

What is Claimed is:

1. Use of an antibody drug conjugate (ADC) in the preparation of a medicament for ~~use in a method of preventing or~~ treating cancer in a human subject, wherein (a) the ADC is to be administered to the subject for a first regimen comprising an effective amount of the ADC,

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

wherein the subject has urothelial cancer; and

wherein the subject has received an immune checkpoint inhibitor therapy and received a chemotherapy; and

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°C.

2. Use of an antibody drug conjugate (ADC) in the preparation of a medicament for treating cancer in a human subject, wherein (a) the ADC is to be administered to the subject for a first regimen comprising an effective amount of the ADC.

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

wherein the subject has urothelial cancer; and

wherein the subject has received an immune checkpoint inhibitor therapy and received a chemotherapy; and

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°C.

3. Use of an antibody drug conjugate (ADC) in the preparation of a medicament for treating cancer in a human subject, wherein (a) the ADC is to be administered to the subject for a first regimen comprising an effective amount of the ADC,

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

wherein the subject has urothelial cancer; and

wherein the subject has received an immune checkpoint inhibitor therapy and received a chemotherapy; and

wherein the ADC is formulated at about 10 mg/ml in a pharmaceutical composition comprising about 1.4 mg/ml histidine, about 2.31 mg/ml histidine hydrochloride monohydrate,

about 0.2 mg/ml polysorbate 20 (TWEEN-20), and about 55 mg/ml trehalose dihydrate, and wherein the pH of the pharmaceutical composition is about 6.0 at 25°C.

4. Use of an antibody drug conjugate (ADC) in the preparation of a medicament for treating cancer in a human subject, wherein (a) the ADC is to be administered to the subject for a first regimen comprising an effective amount of the ADC,

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

wherein the subject has urothelial cancer; and

wherein the subject has received an immune checkpoint inhibitor therapy and received a chemotherapy; and

wherein the ADC is formulated in a vial comprising a pharmaceutical composition comprising about 20 mg of the ADC, about 2.8 mg histidine, about 4.62 mg histidine hydrochloride monohydrate, about 0.4 mg polysorbate 20 (TWEEN-20), and about 110 mg trehalose dihydrate.

5. Use of an antibody drug conjugate (ADC) in the preparation of a medicament for treating cancer in a human subject, wherein (a) the ADC is to be administered to the subject for a first regimen comprising an effective amount of the ADC,

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

wherein the subject has urothelial cancer; and

wherein the subject has received an immune checkpoint inhibitor therapy and received a chemotherapy; and

wherein the ADC is formulated in a vial comprising a pharmaceutical composition comprising about 30 mg of the ADC, about 4.2 mg histidine, about 6.93 mg histidine hydrochloride monohydrate, about 0.6 mg polysorbate 20 (TWEEN-20), and about 165 mg trehalose dihydrate.

62. The use of any one of claims ~~claim~~ 1 to 5, wherein the ADC is to be administered three times within a 28 day cycle.

73. The use of any one of claims ~~claim~~ 1 to 6 or 2, wherein the ADC is to be administered on Days 1, 8 and 15 of a 28 day cycle.

84. The use of any one of claims 1 to 73, wherein the urothelial cancer is locally advanced urothelial cancer.

95. The use of any one of claims 1 to 73, wherein the urothelial cancer is metastatic urothelial cancer.

106. The use of any one of claims 1 to 95, wherein the immune checkpoint inhibitor therapy is a programmed death receptor-1 (PD-1) inhibitor.

117. The use of any one of claims 1 to 95, wherein the immune checkpoint inhibitor

therapy is programmed death-ligand 1 (PD-L1) inhibitor.

128. The use of any one of claims 1 to 117, wherein the chemotherapy is platinum-containing chemotherapy.

139. The use of claim 128, wherein the platinum-containing chemotherapy is platinum-containing chemotherapy in a neoadjuvant setting.

1410. The use of claim 128, wherein the platinum-containing chemotherapy is platinum-containing chemotherapy in an adjuvant setting.

1511. The use of any one of claims 128 to 1410, wherein the platinum-containing chemotherapy is platinum-containing chemotherapy in a locally advanced setting.

1612. The use of any one of claims 128 to 1410, wherein the platinum-containing chemotherapy is platinum-containing chemotherapy in a metastatic setting.

1713. The use of any one of claims 1 to 1612, wherein the first regimen comprises an ADC dose of about 1.25 milligram/kilogram (mg/kg) of the subject's body weight.

1814. The use of claim 1713, wherein the subject has a body weight of less than 100 kg.

1915. The use of any one of claims 1 to 1612, wherein the first regimen comprises an ADC dose of about 125 mg to the subject, wherein the subject has a body weight of no less than 100 kg.

2016. The use of any one of claims 1 to 1915, wherein
(b) the ADC is to be administered after determining blood glucose level in the subject, and
(c) if the blood glucose level from (b) is higher than 250 mg/dL, the administration of the antibody drug conjugate is withheld.

2117. The use of claim 2016, wherein
(d) the ADC is to be administered after waiting for a period sufficient for the blood glucose level to reduce to no more than 250 mg/dL.

2218. The use of claim 2016 or 2117, wherein
(e) the ADC is to be administered after determining blood glucose level in the subject, and
(f) if the blood glucose level from (e) is no more than 250 mg/dL, the ADC is to be administered to the subject for a second regimen comprising an effective amount of the antibody drug conjugate.

2319. The use of any one of claims 2016 to 2218, wherein if the blood glucose level from (b) or (e) is more than 500 mg/dL, the administration of the ADC is discontinued permanently.

2420. The use of ~~any one of claims 16 to 2319~~ claim 22 or 2319, wherein the ADC is to be administered following the steps repeating from (a) to (f).

2521. The use of any one of claims 2016 to 2420, wherein the subject has hyperglycemia.

2622. The use of claim 2521, wherein the subject has diabetic ketoacidosis (DKA).

2723. The use of any one of claims 2016 to 2622, wherein the subject additionally has higher body mass index and/or higher baseline A1C.

2824. The use of any one of claims 2218 to 2723, wherein the second regimen is identical to the first regimen.

2925. The use of any one of claims 2216 to 2824, wherein the blood glucose level is determined daily.

3026. The use of any one of claims 2246 to 2824, wherein the blood glucose level is determined once every two days, once every three days, once every four days, or once every five days, once every six days.

3127. The use of any one of claims 2246 to 2824, wherein the blood glucose level is determined weekly, bi-weekly, once every three weeks, or once every four weeks.

3228. The use of any one of claims 2246 to 2824, wherein the blood glucose level is determined monthly, once every two months, or once every three months.

3329. The use of any one of claims 1 to 3228, wherein
(g) the ADC is to be administered after determining peripheral neuropathy in the subject, and
(h) if the peripheral neuropathy from (g) is no less than Grade 2, the administration of the antibody drug conjugate is withheld.

3430. The use of claim 3329, wherein
(i) the ADC is to be administered after waiting for a period sufficient for the peripheral neuropathy to reduce to no more than Grade 1.

3531. The use of claim 3329 or 3430, wherein
(j) the ADC is to be administered after determining peripheral neuropathy in the subject, and
(k) if the peripheral neuropathy from (j) is no more than Grade 1, the ADC is to be administered to the subject for a second regimen comprising an effective amount of the ADC, wherein the second regimen comprises an ADC dose equal to or lower than the first regimen.

3632. The use of any one of claims 3329 to 3531, wherein if the peripheral neuropathy from (g) or (j) is no less than Grade 3, the administration of the ADC is discontinued permanently.

3733. The use of any one of claims 3329 to 3632, wherein the peripheral neuropathy is predominantly sensory neuropathy.

3834. The use of ~~any one of claims 29 to claim 3531, and or 3733~~, wherein if the use comprises steps (g) to (k), the ADC is to be administered following steps repeating from (g) to (k).

3935. The use of any one of claims 3534, and 3733 to 3834, wherein if the use comprises a second regimen, the ADC is to be administered after determining the number of times the condition for the administration of the second regimen has been satisfied.

4036. The use of any one of claims 3534, and 3733 to 3935, wherein if the use comprises a second regimen, and wherein in (k) if the second regimen is to be administered for the first time, the second regimen is identical to the first regimen.

4137. The use of any one of claims 3534, and 3733 to 4036, wherein if the use comprises a second regimen, and wherein in (k) if the second regimen has been administered once and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 1.0 mg/kg of the subject's body weight.

4238. The use of any one of claims 3534, and 3733 to 4036, wherein if the use comprises a second regimen, and wherein in (k) if the second regimen has been administered once and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 100 mg to the subject.

4339. The use of any one of claims 3534, and 3733 to 4238, wherein if the use comprises a second regimen, and wherein in (k) if the second regimen has been administered twice and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.75 mg/kg of the subject's body weight.

4440. The use of any one of claims 3531, and 3733 to 4238, wherein if the use comprises a second regimen, and wherein in (k) if the second regimen has been administered once and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 75 mg to the subject.

4541. The use of any one of claims 3531, and 3733 to 3640, wherein if the use comprises a second regimen, and wherein in (k) if the second regimen has been administered three times and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.5 mg/kg of the subject's body weight.

4642. The use of any one of claims 3531, and 3733 to 3640, wherein if the use comprises a second regimen, and wherein in (k) if the second regimen has been administered three times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 50 mg to the subject.

4743. The use of any one of claims 3531 and 3733 to 4642, wherein if the use comprises a second regimen, and wherein the ADC dose in the second regimen is increased by an amount of about 0.25 mg/kg for the subject having a body weight of less than 100 kg or increased by an amount of about 25 mg for the subject having a body weight of no less than 100 kg, if

(1) the administration of the ADC has not been discontinued permanently,

(2) the ADC dose in the second regimen is lower than the ADC dose in the first regimen,
and

(3) the peripheral neuropathy has returned to no more than Grade 1.

4844. The use of any one of claims 3329 to 4743, wherein the peripheral neuropathy is determined daily.

4945. The use of any one of claims 3329 to 4743, wherein the peripheral neuropathy is

determined once every two days, once every three days, once every four days, or once every five days, once every six days.

5046. The use of any one of claims 3329 to 4743, wherein the peripheral neuropathy is determined weekly, bi-weekly, once every three weeks, or once every four weeks.

5147. The use of any one of claims 3329 to 4743, wherein the peripheral neuropathy is determined monthly, once every two months, or once every three months.

5248. The use of any one of claims 1 to 5147, wherein
(l) the ADC is to be administered after determining a skin reaction in the subject,
and
(m) if the skin reaction from (l) is no less than Grade 3, the administration of the ADC is withheld.

5349. The use of claim 5248, wherein (n) the ADC is to be administered after waiting for a period sufficient for the skin reaction to reduce to no more than Grade 1.

5450. The use of claim 5248 or 5349, wherein
(o) the ADC is to be administered after determining the skin reaction in the subject, and
(p) if the skin reaction in (o) is no more than Grade 1, the ADC is to be administered to the subject for a second regimen comprising an effective amount of the ADC, wherein the second regimen comprises an ADC dose equal to or lower than the first regimen.

5551. The use of any one of claims 5248 to 5450, wherein if the skin reaction from (l) or (o) is no less than Grade 4, the administration of the ADC is discontinued permanently.

5652. The use of any one of claims 5248 to 5551, wherein the skin reaction is selected from the group consisting of maculopapular rash, pruritus, symmetrical drug-related

intertriginous, flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia.

5753. The use of any one of claims 5248 to 5551, wherein the no less than Grade 3 skin reaction is selected from the group consisting of symmetrical drug-related intertriginous, flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia.

5854. The use of any one of claims ~~48 to 50~~54, and ~~56~~, and ~~5752 to 53~~, wherein if the use comprises steps (l) to (p), the ADC is to be administered following the steps repeating from (l) to (p).

5955. The use of 5854, wherein if Grade 3 skin reaction reoccurs in (l) or (o), the administration of the ADC is discontinued permanently.

6056. The use of any one of claims 5248 to 5450, and ~~5652~~ to 5955, wherein if the use comprises a second regimen, the ADC is to be administered after determining the number of times the condition for the administration of the second regimen has been satisfied.

6157. The use of any one of claims ~~48 to 50~~54, and ~~5652 to 6056~~, wherein if the use comprises a second regimen, wherein if the use comprises step (p), and wherein in (p) if the second regimen is to be administered for the first time, the second regimen is identical to the first regimen.

6258. The use of any one of claims 5248 to 5450, and ~~5652~~ to 6157, wherein if the use comprises a second regimen, and wherein in (p) if the second regimen has been administered one or more times and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 1.0 mg/kg of the subject's body weight.

6359. The use of any one of claims 5248 to 5450, and ~~5652~~ to 6157, wherein if the use

comprises a second regimen, and wherein in (p) if the second regimen has been administered one or more times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 100 mg to the subject.

6460. The use of any one of claims 5248 to 5450, and 5652 to 6359, wherein if the use comprises a second regimen, and wherein in (p) if the second regimen has been administered two or more times and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.75 mg/kg of the subject's body weight.

6561. The use of any one of claims 5248 to 5450, and 5652 to 6359, wherein if the use comprises a second regimen, and wherein in (p) if the second regimen has been administered two or more times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 75 mg to the subject.

6662. The use of any one of claims 5248 to 5450, and 5652 to 6561, wherein if the use comprises a second regimen, and wherein in (p) if the second regimen has been administered three or more times and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.5 mg/kg of the subject's body weight.

6763. The use of any one of claims 5248 to 5450, and 5652 to 6561, wherein if the use comprises a second regimen, and wherein in (p) if the second regimen has been administered three or more times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 50 mg to the subject.

6864. The use of any one of claims 5248 to 5450, and 5652 to 6056, wherein if the use comprises a second regimen, and wherein in (p) if the subject has a body weight of less than 100 kg, the second regimen comprises an ADC dose of about 1.0 mg/kg of the subject's body weight.

6965. The use of any one of claims 5248 to 5450, and 5652 to 6056, wherein if the use comprises a second regimen, and wherein in (p) if the subject has a body weight of no less than

100 kg, the second regimen comprises an ADC dose of about 100 mg to the subject.

7066. The use of any one of claims 5248 to 5450, 5652 to 6056, and 6864 to 6965, wherein if the use comprises a second regimen, and wherein in (p) if the second regimen has been administered one or more times and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.75 mg/kg of the subject's body weight.

7167. The use of any one of claims 5248 to 5450, 5652 to 6056, and 6864 to 6965, wherein if the use comprises a second regimen, and wherein in (p) if the second regimen has been administered one or more times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 75 mg to the subject.

7268. The use of any one of claims 5248 to 5450, 5652 to 6056, and 6864 to 7167, wherein if the use comprises a second regimen, and wherein in (p) if the second regimen has been administered two or more times and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.5 mg/kg of the subject's body weight.

7369. The use of any one of claims 5248 to 5450, 5652 to 6056, and 6864 to 7167, wherein if the use comprises a second regimen, and wherein in (p) if the second regimen has been administered two or more times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 50 mg to the subject.

7470. The use of any one of claims 5450 and 5652 to 7369, wherein the ADC dose in the second regimen is increased by an amount of about 0.25 mg/kg for the subject having a body weight of less than 100 kg or increased by an amount of about 25 mg for the subject having a body weight of no less than 100 kg, if

(1) the administration of the ADC has not been discontinued permanently,

(2) the ADC dose in the second regimen is lower than the ADC dose in the first regimen,

and

(3) the skin reaction has returned to no more than Grade 1.

7571. The use of any one of claims 5248 to 7470, wherein the skin reaction is determined daily.

7672. The use of any one of claims 5248 to 7470, wherein the skin reaction is determined once every two days, once every three days, once every four days, or once every five days, once every six days.

7773. The use of any one of claims 5248 to 7470, wherein the skin reaction is determined weekly, bi-weekly, once every three weeks, or once every four weeks.

7874. The use of any one of claims 5248 to 7470, wherein the skin reaction is determined monthly, once every two months, or once every three months.

7975. The use of any one of claims 1 to 7874, wherein
(q) the ADC is to be administered after determining non-hematologic toxicity in the subject, and
(s) if the non-hematologic toxicity from (q) is no less than Grade 3, the administration of the ADC is withheld.

8076. The use of claim 7975, wherein
(t) the ADC is to be administered after waiting for a period sufficient for the non-hematologic toxicity to reduce to no more than Grade 1.

8177. The use of claim 7975 or 8076, wherein
(u) the ADC is to be administered after determining the non-hematologic toxicity in the subject, and
(v) if the non-hematologic toxicity in (u) is no more than Grade 1, the ADC is to

be administered to the subject for a second regimen comprising an effective amount of the ADC, wherein the second regimen comprises an ADC dose equal to or lower than the first regimen.

8278. The use of any one of claims 7975 to 8177, wherein if the non-hematologic toxicity in (q) or (u) is no less than Grade 4, the administration of the ADC is discontinued permanently.

8379. The use of any one of claims 7975 to 8278, wherein the non-hematologic toxicity is dysgeusia.

8480. The use of any one of claims 7975 to 8278, wherein the non-hematologic toxicity is anorexia.

8581. The use of any one of claims 7975 to 8278, wherein the non-hematologic toxicity is loss of appetite.

8682. The use of any one of claims 7975 to 8278, wherein the non-hematologic toxicity is an ocular disorder.

8783. The use of claim 8679, wherein the ocular disorder is one or more selected from the group consisting of punctate keratitis, keratitis, keratopathy, limbal stem cell deficiency, dry eye, and blurred vision.

8884. The use of any one of claims 75 to 77, 81 and 8379 to 8783, wherein if the use comprises steps (q) to (v), the ADC is to be administered following the steps repeating from (q) to (v).

8985. The use of any one of claims 7975 to 8177, and 8379 to 8884, wherein if the use comprises a second regimen, the ADC is to be administered after determining the number of times the condition for the administration of the second regimen has been satisfied.

9086. The use of any one of claims 7975 to 8177, and 8379 to 8985, wherein if the use comprises a second regimen, in (v) the second regimen is identical to the first regimen.

9187. The use of any one of claims 7975 to 8177, and 8379 to 9086, wherein if the use comprises a second regimen, and wherein in (v) if the second regimen has been administered one or more times and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 1.0 mg/kg of the subject's body weight.

9288. The use of any one of claims 7975 to 8177, and 8379 to 9086, wherein if the use comprises a second regimen, and wherein in (v) if the second regimen has been administered one or more times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 100 mg to the subject.

9389. The use of any one of claims 7975 to 8177, and 8379 to 9288, wherein if the use comprises a second regimen, and wherein in (v) if the second regimen has been administered two or more times and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.75 mg/kg of the subject's body weight.

9490. The use of any one of claims 7975 to 8177, and 8379 to 9288, wherein if the use comprises a second regimen, and wherein in (v) if the second regimen has been administered two or more times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 75 mg to the subject.

9594. The use of any one of claims 7975 to 8177, and 8379 to 9490, wherein if the use comprises a second regimen, and wherein in (v) if the second regimen has been administered three or more times and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.5 mg/kg of the subject's body weight.

9692. The use of any one of claims 7975 to 8177, and 8379 to 9490, wherein if the use comprises a second regimen, and wherein in (v) if the second regimen has been administered

three or more times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 50 mg to the subject.

9793. The use of any one of claims 7975 to 8177, and 8379 to 8985, wherein if the use comprises a second regimen, and wherein in (v) if the subject has a body weight of less than 100 kg, the second regimen comprises an ADC dose of about 1.0 mg/kg of the subject's body weight.

9894. The use of any one of claims 7975 to 8177, and 8379 to 8985, wherein if the use comprises a second regimen, and wherein in (v) if the subject has a body weight of no less than 100 kg, the second regimen comprises an ADC dose of about 100 mg to the subject.

9995. The use of any one of claims 7975 to 8177, and 8379 to 8985, 97 and 9893 to 94, wherein if the use comprises a second regimen, and wherein in (v) if the second regimen has been administered one or more times and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.75 mg/kg of the subject's body weight.

10096. The use of any one of claims 7975 to 8177, and 8379 to 8985, 97 and 9893 to 94, wherein if the use comprises a second regimen, and wherein in (v) if the second regimen has been administered one or more times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 75 mg to the subject.

10197. The use of any one of claims 7975 to 8177, and 8379 to 8985, 9793 to 10096, wherein if the use comprises a second regimen, and wherein in (v) if the second regimen has been administered two or more times and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.5 mg/kg of the subject's body weight.

10298. The use of any one of claims 7975 to 8177, and 8379 to 8985, 9793 to 10096, wherein if the use comprises a second regimen, and wherein in (v) if the second regimen has been administered two or more times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 50 mg to the subject.

10399. The use of any one of claims 8177 and 8379 to 10298, wherein if the use comprises a second regimen, and wherein the ADC dose in the second regimen is increased by an amount of about 0.25 mg/kg for the subject having a body weight of less than 100 kg or increased by an amount of about 25 mg for the subject having a body weight of no less than 100 kg, if

(1) the administration of the ADC has not been discontinued permanently,

(2) the ADC dose in the second regimen is lower than the ADC dose in the first regimen, and

(3) the non-hematologic toxicity has returned to no more than Grade 1.

104100. The use of any one of claims 7975 to 10399, wherein the non-hematologic toxicity is determined daily.

105101. The use of any one of claims 7975 to 10399, wherein the non-hematologic toxicity is determined once every two days, once every three days, once every four days, or once every five days, once every six days.

106102. The use of any one of claims 7975 to 10399, wherein the non-hematologic toxicity is determined weekly, bi-weekly, once every three weeks, or once every four weeks.

107103. The use of any one of claims 7975 to 10399, wherein the non-hematologic toxicity is determined monthly, once every two months, or once every three months.

108104. The use of any one of claims 1 to 107103, wherein

(w) the ADC is to be administered after determining hematologic toxicity in the subject, and

(x) if the hematologic toxicity from (w) is no less than Grade 2, the administration of the ADC is withheld.

109105. The use of claim 108104, wherein
(y) the ADC is to be administered after waiting for a period sufficient for the hematologic toxicity to reduce to no more than Grade 1.

110106. The use of claim 108104 or 109105, wherein
(z) the ADC is to be administered after determining the hematologic toxicity in the subject, and
(aa) if the hematologic toxicity in (z) is no more than Grade 1, the ADC is to be administered to the subject for a second regimen comprising an effective amount of the ADC, wherein the second regimen comprises an ADC dose equal to or lower than the first regimen.

111107. The use of any one of claims 108104 to 110106, wherein if the hematologic toxicity in (w) or (z) is no less than Grade 4, the administration of the ADC is discontinued permanently.

112108. The use of any one of claims 108104 to 111107, wherein the hematologic toxicity is thrombocytopenia.

113109. The use of any one of claims 108104 to 111107, wherein the hematologic toxicity is selected from the group consisting of anemia, thrombocytopenia, neutropenia, and febrile neutropenia.

114110. The use of any one of claims ~~104 to 106~~, 110 and 112108 to 113109, wherein if the use comprises steps (w) to (aa), and wherein the ADC is to be administered following the steps repeating from (w) to (aa).

115111. The use of any one of claims 110106, and 112108 to 114110, wherein if the hematologic toxicity in (w) is no less than Grade 4 and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 1.0 mg/kg of the subject's body weight.

116112. The use of any one of claims 110106, and 112108 to 114110, wherein if the hematologic toxicity in (w) is no less than Grade 4 and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 100 mg to the subject

117113. The use of any one of claims 110106, and 112108 to 114110, wherein the hematologic toxicity in (w) is Grade 3 or Grade 2.

118114. The use of any one of claims 110106, and 112108 to 114110, wherein the hematologic toxicity in (w) is Grade 3 thrombocytopenia or Grade 2 thrombocytopenia.

119115. The use of claim 117113 or 118114, wherein the ADC is to be administered after determining the number of times the condition for the administration of the second regimen has been satisfied.

120116. The use of any one of claims 117113 to 119115, wherein in (aa) the second regimen is identical to the first regimen.

121117. The use of any one of claims 117113 to 120116, wherein in (aa) if the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 1.0 mg/kg of the subject's body weight.

122118. The use of any one of claims 117113 to 120116, wherein in (aa) if the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 100 mg to the subject.

123119. The use of any one of claims 117113 to 122118, wherein in (aa) if the second regimen has been administered at the ADC dose of about 1.0 mg/kg or 100 mg and if the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.75 mg/kg of the subject's body weight.

124120. The use of any one of claims 117113 to 122118, wherein in (aa) if the

second regimen has been administered at the ADC dose of about 1.0 mg/kg or 100 mg and if the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 75 mg to the subject.

125124. The use of any one of claims 117113 to 124120, wherein in (aa) if the second regimen has been administered at the ADC dose of about 0.75 mg/kg or 75 mg and if the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.5 mg/kg of the subject's body weight.

126122. The use of any one of claims 117113 to 124120, wherein in (aa) if the second regimen has been administered at the ADC dose of about 0.75 mg/kg or 75 mg and if the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 50 mg to the subject.

127123. The use of any one of claims 110106 and 112108 to 126122, wherein the ADC dose in the second regimen is increased by an amount of about 0.25 mg/kg for the subject having a body weight of less than 100 kg or increased by an amount of about 25 mg for the subject having a body weight of no less than 100 kg, if

- (1) the administration of the ADC has not been discontinued permanently,
- (2) the ADC dose in the second regimen is lower than the ADC dose in the first regimen, and
- (3) the hematologic toxicity has returned to no more than Grade 1.

128124. The use of any one of claims 108104 to 127123, wherein the hematologic toxicity is determined daily.

129125. The use of any one of claims 108104 to 127123, wherein the hematologic toxicity is determined once every two days, once every three days, once every four days, or once

every five days, once every six days.

130126. The use of any one of claims 108104 to 127123, wherein the hematologic toxicity is determined weekly, bi-weekly, once every three weeks, or once every four weeks.

131127. The use of any one of claims 108104 to 127123, wherein the hematologic toxicity is determined monthly, once every two months, or once every three months.

132128. The use of any one of claims 1 to 131127, wherein
(ab) the ADC is to be administered after determining fatigue in the subject, and
(ac) if the fatigue from (ab) is no less than Grade 3, the administration of the ADC is withheld.

133129. The use of claim 132128, wherein
(ad) the ADC is to be administered after waiting for a period sufficient for the fatigue to reduce to no more than Grade 1.

134130. The use of claim 132128 or 133129, wherein
(ae) the ADC is to be administered after determining the fatigue in the subject, and
(af) if the fatigue in (ae) is no more than Grade 1, the ADC is to be administered to the subject for a second regimen comprising an effective amount of the ADC, wherein the second regimen comprises an ADC dose equal to or lower than the first regimen.

135131. The use of any one of claims 132128 to 134130, wherein if the fatigue in (ab) or (ae) is no less than Grade 4, the administration of the ADC is discontinued permanently.

136132. The use claim 134~~of any one of claims 128 to 130~~, wherein the ADC is to be administered following the steps repeating from (ab) to (af).

137133. The use of any one of claims 132128 to 134130 and 136132, wherein if

the use comprises a second regimen, the ADC is to be administered after determining the number of times the condition for the administration of the second regimen has been satisfied.

138134. The use of any one of claims 132128 to 134130 and 136132 to 137133, wherein ~~in~~ if the use comprises a second regimen, and wherein if the fatigue in (ab) is Grade 3, the second regimen is identical to the first regimen.

139135. The use of any one of claims 132128 to 134130 and 136132 to 137134, wherein if the use comprises a second regimen, and wherein if the fatigue in (ab) is Grade 3 and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 1.0 mg/kg of the subject's body weight.

140136. The use of any one of claims 132128 to 134130 and 136132 to 137134, wherein if the use comprises a second regimen, and wherein if the fatigue in (ab) is Grade 3 and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 100 mg to the subject.

141137. The use of any one of claims 132128 to 134130 and 136132 to 137136, wherein if the use comprises a second regimen, and wherein in (af) if the second regimen has been administered at the ADC dose of about 1.0 mg/kg or 100 mg and if the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.75 mg/kg of the subject's body weight.

142138. The use of any one of claims 132128 to 134130 and 136132 to 137136, wherein if the use comprises a second regimen, and wherein in (af) if the second regimen has been administered at the ADC dose of about 1.0 mg/kg or 100 mg and if the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 75 mg to the subject.

143139. The use of any one of claims 132128 to 134130 and 136132 to 137138,

wherein if the use comprises a second regimen, and wherein in (af) if the second regimen has been administered at the ADC dose of about 0.75 mg/kg or 75 mg and if the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.5 mg/kg of the subject's body weight.

144140. The use of any one of claims 132128 to 134130 and 136132 to 142138, wherein in (af) if the second regimen has been administered at the ADC dose of about 0.75 mg/kg or 75 mg and if the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 50 mg to the subject.

145141. The use of any one of claims 134130 and 136132 to 144140, wherein the ADC dose in the second regimen is increased by an amount of about 0.25 mg/kg for the subject having a body weight of less than 100 kg or increased by an amount of about 25 mg for the subject having a body weight of no less than 100 kg, if

- (1) the administration of the ADC has not been discontinued permanently,
- (2) the ADC dose in the second regimen is lower than the ADC dose in the first regimen, and
- (3) the fatigue has returned to no more than Grade 1.

146142. The use of any one of claims 132128 to 145141, wherein the fatigue is determined daily.

147143. The use of any one of claims 132128 to 145141, wherein the fatigue is determined once every two days, once every three days, once every four days, or once every five days, once every six days.

148144. The use of any one of claims 132128 to 145141, wherein the fatigue is determined weekly, bi-weekly, once every three weeks, or once every four weeks.

149145. The use of any one of claims 132128 to 145141, wherein the fatigue is determined monthly, once every two months, or once every three months.

150146. The use of any one of claims 1 to 149145, wherein
(ag) the ADC is to be administered after determining diarrhea in the subject, and
(ah) if the diarrhea from (ag) is no less than Grade 3, the administration of the ADC is withheld.

151147. The use of claim 150146, wherein
(ai) the ADC is to be administered after waiting for a period sufficient for the diarrhea to reduce to no more than Grade 1.

152148. The use of claim 150146 or 151147, wherein
(aj) the ADC is to be administered after determining the diarrhea in the subject, and
(ak) if the diarrhea in (aj) is no more than Grade 1, the ADC is to be administered to the subject for a second regimen comprising an effective amount of the ADC, wherein the second regimen comprises an ADC dose equal to or lower than the first regimen.

153149. The use of any one of claims 150146 to 152148, wherein if the diarrhea in (ag) or (ai) is no less than Grade 4 and the diarrhea does not improve to no more than Grade 2 within 72 hours with supportive management, the administration of the ADC is discontinued permanently.

154150. The use of claim 152 ~~any one of claims 146 to 148~~, wherein the ADC is to be administered following the steps repeating from (ag) to (ak).

155151. The use of any one of claims 150146 to 152148 and 154150, wherein if the use comprises a second regimen, the ADC is to be administered after determining the number of times the condition for the administration of the second regimen has been satisfied.

156152. The use of any one of claims 150146 to 152148 and 154150 to 155151, wherein if the use comprises a second regimen, in (ak) the second regimen is identical to the first regimen.

157153. The use of any one of claims 150146 to 152148 and 154150 to 156152, wherein if the use comprises a second regimen, and wherein in (ak) if the second regimen has been administered one or more times and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 1.0 mg/kg of the subject's body weight.

158154. The use of any one of claims 150146 to 152148 and 154150 to 156152, wherein if the use comprises a second regimen, and wherein in (ak) if the second regimen has been administered one or more times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 100 mg to the subject.

159155. The use of any one of claims 150146 to 152148 and 154150 to 158154, wherein if the use comprises a second regimen, and wherein in (ak) if the second regimen has been administered two or more times and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.75 mg/kg of the subject's body weight.

160156. The use of any one of claims 150146 to 152148 and 154150 to 158154, wherein if the use comprises a second regimen, and wherein in (ak) if the second regimen has been administered two or more times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 75 mg to the subject.

161157. The use of any one of claims 150146 to 152148 and 154150 to 160156, wherein if the use comprises a second regimen, and wherein in (ak) if the second regimen has been administered three or more times and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.5 mg/kg of the subject's body weight.

162158. The use of any one of claims 150146 to 152148 and 154150 to 160156,

wherein if the use comprises a second regimen, and wherein in (ak) if the second regimen has been administered three or more times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 50 mg to the subject.

163159. The use of any one of claims 150146 to 152148 and 154150 to 155151, wherein if the use comprises a second regimen, and wherein in (ak) if the subject has a body weight of less than 100 kg, the second regimen comprises an ADC dose of about 1.0 mg/kg of the subject's body weight.

164160. The use of any one of claims 150146 to 152148 and 154150 to 155151, wherein if the use comprises a second regimen, and wherein in (ak) if the subject has a body weight of no less than 100 kg, the second regimen comprises an ADC dose of about 100 mg to the subject.

165161. The use of any one of claims 150146 to 152148, 154150 to 155151, and 163159 to 164160, wherein if the use comprises a second regimen, and wherein in (ak) if the second regimen has been administered one or more times and the subject has a body weight of less than 100 kg, the ADC dose in the second regimen is lowered to about 0.75 mg/kg of the subject's body weight.

166162. The use of any one of claims 150146 to 152148, 154150 to 155151, and 163159 to 164160, wherein if the use comprises a second regimen, and wherein in (ak) if the second regimen has been administered one or more times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 75 mg to the subject.

167163. The use of any one of claims 150146 to 152148, 154150 to 155151, and 163159 to 166162, wherein if the use comprises a second regimen, and wherein in (ak) if the second regimen has been administered two or more times and the subject has a body weight of

less than 100 kg, the ADC dose in the second regimen is lowered to about 0.5 mg/kg of the subject's body weight.

168164. The use of any one of claims 150146 to 152148, 154150 to 155151, and 163159 to 166162, wherein if the use comprises a second regimen, and wherein in (ak) if the second regimen has been administered two or more times and the subject has a body weight of no less than 100 kg, the ADC dose in the second regimen is lowered to about 50 mg to the subject.

169165. The use of any one of claims 152148 and 154150 to 168164, wherein the ADC dose in the second regimen is increased by an amount of about 0.25 mg/kg for the subject having a body weight of less than 100 kg or increased by an amount of about 25 mg for the subject having a body weight of no less than 100 kg, if

- (1) the administration of the ADC has not been discontinued permanently,
- (2) the ADC dose in the second regimen is lower than the ADC dose in the first regimen, and
- (3) the diarrhea has returned to no more than Grade 1.

170166. The use of any one of claims 150146 to 169165, wherein the diarrhea is determined daily.

171167. The use of any one of claims 150146 to 169165, wherein the diarrhea is determined once every two days, once every three days, once every four days, or once every five days, once every six days.

172168. The use of any one of claims 150146 to 169165, wherein the diarrhea is determined weekly, bi-weekly, once every three weeks, or once every four weeks.

173169. The use of any one of claims 150146 to 169165, wherein the diarrhea is determined monthly, once every two months, or once every three months.

174170. The use of any one of claims 1 to 173169, 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.

175171. The use of any one of claims 1 to 173169, 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.

176172. The use of any one of claims 1 to 173169, 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.

177173. The use of any one of claims 1 to 173169, 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.

178174. The use of any one of claims 1 to 177173, 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.

179175. The use of any one of claims 1 to 178174, 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.

180176. The use of any one of claims 1 to 179175, wherein the antigen binding fragment is an Fab, F(ab')₂, Fv or scFv fragment.

181177. The use of any one of claims 1 to 180176, wherein the antibody is a fully human antibody.

182178. The use of any one of claims 1 to 181177, wherein the antibody or antigen binding fragment thereof is recombinantly produced.

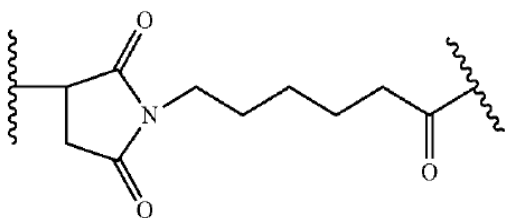
183179. The use of any one of claims 1 to 182178, wherein the antibody or antigen binding fragment is linked to each unit of monomethyl auristatin E (MMAE) via a linker.

184180. The use of claim 183179, 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.

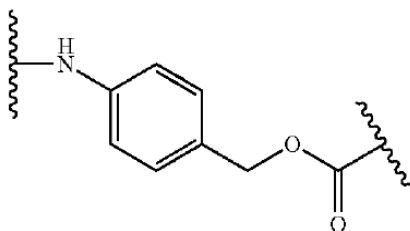
185181. The use of claim 183179 or 184180, wherein the linker has a formula of: –Aa–W_w–Yy–; wherein –A– is a stretcher unit, a is 0 or 1; –W– is an amino acid unit, w is an

integer ranging from 0 to 12; and –Y– is a spacer unit, y is 0, 1, or 2.

186182. The use of claim 185181, 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).

187183. The use of claim 185181 or 186182, 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.

188184. The use of any one of claims 1 to 187183, wherein the antibody is a fully human monoclonal antibody and wherein the antibody is an IgG1.

189185. The use of any one of claims 1 to 188184, wherein the ADC comprises from 1 to 10 units of MMAE per antibody or antigen binding fragment thereof.

190186. The use of any one of claims 1 to 189185, wherein the ADC comprises

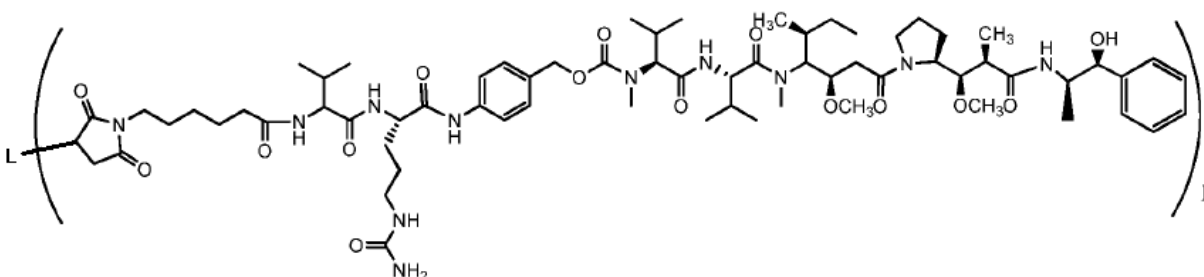
from 2 to 8 units of MMAE per antibody or antigen binding fragment thereof.

191487. The use of any one of claims 1 to 190486, wherein the ADC comprises from 3 to 5 units of MMAE per antibody or antigen binding fragment thereof.

192488. The use of any one of claims 1 to 191487, wherein the ADC comprises from 3 to 4 units of MMAE per antibody or antigen binding fragment thereof.

193489. The use of any one of claims 1 to 192488, wherein the ADC comprises about 4 units of MMAE per antibody or antigen binding fragment thereof.

194490. The use of any one of claims 1 to 189485, wherein the ADC has the following structure:



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

195491. The use of claim 194490, wherein p is from 2 to 8.

196492. The use of claim 194490 or 195491, wherein p is from 3 to 5.

197493. The use of claim 194490 to 196492, wherein p is from 3 to 4.

198494. The use of claim 194490 to 197493, wherein p is about 4.

199495. The use of claim 194490 to 197493, wherein p is about 3.8.

~~196.—The use of any one of claims 1 to 195, 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°C.~~

~~197.—The use of any one of claims 1 to 195, 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°C.~~

~~198.—The use of any one of claims 1 to 195, wherein the ADC is formulated at about 10 mg/ml in a pharmaceutical composition comprising about 1.4 mg/ml histidine, about 2.31 mg/ml histidine hydrochloride monohydrate, about 0.2 mg/ml polysorbate 20 (TWEEN-20), and about 55 mg/ml trehalose dihydrate, and wherein the pH of the pharmaceutical composition is about 6.0 at 25°C.~~

~~199.—The use of any one of claims 1 to 195, wherein the ADC is formulated in a vial comprising a pharmaceutical composition comprising about 20 mg of the ADC, about 2.8 mg histidine, about 4.62 mg histidine hydrochloride monohydrate, about 0.4 mg polysorbate 20 (TWEEN-20), and about 110 mg trehalose dihydrate.~~

~~200.—The use of any one of claims 1 to 195, wherein the ADC is formulated in a vial comprising a pharmaceutical composition comprising about 30 mg of the ADC, about 4.2 mg histidine, about 6.93 mg histidine hydrochloride monohydrate, about 0.6 mg polysorbate 20 (TWEEN-20), and about 165 mg trehalose dihydrate.~~

~~200~~201. The use of any one of claims 1 to ~~199~~200, wherein the ADC is to be administered by an intravenous (IV) injection or infusion.

~~2012~~202. The use of any one of claims 1 to ~~2002~~201, wherein the ADC or the ADC formulated in the pharmaceutical composition is to be administered by an intravenous (IV) injection or infusion over about 30 minutes.

~~2022~~203. Use of an antibody drug conjugate (ADC) in the preparation of a medicament for ~~use in a method of~~ treating cancer in a subject, wherein the ADC is to be administered through a treatment regimen to the subject, wherein the treatment regimen comprises:

- a. administering one or more doses of an antibody drug conjugate (ADC) to the subject, wherein the one or more doses are to be administered at a first dose level that contains an effective amount of the ADC;
- b. determining whether the subject experiences an adverse reaction in response to administration of the ADC in (a), wherein the adverse reaction is selected from the group consisting of hyperglycemia, peripheral neuropathy, a skin reaction, a nonhematologic toxicity, and a hematologic toxicity;
- c. administering one or more subsequent doses of the ADC, each containing an effective amount of the ADC, or discontinuing administration of the ADC based upon the determination in (b), wherein
 - i. if the subject is determined not to have experienced an adverse reaction to the ADC or the adverse reaction is determined to be below a defined level, then the one or more subsequent doses of the ADC are to be administered to the subject at the first dose level; and
 - ii. if the subject is determined to have experienced an adverse reaction to the ADC at or above a defined level, the treatment regimen is permanently discontinued or administration of the one or more subsequent doses of the ADC are withheld for a period of time sufficient to reduce the adverse reaction to a desired level and then administration of the one or more

subsequent doses of ADC are to be administered at the first dose level or a reduced dose level that is reduced relative to the first dose level; and

wherein:

A. the first dose level for the initial treatment round is the starting dose level as indicated in the dose reduction schedule below; and

B. the reduced dose level in c(ii) for each treatment round is reduced to the first dose reduction, the second dose reduction, or the third dose reduction level as set forth in the dose reduction schedule below depending upon whether the dose reduction in c(ii) is the first, second or third dose reduction in the collective treatment rounds, respectively.

	<u>Dose Level</u>
<u>Starting Dose</u>	<u>1.25 mg/kg if the subject weighs less than 100 kg and up to 125 mg if the subject weighs 100 kg or more</u>
<u>First Dose Reduction</u>	<u>1.0 mg/kg if the subject weighs less than 100 kg, and up to 100 mg if the subject weighs 100 kg or more</u>
<u>Second Dose Reduction</u>	<u>0.75 mg/kg if the subject weighs less than 100 kg, and up to 75 mg if the subject weighs 100 kg or more</u>
<u>Third Dose Reduction</u>	<u>0.5 mg/kg if the subject weighs less than 100 kg, and up to 50 mg if the subject weighs 100 kg or more</u>

~~d. optionally repeating (a) — (c) one or more times, each repetition of (a) — (c) defining a treatment round, wherein the first dose level in (a) of each subsequent treatment round is either the first dose level from (a) from the immediately preceding round or the reduced dose level of c(ii) from the immediately preceding round, and wherein if the subject is found to have a recurrence of the adverse reaction in two successive treatment rounds, the one or more subsequent doses of~~

~~the ADC administered in c(ii) is reduced relative to the dose administered in (a) during that treatment round, or administration of the ADC is permanently discontinued; and wherein:~~

- ~~i. the subject has urothelial cancer, optionally selected from the group of locally advanced or metastatic urothelial cancer, and has previously been treated with an immune checkpoint inhibitor and a chemotherapy agent, wherein the immune checkpoint inhibitor is optionally a programmed death receptor 1 (PD-1) inhibitor, or a programmed death ligand 1 (PD-L1) inhibitor, and wherein the immune checkpoint inhibitor was optionally administered in a neoadjuvant or adjuvant setting; and~~
- ~~ii. the ADC comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE), wherein the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 and a light chain variable region comprising the CDRs the light chain variable region set forth in SEQ ID NO:23.~~

203. The use of claim 202, further comprising:

- d. repeating (a) – (c) one or more times, each repetition of (a) – (c) defining a treatment round, wherein the first dose level in (a) of each subsequent treatment round is either the first dose level from (a) from the immediately preceding round or the reduced dose level of c(ii) from the immediately preceding round, and wherein if the subject is found to have a recurrence of the adverse reaction in two successive treatment rounds, the one or more subsequent doses of the ADC administered in c(ii) is reduced relative to the dose administered in (a) during that

treatment round, or administration of the ADC is permanently discontinued; and
wherein:

- i. the subject has urothelial cancer; and
- ii. the ADC comprises an antibody or antigen binding fragment thereof that binds to 191P4D12 and is conjugated to one or more units of monomethyl auristatin E (MMAE), wherein the antibody or antigen binding fragment thereof comprises a heavy chain variable region comprising complementarity determining regions (CDRs) comprising the CDRs of the heavy chain variable region set forth in SEQ ID NO:22 and a light chain variable region comprising the CDRs the light chain variable region set forth in SEQ ID NO:23.

204. The use of claim 203, wherein the urothelial cancer is selected from the group of locally advanced or metastatic urothelial cancer, and has previously been treated with an immune checkpoint inhibitor and a chemotherapy agent.

205. The use of claim 204, wherein the immune checkpoint inhibitor is a programmed death receptor-1 (PD-1) inhibitor, or a programmed death-ligand 1 (PD-L1) inhibitor.

206. The use of claim 205, wherein the immune checkpoint inhibitor was administered in a neoadjuvant or adjuvant setting.

~~204. The use of claim 203, wherein~~

- ~~A. the treatment regimen comprises (a) —(d);~~
- ~~B. the first dose level for the initial treatment round is the starting dose level as indicated in the dose reduction schedule below; and~~
- ~~C. the reduced dose level in c(ii) for each treatment round is reduced to the first dose reduction, the second dose reduction, or the third dose reduction level as set forth in the dose reduction schedule below depending upon whether the dose reduction~~

in c(ii) is the first, second or third dose reduction in the collective treatment rounds, respectively.

	Dose Level
Starting Dose	1.25 mg/kg if the subject weighs less than 100 kg and up to 125 mg if the subject weighs 100 kg or more
First Dose Reduction	1.0 mg/kg if the subject weighs less than 100 kg, and up to 100 mg if the subject weighs 100 kg or more
Second Dose Reduction	0.75 mg/kg if the subject weighs less than 100 kg, and up to 75 mg if the subject weighs 100 kg or more
Third Dose Reduction	0.5 mg/kg if the subject weighs less than 100 kg, and up to 50 mg if the subject weighs 100 kg or more

207205. The use of any one of claims claim 202 to 206203 or 204, wherein

- I. the adverse reaction in (b) is hyperglycemia and determining comprises determining the blood glucose level of the subject;
- II. the determination to continue or discontinue administration of the ADC in (c) is made as follows:
 - i. if the blood glucose level of the subject is equal to or below 250 mg/dL, then the one or more subsequent doses are to be administered at the first dose level;
 - ii. if the blood glucose level of the subject is greater than 250 mg/dL, then administration of the one or more subsequent doses of the ADC are withheld for a period of time sufficient to reduce the blood glucose level to less than or equal to 250 mg/dL, and then the one or more subsequent doses of the ADC are to be administered at the first dose level; and
 - iii. if the blood glucose level of the subject is greater than 500 mg/dL, then

the treatment regimen is permanently discontinued.

208206. The use of ~~claim~~ any one of claims 202 to 206204, wherein

- I. the determination of an adverse reaction in (b) comprises determining if the subject experiences new or worsening symptoms of peripheral neuropathy; and
- II. the determination to continue or discontinue administration of the ADC in (c) is made as follows:
 - i. if the subject experiences no symptoms of peripheral neuropathy or has symptoms of peripheral neuropathy below Grade 2, then the one or more subsequent doses of the ADC are to be administered at the first dose level;
 - ii. if the subject experiences a first occurrence of symptoms of Grade 2 peripheral neuropathy at the first dose level administered in (a), then administration of the one or more subsequent doses of the ADC are withheld for a period sufficient to reduce the symptoms of peripheral neuropathy to Grade 1 or lower, and then administration of the one or more subsequent doses of the ADC at the dose level administered in (a) is resumed;
 - iii. if the subject has recurrent symptoms of peripheral neuropathy after two successive treatment rounds at the same dose level in (a), then the dose is reduced by one dose level in accordance with the dose reduction schedule; and
 - iv. ~~If~~ if the subject experiences symptoms of peripheral neuropathy at Grade 3 or higher, then the treatment regimen is permanently discontinued.

209207. The use of ~~claim~~ any one of claims 202 to 206204, wherein

- I. the determination of an adverse reaction in (b) comprises determining if the subject experiences a skin reaction; and
- II. the decision to continue or discontinue administration of the ADC in (c) is made as follows:
 - i. if the subject experiences no skin reaction or has a skin reaction below Grade 3, then the one or more subsequent doses of the ADC are to be administered at the first dose level;
 - ii. if the subject experiences a Grade 3 skin reaction, then the one or more subsequent doses of the ADC are withheld for a period sufficient to reduce the skin reaction to Grade 1 or less and then administration of the one or more subsequent doses of the ADC at the dose level administered in (a) is resumed or reduced by one dose level in accordance with the dose reduction schedule;
 - iii. if the subject experiences a Grade 4 skin reaction or has recurrent Grade 3 skin reactions following multiple administrations of the ADC, then the treatment regimen is permanently discontinued.

210208. The use of ~~claim~~ any one of claims 202 to 206204, wherein

- I. the determination of an adverse reaction in (b) comprises determining if the subject has symptoms of a nonhematologic toxicity; and
- II. the decision to continue or discontinue administration of the ADC in (c) is made as follows:
 - i. if the subject experiences a nonhematological toxicity that is below Grade 3, then the one or more subsequent doses of the ADC are to be administered at the first dose level;
 - ii. if the subject experiences a Grade 3 nonhematological toxicity, then the one or more subsequent doses of the ADC are withheld for

a period sufficient to reduce the nonhematological to Grade 1 or less and then administration of the one or more subsequent doses of the ADC at the dose level administered in (a) is resumed or reduced by one dose level in accordance with the dose reduction schedule;

- iii. if the subject experiences a Grade 4 nonhematological toxicity, then the treatment regimen is permanently discontinued.

211209. The use of ~~claim~~ any one of claims 202 to 206204, wherein

- I. the determination of an adverse reaction in (b) comprises determining if the subject has symptoms of a hematologic toxicity, wherein the hematological toxicity is optionally thrombocytopenia; and
- II. the decision to continue or discontinue administration of the ADC in (c) is made as follows:
 - i. if the subject experiences a hematological toxicity that is below Grade 3 and the hematological toxicity is not thrombocytopenia, then the one or more subsequent doses of the ADC are to be administered at the first dose level;
 - ii. if the subject experiences a Grade 2 or Grade 3 hematological toxicity, wherein the hematological toxicity is thrombocytopenia, then the one or more subsequent doses of the ADC are withheld for a period sufficient to reduce the thrombocytopenia to Grade 1 or less and then administration of the one or more subsequent doses of the ADC at the dose level administered in (a) is resumed or reduced by one dose level in accordance with the dose reduction schedule;
 - iii. if the subject experiences a Grade 4 hematological

~~nonhematological~~ toxicity that is not thrombocytopenia, then administration of the one or more subsequent doses of the ADC at the dose level administered in (a) is reduced by one dose level in accordance with the dose reduction schedule or the treatment regimen is permanently discontinued.

212240. The use of any one of claims 202203 to 211209, wherein the antibody or antigen binding fragment thereof comprises a CDR H1 comprising the amino acid sequence of SEQ ID NO:9, a CDR H2 comprising the amino acid sequence of SEQ ID NO:10, a CDR H3 comprising the amino acid sequence of SEQ ID NO:11; a CDR L1 comprising the amino acid sequence of SEQ ID NO:12, a CDR L2 comprising the amino acid sequence of SEQ ID NO:13, and a CDR L3 comprising the amino acid sequence of SEQ ID NO:14.

213244. The use of any one of claims 202203 to 211209, wherein the antibody or antigen binding fragment thereof comprises a CDR H1 comprising the amino acid sequence of SEQ ID NO:16, a CDR H2 comprising the amino acid sequence of SEQ ID NO:17, a CDR H3 comprising the amino acid sequence of SEQ ID NO:18; a CDR L1 comprising the amino acid sequence of SEQ ID NO:19, a CDR L2 comprising the amino acid sequence of SEQ ID NO:20, and a CDR L3 comprising the amino acid sequence of SEQ ID NO:21.

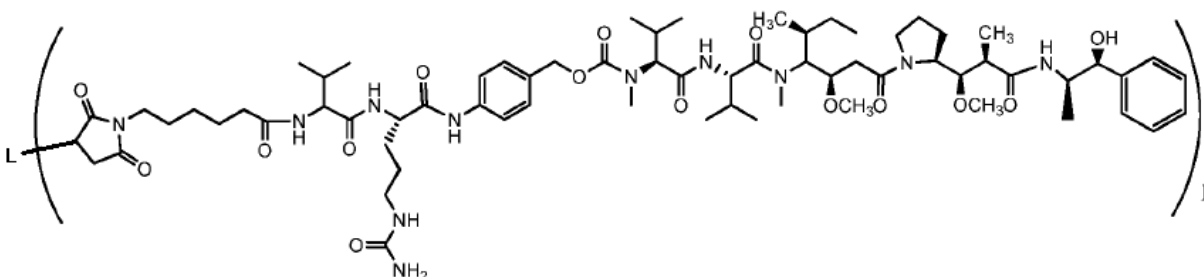
214242. The use of any one of claims 202203 to 211209, wherein the antibody or antigen binding fragment thereof comprises a CDR H1 consisting of the amino acid sequence of SEQ ID NO:9, a CDR H2 consisting of the amino acid sequence of SEQ ID NO:10, a CDR H3 consisting of the amino acid sequence of SEQ ID NO:11; a CDR L1 consisting of the amino acid sequence of SEQ ID NO:12, a CDR L2 consisting of the amino acid sequence of SEQ ID NO:13, and a CDR L3 consisting of the amino acid sequence of SEQ ID NO:14.

215243. The use of any one of claims 202203 to 211209, wherein the antibody or antigen binding fragment thereof comprises a CDR H1 consisting of the amino acid sequence of

SEQ ID NO:16, a CDR H2 consisting of the amino acid sequence of SEQ ID NO:17, a CDR H3 consisting of the amino acid sequence of SEQ ID NO:18; a CDR L1 consisting of the amino acid sequence of SEQ ID NO:19, a CDR L2 consisting of the amino acid sequence of SEQ ID NO:20, and a CDR L3 consisting of the amino acid sequence of SEQ ID NO:21.

216214. The use of any one of claims 202203 to 211209, 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.

217215. The use of any one of claims 202203 to 216214, wherein the ADC has the following structure:



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

218216. The use of claim 217215, wherein p is from 3 to 5.

219217. The use of claim 217215 or 218216, wherein p is from 3 to 4.

220218. The use of any one of claims 217215 to 219217, wherein p is about 4.

221219. The use of any one of claims 217215 to 219217, wherein p is about 3.8.