Qeios

Peer Review

Review of: "A Novel Bispecific Antibody CVL006 Superior to AK112 for Dual Targeting of PD-L1 and VEGF in Cancer Therapy"

Liusong Yin[1]

1. Independent researcher

In this study, Wang et al. described a novel bispecific antibody, CVL006, targeting both the PDL1 and VEGF pathways for enhanced anti-tumor efficacy, which is of great significance in addressing the resistance of current immunotherapies.

A few comments need to be addressed:

1. The authors claimed CVL006 to be superior to the clinically validated AK112. More specifically, the authors mentioned that CVL006 outperformed AK112 in both VEGF and PDL1 (or PD1) binding activities (Page 9).

However, as shown in Figure 1, both CVL006 and AK112 are tetravalent bispecific antibodies based on bevacizumab, with CVL006 incorporating an αPD-L1 VHH domain fused at the N-terminus of the light chain (LC), while AK112 employs an anti-PD1 scFv at the C-terminus of the heavy chain (HC). In terms of VEGF binding, CVL006's LC N-terminus fusion may influence the VEGF binding, as demonstrated in Supplementary Table 2; on the other hand, AK112's HC C-terminus fusion may have less influence on VEGF binding. Therefore, it does not make sense that CVL006 has a better binding affinity for VEGF than AK112, only based on separate non-head-to-head comparison data, which is also validated by the comparable VEGF inhibition activity of both molecules (Figure 3, Page 12). The authors need to perform a very straightforward experiment by directly comparing CVL006's and AK112's binding affinity to VEGF, either through ELISA or SPR.

doi.org/10.32388/A75LT4

In terms of PDL1 or PD1 binding, it does not make sense to directly compare, especially for FACS data, as PDL1 or PD1 binding also relies on the abundance of PDL1 or PD1 on the overexpressed cell line; more importantly, in physiological conditions, PDL1's expression profile and that of PD1 are totally different, making the comparison of the affinity of CVL006 and AK112 to PDL1 or PD1 meaningless.

In the NCI-H1048 lung cancer xenograft model, the authors mentioned that CVL006 exhibited significantly superior efficacy compared to AK112 (Page 14). However, since this is an immunodeficient mice model and both CLV006 and AK112 leverage the anti-tumor immunity through the PD(L)1 axis, it is not clinically relevant to only assess the VEGF function. The authors are suggested to perform a direct comparison of CVL006 with AK112 in the immune-competent models, as in Figure 5.

2. Figure 4, please plot as Lysis (%) for the ADCC effects.

3. Page 14, Figure 5, the authors mentioned that the combination of CVL006 with paclitaxel demonstrated a synergistic effect. However, "synergistic effect" is a very specific term compared with "additive effect." The authors need to justify in Figure 5 whether it is just a simple "additive effect" of the combination, as both CVL006 and paclitaxel have significant anti-tumor efficacy.

4. AK112's MOA has just been published with the cooperative binding of AK112 to both VEGF and PD1 (Figure 7, Zhong et al., 2025, iScience). The authors are suggested to evaluate with specific experiments whether CVL006 also leverages a similar cooperative MOA.

5. PD1 and PDL1 are largely different in expression profiles, MOAs, and clinical efficacy of anti-PD1 and -PDL1 antibodies. The authors are suggested to discuss the difference between PD1/VEGF and PDL1/VEGF in those aspects.

6. Minor point: there are some mismatches in the downloaded PDF of the manuscript regarding chemical names and exponential numbers, especially in the Experimental Methods section.

Declarations

Potential competing interests: No potential competing interests to declare.