**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** <77>7NR | **(N, %)**3, 7%9, 21%30, 70%1, 2% |
| **Metastatic at diagnosis** M0M1NR | **(N, %)**19, 44%18, 42%6, 14% |
| **Treatment intent** RadicalPalliative | **(N, %)**16, 37%27, 63% |
| **Paired metastatic castration resistant biopsy** |
| **Biopsy site** Bone Lymph nodeOther | **(N, %)**26, 60%15, 35%2, 5% |
| **Systemic therapies prior to biopsy^**01234 | **(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.**