SUMMARY

[0002a] In one aspect, there is provided a use of rinatabart sesutecan (Rina-S) in the manufacture of a medicament for treating a solid tumor that is folate receptor 1 (FOLR1) positive, wherein the Rin-S is to be administered at a dosage of between 40 mg/m^2 and 200 mg/m^2 to a human subject with the solid tumor.

[0002b] In another aspect, there is provided a use of rinatabart sesutecan (Rina-S) in the manufacture of a medicament for treating a solid tumor, wherein the medicament is to be administered with 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.

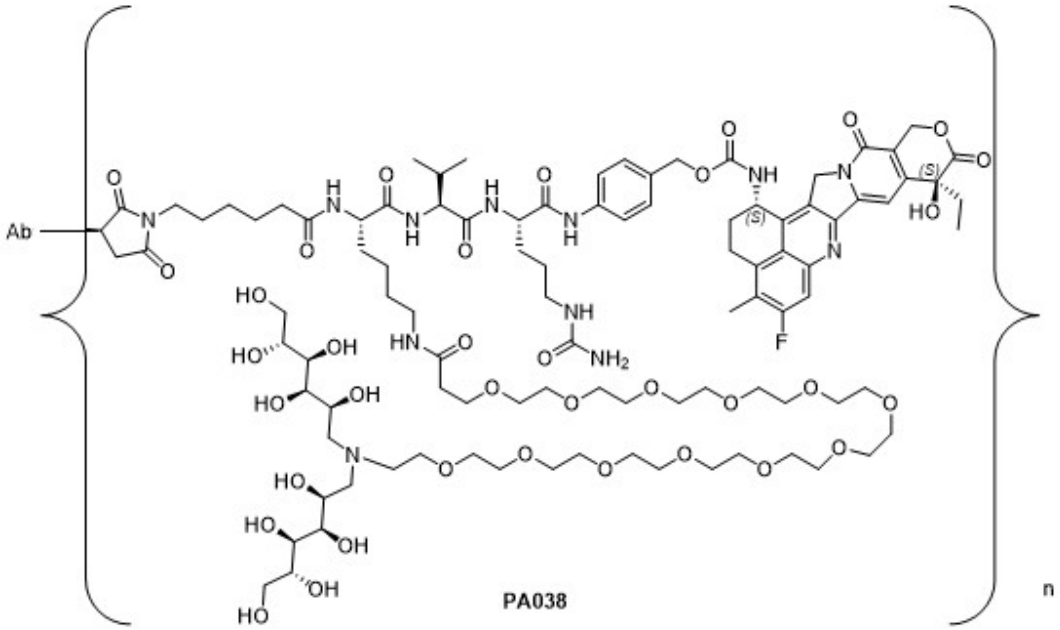
[0002c] In yet another aspect, there is provided a use of rinatabart sesutecan (Rina-S) for the manufacture of a medicament for treatment of a solid tumor, wherein the medicament is to be administered to a human subject with the solid tumor at a dosage of the Rina-S of between 40 mg/m^2 and 200 mg/m^2, for example between 60 mg/m^2 and 140 mg/m^2, for example 100 mg/m^2 or 120 mg/m^2.

[0003] In one example, the present disclosure 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 examples 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 example, the disclosure 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/m^2 and 200 mg/m^2, e.g. between 60 mg/m^2 and 140 mg/m^2. In certain examples the human subject has an ovarian cancer. In certain examples the human subject has an endometrial cancer. In one example the disclosure 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/m^2 and 200 mg/m^2, e.g. between 60 mg/m^2 and 140 mg/m^2. In certain examples the cancer is an ovarian cancer. In certain examples the cancer is an endometrial cancer. In certain examples the ADC is administered at a dosage of 100 mg/m^2. In certain examples the ADC is administered at a dosage of 120 mg/m^2. In certain examples the ADC is administered every three weeks. In certain examples, 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 examples 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 examples, 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 examples 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 example of the current disclosure involves 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/m^2 and 200 mg/m^2, and the solid tumor is folate receptor 1 (FOLR1) positive.

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

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

[0008] In some examples, another example of the current disclosure involves treatment with the ADC Rina-S, wherein the ADC is administered at a dosage of between 60 mg/m^2 and 180 mg/m^2. In certain examples, the ADC is administered at a dosage of 140 mg/m^2. In certain examples, the ADC is administered at a dosage of between 100 mg/m^2 and 140 mg/m^2. In certain examples, the ADC is administered at a dosage of between 100 mg/m^2 and 120 mg/m^2. In certain examples, the ADC is administered at a dosage of about 100 mg/m^2. In certain examples, the ADC is administered at a dosage of about 120 mg/m^2.

[0009] Another example of the current disclosure 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 examples, 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 examples, the ADC dosage is administered to the human subject on Day 1 of a 21-day treatment cycle. In certain examples, the ADC dosage is administered to the human subject as a 30-minute intravenous (IV) infusion.

[0010] In certain examples, 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 examples the ADC dosage is administered to the human subject once every three weeks. In certain examples thereof, the dosage is 120 mg/m^2. In certain examples the ADC is dosage is administered as an intravenous infusion.

[0012] In another example of the current disclosure, the cycle of treatment is repeated 2, 4, 6, 8, 10, 12, 16 or 20 times. In one example, the treatment is continued as long as needed. In certain examples 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 example of the current disclosure, the human subject has previously been treated with at least one anti-cancer therapy. In some examples, the human subject has previously been treated with 1 to 4 anti-cancer therapies. In some examples, the at least one anti-cancer therapy includes treatment with a chemotherapeutic agent. In some examples, 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 examples, the human subject has failed to respond to the at least one anti-cancer therapy prior to treatment of the ADC. In certain examples, the human subject has previously been treated with mirvetuximab soravtansine. In certain examples, the human subject is not eligible for treatment with mirvetuximab soravtansine.

[0014] In yet another example of the current disclosure, 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 example of the current disclosure, 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 example of the current disclosure, with a treatment of the ADC Rina-S, the outcome of the subject is improved. In some examples, the improved treatment outcome is an objective response selected from stable disease, a partial response or a complete response. In certain examples, the improved treatment outcome is reduced tumor burden. In certain examples, the improved treatment outcome is progression-free survival or disease-free survival. In certain examples, 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 example, the disclosure 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 examples thereof, the human subject has ovarian cancer. In certain examples, 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 examples, the human subjects are treated with Rina-S at a dose level of 100 mg/m^2. In certain examples, the human subjects are treated with Rina-S at a dose level of 120 mg/m^2. In certain examples, the dosage is administered to the human subjects about every three weeks (Q3W). In certain examples, the administration of the Rina-S is via intravenous administration, e.g., intravenous infusion.

[0018] In yet another example, the disclosure 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 example, the combination therapy comprises

Rina-S in combination with platinum-based chemotherapy, such as carboplatin, cisplatin, or oxaliplatin. In one example, the combination therapy comprises Rina-S in combination with an anti-angiogenic agent, such as an anti-VEGF antibody, such as bevacizumab. In one example, the combination therapy comprises Rina-S in combination with a PARP inhibitor, such as olaparib or niraparib. In one example, 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, retinfanlimab, toripalimab, and the like, or an anti-PD-L1 antibody such as atezolizumab, avelumab, durvalumab, and the like. In certain examples, the subjects are treated with Rina-S at a dose level of 100 mg/m^2. In certain examples, the subjects are treated with Rina-S at a dose level of 120 mg/m^2. In certain examples, these dosages are administered to the subjects about every three weeks (Q3W). In certain examples, the administration of the Rina-S is via intravenous administration. Dosing and administration regimen of the other therapy in the combinations of the disclosure is performed according to an approved label of the other respective therapy.

[0019] The disclosure 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 examples above and below. In alternative examples, the disclosure also provides Rina-S, optionally in combination with other anti-cancer drugs, for use in treatment of cancer, according to various examples of the methods of treatment according to the disclosure. In other alternative examples, the disclosure also provides Rina-S, optionally in combination with other anti-cancer drugs, for manufacturing a medicament for the treatment of cancer, according to various examples of the methods of treatment according to the disclosure. In further examples, the disclosure 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 disclosure 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 examples 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 example, 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 examples, Rina-S and the second drug may be administered in the same composition. In further examples, 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/m^2 and Rina-S 120 mg/m^2 groups.

[0028] FIG. 6 is a graph illustrating best changes in target lesion (best change from baseline in sum

WHAT IS CLAIMED IS:

1. Use of rinatabart sesutecan (Rina-S) in the manufacture of a medicament for treating a solid tumor that is folate receptor 1 (FOLR1) positive, wherein the Rin-S is to be administered at a dosage of between 40 mg/m^2 and 200 mg/m^2 to a human subject with the solid tumor.

2. The use 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 use of claim 1 or 2, wherein the solid tumor is ovarian epithelial cancer, primary peritoneal cancer, or fallopian tube cancer.

4. The use of claim 1 or 2, wherein the solid tumor is endometrial cancer.

5. The use of claim 1 or 2, wherein the solid tumor is ovarian cancer.

6. The use 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 use 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 use of any one of the preceding claims, wherein the solid tumor is platinum-resistant ovarian cancer.

9. The use of any one of claims 1-3 or 5, wherein the solid tumor is platinum-sensitive ovarian cancer.

10. The use 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 use of any one of the preceding claims, wherein Rina-S is to be administered at a dosage of between 60 mg/m^2 and 180 mg/m^2.

12. The use of any one of the preceding claims, wherein Rina-S is to be administered at a dosage of between 100 mg/m^2 and 140 mg/m^2.

13. The use of any one of the preceding claims, wherein Rina-S is to be administered at a dosage of between 100 mg/m^2 and 120 mg/m^2.

14. The use of any one of the preceding claims, wherein Rina-S is to be administered at a dosage of about 100 mg/m^2.

15. The use of any one of the preceding claims, wherein Rina-S is to be administered at a dosage of about 120 mg/m^2.

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

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

19. The use 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 use of any one of the preceding claims, wherein Rina-S is to be 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 use of any one of the preceding claims, wherein Rina-S is to be 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 use of any of the previous claims, wherein a treatment outcome of the subject is improved, optionally wherein

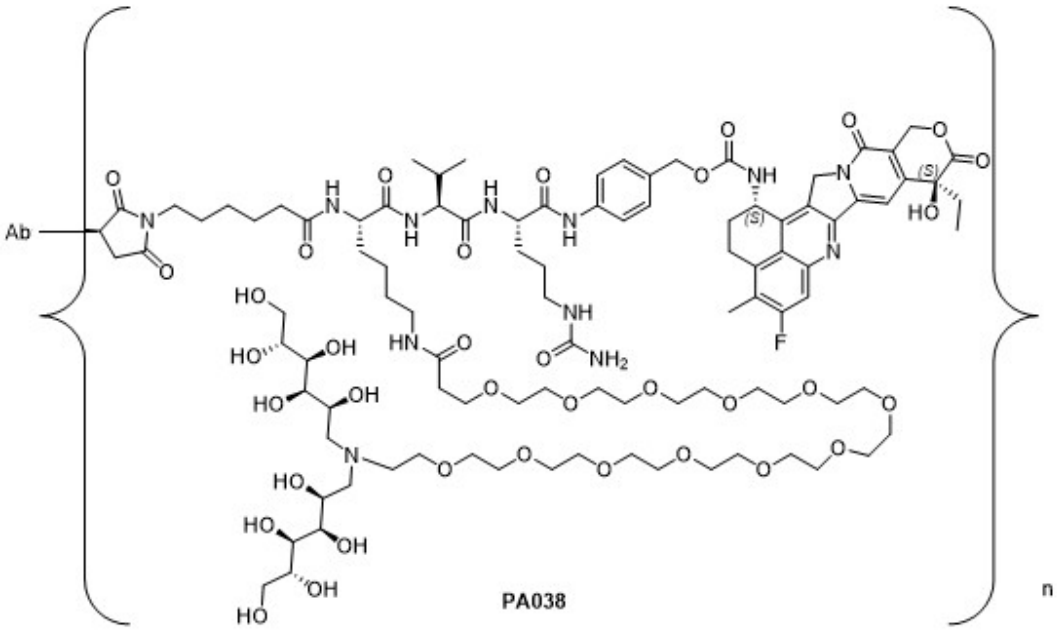
(a) the improved treatment outcome is an objective response selected from stable disease, a partial response or a complete response;

(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. Use of rinatabart sesutecan (Rina-S) in the manufacture of a medicament for treating a solid tumor, wherein the medicament is to be administered with 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 use 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 use 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 use according to any one of the preceding claims, wherein the Rina-S is to be administered to the human subject by intravenous administration.

27. A use 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 use 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 use 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 use according to any one of claims 1-26 and 28, wherein the human subject is not eligible for treatment with mirvetuximab soravtansine.

31. Use of rinatabart sesutecan (Rina-S) for the manufacture of a medicament for treatment of a solid tumor, wherein the medicament is to be administered to a human subject with the solid tumor at a dosage of the Rina-S of between 40 mg/m^2 and 200 mg/m^2, for example between 60 mg/m^2 and 140 mg/m^2, for example 100 mg/m^2 or 120 mg/m^2.