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Low gene expression of *TNF, IL17A, IL23A, and IL12B* in tumors: a safety surrogate to predict cancer survival associated with biologic therapies

Nikolai Klebanov, MD, Lourdes M. Perez-Chada, MD MMSc, Sameer Gupta, MD MPhil, Alice B. Gottlieb, MD PhD, Joseph F. Merola, MD MMSc

PII: S0190-9622(20)32441-5

DOI: https://doi.org/10.1016/j.jaad.2020.08.050

Reference: YMJD 15110

To appear in: Journal of the American Academy of Dermatology

Received Date: 25 May 2020

Revised Date: 10 August 2020

Accepted Date: 13 August 2020

Please cite this article as: Klebanov N, Perez-Chada LM, Gupta S, Gottlieb AB, Merola JF, Low gene expression of *TNF*, *IL17A*, *IL23A*, and *IL12B* in tumors: a safety surrogate to predict cancer survival associated with biologic therapies, *Journal of the American Academy of Dermatology* (2020), doi: https://doi.org/10.1016/j.jaad.2020.08.050.

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- 1 Article type: Research Letter
- 2 Title: Low gene expression of TNF, IL17A, IL23A, and IL12B in tumors: a safety surrogate to
- 3 predict cancer survival associated with biologic therapies
- 4 **Date of revision:** August 9, 2020
- 5 Nikolai Klebanov MD<sup>1,2\*</sup>, Lourdes M. Perez-Chada MD MMSc<sup>1\*</sup>, Sameer Gupta MD MPhil<sup>1</sup>,
- 6 Alice B. Gottlieb MD PhD<sup>3</sup>, Joseph F. Merola MD MMSc<sup>1</sup>
- <sup>7</sup> <sup>1</sup>Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School,
- 8 Boston, MA
- 9 <sup>2</sup>Signature Healthcare Brockton Hospital, Brockton, MA
- <sup>3</sup>Department of Dermatology, Icahn School of Medicine at Mt. Sinai, New York, NY
- <sup>\*</sup>These authors contributed equally to this work
- 12 **Twitter handle:** @josephmerolamd
- 13
- 14 **Corresponding author:**
- 15 Joseph F. Merola MD MMSc
- 16 Brigham and Women's Hospital
- 17 41 Avenue Louis Pasteur, 319
- 18 Boston, Massachusetts 02115
- 19 Phone: (617) 264-5943
- 20 Fax: (617) 264-3021
- 21 Email: jfmerola@bwh.harvard.edu
- 22
- 23 **Funding sources:** We did not receive funding for this study.

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Conflicts of interest: JFM is a consu	ultant and/or investigator for Merck, Abbyie, Dermayant, Eli							
	,,,							
Lilly, Novartis, Janssen, UCB, Celgene, Sanofi, Regeneron, Arena, Sun Pharma, Biogen, Pfizer,								
EMD Sorono, Avotres and Leo Pharma. ABG has served as a consultant/investigator for Janssen								
Inc., Celgene, Beiersdorf, BMS, Abbvie, UCB, Novartis, Incyte Corporation, Lilly, Reddy Labs,								
Valeant, Dermira, Allergan, Sun Pharmaceutical Industries, XBiotech, Leo, Avotres								
Therapeutics, Boehringer Ingelheim.	She received research/educational grants from Janssen,							
Incyte Corporation, XBiotech, Novar	tis, Boehringer Ingelheim, and UCB. Other authors report							
no conflicts of interest.								
<b>RB approval status:</b> Exempt given	no human subjects.							
Reprint requests: Joseph F. Merola	MD MMSc							
Manuscript word count:	499							
Figures:	1							
Supplementary figures:	0							
Tables:	1							
Supplementary tables:	0							
Keywords: psoriasis, biologics, TNF	F, IL17, IL23, IL12, IL12/23, biologics cancer risk, cancer							
risk with psoriasis treatment, cancer s	survival, immune pathway dysregulation, biologics							
compatibility in active malignancy, b	viologics safety in active malignancy							
	<ul> <li>iilly, Novartis, Janssen, UCB, Celge</li> <li>MD Sorono, Avotres and Leo Pharanc., Celgene, Beiersdorf, BMS, Abb /aleant, Dermira, Allergan, Sun Pha 'herapeutics, Boehringer Ingelheim.</li> <li>ncyte Corporation, XBiotech, Novar o conflicts of interest.</li> <li><b>RB approval status:</b> Exempt given</li> <li><b>Reprint requests:</b> Joseph F. Merola</li> <li><b>Manuscript word count:</b></li> <li><b>Figures:</b></li> <li>Supplementary figures:</li> <li><b>Cables:</b></li> <li>Supplementary tables:</li> <li>Keywords: psoriasis, biologics, TNF isk with psoriasis treatment, cancer status the psoriasis treatment, cancer status in active malignancy, biologica, the particular of the provided and t</li></ul>							

47	
48	Acknowledgements: none
49	
50	The results published here are in whole based upon data generated by the TCGA Research
51	Network: <u>https://www.cancer.gov/tcga</u>
52	
53	Nikolai Klebanov and Joseph Merola had full access to the data in the study and take full
54	responsibility for the integrity of the data and the accuracy of the data analysis.
55	
56	Meeting presentation: results from this study have been accepted as a late-breaking abstract
57	(presentation date 3/21/2020) at 2020 AAD annual meeting in Denver, CO, which has been
58	cancelled due to COVID-19 concerns.

#### 59 **Research letter**

60 While tumor necrosis factor (TNF), interleukin (IL)17, IL23, and IL12/23 inhibitors have revolutionized psoriasis management, their safety in patients with active or recent malignancy 61 remains an area of unmet need.<sup>1</sup> We explored the relationship between low expression of key 62 genes encoding the respective targets of these biologic molecules, as a surrogate for targeted 63 biologic therapy, and overall survival across multiple cancers using data from The Cancer 64 65 Genome Atlas (TCGA). We retrieved clinical data and tumor RNA-Seq gene expression data for 66 31 malignancies. All patients had active cancer during sample collection. We used cox-67 proportional hazards to model overall survival as a function of low and high TNF, IL17A, IL23A, 68 and *IL12B* expression (split by median expression value). To mitigate the false discovery rate 69 (FDR) owing to multiple testing among distinct cancers, we applied a highly-conservative FDR p-value correction to the results of the multivariate hazards models after adjusting for sex, age at 70 71 diagnosis, and pathologic tumor stage. After removing cohorts that had relatively low (<10<sup>th</sup> percentile) numbers of patients, 27 72 malignancies were evaluated (9274 patients, **Table 1**). In general, we found a reassuring pattern 73 of no impact on survival across multiple malignancies. Four potentially 'harmful' associations 74 75 were identified (Figure 1): low *TNF*-expression in cutaneous melanoma (n=430) had a survival 76 hazard ratio (HR) of 1.65 [1.24-2.19] (p-FDR=0.017), and low TNF-expression in sarcoma 77 (n=262) had HR=1.92 [1.27-2.89] (p-FDR=0.025); low IL12B-expression in cutaneous 78 melanoma had HR=1.64 [1.23-2.17], p-FDR=0.006, and in breast invasive carcinoma (n=1076) 79 had HR=1.72 [1.24-2.41], p-FDR=0.009. 80 Conversely, low expression of IL17A had no impact on cancer survival. Low IL23A

81 expression was associated with survival 'benefit' in renal clear cell carcinoma (ccRCC, n=531)

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82	with HR=0.53 [0.38-0.73] (p-FDR=0.003). Low <i>IL12B</i> was associated with "benefit" in brain
83	lower grade glioma (n=527, HR=0.53 [0.37-0.76], p-FDR=0.006) and uveal melanoma (n=80,
84	HR= 0.17 [0.07-0.42], p-FDR=0.004).
85	Overall, these findings suggest safety/clinical compatibility of TNF, IL17, IL23, and
86	IL12/23 inhibitors with many malignancies, from a mechanistic standpoint. Indeed, TNF and
87	IL12/23 inhibitors appear to affect the oncogenic pathways underlying only a few specific
88	malignancies. Intriguingly, several of the associations found in our study correlate with pre-
89	clinical and clinical data of malignacy risk with targeted molecules. <sup>2-4</sup>
90	Study limitations include that confounding by treatment could not be estimated due to
91	limited data in TCGA. Expression of key psoriasis pathway mediators were used as proxies for
92	the likely effects of biologics, but actual data on biologic use was not available and the patient
93	population was not known to have psoriasis. While tumors present a complex cytokine network,
94	we limited our analysis to individual cytokine levels which we believe represents the closest
95	surrogate to individual targeted cytokine therapy. Finally, we excluded proteomic data as these
96	are inconsistently available in TCGA. However, evidence suggests that clinical phenotypic traits
97	may correlate better with transcript rather than protein levels. <sup>5</sup>
98	This study represents a novel surrogate and conceptual approach to assessing
99	pharmacologic safety in this population. This hypothesis-generating work should lead to
100	mechanistic, pre-clinical/clinical studies to confirm our findings and, together, provide evidence
101	to guide clinical decisions.

5

### **Table I. Clinical characteristics of cancer patient cohorts.**

Cancer	n (total= 9274)	E x	Age at diagnosis, years, median (IQR)	Male n (%)	Femal e n (%)	Stage 0- II n (%)	Stage III-IV n (%)	Alive n (%)	Dead n (%)	Time-to-follow-up, months, median (IQR)
Adrenocortical CA	77		49 (25)	29 (38% )	48 (62% )	46 (60%)	31 (40%)	50 (65 %)	27 (35 %)	38.5 (45.8)
Bladder CA	405		69 (16)	299 (74% )	106 (26% )	131 (32%)	274 (68%)	228 (56 %)	177 (44 %)	17.6 (20.3)
Breast invasive CA	1076		59 (19)	12 (1%)	1064 (99% )	792 (74%)	284 (26%)	924 (86 %)	152 (14 %)	28.2 (40.4)
Cervical SCC	295		46 (18)	0 (0%)	295 (100 %)	229 (78%)	66 (22%)	223 (76 %)	72 (24 %)	21.6 (30.3)
Cholangiocarcin oma	36	*	67 (16)	16 (44%	20 (56%	28 (78%)	8 (22%)	18 (50 %)	18 (50 %)	21.2 (26.7)
Colon adenocarcinoma	189		72 (17)	91 (48%	98 (52%	109 (58%)	80 (42%)	151 (80 %)	38 (20 %)	24 (22.5)
Diffuse large B- cell lymphoma	41	*	56 (22)	) 18 (44%	) 23 (56%	24 (59%)	17 (41%)	34 (83	7 (17 %)	31.7 (32.4)
Esophageal CA	162		60 (19)	) 138 (85%	) 24 (15%	97 (60%)	65 (40%)	97 (60	65 (40	13.4 (14.3)
Glioblastoma multiforme	171		60 (19)	) 111 (65%	) 60 (35%	Stage unavail	Stage unavail	%) 32 (19	%) 139 (81	12.3 (12.3)
Head and Neck	521		61 (15)	) 385 (74%	) 136 (26%	able 111 (21%)	410 (79%)	%) 300 (58	%) 221 (42	21.2 (26.3)
Kidney	65	*	50 (19)	) 38 (58%	) 27 (42%	45 (69%)	20 (31%)	%) 56 (86	%) 9 (14	73.9 (70.6)
Kidney RCC	531		61 (18)	) 343 (65%	) 188 (35%	325 (61%)	206 (30%)	%) 358 (67	%) 173 (33	39.4 (45.2)
Kidney renal papillary cell	286		62 (18)	) 211 (74%	) 75 (26%	201	(39%) 85	%) 242 (85	%) 44 (15	25.2 (35.7)
CA Acute myeloid leukemia	163		59 (23)	) 88 (54%	) 75 (46%	(70%) Stage unavail	(30%) Stage unavail	%) 58 (36	%) 105 (64	11 (21)
(AML) Brain lower	527		41 (21)	) 290 (55%	) 237 (45%	able Stage	able Stage	(30 %) 394 (75	(01 %) 133 (25	23.2 (27.1)
(LGG)	327		(1 (17)	) 236	(45%) ) 110 (22%)	able 256	able 90	(73 %) 232	(23 %) 114 (22	10 (25.7)
Liver HCC	340		01 (17)	(68% ) 221	(32% ) 259	(74%) 374	(26%) 106	(67 %) 308	(33 %) 172	19 (25.7)
adenocarcinoma	480		66 (13)	(46% ) 358	(54% ) 127	(78%)	(22%)	(64 %) 275	(36 %) 210	21.1 (21.6)
Lung SCC	485		68 (11)	(74% )	(26% ) 293	(81%)	(19%)	(57 %) 115	(43 %) 178	21.4 (29.6)
CA	293		58 (16)	0 (0%)	(100 %)	21 (7%)	(93%)	(39 %)	(61 %)	31.6 (37.1)

Pancreatic adenocarcinoma	177		65 (16)	97 (55%	80 (45% )	168 (95%)	9 (5%)	84 (47 %)	93 (53 %)	15.2 (12.8)
Pheochromocyt oma/paraganglio ma	184		46 (23)	82 (45% )	102 (55% )	Stage unavail able	Stage unavail able	176 (96 %)	8 (4%)	24.7 (32.3)
Prostate adenocarcinoma	487		61 (10)	487 (100 %)	0 (0%)	Stage unavail able	Stage unavail able	477 (98 %)	10 (2%)	30.4 (31.4)
Rectum adenocarcinoma	72		67 (11)	39 (54% )	33 (46% )	43 (60%)	29 (40%)	63 (88 %)	9 (13 %)	17.5 (28.6)
Sarcoma	262		61 (19)	119 (45% )	143 (55% )	Stage unavail able	Stage unavail able	164 (63 %)	98 (37 %)	31.3 (35.8)
Skin cutaneous melanoma	430		58 (23)	268 (62% )	162 (38% )	235 (55%)	195 (45%)	225 (52 %)	205 (48 %)	34.5 (58.8)
Stomach adenocarcinoma	382		67 (15)	243 (64% )	139 (36% )	173 (45%)	209 (55%)	232 (61 %)	150 (39 %)	14.8 (16.5)
Thyroid carcinoma	507		46 (23)	139 (27% )	368 (73% )	339 (67%)	168 (33%)	491 (97 %)	16 (3%)	30.9 (31.9)
Thymoma	119		60 (20)	63 (53% )	56 (47% )	Stage unavail able	Stage unavail able	110 (92 %)	9 (8%)	40.1 (41.1)
Endometrial CA	369		63 (13)	0 (0%)	369 (100 %)	271 (73%)	98 (27%)	310 (84 %)	59 (16 %)	33.4 (41.2)
Uterine carcinosarcoma	56	*	69 (14)	0 (0%)	56 (100 %)	26 (46%)	30 (54%)	22 (39 %)	34 (61 %)	20 (19.3)
Uveal melanoma	80		62 (23)	45 (56% )	35 (44% )	39 (49%)	41 (51%)	57 (71 %)	23 (29 %)	25.8 (24.1)

103

Ex., excluded; IQR, interquartile range; CA, carcinoma; SCC, squamous cell carcinoma; RCC, renal clear cell
 carcinoma; HCC, hepatocellular carcinoma

106

107 \* Cholangiocarcinoma, lymphoma, kidney chromophobe, uterine carcinosarcoma excluded from analysis due

108 to low number of patients/survival events (n < 10th percentile of n)

109

#### 110 FIGURE LEGENDS

#### 111 Figure 1. Associations between overall survival among 27 types of cancer with low and high

#### 112 tumor gene expression of *TNF*, *IL17A*, *IL23A*, and *IL12B*.

113 Effects of low tumor expression of TNF, IL17A, IL23A, and IL12B on survival in patients with

114 malignancy. P-values were adjusted using a stringent false discovery rate (FDR) correction for

- 115 27 comparisons (27 unique cancer cohorts). Hazard ratios were adjusted for age, sex, and tumor
- 116 stage when available, and are reported with 95% confidence intervals.

117

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Gene, Cancer	Hazard Ratio (HR) p	p (FDR)	Forest Plot of Hazard Ratio
Acute myeloid leukemia (n=163)	1.33 [0.90, 1.96] 0.154	0.462	
L17A L23A L12B	0.76 [0.33, 1.74] 0.513 1.13 [0.76, 1.66] 0.552 1.18 [0.80, 1.74] 0.406	0.858 0.739 0.739	
Adrenocortical carcinoma (n=77) TNF IL17A	0.64 [0.29, 1.42] 0.276 0.26 [0.03, 2.07] 0.201	0.677 0.777	
IL23A IL12B Bladder carcinoma (n=405)	0.41 [0.17, 1.00] 0.05 1.08 [0.45, 2.58] 0.867	0.269 0.909	
TNF 1L17A	1.05 [0.78, 1.42] 0.727 1.28 [0.92, 1.77] 0.137 1.42 [1.05, 1.93] 0.037	0.947	
ILI38 Brain lower grade glioma (n=527)	103 0 76 139 0 857	0.909	
117A 1123A	1 05 0 33, 3 30 0 933 1 35 0 96, 1 91 0 087	0.993 0.318	
Breast invasive carcinoma (n=1076)	1.03 [0.75, 1.43] 0.843	0.006	
	0.83 0.51 1.35 0.449 0.96 0.69, 1.32 0.788 1.72 1.24, 2.41 0.001	0.858 0.857 0.009	
TNF IL17A	0.72 [0.45, 1.17] 0.185 1.14 [0.71, 1.81] 0.592	0.499	
L123A L12B Colon adenocarcinoma (n=189)	0.94 [0.59, 1.52] 0.813 1.39 [0.87, 2.23] 0.168	0.857 0.503	
TNF IL17A II 23A	0.88 [0.46, 1.69] 0.703 1.02 [0.53, 1.94] 0.957 1.06 [0.56, 2.02] 0.857	0.947 0.993 0.857	
L12B Cutaneous melanoma (n=430) TNE	0.96 [0.51, 1.83] 0.909	0,909	
L17A L23A	0.55 0.36 0.84 0.006 1.28 0.97 1.70 0.06 1.64 1.23 2.17 0.001	0.165	
Endometrial carcinoma (n=369)	0.96 [0.57, 1.61] 0.877	0.947	
IL23A IL12B Esonbargesi carcinoma (n=162)	1.22 [0.73, 2.06] 0.449 1.28 [0.76, 2.14] 0.348	0.739 0.739	
The IL17A	1.27 [0.78, 2.07] 0.345 0.92 [0.55, 1.54] 0.754	0.775	
IL23A IL12B Glioblastoma multiforme (n=171)		0.834	
INF L17A L23A	0.44 0.16 1.23 0.117 0.79 0.56 1.12 0.181	0.614 0.488	
Head and neck squamous carcinoma (n=521) TNF	1.06 [0.81, 1.39] 0.689	0,909	
L17A L23A L128	1.31 [1.00, 1.72] 0.051 1.35 [1.03, 1.76] 0.029 1.27 [0.98, 1.66] 0.076	0.519 0.258 0.256	
Hepatoce∎ular carcinoma (n=346) TNF IL17A	0.95 0.66, 1.37 0.784	0.947	
IL23A IL12B Kidney renal clear cell carcinoma (n=531)	1.11 [0.77, 1.61] 0.575 1.10 [0.76, 1.59] 0.623	0.739 0.909	
TNF IL17A IL23A	0.98 [0.72, 1.32] 0.874 1.25 [0.78, 2.00] 0.35 0.53 [0.38, 0.73] 1e-04	0.947 0.858 0.003	
IL12B Kidney renal papillary cell carcinoma (n=286) TNF	0.95 [0.71, 1.29] 0.759	0,909	
L17A L23A L12B	1.45 [0.56, 3.73] 0.441 0.88 [0.48, 1.62] 0.685 0.46 [0.24, 0.90] 0.022	0.858 0.804 0.1	
Lung adenocarcinoma (n=480) TNF IL17A	1.31 [0.96, 1.78] 0.092 1.17 [0.86, 1.59] 0.316	0.412	
IL23A IL12B Lung squamous cell carcinoma (n=485)	0.74 [0.54, 1.00] 0.05 1.51 [1.10, 2.06] 0.011	0.269 0.059	
TNF	0.76 [0.58, 1.00] 0.054 1.13 [0.86, 1.48] 0.397 1.18 [0.90, 1.55] 0.236	0.291 0.858 0.497	
IL12B Ovarian serous cystadenocarcinoma (n=293) TNF	_ 0.92 [0.70, 1.21] _ 0.538 1.10 [0.81, 1.48] 0.543	0.855	
L17A L23A L128	1.13 0.66, 1.92 0.665 0.80 0.59, 1.09 0.162 1.14 0.84, 1.54 0.406	0.884 0.486 0.739	
Pancreatic adenocarcinoma (n=177) TNF III 74	1.58 [1.04, 2.41] 0.034 0.86 [0.53, 1.40] 0.555	0.229	
IL23A IL12B Pheochromocytoma/paraganglioma (n=184)	0.90 [0.60, 1.36] 0.616 1.19 [0.79, 1.80] 0.41	0.756 0.739	
TNF IL17A II 23A	1.47 [0.35, 6,23] 0.6 1.00 [0.00, Inf.] 0.999 2.67 [0.52, 13,7] 0.239	0.947 0.999 0.497	
IL12B Prostate adenocarcinoma (n=487)	2.95 [0.58, 15.0] 0.191	0.517	
L17A L23A L128	1.61 0.42 6.27 0.49 0.64 0.18 2.31 0.5 1.16 0.33 4.10 0.818	0.858	
Rectum adenocarcinoma (n=72)	4.18 [0.66, 26.5] 0.129	0.448	
IL23A IL12B Sarcoma (n=262)	1.20 [0.19, 7.54] 0.84e 0.48 [0.11, 2.11] 0.33	0.857 0.739	
TNF IL17A	1.92 [1.27, 2.89] 0.002 0.94 [0.47, 1.87] 0.85 1.22 [0.82, 1.83] 0.225	0.025	
IL12B Stomach adenocarcinoma (n=382)		0.178	······································
L17A L23A	0.87 0.63, 1.20 0.406 1.14 0.82, 1.57 0.442 0.94 0.68 1.30 0.69	0.858	
Thymoma (n=119)	0.31 [0.07, 1.43] 0.133	0,448	
L123A LL12B Thirstel carcinoma (n=607)	1.71 [0.40, 7.25] 0.466 _ 0.91 [0.22, 3.86] _ 0.903	0.739	
TNF 1L17A	1.00 [0.37, 2.68] 0.996 0.69 [0.21, 2.23] 0.532 2.51 [0.85, 7.40] 0.053	0.996	
Uveal melanoma (n=80)	1.11 0.40 3.07 0.834	0.909	
L17A L23A	0.47 0.20 1.10 0.083 0.59 0.25 1.40 0.231	0.558 0.497	
ALL CANCERS (n=9076)	1.08 [0.96, 1.21] 0.184	0.004	
123A 1128	1.02 [0.91, 1.14] 0.821 1.02 [0.91, 1.16] 0.704 1.07 [0.93, 1.23] 0.365		
		0.	031 0.062 0.125 0.250 0.500 1.00 2.00 4.00 8.00 16.00

<---Low Expression Better--- ---Low Expression Worse-->