METHODS OF USING ANTI-STEAP1 ANTIBODIES AND IMMUNOCONJUGATES

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 61/931,478, filed 24 January 2014, the disclosure of which is incorporated herein by reference in its entirety.

FIELD

[0002] Provided herein are methods of treating prostate cancer in particular androgen receptor inhibitor naïve prostate cancer using anti-STEAP1 antibodies and immunoconjugates thereof.

BACKGROUND

[0003] An estimated 241,740 new cases of prostate cancer will occur in the US during 2012. Prostate cancer is the most frequently diagnosed cancer in men aside from skin cancer. With an estimated 28,170 deaths in 2012, prostate cancer is the second-leading cause of cancer death in men. Hormonal therapy, chemotherapy, radiation, or a combination of these treatments is used to treat more advanced disease. Despite the above identified advances in prostate cancer therapy, there is a great need for additional therapeutic agents capable of effectively inhibiting prostate cancer progression including in androgen receptor inhibitor naïve prostate cancer.

[0004] All references cited herein, including patent applications and publications, are incorporated by reference in their entirety.

SUMMARY

[0005] In one aspect, there is provided use of an immunoconjugate comprising an antibody which binds a prostate-specific cell surface protein linked to a cytotoxic agent, in the manufacture of a medicament for treating an androgen receptor inhibitor naïve prostate cancer. Also p~~P~~rovided herein are methods of treating an androgen receptor inhibitor naïve prostate cancer using an immunoconjugate comprising an antibody which binds a prostate-specific cell surface protein linked to a cytotoxic agent.

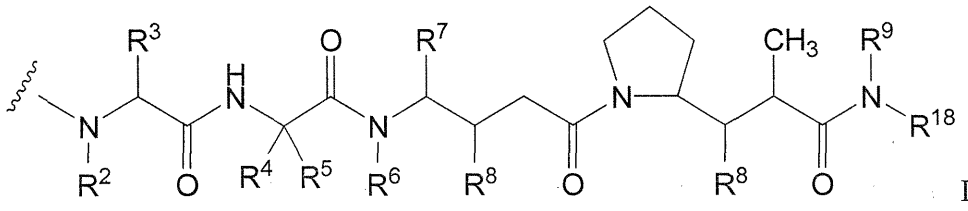
[0006] In some embodiments of any of the uses or methods, the prostate cancer is metastatic prostate cancer. In some embodiments, the metastatic prostate cancer is metastatic castration-resistant prostate cancer. In some embodiments of any of the uses or methods, the androgen receptor inhibitor inhibits androgen binding to androgen receptors and/or inhibits androgen receptor nuclear translocation and interaction with DNA. In some embodiments of any of the uses or methods, the androgen receptor inhibitor is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-N-methylbenzamide or a salt thereof. In some embodiments, the androgen receptor inhibitor is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-N-methylbenzamide. In some embodiments, the androgen receptor inhibitor is enzalutamide.

[0007] In some embodiments of any of the uses or methods, the cytotoxic agent is an antimitotic agent. In some embodiments, the antimitotic agent is an inhibitor of the polymerization of tubulin.

[0008] In some embodiments of any of the uses or methods, the immunoconjugate has the formula Ab-(L-D)p, wherein: (a) Ab is the antibody which binds a prostate-specific cell surface protein; (b) L is a

linker; (c) D is the cytotoxic agent and the cytotoxic agent is selected from a maytansinoid or an auristatin; and (d) p ranges from 1-8. In some embodiments, D is an auristatin.

[0009] In some embodiments, D has formula D_E



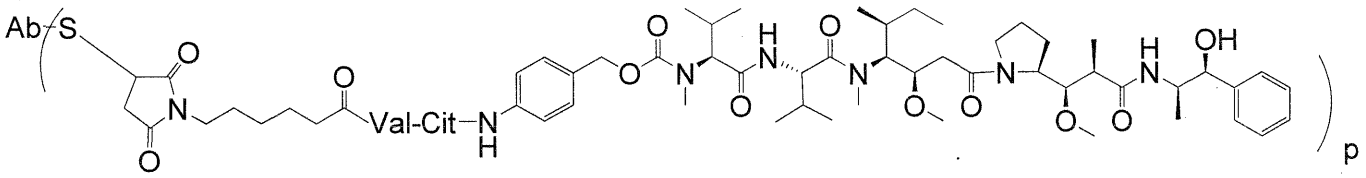
D_E

and wherein R^2 and R^6 are each methyl, R^3 and R^4 are each isopropyl, R^5 is H, R^7 is sec-butyl, each R^8 is independently selected from CH_3, O-CH_3, OH, and H; R^9 is H; and R^{18} is $–C(R^8)_2–C(R^8)_2–$aryl. In some embodiments, D is MMAE.

[0010] In some embodiments of any of the uses or methods, the linker is cleavable by a protease. In some embodiments, the linker comprises a val-cit dipeptide or a Phe-homoLys dipeptide.

[0011] In some embodiments of any of the uses or methods, the linker is acid-labile. In some embodiments, the linker comprises hydrazone.

[0012] In some embodiments of any of the uses or methods, the formula is:



wherein S is a sulfur atom.

[0013] In some embodiments of any of the uses or methods, p ranges from 2-5.

[0014] In some embodiments of any of the uses or methods, the prostate-specific cell surface protein is one or more of prostate-specific membrane antigen (PSM), prostate carcinoma tumor antigen (PCTA-1), prostate stem cell antigen (PSCA), solute carrier family 44, member 4 (SLC44A4), and six transmembrane epithelial antigen of the prostate 1 (STEAP-1). In some embodiments, the prostate-specific cell surface protein is STEAP-1.

[0015] In some embodiments of any of the uses or methods, the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:5; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:6; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:7; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:2; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:3; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:4. In some embodiments, the antibody comprises comprising a VH sequence of SEQ ID NO:9 and a VL sequence of SEQ ID NO:8.

[0016] In some embodiments of any of the uses or methods, the antibody is a monoclonal antibody. In some embodiments, the antibody is a human, humanized, or chimeric antibody.

[0017] In some embodiments of any of the uses or methods, the prostate cancer is also positive for expression of the prostate-specific cell surface protein. In some embodiments, the prostate-specific cell surface protein is STEAP-1.

[0018] In some embodiments of any of the uses or methods, the use or method further comprises administration of an additional therapeutic agent.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] None

DETAILED DESCRIPTION

[0020] Provided herein are methods of treating prostate cancer in particular androgen receptor inhibitor naïve prostate cancer using antibodies which bind a prostate-specific cell surface protein and immunoconjugates thereof, in particular immunoconjugates comprising an antimitotic agent such as an inhibitor of the polymerization of tubulin.

I. *General Techniques*

[0021] The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry, and immunology, which are within the skill of the art. Such techniques are explained fully in the literature, such as, "Molecular Cloning: A Laboratory Manual", second edition (Sambrook et al., 1989); "Oligonucleotide Synthesis" (M. J. Gait, ed., 1984); "Animal Cell Culture" (R. I. Freshney, ed., 1987); "Methods in Enzymology" (Academic Press, Inc.); "Current Protocols in Molecular Biology" (F. M. Ausubel et al., eds., 1987, and periodic updates); "PCR: The Polymerase Chain Reaction", (Mullis et al., ed., 1994); "A Practical Guide to Molecular Cloning" (Perbal Bernard V., 1988); "Phage Display: A Laboratory Manual" (Barbas et al., 2001).

II. *Definitions*

[0022] The term "prostate-specific" as used herein indicates that, the marker is preferentially found in prostate tissues, and substantially distinguishes prostate tissues or cells from other tissues or cells. In certain embodiments, the prostate-specific marker is a surface or membrane marker of prostate cells. In certain embodiments, the prostate-specific marker is selected from the group consisting of: Six-transmembrane epithelial antigen of the prostate (STEAP-1) (*see, e.g.* Hubert et al., (1999) *Proc. Natl. Acad. Sci. USA,* 96, 14523-14528), solute carrier family 44, member 4 (SLC44A4) (*e.g.*, Q53GD3), Prostate-specific membrane antigen (PSM) (*see, e.g.*, Israeli, R. S. et al., (1993) *Cancer Res.* 53, 227–230), Prostate carcinoma tumor antigen (PCTA-1) (*see, e.g.*, Su, Z. Z. et al., (1996) *Proc. Natl. Acad. Sci. USA* 93, 7252–7257), and Prostate stem cell antigen (PSCA) (*see, e.g.*, Reiter, R. E. et al. (1998) *Proc. Natl. Acad. Sci USA* 95, 1735–1740).

[0023] The term "Six-Transmembrane Epithelial Antigen of the Prostate 1" or "STEAP-1", as used herein, refers to any native STEAP-1 from any vertebrate source, including mammals such as primates (*e.g.*, humans, cynomologus monkey (cyno)) and rodents (*e.g.*, mice and rats), unless otherwise indicated. STEAP-1 refers to a cell surface antigen predominantly expressed in prostate

WHAT IS CLAIMED IS:

1. A method of treating an androgen receptor inhibitor naïve prostate cancer using an immunoconjugate comprising an antibody which binds a prostate-specific cell surface protein linked to a cytotoxic agent.

2. The method of claim 1, wherein the prostate cancer is metastatic prostate cancer.

3. The method of claim 2, wherein the metastatic prostate cancer is metastatic castration-resistant prostate cancer.

4. The method of any one of claim 1-3, wherein the androgen receptor inhibitor inhibits androgen binding to androgen receptors and/or inhibits androgen receptor nuclear translocation and interaction with DNA.

5. The method of claim 4, wherein the androgen receptor inhibitor is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-N-methylbenzamide or a salt thereof.

6. The method of any one of claims 1-5, wherein the cytotoxic agent is an antimitotic agent.

7. The method of any one of claims 1-7, wherein the antimitotic agent is an inhibitor of the polymerization of tubulin.

8. The method of any one of claims 1-7, wherein the immunoconjugate has the formula Ab-(L-D)p, wherein:

(a) Ab is the antibody which binds a prostate-specific cell surface protein;

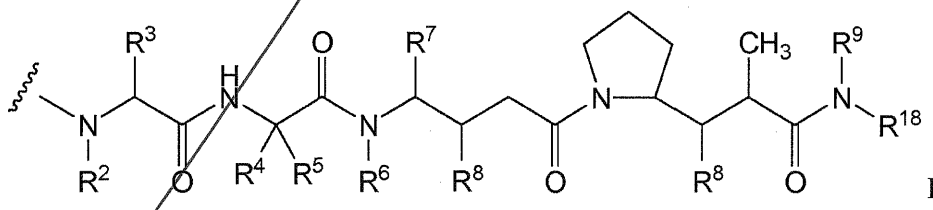
(b) L is a linker;

(c) D is the cytotoxic agent and the cytotoxic agent is selected from a maytansinoid or an auristatin; and

(d) p ranges from 1-8.

9. The method of claim 8, wherein D is an auristatin.

10. The method of claim 9, wherein D has formula D_E



D_E

and wherein R^2 and R^6 are each methyl, R^3 and R^4 are each isopropyl, R^5 is H, R^7 is sec-butyl, each R^8 is independently selected from CH_3, O-CH_3, OH, and H; R^9 is H; and R^{18} is $-C(R^8)_2-C(R^8)_2-$aryl.

11. The method of claim 10, wherein D is MMAE.

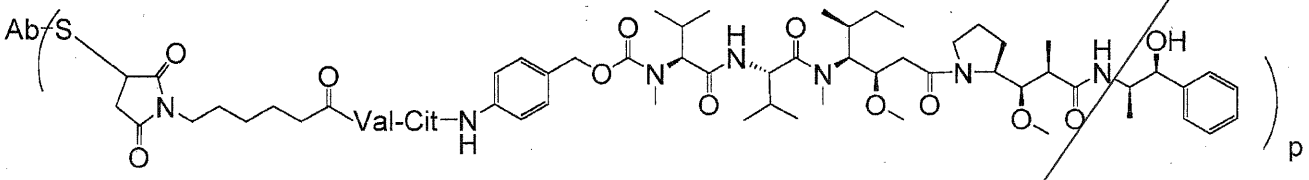
12. The method of any one of claims 8 to 11, wherein the linker is cleavable by a protease.

13. The method of claim 12, wherein the linker comprises a val-cit dipeptide or a Phe-homoLys dipeptide.

14. The method of any one of claims 8 to 11, wherein the linker is acid-labile.

15. The method of claim 14, wherein the linker comprises hydrazone.

16. The method of claim 8 having the formula:



wherein S is a sulfur atom.

17. The method of any one of claims 8 to 16, wherein p ranges from 2-5.

18. The method of any one of claims 1-17, wherein the prostate-specific cell surface protein is one or more of prostate-specific membrane antigen (PSM), prostate carcinoma tumor antigen (PCTA-1), prostate stem cell antigen (PSCA), solute carrier family 44, member 4 (SLC44A4), and six transmembrane epithelial antigen of the prostate 1 (STEAP-1).

19. The method of claim 18, wherein the prostate-specific cell surface protein is STEAP-1.

20. The method of any one of claims 1-19, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:5; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:6; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:7; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:2; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:3; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:4.

21. The method of claim 20, wherein the antibody comprises comprising a VH sequence of SEQ ID NO:9 and a VL sequence of SEQ ID NO:8.

22. The method of any one of claims 1-21, wherein the antibody is a monoclonal antibody.

23. The method of any one of claims 1-22, wherein the antibody is a human, humanized, or chimeric antibody.

24. The method of any one of claims 1-23, wherein the prostate cancer is also positive for expression of the prostate-specific cell surface protein.

25. The method of claim 24, wherein the prostate-specific cell surface protein is STEAP-1.

26. The method of any one of claims 1-25, wherein the method further comprises administration of an additional therapeutic agent.

WHAT IS CLAIMED IS:

1. Use of an immunoconjugate comprising an antibody which binds a prostate-specific cell surface protein linked to a cytotoxic agent, in the manufacture of a medicament for treating an androgen receptor inhibitor naïve prostate cancer.

2. The use of claim 1, wherein the prostate cancer is metastatic prostate cancer.

3. The use of claim 2, wherein the metastatic prostate cancer is metastatic castration-resistant prostate cancer.

4. The use of any one of claim 1-3, wherein the androgen receptor inhibitor inhibits androgen binding to androgen receptors and/or inhibits androgen receptor nuclear translocation and interaction with DNA.

5. The use of claim 4, wherein the androgen receptor inhibitor is 4-{3-[4-cyano-3-(t rifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-N-methylbenzamide or a salt thereof.

6. The use of any one of claims 1-5, wherein the cytotoxic agent is an antimitotic agent.

7. The use of any one of claims 1-7, wherein the antimitotic agent is an inhibitor of the polymerization of tubulin.

8. The use of any one of claims 1-7, wherein the immunoconjugate has the formula Ab-(L-D)p, wherein:

(a) Ab is the antibody which binds a prostate-specific cell surface protein;

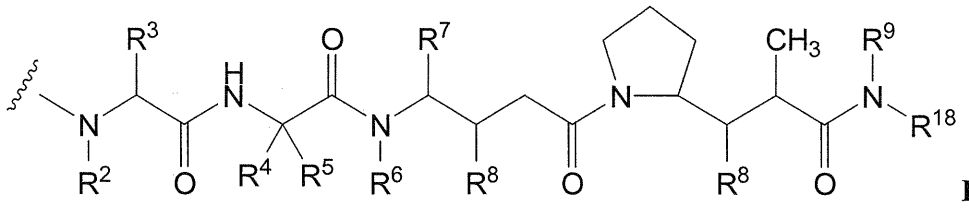
(b) L is a linker;

(c) D is the cytotoxic agent and the cytotoxic agent is selected from a maytansinoid or an auristatin; and

(d) p ranges from 1-8.

9. The use of claim 8, wherein D is an auristatin.

10. The use of claim 9, wherein D has formula D_E



D_E

and wherein R^2 and R^6 are each methyl, R^3 and R^4 are each isopropyl, R^5 is H, R^7 is sec-butyl, each R^8 is independently selected from CH_3, O-CH_3, OH, and H; R^9 is H; and R^{18} is $-C(R^8)_2-C(R^8)_2-$aryl.

11. The use of claim 10, wherein D is MMAE.

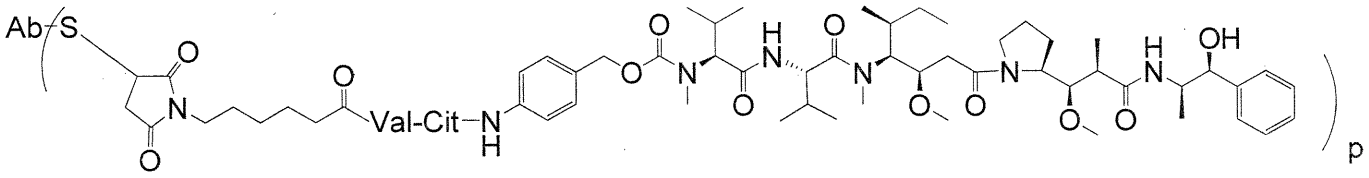
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13. The use of claim 12, wherein the linker comprises a val-cit dipeptide or a Phe-homoLys dipeptide.

14. The use of any one of claims 8 to 11, wherein the linker is acid-labile.

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21. The use of claim 20, wherein the antibody comprises comprising a VH sequence of SEQ ID NO:9 and a VL sequence of SEQ ID NO:8.

22. The use of any one of claims 1-21, wherein the antibody is a monoclonal antibody.

23. The use of any one of claims 1-22, wherein the antibody is a human, humanized, or chimeric antibody.

24. The use of any one of claims 1-23, wherein the prostate cancer is also positive for expression of the prostate-specific cell surface protein.

25. The use of claim 24, wherein the prostate-specific cell surface protein is STEAP-1.

26. The use of any one of claims 1-25, wherein the medicament is to be administered with an additional therapeutic agent.