**[0004]** Patients with SCLC typically respond well to the current front-line therapy, which includes etoposide and cisplatin, but invariably quickly relapse with chemoresistant disease, for which no therapeutic options are currently available. Prognosis in the relapsed refractory setting is extremely poor, with rapid disease progression and short median survival of less than six months. Patients with extended disease SCLC develop drug resistance and die as a result of disease at a median time of 10 to 12 months from diagnosis.

**[0005]** AMG 757 is a bispecific T-cell engager (BiTE®) molecule targeting DLL3 on cancer cells and CD3 on T-cells. It is developed for the treatment of neuroendocrine cancers such as SCLC. AMG 757 is being evaluated in a clinical trial for treating SCLC.

**[0006]** Pembrolizumab (Keytruda®) and nivolumab (Opdivo®) are antibodies against programmed cell death-1 (PD-1). Both have been approved in the US for the treatment of patients with metastatic SCLC who have progression after platinum-based chemotherapy and at least 1 other line of therapy. However, the approvals were based on relatively low response rates (19% with pembrolizumab and 12% with nivolumab). Studies evaluating nivolumab as second-line or maintenance therapy have failed to meet their primary endpoints (Reck et al., Annals of Oncology. 29:x39-x43 (2018)).

**[0007]** There is an unmet medical need for the development of therapies for the treatment of SCLC.

## SUMMARY

**[0008]** Based on the disclosure provided herein, those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific examples of the disclosure described herein. Such equivalents are intended to be encompassed by the following examples (E).

**[0009]** E1: A method of treating DLL3-positive cancer, comprising administering to a subject in need thereof an anti-DLL3 agent and an anti-PD-1 antibody, wherein the anti-DLL3 agent is administered at a dose of from 0.3 mg to 30 mg or from 3 mg to 100 mg once every two weeks, and wherein the anti-PD-1 antibody is administered at a dose of 480 mg once every four weeks.

**[0010]** E2: A method of treating DLL3-positive cancer, comprising administering to a subject in need thereof an anti-DLL3 agent and an anti-PD-1 antibody, wherein the anti-DLL3 agent is administered in a 28-day cycle according to the following schedule: a) a first dose of from 0.3 or 1 mg on cycle 1 day 1, b) a second dose on cycle 1 day 8, and c) a third dose on cycle 1 day 15, and e) one or more subsequent doses starting on cycle 2 day 1 and once every two weeks thereafter, and wherein the second, third, and subsequent doses are the same, are each from 0.3 mg to 30 mg or from 3 mg to 100 mg, and are higher than the first dose, and wherein the anti-PD-1 antibody is administered at a dose of 480 mg once every four weeks.

**[0032]** E24: The method of any one of E5-E22, the DLL3-binding domain comprises a VH that comprises the amino acid sequence of SEQ ID NO:11, and a VL that comprises the amino acid sequence of SEQ ID NO:12, and the CD3-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.

**[0033]** E25: The method of any one of E5-E23, wherein the DLL3-binding domain comprises the amino acid of SEQ ID NO:9 and the CD3-binding domain comprises the amino acid of SEQ ID NO: 23.

**[0034]** E26: The method of any one of E5-E21 or E24, the DLL3-binding domain comprises the amino acid of SEQ ID NO:13 and the CD3-binding domain comprises the amino acid of SEQ ID NO:23.

**[0034a]** E26a: In one aspect, the present disclosure refers to the use of an anti-DLL3 agent and an anti-PD-1 antibody in the manufacture of a medicament for combination therapy for treating small cell lung cancer (SCLC), wherein the anti-DLL3 agent comprises the amino acid sequence of SEQ ID NOs: 13 and 23 and an anti-PD-1 antibody, wherein the anti-DLL3 agent is to be administered at a dose of from 0.3 mg to 30 mg or from 3 mg to 100 mg once every two weeks, and wherein the SCLC recurred in the subject after at least one prior platinum-based chemotherapy.

**[0034b]** E26b: In another aspect, the present disclosure refers to the use of an anti-DLL3 agent in the manufacture of a first medicament and use of an anti-PD-1 antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating small cell lung cancer (SCLC), wherein the anti-DLL3 agent comprises the amino acid sequence of SEQ ID NOs: 13 and 23, wherein the anti-DLL3 agent is to be administered at a dose of from 0.3 mg to 30 mg or from 3 mg to 100 mg once every two weeks, and wherein the SCLC recurred in the subject after at least one prior platinum-based chemotherapy.

**[0034c]** E26c: In yet another aspect, the present disclosure refers to the use of an anti-DLL3 agent in the manufacture of a medicament for use in combinatorial therapy for treating small cell lung cancer (SCLC), wherein said medicament is to be administered in combination with an anti-PD-1 antibody, wherein the anti-DLL3 agent comprises the amino acid sequence of SEQ ID NOs: 13 and 23, wherein the anti-DLL3 agent is to be administered at a dose of from 0.3 mg to 30 mg or from 3 mg to 100 mg once every two weeks, and wherein the SCLC recurred in the subject after at least one prior platinum-based chemotherapy.

**[0035]** E27: The method of E25, wherein the anti-DLL3 agent comprises the amino acid sequence of SEQ ID NO:10.

**[0036]** E28: The method of E27, wherein the anti-DLL3 agent comprises the amino acid sequence of SEQ ID NO:14.

**[0037]** E29: The method of any one of E5-E28, wherein the anti-DLL3 agent further comprises a third domain that extends or enhance the serum half-life of the anti-DLL3 agent.

**[0038]** E30: The method of E29, wherein the third domain comprises the amino acid sequence selected from any one of SEQ ID NOs:51-58.

**[0039]** E31: The method of any one of E5-E22, E24, E26, E28-E30, wherein the anti-DLL3 agent comprises the amino acid of SEQ ID NO:27 or 59.

**[0040]** E32: The method of any one of E5-E31, wherein the anti-PD-1 antibody comprises (a) a VH that comprises: (i) a 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, (iii) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 34; and (b) a VL that comprises: (i) a 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, (iii) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 37.

**[0041]** E33: The method of any one of E5-E32, wherein the anti-PD-1 antibody comprises a VH that comprises the amino acid sequence of SEQ ID NO: 38, and a VL that comprises the amino acid sequence of SEQ ID NO: 39.

**[0042]** E34: The method of any one of E5-E33, wherein the anti-PD-1 antibody comprises a heavy chain (HC) that comprises the amino acid sequence of EQ ID NO:40, and a light chain (LC) that comprises the amino acid sequence of SEQ ID NO:41.

**[0043]** E35: The method of any one of E1or E3-E34, wherein the anti-DLL3 agent is administered once every two weeks at a dose of: from about 0.3 mg to about 30 mg, from about 1 mg to about 30 mg, from about 3 mg to about 30 mg or from about 10 mg to about 30 mg.

**[0044]** E36: The method of E35, wherein the anti-DLL3 agent is administered once every two weeks at a dose of about 0.3 mg, 1 mg, 3 mg, 10 mg, 25 mg or 30 mg.

DLL3 agent is then recovered from the cell culture, and wherein the anti-PD-1 antibody is prepared by a process wherein a host cell comprising a nucleic acid encoding the anti-PD-1 antibody described in any one of E32-E34 is cultured under conditions allowing the expression of the antibody and the expressed anti-PD-1 antibody is then recovered from the cell culture

**[0059]** E51: The method of any one of E1-E50, wherein the subject is a human.

**[0060]** E52: An anti-DLL3 agent and an anti-PD-1 antibody for use in a method as set forth in any one of examples E1-E51.

**[0061]** E53: An anti-DLL3 agent and an anti-PD-1 antibody for use in the treatment of DLL3-positive cancer (e.g., SCLC), wherein the anti-DLL3 agent and the anti-PD-1 antibody are administered as set forth in any one of examples E1-E51.

**[0062]** E54: Use of an anti-DLL3 agent and an anti-PD-1 antibody for the manufacture of a medicament for the treatment of SCLC, wherein the medicament is prepared to be administered as set forth in any one of examples E1-E51.

**[0063]** E55: Use of an anti-DLL3 agent and an anti-PD-1 antibody in the preparation of a medicament for the treatment of an DLL3-positive cancer, wherein the anti-DLL3 agent and the anti-PD-1 antibody are administered as set for in any one of examples E1-E51.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0064]** Figure 1 shows AMG 757 and AMG 404 dose levels in the clinical study exemplified in Example 2.

## DETAILED DESCRIPTION

**[0065]** AMG 757 is a half-life-extended BiTE® (bispecific T cell engager) molecule developed for the treatment of SCLC. The activity of AMG 757 requires the simultaneous binding to both target cells ($DLL3^+$ cells) and T cells. The pharmacological effect of AMG 757 is mediated by specific redirection of previously primed cytotoxic $CD8^+$ or $CD4^+$ T lymphocytes to kill $DLL3^+$ cells. AMG 757 is being evaluated in a first-in-human study in subjects with SCLC (Study 20160323) and was found to have anti-tumor activity starting at dose level of 0.3 mg once every two weeks (Q2W) and with acceptable safety at doses up to 100 mg Q2W.

**[0066]** AMG 404 is a fully human antibody that binds human PD-1 with high affinity and blocks the ability of this receptor to interact with its ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2). AMG 404 is being evaluated in a phase 1 study (Study 20180143) of subjects with solid tumors and was found to be effective against solid tumors.

**[0067]** A number of clinical trials were initiated recently for the treatment of small cell lung cancer using PD1/PDL1 inhibitors in combination with other anti-cancer agents. See e.g., NCT04702880 and

# CLAIMS

What is claimed:

1. Use of an anti-DLL3 agent and an anti-PD-1 antibody in the manufacture of a medicament for combination therapy for treating small cell lung cancer (SCLC), wherein the anti-DLL3 agent comprises the amino acid sequence of SEQ ID NOs: 13 and 23 and an anti-PD-1 antibody, wherein the anti-DLL3 agent is to be administered at a dose of from 0.3 mg to 30 mg or from 3 mg to 100 mg once every two weeks, and wherein the SCLC recurred in the subject after at least one prior platinum-based chemotherapy.

2. Use of an anti-DLL3 agent in the manufacture of a first medicament and use of an anti-PD-1 antibody in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy for treating small cell lung cancer (SCLC), wherein the anti-DLL3 agent comprises the amino acid sequence of SEQ ID NOs: 13 and 23, wherein the anti-DLL3 agent is to be administered at a dose of from 0.3 mg to 30 mg or from 3 mg to 100 mg once every two weeks, and wherein the SCLC recurred in the subject after at least one prior platinum-based chemotherapy.

3. Use of an anti-DLL3 agent in the manufacture of a medicament for use in combinatorial therapy for treating small cell lung cancer (SCLC), wherein said medicament is to be administered in combination with an anti-PD-1 antibody, wherein the anti-DLL3 agent comprises the amino acid sequence of SEQ ID NOs: 13 and 23, wherein the anti-DLL3 agent is to be administered at a dose of from 0.3 mg to 30 mg or from 3 mg to 100 mg once every two weeks, and wherein the SCLC recurred in the subject after at least one prior platinum-based chemotherapy.

4. The use of any one of claims 1 to 3, wherein the anti-DLL3 agent is to be administered at a dose of from 1 mg to 30 mg once every two weeks.

5. The use of any one of claims 1 to 4, wherein the anti-DLL3 agent is to be administered at a dose of 3 mg, 10 mg, 25 mg or 30 mg once every two weeks.

6. The use of any one of claims 1 to 3, wherein the anti-DLL3 agent is to be administered at a dose of from 10 mg to 100 mg once every two weeks.

7. The use of any one of claims 1 to 3 or 6, wherein the anti-DLL3 agent is to be administered at a dose of 10 mg, 25 mg, 30 mg, 50 mg, 75 mg or 100 mg once every two weeks.

8. The use of any one of claims 1 to 7, wherein the anti-DLL3 agent is to be administered on day 1 and day 15 of a 28-day cycle.

9. The use of claim 8, wherein the anti-PD-1 antibody is nivolumab, pembrolizumab, or zeluvalimab.

10. The use of claim 9, wherein the anti-PD-1 antibody is pembrolizumab and wherein the pembrolizumab is to be administered at a dose of 200 mg once every three weeks.

11. The use of claim 9, wherein the anti-PD-1 antibody is nivolumab and wherein the nivolumab is to be administered at a dose of 240 mg once every two weeks.

12. The use of claim 9, wherein the anti-PD-1 antibody is zeluvalimab and wherein the zeluvalimab is to be administered at a dose of 480 mg once every three weeks.

13. The use of claim 10, wherein pembrolizumab is to be administered before the anti-DLL3 agent if both are to be administered on the same day.

14. The use of any one of claims 1 to 13, the method further comprises one or more additional therapeutic agent to be administered to the subject.

15. The use of claim 14, wherein the one or more additional therapeutic agent is a corticosteroid, saline, or tocilizumab.

16. The use of claim 15, wherein the corticosteroid is dexamethasone.

17. The use of any one of claims 14 to 16, wherein the one or more additional therapeutic agent is to be administered in cycle 1 wherein the anti-DLL3 agent is to be administered.

18. The use of any one of claims 1 to 17, wherein the platinum-based chemotherapy is platinum-etoposide therapy.

19. The use of any one of claims 1 to 18, wherein the anti-DLL3 agent is to be administered by IV infusion.

20. The use of any one of claims 1 to 19, wherein the subject is a human.