

Supplementary Table 1. Description of the gene signature in Figure 5

Signature*	Source	Genes
Luminal markers	PMID: 30096301	<i>CYP2J2, ERBB2, ERBB3, FGFR3, FOXA1, GATA3, GPX2, KRT18, KRT19, KRT20, KRT7, KRT8, PPARG, XBP1, UPK1A, UPK2</i>
Basal markers	PMID: 30096301	<i>CD44, CDH3, KRT1, KRT14, KRT16, KRT5, KRT6A, KRT6B, KRT6C</i>
p53-like markers	PMID: 30096301	<i>ACTG2, CNN1, MYH11, MFAP4, PGM5, FLNC, ACTC1, DES, PCP4</i>
TP53/Cell Cycle pathway	PMID: 30096301	<i>ATM, TP53, MDM2, CDKN2A, RB1, CCND1, CDKN1A, PTEN, CCNE1, FBXW7, CDKN1B, CCND1, CCND2, CCND3, CDK4, CDK6</i>
Proliferation	PMID: 30213523	<i>ANLN, ASF1B, ASPM, ATAD2, AURKA, AURKB, BUB1, BUB1B, C12orf48, C15orf23, C16orf59, C17orf53, C1orf112, CCNA2, CCNB1, CCNB2, CCNE2, CDC20, CDC25A, CDC25C, CDC45, CDCA2, CDCA3, CDCA5, CDCA8, CDK1, CDKN3, CENPA, CENPE, CENPF, CENPL, CENPN, CEP55, CHAF1B, CHEK1, CKAP2L, CKS1B, DEPDC1, DEPDC1B, DLGAP5, DONSON, E2F2, EXO1, FAM64A, FAM83D, GINS2, HJURP, HMGB2, HMMR, KIAA1524, KIF11, KIF14, KIF18A, KIF20A, KIF20B, KIF23, KIF2C, KIF4A, MCM2, MCM7, MELK, NCAPG, NUF2, NUSAP1, OIP5, PKMYT1, PLK4, POLA2, POLE2, POLQ, PRC1, PRR11, RACGAP1, RAD51AP1, RFC3, RRM2, SKA3, TK1, TOP2A, TRIP13, TTK, TYMS, UBE2T, UHRF1, ZWINT</i>
FGFR3 activation	Reactome hsa190239	<i>FGF1, FGF16, FGF17, FGF18, FGF2, FGF20, FGF23, FGF4, FGF5, FGF8, FGF9, FGFR3, GALNT3</i>
FGFR3-coexpressed genes	PMID: 22553347	<i>FGFR3, TP63, IRS1, SEMA4B, PTPN13, TMPRSS4</i>
EGFR signaling	Reactome hsa1643713	<i>AREG, BTC, CBL, EGF, EGFR, EPGN, EREG, GAB1, GRB2, HBEGF, HRAS, HSP90AA1, KRAS, NRAS, PIK3CA, PIK3R1, PLCG1, RPS27A, SHC1, SOS1, TGFA, UBA52, UBB, UBC</i>
EGFR ligands	PMID: 25009231	<i>EGFR, AREG, AREGB, EREG, HBEGF, TGFA</i>
Immune checkpoint	PMID: 31563503	<i>CD274, CTLA4, HAVCR2, LAG3, PDCD1, PDCD1LG2, TIGIT</i>
Antigen presenting machinery	PMID: 27855702	<i>B2M, HLA-A, HLA-B, HLA-C, TAP1, TAP2</i>

* Signature score was defined as the mean of normalized expression of related genes; normalized gene expression was calculated as $\log_2(\text{FPKM}+1)$.

Supplementary Table 2. IHC evaluation

Identified cells	Evaluation	IHC antibody	Clonality Species	Company	Product No.	Diluted
LAG-3 ⁺ cells	Cell number (400x)	Anti-Lymphocyte Activation Gene 3 antibody	Monoclonal; Rb	Abcam	ab209236	1:500
CD45 ⁺ cells	Cell number (200x)	Anti-CD45 antibody	Polyclonal; Rb	Abcam	ab10558	1:50
NK cells	Cell percentage (per specimen)	Anti-CD56 antibody	Monoclonal; Ms	Dako	M7304	prediluted
B cells	Cell number (200x)	Anti-CD19 antibody	Monoclonal; Ms	Abcam	ab31947	1:400
T cells	Cell number (200x)	Anti-CD3 antibody	Monoclonal; Rb	Abcam	ab16669	1:200
CD8 ⁺ T cells	Cell number (200x)	Anti-CD8 alpha antibody	Monoclonal; Ms	Abcam	ab17147	1:100
CD4 ⁺ T cells	Cell number (200x)	Anti-CD4 antibody	Monoclonal; Ms	Abcam	ab67001	1:50
Th1 cells	Cell number (per specimen)	Anti-CD4 antibody Anti-T-bet antibody	Monoclonal; Ms Monoclonal; Rb	Abcam Abcam	ab67001 ab150440	1:50 1:500
Th2 cells	Cell number (per specimen)	Anti-CD4 antibody Anti-GATA3 antibody	Monoclonal; Ms Monoclonal; Rb	Abcam Abcam	ab67001 ab186371	1:50 1:100
Treg cells	Cell number (200x)	Anti-FOXP3 antibody	Monoclonal; Ms	Abcam	ab22510	1:100
Mast cells	Cell number (per specimen)	Anti-Mast Cell Tryptase antibody	Monoclonal; Ms	Abcam	ab2378	1:10000
Macrophages	Cell number (200x)	Anti-CD68 antibody	Monoclonal; Rb	Abcam	ab955	1:400
M1	Cell number (200x)	Anti-CD68 antibody Anti-HLA-DR antibody	Monoclonal; Ms Monoclonal; Rb	Dako Abcam	IR604 ab92511	prediluted 1:250
M2	Cell number (200x)	Anti-MRC1 antibody	Monoclonal; Rb	Sigma	HPA004114	1:500
Neutrophils	Cell number (per specimen)	Anti-CD66b antibody	Polyclonal; Rb	Abcam	ab197678	1:1000
DCs	Cell number (200x)	Anti-HLA-DR antibody Anti-CD11c antibody	Monoclonal; Ms Monoclonal; Rb	Abcam Abcam	ab20181 ab52632	1:200 1:200
IL-10 ⁺ cells	Cell number (200x)	Anti-IL-10 antibody	Monoclonal; Ms	Abcam	ab134742	1:200
TGF- β ⁺ cells	Cell number (200x)	Anti-LAP antibody	Polyclonal; Go	R&D	AB-246-NA	1:100
PD-1 ⁺ cells	Cell number (200x)	Anti-PD1 antibody	Monoclonal; Ms	Abcam	ab52587	1:100
PD-L1 ⁺ cells	Cell number (200x)	Anti-PD-L1 antibody	Monoclonal; Rb	Abcam	ab228415	1:500
CTLA-4 ⁺ cells	Cell number (200x)	Anti-CTLA-4 antibody	Monoclonal; Ms	Santa-Cruz	sc-376016	1:100
TIM-3 ⁺ cells	Cell number (200x)	Anti-TIM 3 antibody	Polyclonal; Rb	Abcam	ab185703	1:100
TIGIT ⁺ cells	Cell number (200x)	Anti-TIGIT antibody	Monoclonal; Rb	Abcam	ab243903	1:100

Abbreviation: NK cells; natural killer cells; Th1 cells, type 1 helper T cells; Th2 cells, type 2 helper T cells; M1, type 1 macrophages; M2, type 2 macrophages; DCs, dendritic cells.

Supplementary Table 3. Association of LAG-3⁺ cells and clinicopathologic features with prognosis in univariate and multivariate analyses

Cox regression analyses (n = 141)	OS						DFS					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95%CI	P	HR	95%CI	P	HR	95%CI	P	HR	95%CI	P
Tumor size (≥4cm vs. <4cm)	0.90	0.57-1.42	0.644	0.96	0.61-1.56	0.916	0.80	0.49-1.29	0.352	0.96	0.59-1.58	0.882
AJCC stage			0.053			0.112			0.019			0.050
III vs. II	1.46	0.90-2.35	0.127	1.39	0.85-2.28	0.186	1.40	0.83-2.35	0.206	1.33	0.79-2.26	0.288
IV vs. II	2.60	1.10-6.16	0.030	2.35	0.97-5.68	0.058	3.13	1.39-7.06	0.006	2.81	1.21-6.55	0.017
Grade (high vs. low)	2.66	1.27-5.56	0.009	1.83	0.85-3.94	0.123	3.86	1.55-9.63	0.004	2.90	1.13-7.44	0.027
LVI (present vs. absent)	1.63	1.00-2.66	0.049	1.47	0.88-2.45	0.144	1.38	0.83-2.28	0.213	1.14	0.68-1.92	0.619
LAG-3⁺ cells infiltration (high vs. low)	2.03	1.27-3.24	0.003	2.00	1.23-3.28	0.006	1.89	1.16-3.09	0.010	1.71	1.04-2.82	0.036

Abbreviation: OS, overall survival; DFS, disease-free survival; HR, Hazard Ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; LVI, lymphovascular invasion; ACT, adjuvant chemotherapy.

Supplementary Table 4. Association of sLAG-3⁺ cells and clinicopathologic features with prognosis in univariate and multivariate analyses

Cox regression analyses (n = 141)	OS						DFS					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95%CI	P	HR	95%CI	P	HR	95%CI	P	HR	95%CI	P
Tumor size (≥4cm vs. <4cm)	0.90	0.57-1.42	0.644	1.05	0.66-1.69	0.823	0.80	0.49-1.29	0.352	1.02	0.62-1.68	0.934
AJCC stage			0.053			0.132			0.019			0.051
III vs. II	1.46	0.90-2.35	0.127	1.33	0.82-2.18	0.251	1.40	0.83-2.35	0.206	1.28	0.76-2.18	0.354
IV vs. II	2.60	1.10-6.16	0.030	2.33	0.97-5.63	0.060	3.13	1.39-7.06	0.006	2.83	1.22-6.57	0.016
Grade (high vs. low)	2.66	1.27-5.56	0.009	2.00	0.94-4.23	0.070	3.86	1.55-9.63	0.004	3.03	1.20-7.69	0.020
LVI (present vs. absent)	1.63	1.00-2.66	0.049	1.41	0.85-2.34	0.188	1.38	0.83-2.28	0.213	1.14	0.68-1.92	0.624
Stromal LAG-3⁺ cells infiltration (high vs. low)	2.19	1.36-3.51	0.001	2.13	1.32-3.46	0.002	2.03	1.24-3.30	0.005	1.88	1.14-3.09	0.013

Abbreviation: OS, overall survival; DFS, disease-free survival; HR, Hazard Ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; LVI, lymphovascular invasion; ACT, adjuvant chemotherapy.

Supplementary Table 5. Association of iLAG-3⁺ cells and clinicopathologic features with prognosis in univariate and multivariate analyses

Cox regression analyses (n = 141)	OS						DFS					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95%CI	P	HR	95%CI	P	HR	95%CI	P	HR	95%CI	P
Tumor size (≥4cm vs. <4cm)	0.90	0.57-1.42	0.644	0.97	0.60-1.56	0.902	0.80	0.49-1.29	0.352	0.90	0.57-1.42	0.644
AJCC stage			0.053			0.170			0.019			0.068
III vs. II	1.46	0.90-2.35	0.127	1.34	0.82-2.18	0.247	1.40	0.83-2.35	0.206	1.33	0.79-2.26	0.286
IV vs. II	2.60	1.10-6.16	0.030	2.16	0.89-5.23	0.087	3.13	1.39-7.06	0.006	2.64	1.14-6.13	0.024
Grade (high vs. low)	2.66	1.27-5.56	0.009	2.24	1.05-4.80	0.038	3.86	1.55-9.63	0.004	3.36	1.32-8.53	0.011
LVI (present vs. absent)	1.63	1.00-2.66	0.049	1.33	0.80-2.21	0.278	1.38	0.83-2.28	0.213	1.08	0.64-1.82	0.767
Intra-epithelial LAG-3⁺ cells infiltration (high vs. low)	1.17	0.74-1.84	0.511	1.15	0.72-1.84	0.565	1.34	0.83-2.16	0.230	1.34	0.83-2.18	0.232

Abbreviation: OS, overall survival; DFS, disease-free survival; HR, Hazard Ratio; CI, confidence interval; AJCC, American Joint Committee on Cancer; LVI, lymphovascular invasion; ACT, adjuvant chemotherapy.

Supplementary Table 6. Hazard ratio of mortality and recurrence for patients applying ACT or not according to LAG-3⁺ cells infiltration

Cox regression analyses (n = 141)	Number	OS				DFS			
		HR	95%CI	P	P ^{interaction}	HR	95%CI	P	P ^{interaction}
ACT (yes vs. no)	141 (69/72)	0.79	0.49-1.25	0.309	0.136	0.72	0.44-1.17	0.181	0.115
ACT in high LAG-3 ⁺ cells subgroup (yes vs. no)	72 (38/34)	0.97	0.52-1.81	0.927		0.97	0.52-1.79	0.911	
ACT in low LAG-3 ⁺ cells subgroup (yes vs. no)	69 (31/38)	0.54	0.26-1.12	0.096		0.42	0.18-0.95	0.038	
ACT (yes vs. no)	141 (69/72)	0.79	0.49-1.25	0.309	0.014	0.72	0.44-1.17	0.181	0.027
ACT in high sLAG-3 ⁺ cells subgroup (yes vs. no)	71 (37/34)	1.13	0.62-2.07	0.685		1.16	0.63-2.15	0.636	
ACT in low sLAG-3 ⁺ cells subgroup (yes vs. no)	70 (32/38)	0.45	0.21-0.96	0.038		0.31	0.13-0.73	0.007	
ACT (yes vs. no)	141 (69/72)	0.79	0.49-1.25	0.309	0.886	0.72	0.44-1.17	0.181	0.795
ACT in positive iLAG-3 ⁺ cells subgroup (yes vs. no)	68 (36/32)	0.82	0.42-1.58	0.544		0.70	0.36-1.33	0.275	
ACT in negative iLAG-3 ⁺ cells subgroup (yes vs. no)	73 (33/40)	0.70	0.36-1.38	0.305		0.74	0.36-1.52	0.404	

Abbreviation: OS, overall survival; DFS, disease-free survival; HR, Hazard Ratio; CI, confidence interval; ACT, adjuvant chemotherapy; sLAG-3⁺ cells, stromal LAG-3⁺ cells; iLAG-3⁺ cells, intra-epithelial LAG-3⁺ cells.