

**Supplementary table 1.** Tumour CD274 expression in the cytoplasm and membrane in colorectal carcinoma

|                           | Total No.<br>(n=823) | Cytoplasmic expression level |              |              |             | <i>P</i> value* |
|---------------------------|----------------------|------------------------------|--------------|--------------|-------------|-----------------|
|                           |                      | 0<br>(n=92)                  | 1<br>(n=249) | 2<br>(n=432) | 3<br>(n=50) |                 |
| Membrane expression level |                      |                              |              |              |             | <0.0001         |
| 0                         | 534 (65%)            | 92 (100%)                    | 234 (94%)    | 201 (47%)    | 7 (14%)     |                 |
| 1                         | 289 (35%)            | 0 (0%)                       | 15 (6%)      | 231 (53%)    | 43 (86%)    |                 |

\* *P* value was calculated by the chi-square test.

**Supplementary table 2.** Clinical, pathological, and tumour molecular features according to CD274 expression in stromal cells

| Characteristic  | Total No.<br>(n=823) | CD274 expression in<br>stromal cells |                   | P value* |
|---|----------------------|--------------------------------------|-------------------|----------|
|   |                      | Absent<br>(n=779)                    | Present<br>(n=44) |          |
| Mean age±SD (yr)  | 69.1±9.0             | 69.0±9.0                             | 70.8±8.4          | 0.18     |
| Sex   |                      |                                      |                   | 0.87     |
| Men   | 365 (44%)            | 346 (44%)                            | 19 (43%)          |          |
| Women   | 458 (56%)            | 433 (56%)                            | 25 (57%)          |          |
| Year of diagnosis   |                      |                                      |                   | 0.99     |
| Prior to 1999   | 407 (50%)            | 385 (50%)                            | 22 (50%)          |          |
| 1999 to 2008  | 408 (50%)            | 386 (50%)                            | 22 (50%)          |          |
| Family history of colorectal<br>cancer in a first-degree relative |                      |                                      |                   | 0.27     |
| Absent  | 642 (79%)            | 610 (80%)                            | 32 (73%)          |          |
| Present   | 168 (21%)            | 156 (20%)                            | 12 (27%)          |          |
| Tumour location   |                      |                                      |                   | 0.52     |
| Proximal colon  | 412 (50%)            | 387 (50%)                            | 25 (57%)          |          |
| Distal colon  | 242 (30%)            | 229 (30%)                            | 13 (30%)          |          |
| Rectum  | 163 (20%)            | 157 (20%)                            | 6 (14%)           |          |
| pT stage  |                      |                                      |                   | 0.62     |
| pT1   | 74 (10%)             | 69 (10%)                             | 5 (12%)           |          |
| pT2   | 150 (20%)            | 139 (19%)                            | 11 (26%)          |          |
| pT3   | 496 (65%)            | 470 (66%)                            | 26 (60%)          |          |
| pT4   | 38 (5%)              | 37 (5%)                              | 1 (2%)            |          |
| pN stage  |                      |                                      |                   | 0.33     |
| pN0   | 450 (61%)            | 424 (61%)                            | 26 (62%)          |          |
| pN1   | 180 (25%)            | 167 (24%)                            | 13 (31%)          |          |
| pN2   | 102 (14%)            | 99 (14%)                             | 3 (7%)            |          |
| M stage   |                      |                                      |                   | 0.24     |
| M0  | 641 (84%)            | 602 (84%)                            | 39 (91%)          |          |
| M1  | 118 (16%)            | 114 (16%)                            | 4 (9%)            |          |
| Disease stage   |                      |                                      |                   | 0.45     |
| I   | 175 (23%)            | 162 (23%)                            | 13 (30%)          |          |
| II  | 245 (32%)            | 233 (33%)                            | 12 (28%)          |          |
| III   | 221 (29%)            | 207 (29%)                            | 14 (33%)          |          |
| IV  | 118 (16%)            | 114 (16%)                            | 4 (9%)            |          |

|                               |           |           |          |       |
|-------------------------------|-----------|-----------|----------|-------|
| No. of negative lymph nodes   |           |           |          | 0.66  |
| 0-4                           | 159 (23%) | 152 (24%) | 7 (20%)  |       |
| 5-8                           | 156 (23%) | 145 (23%) | 11 (31%) |       |
| 9-14                          | 178 (26%) | 169 (26%) | 9 (26%)  |       |
| ≥15                           | 185 (27%) | 177 (28%) | 8 (23%)  |       |
| Tumour differentiation        |           |           |          | 0.040 |
| Well to moderate              | 744 (91%) | 708 (91%) | 36 (82%) |       |
| Poor                          | 77 (9%)   | 69 (9%)   | 8 (18%)  |       |
| Extent of extracellular mucin |           |           |          | 0.62  |
| 0%                            | 482 (60%) | 454 (59%) | 28 (67%) |       |
| 1-50%                         | 238 (29%) | 228 (27%) | 10 (24%) |       |
| ≥50%                          | 90 (11%)  | 86 (11%)  | 4 (10%)  |       |
| Extent of signet ring cells   |           |           |          | 0.75  |
| 0%                            | 714 (88%) | 675 (88%) | 39 (93%) |       |
| 1-50%                         | 87 (11%)  | 84 (11%)  | 3 (7%)   |       |
| ≥50%                          | 8 (1%)    | 8 (1%)    | 0 (0%)   |       |
| Extent of solid tumour areas  |           |           |          | 0.77  |
| 0%                            | 583 (83%) | 550 (82%) | 33 (85%) |       |
| 1-50%                         | 96 (14%)  | 92 (14%)  | 4 (10%)  |       |
| ≥50%                          | 27 (4%)   | 25 (4%)   | 2 (5%)   |       |
| Tumour growth pattern         |           |           |          | 0.17  |
| Expansile                     | 216 (29%) | 208 (30%) | 8 (22%)  |       |
| Intermediate                  | 413 (56%) | 387 (55%) | 26 (70%) |       |
| Infiltrative                  | 113 (15%) | 110 (16%) | 3 (8%)   |       |
| MSI status                    |           |           |          | 0.05  |
| MSI-low/MSS                   | 663 (83%) | 632 (84%) | 31 (72%) |       |
| MSI-high                      | 136 (17%) | 124 (16%) | 12 (28%) |       |
| CIMP status                   |           |           |          | 0.024 |
| Low/negative                  | 622 (83%) | 595 (83%) | 27 (69%) |       |
| High                          | 131 (17%) | 119 (17%) | 12 (31%) |       |
| <i>BRAF</i> mutation          |           |           |          | 0.12  |
| Wild-type                     | 683 (85%) | 650 (86%) | 33 (77%) |       |
| Mutant                        | 120 (15%) | 110 (14%) | 10 (23%) |       |
| <i>KRAS</i> mutation          |           |           |          | 0.27  |
| Wild-type                     | 475 (59%) | 446 (59%) | 29 (67%) |       |
| Mutant                        | 324 (41%) | 310 (41%) | 14 (33%) |       |

|                                      |           |           |          |      |
|--------------------------------------|-----------|-----------|----------|------|
| <i>PIK3CA</i> mutation               |           |           |          | 0.56 |
| Wild-type                            | 641 (85%) | 609 (85%) | 32 (82%) |      |
| Mutant                               | 111 (15%) | 104 (15%) | 7 (18%)  |      |
| Mean LINE-1 methylation level±SD (%) | 62.3±9.7  | 62.2±9.8  | 62.9±8.1 | 0.68 |
| <i>Fusobacterium nucleatum</i> DNA   |           |           |          | 0.59 |
| Negative                             | 574 (87%) | 543 (86%) | 31 (89%) |      |
| Low                                  | 45 (7%)   | 44 (7%)   | 1 (3%)   |      |
| High                                 | 44 (7%)   | 41 (7%)   | 3 (9%)   |      |

Abbreviations: CIMP, CpG island methylator phenotype; LINE-1, long interspersed nucleotide element-1; MSI, microsatellite instability; MSS, microsatellite stable; SD, standard deviation.

\* Percentage indicates the proportion of cases with a specific clinical, pathological, or molecular feature in colorectal cancer cases with each tumour CD274 expression score category. There were cases that had missing values for any of the characteristics except for age and sex.

† To assess associations between the presence of CD274-expressing stromal cells and categorical variables (except for the extents of signet ring cells and solid tumour areas, for which Fisher's exact test was performed), the chi-square test was performed. To compare mean age and mean LINE-1 methylation levels, an analysis of variance was performed. We adjusted two-sided  $\alpha$  level to 0.002 ( $=0.05/22$ ) by simple Bonferroni correction for multiple hypothesis testing.

**Supplementary table 3.** Clinical, pathological, and molecular features according to the tumour CD274 expression score in 823 colorectal cancer cases

| Characteristic*  | Total No.<br>(n=823) | Tumour CD274 expression score |              |              |              |             | P value† |
|--|----------------------|-------------------------------|--------------|--------------|--------------|-------------|----------|
|  |                      | 0<br>(n=92)                   | 1<br>(n=234) | 2<br>(n=216) | 3<br>(n=238) | 4<br>(n=43) |          |
| Mean age±SD (yr)   | 69.1 ± 9.0           | 69.9 ± 9.5                    | 68.8 ± 8.8   | 70.4 ± 9.1   | 68.0 ± 9.0   | 68.8 ± 7.9  | 0.05     |
| Sex  |                      |                               |              |              |              |             | 0.08     |
| Men  | 365 (44%)            | 45 (49%)                      | 106 (45%)    | 103 (48%)    | 100 (42%)    | 11 (26%)    |          |
| Women  | 458 (56%)            | 47 (51%)                      | 128 (55%)    | 113 (52%)    | 138 (58%)    | 32 (74%)    |          |
| Year of diagnosis  |                      |                               |              |              |              |             | 0.004    |
| Prior to 1999  | 407 (50%)            | 41 (45%)                      | 115 (50%)    | 89 (41%)     | 139 (59%)    | 23 (53%)    |          |
| 1999 to 2008   | 408 (50%)            | 50 (55%)                      | 115 (50%)    | 127 (59%)    | 96 (41%)     | 20 (47%)    |          |
| Family history of colorectal cancer in a first-degree relative |                      |                               |              |              |              |             | 0.90     |
| Absent   | 642 (79%)            | 73 (80%)                      | 180 (79%)    | 174 (81%)    | 184 (79%)    | 31 (74%)    |          |
| Present  | 168 (21%)            | 18 (20%)                      | 48 (21%)     | 42 (19%)     | 49 (21%)     | 11 (26%)    |          |
| Tumour location  |                      |                               |              |              |              |             | 0.15     |
| Proximal colon   | 412 (50%)            | 42 (46%)                      | 128 (55%)    | 105 (49%)    | 115 (49%)    | 22 (51%)    |          |
| Distal colon   | 242 (30%)            | 22 (24%)                      | 58 (25%)     | 69 (32%)     | 79 (33%)     | 14 (33%)    |          |
| Rectum   | 163 (20%)            | 28 (30%)                      | 45 (19%)     | 40 (19%)     | 43 (18%)     | 7 (16%)     |          |
| pT stage   |                      |                               |              |              |              |             | 0.15     |
| pT1  | 74 (10%)             | 16 (19%)                      | 26 (10%)     | 17 (8%)      | 12 (6%)      | 3 (7%)      |          |
| pT2  | 150 (20%)            | 17 (20%)                      | 38 (18%)     | 44 (21%)     | 45 (21%)     | 6 (14%)     |          |
| pT3  | 496 (65%)            | 47 (55%)                      | 138 (65%)    | 134 (65%)    | 146 (69%)    | 31 (74%)    |          |
| pT4  | 38 (5%)              | 5 (6%)                        | 11 (5%)      | 11 (5%)      | 9 (4%)       | 2 (5%)      |          |
| pN stage   |                      |                               |              |              |              |             | 0.13     |
| pN0  | 450 (61%)            | 52 (67%)                      | 133 (65%)    | 126 (62%)    | 122 (59%)    | 17 (43%)    |          |
| pN1  | 180 (25%)            | 16 (21%)                      | 46 (22%)     | 43 (21%)     | 58 (28%)     | 17 (43%)    |          |
| pN2  | 102 (14%)            | 10 (13%)                      | 26 (13%)     | 33 (16%)     | 27 (13%)     | 6 (15%)     |          |
| M stage  |                      |                               |              |              |              |             | 0.36     |
| M0   | 641 (84%)            | 73 (91%)                      | 178 (84%)    | 173 (85%)    | 185 (83%)    | 32 (78%)    |          |
| M1   | 118 (16%)            | 7 (9%)                        | 34 (16%)     | 31 (15%)     | 37 (17%)     | 9 (22%)     |          |
| Disease stage  |                      |                               |              |              |              |             | 0.22     |
| I  | 175 (23%)            | 23 (29%)                      | 52 (25%)     | 47 (23%)     | 49 (22%)     | 4 (10%)     |          |
| II   | 245 (32%)            | 27 (34%)                      | 73 (34%)     | 70 (34%)     | 65 (29%)     | 10 (24%)    |          |
| III  | 221 (29%)            | 23 (29%)                      | 53 (25%)     | 56 (27%)     | 71 (32%)     | 18 (44%)    |          |
| IV   | 118 (16%)            | 7 (9%)                        | 34 (16%)     | 31 (15%)     | 37 (17%)     | 9 (22%)     |          |

|                               |           |          |           |           |           |          |         |
|-------------------------------|-----------|----------|-----------|-----------|-----------|----------|---------|
| No. of negative lymph nodes   |           |          |           |           |           |          | 0.36    |
| 0-4                           | 159 (23%) | 20 (27%) | 47 (25%)  | 39 (21%)  | 46 (23%)  | 7 (22%)  |         |
| 5-8                           | 156 (23%) | 12 (16%) | 39 (21%)  | 48 (26%)  | 48 (24%)  | 9 (28%)  |         |
| 9-14                          | 178 (26%) | 24 (32%) | 47 (25%)  | 39 (21%)  | 57 (29%)  | 11 (34%) |         |
| ≥15                           | 185 (27%) | 19 (25%) | 57 (30%)  | 58 (32%)  | 46 (23%)  | 5 (16%)  |         |
| Tumour differentiation        |           |          |           |           |           |          | 0.11    |
| Well to moderate              | 744 (91%) | 78 (86%) | 209 (90%) | 200 (93%) | 221 (93%) | 36 (84%) |         |
| Poor                          | 77 (9%)   | 13 (14%) | 24 (10%)  | 16 (7%)   | 17 (7%)   | 7 (16%)  |         |
| Extent of extracellular mucin |           |          |           |           |           |          | <0.0001 |
| 0%                            | 482 (60%) | 45 (51%) | 117 (51%) | 132 (62%) | 162 (69%) | 26 (63%) |         |
| 1-50%                         | 238 (29%) | 22 (25%) | 77 (33%)  | 67 (31%)  | 60 (25%)  | 12 (29%) |         |
| ≥50%                          | 90 (11%)  | 22 (25%) | 36 (16%)  | 15 (7%)   | 14 (6%)   | 3 (7%)   |         |
| Extent of signet ring cells   |           |          |           |           |           |          | 0.002   |
| 0%                            | 714 (88%) | 73 (83%) | 191 (83%) | 195 (91%) | 216 (92%) | 39 (95%) |         |
| 1-50%                         | 87 (11%)  | 11 (13%) | 35 (15%)  | 19 (9%)   | 20 (8%)   | 2 (5%)   |         |
| ≥50%                          | 8 (1%)    | 4 (5%)   | 4 (2%)    | 0 (0%)    | 0 (0%)    | 0 (0%)   |         |
| Extent of solid tumour areas  |           |          |           |           |           |          | 0.20    |
| 0%                            | 583 (83%) | 61 (80%) | 160 (78%) | 148 (82%) | 180 (87%) | 34 (94%) |         |
| 1-50%                         | 96 (14%)  | 10 (13%) | 36 (18%)  | 27 (15%)  | 22 (11%)  | 1 (3%)   |         |
| ≥50%                          | 27 (4%)   | 5 (7%)   | 9 (4%)    | 6 (3%)    | 6 (3%)    | 1 (3%)   |         |
| Tumour growth pattern         |           |          |           |           |           |          | 0.25    |
| Expansile                     | 216 (29%) | 33 (41%) | 58 (28%)  | 60 (30%)  | 58 (27%)  | 7 (18%)  |         |
| Intermediate                  | 413 (56%) | 38 (48%) | 122 (58%) | 109 (55%) | 121 (57%) | 23 (59%) |         |
| Infiltrative                  | 113 (15%) | 9 (11%)  | 30 (14%)  | 31 (16%)  | 34 (16%)  | 9 (23%)  |         |
| MSI status                    |           |          |           |           |           |          | 0.006   |
| MSI-low/MSS                   | 663 (83%) | 64 (70%) | 188 (83%) | 170 (83%) | 205 (88%) | 36 (84%) |         |
| MSI-high                      | 136 (17%) | 27 (30%) | 39 (17%)  | 35 (17%)  | 28 (12%)  | 7 (16%)  |         |
| CIMP status                   |           |          |           |           |           |          | 0.09    |
| Low/negative                  | 622 (83%) | 62 (76%) | 176 (83%) | 154 (80%) | 195 (88%) | 35 (81%) |         |
| High                          | 131 (17%) | 20 (24%) | 37 (17%)  | 39 (20%)  | 27 (12%)  | 8 (19%)  |         |
| <i>BRAF</i> mutation          |           |          |           |           |           |          | 0.64    |
| Wild-type                     | 683 (85%) | 77 (84%) | 189 (83%) | 179 (87%) | 203 (87%) | 35 (81%) |         |
| Mutant                        | 120 (15%) | 15 (16%) | 39 (17%)  | 27 (13%)  | 31 (13%)  | 8 (19%)  |         |

|                                      |           |          |           |           |           |          |      |
|--------------------------------------|-----------|----------|-----------|-----------|-----------|----------|------|
| <i>KRAS</i> mutation                 |           |          |           |           |           |          | 0.29 |
| Wild-type                            | 475 (59%) | 64 (70%) | 136 (60%) | 117 (57%) | 132 (57%) | 26 (60%) |      |
| Mutant                               | 324 (41%) | 28 (30%) | 92 (40%)  | 89 (43%)  | 98 (43%)  | 17 (40%) |      |
| <i>PIK3CA</i> mutation               |           |          |           |           |           |          | 0.56 |
| Wild-type                            | 641 (85%) | 74 (86%) | 193 (88%) | 166 (85%) | 177 (83%) | 31 (82%) |      |
| Mutant                               | 111 (15%) | 12 (14%) | 26 (12%)  | 29 (15%)  | 37 (17%)  | 7 (18%)  |      |
| Mean LINE-1 methylation level±SD (%) | 62.3±9.7  | 63.6±9.4 | 62.3±9.8  | 63.2±10.3 | 60.8±9.2  | 62.5±8.8 | 0.06 |
| <i>Fusobacterium nucleatum</i> DNA   |           |          |           |           |           |          | 0.09 |
| Negative                             | 574 (87%) | 60 (77%) | 163 (84%) | 143 (88%) | 172 (89%) | 36 (97%) |      |
| Low                                  | 45 (7%)   | 9 (12%)  | 15 (8%)   | 8 (5%)    | 13 (7%)   | 0 (0%)   |      |
| High                                 | 44 (7%)   | 9 (12%)  | 15 (8%)   | 11 (7%)   | 8 (4%)    | 1 (3%)   |      |

Abbreviations: CIMP, CpG island methylator phenotype; LINE-1, long interspersed nucleotide element-1; MSI, microsatellite instability; MSS, microsatellite stable; SD, standard deviation.

\* Percentage indicates the proportion of cases with a specific clinical, pathological, or molecular feature in colorectal cancer cases with each tumour CD274 expression score. There were cases that had missing values for any of the characteristics except for age and sex.

† To assess associations between the ordinal categories (0 to 4) of the tumour CD274 expression score and categorical data (except for the extents of signet ring cells and solid tumour areas, for which Fisher's exact test was performed), the chi-square test was performed. To compare mean age and mean LINE-1 methylation levels, an analysis of variance was performed. We adjusted two-sided  $\alpha$  level to 0.002 ( $=0.05/22$ ) by simple Bonferroni correction for multiple hypothesis testing.

**Supplementary table 4.** Multivariable ordinal logistic regression model for the density of FOXP3<sup>+</sup> cells

|   |                                       | Multivariable OR<br>(95% CI)* |
|---|---------------------------------------|-------------------------------|
| <b>Model for FOXP3<sup>+</sup> cell density (n=549, as an outcome variable)</b> |                                       |                               |
| Tumour CD274 expression score   | 0                                     | 1 (reference)                 |
|   | 1                                     | 0.46 (0.26-0.82)              |
|   | 2                                     | 0.39 (0.22-0.70)              |
|   | 3                                     | 0.36 (0.21-0.63)              |
|   | 4                                     | 0.22 (0.10-0.47)              |
|   | $P_{\text{trend}}^{\dagger}$          | 0.0002                        |
| Other variable remaining in the final model                                     |                                       |                               |
|   | Year of diagnosis (5 years as a unit) | 1.42 (1.22-1.66)              |

Abbreviations: CI, confidence interval; OR, odds ratio.

\* The multivariable ordinal logistic regression analysis model initially included age, sex, year of diagnosis, family history of colorectal carcinoma in any parent or sibling, tumour location, microsatellite instability, CpG island methylator phenotype, *KRAS*, *BRAF*, and *PIK3CA* mutations, and LINE-1 methylation level. A backward elimination with a threshold of  $P=0.05$  was used to select variables in the final models.

$\dagger P_{\text{trend}}$  value was calculated by the linear trend across the ordinal categories of the tumour CD274 expression score (0 to 4, as an ordinal predictor variable) in the ordinal logistic regression model for the density of FOXP3<sup>+</sup> cells (an ordinal quartile outcome variable).



**Supplementary table 5.** Distribution of colorectal cancer cases according to the tumour CD274 expression score and the densities of T cells

|  | Total No. | Tumour CD274 expression score |          |          |          |          | <i>P</i> value* |
|--|-----------|-------------------------------|----------|----------|----------|----------|-----------------|
|  |           | 0                             | 1        | 2        | 3        | 4        |                 |
| <b>CD3<sup>+</sup> cell density (n=571)</b>    |           |                               |          |          |          |          | 0.39            |
| Low  | 284 (50%) | 28 (50%)                      | 84 (54%) | 61 (42%) | 93 (53%) | 18 (50%) |                 |
| High   | 286 (50%) | 28 (50%)                      | 71 (46%) | 85 (58%) | 84 (47%) | 18 (50%) |                 |
| <b>CD8<sup>+</sup> cell density (n=564)</b>    |           |                               |          |          |          |          | 0.13            |
| Low  | 281 (50%) | 26 (48%)                      | 85 (56%) | 70 (48%) | 85 (48%) | 15 (44%) |                 |
| High   | 282 (50%) | 28 (52%)                      | 68 (44%) | 76 (52%) | 91 (52%) | 19 (56%) |                 |
| <b>CD45RO<sup>+</sup> cell density (n=577)</b> |           |                               |          |          |          |          | 0.031           |
| Low  | 288 (50%) | 31 (55%)                      | 88 (55%) | 73 (50%) | 80 (45%) | 16 (46%) |                 |
| High   | 288 (50%) | 25 (45%)                      | 72 (45%) | 74 (50%) | 98 (55%) | 19 (54%) |                 |
| <b>FOXP3<sup>+</sup> cell density (n=549)</b>  |           |                               |          |          |          |          | <0.0001         |
| Low  | 273 (50%) | 17 (31%)                      | 68 (45%) | 68 (50%) | 97 (57%) | 23 (64%) |                 |
| High   | 275 (50%) | 38 (69%)                      | 82 (55%) | 69 (50%) | 73 (43%) | 13 (36%) |                 |

\* *P* value was calculated by Spearman correlation test between the tumour CD274 expression score (ranging from 0 to 4) and the densities of T cells (cells/mm<sup>2</sup>; as continuous variables). Because we assessed eight primary tumour immunity status variables, we adjusted two-sided  $\alpha$  level to 0.006 (=0.05/8) by simple Bonferroni correction.

**Supplementary table 6.** Logistic regression analysis to assess the association of the tumour CD274 expression score (predictor) with the density of T cells (outcome)

|   |                              | Univariable OR<br>(95% CI) | Multivariable OR<br>(95% CI)* |
|---|------------------------------|----------------------------|-------------------------------|
| <b>Model for CD3<sup>+</sup> cell density (n=571, as a binary outcome variable [Low vs. High])</b>    |                              |                            |                               |
| Tumour CD274 expression score   | 0                            | 1 (reference)              | 1 (reference)                 |
|   | 1                            | 0.85 (0.46-1.56)           | 0.85 (0.46-1.56)              |
|   | 2                            | 1.39 (0.75-2.59)           | 1.39 (0.75-2.59)              |
|   | 3                            | 0.90 (0.50-1.65)           | 0.90 (0.50-1.65)              |
|   | 4                            | 1.00 (0.43-2.31)           | 1.00 (0.43-2.31)              |
|   | $P_{\text{trend}}^{\dagger}$ | 0.88                       | 0.88                          |
| <b>Model for CD8<sup>+</sup> cell density (n=564, as a binary outcome variable [Low vs. High])</b>    |                              |                            |                               |
| Tumour CD274 expression score   | 0                            | 1 (reference)              | 1 (reference)                 |
|   | 1                            | 0.74 (0.40-1.38)           | 0.78 (0.41-1.48)              |
|   | 2                            | 1.01 (0.54-1.88)           | 1.13 (0.59-2.14)              |
|   | 3                            | 0.99 (0.54-1.83)           | 1.04 (0.56-1.96)              |
|   | 4                            | 1.18 (0.50-2.79)           | 1.39 (0.57-3.36)              |
|   | $P_{\text{trend}}^{\dagger}$ | 0.30                       | 0.20                          |
| <b>Model for CD45RO<sup>+</sup> cell density (n=577, as a binary outcome variable [Low vs. High])</b> |                              |                            |                               |
| Tumour CD274 expression score   | 0                            | 1 (reference)              | 1 (reference)                 |
|   | 1                            | 1.12 (0.55-1.87)           | 1.21 (0.64-2.29)              |
|   | 2                            | 1.26 (0.68-2.33)           | 1.54 (0.81-2.94)              |
|   | 3                            | 1.52 (0.83-2.78)           | 1.89 (1.00-3.57)              |
|   | 4                            | 1.47 (0.63-3.44)           | 1.71 (0.71-4.11)              |
|   | $P_{\text{trend}}^{\dagger}$ | 0.05                       | 0.019                         |
| <b>Model for FOXP3<sup>+</sup> cell density (n=549, as a binary outcome variable [Low vs. High])</b>  |                              |                            |                               |
| Tumour CD274 expression score   | 0                            | 1 (reference)              | 1 (reference)                 |
|   | 1                            | 0.54 (0.28-1.04)           | 0.54 (0.28-1.05)              |
|   | 2                            | 0.45 (0.23-0.88)           | 0.41 (0.21-0.80)              |
|   | 3                            | 0.34 (0.18-0.64)           | 0.36 (0.19-0.70)              |
|   | 4                            | 0.25 (0.10-0.62)           | 0.25 (0.10-0.62)              |
|   | $P_{\text{trend}}^{\dagger}$ | 0.0002                     | 0.0005                        |

Abbreviations: CI, confidence interval; OR, odds ratio.

\* The multivariable binary logistic regression analysis model initially included age, sex, year of diagnosis, family history of colorectal carcinoma in any parent or sibling, tumour location, microsatellite instability, CpG island methylator phenotype, *KRAS*, *BRAF*, and *PIK3CA* mutations, and LINE-1 methylation level. A backward elimination with a threshold of  $P=0.05$  was used to select variables in the final models.

$\dagger P_{\text{trend}}$  value was calculated by the linear trend across the ordinal categories of the tumour CD274 expression score (0 to 4, as an ordinal predictor variable) in the binary logistic regression model for the density of CD3<sup>+</sup> cells, CD8<sup>+</sup> cells, CD45RO<sup>+</sup> cells, or FOXP3<sup>+</sup> cells (a binary outcome variable). Because we assessed eight primary outcome variables, we adjusted two-sided  $\alpha$  level to 0.006 (=0.05/8) by simple Bonferroni correction.

**Supplementary table 7.** Clinical, pathological, and molecular features according to PDCD1 (PD-1)<sup>+</sup> cell density in 793 colorectal cancer cases

| Characteristic*  | Total No.<br>(n=793) | PDCD1 <sup>+</sup> cell density |                     |                |                         |                 | P value† |
|--|----------------------|---------------------------------|---------------------|----------------|-------------------------|-----------------|----------|
|  |                      | Absent<br>(n=230)               | Very low<br>(n=194) | Low<br>(n=140) | Intermediate<br>(n=102) | High<br>(n=127) |          |
| Mean age±SD (yr)   | 69.1±9.0             | 69.1±8.7                        | 68.1±9.7            | 68.6±9.6       | 70.4±8.3                | 70.1±7.8        | 0.19     |
| Sex  |                      |                                 |                     |                |                         |                 | 0.90     |
| Men  | 353 (45%)            | 108 (47%)                       | 82 (42%)            | 62 (44%)       | 46 (45%)                | 55 (43%)        |          |
| Women  | 440 (55%)            | 122 (53%)                       | 112 (58%)           | 78 (56%)       | 56 (55%)                | 72 (57%)        |          |
| Year of diagnosis  |                      |                                 |                     |                |                         |                 | 0.79     |
| Prior to 1999  | 391 (50%)            | 117 (52%)                       | 94 (49%)            | 70 (50%)       | 53 (52%)                | 57 (45%)        |          |
| 1999 to 2008   | 394 (50%)            | 110 (48%)                       | 98 (51%)            | 69 (50%)       | 48 (48%)                | 69 (55%)        |          |
| Family history of colorectal cancer in a first-degree relative |                      |                                 |                     |                |                         |                 | 0.71     |
| Absent   | 613 (79%)            | 175 (77%)                       | 156 (82%)           | 109 (79%)      | 79 (79%)                | 94 (75%)        |          |
| Present  | 167 (21%)            | 51 (23%)                        | 35 (18%)            | 29 (21%)       | 21 (21%)                | 31 (25%)        |          |
| Tumour location  |                      |                                 |                     |                |                         |                 | 0.15     |
| Proximal colon   | 400 (51%)            | 112 (49%)                       | 88 (46%)            | 71 (51%)       | 50 (49%)                | 79 (63%)        |          |
| Distal colon   | 237 (30%)            | 71 (31%)                        | 63 (33%)            | 44 (31%)       | 28 (27%)                | 31 (25%)        |          |
| Rectum   | 151 (19%)            | 46 (20%)                        | 41 (21%)            | 25 (18%)       | 24 (24%)                | 15 (12%)        |          |
| pT stage   |                      |                                 |                     |                |                         |                 | 0.45     |
| pT1  | 69 (10%)             | 21 (10%)                        | 13 (13%)            | 17 (13%)       | 8 (8%)                  | 10 (9%)         |          |
| pT2  | 142 (20%)            | 31 (15%)                        | 37 (21%)            | 24 (18%)       | 21 (22%)                | 29 (25%)        |          |
| pT3  | 478 (66%)            | 136 (67%)                       | 124 (69%)           | 85 (64%)       | 63 (66%)                | 70 (61%)        |          |
| pT4  | 37 (5%)              | 15 (7%)                         | 6 (3%)              | 7 (5%)         | 3 (3%)                  | 6 (5%)          |          |
| pN stage   |                      |                                 |                     |                |                         |                 | 0.026    |
| pN0  | 431 (62%)            | 105 (55%)                       | 101 (58%)           | 79 (62%)       | 59 (65%)                | 87 (76%)        |          |
| pN1  | 169 (24%)            | 54 (28%)                        | 45 (26%)            | 29 (23%)       | 23 (25%)                | 18 (16%)        |          |
| pN2  | 100 (14%)            | 33 (17%)                        | 29 (17%)            | 20 (16%)       | 9 (10%)                 | 9 (8%)          |          |
| M stage  |                      |                                 |                     |                |                         |                 | <0.0001  |
| M0   | 608 (84%)            | 150 (74%)                       | 149 (83%)           | 113 (84%)      | 86 (90%)                | 110 (96%)       |          |
| M1   | 119 (16%)            | 52 (26%)                        | 31 (17%)            | 21 (16%)       | 10 (10%)                | 5 (4%)          |          |
| Disease stage  |                      |                                 |                     |                |                         |                 | 0.0003   |
| I  | 165 (23%)            | 37 (18%)                        | 40 (22%)            | 32 (24%)       | 23 (24%)                | 33 (29%)        |          |
| II   | 236 (32%)            | 55 (27%)                        | 54 (30%)            | 41 (31%)       | 35 (36%)                | 51 (44%)        |          |
| III  | 207 (28%)            | 58 (29%)                        | 55 (31%)            | 40 (30%)       | 28 (29%)                | 26 (23%)        |          |
| IV   | 119 (16%)            | 52 (26%)                        | 31 (17%)            | 21 (16%)       | 10 (10%)                | 5 (4%)          |          |

|                               |           |           |           |           |          |           |         |
|-------------------------------|-----------|-----------|-----------|-----------|----------|-----------|---------|
| No. of negative lymph nodes   |           |           |           |           |          |           | 0.33    |
| 0-4                           | 151 (23%) | 45 (25%)  | 47 (30%)  | 24 (20%)  | 18 (23%) | 17 (15%)  |         |
| 5-8                           | 148 (23%) | 43 (24%)  | 33 (21%)  | 26 (21%)  | 17 (21%) | 29 (25%)  |         |
| 9-14                          | 172 (26%) | 40 (22%)  | 42 (27%)  | 37 (31%)  | 20 (25%) | 33 (29%)  |         |
| ≥15                           | 181 (28%) | 53 (29%)  | 34 (22%)  | 34 (28%)  | 25 (31%) | 35 (31%)  |         |
| Tumour differentiation        |           |           |           |           |          |           | 0.15    |
| Well to moderate              | 717 (91%) | 209 (91%) | 181 (94%) | 128 (91%) | 87 (85%) | 112 (88%) |         |
| Poor                          | 74 (9%)   | 20 (9%)   | 12 (6%)   | 12 (9%)   | 15 (15%) | 15 (12%)  |         |
| Extent of extracellular mucin |           |           |           |           |          |           | 0.35    |
| 0%                            | 465 (60%) | 126 (56%) | 118 (61%) | 91 (70%)  | 65 (64%) | 65 (52%)  |         |
| 1-50%                         | 231 (30%) | 69 (31%)  | 53 (28%)  | 35 (25%)  | 28 (27%) | 46 (37%)  |         |
| ≥50%                          | 85 (11%)  | 30 (13%)  | 21 (11%)  | 12 (9%)   | 9 (9%)   | 13 (10%)  |         |
| Extent of signet ring cells   |           |           |           |           |          |           | 0.14    |
| 0%                            | 685 (88%) | 186 (83%) | 176 (92%) | 123 (89%) | 91 (89%) | 109 (88%) |         |
| 1-50%                         | 87 (11%)  | 33 (15%)  | 16 (8%)   | 13 (9%)   | 10 (10%) | 15 (12%)  |         |
| ≥50%                          | 8 (1%)    | 5 (2%)    | 0 (0%)    | 2 (1%)    | 1 (1%)   | 0 (0%)    |         |
| Extent of solid tumour areas  |           |           |           |           |          |           | 0.23    |
| 0%                            | 565 (83%) | 161 (83%) | 141 (86%) | 107 (86%) | 72 (80%) | 84 (76%)  |         |
| 1-50%                         | 92 (13%)  | 29 (15%)  | 18 (11%)  | 12 (10%)  | 12 (13%) | 21 (19%)  |         |
| ≥50%                          | 26 (4%)   | 4 (2%)    | 5 (3%)    | 5 (4%)    | 6 (7%)   | 6 (5%)    |         |
| Tumour growth pattern         |           |           |           |           |          |           | 0.0006  |
| Expansile                     | 204 (29%) | 55 (27%)  | 60 (34%)  | 33 (25%)  | 21 (23%) | 35 (31%)  |         |
| Intermediate                  | 399 (56%) | 102 (50%) | 85 (48%)  | 85 (65%)  | 56 (62%) | 71 (63%)  |         |
| Infiltrative                  | 112 (16%) | 47 (23%)  | 32 (18%)  | 13 (10%)  | 13 (14%) | 7 (6%)    |         |
| MSI status                    |           |           |           |           |          |           | <0.0001 |
| MSI-low/MSS                   | 642 (83%) | 204 (90%) | 165 (87%) | 116 (87%) | 77 (79%) | 80 (65%)  |         |
| MSI-high                      | 128 (17%) | 22 (10%)  | 24 (13%)  | 18 (13%)  | 20 (21%) | 44 (35%)  |         |
| CIMP status                   |           |           |           |           |          |           | <0.0001 |
| Low/negative                  | 600 (83%) | 186 (89%) | 159 (88%) | 113 (86%) | 66 (75%) | 76 (66%)  |         |
| High                          | 124 (17%) | 23 (11%)  | 22 (12%)  | 18 (14%)  | 22 (25%) | 39 (34%)  |         |
| <i>BRAF</i> mutation          |           |           |           |           |          |           | 0.039   |
| Wild-type                     | 661 (86%) | 201 (88%) | 164 (87%) | 117 (87%) | 85 (86%) | 94 (76%)  |         |
| Mutant                        | 112 (14%) | 27 (12%)  | 24 (13%)  | 18 (13%)  | 14 (14%) | 29 (24%)  |         |

|  |                |                |                 |                |                |                |         |
|--|----------------|----------------|-----------------|----------------|----------------|----------------|---------|
| <i>KRAS</i> mutation                       |                |                |                 |                |                |                | 0.07    |
| Wild-type                                  | 452 (59%)      | 128 (56%)      | 108 (57%)       | 72 (54%)       | 58 (60%)       | 86 (70%)       |         |
| Mutant                                     | 318 (41%)      | 100 (44%)      | 81 (43%)        | 62 (46%)       | 38 (40%)       | 37 (30%)       |         |
| <i>PIK3CA</i> mutation                     |                |                |                 |                |                |                | 0.22    |
| Wild-type                                  | 617 (85%)      | 176 (84%)      | 158 (87%)       | 102 (79%)      | 80 (89%)       | 101 (86%)      |         |
| Mutant                                     | 110 (15%)      | 34 (16%)       | 23 (13%)        | 27 (21%)       | 10 (11%)       | 16 (14%)       |         |
| Mean LINE-1 methylation level $\pm$ SD (%) | 62.3 $\pm$ 9.7 | 61.8 $\pm$ 9.3 | 61.2 $\pm$ 10.6 | 62.0 $\pm$ 9.0 | 62.3 $\pm$ 9.6 | 64.9 $\pm$ 9.1 | 0.014   |
| <i>Fusobacterium nucleatum</i> DNA         |                |                |                 |                |                |                | 0.85    |
| Negative                                   | 558 (87%)      | 159 (86%)      | 137 (88%)       | 105 (90%)      | 67 (85%)       | 90 (87%)       |         |
| Low  | 42 (7%)        | 15 (8%)        | 10 (6%)         | 4 (3%)         | 7 (9%)         | 6 (6%)         |         |
| High                                       | 40 (6%)        | 11 (6%)        | 8 (5%)          | 8 (7%)         | 5 (6%)         | 8 (8%)         |         |
| Tumour CD274 expression score              |                |                |                 |                |                |                | <0.0001 |
| 0  | 80 (10%)       | 35 (16%)       | 23 (12%)        | 8 (6%)         | 5 (5%)         | 9 (7%)         |         |
| 1  | 220 (28%)      | 75 (33%)       | 55 (29%)        | 39 (28%)       | 25 (25%)       | 26 (21%)       |         |
| 2  | 207 (27%)      | 46 (20%)       | 54 (28%)        | 38 (28%)       | 17 (17%)       | 52 (41%)       |         |
| 3  | 231 (30%)      | 60 (27%)       | 54 (28%)        | 38 (28%)       | 46 (45%)       | 33 (26%)       |         |
| 4  | 42 (5%)        | 9 (4%)         | 4 (2%)          | 14 (10%)       | 9 (21%)        | 6 (5%)         |         |

Abbreviations: CIMP, CpG island methylator phenotype; LINE-1, long interspersed nucleotide element-1; MSI, microsatellite instability; MSS, microsatellite stable; SD, standard deviation.

\* Percentage indicates the proportion of cases with a specific clinical, pathological, or molecular feature in colorectal cancer cases with each PDCD1<sup>+</sup> cell density. There were cases that had missing values for any of the characteristics except for age and sex.

† To assess associations between the ordinal categories of PDCD1<sup>+</sup> cell density and categorical data (except for the extents of signet ring cells and solid tumour areas, for which Fisher's exact test was performed), the chi-square test was performed. To compare mean age and mean LINE-1 methylation levels, an analysis of variance was performed. We adjusted two-sided  $\alpha$  level to 0.002 (=0.05/23) by simple Bonferroni correction for multiple hypothesis testing.

**Supplementary table 8.** CD274 expression in stromal cells and colorectal cancer patient mortality

| CD274 expression in stromal cells | Total No. | Colorectal cancer-specific mortality |                         | Overall mortality          |               |                         |                            |
|-----------------------------------|-----------|--------------------------------------|-------------------------|----------------------------|---------------|-------------------------|----------------------------|
|                                   |           | No. of events                        | Univariable HR (95% CI) | Multivariable HR (95% CI)* | No. of events | Univariable HR (95% CI) | Multivariable HR (95% CI)* |
| Absent                            | 771       | 238                                  | 1 (reference)           | 1 (reference)              | 429           | 1 (reference)           | 1 (reference)              |
| Present                           | 44        | 8                                    | 0.54 (0.27-1.09)        | 0.60 (0.29-1.22)           | 21            | 0.77 (0.50-1.19)        | 0.70 (0.45-1.09)           |
| <i>P</i> value                    |           |                                      | 0.08                    | 0.16                       |               | 0.24                    | 0.11                       |

Abbreviations: CI, confidence interval; HR, hazard risk.

\* The multivariable Cox regression model initially included age, sex, year of diagnosis, family history of colorectal carcinoma in any parent or sibling, tumour location, disease stage, microsatellite instability, CpG island methylator phenotype, *KRAS*, *BRAF*, and *PIK3CA* mutations, and LINE-1 methylation level. A backward stepwise elimination with a threshold of  $P=0.05$  was used to select variables in the final models.

**Supplementary table 9.** T-cell density and colorectal cancer mortality according to tumour CD274 expression level

|  | Total<br>No. | Colorectal cancer-specific mortality |                            |                               | Overall mortality   |                            |                               |
|--|--------------|--------------------------------------|----------------------------|-------------------------------|---------------------|----------------------------|-------------------------------|
|  |              | No.<br>of<br>events                  | Univariable HR<br>(95% CI) | Multivariable HR<br>(95% CI)* | No.<br>of<br>events | Univariable HR<br>(95% CI) | Multivariable HR<br>(95% CI)* |
| Tumour with low-level CD274 expression (tumour CD274 expression score 0/1/2) |              |                                      |                            |                               |                     |                            |                               |
| CD3 <sup>+</sup> cell density  |              |                                      |                            |                               |                     |                            |                               |
| Low  | 172          | 54                                   | 1 (reference)              | 1 (reference)                 | 103                 | 1 (reference)              | 1 (reference)                 |
| High   | 183          | 52                                   | 0.87 (0.59-1.27)           | 0.88 (0.60-1.28)              | 101                 | 0.92 (0.70-1.21)           | 0.88 (0.67-1.16)              |
| <i>P</i> value   |              |                                      | 0.47                       | 0.50                          |                     | 0.55                       | 0.37                          |
| Tumour with high-level CD274 expression (tumour CD274 expression score 3/4)  |              |                                      |                            |                               |                     |                            |                               |
| CD3 <sup>+</sup> cell density  |              |                                      |                            |                               |                     |                            |                               |
| Low  | 111          | 41                                   | 1 (reference)              | 1 (reference)                 | 72                  | 1 (reference)              | 1 (reference)                 |
| High   | 101          | 27                                   | 0.70 (0.43-1.13)           | 0.63 (0.38-1.04)              | 54                  | 0.77 (0.54-1.10)           | 0.81 (0.56-1.17)              |
| <i>P</i> value   |              |                                      | 0.14                       | 0.07                          |                     | 0.15                       | 0.26                          |
| <i>P</i> <sub>interaction</sub> †  |              |                                      | 0.26                       | 0.11                          |                     | 0.34                       | 0.35                          |
| Tumour with low-level CD274 expression (tumour CD274 expression score 0/1/2) |              |                                      |                            |                               |                     |                            |                               |
| CD8 <sup>+</sup> cell density  |              |                                      |                            |                               |                     |                            |                               |
| Low  | 180          | 58                                   | 1 (reference)              | 1 (reference)                 | 107                 | 1 (reference)              | 1 (reference)                 |
| High   | 171          | 47                                   | 0.82 (0.56-1.20)           | 0.88 (0.60-1.30)              | 92                  | 0.82 (0.62-1.08)           | 0.78 (0.59-1.04)              |
| <i>P</i> value   |              |                                      | 0.31                       | 0.51                          |                     | 0.15                       | 0.09                          |
| Tumour with high-level CD274 expression (tumour CD274 expression score 3/4)  |              |                                      |                            |                               |                     |                            |                               |
| CD8 <sup>+</sup> cell density  |              |                                      |                            |                               |                     |                            |                               |
| Low  | 99           | 42                                   | 1 (reference)              | 1 (reference)                 | 64                  | 1 (reference)              | 1 (reference)                 |
| High   | 110          | 28                                   | 0.53 (0.33-0.86)           | 0.59 (0.36-0.98)              | 59                  | 0.66 (0.46-0.94)           | 0.70 (0.48-1.02)              |
| <i>P</i> value   |              |                                      | 0.010                      | 0.042                         |                     | 0.022                      | 0.06                          |
| <i>P</i> <sub>interaction</sub> †  |              |                                      | 0.15                       | 0.17                          |                     | 0.30                       | 0.74                          |

|  |     |    |                  |                  |     |                  |                  |
|--|-----|----|------------------|------------------|-----|------------------|------------------|
| Tumour with low-level CD274 expression (tumour CD274 expression score 0/1/2) |     |    |                  |                  |     |                  |                  |
| CD45RO <sup>+</sup> cell density   |     |    |                  |                  |     |                  |                  |
| Low  | 192 | 69 | 1 (reference)    | 1 (reference)    | 119 | 1 (reference)    | 1 (reference)    |
| High   | 169 | 40 | 0.64 (0.43-0.94) | 0.62 (0.42-0.92) | 89  | 0.80 (0.61-1.05) | 0.77 (0.58-1.01) |
| <i>P</i> value   |     |    | 0.023            | 0.016            |     | 0.11             | 0.06             |
| Tumour with high-level CD274 expression (tumour CD274 expression score 3/4)  |     |    |                  |                  |     |                  |                  |
| CD45RO <sup>+</sup> cell density   |     |    |                  |                  |     |                  |                  |
| Low  | 95  | 34 | 1 (reference)    | 1 (reference)    | 57  | 1 (reference)    | 1 (reference)    |
| High   | 117 | 33 | 0.75 (0.46-1.21) | 0.95 (0.59-1.55) | 69  | 0.89 (0.62-1.23) | 0.96 (0.66-1.38) |
| <i>P</i> value   |     |    | 0.24             | 0.85             |     | 0.51             | 0.80             |
| <i>P</i> <sub>interaction</sub> <sup>†</sup>                                 |     |    | 0.91             | 0.59             |     | 0.60             | 0.43             |
| Tumour with low-level CD274 expression (tumour CD274 expression score 0/1/2) |     |    |                  |                  |     |                  |                  |
| FOXP3 <sup>+</sup> cell density  |     |    |                  |                  |     |                  |                  |
| Low  | 152 | 61 | 1 (reference)    | 1 (reference)    | 107 | 1 (reference)    | 1 (reference)    |
| High   | 188 | 38 | 0.44 (0.29-0.65) | 0.52 (0.35-0.79) | 85  | 0.53 (0.40-0.70) | 0.59 (0.44-0.78) |
| <i>P</i> value   |     |    | <0.0001          | 0.002            |     | <0.0001          | 0.0003           |
| Tumour with high-level CD274 expression (tumour CD274 expression score 3/4)  |     |    |                  |                  |     |                  |                  |
| FOXP3 <sup>+</sup> cell density  |     |    |                  |                  |     |                  |                  |
| Low  | 119 | 45 | 1 (reference)    | 1 (reference)    | 80  | 1 (reference)    | 1 (reference)    |
| High   | 86  | 20 | 0.53 (0.31-0.90) | 0.50 (0.29-0.85) | 39  | 0.58 (0.40-0.86) | 0.54 (0.36-0.80) |
| <i>P</i> value   |     |    | 0.018            | 0.011            |     | 0.006            | 0.002            |
| <i>P</i> <sub>interaction</sub> <sup>†</sup>                                 |     |    | 0.42             | 0.46             |     | 0.71             | 0.53             |

Abbreviations: CI, confidence interval; HR, hazard risk.

\* The multivariable stage-stratified Cox regression model initially included age, sex, year of diagnosis, family history of colorectal carcinoma in any parent or sibling, tumour location, disease stage, microsatellite instability, CpG island methylator phenotype, *KRAS*, *BRAF*, and *PIK3CA* mutations, and LINE-1 methylation level. A backward stepwise elimination with a threshold of  $P=0.05$  was used to select variables in the final models.

<sup>†</sup>  $P_{\text{interaction}}$  value (two-sided) was calculated by the Wald test on the cross-product term of the tumour CD274 expression score (ordinal categories ranging from 0 to 4) and each T-cell density variable (ordinal quartile categories) in a Cox proportional hazards regression model.