PLATINUM-RESISTANT CANCER TREATMENT

The present invention relates to novel treatment for cancer, more particularly for cancers that often show resistance to, or are otherwise refractory to, platinum based therapy. Particular cancers that are to be treated include ovarian, endometrial, mesothelial and non-small cell lung (NSCL), and cancers derived from these. More particularly preferred treatment is provided for ovarian derived cancers such as epithelial ovarian, fallopian tube and peritoneal.

Most particularly the present invention provides novel treatment for such cancers that carry α-folate receptors (FR-α), and especially those showing higher than background non-cancerous tissue levels of α-folate receptors, and particularly those having those FR-α on the surface of their cellular membranes. Cancers suitable for the present treatment also include FR-α expressing breast and lung cancers, particularly triple negative breast cancer.

The α-folate receptor is overexpressed in many carcinomas, particularly those of ovarian origin where it is overexpressed highly and homogeneously in 90% of cases; see *Cancer Res.* **51**, 5329–5338, 1991 (Campbell *et al.*, 1991). Furthermore, high α-FR expression has been linked to aggressive, platinum resistant disease and poor prognosis—see *Int. J. Cancer* **74**, 193–198, 1997 and *Int. J. Cancer* **79**, 121–126, 1998 (both Toffoli *et al.*). The β-isoform is widely expressed in tumours of epithelial and non-epithelial origin with expression levels being generally low/moderate and high, respectively, reviewed in *Critical Rev. Therap.* in *Drug Carrier Systems* **15**, 587–627, 1998 (Reddy and Low).

The present invention particularly advantageously provides a treatment for patients with High-Grade Serous Ovarian Carcinoma (HGSOC), such as in the salvage setting where there is high unmet medical need for products that are able to extend life.

Ovarian cancer is a term for a group of tumours that arise from diverse types of tissue contained in the ovary. The most common type of ovarian cancer arises from epithelial cells on the surface of the ovary, and can often spread to any surface within the abdominal cavity including the fallopian tubes and peritoneal cavity. Fallopian tube cancer and primary peritoneal cancer are histologically equivalent diseases to epithelial ovarian cancer. Ovarian cancer is classified from Stage I to Stage IV. Advanced ovarian cancer falls within Stages III and IV; Stage III denotes disease that

is locally advanced and has spread outside the pelvis into the abdominal cavity and Stage IV denotes that distant metastasis to other body organs such as the liver and lungs has occurred.

Epithelial ovarian cancers (EOCs) are the most common cause of death from gynaecological malignancy in the developed world. EOCs comprise a heterogeneous group of neoplasms including serous (68%), clear cell (13%), endometrioid (9%) and mucinous (3%) pathological subtypes. Serous ovarian carcinomas are further divided into low-grade (type I) and high-grade (type II) serous ovarian carcinomas (LGSOC and HGSOC, respectively). Most deaths are attributable to HGSOC which is approximately 20 times more common than LGSOC.

Ovarian cancer may be categorised according to the response to initial platinum chemotherapy as follows:

- platinum-sensitive- disease responds to platinum-based therapy but may relapse after 6 months or more, which can be subdivided into
    - fully platinum-sensitive - disease responds to platinum-based therapy but relapses after 12 months or more and
    - partially platinum-sensitive - disease responds to platinum-based therapy but relapses between 6 and 12 months; and
- platinum-resistant - disease which relapses within 6 months of completion of platinum-based chemotherapy and
- platinum-refractory - disease does not respond to initial platinum-based chemotherapy.

Although a significant percentage of people have disease that responds to initial chemotherapy, between 55% and 75% of these relapse within 2 years of completing treatment. In addition to these scenarios, some patients are intolerant to treatment with platinum based drugs and thus will also need alternate options to platinum that the regimens of the present invention now provide.

The initial therapeutic approach for HGSOCs is usually surgical tumor debulking followed by chemotherapy. Optimal debulking, with no macroscopic residual disease, is the most important prognostic indicator. However, as HGSOC is asymptomatic in the early stages most patients present with advanced stage disease.

Most HGSOCs (80%) respond well to platinum/taxane therapy initially, with drug resistance emerging during subsequent treatment cycles. However, a minority of

HGSOC cases (20%) are refractory to platinum-based chemotherapy from the time of presentation, but the basis for this drug resistance is not known. Disease Stages III and IV, a preferred target population for the present treatment, have a high rate of recurrence.

Patients with optimally debulked (≤1 cm) Stage III ovarian cancer are typically offered intraperitoneal (IP) chemotherapy after front-line surgery. At this time, there is no standardized regimen for IP therapy; however, dosing regimens with drugs such as paclitaxel and cisplatin, or a carboplatin regimen may be used. If the patient cannot tolerate IP delivery then intravenous drug may be given such as paclitaxel and carboplatin or docetaxel plus carboplatin.

Treatment of Stage III and IV disease is usually with chemotherapy; the treatment choice depends on the time elapsed since previous complete response to platinum-containing chemotherapy. Although liposomal doxorubicin is a good first choice, there are many agents with similar efficacy and the final choice depends on individual circumstance and patient and physician preference. Some of the drugs available include Gemcitabine, Topetecan, Paclitaxel, Docetaxel, Etoposide and Nanoparticle albumin-bound paclitaxel. Consideration may also be given to bevacizumab as a single agent or in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan.

Other possible therapies in drug company pipelines include PARP inhibitors, such as Lynparza (olaparib) and Rubraca (rucaparib) (both labels limited to BRCA mutations) and Zejula (niraparib); and check point inhibitors such as Tecentriq (atezoizumab) and Bavercio (avelumab) for non BRCA mutations. However many key opinion leaders have expressed the belief that such drugs need to be used with more clearly identified populations to be capable of increasing overall response rates. Keytruda (pembrolizumab) has also been found to have some efficacy where high levels of PD-1 are found on T-lymphocytes and tumours.

Several FR-α targeted drugs have been put into clinical trials. The FR-α targeted monoclonal antibody Farletuzumab failed to improve progression free survival (PFS) in patients with platinum-sensitive epithelial ovarian cancer in a 1,100 patient Phase III clinical in combination with paclitaxel and carboplatin. Vintafolide, a conjugate of an α-folate receptor targeting moiety with Vinblastine, has shown some success at improving PFS in combination with docetaxel in folate receptor positive non-small cell lung cancer (NSCLC) and has been trialled together with

pegylated liposomal doxorubicin (PLD) in ovarian cancer but the Phase III trial failed to meet the prespecified criteria for PFS to allow continuation of the study. Antibody-drug conjugate IMGN853 (mirvetuximab soravtansine) has also been through Phase I trial in platinum resistant epithelial ovarian cancer with some indication of potential for increasing PFS at a dose of 6mg/kg every three weeks with PFS of 6.7 months in 39% of patients who had three or less prior lines of therapy.

Despite the possibility that combinations of these agents may prove useful in the platinum resistant setting, there remains a need for treatment of platinum resistant cancers and particularly ovarian cancers such as HGSOC as it accounts for the most ovarian deaths and has shown little improvement in overall survival for decades. Whereas potential blockbuster drugs such as immune checkpoint inhibitors have yielded impressive clinical responses in melanoma and non-small cell lung cancer, possibly due to exceptionally high mutational loads, by contrast HGSOC has intermediate mutational load with lower numbers of neoantigens expected. (Bowtell et al. Nat Rev Cancer 2016 June). Current single agent HGSOC therapies have overall response rates (ORR) of 15-20% and progression free survival (PFS) of only 3 to 4 months.

A further drug class includes the thymidylate synthase (TS) inhibitors CB3717, ZD1694 (raltitrexed), LY231514 Alimta (pemetrexed) and ZD9331 (plevitrexed). All of these TS inhibitors have demonstrable clinical activity in a range of solid tumours (see *Cancer Treatment Reports*, 1986, **70**, 1335 and Beale *et al.*, "Tomudex: Clinical Development" in *Antifolate Drugs in Cancer Therapy* (ed. Jackman), Humana Press, Totowa, New Jersey, USA, pp. 177–181, 1999). Side-effects of raltitrexed and ZD9331 are predominantly related to inhibition of TS in gut and bone-marrow.

Raltitrexed and pemetrexed are examples of "classical" TS inhibitors defined by the following properties: the reduced foliate carrier (RFC) is the main transporter into cells; they are excellent substrates for folylpolyglutamate synthase (FPGS) and thus extensively polyglutamated in tissues/tumours to polyglutamates which are effective cytotoxic drug species; and they have fairly short half-life in plasma. Because these classical inhibitors are cleared slowly from tissues because of polyglutamation, they are often cytotoxic and are used in an infrequent short-infusion, eg. about 15 min, dosing regimen at high dosages.

Plevitrexed is a "non-classical" TS inhibitor in that it is not polyglutamated and is has the following properties: the RFC is the main transporter into cells; it is not a substrate for FPGS; TS Ki ~0.4nM, i.e. similar to polyglutamates of raltitexed and pemetrexed; it is readily effluxed from cells and thus not retained well in tissues/tumours; and has a long plasma half life.

Whilst pemetrexed has been approved for use in non-small cell lung cancer and pleural mesothelioma, it has also been proposed as a treatment for platinum-resistant ovarian cancer. For example in this indication 500mg/m^2 pemetrexed was given on day 1 and gemcitabine on day 8 of a 21 day cycle (Clin Transl. Oncol (2009) 11:35-40 and at 900mg/m^2 once every 21 days (J. Clin Oncol 27: 2686-2691). Further discussion of these trials and others is provided in Expert Opin. Investig. Drugs (2012) 21(4) and Expert Opin. Investig. Drugs (2013) 22((9) the latter of which notes a recommended single agent pemetrexed dose of 600mg/m^2. This paper also notes that at that date no antifolate drug, which TS inhibitors are, had been approved for the treatment of ovarian cancer.

A further subset of this group of TS inhibitor compounds are FR-α targeted cyclopenta[*g*]quinazolines, described in patent applications WO-A-94/11354, WO-A-95/30673 and WO-A-03/020748. US5789417, US5747499, US7250511, US7297701, US7528141, US7705006, US7863284, US8063056, US8486955 and US8552016 are incorporated herein by reference for purposes of US patent rights. These documents teach that these compounds be administered at a dose within a range of 50–25000, particularly 50–5000, mg per square metre body area patient (mg/m^2), i.e. approximately 1500mg/m^2, particularly 1–100 mg/kg. Higher dosages are taught could be employed and where subcutaneous infusion is used that the dose range may be increased to 1–1000 mg/kg, preferably 10–250 mg/kg, particularly 30–150 mg/kg.

These inhibitors may also be used against other cells expressing FR-β, in contrast to FR-α, particularly those involved in rheumatoid arthritis and acute myeloid leukemia. For this purpose US8466111 teaches a dose within the range 50-25000mg/m^2, but also lists 5-25000mg/m^2 but states that for subcutaneous administration the dose is increased to 1-1000mg/kg or 0.1-10mg/kg. There is discussion of topical administration at 0.1 to 10mg/kg and oral tablets containing 1, 10, 50 and 100mg of compound are disclosed as is an injection solution of 1, 10 and 50mg/ml.

The higher dosages used are consistent with raltitrexed and pemetrexed and this subset of TS inhibitor compounds share similar properties such as: FR is the main transporter; uptake via FR is slower and more easily saturable than is RFC-mediated uptake of other antifolates; they are not a substrate for FPGS; and TS Ki ~1.4nM, which is similar to polyglutamates of raltitexed and pemetrexed. But because the compounds are readily effluxed from cells not retained in tissues/tumours, it was taught that high dosages should be tolerable.

Typically, TS requires inhibition for at least 24hours to induce antiproliferative effects, and adequate intracellular exposure to drug of at least 2 to 3 days repeated frequently e.g. weekly for TS inhibitors to be effective. This is achieved by polyglutamation of raltitrexed and pemetrexed which overcomes the short plasma half-life and short extracellular exposure. Long intracellular exposure with plevitrexed, for example, is achieved by the unusually long plasma final half-life providing prolonged extracellular exposure.

Surprisingly on administration of the lead compound of this newer class FR-α targeted TS inhibitors to man half life levels were found to be unusually long. This compound, ONX-0801 (hereafter BTG945) has a high affinity for the alpha-folate receptor (FR-α) and enters cells via FR-α mediated transport. It has a modified glutamate ligand, L-glu-y-D-glu dipeptide, and so is not a substrate for FPGS. It binds the α-FR with an affinity that is 70% of folic acid (FA) (Theti et al., 2003); it binds FR-β with similar affinity (van der Heijden et al., 2009) and it appears to have negligible affinity for the ubiquitous reduced folate carrier (RFC) except at high concentrations (Gibbs et al., 2005). This, it has been found, leads to a targeted concentration and time-dependent inhibition of tumour cell proliferation in vitro.

Once inside the cell, BTG945 binds irreversibly to the active site of thymidylate synthase, which is then prevented from performing its normal role in generating thymidine monophosphate (dTMP), a key step in DNA synthesis and repair similarly exploited by the approved TS-inhibitors.

A first in human Phase I clinical trial of BTG945, identified therein as ONX801, was initiated 30/09/2009 with trial registration number ISRCCTN79302332 with the aim of finding a tolerable dose for 3 hour infusion on days 1, 8 and 15 of a 21 day cycle which would inhibit tumour cell growth. However, this trial was abandoned 30/03/2011 due to toxicity at the predicted therapeutically effective dose of 45mg/m^2 with incidence of Brochiolitis Obliterans with Organising

Pneumonia (BOOP), irreversible and believed to increase with culmulative dose. This lead to the conclusion that the drug could not be used at the preconceived dose and regimen as this toxic dose was less than that taught as preferred minimal dose for treatment.

Given the high unmet need for the target treatment cohort, the present inventor has reassessed the dosage regimen that might be applied to the drug BTG945 to render it clinically useful. Analysis of unpublished human plasma drug levels suggested that much lower doses of drug would be necessary to avoid toxicity. The inventor and applicant initiated a new Phase I trial, EudraCT3941, at these presumed safe but predicted non-therapeutic doses wherein it has now been found that unexpected efficacy against platinum resistant tumours, particularly FR-α expressing tumours, in human patients is provided at far lower levels of drug than had previously been thought necessary and without occurrence of the treatment limiting BOOP. This efficacy has been exhibited as partial responses, using RECIST criteria, and stable disease, providing periods of progression free survival, particularly providing partial responses and/or objective response rates (ORR) in high percentages of ovarian cancer patients showing α-folate receptor expression, particularly when such expression exibits receptor on tumour membranes.

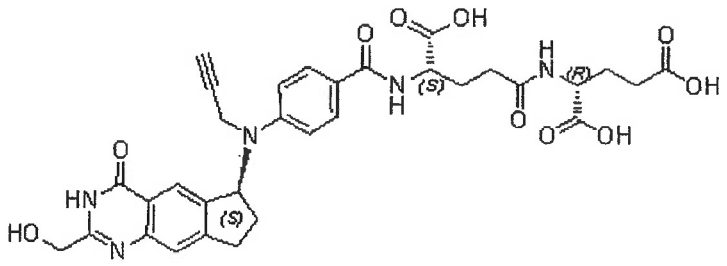
So, whilst BTG945 has comparable Ki to raltitrexed and pemetrexed against isolated target thymidine synthase (1.2nM as compared to 1.4nM), the doses required to have efficacy in man are considerably less than those previously envisioned yet in the FR-α expressing preferred target group the compound appears to have efficacy far superior to that seen with other members of the TS inhibitor class.

Particularly surprising and advantageous is the finding that the side effect profile of BTG945 is unusually favourable. Dose limiting effects other than BOOP were not seen and BOOP itself has proven manageable and/or may be eliminated by optimised regimens using for example 2 or 3 weekly dosing. Side effects such as neutropenia, diarrhoea and hair loss, normally associated with thymidine synthase inhibitors, were not observed, nor were side effects associated with α-folate receptor antibody conjugates, such as diarrhoea, blurred vision and nausea. Furthermore conventional toxicities associated with cytotoxic chemotherapy, such as myelotoxicity, nephrotoxicity and neurotoxicity, were not observed.

Some trial patients' cancers were shown to respond at as low as 1mg/m^2 in the treatment regimen outlined below. Side effects determined to date suggest that this

regimen may be employed as monotherapy or in combination with any of the currently employed therapies described herein as toxicities are not overlapping. Such findings in the clinical setting now provide treatment of platinum resistant cancer that can be used as monotherapy or in combination with other available treatments with promise of extending PFS in a patient group with remaining high unmet need. Combination of the present treatment with first line treatments such as paclitaxel or carboplatin particularly are made available.

In a first aspect the present invention provides a compound of formula I



or a pharmaceutically acceptable salt or ester thereof for the treatment of cancer 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 and

(ii) the treatment is with a dose of between 1mg/m^2 and 30mg/m^2 of compound per patient body surface area per administration.

The treatment is preferably with a dosage regimen that results in plasma concentration of drug 0.5μM or greater for at least 72 hours. More preferably the dosage regimen results in a plasma concentration of drug immediately after dosing that is from 1μM to 5μM for no more than 72 hours, preferably for no more than 60 hours. Most preferably the dosage regimen maintains the plasma concentration of drug from 0.1μM to 2μM for at least 50% of the treatment cycle period.

The treatment is preferably with a dosage regimen selected from

- a dose of 1 to 10mg/m^2 administered in a 28 day cycle at 7 day intervals on day 1, 8, 15 and 22.
- a dose of 6 to 14mg/m^2 administered in a 28 day cycle at 14 day intervals on day 1 and 15
- a dose of 10 to 30mg/m^2 administered in a 21 day cycle on day 1.

The cancer is preferably one that is platinum refractory or resistant. Preferably the cancer is selected from ovarian, endometrial, mesothelial, non-small cell lung or a cancer derived from one of those.

More preferably the cancer is selected from those expressing α-folate receptors (FR-α) and especially those showing higher than background non-cancerous tissue levels of α-folate receptors. Most preferably the FR-α is expressed on the surface membranes of the cancer cells. Most preferably the cancer is an ovarian cancer such as epithelial ovarian, fallopian tube or peritoneal cancer, but may also be breast or lung cancer, for example triple negative breast or non-small cell lung. Specifically preferred cancer to be treated is serous ovarian cancer such as High-Grade Serous Ovarian Cancer (HGSOC) such as found in the salvage setting.

For the avoidance of doubt, platinum drug based therapy includes, but is not limited to, that with drugs Cis-platin or Carboplatin.

Whilst treatment with doses from 1mg/m^2 to 30mg/m^2 is included in the scope of the invention, preferred doses are from 3mg/m^2 to 30mg/m^2 of compound per patient body surface area per administration, more preferably doses of 5mg/m^2 to 20mg/m^2 of compound per patient body surface area per administration, still more preferably a dose of 8mg/m^2 to 15mg/m^2 , most preferably 10mg/m^2 to 15mg/m^2 and particularly about 12mg/m^2, eg. 11.5mg/m^2 to 12.5mg/m^2 of compound per patient body surface area per administration.

The dose is preferably administered intraperitoneally (IP) or intravenously (IV). IP administration will allow dosing with less risk of systemic side effects, particularly those that would affect the lungs such as BOOP. Typically the dose is administered intravenously.

In one preferred embodiment of the invention the compound is administered intraperitoneally (IP) as an injection, particularly a single injection, in a suitably sized volume, for example from 1ml to 10ml, more preferably 2ml to 6ml containing an appropriate amount of compound to meet the mg/m^2 dosage requirement. Typical such doses will be 2, 3, 4 or 5 ml of solution. Typically being an aqueous solution which may be in saline or in water for injection. The compound here is the 'Drug Substance' and the 'Drug Product' is a vial with the appropriate volume for a single IP administration. In a further preferred embodiment, multiple IP injections are given each as from 1ml to 10ml, but more preferably 2ml to 6ml solution containing the appropriate mg of Drug Substance. Typical such doses will be 2, 3, 4 or 5 ml of

solution. Each 'Drug Product' provides for single or multiple IP injections and the Drug Product is a vial containing the Drug Substance, for example being a glass vial, eg a clear glass vial, with a stopper and suitable fixing to maintain the stopper in place such as an aluminium crimp seal.

In a further preferred embodiment, the compound is conveniently administered by injecting the content of a vial provided by pharmaceutical company supplier into a sterile saline bag as part of a saline drip. Typically the 'Drug Product' is a sterile aqueous solution of the Drug Substance BTG945 as trisodium salt, preferably being the dihydrate in solid form. The Drug Product is contained for example in a Type 1 clear glass vial, with a stopper and aluminium crimp seal. The labelled strength of each vial includes for example a 2-mL solution containing the appropriate mg of the Drug Substance. Conveniently, the only excipient in the BTG945 trisodium salt Drug Product can be sterile water for injection. Other components conventional in pharmaceutical compositions may of course be provided.

Drug Product vials are typically stored at low temperature and they are thawed prior to use, then the desired aliquot is withdrawn from 1 or multiple stoppered vials using a sterile syringe. This aliquot is then directly added to an infusion bag for further dilution in 250 mL of 0.9% sterile saline (USP) for injection, whether IP or IV. Once diluted into infusion bags, the prepared solution should preferably be administered to patients at ambient temperature within 24 hours. Prior to administration, the vials and bags should be protected from light.

In one preferred embodiment for IP infusion the aliquot is directly added to an infusion bag for further dilution in 10ml, 15ml, 25ml or 50ml of 0.9% sterile saline (USP) for IP injection or infusion. Once diluted these bags are treated as previously described.

More particularly the invention treats with the said calculated dose by infusions, particularly intravenous infusions (IV) or as single or multiple injections, as set out above spaced between 10 and 28 days apart, more preferably between 10 and 21 days apart and most preferably at dosing interval of about 14 days or 21 days. Still more preferably, when administered IV, the invention treats with a cumulative maximum of 150mg/m^2 of compound per patient body surface area over the course of all infusions. More preferably this limit also applies to IP dosaging. More preferably the maximum cumulative dose is 144mg/m^2.

Treatment in accordance with the present invention provides the compound preferably in infusions 14 or 21 days apart in 21 or 28 day cycles, most preferably 28 day cycles of two infusions each cycle, one on day 1 and one on day 15. These cycles are preferably repeated until the maximum cumulative dose is reached. Infusions are preferably carried out over 0.5 to 3 hours. As the treatment may be effective using as little as 1mg/m^2 it will be realised that infusion rates of 1 hour will be sufficient. Thus infusions may be carried out over 0.5 to 1 hour, over 1 hour, but fewer than 3 hours.

More preferred dosages for each administration, eg infusion, are 1mg/m^2 to 20mg/m^2, preferably 3mg/m^2 to 20mg/m^2, more preferably 6mg/m^2 to 18 mg/m^2, still more preferably from 8mg/m^2 to 16mg/m^2, eg from 10mg/m^2 to 15mg/m^2 and from 10mg/m^2 to 12mg/m^2. The most preferred dose is about 12mg/m^2. At a 12mg/m^2 dose given in 28 day cycle once every 14 days it can be seen that the maximum cumulative recommended dose will be reached in just under 6 months. A further preferred dose is a 12mg/m^2 dose given once every 21 days in 21 day cycles. Further dosing may considered if the attending clinician is monitoring for the irreversible BOOP or similar side effect. When patients show signs of BOOP, for example if there is evidence of accumulation of inflammatory cellular exudate (AICE) on CT scan, the dose of drug compound should be reduced. It may also be prudent to stop drug administration for a short period, eg. 2 or 4 weeks, and then recommence with a lower preferred dose. ACIE has been observed on radiological scans, and it has been found that the condition stopped development or was reduced by halting dosing at 12mg/m^2 for 2 weeks and then recommencing at 6mg/m^2 until the maximum cumulative dose of 144 mg/m^2 is achieved.

In a particularly preferred embodiment, the preferred dosage administered achieves a blood concentration of about 0.5 μM or greater of the compound for at least 72 hrs, preferably less than 2.0μM and more preferably about 0.7 μM or greater is achieved for at least 36hrs or even more preferably about 0.9 μM or greater is achieved for at least 24hrs, more preferably also being less than about 1.5μM. This level is particularly preferred for IV administration. It is preferred that blood plasma levels of drug do not remain over 1μM for more than 72 hours. Most preferably the dosage regimen maintains the plasma concentration of drug from 0.1 to 2μM for at least 50% of the treatment cycle period. More preferably 0.1 to 1μM for 50% of said period.

One particularly preferred cohort of suitable cancers for the treatment of the invention are those of female patients with newly diagnosed, histologically confirmed, high risk advanced (FIGO stage III - IV) BRCA mutated high grade serous or high grade endometrioid ovarian cancer, primary peritoneal cancer and/or fallopian-tube cancer.

Stage III patients preferably have had one attempt at optimal debulking surgery (upfront or interval debulking). Stage IV patients preferably have had either a biopsy and/or upfront or interval debulking surgery.

Particularly preferred are cancers of patients who have completed first line platinum (e.g. carboplatin or cisplatin) therapy (intravenous or intraperitoneal).

Most effectively treated by the present treatment are cancers that express α-folate receptors, particularly those expressing α-folate receptors on the membranes and/or in cytoplasm of at least 25% of cells of the cancer. More effectively treated are cancers that express α-folate receptors on or in at least 50% of the cells of the cancer and most effectively those expressing α-folate receptors on or in at least 75% of the cells of the cancer. Such levels may be determined by histological investigation of biopsy tissue using α-folate specific antibodies linked to visualisation agents as known in the art. For maximal efficacy the cancers are those that express FR-α on the cell membranes.

An example of a method for assessing α-folate receptor expression on membranes and in cyctoplasm is described in Kurosaki et al (2016) Int. J. Cancer: 138, 1994–2002 VC 2015 UICC where the tumour FR-α expression on FFPE (formalin-fixed paraffin-embedded) specimens was investigated using a specific antibody NCL-L-FRalpha (clone BN3.2; Leica Biosystems, UK) on a total of 164 EOCs, including borderline malignancies. Immunohistochemical staining was performed on full section slides using a BenchMark XT automated slide stainer and an iView DAB detection kit according to the manufacturer's instructions (Ventana Medical Systems, Tucson, AZ). Sections were deparaffinized, hydrated and antigen retrieval with Cell Conditioning Solution 1 (Ventana Medical Systems), followed by the mouse monoclonal anti-FRA antibody (1:40 dilution) incubation for 30 min. Positive staining was defined as the presence of membranous or membranous with cytoplasmic stain in tumor cells. Slides were scored as <1% positive tumor cells staining as negative, 1–25% positive tumor cells staining as weak (11), 25–75% staining as moderate (21) and greater than 75% staining as strong (31). The scoring of

FR-α staining was evaluated in a blinded fashion by two independent observers. Any discrepancies were resolved by joint review over a double-headed microscope.

An alternative method for non-invasively ascertaining the suitability of a patient for treatment using the present invention assays for α-folate receptors in the blood. Such assays are described for example Basal et al (2009) PLoS ONE 4(7): e6292. Doi:10.1371/journal.pone.0006292, at least for ovarian cancers. Where α-folate receptor is found on membranes, it can be shed into circulating physiological fluids such as blood serum. In the case of ovarian cancer that team have found that patients with ovarian cancer have elevated levels of circulating α-folate receptor (FRα). This was found to be the case even where the cancer was in its early stages.

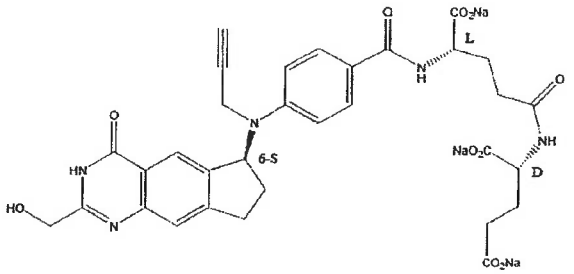
Kurosaki et al (2016) Int. J. Cancer: 138, 1994-2002 further confirm the applicability of serum α-folate receptor levels for diagnosing ovarian cancers of epithelial origin and correlated high serum FR-α with shorter PFS.

In addition to the ovarian tissue derived cancers specified above, FR-α overexpressing cancers that are suitable for treatment by the method and regimens of the invention also include cancers of the uterus, mesothelium, kidney, stomach, lung, colon, choroid plexus and brain. The highest levels of overexpression have been detected in non-mucinous ovarian cancer (Toffoli et al., 1998) where > 90% of patients' tumours exhibit overexpression of the FR- α, but high levels have also been demonstrated in papillary serous endometrial cancer (Allard et al., 2007) renal cell cancer, and NSCLC (Parker et al., 2005). In addition, breast, primary CNS, colon and gastric cancers show varying degrees of expression (Low and Kularatne, 2009).

Tumour Type	% tumours overexpressing FR-α
Ovary	92%
Uterus	91%
Mesothelium	70%
Kidney	50%
Stomach	38%
Lung	33%
Colon	22%
Choroid plexus	80% (ependymal)
Brain	80% (metastases)

Table 1: Alpha-Folate Receptor Expression in Selected Tumours (Weitman 1994; Garin-Chesa 1993; Bueno 2001)

The compound for use in the present invention has IUPAC nomenclature *N*-{*N*-{4-[*N*-((6*S*)-2-Hydroxymethyl -4-oxo- 3,4,7,8-tetrahydro-6*H*-cyclopenta[*g*]quinazolin-6-yl)-*N*-(prop-2-ynyl)amino]benzoyl} -L-γ-glutamyl}-D-glutamic acid or is a salt thereof and is herein referred to as BTG945, of which the trisodium salt thereof has the general formula II



Alternate nomenclature is D-glutamic acid, N-[4-[2-propyn-1-yl-[(6S)-4,6,7,8-tetrahydro-2-(hydroxymethyl)-4-oxo-3H-cyclopenta[g]quinazolin-6-yl]amino]benzoyl]-L-gamma-glutamyl-, sodium salt.

The (6RS) racemate is also known to be an active form containing the active (6S) as described. It will be realised that doses may need to be at the higher end of the described ranges if they use the racemate as it contains only 50% of the (6S) form.

Where the compound is provided as an ester, this may be of a simple alcohol conjugated with one or more of the carboxylate moieties, which otherwise would be sites of sodium linkage in the formula above. The resulting alkyl esters may be any of those equivalent to the parent compound for regulatory purposes. A suitable pharmaceutically-acceptable ester form of the cyclopenta[*g*]quinazoline for the treatment of the invention is, for example, an ester with an aliphatic alcohol of up to 6 carbon atoms, for example a methyl, ethyl or *tert*-butyl ester. As three carboxy groups are present a salt or ester may be mono-acid-di-salt or -ester, di-acid-mono-salt or -ester or even tri-salt or –ester may be used.

A suitable pharmaceutically-acceptable salt form of the compound for the treatment of the invention is, for example, an acid addition salt with an inorganic or organic acid, for example hydrochloric, hydrobromic, trifluoroacetic or maleic acid; or an alkali metal, for example sodium, an alkaline earth metal, for example calcium, or ammonium, for example tetra(2-hydroxyethyl)ammonium, salt. Most preferred is the trisodium salt.

The cyclopenta[g]quinazoline or salt described in the treatment of the present invention are believed in part at least to function as anti-cancer agents due to its ability to inhibit the enzyme thymidylate synthase.

The cyclopenta[g]quinazoline or salt composition may be in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; a form suitable for topical use, for example a cream, ointment, gel or aqueous or oily solution or suspension; a form suitable for nasal use, for example a snuff, nasal spray or nasal drops; a form suitable for vaginal or rectal use, for example a suppository; a form suitable for administration by inhalation, for example as a finely divided powder such as a dry powder, a microcrystalline form or a liquid aerosol; a form suitable for sub-lingual or buccal use, for example a tablet or capsule; or a form suitable for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion use), for example a sterile aqueous or oily solution, emulsion or suspension. In general the above compositions may be prepared in a conventional manner using conventional excipients.

The preferred form of compound is for parenteral administration. Particularly preferred is compound for infusion, where the compound is preferably formulated with saline or water for injection. Alternatively it is provided in solid format ready to be admixed with said water or saline. For example the dihydrate of the trisodium salt.

The composition may contain, in addition to the cyclopenta[g]quinazoline used in the invention, one or more other anti-cancer substances or palliative substances selected from, for example, other antimetabolites, DNA interacting agents, immune-oncological agents, tumour blood vessel inhibiting agents or signal transduction inhibitors or other inhibitors of deregulated pathways in tumours.

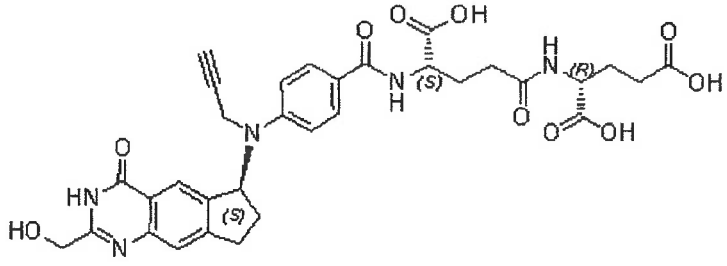
However, those skilled in the art will realise that more conventionally, such combinations are administered separately but coordinated in time with treatment visits to the site of administration.

Particular regimens that are preferred to be employed with the compound for treatment of cancer of the first aspect of the invention are with one or more further anticancer agents 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)

Multiple combinations may also include bevacizumab in combination with paclitaxel, PEGylated liposomal doxorubicin, or topotecan. Further such examples of combinations are exemplified in the examples below.

Particularly advantageously the first aspect of the present invention employs doses of these combined drugs that are lower than those presently prescribed. This is particularly because there has been found not to be cross resistance to BTG945 with that to these other drugs and desired toxic effects on target cancer cells will often be cumulative. Thus in addition to exemplary dosage regimens provided in the examples herein, lower doses or less frequent doses of additional drugs may be exployed.

In a second aspect the present invention provides a method for treating a patient suffering from a cancer that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy and wherein the treatment is with a dose of between 1mg/m^2 and 30mg/m^2 of compound per patient body surface area per administration of a compound of formula I



or a pharmaceutically acceptable salt or ester thereof for the treatment of cancer.

The cancer to be treated is as described above for the first aspect of the invention. The method preferably treats by administering the compound, salt or ester intraperitoneally (IP) or intravenously (IV).

The treatment is preferably with a dosage regimen that results in plasma concentration of drug of 0.5μM or greater for at least 72 hours. More preferably the dosage regimen results in a plasma concentration of drug immediately after dosing that is from 1 to 5μM for no more than 72 hours, preferably for no more than 60 hours. Most preferably the dosage regimen maintains the plasma concentration of drug of 0.1 to 2μM for at least 50% of the treatment cycle period.

The treatment is preferably with a dosage regimen selected from

- a dose of from 1 to 10mg/m^2 administered in a 28 day cycle at 7 day intervals on day 1, 8, 15 and 22.

- A dose of from 6 to 14mg/m^2 administered in a 28 day cycle at 14 day intervals on day 1 and 15
- A dose of from 10 to 30mg/m^2 administered in a 21 day cycle on day 1.

Whilst treatment with doses from 1mg/m^2 to 30mg/m^2 is included in the scope of the invention, preferred doses are from 3mg/m^2 to 30mg/m^2 of compound per patient body surface area per administration, more preferably doses of 5mg/m^2 to 20mg/m^2 of compound per patient body surface area per administration, still more preferably doses of 6mg/m^2 to 18mg/m^2 of compound per patient body surface area per administration, yet more preferably a dose of 8mg/m^2 to 15mg/m^2 , most preferably 10mg/m^2 to 15mg/m^2 and particularly about 12mg/m^2, eg. 11.5mg/m^2 to 12.5mg/m^2 of compound per patient body surface area per administration.

More preferably and particularly the method treats by infusions of the dose spaced between 10 and 28 days apart, more preferably between 10 and 21 days apart and most preferably at dosing interval of about 14 days or 21 days. Still more preferably, when administered IV, the invention treats with a cumulative maximum of 150mg/m^2 of compound per patient body surface area taking into account all of the infusions. More preferably this limit also applies to IP dosaging. More preferably the maximum cumulative dose is 144mg/m^2.

The method in accordance with the present invention provides the compound preferably as infusions 14 or 21 days apart in 21 or 28 day cycles, most preferably 28 days. These cycles are preferably repeated until the maximum cumulative dose is reached. Infusions are preferably carried out over 0.5 to 3 hours. Infusions can be carried out over 0.5 to 1 hour, over 1 hour or from to 1 to fewer than 3 hours. As the treatment may be effective using as little as 1mg/m^2 or 3mg/m^2 it will be realised that infusion rates of 1 hour will be sufficient.

More preferred dosages for each infusion are 1mg/m^2 to 20mg/m^2, more preferably from 10mg/m^2 to 15mg/m^2. The most preferred dose is about 12mg/m^2. At a 12mg/m^2 dose given once every 14 days in 28 day cycles it can be seen that the maximum cumulative recommended dose will be reached in just under 6 months. This is composed of 12 infusions of 12mg/m^2 of compound providing cumulative total 144mg/m^2. A further preferred dosing schedule is a 12mg/m^2 dose given once

every 21 days in 21 day cycles. Further dosing may considered preferably only if the attending clinician is monitoring for the irreversible BOOP or similar side effect.

The method of the second aspect of the present invention further provides for treatment with the compound of the formula I in combination with a therapeutically effective amount of one or more further anticancer agents.

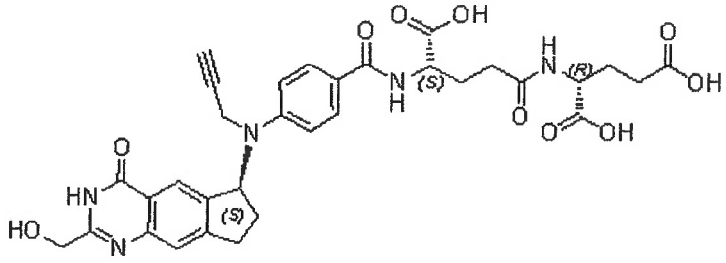
The one or more further anticancer agents used in this combination therapy are preferably selected from Cisplatin, Carboplatin, Doxorubicin, Bevacizumab Gemcitabine, Topetecan, Paclitaxel, Docetaxel, Etoposide, Nanoparticle albumin-bound paclitaxel, Lynparza (olaparib), Rubraca (rucaparib), Zejula (niraparib). Tecentriq (atezoizumab), Bavercio (avelumab) and Keytruda (pembrolizumab).

Multiple combinations may also include bevacizumab in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan. Further such examples of combinations are exemplified in the examples below.

Preferred combinations are with paclitaxel or carboplatin or both.

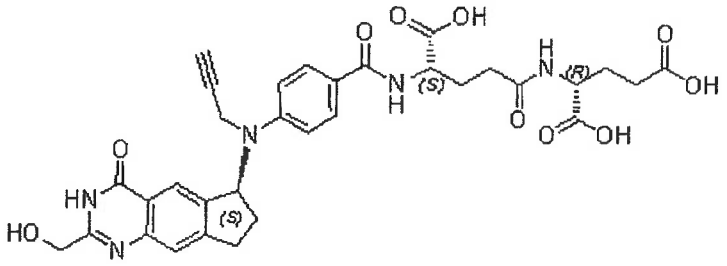
Given the nature of the side effects seen in lung in the failed trial, the inventor also contemplates that the dosage regimen of the invention may also incorporate administration of a steroid to alleviate inflammation of the lung.

A third aspect of the present invention provides a method for treating a patient suffering from a cancer that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy and wherein the treatment is with a dose of between 1mg/m^2 and 30mg/m^2 of compound per patient body surface area per administration of a compound of formula I



or a pharmaceutically acceptable salt or ester thereof in combination with an anti-inflammatory corticosteroid. Preferred corticosteroids are selected from the group consisting of prednisone, methylprednisolone, dexamethasone and prednisolone and hydrocortisone.

In a fourth aspect the present invention provides novel dosage forms of the compound of formula I



comprising a single dosage unit containing said compound or a pharmaceutically acceptable salt or ester thereof characterised in that the amount of said compound in the dosage unit is between 0.5mg and 40mg.

More preferably the dosage unit of the invention contains between 1mg and 30mg of the compound of formula I or salt or ester thereof. Still more preferably the dosage unit contains between 5mg and 26mg of the compound of formula I. Most preferably the dosage unit contains between 10mg and 24mg of the compound or salt or ester of formula I.

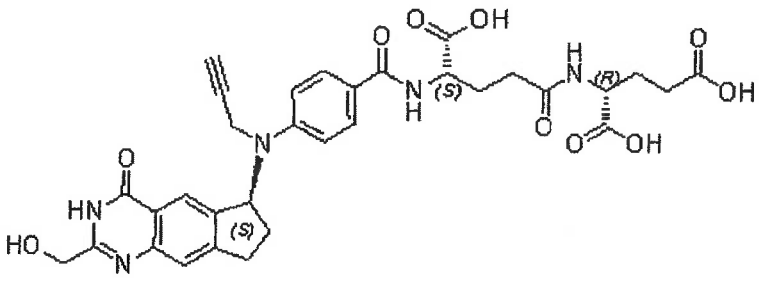
The preferred dosage form will be a container of the compound of formula I or its salt or ester, more preferably the sodium salt, as a sterile solid or aqueous solution in a medium such as water for injection or saline. The sterile solid is preferably BTG945 or a salt or ester thereof free of other materials. Such container would be such that the liquid contained therein, or added thereto when a solid format is provided, could be taken up into a syringe in an amount suited to the body surface area of the patient such as to transfer the required dose of 1mg/m^2 to 30mg/m^2.

Preferably the dose is provided as an aqueous solution in a vial. Such a dosage form or formulation will preferably be a vial containing from 1ml to 30 mls of aqueous solution of the compound for treatment, more preferably from 1ml to 20ml, still more preferably from 1ml to 10ml and most preferably between 2ml and 6ml. Alternatively the dose is provided as solid form of the compound for treatment without liquid. Thus a preferred vial of the invention will contain from 0.5mg to 40mg of compound in 1ml to 30ml of aqueous solution, still more preferably 5mg to 26mg in 1ml to 20ml of aqueous solution and most preferably 10mg to 24mg in 1ml to 10ml of aqueous solution, eg about 6mg or 12mg in 2ml to 6ml of aqueous solution.

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



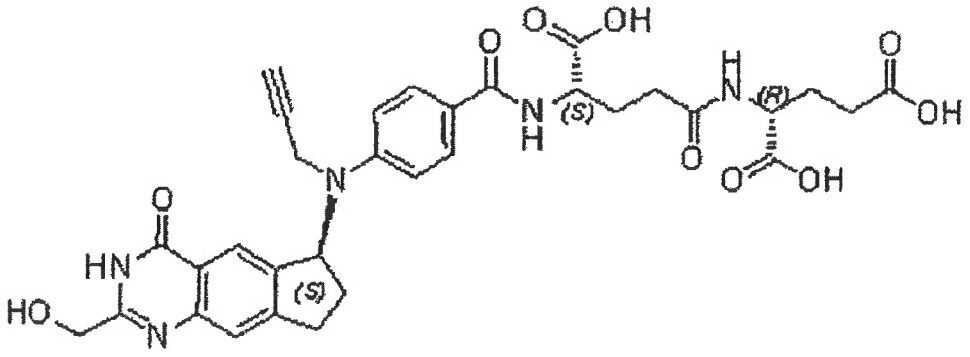
or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for the treatment of ovarian cancer that carries α-folate receptors, wherein

(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

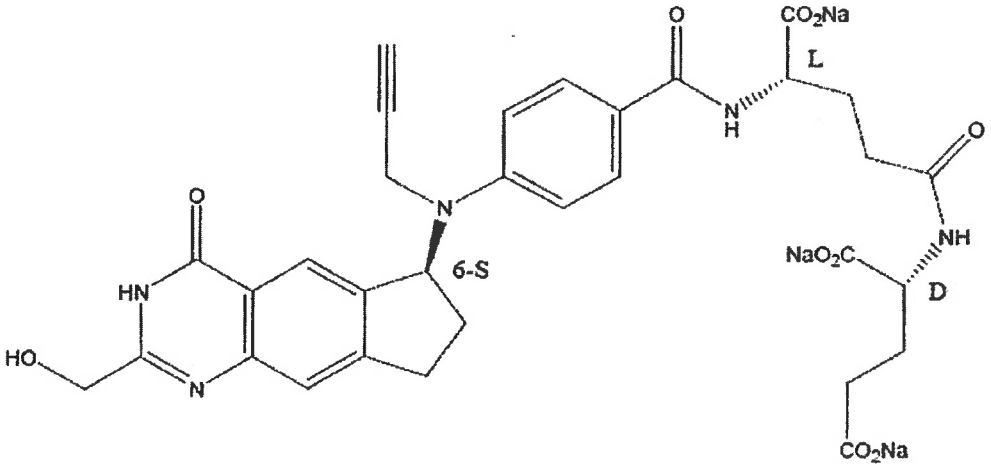
(iii) wherein administration is by infusions of the dose, wherein the infusions are spaced from 10 to 21 days apart.

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

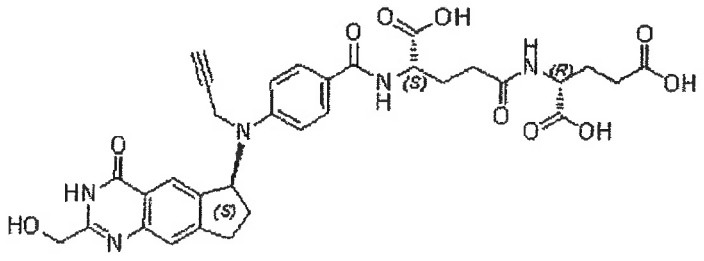
(i) the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(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



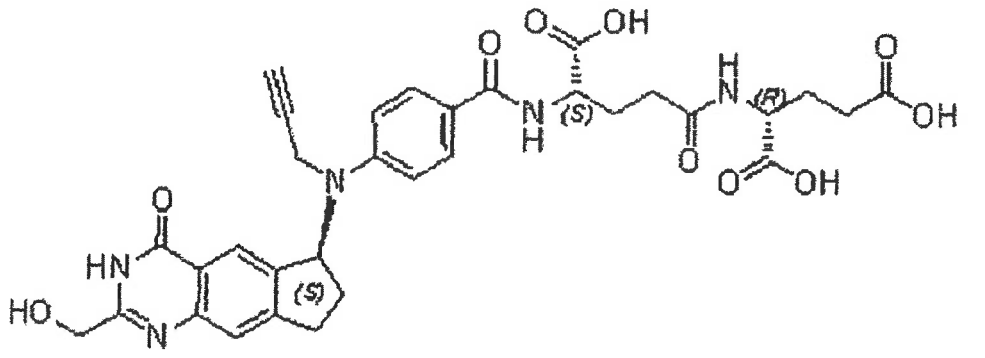
or a pharmaceutically acceptable salt or ester thereof in the manufacture of a medicament for the treatment of ovarian cancer that carries α-folate receptors,

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;

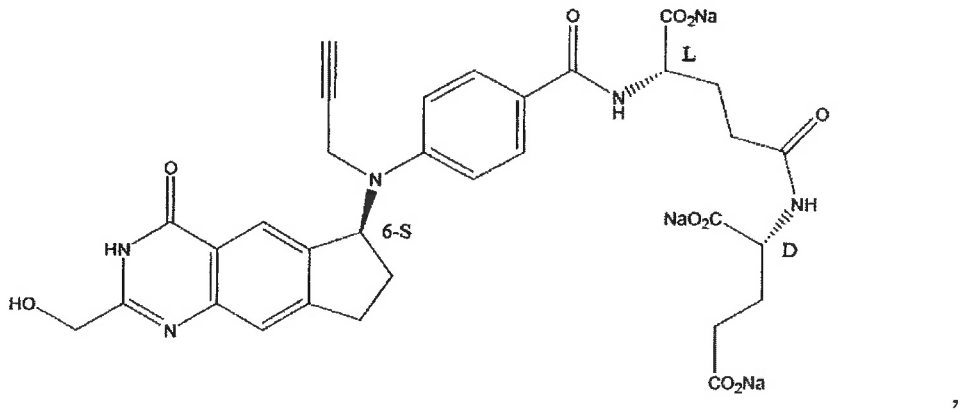
wherein administration is by infusions of the dose, wherein the infusions are spaced from 10 to 21 days apart; and wherein the dose is to be administered intraperitoneally (IP).

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

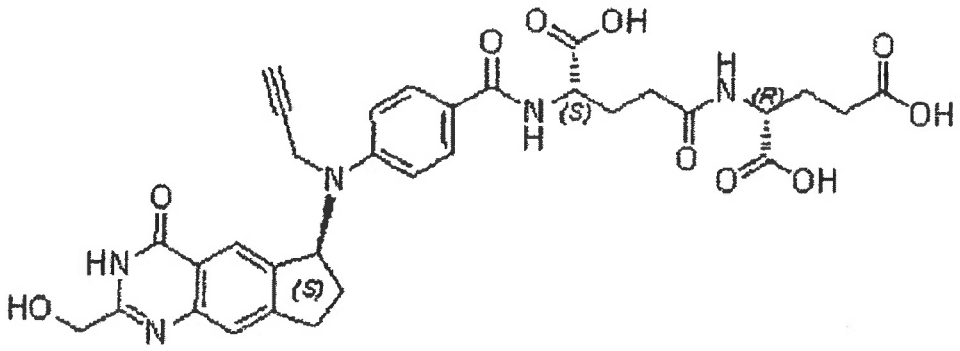
(i) the ovarian cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(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

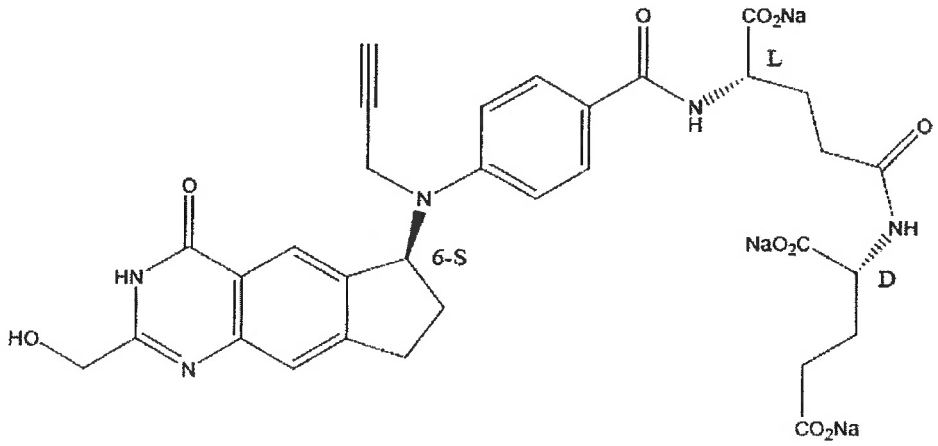
(iv) wherein at least one side effect associated with classical thymidylate synthase inhibitors or alpha folate receptor antibody drug conjugates is not observed

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

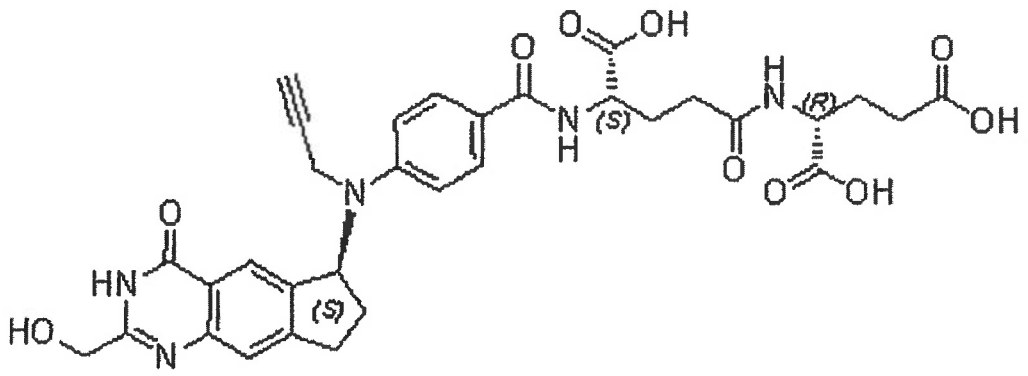
(i) the ovarian cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(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.

FIGURE 4: Shows the % change in tumours as measured using CA125 level 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.

FIGURE 5: Shows the mean blood concentration (μM) of compound ONX-0801/ BTG 945 versus time (hours) for patients under different dose regimens in the escalation phase of the trial before selection of the expansion dose.

EXAMPLES.

The present invention will now be illustrated by the following non-limiting examples. Further embodiments will occur to those skilled in the art in the light of these.

Preferred target cancer to be treated with the following example regimens will be in patients with the following:

•Histologically confirmed epithelial ovarian, fallopian tube, or peritoneal cancer.

•Platinum resistant/refractory disease, defined as disease progression within 180 days following the last administered dose of platinum therapy (resistant), or lack of response or disease progression while receiving the most recent platinum based therapy (refractory), respectively.

•Received up to 3 lines of chemotherapy for platinum sensitive disease, most recently platinum containing, and no prior therapy for platinum resistant disease

Example 1: Treatment of patients with 1mg/m^2 to 12mg/m^2 BTG 945 (trisodium salt form compound of formula II) as monotherapy.

Methods: A 3+3 dose escalation design was used and two IV schedules were explored. Schedule A, weekly dosing (QW) and schedule B, once every 2 weeks dosing (Q2W). A cycle consisted of 4 weeks and treatment was stopped after 6 cycles in both schedules. An expansion cohort to evaluate clinical activity in patients with FR-α overexpressing high grade serous ovarian cancer (HGSOC) was initiated.

Results: 21 patients each were treated in schedule A and B exploring doses ranging from 1-6 mg/m^2 and 2-12 mg/m^2, respectively. The dose limiting toxicity on schedule A was G3 cellulitis; no dose limiting toxicity was seen on schedule B. The most common toxicities were fatigue 15/42 (36%), nausea 9/42 (21%) and dysgeusia 5/42 (12%). Within schedule A at 4 mg/m2, 2 patients developed suspected drug-related changes on pulmonary function tests (drop in Dlco > 15%) at cycles 5 and 6, respectively. No cases of suspected drug-related drop in Dlco were noted in patients treated in schedule B. No grade 3-4 diarrhea, mucositis or neutropenia were seen in either cohort. The Cmax, AUC and half-life at 12 mg/m^2 were 4952 ng/mL, 85170 h*ng/mL and 26 h, respectively. Pre-clinical PK-PD modelling aimed to achieve concentrations between 0.05-1 μM and this was achieved for periods of 48 h at doses of 4 mg/m^2 and above.

Concentrations above 0.5μM were achieved for 72 hours at doses above 6mg/m^2. Evidence of thymidylate synthase inhibition was observed using FLT PET imaging See *Cancer Res* **68.** 3827-3834. 2008 (Pillai et al).

Based on safety and PK, the recommended phase II dose (RP2D) of BTG945 (was ONX801) was 12 mg/m^2 Q2W and an expansion in patients with HGSOC was initiated. 5 patients with HGSOC had partial responses (PRs) in the dose escalation cohort. In the expansion cohort in patients with HGSOC, 5/11 patients had PRs to date of this filing. Archival samples have been analysed from 8/11 patients in the expansion cohort. 4/4 AFR+ve did have PR and 4/4 AFR-ve patients did not have a PR following treatment with BTG945, respectively. RECIST and CA125 responses are shown in Figures 1 to 4.

Conclusions: The RP2D of BTG945 is 12 mg/m^2 Q2W. At the RP2D, multiple patients with AFR overexpressing HGSOC have had PRs and further randomized biomarker prespecified phase II trials are warranted.

Example 2: Combination therapy with BTG945 and other anti-cancer therapies.

12mg/m^2 BTG945 is administered IV in saline for injection on day 1 and day 15 of a 28 day cycle over 1 hour up to a maximum of 6 cycles. One or more of the following exemplary therapeutic regimes are administered in coordination with this treatment as follows:

Example 2.1 Liposomal doxorubicin 40-50 mg/m^2 IV over 30 min; every 21 d

Example 2.2 Gemcitabine 1000 mg/m² IV over 30 min on days 1 and 8; every 21 d

Example 2.3 Topotecan 1.25-1.5 mg/m^2 IV over 30 min on days 1-5; every 21 d

Example 2.4 Paclitaxel 80 mg/m^2 IV over 1 h weekly

Example 2.5 Docetaxel 75-100 mg/m^2 IV over 1 h q 21 days

Example 2.6 Etoposide 50 mg/m^2/day PO for 21 days q 28 days

Example 2.7 Nanoparticle albumin-bound paclitaxel 100 mg/m 2 IV over 30 min given weekly (days 1, 8, and 15) q 28 days

Example 2.8 Keytruda 200mg iv q3 weeks with 945 at any line of chemotherapy.

Example 3: Combination therapy with BTG945 and other anti-cancer therapies for platinum sensitive cancers.

12mg/m^2 BTG945 is administered IV in saline for injection on day 1 and day 15 of a 28 day cycle over 1 hour up to a maximum of 6 cycles. One or more of the following exemplary therapeutic regimes are administered in coordination with this treatment as follows:

Example 3.1 Paclitaxel 135 mg/m^2 IV over 24 h on day 1 plus cisplatin 100 mg/m^2 IP on day 2 (may reduce dose to 75 mg/m^2) plus paclitaxel 60 mg/m^2 IP on day 8 for six or more cycles, provided that the disease is responsive. The cisplatin dose may be reduced to 75 mg/m 2 IP on day 2; some clinicians give paclitaxel 135 mg/m^2 IV over 3 h followed by cisplatin 75 mg/m 2 IP, both on day 1 and on an outpatient basis

Example 3.2 Carboplatin treatment. Normal range of carboplatin AUC for treatment of ovarian carcinoma is from 5 to 7.5; patients who have received extensive prior chemotherapy or radiation should start with an AUC < 5

Example 4: Combination therapy with BTG945 and other anti-cancer therapies for platinum sensitive cancers where patient cannot tolerate IP administration.

12mg/m^2 BTG945 is administered IV in saline for injection on day 1 and day 15 of a 28 day cycle over 1 hour up to a maximum of 6 cycles. One or more of the following exemplary therapeutic regimes are administered in coordination with this treatment as follows:

Example 4.1 Paclitaxel 175 mg/m 2 IV over 3 h plus carboplatin AUC 7.5 IV over 1 h on day 1; every 21 d for six cycles or

Example 4.2 Docetaxel 75 mg/m 2 IV over 1 h plus carboplatin AUC 5 IV over 1 h on day 1; every 21 d for six cycles

Example 5: Combination therapy with BTG945 and other anti-cancer therapies for platinum sensitive Stage III and IV Platinum-sensitive recurrence cancers

Platinum-sensitive recurrence: If recurrence occurs >6 mo from initial or subsequent complete clinical response to platinum-containing chemotherapy, the patient should be treated with 12mg/m^2 BTG945 administered IV in saline for injection on day 1 and day 15 of a 28 day cycle over 1 hour up to a maximum of 6 cycles together with one of the IV platinum-containing combination regimens below. The choice depends on factors such as preexisting comorbidity, prior toxicities, and physician and patient preference. Regimens are as follows:

Example 5.1 Carboplatin AUC 5 IV push plus liposomal doxorubicin 30 mg/m^2 IV over 30 min; every 28 d for six cycles

Example 5.2 Paclitaxel 175 mg/m 2 IV over 3 h plus carboplatin AUC 5 (Calvert) IV over 1 h; every 21 d for six cycles

Example 5.3 Paclitaxel 80 mg/m^2 IV over 1 h weekly days 1, 8, and 15 plus carboplatin AUC 6 IV over 1 h on day 1; every 21 days for six cycles

Example 5.4 Docetaxel 75 mg/m^2 IV over 1 h plus carboplatin AUC 5 IV over 1 h; every 21 d for six cycles

Example 5.5 Gemcitabine 1000 mg/m^2 IV over 30 min on days 1 and 8 plus carboplatin AUC 4 IV over 1 h on day 1; every 21 days for six cycles

Example 6: Combination therapy with BTG945 and other anti-cancer therapies for platinum sensitive Stage III and IV Platinum-sensitive recurrence cancers

Consideration may be given to bevacizumab either alone or with carboplatin/gemcitabine but the use of this agent is still controversial. Platinum-sensitive recurrence: If recurrence occurs >6 mo from initial or subsequent complete clinical response to platinum-containing chemotherapy, the patient should be treated with 12mg/m^2 BTG945 administered IV in saline for injection on day 1 and day 15 of

a 28 day cycle over 1 hour up to a maximum of 6 cycles together with one of the IV platinum-containing combination regimens below.

Example 6.1 Bevacizumab 15 mg/kg IV (initially over 90 min, then over 60 min, and finally over 30 min for subsequent infusions); every 21 d until disease progression, irrespective of prior platinum response

Example 6.2 Gemcitabine 1000 mg/m^2 IV over 30 min on days 1 and 8 plus carboplatin AUC 4 IV push on day 1; every 21 d for 6-10 cycles plus bevacizumab 15 mg/kg IV on day 1 prior to gemcitabine and carboplatin and continued until progression of disease or unacceptable toxicity

Example 6.3 Bevacizumab 10 mg/kg IV every 14 d in combination with one of the following IV chemotherapy regimens: paclitaxel, pegylated liposomal doxorubicin, or topotecan (topotecan is given weekly)

Example 6.4 Bevacizumab 15 mg/kg IV every 21 d in combination with topotecan (every 21 d)

Example 6.5 Bevacizumab 15 mg/kg IV (initially over 90 min, then over 60 min, and finally over 30 min for subsequent infusions); every 21 d until progression

Example 6.6 Bevacizumab 10 mg/kg IV on days 1 and 15 plus topotecan 4 mg/m 2 IV on days 1, 8, and 15, q 28 days

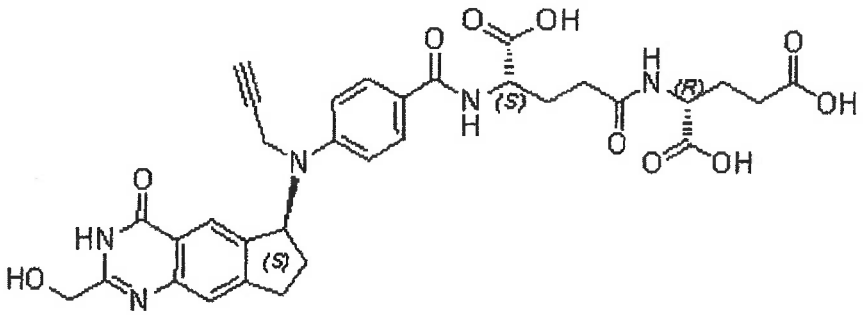
Example 7: Combination therapy with BTG945 and platinum-sensitive or resistant or refractory BRCA-mutated Stage III and IV Platinum-sensitive recurrence cancers

For patients diagnosed as BRCA-mutated (as detected by an FDA-approved test, BRACAnalysis CDxTM) in patients who have been treated with three or more prior lines of chemotherapy: 12mg/m^2 BTG945 administered IV in saline for injection on day 1 and day 15 of a 28 day cycle over 1 hour up to a maximum of 6 cycles whilst Olaparib 400 mg is administered PO BID continuously

In the European Union, olaparib 400 mg PO BID is approved as monotherapy for the maintenance treatment of adult patients with platinum-sensitive, relapsed, BRCA -mutated (germline and/or somatic) high-grade serous epithelial, fallopian tube, or primary peritoneal cancer who are showing response (complete or partial) to platinum-based chemotherapy.

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.

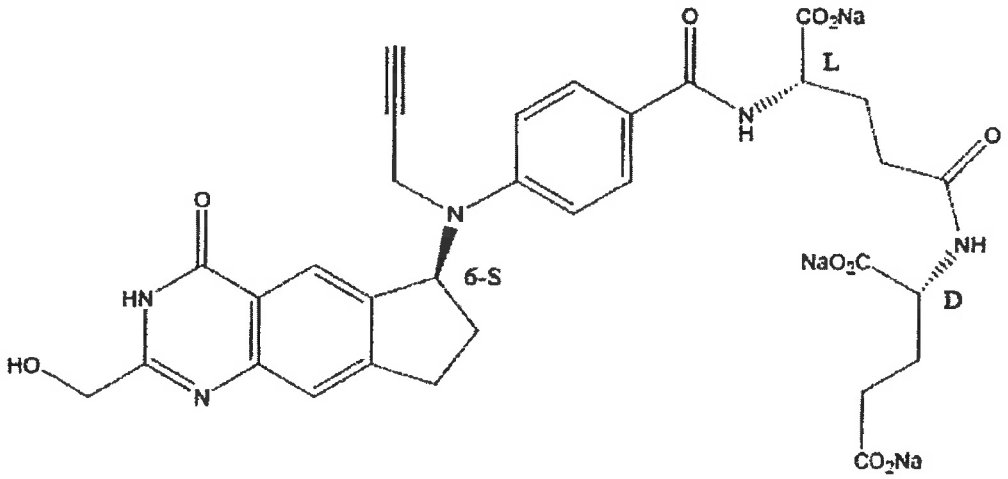
12. A use as claimed in claim 11 characterised in that the maximum cumulative dose is 144mg/m^2.

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.

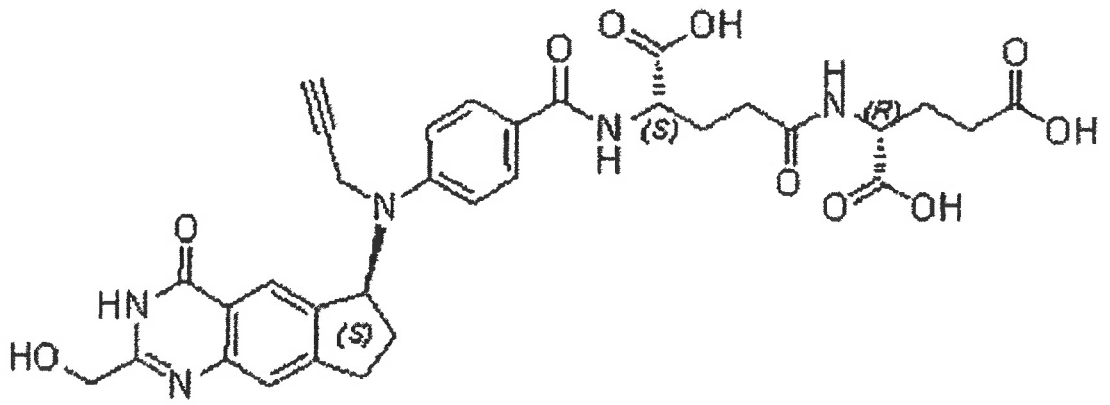
23. A use as claimed in claim 17, wherein the administration of the medicament and the administration of the one or more further anticancer agents are to be performed on alternate weeks of a 14 day dosing schedule.

24. A use as claimed in claims 17 to 23 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).

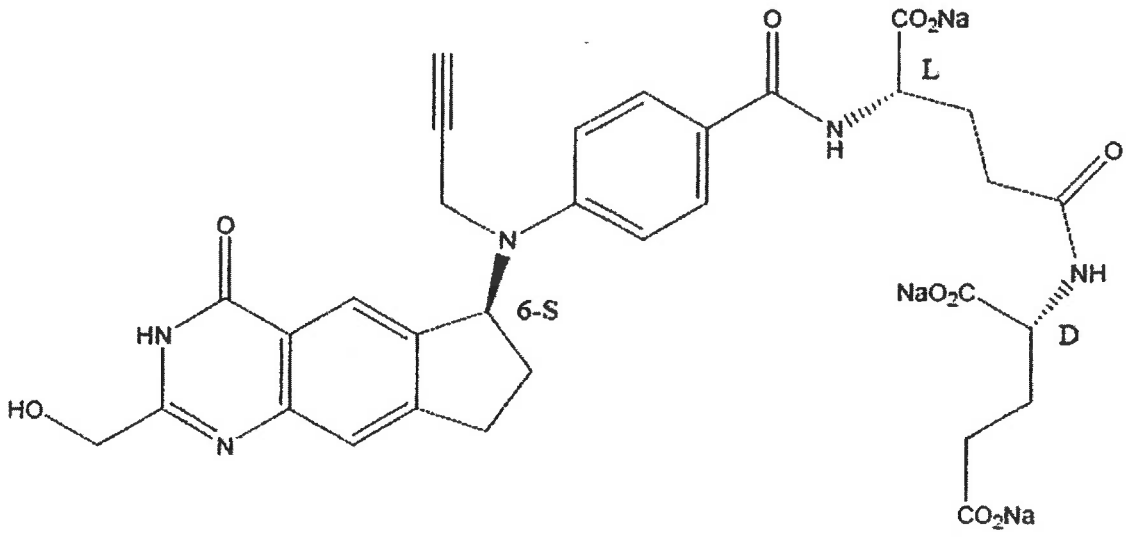
25. A use as claimed in claims 17 to 23 wherein the medicament is to be administered together with bevacizumab in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan.

26. 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

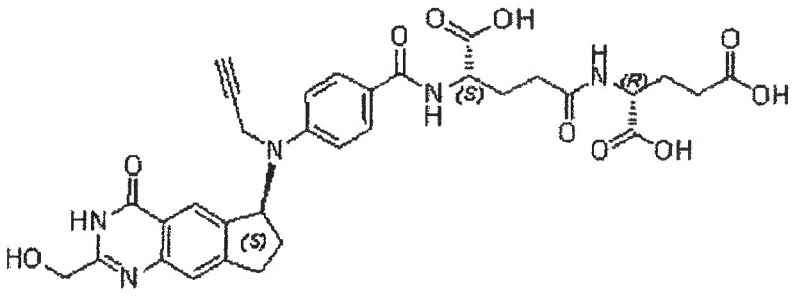
(i) the cancer is one that has the characteristic of being a type prone to being or becoming refractory or resistant to platinum drug based therapy;

(ii) a dose of from 8mg/m² to 15mg/m² 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).

27. 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;

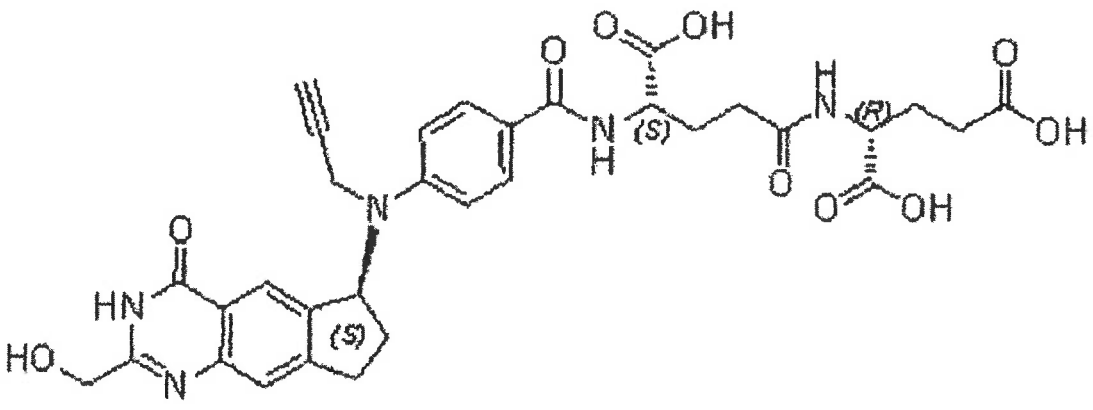
wherein a dose of from 8mg/m² to 15mg/m² of compound per patient body surface area is to be administered per administration;

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

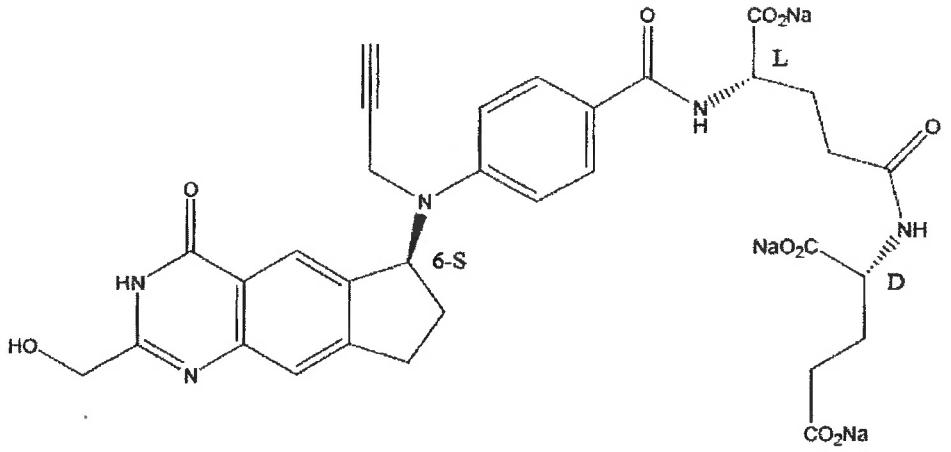
wherein the dose is to be administered intraperitoneally (IP).

28. A use as claimed in claim 27 wherein the medicament is to be administered in combination with a therapeutically effective amount of one or more further anticancer agents.

29. 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.

30. The use according to claim 29, wherein the at least one side effect is chosen from neutropenia, diarrhoea, hair loss, blurred vision or nausea.

31. A use as claimed in claim 29, or 30 characterised in that the ovarian cancer is selected from those expressing α-folate receptors (FR-α).

32. A use as claimed in claim 31characterised in that the ovarian cancer expresses higher than background non-cancerous tissue levels of α-folate receptors.

33. A use as claimed in any one of claims 29 to 32 characterised in that the ovarian cancer is epithelial ovarian, fallopian tube or peritoneal cancer.

34. A use as claimed in claim 33 characterised in that the ovarian cancer is serous ovarian cancer.

35. A use as claimed in claim 34 characterised in that the ovarian cancer is High-Grade Serous Ovarian Cancer (HGSOC).

36. A use as claimed in any one of claims 29 to 35 characterised in that the dose is to be administered intraperitoneally (IP) or intravenously (IV).

37. A use as claimed in any one of claims 29-36 characterised in that the infusions are to be administered at dosing interval of about 14 days.

38. A use as claimed in claim 37 characterised in that a cumulative maximum of 150mg/m^2 of compound per patient body surface area over the course of all the infusions.

39. A use as claimed in claim 38 characterised in that the maximum cumulative dose is 144mg/m^2.

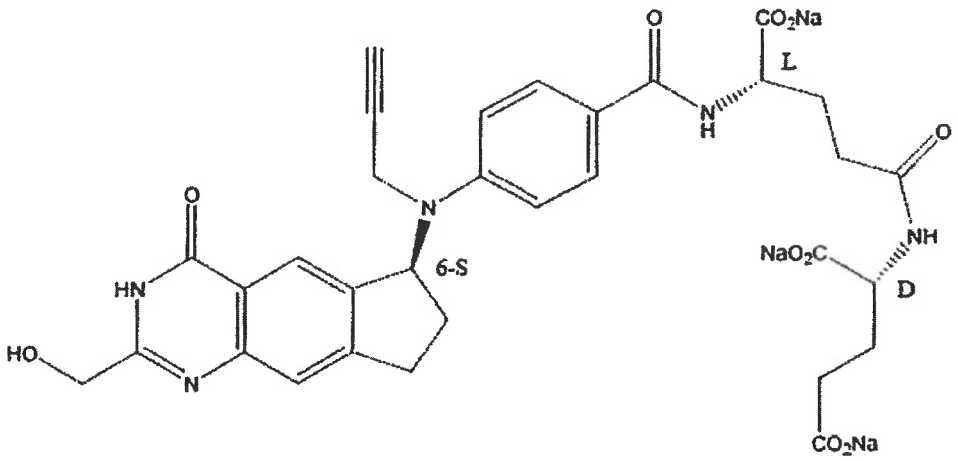
40. A use as claimed in any one of claims 29 to 39 characterised in that an infusion of 10/m^2 to 15mg/m is to be administered per administration.

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.

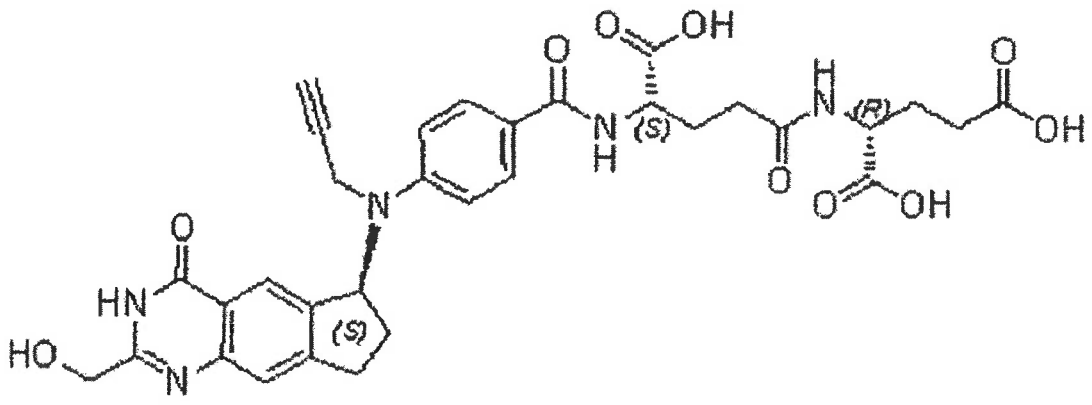
42. A use as claimed in claim 41 characterised in that an infusion of about 12mg/m^2 is to be administered per administration.

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

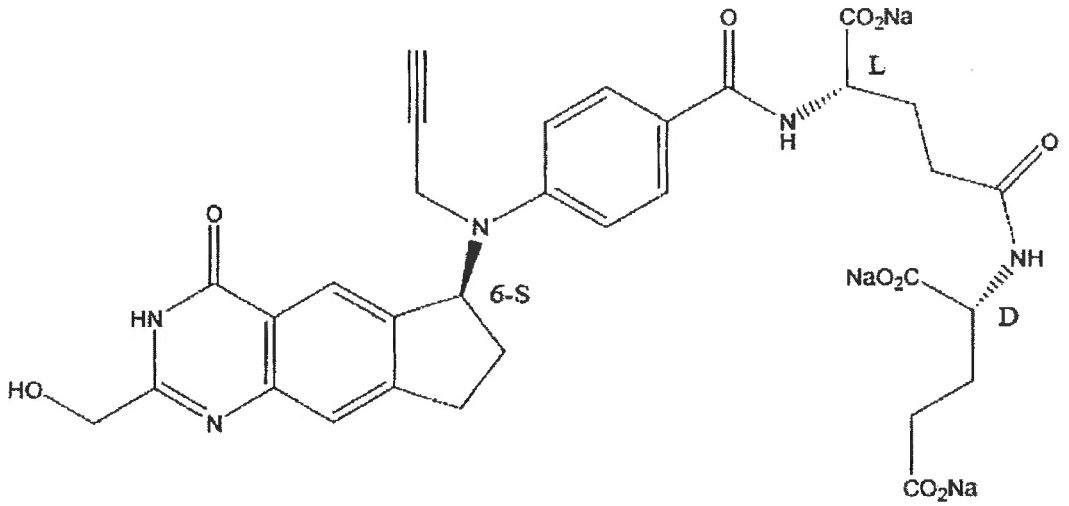
44. A use as claimed in any one of claims 30 to 43 characterised in that the compound is the trisodium salt of formula II



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/m² to 15mg/m² 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/m² 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/m².

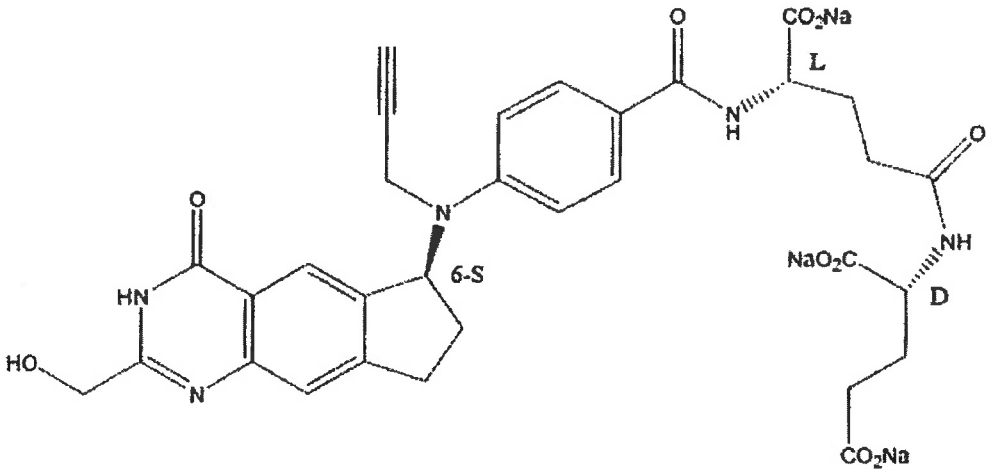
57. A use as claimed in any one of claims 45 to 56 characterised in that an infusion of 10mg/m² to 15mg/m² is to be administered per administration.

58. A use as claimed in claim 57 characterised in that an infusion of 11.5mg/m² to 12.5mg/m² is to be administered per administration.

59. A use as claimed in claim 56 characterised in that an infusion of about 12mg/m² 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



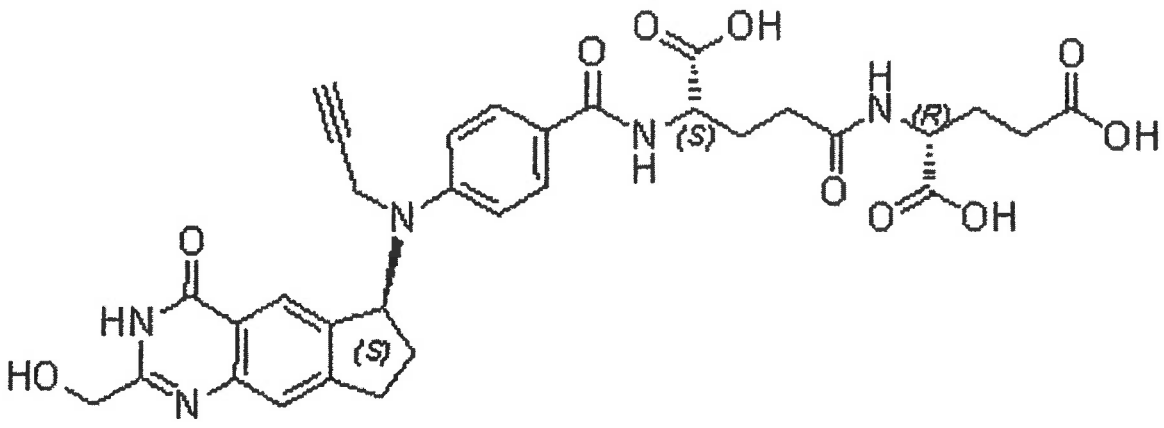
62. A use as claimed in Claim 1 wherein a dosage regimen to be administered is selected from the group

• a dose of 8 to 15mg/m² to be administered in a 28 day cycle at 14 day intervals on day 1 and 15

• a dose of 8 to 15mg/m² 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/m² 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.