wherein medicament is to be administered via an oral route.

3. The use according to any one of claims 1-2 wherein:

(i) the subject is to be treated in an adjuvant setting;

(ii) the subject has had disease progression after treatment with one or more endocrinological agents; optionally wherein said one or more endocrinological agents are selected from the group consisting of SERMs, SERDs, progestins, aromatase inhibitors, and combinations thereof; or

(iii) said subject has had disease progression after treatment with one or more agents selected from the group consisting of CDK4/6 inhibitors, mTOR inhibitors, BCL-2 inhibitors, PI3K inhibitors, and combinations thereof.

4. The use according to any one of claims 1-3 wherein the compound is dosed between 10 and 500 mg, 10 mg and 250 mg, or 25 mg and 250 mg per day.

5. The use according to claim 4 wherein the dose is once per day.

6. The use according to any one of claims 1-5 wherein the subject expresses ESR1 comprising one or more mutations.

7. The use according to claim 6 wherein:

(i) said mutation affects the binding affinity of ligands compared to non-mutated ESR1; optionally wherein said mutation results in reduced estradiol affinity for the mutated ESR1 compared to the non-mutated ESR1; and/or

(ii) said mutation signals ligand dependently or ligand independently through the ESR1 pathway; and/or

(iii) said mutation results in a fusion protein containing at least 10 continuous amino acids from a sequence of a non-mutated ESR1 and at least 10 continuous amino acids from another human protein; and/or

(iv) said mutation results in ESR1 missing 10 or more consecutive amino acids from its normal (non-mutated) ligand binding domain amino acid sequence; and/or

(v) said mutation comprises one or more mutations selected from the group consisting of ESR1-AKAP12, ESR1-CCDC170, ESR1-YAP1, ESR1-POLH, ESR1-PCDH11X, and combinations thereof.

8. The use according to any one of claims 1-6 wherein the treatment further comprises that a CDK4/6 inhibitor is to be administered.

9. The use according to claim 8 wherein said CDK4/6 inhibitor has an IC_{50} of <100 nM against CDK4 and CDK6.

10. The use according to any one of claims 8-9 wherein said CDK4/6 inhibitor is selected from the group consisting of palbociclib, ribociclib, Trilaciclib, abemaciclib and AMG925.

11. The use according to claim 10, wherein said CDK4/6 inhibitor is palbociclib.

12. The use according to any one of claims 1-9 wherein said treatment further comprises that any one of the following is to be administered:

(i) an mTOR inhibitor; optionally wherein said mTOR inhibitor is selected from the group consisting of sirolimus, temsirolimus, everolimus, ridafarolimus, and MLN0128; or

(ii) a PI3K inhibitor; optionally wherein said PI3K inhibitor is BEZ235, GDC-0980, BKM120, GDC-0941, BYL719, GDC-0032, MK2206, GDC-0068, GSK2110183, GSK2141795, AZD5363, AZD2014, MLN0128 or CC-223; or

(iii) a PARP inhibitor; optionally wherein said PARP inhibitor is talazoparib, veliparib, niraparib, beigene290, E7449, KX01, ABT767, CK102, JPI289, KX02, IMP4297, SC10914, NT125, PJ34, VPI289 or ANG-3186; or

(iv) a MCL-1 inhibitor; optionally wherein said MCL-1 inhibitor is 7-(5-((4-(4-(N,N-Dimethylsulfamoyl)piperazin-1-yl)phenoxy)methyl)-1,3-dimethyl-1H-pyrazol-4-yl)-1-(2-morpholinoethyl)-3-(3-(naphthalen-1-yloxy)propyl)-1H-indole-2-carboxylic Acid, S63845, omacataxine, seliciclib, UMI-77, AT101, sabutoclax or TW-37; or

(v) a BCL-2 inhibitor; optionally wherein said BCL-2 inhibitor is venetoclax, navitoclax, ABT737, G3139 or S55746.

13. The use according to any one of claims 1 to 10 wherein said subject is a woman.

14. The use according to claim 13 wherein said woman is a premenopausal woman or a post-menopausal woman.

15. The use according to any one of claims 1 to 14 wherein said breast cancer is localized, advanced or metastatic.

16. The use according to claim 1, wherein said treatment further comprises that a therapeutic agent selected from the group consisting of rapamycin, everolimus, ridaforolimus, temsirolimus, MLN0128, CC115, CC223, OSI-027, AZD8055, AZD2014, GDC-0980, SAR245409, LY3023414, NVP-BEZ235, NVP-BGT226, SF1126 and PKI-587 is to be administered.