~~What is claimed:~~

~~The use of an~~**Claims**

1. An anti-androgen for use in the manufacture of a medicament for treating metastatic castration-sensitive prostate cancer in a male human, ~~wherein the anti-androgen is:~~said treatment comprising or consisting essentially of administering a therapeutically effective amount of an anti-androgen in combination with androgen deprivation therapy to a male human with metastatic castration-sensitive prostate cancer, wherein the anti-androgen is

4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N- methylbenzamide, and

~~4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide,~~

~~4-[7-[4-cyano-3-(trifluoromethyl)phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide, or~~

~~N-{(2S)-1-[3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl]propan-2-yl}-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide.~~

~~5.~~ ~~The use of claim 1,~~ wherein administration of the anti-androgen in combination with androgen deprivation therapy provides an increase in overall survival of the male human, relative to the overall survival rate of a population of male humans with ~~the~~ metastatic castration-sensitive prostate cancer, said population having been administered a placebo in combination with an androgen deprivation therapy~~.~~

~~6.~~ ~~The use of claim 1 or 2, wherein~~, or administration of the anti-androgen in combination with androgen deprivation therapy provides an increase in progression-free survival of the male human, relative to the progression-free survival rate of a population of male humans with ~~the~~ metastatic castration-sensitive prostate cancer, said population having been administered a placebo in combination with an androgen deprivation therapy.

~~7.~~2. The anti-androgen for use ~~of any one of the preceding claims~~according to claim 1, wherein the male human received at least one prior therapy for the treatment of cancer,

wherein the prior therapy for the treatment of cancer is radiation, surgical intervention or docetaxel therapy.

8.3. The anti-androgen for use of any one of claims 1according to 3claim 1, wherein the male human is treatment naïve.

9. The anti-androgen for use ofaccording to any one of the preceding claims, wherein the anti-androgen is 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide.

10.4. The use of claim 6, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered daily to the male human.

11. The use of claim 6, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human.

12. The use of claim 6, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human on a continuous daily dosing schedule.

13. The use of claim 6, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of about 30 mg per day to about 480 mg per day.

14.5. The use of claim 6The anti-androgen for use according to any one of the preceding claims, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of about 180 mg per day to about 480 mg per day, optionally on a continuous daily dosing schedule.

6. The use ofThe anti-androgen for use according to claim 5, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of 30 mg per day to 480 mg per day, optionally at a dose of 180 mg per day to 480 mg per day.

15.7. The anti-androgen for use according to claim 6, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of:

(a) ~~about~~ 30 mg per day;

(b) ~~about~~ 60 mg per day;

(c) ~~about~~ 90 mg per day;

(d) ~~about~~ 120 mg per day; or

(d) ~~about~~ 240 mg per day.

~~16.~~8. The anti-androgen for use ~~of~~according to claim ~~6~~7, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of ~~about~~ 240 mg per day.

~~17.~~9. The anti-androgen for use ~~of~~according to claim ~~13~~8, wherein the dose of 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is decreased to 180 mg per day or 120 mg per day if the male human experiences a greater than or equal to Grade 3 toxicity.

~~18.~~10. The anti-androgen for use according to any one of ~~claim 6~~the preceding claims, wherein ~~4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered~~administration of the anti-androgen in combination with androgen deprivation therapy provides an increase in overall survival and a 33% reduction in risk of death or an increase in progression-free survival and a 52% reduction in risk of radiographic progression or death.

~~19.~~11. The anti-androgen for use according to any one of ~~claim 15~~the preceding claims, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered in combination with at least one gonadotropin-releasing hormone (GnRH) agonist or antagonist.

~~20.~~12. The anti-androgen for use ~~of~~according to claim ~~16~~10, wherein the at least one GnRH agonist or antagonist is or comprises leuprolide, buserelin, naferelin, histrelin, goserelin, deslorelin, degarelix, ozarelix, ABT-620 (elagolix), TAK-385 (relugolix), EP-100, KLH-2109 or triptorelin.

~~21.~~13. The anti-androgen for use according to any one of ~~claim 15~~claims 1 to 10, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is used in combination with bilateral orchiectomy.

~~22.~~14. The anti-androgen for use according to any one of ~~claim 6~~the preceding claims, wherein the 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is not co-administered with:

(a) a medication that is a ~~strong~~ CYP2C8 or CYP3A4 inhibitor;

(b) a medication that is primarily metabolized by CYP3A4, CYP2C19, or CYP2C9;

(c) a medication that is a substrate of UDP-glucuronosyl transferase; or

(d) a medication that is a substrate of P-glycoprotein, breast cancer resistance protein or organic anion transporting polypeptide 1B1.

~~23. The use of claim 1, wherein the anti-androgen is 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide.~~

~~The use of claim 20, wherein the 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide is administered orally to~~ 15. The anti-androgen for use according to any one of the preceding claims, wherein said treatment comprises:

~~24.~~ (a) determining whether the male human ~~at a dose of about 160 mg per day.~~

~~25. The use of claim 1, wherein the anti-androgen is 4-[7-[4-cyano-3-(trifluoromethyl)phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide.~~

~~26. The use of claim 1, wherein the anti-androgen is N-{(2S)-1-[3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl]propan-2-yl}-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide.~~

~~27. The use of an anti-androgen in the manufacture of a medicament for treating~~has metastatic castration-sensitive prostate cancer ~~in a male human, wherein the anti-androgen is one or more of:~~; and

~~4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide,~~

~~4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide,~~

~~4-[7-[4-cyano-3-(trifluoromethyl)phenyl]-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide, or~~

~~N-{(2S)-1-[3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl]propan-2-yl}-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide.~~

~~25. The use of claim 24, wherein at least one of the anti-androgens is 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide.~~

~~26. The use of claim 25, wherein at least one of the androgens is 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally~~(b) administering the anti-androgen in combination with the androgen deprivation therapy to the male human ~~at a dose of:~~

~~(a) about 30 mg per day;~~

~~(b) about 60 mg per day;~~

~~(c) about 90 mg per day;~~

~~(d) about 120 mg per day; or~~

~~(d) about 240 mg per day.~~

~~27. A method of selling an approved drug product comprising apalutamide, said method comprising selling such drug product, wherein a drug product label for a reference listed drug for such drug product includes instructions for treating~~ in the therapeutically effective amount to treat the metastatic castration-sensitive prostate cancer.

~~28. A method of offering for sale an approved drug product comprising apalutamide, said method comprising offering for sale such drug product, wherein a drug product label for a reference listed drug for such drug product includes instructions for treating metastatic castration-sensitive prostate cancer.~~

~~29. The method of claim 27 or 28, wherein the drug product is an ANDA drug product, a supplemental New Drug Application drug product or a 505(b)(2) drug product.~~