

Claims

1. Use of apalutamide (APA) and an androgen deprivation therapy (ADT) (APA+ADT) in the manufacture of a medicament for providing improved treatment benefit of non-metastatic castration resistant prostate cancer (nmCRPC) in a human male, wherein the medicament is to be administered to the human male if a biological sample obtained from the human male is determined to have:
 - a) a luminal-like molecular subtype of prostate cancer;
 - b) a genomic classifier score of greater than about 0.6;
 - c) an increased expression of at least one signature of Class One co-regulated signatures;
 - d) an increased expression of at least one signature of Class Two co-regulated signatures;
 - e) a decreased expression of at least one signature of Class Three co-regulated signatures;
 - f) an increased expression of at least one signature of Class Four co-regulated signatures;or a combination thereof.
2. Use of apalutamide (APA) and an androgen deprivation therapy (ADT) (APA+ADT) in the manufacture of a medicament for treating non-metastatic castration resistant prostate cancer (nmCRPC) in a human male, wherein the medicament is to be administered to the human male if a biological sample originated from the human male is determined to have:
 - a) a luminal-like molecular subtype of prostate cancer;
 - b) a genomic classifier score of greater than about 0.6;
 - c) an increased expression of at least one signature of Class One co-regulated signatures;
 - d) an increased expression of at least one signature of Class Two co-regulated signatures;

- e) a decreased expression of at least one signature of Class Three co-regulated signatures;
 - f) an increased expression of at least one signature of Class Four co-regulated signatures;
- or a combination thereof.
3. A method of predicting whether a human male having a non-metastatic castration resistant prostate cancer (nmCRPC) has an improved benefit from the administration of a therapeutically effective amount of apalutamide (APA) and a therapeutically effective amount of an androgen deprivation therapy (ADT) (APA+ADT), said method comprising
- a) determining if a biological sample obtained from the human male has:
 - i) a luminal-like molecular subtype of prostate cancer;
 - ii) a genomic classifier score of greater than about 0.6;
 - iii) an increased expression level of at least one signature of the Class One, Class Two, and/or Class Four co-regulated signatures;
 - iv) a decreased expression level of at least one signature of the Class Three co-regulated signatures;

or a combination thereof, and
 - b) predicting whether the human male has an improved benefit from the administration of the therapeutically effective amount of APA+ADT based on:
 - i) a luminal-like molecular subtype of prostate cancer;
 - ii) a genomic classifier score of greater than about 0.6;
 - iii) an increased expression level of at least one signature of the Class One, Class Two, and/or Class Four co-regulated signatures;
 - iv) a decreased expression level of at least one signature of the Class Three co-regulated signatures;

or a combination thereof.
4. A method of improving a response to the treatment of non-metastatic castration resistant prostate cancer (nmCRPC) in a human male using a combined administration of a therapeutically effective amount of apalutamide (APA) and a therapeutically effective amount of an androgen deprivation therapy (ADT) (APA+ADT), the method comprising
- a) determining if a biological sample obtained from the human male has:

- i) a luminal-like molecular subtype of prostate cancer;
 - ii) a genomic classifier score of greater than about 0.6;
 - iii) an increased expression level of at least one signature of the Class One, Class Two, and/or Class Four co-regulated signatures;
 - iv) a decreased expression level of at least one signature of the Class Three co-regulated signatures;

or a combination thereof, and
 - b) improving the response to the combined administration of the therapeutically effective amount of APA+ADT, based on:
 - i) a luminal-like molecular subtype of prostate cancer;
 - ii) a genomic classifier score of greater than about 0.6;
 - iii) an increased expression level of at least one signature of the Class One, Class Two, and/or Class Four co-regulated signatures;
 - iv) a decreased expression level of at least one signature of the Class Three co-regulated signatures;

or a combination thereof.
5. The use of claim 1 or 2 or the method of claim 3 or 4, wherein the human male has undergone a prostatectomy.
 6. The use of any one of claims 1, 2 and 5 or the method of any one of claims 3-5, wherein the biological sample is a prostate biopsy sample or a surgical tumor sample.
 7. The use of any one of claims 1, 2 and 5 or the method of any one of claims 3-5, wherein the biological sample is a primary prostate tumor sample.
 8. The use of any one of claims 1, 2 and 5-7 or the method of any one of claims 3-7, wherein metastasis-free survival (MFS) of combined administration of APA+ADT is improved by at least about 6 months relative to sole administration of ADT alone.
 9. The use of any one of claims 1, 2 and 5-8 or the method of any one of claims 3-8, wherein second progression-free survival (PFS2) of combined administration of

APA+ADT is improved by at least about 6 months relative to sole administration of ADT alone.

10. The use of any one of claims 1, 2 and 5-9 or the method of any one of claims 3-9, wherein the APA+ADT is formulated for oral administration.
11. The use of any one of claims 1, 2 and 5-10 or the method of any one of claims 3-10, wherein the biological sample is determined to have a luminal-like molecular subtype of prostate cancer.
12. The use of any one of claims 1, 2 and 5-11 or the method of any one of claims 3-11, wherein the biological sample is determined to have a genomic classifier score of greater than 0.6.
13. The use or method of claim 12, wherein the genomic classifier is a 22-marker genomic classifier comprising, consisting of and/or consisting essentially of markers selected from the group consisting of LASP1, IQGAP3, NFIB, S1PR4, THBS2, ANO7, PCDH7, MYBPC1, EPPK1, TSBP, PBX1, NUSAP1, ZWILCH, UBE2C, CAMKC2N1, RABGAP1, PCAT-32, GYATL1P4/PCAT-80, TNFRSF19 and combinations thereof.
14. The use or method of claim 12 or 13, wherein the human male is determined to have a high risk of metastasis based on the genomic classifier score.
15. The use of any one of claims 1, 2 and 5-14 or the method of any one of claims 3-14, wherein the biological sample is determined to have an increased expression of at least one signature of the Class One co-regulated signatures.
16. The use or method of claim 15, wherein the at least one signature of the Class One co-regulated signatures is selected from the group consisting of: agell2012_1, bibikova2007_1, bismar2006_1, bismar2017_1, cheville2008_1, cuzick2011_1, cuzick2011_lm_1, decipher_1, decipher2_2, genomic_capras_1, genomic_gleason_grade_1, genomic_gleason_grade_2, glinsky2005_1, hallmark_mtorc1_signaling, hallmark_myc_targets_v1, hallmark_myc_targets_v2,

klein2014_1, lapointe2004_1, larkin2012_1, long2014_1, nakagawa2008_1, non_organ_confined_1, normaltumor_1, pam50_luminalB, penney2011_1, penney2011_lm_1, ramaswamy2003_1, saal2007_1, saal2007_pten, sdms_1, singh2002_1, staging_epe_1, staging_lni_1, staging_svi_1, stephenson2005_1, talantov2010_1, varambally2005_1, wu2013_1, yu2007_1, and combinations thereof.

17. The use or method of claim 16, wherein the at least one signature of the Class One co-regulated signatures comprises genomic_gleason_grade_2.
18. The use of any one of claims 1, 2 and 5-17 or the method of any one of claims 3-17, wherein the biological sample is determined to have an increased expression of at least one signature of the Class Two co-regulated signatures.
19. The use or method of claim 18, wherein the at least one signature of the Class Two co-regulated signatures is selected from the group consisting of: ar_related_pathway_ARv7, ar_related_pathway_glucocorticoid_receptor, aros_1, docetaxel_sens_1, ergmodel_1, glinsky2004_1, hallmark_adipogenesis, hallmark_androgen_response, hallmark_angiogenesis_Brauer2013, hallmark_angiogenesis_KeggVEGF, hallmark_angiogenesis_Liberzon2015, hallmark_angiogenesis_Masiero2013, hallmark_angiogenesis_Nolan2013, hallmark_angiogenesis_Uhlik2016, hallmark_apical_surface, hallmark_bile_acid_metabolism, hallmark_cholesterol_homeostasis, hallmark_dna_repair, hallmark_e2f_targets, hallmark_fatty_acid_metabolism, hallmark_g2m_checkpoint, hallmark_glycolysis, hallmark_hedgehog_signaling, hallmark_heme_metabolism, hallmark_mitotic_spindle, hallmark_notch_signaling, hallmark_oxidative_phosphorylation, hallmark_peroxisome, hallmark_pi3k_akt_mtor_signaling, hallmark_protein_secretion, hallmark_spermatogenesis, hallmark_unfolded_protein_response, hallmark_uv_response_dn, hallmark_xenobiotic_metabolism, immunophenoscore_1_CP, immunophenoscore_1_CTLA.4, immunophenoscore_1_IDO1, immunophenoscore_1_LAG3, immunophenoscore_1_PD.1, immunophenoscore_1_PD.L2, immunophenoscore_1_Tem.CD4, immunophenoscore_1_TIGIT, kegg_mismatch_repair,

kegg_non_homologous_end_joining, kegg_nucleotide_excision_repair, long2011_1, nelson_2016_AR_1, pam50_luminalA, pca_vs_mibc_1, race_1, ragnum2015_1, and combinations thereof.

20. The use or method of claim 19, wherein the at least one signature of the Class Two co-regulated signatures comprises hallmark_cholesterol_homeostasis.
21. The use of any one of claims 1, 2 and 5-20 or the method of any one of claims 3-20, wherein the biological sample is determined to have a decreased expression of at least one signature of the Class Three co-regulated signatures.
22. The use or method of claim 21, wherein the at least one signature of the Class Three co-regulated signatures is selected from the group consisting of: ars_1, beltran2016_1, dasatinib_sens_1, estimate2013_2_purity, hallmark_apical_junction, hallmark_apoptosis, hallmark_coagulation, hallmark_epithelial_mesenchymal_transition, hallmark_estrogen_response_early, hallmark_estrogen_response_late, hallmark_hypoxia, hallmark_kras_signaling_dn, hallmark_myogenesis, hallmark_p53_pathway, hallmark_pancreas_beta_cells, hallmark_reactive_oxygen_species_pathway, hallmark_tgf_beta_signaling, hallmark_tnfa_signaling_via_nfkb, hallmark_uv_response_up, hallmark_wnt_beta_catenin_signaling, immunophenoscore_1_ICOS, immunophenoscore_1_MDSC, immunophenoscore_1_PD.L1, immunophenoscore_1_SC, immunophenoscore_1_TIM3, immunophenoscore_1_Treg, kegg_base_excision_repair, kegg_homologous_recombination, lotan2016_1, neg_ctrl_qc, nelson2016_1, pam50_basal, portos_1, portos_2, rbloss_1, smallcell_1, smallcell_2, smallcell_3, torresroca2009_1, zhang2016_basal_1, and combinations thereof.
23. The use or method of claim 22, wherein the at least one signature of the Class Three co-regulated signatures comprises beltran2016_1.
24. The use of any one of claims 1, 2 and 5-23 or the method of any one of claims 3-23, wherein the biological sample is determined to have increased expression of at least one signature of the Class Four co-regulated signatures.

25. The use or method of claim 24, wherein the at least one signature of the Class Four co-regulated signatures is selected from the group consisting of: estimate2013_2_estimate, estimate2013_2_immune, estimate2013_2_stromal, hallmark_allograft_rejection, hallmark_angiogenesis, hallmark_complement, hallmark_IL2_JAK_STAT5_signaling, hallmark_IL6_JAK_STAT3_signaling, hallmark_inflammatory_response, hallmark_interferon_alpha_response, hallmark_interferon_gamma_response, hallmark_kras_signaling_up, immunophenoscore_1_Act.CD4, immunophenoscore_1_Act.CD8, immunophenoscore_1_B2M, immunophenoscore_1_CD27, immunophenoscore_1_EC, immunophenoscore_1_HLA.A, immunophenoscore_1_HLA.B, immunophenoscore_1_HLA.C, immunophenoscore_1_HLA.DPA1, immunophenoscore_1_HLA.DPB1, immunophenoscore_1_HLA.E, immunophenoscore_1_HLA.F, immunophenoscore_1_IPS, immunophenoscore_1_IPS.raw, immunophenoscore_1_MHC, immunophenoscore_1_TAP1, immunophenoscore_1_TAP2, immunophenoscore_1_Tem.CD8, and combinations thereof.
26. The use or method of claim 25, wherein the at least one signature of the Class Four co-regulated signatures comprises hallmark_IL2_JAK_STAT5_signaling.