

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 to human delta-like 3 (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 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: 121, CDR-H2

SEQ ID NO: 136; i) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 131, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 132, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 133, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 443, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 135 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 136; j) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 131, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 132, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 133, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 444, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 135 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 136; k) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 131, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 439, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 133, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 441, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 135 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 136; and l) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 131, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 440, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 133, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 442, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 135 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 136.

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

In yet another aspect, the present disclosure provides for a kit comprising the bispecific antibody construct as disclosed herein and a pharmaceutically acceptable excipient.

In yet another aspect, the present disclosure provides for a bispecific antibody construct, wherein the antibody construct comprises the amino acid sequence of any one of SEQ ID NOs: 525-528.

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 to human delta-like 3 (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 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: 121, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 122, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 123, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 124, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 125 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 126;
 - b) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 131, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 132, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 133, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 134, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 135 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 136;
 - c) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 141, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 142, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 143, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 144, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 145 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 146;
 - d) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 161, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 162, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 163, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 164, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 165 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 166;
 - e) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 131, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 439, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 133, CDR-L1 comprising the amino acid

the amino acid sequence of SEQ ID NO: 133, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 441, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 135 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 136; and

- l) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 131, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 440, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 133, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 442, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 135 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 136.
- 2. The bispecific antibody construct according to claim 1, wherein the first binding domain comprises a VH region comprising the amino acid sequence of SEQ ID NO: 127, SEQ ID NO: 137, SEQ ID NO: 147, SEQ ID NO: 167, SEQ ID NO: 445, SEQ ID NO: 446, SEQ ID NO: 447, SEQ ID NO: 448, SEQ ID NO: 449, SEQ ID NO: 450, SEQ ID NO: 451, SEQ ID NO: 452, SEQ ID NO: 453, SEQ ID NO: 454, or SEQ ID NO: 455.
 - 3. The bispecific antibody construct according to claim 1 or claim 2, wherein the first binding domain comprises a VL region comprising the amino acid sequence of SEQ ID NO: 128, SEQ ID NO: 138, SEQ ID NO: 148, SEQ ID NO: 168, SEQ ID NO: 456, SEQ ID NO: 457, SEQ ID NO: 458, SEQ ID NO: 459, SEQ ID NO: 460, SEQ ID NO: 461, SEQ ID NO: 462, SEQ ID NO: 463, SEQ ID NO: 464, SEQ ID NO: 465, SEQ ID NO: 466, SEQ ID NO: 467, SEQ ID NO: 468, SEQ ID NO: 469, or SEQ ID NO: 470.
 - 4. The bispecific antibody construct according to any one of claims 1-3, wherein the first binding domain comprises a VH region and a VL region comprising the pair of amino acid sequences, respectively, of SEQ ID NOs: 127 and 128; SEQ ID NOs: 137 and 138; SEQ ID NOs: 147 and 148; SEQ ID NOs: 167 and 168; SEQ ID NOs: 137 and 456; SEQ ID NOs: 137 and 457; SEQ ID NOs: 137 and 458; SEQ ID NOs: 137 and 459; SEQ ID NOs: 137 and 460; SEQ ID NOs: 445 and 138; SEQ ID NOs: 446 and 138; SEQ ID NOs: 447 and 138; SEQ ID NOs: 445 and 460; SEQ ID NOs: 448 and 461; SEQ ID NOs: 449 and 462; SEQ ID NOs: 450 and 463; SEQ ID NOs: 450 and 464; SEQ ID NOs: 450 and 465; SEQ ID NOs: 450 and 466; SEQ ID NOs: 450 and 467;

SEQ ID NOs: 450 and 468; SEQ ID NOs: 451 and 463; SEQ ID NOs: 452 and 463; SEQ ID NOs: 453 and 463; SEQ ID NOs: 451 and 468; SEQ ID NOs: 454 and 469; or SEQ ID NOs: 455 and 470.

5. The bispecific antibody construct according to any one of claims 1-4, wherein the first binding domain comprises the amino acid sequence of SEQ ID NO: 129, SEQ ID NO: 139, SEQ ID NO: 149, SEQ ID NO: 169, SEQ ID NO: 471, SEQ ID NO: 472, SEQ ID NO: 473, SEQ ID NO: 474, SEQ ID NO: 475, SEQ ID NO: 476, SEQ ID NO: 477, SEQ ID NO: 478, SEQ ID NO: 479, SEQ ID NO: 480, SEQ ID NO: 481, SEQ ID NO: 482, SEQ ID NO: 483, SEQ ID NO: 484, SEQ ID NO: 485, SEQ ID NO: 486, SEQ ID NO: 487, SEQ ID NO: 488, SEQ ID NO: 489, SEQ ID NO: 490, SEQ ID NO: 491, SEQ ID NO: 492, or SEQ ID NO: 493.
6. The bispecific antibody construct according to any one of claims 1-5 comprising the amino acid sequence of SEQ ID NO: 130, SEQ ID NO: 140, SEQ ID NO: 150, SEQ ID NO: 170; SEQ ID NO: 218, SEQ ID NO: 219, SEQ ID NO: 220, SEQ ID NO: 494, SEQ ID NO: 495, SEQ ID NO: 496, SEQ ID NO: 497, SEQ ID NO: 498, SEQ ID NO: 499, SEQ ID NO: 500, SEQ ID NO: 501, SEQ ID NO: 502, SEQ ID NO: 503, SEQ ID NO: 504, SEQ ID NO: 505, SEQ ID NO: 506, SEQ ID NO: 507, SEQ ID NO: 508, SEQ ID NO: 509, SEQ ID NO: 510, SEQ ID NO: 511, SEQ ID NO: 512, SEQ ID NO: 513, SEQ ID NO: 514, SEQ ID NO: 515, or SEQ ID NO: 516.
7. The bispecific antibody construct according to any one of claims 1-6, wherein the second binding domain comprises a VL region comprising CDR-L1, CDR-L2 and CDR-L3 and a VH region comprising CDR-H1, CDR-H2 and CDR-H3 selected from the group consisting of:
 - a) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 342, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 343, CDR-L3 comprising the amino acid sequence of SEQ ID NO: 344; CDR-H1 comprising the amino acid sequence of SEQ ID NO: 345, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 346, and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 347;
 - b) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 351, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 352, CDR-L3 comprising the amino acid sequence of SEQ ID NO: 353; CDR-H1 comprising the amino acid

- sequence of SEQ ID NO: 354, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 355, and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 356;
- c) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 360, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 361, CDR-L3 comprising the amino acid sequence of SEQ ID NO: 362; CDR-H1 comprising the amino acid sequence of SEQ ID NO: 363, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 364, and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 365;
 - d) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 369, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 370, CDR-L3 comprising the amino acid sequence of SEQ ID NO: 371; CDR-H1 comprising the amino acid sequence of SEQ ID NO: 372, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 373, and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 374;
 - e) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 378, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 379, CDR-L3 comprising the amino acid sequence of SEQ ID NO: 380; CDR-H1 comprising the amino acid sequence of SEQ ID NO: 381, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 382, and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 383;
 - f) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 387, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 388, CDR-L3 comprising the amino acid sequence of SEQ ID NO: 389; CDR-H1 comprising the amino acid sequence of SEQ ID NO: 390, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 391, and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 392;
 - g) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 396, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 397, CDR-L3 comprising the amino acid sequence of SEQ ID NO: 398; CDR-H1 comprising the amino acid sequence of SEQ ID NO: 399, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 400, and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 401;
 - h) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 405, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 406, CDR-L3 comprising the

- amino acid sequence of SEQ ID NO: 407; CDR-H1 comprising the amino acid sequence of SEQ ID NO: 408, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 409, and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 410;
- i) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 414, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 415, CDR-L3 comprising the amino acid sequence of SEQ ID NO: 416; CDR-H1 comprising the amino acid sequence of SEQ ID NO: 417, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 418, and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 419; and
 - j) CDR-L1 comprising the amino acid sequence of SEQ ID NO: 423, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 424, CDR-L3 comprising the amino acid sequence of SEQ ID NO: 425; CDR-H1 comprising the amino acid sequence of SEQ ID NO: 426, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 427, and CDR-H3 comprising the amino acid sequence of SEQ ID NO: 428.
8. The bispecific antibody construct according to any one of claims 1-7, wherein the second binding domain comprises a VL region comprising the amino acid sequence of SEQ ID NO: 349, SEQ ID NO: 358, SEQ ID NO: 367, SEQ ID NO: 376, SEQ ID NO: 385, SEQ ID NO: 394, SEQ ID NO: 403, SEQ ID NO: 412, SEQ ID NO: 421, or SEQ ID NO: 430.
 9. The bispecific antibody construct according to any one of claims 1-8, wherein the second binding domain comprises a VH region comprising the amino acid sequence of SEQ ID NO: 348, SEQ ID NO: 357, SEQ ID NO: 366, SEQ ID NO: 375, SEQ ID NO: 384, SEQ ID NO: 393, SEQ ID NO: 402, SEQ ID NO: 411, SEQ ID NO: 420, or SEQ ID NO: 429.
 10. The bispecific antibody construct according to any one of claims 1-9, wherein the second binding domain comprises a VH region and a VL region comprising the pair of amino acid sequences, respectively, of SEQ ID NOs: 348 and 349; SEQ ID NOs: 357 and 358; SEQ ID NOs: 366 and 367; SEQ ID NOs: 375 and 376; SEQ ID NOs: 384 and 385; SEQ ID NOs: 393 and 394; SEQ ID NOs: 402 and 403; SEQ ID NOs: 411 and 412; SEQ ID NOs: 420 and 421; or SEQ ID NOs: 429 and 430.

11. The bispecific antibody construct according to any one of claims 1-10, wherein the second binding domain comprises the amino acid sequence of SEQ ID NO: 350, SEQ ID NO: 359, SEQ ID NO: 368, SEQ ID NO: 377, SEQ ID NO: 386, SEQ ID NO: 395, SEQ ID NO: 404, SEQ ID NO: 413, SEQ ID NO: 422, or SEQ ID NO: 431.
12. A pharmaceutical composition comprising the bispecific antibody construct according to any one of claims 1-11 and a pharmaceutical acceptable carrier.
13. A kit comprising the bispecific antibody construct according to any one of claims 1-11 and a pharmaceutically acceptable excipient.
14. The kit according to claim 13, further comprising directions for use.
15. The bispecific antibody construct according to any one of claims 1-11, wherein the second binding domain binds to an epitope comprised within amino acids 1-27 of the human CD3 epsilon extracellular domain.
16. The bispecific antibody construct according to any one of claims 1-11, wherein the antibody construct further comprises a third domain that extends serum half-life of the antibody construct.
17. A bispecific antibody construct, wherein the antibody construct comprises the amino acid sequence of any one of SEQ ID NOs: 525-528.