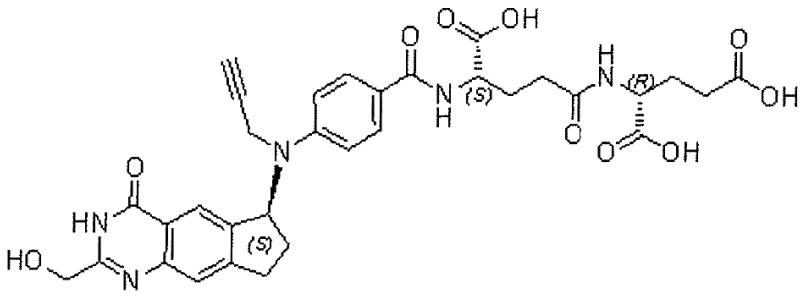
It will be realised by those skilled in the art that pharmaceuticals are expensive commodities and that it is desirable not to waste compound not required for a given treatment. As BTG945 is potentially toxic above the now taught doses it would be inappropriate for more than required to be provided in the clinical setting. Thus as a preferred dose per patient surface area is 6mg/m^2 or 12mg/m^2 and patients typically have surface area between 1m^2 and 2.5m^2 in developed countries, with patients with unusually high BMI often capped at 2m^2, it can be seen that a novel preferred useable vial content, whether in dried solid or solution form, would be between 6mg to 24mg drug compound more preferred between 10mg and 24mg drug compound. Thus vials of drug content 6mg, 8mg, 10mg, 12mg, 14mg, 16mg, 18mg, 20mg and 24mg are disclosed as novel embodiments of the invention. Particularly those where drug is in the form of dried BTG945 salt and/or its dehydrate, or its simple solution in water or saline for injection.

The compound for the treatment of the invention may be synthesised as described in the aforementioned patent applications or as set out in more recent patent US8809526 (Onyx) and patent application US2013/0345423 (Onyx).

In another aspect the present invention provides a use of a compound of formula I



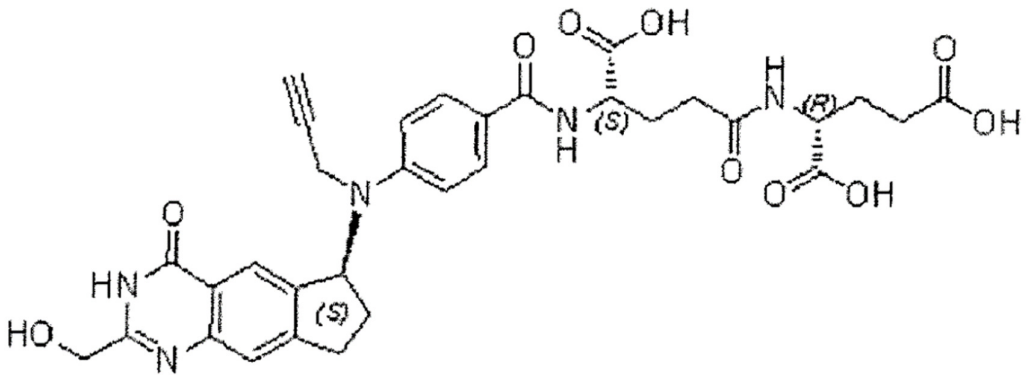
or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for the treatment of ovarian cancer that carries α-folate receptors, wherein

(i) the ovarian cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy,

(ii) a dose of between 8mg/m^2 and 15mg/m^2 of compound per patient body surface area is to be administered per administration; and

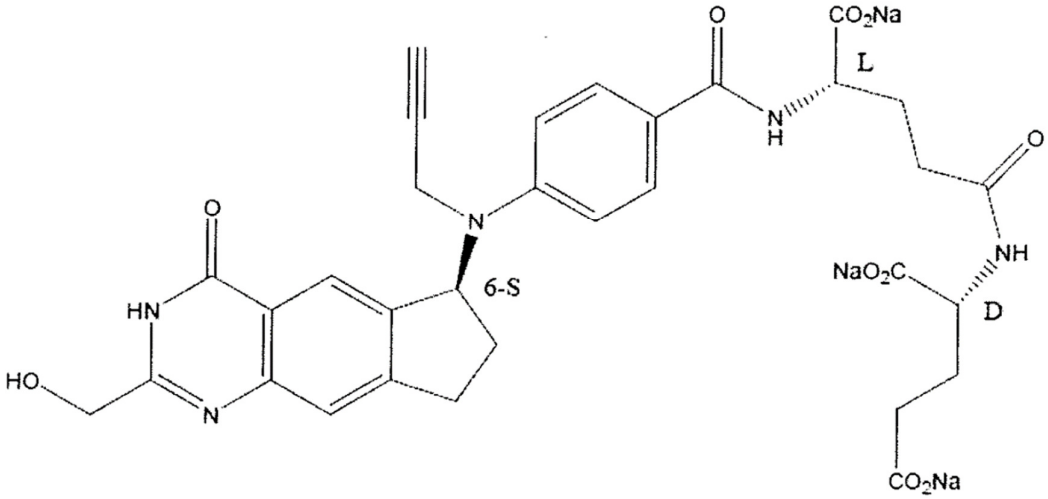
(iii) wherein administration is by infusions of the dose, wherein the infusions are spaced from 10 to 21 days apart.

In another aspect the present invention provides a use of a compound chosen from formula I



,

formula II



and pharmaceutically acceptable salts or esters thereof, in the manufacture of a medicament for the treatment of ovarian cancer that carries α-folate receptors, wherein

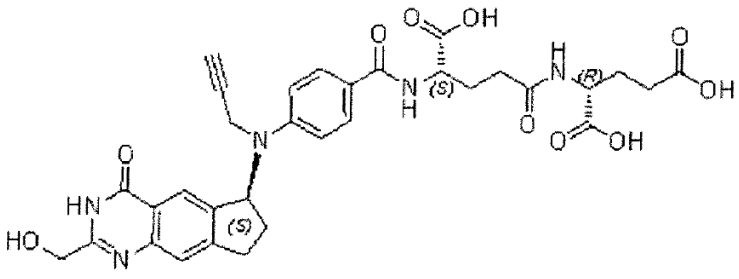
(i) the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(ii) a dose of from 8mg/m^2 to 15mg/m^2 of compound per patient body surface area is to be administered per administration;

(iii) wherein administration is by infusions of the dose, wherein the infusions are spaced from 10 to 21 days apart; and

(iv) the dose is to be administered intraperitoneally (IP).

In another aspect the present invention provides a use of a compound of formula I



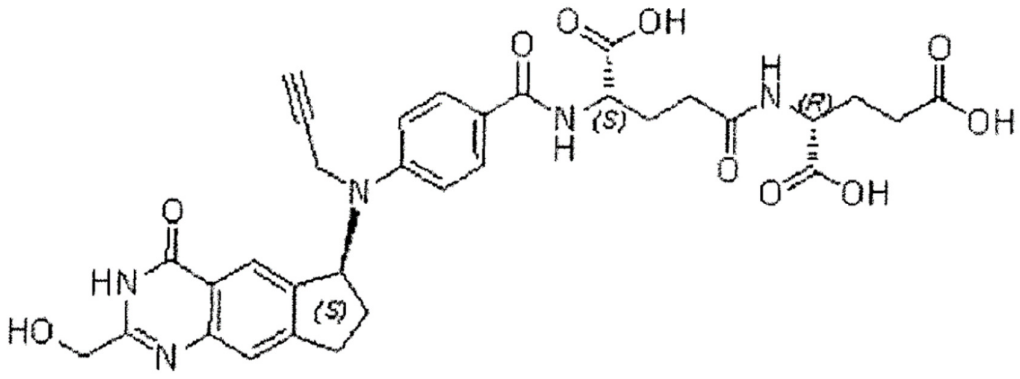
or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for the treatment of ovarian cancer that carries α-folate receptors,

wherein the ovarian cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

wherein a dose of from 8mg/m^2 to 15mg/m^2 of compound per patient body surface area is to be administered per administration;

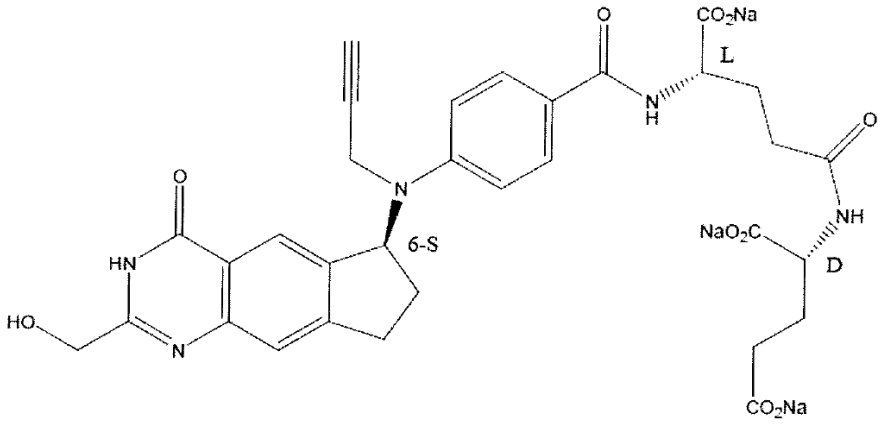
wherein administration is by infusions of the dose, wherein the infusions are spaced from 10 to 21 days apart; and wherein the dose is to be administered intraperitoneally (IP).

In another aspect the present invention provides a use of a compound chosen from formula I



,

formula II



,

and pharmaceutically acceptable salts or esters thereof, in the manufacture of a medicament for the treatment of ovarian cancer that carries α-folate receptors, wherein

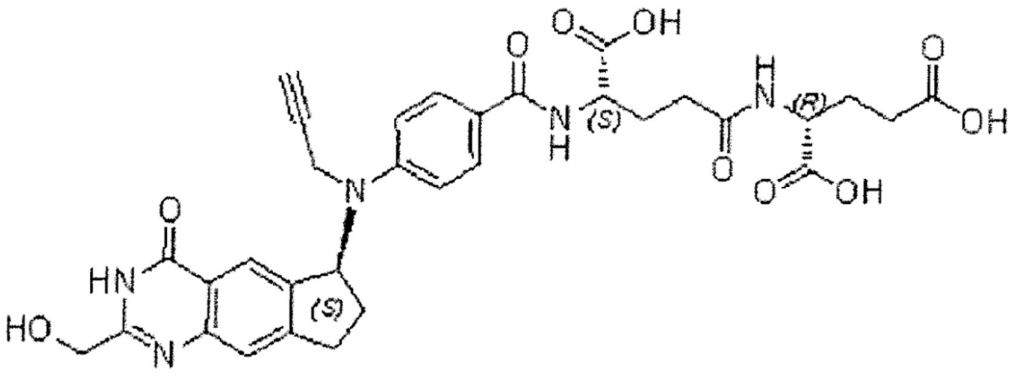
(i) the ovarian cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(ii) a dose of from 8mg/m^2 to 15mg/m^2 of compound per patient body surface area is to be administered per administration;

(iii) wherein administration is by infusions of the dose, wherein the infusions are spaced from 10 to 21 days apart; and

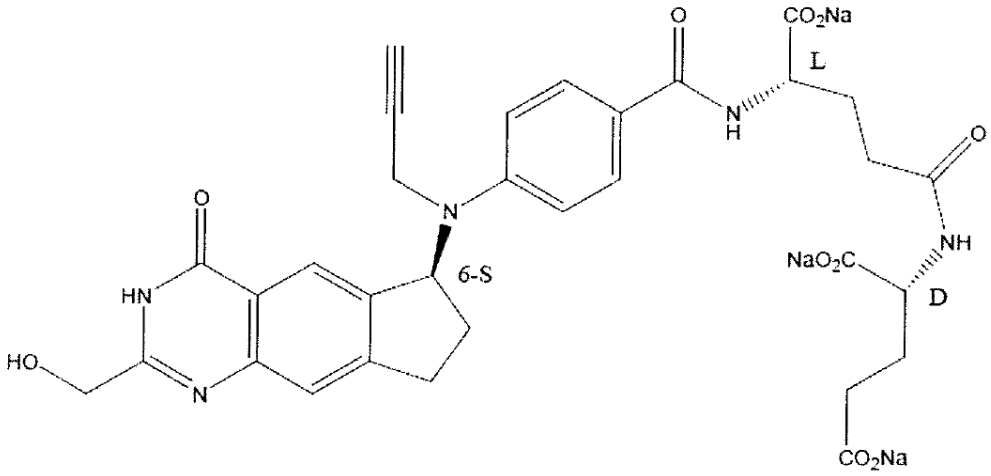
(iv) wherein at least one side effect associated with classical thymidylate synthase inhibitors or alpha folate receptor antibody drug conjugates is not observed

In another aspect the present invention provides a use of a compound chosen from formula I



,

formula II



,

and pharmaceutically acceptable salts or esters thereof, in the manufacture of a medicament for the treatment of ovarian cancer that carries α-folate receptors, wherein

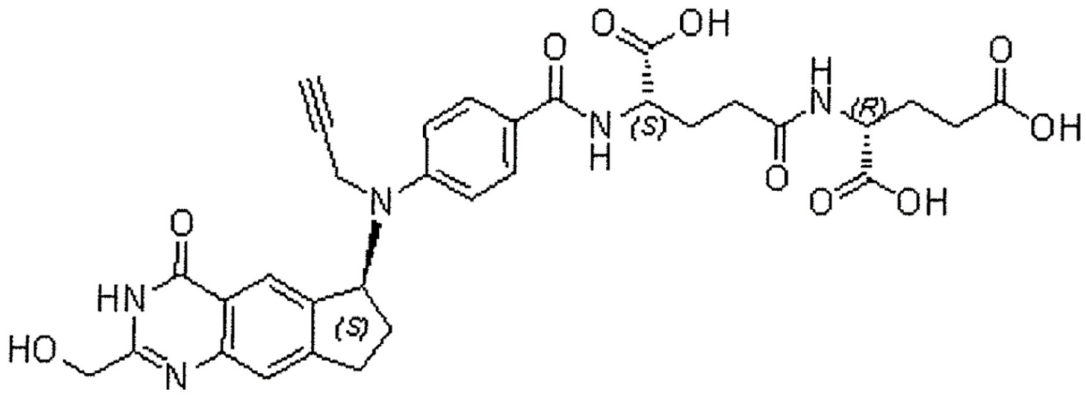
(i) the ovarian cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(ii) a dose of from 8mg/m^2 to 15mg/m^2 of compound per patient body surface area is to be administered per administration;

(iii) wherein administration is by infusions of the dose, wherein the infusions are spaced from 10 to 21 days apart; and

(iv) the dose achieves a concentration of 0.5 μM or greater of the compound for at least 72hrs.

In another aspect the present invention provides a use of a pharmaceutical composition comprising a compound of formula I



or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for the treatment of ovarian cancer that carries α-folate receptors, wherein

(i) the ovarian cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy and

(ii) a dose of between 8 mg/m^2 and 15mg/m^2 of compound per patient body surface area per administration, and

(iii) wherein administration is by infusions of the dose, wherein the infusions are spaced from 10 to 21 days apart.

FIGURES

Figures 1 to 5 show the clinical results of trial with the treatment of the present invention in humans.

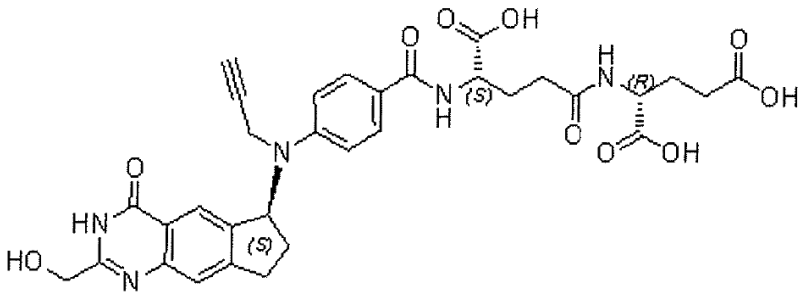
FIGURE 1: Shows the % change in tumours using RECIST criteria in patients in the dose escalation phase of the trial of Example 1 Weekly schedule is indicated by asterisk and an a-folate expressing tumour indicated by a cross.

FIGURE 2: Shows the % change in tumours as measured by CA125 level in escalation phase of the trial of example 1. Numbers represent dose mg/m2 and letters whether weekly (w) or fortnightly (f) and an a-folate expressing tumour indicated by a cross.

FIGURE 3: Shows the % change in tumours using RECIST criteria in patients in the expansion phase of the trial of Example 1 using 12mg/m^2 dose once every 14 days in 28 day cycles. An α-folate expressing tumour is indicated by a cross.

CLAIMS

1. Use of a compound of formula I



or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for the treatment of ovarian cancer that carries α-folate receptors, wherein

(i) the ovarian cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(ii) a dose of between 8mg/m^2 and 15mg/m^2 of compound per patient body surface area is to be administered per administration, and

(iii) wherein administration is by infusions of the dose, wherein the infusions are spaced from 10 to 21 days apart.

2. A use as claimed in claim 1 characterised in that the ovarian cancer is platinum refractory or resistant.

3. A use as claimed in claim 1or 2 characterised in that the ovarian cancer is selected from those expressing α-folate receptors (FR-α).

4. A use as claimed in claim 3 characterised in that the ovarian cancer expresses higher than background non-cancerous tissue levels of α-folate receptors.

5. A use as claimed in claim any one of the preceding claims characterised in that the ovarian cancer is epithelial ovarian, fallopian tube or peritoneal cancer.

6. A use as claimed in claim 5 characterised in that the cancer is serous ovarian cancer.

7. A use as claimed in claim 6 characterised in that the cancer is High-Grade Serous Ovarian Cancer (HGSOC).

8. A use as claimed in any one of the preceding claims characterised in that the dose is to be administered intraperitoneally (IP) or intravenously (IV).

9. A use as claimed in any one of the preceding claims characterised in that the dose is 10mg/m^2 to 15mg/m^2 of compound per patient body surface area per administration.

10. A use as claimed in any one of the preceding claims characterised in that the infusions are to be administered at dosing interval of about 14 days.

11. A use as claimed in claim 10 characterised in that a cumulative maximum of 150mg/m^2 of compound per patient body surface area is to be administered over the course of all the infusions.

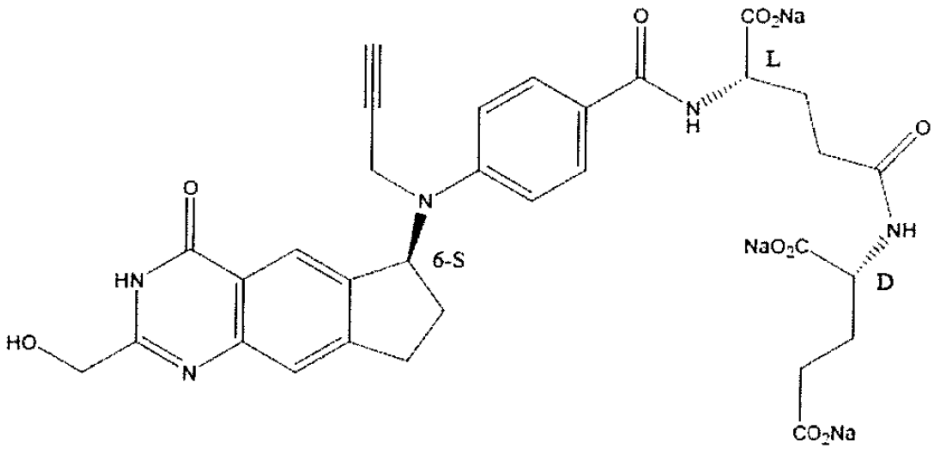
12. A use as claimed in claim 11 characterised in that the maximum cumulative dose is 144mg/m^2.

13. A use as claimed in any one of the preceding claims characterised in that an infusion of 11.5mg/m^2 to 12.5mg/m^2 is to be administered per administration.

14. A use as claimed in claim 13 characterised in that an infusion of about 12mg/m^2 is to be administered per administration.

15. A use as claimed in any one of claims 1 to 14 characterised in that the dose is added to a saline drip.

16. A use as claimed in any one of the preceding claims characterised in that the compound is the trisodium salt of formula II



17. A use as claimed in any one of the preceding claims wherein the medicament is to be administered with a therapeutically effective amount of one or more further anticancer agents.

18. A use as claimed in claim 17, wherein the medicament and the one or more further anticancer agents are to be administered separately.

19. A use as claimed in claim 17, wherein the administration of the medicament and the administration of the one or more further anticancer agents are separated by 12 hours.

20. A use as claimed in claim 17, wherein the administration of the medicament and the administration of the one or more further anticancer agents are separated by 24 hours.

21. A use as claimed in claim 17, wherein the administration of the medicament and the administration of the one or more further anticancer agents are separated by 36 hours.

22. A use as claimed in claim 17, wherein the administration of the medicament and the administration of the one or more further anticancer agents are separated by 38 hours.

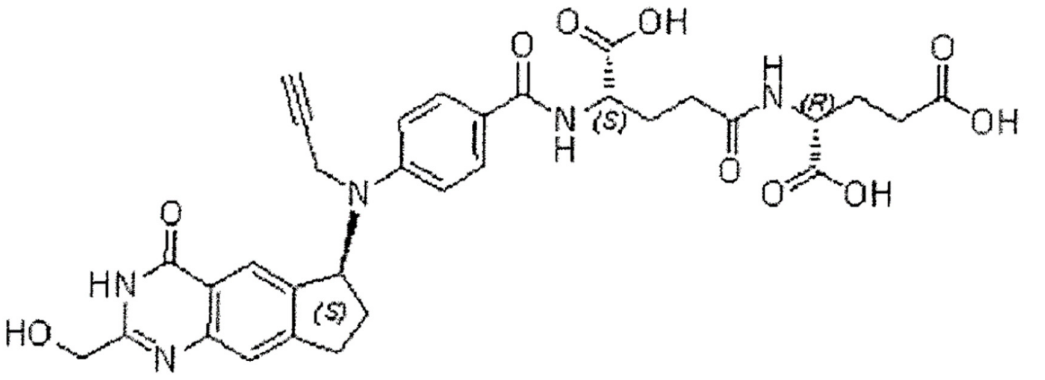
24. A use as claimed in claim 17, wherein the administration of the medicament and the administration of the one or more further anticancer agents are to be performed on alternate weeks of a 14 day dosing schedule.

25. A use as claimed in claims 17 to 24 wherein the one or more further anticancer agents used in this combination therapy are selected from Cisplatin, Carboplatin, Doxorubicin, Bevacizumab Gemcitabine, Topetecan, Paclitaxel, Docetaxel, Etoposide, Nanoparticle albumin-bound paclitaxel,

Lynparza (olaparib), Rubraca (rucaparib), Zejula (niraparib), Tecentriq (atezoizumab), Bavercio (avelumab).

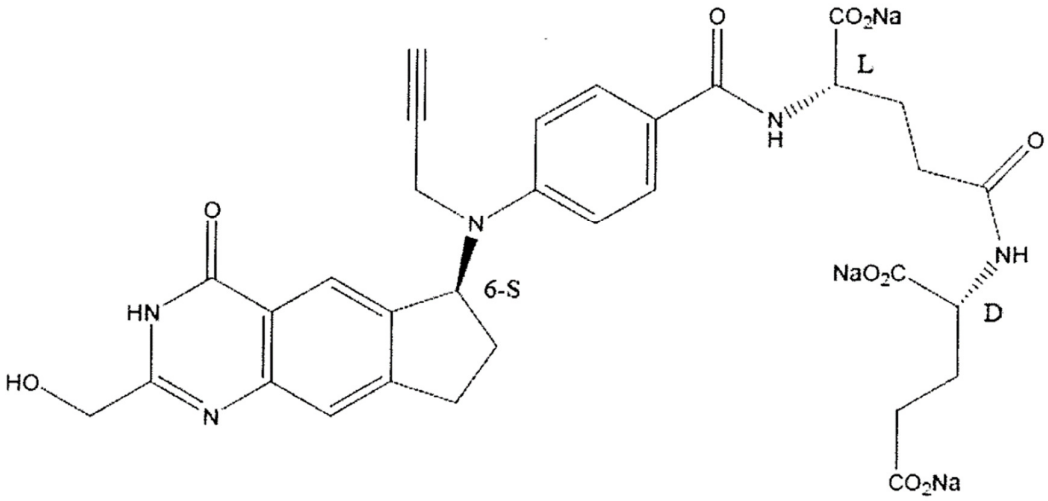
26. A use as claimed in claims 17 to 24 wherein the medicament is to be administered together with bevacizumab in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan.

27. Use of a compound chosen from formula I



,

formula II



and pharmaceutically acceptable salts or esters thereof, in the manufacture of a medicament for the treatment of ovarian cancer that carries α-folate receptors, wherein

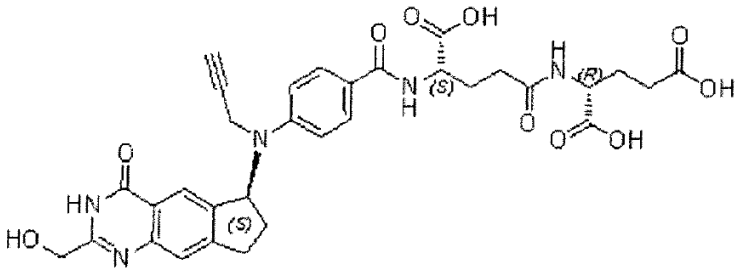
(i) the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(ii) a dose of from 8mg/m^2 to 15mg/m^2 of compound per patient body surface area is to be administered per administration;

(iii) wherein administration is by infusions of the dose, wherein the infusions are spaced from 10 to 21 days apart; and

(iv) the dose is to be administered intraperitoneally (IP).

28. Use of a compound of formula I



or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for the treatment of ovarian cancer that carries α-folate receptors,

wherein the ovarian cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

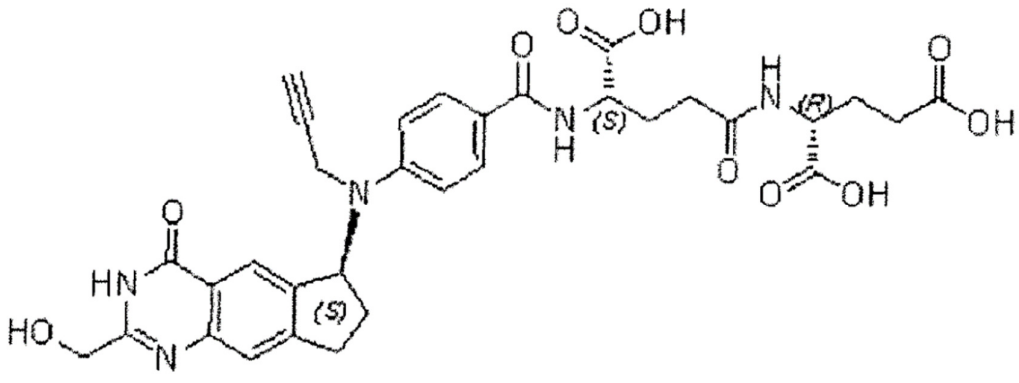
wherein a dose of from 8mg/m^2 to 15mg/m^2 of compound per patient body surface area is to be administered per administration;

wherein administration is by infusions of the dose, wherein the infusions are spaced from 10 to 21 days apart; and

wherein the dose is to be administered intraperitoneally (IP).

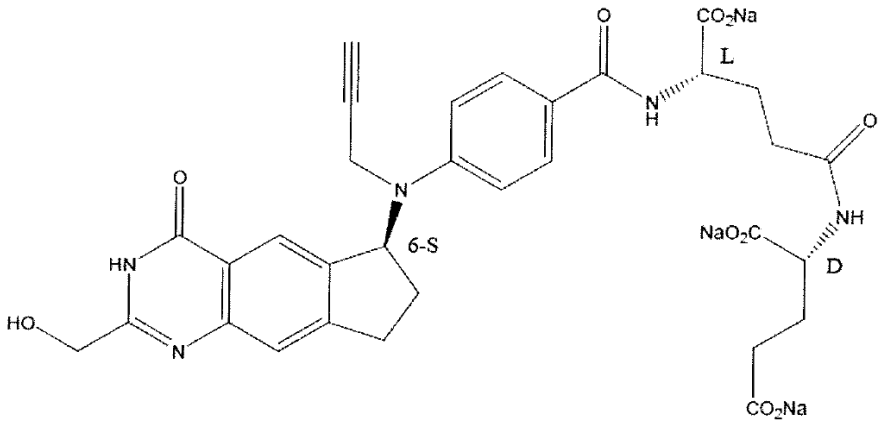
29. A use as claimed in claim 28 wherein the medicament is to be administered in combination with a therapeutically effective amount of one or more further anticancer agents.

30. Use of a compound chosen from formula I



,

formula II



,

and pharmaceutically acceptable salts or esters thereof, in the manufacture of a medicament for the treatment of ovarian cancer that carries α-folate receptors, wherein

(i) the ovarian cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(ii) a dose of from 8mg/m^2 to 15mg/m^2 of compound per patient body surface area is to be administered per administration;

(iii) wherein administration is by infusions of the dose, wherein the infusions are spaced from 10 to 21 days apart; and

(iv) wherein at least one side effect associated with classical thymidylate synthase inhibitors or alpha folate receptor antibody drug conjugates is not observed.

31. The use according to claim 30, wherein the at least one side effect is chosen from neutropenia, diarrhoea, hair loss, blurred vision or nausea.

32. A use as claimed in claim 30, or 31 characterised in that the ovarian cancer is selected from those expressing α-folate receptors (FR-α).

33. A use as claimed in claim 32 characterised in that the ovarian cancer expresses higher than background non-cancerous tissue levels of α-folate receptors.

34. A use as claimed in any one of claims 30 to 33 characterised in that the ovarian cancer is epithelial ovarian, fallopian tube or peritoneal cancer.

35. A use as claimed in claim 34 characterised in that the ovarian cancer is serous ovarian cancer.

36. A use as claimed in claim 35 characterised in that the ovarian cancer is High-Grade Serous Ovarian Cancer (HGSOC).

37. A use as claimed in any one of claims 30 to 36 characterised in that the dose is to be administered intraperitoneally (IP) or intravenously (IV).

38. A use as claimed in any one of claims 30-37 characterised in that the infusions are to be administered at dosing interval of about 14 days.

39. A use as claimed in claim 38 characterised in that a cumulative maximum of 150mg/m^2 of compound per patient body surface area over the course of all the infusions.

40. A use as claimed in claim 39 characterised in that the maximum cumulative dose is 144mg/m^2.

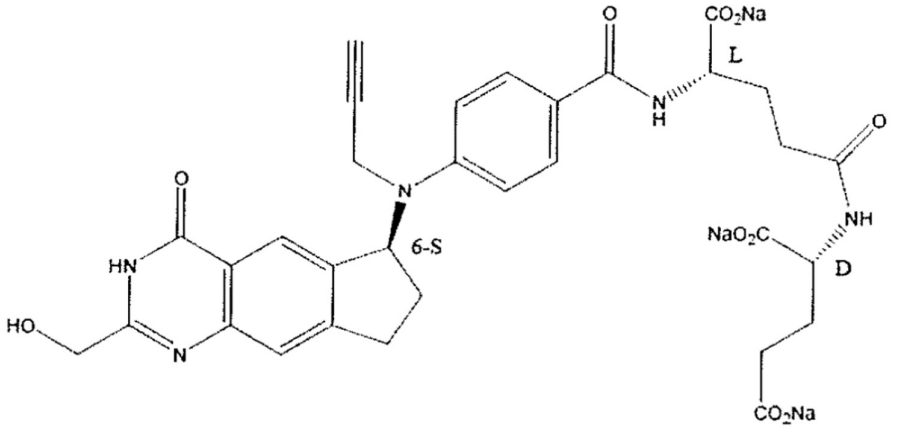
40. A use as claimed in any one of claims 30 to 40 characterised in that an infusion of 10/m^2 to 15mg/m is to be administered per administration.

41. A use as claimed in claim 40 characterised in that an infusion of 11.5mg/m^2 to 12.5mg/m^2 is to be administered per administration.

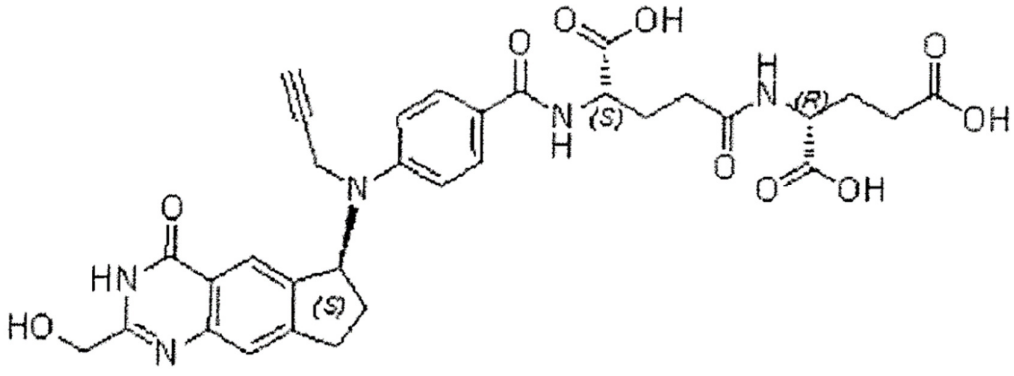
42. A use as claimed in claim 41 characterised in that an infusion of about 12mg/m^2 is to be administered per administration.

43. A use as claimed in any one of claims 30 to 42 characterised in that the dose is added to a saline drip.

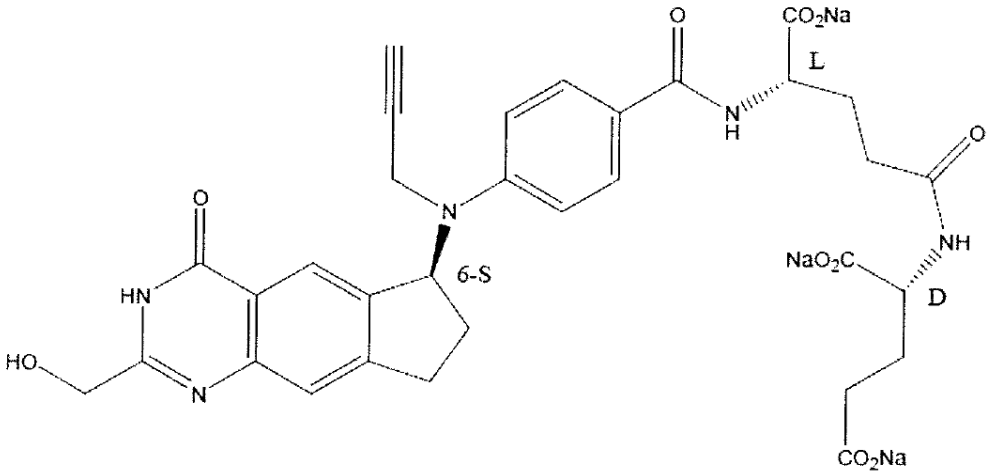
44. A use as claimed in any one of claims 30 to 43 characterised in that the compound is the trisodium salt of formula II



45. Use of a compound chosen from formula I



formula II



,

and pharmaceutically acceptable salts or esters thereof, in the manufacture of a medicament for the treatment of ovarian cancer that carries α-folate receptors, wherein

(i) the ovarian cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(ii) a dose of from 8mg/m^2 to 15mg/m^2 of compound per patient body surface area is to be administered per administration;

(iii) wherein administration is by infusions of the dose, wherein the infusions are spaced from 10 to 21 days apart; and

(iv) the dose achieves a concentration of 0.5 μM or greater of the compound for at least 72hrs.

46. The use according to claim 45, wherein a dose that achieves a concentration of 0.7 μM or greater of the compound for at least 36hrs is to be administered.

47. The use according to claim 45, wherein a dose that achieves a concentration of 0.9 μM or greater of the compound for at least 24hrs is to be administered.

48. A use as claimed in claim 45, 46 or 47 characterised in that it is selected from those expressing α-folate receptors (FR-α).

49. A use as claimed in claim 48 characterised in that the ovarian cancer expresses higher than background non-cancerous tissue levels of α-folate receptors.

50. A use as claimed in any one of claims 45 to 49 characterised in that the ovarian cancer is epithelial ovarian, fallopian tube or peritoneal cancer.

51. A use as claimed in claim 50 characterised in that the ovarian cancer is serous ovarian cancer.

52. A use as claimed in claim 51 characterised in that the ovarian cancer is High-Grade Serous Ovarian Cancer (HGSOC).

53. A use as claimed in any one of claims 45 to 52 characterised in that the dose is to be administered intraperitoneally (IP) or intravenously (IV).

54. A use as claimed in any one of claims 45 to 53 characterised in that the infusions are to be administered at dosing interval of about 14 days.

55. A use as claimed in claim 54 characterised in that a cumulative maximum of 150mg/m^2 of compound per patient body surface area is to be administered over the course of all the infusions.

56. A use as claimed in claim 55 characterised in that the maximum cumulative dose is 144mg/m^2.

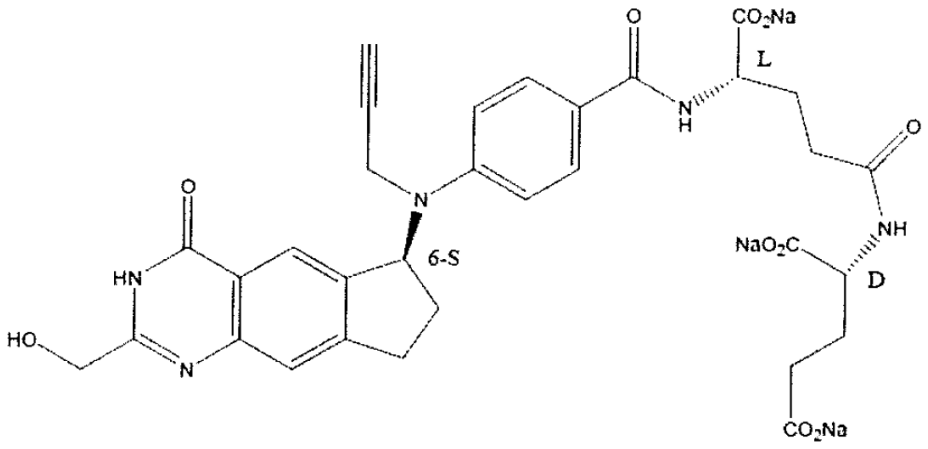
57. A use as claimed in any one of claims 45 to 56 characterised in that an infusion of 10mg/m^2 to 15mg/m^2 is to be administered per administration.

58. A use as claimed in claim 57 characterised in that an infusion of 11.5mg/m^2 to 12.5mg/m^2 is to be administered per administration.

59. A use as claimed in claim 56 characterised in that an infusion of about 12mg/m^2 is to be administered per administration.

60. A use as claimed in any one of claims 45 to 59 characterised in that the dose is added to a saline drip.

61. A use as claimed in any one of claims 45 to 60 characterised in that the compound is the trisodium salt of formula II



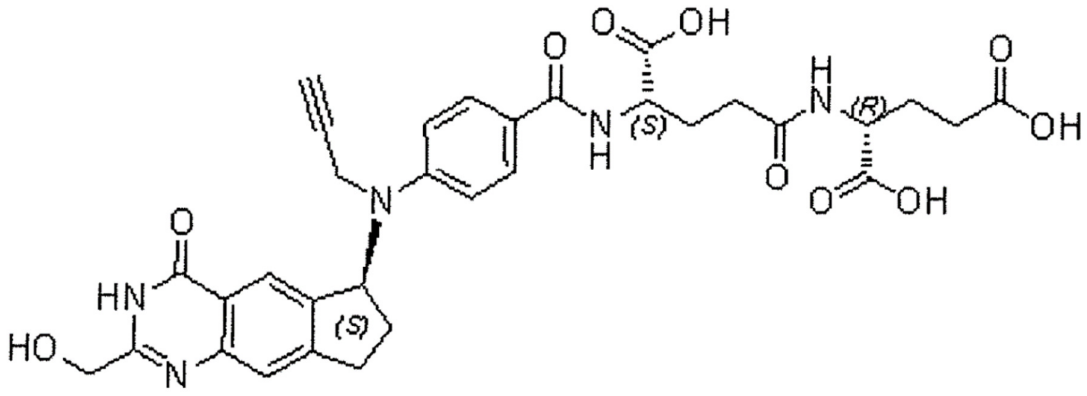
62. A use as claimed in Claim 1 wherein a dosage regimen to be administered is selected from the group

• a dose of 8 to 15mg/m^2 to be administered in a 28 day cycle at 14 day intervals on day 1 and 15

• a dose of 8 to 15mg/m^2 to be administered in a 21 day cycle on day 1.

63. A use as claimed in Claim 62 wherein the dosage regimen is a dose of 10 to 14mg/m^2 to be administered in a 28 day cycle at 14 day intervals on day 1 and 15.

64. Use of a pharmaceutical composition comprising a compound of formula I



or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for the treatment of ovarian cancer that carries α-folate receptors, wherein

(i) the ovarian cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy and

(ii) a dose of between 8 mg/m^2 and 15mg/m^2 of compound per patient body surface area per administration, and

(iii) wherein administration is by infusions of the dose, wherein the infusions are spaced from 10 to 21 days apart.