study, approximately 86% of SCLC tumors analyzed showed evidence of DLL3 expression by RNA-seq (Giffin et al., Clin. Cancer Res., 27(5):1526-1537 (2021). doi: 10.1158/1078-0432.CCR-20-2845). In contrast, only a few normal cell types have been shown to express DLL3 (e.g., neurons, pancreatic islet cells, and pituitary cells), and such expression was predominantly cytoplasmic. Recent studies have reported that DLL3 is also expressed in other tumor types of neuroendocrine origin, including melanoma, glioblastoma multiforme, neuroendocrine prostate cancer (NEPC), and large cell neuroendocrine lung tumors.

[005] Therapies targeting DLL3 are being investigated for treating DLL3-expressing cancers. For example, rovalpituzumab tesirine (Rova-T) is an antibody-drug conjugate (ADC) containing a DLL3-targeting antibody tethered to the cytotoxic agent pyrrolobenzodiazepine via of a protease-cleavable linker. Despite promising results in early clinical trials, development of Rova-T was discontinued after it demonstrated limited efficacy and higher rates of certain toxicities in phase 3 trials (Blackhall et al., *J. Thoracic Oncology*, *16*(9): 1547-1558 (2021); and Upetry et al., *J. Thoracic Oncology*, *16*(9): 1429-1433 (2021)). The therapeutic effects of ADCs are mediated by the cytotoxic/cytostatic agent to which the antibody is conjugated, and ADCs do not generally engage, recruit, and/or activate cells of the immune system. As such, DLL3 remains a promising target for immunotherapeutics that, for example, engage and activate cytotoxic T cells.

[006] There remains a need for methods for identifying and treating patient populations that would benefit from DLL3-targeted immunotherapeutics.

BRIEF SUMMARY

[006a] In one aspect, the disclosure provides a use of a bispecific antigen-binding molecule comprising at least a first binding domain that binds to human delta-like ligand 3 (DLL3) in the manufacture of a medicament for treating small cell lung cancer (SCLC) in a subject, wherein at least 25% of the SCLC cells express DLL3.

[006b] In one aspect, the disclosure provides a use of a bispecific antigen-binding molecule comprising at least a first binding domain that binds to human delta-like ligand 3 (DLL3) in the manufacture of a medicament for treating SCLC in a subject, wherein the SCLC has a DLL3 expression level in which at least 25% of the SCLC cells express DLL3 at an intensity equal to or greater than 2+ as determined by an IHC assay.

[006c] In one aspect, the disclosure provides a use of a bispecific antigen-binding molecule comprising a first binding domain that binds to human delta-like ligand 3 (DLL3) and a second binding domain that binds to human CD3 in the manufacture of a medicament for treating

neuroendocrine prostate cancer (NEPC) in a subject, wherein the NEPC cells express DLL3 as determined by an immunohistochemical (IHC) assay.

[007] The disclosure provides a method of treating small cell lung cancer (SCLC) in a subject, which method comprises administering to the subject a bispecific antigen-binding molecule comprising at least a first binding domain that binds to human delta-like ligand 3 (DLL3), wherein at least 25% of the SCLC cells express DLL3.

[008] In some examples of the method, at least 50% or at least 75% of the SCLC cells express DLL3.

[009] In some examples of the method, DLL3 expression is determined using an immunohistochemical (IHC) assay.

[0010] In some examples of the method, DLL3 expression is determined using Formalin Fixed Paraffin Embedded (FFPE) tissue specimens from the subject.

[0011] In some examples of the method, the SCLC has progressed or recurred in the subject following a platinum-based treatment.

[0012] In some examples of the method, the SCLC has progressed or recurred in the subject following a platinum-based treatment in combination with etoposide, and optionally a PD-L1 inhibitor.

[0013] In some examples of the method, the subject (i) has completed up to two cycles of platinum-based treatment in combination with etoposide and optionally a PD-L1 inhibitor, or (ii) has completed four to six cycles of platinum-based treatment in combination with etoposide and optionally a PD-L1 inhibitor, and has not experienced disease progression.

[0014] In some examples, the method further comprises administering to the subject a PD-L1 inhibitor and optionally a chemotherapeutic agent.

[0015] In some examples of the method, the bispecific antigen-binding molecule comprises a second binding domain that binds to human CD3.

[0016] In some examples of the method, the bispecific antigen-binding molecule is a protein.

[0017] In some examples of the method, the bispecific antigen-binding molecule comprises an antibody, a single chain variable fragment (scFv), tandem single-chain variable fragments (scFv)2, a bispecific T cell engager (BiTE®) molecule, or a heteromultimer.

[0018] In some examples of the method, the bispecific antigen-binding molecule comprises the amino acid sequences of SEQ ID NO: 14 and SEQ ID NO: 15.

[0019] In some examples of the method, the bispecific antigen-binding molecule is tarlatamab.

[0020] In some examples of the method, the bispecific antigen-binding molecule comprises a first heterodimer that binds to human DLL3 and a second heterodimer that binds to human CD3, wherein (a) the first heterodimer comprises a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 17 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 18; and (b) the second heterodimer comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 20.

[0021] In some examples, the method increases progression free survival (PFS) of the subject as compared to a second SCLC subject comprising less than 50% of SCLC cells expressing DLL3 and treated with the same antigen-binding molecule.

[0022] In some examples, the method increases one or more of Overall Survival (OS), Objective Response Rate (ORR), and/or Disease Control Rate (DCR) and Duration of Response (DOR) as compared to the second subject.

[0023] In some examples, the method results in an Objective Response Rate (ORR) in the subject that is greater than about 35%.

[0024] The disclosure also provides a method of treating SCLC in a subject, which method comprises administering to the subject a bispecific antigen-binding molecule comprising at least a first binding domain that binds to human DLL3, wherein the SCLC has a DLL3 expression level in which at least 25% of the SCLC cells express DLL3 at an intensity equal to or greater than 2+ as determined by an IHC assay.

[0025] In some examples of the method, the SCLC has a DLL3 expression level in which at least 50% or at least 75% of the SCLC cells express DLL3 at an intensity equal to or greater than 2+ as determined by an IHC assay.

[0026] In some examples of the method, at least 25% of the SCLC cells express DLL3 at an intensity of 2+ or 3+ as determined by the IHC assay.

[0027] In some examples of the method, DLL3 expression is determined using Formalin Fixed Paraffin Embedded (FFPE) tissue specimens from the subject.

[0028] In some examples of the method, the SCLC has progressed or recurred in the subject following a platinum-based treatment.

[0029] In some examples of the method, the SCLC has progressed or recurred in the subject following a platinum-based treatment in combination with etoposide, and optionally a PD-L1 inhibitor.

[0030] In some examples of the method, the subject (i) has completed up to two cycles of platinum-based treatment in combination with etoposide and optionally a PD-L1 inhibitor, or (ii) has completed four to six cycles of platinum-based treatment in combination with etoposide and optionally a PD-L1 inhibitor, and has not experienced disease progression.

[0031] In some examples, the method further comprises administering to the subject a PD-L1 inhibitor and optionally a chemotherapeutic agent.

[0032] In some examples of the method, the bispecific antigen-binding molecule comprises a second binding domain that binds to human CD3.

[0033] In some examples of the method, the bispecific antigen-binding molecule is a protein.

[0034] In some examples of the method, the bispecific antigen-binding molecule comprises an antibody, a single chain variable fragment (scFv), tandem single-chain variable fragments (scFv)2, a bispecific T cell engager (BiTE®) molecule, or a heteromultimer.

[0035] In some examples of the method, the bispecific antigen-binding molecule comprises SEQ ID NO: 14 and SEQ ID NO: 15.

[0036] In some examples of the method, the bispecific antigen-binding molecule is tarlatamab.

[0037] In some examples of the method, the bispecific antigen-binding molecule comprises a first heterodimer that binds to human DLL3 and a second heterodimer that binds to human CD3,

wherein (a) the first heterodimer comprises a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 17 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 18; and (b) the second heterodimer comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 20.

[0038] In some examples, the method increases progression free survival (PFS) of the subject compared to a second SCLC subject having a lower DLL3 expression level and treated with the same antigen-binding molecule.

[0039] In some examples, the method increases one or more of OS, ORR, and/or DCR and DOR as compared to the second subject.

[0040] In some examples, the method results in an Objective Response Rate (ORR) in the subject that is greater than about 35%.

[0041] In some examples of the method, the cancer cells are viable cancer cells.

[0042] In some examples of the method, the bispecific antigen-binding molecule is tarlatamab, and tarlatamab is administered at a dose of from 10 mg to 100 mg once every two weeks.

[0043] In some examples of the method, tarlatamab is administered at a dose of 10 mg once every two weeks.

[0044] In some examples of the method, tarlatamab is administered at a dose of 100 mg once every two weeks.

[0045] In some examples, the method comprises administering tarlatamab at a dose of 10 mg to 100 mg once a week on weeks 1, 2, and 3 prior to administering tarlatamab once every two weeks.

[0046] In some examples of the method, the bispecific antigen-binding molecule is tarlatamab, and tarlatamab is administered at a dose of from 10 mg to 100 mg twice every three weeks.

[0047] In some examples of the method, tarlatamab is administered at a dose of 10 mg, 30 mg, or 100 mg twice every three weeks.

[0048] In some examples of the method, tarlatamab is administered on day 1 and day 8 of a 21-day cycle.

[0049] In some examples of the method, the bispecific antigen-binding molecule is tarlatamab, and tarlatamab is administered at a dose of from 20 mg to 200 mg once every three weeks.

[0050] In some examples of the method, tarlatamab is administered at a dose of from 20 mg to 100 mg once every three weeks.

[0051] In some examples of the method, tarlatamab is administered at a dose of from 100 mg to 200 mg once every three weeks.

[0052] In some examples of the method, tarlatamab is administered at a dose of 20 mg, 60 mg, 100 mg, or 200 mg.

[0053] In some examples of the method, tarlatamab is administered on day one of a 21-day cycle.

[0054] In some examples, the method comprises administering tarlatamab at a dose of 10 mg to 100 mg once a week on weeks 1 and 2 prior to administering tarlatamab once every three weeks.

[0055] In some examples of the method, the FFPE tissue specimens are prepared from core needle biopsy tissue samples.

[0056] In some examples of the method, the subject is a human. In some examples , the human had at least one prior treatment of the cancer and relapsed. In some examples , the at least one prior treatment is a platinum-based chemotherapy and etoposide, and optionally an anti-PD-L1 antibody. In some examples , the human had no prior systemic treatment of the cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0057] Figure 1A is a graph showing the best percent change from baseline in tumor burden (defined by the sum of the longest diameters (SLD) of all target lesions) in 94 patients whose data cut-off date was at least 9 weeks after the first dose date and for whom postbaseline tumor data were available. CR denotes complete response, PR partial response, SD stable disease, and NE not evaluable. SD^ indicates patients had an initial response but did not have confirmation of response on the subsequent scan and PR** indicates patients had an initial PR and still have potential for future confirmative scans. One confirmed subject in cohort 30 had missing sum of diameters for lesion measurement and was not included in the plot. † Step dosing (i.e., 1 mg run-in dose) was used in these cohorts. Figure 1B is a graph showing the time to response, the duration of treatment, and patient status as of the data cutoff date according to dose of tarlatamab for all patients with confirmed response (N=25).

[0058] Figure 2A shows a Kaplan-Meier curve of progression-free survival for patients whose data cut-off date was at least 9 weeks after the first dose date (N=107). Figure 2B shows a Kaplan-Meier curve of overall survival for patients whose data cut-off date was at least 9 weeks after the first dose date (N=107).

[0059] Figure 3 is ROC curve reflecting True Positive Rate (TPR) and False Positive Rate (FPR) of enrichment of objective response when FIH subjects (1-100 mg cohorts) are retrospectively examined for selection using DLL3 expression assessed with the Ventana SP347

CLAIM(S):

1. Use of a bispecific antigen-binding molecule comprising at least a first binding domain that binds to human delta-like ligand 3 (DLL3) in the manufacture of a medicament for treating small cell lung cancer (SCLC) in a subject, wherein at least 25% of the SCLC cells express DLL3.

2. The use of claim 1, wherein at least 50% or at least 75% of the SCLC cells express DLL3.

3. The use of claim 1 or claim 2, wherein DLL3 expression is determined using an immunohistochemical (IHC) assay.

4. The use of claim 3, wherein DLL3 expression is determined using Formalin Fixed Paraffin Embedded (FFPE) tissue specimens from the subject.

5. The use of any one of claims 1-4, wherein the SCLC has progressed or recurred in the subject following a platinum-based treatment.

6. The use of any one of claims 1-4, wherein the SCLC has progressed or recurred in the subject following a platinum-based treatment in combination with etoposide, and optionally a PD-L1 inhibitor.

7. The use of any one of claims 1-4, which further comprises a PD-L1 inhibitor and optionally a chemotherapeutic agent to be administered to the subject.

8. The use of any one of claims 1-7, wherein the bispecific antigen-binding molecule comprises a second binding domain that binds to human CD3.

9. The use of any one of claims 1-8, wherein the bispecific antigen-binding molecule comprises an antibody, a single chain variable fragment (scFv), tandem single-chain variable fragments $(scFv)_2$, a bispecific T cell engager (BiTE®) molecule, or a heteromultimer.

10. The use of claim 9, wherein the bispecific antigen-binding molecule comprises the amino acid sequences of SEQ ID NO: 14 and SEQ ID NO: 15.

11. The use of claim 10, wherein the bispecific antigen-binding molecule is tarlatamab.

12. The use of claim 9, wherein the bispecific antigen-binding molecule comprises a first heterodimer that binds to human DLL3 and a second heterodimer that binds to human CD3, wherein

(a) the first heterodimer comprises a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 17 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 18; and

(b) the second heterodimer comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 20.

13. Use of a bispecific antigen-binding molecule comprising at least a first binding domain that binds to human delta-like ligand 3 (DLL3) in the manufacture of a medicament for treating SCLC in a subject, wherein the SCLC has a DLL3 expression level in which at least 25% of the SCLC cells express DLL3 at an intensity equal to or greater than 2+ as determined by an IHC assay.

14. The use of claim 13, wherein the SCLC has a DLL3 expression level in which at least 50% or at least 75% of the SCLC cells express DLL3 at an intensity equal to or greater than 2+ as determined by an IHC assay.

15. The use of claim 13, wherein at least 25% of the SCLC cells express DLL3 at an intensity of 2+ or 3+ as determined by the IHC assay.

16. The use of any one of claims 13-15, wherein the SCLC has progressed or recurred in the subject following a platinum-based treatment.

17. The use of any one of claims 13-15, wherein the SCLC has progressed or recurred in the subject following a platinum-based treatment in combination with etoposide, and optionally a PD-L1 inhibitor.

18. The use of any one of claims 13-15, which further comprises a PD-L1 inhibitor and optionally a chemotherapeutic agent to be administered to the subject.

19. The use of any one of claims 13-18, wherein the bispecific antigen-binding molecule comprises a second binding domain that binds to human CD3.

20. The use of any one of claims 13-19, wherein the bispecific antigen-binding molecule comprises an antibody, a single chain variable fragment (scFv), tandem single-chain variable fragments $(scFv)_2$, a bispecific T cell engager (BiTE®) molecule, or a heteromultimer.

21. The use of claim 20, wherein the bispecific antigen-binding molecule comprises SEQ ID NO: 14 and SEQ ID NO: 15.

22. The use of claim 21, wherein the bispecific antigen-binding molecule is tarlatamab.

23. The use of claim 20, wherein the bispecific antigen-binding molecule comprises a first heterodimer that binds to human DLL3 and a second heterodimer that binds to human CD3, wherein

(a) the first heterodimer comprises a heavy chain (HC) comprising the amino acid sequence of SEQ ID NO: 17 and a light chain (LC) comprising the amino acid sequence of SEQ ID NO: 18; and

(b) the second heterodimer comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 19 and a light chain comprising the amino acid sequence of SEQ ID NO: 20.

24. The use of any one of claims 1-11 or 13-22, wherein the bispecific antigen-binding molecule is tarlatamab, and wherein tarlatamab is to be administered at a dose of from 10 mg to 100 mg once every two weeks.

25. The use of claim 24, wherein tarlatamab is to be administered at a dose of 10 mg once every two weeks or 100 mg once every two weeks.

26. The use of claim 24 or claim 25, which comprises tarlatamab to be administered at a dose of 10 mg to 100 mg once a week on weeks 1, 2, and 3 prior to tarlatamab to be administered once every two weeks.

27. The use of any one of claims 1-11 or 13-22, wherein the bispecific antigen-binding molecule is tarlatamab, and wherein tarlatamab is to be administered at a dose of from 10 mg to 100 mg twice every three weeks.

28. The use of claim 27, wherein tarlatamab is to be administered at a dose of 10 mg, 30 mg, or 100 mg twice every three weeks.

29. The use of claim 27 or 28, wherein tarlatamab is to be administered on day 1 and day 8 of a 21-day cycle.

30. The use of any one of claims 1-11 or 13-22, wherein the bispecific antigen-binding molecule is tarlatamab, and wherein tarlatamab is to be administered at a dose of from 20 mg to 200 mg once every three weeks.

31. The use of claim 30, wherein tarlatamab is to be administered at a dose of from 20 mg to 100 mg once every three weeks or from 100 mg to 200 mg once every three weeks.

32. The use of claim 30 or 31, wherein tarlatamab is to be administered at a dose of 20 mg, 60 mg, 100 mg, or 200 mg.

33. The use of any one of claims 30-32, wherein tarlatamab is to be administered on day one of a 21-day cycle.

34. The use of any one of claims 30-32, which comprises tarlatamab to be administered at a dose of 10 mg to 100 mg once a week on weeks 1 and 2 prior to tarlatamab to be administered once every three weeks.

35. The use of any one of claims 1-34, wherein the subject is a human.

36. The use of any one of claims 1-35, wherein the subject had at least one prior treatment of the cancer and relapsed.

37. Use of a bispecific antigen-binding molecule comprising a first binding domain that binds to human delta-like ligand 3 (DLL3) and a second binding domain that binds to human CD3 in the manufacture of a medicament for treating neuroendocrine prostate cancer (NEPC) in a subject, wherein the NEPC cells express DLL3 as determined by an immunohistochemical (IHC) assay.

38. The use of claim 37, wherein the IHC assay is a Ventana SP347 IHC assay.

39. The use of claim 37 or claim 38, wherein the bispecific antigen-binding molecule is a protein that comprises the amino acid sequences of SEQ ID NO: 14 and SEQ ID NO: 15.