Supplementary Table 1. Clinical characteristics of the studied LUAD patients from Hellmann cohort.

| Characteristics          | All patients | EPHA5 Mut | EPHA5 WT | P value |
|--------------------------|--------------|-----------|----------|---------|
| Total (cases)            | 59           | 4         | 55       |         |
| Gender [cases (%)]       |              |           |          | 0.624   |
| Male                     | 22 (37.3)    | 2 (50.0)  | 20 (36.4)|         |
| Female                   | 37 (62.7)    | 2 (50.0)  | 35 (63.6)|         |
| Age (years)              |              | 56.5      | 66       | 0.148   |
| Median                   | 63           | 56.5      | 66       |         |
| IQR                      | 56.00-70.50  | 52.25-61.25| 56.50-71.00 |         |
| Smoking status [cases (%)]|           | 4         |          | 0.566   |
| Current/former           | 46 (78.0)    | 4 (100.0) | 42 (76.4)|         |
| Never                    | 13 (22.0)    | 0 (0.0)   | 13 (23.6)|         |
| Performance status [cases (%)]|              |          |          | 1       |
| ECOG_0                   | 28 (47.5)    | 2 (50.0)  | 26 (47.3)|         |
| ECOG_1                   | 31 (52.5)    | 2 (50.0)  | 29 (52.7)|         |
| Clinical benefit [cases (%)]|            |          |          | 0.114   |
| DCB                      | 31 (52.5)    | 4 (100.0) | 27 (49.1)|         |
| NDB                      | 28 (47.5)    | 0 (0.0)   | 28 (50.9)|         |

DCB: durable clinical benefit, NDB: no durable benefit;
P value: Wilcoxon test rank sum or Fisher’s exact test (two sided) was used for the comparison between the EPHA5 Mut and WT groups.
**Supplementary Table 2. DDR core pathway membership.**

| Base Excision Repair (BER) | Nucleotide Excision Repair (NER, including TC-NER and GC-NER) | Mismatch Repair (MMR) | Fanconi Anemia (FA) | Homologous Recombination (HR) | Non-homologous End Joining (NHEJ) | Direct Repair (DR) | Translesion Synthesis (TLS) | Damage Sensor etc. |
|---------------------------|---------------------------------------------------------------|-----------------------|---------------------|------------------------------|-----------------------------------|-------------------|-----------------------------|-------------------|
| PARP1                     | CUL5                                                          | EXO1                  | FANCA               | MRE11A                       | LIG4                              | ALKBH2            | POLN                         | ATM               |
| POLB                      | ERCC1                                                         | MLH1                  | FANCB               | NBN                          | NHEJ1                             | ALKBH3            | POLQ                         | ATR               |
| APEX1                     | ERCC2                                                         | MLH3                  | FANCC               | RAD50                        | POLL                              | REV1              | REV3L                        | ATRIP             |
| APEX2                     | ERCC4                                                         | MSH2                  | FANCD2              | TP53BP1                      | POLM                              | MGMT              | SHPRH                        | CHEK1             |
| FEN1                      | ERCC5                                                         | MSH3                  | FANCI               | XRCC2                        | PRKDC                             | MDC1              | CHEK2                        | MDC1              |
| TDG                       | ERCC6                                                         | MSH6                  | FANCL               | XRCC3                        | XRCC4                             | MDC1              | CHEK2                        | MDC1              |
| TDP1                      | POLE                                                          | PMS1                  | FANCM               | BARD1                        | XRCC5                             | RNMT              | TOPBP1                       | TOPBP1           |
| UNG                       | POLE3                                                         | PMS2                  | UBE2T               | BRCA1                        | BLM                               | XRCC6             | TPD3A                        | TPD3A             |
|                           |                                                               | XPA                   |                     | BRCA2                        |                                   |                   |                              |                   |
|                           |                                                               | XPC                   |                     | BRIP1                        |                                   |                   |                              |                   |
|                           |                                                               |                       |                     | EME1                         |                                   |                   |                              |                   |
|                           |                                                               |                       |                     | GEN1                         |                                   |                   |                              |                   |
|                           |                                                               |                       |                     | MUS81                        |                                   |                   |                              |                   |
|                           |                                                               |                       |                     | PALB2                        |                                   |                   |                              |                   |
|                           |                                                               |                       |                     | RAD51                        |                                   |                   |                              |                   |
|                           |                                                               |                       |                     | RAD52                        |                                   |                   |                              |                   |
|                           |                                                               |                       |                     | RBBP8                        |                                   |                   |                              |                   |
|                           |                                                               |                       |                     | SHFM1                        |                                   |                   |                              |                   |
|                           |                                                               |                       |                     | SLX1A                        |                                   |                   |                              |                   |
|                           |                                                               |                       |                     | XRCC5                        |                                   |                   |                              |                   |
|                           |                                                               |                       |                     | XRCC6                        |                                   |                   |                              |                   |

**Supplementary Table 3. Clinical characteristics of the studied LUAD patients from MSKCC immunotherapy cohort.**

| Characteristics             | All patients | EPHA5 Mut | EPHA5 WT | P value |
|-----------------------------|--------------|-----------|----------|---------|
| **Total (cases)**           | 271          | 23        | 248      | 0.827   |
| **Gender [cases (%)]**      |              |           |          |         |
| Male                        | 117 (43.2)   | 9 (39.1)  | 108 (43.5)| 0.55    |
| Female                      | 154 (56.8)   | 14 (60.9) | 140 (56.5)|         |
| **Age Group at Diagnosis in Years [cases (%)]** | | | | 0.634 |
| 31-50                       | 28 (10.3)    | 2 (8.7)   | 26 (10.5) |         |
| 50-60                       | 61 (22.5)    | 8 (34.8)  | 53 (21.4) |         |
| 61-70                       | 85 (31.4)    | 6 (26.1)  | 79 (31.9) |         |
| >71                         | 97 (35.8)    | 7 (30.4)  | 90 (36.3) |         |
| **Drug Type [cases (%)]**   |              |           |          |         |
| PD-1/PDL-1                  | 255 (94.1)   | 21 (91.3) | 234 (94.4)|         |
| Combo                       | 16 (5.9)     | 2 (8.7)   | 14 (5.6)  |         |

P value: Fisher’s exact test (two sided) was used for the comparison between the EPHA5 Mut and WT groups.
Supplementary Table 4. Clinical characteristics of the studied LUAD patients from Chinese cohort.

| Characteristics                  | All patients | EPHA5 Mut | EPHA5 WT | P value |
|----------------------------------|--------------|-----------|----------|---------|
| **Total (cases)**                | 143          | 9         | 134      |         |
| **Gender [cases (%)]**           |              |           |          | 0.086   |
| Male                             | 86 (60.1)    | 8 (88.9)  | 78 (58.2)|         |
| Female                           | 57 (39.9)    | 1 (11.1)  | 56 (41.8)|         |
| **Age (years)**                  |              |           |          | 0.206   |
| Median                           | 62.00        | 66.00     | 62.00    |         |
| IQR                              | 55.00-68.00  | 63.00-67.00| 54.25-68.00|         |
| **Smoking status [cases (%)]**   |              |           |          | 0.140   |
| Current/former                   | 58 (40.6)    | 6 (66.7)  | 52 (38.8)|         |
| Never                            | 70 (49.0)    | 2 (22.2)  | 68 (50.7)|         |
| NA                               | 15 (10.5)    | 1 (11.1)  | 14 (10.4)|         |
| **Pathological stage [cases (%)] |              |           |          | 0.921   |
| I                                | 16 (11.2)    | 1 (11.1)  | 15 (11.2)|         |
| II                               | 27 (18.9)    | 2 (22.2)  | 25 (18.7)|         |
| III                              | 59 (41.2)    | 3 (33.3)  | 56 (41.8)|         |
| IV                               | 41 (28.7)    | 3 (33.4)  | 38 (28.3)|         |

NA: not available;
P value: Wilcoxon test rank sum or Fisher's exact test (two sided) was used for the comparison between the EPHA5 Mut and WT groups, and NA was not included in the statistical analysis.
Supplementary Table 5. Gene list of the designed NGS panel.

| Hugo Symbol | Hugo Symbol | Hugo Symbol | Hugo Symbol | Hugo Symbol | Hugo Symbol | Hugo Symbol |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| AMER1       | IP07        | CREBBP      | PDCD1LG2    | HSPA4       | ESR1        | DHFR        |
| ASXL1       | MEDI9       | CRKL        | PDGFRB      | CNOT8       | ETV6        | GSTA1       |
| ATRX        | MARK2       | CRLF2       | PIK3C2G     | GABRP       | FANCA       | SOD2        |
| AURKB       | ANO1        | CSF1R       | PIK3CB      | F13A1       | FBXW7       | SLC22A2     |
| BCOR        | KDM5A       | CSF3R       | PIK3CG      | FLOT1       | FGF19       | SEMA3C      |
| BRD4        | ZDHHC17     | CXCR4       | PIK3R1      | HSPA1B      | FGF3        | ABCB1       |
| CBFB        | VSIG10      | CYLD        | PIK3R2      | MAP3K4      | FGF4        | SLC31A1     |
| CDC73       | CTAEG5      | DAXX        | PLCG2       | TRA2A       | FGF1R       | HSPA5       |
| CDK12       | PRPF39      | DICER1      | PPARG       | ABCA13      | FGF2R       | CYPC21       |
| CDK8        | MAP4K5      | DIS3        | PPP2R1A     | CALD1       | FGF3        | CYP2C8       |
| CIC         | ARID4A      | DOT1L       | PRKCI       | UBE3C       | FH          | SLIT1        |
| CTCF        | TECPR2      | EP300       | PTCH1       | MMP16       | FLT1        | ABCC2        |
| FAM46C      | AOPT1       | EPHA3       | PTPN11      | RIPK2       | HRAS        | RRM1         |
| FAT1        | HAU52       | EPHA5       | RAD51       | RAD21       | IDH1        | GSTP1        |
| FOXL2       | ATP9B       | EPHA7       | RAD51B      | IAR5        | IDH2        | SLCO1B3      |
| FUBP1       | SPC24       | EPBH1       | RAD52       | MAPKAP1     | JAK1        | SLCO1B1      |
| GATA1       | MYADM       | ERBB4       | RAD54L      | UFP2        | JAK2        | CYP19A1      |
| GATA2       | KIR3DX1     | ERG         | RAF1        | PDE6C       | KRAS        | CYBA         |
| IKZF1       | ZNF805      | ETV1        | RARA        | ADBR1       | MAP2K1       | TYSM         |
| KDM5C       | C20orf96    | EZH2        | RPTOR       | ACADSB      | MDM2        | CYP2B6       |
| LMO1        | NCOA6       | FANCC       | RUNX1       | TPH1        | MDM4        | XRC1         |
| MYCL        | TMRPR5S15    | FANCG       | SDHA        | PTPRJ       | MEN1        | ERCC2        |
| NNX2-1      | DSCAM       | FAS         | SETD2       | FOLH1       | MET         | ERCC1        |
| PRDM1       | RRP1B       | FGF4        | SF3B1       | ALG9        | MLH1        | HNF4A        |
| PREX2       | C22orf23    | FLCN        | SMAD2       | HYOU1       | MRE11A       | CBR3         |
| RBBM10      | MOV10L1     | FLT3        | SMAD3       | MAGOHB      | MSH3        | CYP2D6       |
| RNF43       | WWC3        | FLT4        | SMARCA4     | TXNRD1       | MSH6        | GSTM1        |
| SPEN        | ARHGAP6     | FOXP1       | SMARCB1     | HCAR2       | MTO1        | EWSR1        |
| TET2        | BCYRN1      | GATA3       | SMO         | EXOSC8      | MUTYH       | FUS          |
| TOP1        | ZNF711      | GLI1        | SOCS1       | TNFSF13B    | NBN         | HEY1         |
| PDPN        | TBC1D8B     | GNA11       | SOX2        | SNX6        | NF2         | NR4A3        |
| GMEB1       | DOCK11      | GNA13       | SOX9        | AK7         | NOTCH1      | PDGFB        |
| MTF1        | LONRF3      | GNAAQ       | SPOP        | CYFIP1      | NRAS        | SS18         |
| ZZZ3        | KIAA1210    | GNAS        | SRC         | GANC        | NT5C2       | EML4         |
| RABGAP1L    | ARHGAP4     | GRIN2A      | STAT3       | NEO1        | NTRK1       | CD74         |
| IRF6        | BAP1        | GSK3B       | SUFU        | FANCI       | NTRK2       | SLC34A2      |
| PLEKHH2     | DDR2        | H3F3A       | SYK         | ITGAL       | NTRK3       | KIF5B        |
| PNO1        | ERRF11      | HGF         | TXB3        | ARMC5       | PALB2       | RIC1         |
| TSN         | NPM1        | HNF1A       | TGFBR2      | NUP93       | PBRM1       | AGPAT9       |
| ARL6IP6     | ROS1        | ID3         | TMPRSS2     | IRF8        | PDGFR1      | CAST         |
| NAB1        | NR113       | IGF1R       | TNAIP3      | NF1         | PIK3CA      | ZMYM4        |
| ALS2CR11    | OTOS        | IGF2        | TNFRSF14    | RHOT1       | PMS2        | SLC30A5      |
| ULK4        | C8orf34     | IKBKE       | TSHR        | TAF15       | POLD1       | CEP120       |
| KPN4A       | NAB2        | IL7R        | U2AF1       | KPNB1       | POLE        | C5orf15      |
| ZBBX        | PPHLN1      | INHBA       | WHSC1       | ABCA8       | PRKAR1A     | SIMC1        |
| LRRCC34     | ABL1        | INPP4B      | WHSC1L1     | KCNJ2       | PTEN        | PGBD1        |
| SEL1L3      | AKT2        | IRF4        | XPO1        | NUP85       | RAC1        | HAUS6        |
| NFXL1       | AKT3        | IRS2        | CXCL8       | LAMA3       | RAD50       | ZNF367       |
| SHROOM3     | ALOX12B     | JAK3        | EIF4G3      | MALT1       | RAD51C       | SFXN4        |
| FRAS1       | ARID1A      | JUN         | STMN1       | CDC2B5      | RAD51D       | CEP290       |
| CBR4        | ARID1B      | KDM6A       | LEPR        | CD40        | RB1         | STYX         |
| GPM6A       | ARID2       | KDR         | ASH1L       | FGF16       | RET         | MAPKBP1      |
| FAM149A     | ATR         | KEAP1       | FMO1        | RPA4        | RICTOR      | ZNF91        |
| MTRR        | AURKA       | KMT2A       | SIPA1L2     | STAG2       | SDHB        | APOL2        |
| C5orf42 | AXIN1 | KMT2C | RYR2 | BRS3 | SDHC | NKAP |
|---------|-------|-------|------|------|------|------|
| ADAMTS6 | AXL   | KMT2D | ADSS | IRAK1 | SDHD | DBT  |
| BTF3    | BARD1 | LYN   | ID2  | AKT1 | SMAD4 | DIAPH1 |
| ANKRA2  | BCL2  | MAP2K2 | CALM2 | ALK  | STK11 | HLA-DRB1 |
| CHD1    | BCL2L1 | MAP2K4 | MSH2 | APC  | TERT  | COL15A1 |
| CDKL3   | BTG1  | MAP3K1 | PAPOLG | AR  | TP53  | WDR5 |
| PURA    | BTK   | MCL1  | REL  | ARAF | TSC1  | MMP3 |
| RBM27   | CALR  | MED12 | MEIS1 | ATM  | TSC2  | NLRP7 |
| FAM153B | CARD11 | MEF2B | MRPL19 | BLM  | VEGFA | DEPDC5 |
| HNRNPH1 | CASP8 | MITF  | SUCLG1 | BRAF | VHL   | DYNC2H1 |
| ACOT13  | CBL   | MPL   | UBE2E3 | BRCA1 | WT1   | STARD4 |
| PAQR8   | CCND2 | MYC   | NDUF51 | BRCA2 | PIGF  | ZNF2 |
| SASH1   | CCND3 | MYCN  | ARPC2 | BRIP1 | B2M   | TOE1 |
| CNKS1R3 | CCNE1 | MYD88 | CUL3  | CCND1 | MAPK1 | EZR |
| TAGAP   | CD274 | NFE2L2 | CAB39 | CDH1 | MTHFR | HLA-A |
| TNRC18  | CD79A | NFKBIA | FANCD2 | CDK4 | CDA   | HLA-B |
| SUGCT   | CD79B | NOTCH2 | TOP2B | CDKN2A | DPYD | HLA-C |
| TRIM24  | CDK6  | NOTCH3 | CCR4  | CHEK2 | MTR   | SLC7A8 |
| ER1I    | CDKN1A | NSD1  | KIT   | CTNNB1 | GALNT14 | RFC1 |
| TNKS    | CDKN1B | P2RY8 | COX18 | DNMT3A | LRP2  | STRBP |
| TMEM67  | CDKN2B | PARK2 | MYO10 | EGF1R | ATIC  | PLEKHA1 |
| RNF19A  | CDKN2C | PARP1 | DROSHA | ERBB2 | UGT1A1 |
| ANKRD46 | CEBPA | PAX5  | CDK7  | ERBB3 | XPC   |
| C9orf72 | CHEK1 | PDCD1 | CDO1  | ERCC4 | UMP5 |