3. SUMMARY

[006] The therapies described herein target solid tumor cancers in which cMet is overexpressed in at least 10% of the patient population having the cancer. cMet (cellular mesenchymal-epithelial transition factor) is a cell-surface receptor tyrosine kinase that transduces signals from the extracellular matrix into the cytoplasm by binding to hepatocyte growth factor/HGF ligand. This cell surface receptor is expressed in epithelial cells of many organs, including the liver, pancreas, prostate, kidney, muscle and bone marrow, during both embryogenesis and adulthood. cMet regulates many physiological processes including cell proliferation and survival, migration and scattering (cell-cell repulsion), tissue morphogenesis, organ regeneration, and tissue remodeling. In cancer and other pathological processes, cMet is often aberrantly activated via mutation, amplification, or protein overexpression.

[007] Solid tumor cancers in which cMet is overexpressed in at least 10% of the patient population include lung cancer, colorectal cancer, head and neck cancer, pancreatic cancer, gastric cancer, glioblastoma, ovarian, breast, prostate, cervical, and esophageal cancer. Data presented herein demonstrate, for the first time, that antibody drug conjugates ("ADCs") that specifically target cMet overexpression have demonstrated anti-tumor activity in patients diagnosed with non-small cell lung cancer. Data demonstrating in vivo anti-tumor efficacy of anti-cMet ADCs administered as monotherapy or combination are provided in Examples 10-14 and 16, and FIGS. 8-12 and 14-18.

[008] cMet overexpression can be defined by an immunohistorychemistry (IHC) H-score of greater than or equal to 150 when measured according to the assay of Example 17. Briefly, IHC staining protocol for cMet overexpression has been developed using the Ventana cMet CONFIRM (SP44) kit. Tissue samples are stained with the Ventana antibody and then scored by determining the percentages of target tissue cells staining at various intensity levels of low to high. FIG. 20 depicts representative H-scores using the assay described in Example 17.

[009] Alternatively, cMet overexpressing tumor tissue using an IHC score from 0 to 3+ as described in Example 17. FIGS. 19 and 21 depict representative IHC scores using the assay described in Example 17.

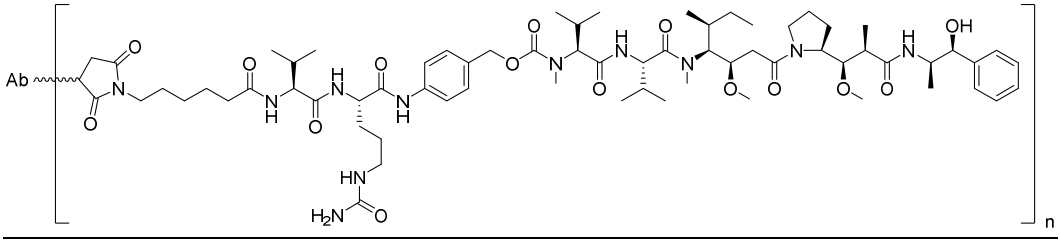
[010] The anti-cMet ADCs may be administered as single therapeutic agents (monotherapy) or adjunctively with or to other anti-cancer treatments and/or therapeutic agents, typically but not necessarily those used to treat the type of cancers being treated. Indeed, data presented herein demonstrate that tumors that exhibit resistance to other targeted or non-targeted chemotherapies retain sensitivity to anti-cMet ADCs (see, e.g., Example 14 and FIGS. 12A-C). Accordingly, the anti-cMet ADCs described herein provide significant benefits over current targeted and non-targeted approaches toward the treatment of solid tumor cancers that overexpress cMet. Adjunctive therapies and/or therapeutic agents typically will be used at their approved dose, route of administration, and frequency of administration, but may be used at lower dosages and/or less frequently. When

administered as monotherapy, the anti-cMet ADC will typically be administered on a schedule that provides therapeutic benefit. It is contemplated that anti-cMet ADCs administered once a week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every seven weeks or once every eight weeks will provide therapeutic benefit, although more or less frequent administration may be beneficial. When administered adjunctive to or with another therapy and/or agent, the anti-cMet ADC may be administered before, after or concurrently with the other therapy or agent.

[011] The anti-cMet ADCs may be administered via a variety of routes or modes of administration, including but not limited to, intravenous infusion and/or injection and subcutaneous injection. The amount administered will depend upon the route of administration, the dosing schedule, the type of cancer being treated, the stage of the cancer being treated, and other parameters such as the age and weight of the patient, as is well known in the art. Specific exemplary dosing schedules expected to provide therapeutic benefit are provided in the Detailed Description. Generally, an amount of anti-cMet ADC in the range of about 0.005 to 15 mg/kg when administered intravenously on a weekly basis from once weekly to and including once every eight weeks is expected to provide therapeutic benefit.

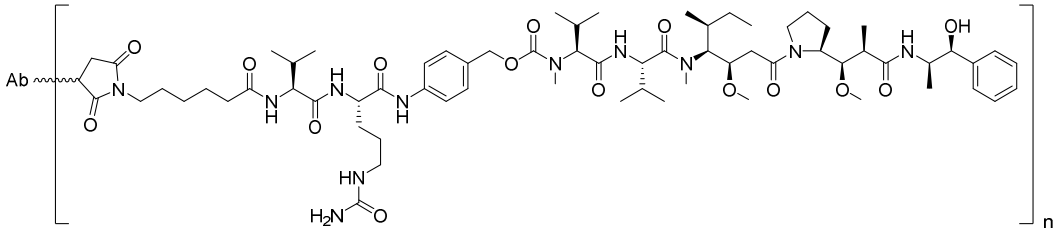
[012] Accordingly, in one example, the present disclosure provides ADCs that specifically bind cMet ("anti-cMet ADCs"). The anti-cMet ADCs comprise cytotoxic and/or cytostatic agents linked by way of linkers to an antigen binding moiety that specifically binds cMet. In some examples, the antigen binding moiety is an antibody and/or an antigen binding fragment.

[012a] In one aspect, there is provided an anti-cMet antibody drug conjugate ("ADC") consisting of an anti-cMet antibody (Ab) conjugated to monomethyl auristatin E ("MMAE") drugs according to the following structure:



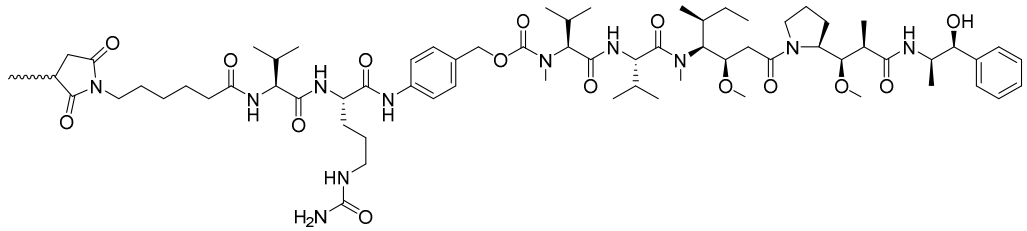
wherein the Ab is an IgG antibody consisting of heavy chains each consisting of the amino acid sequence of SEQ ID NO: 86 and light chains each consisting of the amino acid sequence of SEQ ID NO: 87, n has a value of 2, and conjugation of each of the MMAE drugs to the Ab is via a thioether linkage formed with a sulfhydryl group of a cysteine residue.

[012b] In one aspect, there is provided an anti-cMet antibody drug conjugate ("ADC") consisting of an anti-cMet antibody (Ab) conjugated to monomethyl auristatin E ("MMAE") drugs according to the following structure:



wherein the Ab is an IgG antibody consisting of heavy chains each consisting of the amino acid sequence of SEQ ID NO: 86 and light chains each consisting of the amino acid sequence of SEQ ID NO: 87, n has a value of 4, and conjugation of each of the MMAE drugs to the Ab is via a thioether linkage formed with a sulfhydryl group of a cysteine residue.

[012c] In one aspect, there is provided a composition comprising an anti-cMet antibody drug conjugate ("ADC"), wherein the ADC consists of an anti-cMet antibody (Ab) conjugated to monomethyl auristatin E ("MMAE") drugs according to the following structure:



wherein the Ab is an IgG antibody consisting of heavy chains each consisting of the amino acid sequence of SEQ ID NO:86 and light chains each consisting of the amino acid sequence of SEQ ID NO:87, and conjugation of each of the MMAE drugs to the Ab is via a thioether linkage formed with a sulfhydryl group of a cysteine residue, and
wherein the composition has as an average drug-to-antibody ratio ("DAR") in the range of 2-4.
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[013] Antibodies and/or binding fragments composing the anti-cMet ADCs generally comprise a heavy chain comprising a variable region (V_H) having three complementarity determining regions ("CDRs") referred to herein (in N→C order) as V_H CDR#1, V_H CDR#2, and V_H CDR#3, and a light chain comprising a variable region (V_L) having three complementarity determining regions

referred to herein (in N→C order) as V_L CDR#1, V_L CDR#2, and V_L CDR#3. The amino acid sequences of exemplary CDRs, as well as the amino acid sequence of the V_H and V_L regions of the heavy and light chains of exemplary anti-cMet antibodies and/or binding fragments that can compose the anti-cMet ADCs are provided herein. Specific examples of anti-cMet ADCs include, but are not limited to, ABT-700 and STI-0602.

[014] For therapeutic uses, it may be desirable to utilize anti-cMet ADCs that bind cMet with an affinity of at least 100 nM. Accordingly, in some examples, the anti- cMet ADCs comprise an anti- cMet and/or anti- cMet binding fragment that binds cMet with an affinity of at least about 100 nM, or even higher, for example, at least about 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 30 nM, 25 nM, 20 nM, 15 nM, 10 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.1 nM,

0.01 nM, or greater. Affinity of anti- cMet antibodies and/or binding fragments can be determined using techniques well known in the art or described herein, such as for example, ELISA, isothermal titration calorimetry (ITC), surface plasmon resonance, flow cytometry, or fluorescent polarization assay. In some examples, the affinity refers to apparent affinity EC_{50} values, measured according to Example 5. In one example, the antibody has an apparent affinity EC_{50} value from lower than about 10 nanomol/L, preferably from about 1 picomol/L to 10 nanomol/L, preferably about 0.3 nanomol/L, as determined according to Example 5.

[015] Antibodies may be in the form of full-length antibodies, bispecific antibodies, dual variable domain antibodies, multiple chain or single chain antibodies, surrobodies (including surrogate light chain construct), single domain antibodies, camelized antibodies, scFv-Fc antibodies, and the like. They may be of, or derived from, any isotype, including, for example, IgA (*e.g.*, IgA_1 or IgA_2), IgD, IgE, IgG (*e.g.*, IgG_1, IgG_2, IgG_3 or IgG_4), IgM, or IgY. In some examples, the anti-cMet antibody is an IgG (*e.g.*, IgG_1, IgG_2, IgG_3 or IgG_4). Antibodies may be of human or non-human origin. Examples of non-human origin include, but are not limited to, mammalian origin (*e.g.*, simians, rodents, goats, and rabbits) or avian origin (*e.g.,* chickens). In specific examples, antibodies composing the anti- cMet ADCs are suitable for administration to humans, such as, for example, humanized antibodies and/or fully human antibodies.

[016] Antigen binding fragments composing the anti- cMet ADCs may include any fragment of an antibody capable of specifically binding cMet. Specific examples of antibody binding fragments that may be included in the anti- cMet ADCs include, but are not limited to, Fab, Fab', $(Fab')_2$, Fv and scFv.

[017] Antibodies and/or binding fragments composing the anti-cMet ADCs may include modifications and/or mutations that alter the properties of the antibodies and/or fragments, such as those that increase half-life, increase or decrease ADCC, *etc.*, as is known in the art.

[018] The cytotoxic and/or cytostatic agents composing the anti-cMet ADCs may be any agents known to inhibit the growth and/or replication of, and/or kill cells. Numerous agents having cytotoxic and/or cytostatic properties are known in the literature. Non-limiting examples of classes of cytotoxic and/or cytostatic agents include, by way of example and not limitation, cell cycle modulators, apoptosis regulators, kinase inhibitors, protein synthesis inhibitors, alkylating agents, DNA cross-linking agents, intercalating agents, mitochondria inhibitors, nuclear export inhibitors, topoisomerase I inhibitors, topoisomerase II inhibitors, RNA/DNA antimetabolites and antimitotic agents.

[019] In a specific example, a cytotoxic and/or cytostatic agent composing an anti-cMet ADC is a cell-permeating antimitotic agent, such as, for example, an auristatin. Specific examples of cell-permeating auristatins include, but are not limited to, dolastatin-10 and monomethyl auristatin E

("MMAE"). In another specific example, a cytotoxic and/or cytostatic agent composing an anti-cMet ADC is a cell-permeating DNA cross-linking agent, such as a cell-permeating minor groove-binding DNA cross-linking agent. Specific examples of cell-permeating DNA minor groove-binding agents include, but are not limited to, pyrrolobenzodiazepines ("PBD") and PBD dimers.

[020] The linkers linking the cytotoxic and/or cytostatic agents to the antigen binding moiety of an anti-cMet ADC may be long, short, flexible, rigid, hydrophilic or hydrophobic in nature, or may comprise segments that have different characteristics, such as segments of flexibility, segments of rigidity, *etc.* The linker may be chemically stable to extracellular environments, for example, chemically stable in the blood stream, or may include linkages that are not stable and release the cytotoxic and/or cytostatic agents in the extracellular milieu. In some examples, the linkers include linkages that are designed to release the cytotoxic and/or cytostatic agents upon internalization of the anti- cMet ADC within the cell. In some specific examples, the linkers includes linkages designed to cleave and/or immolate or otherwise breakdown specifically or non-specifically inside cells. A wide variety of linkers useful for linking drugs to antigen binding moieties such as antibodies in the context of ADCs are known in the art. Any of these linkers, as well as other linkers, may be used to link the cytotoxic and/or cytostatic agents to the antigen binding moiety of the anti- cMet ADCs described herein.

[021] The number of cytotoxic and/or cytostatic agents linked to the antigen binding moiety of an anti- cMet ADC can vary (called the "drug-to-antibody ratio," or "DAR"), and will be limited only by the number of available attachments sites on the antigen binding moiety and the number of agents linked to a single linker. Typically, a linker will link a single cytotoxic and/or cytostatic agent to the antigen binding moiety of an anti- cMet ADC. In examples of anti- cMet ADCs which include more than a single cytotoxic and/or cytostatic agent, each agent may be the same or different. As long as the anti- cMet ADC does not exhibit unacceptable levels of aggregation under the conditions of use and/or storage, anti-cMet ADCs with DARs of twenty, or even higher, are contemplated. In some examples, the anti-cMet ADCs described herein may have a DAR in the range of about 1-10, 1-8, 1-6, or 1-4. In certain specific examples, the anti-cMet ADCs may have a DAR of 2, 3, or 4. In other specific examples, the anti-cMet ADCs may have an average DAR of 3.1.

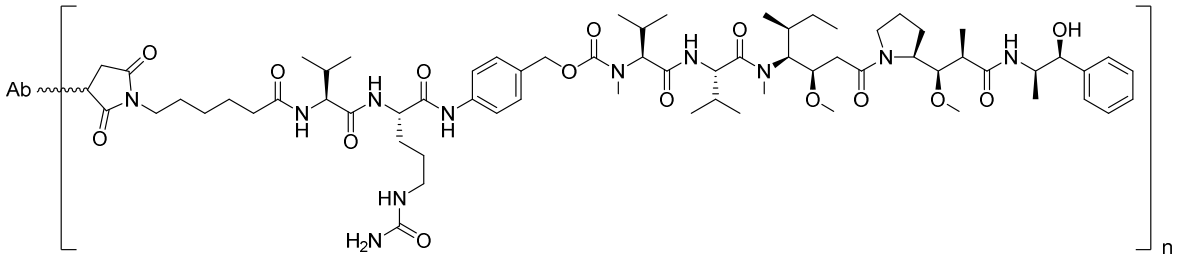
4. BRIEF DESCRIPTION OF THE FIGURES

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[022] FIGS 1A-E show the amino acid sequences of several cMet antibodies.

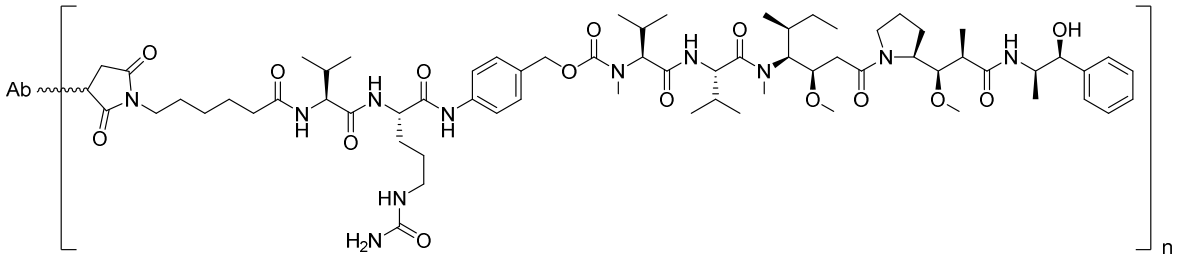
WE CLAIM:

1. An anti-cMet antibody drug conjugate ("ADC") consisting of an anti-cMet antibody (Ab) conjugated to monomethyl auristatin E ("MMAE") drugs according to the following structure:



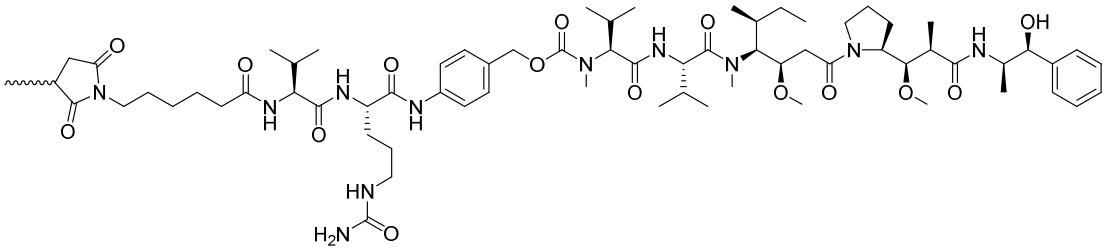
wherein the Ab is an IgG antibody consisting of heavy chains each consisting of the amino acid sequence of SEQ ID NO:86 and light chains each consisting of the amino acid sequence of SEQ ID NO:87, n has a value of 2, and conjugation of each of the MMAE drugs to the Ab is via a thioether linkage formed with a sulfhydryl group of a cysteine residue.

2. An anti-cMet antibody drug conjugate ("ADC") consisting of an anti-cMet antibody (Ab) conjugated to monomethyl auristatin E ("MMAE") drugs according to the following structure:



wherein the Ab is an IgG antibody consisting of heavy chains each consisting of the amino acid sequence of SEQ ID NO:86 and light chains each consisting of the amino acid sequence of SEQ ID NO:87, n has a value of 4, and conjugation of each of the MMAE drugs to the Ab is via a thioether linkage formed with a sulfhydryl group of a cysteine residue.

3. A composition comprising an anti-cMet antibody drug conjugate ("ADC"), wherein the ADC consists of an anti-cMet antibody (Ab) conjugated to monomethyl auristatin E ("MMAE") drugs according to the following structure:



wherein the Ab is an IgG antibody consisting of heavy chains each consisting of the amino acid sequence of SEQ ID NO:86 and light chains each consisting of the amino acid sequence of SEQ ID NO:87, and conjugation of each of the MMAE drugs to the Ab is via a thioether linkage formed with a sulfhydryl group of a cysteine residue, and

wherein the composition has as an average drug-to-antibody ratio ("DAR") in the range of 2-4.

4. The composition of claim 3, having a DAR of about 3.