A combination therapy is described, comprising a dosage regimen for the co-administration of 4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-N-methylbenzamide and a strong CYP3A4 inducer.
COMBINATION THERAPY WITH APALUTAMIDE

[01] This application claims priority to and incorporates by reference U.S. provisional application Serial No. 62/204,287, filed on August 12, 2015.

TECHNICAL FIELD

[02] This disclosure relates generally to cancer treatment.

DETAILED DESCRIPTION

[03] 4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-N-methylbenzamide is an androgen receptor inhibitor and can be used to treat cancers such as prostate cancers, breast cancers, and ovarian cancers. If 4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-N-methylbenzamide is co-administered with a strong CYP3A4 inducer (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine), the daily dose of 4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-N-methylbenzamide may be increased from, e.g., 160 mg/day to 200-300 mg/day (e.g., 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300 mg/day).

[04] "Co-administration" of 4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-N-methylbenzamide and a strong CYP3A4 inhibitor means administration in any manner in which the pharmacological effects of 4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-N-methylbenzamide and the strong CYP3A4 inhibitor overlap in the patient at the same time. Co-administration does not require that both agents be administered in a single pharmaceutical composition, in the same dosage form, by the same route of administration, or for the same length of time.

[05] 4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-N-methylbenzamide is typically formulated for oral administration, for example, in solution in caprylocaproyl polyoxylglycerides.
[06] Patients who can be treated with the disclosed co-administration regimes include patients with prostate cancer (including metastatic prostate cancer, castration-resistant prostate cancer, hormone-sensitive prostate cancer, metastatic castration-resistant prostate cancer, metastatic hormone-sensitive prostate cancer), breast cancer (including triple-negative breast cancer), and ovarian cancer. Prostate cancer patients who can be treated using the disclosed co-administration regimes include patients with metastatic castration-resistant prostate cancer (CRPC) who had previously received chemotherapy (e.g., docetaxel) as well as patients with CRPC who are chemotherapy-naive.
CLAIMS

1. A method of treating cancer, comprising co-administration to a patient in need thereof a therapeutically effective dose of 4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-N-methylbenzamide and a CYP3A4 inducer, wherein the therapeutically effective dose of 4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-N-methylbenzamide is 200-300 mg per day.

2. The method of claim 1, wherein the cancer is selected from the group consisting of prostate cancer, breast cancer, and ovarian cancer.

3. The method of claim 1, wherein the therapeutically effective dose of 4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-N-methylbenzamide is 240 mg per day.

4. A method of treating metastatic castration-resistant prostate cancer, comprising co-administration to a patient in need thereof (i) 240 mg/day of 4-[7-[6-cyano-5-(trifluoromethyl)pyridin-3-yl]-8-oxo-6-sulfanylidene-5,7-diazaspiro[3.4]octan-5-yl]-2-fluoro-N-methylbenzamide and (ii) a CYP3A4 inducer.

5. The method of any of claims 1-4, wherein the CYP3A4 inducer is selected from the group consisting of carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and rifapentine.
# INTERNATIONAL SEARCH REPORT

**International application No**

PCT/US2016/04647O

## A. CLASSIFICATION OF SUBJECT MATTER

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**ADD.**

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

| A61K | A61P |

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>SPIGSET OLAV ET AL: 1 [Cytochrome P-450 3A4--the most important arena for drug interactions in the body].</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

- **“X”** & **“P”** document defining the general state of the art which is not considered to be of particular relevance
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**Date of the actual completion of the international search**

21 October 2016

**Date of mailing of the international search report**

03/11/2016

**Name and mailing address of the ISA/Office**

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

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Rodriguez-Palmero, M

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### DOCUMENTS CONSIDERED TO BE RELEVANT

**Category** | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No.
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Y | WIJ DAN RAMADAN ET AL: "Enzal utami de for patients with metastatic castration-resistant prostate cancer", ONCOTARGETS AND THERAPY, April 1 2015 (2015-04), page 871, XP055310932, DOI: 10.2147/OTT.80488 table 4 | 1-5

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