

cell surface and the reduced performance of ADCs against targets with low expression. Furthermore, ADC molecules often demonstrate toxicity related to free warhead, likely a result of linker degradation, resulting in maximum tolerated dose limitations and potential impacts on efficacy unrelated to the target chosen for the antibody. This is less likely to be an issue for a T cell-engaging bispecific molecule, engineered to engage DLL3 and CD3 simultaneously, given the required sensitivity of T cells for their targets, and highly potent in vitro cytotoxicity has been demonstrated on cell lines expressing several hundred target proteins per cell. Additionally, the usually smaller size of a bispecific T cell engaging antibody construct relative to a normal antibody (full-length IgG) may improve tissue penetration and increase potency due to more efficient engagement of the DLL3 and CD3 targets, resulting in improved synapse formation between the T cell and target tumor cell.

SCLC remains a significant unmet medical need, and new therapeutic options are required to improve the outlook for this sizable patient population. The above discussed bispecific antibody modality is clinically validated, and as such an antibody construct targeting DLL3 and CD3 represents a promising new possibility for the treatment of SCLC and an opportunity to improve the survival of patients suffering with this indication. As there is still a need for having available further options for the treatment of tumor or cancer diseases related to the overexpression of DLL3, there are provided herewith means and methods for the solution of this problem in the form of a bispecific antibody construct with one binding domain directed to DLL3 and a second binding domain directed to CD3 on T cells.

Summary

Thus, in a first example, the present disclosure provides a bispecific antibody construct comprising a first binding domain which binds to human DLL3 on the surface of a target cell and a second binding domain which binds to human CD3 on the surface of a T cell, wherein the first binding domain binds to an epitope of DLL3 which is comprised within the region as depicted in SEQ ID NO: 260.

In one aspect, the present disclosure provides for a bispecific antibody construct comprising a first binding domain which binds an epitope of human delta-like ligand 3 (DLL3) on the surface of a target cell within the amino acid sequence of SEQ ID NO: 269 and a second binding domain which binds to human CD3 on the surface of a T cell, wherein the first binding domain comprises a VH region comprising CDR-H1, CDR-H2 and CDR-H3 and a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from the group

consisting of: a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 171, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 172, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 173, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 174, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 175 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 176; b) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 181, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 182, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 183, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 184, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 185 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 186; c) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 191, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 192, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 193, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 194, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 195 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 196; and d) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 201, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 202, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 203, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 204, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 205 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 206.

In another aspect, the present disclosure provides for a pharmaceutical composition comprising the antibody construct as disclosed herein and a pharmaceutical acceptable carrier.

In yet another aspect, the present disclosure provides for a kit comprising the pharmaceutical composition as disclosed herein.

It must be noted that as used herein, the singular forms “a”, “an”, and “the” include plural references unless the context clearly indicates otherwise. Thus, for example, reference to “a reagent” includes one or more of such different reagents and reference to “the method” includes reference to equivalent steps and methods known to those of ordinary skill in the art that could be modified or substituted for the methods described herein.

Claims

1. A bispecific antibody construct comprising a first binding domain which binds an epitope of human Delta-like Ligand 3 (DLL3) on the surface of a target cell within the amino acid sequence of SEQ ID NO: 269 and a second binding domain which binds to human CD3 on the surface of a T cell,
wherein the first binding domain comprises a VH region comprising CDR-H1, CDR-H2 and CDR-H3 and a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from the group consisting of:
 - a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 171, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 172, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 173, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 174, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 175 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 176;
 - b) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 181, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 182, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 183, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 184, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 185 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 186;
 - c) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 191, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 192, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 193, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 194, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 195 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 196; and
 - d) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 201, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 202, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 203, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 204, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 205 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 206.

2. The antibody construct according to claim 1, wherein the first binding domain comprises a VH region comprising an amino acid sequence comprising:
 - a) at least 85% identity to an amino acid sequence of SEQ ID NO: 177, SEQ ID NO: 187, SEQ ID NO: 197, or SEQ ID NO: 207; or
 - b) the amino acid sequence of SEQ ID NO: 177, SEQ ID NO: 187, SEQ ID NO: 197, or SEQ ID NO: 207.
3. The antibody construct according to claim 1 or claim 2, wherein the first binding domain comprises a VL region comprising an amino acid sequence comprising:
 - a) at least 85% identity to an amino acid sequence of SEQ ID NO: 178, SEQ ID NO: 188, SEQ ID NO: 198, or SEQ ID NO: 208; or
 - b) the amino acid sequence of SEQ ID NO: 178, SEQ ID NO: 188, SEQ ID NO: 198, or SEQ ID NO: 208.
4. The antibody construct according to any one of claims 1-3, wherein the first binding domain comprises a VH region and VL region comprising a pair of amino acid sequences, respectively, comprising:
 - a) at least 85% identity to the amino acid sequences of SEQ ID NOs: 177 and 178, SEQ ID NOs: 187 and 188, SEQ ID NOs: 197 and 198, or SEQ ID NOs: 207 and 208; or
 - b) the amino acid sequences of SEQ ID NOs: 177 and 178, SEQ ID NOs: 187 and 188, SEQ ID NOs: 197 and 198, or SEQ ID NOs: 207 and 208.
5. The antibody construct according to any one of claims 1-4, wherein the first binding domain comprises an amino acid sequence comprising:
 - a) at least 85% identity to an amino acid sequence of SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, and SEQ ID NO: 209; or
 - b) the amino acid sequences of SEQ ID NO: 179, SEQ ID NO: 189, SEQ ID NO: 199, or SEQ ID NO: 209.
6. The antibody construct according to any one of claims 1-5, wherein the antibody construct comprises a polypeptide comprising the amino acid sequence of SEQ ID NO: 180, SEQ ID NO: 190, SEQ ID NO: 200, or SEQ ID NO: 210.
7. The antibody construct according to any one of claims 1-6, wherein the antibody construct is in a format of two single-chain variable fragments ((scFv)₂).

8. The antibody construct according to any one of claims 1-6, wherein the antibody construct is in a format of scFv-single domain monoclonal antibody (Mab).
9. The antibody construct according to any one of claims 1-8, wherein the first binding domain, the second binding domain, or both is in a Fab format.
10. A pharmaceutical composition comprising the antibody construct according to any one of claims 1-9 and a pharmaceutical acceptable carrier.
11. A kit comprising the pharmaceutical composition of claim 10.
12. The kit according to claim 11, further comprising directions for use.