

[0004] Delta-like 3 (DLL3) is a type 1 transmembrane protein and noncanonical Notch ligand that is differentially expressed in SCLC. 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)). DLL3 is a novel and promising target for the development of T-cell-targeted therapies for SCLC.

[0005] There is an unmet medical need for the development of therapies for the treatment of SCLC.

SUMMARY

[0006] 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).

[0007] E1: A method of treating DLL3-positive cancer, comprising administering to a subject in need thereof an anti-DLL3 agent, wherein the anti-DLL3 agent is administered at a dose of from 0.3 mg to 100 mg, from 3 mg to 200 mg, or 100 mg once every two weeks.

[0008] E2: A method of treating DLL3-positive cancer, comprising administering to a subject in need thereof an anti-DLL3 agent, wherein said anti-DLL3 agent is administered according to the following schedule: a) a first dose of from 0.3 mg to 100 mg, 0.5 mg to 10 mg, or 1 mg, on day 1, b) a second dose of from 0.3 mg to 100 mg, from 3 to 200 mg, or 100 mg, on day 8, and c) one or more subsequence doses of from 0.3 mg to 100 mg, from 3 to 200 mg, or 100 mg, starting on day 15 and once every two weeks thereafter, and wherein the second and subsequent doses are the same, and are higher than the first dose.

[0009] E3: A method of treating DLL3-positive cancer, comprising administering to a subject in need thereof an anti-DLL3 agent, wherein said anti-DLL3 agent is administered according to one of the following two schedules:

Schedule I: a) a first dose (run-in dose) of from 0.5 mg to 10 mg or 1 mg, on day 1, b) a second dose (step dose) of from 3 mg to 100 mg or from 25 mg to 50 mg, on day 4, c) a third dose (step dose) of from 3 mg to 200 mg or 100 mg, on day 8, and d) one or more subsequence doses (target dose) of from 3 mg to 200 mg or 100 mg, starting on day 15 and once every two weeks thereafter, and wherein the second dose is higher than the first dose, and the third and subsequent doses are the same, and are the same or higher than the second dose; or

Schedule II: a) a first dose (run-in dose) of from 0.5 mg to 10 mg or 1 mg, on day 1, b) a second dose (step dose) of from 3 mg to 100 mg or 25 mg to 50 mg, on day 8, c) a third dose (step dose) of from 3 mg to 200 mg or 100 mg, on day 15 and c) one or more subsequence doses (target dose) of from

[0055] E49: The method of any one of E1-E48, wherein the method comprises administering one or more additional therapeutic agent to the subject.

[0056] E50: The method of E49, wherein the one or more additional therapeutic agents is a steroid.

[0057] E51: The method of any one of E49 or E50, wherein the additional therapeutic agent is dexamethasone.

[0058] E52: The method of any one of E49-E51, wherein the additional therapeutic agent is administered prior to the treatment with the anti-DLL3 agent.

[0059] E53: The method of any one of E48-E51, wherein the additional therapeutic agent is administered concurrently with the anti-DLL3 agent.

[0060] E54: The method of any one of E2-E53, wherein the anti-DLL3 agent is administered in a 28-day cycle, and the method further comprises administering a fluid (e.g., saline), an anti-inflammatory agent, tocilizumab, or etanercept to the subject in the first cycle wherein the anti-DLL3 agent is administered.

[0061] E55: The method of E54, wherein one-liter saline is administered by IV infusion to the subject after the run-in dose and the step doses of the anti-DLL3 agent.

[0062] E56: The method of E55, wherein the one-liter saline is administered over about 4-5 hours.

[0063] E57: The method of E54, wherein the anti-inflammatory agent is a corticosteroid or acetaminophen.

[0064] E58: The method of E57, wherein the corticosteroid is dexamethasone.

[0065] E59: The method of any one of E54, E57, or E58, wherein the anti-inflammatory agent or tocilizumab is administered to the subject prior to the run-in dose and the step doses of the anti-DLL3 agent.

[0066] E60: The method of E59, wherein the corticosteroid is administered to the subject about 6-16 hours prior to the run-in dose and step doses of the anti-DLL3 agent.

[0067] E61: The method of E59, wherein tocilizumab or acetaminophen is administered to the subject about one hour prior to the run-in dose and step doses of the anti-DLL3 agent.

[0068] E62: The method of E54, wherein etanercept is administered to the subject about 36-60 hours prior to the run-in dose and step doses, except the step dose on day 4, of the anti-DLL3 agent.

[0069] E63: The method of E62, wherein etanercept is administered 2 days prior to the run-in dose and step doses, except the step dose on day 4, of the anti-DLL3 agent.

[0070] E64: The method of any one of E1-E63, wherein the subject is a human.

[0071] E65: An anti-DLL3 agent for use in a method as set forth in any one of examples E1-E64.

[0072] E66: An anti-DLL3 agent for use in the treatment of DLL3-positive cancer (e.g., SCLC), wherein the anti-DLL3 agent is administered as set forth in any one of examples E1-E64.

[0073] E67: Use of an anti-DLL3 agent 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-E64.

[0074] E68: Use of an anti-DLL3 agent in the preparation of a medicament for the treatment of an DLL3-positive cancer, wherein the anti-DLL3 agent is administered as set for in any one of examples E1-E64.

In one aspect, the present disclosure refers to the use of an anti-DLL3 agent comprising the amino acid sequence of SEQ ID NO: 438 in the preparation of a medicament for treating small cell lung cancer (SCLC) in a human subject in need thereof, wherein the medicament is to be administered at a dose of from 10 mg to 100 mg once every two weeks.

In one aspect, the present disclosure refers to the use of an anti-DLL3 agent comprising the amino acid sequence of SEQ ID NO: 438 in the preparation of a medicament for use in combinatorial therapy for treating small cell lung cancer (SCLC) in a human subject in need thereof, wherein the medicament is to be administered according to the following schedule: a) a first dose (run-in dose) of from 0.5 mg to 2 mg on day 1, b) a second dose (step dose) of from 3 mg to 100 mg on day 8, and c) one or more subsequent doses (target dose) of from 3 mg to 100 mg, starting on day 15 and once every two weeks thereafter, and wherein the second and subsequent doses are the same, and are higher than the first dose, wherein said medicament is to be administered in combination with an anti-inflammatory agent and the anti-inflammatory agent is to be administered to the subject on day 1 prior to the run-in dose and on day 8 prior to the step dose of the anti-DLL3.

BRIEF DESCRIPTION OF THE DRAWINGS

[0075] Figure 1 shows predicted serum concentration-time profiles of a single cycle of AMG 757 in humans after administration of short IV-infusions once every two weeks. The dashed lines represent the concentrations required for 50% and 90% maximal effect (EC₅₀ and EC₉₀ values of 0.61 ng/mL and 4.6 ng/mL, respectively) of AMG 757-mediated CD69 upregulation, which was identified as the most sensitive marker of AMG 757 activity (Study 123564).

[0076] Figure 2 shows predicted lung concentration-time profiles of a single cycle of AMG 757 in humans after administration of short IV-infusions once every two weeks. The dashed lines represent the concentrations required for 50% and 90% maximal effect (EC₅₀ and EC₉₀ values of 2.8 ng/mL and 5.7 ng/mL, respectively) of AMG 757-mediated cell killing in SHP-77 cells.

[0077] Figure 3 shows a step dosing example assuming adverse events related to first dose effects occurs at 0.03 mg.

[0078] Figure 4 shows confirmed partial response (PR) of SCLC patients treated with AMG 757.

[0079] Figure 5 shows the mean steady state serum AMG 757 Concentration-Time profiles of SCLC patients treated with the molecule. In Figure 5, *denotes step dosing, data are presented after Cycle 2 Day 15 dose during the 2 week dosing interval. Data from the only patient enrolled in 0.1 mg group were not available as the patient dropped out during cycle 1.

[0080] Figure 6 shows Summary of Objective Response of SCLC patients treated with AMG 757.

DETAILED DESCRIPTION

[0081] As disclosed and exemplified herein, a Phase 1 clinical study was conducted for the treatment of SCLC, using a bispecific protein (AMG 757) that targets DLL3 and CD3.

[0082] 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. The selection of the starting dose for the First in Human (FIH) study was based on the Minimum Anticipated Biological Effect Level (MABEL), which was identified as the EC₅₀ of AMG 757-mediated CD69 upregulation in

CLAIMS

What is claimed:

1. Use of an anti-DLL3 agent comprising the amino acid sequence of SEQ ID NO: 438 in the preparation of a medicament for treating small cell lung cancer (SCLC) in a human subject in need thereof, wherein the medicament is to be administered at a dose of from 10 mg to 100 mg once every two weeks.
2. The use of claim 1, wherein the anti-DLL3 agent is to be administered at a dose of 10 mg, 30 mg, or 100 mg, once every two weeks.
3. The use of claim 1 or claim 2, wherein the anti-DLL3 agent is to be administered on day 1 and day 15 of a 28-day cycle.
4. The use of any one of claims 1-3, wherein the anti-DLL3 agent is to be administered in a 28-day cycle, and is to be used in combination with saline, an anti-inflammatory agent, acetaminophen, an anti-IL6 antibody, or an anti-TNF agent to the subject in the first cycle wherein the anti-DLL3 agent is administered.
5. The use of claim 4, wherein one-liter saline is to be administered by IV infusion to the subject.
6. The use of claim 5, wherein one-liter saline is to be administered by IV infusion over the course of four to five hours.
7. The use of any one of claims 4-6, wherein a corticosteroid is to be administered to the subject.
8. The use of claim 7, wherein the corticosteroid is dexamethasone.
9. The use of claim 8, wherein the corticosteroid is dexamethasone to be administered by IV infusion.
10. The use of any one of claims 1-9, wherein said anti-DLL3 agent is to be administered according to the following schedule:
 - a) a first dose of from 0.3 mg to 3 mg on day 1,
 - b) a second dose of from 10 mg to 100 mg on day 8, and
 - c) one or more subsequent doses of from 10 mg to 100 mg, starting on day 15 and once every two weeks thereafter, and wherein the second and subsequent doses are the same.

11. The use of claim 10, wherein the first dose is about 1 mg to about 3 mg, and the second dose and the subsequent doses are about 10 mg to about 15 mg.
12. Use of an anti-DLL3 agent comprising the amino acid sequence of SEQ ID NO: 438 in the preparation of a medicament for use in combinatorial therapy for treating small cell lung cancer (SCLC) in a human subject in need thereof, wherein the medicament is to be administered according to the following schedule:
 - a) a first dose (run-in dose) of from 0.5 mg to 2 mg on day 1,
 - b) a second dose (step dose) of from 3 mg to 100 mg on day 8, and
 - c) one or more subsequent doses (target dose) of from 3 mg to 100 mg, starting on day 15 and once every two weeks thereafter, and wherein the second and subsequent doses are the same, and are higher than the first dose, wherein said medicament is to be administered in combination with an anti-inflammatory agent and the anti-inflammatory agent is to be administered to the subject on day 1 prior to the run-in dose and on day 8 prior to the step dose of the anti-DLL3.
13. The use of claim 12, wherein the first dose is 1 mg; and wherein the second dose and subsequent doses are each 3 mg, 10 mg, 30 mg, or 100 mg.
14. The use of claim 12 or claim 13, wherein the second dose and subsequent doses are each 10 mg.
15. The use of any one of claims 12-14, wherein the anti-DLL3 agent is to be administered in a 28-day cycle, and the medicament comprising the anti-DLL3 agent is to be administered with saline, an anti-inflammatory agent, acetaminophen, an anti-IL6 antibody, or an anti-TNF agent to the subject in the first cycle wherein the anti-DLL3 agent is to be administered.
16. The use of claim 15, wherein one-liter saline is to be administered by IV infusion to the subject.
17. The use of claim 16, wherein one-liter saline is to be administered by IV infusion over the course of four to five hours.
18. The use of claim 16 or claim 17, wherein one-liter saline is to be administered by IV infusion on day 1, day 8, and day 15.
19. The use of claim 16, wherein the anti-inflammatory agent is a corticosteroid.
20. The use of claim 19, wherein the corticosteroid is dexamethasone.

21. The use of claim 15, 19, or 20, wherein the anti-inflammatory agent, acetaminophen, or anti-IL6 antibody is to be administered to the subject prior to the run-in dose and the step doses of the anti-DLL3 agent.
22. The use of any one of claims 1-21, wherein the anti-DLL3 agent comprises the amino acid sequence of SEQ ID NO: 520.
23. The use of any one of claims 1-22, wherein the cancer is extensive-stage SCLC (ES SCLC).
24. The use of any one of claims 1-23, wherein the cancer is relapsed/refractory SCLC (RR SCLC).
25. The use of any one of claims 1-24, wherein the anti-DLL3 agent is to be administered by IV infusion.
26. The use of claim 25, wherein the anti-DLL3 agent is to be administered via a one hour intravenous (IV) infusion.
27. The use of claim 4, claim 15, or claim 21, wherein the anti-IL6 antibody is tocilizumab.
28. The use of claim 4 or claim 15, wherein the anti-TNF agent is etanercept.