		Cytoplasmic expression level							
	Total No.	Total No. 0 1 2 3							
	(n=823)	(n=92)	(n=249)	(n=432)	(n=50)	P value*			
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%)				

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

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

		CD274 exp	pression in	
	Total No	Absent	Present	
Characteristic	(n=823)	(n=779)	(n=44)	P value*
Mean age+SD (vr)	<u>69.1+9.0</u>	<u>69.0+9.0</u>	70.8+8.4	0.18
(ji)	0,11_,10	0,10_,10	/0.0_011	0.10
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				0.27
cancer in a first-degree relative	(42)(700/)	(200)	22(720/)	
Absent	042(79%)	610(80%)	32(73%)	
Present	168 (21%)	156 (20%)	12(27%)	
Tumour location				0.52
Proximal colon	412 (50%)	387 (50%)	25 (57%)	0.02
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%)	
рТ3	496 (65%)	470 (66%)	26 (60%)	
PT4	38 (5%)	37 (5%)	1 (2%)	
pN stage				0.33
pN0	450 (61%)	424 (61%)	26 (62%)	
pNI	180 (25%)	167 (24%)	13 (31%)	
pN2	102 (14%)	99 (14%)	3 (7%)	
M stage				0.24
MO	641 (84%)	602 (84%)	39 (91%)	0.24
M1	118(16%)	114(16%)	$\frac{37(9170)}{4(9\%)}$	
1721	110(10/0)	117(10/0)	· (270)	
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%)	

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

No. of pagetive lymph pades				0.66
No. of negative lymph nodes	150 (020/)	150 (040/)	7 (2001)	0.00
0-4	159 (23%)	152 (24%)	/ (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%)	0.75
1-50%	87 (11%)	84 (11%)	3(7%)	
>50%	$\frac{3}{8}(1\%)$	8(10)	0(0%)	
<u>~</u> JU/0	0 (170)	σ(170)	U (U70)	
Extent of solid tumour areas	502 (0201)	550 (0 2 01)	22 (050()	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%)	
men	131 (1770)	117(17/0)	12 (3170)	
BRAF mutation	(02 (050))			0.12
wild-type	683 (85%)	650 (86%)	33 (77%)	
Mutant	120 (15%)	110(14%)	10 (23%)	
KRAS 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
Fusobacterium nucleatum 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 α level to 0.002 (=0.05/22) by simple Bonferroni correction for multiple hypothesis testing.

	Tumour CD274 expression score						
	Total No.	0	1	2	3	4	-
Characteristic*	(n=823)	(n=92)	(n=234)	(n=216)	(n=238)	(n=43)	P value†
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
a							0.00
Sex	265 (140)	45 (400())	106 (150/)	102 (400/)	100 (400()	11 (2001)	0.08
Men	365 (44%)	45 (49%)	106 (45%)	103 (48%)	100 (42%)	11 (26%)	
women	438 (36%)	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							0.90
first-degree relative							
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%)	0110
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%)	
nN stage							0.13
nN0	450 (61%)	52 (67%)	133 (65%)	126 (62%)	122 (59%)	17 (43%)	0.15
nN1	180(25%)	16(21%)	46(22%)	43(21%)	58 (28%)	17(43%) 17(43%)	
nN2	100(25%) 102(14%)	10(21%) 10(13%)	26(13%)	$\frac{43}{210}$	27 (13%)	6(15%)	
p112	102 (1470)	10 (1370)	20 (1370)	33 (10/0)	27 (1370)	0(1370)	
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 Iscase stage	175 (23%)	23(200)	57 (25%)	17 (73%)	19 (22%)	(10%)	0.22
I II	173(23%) 245(22%)	23 (27%) 27 (21%)	52(25%) 73(210%)	(23%)	47 (22%) 65 (20%)	+(10%) 10(24%)	
III	2+3(3270) 221(200%)	27(3470) 23(200%)	73 (3470) 53 (75%)	56(34%)	(23%)	10(2470) 18(110(2)	
IV	221(2770) 118(1604)	23(2970) 7(0%)	33(2370) 34(160)	30(2770) 31(1504)	71(3270) 37(170%)	Q(770)	
1 V	110(10%)	1 (970)	J 4 (1070)	51 (1570)	$J_{1}(170)$	7 (2270)	

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

No. ot legative 0^{4} 159 (23%) 20 (27%) 47 (25%) 39 (21%) 46 (23%) 7 (22%) 5-8 156 (23%) 12 (16%) 39 (21%) 58 (22%) 47 (25%) 39 (21%) 57 (29%) 11 (34%) ≥15 185 (27%) 19 (25%) 57 (30%) 58 (32%) 46 (23%) 5 (16%) 0.11 Umour differentiation 744 (91%) 78 (86%) 209 (90%) 200 (93%) 221 (93%) 36 (84%) 0.11 Vell to moderate 744 (91%) 78 (86%) 209 (90%) 200 (93%) 221 (93%) 36 (84%) 0.0001 extracellular mucin 0% 482 (60%) 45 (51%) 117 (51%) 132 (62%) 162 (69%) 26 (63%) 20 (002 250% 90 (11%) 22 (25%) 36 (16%) 15 (7%) 14 (6%) 37 (7%) 20 (0%) 2 (0%) 2 (5%) 2 (0%)									
$ \begin{array}{ $	No. of negative							0.36	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	lymph nodes							0.00	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	0-4	159 (23%)	20 (27%)	47 (25%)	39 (21%)	46 (23%)	7 (22%)		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	5-8	156 (23%)	12 (16%)	39 (21%)	48 (26%)	48 (24%)	9 (28%)		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	9-14	178 (26%)	24 (32%)	47 (25%)	39 (21%)	57 (29%)	11 (34%)		
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	≥15	185 (27%)	19 (25%)	57 (30%)	58 (32%)	46 (23%)	5 (16%)		
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Tumour								
$ \begin{array}{c} \text{Altreemation} \\ \text{Well to moderate} \\ \text{Poor} \\ \hline \text{Poor} \\ \hline \text{T7} (9\%) \\ \text{13} (14\%) \\ 24 (10\%) \\ 24 (10\%) \\ 16 (7\%) \\ 17 (7\%) \\ 17 (7\%) \\ 17 (7\%) \\ 7 (16\%) \\ \hline \text{T7} (3\%) \\ 17 (7\%) \\ 7 (16\%) \\ \hline \text{Column 1} \\ $								0.11	
Well to moderate Poor744 (91%) 77 (9%)78 (80%) 13 (14%)209 (90%) 24 (10%)200 (93%) 16 (7%)221 (93%) 17 (7%)36 (84%) 7 (16%)Extent of extracellular mucin<	<	differentiation					001 (000)	$2 \leq \langle 0, 40 \rangle$	
Poor 77 (9%) 13 (14%) 24 (10%) 16 (7%) 17 (7%) 7 (16%) Extent of extracellular mucin <	Well to moderate	/44 (91%)	/8 (86%)	209 (90%)	200 (93%)	221 (93%)	36 (84%)		
Extent of extracellular mucin <0.0001	Poor	77 (9%)	13 (14%)	24 (10%)	16 (7%)	17(7%)	7 (16%)		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Extent of							<0.0001	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	extracellular mucin							<0.0001	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	0%	482 (60%)	45 (51%)	117 (51%)	132 (62%)	162 (69%)	26 (63%)		
$ \begin{array}{c} \geq 50\% & 90 (11\%) & 22 (25\%) & 36 (16\%) & 15 (7\%) & 14 (6\%) & 3 (7\%) \\ \hline \\ 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\%) \\ \geq 50\% & 8 (1\%) & 4 (5\%) & 4 (2\%) & 0 (0\%) & 0 (0\%) & 0 (0\%) \\ \hline \\ 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\%) \\ \geq 50\% & 27 (4\%) & 5 (7\%) & 9 (4\%) & 6 (3\%) & 6 (3\%) & 1 (3\%) \\ \hline \\ Tumour growth \\ pattern \\ 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\%) \\ Low/negative & 622 (83\%) & 62 (76\%) & 176 (83\%) & 154 (80\%) & 195 (88\%) & 35 (81\%) \\ High & 131 (17\%) & 20 (24\%) & 37 (17\%) & 29 (203 (87\%) & 35 (81\%) \\ BRAF 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\%) \\ \end{array}$	1-50%	238 (29%)	22 (25%)	77 (33%)	67 (31%)	60 (25%)	12 (29%)		
Extent of signet ring cells0.0020%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%)0 (0%)Extent of solid tumour areas 0%583 (83%)61 (80%)160 (78%)148 (82%)180 (87%)34 (94%)34 (94%)1-50%96 (14%)10 (13%)36 (18%)27 (15%)22 (11%)1 (3%)250%1 (3%)250%27 (4%)5 (7%)9 (4%)6 (3%)6 (3%)1 (3%)0.25Tumour growth 	≥50%	90 (11%)	22 (25%)	36 (16%)	15 (7%)	14 (6%)	3 (7%)		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Extent of signet ring								
$\begin{array}{cccc} 0\% & 714 (88\%) & 73 (83\%) & 191 (83\%) & 195 (91\%) & 216 (92\%) & 39 (95\%) \\ 1-50\% & 87 (11\%) & 11 (13\%) & 35 (15\%) & 19 (9\%) & 20 (8\%) & 2 (5\%) \\ \ge 50\% & 8 (1\%) & 4 (5\%) & 4 (2\%) & 0 (0\%) & 0 (0\%) & 0 (0\%) \\ \hline \\ Extent of solid tumour areas & 0.20 \\ 0\% & 583 (83\%) & 61 (80\%) & 160 (78\%) & 148 (82\%) & 180 (87\%) & 34 (94\%) \\ 1-50\% & 96 (14\%) & 10 (13\%) & 36 (18\%) & 27 (15\%) & 22 (11\%) & 1 (3\%) \\ \ge 50\% & 27 (4\%) & 5 (7\%) & 9 (4\%) & 6 (3\%) & 6 (3\%) & 1 (3\%) \\ \hline \\ Tumour growth \\ pattern \\ Expansile & 216 (29\%) & 33 (41\%) & 58 (28\%) & 60 (30\%) & 58 (27\%) & 7 (18\%) \\ Intermediate & 413 (56\%) & 38 (48\%) & 122 (58\%) & 109 (55\%) & 121 (57\%) & 23 (59\%) \\ Infiltrative & 113 (15\%) & 9 (11\%) & 30 (14\%) & 31 (16\%) & 34 (16\%) & 9 (23\%) \\ \hline \\ MSI status & 663 (83\%) & 64 (70\%) & 188 (83\%) & 170 (83\%) & 205 (88\%) & 36 (84\%) \\ MSI-high & 136 (17\%) & 27 (30\%) & 39 (17\%) & 35 (17\%) & 28 (12\%) & 7 (16\%) \\ \hline \\ CIMP status & 622 (83\%) & 62 (76\%) & 176 (83\%) & 154 (80\%) & 195 (88\%) & 35 (81\%) \\ High & 131 (17\%) & 20 (24\%) & 37 (17\%) & 39 (20\%) & 27 (12\%) & 8 (19\%) \\ \hline \\ BRAF mutation & 0.64 \\ \hline \\ Wild-type & 683 (85\%) & 77 (84\%) & 189 (83\%) & 179 (87\%) & 203 (87\%) & 35 (81\%) \\ \hline \\ \end{array}$	colle							0.002	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$		714(990/)	72(920/)	101(920/)	105(010/)	216(020/)	20(050())		
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	0%	/14 (88%)	/3 (83%)	191(83%)	195 (91%)	210(92%)	39 (95%)		
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	1-50%	87 (11%)	11(13%)	35 (15%)	19 (9%)	20 (8%)	2 (5%)		
Extent of solid tumour areas0.200%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%)0.25Tumour growth pattern216 (29%)33 (41%)58 (28%)60 (30%)58 (27%)7 (18%)0.25Intermediate413 (56%)38 (48%)122 (58%)109 (55%)121 (57%)23 (59%)0.06Infiltrative113 (15%)9 (11%)30 (14%)31 (16%)34 (16%)9 (23%)0.006MSI status MSI-high663 (83%)64 (70%)188 (83%)170 (83%)205 (88%)36 (84%)0.09CIMP status Low/negative622 (83%)62 (76%)176 (83%)154 (80%)195 (88%)35 (81%)0.09BRAF mutation Wild-type683 (85%)77 (84%)189 (83%)179 (87%)203 (87%)35 (81%)0.64Wild-type Mutant120 (15%)15 (16%)39 (17%)27 (13%)31 (13%)8 (19%)0.64	<i>≥</i> 50%	8 (1%)	4 (5%)	4 (2%)	0(0%)	0(0%)	0(0%)		
0.200%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%) $\geq 50\%$ 27 (4%)5 (7%)9 (4%)6 (3%)6 (3%)1 (3%)Tumour growth pattern216 (29%)33 (41%)58 (28%)60 (30%)58 (27%)7 (18%)Intermediate413 (56%)38 (48%)122 (58%)109 (55%)121 (57%)23 (59%)Infiltrative113 (15%)9 (11%)30 (14%)31 (16%)34 (16%)9 (23%)MSI status663 (83%)64 (70%)188 (83%)170 (83%)205 (88%)36 (84%)MSI-low/MSS663 (83%)64 (70%)188 (83%)170 (83%)205 (88%)36 (84%)MSI-high136 (17%)27 (30%)39 (17%)35 (17%)28 (12%)7 (16%)CIMP status Low/negative622 (83%)62 (76%)176 (83%)154 (80%)195 (88%)35 (81%)High131 (17%)20 (24%)37 (17%)39 (20%)27 (12%)8 (19%)BRAF mutation Wild-type683 (85%)77 (84%)189 (83%)179 (87%)203 (87%)35 (81%)Mutant120 (15%)15 (16%)39 (17%)27 (13%)31 (13%)8 (19%)	Extent of solid							0.20	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	tumour areas							0.20	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	0%	583 (83%)	61 (80%)	160 (78%)	148 (82%)	180 (87%)	34 (94%)		
$ \ge 50\% \qquad 27 (4\%) \qquad 5 (7\%) \qquad 9 (4\%) \qquad 6 (3\%) \qquad 6 (3\%) \qquad 1 (3\%) \qquad 0.25 $ Tumour growth pattern Expansile $ 216 (29\%) \qquad 33 (41\%) \qquad 58 (28\%) \qquad 60 (30\%) \qquad 58 (27\%) \qquad 7 (18\%) $ Intermediate $ 413 (56\%) \qquad 38 (48\%) \qquad 122 (58\%) \qquad 109 (55\%) \qquad 121 (57\%) \qquad 23 (59\%) $ Infiltrative $ 113 (15\%) \qquad 9 (11\%) \qquad 30 (14\%) \qquad 31 (16\%) \qquad 34 (16\%) \qquad 9 (23\%) \qquad 0.006 $ MSI status $ MSI \text{ status} \qquad \qquad 663 (83\%) \qquad 64 (70\%) \qquad 188 (83\%) \qquad 170 (83\%) \qquad 205 (88\%) \qquad 36 (84\%) $ MSI status $ MSI \text{ status} \qquad \qquad 663 (83\%) \qquad 64 (70\%) \qquad 188 (83\%) \qquad 170 (83\%) \qquad 205 (88\%) \qquad 36 (84\%) $ $ MSI \text{ high} \qquad 136 (17\%) \qquad 27 (30\%) \qquad 39 (17\%) \qquad 35 (17\%) \qquad 28 (12\%) \qquad 7 (16\%) \qquad 0.09 $ $ Low/negative 622 (83\%) \qquad 62 (76\%) \qquad 176 (83\%) \qquad 154 (80\%) \qquad 195 (88\%) \qquad 35 (81\%) High \qquad 131 (17\%) \qquad 20 (24\%) \qquad 37 (17\%) \qquad 39 (20\%) \qquad 27 (12\%) \qquad 8 (19\%) \qquad 0.64 Wild-type \qquad 683 (85\%) \qquad 77 (84\%) \qquad 189 (83\%) \qquad 179 (87\%) \qquad 203 (87\%) \qquad 35 (81\%) $	1-50%	96 (14%)	10 (13%)	36 (18%)	27 (15%)	22 (11%)	1 (3%)		
Tumour growth pattern $216 (29\%)$ $33 (41\%)$ $58 (28\%)$ $60 (30\%)$ $58 (27\%)$ $7 (18\%)$ Intermediate Infiltrative $413 (56\%)$ $38 (48\%)$ $122 (58\%)$ $109 (55\%)$ $121 (57\%)$ $23 (59\%)$ Infiltrative $113 (15\%)$ $9 (11\%)$ $30 (14\%)$ $31 (16\%)$ $34 (16\%)$ $9 (23\%)$ 0.006 MSI status MSI-low/MSS $663 (83\%)$ $64 (70\%)$ $188 (83\%)$ $170 (83\%)$ $205 (88\%)$ $36 (84\%)$ 0.006 CIMP status Low/negative $622 (83\%)$ $62 (76\%)$ $176 (83\%)$ $154 (80\%)$ $195 (88\%)$ $35 (81\%)$ 0.09 BRAF mutation Wild-type $683 (85\%)$ $77 (84\%)$ $189 (83\%)$ $179 (87\%)$ $203 (87\%)$ $35 (81\%)$ 0.64	≥50%	27 (4%)	5 (7%)	9 (4%)	6 (3%)	6 (3%)	1 (3%)		
10001 grown 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-low/MSS $663 (83%)$ $64 (70%)$ $188 (83%)$ $170 (83%)$ $205 (88%)$ $36 (84%)$ 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 Low/negative $622 (83%)$ $62 (76%)$ $176 (83%)$ $154 (80%)$ $195 (88%)$ $35 (81%)$ High $131 (17%)$ $20 (24%)$ $37 (17%)$ $39 (20%)$ $27 (12%)$ $8 (19%)$ BRAF mutation Wild-type $683 (85%)$ $77 (84%)$ $189 (83%)$ $179 (87%)$ $203 (87%)$ $35 (81%)$ Mutant $120 (15%)$ $15 (16%)$ $39 (17%)$ $27 (13%)$ $31 (13%)$ $8 (19%)$	Tumour growth								
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 status663 (83\%) $64 (70\%)$ $188 (83\%)$ $170 (83\%)$ $205 (88\%)$ $36 (84\%)$ MSI-low/MSS663 (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 $622 (83\%)$ $62 (76\%)$ $176 (83\%)$ $154 (80\%)$ $195 (88\%)$ $35 (81\%)$ High $131 (17\%)$ $20 (24\%)$ $37 (17\%)$ $39 (20\%)$ $27 (12\%)$ $8 (19\%)$ BRAF mutation 0.64 Wild-type $683 (85\%)$ $77 (84\%)$ $189 (83\%)$ $179 (87\%)$ $203 (87\%)$ $35 (81\%)$ Mutant $120 (15\%)$ $15 (16\%)$ $39 (17\%)$ $27 (13\%)$ $31 (13\%)$ $8 (19\%)$	nattern							0.25	
LAparisine $210 (27\%)$ $35 (41\%)$ $53 (23\%)$ $50 (21\%)$ $50 (21\%)$ $7 (15\%)$ 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 status0.006MSI-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 Low/negative $622 (83\%)$ $62 (76\%)$ $176 (83\%)$ $154 (80\%)$ $195 (88\%)$ $35 (81\%)$ High $131 (17\%)$ $20 (24\%)$ $37 (17\%)$ $39 (20\%)$ $27 (12\%)$ $8 (19\%)$ BRAF mutation Wild-type $683 (85\%)$ $77 (84\%)$ $189 (83\%)$ $179 (87\%)$ $203 (87\%)$ $35 (81\%)$ Mutant $120 (15\%)$ $15 (16\%)$ $39 (17\%)$ $27 (13\%)$ $31 (13\%)$ $8 (19\%)$	Expansile	216 (29%)	33(41%)	58 (28%)	60 (30%)	58 (27%)	7 (18%)		
Intermediate $413(30\%)$ $38(43\%)$ $122(33\%)$ $109(35\%)$ $121(37\%)$ $23(39\%)$ Infiltrative $113(15\%)$ $9(11\%)$ $30(14\%)$ $31(16\%)$ $34(16\%)$ $9(23\%)$ MSI status	Intermediate	210(2)/0)	33(41%)	122(58%)	100(55%)	121(57%)	7(10%)		
Initiative $113(13\%)$ $9(11\%)$ $30(14\%)$ $31(16\%)$ $34(16\%)$ $9(23\%)$ MSI status0.006MSI-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 $136(17\%)$ $27(30\%)$ $39(17\%)$ $35(17\%)$ $28(12\%)$ $7(16\%)$ Low/negative $622(83\%)$ $62(76\%)$ $176(83\%)$ $154(80\%)$ $195(88\%)$ $35(81\%)$ High $131(17\%)$ $20(24\%)$ $37(17\%)$ $39(20\%)$ $27(12\%)$ $8(19\%)$ BRAF mutation0.64Wild-type $683(85\%)$ $77(84\%)$ $189(83\%)$ $179(87\%)$ $203(87\%)$ $35(81\%)$ Mutant $120(15\%)$ $15(16\%)$ $39(17\%)$ $27(13\%)$ $31(13\%)$ $8(19\%)$	Internetine	413(30%) 112(15%)	38(48%)	122(36%)	109(33%)	121(3770) 24(160())	23(39%)		
MSI status 0.006 MSI-low/MSS MSI-high $663 (83\%) \\ 136 (17\%) \\ 27 (30\%) \\ 27 (30\%) \\ 27 (30\%) \\ 27 (30\%) \\ 39 (17\%) \\ 39 (17\%) \\ 39 (17\%) \\ 39 (17\%) \\ 35 (17\%) \\ 28 (12\%) \\ 7 (16\%) \\ 7 (16\%) \\ 7 (16\%) \\ 7 (16\%) \\ 0.09 \\$	Infiltrative	115 (15%)	9(11%)	30 (14%)	31 (10%)	34 (10%)	9 (23%)		
MSI-low/MSS MSI-high $663 (83\%)$ $136 (17\%)$ $64 (70\%)$ $27 (30\%)$ $188 (83\%)$ 	MSI status							0.006	
MSI-low/Mabb $3000 (0070)$ $301 (1000)$ $100 (0070)$ $100 (0070)$ $200 (0070)$ $300 (0170)$ MSI-high $136 (17\%)$ $27 (30\%)$ $39 (17\%)$ $35 (17\%)$ $28 (12\%)$ $7 (16\%)$ CIMP status $622 (83\%)$ $62 (76\%)$ $176 (83\%)$ $154 (80\%)$ $195 (88\%)$ $35 (81\%)$ High $131 (17\%)$ $20 (24\%)$ $37 (17\%)$ $39 (20\%)$ $27 (12\%)$ $8 (19\%)$ BRAF mutation 0.64 Wild-type $683 (85\%)$ $77 (84\%)$ $189 (83\%)$ $179 (87\%)$ $203 (87\%)$ $35 (81\%)$ Mutant $120 (15\%)$ $15 (16\%)$ $39 (17\%)$ $27 (13\%)$ $31 (13\%)$ $8 (19\%)$	MSI-low/MSS	663 (83%)	64(70%)	188 (83%)	170 (83%)	205 (88%)	36 (84%)	0.000	
Wist-lingh130 (17%) $27 (30\%)$ $33 (17\%)$ $33 (17\%)$ $23 (12\%)$ $7 (10\%)$ CIMP status0.09Low/negative $622 (83\%)$ $62 (76\%)$ $176 (83\%)$ $154 (80\%)$ $195 (88\%)$ $35 (81\%)$ High131 (17\%) $20 (24\%)$ $37 (17\%)$ $39 (20\%)$ $27 (12\%)$ $8 (19\%)$ BRAF mutation0.64Wild-type $683 (85\%)$ $77 (84\%)$ $189 (83\%)$ $179 (87\%)$ $203 (87\%)$ $35 (81\%)$ Mutant120 (15\%) $15 (16\%)$ $39 (17\%)$ $27 (13\%)$ $31 (13\%)$ $8 (19\%)$	MSI-high	136(17%)	27 (30%)	39(17%)	35(17%)	205(00%) 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%) BRAF 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%)	MSI-mgn	130 (1770)	27 (3070)	57 (1770)	55 (1770)	20 (1270)	/(10/0)		
Low/negative High $622 (83\%)$ $131 (17\%)$ $62 (76\%)$ $20 (24\%)$ $176 (83\%)$ 	CIMP status							0.09	
High $131 (17\%)$ $20 (24\%)$ $37 (17\%)$ $39 (20\%)$ $27 (12\%)$ $8 (19\%)$ BRAF mutation0.64Wild-type $683 (85\%)$ $77 (84\%)$ $189 (83\%)$ $179 (87\%)$ $203 (87\%)$ $35 (81\%)$ Mutant $120 (15\%)$ $15 (16\%)$ $39 (17\%)$ $27 (13\%)$ $31 (13\%)$ $8 (19\%)$	Low/negative	622 (83%)	62 (76%)	176 (83%)	154 (80%)	195 (88%)	35 (81%)	-	
BRAF 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%)	High	131 (17%)	20(24%)	37 (17%)	39 (20%)	27 (12%)	8 (19%)		
BRAF 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%)		101 (1770)	20 (2170)	57 (1770)	27 (2070)	2, (12/0)	0 (1770)		
Wild-type683 (85%)77 (84%)189 (83%)179 (87%)203 (87%)35 (81%)Mutant120 (15%)15 (16%)39 (17%)27 (13%)31 (13%)8 (19%)	BRAF mutation							0.64	
Mutant 120 (15%) 15 (16%) 39 (17%) 27 (13%) 31 (13%) 8 (19%)	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%)		

KRAS 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%)	
PIK3CA mutation							0.56
Wild-type	641 (85%)	74 (86%)	193 (88%)	166 (85%)	177 (83%)	31 (82%)	0.00
Mutant	111 (15%)	12(14%)	26(12%)	29 (15%)	37 (17%)	7 (18%)	
Wittent	111 (1570)	12(11/0)	20 (1270)	2) (15/0)	57 (1770)	/ (10/0)	
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
(%)							
Fusobacterium							0.00
nucleatum 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%)	
0	× /	~ /	` '	× /	× /	× /	

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 α level to 0.002 (=0.05/22) by simple Bonferroni correction for multiple hypothesis testing.

		Multivariable OR
		(95% CI)*
Model for FOXP3 ⁺ cell density (n=54	19, as an o	outcome variable)
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_{trend} †	0.0002
Other variable remaining in the final m	nodel	
Year of diagnosis (5 years as a unit	t)	1.42 (1.22-1.66)

Supplementary table 4. Multivariable ordinal logistic regression model for the density of FOXP3⁺ cells

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. † *P*_{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⁺ 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

			Tumour C	D274 expres	ssion score		
	Total No.	0	1	2	3	4	P value*
$CD3^+$ cell d	lensity (n=571	l)					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%)	
CD8 ⁺ cell d	lensity (n=564	I)					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%)	
CD45RO ⁺	cell density (n	h=577)					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%)	
FOXP3 ⁺ ce	ell density (n=	549)					< 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/mm²; as continuous variables). Because we assessed eight primary tumour immunity status variables, we adjusted two-sided α level to 0.006 (=0.05/8) by simple Bonferroni correction.

		Univariable OR	Multivariable OR
		(95% CI)	(95% CI)*
Model for CD3 ⁺ cell density (n=571, as	a binary (outcome variable [Lo	ow vs. High])
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_{trend} †	0.88	0.88
Model for CD8 ⁺ cell density (n=564, as	a binary (outcome variable [Lo	ow vs. High])
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_{trend} †	0.30	0.20
Model for CD45RO ⁺ cell density (n=577	7, as a bin	ary outcome variabl	e [Low vs. High])
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_{trend} †	0.05	0.019
Model for FOXP3 ⁺ cell density (n=549,	as a bina	ry outcome variable	[Low vs. High])
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_{trend} †	0.0002	0.0005

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

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.

[†] P_{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⁺ cells, CD8⁺ cells, CD45RO⁺ cells, or FOXP3⁺ cells (a binary outcome variable). Because we assessed eight primary outcome variables, we adjusted two-sided α level to 0.006 (=0.05/8) by simple Bonferroni correction.

		PDCD1 ⁺ cell density					
	Total No.	Absent	Very low	Low	Intermediate	High	-
Characteristic*	(n=793)	(n=230)	(n=194)	(n=140)	(n=102)	(n=127)	P value [†]
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							0.71
colorectal cancer in a							0.71
Abaant	(12)(700)	175 (770/)	156(920/)	100 (700/)	70(700())	04(750())	
Absent	013(79%)	1/5(7/%)	150(82%)	109(79%)	79 (79%)	94 (75%)	
Present	107 (21%)	51 (25%)	33 (18%)	29 (21%)	21 (21%)	51 (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%)	
nT stage							0.45
nT1	69 (10%)	21 (10%)	13 (13%)	17 (13%)	8 (8%)	10 (9%)	0.45
pT1 nT2	142(20%)	31 (15%)	37(21%)	24(18%)	21(22%)	29(25%)	
pT2 nT3	478 (66%)	136 (67%)	124 (69%)	85 (64%)	63 (66%)	29 (23 %) 70 (61%)	
PT4	37 (5%)	15 (7%)	6 (3%)	7 (5%)	3 (3%)	6 (5%)	
			0 (0.00)				
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
MO	608 (84%)	150 (74%)	149 (83%)	113 (84%)	86 (90%)	110 (96%)	(0.0001
M1	119 (16%)	52 (26%)	31 (17%)	21 (16%)	10 (10%)	5 (4%)	
	- ()	- (/	- (()	- (/-/	- (• • •)	
Disease stage							0.0003
Ι	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%)	

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

No. of negative							0.22
lymph nodes							0.55
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							0.15
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							0.05
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%)	
	00 (11/0)	00 (1070)	()		- (- / 0)	10 (10,0)	
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%)	
	0(170)	5 (270)	0 (070)	2(170)	1 (170)	0 (070)	
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%)	
	20 (170)	1 (270)	5 (570)	5 (170)	0(170)	0 (370)	
Tumour growth							
nattern							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%)	
mmuuive	112 (1070)	+7 (2370)	52 (1070)	15 (1070)	13 (1470)	7 (070)	
MSI status							<0.0001
MSI-low/MSS	642 (83%)	204 (90%)	165 (87%)	116 (87%)	77 (79%)	80 (65%)	<0.0001
MSI_high	128(17%)	20+(90%)	24(13%)	18(13%)	20(21%)	44(35%)	
Misi-iligii	128 (1770)	22 (10%)	24 (1370)	18 (1370)	20 (2170)	44 (33%)	
CIMD status							<0.0001
L ouv/nogotivo	600(920/)	196 (900/)	150 (990/)	112 (960/)	66 (75%)	76(660/)	<0.0001
LOw/negative	100(65%)	100(09%)	139(00%)	113(00%) 18(140/)	00(75%)	70 (00%)	
підіі	124 (17%)	23 (11%)	22 (12%)	18(14%)	22 (23%)	37 (34%)	
DDAE mutation							0.020
DRAF INULATION	((1))	201(000)	164 (070/)	117(070/)	$0 \in (0 \in \mathbb{N})$	04(760)	0.039
wild-type	001(80%)	201(88%)	104(8/%)	11/(8/%)	85 (86%)	94 (76%)	
wutant	112 (14%)	27 (12%)	24 (13%)	18 (15%)	14 (14%)	29 (24%)	

KRAS 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%)	
PIK3CA 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 I INE-1							
methylation level+SD	62 3+9 7	61 8+9 3	61 2+10 6	62 0+9 0	62 3+9 6	64 9+9 1	0.014
(%)	02.5±7.7	01.0±9.5	01.2 ± 10.0	02.0±9.0	02.3±9.0	07.7±7.1	0.014
(/0)							
Fusobacterium							0.95
nucleatum 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							< 0.0001
expression score							(010001
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 $PDCD1^+$ 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⁺ 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 α level to 0.002 (=0.05/23) by simple Bonferroni correction for multiple hypothesis testing.

CD274	Total	Colorectal cancer-specific mortality			Overall mortality				
expression	No.	No.	Univariable HR	Multivariable HR	No.	Univariable HR	Multivariable HR		
in stromal		of	(95% CI)	(95% CI)*	of	(95% CI)	(95% CI)*		
cells		events	events			events			
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)		
P value			0.08	0.16		0.24	0.11		

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

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	Colorectal cancer-specific mortality				Overall mortality			
	No.	No.	Univariable HR	Multivariable HR	No.	Univariable HR	Multivariable HR		
		of	(95% CI)	(95% CI)*	of	(95% CI)	(95% CI)*		
		events			events				
Tumour with low-level CD274 expression (tumour CD274 expression score 0/1/2)									
CD3 ⁺ cell de	nsity								
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)		
P value			0.47	0.50		0.55	0.37		
Tumour with high-level CD274 expression (tumour CD274 expression score $3/4$) CD3 ⁺ 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)		
P value			0.14	0.07		0.15	0.26		
$P_{\text{interaction}}$ †			0.26	0.11		0.34	0.35		
Tumour with low-level CD274 expression (tumour CD274 expression score $0/1/2$) CD8 ⁺ 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)		
P value			0.31	0.51		0.15	0.09		
Tumour with high-level CD274 expression (tumour CD274 expression score $3/4$) CD8 ⁺ 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)		
P value			0.010	0.042		0.022	0.06		
$P_{ m interaction}$ †			0.15	0.17		0.30	0.74		

Tumour with low-level CD274 expression (tumour CD274 expression score 0/1/2)								
$CD45RO^+$ co	ell dens	ity						
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)	
P value			0.023	0.016		0.11	0.06	
Tumour with	high-le	vel CD2	274 expression (tu	mour CD274 express	ion sco	re 3/4)		
$CD45RO^+$ ce	ell dens	ity						
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)	
P value			0.24	0.85		0.51	0.80	
$P_{\text{interaction}}$ †			0.91	0.59		0.60	0.43	
Tumour with	low-lev	vel CD2	74 expression (tur	nour CD274 expression	on scor	e 0/1/2)		
FOXP3 ⁺ cell	densit	У						
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)	
P value			< 0.0001	0.002		< 0.0001	0.0003	
Tumour with high-level CD274 expression (tumour CD274 expression score 3/4)								
FOXP3 ⁺ cell	densit	у	-	_				
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)	
P value			0.018	0.011		0.006	0.002	
$P_{\text{interaction}}$ †			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.

 $\dagger P_{\text{interaction}}$ 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.