

Supplementary materials for High expression of PD-1 in circulating cells of patients with advanced colorectal cancer receiving adjuvant therapy

1 **This file includes:**

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3 Table SI

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27 Table SI. Tested immune genes with their details.

Immune Gene Symbol	Synonym (s)	Cytogenetic Band	Roles in Immunity
IFN γ	Interferon-gamma; IFG; IFI	12q15	IFNγ is related to high susceptibility to different infections and to several autoimmune diseases ¹² . IFN-γ-driven tumor microenvironment shows a better prognostic result in the tumor ³ . It induces Class II major histocompatibility complex (MHC) molecule expression and an activator of macrophages ^{2,4} .
PD-1	Programmed cell death 1; CD279; hPD-1; CD279; SLEB2	2q37.3	In the human body, PD-1 functions in the regulation of the immune system's response to the cells. It works by increasing self-tolerance by suppressing the inflammatory activity of the T cell and down-regulation of the immune system ^{5,6} . Autoimmune diseases prevented by this gene. Besides, it prevents the immune system from killing cancer cells ⁷⁻⁹ . This gene is also expressed in pro-B-cells and may differentiate them ^{10,11} .
β2M	beta-2 microglobulin; Ly-m11; beta2m; beta2-m	15q21.	Altered expression of β2M defines MMR-deficient cancers with a favorable clinical course in addition lack of metastatic diseases ¹²⁻¹⁵ .
CD3e	CD3e Molecule; T3E; TCRE; IMD18	11q23. 3	CD3e is linked cell-surface proteins of the immunoglobulin superfamily. It contains a

			domain of single extracellular immunoglobulin ¹⁶⁻¹⁹ .
CD28	CD28 molecule; Tp44	2q33.2	For cytokine production, T-cell survival and proliferation and T-helper type-2 development, the protein encoded this gene is required ^{20,21} . This gene belongs to a family and that creates a dynamic network which modulates immune response's initiation, maintenance, and termination ²²⁻²⁴ .
HLA-A	Major histocompatibility complex, class I, A	6p22.1	HLA-A presents vaccinia virus antigens to T cells, thus initiates adaptive immune responses ^{25,26} .
ICAM 1	Intercellular adhesion molecule 1; CD54; P3.58; BB2	19p13.2	ICAM 1 gene translates a glycoprotein in the cell surface. Expression of this glycoprotein normally happens on cells of the immune system and endothelial cells ²⁷⁻²⁹ .

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30 **References**

- 31 1. Deniz R, Tulunay-Virlan A, Ture Ozdemir F, et al. Th17-Inducing Conditions Lead to
32 in vitro Activation of Both Th17 and Th1 Responses in Behcet's Disease. *Immunol
33 Invest.* 2017;46(5):518-525. doi:10.1080/08820139.2017.1306865
- 34 2. Mojic M, Takeda K, Hayakawa Y. The Dark Side of IFN- γ : Its Role in Promoting
35 Cancer Immunoevasion. *Int J Mol Sci.* 2017;19(1):89. doi:10.3390/ijms19010089
- 36 3. Grenz S, Naschberger E, Merkel S, et al. IFN- γ -Driven Intratumoral
37 Microenvironment Exhibits Superior Prognostic Effect Compared with an IFN- α -
38 Driven Microenvironment in Patients with Colon Carcinoma. *Am J Pathol.*
39 2013;183(6):1897-1909. doi:10.1016/j.ajpath.2013.08.025
- 40 4. Kosmidis C, Sapalidis K, Koletsas T, et al. Interferon- γ and Colorectal Cancer: an up-to

- 41 date. *J Cancer*. 2018;9(2):232-238. doi:10.7150/jca.22962
- 42 5. Champiat S, Dercle L, Ammari S, et al. Hyperprogressive Disease Is a New Pattern of
43 Progression in Cancer Patients Treated by Anti-PD-1/PD-L1. *Clin Cancer Res*.
44 2017;23(8):1920-1928. doi:10.1158/1078-0432.CCR-16-1741
- 45 6. Syn NL, Teng MWL, Mok TSK, Soo RA. De-novo and acquired resistance to immune
46 checkpoint targeting. *Lancet Oncol*. 2017;18(12):e731-e741. doi:10.1016/S1470-
47 2045(17)30607-1
- 48 7. Weber J. Immune Checkpoint Proteins: A New Therapeutic Paradigm for Cancer—
49 Preclinical Background: CTLA-4 and PD-1 Blockade. *Semin Oncol*. 2010;37(5):430-
50 439. doi:10.1053/J.SEMINONCOL.2010.09.005
- 51 8. Fife BT, Pauken KE. The role of the PD-1 pathway in autoimmunity and peripheral
52 tolerance. *Ann N Y Acad Sci*. 2011;1217(1):45-59. doi:10.1111/j.1749-
53 6632.2010.05919.x
- 54 9. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and
55 autoimmunity. *Immunol Rev*. 2010;236(1):219-242. doi:10.1111/j.1600-
56 065X.2010.00923.x
- 57 10. Mojtabaei Z, Mohmedi M, Rahimifar S, Erfani N, Hosseini SV, Ghaderi A.
58 Programmed death-1 gene polymorphism (PD-1.5 C/T) is associated with colon
59 cancer. *Gene*. 2012;508(2):229-232. doi:10.1016/j.gene.2012.07.059
- 60 11. Zhao Y, Mao Z, Pang H, et al. Association of programmed cell death 1 (PDCD1) gene
61 polymorphisms with colorectal cancer among Han Chinese population. *Zhonghua Yi
62 Xue Yi Chuan Xue Za Zhi*. 2018;35(2):219-223. doi:10.3760/cma.j.issn.1003-
63 9406.2018.02.016
- 64 12. Kloor M, Michel S, Buckowitz B, et al. Beta2-microglobulin mutations in
65 microsatellite unstable colorectal tumors. *Int J Cancer*. 2007;121(2):454-458.
66 doi:10.1002/ijc.22691
- 67 13. Shroud J, Yousefzadeh M, Dodd A, et al. β 2 microglobulin mRNA expression levels
68 are prognostic for lymph node metastasis in colorectal cancer patients. *Br J Cancer*.
69 2008;98(12):1999-2005. doi:10.1038/sj.bjc.6604399
- 70 14. Koelzer VH, Baker K, Kassahn D, Baumhoer D, Zlobec I. Prognostic impact of β -2-
71 microglobulin expression in colorectal cancers stratified by mismatch repair status. *J
72 Clin Pathol*. 2012;65(11):996-1002. doi:10.1136/jclinpath-2012-200742
- 73 15. Pereira C, Gimenez-Xavier P, Pros E, et al. Genomic Profiling of Patient-Derived
74 Xenografts for Lung Cancer Identifies *B2M* Inactivation Impairing
75 Immunorecognition. *Clin Cancer Res*. 2017;23(12):3203-3213. doi:10.1158/1078-
76 0432.CCR-16-1946
- 77 16. Upreti D, Zhang M, Bykova E, Kung SKP, Pathak KA. Change in CD3 ζ -chain
78 expression is an independent predictor of disease status in head and neck cancer
79 patients. *Int J Cancer*. 2016;139(1):122-129. doi:10.1002/ijc.30046
- 80 17. Soudais C, de Villartay J-P, Le Deist F, Fischer A, Lisowska-Gospierre B.
81 Independent mutations of the human CD3- ϵ gene resulting in a T cell receptor/CD3

- 82 complex immunodeficiency. *Nat Genet.* 1993;3(1):77-81. doi:10.1038/ng0193-77
- 83 18. Prado-Garcia H, Aguilar-Cazares D, Meneses-Flores M, Morales-Fuentes J, Lopez-
84 Gonzalez JS. Lung carcinomas do not induce T-cell apoptosis via the Fas/Fas ligand
85 pathway but down-regulate CD3 epsilon expression. *Cancer Immunol Immunother.*
86 2008;57(3):325-336. doi:10.1007/s00262-007-0372-6
- 87 19. Yang X, Liu Y, Zheng D. Overexpression of Bcl-2 inhibited T lymphocyte apoptosis
88 mediated by CD3 epsilon molecule. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao.*
89 1999;21(6):421-424. <http://www.ncbi.nlm.nih.gov/pubmed/12567487>. Accessed
90 September 13, 2018.
- 91 20. Bromley SK, Iaboni A, Davis SJ, et al. The immunological synapse and CD28-CD80
92 interactions. *Nat Immunol.* 2001;2(12):1159-1166. doi:10.1038/ni737
- 93 21. Tavano R, Contento RL, Baranda SJ, et al. CD28 interaction with filamin-A controls
94 lipid raft accumulation at the T-cell immunological synapse. *Nat Cell Biol.*
95 2006;8(11):1270-1276. doi:10.1038/ncb1492
- 96 22. Lee H, Kim JH, Yang SY, et al. Peripheral blood gene expression of B7 and CD28
97 family members associated with tumor progression and microscopic lymphovascular
98 invasion in colon cancer patients. *J Cancer Res Clin Oncol.* 2010;136(9):1445-1452.
99 doi:10.1007/s00432-010-0800-4
- 100 23. Liaskou E, Jeffery LE, Trivedi PJ, et al. Loss of CD28 Expression by Liver-Infiltrating
101 T Cells Contributes to Pathogenesis of Primary Sclerosing Cholangitis.
102 *Gastroenterology.* 2014;147(1):221-232.e7. doi:10.1053/j.gastro.2014.04.003
- 103 24. Pagès F, Ragueneau M, Rottapel R, et al. Binding of phosphatidyl-inositol-3-OH
104 kinase to CD28 is required for T-cell signalling. *Nature.* 1994;369(6478):327-329.
105 doi:10.1038/369327a0
- 106 25. Menon AG, Morreau H, Tollenaar RAEM, et al. Down-Regulation of HLA-A
107 Expression Correlates with a Better Prognosis in Colorectal Cancer Patients. *Lab
108 Investig.* 2002;82(12):1725-1733. doi:10.1097/01.LAB.0000043124.75633.ED
- 109 26. Ovsyannikova IG, Pankratz VS, Salk HM, Kennedy RB, Poland GA. HLA alleles
110 associated with the adaptive immune response to smallpox vaccine: a replication study.
111 *Hum Genet.* 2014;133(9):1083-1092. doi:10.1007/s00439-014-1449-x
- 112 27. Wang Q, Li B, Liu B, et al. Polymorphisms of the ICAM-1 exon 6 (E469K) are
113 associated with differentiation of colorectal cancer. *J Exp Clin Cancer Res.*
114 2009;28(1):139. doi:10.1186/1756-9966-28-139
- 115 28. Novikov V V., Shumilova S V., Novikov D V., Kalugin A V., Fomina SG, Karaulov A
116 V. Genetic Instability in Locus rs5498 E469K (A/G) of ICAM-1 Gene in Patients with
117 Colorectal Cancer and Breast Cancer. *Bull Exp Biol Med.* 2016;160(6):811-813.
118 doi:10.1007/s10517-016-3316-3
- 119 29. Liu L-B, Liu T, Xin F-Z. Correlations of ICAM-1 gene polymorphisms with
120 susceptibility and multidrug resistance in colorectal cancer in a Chinese population.
121 *Medicine (Baltimore).* 2017;96(33):e7481. doi:10.1097/MD.0000000000007481
- 122