Modern Pathology (2020) 33:1234–1235
https://doi.org/10.1038/s41379-020-0522-3

CORRESPONDENCE

Reply to "PD-L1 expression in anaplastic large cell lymphoma"

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Received: 7 January 2020 / Revised: 6 March 2020 / Accepted: 6 March 2020 / Published online: 18 March 2020

To the Editor:

We thank Kong et al. for their comments regarding our study, "PD-L1 expression is associated with ALK positivity and STAT3 activation, but not outcome in patients with systemic anaplastic large cell lymphoma" [1]. In their letter, Kong and colleagues describe PD-L1 expression in 44 patients with ALK-negative anaplastic large cell lymphoma (ALCL) at the Mayo Clinic. They report that PD-L1 positivity is associated with an inferior outcome in ALK-negative ALCL patients, inconsistent with the data we reported earlier.

As was suggested by Kong et al., multiple factors might account for the different results between our cohort and their own patient group. One factor might be the antibody used for PD-L1 immunohistochemistry. We used the 22C3 antibody clone (Dako, Santa Clara, CA, USA) in our study. Using a 5% cutoff as was reported, as well as many other cutoff values not reported, we did not find a significant difference in overall survival between patients with PD-L1+ versus PD-L1-negative ALK-negative ALCL. Another potentially important factor is the different patient cohorts, a well-known factor that can cause differences in survival between studies. These differences may include patient referral patterns, as well as the composition of these cohorts. ALK-negative ALCL has been shown to be heterogeneous with at least three subsets: *DUSP22* rearranged, *TP63* rearranged, and a subset with neither rearrangement. Patients with *DUSP22* rearrangement, representing 19–30% of all ALK-negative ALCL cases [2, 3], has been associated with a good prognosis with a 5-year overall survival of 80–90%, comparable to that of patients with ALK + ALCL [4]. *TP63* rearrangement, by contrast, is associated with a very poor prognosis and the patient group negative for both abnormalities has an intermediate prognosis. In our study, we do not have complete *DUSP22* or *TP63* rearrangement data on the ALK-negative ALCL cases. We agree that the cohort we reported may have had a greater percentage of patients with clinically aggressive disease as compared with the cohort reported by Kong et al.

Although the data reported by Kong et al. suggest that PD-L1 positivity is associated with inferior outcome in patients with ALK-negative ALCL, we believe their data would be strengthened by a multivariate analysis showing that PD-L1 expression is an independent prognostic factor in patients with ALK-negative ALCL. As shown by others, PD-L1 is minimally expressed by *DUSP22*-rearranged ALCLs and this patient subset is reported to have a better prognosis as described above. This leads us to ask about a potential relationship between PD-L1 expression and *DUSP22* rearrangement. From their letter, the possible prognostic role of PD-L1 expression in non-*DUSP22*-rearranged ALK-negative ALCL cannot be determined.

Kong and colleagues commented on the 25% 5-year overall survival in our cohort, being "considerably lower" than their own data. The reported 5-year overall survival of patients with ALK-negative ALCL ranges from 30 to 50% [2, 4]. Therefore the survival rate in our study is a little low, but still consistent with other reports in the literature. Our institution is a referral center and may therefore select for a greater percentage of patients with poorer prognostic features. Kong et al. also noted that the median follow-up of 20 months (range, 0–224 months) in our study was "limited". We agree, however, this follow-up time was sufficient for us to observe the prognostic significance of ALK and the International Prognostic Index score in our cohort [1], two known prognostic factors in ALCL patients. We would think that the prognostic impact of PD-L1 expression would have been detectable, despite the limitations of our study design.

We also think it would be interest for Kong et al. to report the potential prognostic impact of PD-L1 expression in patients with ALK + ALCL. Patients with ALK + ALCL

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are known to generally have a better prognosis than patients with ALK-negative ALCL. In our study, we found that PD-L1 expression in ALK + ALCL cases was significantly higher than in ALK-negative ALCL cases [1]. Higher PD-L1 expression in ALK + ALCL versus ALK-negative ALCL seems somewhat counterintuitive, since ALK + ALCL is associated with a better prognosis. Perhaps ALK expression overpowers any prognostic impact of PD-L1 expression in ALK + ALCL patients.

In summary, we agree with Kong and colleagues that PD-L1 expression in a subset of ALCL cases makes it a potential therapeutic target for PD-1 blockade. However, our data are inconsistent regarding the prognostic impact of PD-L1 expression in ALK-negative ALCL. Our conclusion regarding the prognostic impact of PD-L1 was based on our own data, and was not intended to be the only opinion on this subject, and therefore we welcome additional data and discussion. It should be noted that the numbers of patients with ALK-negative ALCL in our own cohort and that of the Mayo Clinic are not high, and therefore additional studies with greater patient numbers and controlled trials will be helpful to resolve the question. We very much appreciate the insightful letter of Kong and colleagues and this opportunity to respond.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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