measures, such as the number of removed lymph nodes, surgical margins, and operation time, were not compromised by neoadjuvant pembrolizumab. In the ABACUS study, 69 cisplatin-ineligible patients with T2 T4N0M0 MIBC were treated with 2 cycles of 1200 mg neoadjuvant atezolizumab prior to RC, with no significant safety findings (Powles et al., 2018, J Clin Oncol., 36(Suppl 15):Abstract 4506).

[0019] pCR was observed in 29% of the patients and in 40% of patients with PD-L1-positive disease compared to only 16% in the PD-L1-negative cohort. A total of 39% of patients were down staged to non-muscle invasive disease. Both studies lack the long-term follow-up data needed to assess PFS and OS in the postoperative setting for patients who receive neoadjuvant immunotherapy.

[0020] There is currently no standard neoadjuvant or perioperative treatment options for patients with MIBC who are cisplatin-ineligible. Therefore, newer treatment approaches, including new drug combination strategies, are needed for this patient population.

3. Summary

[0021] Provided herein are methods for the treatment of various cancers in human subjects, such as urothelial and bladder cancer, including subjects with muscle invasive bladder cancer (MIBC) and muscle invasive urothelial cancer (MIUC) who are cisplatin-ineligible, using an antibody drug conjugate (ADC) that binds 191P4D12.

[0022] Example 1. A method of treating muscle invasive urothelial cancer (MIUC) or muscle invasive bladder cancer (MIBC) in a human subject, comprising (a) administering to the subject an effective amount of an antibody drug conjugate (ADC); wherein the ADC comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 (Nectin-4) conjugated to one or more units of monomethyl auristatin E (MMAE); wherein the subject is ineligible to receive cisplatin treatment (cisplatin ineligible); and wherein the pathological complete response rate (pCRR) is at least 30%.

[0023] Example 2. A method of treating muscle invasive urothelial cancer (MIUC) or muscle invasive bladder cancer (MIBC) in a human subject, comprising administering to the subject an effective amount of an antibody drug conjugate (ADC); wherein the ADC comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 (Nectin-4) conjugated to one or more units of monomethyl auristatin E (MMAE); wherein the subject is ineligible to receive cisplatin treatment (cisplatin ineligible); and wherein the pathological downstaging rate (pDSR) is at least 50%.

[0024] Example 3. The method of example 1 or example 2, wherein the method comprises administering to the subject 3 cycles of the ADC.

[0025] Example 4. The method of any one of examples 1 to 3, wherein the treatment of the cancer further comprises radical cystectomy and pelvic lymph node dissection (RC+PLND).

[0026] Example 5. The method of example 4, wherein the human subject receives the RC+PLND about four (4) to about twelve (12) weeks after the ADC is administered to the human subject.

[0027] Example 6. The method of example 1 or 2, further comprising (b) performing radical cystectomy and pelvic lymph node dissection (RC+PLND) on the subject.

[0028] Example 7. The method of example 6, wherein (b) is performed about four (4) to about twelve (12) weeks after (a).

[0029] Example 8. A method of treating muscle invasive urothelial cancer (MIUC) or muscle invasive bladder cancer (MIBC) in a human subject, comprising: administering to the subject multiple cycles of an effective amount of an antibody drug conjugate (ADC), wherein

(a) the ADC comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 (Nectin-4) conjugated to one or more units of monomethyl auristatin E (MMAE);

(b) the subject is ineligible to receive cisplatin treatment (cisplatin ineligible); and

(c) the number of cycles of ADC treatment administered to the cisplatin ineligible subject is equal to or less than the number of cycles of standard-of-care (SOC) therapy used to treat cisplatin eligible subjects with MIUC or MIBC.

[0030] Example 9. The method of example 8, wherein the SOC therapy for a cisplatin eligible subject comprises cisplatin.

[0031] Example 10. The method of example 8, wherein the SOC therapy for the cisplatin eligible subject comprises (i) methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), or (ii) gemcitabine plus cisplatin.

[0032] Example 11. The method of example 8, wherein the SOC therapy for the cisplatin eligible subject comprises administering a programmed cell death 1 (PD-1) or a programmed cell death-ligand 1 (PD-L1) inhibitor.

[0033] Example 12. The method of any one of examples 8 to 11, wherein the number of cycles of ADC treatment administered to the cisplatin ineligible subject is 3 or 4.

[0034] Example 13. The method of any one of examples 8 to 11, wherein the number of cycles of ADC treatment administered to the cisplatin ineligible subject is 3.

[0035] Example 14. A method of administering neoadjuvant or perioperative therapy to treat muscle invasive urothelial cancer (MIUC) or muscle invasive bladder cancer (MIBC) in a human subject, comprising: administering to the subject multiple cycles of an effective amount of an antibody drug conjugate (ADC), wherein

(a) the ADC comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 (Nectin-4) conjugated to one or more units of monomethyl auristatin E (MMAE);

(b) the subject is ineligible to receive cisplatin treatment (cisplatin ineligible); and

(c) the subject remains eligible for radical cystectomy and pelvic lymph node dissection (RC+PLND) surgery following the multiple cycles of treatment with the ADC.

[0036] Example 15. The method of example 14, wherein the ADC is administered as a neoadjuvant therapy prior to the surgery.

[0037] Example 16. The method of example 14, wherein the ADC is administered prior to and following the surgery.

[0038] Example 17. A method of treating muscle invasive urothelial cancer (MIUC) or muscle invasive bladder cancer (MIBC) in a human subject, comprising: administering to the subject multiple cycles of an effective amount of an antibody drug conjugate (ADC), wherein

(a) the ADC comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 (Nectin-4) conjugated to one or more units of monomethyl auristatin E (MMAE);

(b) the subject is ineligible to receive cisplatin treatment (cisplatin ineligible); and

(c) the efficacy of the treatment of the subject with the effective amount of the ADC is similar to the efficacy of treatment observed with cisplatin eligible patients treated with standard-of-care (SOC) therapy used to treat cisplatin eligible subjects with MIUC or MIBC.

[0039] Example 18. The method of example 17, wherein the efficacy of the treatment is at least as efficacious as the efficacy of the treatment observed with SOC for cisplatin eligible subjects.

[0040] Example 19. The method of example 17 or 18, wherein the measure of efficacy of treatment is one or more of: pathological complete response rate (pCRR),

pathological downstaging rates (pDSR), disease free survival (DFS), event-free survival (EFS), overall survival (OS), progression free survival (PFS), and duration of response (DoR).

[0041] Example 20. The method of example 19, wherein the pCRR for the cisplatin ineligible subject is at least 30%.

[0042] Example 21. The method of example 19, wherein pDSR for the cisplatin ineligible subject is at least 50%.

[0043] Example 22. The method of any one of examples 18 to 21, wherein the SOC therapy for a cisplatin eligible subject comprises cisplatin.

[0044] Example 23. The method of example 22, wherein the SOC therapy for the cisplatin eligible subject comprises (i) methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), or (ii) gemcitabine plus cisplatin.

[0045] Example 24. The method of example 18, wherein the SOC therapy for the cisplatin eligible subject comprises a programmed cell death 1 (PD-1) or a programmed cell death-ligand 1 (PD-L1) inhibitor.

[0046] Example 25. The method of example 24, wherein the PD-1 inhibitor is nivolumab or pembrolizumab.

[0047] Example 26. The method of example 24, wherein the PD-L1 inhibitor is selected from the group consisting of atezolizumab, avelumab, and durvalumab.

[0048] Example 27. The method of any one of examples 1 to 26, wherein the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23.

[0049] Example 28. The method of any one of examples 1 to 27, wherein the antibody or antigen binding fragment thereof comprises CDR-H1 comprising the amino acid sequence of SEQ ID NO:9, CDR-H2 comprising the amino acid sequence of SEQ ID NO:10, CDR-H3 comprising the amino acid sequence of SEQ ID NO:11; CDR-L1 comprising the amino acid sequence of SEQ ID NO:12, CDR-L2 comprising the amino acid sequence of SEQ ID NO:13, and CDR-L3 comprising the amino acid sequence of SEQ ID NO:14, or

wherein the antibody or antigen binding fragment thereof comprises CDR-H1 comprising the amino acid sequence of SEQ ID NO:16, CDR-H2 comprising the amino acid sequence of SEQ ID NO:17, CDR-H3 comprising the amino acid sequence of SEQ ID

NO:18; CDR-L1 comprising the amino acid sequence of SEQ ID NO:19, CDR-L2 comprising the amino acid sequence of SEQ ID NO:20, and CDR-L3 comprising the amino acid sequence of SEQ ID NO:21.

[0050] Example 29. The method of any one of examples 1 to 27, wherein the antibody or antigen binding fragment thereof comprises CDR-H1 consisting of the amino acid sequence of SEQ ID NO:9, CDR-H2 consisting of the amino acid sequence of SEQ ID NO:10, CDR-H3 consisting of the amino acid sequence of SEQ ID NO:11; CDR-L1 consisting of the amino acid sequence of SEQ ID NO:12, CDR-L2 consisting of the amino acid sequence of SEQ ID NO:13, and CDR-L3 consisting of the amino acid sequence of SEQ ID NO:14, or

wherein the antibody or antigen binding fragment thereof comprises CDR-H1 consisting of the amino acid sequence of SEQ ID NO:16, CDR-H2 consisting of the amino acid sequence of SEQ ID NO:17, CDR-H3 consisting of the amino acid sequence of SEQ ID NO:18; CDR-L1 consisting of the amino acid sequence of SEQ ID NO:19, CDR-L2 consisting of the amino acid sequence of SEQ ID NO:20, and CDR-L3 consisting of the amino acid sequence of SEQ ID NO:21.

[0051] Example 30. The method of any one of examples 1 to 29, wherein the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:22 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:23.

[0052] Example 31. The method of any one of examples 1 to 30, wherein the antibody comprises a heavy chain comprising the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino acid (lysine) of SEQ ID NO:7 and a light chain comprising the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:8.

[0053] Example 32. The method of any one of examples 1 to 30, wherein the antigen binding fragment is an Fab, F(ab′)2, Fv, or scFv.

[0054] Example 33. The method of any one of examples 1 to 31, wherein the antibody is a fully human antibody.

[0055] Example 34. The method of any one of examples 1 to 31 and 33, wherein the antibody is an IgG1 and the light chain is a kappa light chain.

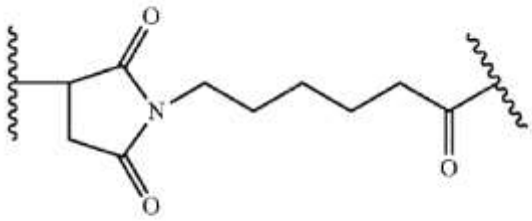
[0056] Example 35. The method of any one of examples 1 to 34, wherein the antibody or antigen binding fragment thereof is recombinantly produced.

[0057] Example 36. The method of any one of examples 1 to 35, wherein the antibody or antigen binding fragment is conjugated to each unit of MMAE via a linker.

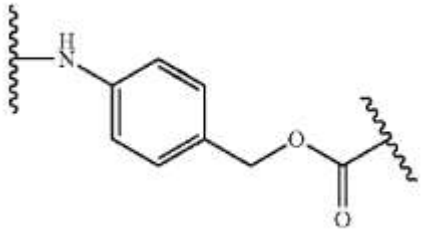
[0058] Example 37. The method of example 36, wherein the linker is an enzyme-cleavable linker, and wherein the linker forms a bond with a sulfur atom of the antibody or antigen binding fragment thereof.

[0059] Example 38. The method of example 36 or 37, wherein the linker has a formula of: –Aa–Ww–Yy–; wherein –A– is a stretcher unit, a is 0 or 1; –W– is an amino acid unit, w is an integer ranging from 0 to 12; and –Y– is a spacer unit, y is 0, 1, or 2.

[0060] Example 39. The method of example 38, wherein the stretcher unit has the structure of Formula (1) below; the amino acid unit is valine-citrulline; and the spacer unit is a PAB group comprising the structure of Formula (2) below:



Formula (1)



Formula (2).

[0061] Example 40. The method of example 38 or 39, wherein the stretcher unit forms a bond with a sulfur atom of the antibody or antigen binding fragment thereof; and wherein the spacer unit is linked to MMAE via a carbamate group.

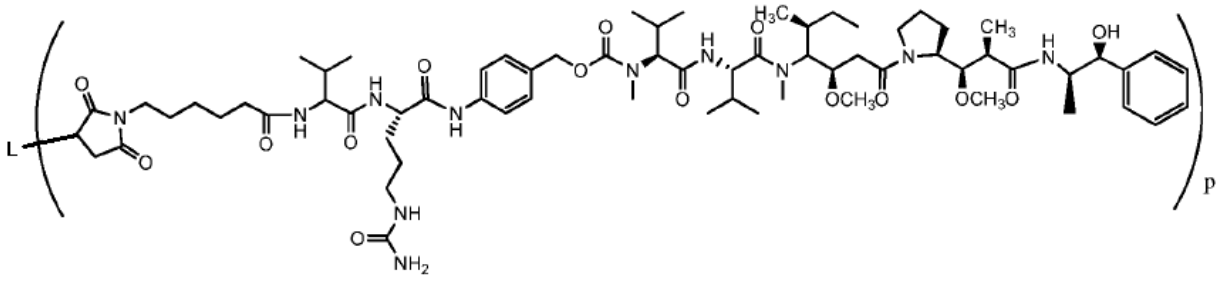
[0062] Example 41. The method of any one of examples 1 to 40, wherein the ADC comprises from 1 to 20 units of MMAE per antibody or antigen binding fragment thereof.

[0063] Example 42. The method of any one of examples 1 to 41, wherein the ADC comprises from 1 to 10 units of MMAE per antibody or antigen binding fragment thereof.

[0064] Example 43. The method of any one of examples 1 to 42, wherein the ADC comprises from 2 to 8 units of MMAE per antibody or antigen binding fragment thereof.

[0065] Example 44. The method of any one of examples 1 to 43, wherein the ADC comprises from 3 to 5 units of MMAE per antibody or antigen binding fragment thereof.

[0066] Example 45. The method of any one of examples 1 to 42, wherein the ADC has the following structure:



wherein L- represents the antibody or antigen binding fragment thereof and p is from 1 to 10.

[0067] Example 46. The method of example 45, wherein p is from 2 to 8.

[0068] Example 47. The method of example 45 or 46, wherein p is from 3 to 5.

[0069] Example 48. The method of any one of examples 45 to 47, wherein p is from 3 to 4.

[0070] Example 49. The method of any one of examples 45 to 48, wherein p is about 4.

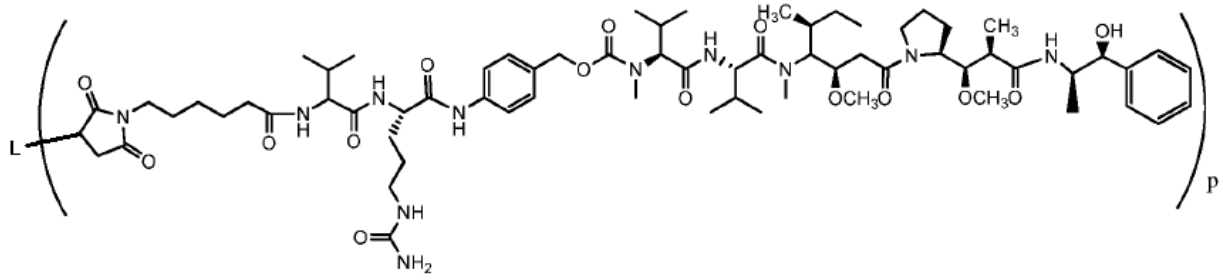
[0071] Example 50. The method of any one of examples 45 to 48, wherein the average p value of the effective amount of the antibody drug conjugates is about 3.8.

[0072] Example 51. The method of any one of examples 1 to 50, wherein the ADC is formulated in a pharmaceutical composition comprising L-histidine, polysorbate-20 (TWEEN-20), and trehalose dehydrate.

[0073] Example 52. The method of any one of examples 1 to 51, wherein the ADC is formulated in a pharmaceutical composition comprising about 20 mM L-histidine, about 0.02% (w/v) TWEEN-20, about 5.5% (w/v) trehalose dihydrate, and hydrochloride, and wherein the pH of the pharmaceutical composition is about 6.0 at 25℃.

[0074] Example 53. The method of any one of examples 1 to 51, wherein the ADC is formulated in a pharmaceutical composition comprising about 9 mM histidine, about 11 mM histidine hydrochloride monohydrate, about 0.02% (w/v) TWEEN-20, and about 5.5% (w/v) trehalose dihydrate, and wherein the pH of the pharmaceutical composition is about 6.0 at 25℃.

[0075] Example 54. The method of any one of examples 1 to 53, wherein the ADC has the following structure:



wherein L- represents the antibody or antigen binding fragment thereof and p is from about 3 to about 4, the antibody comprises a heavy chain comprising the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino acid (lysine) of SEQ ID NO:7 and a light chain comprising the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:8, wherein the ADC is administered at a dose of about 1.25 mg/kg of the subject's body weight, and wherein the dose is administered by an IV infusion on Days 1 and 8 of every three-week cycle.

[0076] Example 55. The method of any one of examples 1 to 54, wherein the subject has cT2-T4aN0M0 stage MIBC.

[0077] Example 56. The method of any one of examples 1 to 55, wherein the subject is considered cis-platin ineligible if one or more of the following criteria are satisfied: (a) GFR <60 mL/min but ≥30 mL/min, (wherein the GFR is measured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease equations (MDRD), or 24-hour urine collection); (b) ECOG performance status of 2; (c) NCI CTCAE Version 4.03 Grade ≥2 hearing loss; and (d) NYHA Class III heart failure.

[0078] Example 57. The method of any one of examples 1 to 56, wherein the subject has not received prior systemic treatment, chemoradiation, and/or radiation therapy for MIBC.

[0079] Example 58. The method of any one of examples 1 to 57, wherein the subject has not received an immune checkpoint inhibitor (CPI).

[0080] Example 59. The method of example 58, wherein the CPI is a programmed cell death 1 (PD-1) inhibitor or a programmed cell death-ligand 1 (PD-L1) inhibitor.

[0081] Example 60. The method of any one of examples 1 to 59, wherein the subject has not received a CD137 agonist, a CTLA-4 inhibitor, or an OX-40 agonist.

[0082] Example 61. The method of any one of examples 1 to 60, wherein the effective amount of the ADC is about 1 to about 10 mg/kg of the subject's body weight, about 1 to about 5 mg/kg of the subject's body weight, about 1 to about 2.5 mg/kg of the subject's body weight, or about 1 to about 1.25 mg/kg of the subject's body weight.

[0083] Example 62. The method of any one of examples 1 to 60, wherein the effective amount of the ADC is about 0.25 mg/kg, about 0.5 mg/kg, about 0.75 mg/kg, about 1.0 mg/kg, about 1.25 mg/kg, about 1.5 mg/kg, about 1.75 mg/kg, about 2.0 mg/kg, about 2.25 mg/kg, or about 2.5 mg/kg of the subject's body weight.

[0084] Example 63. The method of any one of examples 1 to 60, wherein the effective amount of the ADC is about 1 mg/kg of the subject's body weight.

[0085] Example 64. The method of any one of examples 1 to 60, wherein the effective amount of ADC is about 1.25 mg/kg of the subject's body weight.

[0086] Example 65. The method of any one of examples 1 to 60, wherein in (a) the effective amount of the ADC is administered to the subject on days 1 and 8 of every 3 week cycle for a total of 3 cycles.

[0087] Example 66. The method of example 65, wherein the effective amount of the ADC is about 1.25 mg/kg of the subject's body weight.

[0088] Example 67. The method of example 4 or 5, wherein in (a) the effective amount of the ADC is administered to the subject on days 1 and 8 of every 3 week cycle for a total of 3 cycles.

[0089] Example 68. The method of any one of examples 4, 5, or 67, wherein the method further comprises (b) about 8 weeks after the subject receives the RC+PLND, administering to the subject on days 1 and 8 of every 3 week cycle the effective amount of the ADC for a total of 6 cycles.

[0090] Example 69. The method of example 67 or 68, wherein the effective amount of the ADC is about 1.25 mg/kg of the subject's body weight.

[0091] Example 70. The method of example 6 or 7, wherein in (a) the effective amount of the ADC is administered to the subject on days 1 and 8 of every 3 week cycle for a total of 3 cycles.

[0092] Example 71. The method of any one of examples 5, 7, or 70, further comprising (c) about 8 weeks after (b), administering to the subject on days 1 and 8 of every 3 week cycle the effective amount of the ADC for a total of 3 cycles.

[0093] Example 72. The method of example 70 or 71, wherein the effective amount of the ADC is about 1.25 mg/kg of the subject's body weight.

[0094] Example 73. The method of any one of examples 8 to 64, wherein the effective amount of the ADC is administered to the human subject on days 1 and 8 of a 3 week cycle for a total of 3 cycles.

[0095] Example 74. The method of any one of examples 1 to 73, wherein wherein the ADC is administered by intravenous (IV) injection or infusion.

[0096] Example 75. The method of any one of examples 1 to 74, wherein the cancer is muscle invasive urothelial cancer (MIUC).

[0097] Example 76. The method of any one of examples 1 to 74, wherein the cancer is muscle invasive bladder cancer (MIBC).

[0098] Example 77. The method of any one of examples 1 to 76, wherein the ADC is enfortumab vedotin (EV).

[0099] Example 78. The method of any one of examples 1 to 77, wherein the overall survival of the subject is extended by at least 2, at least 4, at least 6, at least 8, at least 10, or at least 12 months.

[00100] Example 79. The method of any one of examples 1 to 78, wherein the ADC is administered as a monotherapy.

[00100a] In one aspect, the present disclosure provides use of an antibody drug conjugate (ADC) in the manufacture of a medicament for treating muscle invasive urothelial cancer (MIUC) or muscle invasive bladder cancer (MIBC) in a human subject, wherein (a) an effective amount of the ADC is to be administered to the human subject;

wherein the ADC comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 (Nectin-4) conjugated to one or more units of monomethyl auristatin E (MMAE);

wherein the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible); and

wherein:

(i) the pathological complete response rate (pCRR) is at least 30%; or

(ii) the pathological downstaging rate (pDSR) is at least 50%.

[00100b] In another aspect, the present disclosure provides use of an antibody drug conjugate (ADC) in the manufacture of a medicament for treating muscle invasive urothelial cancer (MIUC) or muscle invasive bladder cancer (MIBC) in a human subject, wherein multiple cycles of an effective amount of the ADC are to be administered to the human subject, and wherein:

(a) the ADC comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 (Nectin-4) conjugated to one or more units of monomethyl auristatin E (MMAE);

(b) the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible); and

(c) the number of cycles of ADC treatment to be administered to the cisplatin ineligible human subject is equal to or less than the number of cycles of standard-of-care (SOC) therapy used to treat cisplatin eligible human subjects with MIUC or MIBC.

[00100c] In another aspect, the present disclosure provides use of an antibody drug conjugate (ADC) in the manufacture of a medicament for treating muscle invasive urothelial cancer (MIUC) or muscle invasive bladder cancer (MIBC) in a human subject, wherein multiple cycles of an effective amount of the ADC are to be administered to the human subject as a neoadjuvant or perioperative therapy, wherein:

(a) the ADC comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 (Nectin-4) conjugated to one or more units of monomethyl auristatin E (MMAE);

(b) the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible); and

(c) the human subject remains eligible for radical cystectomy and pelvic lymph node dissection (RC+PLND) surgery following the multiple cycles of treatment with the ADC.

[00100d] In another aspect, the present disclosure provides use of an antibody drug conjugate (ADC) in the manufacture of a medicament for treating muscle invasive urothelial cancer (MIUC) or muscle invasive bladder cancer (MIBC) in a human subject, wherein multiple cycles of an effective amount of the ADC are to be administered to the human subject, wherein:

(a) the ADC comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 (Nectin-4) conjugated to one or more units of monomethyl auristatin E (MMAE);

(b) the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible); and

(c) the efficacy of the treatment of the human subject with the effective amount of the ADC is similar to the efficacy of treatment observed with cisplatin eligible human subjects treated with standard-of-care (SOC) therapy used to treat cisplatin eligible human subjects with MIUC or MIBC.

4. Brief Description of the Drawings

[00101] **FIGS. 1A-1E** depict the nucleotide and amino acid sequences of nectin-4 protein (**FIG. 1A**), the nucleotide and amino acid sequences of the heavy chain (**FIG. 1B**) and light chain (**FIG. 1C**) of Ha22-2(2.4)6.1, and the amino acid sequences of the heavy chain (**FIG. 1D**) and light chain of Ha22-2(2.4)6.1 (**FIG. 1E**).

[00102] **FIG. 2** depicts the overall study design of the clinical study described in Section 6.1. TURBT, trans urethral resection of bladder tumour.

[00103] **FIG. 3** depicts the European Organization for the Research and Treatment (EORTC) Core Quality of Life (QLQ-C-30) assessment (EORTC-QLQ-C-30, current version, Version 3), as described in Section 6.1.

[00104] **FIG. 4** depicts the EuroQol-5 Dimensions (EQ-5D-5L) described in Section 6.1.

[00105] **FIG. 5** depicts the MIUC disease stages (shown in **FIG. 5** are Tis, Ta, T1, T2a, T2b, T3a, T3b, T4a, and T4b) relative to the anatomy of the bladder and pelvic region described in Section 6.2 (*See, e.g.*, www.cancer.org/cancer/bladder-cancer/detection-diagnosis-staging/staging.html).

Claims

1. Use of an antibody drug conjugate (ADC) in the manufacture of a medicament for treating muscle invasive urothelial cancer (MIUC) or muscle invasive bladder cancer (MIBC) in a human subject, wherein (a) an effective amount of the ADC is to be administered to the human subject;

wherein the ADC comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 (Nectin-4) conjugated to one or more units of monomethyl auristatin E (MMAE);

wherein the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible); and

wherein:

(i) the pathological complete response rate (pCRR) is at least 30%; or

(ii) the pathological downstaging rate (pDSR) is at least 50%.

2. The use of claim 1, wherein 3 cycles of the ADC are to be administered to the human subject.

3. The use of claim 1 or claim 2, wherein the treatment of the cancer further comprises radical cystectomy and pelvic lymph node dissection (RC+PLND).

4. The use of claim 3, wherein the human subject receives the RC+PLND about four (4) to about twelve (12) weeks after the ADC has been administered to the human subject.

5. The use of claim 1, wherein (b) radical cystectomy and pelvic lymph node dissection (RC+PLND) are to be further performed on the human subject.

6. The use of claim 5, wherein (b) is to be performed about four (4) to about twelve (12) weeks after (a).

7. Use of an antibody drug conjugate (ADC) in the manufacture of a medicament for treating muscle invasive urothelial cancer (MIUC) or muscle invasive bladder cancer (MIBC) in a human subject, wherein multiple cycles of an effective amount of the ADC are to be administered to the human subject, and wherein:

(a) the ADC comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 (Nectin-4) conjugated to one or more units of monomethyl auristatin E (MMAE);

(b) the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible); and

(c) the number of cycles of ADC treatment to be administered to the cisplatin ineligible human subject is equal to or less than the number of cycles of standard-of-care (SOC) therapy used to treat cisplatin eligible human subjects with MIUC or MIBC.

8. The use of claim 7, wherein the SOC therapy for a cisplatin eligible human subject comprises:

i. cisplatin;

ii. methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC);

iii. gemcitabine plus cisplatin;

iv. a programmed cell death 1 (PD-1) inhibitor; or

v. a programmed cell death-ligand 1 (PD-L1) inhibitor.

9. The use of claim 7 or claim 8, wherein the number of cycles of ADC treatment to be administered to the cisplatin ineligible human subject is 3 or 4.

10. Use of an antibody drug conjugate (ADC) in the manufacture of a medicament for treating muscle invasive urothelial cancer (MIUC) or muscle invasive bladder cancer (MIBC) in a human subject, wherein multiple cycles of an effective amount of the ADC are to be administered to the human subject as a neoadjuvant or perioperative therapy, wherein:

(a) the ADC comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 (Nectin-4) conjugated to one or more units of monomethyl auristatin E (MMAE);

(b) the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible); and

(c) the human subject remains eligible for radical cystectomy and pelvic lymph node dissection (RC+PLND) surgery following the multiple cycles of treatment with the ADC.

11. The use of claim 10, wherein the ADC is to be administered as a neoadjuvant therapy (i) prior to the surgery or (ii) prior to and following the surgery.

12. Use of an antibody drug conjugate (ADC) in the manufacture of a medicament for treating muscle invasive urothelial cancer (MIUC) or muscle invasive bladder cancer (MIBC) in a human subject, wherein multiple cycles of an effective amount of the ADC are to be administered to the human subject, wherein:

(a) the ADC comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 (Nectin-4) conjugated to one or more units of monomethyl auristatin E (MMAE);

(b) the human subject is ineligible to receive cisplatin treatment (cisplatin ineligible); and

(c) the efficacy of the treatment of the human subject with the effective amount of the ADC is similar to the efficacy of treatment observed with cisplatin eligible human subjects treated with standard-of-care (SOC) therapy used to treat cisplatin eligible human subjects with MIUC or MIBC.

13. The use of claim 12, wherein the efficacy of the treatment is at least as efficacious as the efficacy of the treatment observed with SOC for cisplatin eligible human subjects.

14. The use of claim 12 or claim 13, wherein the measure of efficacy of treatment is one or more of: pathological complete response rate (pCRR), pathological downstaging rates (pDSR), disease free survival (DFS), event-free survival (EFS), overall survival (OS), progression free survival (PFS), and duration of response (DoR).

15. The use of claim 14, wherein:

(i) the pCRR for the cisplatin ineligible human subject is at least 30%; or

(ii) the pDSR for the cisplatin ineligible human subject is at least 50%.

16. The use of any one of claims 13 to 15, wherein the SOC therapy for the cisplatin eligible human subject comprises:

(i) cisplatin;

(ii) methotrexate, vinblastine, doxorubicin, and ciasplatin (MVAC);

(iii) gemcitabine plus cisplatin;

(iv) a programmed cell death 1 (PD-1) inhibitor; or

(v) a programmed cell death-ligand 1 (PD-L1) inhibitor.

17. The use of claim 16, wherein: (i) the PD-1 inhibitor is nivolumab or pembrolizumab, or (ii) the PD-L1 inhibitor is selected from the group consisting of atezolizumab, avelumab, and durvalumab.

18. The use of any one of claims 1 to 17, wherein the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the amino acid sequences of the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 and a light chain variable region comprising CDRs comprising the amino acid sequences of the CDRs of the light chain variable region set forth in SEQ ID NO:23.

19. The use of any one of claims 1 to 18, wherein:

(i) the antibody or antigen binding fragment thereof comprises CDR-H1 comprising the amino acid sequence of SEQ ID NO:9, CDR-H2 comprising the amino acid sequence of SEQ ID NO:10, CDR-H3 comprising the amino acid sequence of SEQ ID NO:11; CDR-L1 comprising the amino acid sequence of SEQ ID NO:12, CDR-L2 comprising the amino acid sequence of SEQ ID NO:13, and CDR-L3 comprising the amino acid sequence of SEQ ID NO:14;

(ii) the antibody or antigen binding fragment thereof comprises CDR-H1 comprising the amino acid sequence of SEQ ID NO:16, CDR-H2 comprising the amino acid sequence of SEQ ID NO:17, CDR-H3 comprising the amino acid sequence of SEQ ID NO:18; CDR-L1 comprising the amino acid sequence of SEQ ID NO:19, CDR-L2 comprising the amino acid sequence of SEQ ID NO:20, and CDR-L3 comprising the amino acid sequence of SEQ ID NO:21;

(iii) the antibody or antigen binding fragment thereof comprises CDR-H1 consisting of the amino acid sequence of SEQ ID NO:9, CDR-H2 consisting of the amino acid sequence of SEQ ID NO:10, CDR-H3 consisting of the amino acid sequence of SEQ ID NO:11; CDR-L1 consisting of the amino acid sequence of SEQ ID NO:12, CDR-L2 consisting of the amino acid sequence of SEQ ID NO:13, and CDR-L3 consisting of the amino acid sequence of SEQ ID NO:14, or

(iv) the antibody or antigen binding fragment thereof comprises CDR-H1 consisting of the amino acid sequence of SEQ ID NO:16, CDR-H2 consisting of the amino acid sequence of SEQ ID NO:17, CDR-H3 consisting of the amino acid sequence of SEQ ID NO:18; CDR-L1 consisting of the amino acid sequence of SEQ ID NO:19, CDR-L2 consisting of the amino acid sequence of SEQ ID NO:20, and CDR-L3 consisting of the amino acid sequence of SEQ ID NO:21.

20. The use of any one of claims 1 to 19, wherein the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO:22 and a light chain variable region comprising the amino acid sequence of SEQ ID NO:23.

21. The use of any one of claims 1 to 20, wherein the antibody comprises a heavy chain comprising the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino acid (lysine) of SEQ ID NO:7 and a light chain comprising the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:8.

22. The use of any one of claims 1 to 20, wherein the antigen binding fragment is:

(i) an Fab, F(ab′)2, Fv, or scFv; or

(ii) a recombinant antigen binding fragment.

23. The use of any one of claims 1 to 21, wherein the antibody is:

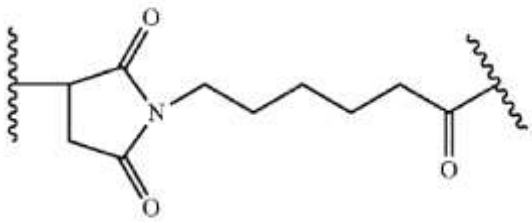
(i) a fully human antibody;

(ii) an IgG1 and the light chain is a kappa light chain; or

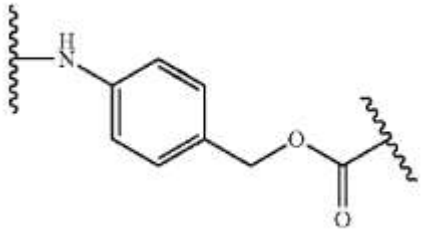
(iii) a recombinant antibody.

24. The use of any one of claims 1 to 23, wherein the antibody or antigen binding fragment is conjugated to each unit of MMAE via a linker; optionally wherein the linker is an enzyme-cleavable linker, and wherein the linker forms a bond with a sulfur atom of the antibody or antigen binding fragment thereof; and optionally wherein the linker has a formula of: –Aa–Ww–Yy–; wherein –A– is a stretcher unit, a is 0 or 1; –W– is an amino acid unit, w is an integer ranging from 0 to 12; and –Y– is a spacer unit, y is 0, 1, or 2.

25. The use of claim 24, wherein the stretcher unit has the structure of Formula (1) below; the amino acid unit is valine-citrulline; and the spacer unit is a PAB group comprising the structure of Formula (2) below:



Formula (1)



Formula (2);

wherein optionally the stretcher unit forms a bond with a sulfur atom of the antibody or antigen binding fragment thereof; and wherein the spacer unit is linked to MMAE via a carbamate group.

26. The use of any one of claims 1 to 25, wherein the ADC comprises:

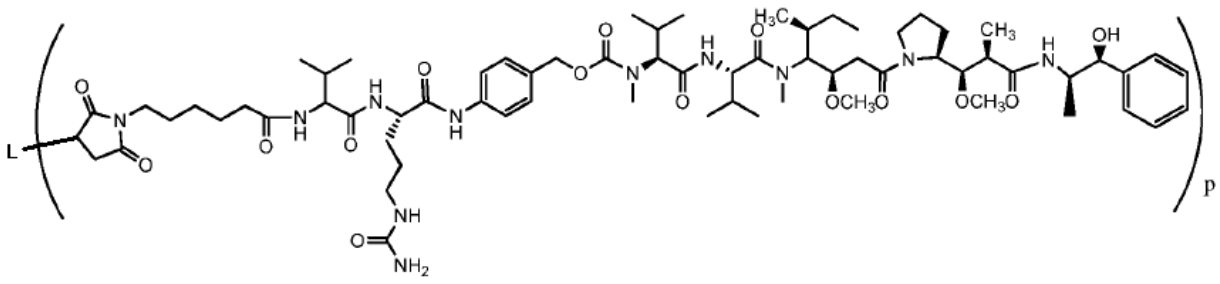
(i) from 1 to 20 units of MMAE per antibody or antigen binding fragment thereof;

(ii) from 1 to 10 units of MMAE per antibody or antigen binding fragment thereof;

(iii) from 2 to 8 units of MMAE per antibody or antigen binding fragment thereof; or

(iv) from 3 to 5 units of MMAE per antibody or antigen binding fragment thereof.

27. The use of any one of claims 1 to 26, wherein the ADC has the following structure:



wherein L- represents the antibody or antigen binding fragment thereof and p is from 1 to 10.

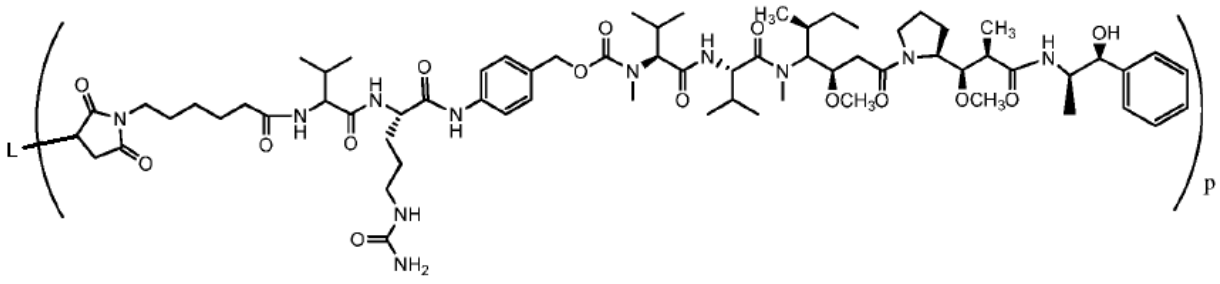
28. The use of claim 27, wherein:

(i) p is from 2 to 8;
(ii) p is from 3 to 5;
(iii) p is from 3 to 4; or
(iv) p is about 4.

29. The use of claim 27 or 28, wherein the average p value of the effective amount of the antibody drug conjugate is about 3.8.

30. The use of any one of claims 1 to 29, wherein the ADC is formulated in a pharmaceutical composition comprising L-histidine, polysorbate-20 (TWEEN-20), and trehalose dehydrate; optionally wherein the ADC is formulated in (i) a pharmaceutical composition comprising about 20 mM L-histidine, about 0.02% (w/v) TWEEN-20, about 5.5% (w/v) trehalose dihydrate, and hydrochloride, and wherein the pH of the pharmaceutical composition is about 6.0 at 25℃; or (ii) a pharmaceutical composition comprising about 9 mM histidine, about 11 mM histidine hydrochloride monohydrate, about 0.02% (w/v) TWEEN-20, and about 5.5% (w/v) trehalose dihydrate, and wherein the pH of the pharmaceutical composition is about 6.0 at 25℃.

31. The use of any one of claims 1 to 30, wherein the ADC has the following structure:



wherein L- represents the antibody or antigen binding fragment thereof and p is from about 3 to about 4,

wherein the antibody comprises a heavy chain comprising the amino acid sequence ranging from the 20th amino acid (glutamic acid) to the 466th amino acid (lysine) of SEQ ID

NO:7 and a light chain comprising the amino acid sequence ranging from the 23rd amino acid (aspartic acid) to the 236th amino acid (cysteine) of SEQ ID NO:8,

wherein the ADC is to be administered at a dose of about 1.25 mg/kg of the human subject's body weight, and

wherein the dose is to be administered by an IV infusion on Days 1 and 8 of every three-week cycle.

32. The use of any one of claims 1 to 31, wherein the human subject has cT2-T4aN0M0 stage MIBC.

33. The use of any one of claims 1 to 32, wherein the human subject is considered cisplatin ineligible if one or more of the following criteria are satisfied: (a) GFR <60 mL/min but ≥30 mL/min, (wherein the GFR is measured by the Cockcroft-Gault formula, Modification of Diet in Renal Disease equations (MDRD), or 24-hour urine collection); (b) ECOG performance status of 2; (c) NCI CTCAE Version 4.03 Grade ≥2 hearing loss; and (d) NYHA Class III heart failure.

34. The use of any one of claims 1 to 33, wherein the human subject has not received prior systemic treatment, chemoradiation, and/or radiation therapy for MIBC.

35. The use of any one of claims 1 to 34, wherein the human subject has not received an immune checkpoint inhibitor (CPI); wherein optionally the CPI is a programmed cell death 1 (PD-1) inhibitor or a programmed cell death-ligand 1 (PD-L1) inhibitor.

36. The use of any one of claims 1 to 35, wherein the human subject has not received a CD137 agonist, a CTLA-4 inhibitor, or an OX-40 agonist.

37. The use of any one of claims 1 to 36, wherein the effective amount of the ADC is about 1 to about 10 mg/kg, about 1 to about 5 mg/kg, about 1 to about 2.5 mg/kg, about 1 to about 1.25 mg/kg, about 0.25 mg/kg, about 0.5 mg/kg, about 0.75 mg/kg, about 1.0 mg/kg, about 1.25 mg/kg, about 1.5 mg/kg, about 1.75 mg/kg, about 2.0 mg/kg, about 2.25 mg/kg, or about 2.5 mg/kg of the human subject's body weight.

38. The use of claim 1, wherein in (a) the effective amount of the ADC is to be administered to the human subject on days 1 and 8 of every 3 week cycle for a total of 3

cycles; optionally wherein the effective amount of the ADC is about 1.25 mg/kg of the human subject's body weight.

39. The use of claim 3 or claim 4, wherein in (a) the effective amount of the ADC is to be administered to the human subject on days 1 and 8 of every 3 week cycle for a total of 3 cycles; optionally wherein the effective amount of the ADC is about 1.25 mg/kg of the human subject's body weight.

40. The use of any one of claims 3, 4, or 39, wherein (b) about 8 weeks after the human subject has received the RC+PLND, the effective amount of the ADC is to be further administered to the human subject on days 1 and 8 of every 3 week cycle for a total of 6 cycles; optionally wherein the effective amount of the ADC is about 1.25 mg/kg of the human subject's body weight.

41. The use of claim 5 or claim 6, wherein in (a) the effective amount of the ADC is to be administered to the human subject on days 1 and 8 of every 3 week cycle for a total of 3 cycles; optionally wherein the effective amount of the ADC is about 1.25 mg/kg of the human subject's body weight.

42. The use of any one of claims 5, 6, or 41, wherein (c) about 8 weeks after (b), the effective amount of the ADC is to be further administered to the human subject on days 1 and 8 of every 3 week cycle for a total of 3 cycles; optionally wherein the effective amount of the ADC is about 1.25 mg/kg of the human subject's body weight.

43. The use of any one of claims 7 to 37, wherein the effective amount of the ADC is to be administered to the human subject on days 1 and 8 of a 3 week cycle for a total of 3 cycles.

44. The use of any one of claims 1 to 43, wherein the ADC is to be administered by intravenous (IV) injection or infusion.

45. The use of any one of claims 1 to 44, wherein the cancer is muscle invasive urothelial cancer (MIUC) or muscle invasive bladder cancer (MIBC).

46. The use of any one of claims 1 to 45, wherein the ADC is enfortumab vedotin (EV).

47. The use of any one of claims 1 to 46, wherein the overall survival of the human subject is extended by at least 2, at least 4, at least 6, at least 8, at least 10, or at least 12 months.

48. The use of any one of claims 1 to 47, wherein the ADC is to be administered as a monotherapy.