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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

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Research letter

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 remains an area of unmet need.[1] We explored the relationship between low expression of key genes encoding the respective targets of these biologic molecules, as a surrogate for targeted biologic therapy, and overall survival across multiple cancers using data from The Cancer Genome Atlas (TCGA). We retrieved clinical data and tumor RNA-Seq gene expression data for 31 malignancies. All patients had active cancer during sample collection. We used cox-proportional hazards to model overall survival as a function of low and high *TNF, IL17A, IL23A,* and *IL12B* expression (split by median expression value). To mitigate the false discovery rate (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 diagnosis, and pathologic tumor stage.

After removing cohorts that had relatively low (<10th percentile) numbers of patients, 27 malignancies were evaluated (9274 patients, **Table 1**). In general, we found a reassuring pattern of no impact on survival across multiple malignancies. Four potentially 'harmful' associations were identified (**Figure 1**): low *TNF*-expression in cutaneous melanoma (n=430) had a survival hazard ratio (HR) of 1.65 [1.24-2.19] (p-FDR=0.017), and low *TNF*-expression in sarcoma (n=262) had HR=1.92 [1.27-2.89] (p-FDR=0.025); low *IL12B*-expression in cutaneous melanoma had HR=1.64 [1.23-2.17], p-FDR=0.006, and in breast invasive carcinoma (n=1076) had HR=1.72 [1.24-2.41], p-FDR=0.009.

Conversely, low expression of *IL17A* had no impact on cancer survival. Low *IL23A* expression was associated with survival 'benefit' in renal clear cell carcinoma (ccRCC, n=531)

with HR=0.53 [0.38-0.73] (p-FDR=0.003). Low *IL12B* was associated with "benefit" in brain lower grade glioma (n=527, HR=0.53 [0.37-0.76], p-FDR=0.006) and uveal melanoma (n=80, HR= 0.17 [0.07-0.42], p-FDR=0.004).

Overall, these findings suggest safety/clinical compatibility of TNF, IL17, IL23, and IL12/23 inhibitors with many malignancies, from a mechanistic standpoint. Indeed, TNF and IL12/23 inhibitors appear to affect the oncogenic pathways underlying only a few specific malignancies. Intriguingly, several of the associations found in our study correlate with pre-clinical and clinical data of malignacy risk with targeted molecules.[2-4]

Study limitations include that confounding by treatment could not be estimated due to limited data in TCGA. Expression of key psoriasis pathway mediators were used as proxies for the likely effects of biologics, but actual data on biologic use was not available and the patient population was not known to have psoriasis. While tumors present a complex cytokine network, we limited our analysis to individual cytokine levels which we believe represents the closest surrogate to individual targeted cytokine therapy. Finally, we excluded proteomic data as these are inconsistently available in TCGA. However, evidence suggests that clinical phenotypic traits may correlate better with transcript rather than protein levels.[5]

This study represents a novel surrogate and conceptual approach to assessing pharmacologic safety in this population. This hypothesis-generating work should lead to mechanistic, pre-clinical/clinical studies to confirm our findings and, together, provide evidence to guide clinical decisions.

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

Cancer	n (total= 9274)	Ex.	Age at diagnosis, years, median (IQR)	Male n (%)	Female 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)
Cholangiocarcinoma	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 unavailable	Stage unavailable	32 (19%)	139 (81%)	12.3 (12.3)
Head and Neck SCC	521		61 (15)	385 (74%)	136 (26%)	111 (21%)	410 (79%)	300 (58%)	221 (42%)	21.2 (26.3)
Kidney chromophobe	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 (39%)	358 (67%)	173 (33%)	39.4 (45.2)
Kidney renal papillary cell CA	286		62 (18)	211 (74%)	75 (26%)	201 (70%)	85 (30%)	242 (85%)	44 (15%)	25.2 (35.7)
Acute myeloid leukemia (AML)	163		59 (23)	88 (54%)	75 (46%)	Stage unavailable	Stage unavailable	58 (36%)	105 (64%)	11 (21)
Brain lower grade glioma (LGG)	527		41 (21)	290 (55%)	237 (45%)	Stage unavailable	Stage unavailable	394 (75%)	133 (25%)	23.2 (27.1)
Liver HCC	346		61 (17)	236 (68%)	110 (32%)	256 (74%)	90 (26%)	232 (67%)	114 (33%)	19 (25.7)
Lung adenocarcinoma	480		66 (13)	221 (46%)	259 (54%)	374 (78%)	106 (22%)	308 (64%)	172 (36%)	21.1 (21.6)
Lung SCC	485		68 (11)	358 (74%)	127 (26%)	395 (81%)	90 (19%)	275 (57%)	210 (43%)	21.4 (29.6)
Ovarian serous CA	293		58 (16)	0 (0%)	293 (100%)	21 (7%)	272 (93%)	115 (39%)	178 (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)
Pheochromocytoma/paraganglioma	184		46 (23)	82 (45%)	102 (55%)	Stage unavailable	Stage unavailable	176 (96%)	8 (4%)	24.7 (32.3)
Prostate adenocarcinoma	487		61 (10)	487 (100%)	0 (0%)	Stage unavailable	Stage unavailable	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 unavailable	Stage unavailable	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 unavailable	Stage unavailable	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)

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

* Cholangiocarcinoma, lymphoma, kidney chromophobe, uterine carcinosarcoma excluded from analysis due to low number of patients/survival events (n < 10th percentile of n)

FIGURE LEGENDS

Figure 1. Associations between overall survival among 27 types of cancer with low and high tumor gene expression of *TNF*, *IL17A*, *IL23A*, and *IL12B*.

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