Figure S1. Flow chart of the methods in the present study. A total of 4,534 genes associated with the overall survival in patients with non-small cell lung cancer were first produced by Cox PH survival analysis. Next LASSO regression was used to select the optimal gene signature for prognosis prediction. The survival risk score system was built based on 21 CpG signatures. Overall, 2,000 CpG sites, 1,505 copy number variations regions, 1,841 genes and 527 miRNAs were screened for multi-omics integrative clustering after pre-processing. A total of 6 iCluster subtypes were identified and the features of these were characterized. Through integrating multi-omics data and survival risk scores of the patients, survival risk score-related copy number variation regions and mutations were identified. del, deletion; amp, amplification; CN, copy number; miRNA, microRNA; PH, proportional hazard; LASSO, least absolute shrinkage and selection operator.

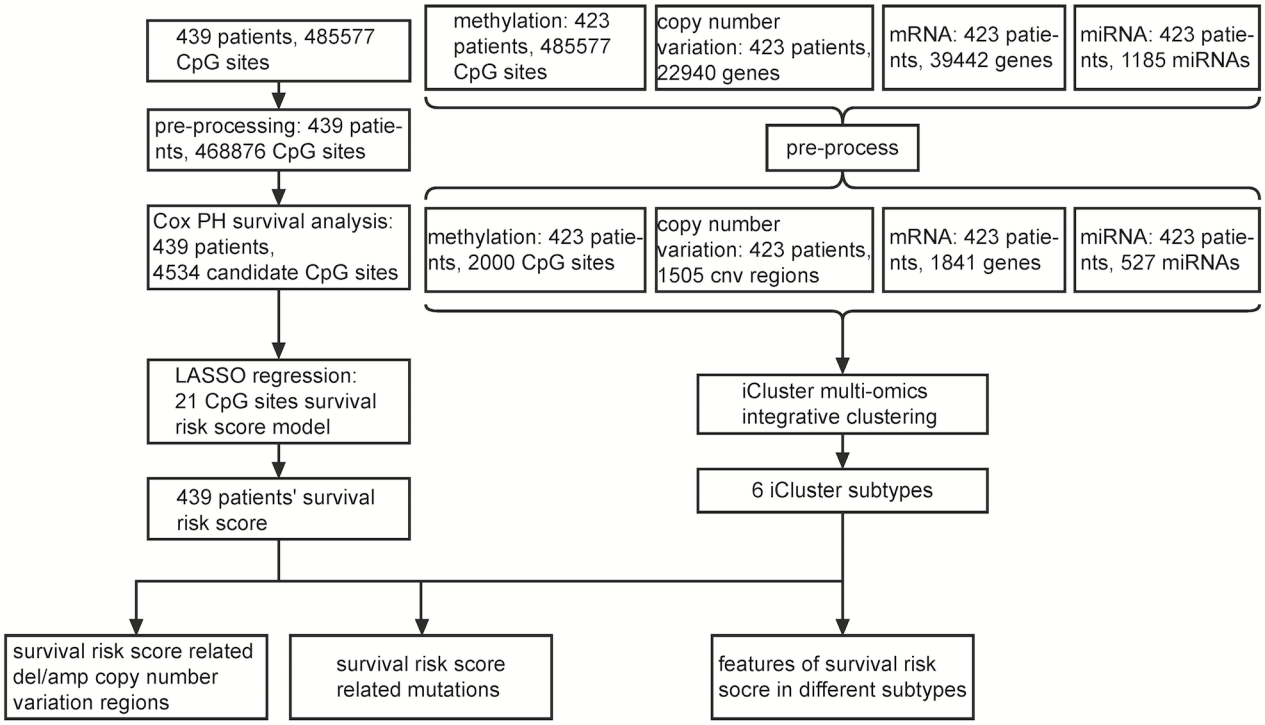

Figure S2. Number of clusters vs. percentage of explained variation. The Bayesian Information Criterion of the different number of clusters did not show an elbow point. According to the of iCluster algorithm manual, the heatmaps of the outcome with the different number of clusters were compared to determine the optimal number of clusters based on the features pattern.

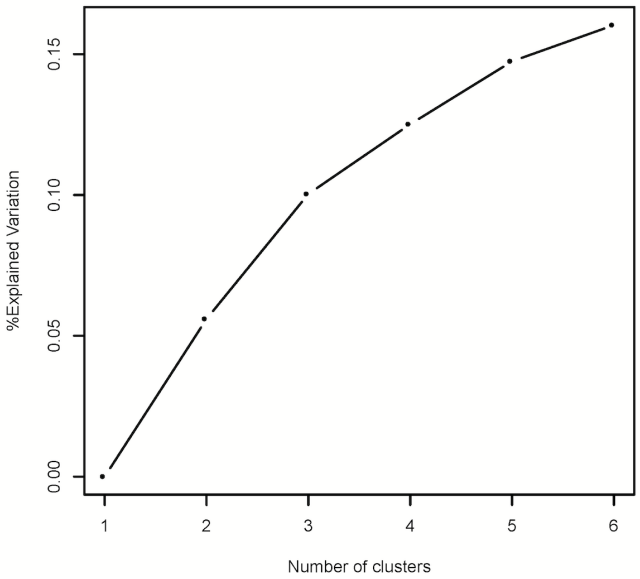

Figure S3. Heatmaps organized by iCluster groupings. (A-E) Two-iCluster solutions to six-iCluster solutions. From top to bottom in each figure, the heatmaps represent, in order, the copy number, mRNA expression, methylation and miRNA expression. Red represents copy number amplification or high expression/methylation levels. Blue represents copy number deletion or low expression/methylation levels. Patients were divided into different iClusters using black vertical lines. A six-iCluster solution was selected. cnv, copy number variation; mRNA, mRNA expression; meth, methylation; miRNA, miRNA expression.

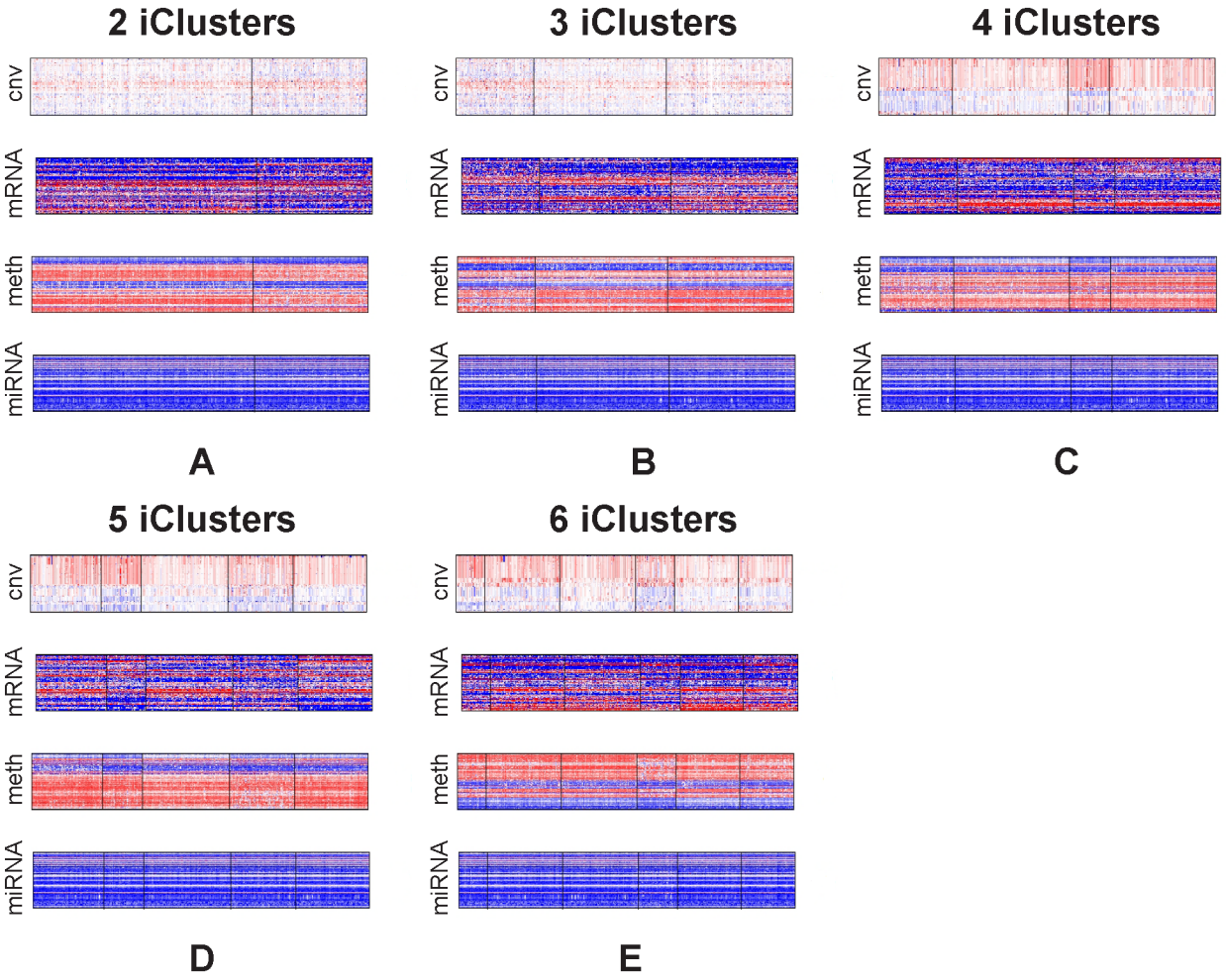

Figure S4. Distribution of patients' risk scores across stages and subtypes. (A) Distribution of patients' risk scores across stages. Patients in stage 2 and stage 3 had significant higher risk scores than patients in stage 1. The significance level was adjusted using Bonferroni's correction ($\alpha'=8.3x10^{-3}$). (B) Distribution of patients' risk scores across subtypes. Patients in iClusters 4-6 had significant higher risk scores than patients in iCluster 3. Patients in iCluster 6 had significant higher risk scores than patients in iClusters 1-3 and iCluster 5. The significance level was adjusted using Bonferroni's correction ($\alpha'=3.3x10^{-3}$).

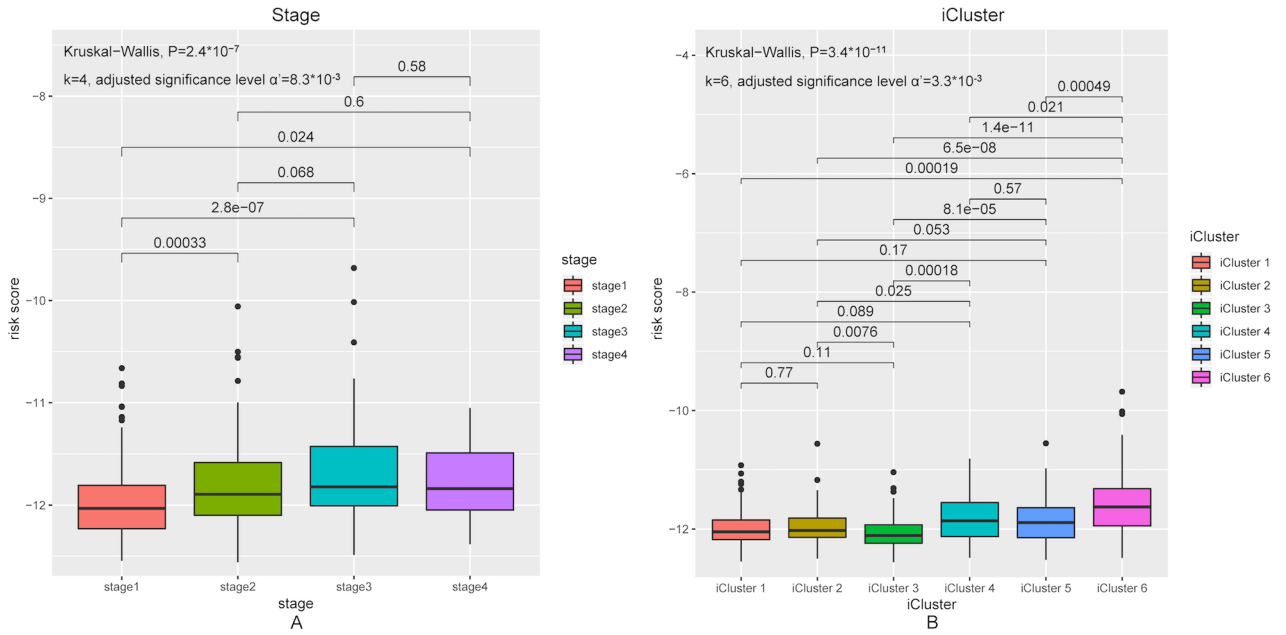

Table SI. Summary table of patients' detailed clinical information.

| Characteristics | Patients, n |
|---|---|
| Age, years | |
| ≤60 | 145 |
| >60 | 284 |
| NA | 10 |
| Sex | |
| Female | 236 |
| Male | 203 |
| Pathology stage | |
| I | 238 |
| II | 107 |
| III | 70 |
| IV | 20 |
| NA | 4 |
| Risk | |
| High | 114 |
| Low | 325 |

NA, not available.

Table SII. Summary table of features of different iClusters.

| Category | iClsuter1 | iClsuter2 | iClsuter3 | iClsuter4 | iClsuter5 | iClsuter6 |
|---|---|---|---|---|---|---|
| Male | 63.89% | 44.68% | 30.53% | 58% | 38.75% | 63.24% |
| Female | 36.11% | 55.32% | 69.47% | 42% | 61.25% | 36.76% |
| Stage1 | 58.33% | 54.26% | 67.37% | 54% | 50% | 39.71% |
| Stage2 | 19.44% | 25.53% | 16.84% | 22% | 30% | 26.47% |
| Stage3 | 13.89% | 15.96% | 11.58% | 14% | 17.50% | 26.47% |
| Stage4 | 8.33% | 3.19% | 2.11% | 8% | 1.25% | 7.35% |
| M0 | 75% | 64.89% | 62.11% | 56% | 66.25% | 66.18% |
| M1 | 8.33% | 3.19% | 2.11% | 8% | 1.25% | 7.35% |
| Mx | 16.67% | 30.85% | 33.68% | 34% | 32.50% | 26.47% |
| N0 | 75% | 64.89% | 62.11% | 56% | 66.25% | 66.18% |
| N1 | 8.33% | 3.19% | 2.11% | 8% | 1.25% | 7.35% |
| N2 | 16.67% | 30.85% | 33.68% | 34% | 32.50% | 26.47% |
| N3 | 0 | 1.06% | 2.11% | 2% | 0 | 0 |
| Nx | 0 | 0 | 0 | 0 | 0 | 0 |
| T1 | 30.56% | 24.47% | 53.68% | 32% | 30% | 25% |
| T2 | 52.78% | 63.83% | 35.79% | 60% | 58.75% | 55.88% |
| T3 | 8.33% | 8.51% | 6.32% | 6% | 8.75% | 13.24% |
| T4 | 8.33% | 3.19% | 4.21% | 2% | 2.50% | 4.41% |
| Tx | 0 | 0 | 0 | 0 | 0 | 1.47% |
| TTN mutation | 30.56% | 56.38% | 25.26% | 70% | 57.50% | 66.18% |
| KRAS mutation | 52.78% | 32.98% | 30.53% | 32% | 27.50% | 26.47% |
| TP53 mutation | 11.11% | 75.53% | 24.21% | 64% | 68.75% | 66.18% |
| KEAP1 mutation | 63.89% | 8.51% | 3.16% | 26% | 8.75% | 38.24% |

Table SIII. Detailed information of the selected CpG sites.

| CpG | Chromosome | Start | End | Gene symbol | Gene type | Region type |
|---|---|---|---|---|---|---|
| *cg01467592* | 8 | 144423973 | 144423974 | *VPS28* | Protein coding | N Shore |
| *cg02967813* | 2 | 3633738 | 3633739 | *COLEC11* | Protein coding | N Shore |
| *cg04391569* | 10 | 132781797 | 132781798 | *INPP5A* | Protein coding | Island |
| *cg05406101* | 21 | 29019898 | 29019899 | *RWDD2B* | Protein coding | S Shore |
| *cg06860998* | 4 | 4396367 | 4396368 | *D4S234E* | Protein coding | - |
| *cg06933711* | 10 | 30052194 | 30052195 | *KIAA1462* | Protein coding | - |
| *cg12193943* | 12 | 1776695 | 1776696 | *ADIPOR2* | Protein coding | - |
| *cg13372811* | 1 | 110084968 | 110084969 | *LINC01397* | Antisense | S Shore |
| *cg19160958* | 17 | 37447782 | 37447783 | *TADA2A* | Protein coding | - |
| *cg21749275* | 4 | 109539742 | 109539743 | *SEC24B* | Protein coding | - |
| *cg22697853* | 1 | 148264933 | 148264934 | | | Island |
| *cg27018309* | 16 | 8849265 | 8849266 | *PMM2; RP11-152P23.2; RP11-77H9.2* | Protein coding | - |
| *cg27529004* | 2 | 236582165 | 236582166 | *ACKR3* | Protein coding | - |
| *cg00278107* | 5 | 1061138 | 1061139 | *SLC12A7* | Protein coding | Island |
| *cg03723506* | 5 | 38557041 | 38557042 | *LIFR; LIFR-AS1* | Protein coding | Island |
| *cg04973915* | 5 | 171927687 | 171927688 | *FBXW11* | Protein coding | - |
| *cg06720244* | 3 | 45968967 | 45968968 | *ZC3H13* | Protein coding | - |
| *cg11302293* | 4 | 3784045 | 3784046 | | | - |
| *cg13354228* | 8 | 658673 | 658674 | *RP11-806L2.5*; *TYMS; TYMSOS* | Sense intronic | Island |
| *cg17510645* | 1 | 243236587 | 243236588 | *CEP170* | Protein coding | - |
| *cg20981791* | 8 | 23293556 | 23293557 | *R3HCC1* | Protein coding | - |

N Shore, 0-2 kb up-stream of a CpG island; S Shore, 0-2 kb down-stream of a CpG island; Island, Cpg Island; -, more than 4 kb up- and down-stream of a CpG island.

Table SIV. Multivariate analysis of methylation risk score and other confounders.

| Characteristic | Hazard ratio | 95% CI | P-Value |
|---|---|---|---|
| Risk score | 15.3 | 8.43-27.78 | $<2x10^{-16}$ |
| Age | 1.03 | 1.01-1.06 | 0.01 |
| Sex (male) | 1.71 | 1.01-2.88 | 0.05 |
| Stage2 | 2.16 | 1.16-4.03 | 0.01 |
| Stage3 | 2.18 | 1.18-4.03 | 0.01 |
| Stage4 | 4.28 | 1.73-10.6 | <0.01 |
| Smoke (yes) | 1.21 | 0.61-2.39 | 0.58 |
| *AC005152_3* normal | 183563299.2 | 0-Inf | 0.99 |
| *AC005152_3* amplification | 0.43 | 0.01-19.03 | 0.66 |
| *SLC39A11* normal | 0.01 | 0-0.23 | 0.01 |
| *SLC39A11* amplification | 1.02 | 0.04-25.16 | 0.99 |
| *KCNJ2_AS1* normal | 0 | 0-Inf | 0.99 |
| *KCNJ2_AS1* amplification | 1.53 | 0.15-15.96 | 0.72 |
| *MOB2* normal | 1.41 | 0.82-2.43 | 0.22 |
| *MOB2* amplification | 1.67 | 0.83-3.38 | 0.15 |
| *TP53* mutation | 0.99 | 0.6-1.63 | 0.98 |
| *MUC16* mutation | 1.13 | 0.69-1.85 | 0.63 |
| *CSMD3* mutation | 0.98 | 0.55-1.72 | 0.93 |
| *LRP1B* mutation | 0.66 | 0.37-1.17 | 0.16 |
| *ZFHX4* mutation | 0.7 | 0.39-1.23 | 0.21 |
| *KEAP1* mutation | 0.52 | 0.28-0.97 | 0.04 |
| *COL11A1* mutation | 1.73 | 0.93-3.19 | 0.08 |
| *RYR3* mutation | 0.75 | 0.4-1.43 | 0.38 |
| *APOB* mutation | 0.53 | 0.24-1.16 | 0.11 |
| *NLRP3* mutation | 0.89 | 0.42-1.89 | 0.76 |
| *COL22A1* mutation | 3.09 | 1.54-6.18 | <0.01 |
| *TNN* mutation | 0.95 | 0.47-1.92 | 0.88 |
| *FAM47B* mutation | 0.75 | 0.31-1.77 | 0.51 |
| *DNAH3* mutation | 1.01 | 0.42-2.45 | 0.98 |
| *FMN2* mutation | 0.95 | 0.48-1.9 | 0.89 |
| *PKD1L1* mutation | 1.04 | 0.42-2.57 | 0.94 |
| *TRPS1* mutation | 2.63 | 1.13-6.09 | 0.02 |
| *HYDIN* mutation | 1.03 | 0.41-2.61 | 0.95 |
| *SMARCA4* mutation | 1.1 | 0.47-2.57 | 0.83 |
| *KCNU1* mutation | 2.31 | 0.91-5.88 | 0.08 |
| *ERBB4* mutation | 0.58 | 0.18-1.82 | 0.35 |
| *RBP3* mutation | 1.61 | 0.64-4.02 | 0.31 |
| *PCDHB5* mutation | 0.69 | 0.28-1.7 | 0.42 |
| *BSN* mutation | 0.92 | 0.34-2.51 | 0.87 |
| *SCN1A* mutation | 1.42 | 0.44-4.52 | 0.56 |
| *MTCL1* mutation | 0.75 | 0.28-1.99 | 0.57 |
| *RGPD4* mutation | 1.11 | 0.38-3.31 | 0.84 |
| *USP9X* mutation | 1.66 | 0.43-6.4 | 0.46 |
| *POTEG* mutation | 0 | 0-Inf | 0.99 |

Inf, Infinity. CI, confidence interval.