

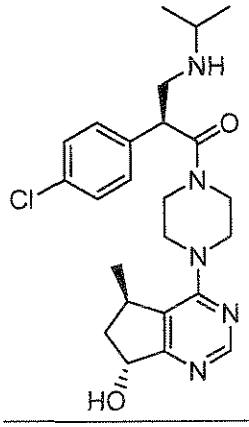
(I).

Currently, there remains a need for improved methods and compositions that can be used to treat hyperproliferative diseases such as cancer.

SUMMARY ~~OF THE INVENTION~~

It has been determined that additive or synergistic effects in inhibiting the growth of cancer cells *in vitro* and *in vivo* can be achieved by administering a compound of formula I or a pharmaceutically acceptable salt thereof in combination with certain other specific chemotherapeutic agents. The combinations and methods may be useful in the treatment of hyperproliferative disorders such as cancer.

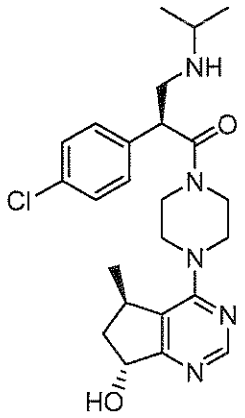
In one example, the present invention refers to a combination of a) a compound of Formula Ia:



Ia,

or a pharmaceutically acceptable salt thereof, and b) abiraterone or a pharmaceutically acceptable salt thereof for use in the therapeutic treatment of a hyperproliferative disorder.

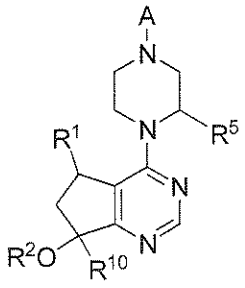
In another example, the present invention refers to a compound of formula Ia



Ia,

or a pharmaceutically acceptable salt thereof, for therapeutic use for improving the quality of life of a patient treated for a hyperproliferative disorder with abiraterone or a pharmaceutically acceptable salt thereof.

One exampleaspect of the disclosure describesinvention provides a method for treating a hyperproliferative disorder in a mammal comprising, administering to the mammal, a) a compound of formula I:



(I)

or a pharmaceutically acceptable salt thereof; and b) one or more agents selected from 5-FU, a platinum agent (carboplatin, cisplatnin, oxaliplatin, etc.) irinotecan, docetaxel, doxorubicin, gemcitabine, SN-38, capecitabine, temozolomide, erlotinib, PD-0325901, paclitaxel, bevacizumab, pertuzumab, tamoxifen, rapamycin, lapatinib, PLX-4032, MDV3100, abiraterone, and GDC-0973.

The compound of formula I or the pharmaceutically acceptable salt thereof and the chemotherapeutic agent may be co-formulated for administration in a combination as a pharmaceutical composition or they may be administered separately in alternation (sequentially) as a therapeutic combination.

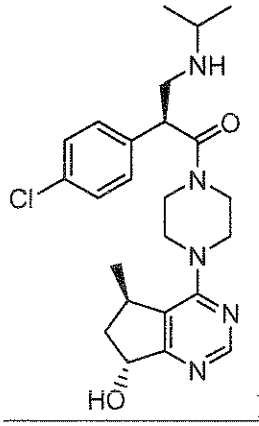
One exampleaspect of the disclosure describesinvention provides a method for treating a disease or condition

modulated by AKT kinase in a mammal comprising, administering to the mammal, a) a compound of formula I or a pharmaceutically acceptable salt thereof; and b) one or more agents selected from 5-FU, a platinum agent, irinotecan, docetaxel, doxorubicin, gemcitabine, SN-38, capecitabine, temozolomide, erlotinib, PD-0325901, paclitaxel, bevacizumab, pertuzumab, tamoxifen, rapamycin, lapatinib, PLX-4032, MDV3100, abiraterone, and GDC-0973.

One example~~aspect~~ of the disclosure describes~~invention provides~~ the combination of a) a compound of formula I or a pharmaceutically acceptable salt thereof; and b) one or more agents selected from 5-FU, a platinum agent, irinotecan, docetaxel, doxorubicin, gemcitabine, SN-38, capecitabine, temozolomide, erlotinib, PD-0325901, paclitaxel, bevacizumab, pertuzumab, tamoxifen, rapamycin, lapatinib, PLX-4032, MDV3100, abiraterone, and GDC-0973 for treating a hyperproliferative disorder.

One example~~aspect~~ of the disclosure describes~~invention provides~~ the combination of a) a compound of formula I or a pharmaceutically acceptable salt thereof; and b) one or more agents selected from 5-FU, a platinum agent, irinotecan, docetaxel, doxorubicin, gemcitabine, SN-38, capecitabine, temozolomide, erlotinib, PD-0325901, paclitaxel, bevacizumab, pertuzumab, tamoxifen, rapamycin, lapatinib, PLX-4032, MDV3100, abiraterone, and GDC-0973 for treating a disease or condition modulated by AKT kinase.

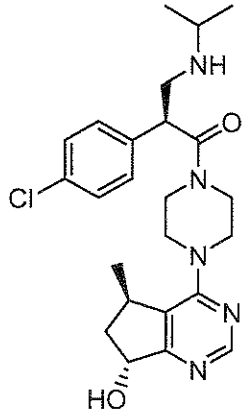
In one aspect, the present invention refers to the use of a combination of, a) a compound of Formula Ia:



Ia,

or a pharmaceutically acceptable salt thereof; and b) abiraterone or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating a hyperproliferative disorder in a mammal.

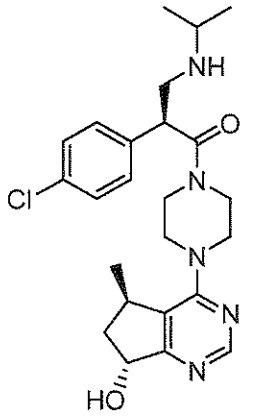
In another aspect, the present invention refers to a kit comprising a compound of formula Ia



Ia

or a pharmaceutically acceptable salt thereof, a container, and a package insert or label indicating the administration of the compound of formula Ia with abiraterone or a pharmaceutically acceptable salt thereof for treating a hyperproliferative disorder.

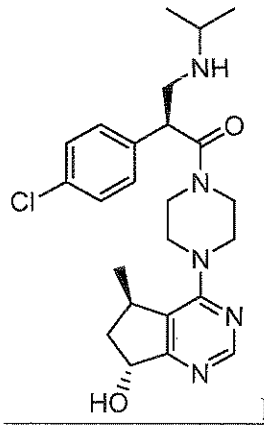
In yet another aspect, the present invention refers to a product comprising a compound having formula Ia



Ia,

or a pharmaceutically acceptable salt thereof, and abiraterone or a pharmaceutically acceptable salt thereof as a combined preparation for separate, simultaneous or sequential use in the treatment of a hyperproliferative disorder.

In a further aspect, the present invention refers to a medicament for use in treating a hyperproliferative disorder in a mammal comprising, a combination of, a) a compound of Formula Ia:



Ia,

or a pharmaceutically acceptable salt thereof; and b) abiraterone or a pharmaceutically acceptable salt thereof.

One exampleaspeet of the disclosure describesinvention provides the use of a compound of formula I or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a hyperproliferative disorder in a mammal, wherein one or more agents selected from 5-FU, a platinum agent, irinotecan, docetaxel, doxorubicin, gemcitabine, SN-38, capecitabine, temozolomide, erlotinib, PD-0325901, paclitaxel, bevacizumab, pertuzumab, tamoxifen, rapamycin, lapatinib, PLX-4032, MDV3100, abiraterone, and GDC-0973 are administered to the mammal.

One exampleaspeet of the disclosure describesinvention provides the use of a compound of formula I or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a disease or condition modulated by AKT kinase in a mammal, wherein one or more agents selected from 5-FU, a platinum agent, irinotecan, docetaxel, doxorubicin, gemcitabine, SN-38, capecitabine, temozolomide, erlotinib, PD-0325901, paclitaxel, bevacizumab, pertuzumab, tamoxifen, rapamycin, lapatinib, PLX-4032, MDV3100, abiraterone, and GDC-0973 are administered to the mammal.

One exampleaspeet of the invention disclosure describesprovides a kit comprising a compound of formula I or a pharmaceutically acceptable salt thereof, a container, and a package insert or label indicating

the administration of the compound of formula I or a pharmaceutically acceptable salt thereof with one or more agents selected from 5-FU, a platinum agent, irinotecan, docetaxel, doxorubicin, gemcitabine, SN-38, capecitabine, temozolomide, erlotinib, PD-0325901, paclitaxel, bevacizumab, pertuzumab, tamoxifen, rapamycin, lapatinib, PLX-4032, MDV3100, abiraterone, and GDC-0973 for treating a hyperproliferative disorder.

One exampleaspect of the disclosure describesinvention provides a product comprising a compound having formula I or a pharmaceutically acceptable salt thereof, and a chemotherapeutic agent selected from 5-FU, a platinum agent, irinotecan, docetaxel, doxorubicin, gemcitabine, SN-38, capecitabine, temozolomide, erlotinib, PD-0325901, paclitaxel, bevacizumab, pertuzumab, tamoxifen, rapamycin, lapatinib, PLX-4032, MDV3100, abiraterone, and GDC-0973; as a combined preparation for separate, simultaneous or sequential use in the treatment of a hyperproliferative disorder.

One exampleaspect of the disclosure describesinvention provides a product comprising a compound having formula I or a pharmaceutically acceptable salt thereof, and abiraterone or a pharmaceutically acceptable salt thereof; as a combined preparation for separate, simultaneous or sequential use in the treatment of a hyperproliferative disorder, such as prostate cancer.

In addition to providing improved treatment for a given hyperproliferative disorder, administration of certain combinations of the disclosureinvention may improve the quality of life for a patient compared to the quality of life experienced by the same patient receiving a different treatment. For example, administration of a combination of a compound of formula I or a pharmaceutically acceptable salt thereof, and a chemotherapeutic agent as described herein to a patient may provide an improved quality of life compared to the quality of life the same patient would experience if they received only the chemotherapeutic agent as therapy. For example, the combined therapy with the combination described herein may lower the dose of chemo agents needed, thereby lessening the side-effects associated with high-dose chemotherapeutic agents (e.g., nausea, vomiting, hair loss, rash, decreased appetite, weight loss, etc.). The combination may also cause reduced tumor burden and the associated adverse events, such as pain, organ dysfunction, weight loss, etc. Accordingly, one exampleaspect of the disclosure describesinvention provides a compound of formula I or a pharmaceutically acceptable salt thereof, for therapeutic use for improving the quality of life of a patient treated for a hyperproliferative disorder with an agent selected from 5-FU, a platinum agent, irinotecan, docetaxel, doxorubicin, gemcitabine, SN-38, capecitabine, temozolomide, erlotinib, PD-0325901, paclitaxel, bevacizumab, pertuzumab, tamoxifen, rapamycin, lapatinib, PLX-4032, MDV3100, abiraterone, and GDC-0973. Accordingly, another exampleaspect of the disclosureinvention

describesprovides a compound of formula I or a pharmaceutically acceptable salt thereof, for therapeutic use for improving the quality of life of a patient treated for a hyperproliferative disorder with abiraterone or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates data for the compound of formula Ia (GDC-0068) dosed PO + *abiraterone in LuCaP35V Primary Prostate Tumors.*

Figure 2 illustrates data for the compound of formula Ia (GDC-0068) dosed PO + abiraterone in DU-145.x1 Primary Prostate Tumors.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS AND DEFINITIONS

The words "comprise," "comprising," "include," "including," and "includes" when used in this specification and claims are intended to specify the presence of stated features, integers, components, or steps, but they do not preclude the presence or addition of one or more other features, integers, components, steps, or groups thereof.

The activity of anti-androgen therapies, including bicalutamide, GnRH agonist, and abiraterone, has resulted in improved survival for patients with prostate cancer. However, nearly all patients who present with hormone-sensitive advanced prostate cancer progress to CRPC and require other forms of therapy. Activation of PI3K/Akt signaling, often manifested by PTEN loss, is a frequent hallmark of CRPC. Deregulation of this pathway results in activation of downstream targets (e.g., PRAS40, MTOR, GSK3b, FOXO, etc.) involved in survival, proliferation, cell cycle progression, growth, migration, and angiogenesis. Notably, prostate-specific deletion of PTEN in mouse models faithfully recapitulates features of human prostate cancer, and Akt1 deletion in a conditional Pten knockout model significantly reduces prostate cancers (Chen et al. 2006; Guertin et al. 2009; Nardella et al. 2009). Additionally, Pten deletion promotes androgen independence in cell lines and mouse models of prostate cancer (Gao et al. 2006; Jiao et al. 2007). In prostate cancer patients, PTEN loss is associated with higher Gleason scores, recurrence post-prostectomy, bone metastasis, and progression to castrateresistance. Additionally, PTEN loss is associated with a decrease in overall survival. Collectively, these results suggest that activation of the PI3K/Akt pathway is an important driver for prostate cancer.

Recent nonclinical data suggest that reciprocal crosstalk between the AR and PI3K/Akt pathways occurs in PTEN-deficient CRPC. Specifically, activation of the PI3K/Akt pathway is associated with repressed androgen signaling, and inhibition of the PI3K/Akt