265 CD47XPD-L1 BISPECIFIC ANTIBODIES FOR CANCER THERAPY

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Background PD-1/PD-L1 blockade can significantly improve survival across many types of cancer, but only in a minority of patients. To broaden its therapeutic efficacy, several combination partners are now being evaluated together with PD-1/PD-L1 blockade. Agents blocking CD47/SIRPα innate immune checkpoint are one such example, and co-targeting PD-1/PD-L1 and CD47 with monoclonal antibody (mAb) combinations showed increased antitumor responses in preclinical studies. However, CD47 mAbs are hindered by ubiquitous CD47 expression leading to rapid target-mediated clearance and safety concerns. Consequently, dual-targeting CD47xPD-L1 bispecific antibodies (bsAbs) enabling preferential inhibition of CD47 on PD-L1-positive cells are being tested as an alternative approach. We compare here two distinct bsAbs, based on a common PD-L1 antibody arm, with differing FcgR-enabling effector functions and CD47-binding arm affinities.

Methods An array of fully human bsAbs associating a high affinity PD-L1 arm to CD47 arms with varying affinities were generated using the κλ-body platform.[1] CD47xPD-L1 bsAbs of human IgG1 isotype (CD47 low affinities) or IgG4 isotype (CD47 high affinities) were screened in various binding assays (including to red blood cells (RBC)) and in receptor-blocking assays, and then tested for their Fc-mediated killing and T-cell activation activity (SEA-stimulated PBMC assay). Selected molecules were evaluated in vivo.

Results Both bsAb approaches demonstrated strong blockade of PD-1/PD-L1 interaction and significantly enhanced T-cell activation in vitro. CD47lowxPD-L1 IgG1 bsAbs did not bind to RBC and showed PD-L1-guided inhibition of CD47. ADCP and ADCC experiments with a panel of tumor cell lines expressing various target levels showed superior killing activity with CD47lowxPD-L1 IgG1 bsAbs as compared to the anti-PD-L1 IgG1 mAb, avelumab. On the other hand, CD47highxPD-L1 IgG4 bsAbs showed residual RBC binding and PD-L1-independent blocking of CD47/SIRPα These CD47high IgG4 bsAbs were able to enhance the anti-tumor activity of anti-tumor-associated antigen (TAA) mAbs in vitro (phagocytosis), and in vivo (Raji lymphoma xenograft model). In addition, anti-tumor activity of mouse CD47xPD-L1 bsAbs in a syngeneic MC38 colon carcinoma model was demonstrated.

Conclusions With the objective of finding the optimal CD47xPD-L1 bsAb design, two approaches targeting CD47 and PD-L1 inhibition were tested. Both the CD47lowxPD-L1 IgG1 bsAbs and CD47highxPD-L1 IgG4 bsAbs were able to mediate enhanced antitumor responses, the former as a standalone treatment, the latter in conjunction with an anti-TAA mAb. To further characterize the CD47lowxPD-L1 and CD47highxPD-L1 bsAbs, lead candidates will be tested in PK and tolerability studies in non-human primates.

REFERENCES

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