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PD-L1 expression in anaplastic large cell lymphoma

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To the editor: We read with interest the recent article "PD-L1 expression is associated with ALK positivity and STAT3 activation, but not outcome in patients with systemic anaplastic large cell lymphoma" [1]. Shen et al examined PD-L1 expression by immunohistochemistry in 95 systemic anaplastic large cell lymphomas (ALCLs) and concluded that PD-L1 expression has no prognostic significance in ALCL, including ALK-negative ALCL.

In a previous study that examined PD-L1 expression in 152 ALCLs, we found that ALK- ALCLs with *DUSP22* rearrangements expressed minimal PD-L1 and pSTAT3^{Tyr705} [2], a finding subsequently replicated [3]. We hypothesized that the lack of PD-L1 might be one component of an immunogenic phenotype contributing to the excellent outcomes usually seen in *DUSP22*-rearranged ALCLs [4, 5]. In light of the data of Shen et al, we examined the association of PD-L1 expression and outcome in our previous series [2]. Of the 152 ALCLs stained for PD-L1, 62 were systemic ALCLs with available outcome data (18 ALK-positive, 44 ALK-negative; M:F, 38:24; mean age, 55 y; median follow-up, 43 months). Using the cutoff of 5% for PD-L1 positivity employed by Shen et al, we found that PD-L1 positivity was associated with inferior outcomes in ALK-negative ALCL (median survival, 38 months vs. 262 months in PD-L1-negative cases; P=0.03, log-rank test; Fig. 1A).

Several factors might account for the different results in our series and that of Shen et al. While used in several studies, the 5% cutoff for PD-L1 positivity may have difficulties with reproducibility, potentially accentuated by antibody/protocol differences ([2]; not specified in Shen et al). Only 27% of our ALK-negative ALCLs were PD-L1-negative using this cutoff, compared to 58% in Shen et al. Analyzing our data with a cutoff based on the median PD-L1 value of 55%, we found an even stronger association of PD-L1 positivity with outcome (median survival, 7 months vs. 216 months in PD-L1-negative cases; P=0.002; Fig. 1B). Differences in the composition of the study groups may also contribute to the different results. Although median follow-up was only 20 months in Shen et al and 5-year overall survival in ALK-negative ALCL is not provided, from their Fig. 4, it appears to be ~25%, which is considerably poorer than the 52% in our data and references they cite (e.g., [6], 49%). Possibly, the more clinically aggressive disease in the series of Shen et al masked

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contributions of PD-L1. Though not reported, the series by Shen et al might have fewer *DUSP22*-rearranged ALCLs than ours (24%), or might be enriched for “high-risk” *DUSP22*-rearranged ALCLs as recently described [3].

Based on these discrepancies and the features of the series analyzed by Shen et al including limited follow-up, we believe the conclusion that PD-L1 is not associated with outcome in ALK-negative ALCL is premature. The collective literature is in agreement that ALCLs demonstrate variable expression of PD-L1. As Shen et al note, the most important implication of this variable expression is the hypothesis that PD-L1 functionally promotes immune escape in some ALCLs but not others and might serve as a biomarker to individualize immunotherapeutic approaches. Our data showing poorer outcomes in PD-L1-positive ALK-negative ALCLs are consistent with this hypothesis and with data from other cancers as reviewed by Shen et al. Future work should examine the functional role of PD-L1 in ALCL and its relationship to immunotherapy response in pre-clinical models and clinical trials.

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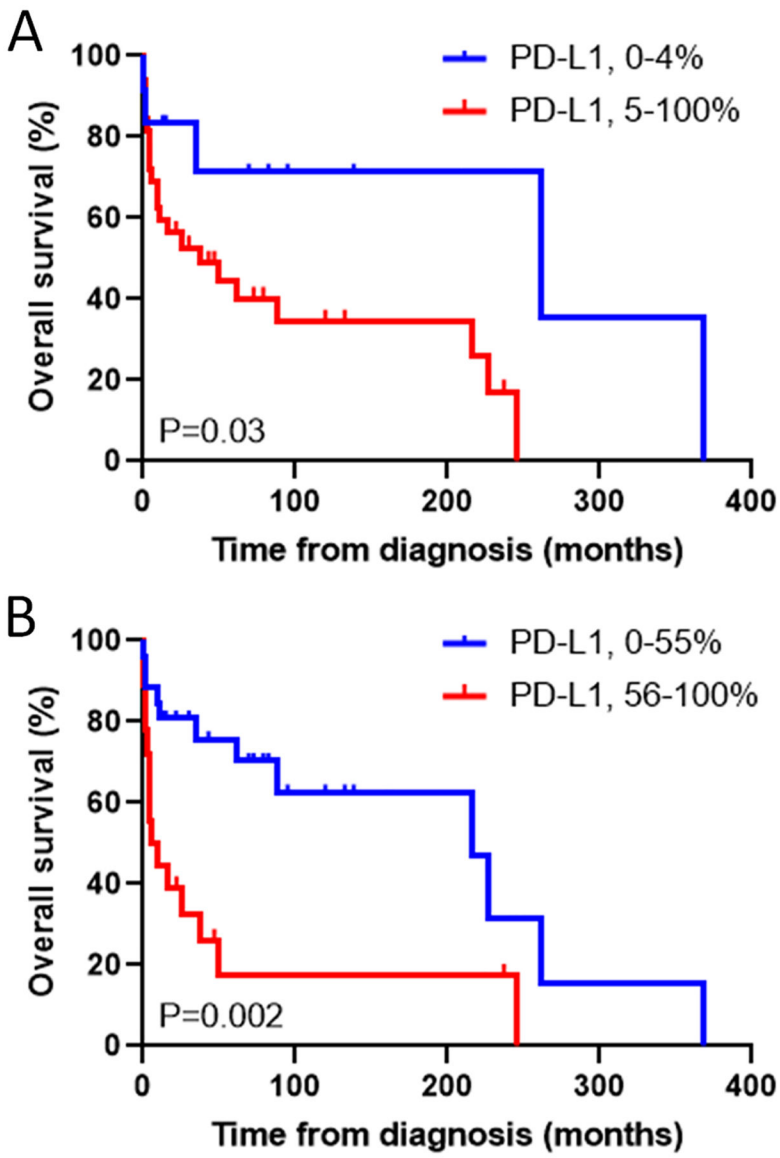

Fig. 1.

Overall survival in systemic ALK-negative anaplastic large cell lymphoma, stratified by PD-L1 expression. (A) Based on a cutoff for positivity of 5% of the neoplastic cells staining, as per Shen et al [1]. (B) Based on a cutoff of 55%, the median PD-L1 value in our series.