Supplement Figure 1:

A. The enriched immune-related pathways in GO of KEAP1/NFE2L2-mutant P2 patient subgroup.

B. The enriched immune-related pathways in GO of KEAP1/NFE2L2-mutant C2 patient subgroup.
Supplement Figure 2:
A. Four subgroups with distinct mutational signatures were retrieved from the mutational profiles of TCGA lung adenocarcinoma patients. W2 subgroup was closely associated with smoking-related mutational signatures.
B. Differential activities of the smoking-related mutational signature between the subtypes of \textit{KEAP1}/\textit{NFE2L2}-mutant lung adenocarcinoma patients ($P = 0.004$).
Supplement Table 1: Comparisons of common mutations between KEAP1/NFE2L2-mutant subgroups of patients (P1 and P2).

| Mutation          | P1       | P2       | P-value  |
|-------------------|----------|----------|----------|
| Number            | 26       | 63       |          |
| EGFR mutation     |          |          | 1.000*   |
| Yes               | 1 (3.8)  | 2 (3.2)  |          |
| No                | 25 (96.2)| 61 (96.8)|          |
| KRAS mutation     |          |          | 0.081    |
| Yes               | 10 (38.5)| 13 (20.6)|          |
| No                | 16 (61.5)| 50 (79.4)|          |
| TP53 mutation     |          |          | <0.001*  |
| Yes               | 3 (11.5) | 37 (58.7)|          |
| No                | 23 (88.5)| 26 (41.3)|          |
| STK11 mutation    |          |          | 0.008    |
| Yes               | 11 (42.3)| 10 (15.9)|          |
| No                | 15 (57.7)| 53 (84.1)|          |
| LRP1B mutation    |          |          | 0.113*   |
| Yes               | 4 (15.4) | 22 (34.9)|          |
| No                | 22 (84.6)| 41 (64.1)|          |
| PCLO mutation     |          |          | 0.011*   |
| Yes               | 1 (3.8)  | 20 (31.7)|          |
| No                | 25 (96.2)| 43 (68.3)|          |
| PTPRD mutation    |          |          | 0.756*   |
| Yes               | 2 (7.7)  | 8 (12.7) |          |
| No                | 24 (92.3)| 55 (87.3)|          |
| RELN mutation     |          |          | 0.550*   |
| Yes               | 4 (15.4) | 15 (23.8)|          |
| No                | 22 (84.6)| 48 (76.2)|          |
| FAT4 mutation     |          |          | 0.476*   |
| Yes               | 3 (11.5) | 13 (20.6)|          |
| No                | 23 (88.5)| 50 (79.4)|          |
| KMT2D mutation    |          |          | 0.316#   |
| Yes               | 0 (0)    | 5 (7.9)  |          |
| No                | 26 (100) | 58 (92.1)|          |
| EPHA5 mutation    |          |          | 0.129*   |
| Yes               | 1 (3.8)  | 12 (19.0)|          |
| No                | 25 (96.2)| 51 (81.0)|          |
| CPS1 mutation     |          |          | 0.920*   |
| Yes               | 2 (7.7)  | 7 (11.1) |          |
| No                | 24 (92.3)| 56 (88.9)|          |
| NF1 mutation      |          |          | 0.029#   |
|                  | Yes | No     |  |  |  |  |  |
|------------------|-----|--------|---|---|---|---|---|
|                  | 0 (0)| 26 (100)|   |   |   |   |   |
| SETBP1 mutation  | 1.000* |  |  |  |  |  |  |
| Yes              | 4 (15.4)| 9 (14.3)|   |   |   |   |   |
| No               | 22 (84.6)| 54 (85.7)|   |   |   |   |   |
| FAT1 mutation    | 0.613* |  |  |  |  |  |  |
| Yes              | 2 (7.7)| 9 (14.3)|   |   |   |   |   |
| No               | 24 (92.3)| 54 (85.7)|   |   |   |   |   |
| PTPRT mutation   | 0.040* |  |  |  |  |  |  |
| Yes              | 1 (3.8)| 16 (25.4)|   |   |   |   |   |
| No               | 25 (96.2)| 47 (74.6)|   |   |   |   |   |
| GRIN2A mutation  | 1.000* |  |  |  |  |  |  |
| Yes              | 2 (7.7)| 5 (7.9)|   |   |   |   |   |
| No               | 24 (92.3)| 58 (92.1)|   |   |   |   |   |
| ZNF521 mutation  | 0.054# |  |  |  |  |  |  |
| Yes              | 0 (0)| 9 (14.3)|   |   |   |   |   |
| No               | 26 (100)| 54 (85.7)|   |   |   |   |   |
| MGAM mutation    | 0.175# |  |  |  |  |  |  |
| Yes              | 0 (0)| 6 (9.5)|   |   |   |   |   |
| No               | 26 (100)| 57 (90.5)|   |   |   |   |   |

All comparisons were based on the chi-square test.

* represents the chi-square test with continuity correction.

# represents the Fisher’s exact test.

Supplement Table 2: The list of identified mutant-specific compounds based on the GDSC database.
| GDSC database | Drug ID | Drug Name      | Putative Target                      | Pathway Name          | Subgroup Specific |
|---------------|---------|----------------|--------------------------------------|-----------------------|-------------------|
| GDSC2         | 1576    | IWP-2          | PORCN                                | WNT signaling         | C2                |
| GDSC2         | 1854    | MN-64          | TNKS1, TNKS2                         | WNT signaling         | C2                |
| GDSC1         | 1268    | XAV939         | TNKS1, TNKS2                         | WNT signaling         | C2                |
| GDSC2         | 1268    | XAV939         | TNKS1, TNKS2                         | WNT signaling         | C2                |
| GDSC1         | 308     | Foretinib      | MET, KDR, TIE2, VEGFR3/FLT4, RON, PDGFR, FGFR1, EGFR | RTK signaling        | C2                |
| GDSC1         | 1029    | Motesanib      | VEGFR, RET, KIT, PDGFR               | RTK signaling         | C2                |
| GDSC1         | 1049    | PD173074       | FGFR1, FGFR3                         | RTK signaling         | C2                |
| GDSC1         | 1194    | SB505124       | TGFBR1, ACVR1B, ACVR1C               | RTK signaling         | C2                |
| GDSC2         | 1912    | Afuresertib    | AKT1, AKT2, AKT3                     | PI3K/MTOR signaling   | C2                |
| GDSC1         | 228     | AKT inhibitor VIII | AKT1, AKT2, AKT3                  | PI3K/MTOR signaling   | C2                |
| GDSC2         | 2045    | AMG-319        | PI3Kalpha, PI3Kbeta, PI3Kgamma       | PI3K/MTOR signaling   | C2                |
| GDSC2         | 1918    | AZD8186        | PI3Kalpha, PI3Kbeta                 | PI3K/MTOR signaling   | C2                |
| GDSC2         | 1053    | MK-2206        | AKT1, AKT2                          | PI3K/MTOR signaling   | C2                |
| GDSC1         | 1527    | Pictilisib     | PI3K (class 1)                      | PI3K/MTOR signaling   | C2                |
| GDSC1         | 223     | ZSTK474        | PI3K (class 1)                      | PI3K/MTOR signaling   | C2                |
| GDSC2         | 1916    | AZD5363        | AKT1, AKT2, AKT3, ROCK2             | Other, kinases        | C2                |
| GDSC1         | 229     | Enzastaurin    | PKCB                                 | Other, kinases        | C2                |
| GDSC1         | 253     | XMD14-99       | ALK, CDK7, LTK, others              | Other, kinases        | C2                |
| GDSC1         | 332     | XMD15-27       | CAMK2                                | Other, kinases        | C2                |
| GDSC1         | 186     | Bexarotene     | Retinoic X receptor (RXR) agonist    | Other                 | C2                |
| GDSC2         | 1998    | BPD-00008900   | Other                                | Other                 | C2                |
| GDSC1         | 166     | FTI-277        | Farnesyl-transferase (FNTA)          | Other                 | C2                |
| GDSC1         | 180     | Thapsigargin   | SERCA                                | Other                 | C2                |
| GDSC2         | 1007    | Docetaxel      | Microtubule stabiliser               | Mitosis               | C2                |
|     |     |                           |                  |                      |               |
|-----|-----|---------------------------|------------------|----------------------|---------------|
| GDSC1 | 201 | Epothilone B              | Microtubule      | Mitosis              | C2            |
|     |     |                            | stabiliser       |                      |               |
| GDSC1 | 225 | Genentech Cpd 10          | AURKA, AURKB     | Mitosis              | C2            |
|     |     |                            |                  |                      |               |
| GDSC1 | 140 | Vinorelbine                | Microtubule      | Mitosis              | C2            |
|     |     |                            | destabiliser     |                      |               |
| GDSC2 | 1913| AGI-5198                  | IDH1 (R132H)     | Metabolism           | C2            |
|     |     |                            |                  |                      |               |
| GDSC2 | 1091| BMS-536924                | IGF1R, IR        | IGF1R signaling      | C2            |
|     |     |                            |                  |                      |               |
| GDSC2 | 1510| Linsitinib                | IGF1R            | IGF1R signaling      | C2            |
|     |     |                            |                  |                      |               |
| GDSC2 | 1932| NVP-ADW742                | IGF1R            | IGF1R signaling      | C2            |
|     |     |                            |                  |                      |               |
| GDSC2 | 1036| PLX-4720                  | BRAF             | ERK MAPK signaling   | C2            |
|     |     |                            |                  |                      |               |
| GDSC1 | 1061| SB590885                  | BRAF             | ERK MAPK signaling   | C2            |
|     |     |                            |                  |                      |               |
| GDSC1 | 1069| EHT-1864                  | RAC1, RAC2,      | Cytoskeleton         | C1            |
|     |     |                            | RAC3             |                      |               |
| GDSC2 | 1928| I-BRD9                    | BRD9             | Chromatin other      | C2            |
|     |     |                            |                  |                      |               |
| GDSC2 | 1237| EPZ004777                 | DOT1L            | Chromatin histone    | C2            |
|     |     |                            |                  | methylation          |               |
| GDSC2 | 1563| EPZ5676                   | DOT1L            | Chromatin histone    | C2            |
|     |     |                            |                  | methylation          |               |
| GDSC1 | 271 | VNLG/124                  | HDAC,RAR         | Chromatin histone    | C2            |
|     |     |                            |                  | acetylation          |               |
| GDSC2 | 1997| WEHI-539                  | BCL-XL           | Apoptosis regulation | C2            |
|     |     |                            |                  |                      |               |