

**Table S1. The clinicopathological characteristics of the TCGA and ICGC cohorts**

| Variables                      | TCGA<br>N(%) | ICGC<br>N(%) |
|--------------------------------|--------------|--------------|
| <b>Age</b>                     |              |              |
| <60                            | 53(30.64)    | 39(22.41)    |
| ≥60                            | 120(69.36)   | 134(77.01)   |
| Missing                        | 0(0.00)      | 1(0.57)      |
| <b>Sex</b>                     |              |              |
| Male                           | 95(54.91)    | 93(53.45)    |
| Female                         | 78(45.09)    | 81(46.55)    |
| <b>Race</b>                    |              |              |
| Asian                          | 12(6.94)     | NA           |
| African American               | 6(3.47)      | NA           |
| White                          | 151(87.28)   | NA           |
| Missing                        | 4(2.31)      | NA           |
| <b>Tumor Location</b>          |              |              |
| Head                           | 128(73.99)   | NA           |
| Body & Tail                    | 27(15.61)    | NA           |
| Overlapping                    | 18(10.40)    | NA           |
| <b>T Stage</b>                 |              |              |
| T1-T2                          | 25(14.45)    | 24(13.79)    |
| T3-T4                          | 147(84.97)   | 144(82.76)   |
| Missing                        | 1(0.58)      | 6(3.45)      |
| <b>N Stage</b>                 |              |              |
| N0                             | 46(26.59)    | 45(25.86)    |
| N1                             | 124(71.68)   | 122(70.11)   |
| NX                             | 3(1.73)      | 7(4.02)      |
| <b>M Stage</b>                 |              |              |
| M0                             | 80(46.24)    | 3(1.72)      |
| M1                             | 5(2.89)      | 8(4.60)      |
| MX                             | 88(50.87)    | 163(93.68)   |
| <b>Histologic Grade</b>        |              |              |
| G1-G2                          | 119(68.79)   | 113(64.94)   |
| G3-G4                          | 52(30.06)    | 55(31.61)    |
| GX                             | 2(1.16)      | 6(3.45)      |
| <b>Maximum Tumor Dimension</b> |              |              |
| <4cm                           | 92(53.18)    | NA           |
| ≥4cm                           | 67(38.73)    | NA           |
| Missing                        | 14(8.09)     | NA           |

TCGA, The Cancer Genome Atlas; ICGC, International Cancer Genome Consortium; NA, not applicable.

**Table S2. The clinicopathological characteristics of 291 PDAC patients in the PUMCH cohort**

| <b>Variables</b>        | <b>N(%)</b> |
|-------------------------|-------------|
| <b>Age</b>              |             |
| <60                     | 126(43.30)  |
| ≥60                     | 165(56.70)  |
| <b>Sex</b>              |             |
| Male                    | 160(54.98)  |
| Female                  | 131(45.02)  |
| <b>Histologic Grade</b> |             |
| G1-G2                   | 182(62.54)  |
| G3-G4                   | 109(37.46)  |
| <b>Tumor Location</b>   |             |
| Head                    | 178(61.17)  |
| Body & Tail             | 113(38.83)  |
| <b>PNI</b>              |             |
| No                      | 96(32.99)   |
| Yes                     | 195(67.01)  |
| <b>LVI</b>              |             |
| No                      | 182(62.54)  |
| Yes                     | 109(37.46)  |
| <b>T Stage</b>          |             |
| T1-T2                   | 213(73.20)  |
| T3-T4                   | 78(26.80)   |
| <b>M Stage</b>          |             |
| M0                      | 281(96.56)  |
| M1                      | 10(3.44)    |

PNI, perineural invasion; LVI, lymphovascular invasion.

Table S3. Details of 6 probes located in PD-L1/PD-L2

| Probe      | chr  | pos     | strand | Address  | Type | Islands_Name         | Relation_to_Island | RefGene_Name | RefGene_Accession | RefGene_Group | Regulatory_Feature              |
|------------|------|---------|--------|----------|------|----------------------|--------------------|--------------|-------------------|---------------|---------------------------------|
| cg02823866 | chr9 | 5450410 | -      | 6691157  | II   | chr9:5450409-5450629 | Island             | CD274        | NM_014143         | TSS200        | Promoter Associated             |
| cg19724470 | chr9 | 5450936 | +      | 86696312 | II   | chr9:5450409-5450629 | S_Shore            | CD274        | NM_014143         | 5'UTR         | Promoter Associated             |
| cg14351952 | chr9 | 5515324 | +      | 97619110 | II   | NA                   | OpenSea            | PDCD1LG2     | NM_025239         | 5'UTR         | NA                              |
| cg14374994 | chr9 | 5543782 | +      | 22666921 | II   | NA                   | OpenSea            | PDCD1LG2     | NM_025239         | Body          | NA                              |
| cg07211259 | chr9 | 5510497 | -      | 89663916 | II   | NA                   | OpenSea            | PDCD1LG2     | NM_025239         | TSS200        | Unclassified Cell type specific |
| cg14133064 | chr9 | 5530115 | +      | 30610977 | II   | NA                   | OpenSea            | PDCD1LG2     | NM_025239         | Body          | NA                              |

NA, not applicable.

Table S4. Association of cg17924470, cg02823866, cg14351952, cg14374994, cg07211259, and cg14133064 methylation subgroups with clinicopathological characteristics in the ICGC cohort

| Variables        | N   | PD-L1      |           |          |            |           |          | PD-L2      |           |          |            |           |          |            |           |          |            |           |          |
|------------------|-----|------------|-----------|----------|------------|-----------|----------|------------|-----------|----------|------------|-----------|----------|------------|-----------|----------|------------|-----------|----------|
|                  |     | cg02823866 |           |          | cg19724470 |           |          | cg14351952 |           |          | cg14374994 |           |          | cg07211259 |           |          | cg14133064 |           |          |
|                  |     | Hyper      | Hypo      | <i>p</i> | Hyper      | Hypo      | <i>p</i> | Hyper      | Hypo      | <i>p</i> | Hyper      | Hypo      | <i>p</i> | Hyper      | Hypo      | <i>p</i> | Hyper      | Hypo      | <i>p</i> |
| Age              |     |            |           | 0.857    |            |           | 0.104    |            |           | 0.467    |            |           | 0.589    |            |           | 0.716    |            |           | 0.207    |
| <60              | 39  | 19(48.72)  | 20(51.28) |          | 24(61.54)  | 15(38.46) |          | 22(56.41)  | 17(43.59) |          | 21(53.85)  | 18(46.15) |          | 18(46.15)  | 21(53.85) |          | 16(41.03)  | 23(58.97) |          |
| ≥60              | 134 | 68(50.75)  | 66(49.25) |          | 62(46.27)  | 72(53.73) |          | 65(48.51)  | 69(51.49) |          | 65(48.51)  | 69(51.49) |          | 68(50.75)  | 66(49.25) |          | 71(52.99)  | 63(47.01) |          |
| Missing          | 1   | 0(0.00)    | 1(100.00) |          | 1(100)     | 0(0.00)   |          | 0(0%)      | 1(100.00) |          | 1(100.00)  | 0(0.00)   |          | 1(100.00)  | 0(0.00)   |          | 0(0.00)    | 1(100.00) |          |
| Sex              |     |            |           | 0.181    |            |           | 0.034    |            |           | 0.181    |            |           | 0.381    |            |           | 0.381    |            |           | 0.064    |
| Male             | 93  | 43(46.24)  | 50(53.76) |          | 53(56.99)  | 40(43.01) |          | 50(53.76)  | 43(46.24) |          | 45(48.39)  | 48(51.61) |          | 45(48.39)  | 48(51.61) |          | 52(55.91)  | 41(44.09) |          |
| Female           | 81  | 44(54.32)  | 37(45.68) |          | 34(41.98)  | 47(58.02) |          | 37(45.68)  | 44(54.32) |          | 42(51.85)  | 39(48.15) |          | 42(51.85)  | 39(48.15) |          | 35(43.21)  | 46(56.79) |          |
| T Stage          |     |            |           | 0.537    |            |           | 0.685    |            |           | 0.275    |            |           | 1        |            |           | 0.275    |            |           | 0.275    |
| T1-T2            | 24  | 10(41.67)  | 14(58.33) |          | 10(41.67)  | 14(58.33) |          | 13(54.17)  | 11(45.83) |          | 12(50.00)  | 12(50.00) |          | 13(54.17)  | 11(45.83) |          | 13(54.17)  | 11(45.83) |          |
| T3-T4            | 144 | 73(50.69)  | 71(49.31) |          | 74(51.39)  | 70(48.61) |          | 73(50.69)  | 71(49.31) |          | 72(50.00)  | 72(50.00) |          | 73(50.69)  | 71(49.31) |          | 73(50.69)  | 71(49.31) |          |
| Missing          | 6   | 4(66.67)   | 2(33.33)  |          | 3(50.00)   | 3(50.00)  |          | 1(16.67)   | 5(83.33)  |          | 3(50.00)   | 3(50.00)  |          | 1(16.67)   | 5(83.33)  |          | 1(16.67)   | 5(83.33)  |          |
| N Stage          |     |            |           | 0.52     |            |           | 0.78     |            |           | 0.041    |            |           | 0.714    |            |           | 0.439    |            |           | 0.52     |
| N0               | 45  | 21(46.67)  | 24(53.33) |          | 24(53.33)  | 21(46.67) |          | 28(62.22)  | 17(37.78) |          | 25(55.56)  | 20(44.44) |          | 21(46.67)  | 24(53.33) |          | 24(53.33)  | 21(46.67) |          |
| N1               | 122 | 61(50.00)  | 61(50.00) |          | 59(48.36)  | 63(51.64) |          | 58(47.54)  | 64(52.46) |          | 59(48.36)  | 63(51.64) |          | 64(52.46)  | 58(47.54) |          | 61(50.00)  | 61(50.00) |          |
| NX & Missing     | 7   | 5(71.43)   | 2(28.57)  |          | 4(57.14)   | 3(42.86)  |          | 1(14.29)   | 6(85.71)  |          | 3(42.86)   | 4(57.14)  |          | 2(28.57)   | 5(71.43)  |          | 2(28.57)   | 5(71.43)  |          |
| M Stage          |     |            |           | 0.789    |            |           | 0.455    |            |           | 0.455    |            |           | 0.62     |            |           | 0.169    |            |           | 0.294    |
| M0               | 3   | 1(33.33)   | 2(66.67)  |          | 2(66.67)   | 1(33.33)  |          | 1(33.33)   | 2(66.67)  |          | 1(33.33)   | 2(66.67)  |          | 0(0.00)    | 3(100.00) |          | 0(0.00)    | 3(100.00) |          |
| M1               | 8   | 5(62.50)   | 3(37.50)  |          | 2(25.00)   | 6(75.00)  |          | 6(75.00)   | 2(25.00)  |          | 3(37.50)   | 5(62.50)  |          | 3(35.50)   | 5(62.50)  |          | 4(50.00)   | 4(50.00)  |          |
| MX & Missing     | 163 | 81(49.69)  | 82(50.31) |          | 83(50.92)  | 80(49.08) |          | 80(49.08)  | 83(50.92) |          | 83(50.92)  | 80(49.08) |          | 84(51.53)  | 79(48.47) |          | 83(50.92)  | 80(49.08) |          |
| Histologic Grade |     |            |           | 1        |            |           | 0.508    |            |           | 0.308    |            |           | 0.167    |            |           | 0.002    |            |           | 0.284    |
| G1-G2            | 113 | 56(49.56)  | 57(50.44) |          | 53(46.90)  | 60(53.10) |          | 58(51.33)  | 55(48.67) |          | 58(51.33)  | 55(48.67) |          | 67(59.29)  | 46(40.71) |          | 57(50.44)  | 56(49.56) |          |
| G3-G4            | 55  | 28(50.91)  | 27(49.09) |          | 31(56.36)  | 24(43.64) |          | 28(50.91)  | 27(49.09) |          | 24(43.64)  | 31(56.36) |          | 18(32.73)  | 37(67.27) |          | 29(52.73)  | 26(47.27) |          |
| GX & Missing     | 6   | 3(50.00)   | 3(50.00)  |          | 3(50.00)   | 3(50.00)  |          | 1(16.67)   | 5(83.33)  |          | 5(83.33)   | 1(16.17)  |          | 2(33.33)   | 4(66.67)  |          | 1(16.67)   | 5(83.33)  |          |

PD-L1, programmed cell death ligand 1; PD-L2, programmed cell death ligand 2.

*p* values < 0.05 are bolded.

Table S5. Association of cg17924470, cg02823866, cg14351952, cg14374994, cg07211259, and cg14133064 methylation subgroups with clinicopathological characteristics in the TCGA cohort

| Variables               | N   | PD-L1      |           |       |            |           |       | PD-L2      |           |       |            |           |       |            |           |       |            |           |       |
|-------------------------|-----|------------|-----------|-------|------------|-----------|-------|------------|-----------|-------|------------|-----------|-------|------------|-----------|-------|------------|-----------|-------|
|                         |     | cg02823866 |           |       | cg19724470 |           |       | cg14351952 |           |       | cg14374994 |           |       | cg07211259 |           |       | cg14133064 |           |       |
|                         |     | Hyper      | Hypo      | p     | Hyper      | Hypo      | p     | Hyper      | Hypo      | p     | Hyper      | Hypo      | p     | Hyper      | Hypo      | p     | Hyper      | Hypo      | p     |
| Age                     |     |            |           | 0.657 |            |           | 0.125 |            |           | 0.381 |            |           | 0.83  |            |           | 0.439 |            |           | 0.381 |
| <60                     | 53  | 25(47.17)  | 28(52.83) |       | 31(59.49)  | 22(41.51) |       | 29(54.72)  | 24(45.28) |       | 27(50.94)  | 26(49.06) |       | 24(45.28)  | 29(54.72) |       | 29(54.72)  | 24(45.28) |       |
| ≥60                     | 120 | 61(50.83)  | 59(49.17) |       | 55(45.83)  | 65(54.17) |       | 57(47.50)  | 63(52.50) |       | 59(49.17)  | 61(50.83) |       | 62(51.67)  | 58(48.33) |       | 57(47.50)  | 63(52.50) |       |
| Sex                     |     |            |           | 0.013 |            |           | 0.759 |            |           | 0.11  |            |           | 0.2   |            |           | 0.396 |            |           | 0.813 |
| Male                    | 95  | 55(57.89)  | 40(42.11) |       | 46(48.42)  | 49(51.58) |       | 42(44.21)  | 53(55.79) |       | 43(45.26)  | 52(54.74) |       | 50(52.63)  | 45(47.37) |       | 48(50.53)  | 47(49.47) |       |
| Female                  | 78  | 31(39.74)  | 47(60.26) |       | 40(51.28)  | 38(48.72) |       | 44(56.41)  | 34(43.59) |       | 43(55.13)  | 35(44.87) |       | 36(46.15)  | 42(53.85) |       | 38(48.72)  | 40(51.28) |       |
| Race                    |     |            |           | 0.726 |            |           | 0.591 |            |           | 0.207 |            |           | 0.244 |            |           | 0.044 |            |           | 0.591 |
| Asian                   | 12  | 7(58.33)   | 5(41.67)  |       | 7(58.33)   | 5(41.67)  |       | 6(50.00)   | 6(50.00)  |       | 5(41.67)   | 7(58.33)  |       | 10(83.33)  | 2(16.67)  |       | 5(41.67)   | 7(58.33)  |       |
| African American        | 6   | 3(50.00)   | 3(50.00)  |       | 2(33.33)   | 4(66.67)  |       | 2(33.33)   | 4(66.67)  |       | 3(50.00)   | 3(50.00)  |       | 4(66.67)   | 2(33.33)  |       | 4(66.67)   | 2(33.33)  |       |
| White                   | 151 | 73(48.34)  | 78(51.66) |       | 74(49.01)  | 77(50.99) |       | 74(49.01)  | 77(50.99) |       | 74(49.01)  | 77(50.99) |       | 71(47.02)  | 80(52.98) |       | 74(49.01)  | 77(50.99) |       |
| Missing                 | 4   | 3(75.00)   | 1(25.00)  |       | 3(75.00)   | 1(25.00)  |       | 4(100.00)  | 0(0.00)   |       | 4(100.00)  | 0(0.00)   |       | 1(25.00)   | 3(75.00)  |       | 3(75.00)   | 1(25.00)  |       |
| Tumor Location          |     |            |           | 0.315 |            |           | 0.338 |            |           | 0.286 |            |           | 0.296 |            |           | 0.593 |            |           | 0.822 |
| Head                    | 128 | 60(46.88)  | 68(53.13) |       | 61(47.66)  | 67(52.34) |       | 60(46.88)  | 68(53.13) |       | 62(48.44)  | 66(51.56) |       | 65(50.78)  | 63(49.22) |       | 62(48.44)  | 66(51.56) |       |
| Body & Tail             | 27  | 17(62.96)  | 10(37.04) |       | 13(48.15)  | 14(51.85) |       | 14(51.85)  | 13(48.15) |       | 12(44.44)  | 15(55.56) |       | 11(40.74)  | 16(59.26) |       | 14(51.85)  | 13(48.15) |       |
| Overlapping             | 18  | 9(50.00)   | 9(50.00)  |       | 12(66.67)  | 6(33.33)  |       | 12(66.67)  | 6(33.33)  |       | 12(66.67)  | 6(33.33)  |       | 10(55.56)  | 8(44.44)  |       | 10(55.56)  | 8(44.44)  |       |
| T Stage                 |     |            |           | 0.336 |            |           | 1     |            |           | 0.748 |            |           | 0.748 |            |           | 0.107 |            |           | 0.239 |
| T1-T2                   | 25  | 10(40.00)  | 15(60.00) |       | 12(48.00)  | 13(52.00) |       | 13(52.00)  | 12(48.00) |       | 13(52.00)  | 12(48.00) |       | 16(64.00)  | 9(36.00)  |       | 15(60.00)  | 10(40.00) |       |
| T3-T4                   | 147 | 76(51.70)  | 71(48.30) |       | 73(49.66)  | 74(50.34) |       | 72(48.98)  | 75(51.02) |       | 72(48.98)  | 75(51.02) |       | 69(46.94)  | 78(53.06) |       | 70(47.62)  | 77(52.38) |       |
| Missing                 | 1   | 0(0.00)    | 1(100.00) |       | 1(100.00)  | 0(0.00)   |       | 1(100.00)  | 0(0.00)   |       | 1(100.00)  | 0(0.00)   |       | 1(100.00)  | 0(0.00)   |       | 1(100.00)  | 0(0.00)   |       |
| N Stage                 |     |            |           | 0.897 |            |           | 0.948 |            |           | 0.659 |            |           | 0.897 |            |           | 0.749 |            |           | 0.417 |
| N0                      | 46  | 22(47.83)  | 24(52.17) |       | 23(50.00)  | 23(50.00) |       | 21(45.65)  | 25(54.35) |       | 22(47.83)  | 24(52.17) |       | 24(52.17)  | 22(47.83) |       | 19(41.30)  | 27(58.70) |       |
| N1                      | 124 | 62(50.00)  | 62(50.00) |       | 61(49.19)  | 63(50.81) |       | 64(51.61)  | 60(48.39) |       | 62(50.00)  | 62(50.00) |       | 60(48.39)  | 64(51.61) |       | 65(52.42)  | 59(47.58) |       |
| NX                      | 3   | 2(66.67)   | 1(33.33)  |       | 2(66.67)   | 1(33.33)  |       | 1(33.33)   | 2(66.67)  |       | 2(66.67)   | 1(33.33)  |       | 2(66.67)   | 1(33.33)  |       | 2(66.67)   | 1(33.33)  |       |
| M Stage                 |     |            |           | 0.676 |            |           | 0.546 |            |           | 0.396 |            |           | 0.885 |            |           | 0.885 |            |           | 0.741 |
| M0                      | 80  | 42(52.50)  | 38(47.50) |       | 36(45.00)  | 44(55.00) |       | 39(48.75)  | 41(51.25) |       | 41(51.25)  | 39(48.75) |       | 41(51.25)  | 39(48.75) |       | 42(52.50)  | 38(47.50) |       |
| M1                      | 5   | 3(60.00)   | 2(40.00)  |       | 3(60.00)   | 2(40.00)  |       | 1(20.00)   | 4(80.00)  |       | 2(40.00)   | 3(60.00)  |       | 2(40.00)   | 3(60.00)  |       | 2(40.00)   | 3(60.00)  |       |
| MX                      | 88  | 41(46.59)  | 47(53.41) |       | 47(53.41)  | 41(46.59) |       | 46(52.27)  | 42(47.73) |       | 43(48.86)  | 45(51.14) |       | 43(48.86)  | 45(51.14) |       | 42(47.73)  | 46(52.27) |       |
| Histologic Grade        |     |            |           | 0.491 |            |           | 0.271 |            |           | 0.808 |            |           | 0.702 |            |           | 0.555 |            |           | 0.374 |
| G1-G2                   | 119 | 61(51.26)  | 58(48.74) |       | 61(51.26)  | 58(48.74) |       | 61(51.26)  | 58(48.74) |       | 62(52.10)  | 57(47.90) |       | 59(49.58)  | 60(50.42) |       | 58(48.74)  | 61(51.26) |       |
| FG3-G4                  | 52  | 25(48.08)  | 27(51.92) |       | 23(44.23)  | 29(55.77) |       | 24(46.15)  | 28(53.85) |       | 23(44.23)  | 29(55.77) |       | 25(48.08)  | 27(51.92) |       | 28(53.85)  | 24(46.15) |       |
| GX                      | 2   | 0(0.00)    | 2(100.00) |       | 2(100.00)  | 0(0.00)   |       | 1(50.00)   | 1(50.00)  |       | 1(50.00)   | 1(50.00)  |       | 2(100.00)  | 0(0.00)   |       | 0(0.00)    | 2(100.00) |       |
| Maximum Tumor Dimension |     |            |           | 0.675 |            |           | 0.098 |            |           | 0.373 |            |           | 0.778 |            |           | 0.267 |            |           | 0.972 |
| <4cm                    | 92  | 43(46.74)  | 49(53.26) |       | 48(52.17)  | 44(47.83) |       | 42(45.65)  | 50(54.35) |       | 44(47.83)  | 48(52.17) |       | 50(54.35)  | 42(45.65) |       | 45(48.91)  | 47(51.09) |       |
| ≥4cm                    | 67  | 35(52.24)  | 32(47.76) |       | 33(49.25)  | 34(50.75) |       | 35(52.24)  | 32(47.76) |       | 34(50.75)  | 33(49.25) |       | 28(41.79)  | 39(58.21) |       | 34(50.75)  | 33(49.25) |       |
| Missing                 | 14  | 8(57.14)   | 6(42.86)  |       | 5(35.71)   | 9(64.29)  |       | 9(64.29)   | 5(35.71)  |       | 8(57.14)   | 6(42.86)  |       | 8(57.14)   | 6(42.86)  |       | 7(50.00)   | 7(50.00)  |       |

PD-L1, programmed cell death ligand 1; PD-L2, programmed cell death ligand 2.

*p* values < 0.05 are bolded.

**Table S6. Univariate Cox analysis of cg17924470, cg02823866, cg14351952, cg14374994, cg07211259, and cg14133064 from the TCGA and ICGC cohorts**

| Gene  | methylation loci<br>(low vs high expression) | TCGA              |              | ICGC             |              |
|-------|----------------------------------------------|-------------------|--------------|------------------|--------------|
|       |                                              | HR(95%CI)         | <i>p</i>     | HR(95%CI)        | <i>p</i>     |
| PD-L1 | cg02823866                                   | 0.933 (0.62-1.41) | 0.743        | 1.23 (0.91-1.67) | 0.175        |
|       | cg19724470                                   | 1.92 (1.25-2.95)  | <b>0.003</b> | 1.14 (0.84-1.54) | 0.405        |
|       | cg14351952                                   | 1.14 (0.58-1.33)  | 0.537        | 1.00 (0.74-1.35) | 0.988        |
| PD-L2 | cg14374994                                   | 1.10 (0.60-1.38)  | 0.657        | 0.95 (0.70-1.28) | 0.716        |
|       | cg07211259                                   | 1.40 (0.92-2.13)  | 0.121        | 1.62 (1.19-2.19) | <b>0.002</b> |
|       | cg14133064                                   | 0.99 (0.67-1.53)  | 0.944        | 1.19 (0.88-1.61) | 0.254        |

PD-L1, programmed cell death ligand 1; PD-L2, programmed cell death ligand 2; TCGA, The Cancer Genome Atlas; ICGC, International Cancer Genome Consortium; HR, hazard ratio; CI, confidence interval.

*p* values < 0.05 are bolded.

**Table S7. Univariate Cox analysis of clinicopathological characteristics from the TCGA and ICGC cohorts**

| Variables              | TCGA               |              | ICGC               |                  |
|------------------------|--------------------|--------------|--------------------|------------------|
|                        | HR(95%CI)          | <i>p</i>     | HR(95%CI)          | <i>p</i>         |
| <b>Age</b>             |                    |              |                    |                  |
| <60                    | reference          |              | reference          |                  |
| ≥60                    | 1.32 (0.82 - 2.13) | 0.246        | 0.96 (0.67 - 1.37) | 0.820            |
| <b>Sex</b>             |                    |              |                    |                  |
| Female                 | reference          |              | reference          |                  |
| Male                   | 0.75 (0.49 - 1.13) | 0.172        | 1.22 (0.90 - 1.66) | 0.196            |
| <b>Grade</b>           |                    |              |                    |                  |
| G1-G2                  | reference          |              | reference          |                  |
| G3-G4                  | 1.31 (0.85 - 2.03) | 0.213        | 1.98 (1.41 - 2.79) | <b>&lt;0.001</b> |
| GX                     | 0.89 (0.12 - 6.51) | 0.915        | 2.75 (1.19 - 6.38) | <b>0.018</b>     |
| <b>T Stage</b>         |                    |              |                    |                  |
| T1-T2                  | reference          |              | reference          |                  |
| T3-T4                  | 1.16 (0.61 - 2.18) | 0.657        | 1.62 (1.03 - 2.57) | <b>0.038</b>     |
| TX                     | NA                 |              | 3.64 (1.45 - 9.16) | <b>0.006</b>     |
| <b>N Stage</b>         |                    |              |                    |                  |
| N0                     | reference          |              | reference          |                  |
| N1                     | 1.76 (1.05 - 2.96) | <b>0.031</b> | 1.11 (0.79 - 1.57) | 0.548            |
| NX                     | NA                 |              | 2.99 (1.33 - 6.73) | <b>0.008</b>     |
| <b>M Stage</b>         |                    |              |                    |                  |
| M0                     | reference          |              | reference          |                  |
| M1                     | 0.72 (0.17 - 2.98) | 0.648        | 0.68 (0.18 - 2.59) | 0.577            |
| MX                     | 1.05 (0.69 - 1.60) | 0.803        | 0.38 (0.12 - 1.19) | 0.096            |
| <b>Tumor Location</b>  |                    |              |                    |                  |
| Head                   | reference          |              | NA                 |                  |
| Body & tail            | 0.61 (0.31 - 1.20) | 0.151        | NA                 |                  |
| Overlapping            | 1.06 (0.57 - 1.96) | 0.858        | NA                 |                  |
| <b>Tumor Dimension</b> |                    |              |                    |                  |
| <4cm                   | reference          |              | NA                 |                  |
| ≥4cm                   | 1.28 (0.84 - 1.95) | 0.254        | NA                 |                  |
| Missing                | 0.40 (0.12 - 1.30) | 0.129        | NA                 |                  |

TCGA, The Cancer Genome Atlas; ICGC, International Cancer Genome Consortium; HR, hazard ratio; CI, confidence interval; NA, not applicable.

*p* values < 0.05 are bolded.

**Table S8. Association of cg17924470 methylation and PD-L1 expression with clinicopathological characteristics in the PUMCH cohort**

| Variables               | N   | cg17924470 |            | <i>p</i>         | PD-L1 expression |            | <i>p</i>         |
|-------------------------|-----|------------|------------|------------------|------------------|------------|------------------|
|                         |     | Hyper      | Hypo       |                  | Positive         | Negative   |                  |
| <b>Age</b>              |     |            |            | 0.235            |                  |            | 0.898            |
| <60                     | 126 | 30(23.81)  | 96(76.19)  |                  | 37(29.37)        | 89(70.63)  |                  |
| ≥60                     | 165 | 50(30.30)  | 115(69.70) |                  | 50(30.30)        | 115(69.70) |                  |
| <b>Sex</b>              |     |            |            | 0.895            |                  |            | 0.608            |
| Male                    | 160 | 43(26.88)  | 117(73.13) |                  | 50(31.25)        | 110(68.75) |                  |
| Female                  | 131 | 37(28.24)  | 94(71.76)  |                  | 37(28.24)        | 94(71.76)  |                  |
| <b>Histologic Grade</b> |     |            |            | <b>0.031</b>     |                  |            | 0.186            |
| G1-G2                   | 182 | 58(31.87)  | 124(68.13) |                  | 49(26.92)        | 133(73.08) |                  |
| G3-G4                   | 109 | 22(20.18)  | 87(79.82)  |                  | 38(34.86)        | 71(65.14)  |                  |
| <b>Tumor Location</b>   |     |            |            | 0.429            |                  |            | 0.359            |
| Head                    | 178 | 46(25.84)  | 132(74.16) |                  | 57(32.02)        | 121(67.98) |                  |
| Body&Tail               | 113 | 34(30.09)  | 79(69.91)  |                  | 30(26.55)        | 83(73.45)  |                  |
| <b>PNI</b>              |     |            |            | 0.314            |                  |            | 0.414            |
| No                      | 96  | 30(31.25)  | 66(68.75)  |                  | 32(33.33)        | 64(66.67)  |                  |
| Yes                     | 195 | 50(25.64)  | 145(74.36) |                  | 55(28.21)        | 140(71.79) |                  |
| <b>LVI</b>              |     |            |            | 0.684            |                  |            | 0.512            |
| No                      | 182 | 52(28.57)  | 130(71.43) |                  | 57(31.32)        | 125(68.68) |                  |
| Yes                     | 109 | 28(25.69)  | 81(74.31)  |                  | 30(27.52)        | 79(72.48)  |                  |
| <b>T Stage</b>          |     |            |            | 1                |                  |            | 0.885            |
| T1-T2                   | 213 | 59(27.70)  | 154(72.30) |                  | 63(29.58)        | 150(70.42) |                  |
| T3-T4                   | 78  | 21(26.92)  | 57(73.08)  |                  | 24(30.77)        | 54(69.23)  |                  |
| <b>N Stage</b>          |     |            |            | <b>&lt;0.001</b> |                  |            | <b>&lt;0.001</b> |
| N0                      | 103 | 58(56.31)  | 45(43.69)  |                  | 17(16.50)        | 86(83.50)  |                  |
| N1-N2                   | 169 | 16(9.47)   | 153(90.53) |                  | 63(37.28)        | 106(62.72) |                  |
| <b>M Stage</b>          |     |            |            | 1                |                  |            | 0.728            |
| M0                      | 281 | 77(27.40)  | 204(72.60) |                  | 85(30.25)        | 196(69.75) |                  |
| M1                      | 10  | 3(30.00)   | 7(70.00)   |                  | 2(20.00)         | 8(80.00)   |                  |

PNI, perineural invasion; LVI, lymphovascular invasion; PD-L1, programmed cell death ligand 1.  
*p* values < 0.05 are bolded.

**Table S9. Univariate Cox analysis of cg19724470 methylation, PD-L1 expression and clinicopathological characteristics in the PUMCH cohort**

| Variables             | HR(95%CI)          | <i>p</i>     |
|-----------------------|--------------------|--------------|
| <b>Age</b>            |                    |              |
| <60                   | reference          |              |
| ≥60                   | 1.17 (0.87 - 1.59) | 0.304        |
| <b>Sex</b>            |                    |              |
| Female                | reference          |              |
| Male                  | 1.34 (0.99 - 1.82) | 0.0559       |
| <b>LVI</b>            |                    |              |
| No                    | reference          |              |
| Yes                   | 1.21 (0.89 - 1.65) | 0.214        |
| <b>PNI</b>            |                    |              |
| No                    | reference          |              |
| Yes                   | 1.15 (0.83 - 1.58) | 0.41         |
| <b>AJCC</b>           |                    |              |
| I-III                 | reference          |              |
| IV                    | 2.44 (1.24 - 4.79) | <b>0.010</b> |
| <b>Tumor Location</b> |                    |              |
| Head                  | reference          |              |
| Body & tail           | 0.63 (0.46 - 0.87) | <b>0.004</b> |
| <b>cg19724470</b>     |                    |              |
| hypermethylation      | reference          |              |
| hypomethylation       | 1.53 (1.07-2.18)   | <b>0.018</b> |
| <b>PD-L1 (TC)</b>     |                    |              |
| ≤1%                   | reference          |              |
| >1%                   | 1.44 (1.05 - 1.96) | <b>0.024</b> |

LVI: lymphovascular invasion; PNI: perineural invasion; AJCC, American Joint Committee on Cancer; PD-L1, programmed cell death ligand 1; TC, tumor cell; HR, hazard ratio; CI, confidence interval.

*p* values < 0.05 are bolded.