

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

In one aspect, the present disclosure relates to a polypeptide 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 binds to an epitope of DLL3 within the amino acid sequence of SEQ ID NO: 258, and 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.

In another aspect, the present disclosure relates to a A polypeptide 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 comprises a VH region comprising CDR-H1, CDR-H2 and CDR-H3 and a VL region comprising CDR-L1, CDR-L2 and CDR-L3, and the second 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, wherein the CDR-H1, CDR-H2 and CDR-H3 and CDR-L1, CDR-L2 and CDR-L3 of the first binding domain are selected from the group consisting of:

a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 31, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 32, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 33, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 34, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 35, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 36;

- b) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 41, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 42, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 43, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 44, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45[[u]], and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 46;
- c) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 51, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 52, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 53, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 54, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 55, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 56;
- d) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 61[[]]], CDR-H2 comprising the amino acid sequence of SEQ ID NO: 62, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 63, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 64, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 65, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 66;
- e) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 71, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 72, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 73, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 74, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 75, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 76;
- f) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 81, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 82, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 83, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 84, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 85, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 86;
- g) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 91, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 92, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 93, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 94, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 95, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 96;
- h) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 101, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 102, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 103, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 104, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 105, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 106; and
- i) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 111, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 112, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 113, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 114, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 115, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 116; and
- wherein the CDR-H1, CDR-H2 and CDR-H3 and CDR-L1, CDR-L2 and CDR-L3 of the second binding domain are 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.

In another aspect, the present disclosure relates to a polypeptide 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 comprises a VH region comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 33, and a VL region comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 34, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 35, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 36, and wherein the second binding domain comprises a VL domain comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 423, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 424, a CDR-L3 comprising the amino acid sequence of SEQ ID NO:

425, and a VH domain comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 426, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 427, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 428.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising the polypeptide as disclosed herein and a pharmaceutically acceptable carrier.

In another aspect, the present disclosure relates to use of the polypeptide as disclosed herein in the manufacture of a medicament for treating a tumor or cancer disease or a metastatic cancer disease.

In another aspect, the present disclosure relates to a kit comprising the polypeptide as disclosed herein and a pharmaceutically acceptable excipient.

In another aspect, the present disclosure relates to a polypeptide 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 binds to an epitope of DLL3 within the amino acid sequence of SEQ ID NO: 258, and wherein the second binding domain binds to an extracellular epitope comprised within amino acids 1-27 of the human CD3 epsilon extracellular domain.

Thus, in a first aspect, the present invention 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.

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 polypeptide 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 binds to an epitope of DLL3 within the amino acid sequence of SEQ ID NO: 258,

and 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.
2. The polypeptide according to claim 1, wherein the second binding domain comprises a VL region comprising the amino acid sequence selected from the group consisting 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, and SEQ ID NO: 430.

3. The polypeptide according to claim 1, wherein the second binding domain comprises a VH region comprising the amino acid sequence selected from the group consisting 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, and SEQ ID NO: 429.
4. The polypeptide according to claim 1, wherein the second binding domain comprises a VH region and a VL region comprising the pair of amino acid sequences, respectively, selected from the group consisting 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; and SEQ ID NOs: 429 and 430.
5. The polypeptide according to claim 1, wherein the second binding domain comprises an amino acid sequence selected from the group consisting 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, and SEQ ID NO: 431.
6. The polypeptide according to claim 1, 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: 31, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 32, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 33, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 34, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 35 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 36;
 - b) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 41, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 42, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 43, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 44, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 46;
 - c) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 51, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 52, CDR-H3 comprising the amino acid

sequence of SEQ ID NO: 53, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 54, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 55 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 56;

d) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 61, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 62, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 63, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 64, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 65 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 66;

e) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 71, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 72, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 73, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 74, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 75 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 76;

f) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 81, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 82, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 83, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 84, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 85 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 86;

g) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 91, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 92, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 93, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 94, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 95 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 96;

h) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 101, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 102, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 103, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 104, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 105 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 106; and

i) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 111, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 112, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 113, CDR-L1 comprising the amino acid sequence of SEQ ID

NO: 114, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 115 and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 116.

7. The polypeptide according to claim 1, wherein the first binding domain comprises a VH region comprising the amino acid sequence selected from the group consisting of: SEQ ID NO: 37, SEQ ID NO: 47, SEQ ID NO: 57, SEQ ID NO: 67, SEQ ID NO: 77, SEQ ID NO: 87, SEQ ID NO: 97, SEQ ID NO: 107, SEQ ID NO: 117, SEQ ID NO: 435 and SEQ ID NO: 529.
8. The polypeptide according to claim 1, wherein the first binding domain comprises a VL region comprising the amino acid sequence selected from the group consisting of: SEQ ID NO: 38, SEQ ID NO: 48, SEQ ID NO: 58, SEQ ID NO: 68, SEQ ID NO: 78, SEQ ID NO: 88, SEQ ID NO: 98, SEQ ID NO: 108, SEQ ID NO: 118, SEQ ID NO: 436, and SEQ ID NO: 530.
9. The polypeptide according to claim 1, wherein the first binding domain comprises a VH region and a VL region comprising the pair of amino acid sequences, respectively, selected from the group consisting of: SEQ ID NOs: 37 and 38; SEQ ID NOs: 47 and 48; SEQ ID NOs: 57 and 58; SEQ ID NOs: 67 and 68; SEQ ID NOs: 77 and 78; SEQ ID NOs: 87 and 88; SEQ ID NOs: 97 and 98; SEQ ID NOs: 107 and 108; SEQ ID NOs: 117 and 118; SEQ ID NOs: 435 and 436; and SEQ ID NOs: 529 and 530 .
10. The polypeptide according to claim 1, wherein the first binding domain comprises a polypeptide comprising the amino acid sequence selected from the group consisting of: SEQ ID NO: 39, SEQ ID NO: 49, SEQ ID NO: 59, SEQ ID NO: 69, SEQ ID NO: 79, SEQ ID NO: 89, SEQ ID NO: 99, SEQ ID NO: 109, SEQ ID NO: 119, SEQ ID NO: 437 and SEQ ID NO: 531.
11. A polypeptide 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 comprises a VH region comprising CDR-H1, CDR-H2 and CDR-H3 and a VL region comprising CDR-L1, CDR-L2 and CDR-L3, and the second 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,

wherein the CDR-H1, CDR-H2 and CDR-H3 and CDR-L1, CDR-L2 and CDR-L3 of the first binding domain are selected from the group consisting of:

- a) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 31, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 32, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 33, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 34, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 35, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 36;
- b) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 41, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 42, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 43, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 44, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45[[u]], and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 46;
- c) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 51, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 52, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 53, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 54, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 55, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 56;
- d) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 61[[]]], CDR-H2 comprising the amino acid sequence of SEQ ID NO: 62, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 63, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 64, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 65, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 66;
- e) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 71, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 72, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 73, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 74, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 75, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 76;
- f) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 81, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 82, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 83, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 84, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 85, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 86;
- g) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 91, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 92, CDR-H3 comprising the amino acid sequence of

SEQ ID NO: 93, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 94, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 95, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 96;

- h) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 101, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 102, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 103, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 104, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 105, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 106; and
- i) CDR-H1 comprising the amino acid sequence of SEQ ID NO: 111, CDR-H2 comprising the amino acid sequence of SEQ ID NO: 112, CDR-H3 comprising the amino acid sequence of SEQ ID NO: 113, CDR-L1 comprising the amino acid sequence of SEQ ID NO: 114, CDR-L2 comprising the amino acid sequence of SEQ ID NO: 115, and CDR-L3 comprising the amino acid sequence of SEQ ID NO: 116; and

wherein the CDR-H1, CDR-H2 and CDR-H3 and CDR-L1, CDR-L2 and CDR-L3 of the second binding domain are 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.
12. The polypeptide of claim 11, wherein the CDR-H1, CDR-H2 and CDR-H3 and CDR-L1, CDR-L2 and CDR-L3 of the second binding domain are 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.
 13. The polypeptide of claim 12, wherein the first binding domain comprising a VH and a VL region comprising a pair of amino acid sequences, respectively, selected from the group consisting of: SEQ ID NOs: 37 and 38; SEQ ID NOs: 47 and 48; SEQ ID NOs: 57 and 58; SEQ ID NOs: 67 and 68; SEQ ID NOs: 77 and 78; SEQ ID NOs: 87 and 88; SEQ ID NOs: 97 and 98; SEQ ID NOs: 107 and 108; SEQ ID NOs: 117 and 118; SEQ ID NOs: 435 and 436; and SEQ ID NOs: 529 and 530.
 14. The polypeptide of claim 13, wherein the second binding domain comprises a VH comprising the amino acid sequence of SEQ ID NO: 429 and a VL region comprising the amino acid sequence of SEQ ID NO: 430.
 15. The polypeptide of claim 14, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 40, SEQ ID NO: 50, SEQ ID NO: 60, SEQ ID NO: 70, SEQ ID NO: 80, SEQ ID NO: 90, SEQ ID NO: 100, SEQ ID NO: 110, SEQ ID NO: 120, SEQ ID NO: 211, SEQ ID NO: 212, SEQ ID NO: 213, SEQ ID NO: 214, SEQ ID NO: 215, SEQ ID NO: 216, SEQ ID NO: 217, SEQ ID NO: 438 or SEQ ID NO: 532.
 16. The polypeptide of claim 15, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 517, SEQ ID NO: 518, SEQ ID NO: 519, SEQ ID NO: 520, SEQ ID NO: 521, SEQ ID NO: 522, SEQ ID NO: 523 or SEQ ID NO: 524.
 17. The polypeptide according to claim 12, wherein the first binding domain comprises the amino acid sequence of SEQ ID NO: 39 or SEQ ID NO: 437, and wherein the second binding domain comprises the amino acid sequence of SEQ ID NO: 431.
 18. A polypeptide 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 comprises a VH region comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 31, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 32, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 33, and a VL region comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 34, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 35, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 36, and wherein the second binding domain comprises a VL domain comprising a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 423, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 424, a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 425, and a VH domain comprising a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 426, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 427, and a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 428.

19. The polypeptide according to claim 18, wherein the first binding domain comprises a VH region comprising the amino acid sequence of SEQ ID NO: 435 and a VL region comprising the amino acid sequence of SEQ ID NO: 436, and the second binding domain comprises a VH region comprising the amino acid sequence of SEQ ID NO: 429 and a VL region comprising the amino acid sequence of SEQ ID NO: 430, or

wherein first binding domain comprising a VH comprising the amino acid sequence of SEQ ID NO: 37 and a VL comprising the amino acid sequence of SEQ ID NO: 38, and the second binding domain comprising a VH comprising the amino acid sequence of SEQ ID NO: 429 and a VL region comprising the amino acid sequence of SEQ ID NO: 430.

20. The polypeptide of claim 1, 11, or 18, wherein the polypeptide is in a format of two single-chain variable fragments ((scFv)₂), a scFv-single domain monoclonal antibody (mAb), or a diabody or an oligomer of any of the foregoing formats.
21. A pharmaceutical composition comprising the polypeptide of claim 1, 11, 16 or 18 and a pharmaceutically acceptable carrier.
22. Use of the polypeptide according to claims 1, 11, 16 or 18 in the manufacture of a medicament for treating a tumor or cancer disease or a metastatic cancer disease.
23. The use according to claim 22, wherein the tumor or cancer disease is small cell lung cancer (SCLC), melanoma or neuroendocrine prostate cancer.

24. A kit comprising the polypeptide according to claims 1, 11, 16 or 18 and a pharmaceutically acceptable excipient.
25. The kit according to claim 24 further comprising directions for use.
26. A polypeptide 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 binds to an epitope of DLL3 within the amino acid sequence of SEQ ID NO: 258, and wherein the second binding domain binds to an extracellular epitope comprised within amino acids 1-27 of the human CD3 epsilon extracellular domain.
27. The polypeptide of claim 26, wherein the epitope comprised within amino acids 1-27 of the human CD3 epsilon extracellular domain comprises at least the amino acid sequence Gln-Asp-Gly-Asn-Glu set forth in SEQ ID NO: 577.
28. The polypeptide of claim 26, wherein the first binding domain further binds to macaque DLL3.
29. The polypeptide of claim 26, wherein the second binding domain further binds to macaque CD3.
30. The polypeptide of claim 29, wherein the macaque CD3 is *Macaca fascicularis* CD3.
31. The polypeptide of claim 26, wherein the second binding domain binds to human CD3 epsilon and to *Callithrix jacchus*, *Saguinus oedipus* or *Saimiri sciureus* CD3 epsilon.
32. The polypeptide of claim 26, wherein the polypeptide is in a format of two single-chain variable fragments ((scFv)₂), a scFv-single domain monoclonal antibody (mAb), or a diabody, or an oligomer of any of the foregoing formats.
33. The polypeptide of claims 1, 11, 18, or 26, wherein the polypeptide comprises two single-chain variable fragments ((scFv)₂).
34. The polypeptide of claims 1, 11, 16 or 18, or the pharmaceutical composition of claim 21 for use in therapy.