# METHOD OF TREATING BRAIN METASTASES IN SUBJECTS WITH A DLL3-POSITIVE CANCER

## FIELD OF THE INVENTION

**[0001]** The present application relates to dosage and administration of anti-DLL3 agents for the treatment of cancer.

## CROSS-REFERENCE TO RELATED APPLICATIONS

**[0002]** This application claims the benefit of U.S. Provisional Patent Application No. 63/563,793, filed March 11, 2024, the entire contents of which is hereby incorporated herein by reference.

## INCORPORATION BY REFERENCE OF MATERIAL ELECTRONICALLY SUBMITTED

**[0003]** This application is filed with a sequence listing in electronic form which is incorporated herein by reference in its entirety and identified as follows: file name: 70115_SeqListing.xml, created: March 6, 2025, size: 60,989 bytes.

## BACKGROUND OF THE INVENTION

**[0004]** Cancers residing in the central nervous system are among the most difficult to treat. Metastases to the brain, caused by the spread of cancer cells from their original location to the brain, can be a devastating step in disease progression. Metastatic brain tumors are the most common cause of brain tumors in adults. Al Tamimi et al., Cureus, 14(11): e31197 (2022). Lung cancer and breast cancer are among the most common cancer types that lead to brain metastases, although any type of cancer can result in brain metastases, including melanoma, colon cancer, kidney cancer, and thyroid cancer. Treatment of brain metastases with biopharmaceuticals, such as antibody constructs, remains challenging for a number of reasons, including limited penetration through the blood-brain barrier (BBB).

## SUMMARY OF THE INVENTION

**[0005]** The disclosure provides a method of treating brain metastases in a human subject with a DLL3-positive cancer in need thereof. The method comprises administering to the subject an anti-DLL3 agent comprising a first binding domain that binds to human DLL3 on the surface of a target cell and a second binding domain that binds to human CD3 on the surface of a T

cell, wherein the anti-DLL3 agent is administered at a dose of from 3 mg to 200 mg once a week, once every two weeks, or once every three weeks. In various aspects, the DLL3-positive cancer is small cell lung cancer (SCLC), such as relapsed SCLC, extensive stage SCLC (which may be relapsed or refractory), or limited-stage SCLC (which may be relapsed or refractory). In alternative aspects, the DLL3-positive cancer is an extrapulmonary neuroendocrine cancer, such as neuroendocrine prostate cancer. Optionally, the subject has not been previously treated for the brain metastases prior to the administration of the anti-DLL3 agent. The disclosure also contemplates aspects wherein the subject has been previously treated for the brain metastases prior to the administration of the anti-DLL3 agent, and suffers from asymptomatic, stable brain metastases.

**[0006]** In various aspects, the anti-DLL3 agent is administered at a dose of from 3 mg to 100 mg once every two weeks (e.g., a dose of 3 mg, 10 mg, 20 mg, 30 mg, or 100 mg once every two weeks, such as a dose of 10 mg once every two weeks). Optionally, 1 mg of the anti-DLL3 agent is administered on day 1, 10 mg of the anti-DLL3 agent is administered on day 8, and 10 mg of the anti-DLL3 agent is administered on day 15 of a first 28-day cycle, and 10 mg of the anti-DLL3 agent is administered once every two weeks in one or more additional 28-day cycles.

**[0007]** Alternatively or in addition, the anti-DLL3 agent is administered at a dose of from 3 mg to 100 mg once every week.

**[0008]** Alternatively or in addition, the anti-DLL3 agent is administered at a dose of from 10 mg to 200 mg once every three weeks (e.g., at a dose of 10 mg, 20 mg, 60 mg, or 200 mg once every three weeks, such as a dose of 20 mg once every three weeks). Optionally, 1 mg of the anti-DLL3 agent is administered on day 1 and 20 mg of the anti-DLL3 agent is administered on day 8 of a first 21-day cycle, and 20 mg of the anti-DLL3 agent is administered once every three weeks in one or more additional 21-day cycles.

**[0009]** In various aspects, the anti-DLL3 agent of the method comprises the amino acid sequences of SEQ ID NOs: 23 and 20. Optionally, the anti-DLL3 agent comprises the amino acid sequence of SEQ ID NO: 28. Optionally, the anti-DLL3 agent comprises the amino acid sequence of SEQ ID NO: 29.

**[0010]** The disclosure further provides a method of treating brain metastases in a human subject with a DLL3-positive cancer. The method comprises administering to the subject an anti-DLL3 agent comprising a first binding domain that binds to human DLL3 and comprises SEQ ID NOs: 32-37 (e.g., the first binding domain comprises SEQ ID NO: 28 or 29) and a second binding domain that binds to human CD3 and comprises SEQ ID NOs: 42-47. The anti-DLL3 agent is administered via IV infusion according to the following schedule: 1 mg on day 1 of a first 28 day cycle; 10 mg on day 8 of a first 28 day cycle 1; 10 mg on day 15 of a

first 28 day cycle; and 10 mg once every two weeks thereafter in one or more subsequent 28 day cycles. Optionally, the anti-DLL3 agent is administered in a 28-day cycle, and the method further comprises administering saline, an anti-inflammatory agent, tocilizumab, or etanercept to the subject in the first cycle wherein the anti-DLL3 agent is administered. For instance, the method may comprise administering dexamethasone to the subject, optionally on day 1 and day 8 in the first cycle wherein the anti-DLL3 agent is administered. The method also optionally comprises administering one liter of saline to the subject following administration of the anti-DLL3 agent. The subject (i) has not been previously treated for the brain metastases prior to the administration of the anti-DLL3 agent or (ii) has been previously treated for the brain metastases prior to the administration of the anti-DLL3 agent and suffers from asymptomatic, stable brain metastases.

**[0011]** It should be understood that while various embodiments in the specification are presented using "comprising" language, under various circumstances, a related embodiment may also be described using "consisting of" or "consisting essentially of" language. The disclosure contemplates embodiments described as "comprising" a feature to include embodiments which "consist of" or "consists essentially of" the feature. The term "a" or "an" refers to one or more; for example, "an immunoglobulin molecule," is understood to represent one or more immunoglobulin molecules. As such, the terms "a" (or "an"), "one or more," and "at least one" can be used interchangeably herein.

**[0012]** It should also be understood that when describing a range of values, the characteristic being described could be an individual value found within the range. For example, "a dose from about 3 mg to about 100 mg," could be, but is not limited to, 5 mg, 10 mg, 25 mg, 50 mg, etc. and any value in between such values. In any of the ranges described herein, the endpoints of the range are included in the range. However, the description also contemplates the same ranges in which the lower and/or the higher endpoint is excluded.

**[0013]** "About" or "approximately," when used in connection with a measurable numerical variable, refers to the indicated value of the variable and to all values of the variable that are within the experimental error of the indicated value (e.g., within the 95% confidence interval for the mean) or ±10% of the indicated value, whichever is greater.

**[0014]** The use of section headings is merely for the convenience of reading. The entire document is intended to be related as a unified disclosure, and it should be understood that all combinations of features described herein are contemplated, even if the combination of features are not found together in the same sentence, or paragraph, or section of this document.

**[0015]** Additional features and variations of the disclosure will be apparent to those skilled in the art from the entirety of this application, including the drawings, detailed description, and

appended claims, and all such features are intended as aspects of the disclosure. Likewise, features of the disclosure described herein can be re-combined into additional embodiments that also are intended as aspects of the disclosure, irrespective of whether the combination of features is specifically mentioned above as an aspect or embodiment of the disclosure. The invention includes, as an additional aspect, all aspects of the invention narrower in scope in any way than the variations specifically mentioned. Also, only such limitations which are described herein as critical to the invention should be viewed as such; variations of the invention lacking limitations which have not been described herein as critical are intended as aspects of the invention.

**[0016]** All of the references cited herein, including patents, patent applications, literature publications, and the like, are hereby incorporated in their entireties by reference.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0017]** FIG. 1 is a swimmer plot of responders (n = 38) illustrating extended follow-up efficacy outcomes following tarlatamab treatment. Overall, the ORR was 25.0% (95% CI, 18.3, 32.7), median DOR was 11.2 months (95% CI, 6.6 to 22.3). In the group administered 10 mg tarlatamab (n = 17), ORR was 35.3% (95% CI, 14.2 to 61.7) and median DOR was 14.9 months (95% CI, 3.0, not estimable). CI: confidence interval; CR: complete response; DOR: duration of response, eIV: extended IV infusion; PR: partial response; ORR: objective response rate.

**[0018]** FIG. 2 is a Kaplan-Meier estimate of duration of response. Among 17 patients receiving the tarlatamab 10 mg dose, median OS was 20.3 months (95% CI: 5.1, NE).

**[0019]** FIG. 3 is a waterfall plot showing the best percentage change from baseline in the sum of diameters of central nervous system (CNS) lesion(s) (y-axis) in patients receiving five different tarlatamab regimens, sorted by interval from prior brain radiotherapy (RT) to cycle 1 day 1 (C1D1) of tarlatamab (x-axis). Two patients, noted with an asterisk, had brain radiotherapy following disease progression; the best CNS tumor shrinkage occurred prior to this subsequent brain RT. Modified response assessment in neuro-oncology brain metastases (mRANO BM) was determined, representing RANO BM criteria with the following modifications: (1) corticosteroid data and clinical status were not incorporated into imaging reads and (2) diffusion weighted imaging MRI sequences were not required but were made available to the independent reviewer if received. CNS tumor shrinkage of ≥ 30% was observed in 10 of 16 patients (62.5%) with baseline lesion of ≥ 10 mm. CNS progression occurred in 9 of 112 patients (8.0%). Intracranial disease control was observed in 89.3% of patients (95% CI, 71.8, 97.7). The median duration of intracranial disease control was

determined to be 7.4 months (95% CI, 2.8, NE). CI, confidence interval; DOR, duration of response; mRANO-BM, modified Response Assessment in Neuro-Oncology Brain Metastases; NE, not evaluable; ORR, objective response rate; OS, overall survival; PR, partial response.

**[0020]** FIG. 4 is a graph illustrating time from last radiotherapy session and duration of tarlatamab treatment. CNS tumor shrinkage was observed in multiple subjects, and tumor shrinkage observed following treatment more than 50 days after radiotherapy further evidences intracranial activity of tarlatamab. BOR: best overall response; CNS: central nervous system; eIV: extended intravenous infusion; NE: not estimable; PD: progressive disease; PR: partial response; Q2W, once every 2 weeks; SD: stable disease.

**[0021]** FIG. 5 is a swimmer plot of responders (n = 17) illustrating extended follow-up efficacy outcomes following tarlatamab treatment. Patients with a baseline CNS lesion of ≥ 10 mm were administered (i) 1 mg of tarlatamab on day 1, followed by 10 mg of tarlatamab on days 8, 15, and every two weeks thereafter (n=3), or (ii) 1 mg of tarlatamab on day 1, followed by 100 mg of tarlatamab on days 8, 15, and every two weeks thereafter (n=14). BOR: best overall response; CI: confidence interval; CR: complete response; DOR: duration of response, ORR: objective response rate; PR: partial response; SBRT: stereotactic body radiation therapy; SD: stable disease; SRS: stereotactic radiosurgery; WBRT: whole brain radiation therapy.

**[0022]** FIG. 6 is a chart summarizing baseline demographics and disease characteristics of patients participating in the extended follow-up study illustrated in FIGs. 7A-7B.

**[0023]** FIGs. 7A-7B illustrate intracranial activity of tarlatamab assessed per mRANO-BM by blinded independent central review in 16 patients with a baseline CNS lesion ≥10 mm. FIG. 7A is a waterfall plot showing the best percentage change from baseline in the sum of diameters of CNS lesion(s) in patients receiving five different tarlatamab regimens, sorted by interval from previous brain RT to cycle 1 day 1 (C1D1) of tarlatamab. Two patients, noted with an asterisk, had brain RT after disease progression; the best CNS tumor shrinkage occurred before this subsequent brain RT. FIG. 7B illustrates data considering the time from last brain RT and duration of tarlatamab treatment. The last previous brain RT is denoted by a diamond, with diamond shading designating previous SBRT or SRS and no diamond shading designating previous WBRT. A postbaseline response assessment per modified RECIST 1.1 was not available for one patient. BOR: best overall response; C1D1: cycle 1 day 1 of tarlatamab treatment; eIV: extended intravenous; mRANO-BM: modified Response Assessment in Neuro-Oncology Brain Metastases; NA: not available; PD: progressive disease; PR: partial response; RT: radiotherapy; SBRT: stereotactic body radiation therapy; SD: stable disease; SLD: sum of the longest diameters of lesions; SRS: stereotactic radiosurgery; WBRT: whole-brain radiation therapy.

**[0024]** FIG. 8 is a chart summarizing intracranial activity in patients with CNS metastases participating in the extended follow-up study illustrated in FIGs. 7A-7B.

## DETAILED DESCRIPTION

**[0025]** The disclosure is directed to use of an anti-DLL3 agent described herein to brain metastases in a human subject with a DLL3-positive cancer. Surprisingly, a bispecific protein (AMG 757, also referred to as tarlatamab) that targets DLL3 and CD3 demonstrated intracranial activity when administered to human subjects with metastases in the brain associated with a DLL3-positive cancer (here, SCLC), reducing the size of tumors by more than 30% in some patients. The materials and methods described herein provide a new treatment option for brain metastases in subjects suffering from DLL3-expressing neuroendocrine cancers (e.g., brain metastases in a subject suffering from SCLC).

### *TREATMENT*

**[0026]** The disclosure provides a method of treating brain metastases in a human subject with a DLL3-positive cancer in need thereof. Delta-like 3 (DLL3) is a type 1 transmembrane protein and noncanonical Notch ligand that is differentially expressed in some cancer types, including SCLC. For instance, using immunohistochemistry (IHC), 85% of SCLC tumors stained positive for DLL3 in a pattern consistent with both membranous and cytoplasmic expression. In contrast, low levels of DLL3 protein expression were detected in normal brain, pancreatic islets, and pituitary gland with a cytoplasmic staining pattern (Saunders et al., Sci Transl Med., 7:302ra136 (2015)). The amino acid sequence of human DLL3 is set forth in the sequence table provided below as SEQ ID NO: 1.

**[0027]** The subject may suffer from brain metastases stemming from any DLL3-positive cancer. In some instances, the DLL3-positive cancer is a neuroendocrine cancer (i.e., neuroendocrine neoplasm). Optionally, the DLL3-positive cancer is a pulmonary neuroendocrine cancer, although the disclosure also contemplates extrapulmonary neuroendocrine cancers. In various aspects of the disclosure, the subject is suffering from lung cancer, such as small cell lung cancer (SCLC), examples of which include relapsed/refractory SCLC (RR SCLC), extensive stage SCLC (ES SCLC) (which may be relapsed or refractory), and limited-stage SCLC (LS SCLC) (which may be relapsed or refractory). In this respect, the brain metastases may be associated with SCLC. LS SCLC often refers to SCLC cancers found only on one side of the chest (e.g., only in one lung), enabling treatment with a single radiation field. In various aspects of the disclosure, LS SCLC has not progressed in the subject following concurrent chemoradiation therapy. ES SCLC includes cancers that have spread more widely throughout the lung and/or to the other lung,

and often to other locations within the body. Relapsed SCLC include cancers which, e.g., reemerge within three months of a first line of treatment (e.g., chemotherapy and/or radiation). The brain metastases may be derived from other DLL3-positive cancer types, such as prostate cancer (e.g., neuroendocrine prostate cancer), bladder cancer (e.g., small cell bladder cancer), ovarian cancer, pancreatic cancer, liver cancer (e.g., hepatoblastoma or hepatocellular carcinoma), or melanoma.

**[0028]** Optionally, the subject suffers from SCLC which has recurred after one or more prior lines of treatment in the subject, such as a SCLC recurrence after two or more prior lines of treatment in the subject. For example, the subject has, in various aspects, received at least one, two, three, four, five, or six prior lines of treatment for the SCLC (or other DLL3-positive cancer). By "prior line of treatment" is meant a previous treatment with another anticancer therapeutic, e.g., a first- or second-line cancer therapy or standard of care therapy, before administration of the anti-DLL3 agent. In various aspects, at least one of the prior lines of treatment is a platinum-based chemotherapeutic. Alternatively or in addition, at least one of the prior lines of treatment is anti-PD1 antibody or anti-PD-L1 antibody therapy. For instance, the subject may have undergone a combination of therapies including platinum-based chemotherapy and anti-PD1 antibody or anti-PD-L1 antibody therapy. Where the subject has undergone prior lines of treatment, administration of the anti-DLL3 agent may occur at any timepoint following completion of the prior lines of treatment. For instance, the anti-DLL3 agent may be administered at least 28 days (e.g., at least 60 days or at least 90 days) after the completion of any prior lines of treatment for SCLC (or other DLL3-positive cancer).

**[0029]** Optionally, the subject has not been previously treated for the brain metastases prior to the administration of the anti-DLL3 agent. By "not previously treated" is meant that the subject has not previously undergone radiation therapy or surgery to treat the brain metastases prior to administration of the anti-DLL3 agent.

**[0030]** Alternatively, the subject may have been previously treated for the brain metastases prior to the administration of the anti-DLL3 agent. In this regard, the subject optionally suffers from asymptomatic, stable brain metastases when treatment with the anti-DLL3 agent commences. Put another way, in various aspects of the disclosure, the subject has prior-treated, asymptomatic, stable brain metastases (i.e., no further metastases growth following radiation or surgery).

**[0031]** Optionally, the subject has received radiation therapy or surgery for the DLL3-positive tumor prior to the method of the disclosure. In this regard, the subject may have completed a course of radiation therapy at least about or no more than about 10 weeks prior to treatment with the anti-DLL3 agent, at least about or no more than about 20 weeks prior to treatment with the anti-DLL3 agent, at least about or no more than about 30 weeks prior to treatment

with the anti-DLL3 agent, at least about or no more than about 40 weeks prior to treatment with the anti-DLL3 agent, at least about or no more than about 50 weeks prior to treatment with the anti-DLL3 agent, at least about or no more than about 60 weeks prior to treatment with the anti-DLL3 agent, at least about or no more than about 70 weeks prior to treatment with the anti-DLL3 agent, at least about or no more than about 80 weeks prior to treatment with the anti-DLL3 agent, at least about or no more than about 90 weeks prior to treatment with the anti-DLL3 agent, or at least about or no more than about 100 weeks prior to treatment with the anti-DLL3 agent.

**[0032]** In various aspects, the subject may have completed radiation therapy less than 50 days prior to treatment with the anti-DLL3 agent, or may have completed radiation treatment more than 50 days prior to treatment with the anti-DLL3 agent. For instance, the subject may have completed radiation therapy about 14 days to about 40 days (e.g., about 15 days, about 18 days, about 20 days, about 23 days, about 25 days, about 31 days, about 33 days, or about 39 days) prior to a first administration of anti-DLL3 agent to treat the brain metastases. Alternatively, the subject may have completed radiation therapy about 50 days to about 160 days (e.g., about 50 days, about 114 days, about 127 days, or about 160 days) prior to a first administration of anti-DLL3 agent to treat the brain metastases. In various aspects, the subject may have completed radiation therapy more than about 160 days prior to a first administration of anti-DLL3 agent to treat the brain metastases.

**[0033]** The term “treatment” includes prophylactic and/or therapeutic treatments. If it is administered prior to clinical manifestation of a condition (e.g., prior to occurrence of measurable brain metastases), the treatment is considered prophylactic. The term “treat,” as well as words related thereto, do not necessarily imply 100% or complete treatment or remission. Rather, there are varying degrees of treatment of which one of ordinary skill in the art recognizes as having a potential benefit or therapeutic effect. In this respect, the methods of treating a disease or disorder can provide any amount or any level of improvement in the subject’s wellbeing.

**[0034]** The method of treating a subject described herein is intended to provide an improvement in a disease or condition (e.g., ameliorating or reducing the severity of the brain metastases or shortening the length of affliction) and/or an improvement in the symptoms associated with the disease or condition. For example, a therapeutic response would refer to one or more of the following improvements in the disease: (1) a reduction in the number of neoplastic cells; (2) an increase in neoplastic cell death; (3) inhibition of neoplastic cell survival; (4) decrease in tumor size or load (i.e., burden), (5) inhibition (i.e., slowing to some extent, preferably halting) of metastases growth or appearance of new lesions; (6) an increased patient survival rate; (7) inhibit the reoccurrence of brain metastases, and/or (8)

some relief from one or more symptoms associated with the disease or condition. In various aspects, the method reduces the size of at least one CNS tumor by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, or at least 30% compared to pre-treatment.

**[0035]** Therapeutic responses in any given disease or condition, including treatment of brain metastases, can be determined by, e.g., standardized response criteria specific to that disease or condition. Tumor response can be assessed using screening techniques such as magnetic resonance imaging (MRI) scan, x-radiographic imaging, computed tomographic (CT) scan, positron emission tomography (PET) scan, or tumor biopsy sampling. In addition to these therapeutic responses, the subject undergoing therapy may experience the beneficial effect of an improvement in symptoms associated with the disease.

**[0036]** It will be appreciated that the disclosure further provides use of an anti-DLL3 agent comprising a first binding domain that binds to human DLL3 on the surface of a target cell and a second binding domain that binds to human CD3 on the surface of a T cell for the treatment of brain metastases in a human subject with a DLL3-positive cancer in need thereof, wherein the anti-DLL3 agent is administered at a dose of from 3 mg to 200 mg once a week, once every two weeks, or once every three weeks. The disclosure also provides use of an anti-DLL3 agent comprising a first binding domain that binds to human DLL3 on the surface of a target cell and a second binding domain that binds to human CD3 on the surface of a T cell in the preparation of a medicament for the treatment of brain metastases in a human subject with a DLL3-positive cancer in need thereof, wherein the anti-DLL3 agent medicament is administered at a dose of from 3 mg to 200 mg once a week, once every two weeks, or once every three weeks. Further provided is an anti-DLL3 agent comprising a first binding domain that binds to human DLL3 on the surface of a target cell and a second binding domain that binds to human CD3 on the surface of a T cell for use in the treatment of brain metastases in a human subject with a DLL3-positive cancer in need thereof, wherein the anti-DLL3 agent is administered at a dose of from 3 mg to 200 mg once a week, once every two weeks, or once every three weeks.

***ANTI-DLL3 AGENTS***

**[0037]** The method of treating brain metastases in a human subject with a DLL3-positive cancer comprises administering to the subject an anti-DLL3 agent, such as an anti-DLL3 agent comprising a first binding domain that binds to human DLL3 on the surface of a target cell and a second binding domain that binds to human CD3 on the surface of a T cell. The human DLL3 protein comprises eight extracellular domains: signal peptide, N-terminus, DSL, EGF1, EGF2, EGF3, EGF4, EGF5 and EGF6. Preferably, the first domain binds to an epitope of DLL3 comprised within the amino acid sequence of SEQ ID NO: 52. More preferably, the first

domain binds to an epitope of DLL3 comprised within the amino acid sequence of SEQ ID NO: 53.

**[0038]** An exemplary anti-DLL3 agent is a BiTE® (bispecific T cell engager) molecule. BiTE® molecules are recombinant protein constructs made from two flexibly linked binding domains, each domain derived from antibodies. Antigen-binding domains retain the ability to specifically bind to an antigen (preferably with substantially the same binding affinity). Examples of antigen-binding fragments include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; and (v) a dAb fragment (Ward et al., Nature 341:544-546 (1989)), which consists of a VH domain. Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. Science 242:423-426 (1988) and Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988). One binding domain of a BiTE® molecule is specific for a tumor-associated surface antigen (such as DLL3); the second binding domain is specific for CD3, a subunit of the T cell receptor complex on T cells. By their design, BiTE® molecules are uniquely suited to transiently connect T cells with target cells and, at the same time, potently activate the inherent cytolytic potential of T cells against target cells. See e.g., International Patent Publication Nos. WO 99/54440, WO 2005/040220, and WO 2008/119567, each of which is incorporated by reference in its entirety.

**[0039]** The “complementarity determining regions” (CDRs) of exemplary DLL3-binding domains and CD3-binding domains are provided in Table 6. The CDRs can be defined according to Kabat, Chothia, the accumulation of both Kabat and Chothia, AbM, contact, North, and/or conformational definitions or any method of CDR determination well known in the art. See, e.g., Kabat et al., 1991, Sequences of Proteins of Immunological Interest, 5$^{th}$ ed. (hypervariable regions); Chothia et al., 1989, Nature 342:877-883 (structural loop structures). AbM definition of CDRs is a compromise between Kabat and Chothia and uses Oxford Molecular’s AbM antibody modeling software (Accelrys®). The identity of the amino acid residues in a particular antibody that make up a CDR can be determined using methods well known in the art.

**[0040]** In certain embodiments, the DLL3-binding domain comprises (a) a heavy chain variable region (VH) that comprises (i) a VH complementarity determining region one (CDR-H1) comprising the amino acid sequence of SEQ ID NO:3, (ii) a CDR-H2 comprising the amino

acid sequence of SEQ ID NO:4, and (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO:5; and (b) a light chain variable region (VL) that comprises (i) a VL complementarity determining region one (CDR-L1) comprising the amino acid sequence of SEQ ID NO:6, (ii) a CDR-L2 comprising the amino acid sequence of SEQ ID NO:7, and (iii) a CDR-L3 comprising the amino acid sequence of SEQ ID NO:8.

**[0041]** In certain embodiments, the DLL3-binding domain comprises a VH that comprises the amino acid sequence of SEQ ID NO:9, and a VL that comprises the amino acid sequence of SEQ ID NO:10. In certain preferred embodiments, the DLL3-binding domain comprises a VH that comprises the amino acid sequence of SEQ ID NO:21, and a VL that comprises the amino acid sequence of SEQ ID NO:22. In some embodiments, the VH and VL are joined by a linker to form a single chain Fv (scFv). Linkers are known in the art and further described in, e.g., U.S. Patent Publication No. 2023/0174643, hereby incorporated by reference in its entirety.

**[0042]** In various aspects, the DLL3-binding domain comprises the amino acid sequence of SEQ ID NO: 11. In certain embodiments, the DLL3-binding domain comprises the amino acid sequence of SEQ ID NO: 23.

**[0043]** In various aspects, the CD3-binding domain comprises (a) a VH that comprises (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:15, (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO:16, and (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO:17; and a VL that comprises (i) a CDR-L1 comprising the amino acid sequence of SEQ ID NO:12, (ii) a CDR-L2 comprising the amino acid sequence of SEQ ID NO:13, and (iii) a CDR-L3 comprising the amino acid sequence of SEQ ID NO:14.

**[0044]** In certain embodiments, the CD3-binding domain comprises a VH that comprises the amino acid sequence of SEQ ID NO:18, and a VL that comprises the amino acid sequence of SEQ ID NO:19. In some embodiments, the VH and VL are joined by a linker to form a single chain Fv (scFv). In some embodiments, the linker is a peptide linker. In certain embodiments, the CD3-binding domain comprises the amino acid sequence of SEQ ID NO: 20.

**[0045]** In certain embodiments, the anti-DLL3 agent disclosed herein comprises two domains. The first domain binds to DLL3 (preferably human DLL3) and comprises (a) a heavy chain variable region (VH) that comprises (i) a VH complementarity determining region one (CDR-H1) comprising the amino acid sequence of SEQ ID NO:3, (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO:4, and (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO:5; and (b) a light chain variable region (VL) that comprises (i) a VL complementarity determining region one (CDR-L1) comprising the amino acid sequence of SEQ ID NO:6; (ii) a CDR-L2 comprising the amino acid sequence of SEQ ID NO:7, and (iii) a CDR-L3 comprising the amino acid sequence of SEQ ID NO:8. The second domain binds to CD3 (preferably human CD3), and comprises (a) a VH that comprises (i) a CDR-H1

comprising the amino acid sequence of SEQ ID NO:15, (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO:16, and (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO:17; and (b) a VL that comprises (i) a CDR-L1 comprising the amino acid sequence of SEQ ID NO:12, (ii) a CDR-L2 comprising the amino acid sequence of SEQ ID NO:13, and (iii) a CDR-L3 comprising the amino acid sequence of SEQ ID NO:14.

**[0046]** In certain embodiments, the anti-DLL3 agent described herein comprises two domains: (a) the first domain binds DLL3 (preferably human DLL3) and comprises a VH that comprises the amino acid sequence of SEQ ID NO:9, and a VL that comprises the amino acid sequence of SEQ ID NO:10; and (b) the second domain binds CD3 (preferably human CD3) and comprises a VH that comprises the amino acid sequence of SEQ ID NO:18, and a VL that comprises the amino acid sequence of SEQ ID NO:19. In certain aspects, the anti-DLL3 agent described herein comprises two domains: (a) the first domain binds DLL3 (preferably human DLL3) and comprises a VH that comprises the amino acid sequence of SEQ ID NO:21, and a VL that comprises the amino acid sequence of SEQ ID NO: 22; and (b) the second domain binds CD3 (preferably human CD3) and comprises a VH that comprises the amino acid sequence of SEQ ID NO:18, and a VL that comprises the amino acid sequence of SEQ ID NO:19.

**[0047]** In certain aspects, the anti-DLL3 agent described herein comprises (a) a first domain that binds DLL3 (preferably human DLL3) and comprises the amino acid sequence of SEQ ID NO: 11, and (b) a second domain that binds CD3 (preferably human CD3) and comprises the amino acid of SEQ ID NO: 20. In certain aspects, the anti-DLL3 agent described herein comprises two domains: (a) the first domain binds DLL3 (preferably human DLL3) and comprises the amino acid sequence of SEQ ID NO: 23, and (b) the second domain binds CD3 (preferably human CD3) and comprises the amino acid of SEQ ID NO: 20.

**[0048]** In certain aspects, the anti-DLL3 agent described herein comprises the amino acid sequence of SEQ ID NO: 55. In certain embodiments, the anti-DLL3 agent described herein comprises the amino acid sequence of SEQ ID NO: 24.

**[0049]** In certain embodiments, the anti-DLL3 agent described herein comprises the amino acid sequence of SEQ ID NO: 28. In certain embodiments, the anti-DLL3 agent described herein comprises the amino acid sequence of SEQ ID NO: 29.

**[0050]** In various aspects, the anti-DLL3 agent is tarlatamab.

**[0051]** In other aspects of the disclosure, the anti-DLL3 agent is a single chain polypeptide comprising one or more scFvs fused to one or more single domain monoclonal antibodies (sdmAb). Optionally, the scFv-sdmAb format may comprise a domain that serves to extend the half-life of the protein. In this regard, the anti-DLL3 agent may comprise, from N to C terminus, an scFv that binds CD3, a linker peptide, a sdmAb that binds serum albumin, a

peptide linker, and a sdmAb that binds DLL3. The disclosure contemplates an anti-DLL3 agent comprising the amino acid sequence of SEQ ID NO: 30. An alternate format comprises, from N- to C- terminus, a sdmAb that binds DLL3, a peptide linker, a sdmAb that binds serum albumin, a peptide linker, and an scFv that binds CD3. An example of such an anti-DLL3 agent comprises the amino acid sequence of SEQ ID NO: 31. Anti-DLL3 agents comprising these formats are further described in, e.g., International Patent Publication No. WO 2020/069028, incorporated by reference in its entirety and particularly with respect to disclosure relating to anti-DLL3 agents and associated amino acid sequences.

**[0052]** The anti-DLL3 agent of the method also may take the form of a traditional bispecific IgG-like antibody, wherein one arm binds DLL3 and the second arm binds CD3. In various aspects, the antibody construct comprises two arms comprising, from N- to C- terminus, a VL domain, a CL domain, a peptide linker, a VH domain, a CH1domain, a peptide linker, and an Fc domain (scFab-Fc). In various aspects, the anti-DLL3 agent disclosed herein comprises a first domain binds to DLL3 (preferably human DLL3) and comprises (a) a heavy chain variable region (VH) that comprises (i) a VH complementarity determining region one (CDR-H1) comprising the amino acid sequence of SEQ ID NO:32, (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO:33, and (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO:34; and (b) a light chain variable region (VL) that comprises (i) a VL complementarity determining region one (CDR-L1) comprising the amino acid sequence of SEQ ID NO:35, (ii) a CDR-L2 comprising the amino acid sequence of SEQ ID NO:36, and (iii) a CDR-L3 comprising the amino acid sequence of SEQ ID NO:37. Optionally, the first domain binds DLL3 and comprises a VH region comprising the amino acid sequence of SEQ ID NO: 38 and a VL region comprising the amino acid sequence of SEQ ID NO: 39. In various aspects, the DLL3 binding region of the agent comprises SEQ ID NO: 40. The second domain binds to CD3 (preferably human CD3), and comprises (a) a VH that comprises (i) a CDR-H1 comprising the amino acid sequence of SEQ ID NO:42, (ii) a CDR-H2 comprising the amino acid sequence of SEQ ID NO:43, and (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO:44; and (b) a VL that comprises (i) a CDR-L1 comprising the amino acid sequence of SEQ ID NO:45, (ii) a CDR-L2 comprising the amino acid sequence of SEQ ID NO:46, and (iii) a CDR-L3 comprising the amino acid sequence of SEQ ID NO:47. Optionally, the second domain binds CD3 and comprises a VH region comprising the amino acid sequence of SEQ ID NO: 48 and a VL region comprising the amino acid sequence of SEQ ID NO: 49. In various aspects, the CD3 binding region of the agent comprises SEQ ID NO: 50. The anti-DLL3 agent optionally comprises the amino acid sequence of SEQ ID NO: 41 and the amino acid sequence of SEQ ID NO: 51. Anti-DLL3 agents are further described in, e.g., International Patent Publication No. WO 2019/234220, incorporated by reference in its entirety and

particularly with respect to disclosure relating to anti-DLL3 agents and associated amino acid sequences.

***THERAPEUTIC REGIMEN***

**[0053]** Disclosed herein are methods of treating brain metastases in a human subject with a DLL3-positive cancer comprising administering to the subject in need thereof an anti-DLL3 agent at a dose of from 3 mg to 200 mg once a week, once every two weeks, or once every three weeks. In certain aspects, the anti-DLL3 agent is administered at a dose of from about 3 mg to about 100 mg, from about 3 mg to about 90 mg, from about 3 mg to about 80 mg, from about 3 mg to about 70 mg, from about 3 mg to about 60 mg, from about 3 mg to about 50 mg, from about 3 mg to about 40 mg, from about 3 mg to about 30 mg, from about 3 mg to about 20 mg, from about 3 mg to about 10 mg, from about 3 mg to about 12 mg, from about 3 mg to about 15 mg, from about 10 mg to about 100 mg, from about 10 mg to about 90 mg, from about 10 mg to about 80 mg, from about 10 mg to about 70 mg, from about 10 mg to about 60 mg, from about 10 mg to about 50 mg, from about 10 mg to about 40 mg, from about 10 mg to about 30 mg, from about 10 mg to about 20 mg, from about 10 mg to about 15 mg, from about 20 mg to about 100 mg, from about 20 mg to about 90 mg, from about 20 mg to about 80 mg, from about 20 mg to about 70 mg, from about 20 mg to about 60 mg, from about 20 mg to about 50 mg, from about 20 mg to about 40 mg, from about 20 mg to about 30 mg, from about 30 mg to about 100 mg, from about 30 mg to about 90 mg, from about 30 mg to about 80 mg, from about 30 mg to about 70 mg, from about 30 mg to about 60 mg, from about 30 mg to about 50 mg, from about 60 mg to about 200 mg, or from about 100 mg to about 200 mg. The dose is administered once a week, once every two weeks, or once every three weeks.

**[0054]** In various aspects of the disclosure, the anti-DLL3 agent is administered once every two weeks at a dose of about 3 mg to about 100 mg, such as a dose of 3 mg, 10 mg, 30 mg, or 100 mg. For example, the method may comprise administering the anti-DLL3 agent at a dose of 10 mg once every two weeks.

**[0055]** The anti-DLL3 agent may be administered to the subject in accordance with a treatment regimen that involves cycles of periodic administration of the agent to the subject. A cycle may comprise any appropriate period of time, and multiple cycles may be employed which entail different frequency of administration and/or different doses administered. One cycle in the course of treatment comprises administering the anti-DLL3 agent at the dose described herein once a week, once every two weeks, or once every three weeks; other cycles with different dosing regimens may be part of the overall course of treatment. In one example, repeated administrations of the anti-DLL3 agent are administered over the course of one or more 28 day cycles. A first cycle may be employed to administer a “run-in dose” of agent, which refers to the initial dose of an anti-DLL3 agent equal to or lower than a dose at which a

first dose effect (e.g., cytokine release syndrome (CRS)) is observed. For example, a run-in dose can be a maximum tolerated dose (MTD) of an anti-DLL3 agent where no CRS or a CRS lower than a certain grade (e.g., Grade 2) is observed. A first cycle may also be employed to offer a "step dose" of agent, which refers to a dose that is higher than the previous dose at which an anti-DLL3 agent is administered. Step dose includes one or more doses that increase from a run-in dose to reach a target dose. As merely an example, 1 mg of the anti-DLL3 agent is administered on day 1, 10 mg the anti-DLL3 agent is administered on day 8, and 10 mg of the anti-DLL3 agent is administered on day 15 of a first 28-day cycle, after which and 10 mg of the anti-DLL3 agent is administered once every two weeks in one or more additional 28-day cycles.

**[0056]** In various aspects of the disclosure, the anti-DLL3 agent is administered once every week at a dose of about 3 mg to about 100 mg (e.g., about 3 mg to about 30 mg), such as a dose of about 3 mg, about 6 mg, about 10 mg, about 12 mg, about 20 mg, about 24 mg, about 30 mg, or about 100 mg. For example, the method may comprise administering the anti-DLL3 agent at a dose of about 6 mg, about 12 mg, or about 24 mg, once a week.

**[0057]** In other aspects of the disclosure, the anti-DLL3 agent is administered at a dose of from about 10 mg to about 200 mg once every three weeks, such as at a dose of about 10 mg, about 20 mg, about 60 mg, or about 200 mg, once every three weeks. For instance, the method may comprise administering the anti-DLL3 agent at a dose of about 20 mg once every three weeks. Multiple cycles of administration may be employed. As merely an example, the method comprises, in various aspects, administering 1 mg of the anti-DLL3 agent on day 1 and administering 20 mg of the anti-DLL3 agent on day 8 (with an optional further administration of 20 mg of the anti-DLL3 agent on day 15) of a first 21-day cycle, after which 20 mg of the anti-DLL3 agent is administered once every three weeks in one or more additional 21-day cycles. As an additional example, the method comprises, in various aspects, administering 1 mg of the anti-DLL3 agent on day 8 and administering 20 mg of the anti-DLL3 agent on day 15 of a first 21-day cycle, after which 20 mg of the anti-DLL3 agent is administered once every three weeks in one or more additional 21-day cycles. Optionally, an anti-PD-L1 agent is administered as part of the therapeutic regimen, further optionally administered on day 1 of the first 21 day cycle.

**[0058]** Alternative dosing regimens contemplated by the disclosure include administration of about 0.015 mg to about 24 mg (e.g., about 2 mg to about 20 mg, about 6 mg to about 24 mg, about 6 mg to about 12 mg, or about 12 mg to about 24 mg) of the anti-DLL3 agent in any interval (e.g., once every one to six weeks), and preferable at an interval of once a week, once every two weeks, or once every three weeks. For instance, the anti-DLL3 agent may be

administered at a dose of about 6 mg, about 12 mg, or about 24 mg once a week, or about 12 mg or about 24 mg once every two weeks.

**[0059]** The anti-DLL3 agent can be administered by any suitable means, including parenteral, subcutaneous, intraperitoneal, intrapulmonary, intranasal, and/or intralesional administration. Parenteral administration includes intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. In some embodiments, the anti-DLL3 agent is administered by intravenous (IV) infusion, such as a short IV infusion (approximately 60 minutes), once a week, once every two weeks, or once every three weeks.

***CO-THERAPY***

**[0060]** In some embodiments, the method of the disclosure provides for the use of an anti-DLL3 agent in combination with one or more additional therapeutic agents. In certain embodiments, the one or more additional therapeutic agents is an agent that mitigates CRS of anti-DLL3 agents (e.g., tarlatamab). In certain embodiments, the one or more additional therapeutic agents include an anti-inflammatory agent, a fluid (e.g., saline), an anti-IL6 antibody (e.g., tocilizumab or siltuximab) and/or an anti-TNF agent (e.g., etanercept). Optionally, the additional agent(s) is administered to the subject in the first cycle wherein the anti-DLL3 agent is administered, although one or more additional agents may be administered in subsequent cycles (i.e., after the first cycle wherein the ant-DLL3 agent is administered).

**[0061]** In some aspects, the one or more additional therapeutic agents may be an anti-inflammatory agent (for example, to prophylactically treat CRS). The anti-inflammatory agent may be administered prior to, concurrently, or after the administration of the anti-DLL3 agent. Exemplary anti-inflammatory agent includes acetaminophen, naproxen sodium, ibuprofen, tramadol, aspirin, celecoxib, valdecoxib, indomethacin, or other Non-steroidal anti-inflammatory drugs (NSAIDs). Other anti-inflammatory agent includes, e.g., beclomethasone, hydroxycortisone, betamethasone, methylprednisolone, budesonide, prednisolone, cortisone, prednisone, dexamethasone, and triamcinolone, or other glucocorticoids. In certain embodiments, the anti-inflammatory agent is a corticosteroid. In certain embodiments, the corticosteroid is dexamethasone. In certain embodiments, the anti-inflammatory agent is acetaminophen. In certain embodiments, the anti-inflammatory agent (e.g., a corticosteroid such as dexamethasone or acetaminophen) is administered before the administration of the anti-DLL3 agent. In certain embodiments, dexamethasone is administered intravenously, e.g., prior to a first cycle of doses of the anti-DLL3 agent. In certain embodiments, dexamethasone is administered orally. For instance, in various aspects, an anti-inflammatory, such as a corticosteroid (e.g., dexamethasone) is administered to the subject on day 1 and day 8 in the first cycle wherein the anti-DLL3 agent is administered. In various aspects, 8 mg of

dexamethasone is administered intravenously (or an equivalent dose and route of administration is employed).

**[0062]** In some embodiments, the one or more additional therapeutic agents (e.g., agents that mitigate CRS) are a fluid (e.g., saline), an anti-IL6 antibody (e.g., tocilizumab or siltuximab) or an anti-TNF agent (e.g., etanercept). Each of these agents may be administered prior to, concurrently, or after the administration of the anti-DLL3 agent. In certain embodiments, saline is administered (e.g., by IV administration) after the administration of the anti-DLL3 agent, preferably in the first cycle of doses of the anti-DLL3 agent. Optionally, one liter of saline is administered, further optionally over the course of four to five hours. In certain embodiments, the anti-IL6 antibody (e.g., tocilizumab or siltuximab) or the anti-TNF agent (e.g., etanercept) is administered prior to the administration of the anti-DLL3 agent.

**[0063]** The method also optionally comprises administering the anti-DLL3 agent in combination with an anti-PD1 antibody (or other antagonist) or anti-PD-L1 antibody (or other antagonist). Programmed Cell Death protein 1 (PD-1), also known as CD279, SLEB2, and hSLEI, is a transmembrane protein expressed on activated T, natural killer (NK) and B lymphocytes, macrophages, dendritic cells (DCs) and monocytes. PD-1 binds to B7 protein family members, PD-1 Ligand 1 (PD-L1; also referred to as CD279 and B7-H1) and PD-1 Ligand 2 (also known as PD-L2, CD273, and B7-DC). PD-L1 is constitutively expressed on T and B cells, macrophages and dendritic cells, whereas PD-L2 expression is typically restricted to activated DC and macrophages (Xing et al., Oncoimmunology 7(3): el356144 (2017) (doi: 10.1080/2162402X.2017.1356144)). PD-1 inhibits both adaptive and innate immune responses. The PD-1/PD-L1 axis is involved in the suppression of T cell immune responses in cancer. Antagonists of this pathway have been clinically validated across a number of solid tumor indications. PD-1 inhibitors, e.g., nivolumab, pembrolizumab, tislelizumab, and cemiplimab, and PD-L1 inhibitors, e.g., atezolizumab, avelumab, and durvalumab, target the PD-1/PD-L1 pathway, and each has been approved by the U.S. Food and Drug Administration (FDA) or other regulatory agencies for the treatment of various cancers. Exemplary agents targeting PD1 include nivolumab, pembrolizumab, and tislelizumab. Exemplary agents targeting PD-L1 include anti-PD-L1 antibodies such as atezolizumab, avelumab, and durvalumab. In various aspects of the disclosure, the method comprises administering durvalumab to the subject. While any order of administration of the anti-DLL3 agent and the anti-PD1 antibody (or other PD1 antagonist) or anti-PD-L1 antibody (or other PD-L1 antagonist) is contemplated (prior to, concurrently, or after the administration), the anti-PD1 or anti-PD-L1 agent is administered before the anti-DLL3 agent in various aspects of the method.

**[0064]** The method also optionally comprises administering the anti-DLL3 agent in combination with an antibody-drug conjugate, such as an antibody drug conjugate that targets

B7-H3 (e.g., Ifinatamab Deruxtecan (I-DXd)). I-DXd is an IgG antibody which binds human B7-H3 and which is conjugated to deruxtecan, a DNA topoisomerase I inhibitor attached to a cleavable tetrapeptide linker. The dosing and timing of administration of Ifinatamab Deruxtecan may, in various aspects, comprises administering about 4 mg/kg to about 18 mg/kg, such as about 8 mg/kg to about 12 mg/kg, to the subject, at an interval of once per week, once every two weeks, once every three weeks, or once every four weeks. In various aspects, Ifinatamab Deruxtecan is administered at a dose of about 8 mg/kg or about 12 mg/kg once every three weeks (e.g., day 1 of a 21 day cycle). The combination treatment may comprise administering any of the anti-DLL3 agents described above. For instance, in various aspects, the anti-DLL3 agent comprises SEQ ID NO: 30 or SEQ ID NO: 31. The disclosure contemplates a method of treating brain metastases in a subject suffering from a DLL3-positive cancer using any of the anti-DLL3 agents described herein in combination with I-DXd. The disclosure further contemplates treating a subject suffering from a DLL3-positive cancer, such as SCLC, with any of the anti-DLL3 agents described herein administered as disclosed herein in combination with administering I-DXd, including optionally administering I-DXd at a dose of about 8 mg/kg or about 12 mg/kg once every three weeks.

**[0065]** The anti-DLL3 agent may also be part of a therapeutic regimen that comprises administration of a chemotherapeutic agent to the subject. Examples of chemotherapeutic agents include, but are not limited to, amrubicin, altretamine, amsacrine, L-asparaginase, colaspase, bleomycin, busulfan, capecitabine, carboplatin, carmustine, chlorambucil, cisplatin, cladribine, cyclophosphamide, cytophosphane, cytarabine, dacarbazine, dactinomycin, daunorubicin, docetaxel, doxorubicin, epirubicin, etoposide, fluorouracil, fludarabine, fotemustine, ganciclovir, gemcitabine, hydroxyurea, idarubicin, ifosfamaide, irinotecan, lomustine, lurbinectedin, melphalan, mercaptopurine, methotrexate, mitoxantrone, mitomycin C, nimustine, oxaliplatin, paclitaxel, pemetrexed, procarbazine, raltitrexed, temozolomide, teniposide, tioguanine, thiotepa, topotecan, vinblastine, vincristine, vindesine, and vinorelbine.

**[0066]** The disclosure further provides a kit or article of manufacture comprising: (a) a container comprising an anti-DLL3 agent; and (b) a package insert with instructions for treating brain metastases associated with DLL3-positive cancer in a subject. The package insert optionally includes instructions specifying the dosage regimen for the anti-DLL3 agent according to any of the dosage regimens described above. In various aspects, the package insert may comprise instructions for administration of an immune checkpoint inhibitor, an anti-inflammatory agent (e.g., a corticosteroid such as dexamethasone or acetaminophen), saline, an anti-IL6 antibody (e.g., tocilizumab or siltuximab), or an anti-TNF agent (e.g., etanercept).

**[0067]** The following example is given merely to illustrate the present invention and not in any way to limit its scope.

## EXAMPLES

**[0068]** Patients with small cell lung cancer (SCLC) face a poor prognosis, with two-thirds having extensive-stage (ES) disease at diagnosis and approximately 40–80% of patients developing brain metastases during the disease course. While most patients with ES SCLC respond to frontline therapy, disease progression often occurs within six months. Current second-line treatments impart short duration of response (DOR) (median DOR: 3.6–5.3 months) and limited survival (median overall survival [OS]: 5.8–9.3 months). No therapies are currently approved in third line and beyond.

**[0069]** Tarlatamab, a BiTE® (bispecific T-cell engager) immunotherapy that redirects cytotoxic T cells to cancer cells expressing delta-like ligand 3 (DLL3), is a novel therapeutic approach. Tarlatamab (sequences set forth in Table 6) has demonstrated durable anticancer activity with a manageable safety profile in patients with previously treated SCLC. The results of a phase I study evaluating tarlatamab in subjects with small cell lung cancer (SCLC) is provided herein, demonstrating a sustained clinical benefit as well as the surprising observation of intracranial activity of tarlatamab against brain metastases.

**[0070]** The primary endpoints for the study included safety and dose limiting toxicities (DLTs), treatment-emergent adverse events (AEs), treatment-related AEs, and clinically significant changes in vital signs, ECG, physical examinations, and clinical laboratory tests. Secondary endpoints included (1) pharmacokinetic (PK) parameters for tarlatamab following intravenous administration including, but not limited to, maximum observed concentration (Cmax), minimum observed concentration (Cmin), area under the concentration-time curve (AUC) over the two week dosing interval, accumulation following multiple dosing, and, if feasible, half-life (t1/2); (2) Objective Response (OR) per modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1; (3) Duration of Response (DOR); (4) time to response (TTR); (5) nine-month Progression-Free Survival (PFS); and (6) Overall Survival (OS). Exploratory endpoints included (1) cell surface target protein expression, gene expression signatures and/or tumor infiltrating lymphocyte status in tumor tissue at baseline; (2) effect of prior chemotherapy on T cell cytokine production pre-tarlatamab treatment, (3) incidence of CRS for subjects with relapsed/refractory small cell lung cancer (R/R SCLC) who progressed or recurred following platinum-based regimen, and (4) changes in blood oxygen saturation, blood pressure, pulse rate, respiratory rate, body temperature, cardiac output, and stroke volume following tarlatamab administration via continuous wireless data recording device during first 48 hours post-infusion.

**[0071]** Central nervous system (CNS) tumor sum of diameters (SOD) was assessed per modified Response Assessment in Neuro-Oncology Brain Metastases (mRANO-BM) criteria

(Lin et al., Lancet Oncol, 16:e270-8 (2015)) by blinded independent central review (BICR) in patients with ≥ 1 brain lesion at baseline and ≥ 2 brain scans; all CNS tumors were considered non-target lesions given prior definitive treatment.

**[0072]** Key Eligibility Criteria for the study are summarized in Table 1 below. Patients with asymptomatic, treated, stable brain metastases were eligible (i.e., patients with brain metastases at baseline were require to have completed definitive therapy (radiation and/or surgery), be without evidence of radiographic CNS progression (no further metastases growth following radiation or surgery), and be asymptomatic).

**TABLE 1**

| Key inclusion criteria | Key exclusion criteria |
|---|---|
| Male or female ≥ 18 years of age with Histologically or cytologically confirmed Small Cell Lung Cancer (SCLC) | History of other malignancy within the past 2 years prior to first dose of tarlatamab with exceptions |
| Parts A and C-G: relapsed/refractory small cell lung cancer (R/R SCLC) who progressed or recurred following platinum-based regimen | Major surgery within 28 days of first dose tarlatamab |
| Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 | Untreated or symptomatic brain metastases and leptomeningeal disease |
| Subjects with treated, asymptomatic, stable brain metastases are eligible provided they meet defined criteria | Prior anti-cancer therapy: at least 28 days must have elapsed between any prior anti-cancer therapy and first dose of tarlatamab |
| Adequate organ function as defined in protocol | |

**[0073]** For Parts A and C-F, tarlatamab (0.003 mg, 0.01 mg, 0.03 mg, 0.1 mg, 0.3 mg, 1 mg, 3 mg, 10 mg, 30 mg, and 100 mg) was administered intravenously every two weeks ± step dosing in patients with SCLC that progressed after ≥1 platinum-based chemotherapeutic regimen. Alternative dosing was used in Part G, including 1 mg to 25 mg to 100 mg regimen (two-step-dosing Q2W), 1 mg to 100 mg to 200 mg increased regimen (Q3W), and 1 mg to 100 mg (D1/D8) cohorts.

**[0074]** The analysis described herein included fully enrolled cohorts of patients treated with doses of 10 mg, 30 mg, 100 mg, and the alternate dosing regimen of tarlatamab (≥ 10 mg).

**[0075]** Patients had a median of two prior lines of therapy (range, 1–7); 28.9% had received ≥ three lines. At baseline, 38 patients (25.0%) had brain metastases. DLL3 expression was detected in 121 out of 129 patients (93.8%) with evaluable baseline tumor sample. Median follow-up was 12.1 months (range, 0.2–34.3); median duration of treatment was 2.8 months (range, <1–34.5). Overall, 56 patients (36.8%) received subsequent anticancer therapy, including 2 of 17 patients (11.8%) in the 10 mg cohort. Chemotherapy was the most common subsequent therapy, administered to 52 of 56 patients (92.9%).

**[0076]** Antitumor activity was assessed using modified RECIST 1.1. Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan-Meier methods. Tumor DLL3 expression was assessed by immunohistochemistry. T-cell activation and cytokine profiles

were evaluated. Tarlatamab administration continued until disease progression, unacceptable side effects, or consent withdrawal.

**[0077]** The most common treatment-emergent adverse events were consistent with that reported previously and included cytokine release syndrome (CRS; 66.4%), pyrexia (48.7%), and decreased appetite (43.4%). Treatment-related adverse events (TRAEs) led to discontinuation in nine patients (5.9%), only occurring among patients dosed with 100 mg tarlatamab. There were no fatal TRAEs.

**[0078]** Most CRS events were grade 1 or 2 and occurred most often following the first or second tarlatamab administrations in cycle 1. Grade 3 CRS occurred in 4.4% of patients (6/135) dosed with >10 mg tarlatamab and in no patients dosed with 10 mg tarlatamab; no grade ≥ 4 CRS events occurred. The incidence of immune effector cell-associated neurotoxicity syndrome (ICANS) and associated neurological events was similar in patients with or without brain metastases at baseline (any grade: 10.5% [4/38] versus 12.3% [14/114]; grade 3–4: 5.3% [2/38] versus 5.3% [6/114]), primarily occurring in patients treated with > 10 mg tarlatamab (94.4% [17/18]). No grade 5 events occurred. There were no occurrences of late-onset CRS or ICANS and associated neurological events among the 25 patients treated with tarlatamab for ≥ 52 weeks.

**[0079]** Across all cohorts dosed with ≥ 10 mg tarlatamab, ORR was 25.0% (95% CI, 18.3 to 32.7), including four patients with complete response (CR) and 34 with partial response (PR); disease control rate (DCR) was 57.2% (95% CI, 49.0 to 65.2). Of 38 confirmed responders, the median DOR was 11.2 months (95% CI, 6.6 to 22.3), with 13 patients (34.2%) with DOR ≥ 12 months and 4 patients (10.5%) with DOR ≥ 24 months (FIGs. 1 and 2). Three of four patients with CR had a DOR of at least 20 months, with the response ongoing. Twelve patients (31.6%) had ongoing response at data cutoff.

**[0080]** Overall median PFS was 3.5 months (95% CI, 2.7 to 3.8) and overall median OS was 17.5 months (95% CI, 11.4 to not estimable [NE]). The Kaplan-Meier estimates of PFS and OS at 12 months were 16.7% and 57.9%, respectively.

**[0081]** Among 17 patients receiving the dose of 10 mg tarlatamab, ORR was 35.3% (95% CI, 14.2 to 61.7), DCR was 58.8% (95% CI, 32.9 to 81.6), and median DOR was 14.9 months (95% CI, 3.0, NE). Patients treated with 10 mg tarlatamab had the longest median OS among all dose cohorts, 20.3 months (95% CI, 5.1 to NE).

**[0082]** Overall, 25 patients (15.1%; 4 CR, 17 PR, 4 stable disease) had sustained disease control (SDC) with time on treatment (TOT) ≥ 52 weeks (range, 52-150), including eight patients treated ≥ 104 weeks. Tarlatamab 10 mg dosing had the highest frequency of patients with SDC with TOT ≥ 52 weeks (29.4% [5/17]). Of 24 patients with SDC with TOT ≥ 52 weeks with evaluable baseline tumor sample, 23 (95.8%) had detectable DLL3 expression and one

(4.2%) had undetectable DLL3 expression. Patients with SDC with TOT ≥ 52 weeks, compared to either patients with best response of progressive disease (PD) or to responders without SDC, had a lower incidence of liver metastases (32.0% versus 45.3%; 47.1%), lower tumor burden (median tumor SOD: 47.0 mm versus 89.0 mm; 101.0 mm), and better performance status (ECOG PS 0: 60.0% versus 39.6%; 29.4%) at baseline.

**[0083]** Of the 112 patients with PD, the most common sites of disease progression were thorax (50/112, 44.6%), lymph nodes (43/112, 38.4%), liver (38/112, 33.9%), and other visceral organs (19/112, 17.0%). PD in the brain occurred infrequently (8.0%), including five patients with PD in the CNS only and four patients with PD in the CNS and systemic sites.

**[0084]** Of 38 patients with stable, treated brain metastases at baseline, 28 patients (73.7%) were evaluable, having a baseline scan and ≥ 1 post-baseline scan(s); all received prior brain radiotherapy (RT). Median time from prior RT to first tarlatamab dose was 44.5 days (Q1: 23.0, Q3: 87.0).

**[0085]** Considering all 28 patients with evaluable brain metastases, one patient had confirmed CR and only one patient had PD as best intracranial response to tarlatamab.

**[0086]** Of 16 patients with a baseline CNS lesion ≥ 10 mm, CNS tumor shrinkage of ≥ 30% was observed in 10 patients (62.5%) (FIGs. 3 and 4). Intracranial disease control was seen in 87.5% of patients (95% CI, 61.7 to 98.4). The median duration of intracranial disease control was 7.4 months (95% CI, 2.8 to NE). Three of eight patients (37.5%) who completed RT ≥ 50 days before tarlatamab initiation had ≥ 30% CNS tumor shrinkage, including one patient with RT 161 days prior to tarlatamab initiation and treatment duration of 12 months (FIGs. 3 and 4). Concordance was seen between systemic disease control and brain metastasis shrinkage; nine of ten patients (90%) with ≥ 30% CNS tumor shrinkage had SD or better systemically.

**[0087]** In an extended follow-up of the clinical study described above, tarlatamab demonstrated sustained clinical benefit in previously treated SCLC, including long DOR, unprecedented OS, and SDC with TOT ≥ 52 weeks. Across all doses, ORR was 25.0% and median OS was 17.5 months. With tarlatamab 10 mg, 35.3% of patients responded, responses were durable (median DOR: 14.9 months), and long-term survival was achieved (median OS: 20.3 months). Additionally, 29.4% of patients treated with tarlatamab 10 mg had SDC with TOT ≥ 52 weeks.

**[0088]** Additional information regarding the follow-up analysis is as follows. Of 28 patients evaluable for mRANO-BM analyses, 16 had a baseline CNS lesion ≥10 mm. Intracranial disease control occurred in 87.5% (14 of 16), with a median duration of 7.4 months (95% CI, 2.8 to NE; FIG. 8). CNS tumor shrinkage of ≥ 30% was observed in 62.5% (10 of 16) of patients (FIG. 7A). All 16 patients had brain radiotherapy (RT) before study initiation. Three of eight patients (37.5%) who completed RT ≥50 days before tarlatamab initiation had ≥ 30%

CNS tumor shrinkage. In addition, for a subset of patients, the nadir in CNS tumor shrinkage occurred long after previous RT (FIG. 7B). Concordance was seen between systemic disease control and brain metastasis shrinkage; 9 of 10 patients (90%) with ≥ 30% CNS tumor shrinkage had stable disease or better systemically.

**[0089]** Remarkably, with tarlatamab treatment, CNS tumor shrinkage of ≥ 30% occurred in 62.5% of patients with baseline CNS lesions ≥ 10 mm, including in a subset long after prior brain RT, demonstrating intracranial activity of tarlatamab. The ability of tarlatamab to cross the BBB and achieve a therapeutic effect against brain metastases was surprising, given the unpredictability associated with penetration of large proteins (~100 KD) to the CNS. The results of the study demonstrate the ability of an anti-DLL3 agent described herein to provide a therapeutic benefit to subjects suffering from brain metastases associated with DLL3-expressing cancer.

**[0090]** A phase 2 study was conducted in patients previously treated for SCLC, which again established CNS tumor shrinkage in patients treated with tarlatamab. Key inclusion criteria of the phase 2 study included R/R SCLC, previous treatment with ≥ two lines of treatment (including platinum-doublet), Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1, available tumor tissue, and measurable disease; patients with treated and stable brain metastases were allowed. The study was conducted in three parts. In the first part, patients were randomized to one of two possible therapeutic regimens: (i) 1 mg of tarlatamab on day 1, followed by 10 mg of tarlatamab on days 8, 15, and every two weeks thereafter, or (ii) 1 mg of tarlatamab on day 1, followed by 100 mg of tarlatamab on days 8, 15, and every two weeks thereafter. Each cohort enrolled 88 patients. Two subsequent parts enrolled patients using the regimen of 1 mg of tarlatamab on day 1, followed by 10 mg of tarlatamab on days 8 and 15, and every two weeks thereafter. Twelve patients were enrolled in Part 2 and included in efficacy analyses along with patients enrolled in Part 1. Patients enrolled in Part 3 were evaluated for safety of reduced inpatient monitoring. Primary endpoints were ORR (Parts 1 & 2), incidence of TEAEs (Parts 1 & 3) and serum concentrations of tarlatamab (Part 1). Secondary endpoints for all parts included additional efficacy endpoints, safety, pharmacokinetics, and immunogenicity. A post-hoc analysis of intracranial activity was evaluated by blinded independent central review (BICR) and safety was additionally evaluated, stratified by the presence or absence of baseline brain metastases.

**[0091]** The patient baseline clinical characteristics of the study were as set forth in Table 2 (10 mg Q2W) and Table 3 (100 mg Q2W).

**TABLE 2**

| **Baseline brain metastases** | **Tarlatamab – 1 mg d1, 10 mg d8 and d15, 10 mg Q2W (n = 100)†** | |
|---|---|---|
| | **Yes (n = 23)** | **No (n = 77)** |
| ECOG PS 0 / 1, n (%) | 4 (17) / 19 (83) | 22 (29) / 55 (71) |
| Median prior lines of therapy, n (range) | 2 (2–5) | 2 (1–6) |
| Prior anti-PD-(L)1 treatment, n (%) | 19 (83) | 55 (71) |
| DLL3 expression (> 0% of tumor cells), x/X (%) | 21/22 (95) | 59/61 (97) |

**TABLE 3**

| **Baseline brain metastases** | **Tarlatamab – 1 mg d1, 100 mg d8 and d15, 100 mg Q2W (n = 88)†** | |
|---|---|---|
| | **Yes (n = 32)** | **No (n = 56)** |
| ECOG PS 0 / 1, n (%) | 7 (22) / 25 (78) | 17 (30) / 39 (70) |
| Median prior lines of therapy, n (range) | 2 (2–8) | 2 (1–6) |
| Prior anti-PD-(L)1 treatment, n (%) | 24 (75) | 38 (68) |
| DLL3 expression (> 0% of tumor cells), x/X (%) | 25/25 (100) | 46/49 (94) |

**[0092]** The study demonstrated that tarlatamab elicited durable response with promising survival, regardless of the presence of treated, stable brain metastases at baseline. The results of the study (median follow-up period 10.6 months) are provided in Table 4 (10 mg Q2W) and Table 5 (100 mg Q2W). NE=not estimable at time of study.

**TABLE 4**

| Brain metastases | Tarlatamab 10 mg Q2W (n = 100) | |
|---|---|---|
| | **Yes (n = 23)** | **No (n = 77)** |
| ORR, % (95% CI) | 52 (31–73) | 38 (27–49) |
| Median DOR, months (range) | NE (3–12+) | NE (2–12+) |
| DOR probability at 12 months, Kaplan-Meier (KM) estimate, % (95% CI) | 55 (22–78) | 50 (29–68) |
| Median PFS, months (95% CI) | 6.7 (3–NE) | 4.0 (3–6) |
| Median OS, months (95% CI) | 14.3 (14–NE) | NE (9–NE) |

**TABLE 5**

| Brain metastases | Tarlatamab 100 mg Q2W (n = 88) | |
|---|---|---|
| | **Yes (n = 32)** | **No (n = 56)** |
| ORR, % (95% CI) | 41 (24–59) | 29 (17–42) |
| Median DOR, months (range) | 7 (1+–12+) | 8 (3–13+) |
| DOR probability at 12 months, Kaplan-Meier (KM) estimate, % (95% CI) | 48 (18–72) | 42 (16–66) |
| Median PFS, months (95% CI) | 4 (3–8) | 3 (2–4) |
| Median OS, months (95% CI) | NE (NE–NE) | NE (9–NE) |

**[0093]** In the post-hoc analysis of intracranial antitumor activity, CNS tumor shrinkage was observed in patients with previously treated brain metastases. Indeed, the analysis revealed CNS tumor shrinkage of ≥ 30% in 10 of 17 patients (59%) with baseline brain metastases that met criteria for evaluation. Intracranial disease control was achieved in 94% (16 of 17) patients (95% CI, 71.3–99.9). The median duration of intracranial disease control was in the range of 2.6–13.9+ months. CNS disease progression per modified RANO-BM (modified response assessment in neuro-oncology criteria for brain metastases) occurred in 3 of 17 patients (18%). The results are illustrated in FIG. 5.

**[0094]** Tarlatamab treatment, including patients receiving the 10 mg Q2W regimen, demonstrated a favorable benefit-risk profile in patients with previously treated SCLC irrespective of the presence of treated and stable brain metastases (BM) at baseline. ORR was 52% in patients with BM (n = 23) and 38% in patients without BM (n = 77). In patients with BM, median progression-free survival (PFS) was 6.7 months and median overall survival (OS) was 14.3 months. CNS tumor shrinkage was observed in patients treated with tarlatamab, regardless of time interval between prior radiotherapy and start of tarlatamab.

**[0095]** The results of the extended follow-up analysis and phase 2 analysis further demonstrate the ability of an anti-DLL3 agent described herein to provide a therapeutic benefit to subjects suffering from brain metastases associated with DLL3-expressing cancer.

**[0096]** While this invention has been described with an emphasis upon preferred aspects, it will be obvious to those of ordinary skill in the art that variations of the preferred methods may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

**TABLE 6: Amino Acid Sequences**

| SEQ ID NO: | Name | Format / Source | Amino acid sequence |
|---|---|---|---|
| 1 | Human DLL3 | human | MVSPRMSGLLSQTVILALIFLPQTRPAGVFELQIHSFGPGPG PGAPRSPCSARLPCRLFFRVCLKPGLSEEAAESPCALGAAL SARGPVYTEQPGAPAPDLPLPDGLLQVPFRDAWPGTFSFII ETWREELGDQIGGPAWSLLARVAGRRRLAAGGPWARDIQR AGAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCGPGL RPCAPLEDECEAPLVCRAGCSPEHGFCEQPGECRCLEGW TGPLCTVPVSTSSCLSPRGPSSATTGCLVPGPGPCDGNPC ANGGSCSETPRSFECTCPRGFYGLRCEVSGVTCADGPCFN GGLCVGGADPDSAYICHCPPGFQGSNCEKRVDRCSLQPC RNGGLCLDLGHALRCRCRAGFAGPRCEHDLDDCAGRACA NGGTCVEGGGAHRCSCALGFGGRDCRERADPCAARPCAH GGRCYAHFSGLVCACAPGYMGARCEFPVHPDGASALPAA PPGLRPGDPQRYLLPPALGLLVAAGVAGAALLLVHVRRRGH SQDAGSRLLAGTPEPSVHALPDALNNLRTQEGSGDGPSSS VDWNRPEDVDPQGIYVISAPSIYAREVATPLFPPLHTGRAG QRQHLLFPYPSSILSVK |
| 2 | Human DLL3 ECD | human | MVSPRMSGLLSQTVILALIFLPQTRPAGVFELQIHSFGPGPG PGAPRSPCSARLPCRLFFRVCLKPGLSEEAAESPCALGAAL SARGPVYTEQPGAPAPDLPLPDGLLQVPFRDAWPGTFSFII ETWREELGDQIGGPAWSLLARVAGRRRLAAGGPWARDIQR AGAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCGPGL RPCAPLEDECEAPLVCRAGCSPEHGFCEQPGECRCLEGW TGPLCTVPVSTSSCLSPRGPSSATTGCLVPGPGPCDGNPC ANGGSCSETPRSFECTCPRGFYGLRCEVSGVTCADGPCFN GGLCVGGADPDSAYICHCPPGFQGSNCEKRVDRCSLQPC RNGGLCLDLGHALRCRCRAGFAGPRCEHDLDDCAGRACA NGGTCVEGGGAHRCSCALGFGGRDCRERADPCAARPCAH |

| | | | |
|---|---|---|---|
| | | | GGRCYAHFSGLVCACAPGYMGARCEFPVHPDGASALPAA PPGLRPGDPQRYL |
| 3 | DLL3-4 | VH CDR1 | SYYWS |
| 4 | DLL3-4 | VH CDR2 | YVYYSGTTNYNPSLKS |
| 5 | DLL3-4 | VH CDR3 | IAVTGFYFDY |
| 6 | DLL3-4 | VL CDR1 | RASQRVNNNYLA |
| 7 | DLL3-4 | VL CDR2 | GASSRAT |
| 8 | DLL3-4 | VL CDR3 | QQYDRSPLT |
| 9 | DLL3-4 | VH | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPP GKGLEWIGYVYYSGTTNYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCASIAVTGFYFDYWGQGTLVTVSS |
| 10 | DLL3-4 | VL | EIVLTQSPGTLSLSPGERVTLSCRASQRVNNNYLAWYQQRP GQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPED FAVYYCQQYDRSPLTFGGGTKLEIK |
| 11 | DLL3-4 (EGF-3 epitope) | scFv | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPP GKGLEWIGYVYYSGTTNYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCASIAVTGFYFDYWGQGTLVTVSSGGGGS GGGGSGGGGSEIVLTQSPGTLSLSPGERVTLSCRASQRVN NNYLAWYQQRPGQAPRLLIYGASSRATGIPDRFSGSGSGT DFTLTISRLEPEDFAVYYCQQYDRSPLTFGGGTKLEIK |
| 12 | CDR-L1 of I2C | artificial | GSSTGAVTSGNYPN |
| 13 | CDR-L2 of I2C | artificial | GTKFLAP |
| 14 | CDR-L3 of I2C | artificial | VLWYSNRWV |
| 15 | CDR-H1 of I2C | artificial | KYAMN |
| 16 | CDR-H2 of I2C | artificial | RIRSKYNNYATYYADSVKD |
| 17 | CDR-H3 of I2C | artificial | HGNFGNSYISYWAY |
| 18 | VH of I2C | artificial | EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQ APGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTL VTVSS |
| 19 | VL of I2C | artificial | QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQ KPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQ PEDEAEYYCVLWYSNRWVFGGGTKLTVL |
| 20 | VH-VL of I2C | artificial | EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQ APGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTL VTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVT LTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPG TPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWV FGGGTKLTVL |
| 21 | DLL3-4-001 (G44C) | VH | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPP GKCLEWIGYVYYSGTTNYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCASIAVTGFYFDYWGQGTLVTVSS |
| 22 | DLL3-4-001 (G234C) | VL | EIVLTQSPGTLSLSPGERVTLSCRASQRVNNNYLAWYQQRP GQAPRLLIYGASSRATGIPDRFSGSGSGTDFTLTISRLEPED FAVYYCQQYDRSPLTFGCGTKLEIK |

| | | | |
|---|---|---|---|
| 23 | DLL3-4-001 (G44C-G243C) | scFv | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPP<br>GKCLEWIGYVYYSGTTNYNPSLKSRVTISVDTSKNQFSLKLS<br>SVTAADTAVYYCASIAVTGFYFDYWGQGTLVTVSSGGGGS<br>GGGGSGGGGSEIVLTQSPGTLSLSPGERVTLSCRASQRVN<br>NNYLAWYQQRPGQAPRLLIYGASSRATGIPDRFSGSGSGT<br>DFTLTISRLEPEDFAVYYCQQYDRSPLTFGCGTKLEIK |
| 24 | DLL3-4-001 (CC) xI2C | bispecific molecule | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPP<br>GKCLEWIGYVYYSGTTNYNPSLKSRVTISVDTSKNQFSLKLS<br>SVTAADTAVYYCASIAVTGFYFDYWGQGTLVTVSSGGGGS<br>GGGGSGGGGSEIVLTQSPGTLSLSPGERVTLSCRASQRVN<br>NNYLAWYQQRPGQAPRLLIYGASSRATGIPDRFSGSGSGT<br>DFTLTISRLEPEDFAVYYCQQYDRSPLTFGCGTKLEIKSGGG<br>GSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWV<br>RQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSK<br>NTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQ<br>GTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGG<br>TVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFL<br>APGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSN<br>RWVFGGGTKLTVL |
| 25 | DLL3-4 xI2C - scFc | bispecific HLE molecule | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPP<br>GKGLEWIGYVYYSGTTNYNPSLKSRVTISVDTSKNQFSLKLS<br>SVTAADTAVYYCASIAVTGFYFDYWGQGTLVTVSSGGGGS<br>GGGGSGGGGSEIVLTQSPGTLSLSPGERVTLSCRASQRVN<br>NNYLAWYQQRPGQAPRLLIYGASSRATGIPDRFSGSGSGT<br>DFTLTISRLEPEDFAVYYCQQYDRSPLTFGGGTKLEIKSGGG<br>GSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWV<br>RQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSK<br>NTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQ<br>GTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGG<br>TVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFL<br>APGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSN<br>RWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLF<br>PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVS<br>NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT<br>CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY<br>SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK<br>GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCP<br>PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE<br>DPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVL<br>HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT<br>LPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN<br>YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE<br>ALHNHYTQKSLSLSPGK |
| 26 | DLL3-4 xI2C - scFc_del GK | bispecific HLE molecule | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPP<br>GKGLEWIGYVYYSGTTNYNPSLKSRVTISVDTSKNQFSLKLS<br>SVTAADTAVYYCASIAVTGFYFDYWGQGTLVTVSSGGGGS<br>GGGGSGGGGSEIVLTQSPGTLSLSPGERVTLSCRASQRVN<br>NNYLAWYQQRPGQAPRLLIYGASSRATGIPDRFSGSGSGT<br>DFTLTISRLEPEDFAVYYCQQYDRSPLTFGGGTKLEIKSGGG<br>GSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWV<br>RQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSK<br>NTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQ<br>GTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGG<br>TVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFL<br>APGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSN<br>RWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLF<br>PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV |

| | | | |
|---|---|---|---|
| | | | HNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVS<br>NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT<br>CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY<br>SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGG<br>GGSGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPC<br>PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP<br>EVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQ<br>DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP<br>PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK<br>TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL<br>HNHYTQKSLSLSPGK |
| 27 | DLL3-4-001 (CC) xI2C - scFc | bispecific HLE molecule | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPP<br>GKCLEWIGYVYYSGTTNYNPSLKSRVTISVDTSKNQFSLKLS<br>SVTAADTAVYYCASIAVTGFYFDYWGQGTLVTVSSGGGGS<br>GGGGSGGGGSEIVLTQSPGTLSLSPGERVTLSCRASQRVN<br>NNYLAWYQQRPGQAPRLLIYGASSRATGIPDRFSGSGSGT<br>DFTLTISRLEPEDFAVYYCQQYDRSPLTFGCGTKLEIKSGGG<br>GSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWV<br>RQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSK<br>NTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQ<br>GTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGG<br>TVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFL<br>APGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSN<br>RWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLF<br>PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVS<br>NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT<br>CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY<br>SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK<br>GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCP<br>PCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE<br>DPEVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVL<br>HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYT<br>LPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN<br>YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHE<br>ALHNHYTQKSLSLSPGK |
| 28 | DLL3-4-001 (CC) xI2C - scFc _delGK | bispecific HLE molecule | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPP<br>GKCLEWIGYVYYSGTTNYNPSLKSRVTISVDTSKNQFSLKLS<br>SVTAADTAVYYCASIAVTGFYFDYWGQGTLVTVSSGGGGS<br>GGGGSGGGGSEIVLTQSPGTLSLSPGERVTLSCRASQRVN<br>NNYLAWYQQRPGQAPRLLIYGASSRATGIPDRFSGSGSGT<br>DFTLTISRLEPEDFAVYYCQQYDRSPLTFGCGTKLEIKSGGG<br>GSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWV<br>RQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSK<br>NTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQ<br>GTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGG<br>TVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFL<br>APGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSN<br>RWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLF<br>PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV<br>HNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVS<br>NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT<br>CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY<br>SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGG<br>GGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPC<br>PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP<br>EVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQ<br>DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP |

| | | | |
|---|---|---|---|
| | | | PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK |
| 29 | DLL3-4-001 (CC) xI2C - scFc _delGK (terminal clip) | bispecific HLE molecule | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPP GKCLEWIGYVYYSGTTNYNPSLKSRVTISVDTSKNQFSLKLS SVTAADTAVYYCASIAVTGFYFDYWGQGTLVTVSSGGGGS GGGGSGGGGSEIVLTQSPGTLSLSPGERVTLSCRASQRVN NNYLAWYQQRPGQAPRLLIYGASSRATGIPDRFSGSGSGT DFTLTISRLEPEDFAVYYCQQYDRSPLTFGCGTKLEIKSGGG GSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWV RQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSK NTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQ GTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGG TVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFL APGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSN RWVFGGGTKLTVLGGGGDKTHTCPPCPAPELLGGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPCEEQYGSTYRCVSVLTVLHQDWLNGKEYKCKVS NKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGG GGSGGGGSGGGGSGGGGSGGGGSGGGGSDKTHTCPPC PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAKTKPCEEQYGSTYRCVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYK TTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPG |
| 30 | DLL3x CD3 | scFv – single domain mAb (sdmAb) format; anti-CD3 scFv - anti-DLL3 sdmAb | EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAINWVRQA PGKGLEWVARIRSKYNNYATYYADQVKDRFTISRDDSKNTA YLQMNNLKTEDTAVYYCVRHANFGNSYISYWAYWGQGTL VTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVT LTCASSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLVPG TPARFSGSLLGGKAALTLSGVQPEDEAEYYCTLWYSNRWV FGGGTKLTVLGGGGSGGGSEVQLVESGGGLVQPGNSLRL SCAASGFTFSKFGMSWVRQAPGKGLEWVSSISGSGRDTLY ADSVKGRFTISRDNAKTTLYLQMNSLRPEDTAVYYCTIGGSL SVSSQGTLVTVSSGGGGSGGGSEVQLVESGGGLVQPGGS LTLSCAASSSSVSLLSLAWYRQAPGKKRELVAGISDDGSIVY MDSVKGRFTISRDNAKNSVYLQMNSLRAEDTAVYYCYAY SWITRSPYWGQGTLVTVSSHHHHHH |
| 31 | DLL3x CD3 | scFv – single domain mAb (sdmAb) format; anti-DLL3 sdmAb - anti-CD3 scFv | EVQLVESGGGLVQPGGSLTLSCAASSSSVSLLSLAWYRQA PGKKRELVAGISDDGSIVYMDSVKGRFTISRDNAKNSVYLQ MNSLRAEDTAVYYCYAYSWITRSPYWGQGTLVTVSSGGG GSGGGSEVQLVESGGGLVQPGNSLRLSCAASGFTFSKFG MSWVRQAPGKGLEWVSSISGSGRDTLYADSVKGRFTISRD NAKTTLYLQMNSLRPEDTAVYYCTIGGSLSVSSQGTLVTVS SGGGGSGGGSEVQLVESGGGLVQPGGSLKLSCAASGFTF NKYAINWVRQAPGKGLEWVARIRSKYNNYATYYADQVKDR FTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHANFGNSYIS YWAYWGQGTLVTVSSGGGGSGGGGSGGGGSQTVVTQEP SLTVSPGGTVTLTCASSTGAVTSGNYPNWVQQKPGQAPRG LIGGTKFLVPGTPARFSGSLLGGKAALTLSGVQPEDEAEYY CTLWYSNRWVFGGGTKLTVLHHHHHH |
| 32 | DLL3 | VH CDR1 | GYTFTSYYVH |
| 33 | DLL3 | VH CDR2 | IINPGGGTTSYAQKFLG |

| | | | |
|---|---|---|---|
| 34 | DLL3 | VH CDR3 | GEAVTGNYFYYGMDV |
| 35 | DLL3 | VL CDR1 | RASQGISNYLV |
| 36 | DLL3 | VL CDR2 | AVSSLYS |
| 37 | DLL3 | VL CDR3 | LQHDSYPYT |
| 38 | DLL3 | VH | QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYVHWVRQA PGQGLEWMVIINPGGGTTSYAQKFLGRVTMTRDTSTNTVY MELKSLRSEDTAVYYCARGEAVTGNYFYYGMDVWGQGTT VTVSS |
| 39 | DLL3 | VL | DIQMTQSPSAMSASVGDRVTITCRASQGISNYLVWFQQKP GKAPKRLIYAVSSLYSGVPSRFSGSGSGTEFTLTISSLQPED FATYYCLQHDSYPYTFGQGTKLEIK |
| 40 | DLL3 | scFab | DIQMTQSPSAMSASVGDRVTITCRASQGISNYLVWFQQKP GKAPKRLIYAVSSLYSGVPSRFSGSGSGTEFTLTISSLQPED FATYYCLQHDSYPYTFGQGTKLEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQ ESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGECGGGGSEGKSSGSGSESKSTEGKSSGS GSESKSTGGGGSQVQLVQSGAEVKKPGASVKVSCKASGY TFTSYYVHWVRQAPGQGLEWMVIINPGGGTTSYAQKFLGR VTMTRDTSTNTVYMELKSLRSEDTAVYYCARGEAVTGNYF YYGMDVWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTA ALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYS LSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSC |
| 41 | DLL3 | scFab-Fc | DIQMTQSPSAMSASVGDRVTITCRASQGISNYLVWFQQKP GKAPKRLIYAVSSLYSGVPSRFSGSGSGTEFTLTISSLQPED FATYYCLQHDSYPYTFGQGTKLEIKRTVAAPSVFIFPPSDEQ LKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPV TKSFNRGECGGGGSEGKSSGSGSESKSTEGKSSGSGSES KSTGGGGSQVQLVQSGAEVKKPGASVKVSCKASGYTFTSY YVHWVRQAPGQGLEWMVIINPGGGTTSYAQKFLGRVTMTR DTSTNTVYMELKSLRSEDTAVYYCARGEAVTGNYFYYGMD VWGQGTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCP PCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLWCLVKGFYPSDIAVEWESNGQPEN NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPG |
| 42 | CD3 | VH CDR1 | GFTFNTYAMN |
| 43 | CD3 | VH CDR2 | RIRSKYNNYATYYADSVKD |
| 44 | CD3 | VH CDR3 | HGNFGNSYVSWFAY |
| 45 | CD3 | VL CDR1 | RSSTGAVTTSNYAN |
| 46 | CD3 | VL CDR2 | GTNKRAP |
| 47 | CD3 | VL CDR3 | ALWYSNLWV |
| 48 | CD3 | VH | EVQLVESGGGLVQPGGSLKLSCAASGFTFNTYAMNWVRQ APGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNT AYLQMNNLKTEDTAVYYCVRHGNFGNSYVSWFAYWGQGT LVTVSA |

| | | | |
|---|---|---|---|
| 49 | CD3 | VL | EAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQE<br>KPGQLPRGLIGGTNKRAPWVPARFSGSLLGGKAALTLSGA<br>QPEDEAEYFCALWYSNLWVFGGGTKLTVL |
| 50 | CD3 | scFab | EAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQE<br>KPGQLPRGLIGGTNKRAPWVPARFSGSLLGGKAALTLSGA<br>QPEDEAEYFCALWYSNLWVFGGGTKLTVLGQPKAAPSVTL<br>FPPSSEELQANKATLVCLISDFYPGAVKVAWKADGSPVNTG<br>VETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE<br>GSTVEKTVAPAECSGGGGSEGKSSGSGSESKSTEGKSSG<br>SGSESKSTGGGGSEVQLVESGGGLVQPGGSLKLSCAASGF<br>TFNTYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVK<br>DRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNS<br>YVSWFAYWGQGTLVTVSAASTKGPSVFPLAPSSKSTSGGT<br>AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY<br>SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS |
| 51 | CD3 | scFab-Fc | EAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQE<br>KPGQLPRGLIGGTNKRAPWVPARFSGSLLGGKAALTLSGA<br>QPEDEAEYFCALWYSNLWVFGGGTKLTVLGQPKAAPSVTL<br>FPPSSEELQANKATLVCLISDFYPGAVKVAWKADGSPVNTG<br>VETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHE<br>GSTVEKTVAPAECSGGGGSEGKSSGSGSESKSTEGKSSG<br>SGSESKSTGGGGSEVQLVESGGGLVQPGGSLKLSCAASGF<br>TFNTYAMNWVRQAPGKGLEWVARIRSKYNNYATYYADSVK<br>DRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNS<br>YVSWFAYWGQGTLVTVSAASTKGPSVFPLAPSSKSTSGGT<br>AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLY<br>SLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCD<br>KTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCV<br>VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV<br>VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP<br>REPQVYTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWES<br>NGQPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVF<br>SCSVMHEALHNRFTQKSLSLSPG |
| 52 | DLL3 EGF-3+4 | Human | SGVTCADGPCFNGGLCVGGADPDSAYICHCPPGFQGSNC<br>EKRVDRCSLQPCRNGGLCLDLGHALRCRCRAGFAGPRCE |
| 53 | DLL3 EGF-3 | Human | SGVTCADGPCFNGGLCVGGADPDSAYICHCPPGFQGSNC<br>E |
| 54 | CD3 epsilon chain | Human | MQSGTHWRVLGLCLLSVGVWGQDGNEEMGGITQTPYKVSI<br>SGTTVILTCPQYPGSEILWQHNDKNIGGDEDDKNIGSDEDH<br>LSLKEFSELEQSGYYVCYPRGSKPEDANFYLYLRARVCENC<br>MEMDVMSVATIVIVDICITGGLLLLVYYWSKNRKAKAKPVTR<br>GAGAGGRQRGQNKERPPPVPNPDYEPIRKGQRDLYSGLN<br>QRRI |
| 55 | DLL3-4 xI2C | bispecific molecule | QVQLQESGPGLVKPSETLSLTCTVSGGSISSYYWSWIRQPP<br>GKGLEWIGYVYYSGTTNYNPSLKSRVTISVDTSKNQFSLKLS<br>SVTAADTAVYYCASIAVTGFYFDYWGQGTLVTVSSGGGGS<br>GGGGSGGGGSEIVLTQSPGTLSLSPGERVTLSCRASQRVN<br>NNYLAWYQQRPGQAPRLLIYGASSRATGIPDRFSGSGSGT<br>DFTLTISRLEPEDFAVYYCQQYDRSPLTFGGGTKLEIKSGGG<br>GSEVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWV<br>RQAPGKGLEWVARIRSKYNNYATYYADSVKDRFTISRDDSK<br>NTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQ<br>GTLVTVSSGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGG<br>TVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFL<br>APGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSN<br>RWVFGGGTKLTVL |

CLAIMS

What is claimed:

1. A method of treating brain metastases in a human subject with a DLL3-positive cancer in need thereof, the method comprising administering to the subject an anti-DLL3 agent comprising a first binding domain that binds to human DLL3 on the surface of a target cell and a second binding domain that binds to human CD3 on the surface of a T cell, wherein the anti-DLL3 agent is administered at a dose of from 3 mg to 200 mg once a week, once every two weeks, or once every three weeks.

2. The method of claim 1, wherein the anti-DLL3 agent is administered at a dose of from 3 mg to 100 mg once every two weeks.

3. The method of claim 1, wherein the anti-DLL3 agent is administered at a dose of 3 mg, 10 mg, 20 mg, 30 mg, or 100 mg once every two weeks.

4. The method of claim 3, wherein the anti-DLL3 agent is administered at a dose of 10 mg once every two weeks.

5. The method of any one of claims 1-4, wherein the anti-DLL3 agent is administered over the course of multiple 28-day cycles.

6. The method of any one of claims 1-5, wherein 1 mg of the anti-DLL3 agent is administered on day 1, 10 mg the anti-DLL3 agent is administered on day 8, and 10 mg of the anti-DLL3 agent is administered on day 15 of a first 28-day cycle, and 10 mg of the anti-DLL3 agent is administered once every two weeks in one or more additional 28-day cycles.

7. The method of claim 1, wherein the anti-DLL3 agent is administered at a dose of from 3 mg to 100 mg once every week.

8. The method of claim 1, wherein the anti-DLL3 agent is administered at a dose of from 10 mg to 200 mg once every three weeks.

9. The method of claim 1 or claim 8, wherein the anti-DLL3 agent is administered at a dose of 10 mg, 20 mg, 60 mg, or 200 mg once every three weeks.

10. The method of claim 9, wherein the anti-DLL3 agent is administered at a dose of 20 mg once every three weeks.

11. The method of any one of claims 1 and 8-10, wherein 1 mg of the anti-DLL3 agent is administered on day 1 and 20 mg of the anti-DLL3 agent is administered on day 8 of a first 21-day cycle, and 20 mg of the anti-DLL3 agent is administered once every three weeks in one or more additional 21-day cycles.

12. The method of any one of claims 1-11, wherein the DLL3-positive cancer is small cell lung cancer (SCLC).

13. The method of claim 12, wherein the SCLC is relapsed SCLC or extensive stage SCLC.

14. The method of claim 12, wherein the SCLC is limited-stage SCLC (LS SCLC).

15. The method of claim 12 or claim 13, wherein the SCLC recurred after one or more prior lines of treatment in the subject.

16. The method of claim 14, wherein the SCLC recurred after two or more prior lines of treatment in the subject.

17. The method of claim 15 or claim 16, wherein at least one prior line of treatment comprises a platinum-based chemotherapeutic.

18. The method of any one of claims 15-17, wherein at least one prior line of treatment comprises an anti-PD1 antibody or anti-PD-L1 antibody therapy.

19. The method of any one of claims 1-18, wherein the anti-DLL3 agent is administered at least 28 days after the completion of any prior lines of treatment of SCLC in the subject.

20. The method of any one of claims 1-11, wherein the DLL3-positive cancer is an extrapulmonary neuroendocrine cancer.

21. The method of claim 20, wherein the DLL3-positive cancer is neuroendocrine prostate cancer.

22. The method of any one of claims 1-21, wherein the subject has not been previously treated for the brain metastases prior to the administration of the anti-DLL3 agent.

23. The method of any one of claims 1-21, wherein the subject has been previously treated for the brain metastases prior to the administration of the anti-DLL3 agent, and suffers from asymptomatic, stable brain metastases.

24. The method of any one of claims 1-23, wherein the anti-DLL3 agent is administered in combination with an anti-PD1 antibody or anti-PD-L1 antibody.

25. The method of claim 24, wherein the anti-PD-L1 antibody is durvalumab.

26. The method of any one of claims 1-25, wherein the anti-DLL3 agent comprises the amino acid sequences of SEQ ID NOs: 23 and 20.

27. The method of any one of claims 1-25, wherein the anti-DLL3 agent comprises the amino acid sequence of SEQ ID NO: 28.

28. The method of any one of claims 1-25, wherein the anti-DLL3 agent comprises the amino acid sequence of SEQ ID NO: 29.

29. The method of any one of claims 1-28, wherein the anti-DLL3 agent is administered by IV infusion.

30 A method of treating brain metastases in a human subject with a DLL3-positive cancer in need thereof, the method comprising administering to the subject an anti-DLL3 agent comprising a first binding domain that binds to human DLL3 and comprises SEQ ID NOs: 32-37 and a second binding domain that binds to human CD3 and comprises SEQ ID NOs: 42-47, wherein the anti-DLL3 agent is administered via IV infusion according to the following schedule:

1 mg on day 1 of a first 28 day cycle;

10 mg on day 8 of a first 28 day cycle 1;

10 mg on day 15 of a first 28 day cycle;

and 10 mg once every two weeks thereafter in one or more subsequent 28 day cycles;

wherein the subject (i) has not been previously treated for the brain metastases prior to the administration of the anti-DLL3 agent or (ii) has been previously treated for the brain metastases prior to the administration of the anti-DLL3 agent and suffers from asymptomatic, stable brain metastases.

31. The method of claim 30, wherein the anti-DLL3 agent comprises SEQ ID NO: 28.

32. The method of claim 30, wherein the anti-DLL3 agent comprises SEQ ID NO: 29.

33. The method of any one of claims 1-32, wherein the anti-DLL3 agent is administered in a 28-day cycle, and the method further comprises administering saline, an anti-inflammatory

agent, tocilizumab, or etanercept to the subject in the first cycle wherein the anti-DLL3 agent is administered.

34. The method of claim 33, wherein dexamethasone is administered to the subject.

35. The method of claim 34, wherein dexamethasone is administered to the subject on day 1 and day 8 in the first cycle wherein the anti-DLL3 agent is administered.

36. The method of any one of claims 1-35, wherein one liter of saline is administered to the subject following administration of the anti-DLL3 agent.