**SUPPLEMENTARY TABLES**

|  |  |  |  |
| --- | --- | --- | --- |
| ABCC4 | ACSL3 | ADAM7 | APPBP2 |
| ATXN3 | BMPR1B | C1orf116 | CAMKK2 |
| CENPN | CRLS1 | DYNLL2 | EAF2 |
| ELK4 | ELL2 | EVI5 | FADS1 |
| FKBP5 | GNAI3 | GNMT | HERC3 |
| HMGCR | INSIG1 | KLK2 | KLK3 |
| MAF | MAP7 | MED28 | MPHOSPH9 |
| MTERFD2 | NGLY1 | NKX3-1 | NNMT |
| PIAS1 | PMEPA1 | PTGER4 | RRP12 |
| SLC30A7 | SPCS3 | TARP | TMEM50A |
| TMPRSS2 | UBE2J1 | ZBTB10 |  |

***Supplementary Table 1:* Genes included in the AR signature.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| FLJ39080 | ANK3 | SBF2 | UBE2R2 | AGBL4 |
| DNER | RPH3AL | HIF3A | KRTAP19-7 | KLF9 |
| RERE | ASPH | CLSTN1 | RALA | MAML3 |
| ATP6V1H | THADA | LIMD1 | CAM1KD | PDE6A |
| CNTNAP2 | EXT2 | PTGFR | PARD3B | DGKB |
| LARS2 | AMOTL1 | ARHGAP6 | TOP2B | KIF5C |
| PNKD | COBLL1 | XBP1 | GPC6 | RECK |
| LPP | RBM33 | DNAH5 | BCAT2 | IL20RA |
| NSMCE2 | MBNL1 | PMFBP1 | HSD17B14 | AGTPBP1 |
| NFIC | ZBTB20 | ATG16L1 | TK2 |  |

***Supplementary Table 2:* Genes included in the acquired ADT resistance signature.**

|  |  |
| --- | --- |
| **Clinical characteristics (n=43)** | |
| **Archival (castration sensitive) biopsy** | |
| **Histology**  Adenocarcinoma | **(N, %)**  43, 100% |
| **Gleason score**  <7  7  >7  NR | **(N, %)**  3, 7%  9, 21%  30, 70%  1, 2% |
| **Metastatic at diagnosis**  M0  M1  NR | **(N, %)**  19, 44%  18, 42%  6, 14% |
| **Treatment intent**  Radical  Palliative | **(N, %)**  16, 37%  27, 63% |
| **Paired metastatic castration resistant biopsy** | |
| **Biopsy site**  Bone  Lymph node  Other | **(N, %)**  26, 60%  15, 35%  2, 5% |
| **Systemic therapies prior to biopsy^**  0  1  2  3  4 | **(N, %)**  5, 12%  6, 14%  13, 30%  12, 28%  7, 16% |
| **AR targeting therapy prior to biopsy**  Post abiraterone or enzalutamide | **(N, %)**  36, 84% |

***Supplementary Table 3*: Clinical characteristics of prostate cancer patients with matched, same patient, diagnostic (archival) castration sensitive and metastatic castration resistant tissue biopsies.** N – number, NR – not recorded, AR – androgen receptor, ^ - systemic therapies include docetaxel, cabazitaxel, abiraterone and enzalutamide.

|  |  |  |
| --- | --- | --- |
| ATAD2A | BRD7 | PBRM1(2) |
| ATAD2B | BRD9 | PBRM1(5) |
| BAZ2A | BRDT(1) | PCAF |
| BAZ2B | BRDT(2) | SMARCA2 |
| BRD1 | BRPF1 | SMARCA4 |
| BRD2(1) | BRPF3 | TAF1(2) |
| BRD2(2) | CECR2 | TAF1L(2) |
| BRD3(1) | CREBBP | TRIM24 |
| BRD3(2) | EP300 | TRIM33 |
| BRD4(1) | FALZ | WDR9(2) |
| BRD4(2) | GCN5L2 |  |

***Supplementary Table 4:* Bromoscan** **assay** **list** **of bromodomains tested with CCS1477.** Number in parenthesis denotes bromodomain tested.

|  |  |  |
| --- | --- | --- |
| ABL1(E255K)-phosphorylated | FAK | PDGFRA |
| ABL1(T315I)-phosphorylated | FGFR2 | PDGFRB |
| ABL1-nonphosphorylated | FGFR3 | PDPK1 |
| ABL1-phosphorylated | FLT3 | PIK3C2B |
| ACVR1B | GSK3B | PIK3CA |
| ADCK3 | IGF1R | PIK3CG |
| AKT1 | IKK-alpha | PIM1 |
| AKT2 | IKK-beta | PIM2 |
| ALK | INSR | PIM3 |
| AURKA | JAK2(JH1domain-catalytic) | PKAC-alpha |
| AURKB | JAK3(JH1domain-catalytic) | PLK1 |
| AXL | JNK1 | PLK3 |
| BMPR2 | JNK2 | PLK4 |
| BRAF | JNK3 | PRKCE |
| BRAF(V600E) | KIT | RAF1 |
| BTK | KIT(D816V) | RET |
| CDK11 | KIT(V559D,T670I) | RIOK2 |
| CDK2 | LKB1 | ROCK2 |
| CDK3 | MAP3K4 | RSK2(Kin.Dom.1-N-terminal) |
| CDK7 | MAPKAPK2 | SNARK |
| CDK9 | MARK3 | SRC |
| CHEK1 | MEK1 | SRPK3 |
| CSF1R | MEK2 | TGFBR1 |
| CSNK1D | MET | TIE2 |
| CSNK1G2 | MKNK1 | TRKA |
| DCAMKL1 | MKNK2 | TSSK1B |
| DYRK1B | MLK1 | TYK2(JH1domain-catalytic) |
| EGFR | p38-alpha | ULK2 |
| EGFR(L858R) | p38-beta | VEGFR2 |
| EPHA2 | PAK1 | YANK3 |
| ERBB2 | PAK2 | ZAP70 |
| ERBB4 | PAK4 |  |
| ERK1 | PCTK1 |  |

***Supplementary Table 5:* List of kinases tested with CCS1477.**

|  |  |  |  |
| --- | --- | --- | --- |
| 5-HT transporter | CB1 | H2 | PDE3A |
| 5-HT1A | CB2 | KV channel | PDE4D2 |
| 5-HT1B | CCK1 (CCKA) | Lck kinase | Potassium Channel hERG |
| 5-HT2A | COX1 | M1 | V1 a |
| 5-HT2B | COX2 | M2 | α1A |
| 5-HT3 | D1 | M3 | α2A |
| A2A | D2S | MAO-A | β1 |
| Acetylcholinesterase | Dopamine transporter | N neuronal α4β2 | β2 |
| AR | ETA | Na+ channel | δ (DOP) |
| BZD (central) | GR | NMDA | κ (KOP) |
| Ca2+ channel (L, dihydropyridine site) | H1 | Norepinephrine transporter | μ (MOP) |

***Supplementary Table 6:* List of Receptor/Enzyme/Ion channel bindings tested with CCS1477.**

|  |  |  |
| --- | --- | --- |
| **Pathway** | **NES** | **FDR** |
| HALLMARK\_HYPOXIA | -2.21 | 0.001 |
| HALLMARK\_TNFA\_SIGNALING\_VIA\_NFKB | -1.86 | 0.019 |
| HALLMARK\_ANDROGEN\_RESPONSE | -1.77 | 0.023 |
| HALLMARK\_MITOTIC\_SPINDLE | -1.7 | 0.031 |
| HALLMARK\_ESTROGEN\_RESPONSE\_EARLY | -1.61 | 0.05 |

***Supplementary Table 7*: Cellular pathways de-enriched by CCS1477 treatment in 22Rv1 mouse xenografts.** Normalized enrichment score (NES) for cellular pathways de-enriched by CCS1477 with a false discovery rate (FDR) <0.05 are shown.

|  |  |  |
| --- | --- | --- |
| **Pathway** | **NES** | **FDR** |
| HALLMARK\_ESTROGEN\_RESPONSE\_EARLY | -2.41 | <0.001 |
| HALLMARK\_ANGIOGENESIS | -2.34 | <0.001 |
| HALLMARK\_TNFA\_SIGNALING\_VIA\_NFKB | -2.32 | <0.001 |
| HALLMARK\_UV\_RESPONSE\_DN | -2.27 | <0.001 |
| HALLMARK\_NOTCH\_SIGNALING | -2.26 | <0.001 |
| HALLMARK\_WNT\_BETA\_CATENIN\_SIGNALING | -2.19 | <0.001 |
| HALLMARK\_HYPOXIA | -2.1 | <0.001 |
| HALLMARK\_G2M\_CHECKPOINT | -2.01 | 0.001 |
| HALLMARK\_EPITHELIAL\_MESENCHYMAL\_TRANSITION | -1.99 | 0.001 |
| HALLMARK\_ESTROGEN\_RESPONSE\_LATE | -1.92 | 0.001 |
| HALLMARK\_MYC\_TARGETS\_V2 | -1.81 | 0.004 |
| HALLMARK\_HEDGEHOG\_SIGNALING | -1.75 | 0.007 |
| HALLMARK\_APICAL\_SURFACE | -1.73 | 0.008 |
| HALLMARK\_APICAL\_JUNCTION | -1.66 | 0.01 |
| HALLMARK\_ANDROGEN\_RESPONSE | -1.64 | 0.012 |
| HALLMARK\_TGF\_BETA\_SIGNALING | -1.62 | 0.013 |
| HALLMARK\_MITOTIC\_SPINDLE | -1.55 | 0.018 |
| HALLMARK\_IL2\_STAT5\_SIGNALING | -1.54 | 0.02 |
| HALLMARK\_GLYCOLYSIS | -1.45 | 0.038 |
| HALLMARK\_APOPTOSIS | -1.41 | 0.047 |

***Supplementary Table 8:* Cellular pathways de-enriched by CCS1477 treatment in CP50c patient derived mouse xenografts.** Normalized enrichment score (NES) for cellular pathways de-enriched by CCS1477 with a false discovery rate (FDR) <0.05 are shown.



***Supplementary Table 9:* Primary antibodies and protocols for immunohistochemistry assays.** AR-FL and AR-V7 IHC was carried out as previously reported (44).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Cell line** | **Supplier** | **Catalogue No.** | **Media** | **Serum** |
| 22Rv1 | ATCC | CRL-2505 | RMPI | FBS |
| VCaP | ATCC | CRL-2876 | DMEM | FBS |
| LNCaP | ATCC | CRL-1740 | RMPI | FBS |
| LNCaP-AR | ATCC/AR over-expression done in house | CRL-1740 | RMPI | FBS |
| LNCaP95 | Dr Meeker/Dr Luo\* | NA | RMPI^ | CSS |
| LNCaP-Bic | Dr Worthington – Axis Bioservices Ltd | NA | RPMI | FBS |
| C4-2 | ATCC | CRL-3314 | DMEM/F12 | FBS |
| DU145 | ATCC | HTB-81 | DMEM | FBS |
| PC3 | ATCC | CRL-1345 | F12 | FBS |

***Supplementary Table 10:* Cell lines**

ATCC – American Type Culture Collection, FBS – fetal bovine serum, CSS – charcoal stripped serum, \* - LNCaP95 cells were a kind gift from Drs. Alan K Meeker and Jun Luo (Johns Hopkins University, Baltimore, Maryland, USA), NA – non-applicable, ^ - phenol red free.

|  |  |  |
| --- | --- | --- |
| **Protein target** | **Company** | **Catalogue ID** |
| AR-FL | DAKO/ Abcam | M3562/ AB74272 |
| AR-V7 | RevMab | 31-1109-00 |
| C-MYC | Menarini/ Abcam | MP-415-CMEK/ AB32072 |
| B-actin | New England Biolabs | 4970S |
| GAPDH | Millipore | MAB374 |
| CBP | Cell signaling | 7389 |
| p300 | Merck | 05-257 |
| KLK3 | DAKO | A0562 |

***Supplementary Table 11:*** **Antibodies used for Western blot analysis.**

|  |  |  |
| --- | --- | --- |
| **Gene target** | **Supplier** | **Catalogue ID** |
| Control | Dharmacon (Horizon) | D-001810-10 |
| CBP | L-003477 |
| p300 | L-003486 |
| C-MYC | L-003282 |

***Supplementary Table 12:* ON-TARGETplus siRNA pools for gene expression knockdown.**

|  |  |  |
| --- | --- | --- |
| **Gene target** | **Supplier** | **Assay ID** |
| CBP | Thermo Fisher Scientific | Hs00932878\_m1 |
| p300 | Hs00914212\_m1 |
| AR | Hs00171172\_m1 |
| AR-V7 | Hs04260217\_m1 |
| C-MYC | Hs00153408\_m1 |
| KLK2 | Hs00428384\_g1 |
| KLK3 | Hs02576345\_m1 |
| FKBP5 | Hs01561006\_m1 |
| TMPRSS2 | Hs01122322\_m1/ Hs01120965\_m1 |
| GAPDH | Hs02786624\_g1/ Hs01922876\_u1 |
| HPRT1 | Hs02800695\_m1 |
| B2M | Hs00187842\_m1 |
| RPLP0 | Hs00420895\_gH |

***Supplementary Table 13:*** **TaqMan probes for qRT-PCR analysis (cell line, 22Rv1 xenograft model and CP50c mouse xenograft model).**

|  |  |  |
| --- | --- | --- |
| **Gene target** | **Forward** | **Reverse** |
| 18S | GCAATTATTCCCCATGAACG | GGCCTCACTAAACCATCCAA |
| CBP | ATTCAGTGCTAAGAGGCTG | GGAAAGATTCAGACATTTCCC |
| P300 | GATGCCCAATGTATCTAACGA | CGGATCACAAAGAAGACCTC |
| AR | CCTGGCTTCCGCAACTTACAC | GGACTTGTGCATGCGGTACTCA |
| KLK3 | TGTGTGCTGGACGCTGGA | CACTGCCCCATGACGTGAT |
| FKBP5 | GCAACAGTAGAAATCCACCTG | CTCCAGAGCTTTGTCAATTCC |
| C-MYC | ACTATGACCTCGACTACGACTC | TCGTCGCAGTAGAAATACGGC |
| CAD | GAGCTCAGGAACTCTGTGAC | TCAAATGAACGCCCAATGCC |
| ODC | CCATGGGGCTGGCCT | TTCCAAATCCCTCTGCGTGT |

***Supplementary Table 14:* Primers for PCR analysis (doxycycline-inducible cell lines and CBP/p300 re-expression).**

|  |  |  |
| --- | --- | --- |
| **Gene target** | **Forward** | **Reverse** |
| KLK3 | ACAGACCTACTCTGGAGGAAC | AGACAAGGGTGGAAGGCTCT |
| TMPRSS2 | CCAGGGAAGGAAGGAACACC | CTGACTTGGGCACACGGAAT |
| FKBP5 | GCGAGCTGCAAAACATCACT | GTGCCAGCCACATTCAGAAC |
| ANKRD30B | TCAAAGTCAACCAAGAGGACTCA | ACGGCAGGCTAAATGGGTTT |
| CHRNA2 | GTCCAGTCACCACGATGCT | GCAGCTCTGTCCTTACTCCAA |
| TFF1 | GTTGTCACGGCCAAGCCTTTT | GGCAGGCTCTGTTTGCTTAAAGAGCG |
| TGCA enhancer | GGAGAAAGGAGGTGGAACGG | GACTCAAAGTGACAGGGGCA |
| Dessert (negative control) | CTAGGAGGGTGGAGGTAGGG | GCCCCAAACAGGAGTAATGA |

***Supplementary Table 15:* Primers for ChIP-PCR analysis.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ABCC4 | CDK6 | HSD17B14 | NKX3-1 | SORD |
| ABHD2 | CENPN | IDI1 | PA2G4 | SPCS3 |
| ACSL3 | DBI | INPP4B | PDLIM5 | SPDEF |
| ACTN1 | DHCR24 | INSIG1 | PGM3 | SRF |
| ADAMTS1 | DNAJB9 | IQGAP2 | PIAS1 | SRP19 |
| ADRM1 | ELK4 | ITGAV | PLPP1 | STEAP4 |
| AKAP12 | ELL2 | KLK2 | PMEPA1 | STK39 |
| AKT1 | ELOVL5 | KLK3 | PTK2B | TMEM50A |
| ALDH1A3 | FADS1 | KRT19 | PTPN21 | TMPRSS2 |
| ANKH | FKBP5 | KRT8 | RAB4A | TNFAIP8 |
| APPBP2 | GNAI3 | LIFR | RPS6KA3 | TPD52 |
| ARID5B | GPD1L | LMAN1 | RRP12 | TSC22D1 |
| AZGP1 | GSR | MAF | SAT1 | UAP1 |
| B2M | GUCY1A1 | MAK | SCD | UBE2I |
| B4GALT1 | H1-0 | MAP7 | SEC24D | UBE2J1 |
| BMPR1B | HERC3 | MERTK | SELENOP | VAPA |
| CAMKK2 | HMGCR | MYL12A | SGK1 | XRCC5 |
| CCND1 | HMGCS1 | NCOA4 | SLC26A2 | XRCC6 |
| CCND3 | HOMER2 | NDRG1 | SLC38A2 | ZBTB10 |
| CDC14B | HPGD | NGLY1 | SMS | ZMIZ1 |

***Supplementary Table 16:* Genes included in the AR (Hallmark; H) response score.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| AKAP12 | CS | HOXB13 | SMPDL3A | WWC1 | ZNF726 |
| ANKRD30B | CTPS2 | IFT57 | SNX1 | ZFX | ZNF761 |
| AR | CYP4F8 | LRRC41 | SPATS2 | ZNF138 | ZNF813 |
| ATF7 | DCAF6 | MALT1 | SRC | ZNF174 | ZNF85 |
| BAZ2A | DOPEY2 | NUDT4 | STEAP1 | ZNF285 |  |
| C4orf36 | ELL2 | PITPNA | STEAP2 | ZNF43 |  |
| CAPN7 | FASN | PPP2R3A | TMBIM6 | ZNF525 |  |
| CBR4 | GALNT7 | PPP3CA | TMSB4Y | ZNF528 |  |
| CCDC115 | GRIN3A | PTER | TTTY15 | ZNF583 |  |
| CDYL2 | GSPT1 | RAB40B | UBE2E3 | ZNF680 |  |
| CROT | HOMER2 | RAB5B | USP54 | ZNF682 |  |

***Supplementary Table 17:* Genes included in the AR-V7 signature.**