

DOSAGE OF ANTIBODY DRUG CONJUGATE RINATABART SESUTECAN

TECHNICAL FIELD

[0001] The present disclosure generally relates to dosage schedules for antibody-drug conjugates (ADC) for human subjects, and in particular, to the dosage schedule of ADC rinatabart sesutecan (Rina-S) for human subjects in the treatment of cancer, such as solid tumors. It also relates to such ADCs for use in such dosage regimens. It also relates to combination therapies, where the ADC is used in combination with a further anti-cancer drug.

BACKGROUND

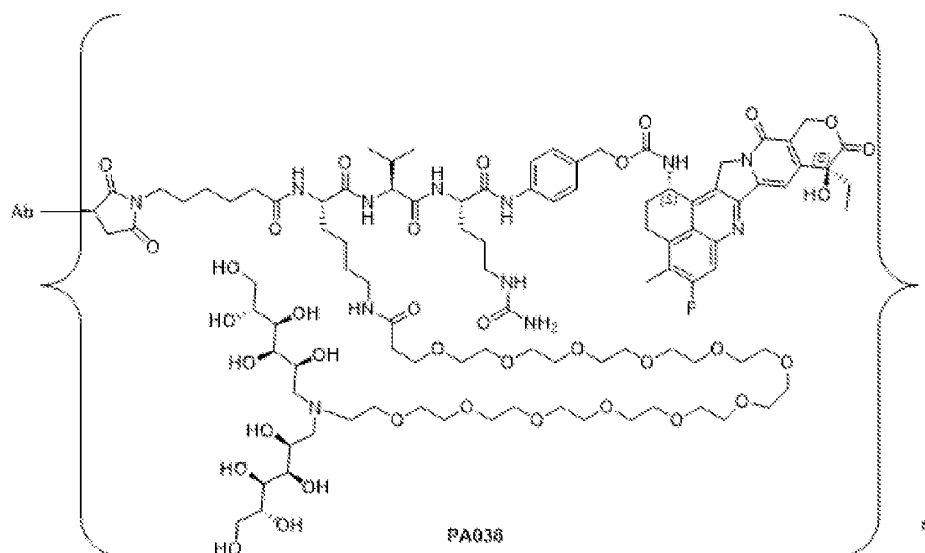
[0002] Folate Receptor 1 (FOLR1), also known as Folate Receptor-alpha ($FR\alpha$), or Folate Binding Protein (FBP), is an N-glycosylated protein expressed on the plasma membrane of cells. FOLR1 is overexpressed in the vast majority of ovarian cancers, as well as in many uterine, endometrial, pancreatic, renal, lung, and breast cancers, while the expression of FOLR1 on normal tissues is restricted to the apical membrane of epithelial cells in the kidney proximal tubules, alveolar pneumocytes of the lung, bladder, testes, choroid plexus, and thyroid (Weitman S D, et al., Cancer Res 52: 3396-3401 (1992); Antony A C, Annu Rev Nutr 16: 501-521 (1996); Kalli K R, et al. Gynecol Oncol 108: 619-626 (2008)). The antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S; previously also referred to as PRO1184) is developed to target FOLR1 and includes a FOLR1 antibody and drug units, each of which comprises exatecan connected to the antibody through a hydrophilic linker. Rina-S has been shown to induce cytotoxicity in cancer cells and demonstrate anti-tumor activities, both *in vitro* and *in vivo*. However, there is still a need for effective methods of administering Rina-S to human subjects. Preferably, the methods comprise optimized dosage and administration schedules that maximize efficacy and minimize toxicity of Rina-S for therapeutic use in human subjects. There is also a need to provide combination therapies for treating cancers which are positive for FOLR1.

SUMMARY

[0003] In one aspect, the present invention provides methods of treating a solid tumor comprising administering to a human subject with the solid tumor an antibody-drug conjugate (ADC) with the characteristics set forth herein comprising an antibody to FOLR1 conjugated via a hydrophilic linker to the anti-cancer drug exatecan. In any of the embodiments set out herein, the ADC may be Rina-S.

[0004] Provided herein are methods and dosage schedules for administering Rina-S to human subjects in the treatment of cancers, such as but not limited to solid tumors.

[0005] In one aspect, the invention provides a method for treating a solid tumor that is folate receptor 1 (FOLR1) positive, the method comprising administering to a human subject with the solid tumor an antibody-drug conjugate (ADC), wherein the ADC has the structure (structure 1):



wherein Ab is an antibody that binds to FOLR1 and that comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH and VL regions has amino acid sequences that are set forth in SEQ ID NO: 1 and SEQ ID NO: 2, respectively, and wherein n is 8, and wherein the ADC is administered at a dosage of between 40 mg/m² and 200 mg/m², e.g. between 60 mg/m² and 140 mg/m². In certain embodiments the human subject has an ovarian cancer. In certain embodiments the human subject has an endometrial cancer. In one aspect the invention provides a method for treating a human subject having a cancer that includes a solid tumor that is

FOLR1 positive, the method comprising administering to the subject an ADC having structure 1, wherein Ab is an antibody that comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH and VL regions has amino acid sequences that are set forth in SEQ ID NO: 1 and SEQ ID NO: 2, respectively, and wherein n is 8, and wherein the ADC is administered at a dosage of between 40 mg/m² and 200 mg/m², e.g. between 60 mg/m² and 140 mg/m². In certain embodiments the cancer is an ovarian cancer. In certain embodiments the cancer is an endometrial cancer. In certain embodiments the ADC is administered at a dosage of 100 mg/m². In certain embodiments the ADC is administered at a dosage of 120 mg/m². In certain embodiments the ADC is administered every three weeks. In certain embodiments, the ADC has the structure of structure 1 wherein Ab is an antibody that comprises a heavy chain (HC) and a light chain (LC), wherein the HC and LC have amino acid sequences that are set forth in SEQ ID NO: 6 and SEQ ID NO: 5, respectively, and wherein n is 8. In certain embodiments said HC and LC have amino acid sequences that are set forth in SEQ ID NO: 4 and SEQ ID NO: 5, respectively. In certain embodiments, the ADC has the structure of structure 1 wherein Ab is an antibody that comprises two HCs each having the amino acid sequence set forth in SEQ ID NO: 6 and two LCs each having the amino acid sequence set forth in SEQ ID NO: 5, and wherein n is 8. In certain embodiments each of said two HCs have the amino acid sequence set forth in SEQ ID NO: 4 and each of said two LCs have the amino acid sequence set forth in SEQ ID NO: 5.

[0006] One aspect of the current invention involves a method of treating a solid tumor comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatbart sesutecan (Rina-S), wherein the ADC is administered at a dosage of between 40 mg/m² and 200 mg/m², and the solid tumor is folate receptor 1 (FOLR1) positive.

[0007] In some embodiments of the present invention, the solid tumor is selected from the group consisting of: ovarian cancer, endometrial cancer, breast cancer, lung cancer, and mesothelioma. In certain embodiments, the solid tumor is ovarian cancer. In certain embodiments, the solid tumor is platinum-resistant ovarian cancer (PROC). In certain embodiments, the solid tumor is platinum-sensitive ovarian cancer (PSOC). In certain embodiments, the solid tumor is ovarian epithelial

cancer, primary peritoneal cancer, or fallopian tube cancer. In certain embodiments, the solid tumor is endometrial cancer. In certain embodiments, the solid tumor is non-small-cell lung cancer (NSCLC). In certain embodiments, the solid tumor is breast cancer, including HER2-negative breast cancer. In certain embodiments, the solid tumor is pleural mesothelioma or peritoneal mesothelioma. In certain embodiments, the solid tumor is localized or metastatic.

[0008] In some embodiments, another aspect of the current invention involves treatment with the ADC Rina-S, wherein the ADC is administered at a dosage of between 60 mg/m² and 180 mg/m². In certain embodiments, the ADC is administered at a dosage of 140 mg/m². In certain embodiments, the ADC is administered at a dosage of between 100 mg/m² and 140 mg/m². In certain embodiments, the ADC is administered at a dosage of between 100 mg/m² and 120 mg/m². In certain embodiments, the ADC is administered at a dosage of about 100 mg/m². In certain embodiments, the ADC is administered at a dosage of about 120 mg/m².

[0009] Another aspect of the current invention concerns the dosage schedule of the ADC Rina-S, wherein the ADC is administered to the human subject once or twice a week on a schedule with a cycle selected from the group consisting of: (i) weekly; (ii) every other week; (iii) one week of therapy followed by two, three or four weeks off; (iv) two weeks of therapy followed by one, two, three or four weeks off; (v) three weeks of therapy followed by one, two, three, four or five weeks off; (vi) four weeks of therapy followed by one, two, three, four or five weeks off; (vii) five weeks of therapy followed by one, two, three, four or five weeks off; and (viii) monthly. In certain embodiments, the ADC dosage is administered to the human subject once a week on a schedule with a cycle selected from the group consisting of: (i) weekly; (ii) every other week; (iii) one week of therapy followed by two, three or four weeks off. In certain embodiments, the ADC dosage is administered to the human subject on Day 1 of a 21-day treatment cycle. In certain embodiments, the ADC dosage is administered to the human subject as a 30-minute intravenous (IV) infusion.

[0010] In certain embodiments, the ADC is administered to the human subject with a cycle consisting of (i) once a week for two weeks of therapy followed by two, three or four weeks off; (ii) once a week for three weeks of therapy followed by two, three or four weeks off; (iii) once a week

for four weeks of therapy followed by two, three or four weeks off; (iv) every other week for four weeks of therapy followed by two, three or four weeks off; (v) once a week for five weeks of therapy followed by two, three or four weeks off.

[0011] In certain embodiments the ADC dosage is administered to the human subject once every three weeks. In certain embodiments thereof, the dosage is 120 mg/m². In certain embodiments the ADC dosage is administered as an intravenous infusion.

[0012] In another aspect of the current invention, the cycle of treatment is repeated 2, 4, 6, 8, 10, 12, 16 or 20 times. In one embodiment, the treatment is continued as long as needed. In certain embodiments the treatment is continued, for example, while the subject demonstrates a reduction in tumor size or stable tumor size (e.g., by RECIST v1.1 criteria), and/or a positive Duration of Objective Response (DOR), Overall Response rate (ORR), Disease Control Rate (DCR), Progression Free Survival time (PFS) and/or Overall Survival. Treatment with the ADC may be continued, for example, up to disease progression or unacceptable toxicity.

[0013] In yet another aspect of the current invention, the human subject has previously been treated with at least one anti-cancer therapy. In some embodiments, the human subject has previously been treated with 1 to 4 anti-cancer therapies. In some embodiments, the at least one anti-cancer therapy includes treatment with a chemotherapeutic agent. In some embodiments, the at least one anti-cancer therapy includes treatment with at least one anti-cancer therapy selected from the group consisting of platinum chemotherapy, bevacizumab, poly ADP-ribose polymerase (PARP) inhibitor, and mirvetuximab soravtansine. In certain embodiments, the human subject has failed to respond to the at least one anti-cancer therapy prior to treatment of the ADC. In certain embodiments, the human subject has previously been treated with mirvetuximab soravtansine. In certain embodiments, the human subject is not eligible for treatment with mirvetuximab soravtansine.

[0014] In yet another aspect of the current invention, the treatment with the ADC Rina-S results in a reduction in a size of the solid tumor of at least 15%, at least 20%, at least 30%, at least 40%, or at least 50%.

[0015] In yet another aspect of the current invention, the ADC is administered in combination with one or more therapeutic modalities selected from the group consisting of unconjugated antibodies, radiolabeled antibodies, drug-conjugated antibodies, toxin-conjugated antibodies, gene therapy, chemotherapy, therapeutic peptides, cytokine therapy, oligonucleotides, localized radiation therapy, surgery and interference RNA therapy.

[0016] In yet another aspect of the current invention, with a treatment of the ADC Rina-S, the outcome of the subject is improved. In some embodiments, the improved treatment outcome is an objective response selected from stable disease, a partial response or a complete response. In certain embodiments, the improved treatment outcome is reduced tumor burden. In certain embodiments, the improved treatment outcome is progression-free survival or disease-free survival. In certain embodiments, the improved treatment outcome is improved overall survival.

[0017] Treatment with the ADC Rina-S has been shown herein to provide clinical benefit in patients with tumors across all levels of FOLR1 expression, generating the possibility to treat patients with Rina-S irrespective of establishing FOLR1 expression levels prior to treatment. Accordingly, in another aspect, the invention provides for treatment of human subjects having a solid tumor with Rina-S, wherein the FOLR1 expression level in the solid tumor has not been determined. In certain embodiments thereof, the human subject has ovarian cancer. In certain embodiments, the human subjects have been pretreated with other anti-cancer therapies, e.g. with at least 1, 2, 3, 4, or more lines of therapy. In certain embodiments, the human subjects are treated with Rina-S at a dose level of 100 mg/m². In certain embodiments, the human subjects are treated with Rina-S at a dose level of 120 mg/m². In certain embodiments, the dosage is administered to the human subjects about every three weeks (Q3W). In certain embodiments, the administration of the Rina-S is via intravenous administration, e.g., intravenous infusion.

[0018] In yet another aspect, the invention provides combination therapies for subjects having a solid tumor, including methods of combination treatments comprising administering to the subject Rina-S in combination with either one of platinum-based chemotherapy, anti-angiogenic agents, PARP inhibitors, or checkpoint inhibitors. In one embodiment, the combination therapy comprises

Rina-S in combination with platinum-based chemotherapy, such as carboplatin, cisplatin, or oxaliplatin. In one embodiment, the combination therapy comprises Rina-S in combination with an anti-angiogenic agent, such as an anti-VEGF antibody, such as bevacizumab. In one embodiment, the combination therapy comprises Rina-S in combination with a PARP inhibitor, such as olaparib or niraparib. In one embodiment, the combination therapy comprises Rina-S in combination with a checkpoint inhibitor, such as an inhibitor of the PD-1 or PD-L1 immune checkpoint proteins, such as an anti-PD1 antibody such as pembrolizumab, nivolumab, cemiplimab, dostarlimab, retinfolimab, toripalimab, and the like, or an anti-PD-L1 antibody such as atezolizumab, avelumab, durvalumab, and the like. In certain embodiments, the subjects are treated with Rina-S at a dose level of 100 mg/m². In certain embodiments, the subjects are treated with Rina-S at a dose level of 120 mg/m². In certain embodiments, these dosages are administered to the subjects about every three weeks (Q3W). In certain embodiments, the administration of the Rina-S is via intravenous administration. Dosing and administration regimen of the other therapy in the combinations of the invention is performed according to an approved label of the other respective therapy.

[0019] The invention thus provides various methods for treatment of cancer by administering to a subject Rina-S, optionally in combination with other anti-cancer drugs, as described in the aspects above and below. In alternative aspects, the invention also provides Rina-S, optionally in combination with other anti-cancer drugs, for use in treatment of cancer, according to various aspects of the methods of treatment according to the invention. In other alternative aspects, the invention also provides Rina-S, optionally in combination with other anti-cancer drugs, for manufacturing a medicament for the treatment of cancer, according to various aspects of the methods of treatment according to the invention. In further aspects, the invention further provides an agent for the treatment of cancer comprising Rina-S as an active agent, optionally in combination with other anti-cancer drugs. Where a method of treatment is set out herein, the invention also provides the corresponding product for use in the method, as well as use of the product for the manufacture of a medicament for the stated method and *vice versa*.

[0020] In embodiments set out herein where two drugs are being referred to as administered in

combination, the drugs may be, for instance, administered simultaneously, separately, or sequentially. In one embodiment, administration of drugs in combination may mean that they are both administered in the method provided. The drugs may be administered in the same pharmaceutical composition. Alternatively, the drugs may be administered as separate compositions. Where a regimen is set out herein for the administration of Rina-S, it may be any further drug is administered at the same time point, but in a separate composition. In other embodiments, Rina-S and the second drug may be administered in the same composition. In further embodiments, it may be that Rina-S is administered in the regimen set out herein for it, but the second drug is administered in its own separate regimen.

[0021] Additional features will be set forth in part in the description which follows, and in part will become apparent to those skilled in the art upon examination of the following and the accompanying drawings or may be learned by production or operation of the examples. The features of the present disclosure may be realized and attained by practice or use of various aspects of the methodologies, instrumentalities, and combinations set forth in the detailed examples discussed below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] The present disclosure is further described in terms of exemplary embodiments. These exemplary embodiments are described in detail with reference to the drawings. It should be noted that the drawings are not to scale. These embodiments are non-limiting exemplary embodiments, in which like reference numerals represent similar structures throughout the several views of the drawings, and wherein:

[0023] FIG. 1 is a graph illustrating the study 1 design for the PRO1184-001 drug dosage schedule.

[0024] FIG. 2 is a graph illustrating the change from baseline in target lesion tumor burden.

[0025] FIG. 3 is a graph illustrating the percentage change in tumor size over time for each dose level.

[0026] FIG. 4 is a graph illustrating the reduction in CA-125 (cancer antigen 125) levels per subject.

[0027] FIG. 5 is a graph illustrating treatment emergent adverse events (TEAEs) in the Rina-S 100 mg/m² and Rina-S 120 mg/m² groups.

[0028] FIG. 6 is a graph illustrating best changes in target lesion (best change from baseline in sum of tumor diameter) for ovarian cancer patients and endometrial cancer patients.

[0029] FIG. 7 is a graph illustrating best changes in target lesion (best change from baseline in sum of tumor diameter) for ovarian cancer patients treated with Rina 100 mg/m² or Rina-S 120 mg/m².

[0030] FIG. 8 is a graph illustrating treatment responses for ovarian cancer patients treated with Rina 100 mg/m² or Rina-S 120 mg/m² over time. One patient in the 120 mg/m² cohort with prior mirvetuximab soravtansine was not response-evaluable. Reasons for discontinuation included alanine aminotransferase increased (n=1; not related to treatment), neutrophil count decreased (n=1; related to treatment), small intestinal perforation (n=1; not related to treatment), and rectal hemorrhage (n=1; not related to treatment). CR: complete response, MIRV: mirvetuximab soravtansine, OC: ovarian cancer, PD: progressive disease, PR: partial response, Rina-S: rinatabart sesutecan, SD: stable disease, tx: treatment.

[0031] FIG. 9 is a graph illustrating best changes in target lesion (best change from baseline in sum of tumor diameter) for ovarian cancer patients treated with Rina-S 100 mg/m² or Rina-S 120 mg/m² by FR α PS2+ status. FR α : folate receptor, OC: ovarian cancer, PS: positive staining, SoD: sum of diameter, Rina-S: rinatabart sesutecan.

[0032] FIG. 10A is a graph of cell viability versus drug concentration for human ovarian cancer cell line OVCAR-8 cells treated with either Rina-S alone, Carboplatin alone, or the two in combination. FIG. 10B is a graph of cell viability versus drug concentration for human endometrial carcinoma cells line HEC-1-A cells after treatment with Rina-S alone, Olaparib alone, or the two drugs in combination.

[0033] FIG. 11 provides graphs for various markers following treatment of KB cells (a subline of human HeLa cells) or 3LL-FR- α cells (mouse Lewis Lung Carcinoma cells expressing FR- α) with Exatecan or Rina-S. FIG. 11A to FIG. 11C show results for KB cells treated with Exatecan or Rina-S, with the markers measured being extracellular ATP (FIG. 11A), % cells positive for calreticulum

(FIG. 11B), and HMGB1 levels (FIG. 11C). FIG. 11D to FIG. 11F show the corresponding results for 3LL-FR- α cells.

[0034] FIG. 12 provides graphs of tumor volumes in mouse tumor models treated with Rina-S alone or in combination with various other cancer drugs, namely carboplatin (“+carbo”), bevacizumab (“+Bev”), olaparib (“+PARP”), and CS1003 (an anti PD-1 antibody, “+IO”). The results for a PBS control are also included in each graph. The xenograft cancers involved in each model are the ovarian carcinoma line OVCAR-8 (FIG. 12A and FIG. 12B), the human endometrial carcinoma cells line HEC-1-A (FIG. 12C), mouse 3LL-FR- α Lewis Lung Carcinoma cells (FIG. 12D), and the mouse colon adenocarcinoma cell line MC-38- FR- α (FIG. 12E).

DETAILED DESCRIPTION

[0035] The following description is presented to enable any person skilled in the art to make and use the present disclosure and is provided in the context of a particular application and its requirements. Various modifications to the disclosed embodiments will be readily apparent to those skilled in the art, and the general principles defined herein may be applied to other embodiments and applications without departing from the spirit and scope of the present disclosure. Thus, the present disclosure is not limited to the embodiments shown but is to be accorded the widest scope consistent with the claims.

[0036] The terminology used herein is to describe particular example embodiments only and is not intended to be limiting. As used herein, the singular forms “a,” “an,” and “the” may be intended to include the plural forms as well, unless the context clearly indicates otherwise. It will be further understood that the terms “comprises,” “comprising,” “includes,” and/or “including” when used in this specification, specify the presence of stated features, integers, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof.

[0037] These and other features, and characteristics of the present disclosure, as well as the methods of operation and functions of the related elements of structure and the combination of parts

and economies of manufacture, may become more apparent upon consideration of the following description with reference to the accompanying drawing(s), all of which form a part of this specification. It is to be expressly understood, however, that the drawing(s) is for the purpose of illustration and description only and are not intended to limit the scope of the present disclosure. It is understood that the drawings are not to scale.

[0038] For convenience, certain terms in the specification, examples and claims are defined here. Unless stated otherwise, or implicit from context, the following terms and phrases have the meanings provided below. The definitions are provided to aid in describing particular embodiments, and are not intended to limit the claimed invention, because the scope of the invention is limited only by the claims. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs.

[0039] As used herein and unless otherwise indicated, the terms "a" and "an" are taken to mean "one", "at least one" or "one or more". Unless otherwise required by context, singular terms used herein shall include pluralities and plural terms shall include the singular.

[0040] Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to". Where an embodiment is set out using "comprises", "comprising" or similar wording, the invention also provides embodiments "*consisting essentially of*" what is set out. The invention also provides embodiments "*consisting of*" what is set out.

[0041] The terms "decreased," "reduce," "reduced", "reduction", "decrease," and "inhibit" are all used herein generally to mean a decrease by a statistically significant amount relative to a reference.

[0042] The terms "increased", "increase" or "enhance" or "activate" are all used herein to generally mean an increase by a statically significant amount relative to a reference.

[0043] The term "about", may, for instance, allow up to 10% variation of what is set out. In some embodiments, it may allow for up to 5% variation. In some embodiments, up to 2% variation may

be allowed. In some embodiments up to 1% variation may be allowed. In some embodiments, where the term “about” is used, also provided is an embodiment with exactly what is set out.

[0044] As used herein, the terms "protein" and "polypeptide" are used interchangeably herein to designate a series of amino acid residues each connected to each other by peptide bonds between the alpha-amino and carboxyl groups of adjacent residues. The terms "protein" and "polypeptide" also refer to a polymer of amino acids, including modified amino acids (e.g., phosphorylated, glycosylated, glycosylated, etc.) and amino acid analogs, regardless of its size or function. "Protein" and "polypeptide" are often used in reference to relatively large polypeptides, whereas the term "peptide" is often used in reference to small polypeptides, but usage of these terms in the art overlaps. The terms "protein" and "polypeptide" are used interchangeably herein when referring to an encoded gene product and fragments thereof. Thus, exemplary polypeptides or proteins include gene products, naturally occurring proteins, homologs, orthologs, paralogs, fragments and other equivalents, variants, fragments, and analogs of the foregoing.

[0045] FOLR1, or folate receptor alpha, is a cell surface protein that binds to folate and reduced folic acid derivatives and mediates delivery of 5-methyltetrahydrofolate and folate analogs into the interior of cells. It is also referred to as FR α , adult folate-binding protein, FBP, Folate receptor 1, Folate receptor-adult, KB cells FBP, and ovarian tumor-associated antigen MOv18. Human FOLR1 polypeptides include, but are not limited to, those having the amino acid sequence set forth in UniProt identifier P15328-1; this sequence is incorporated by reference herein.

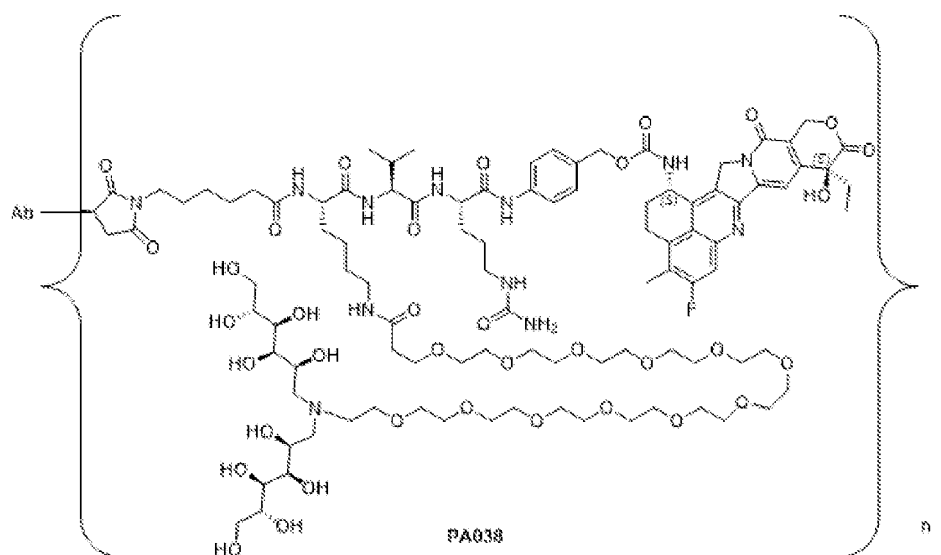
[0046] An antibody drug conjugate (ADC) comprises an antibody conjugated to a drug. The antibody and drug may be conjugated via any suitable means. It may be that the antibody and drug are conjugated via a linker. Alternatively, the antibody and drug may be conjugated directly to each other. The ADCs discussed herein comprise an anti-cancer drug as the drug portion of the ADC.

Antibodies and Antibody-Drug Conjugates (ADCs)

[0047] In one embodiment, the present invention provides a method of treating solid tumor comprising administering to a human subject with a tumor an antibody-drug conjugate (ADC) with

the characteristics described herein comprising an antibody to FOLR1 conjugated via a hydrophilic linker to the drug exatecan, wherein the ADC is administered at a dosage of between 40 mg/m² and 200 mg/m². In certain embodiments the dosage is between 60 mg/m² and 140 mg/m². In certain embodiments the dosage is 100 mg/m². In certain embodiments the dosage is 120 mg/m². In any of the embodiments set out herein, the tumor may be a solid tumor. In any of the embodiments set out herein, the ADC employed may be Rina-S as set out in detail herein. The term “Rina-S” as used herein encompasses embodiments of the ADCs described herein, including a biosimilar of Rina-S.

[0048] Rinatabart sesutecan (Rina-S; sometimes this has also been referred to as PRO1184) as used herein is an antibody-drug conjugate (ADC) that includes an antibody to FOLR1, and exatecan drug units, each of which is connected to the antibody through a hydrophilic linker. In certain embodiments, Rina-S has the following structure (structure 1):



wherein Ab is an antibody that binds to FOLR1 and comprises a heavy chain that comprises three CDRs having the amino acid sequences of the 3 CDRs as present in SEQ ID NO: 1 (respective CDRs underlined in the sequence shown below) and a light chain that comprises three CDRs having the amino acid sequences as present in SEQ ID NO: 2 (respective CDRs underlined in the sequence shown below). In certain embodiments the Ab is an antibody that comprises a heavy chain variable region having an amino acid sequence as set forth in SEQ ID NO: 1 and a light chain variable region

having an amino acid sequence as set forth in SEQ ID NO: 2. In certain embodiments the Ab is an IgG1 antibody. In certain embodiments the Ab is an antibody that comprises a heavy chain having an amino acid sequence as set forth in SEQ ID NO: 6 (or optionally an amino acid sequence further including an additional C-terminal lysine (K), i.e. a heavy chain having an amino acid sequence as set forth in SEQ ID NO: 4) and a light chain having an amino acid sequence as set forth in SEQ ID NO: 5. In structure 1, n is p^{load} , which is the average drug loading (e.g., drug to antibody ratio; or DAR). In certain embodiments n is 8.

[0049] In some embodiments, the ADC comprises an antibody component which comprises an Fc domain or region with one or more amino acid substitutions which diminish IgG Fc receptor (FcγR) binding (as compared to an IgG1 constant region having the amino acid sequence set forth in SEQ ID NO: 3), e.g., substitutions at positions 234 and 235 of the Fc region (EU numbering of residues). In some embodiments, the substitutions are L234A and L235A (LALA), according to the EU number of Kabat. In some alternative forms, the Fc domain may comprise D265A and/or P329G in an Fc region derived from a human IgG1 Fc region, according to the EU numbering of Kabat. In certain embodiments, the substitutions are L234A, L235A and P329G (LALA-PG) in an Fc region derived from a human IgG1 Fc region, according to the EU numbering of Kabat. (See, e.g., WO 2012/130831). In some embodiments, the substitutions are L234A, L235A and D265A (LALA-DA) in an Fc region derived from a human IgG1 Fc region, according to the EU number of Kabat. In certain embodiments, the Ab comprises a light chain constant region of the kappa isotype.

[0050] In some embodiments, the ADC is a biosimilar of Rina-S. The term "biosimilar" (e.g., of an approved reference product/biological drug) as used herein refers to a biologic product that is similar to the reference product based on data from (a) analytical studies demonstrating that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; (b) animal studies (including the assessment of toxicity); and/or (c) a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is approved and intended to be used

and for which approval is sought (e.g., that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product). In some embodiments, the biosimilar biological product and reference product utilizes the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product. In some embodiments, the condition or conditions of use prescribed, recommended, or suggested in the labeling proposed for the biological product have been previously approved for the reference product. In some embodiments, the route of administration, the dosage form, and/or the strength of the biological product are the same as those of the reference product. A biosimilar can be, e.g., a presently known antibody having the same primary amino acid sequence as a marketed antibody, but may be made in different cell types or by different production, purification, or formulation methods. A biosimilar ADC typically is structurally highly similar to the reference product, including the antibody part, the cytotoxic payload, and the linker, but may be produced via slightly different production processes.

[0051] SEQ ID NO: 1 F131 VH amino acid sequence (wherein the three CDRs are indicated by underlining):

EVQLLESGGGVVPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYY
ADSVKGRFTISRANSKNTLYLQMNSLRAEDTAVYYCARPRAYYGAYGSSFDYWGQGTQV
 TVSS

SEQ ID NO: 2 F131 VL amino acid sequence (wherein the three CDRs are indicated by underlining):

EIVMTQSPSSVSASVGDRVAITCRASQGSSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRF
SGSGSGTDFTLTISLQPEDFATYYCQQSYSTPLTFGGGTKVDIK

SEQ ID NO: 3 human IgG1 heavy chain constant region UniProt P01857-1:

ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS

GLYSLSSVVT VPSSSLGTQT YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG
PSVFLFPPKP KDTLMIS RTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA
KTKPREEQYN STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS
KAKGQPREPQ VYTLPPSRDE LTKNQVSLTCLVKGFYPSDI AVEWESNGQP ENNYKTTTPV
LDS DGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK

SEQ ID NO: 4 F131 heavy chain amino acid sequence (including C-terminal K):

EVQLLESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYY
ADSVKGRFTISRANSKNTLYLQMNSLRAEDTAVYYCARPRAYYGAYGSSFDYWGQGTQVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPS
VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDS DGSFFLYSKLTVDKSRWQQGN
VFSCSV MHEALHNHYTQKSLSLSPGK

SEQ ID NO: 5 F131 light chain amino acid sequence:

EIVMTQSPSSVSASVGDRVAITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQSGVPSRFS
GSGSGTDFLTISLQPEDFATYYCQQSYSTPLTFGGGTKVDIKRTVAAPSVFIFPPSDEQLKS
GTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEK
HKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 6 F131 heavy chain amino acid sequence (without C-terminal K):

EVQLLESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYDGSNKYY
ADSVKGRFTISRANSKNTLYLQMNSLRAEDTAVYYCARPRAYYGAYGSSFDYWGQGTQVT
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPS

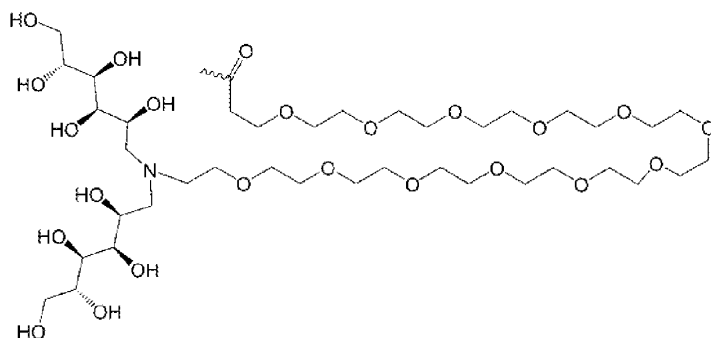
VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST
YRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGN
VFSCSVMHREALHNHYTQKSLSLSPG

[0052] In some embodiments, the heavy chain of the antibody component of Rina-S described herein does not contain a C-terminal lysine at the C-terminus of the CH3 region (i.e., corresponding to the C-terminal lysine at position 453 of SEQ ID NO: 4, or the C-terminal lysine at position 330 of SEQ ID NO: 3). The heavy chain of SEQ ID NO: 4 without the C-terminal lysine is provided as SEQ ID NO: 6. The C-terminal lysine may be removed, for example, by engineering the heavy chain to not contain a C-terminal lysine, or by removing the C-terminal lysine (e.g., with a carboxypeptidase, e.g. during production or processing of the antibody). Accordingly, in some embodiments, the heavy chain of the antibody component of Rina-S has the amino acid sequence of SEQ ID NO: 6. For any of the aspects and embodiments of the invention, the heavy chain of the antibody component may thus comprise either SEQ ID NO: 6 or SEQ ID NO: 4.

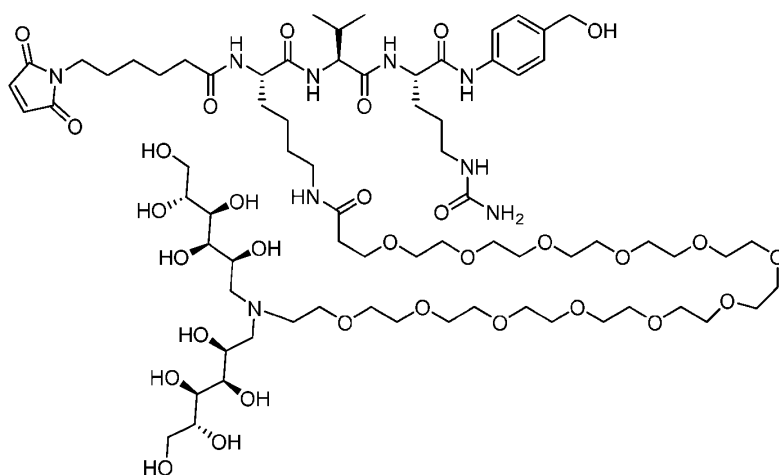
[0053] In some embodiments, the antibody component of Rina-S is the F131 antibody of PCT application WO/2022/217022. WO/2022/217022 is incorporated by reference in its entirety. WO/2022/217022 is also incorporated specifically in relation to the antibodies disclosed therein and in particular in relation to F131 and related antibodies.

[0054] In some embodiments, the average DAR (drug antibody ratio) of Rina-S is about 8. In some embodiments, the average DAR of Rina-S is 8.

[0055] In various embodiments, the present invention concerns treatment of cancer with ADCs provided herein. In some embodiments, the ADC includes the antibody or antibody fragment that comprises VH and VL regions having amino acid sequences that are set forth in SEQ ID NO: 1 and SEQ ID NO: 2. The ADC includes drug units (exatecan). The ADC includes linkers that connect the drug units to the antibody or antibody fragment. In certain embodiments, the linker includes a polar unit having the following structure (structure 2):



[0056] In some embodiments, the linker is derived from a linker compound having the following structure (structure 3):

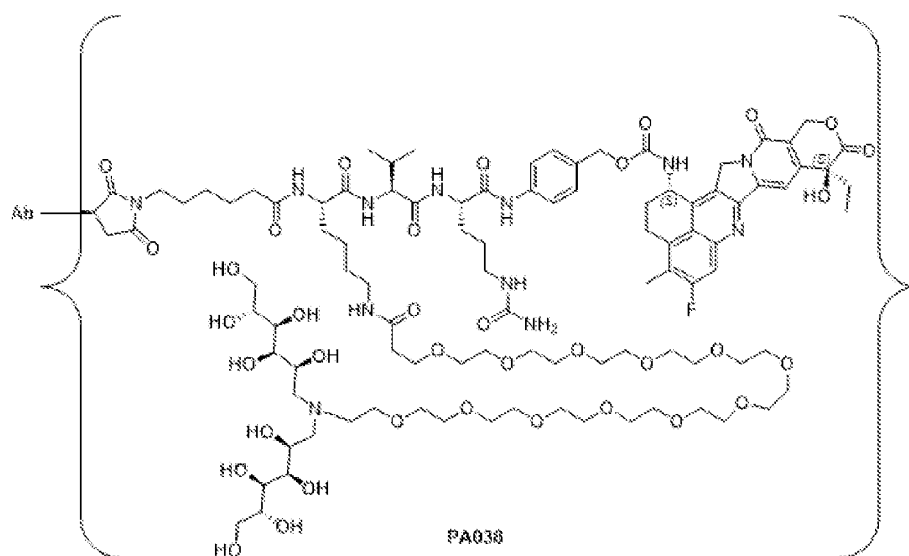


wherein the H on the benzylic OH is optionally replaced with a bond to one of the drug units (exatecan).

[0057] In some embodiments, the ADC of the present invention has an average DAR of about 4, about 6, or about 8. In some embodiments, the ADC has an average DAR of about 8.

[0058] In various embodiments, the present invention concerns treatment of cancer with Rina-S or other ADCs noted above or disclosed in PCT applications WO2023280227 and WO2022217022. Both are disclosed in their entirety and specifically in relation to Rina-S and ADCs.

[0059] In any of the embodiments set out herein, the preferred ADC is Rina-S or a biosimilar thereof. In a particularly preferred embodiment Rina-S (or a biosimilar thereof) has the following structure:



wherein Ab is an antibody that comprises a heavy chain and a light chain that have amino acid sequences that are set forth in SEQ ID NO: 6 and SEQ ID NO: 5, respectively, and wherein n is 8. In one embodiment, the Ab has two such heavy chains of SEQ ID NO: 6 and two such light chains of SEQ ID NO: 5. In certain embodiments, Rina-S may instead of the heavy chain sequence set forth in SEQ ID NO: 6, comprise the heavy chain sequence set forth in SEQ ID NO: 4 (i.e. having the additional C-terminal lysine). In certain embodiments, Rina-S (or a biosimilar thereof) is formulated into a pharmaceutical composition that can be administered to the subject according to the invention, and said pharmaceutical composition may further comprise one or more pharmaceutically acceptable carriers, excipients, and/or diluents.

Patients and cancer types

[0060] In various embodiments, the present invention concerns method of treating cancer, such as but not limited to solid tumor; the method comprises administering to a human subject the ADC Rina-S, wherein the ADC is administered at a dosage of between 40 mg/m² and 200 mg/m². Here, “m²” (square meter) is a measurement of the patient’s body surface area (BSA).

[0061] In some embodiments, the method of the present invention can be used to treat a solid tumor. In some embodiments, the subject has a plurality of solid tumors. In some embodiments, the

subject has a plurality of solid tumors because the cancer has metastasized. In some embodiments, the solid tumor is a primary tumor. In some embodiments, the solid tumor is a secondary tumor. In some embodiments, the subject has a plurality of solid tumors with both the primary solid tumor and secondary solid tumor(s) present. In certain embodiments, the solid tumor is present in a human subject having a cancer selected from the group consisting of: ovarian cancer, endometrial cancer, breast cancer, lung cancer, and mesothelioma. In certain embodiments, the solid tumor is ovarian cancer. In certain embodiments, the solid tumor is platinum-resistant ovarian cancer (PROC). In certain embodiments, the solid tumor is platinum-sensitive ovarian cancer (PSOC). In certain embodiments, the solid tumor may be ovarian epithelial cancer, primary peritoneal cancer, or fallopian tube cancer. In some embodiments, the solid tumor may be a primary peritoneal carcinoma. In some embodiments, the solid tumor may be a fallopian tube cancer. In certain embodiments, the solid tumor may be endometrial cancer. In certain embodiments, the solid tumor may be lung cancer, such as non-small-cell lung cancer (NSCLC). In certain embodiments, the solid tumor may be breast cancer, including HER2-negative breast cancer. In some embodiments, the solid tumor may be a mesothelioma. In certain embodiments, the solid tumor may be pleural mesothelioma or peritoneal mesothelioma. In some embodiments, the methods of the present invention can be used to treat cancer (e.g., solid tumor) that is FOLR1 positive. As used herein, the tumor being “FOLR1 positive” means that at least a portion of the tumor cells are expressing the FOLR1 protein that can be detected by standard methods such as immunohistochemistry (IHC); a cell being “FOLR1 positive” means that the cell is expressing the FOLR1 protein that can be detected by standard methods such as IHC. In certain embodiments, FOLR1 expression in a tumor is determined by applying a regulatory approved test (e.g. an FDA approved Ventana FOLR1-2.1 RxDx Assay, or a local equivalent thereof) on a tumor sample. In some embodiments, at least 10%, 15%, 20%, 25%, 30%, 40%, or 50% of the cells in a sample from the tumor are FOLR1 positive. In certain embodiments, in a sample from the solid tumor of the human subject, at least 25% of cancer cells are FOLR1 positive. In certain embodiments, in a sample from the solid tumor of the human subject, at least 75% of cancer cells are FOLR1 positive. In certain embodiments, in a sample from

the solid tumor of the human subject, less than 75% of cancer cells are FOLR1 positive. In certain embodiments, in a sample from the solid tumor of the human subject, less than 25% of cancer cells are FOLR1 positive. In certain embodiments the tumor in the human subject has high FOLR1 expression, identified as FR α membrane staining intensity $\geq 2+$ ("PS2+") in $\geq 75\%$ of tumor cells in an IHC assay such as the Ventana FOLR1 (FOLR1-2.1) RxDx Assay. In certain embodiments the tumor in the human subject has medium FOLR1 expression, identified as FR α membrane staining intensity $\geq 1+$ ("PS1+") in $\geq 25\%$ of tumor cells and PS2+ in $< 75\%$ of tumor cells in an IHC assay such as the Ventana FOLR1 (FOLR1-2.1) RxDx Assay. In certain embodiments the tumor in the human subject has low FOLR1 expression, identified as PS1+ in $< 25\%$ of tumor cells in an IHC assay such as the Ventana FOLR1 (FOLR1-2.1) RxDx Assay. In certain embodiments, the human subject is treated with Rina-S according to the invention at a time where there has not been a determination of the percentage of cancer cells which are FOLR1 positive in a sample of the solid tumor of the human subject; in certain embodiments thereof, the human subject has an ovarian cancer.

[0062] In some embodiments, the methods of the present invention can be used to treat cancer (e.g., solid tumor) that is localized. In some embodiments, the method of the present invention can be used to treat cancer (e.g., solid tumor) that is metastatic. In some embodiments the patient has an advanced solid tumor. In some embodiments, the patient has a locally advanced tumor. In some embodiments the tumor has spread so that the patient has secondary solid tumors in addition to the primary tumor. In some embodiments, the tumor cannot be removed by surgery, i.e. the tumor is unresectable. In some embodiments, the tumor has both spread (the cancer is metastatic) and at least one solid tumor is present which is unresectable.

[0063] In some embodiments, the subject may have high-grade epithelial ovarian cancer. In some embodiments, the subject may have a high-grade serous ovarian cancer.

[0064] In certain of the embodiments set out herein, the subject may have a tumor that is a platinum-resistant tumor. In some embodiments, the subject may have high-grade serous or endometrioid EOC (epithelial ovarian cancer), primary peritoneal cancer, or fallopian tube cancer,

resistant to platinum chemotherapy. In one preferred embodiment, the subject has platinum-resistant ovarian cancer. Alternatively, the subject may have a tumor that is platinum-sensitive. In some embodiments, the subject may have platinum-sensitive ovarian cancer.

[0065] In some embodiments, the subject to be treated has a histologically or cytologically confirmed metastatic or unresectable solid malignancy. In some embodiments, the subject has ovarian cancer and also epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. In some embodiments, the subject has endometrial cancer. In some embodiments, the subject has non-small cell lung cancer (NSCLC). In some embodiments, the subject has EGFR-mutated NSCLC. In some embodiments, the subject has breast cancer. In some embodiments, the subject has hormone receptor-positive, HER2-negative or triple-negative breast cancer. In some embodiments the subject has mesothelioma. In one embodiment, the cancer is selected from histologically or cytologically confirmed metastatic or unresectable solid malignancy including ovarian cancer (must have epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer), endometrial cancer, non-small cell lung cancer, epidermal growth factor receptor (EGFR)-mutated NSCLC, breast cancer (hormone receptor-positive, HER2-negative and triple-negative), and mesothelioma.

[0066] In some embodiments, the subject to be treated is selected from one with high-grade serious ovarian cancer, primary peritoneal cancer or fallopian tube cancer (in particular excluding endometrioid, clear cell carcinoma, mucinous, low grade, and those with a sarcomatous or neuroendocrine element).

[0067] In one embodiment, the patient has already had their FR α expression status determined, for instance using the Ventana FOLR1-2.1 RxDx Assay. In one embodiment, the patient has high FR α expression (ie, FR α expression $\geq 75\%$ PS2+), for instance as measured using the Ventana FOLR1-2.1 RxDx Assay. In another embodiment, the patient does not have high FR α expression, and in particular has a FR α expression $< 75\%$ PS2+, for instance as measured using the Ventana FOLR1-2.1 RxDx Assay. In further embodiments, the patient has a FR α expression $< 25\%$ PS2+, for instance as measured using the Ventana FOLR1-2.1 RxDx Assay. In certain embodiments, the patient has not already had their FR α expression status determined. In such embodiments the patient may be treated

with Rina-S according to the invention absent predetermination of FR α expression status, e.g. in patients having ovarian cancer.

[0068] In some embodiments, a method of the present invention may comprise a step of determining whether or not the tumor expresses FOLR1. In further embodiments, it may comprise the step of determining the level of expression of FOLR1. In other embodiments, it may not comprise either of those steps. In certain embodiments thereof, the human subject has ovarian cancer. In certain embodiments, the patients have been pretreated with other therapies against the tumor, e.g. with at least 1, 2, 3, 4, or more lines of therapy. In certain embodiments, the patients are treated with the ADC, in particular Rina-S, at a dose level of 100 mg/m². In certain embodiments, the patients are treated with the ADC, in particular Rina-S, at a dose level of or 120 mg/m². In certain embodiments, the dosage is administered to the patients about every three weeks (Q3W). In certain embodiments, the administration of the ADC, in particular Rina-S, is via intravenous administration.

[0069] In some embodiments, whether or not there is FOLR1 expression is not determined beyond determining the presence or absence of any expression of FOLR1. In some embodiments, the level of FOLR1 expression in the solid tumor is not determined at all prior to treatment. For instance, as a large majority of ovarian cancers display FOLR1 expression it may be that a subject with ovarian cancer is simply treated according to the invention without determining the presence, or absence, or level of FOLR1 expression, because of the high chance the tumor will express FOLR1 and also because the exact level of FOLR1 expression may be less important for Rina-S than for other cancer drugs.

[0070] In one embodiment, a patient with one of the recited cancer types herein is treated without any determination of whether or not the solid tumor displays FOLR1 expression. In certain embodiments thereof, the human subject has ovarian cancer. In certain embodiments, the human subjects have been pretreated with other therapies against the tumor, e.g. with at least 1, 2, 3, 4, or more lines of therapy. In certain embodiments, the human subjects are treated with ADC, in particular Rina-S, at a dose level of 100 mg/m². In certain embodiments, the human subjects are

treated with the ADC, in particular Rina-S, at a dose level of or 120 mg/m². In certain embodiments, the dosage is administered to the human subjects about every three weeks (Q3W). In certain embodiments, the administration of the ADC, in particular Rina-S, is via intravenous administration.

Dosages, dosage regimens, routes of administration, and patient assessment

[0071] In some embodiments, the dosage range of the ADCs (e.g., Rina-S) used to treat cancer (e.g., solid tumor) in the present invention may be between 40 mg/m² and 200 mg/m². In some embodiments, the dosage range may be between 60 mg/m² and 180 mg/m². In certain embodiments, the dosages are 40 mg/m², 60 mg/m², 100 mg/m², 120 mg/m², 140 mg/m², or 180 mg/m². In certain embodiments, the dosages may be 60 mg/m²-180 mg/m², 100 mg/m²-140 mg/m², 100 mg/m²-120 mg/m². In certain embodiments, the ADC is administered at a dosage of 140 mg/m². In certain embodiments, the dosage is about 60 mg/m². In certain embodiments, the dosage is about 100 mg/m². In certain embodiments, the dosage is about 120 mg/m². Doses expressed in mg/m² are based on the body surface area (BSA) of the patient which may be calculated by the Mosteller's equation (BSA in m² is $\sqrt{(\text{height (cm)} \times \text{weight (kg)})/3600}$)

[0072] In some embodiments, the ADCs (e.g., Rina-S) may be given either weekly, twice weekly or every other week. The dosing schedule may include treatment cycles of two consecutive weeks of therapy followed by one, two, three or four weeks of rest, or alternating weeks of therapy and rest, or one week of therapy followed by two, three or four weeks of rest, or three weeks of therapy followed by one, two, three or four weeks of rest, or four weeks of therapy followed by one, two, three or four weeks of rest, or five weeks of therapy followed by one, two, three, four or five weeks of rest, or administration once every two weeks, once every three weeks or once a month. Treatment may be extended for any number of cycles, such as at least 2, at least 4, at least 6, at least 8, at least 10, at least 12, at least 16, or at least 20 cycles (e.g., 2-20 cycles, 2-16 cycles, 2-10 cycles, 2-4 cycles, 4-20 cycles, 4-16 cycles, 4-10 cycles, 6-20 cycles, 6-16 cycles, 6-10 cycles, 8-20 cycles, 8-16 cycles, 8-10 cycles, 10-20 cycles, 10-16 cycles, 12-20 cycles, 12-16 cycles, or 16-20 cycles, or more than 20 cycles). In some embodiments, the ADC dosage is administered to the human subject

on Day 1 of a 21-day treatment cycle. In some embodiments, the ADC is administered every 2 to 4 weeks. In some embodiments, the ADC is administered about every 3 weeks. In some embodiments, the ADC is administered every 3 weeks. Dosing every 3 weeks may also be referred to as Q3W.

[0073] In some embodiments, the ADC dosage is administered to the human subject as a 10-minute, 20-minute, 30-minute, 40-minute, 50-minute, 60-minute intravenous (IV) infusion. In some embodiments, the ADC dosage is administered to the human subject as a 30-minute intravenous (IV) infusion.

[0074] In some embodiments, the treatment with the ADC results in a reduction in a size of the solid tumor of at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, or at least 50%. In certain embodiments, the treatment with the ADC results in a reduction in a size of the solid tumor of at least 15%. In certain embodiments, the treatment with the ADC results in a reduction in a size of the solid tumor of at least 20%. In certain embodiments, the treatment with the ADC results in a reduction in a size of the solid tumor of at least 25%. In certain embodiments, the treatment with the ADC results in a reduction in a size of the solid tumor of 15-90%, for example, 15-75%, 15-50%, 15-40%, 15-30%, 30-90%, 30-75%, 30-50%, 30-40%, 40-90%, 40-75%, 40-50%, 50-90%, or 50-75%. The person of ordinary skill will realize that a variety of factors, such as age, general health, specific organ function or weight, as well as effects of prior therapy on specific organ systems may be considered in selecting an optimal dosage of ADC, and that the dosage and/or frequency of administration may be increased or decreased during the course of therapy.

[0075] In some embodiments, the treatments of the present invention result in an improved treatment outcome for the subject. Such is especially the case when the human subject has failed a previous treatment. In certain embodiments, the improved treatment outcome is an objective response selected from stable disease, a partial response, or a complete response. In certain embodiments, the improved treatment outcome is a stable disease, indicating the progression of the solid tumor has been halted. In certain embodiments, the improved treatment outcome is a partial response. In certain embodiments, the partial response indicates that the solid tumor size has been reduced by at least 20%, at least 25%, at least 30%, at least 40%, or at least 50%. In certain

embodiments, the partial response indicates that the solid tumor size has been reduced by at least 30%. As discussed further below, the RECIST ver 1.1 criteria may be used to assess tumor size and in one embodiment, the partial response indicates that the solid tumor size has been reduced by at least 20%, at least 25%, at least 30%, at least 40%, or at least 50% according to those criteria. In one embodiment, it has been reduced by at least 30% according to those criteria. In certain embodiments, the improved treatment outcome is a complete response. In certain embodiments, the complete response indicates that there is no detectable cancer. In certain embodiments, the improved treatment outcome is reduced tumor burden. In certain embodiments, the reduce tumor burden indicates a reduction of the solid tumor size by at least 20%, at least 25%, at least 30%, at least 40%, or at least 50%. In certain embodiments, the improved treatment outcome is progression-free survival or disease-free survival. In certain embodiments, the progression-free survival or disease-free survival is assessed after 1, 2, 3, 4, 5, or 10 years.

[0076] Any appropriate approach may be used to assess tumors and the treatment. In some embodiments the treatment is assessed per RECIST v1.1. In embodiments, where the cancer is pleural mesothelioma treatment may be assessed using mRECIST v1.1. The RECIST ver 1.1 criteria were published by Eisenhauer *et al* in the European Journal of Cancer (2009) 228-247 and may be used to define the degree of response. Eisenhauer *et al* is incorporated in its entirety and specifically in relation to the RECIST ver 1.1 criteria. In some embodiments, Best Overall Response (BOR) may be assessed. In some embodiments, overall response rate (ORR) may be assessed. In some embodiments Disease Control Rate (DCR) may be assessed. In some embodiments, Progression Free Survival time (PFS) may be assessed. In some embodiments, Overall Survival may be assessed. In some embodiments, the Duration of Objective Response (DOR) may be assessed.

[0077] The optimized dosages and schedules of administration disclosed herein show unexpected superior efficacy and reduced toxicity in human subjects, which could not have been predicted from animal model studies. The superior efficacy allows the treatment of tumors that were previously found to be resistant to one or more standard anti-cancer therapies.

[0078] Generally, the dosage of an administered ADC (e.g., Rina-S) for human subjects can be

varied depending upon such factors as the patient's age, weight, height, sex, general medical condition and previous medical history. As discussed above, dosages of Rina-S may vary from 40 mg/m² to 200 mg/m², 60 mg/m² to 180 mg/m², 100 mg/m² -140 mg/m², 100 mg/m² -120 mg/m², or about 60 mg/m², about 100 mg/m², or about 120 mg/m². In certain embodiments, Rina-S is administered IV on Day 1 of a 21-day cycle and may be continued until disease progression, unacceptable toxicity, or other reasons for treatment discontinuation. Dose-limiting toxicities were observed at the 140 mg/m² and 180 mg/m² dose levels and were all hematologic cytopenias. The schedule of administration may comprise administration once or twice a week, on a cycle selected from the group consisting of: (i) weekly; (ii) every other week; (iii) one week of therapy followed by two, three or four weeks off; (iv) two weeks of therapy followed by one, two, three or four weeks off; (v) three weeks of therapy followed by one, two, three, four or five week off; (vi) four weeks of therapy followed by one, two, three, four or five week off; (vii) five weeks of therapy followed by one, two, three, four or five week off; and (viii) monthly. The cycle may be repeated 2, 4, 6, 8, 10, 12, 16 or 20 times. The treatment with the ADC results in a reduction in a size of the solid tumor of at least 15%, at least 20%, at least 30%, at least 40%, or at least 50%.

[0079] In some embodiments, the subjects that are treated with the ADC Rina-S according to the present invention have previously been treated with other lines of therapy, e.g. 1, 2, 3, 4, 5, 6, or 7 prior other cancer therapies. In certain embodiments, a subject having ovarian cancer that is treated with the ADC Rina-S according to the present invention has been previously treated with one or more of bevacizumab, PARP inhibitor, platinum-based chemotherapy (e.g. cisplatin, carboplatin, oxaliplatin), and/or mirvetuximab soravtansine. In certain embodiments, a subject having endometrial cancer that is treated with the ADC Rina-S according to the present invention has been previously treated with a PD-1 inhibitor (e.g. pembrolizumab).

[0080] In one embodiment, the present invention provides a method of treating a solid tumor comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every three weeks (Q3W) to about every six weeks (Q6W), and the solid

tumor is folate receptor 1 (FOLR1) positive.

[0081] In one embodiment in such a method, the doses are administered every 3 weeks (Q3W). In another embodiment, they are administered every 4 weeks (Q4W). In another embodiment, they are administered every 5 weeks (Q5W). In another embodiment, they are administered every 6 weeks (Q6W).

[0082] In one embodiment, the present invention provides a method of treating a solid tumor comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every three weeks (Q3W) to about every six weeks (Q6W), and the solid tumor is folate receptor 1 (FOLR1) positive.

[0083] In a further embodiment, the present invention provides a method of treating a solid tumor comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered every three weeks (Q3W) to every six weeks (Q6W), and the solid tumor is folate receptor 1 (FOLR1) positive.

[0084] In one embodiment, the present invention provides a method of treating a solid tumor comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every three weeks (Q3W), and the solid tumor is folate receptor 1 (FOLR1) positive.

[0085] In one embodiment, the present invention provides a method of treating a solid tumor comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every three weeks (Q3W), and the solid tumor is folate receptor 1 (FOLR1) positive.

[0086] Such regimens may in particular be administered to a human subject having ovarian cancer. In one embodiment, they may be administered to a human subject having platinum-resistant ovarian

cancer. In an alternative embodiment, they may be administered to a human subject having platinum-sensitive ovarian cancer. In further embodiments, they may be administered to a human subject having endometrial cancer.

[0087] In one embodiment, the present invention provides a method of treating ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every three weeks (Q3W) to about every six weeks (Q6W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0088] In one embodiment, the present invention provides a method of treating ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every three weeks (Q3W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0089] In one embodiment, the present invention provides a method of treating ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every three weeks (Q3W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0090] In one embodiment, the present invention provides a method of treating platinum-resistant ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every three weeks (Q3W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0091] In one embodiment, the present invention provides a method of treating platinum-resistant ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every three weeks (Q3W), and the ovarian cancer is folate receptor 1

(FOLR1) positive.

[0092] In one embodiment, the present invention provides a method of treating platinum-sensitive ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every three weeks (Q3W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0093] In one embodiment, the present invention provides a method of treating platinum-sensitive ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every three weeks (Q3W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0094] In one embodiment, the present invention provides a method of treating endometrial cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every three weeks (Q3W), and the endometrial cancer is folate receptor 1 (FOLR1) positive.

[0095] In one embodiment, the present invention provides a method of treating endometrial cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every three weeks (Q3W), and the endometrial cancer is folate receptor 1 (FOLR1) positive.

[0096] In other embodiments, dosing about every 3 weeks (Q3W) is employed in the treatment of breast cancer. Hence, further embodiments employing Q3W in relation to breast cancer are set out below.

[0097] In one embodiment, the present invention provides a method of treating breast cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120

mg/m² administered about every three weeks (Q3W) to about every six weeks (Q6W), and the breast cancer is folate receptor 1 (FOLR1) positive.

[0098] In one embodiment, the present invention provides a method of treating breast cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every three weeks (Q3W), and the breast cancer is folate receptor 1 (FOLR1) positive.

[0099] In one embodiment, the present invention provides a method of treating breast cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every three weeks (Q3W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0100] In other embodiments, dosing about every 3 weeks (Q3W) is employed in the treatment of non-small-cell lung carcinoma (NSCLC) cancer. Hence, further embodiments, employing Q3W in treating NSCLC are set out below.

[0101] In one embodiment, the present invention provides a method of treating NSCLC cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every three weeks (Q3W) to about every six weeks (Q6W), and the NSCLC cancer is folate receptor 1 (FOLR1) positive.

[0102] In one embodiment, the present invention provides a method of treating NSCLC cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every three weeks (Q3W), and the NSCLC cancer is folate receptor 1 (FOLR1) positive.

[0103] In one embodiment, the present invention provides a method of treating NSCLC cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC)

rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every three weeks (Q3W), and the NSCLC cancer is folate receptor 1 (FOLR1) positive.

[0104] In other embodiments, dosing about every 3 weeks (Q3W) is employed in the treatment of mesothelioma. Hence, further embodiments, employing Q3W in treating mesothelioma are set out below.

[0105] In one embodiment, the present invention provides a method of treating mesothelioma comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every three weeks (Q3W) to about every six weeks (Q6W), and the mesothelioma is folate receptor 1 (FOLR1) positive.

[0106] In one embodiment, the present invention provides a method of treating mesothelioma comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every three weeks (Q3W), and the mesothelioma is folate receptor 1 (FOLR1) positive.

[0107] In one embodiment, the present invention provides a method of treating mesothelioma comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every three weeks (Q3W), and the mesothelioma is folate receptor 1 (FOLR1) positive.

Combination therapies

[0108] In some embodiments of the methods of the present invention, the ADC may be used alone or as a combination therapy with one or more therapeutic modalities selected from the group consisting of unconjugated antibodies, radiolabeled antibodies, drug-conjugated antibodies, toxin-conjugated antibodies, gene therapy, chemotherapy, therapeutic peptides, cytokine therapy,

oligonucleotides, localized radiation therapy, surgery and interference RNA therapy.

[0109] In one embodiment, where the ADC is used in combination with another drug it may be that they are administered simultaneously, it may be that ADC and further drug are given simultaneously, separately, or sequentially. In one embodiment, they may be given in the same pharmaceutical composition. In an alternative embodiment, the ADC and further drug may be given in separate compositions. In one embodiment, although the ADC and further drug are administered separately, it may be that they are packaged together, for instance in the form of a kit comprising both. In one embodiment, an ADC for use in a method as set out herein is provided. In an alternative embodiment, the invention provides the further drug for use in a method as set out herein wherein the ADC is also administered. Various regimens are set out herein involving administration of an ADC as described herein and the invention provides such regimens where the second drug is administered as part of the regimen. It may be, for instance, that the second drug is administered as the same time as the ADC. Alternatively, the further drug may be administered according to the standard regimen for that drug. The present invention also provides regimens which alternate administration of the ADC with the further drug.

[0110] In some embodiments, the ADC may be used in combination with a platinum-based chemotherapy drug. Examples of such drugs include cisplatin, carboplatin, and oxaliplatin. In some embodiments, the ADC may be used in combination with carboplatin.

[0111] In some embodiments, the ADC may be used in combination with a drug that is a VEGF inhibitor. In some embodiments, the ADC is used in combination with bevacizumab.

[0112] In some embodiments, the ADC may be used in combination with an immuno-oncology therapy agent. In some embodiments, the ADC may be used in combination with a drug that inhibits PD-1. Non-limiting examples of a drug that inhibits PD-1 include pembrolizumab, nivolumab, nofazinlimab, and cemiplimab. In some embodiments, the ADC may be used in combination with pembrolizumab. In some embodiments, the ADC may be used in combination with nofazinlimab. In some embodiments, the ADC may be used in combination with pembrolizumab. In some embodiments, the ADC may be used in combination with a drug that inhibits PD-L1. Non-limiting

examples of a drug that inhibits PD-1 include atezolizumab, avelumab, and durvalumab.

[0113] In some embodiments, the ADC may be used in combination with a drug that is a PARP inhibitor. In some embodiments, the ADC is used in combination with olaparib.

[0114] In preferred embodiments, the ADC may be of use for treatment of cancers for which standard therapies are not effective, such as ovarian cancer, endometrial cancer, breast cancer, lung cancer, and mesothelioma. More preferably, the combination of ADC and other therapeutic modality is more efficacious than either alone, or the sum of the effects of individual treatments. In one embodiment, a combination is synergistic.

[0115] In one embodiment, an ADC as set out herein may be used in combination with olaparib. In one embodiment, the ADC is Rina-S. In certain embodiments, the human subject has endometrial adenocarcinoma. In certain embodiments, the human subjects have been pretreated with other therapies against the tumor, e.g. with at least 1, 2, 3, 4, or more lines of therapy. In certain embodiments, the human subjects are treated with Rina-S at a dose level of 100 mg/m². In certain embodiments, the human subjects are treated with Rina-S at a dose level of or 120 mg/m². In certain embodiments, the dosage is administered to the human subjects about every three weeks (Q3W). In certain embodiments, the administration of the Rina-S is via intravenous administration.

[0116] In one embodiment, an ADC as set out herein may be used in combination with carboplatin. In one embodiment, the ADC is Rina-S. In certain embodiments, the human subject has endometrial adenocarcinoma. In certain embodiments, the human subjects have been pretreated with other therapies against the tumor, e.g. with at least 1, 2, 3, 4, or more lines of therapy. In certain embodiments, the human subjects are treated with Rina-S at a dose level of 100 mg/m². In certain embodiments, the human subjects are treated with Rina-S at a dose level of or 120 mg/m². In certain embodiments the dosage is administered to the human subjects about every three weeks (Q3W). In certain embodiments, the administration of the Rina-S is via intravenous administration.

[0117] In one embodiment, an ADC as set out herein may be used in combination with carboplatin when treating ovarian cancer. In one embodiment, the ADC is Rina-S. In certain embodiments, the human subjects have been pretreated with other therapies against the tumor, e.g. with at least 1, 2, 3,

4, or more lines of therapy. In certain embodiments, the human subjects are treated with Rina-S at a dose level of 100 mg/m². In certain embodiments, the human subjects are treated with Rina-S at a dose level of or 120 mg/m². In certain embodiments, the dosage is administered to the human subjects about every three weeks (Q3W). In certain embodiments, the administration of the Rina-S is via intravenous administration.

[0118] In one embodiment, an ADC as set out herein may be used in combination with bevacizumab. In one embodiment, the ADC is Rina-S. In certain embodiments, the human subject has endometrial adenocarcinoma. In certain embodiments, the human subjects have been pretreated with other therapies against the tumor, e.g. with at least 1, 2, 3, 4, or more lines of therapy. In certain embodiments, the human subjects are treated with Rina-S at a dose level of 100 mg/m². In certain embodiments, the human subjects are treated with Rina-S at a dose level of or 120 mg/m². In certain embodiments, the dosage is administered to the human subjects about every three weeks (Q3W). In certain embodiments, the administration of the Rina-S is via intravenous administration.

[0119] In one embodiment, an ADC as set out herein may be used in combination with bevacizumab to treat ovarian cancer. In one embodiment, the ADC is Rina-S. In certain embodiments, the human subject has endometrial adenocarcinoma. In certain embodiments, the human subjects have been pretreated with other therapies against the tumor, e.g. with at least 1, 2, 3, 4, or more lines of therapy. In certain embodiments, the human subjects are treated with Rina-S at a dose level of 100 mg/m². In certain embodiments, the human subjects are treated with Rina-S at a dose level of or 120 mg/m². In certain embodiments, the dosage is administered to the human subjects about every three weeks (Q3W). In certain embodiments, the administration of the Rina-S is via intravenous administration.

[0120] In one embodiment, an ADC as set out herein may be used in combination with immunotherapy. In one embodiment, the ADC is Rina-S. In certain embodiments, the human subject has endometrial adenocarcinoma. In certain embodiments, the human subjects have been pretreated with other therapies against the tumor, e.g. with at least 1, 2, 3, 4, or more lines of therapy. In certain embodiments, the human subjects are treated with Rina-S at a dose level of 100 mg/m². In certain

embodiments, the human subjects are treated with Rina-S at a dose level of or 120 mg/m^2 . In certain embodiments, the dosage is administered to the human subjects about every three weeks (Q3W). In certain embodiments, the administration of the Rina-S is via intravenous administration.

[0121] In one embodiment, an ADC as set out herein may be used in combination with immunotherapy. In one embodiment, the ADC is Rina-S. In certain embodiments, the human subject has ovarian cancer. In certain embodiments, the human subjects have been pretreated with other therapies against the tumor, e.g. with at least 1, 2, 3, 4, or more lines of therapy. In certain embodiments, the human subjects are treated with Rina-S at a dose level of 100 mg/m^2 . In certain embodiments, the human subjects are treated with Rina-S at a dose level of or 120 mg/m^2 . In certain embodiments, the dosage is administered to the human subjects about every three weeks (Q3W). In certain embodiments, the administration of the Rina-S is via intravenous administration.

[0122] In one embodiment, an ADC as set out herein may be used in combination with an anti-PD-1 antibody. In one embodiment, the ADC is Rina-S. In certain embodiments, the human subject has endometrial adenocarcinoma. In certain embodiments, the human subjects have been pretreated with other therapies against the tumor, e.g. with at least 1, 2, 3, 4, or more lines of therapy. In certain embodiments, the human subjects are treated with Rina-S at a dose level of 100 mg/m^2 . In certain embodiments, the human subjects are treated with Rina-S at a dose level of or 120 mg/m^2 . In certain embodiments, the dosage is administered to the human subjects about every three weeks (Q3W). In certain embodiments, the administration of the Rina-S is via intravenous administration.

[0123] In one embodiment, an ADC as set out herein may be used in combination with an anti-PD-1 antibody to treat ovarian cancer. In one embodiment, the ADC is Rina-S. In certain embodiments, the human subjects have been pretreated with other therapies against the tumor, e.g. with at least 1, 2, 3, 4, or more lines of therapy. In certain embodiments, the human subjects are treated with Rina-S at a dose level of 100 mg/m^2 . In certain embodiments, the human subjects are treated with Rina-S at a dose level of or 120 mg/m^2 . In certain embodiments, the dosage is administered to the human subjects about every three weeks (Q3W). In certain embodiments, the administration of the Rina-S is via intravenous administration.

Patient groups and histories

[0124] The human subject has previously been treated with at least one anti-cancer therapy. In one embodiment, the subject may previously have been treated with at least one anti-cancer therapy that was not effective in treating the cancer. In one embodiment, the subject may previously have been treated with at least one anti-cancer therapy that was initially effective, but which now has reduced or no efficacy. In some embodiments, the subject may have become resistant to the previous therapy when it is administered on its own.

[0125] In some embodiments, the human subject has previously been treated with 1 to 4 anti-cancer therapies. In some embodiments, the at least one anti-cancer therapy includes treatment with a chemotherapeutic agent. In some embodiments, the at least one anti-cancer therapy includes treatment with at least one anti-cancer therapy selected from the group consisting of platinum chemotherapy, bevacizumab, poly ADP-ribose polymerase (PARP) inhibitor, and mirvetuximab soravtansine. The human subject has failed to respond to the at least one anti-cancer therapy prior to treatment of the ADC.

[0126] In some embodiments, the subject to be treated is selected from one with high-grade serious ovarian cancer, primary peritoneal cancer or fallopian tube cancer (in particular excluding endometrioid, clear cell carcinoma, mucinous, low grade, and those with a sarcomatous or neuroendocrine element). In some embodiments, the subject is selected from a subject with such a solid tumor and the subject has received 1 to 3 lines of therapy with a different anti-cancer therapy (prior induction plus maintenance is considered 1 line of therapy, even if parts of the treatment regimen, induction or maintenance, are interrupted and/or resumed at a later date, in the absence of disease progression while on active treatment – a switch/change in regimen due solely to toxicity or participant preference, and not disease progression is not considered a separate line of therapy). In some embodiments, where, the cancer is ovarian cancer, it is platinum-resistant/refractory ovarian cancer. In some embodiments, the subject has received prior bevacizumab. In some embodiments, the subject has breast cancer with known or suspected deleterious germline or somatic BRCA

mutations (e.g. as determined by an FDA-approved test) and has been treated with a poly ADP-ribose polymerase (PARP) inhibitor. In some embodiments, the subject has an FR α status based on an FDA approved test (e.g. the Ventana FOLR1 RxDx Assay) – subjects who are FR α positive may have previously received mirvetuximab soravtansine, (MIRV). In some embodiments, the subjects are FR α positive but not eligible for treatment by MIRV, e.g. because the FR α expression is too low. In some embodiments, the subject is treated according to the invention when the FR α expression level of the tumor in the subject has not been determined by a regulatory (e.g. FDA-) approved test. In some embodiments, whether or not the tumor expresses FR α is not determined. For example, it may be that a high proportion of that cancer will express FR α so it is not considered necessary to determine the presence of FR α or at least it is not considered necessary to determine the level of FR α expression. In one embodiment, the cancer in such embodiments is ovarian cancer.

[0127] In some embodiments, the subject has platinum-sensitive ovarian cancer (PSOC) and has received 1 to 3 prior lines of therapy, in particular where the prior lines of therapy are with a platinum-based chemotherapeutic.

[0128] In some embodiments, the subject has platinum-resistant or platinum-refractory cancer. In some embodiments, the subject will have high grade serous or endometrioid EOC, primary peritoneal cancer, or fallopian tube cancer, resistant to platinum chemotherapy. In some embodiments, the subject will have platinum-resistant or platinum-refractory cancer, wherein the subject has received prior platinum chemotherapy drug-based therapy. In some embodiments, the subject will have received 1 to 2 prior lines of such therapy. In some embodiments, the subject will have endometrial cancer and in particular any subtype of endometrial cancer excluding sarcoma. In some embodiments, the subject will have such endometrial cancer and have received prior platinum-based chemotherapy for recurrent or advanced disease. In some embodiments, for any of the subjects mentioned in this paragraph they will not have any of the following: (i) another malignancy within 3 years; (ii) Active central nervous system (CNS) metastases (treated, stable CNS metastases are allowed); (iii) Uncontrolled Grade 3 or greater infection within 2 weeks of commencing treatment; (iv) testing positive for hepatitis B virus (HBV), hepatitis C virus (HCV) or human

immunodeficiency virus (HIV); (v) a history of (non-infectious) interstitial lung disease (ILD)/pneumonitis that required steroids within the past 2 years, has current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening; (v) use of a strong CYP3A inhibitor within 14 days (dose escalation only); or (vi) Prior therapy with a topoisomerase 1 inhibitor-based antibody drug conjugate.

[0129] In one embodiment, the subject will have histologically or cytologically confirmed high-grade serous or endometrioid epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. In one embodiment, such a subject will have received 1 to 4 prior lines of therapy. In one preferred embodiment the patient will have received at least one of:

- a) Platinum chemotherapy
- b) Bevacizumab, unless the patient has a documented contraindication
- c) A poly ADP-ribose polymerase (PARP) inhibitor (for patients with known or suspected deleterious germline or somatic BRCA mutations)
- d) Mirvetuximab soravtansine, if:
 - i. Mirvetuximab soravtansine is available in the enrollment region, and
 - ii. the patient is eligible based on positive FR α expression per an FDA-approved (or local equivalent) test, and
 - iii. the patient does not have a documented medical exception, including chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring, such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic retinopathy with macular edema, macular degeneration, presence of papilledema, and/or monocular vision.

[0130] In one embodiment, a subject that has only had one line of platinum-based therapy will have received at least 4 cycles of platinum therapy, and must have either had a response (complete response [CR] or partial response [PR]) or had non-measurable disease at the start of platinum-based therapy, and then progressed between > 91 days and $\leq$ 183 days after the date of the last dose of

platinum. In a further embodiment, patients who have received 2 to 4 lines of platinum-based therapy will have progressed on or within 183 days after the date of the last dose of platinum.

[0131] In one embodiment, the subject will not have one or more of the following exclusion criteria (particularly where the subject is being treated for PROC):

- Prior therapy with an antibody-drug conjugate containing a topoisomerase 1 inhibitor.
- Have primary platinum-refractory disease, defined as ovarian cancer that did not respond (CR or PR) to or progressed $\leq$ 91 days after the last dose of a first-line platinum-containing regimen.
- History of another malignancy within 3 years before the first dose of Rina-S, or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (e.g., 5-year OS $\geq$ 90%), including, but not limited to, adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, ductal carcinoma in situ, or Stage I uterine cancer.
- Known active central nervous system metastases or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are clinically stable for at least 4 weeks prior to study entry after brain metastasis treatment, they have no new or enlarging brain metastases, and are off corticosteroids and anticonvulsants prescribed for symptoms associated with brain metastases for at least 7 days prior to the first dose of study drug. Patients with suspected brain metastases at screening may undergo a computed tomography (CT)/magnetic resonance imaging (MRI) of the brain prior to study entry.
- Hospitalization or clinical symptoms due to gastrointestinal obstruction within the past 91 days or radiographic evidence of gastrointestinal obstruction at the time of screening. Enrollment of patients who currently require parenteral nutrition must be discussed with the study medical monitor to determine eligibility.

- Ascites requiring frequent paracentesis (more often than approximately every 4 weeks) for symptomatic management. Enrollment of patients with an indwelling peritoneal catheter must be discussed with the medical monitor to determine eligibility.

[0132] In one embodiment, the subject may have a particular level of FR α expression, for instance as measured by the Ventana FOLR1-2.1 RxDx Assay. In one embodiment, the subject has a tumor that does not have high FR α expression per the Ventana FOLR1-2.1 RxDx Assay (or local equivalent test), for instance the patient may have a FR α expression of <75% PS2+. In one embodiment, the subject has an FR α expression of <25% PS2+. In one embodiment, the subject has a tumor that does have high FR α expression per the Ventana FOLR1-2.1 RxDx Assay and in particular a FR α expression level of $\geq$ 75% PS2+. In one embodiment, the subject has a FR α expression level of $\geq$ 75% PS2+ per the Ventana FOLR1-2.1 RxDx Assay and not have previously received mirvetuximab soravtansine.

[0133] In one embodiment, the subject has a tumor with FR α expression and is further defined by whether the subject has been previously treated with mirvetuximab soravtansine. In one embodiment, the subject is mirvetuximab soravtansine naïve and FR α expression non-high [ie, <75% PS2+]. In one embodiment, the subject is mirvetuximab soravtansine naïve and FR α expression high [i.e., $\geq$ 75% PS2+]. In one embodiment, the subject has been mirvetuximab soravtansine-treated previously.

[0134] In one embodiment, the subject will have received 1 to 4 prior lines of therapy, which must include platinum-based chemotherapy, bevacizumab, and/or mirvetuximab soravtansine.

Further embodiments

[0135] The following section sets out a number of illustrative embodiments.

[0136] In one embodiment, the present invention provides a method of treating epithelial ovarian cancer, endometrial cancer, breast cancer, non-small cell lung cancer, and mesothelioma, the method comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC)

rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of from 40 mg/m² to 200 mg/m², and the solid tumor is folate receptor 1 (FOLR1) positive. In one embodiment, the dosage is from about 100 mg/m² to about 140 mg/m². In one embodiment, the dosage is from about 110 mg/m² to about 130 mg/m². In one embodiment, the dosage is about 120 mg/m².

[0137] In one embodiment, the present invention provides a method of treating a subject with high grade serous or endometrioid EOC, primary peritoneal cancer, or fallopian tube cancer, resistant to platinum chemotherapy comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of from 40 mg/m² to 200 mg/m², and the solid tumor is folate receptor 1 (FOLR1) positive. In one embodiment, the dosage is from about 100 mg/m² to about 140 mg/m². In one embodiment, the dosage is from about 110 mg/m² to about 130 mg/m². In one embodiment, the dosage is about 120 mg/m².

[0138] In one embodiment, the present invention employs about 4 weekly dosing. In one embodiment, 4 weekly dosing (Q4W) is employed. Hence, further embodiments employing Q4W are set out below.

[0139] In one embodiment, the present invention further provides a method of treating a solid tumor comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² about every four weeks (Q4W), and the solid tumor is folate receptor 1 (FOLR1) positive.

[0140] In one embodiment, the present invention provides a method of treating ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every four weeks (Q4W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0141] In one embodiment, the present invention provides a method of treating ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC)

rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every four weeks (Q4W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0142] In one embodiment, the present invention provides a method of treating ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every four weeks (Q4W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0143] In one embodiment, the present invention provides a method of treating platinum-resistant ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 100 mg/m² administered about every four weeks (Q4W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0144] In one embodiment, the present invention provides a method of treating platinum resistant ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every four weeks (Q4W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0145] In one embodiment, the present invention provides a method of treating platinum sensitive ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every four weeks (Q4W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0146] In one embodiment, the present invention provides a method of treating platinum sensitive ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every four weeks (Q4W), and the ovarian cancer is folate receptor 1

(FOLR1) positive.

[0147] In one embodiment, the present invention provides a method of treating endometrial cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every four weeks (Q4W), and the endometrial cancer is folate receptor 1 (FOLR1) positive.

[0148] In one embodiment, the present invention provides a method of treating endometrial cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every four weeks (Q4W), and the endometrial cancer is folate receptor 1 (FOLR1) positive.

[0149] In one embodiment, the present invention provides a method of treating endometrial cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every four weeks (Q4W), and the endometrial is folate receptor 1 (FOLR1) positive.

[0150] In one embodiment, the present invention employs about 5 weekly dosing. In one embodiment, 5 weekly dosing (Q5W) is employed. Hence, further embodiments employing Q5W are set out below.

[0151] In one embodiment, the present invention further provides a method of treating a solid tumor comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² about every five weeks (Q5W), and the solid tumor is folate receptor 1 (FOLR1) positive.

[0152] In one embodiment, the present invention provides a method of treating ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120

mg/m² administered about every five weeks (Q5W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0153] In one embodiment, the present invention provides a method of treating ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every five weeks (Q5W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0154] In one embodiment, the present invention provides a method of treating ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every five weeks (Q5W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0155] In one embodiment, the present invention provides a method of treating platinum resistant ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 100 mg/m² administered about every five weeks (Q5W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0156] In one embodiment, the present invention provides a method of treating platinum resistant ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every five weeks (Q5W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0157] In one embodiment, the present invention provides a method of treating platinum sensitive ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every five weeks (Q5W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0158] In one embodiment, the present invention provides a method of treating platinum sensitive ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every five weeks (Q5W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0159] In one embodiment, the present invention provides a method of treating endometrial cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every five weeks (Q5W), and the endometrial cancer is folate receptor 1 (FOLR1) positive.

[0160] In one embodiment, the present invention provides a method of treating endometrial cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every five weeks (Q5W), and the endometrial cancer is folate receptor 1 (FOLR1) positive.

[0161] In one embodiment, the present invention provides a method of treating endometrial cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every five weeks (Q5W), and the endometrial is folate receptor 1 (FOLR1) positive.

[0162] In one embodiment, the present invention employs about 6 weekly dosing. In one embodiment, 6 weekly dosing (Q6W) is employed. Hence, further embodiments employing Q6W are set out below.

[0163] In one embodiment, the present invention further provides a method of treating a solid tumor comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² about every six weeks (Q6W), and the solid tumor is folate receptor 1 (FOLR1) positive.

[0164] In one embodiment, the present invention provides a method of treating ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every six weeks (Q6W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0165] In one embodiment, the present invention provides a method of treating ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every six weeks (Q6W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0166] In one embodiment, the present invention provides a method of treating ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every six weeks (Q6W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0167] In one embodiment, the present invention provides a method of treating platinum resistant ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 100 mg/m² administered about every six weeks (Q6W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0168] In one embodiment, the present invention provides a method of treating platinum resistant ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every six weeks (Q6W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0169] In one embodiment, the present invention provides a method of treating platinum sensitive ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug

conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every six weeks (Q6W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0170] In one embodiment, the present invention provides a method of treating platinum sensitive ovarian cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every six weeks (Q6W), and the ovarian cancer is folate receptor 1 (FOLR1) positive.

[0171] In one embodiment, the present invention provides a method of treating endometrial cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every six weeks (Q6W), and the endometrial cancer is folate receptor 1 (FOLR1) positive.

[0172] In one embodiment, the present invention provides a method of treating endometrial cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every six weeks (Q6W), and the endometrial cancer is folate receptor 1 (FOLR1) positive.

[0173] In one embodiment, the present invention provides a method of treating endometrial cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every six weeks (Q6W), and the endometrial cancer is folate receptor 1 (FOLR1) positive.

[0174] The present invention may also be employed in the treatment of breast cancer.

[0175] In one embodiment, the present invention employs about 4 weekly dosing in the treatment of breast cancer. In one embodiment, 4 weekly dosing (Q4W) is employed in the treatment of breast cancer. Hence, further embodiments employing Q4W dosing in relation to breast cancer are set out

below.

[0176] In one embodiment, the present invention provides a method of treating breast cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every four weeks (Q4W), and the breast cancer is folate receptor 1 (FOLR1) positive.

[0177] In one embodiment, the present invention provides a method of treating breast cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every four weeks (Q4W), and the breast cancer is folate receptor 1 (FOLR1) positive.

[0178] In one embodiment, the present invention provides a method of treating breast cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every four weeks (Q4W), and the breast cancer is folate receptor 1 (FOLR1) positive.

[0179] In one embodiment, the present invention employs about 5 weekly dosing in the treatment of breast cancer. In one embodiment, 5 weekly dosing (Q4W) is employed in the treatment of breast cancer. Hence, further embodiments employing Q4W dosing in relation to breast cancer are set out below.

[0180] In one embodiment, the present invention provides a method of treating breast cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every five weeks (Q5W), and the breast cancer is folate receptor 1 (FOLR1) positive.

[0181] In one embodiment, the present invention provides a method of treating breast cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC)

rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every five weeks (Q5W), and the breast cancer is folate receptor 1 (FOLR1) positive.

[0182] In one embodiment, the present invention provides a method of treating breast cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every five weeks (Q5W), and the breast cancer is folate receptor 1 (FOLR1) positive.

[0183] In one embodiment, the present invention employs about 6 weekly dosing in the treatment of breast cancer. In one embodiment, 6 weekly dosing (Q6W) is employed in the treatment of breast cancer. Hence, further embodiments employing Q6W dosing in relation to breast cancer are set out below.

[0184] In one embodiment, the present invention provides a method of treating breast cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every six weeks (Q6W), and the breast cancer is folate receptor 1 (FOLR1) positive.

[0185] In one embodiment, the present invention provides a method of treating breast cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every six weeks (Q6W), and the breast cancer is folate receptor 1 (FOLR1) positive.

[0186] In one embodiment, the present invention provides a method of treating breast cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every six weeks (Q6W), and the breast cancer is folate receptor 1 (FOLR1) positive.

[0187] The present invention may also be employed in the treatment of NSCLC cancer.

[0188] In one embodiment, the present invention employs about 4 weekly dosing in the treatment of NSCLC cancer. In one embodiment, 4 weekly dosing (Q4W) is employed in the treatment of NSCLC cancer. Hence, further embodiments employing Q4W dosing in relation to NSCLC cancer are set out below.

[0189] In one embodiment, the present invention provides a method of treating NSCLC cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every four weeks (Q4W), and the NSCLC cancer is folate receptor 1 (FOLR1) positive.

[0190] In one embodiment, the present invention provides a method of treating NSCLC cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every four weeks (Q4W), and the NSCLC cancer is folate receptor 1 (FOLR1) positive.

[0191] In one embodiment, the present invention provides a method of treating NSCLC cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every four weeks (Q4W), and the NSCLC cancer is folate receptor 1 (FOLR1) positive.

[0192] In one embodiment, the present invention employs about 5 weekly dosing in the treatment of NSCLC cancer. In one embodiment, 5 weekly dosing (Q4W) is employed in the treatment of NSCLC cancer. Hence, further embodiments employing Q4W dosing in relation to NSCLC cancer are set out below.

[0193] In one embodiment, the present invention provides a method of treating NSCLC cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120

mg/m² administered about every five weeks (Q5W), and the NSCLC cancer is folate receptor 1 (FOLR1) positive.

[0194] In one embodiment, the present invention provides a method of treating NSCLC cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/ m² administered about every five weeks (Q5W), and the NSCLC cancer is folate receptor 1 (FOLR1) positive.

[0195] In one embodiment, the present invention provides a method of treating NSCLC cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/ m² administered about every five weeks (Q5W), and the NSCLC cancer is folate receptor 1 (FOLR1) positive.

[0196] In one embodiment, the present invention employs about 6 weekly dosing in the treatment of NSCLC cancer. In one embodiment, 6 weekly dosing (Q6W) is employed in the treatment of NSCLC cancer. Hence, further embodiments employing Q6W dosing in relation to NSCLC cancer are set out below.

[0197] In one embodiment, the present invention provides a method of treating NSCLC cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every six weeks (Q6W), and the NSCLC cancer is folate receptor 1 (FOLR1) positive.

[0198] In one embodiment, the present invention provides a method of treating NSCLC cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/ m² administered about every six weeks (Q6W), and the NSCLC cancer is folate receptor 1 (FOLR1) positive.

[0199] In one embodiment, the present invention provides a method of treating NSCLC cancer

comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every six weeks (Q6W), and the NSCLC cancer is folate receptor 1 (FOLR1) positive.

[0200] The present invention may also be employed in the treatment of mesothelioma.

[0201] In one embodiment, the present invention employs about 4 weekly dosing in the treatment of mesothelioma. In one embodiment, 4 weekly dosing (Q4W) is employed in the treatment of mesothelioma. Hence, further embodiments employing Q4W dosing in relation to mesothelioma are set out below.

[0202] In one embodiment, the present invention provides a method of treating mesothelioma comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every four weeks (Q4W), and the mesothelioma is folate receptor 1 (FOLR1) positive.

[0203] In one embodiment, the present invention provides a method of treating mesothelioma comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every four weeks (Q4W), and the mesothelioma is folate receptor 1 (FOLR1) positive.

[0204] In one embodiment, the present invention provides a method of treating mesothelioma comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every four weeks (Q4W), and the mesothelioma is folate receptor 1 (FOLR1) positive.

[0205] In one embodiment, the present invention employs about 5 weekly dosing in the treatment of mesothelioma. In one embodiment, 5 weekly dosing (Q5W) is employed in the treatment of mesothelioma. Hence, further embodiments employing Q5W dosing in relation to mesothelioma are

set out below.

[0206] In one embodiment, the present invention provides a method of treating mesothelioma comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every five weeks (Q5W), and the mesothelioma is folate receptor 1 (FOLR1) positive.

[0207] In one embodiment, the present invention provides a method of treating mesothelioma comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every five weeks (Q5W), and the mesothelioma is folate receptor 1 (FOLR1) positive.

[0208] In one embodiment, the present invention provides a method of treating mesothelioma comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every five weeks (Q5W), and the mesothelioma is folate receptor 1 (FOLR1) positive.

[0209] In one embodiment, the present invention employs about 6 weekly dosing in the treatment of mesothelioma. In one embodiment, 6 weekly dosing (Q6W) is employed in the treatment of mesothelioma. Hence, further embodiments employing Q6W dosing in relation to mesothelioma are set out below.

[0210] In one embodiment, the present invention provides a method of treating mesothelioma comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² to 120 mg/m² administered about every six weeks (Q6W), and the mesothelioma is folate receptor 1 (FOLR1) positive.

[0211] In one embodiment, the present invention provides a method of treating NSCLC cancer comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC)

rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 100 mg/m² administered about every six weeks (Q6W), and the NSCLC cancer is folate receptor 1 (FOLR1) positive.

[0212] In one embodiment, the present invention provides a method of treating mesothelioma comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of 120 mg/m² administered about every six weeks (Q6W), and the NSCLC cancer is folate receptor 1 (FOLR1) positive.

Further numbered embodiments

The following represent numbered embodiments of the invention:

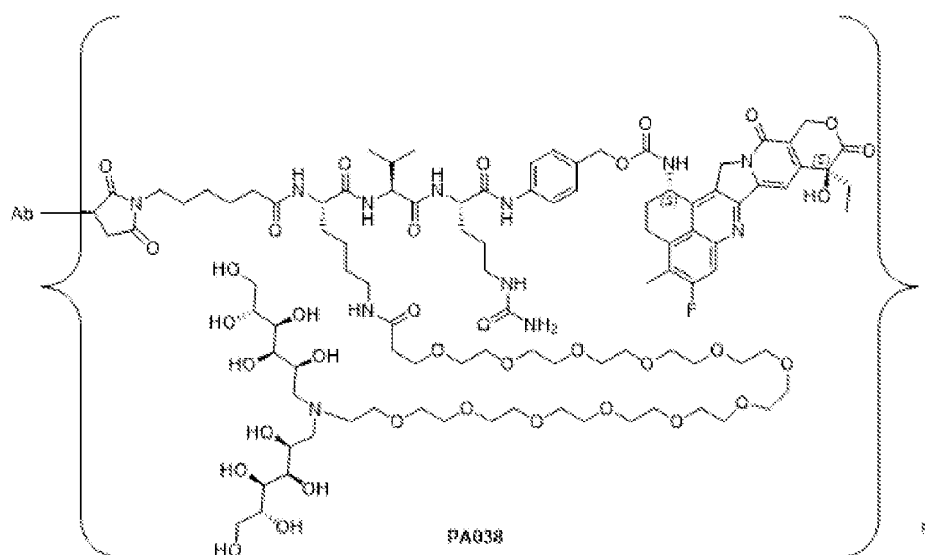
1. A method of treating a solid tumor comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S), wherein the ADC is administered at a dosage of between 40 mg/m² and 200 mg/m², and the solid tumor is folate receptor 1 (FOLR1) positive.
2. The method of [1], wherein the solid tumor is selected from the group consisting of: ovarian cancer, endometrial cancer, breast cancer, lung cancer, and mesothelioma.
3. The method of [1], wherein the solid tumor is ovarian epithelial cancer, primary peritoneal cancer, or fallopian tube cancer.
4. The method of [1], wherein the solid tumor is endometrial cancer.
5. The method of [1], wherein the solid tumor is non-small-cell lung cancer (NSCLC).
6. The method of [1], wherein the solid tumor is breast cancer, including HER2-negative breast cancer.
7. The method of [1], wherein the solid tumor is pleural mesothelioma or peritoneal mesothelioma.
8. The method of [1], wherein the solid tumor is a platinum resistant tumor.

9. The method of [8], wherein the solid tumor is a high grade serous or endometrioid EOC, primary peritoneal cancer, or fallopian tube cancer, resistant to platinum chemotherapy.
10. The method of any one of [1]- [7], wherein the solid tumor is localized or metastatic.
11. The method of any one of [1]-[10], wherein at least one tumor is not removable by surgery.
12. The method of any one of [1]-[11], wherein the ADC is administered at a dosage of between 60 mg/m² and 180 mg/m².
13. The method of any one of [1]-[11], wherein the ADC is administered at a dosage of between 100 mg/m² and 140 mg/m².
14. The method of any one of [1]-[11], wherein the ADC is administered at a dosage of between 100 mg/m² and 120 mg/m².
15. The method of any one of [1]-[11], wherein the ADC is administered at a dosage of about 120 mg/m².
16. The method of any one of [1]-[15], wherein the ADC dosage is administered to the human subject once or twice a week on a schedule with a cycle selected from the group consisting of: (i) weekly; (ii) every other week; (iii) one week of therapy followed by two, three or four weeks off; (iv) two weeks of therapy followed by one, two, three or four weeks off; (v) three weeks of therapy followed by one, two, three, four or five weeks off; (vi) four weeks of therapy followed by one, two, three, four or five weeks off; (vii) five weeks of therapy followed by one, two, three, four or five weeks off; and (viii) monthly.
17. The method of any one of [1]-[15], wherein the ADC dosage is administered to the human subject once a week on a schedule with a cycle selected from the group consisting of: (i) weekly; (ii) every other week; (iii) one week of therapy followed by two, three or four weeks off.
18. The method of any one of [16]-[17], wherein the cycle is repeated 2, 4, 6, 8, 10, 12, 16 or 20 times.
19. The method of any one of [1]-[18], wherein the human subject has previously been treated with at least one anti-cancer therapy.
20. The method of [19], wherein the at least one anti-cancer therapy includes treatment with a chemotherapeutic agent.

21. The method of any one of [19]-[20], wherein the human subject has failed to respond to the at least one anti-cancer therapy prior to treatment of the ADC.
22. The method of any one of [1]-[21], wherein the treatment with the ADC results in a reduction in a size of the solid tumor of at least 15%, at least 20%, at least 30%, at least 40%, or at least 50%.
23. The method of any one of [1]-[22], wherein the ADC is administered in combination with one or more therapeutic modalities selected from the group consisting of unconjugated antibodies, radiolabeled antibodies, drug-conjugated antibodies, toxin-conjugated antibodies, gene therapy, chemotherapy, therapeutic peptides, cytokine therapy, oligonucleotides, localized radiation therapy, surgery and interference RNA therapy.
24. The method of any one of [1]-[23], wherein the ADC is administered in combination with a platinum-based chemotherapy.
25. The method of [24], wherein the ADC is administered in combination with carboplatin.
26. The method of any one of [1]-[23], wherein the ADC is administered in combination with a VEGF antagonist-based chemotherapy.
27. The method of [26], wherein the ADC is administered in combination with bevacizumab.
28. The method of any one of [1]-[23], wherein the ADC is administered in combination with a PD-1 inhibitor.
29. The method of [28], wherein the ADC is administered in combination with pembrolizumab.
30. The method of any of [1] to [29], wherein a treatment outcome of the subject is improved.
31. The method of [30], wherein the improved treatment outcome is an objective response selected from stable disease, a partial response or a complete response.
32. The method of [31], wherein the improved treatment outcome is reduced tumor burden.
33. The method of [31], wherein the improved treatment outcome is progression-free survival or disease-free survival.
34. The method of any one of [1] to [15], wherein the ADC dosage is administered to the human subject every three weeks.

35. A method of treating a solid tumor comprising administering to a human subject with a solid tumor an antibody-drug conjugate (ADC) rinatabart sesutecan (Rina-S) and either one of: (i) a platinum-based chemotherapy, (ii) an anti-angiogenic agent, (iii) a PARP inhibitor, or (iv) an immune checkpoint inhibitor.
36. The method of [35] comprising administering to the human subject Rina-S and a platinum-based chemotherapy.
37. The method of [36] wherein the platinum-based chemotherapy is chosen from carboplatin, cisplatin, and oxaliplatin.
38. The method of [37] wherein the platinum-based chemotherapy is carboplatin.
39. The method of [35] comprising administering to the human subject Rina-S and an anti-angiogenic agent.
40. The method of [39] wherein the anti-angiogenic agent is an anti-VEGF antibody.
41. The method of [40] wherein the anti-VEGF antibody is bevacizumab.
42. The method of [35] comprising administering to the human subject Rina-S and a PARP inhibitor.
43. The method of [42] wherein the PARP inhibitor is olaparib.
44. The method of [35] comprising administering to the human subject Rina-S and an immune checkpoint inhibitor.
45. The method of [44] wherein the immune checkpoint inhibitor is an inhibitor of the PD-1 or PD-L1 immune checkpoint proteins.
46. The method of [45] wherein the immune checkpoint inhibitor is an anti-PD-1 antibody.
47. The method of [46] wherein the anti-PD-1 antibody is chosen from the group consisting of pembrolizumab, nivolumab, cemiplimab, dostarlimab, retinofanlimab, and toripalimab.
48. The method of [47] wherein the anti-PD-1 antibody is pembrolizumab.
49. The method of [45] wherein the immune checkpoint inhibitor is an anti-PD-L1 antibody.
50. The method of [49] wherein the anti-PD-L1 antibody is chosen from the group consisting of atezolizumab, avelumab, and durvalumab.

51. The method of any one of [35]-[50], wherein the Rina-S is administered at a dosage of between 60 mg/m² and 180 mg/m².
52. The method of any one of [35]-[50], wherein the Rina-S is administered at a dosage of between about 100 mg/m² and about 140 mg/m².
53. The method of any one of [35]-[50], wherein the Rina-S is administered at a dosage of 100 mg/m².
54. The method of any one of [35]-[50], wherein the Rina-S is administered at a dosage of 120 mg/m².
55. The method of any one of [1]-[54], wherein the Rina-S is administered to the subject by intravenous administration.
56. The method of any one of [35]-[55], wherein the Rina-S is administered to the subject every three weeks (Q3W).
57. The method of any one of [35]-[43] or any one of [51]-[56], wherein the human subject has ovarian cancer.
58. The method of any one of [35]-[56], wherein the human subject has endometrial cancer.
59. The method of [35] or of any one of [44]-[56], wherein the subject has lung cancer.
60. The method of [35] or of any one of [44]-[56], wherein the subject has colorectal cancer.
61. A method for treating a solid tumor, the method comprising administering to a human subject with the solid tumor an antibody-drug conjugate (ADC), wherein the ADC has the structure (structure 1):



wherein Ab is a folate receptor 1 (FOLR1)-binding antibody that comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH and VL regions has amino acid sequences that are set forth in SEQ ID NO: 1 and SEQ ID NO: 2, respectively, and wherein n is 8, and wherein the ADC is administered at a dosage of between 40 mg/m² and 200 mg/m².

62. A method of treating cancer that comprises a solid tumor, the method comprising administering to a human subject having cancer an antibody-drug conjugate (ADC) having structure 1 wherein Ab is a FOLR1-binding antibody that comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH and VL regions has amino acid sequences that are set forth in SEQ ID NO: 1 and SEQ ID NO: 2, respectively, and wherein n is 8, and wherein the ADC is administered at a dosage of between 40 mg/m² and 200 mg/m².

63. An ADC having structure 1 wherein Ab is a FOLR1-binding antibody that comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH and VL regions has amino acid sequences that are set forth in SEQ ID NO: 1 and SEQ ID NO: 2, respectively, and wherein n is 8, for use in a method of treating a solid tumor, the method comprising administering to a human subject with the solid tumor the ADC at a dosage of between 40 mg/m² and 200 mg/m².

64. An ADC having structure 1 wherein Ab is a FOLR1-binding antibody that comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH and VL regions has amino acid sequences that are set forth in SEQ ID NO: 1 and SEQ ID NO: 2, respectively, and wherein n is 8, for use in a method of treating a cancer that comprises a solid tumor, the method comprising administering to a human subject having the cancer the ADC at a dosage of between 40 mg/m² and 200 mg/m².

65. Use of an ADC having structure 1 wherein Ab is a FOLR1-binding antibody that comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH and VL regions has amino acid sequences that are set forth in SEQ ID NO: 1 and SEQ ID NO: 2, respectively, and wherein n is 8, for the manufacture of a medicament for treatment of a solid tumor, wherein the medicament is for administration to a human subject with the solid tumor at a dosage of the ADC of between 40 mg/m² and 200 mg/m².

66. Use of an ADC having structure 1 wherein Ab is a FOLR1-binding antibody that comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH and VL regions has amino acid

sequences that are set forth in SEQ ID NO: 1 and SEQ ID NO: 2, respectively, and wherein n is 8, for the manufacture of a medicament for treatment of a cancer that comprises a solid tumor, wherein the medicament is for administration to a human subject with the cancer at a dosage of the ADC of between 40 mg/m² and 200 mg/m².

67. The method, the ADC for use in a method, or the use according to any one of [61]-[66], wherein the solid tumor is folate receptor 1 (FOLR1) positive.

68. The method, the ADC for use in a method, or the use according to [67], wherein prior to administering the ADC to the human subject, it has been determined that the solid tumor is FOLR1 positive by a regulatory approved test.

69. The method, the ADC for use in a method, or the use according to any one of [61]-[66], wherein there has not been a step to determine FOLR1 expression levels prior to administering the ADC to the human subject.

70. The method, the ADC for use in a method, or the use according to any one of [61]-[69], wherein the ADC is administered at dosage of between 60 mg/m² and 140 mg/m².

71. The method, the ADC for use in a method, or the use according to any one of [61]-[70], wherein the ADC is administered at dosage of 100 mg/m².

72. The method, the ADC for use in a method, or the use according to any one of [61]-[70], wherein the ADC is administered at dosage of 120 mg/m².

73. The method, the ADC for use in a method, or the use according to any one of [61]-[72], wherein the human subject has a cancer selected from the group consisting of: ovarian cancer, endometrial cancer, breast cancer, lung cancer, and mesothelioma.

74. The method, the ADC for use in a method, or the use according to any one of [61]-[73], wherein the human subject has ovarian cancer.

75. The method, the ADC for use in a method, or the use according to [74], wherein the subject has platinum-resistant ovarian cancer (PROC).

76. The method, the ADC for use in a method, or the use according to [74], wherein the subject has platinum-sensitive ovarian cancer (PSOC).

77. The method, the ADC for use in a method, or the use according to any one of [61]-[73], wherein the human subject has endometrial cancer.
78. The method, the ADC for use in a method, or the use according to any one of [61]-[77], wherein the ADC is administered to the subject every three weeks (Q3W).
79. The method, the ADC for use in a method, or the use according to any one of [61]-[78], wherein the Ab is an IgG1 antibody comprising an Fc domain with one or more amino acid substitutions which diminish IgG Fc receptor (FcγR) binding as compared to an IgG1 constant region having the amino acid sequence set forth in SEQ ID NO: 3.
80. The method, the ADC for use in a method, or the use according to [79], wherein the antibody comprises substitutions L234A and L235A (LALA), according to the EU numbering of Kabat.
81. The method, the ADC for use in a method, or the use according to any one of [61]-[80], wherein the Ab comprises a heavy chain comprising SEQ ID NO: 6 and a light chain comprising SEQ ID NO: 5.
82. The method, the ADC for use in a method, or the use according to any one of [61]-[80], wherein the Ab comprises a heavy chain comprising SEQ ID NO: 4 and a light chain comprising SEQ ID NO: 5.
83. The method, the ADC for use in a method, or the use according to any one of [61]-[82], wherein the method further comprises administering to the human subject either one of: (i) a platinum-based chemotherapy, (ii) an anti-angiogenic agent, (iii) a PARP inhibitor, or (iv) a checkpoint inhibitor, or wherein the use is for manufacture of a medicament for administration to the human subject of the ADC and further administration to the human subject either one of: (i) a platinum-based chemotherapy, (ii) an anti-angiogenic agent, (iii) a PARP inhibitor, or (iv) an immune checkpoint inhibitor.
84. The method, the ADC for use in a method, or the use according to [83], wherein the method further comprises administering carboplatin to the human subject, or wherein the use is for manufacture of a medicament for administration to the human subject of the ADC and carboplatin.
85. The method, the ADC for use in a method, or the use according to [83], wherein the method further comprises administering bevacizumab to the human subject, or wherein the use is for manufacture of a medicament for administration to the human subject of the ADC and bevacizumab.

86. The method, the ADC for use in a method, or the use according to [83], wherein the method further comprises administering olaparib to the human subject, or wherein the use is for manufacture of a medicament for administration to the human subject of the ADC and olaparib.

87. The method, the ADC for use in a method, or the use according to [83], wherein the method further comprises administering an anti-PD-1 or anti-PD-L1 antibody to the human subject, or wherein the use is for manufacture of a medicament for administration to the human subject of the ADC and an anti-PD-1 or anti-PD-L1 antibody.

EXAMPLES

- [0213] Abbreviations
- [0214] CNS: central nervous system
- [0215] HIV: human immunodeficiency virus
- [0216] IHC: immunohistochemistry
- [0217] EOC: epithelial ovarian cancer
- [0218] FR α : folate receptor α (also “FOLR1”)
- [0219] HER2: human epidermal growth factor receptor 2
- [0220] HR: hormone receptor
- [0221] NSCLC: non-small cell lung cancer
- [0222] RECIST: response evaluation criteria in solid tumors
- [0223] TRAE: treatment related adverse event
- [0224] ECOG: Eastern Cooperative Oncology Group

Example 1: Recruitment of patients for the study 1

[0225] Table 1 shows the inclusion and exclusion criteria for subjects. Twenty-three patients have been treated with Rina-S. Table 2 shows patient disposition and demographics.

Table 1: Inclusion and Exclusion criteria (Part A only)

Inclusion Criteria	Exclusion Criteria
- Adults with confirmed metastatic/unresectable solid tumor of one of the following types: ➤ Ovarian: epithelial, primary peritoneal, or fallopian tube cancer ➤ Endometrial cancer ➤ Breast cancer (excluding HER2+) ➤ NSCLC ➤ Mesothelioma (pleural or peritoneal) - Previously received all therapies known to confer clinical benefit - Measurable disease per RECIST 1.1 - Willing to provide pre-treatment tumor specimen (archival or fresh biopsy) for FOLR1 expression testing - Patients enrolled in Part B must have FOLR1 expression in $\geq 25\%$ of tumor cells with at least 1+ intensity by IHC.	- History of another malignancy within 3 years - Known active CNS metastases - HIV infection, active hepatitis B or hepatitis C infection

Table 2: Patient Disposition and Demographics (All Treated Patients)

	Rina-S dose level					
	60	100	120	140	180	Total

	mg/m² (N=4)	mg/m²	mg/m² (N=14)	mg/m² (N=1)	mg/m² (N=4)	(N=23)
Age, median (range) (years)	59.5 (51,73)	N/A	66.5 (52,87)	52.0 (52,52)	57.0 (43,67)	66.0 43,87)
Gender, female, n (%)	4 (100.0)	N/A	12 (85.7)	1 (100.0)	4 (100.0)	21 (91.3)
Race, n (%)^a	-	-	-	-	-	-
White	3 (75.0)	N/A	11 (78.6)	0	4 (100.0)	18 (78.3)
Asian	1 (25.0)	N/A	2 (14.3)	0	0	3 (13.0)
Black or African-American	0	N/A	1 (7.1)	0	0	1 (4.3)
Other	0	N/A	0	1 (100.0)	0	1 (4.3)
ECOG PS, n (%)	-	-	-	-	-	-
0	3 (75.0)	N/A	2 (14.3)	0	1 (25.0)	6 (26.1)
1	1 (25.0)	N/A	12 (85.7)	1 (100.0)	3 (75.0)	17 (73.9)

[0226] The total number of subjects was 23 with an age range of 43-87 years. Of these, 21 were female, 18 were white, 3 were Asian, 1 was black or African-American, and 1 was of others. Table 3 shows the patient baseline characteristics.

Table 3: Patient Baseline Disease Characteristics (All Treated Patients)

	Rina-S dose level					
	60 mg/m² (N=4)	100 mg/m²	120 mg/m² (N=14)	140 mg/m² (N=1)	180 mg/m² (N=4)	Total (N=23)
Tumor type, n (%)	-	-	-	-	-	-
Ovarian cancer	3 (75.0)	N/A	9 (64.3)	1 (100.0)	0	13 (56.5)

Endometrial cancer	1 (25.0)	N/A	2 (14.3)	0	3 (75.0)	6 (26.1)
Breast cancer	0	N/A	0	0	1 (25.0)	1 (4.3)
NSCLC	0	N/A	2 (14.3)	0	0	2 (8.7)
Mesothelioma	0	N/A	1 (7.1)	0	0	1 (4.3)
Prior systemic therapies, n	4	N/A	13	0	3	20
All patients, median (range)	7.5 (3,9)	N/A	4.0 (1,13)	NA	3 (3,4)	4.0 (1,13)
Ovarian cancer	N/A	N/A	N/A	N/A	N/A	N/A
Bevacizumab	N/A	N/A	N/A	N/A	N/A	N/A
PARP inhibitors	N/A	N/A	N/A	N/A	N/A	N/A
Endometrial cancer	N/A	N/A	N/A	N/A	N/A	N/A

Example 2: Safety, tolerability and maximum tolerated dose (MTD) testing of Rina- S

[0227] The goal of this study 1 is to determine the safety, tolerability and maximum tolerated dose (MTD) of rinatabart sesutecan (Rina-S; PRO1184).

[0228] FIG. 1 shows the study 1 design for the PRO1184-001 drug dosage schedule. Part A (dose escalation) included five tumor types. Part B (dose expansion) included four tumor specific cohorts and one basket cohort. Incremental doses of Rina-S were administered to 5 different cancer patients over 21 days, ranging from 60 mg/m², to 180 mg/m² at the end of the maximum therapeutic dose. Four tumor-specific cohorts and one basket cohort (ovarian cancer) were included in the study 1.

[0229] Safety assessments include physical examination, vital signs and body measurements, standard clinical laboratory assessments such as hematology, blood biochemistry, and monitoring of adverse events and serious adverse events. Table 4 shows the summary of safety data.

Table 4: Summary of Safety Data

	Rina-S dose level									
	60 mg/m ² (N=4)		100 mg/m ²		120 mg/m ² (N=14)		140 mg/m ² (N=1)		180 mg/m ² (N=4)	
Grade	Any	≥3	Any	≥3	Any	≥3	Any	≥3	Any	≥3
Any TRAE	3 (75.0)	0	N/A	N/A	10 (71.4)	4 (28.6)	0	0	4 (100.0)	1 (25.0)
Most common^a TRAEs	-	-	-	-	-	-	-	-	-	-
Nausea	2 (50.0)	0	N/A	N/A	6 (42.9)	0	0	0	1 (25.0)	0
Fatigue	0	0	N/A	N/A	3 (21.4)	0	0	0	2 (50.0)	0
Anemia	0	0	N/A	N/A	2 (14.3)	1 (7.1)	0	0	2 (50.0)	2 (50.0)
Neutropenia	0	0	N/A	N/A	3 (21.4)	3 (21.4)	0	0	1 (25.0)	1 (25.0)
Neutrophil count decreased	0	0	N/A	N/A	2 (14.3)	1 (7.1)	0	0	2 (50.0)	2 (50.0)
Diarrhea	1 (25)	0	N/A	N/A	1	0	0	0	1	0

					(7.1)				(25.0)	
Thrombocytopenia	0	0	N/A	N/A	2 (14.3)	2 (14.3)	0	0	1 (25.0)	1 (25.0)

[0230] Rina-S was well tolerated at least up to 120 mg/m² (140 mg/m² is under evaluation), with common adverse events including hematologic cytopenias, gastrointestinal adverse events and fatigue. Most TRAEs were mild or moderate. Grade $\geq$ 3 treatment related adverse events occurred in 8 (34.8%) patients. Treatment-related Serious Adverse Events (SAEs) occurred in 3 patients and were all cytopenias. Dose-limiting toxicities were observed at the 140 mg/m² and 180 mg/m² dose levels and were all hematologic cytopenias. No interstitial lung disease/pneumonitis, infusion-related reactions, keratopathy was observed.

[0231] The most common treatment-related adverse events (AEs) were nausea (n=5), decreased white blood cell counts (n=3), and fatigue, decreased lymphocyte counts, and decreased neutrophil counts (n=2 each); most events were Grade 1 or 2. Treatment-related $\geq$ Grade 3 hematologic AEs were reported for 2 patients treated at 120 mg/m². No ocular toxicity or interstitial lung disease was observed. No DLTs were observed.

Example 3: Determination of anti-tumor activity of Rina-S in the study 1

[0232] Fifteen patients with at least one post-baseline scan tumor assessment. Ten patients were considered efficacy evaluable (had a baseline scan and at least 1 post-baseline tumor assessment). Treatment duration ranged from 0.6 weeks to 31.0 weeks. Seventeen of 23 patients remain on treatment. FIG. 2 shows the best change from baseline in target lesion tumor burden: ovarian and endometrial cancer. FIG. 3 shows the percentage change in tumor size over time: ovarian and endometrial cancer. FIG. 4 shows the reduction in CA-125 levels.

[0233] The overall response rate was 20.0% (95% CI: 2.5, 55.6), with 2 patients with partial response (including 1 confirmed response) and 4 patients with stable disease. Anti-tumor responses appeared to deepen over time.

[0234] Rina- S showed encouraging antitumor activity across FOLR1 expression levels in this heavily pretreated patient population and most patients had a reduction in target lesion.

[0235] Antitumor activity was observed at both dose levels and in patients with high, medium, and low FOLR1 expression, including an ongoing confirmed partial response in a patient with endometrial cancer and decreased tumor measurements in additional patients.

Example 4: Recruitment of patients for the study 2

[0236] Approximately 530 patients with platinum resistant ovarian cancer (PROC) across approximately 90 global sites were randomized. The inclusion and exclusion criteria for subjects are as shown below.

[0237] Key Inclusion Criteria

- Patients must have histologically or cytologically confirmed high grade serous or endometrioid epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer.
- Patients must have received 1 to 4 prior lines of therapy.
- Patients must have received prior treatment with at least 1 of the following therapies:
 - Platinum chemotherapy
 - Bevacizumab, unless the patient has a documented contraindication
 - Patients with known or suspected deleterious germline or somatic BRCA mutations must have been treated with a poly ADP-ribose polymerase (PARP) inhibitor
 - Mirvetuximab soravtansine, if:
 - Mirvetuximab soravtansine is available in the enrollment region, and
 - The patient is eligible based on positive FR α expression per an FDA-approved (or local equivalent) test, and
 - The patient does not have a documented medical exception, including chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment/monitoring, such as uncontrolled glaucoma, wet age-related macular degeneration requiring intravitreal injections, active diabetic

retinopathy with macular edema, macular degeneration, presence of papilledema, and /or monocular vision.

NOTE: Diagnostic testing (e.g., for FR α and BRCA) should be performed in a laboratory certified by Clinical Laboratory Improvement Amendments (CLIA; or local equivalent) using a test approved by the relevant regulatory body (FDA or local equivalent).

- Patients must have platinum-resistant disease:
 - Patients who have only had 1 line of platinum-based therapy must have received at least 4 cycles of platinum therapy, and must have either had a response (complete response [CR] or partial response [PR]) or had non-measurable disease at the start of platinum-based therapy, and then progressed between > 91 days and ≤ 183 days after the date of the last dose of platinum.
 - Patients who have received 2 to 4 lines of platinum-based therapy must have progressed on or within 183 days after the date of the last dose of platinum.

[0238] Key Inclusion Criteria

- Prior therapy with an antibody-drug conjugate containing a topoisomerase 1 inhibitor.
- Have primary platinum-refractory disease, defined as ovarian cancer that did not respond (CR or PR) to or progressed ≤ 91 days after the last dose of a first-line platinum-containing regimen.
- History of another malignancy within 3 years before the first dose of study drug, or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (e.g., 5-year OS $\geq 90\%$), including, but not limited to, adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, ductal carcinoma in situ, or Stage I uterine cancer.
- Known active central nervous system metastases or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are clinically stable for at least 4 weeks prior to study entry after brain metastasis treatment, they have no new or enlarging

brain metastases, and are off corticosteroids and anticonvulsants prescribed for symptoms associated with brain metastases for at least 7 days prior to the first dose of study drug. Patients with suspected brain metastases at screening should undergo a computed tomography (CT)/magnetic resonance imaging (MRI) of the brain prior to study entry.

- Hospitalization or clinical symptoms due to gastrointestinal obstruction within the past 91 days or radiographic evidence of gastrointestinal obstruction at the time of screening. Enrollment of patients who currently require parenteral nutrition must be discussed with the study medical monitor to determine eligibility.
- Ascites requiring frequent paracentesis (more often than approximately every 4 weeks) for symptomatic management. Enrollment of patients with an indwelling peritoneal catheter must be discussed with the medical monitor to determine eligibility.

[0239] The 530 patients with PROC consists of: approximately 420 patients, including: patients whose tumors do not have high FR α expression per the Ventana FOLR1-2.1 RxDx Assay (or local equivalent test) (i.e., FR α expression <75% PS2+), patients previously treated with mirvetuximab soravtansine, and patients who are not candidates for mirvetuximab soravtansine due to medical conditions; and approximately 110 patients with high FR α expression (i.e., FR α expression $\geq$ 75% PS2+) who have not previously received mirvetuximab soravtansine, but are enrolled in regions where mirvetuximab soravtansine is not available therapy.

Example 5: Test Product, Dose, and Mode of Administration of the study 2

[0240] Rinatabart Sesutecan (Rina-S): Rina-S will be administered on Day 1 of a 21-day treatment cycle. Rina-S will be administered as a 30-minute intravenous (IV) infusion.

[0241] Investigator's Choice (IC) Therapies: Patients will receive one of the following chemotherapies on a 4-week cycle at the discretion of the investigator: Paclitaxel 80 mg/m² as a 1-hour IV infusion on Days 1, 8, and 15 every 4 weeks (Q4W); Topotecan 4 mg/m² as a 30-minute IV infusion on Days 1, 8 and 15 Q4W, or 1.25 mg/m² as a 30-minute IV infusion on Days 1-5 Q3W; Pegylated liposomal doxorubicin (PLD) 40 mg/m² as a 1 mg/min IV infusion on Day 1 Q4W. After

Cycle 1, the drug can be delivered as a 1-hour infusion; and Gemcitabine 1000 mg/m², or 800 mg/m² at investigator's discretion, as a 30-minute IV infusion on Days 1, 8, and 15 Q4W.

[0242] There is an estimated 4- to 6-month treatment period (the duration of treatment is expected to vary for each patient). Patients will continue to receive study drug until the first instance of disease progression, unacceptable toxicity, investigator decision, consent withdrawal, pregnancy, death, or premature study termination by the sponsor. Patients who present equivocal findings of progression may be allowed to continue the study drug with approval of the medical monitor and if, in the opinion of the investigator, the patient is clinically stable. If progression is confirmed unequivocally on the next response assessment, study drug will be discontinued.

Example 6: Determination of anti-tumor activity of Rina-S in the study 2

Efficacy Analysis

Primary Endpoint: PFS per Investigator Assessment

[0243] This study is designed to evaluate PFS in patients with PROC receiving either Rina-S or IC, with the hypothesis that Rina-S is superior to IC in PFS. The study is considered to have met this objective if Rina-S is superior to IC in PFS at the final analysis of PFS, using the PAS.

[0244] PFS is defined as the time from randomization to the first documentation of disease progression (PD) per RECIST v1.1 according to investigator assessment, or to death due to any cause, whichever comes first.

[0245] The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment arm. The median PFS and its two-sided 95% confidence interval (CI) using the complementary log-log transformation method (Collett, London: Chapman & Hall, pp. 237-251 (1994)) will be calculated. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The same stratification factors used

for randomization will be applied to both the stratified log-rank test and the stratified Cox model.

[0246] Since progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for patients who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented using RECIST v1.1, regardless of discontinuation of study drug.

[0247] PFS will be calculated as follows:

$$\text{PFS (days)} = (\text{date of first documented PD or death} - \text{date of randomization}) + 1$$

[0248] Patients without documented PD or death will be censored at the last disease assessment date. PFS will also be censored at the date of the last disease assessment documenting absence of PD or death in patients who are given anti-tumor treatment other than the study drug or are removed from the study prior to the documentation of tumor progression. If a patient does not have any on-study tumor assessments, PFS will be censored on Day 1.

[0249] PFS per BICR will be analyzed using the same methodology as a sensitivity analysis. In addition, the concordance in the PD assessment between investigator assessment and BICR assessment will be evaluated. The discordance between the investigator and BICR assessments in censoring status, time to PD, and time to censoring will be tabulated, and the data for the discordance will be listed.

Key Secondary Endpoints:

Overall Survival

[0250] OS is defined as the time from randomization to death due to any cause. OS will be calculated as follows:

$$\text{OS (days)} = (\text{date of death} - \text{date of randomization} + 1).$$

[0251] Patients who are alive (with no OS event) will be censored at the last known date alive.

[0252] The non-parametric Kaplan-Meier method will be used to estimate the OS curve in each treatment arm. The median OS and its two-sided 95% CI using the complementary log-log transformation method (Collett, London: Chapman & Hall, pp. 237-251 (1994)) will be calculated.

The treatment difference in OS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The same stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model. The Kaplan-Meier estimates of OS rate at 12 months will be compared between the Rina-S arm and IC arm and proportionality of hazard ratio over time will be explored.

Objective Response Rate

[0253] ORR is defined as the percentage of the patients who have a best response of confirmed CR or PR using RECIST v1.1. Responses per investigator will be used as the primary analysis of ORR and responses based on BICR, incorporating status of CA-125 normalization for CR, will be used as a sensitivity analysis.

[0254] If PFS per investigator is declared positive at the primary analysis and OS is declared positive, a final analysis of ORR per investigator assessment will be performed. The following hypothesis will be tested at a one-sided α level of 0.025:

$$H_0: ORR_{\text{Rina-S}} = ORR_{\text{IC}} \text{ vs } H_a: ORR_{\text{Rina-S}} > ORR_{\text{IC}}$$

where $ORR_{\text{Rina-S}}$ is the ORR in the Rina-S arm and ORR_{IC} is the ORR in the IC arm.

[0255] ORR will be analyzed using a Cochran-Mantel-Haenszel (CMH) test (Cochran, Biometrics 10, 417-451 (1954); Mantel and Haenszel, J Natl Cancer Inst 22, 719-748 (1959)) stratified by the randomization stratification factors to test for differences between the Rina-S arm and the IC arm. P-value, odds ratio and its 95% CI will be reported. The 95% CIs for ORR by treatment arm based on Clopper-Pearson method (Clopper and Pearson, Biometrika 26, 404-413 (1934)) will also be provided. The PAS population will serve as the primary population for ORR and a supportive analysis of ORR will be carried out using the patients in the ITT and EE analysis set.

[0256] ORR per BICR will be analyzed using the same methodology based on PAS as a sensitivity analysis. In addition, the concordance in the best overall response (BOR) between investigator assessment and BICR assessment will be evaluated. The discordance between the investigator and BICR assessments in BOR and time to BOR will be tabulated, and the data for the discordance will be listed.

Determination of Sample Size

[0257] The primary endpoint of this study is PFS as assessed by the investigator, with OS and ORR as assessed by the investigator as key secondary endpoints.

[0258] The primary analysis will be conducted on the Primary Analysis Set (PAS). This set excludes patients with high FR α expression who would otherwise be candidates for mirvetuximab soravtansine, but who have not received this prior therapy due to being enrolled in regions where it is not available. It is expected that approximately 80% of the study population will be included in the PAS.

[0259] The sample size calculation for the final PFS analysis (PFS primary analysis) focuses on demonstrating superior PFS in the Rina-S arm compared to the IC arm and is based on the following assumptions:

- PFS follows an exponential distribution with a median of 4 months in the IC arm
- The hazard ratio between the Rina-S arm and the IC arm is 0.67 (corresponding to a median PFS of 6 months in the Rina-S arm)

- An enrollment period of 21 months for a total of approximately 530 patients in order to reach approximately 420 patients in the primary population

[0260] A yearly censoring rate of 10% for PFS. A PFS hazard ratio of 0.67 is proposed for hypothesis testing in this study, equivalent to an approximate 2-month improvement in the median PFS assuming exponential distribution, which may be considered clinically meaningful. In patients with PROC, improvement in PFS has been associated with decreased tumor-related symptoms, improvement in patient-reported outcomes, and improvement in overall survival.

[0261] With 262 PFS events, the study has 90% power to demonstrate superiority of the Rina-S arm over the IC arm at a one-sided $\alpha = 0.025$ when the true hazard ratio is 0.67. To ensure sufficient follow-up for the treated patients, the PFS primary analysis will be conducted when at least 262 PFS events have occurred and patients in the PAS have had the opportunity to be followed-up for a minimum of 3 months after randomization (or have documented PD, died, or been withdrawn from the study within 3 months after randomization).

[0262] If the primary endpoint of PFS is statistically significant at a one-sided α level of 0.025, the hierarchical testing procedure will be used to test the two key secondary endpoints in the following order at a one-sided α level of 0.025 to control the study-wide type I error rate.

- OS
- ORR per RECIST v1.1 as assessed by the investigator.

[0263] The key secondary endpoint of OS will be tested only after PFS is declared positive. At that timepoint, an interim analysis of OS will be performed (with approximately 131 OS events [53%] projected), and a final analysis of OS will be performed when at least 248 OS events have occurred, or at the time of study closure, when all treated patients have had the opportunity to be followed for at least 3 years after randomization, or have died or been withdrawn from the study, whichever comes first. The O'Brien-Fleming spending function will be applied to these two OS analysis timepoints at the one-sided α level of 0.025. The exact α allocation at the time of OS interim analysis depends on the number of OS events accrued by that time. With 248 OS events, the study has 80% power to demonstrate superiority of the Rina-S arm over the IC arm at a one-sided $\alpha = 0.025$ when the true hazard ratio is 0.70. In addition, the sample size calculation of OS analyses assumes a median OS in the IC arm of 13 months, a censoring rate of 2% per year, and the same enrollment schedule as specified in the sample size calculation for PFS analysis.

[0264] ORR per investigator will be tested after the efficacy bound for OS has been crossed. Since all patients will be enrolled at that time, the following hypothesis will be tested at 1-sided 2.5% level with no group sequential spending function applied:

$$H_0: \text{ORR}_{\text{Rina-S}} = \text{ORR}_{\text{IC}} \text{ vs } H_a: \text{ORR}_{\text{Rina-S}} > \text{ORR}_{\text{IC}}$$

where $\text{ORR}_{\text{Rina-S}}$ is the ORR in the Rina-S arm and ORR_{IC} is the ORR in the IC arm.

[0265] Assuming the true $\text{ORR}_{\text{Rina-S}}$ is 30% and the true ORR_{IC} is 16%, a sample size of approximately 420 patients (210 patients/arm) achieves approximately 93% power to detect a difference in ORR of 14% (30% vs 16%) using the method of Farrington and Manning (Farrington and Manning, Stat Med 9, 1447-1454 (1990)) for a study to test the difference between two binomial event rates.

[0266] The sample size calculation for PFS, OS, and ORR are carried out using R package *gsDesign*.

Example 7: Dose escalation and dose expansion of the Study 1

[0267] As continuation of the Study 1, 53 patients regardless of FR α expression were treated in Part A (dose escalation), including 32 patients with previously treated ovarian cancer (OC), 11

patients with previously treated endometrial cancer (EC), and 10 patients with other tumor types (NSCLC, breast cancer, and mesothelioma). The median numbers of prior therapies of the patients with ovarian cancer and endometrial cancer were 5 (1-14) and 3 (1-14), respectively. 75% of the patients with ovarian cancer had received bevacizumab, and 91% were platinum resistant. All the patients with endometrial cancer received PD-1 inhibitor. Rina-S doses from 60-180 mg/m² were evaluated in Part A. The MTD was 140 mg/m². Doses of 100 and 120 mg/m² were selected for evaluation in Part B (dose expansion).

[0268] In Part B, 35 patients with ovarian cancer and 13 patients with endometrial cancer were treated. The median numbers of prior therapies of the patients with ovarian cancer and endometrial cancer were 3 (1-4) and 3 (1-7), respectively.

[0269] Planned tumor-specific dose expansion includes OC, EC, and EGFR-mutant NSCLC regardless of FR α expression (FR α levels retrospectively assessed). The patients with ovarian cancer in Part B (cohort B1, ovarian cancer dose expansion) was randomized 1:1 to Rina-S 100 mg/m² or Rina-S 120 mg/m². The inclusion criteria for cohort B1 are as shown below.

- 1) Histologically or cytologically confirmed OC (must have epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer)
- 2) Prior treatment (1-3 lines for PROC or 4 lines regardless of platinum-sensitivity status)
- 3) ECOG PS 0-1
- 4) Measurable disease per RECIST v1.1
- 5) Adequate hematologic, hepatic, renal, and cardiac function

[0270] Table 5 shows patient demographics and disease characteristics in cohort B1.

Table 5: Ovarian Cancer Dose Expansion - Patient Demographics and Disease Characteristics

	Rina-S 100 mg/m ²	Rina-S 120 mg/m ²
Cohort B1: OC Dose Expansion	n = 22	n = 20
Age, median (range), years	62.5 (42-82)	64.5 (37-83)

Prior lines of therapy, median (range)	3 (1-5)	3 (1-4)
Bevacizumab, n (%)	20 (90.9)	18 (90.0)
PARPi, n (%)	15 (68.2)	13 (65.0)
Mirvetuximab soravtansine, n (%)	4 (18.2)	4 (20.0)
Platinum sensitivity status, n (%)		
Resistant	20 (90.9)	19 (95.0)
Sensitive	2 (9.1)	1 (5.0)

Example 8: Overall safety of Rina-S

[0271] As continuation of the Study 1, for Part A patients treated at 100 or 120 mg/m² (n=35), the most common (>20%) treatment-related adverse events (TRAEs) were nausea (n=20.57%), neutropenia (n=18.51%), leukopenia (n=16.46%), anemia (n=15.43%), thrombocytopenia (n=11.31%), and vomiting (n=9.26%); most events were Grade 1/2. The most common (>10%)> Grade 3 TRAEs were neutropenia (n=12.34%), anemia (n=9.26%), leukopenia (n=8.23%), and thrombocytopenia (n=5.14%). Table 6 shows overall safety of cohort B1. OC Dose Expansion at 100 and 120 mg/m²: TEAEs of any grade and grade 3-4 were reported in 100% and 60%-63.6% of patients, respectively; TEAEs leading to dose reductions occurred in 11.1%-16.2% of patients; safety profiles were similar between cohorts. Fig. 5 shows the overall safety in details.

Table 6: Overall Safety of Cohort B1: OC Dose Expansion

Cohort B1: OC Dose Expansion		
	Rina-S (100 mg/m ²) n = 22	Rina-S (120 mg/m ²) n = 18
Overall Safety, %		
Any-grade TEAE	100	100
Grade 3/4b	60.0	63.6
TEAEs leading to dose reductions	11.1	16.2

Prophylactic GCSF use	31.0	48.5
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[0272] As a result, no ocular toxicity, neuropathy, or interstitial lung disease was observed. The emerging safety profile of Rina-S in Part B is consistent with Part A.

Example 9: Determination of anti-tumor activity of Rina-S in the Study 1

[0273] As continuation of the Study 1, the antitumor activity of Rina-S was evaluated in dose escalation and dose expansion.

[0274] In Part A (dose escalation), Rina-S showed encouraging antitumor activity in heavily pretreated patients with OC and EC. Table 7 shows the results of antitumor activity for Part A. Fig. 6 shows the best change in target lesion for OC and EC dose escalation.

Table 7: Part A: OC and EC Dose Escalation

Rina-S (100 mg/m ² and 120 mg/m ²) n = 26 ^a	
Confirmed ORR, ^b % (95% CI)	30.8 (14.3-51.8)
Best overall response, ^b n (%)	
PR	8 (30.8)
SD	15 (57.7)
PD	3 (11.5)
DCR, % (95% CI)	88.5 (69.8-97.6)
Median DOR, weeks (95% CI)	35.3 (20.14-NE)

^aResponse-evaluable population. The response evaluable population set includes all treated patients who had a baseline and at least 1 evaluable postbaseline tumor assessment, or who had documented progression of disease at any time after the first dose of Rina-S. Response assessment per RECIST v1.1.

^bBased on investigator assessment.

[0275] In Part B, Rina-S showed encouraging antitumor activity at 120 mg/m², including a complete response, in heavily pretreated patients with OC. Table 8 shows the results of antitumor activity for cohort B1 of Part B. The Treatment duration range was 3.0-42.0+ weeks. The Median on-study follow-up was 24 weeks. Fig. 7 shows the best change in target lesion for OC dose expansion.

Table 8: Cohort B1: OC Dose Expansion^a

	Rina-S (100 mg/m²) n = 22^b	Rina-S (120 mg/m²) n = 18^b
Confirmed ORR,^b	18.2	50.0
Best overall response, b n (%)		
CR	0	1 (5.6)
PR	4 (18.2)	8 (44.4)
SD	15 (68.2)	7 (38.9)
PD	3 (13.6)	1 (5.6)
Not evaluable	0	1 (5.6)
DCR, % (95% CI)	86.4 (65.1-97.1)	88.9 (65.3-98.6)
Median DOR (95% CI)	NR (NR-NR)	

^aBased on investigator assessment.

^bResponse-evaluable population.

^cOne patient in the 120 mg/m² cohort with prior mirvetuximab soravtansine was not response-evaluable.

[0276] As shown in Fig. 8, most responses with Rina-S 120 mg/m² were observed early (at week

6) and all confirmed responses with 120 mg/m² were ongoing at the time of data cutoff in patients with heavily pretreated OC. As shown in Fig. 9, responses in patients with OC were observed across all FR α expression levels.

Example 9: Activity of combinations between Rina-S and standard-of-care therapy drugs in vitro

[0277] Cells were seeded in a 96-well plate (the wells being flat bottomed) at an appropriate density depending on the cell line (typically 1,000-3,000 cells per well in 100 μ L of appropriate culture media). After overnight incubation, cells were treated with increasing concentrations of Rina-S, carboplatin or olaparib alone or Rina-S in combination with carboplatin (12.5 μ M) or olaparib (30 μ M) (concentrations were chosen based on IC₅₀ values). Cell viability was evaluated after 4 days. Cell-Titer Glo (Promega, CAT# G7572) was added into the wells with luciferase readings collected after 5 minutes and analyzed by Microplate readers. All readings were normalized as percentage of viable cells in the untreated control wells and the IC₅₀ values were calculated by GraphPad Prism® software.

[0278] As shown in Figs. 10A and 10B, the combination of Rina-S with carboplatin did not enhance the cytotoxicity of Rina-S on OVCAR-8, while the combination of Rina-S with olaparib enhanced the cytotoxicity effect of Rina-S on HEC-1-A.

Example 10: Induction of hallmarks of immunogenic cell death (ICD) by exatecan and Rina-S

[0279] Hall markers of ICD induced by Rina-S and exatecan were evaluated in FOLR α -positive cells. KB and 3LL-FR α were seeded at 5*10³ cells per well in a 96-well plate (for ATP and HMGB1 detection) or 4*10⁴ cells per well in a 24-well plate (for cell surface calreticulin detection) and incubated at 37 °C overnight. The wells of the plates used were flat bottomed. For extracellular ATP (Adenosine triphosphate) and HMGB1 (High box group 1 protein) detection, cell supernatants were removed and 200 μ L serially diluted Rina-S (10-fold dilutions; 1000 to 0.1 nM) or exatecan (10-fold dilutions; 800 to 0.8 nM) were added to the wells, and incubated for 24-72 h. ATP and HMGB1

released in the supernatant were detected by CTG kit (Promega; Cat No: G7572) and Lumit HMGB1 Immunoassay kit (Promega; Cat No: W6112) separately. For cell surface calreticulin detection, cell supernatants were removed and 500 μ L serially diluted Rina-S (10-fold dilutions; 100 to 1 nM) or exatecan (10-fold dilutions; 80 to 0.8 nM) were added to the wells and incubated for 48 h. Cell surface calreticulin was detected by flow cytometry using anti-calreticulin monoclonal antibody (Enzolifesciences; Cat No: ADI-SPA-601PE-D).

[0280] Rina-S and exatecan upregulated ICD biomarkers in FOLR α -positive cells in a concentration-dependent manner, as indicated in Figs. 11A-11F.

Example 11: Anti-tumor activity of combinations of Rina-S with SoC agents in mouse models in vivo

[0281] Rina-S shows strong potentiation of anti-tumor activity in combination with carboplatin, bevacizumab, olaparib (PARPi), or immunotherapy. Combinations of Rina-S with standard-of-care (SOC) agents were evaluated in preclinical mouse models of ovarian and endometrial cancer in vivo. Around 15 and 17 days after tumor inoculation, mice with an average tumor size of 100.16~180.86 mm³ were randomized into 4 groups (n = 5–6 per group). On either Day 0 or Day 1, following randomization (defined as Day 0), the mice received the test article or PBS at the indicated concentrations. In detail: female NDG (ultra-immunodeficient phenotype) mice bearing established OVCAR-8 ovarian cancer xenografts (n = 6 mice/group) were treated with Rina-S (3 mg/kg, single dose) or bevacizumab (5 mg/kg, single dose) (Fig. 12A); Rina-S (3 mg/kg single dose) or carboplatin (60 mg/kg, QW * 4) (Fig. 12B), IV, or IP, alone or in combination. Female BALB/c nude mice bearing established HEC-1-A endometrial cancer xenografts (n = 5 mice/group) were treated with Rina-S (5 mg/kg, single dose) or olaparib (50 mg/kg, daily for 5 days X 4 weeks) IV, or by oral gavage, alone or in combination (Fig. 12C).

[0282] Combinations of Rina-S with immuno-oncology therapy agents were evaluated in preclinical models of lung cancer and colorectal cancer. Around 6 days after tumor inoculation, mice with average tumor size of 65~142 mm³ were randomized into 4 or 6 groups (n = 6 per group). On

either Day 0 or Day 1, following randomization (defined as Day 0), the mice received the test article or PBS at indicated concentrations. In detail: female C57BL/6 bearing established lung cancer (3LL-FR α) xenografts (n = 6 mice/group) were treated with Rina-S (2.5 mg/kg, single dose) or CS1003 (nofazinlimab; anti-PD-1) (10 mg/kg, Q3D*4) IV, alone or in combination (Fig. 12D). Female C57BL/6 mice bearing established MC38-FR α colorectal cancer xenografts (n = 6 mice/group) were treated with Rina-S (1.5 or 2.5 mg/kg, single dose) or CS1003 (0.5 mg/kg, Q3D*4) IV, alone or in combination (Fig. 12E).

[0283] Tumor size was measured twice a week in two dimensions using a caliper, and tumor volume was calculated in mm³ using the formula: $V = 0.5a \times b^2$ where a and b are the long and short diameters of the tumor, respectively. Tumor volume exceeding 2000 mm³ was defined as reaching the end of the experiment. Body weight was measured twice a week. Animal body weight was monitored as an indirect measure of tolerability.

[0284] Combination of Rina-S with carboplatin or bevacizumab or olaparib resulted in potentiated antiproliferative effects in the OVCAR-8 and HEC-1-A model in vivo, suggesting a benefit of these combinations in relevant tumor types (such as ovarian cancer and endometrial) in the clinic. No significant weight loss was observed in any of the treatment groups, and there were no reports of morbidity or mortality during the treatment period.

[0285] Combinations of Rina-S with CS1003 (anti-PD-1) resulted in potentiated anti-tumor effects in the 3LL-FR α and MC38-FR α model in vivo, suggesting a benefit for combined treatment of Rina-S and immune checkpoint inhibitors (ICI) in the clinic.

[0286] Having thus described the basic concepts, it may be rather apparent to those skilled in the art after reading this detailed disclosure that the foregoing detailed disclosure is intended to be presented by way of example only and is not limiting. Various alterations, improvements, and modifications may occur and are intended to those skilled in the art, though not expressly stated herein. These alterations, improvements, and modifications are intended to be suggested by this

disclosure and are within the spirit and scope of the exemplary embodiments of this disclosure.

[0287] Moreover, certain terminology has been used to describe embodiments of the present disclosure. For example, the terms “one embodiment,” “an embodiment,” and “some embodiments” mean that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present disclosure. Therefore, it is emphasized and should be appreciated that two or more references to “an embodiment” or “one embodiment” or “an alternative embodiment” in various portions of this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures or characteristics may be combined as suitable in one or more embodiments of the present disclosure.

[0288] Further, it will be appreciated by one skilled in the art, aspects of the present disclosure may be illustrated and described herein in any of a number of patentable classes or context including any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof.

[0289] Furthermore, the recited order of processing elements or sequences, or the use of numbers, letters, or other designations, therefore, is not intended to limit the claimed processes and methods to any order except as may be specified in the claims. Although the above disclosure discusses through various examples what is currently considered to be a variety of useful embodiments of the disclosure, it is to be understood that such detail is solely for that purpose and that the appended claims are not limited to the disclosed embodiments, but, on the contrary, are intended to cover modifications and equivalent arrangements that are within the spirit and scope of the disclosed embodiments.

[0290] Similarly, it should be appreciated that in the foregoing description of embodiments of the present disclosure, various features are sometimes grouped together in a single embodiment, figure, or description thereof to streamline the disclosure aiding in the understanding of one or more of the various embodiments. This method of disclosure, however, is not to be interpreted as reflecting an intention that the claimed subject matter requires more features than are expressly recited in each

claim. Rather, claim subject matter lie in less than all features of a single foregoing disclosed embodiment.

WHAT IS CLAIMED IS:

1. A method of treating a solid tumor that is folate receptor 1 (FOLR1) positive, the method comprising administering to a human subject with the solid tumor rinatabart sesutecan (Rina-S), at a dosage of between 40 mg/m² and 200 mg/m².
2. The method of claim 1, wherein the solid tumor is selected from the group consisting of: ovarian cancer, endometrial cancer, breast cancer, lung cancer, and mesothelioma.
3. The method of claim 1 or 2, wherein the solid tumor is ovarian epithelial cancer, primary peritoneal cancer, or fallopian tube cancer.
4. The method of claim 1 or 2, wherein the solid tumor is endometrial cancer.
5. The method of claim 1 or 2, wherein the solid tumor is ovarian cancer.
6. The method of claim 1, wherein the solid tumor is:
 - a) non-small-cell lung cancer (NSCLC);
 - b) breast cancer, including HER2-negative breast cancer;
 - c) pleural mesothelioma; or
 - d) peritoneal mesothelioma.
7. The method of any one of the preceding claims, wherein the solid tumor is a platinum resistant tumor, optionally a high grade serous or endometrioid EOC, primary peritoneal cancer, or fallopian tube cancer, resistant to platinum chemotherapy.
8. The method of any one of the preceding claims, wherein the solid tumor is platinum-resistant ovarian cancer.
9. The method of any one of claims 1-3 or 5, wherein the solid tumor is platinum-sensitive ovarian cancer.
10. The method of any one of the preceding claims, wherein the solid tumor is localized or metastatic; and/or wherein at least one tumor is not removable by surgery.
11. The method of any one of the preceding claims, wherein Rina-S is administered at a dosage of between 60 mg/m² and 180 mg/m².

12. The method of any one of the preceding claims, wherein Rina-S is administered at a dosage of between 100 mg/m² and 140 mg/m².

13. The method of any one of the preceding claims, wherein Rina-S is administered at a dosage of between 100 mg/m² and 120 mg/m².

14. The method of any one of the preceding claims, wherein Rina-S is administered at a dosage of about 100 mg/m².

15. The method of any one of the preceding claims, wherein Rina-S is administered at a dosage of about 120 mg/m².

16. The method of any one of the preceding claims, wherein the Rina-S dosage is administered to the human subject once or twice a week on a schedule with a cycle selected from the group consisting of: (i) weekly; (ii) every other week; (iii) one week of therapy followed by two, three or four weeks off; (iv) two weeks of therapy followed by one, two, three or four weeks off; (v) three weeks of therapy followed by one, two, three, four or five weeks off; (vi) four weeks of therapy followed by one, two, three, four or five weeks off; (vii) five weeks of therapy followed by one, two, three, four or five weeks off; and (viii) monthly.

17. The method of any one of claims 1-15, wherein the Rina-S dosage is administered to the human subject on a cycle once every three weeks (Q3W).

18. The method of any one of claims 16-17, wherein the cycle is repeated 2, 4, 6, 8, 10, 12, 16 or 20 times.

19. The method of any one of claims 1-18, wherein the human subject has previously been treated with at least one anti-cancer therapy, optionally wherein

- (a) the at least one anti-cancer therapy includes treatment with a chemotherapeutic agent, and/or
- (b) wherein the human subject has failed to respond to the at least one anti-cancer therapy prior to treatment with Rina-S.

20. The method of any one of the preceding claims, wherein Rina-S is administered in combination with one or more therapeutic modalities selected from the group consisting of unconjugated antibodies, radiolabeled antibodies, drug-conjugated antibodies, toxin-conjugated antibodies, gene therapy,

chemotherapy, therapeutic peptides, cytokine therapy, oligonucleotides, localized radiation therapy, surgery and interference RNA therapy.

21. The method of any one of the preceding claims, wherein Rina-S is administered

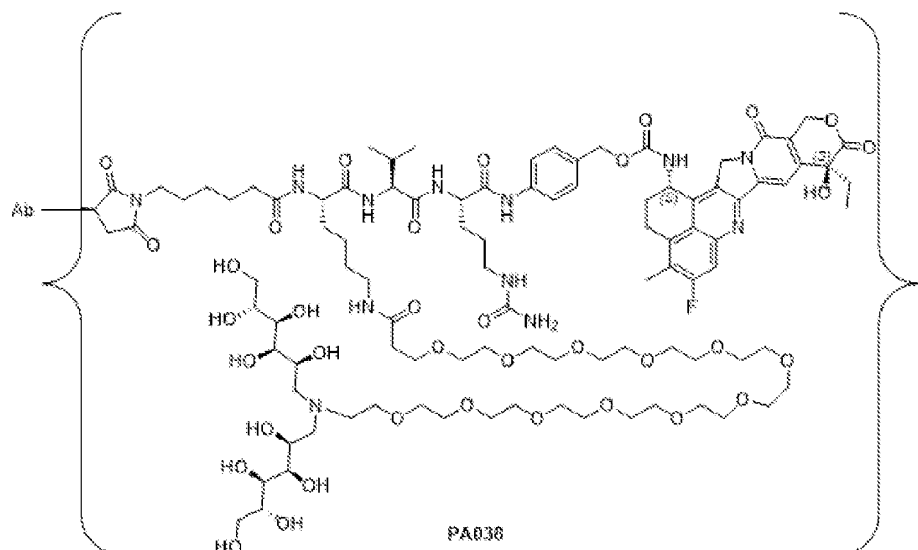
- (a) in combination with a platinum-based chemotherapy, optionally carboplatin;
- (b) in combination with a VEGF antagonist-based chemotherapy, optionally bevacizumab; or
- (c) in combination with a PD-1 inhibitor, optionally pembrolizumab.

22. The method of any of the previous claims, wherein a treatment outcome of the subject is improved, optionally wherein

- (a) the improved treatment outcome is an objective response selected from stable disease, a partial response or a complete response;
- (b) wherein the improved treatment outcome is reduced tumor burden, and/or
- (c) wherein the improved treatment outcome is progression-free survival or disease-free survival.

23. A method of treating a solid tumor comprising administering to a human subject with a solid tumor rinatabart sesutecan (Rina-S) and either one of: (i) a platinum-based chemotherapy, for example carboplatin; (ii) an anti-angiogenic agent, for example an anti-VEGF antibody, for example bevacizumab; (iii) a PARP inhibitor, for example olaparib; or (iv) an immune checkpoint inhibitor, for example an inhibitor of the PD-1 or PD-L1 immune checkpoint proteins, for example an anti-PD-1 antibody, for example pembrolizumab.

24. The method of any one of the preceding claims, wherein Rina-S has the structure (structure 1):



wherein Ab is a folate receptor 1 (FOLR1)-binding antibody that comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH and VL regions has amino acid sequences that are set forth in SEQ ID NO: 1 and SEQ ID NO:2, respectively, and wherein n is 8.

25. The method of claim 24, wherein Ab is a FOLR1-binding antibody that comprises a heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 6 or optionally SEQ ID NO: 4, and comprising a light chain comprising the amino acid sequence set forth in SEQ ID NO: 5.

26. A method according to any one of the preceding claims, wherein the Rina-S is administered to the human subject by intravenous administration.

27. A method according to any one of the preceding claims, wherein the FOLR1 expression level of the tumor has not been determined prior to administration of Rina-S.

28. A method according to any one of claims 1-26, wherein a tumor sample of the subject has high FOLR1 expression, according to a regulatory approved test for FOLR1 expression, optionally a Ventana FOLR1-2.1 RxDx Assay.

29. A method according to any one of claims 1-26, wherein a tumor sample of the subject has medium or low FOLR1 expression, according to a regulatory approved test for FOLR1 expression, optionally a Ventana FOLR1-2.1 RxDx Assay.
30. A method according to any one of claims 1-26 and 28, wherein the human subject is not eligible for treatment with mirvetuximab soravtansine.
31. Rinatabart sesutecan (Rina-S) for use for use in a method of treating a solid tumor, the method comprising administering to a human subject with the solid tumor the Rina-S at a dosage of between 40 mg/m² and 200 mg/m², for example between 60 mg/m² and 140 mg/m², for example 100 mg/m² or 120 mg/m².
32. Use of rinatabart sesutecan (Rina-S) for the manufacture of a medicament for treatment of a solid tumor, wherein the medicament is for administration to a human subject with the solid tumor at a dosage of the Rina-S of between 40 mg/m² and 200 mg/m², for example between 60 mg/m² and 140 mg/m², for example 100 mg/m² or 120 mg/m².