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Expression of IL-4 in Tumors: A Safety Surrogate to Predict Cancer Survival Associated With Biologic Therapies

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INTRODUCTION

Interleukin (IL)-4-targeted therapies have revolutionized management of inflammatory dermatoses. Dupilumab, an IL-4 receptor alpha inhibitor, is approved for moderate-to-severe atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, and eosinophilic esophagitis[1] with ongoing studies including in urticaria, prurigo nodularis, and alopecia.[2] Interleukins are critical mediators of immunosurveillance, and a theoretical increased risk of malignancy exists for any interleukin inhibitor until real-world long-term safety data are explored. Genomic expression studies can help examine if interleukin deficiencies are associated with increased malignancy risk, providing a proxy for long-term interleukin repression.

We utilize data from the Cancer Genome Atlas to investigate if IL-4 expression is correlated with overall survival (OS) in

TABLE 1.

Survival Harm Odds Ratio (OR) With Low IL-4 Expression			
Cancer (n=)	**n**	**OR (high exp=ref)**	***P*-value***
Pheochromocytoma/paraganglioma	184	0.46 [0.11-1.93]	0.291
Adrenocortical CA	77	0.55 [0.22-1.37]	0.198
Brain lower grade glioma	527	0.61 [0.40-0.95]	0.028
Renal cell carcinoma	531	0.74 [0.51-1.09]	0.133
Acute myeloid leukemia	163	0.82 [0.53-1.27]	0.377
Head and Neck CA	521	0.87 [0.55-1.37]	0.542
Glioblastoma multiforme	171	0.87 [0.58-1.31]	0.511
Hepatocellular carcinoma	346	0.87 [0.45-1.69]	0.690
Breast invasive CA	1076	0.90 [0.59-1.38]	0.640
Lung SCC	485	0.94 [0.64-1.37]	0.738
Renal papillary CA	286	0.94 [0.48-1.86]	0.866
Stomach adenocarcinoma	382	0.95 [0.67-1.35]	0.774
Uveal melanoma	80	1.01 [0.29-3.55]	0.988
Bladder CA	405	1.06 [0.69-1.63]	0.790
Colon adenocarcinoma	189	1.09 [0.42-2.84]	0.854
Lung adenocarcinoma	480	1.10 [0.78-1.56]	0.583
Endometrial CA	369	1.12 [0.65-1.95]	0.679
Esophageal CA	162	1.15 [0.61-2.19]	0.661
Cutaneous melanoma	430	1.36 [0.89-2.07]	0.158
Ovarian serous CA	293	1.43 [0.95-2.17]	0.087
Cervical CA	295	1.53 [0.70-3.35]	0.283
Sarcoma	262	1.82 [1.11-2.97]	0.018 (p_{adj}=0.2479)
Pancreatic adenocarcinoma	177	1.94 [1.12-3.37]	0.018 (p_{adj}=0.2479)
Thymoma	119	1.98 [0.46-8.50]	0.358
Thyroid carcinoma	507	2.72 [0.61-12.10]	0.188

Abbreviations: CA, carcinoma
**P*-value adjusted using False Discovery Rate (FDR)

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multiple cancers. After excluding cohorts with <10th percentile of patients, 25 malignancies were evaluated (n=8517). We used odds ratio to model OS with IL-4 expression (high/low, split by median expression value). Multiple testing correction was addressed with highly-conservative false discovery rate (FDR) P-value correction to the results of the multivariate hazards models, adjusted for sex, age at diagnosis, and tumor stage. Sensitivity analyses were performed with IL-4R (receptor) and IL-13. We found no significant adverse survival effects with IL-4, IL-4R, nor IL-13 expression in the examined cohorts.

IL-4 signaling blockade can lead to enhanced functioning of interferon-γ (IFNγ) producing cells.[3] Previous reports reveal extensive anti-tumor effects of IFNγ in bladder carcinoma, colorectal carcinoma, ovarian carcinoma, and adult T-cell lymphoma.[4] IFNγ can enhance the cytotoxic function of natural killer cells and cytotoxic T cells, increase the antigenicity of tumor cells by up-regulation of major histocompatibility complex class I, induce expression of p21 and p27 molecules to inhibit cell proliferation, and regulate PD-L1 expression on the surface of cancer cells. Furthermore, IFNγ-deficient mice are more susceptible to spontaneous neoplasms[5] and low IFNγ expression is a poor prognostic factor in ovarian carcinoma and melanoma. Our findings provide further support that dupilumab is unlikely to be associated with an increased malignancy risk. Limitations include that IL-4 expression levels are unlikely to directly correlate with a dupilumab-treatment phenotype. Additionally, we focus on individual expression of single cytokines, while pathways often involve complex changes in expression of multiple genes. Further prospective work is needed to continually assess the dupilumab safety profile.

DISCLOSURES

JFM was a consultant and/or investigator for Amgen, BMS, AbbVie, Dermavant, Eli Lilly, Novartis, Janssen, UCB, Sanofi, Regeneron, Sun Pharma, Biogen, Pfizer, and Leo Pharma. NK was previously a consultant for BeiGene. JSS was a consultant and/or investigator for Biogen. LPC has no disclosures. CG has no disclosures.

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