**Supplementary Materials**

**Transcriptomic analysis reveals early alterations associated with intrinsic resistance to target therapy in lung adenocarcinoma cell lines**

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**Figure S1. Representative strategy of cytometry analysis for the quantification of viable, apoptotic, and necrotic cells. Effect of erlotinib in EGFR-mutated lung adenocarcinoma cell lines.** (A) Compared to control, erlotinib induces a slight cytotoxic effect in the cell line studied. (B) Percentages of viable, apoptotic and necrotic cells in the HCC827 and HCC4006 cell lines are Indica mainly a cytostatic effect, inducing damage in a low proportion of tumor cells. Percentages of viable, apoptotic, and necrotic cells in HCC827 (B) and HCC4006 (C) cell lines are indicated. Three independent experiments were done. Mean ± SD is shown. \*\*\*\**p* < 0.0001.



**Figure S2.** SA-ß-gal-positive cells evidencing DTP cells showing a senescent-like phenotype. After osimertinib exposure for 48 h, residual cells were cultured in fresh complete media for additional five days and the expression of beta-galactosidase was detected. Micrographs show SA-ß-gal-positive cells evidencing DTP cells with a senescent-like phenotype. Magnification 40x.

**Table S1.** TaqMan® gene expression assays.

|  |  |
| --- | --- |
| **Gene** | **TaqMan assay ID** |
| *AGAP2-AS1* | Hs01096080\_s1 |
| *MEG3* | Hs00292028\_m1 |
| *NKILA* | Hs04937740\_s1 |
| *CERS6-AS1* | Hs01372066\_g1 |
| *LINC01133* | Hs04274447\_m1 |
| *CD74* | Hs00269961\_m1 |
| *NFYC-AS1* | Hs03670565\_s1 |
| *FLJ31104* | Hs01377183\_m1 |
| *SLC25A25-AS1* | Hs05052217\_s1 |
| *ARIH2OS* | Hs03644906\_s1 |
| *GAPDH* | Hs02786624\_g1 |

**Table S2.** DsiRNA sequences employed for knockdown

|  |  |  |
| --- | --- | --- |
| **Name** | **Sequence**  | **Sense** |
| *hs.Ri.AGAP2-AS1.13.1* | *5’ rGrUrCrCrArCrGrCrArGrArUrUrGrArArUrUrCrCrCrCrUTG 3’* | + |
|  | *5’ rCrArArGrGrGrGrArArUrUrCrArArUrCrUrGrCrGrUrGrGrArCrUrG 3’* | - |
|  |  |  |
| *hs.Ri.AGAP2-AS1.13.2* | *5’ rCrCrCrCrArCrUrUrGrUrUrArCrCrUrGrCrUrUrUrArUrAAA 3’* | + |
|  | *5’ rUrUrUrArUrArArArGrCrArGrGrUrArArCrArArGrUrGrGrGrGrArG 3’* | - |
|  |  |  |
| *hs.AGAP2-AS1.13.3* | *5’ rCrCrArCrUrUrGrUrUrArCrCrUrGrCrUrUrUrArUrArArATA 3’* | + |
|  | *5’ rUrArUrUrUrArUrArArArGrCrArGrGrUrArArCrArArGrUrGrGrGrG 3’* | - |
|  |  |  |
| *hs.Ri.LINC01133.13.1* | *5’ rArArArGrCrUrUrGrArCrUrGrArArGrGrUrArCrCrArArGGT 3’* | + |
|  | *5’ rArCrCrUrUrGrGrUrArCrCrUrUrCrArGrUrCrArArGrCrUrUrUrUrA 3’* | - |
|  |  |  |
| *hs.Ri.LINC01133.13.2* | *5’ rCrCrArArArGrUrCrCrArGrCrArUrGrGrUrArGrArCrArUCA 3’* | + |
|  | *5’ rUrGrArUrGrUrCrUrArCrCrArUrGrCrUrGrGrArCrUrUrUrGrGrArG 3’* | - |
|  |  |  |
| *hs.Ri.LINC01133.13.3* | *5’ GrCrArUrGrGrUrArGrArCrArUrCrArGrUrGrGrUrGrGrUAA 3’* | + |
|  | *5’ rUrUrArCrCrArCrCrArCrUrGrArUrGrUrCrUrArCrCrArUrGrCrUrG 3’* | - |
|  |  |  |
| *hs.Ri.NFYC-AS1.13.1* | *5’ rGrArArUrArArArGrArArCrArGrUrArCrUrUrArCrCrArAGA 3’* | + |
|  | *5’ rUrCrUrUrGrGrUrArArGrUrArCrUrGrUrUrCrUrUrUrArUrUrCrUrA 3’* | - |
|  |  |  |
| *hs.Ri.NFYC-AS1.13.2* | *5’ rCrArGrCrUrArUrUrUrArCrCrArGrGrUrArGrUrArCrUrAGA 3’* | + |
|  | *5’ rUrCrUrArGrUrArCrUrArCrCrUrGrGrUrArArArUrArGrCrUrGrCrU 3’* | - |
|  |  |  |
| *hs.Ri.NFYC-AS1.13.3* | *5’ ArGrArArArUrUrUrArUrGrArGrCrUrArUrCrUrUrArCrAAT 3’* | + |
|  | *5’ rArUrUrGrUrArArGrArUrArGrCrUrCrArUrArArArUrUrUrCrUrGrC 3’* | - |

**Table S3.** LncRNAs overexpressed in erlotinib-DTP cells.

|  |  |
| --- | --- |
| **Ensembl ID** | **Gene name** |
| *ENSG00000214548* | *MEG3* |
| *ENSG00000231187* | *SYT15-AS1* |
| *ENSG00000231638* | *LUARIS* |
| *ENSG00000255737* | *AGAP2-AS1* |
| *ENSG00000260604* |  |
| *ENSG00000265666* | *RARA-AS1* |
| *ENSG00000278709* | *NKILA* |
| *ENSG00000280303* | *ERICD* |

**Table S4.** LncRNAs overexpressed in Osimertinib-DTP cells.

|  |  |
| --- | --- |
| **Ensembl ID** | **Gene name** |
| ENSG00000224032 | *EPB41L4A-AS1* |
| ENSG00000224259 | *LINC01133* |
| ENSG00000226200 | *SGMS1-AS1* |
| ENSG00000227617 | *CERS6-AS1* |
| ENSG00000253671 |  |
| ENSG00000254231 | *WWP1-AS1* |
| ENSG00000258634 |  |
| ENSG00000258701 | *LINC00638* |
| ENSG00000259976 |  |
| ENSG00000260604 |  |
| ENSG00000261799 |  |
| ENSG00000273033 | *LINC02035* |
| ENSG00000277496 | *SLCO4A1-AS2* |

**Table S5****.** LncRNAs overexpressed in CDDP-DTP cells.

|  |  |
| --- | --- |
| **Ensembl ID** | **Gene name** |
| ENSG00000170161 | *FAM88B* |
| ENSG00000174365 | *SNHG11* |
| ENSG00000203804 | *ADAMTSL4-AS1* |
| ENSG00000204802 | *FAM88C* |
| ENSG00000215014 |  |
| ENSG00000215458 | *AATBC* |
| ENSG00000221883 | *ARIH2OS* |
| ENSG00000222043 |  |
| ENSG00000224046 | *DMTF1-AS1* |
| ENSG00000224281 | *SLC25A5-AS1* |
| ENSG00000224358 | *TMCO1-AS1* |
| ENSG00000224635 |  |
| ENSG00000227354 | *RBM26-AS1* |
| ENSG00000227518 | *MIR1302-9HG* |
| ENSG00000227896 | *WAPL-DT* |
| ENSG00000227908 | *IL6ST-DT* |
| ENSG00000229178 |  |
| ENSG00000230337 | *EXOSC10-AS1* |
| ENSG00000230736 |  |
| ENSG00000231305 |  |
| ENSG00000232956 | *SNHG15* |
| ENSG00000234912 | *SNHG20* |
| ENSG00000235529 | *AGAP1-IT1* |
| ENSG00000236255 |  |
| ENSG00000242622 | *GSK3B-DT* |
| ENSG00000244945 | *RUFY1-AS1* |
| ENSG00000245748 |  |
| ENSG00000246863 | *GPR176-DT* |
| ENSG00000246889 | *CTTN-DT* |
| ENSG00000247092 | *SNHG10* |
| ENSG00000247373 | *TMED2-DT* |
| ENSG00000252690 |  |
| ENSG00000254473 | *UBQLN1-AS1* |
| ENSG00000254911 | *SCARNA9* |
| ENSG00000255198 | *SNHG9* |
| ENSG00000255224 |  |
| ENSG00000255717 | *SNHG1* |
| ENSG00000258738 | *BAZ1A-AS1* |
| ENSG00000259802 |  |
| ENSG00000259818 | *CZIB-DT* |
| ENSG00000260339 | *HEXA-AS1* |
| ENSG00000260367 |  |
| ENSG00000260589 | *STAM-DT* |
| ENSG00000260778 | *MIR3677HG* |
| ENSG00000260806 | *PAPOLA-DT* |
| ENSG00000260942 | *CAPN10-DT* |
| ENSG00000260948 |  |
| ENSG00000261087 | *ZNNT1* |
| ENSG00000261360 | *OTULIN-DT* |
| ENSG00000261758 | *STAG1-DT* |
| ENSG00000262202 |  |
| ENSG00000263823 |  |
| ENSG00000263990 |  |
| ENSG00000267322 | *SNHG22* |
| ENSG00000267342 |  |
| ENSG00000268403 |  |
| ENSG00000268798 |  |
| ENSG00000269846 |  |
| ENSG00000270332 | *SMC2-DT* |
| ENSG00000270673 | *YTHDF3-DT* |
| ENSG00000272056 |  |
| ENSG00000272103 |  |
| ENSG00000272145 | *NFYC-AS1* |
| ENSG00000272631 |  |
| ENSG00000272677 | *HNRNPD-DT* |
| ENSG00000272768 |  |
| ENSG00000272843 |  |
| ENSG00000272994 | *C2orf49-DT* |
| ENSG00000273199 |  |
| ENSG00000274213 |  |
| ENSG00000274270 |  |
| ENSG00000274292 |  |
| ENSG00000274925 | *ZKSCAN2-DT* |
| ENSG00000275198 | *LINC02960* |
| ENSG00000275401 |  |
| ENSG00000275437 |  |
| ENSG00000275807 |  |
| ENSG00000276603 |  |
| ENSG00000277182 |  |
| ENSG00000277597 |  |
| ENSG00000277895 |  |
| ENSG00000279762 |  |
| ENSG00000280213 | *UCKL1-AS1* |
| ENSG00000280614 |  |
| ENSG00000280800 |  |
| ENSG00000281181 |  |
| ENSG00000281207 | *SLFNL1-AS1* |
| ENSG00000281383 |  |
| ENSG00000282021 |  |
| ENSG00000283078 |  |
| ENSG00000285230 | *RALY-AS1* |
| ENSG00000285763 |  |