

## RESEARCH LETTER

### Histologic subtype of cutaneous immune-related adverse events predicts overall survival in patients receiving immune checkpoint inhibitors

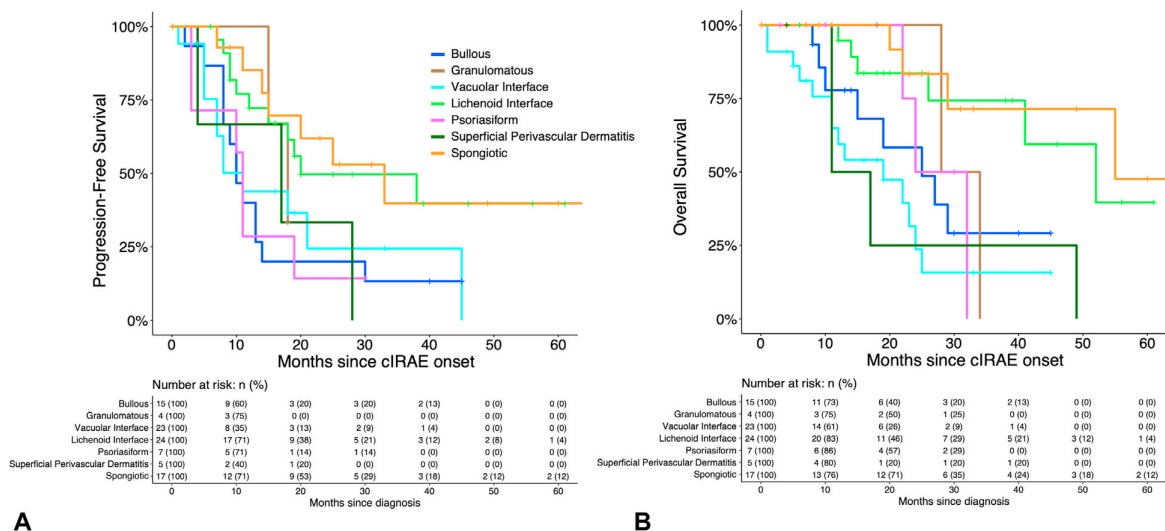
*To the Editor:* Immune-related adverse events due to immune checkpoint inhibitors can lead to treatment interruption or cessation, increasing cancer-related mortality.<sup>1</sup> Cutaneous immune-related adverse events (cIRAEs) typically precede noncutaneous immune-related adverse events (ncIRAEs) and may serve as a clinical indicator for further immune-related adverse event development and overall survival.<sup>1,2</sup> Histopathologic classification is especially critical for cIRAEs because clinical morphology and histopathologic pattern often do not correlate with each other in patients with cIRAEs.<sup>2-5</sup> The goal of our study was to identify associations between histopathologic patterns of cIRAEs with the development of ncIRAEs and patient outcomes.

We performed a 9-year retrospective chart review of patients on immune checkpoint inhibitors at our oncology clinic who underwent a skin biopsy for drug eruption. The skin biopsy's histologic findings were classified based on dominant patterns as follows: bullous (based on positive direct immunofluorescence), granulomatous, vacuolar interface, lichenoid interface, psoriasiform, superficial perivascular dermatitis, and spongiotic. The histology of superficial perivascular dermatitis lacked an epidermal change, and the inflammatory infiltrate was predominantly lymphocytic or

lymphohistiocytic, with or without eosinophils. Logistic regression was used to evaluate associations between the histologic subtypes and other clinical parameters. The Cox proportional hazards analysis was used to calculate progression-free and overall survival hazard ratios (HRs). To address multiple hypothesis testing, only results with a false discovery rate (FDR) of less than 0.15 were considered significant.

Of 95 patients with biopsy-proven cIRAEs (Supplementary Table I, available via Mendeley at <https://data.mendeley.com/datasets/6cvsg3zvg4/1>), at least 1 ncIRAE developed in 48 patients (51%). Forty patients experienced a cIRAE before an ncIRAE developed. The vacuolar interface histology was significantly associated with pneumonitis ( $P = .01$ ). The psoriasiform histology was significantly associated with musculoskeletal ncIRAEs ( $P = .002$ ). Other significant associations included associations between the psoriasiform histology and multiple ncIRAEs ( $P = .02$ ) as well as between ipilimumab/nivolumab combination therapy and the bullous histology ( $P = .03$ ). Majority of ncIRAEs occurred within months of cIRAE onset (Supplementary Fig 1, available via Mendeley at <https://data.mendeley.com/datasets/6cvsg3zvg4/1>).

The spongiotic and lichenoid interface histologic patterns were associated with improved progression-free survival (Fig 1, A), although no subtype reached statistical significance. For overall survival (Fig 1, B), both the spongiotic (HR = 0.28 [0.09-0.82], FDR = 0.07) and lichenoid interface



**Fig 1.** Progression-free survival (A) and overall survival (B) represented using Kaplan-Meier curves stratified by histologic subtype. cIRAE, Cutaneous immune-related adverse events.

(HR = 0.41 [0.17-1.01], FDR = 0.09) subtypes were significantly associated with a decreased mortality risk. In contrast, the vacuolar interface (HR = 3.64 [1.83-7.21], FDR < 0.001) and superficial perivascular dermatitis (HR = 3.07 [0.99-9.43], FDR = 0.09) subtypes were significantly associated with an increased mortality risk.

cIRAEs may serve as an informative and actionable clinical biomarker for the development of ncIRAEs and patient prognosis. In our cohort examining the associations between the biopsy-proven cIRAE histologic subtypes and ncIRAEs, of particular interest was the association of the vacuolar interface histology with pneumonitis because pneumonitis can rapidly progress and increase patient morbidity and mortality. Regarding a significant association between the psoriasiform histology and musculoskeletal ncIRAEs, only 1 of 9 patients with the psoriasiform histology had a prior diagnosis of psoriasis; therefore, exposure to immunotherapy might unmask a predisposition to psoriasis and psoriatic arthritis. The limitations included the fact that this was a single-institution, retrospective, chart-review study; therefore, rarer histologies might not have achieved statistical significance in terms of immune-related adverse event associations. Future studies will need to investigate whether similar cellular and molecular immune mechanisms mediate cIRAEs or ncIRAEs and tumor control.

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#### Conflicts of interest

Dr Kwong is a consultant for Oncoderm and Happy 2nd Birthday. Dr Novoa is a consultant for Enspectra and Stemline therapeutics. Dr Rieger is a consultant for Pfizer and Kyowa Kirin. Drs Hirotsu, Marquez, Robinson, and Zaba and Authors Scott and Tran have no conflicts of interest to declare.

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