AR+ BREAST CANCER TREATMENT METHODS

PRIORITY CLAIM

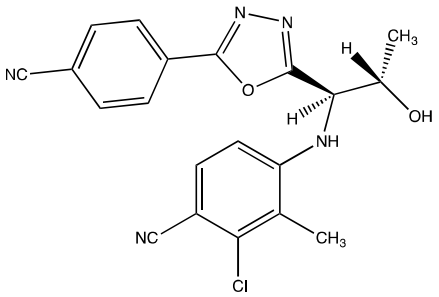
This application claims priority to U.S. Provisional Application No. 62/353,350, filed June 22, 2016, U.S. Provisional Application No. 62/377,497, filed August 19, 2016, and U.S. Provisional Application No. 62/461,546, filed February 21, 2017, all of which are incorporated herein by reference in their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

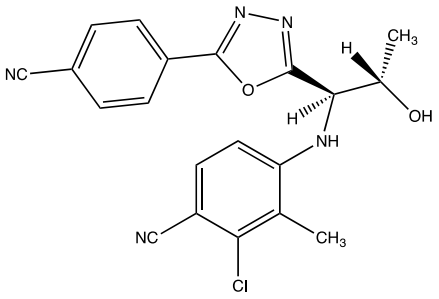
a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof in the manufacture of a medicament for treating AR+/ER+ breast cancer in a subject.

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

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 in a subject.

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 claim 10, wherein the CDK4/6 inhibitor is ribociclib.

14. The use according to claim 10, wherein the CDK4/6 inhibitor is abemaciclib.

15. The use according to claim 12, wherein the mTOR inhibitor is everolimus.

16. The use according to any one of claims 1 to 15 wherein said subject is a woman.

17. The use according to claim 16 wherein said woman is a premenopausal woman or a post-menopausal woman.

18. The use according to any one of claims 1 to 17 wherein said breast cancer is localized, advanced or metastatic.

19. 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.