PRECLINICAL CHARACTERIZATION OF D3L-001, A NOVEL BISPECIFIC ANTIBODY THAT ENHANCE PHAGOCYTOSIS AND ERADICATION OF HER2 POSITIVE SOLID TUMOR VIA HER2 AND CD47 DUAL BLOCKADE

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Background HER2 is overexpressed in different solid tumors, including 15-20% of breast cancer. The advent of HER2-targeted drugs, including antibodies (Ab), TKI and ADC, have revolutionized HER2+ cancer treatment; however, the disease will eventually recur in most patients. Recent studies have suggested efficacy of HER2 target antibodies (Ab) therapy could be further enhanced by antibody-dependent cellular phagocytosis (ADCP) principally regulated by antiphagocytic “don’t-eat-me” CD47 signals. CD47 is overexpressed in many HER2+ cancers, which suppresses phagocytosis through binding to SIRPα.

In this study, an internally discovered anti-HER2×CD47 bispecific antibody (bsAb), D3L-001, demonstrated synergistic anti-tumor effect by HER2 guided CD47 co-blocking. It enhances macrophage mediated phagocytosis and significantly suppresses in vivo tumor growth while sparing hematological toxicities, which are typically induced by anti-CD47 antibodies.

Methods SK-BR-3, HCC1954 and Jurkat cells were used. Cellular binding and in vitro blocking of CD47 and SIRPα interaction by Abs were measured by FACS. Monocytes were isolated from PBMC and differentiated into macrophages, which were then used for ADCP assays. Abs in vivo efficacy were examined in HER2+ tumor models.

Results D3L-001 was designed to have higher HER2 affinity (Kd < 1 nM) than that of CD47 (Kd >10 nM). With this unique design, D3L-001 showed preferential binding to HER2/CD47 double positive tumor cells as compared to CD47 single positive cells (figure 1). This preferential binding prevents D3L-001 from inducing red blood cell hemagglutination in vitro. Moreover, its binding to HER2+ tumor cells wasn’t affected by whole blood cell pre-culture treatment, indicating low systemic CD47 antigen sink effect. Intriguingly, we found that D3L-001 can block the interaction between SIRPα and CD47 on HER2+ tumor cells very effectively, probably due to the avidity effect induced by the addition of HER2 binding arm (figure 2). This potent blocking translated well into enhanced in vitro phagocytosis ability. D3L-001 showed stronger anti-tumor effect than trastuzumab in a panel of HER2+ tumor models. We observed significant tumor growth inhibition and regression in trastuzumab resistant xenograft models in a dose-dependent manner. D3L-001 demonstrated better efficacy than combination of trastuzumab and magrolimab, indicating synergistic effect of co-blocking HER2 and CD47 in bispecific form. In addition, the combination of D3L-001 with pertuzumab also showed synergistic in vivo efficacy.

Conclusions D3L-001 is a novel HER2×CD47 bsAb which demonstrated potent and synergistic anti-tumor effect via HER2 guided CD47 co-blocking in both in vitro and in vivo models. D3L-001 might provide a novel treatment approach for HER2+ cancers and overcome their resistance to current therapies.

Abstract 1377 Figure 1 In vitro cellular binding of D3L-001 to HER2/CD47 double positive SK-BR-3 cell (A) and CD47 single positive red blood cell (B).

Abstract 1377 Figure 2 In vitro cellular blocking of SIRPα and CD47 interaction by D3L-001.