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(54) Title: USE OF DOPAMINE RECEPTOR AGONIST FOR THE TREATMENT OF A COLORECTAL CANCERS

(57) Abstract: The present invention relates to a class of compounds suitable for the treatment of colorectal cancers.



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USE OF DOPAMINE RECEPTOR AGONIST FOR THE TREATMENT OF A COLORECTAL CANCERS

FIELD OF THE INVENTION

The present invention relates to a class of compounds suitable for the treatment of colorectal cancers.

5 BACKGROUND OF THE INVENTION

Colorectal cancer (CRC) is a major worldwide health problem owing to its high prevalence and mortality rates. In the USA, CRC is the third most commonly diagnosed cancer and third leading cause of cancer death in both men and women. It is estimated that over 40,000 of the adult UK population are diagnosed with CRC each year. If diagnosed and treated early
10 CRC is also one of the most curable types of cancer with cure rates as high as 90%.

Advances in the diagnosis and treatment of CRC have had a major impact on management of this malignancy. Developments in screening, prevention, biomarker and genomic analysis, stem-cell research, personalized therapies and chemotherapy have improved detection and mortality statistics. However, despite these advances, many patients with advanced and
15 metastatic tumors will still succumb to the disease. Further diagnosis and treatment advances are therefore needed.

There is still a need in the art for additional, better or just alternative compounds suitable for use in the treatment of CRC either alone or in combination treatments with existing compounds approved or at least known for effect in this indication.

20 OBJECT OF THE INVENTION

It is an object of embodiments of the invention to provide alternative new compounds suitable for use in the treatment of CRC.

SUMMARY OF THE INVENTION

It has been found by the present inventor(s) that dopamine receptor agonists may be used in
25 the treatment of colorectal cancers.

So, in a first aspect the present invention relates to a dopamine receptor agonist for the treatment of a colorectal cancer.

In a second aspect the present invention relates to the use of a dopamine receptor agonist for the treatment of a colorectal cancer.

- 5 In a third aspect the present invention relates to a method of treating a patient suffering from colorectal cancer characterized by administration of effective amounts of a dopamine receptor agonist, or a pharmaceutically acceptable salt thereof, to a patient in need of such treatment.

DETAILED DISCLOSURE OF THE INVENTION

10 *Definitions*

Colorectal cancers

- The term "colorectal cancer" as used herein refers to a cancer also known as colon cancer, rectal cancer, gastrointestinal cancer, or bowel cancer that starts in the colon or rectum (parts of the large intestine), or in the appendix. In some embodiments the colorectal cancer
15 is an adenocarcinoma (Cancer that develops in glandular cells).

- In the context of the present invention, "treatment" or "treating" refers to preventing, alleviating, managing, curing or reducing one or more symptoms or clinically relevant manifestations of a gastrointestinal cancer, unless contradicted by context. For example, "treatment" of a patient in whom no symptoms or clinically relevant manifestations of a
20 gastrointestinal cancer have been identified is preventive or prophylactic therapy, whereas "treatment" of a patient in whom symptoms or clinically relevant manifestations of a gastrointestinal cancer have been identified generally does not constitute preventive or prophylactic therapy.

Dopamine agonists

- 25 Dopamine (3,4-dihydroxyphenylethylamine or 3-hydroxytyramine) is a catecholamine formed in the body by the decarboxylation of dopa (3,4- dihydroxyphenylalanine) and acts as a neurotransmitter in the CNS. Inside the brain, dopamine acts as a neurotransmitter within the synapse of the nerve cell, and outside the brain (or more specifically outside the blood-

brain barrier), it acts as a hormone (like most neurotransmitters) and affects the constriction/dilation of blood vessels.

Due to the side effects of the treatment with L-dopa or with the combination L-dopa/carbidopa, dopamine agonists have been developed or are in development for the treatment of diseases or conditions in which dopamine is involved. The dopamine agonists mimic the activity of dopamine by directly activating the dopamine receptor.

The receptors for dopamine are primarily found in the striatum. There are at least five subtypes of dopamine receptors, called D1 through D5; the D1 and D5 subtypes belong to the dopamine receptor type 1 family and are referred to as "D1-like" or "D1-R" while the D2, D3, and D4 belong to the dopamine receptor type 2 family and are referred to as "D2-like" or "D2-R". The receptors are grouped in this manner because of the common properties of the receptor effects.

The different dopamine agonists may have affinity to both D1-like and D2-like families, albeit with different strength, or they may be specific to the D1 or the D2 family or to one of the receptors within one of the families.

Some of the dopamine agonists that may be suitable in the treatment of colorectal cancers include amantadine, quinagolide, rasagiline, apomorphine (D1 and D2 agonist), the ergoline derivatives bromocriptine (D2 agonist), lisuride (D2 agonist), pergolide (D2/D3 strong agonist), and cabergoline (D2 agonist), and the non-ergoline derivatives ropinirole (D2 agonist) and pramipexole (D2/D3 agonist). Bromocriptine and quinpirole protected cortical neurons from glutamate toxicity via the phosphatidylinositol 3 kinase cascade (Kihara et al. 2002). Other dopamine agonists under investigation include the D1 agonists dihydrexidine (DHX, the first high affinity full D1 dopamine receptor agonist), SKF-38393, SKF-81297, and SKF-82958, and the D2 agonists quinpirole, LY 172555, PPHT [(+)-2-(N-phenylethyl-N-propyl) amino-5-hydroxytetralin] and quinelorane, and TNPA [2,10, 11-trihydroxy-N-propylnoraporphine].

Pergolide (trade names Permax, Prascend) IUPAC name: (8 β)-8-((methylthio)methyl)-6-propyl-ergoline; CAS number: 66104-22-1 is a specifically suitable ergoline-based dopamine receptor agonist.

The above mentioned compounds will normally be administered as single dose or as repeated dosages in solid or fluid form (as tablet, lozenge, granules, powder, sachet, capsule, suppository, emulsion, solution, liniment, tincture, gel, etc.), or via a slow-release

formulation (in or on carriers such as lipids, liposomes or implants, in prodrug-form or in slowly metabolizing derivatives, etc.).

Preferably the compounds according the present invention is administered in tablet form orally, although for the ease of combined administration with other compounds used in the methods and composition of the invention also other dosage forms (gels, liquids, sprays, injection fluids, etc.) and other routes of administration (subcutaneous, intramuscular, intragluteal, intravenous, via local delivery (for example by implants), transdermal, etc.).

For each of the above given substances, suitable dose schemes can be derived from common general knowledge of the compound and possibly adapted according to synergistic effects as is suitable if combined with other compounds.

A typical dose for the dopamine agonist Pergolide mesylate is 0.05-40 mg daily by oral administration (tablet). Similarly for cabergoline oral doses of 0.5- 4.5 mg per week given in one or two doses is suitable. A person skilled in the art will have the knowledge and skill to select suitable doses and administration routes for these and other compounds mentioned above.

The term "pharmaceutical composition" as used herein can have the conventional meaning of a composition of two or more of the drugs as discussed above; however it is also meant to comprise doses for treatments wherein the drugs are administered separately, e.g. at different time intervals, but where the combination of the drugs provides the therapeutical effect.

Pharmaceutical compositions of the present invention can be prepared for storage as aqueous solutions with optional pharmaceutically-acceptable carriers, excipients or stabilizers typically employed in the art (all of which are referred to herein as "carriers"), i.e., buffering agents, stabilizing agents, preservatives, isotonifiers, non-ionic detergents, antioxidants, and other miscellaneous additives. See, e.g., Remington 's Pharmaceutical Sciences, 16th edition (Osol, ed. 1980). Such additives must be nontoxic to the recipients at the dosages and concentrations employed.

Buffering agents help to maintain the pH in the range which approximates physiological conditions. They can be present at concentration ranging from about 2 mM to about 50 mM. Suitable buffering agents for use with the present disclosure include both organic and inorganic acids and salts thereof such as citrate buffers (e.g., monosodium citrate-disodium citrate mixture, citric acid-trisodium citrate mixture, citric acid-monosodium citrate mixture, etc.), succinate buffers (e.g., succinic acid- monosodium succinate mixture, succinic acid-

sodium hydroxide mixture, succinic acid- disodium succinate mixture, etc.), tartrate buffers (e.g., tartaric acid-sodium tartrate mixture, tartaric acid-potassium tartrate mixture, tartaric acid-sodium hydroxide mixture, etc.), fumarate buffers (e.g., fumaric acid-monosodium fumarate mixture, fumaric acid- disodium fumarate mixture, monosodium fumarate-disodium fumarate mixture, etc.), gluconate buffers (e.g., gluconic acid-sodium glyconate mixture, gluconic acid-sodium hydroxide mixture, gluconic acid-potassium glyconate mixture, etc.), oxalate buffer (e.g., oxalic acid-sodium oxalate mixture, oxalic acid-sodium hydroxide mixture, oxalic acid-potassium oxalate mixture, etc.), lactate buffers (e.g., lactic acid-sodium lactate mixture, lactic acid-sodium hydroxide mixture, lactic acid-potassium lactate mixture, etc.) and acetate buffers (e.g., acetic acid-sodium acetate mixture, acetic acid-sodium hydroxide mixture, etc.). Additionally, phosphate buffers, histidine buffers and trimethylamine salts such as Tris can be used.

Preservatives can be added to retard microbial growth, and can be added in amounts ranging from 0.2%- 1% (w/v). Suitable preservatives for use with the present disclosure include phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, octadecyldimethylbenzyl ammonium chloride, benzalconium halides (e.g., chloride, bromide, and iodide), hexamethonium chloride, and alkyl parabens such as methyl or propyl paraben, catechol, resorcinol, cyclohexanol, and 3-pentanol. Isotonicifiers sometimes known as "stabilizers" can be added to ensure isotonicity of liquid compositions of the present disclosure and include polyhydric sugar alcohols, for example trihydric or higher sugar alcohols, such as glycerin, erythritol, arabitol, xylitol, sorbitol and mannitol. Stabilizers refer to a broad category of excipients which can range in function from a bulking agent to an additive which solubilizes the therapeutic agent or helps to prevent denaturation or adherence to the container wall. Typical stabilizers can be polyhydric sugar alcohols (enumerated above); amino acids such as arginine, lysine, glycine, glutamine, asparagine, histidine, alanine, ornithine, L-leucine, 2-phenylalanine, glutamic acid, threonine, etc., organic sugars or sugar alcohols, such as lactose, trehalose, stachyose, mannitol, sorbitol, xylitol, ribitol, myoinositol, galactitol, glycerol and the like, including cyclitols such as inositol; polyethylene glycol; amino acid polymers; sulfur containing reducing agents, such as urea, glutathione, thiocetic acid, sodium thioglycolate, thioglycerol, a-monothioglycerol and sodium thio sulfate; hydrophylic polymers, such as polyvinylpyrrolidone monosaccharides, such as xylose, mannose, fructose, glucose; disaccharides such as lactose, maltose, sucrose and trisaccharides such as raffinose; and polysaccharides such as dextran.

Additional miscellaneous excipients include bulking agents (e.g., starch), chelating agents (e.g., EDTA), antioxidants (e.g., ascorbic acid, methionine, vitamin E), and co-solvents.

The compounds and use according to the present invention may optionally be administered with any other antitumor agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy for treating a colorectal cancer.

Such antitumor agents may include, for instance, alkylating agents, topoisomerase I and II inhibitors, antimicrotubule agents and antimetabolites. As an example, specific antitumor agents are compounds such as melphalan, chlorambucil, mechlorethamine, cyclophosphamide, ifosfamide and busulfan; nitrosoureas such as carmustine, lomustine, semustine and fotemustine; tetrazines such as dacarbazine and temozolomide ; aziridines such as thiotepa and mitomycin C; platinum derivatives such as cisplatin, carboplatin, oxaliplatin, nedaplatin and lobaplatin ; camptothecin derivatives such as CPT-11, Topotecan, 9-amino- camptothecin, 9-nitro-camptothecin and 10,11-methylenedioxy-camptothecin; anthracycline derivatives such as doxorubicin, daunorubicin, epirubicin, nemorubicin and idarubicin ; podophyllotoxin compounds etoposide and teniposide ; anthraquinone derivative like mitoxantrone and losoxantone ; acridine derivatives like amsacrine and actinomycin D; taxanes such as paclitaxel or docetaxel; vinca alkaloids such as vincristine, vinblastine, vindesine, vinorelbine ; estramustine; antifolates such as metotrexate, trimetrexate, tomudex; 5-fluoropyrimidines such as 5-FU, floxuridine, ftorafut and capecitabine; cytidin analogs such as cytatidine, azacitidine and gemcitabine. Other antitumor agents include therapeutic antibodies.

The compounds and use according to the present invention can be administered in combination with, or adjunctive to, one or more other treatments to prevent or delay gastrointestinal cancer. Other treatments include, without limitation, chemotherapeutic treatment, radiation, surgical resection, antibody therapy, and treatment with a second agent, as described herein. Combination treatment as provided herein involves the administration of at least two treatments to a patient, the first of which is treatment with the compounds according to the present invention, and the second of which is treatment with any other therapeutic or prophylactic agent or procedure.

The compounds and use according to the present invention can be combined with surgical procedures, such as surgical resection. The compounds according to the present invention can be administered to subjects found to have, or predisposed to develop, pre-cancerous polyps, such as individuals with familial adenomatous polyposis, in combination with surgical resection of the affected portion(s) of the gastrointestinal tract. Treatment with the compounds according to the present invention can be initiated before, concurrently with, or after surgical resection.

The compounds and use according to the present invention can also be combined with radiation therapy. Radiation therapy is the use of high-energy radiation from x-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy, or brachytherapy). Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body. Radiation therapy may also be called irradiation and radiotherapy. Other radiation therapies include three-dimensional conformal radiation therapy (3D-CRT) and intensity modulated radiation therapy (IMRT). Other radiation therapies are also possible.

Cancer staging

Certain aspects of the methods are provided for patients that are stage II- IV colorectal cancer patients. In particular aspects, the patient is a stage IV patient.

The most common staging system is the TNM (for tumors/nodes/metastases) system, from the American Joint Committee on Cancer (AJCC). The TNM system assigns a number based on three categories. "T" denotes the degree of invasion of the intestinal wall, "N" the degree of lymphatic node involvement, and "M" the degree of metastasis. The broader stage of a cancer is usually quoted as a number I, II, III, IV derived from the TNM value grouped by prognosis; a higher number indicates a more advanced cancer and likely a worse outcome. Details of this system are in the graph below:

AJCC TNM stage TNM stage criteria for colorectal cancer stage:

Stage 0 Tis NO M0 Tis: Tumor confined to mucosa; cancer-in-situ

Stage I T1 NO M0 T1 : Tumor invades submucosa

Stage I T2 NO M0 T2: Tumor invades muscularis propria

Stage II-A T3 NO M0 T3 : Tumor invades subserosa or beyond (without other organs involved)

Stage II-B T4 NO M0 T4: Tumor invades adjacent organs or perforates the visceral peritoneum

Stage III-A T1-2 N1 M0 N1 : Metastasis to 1 to 3 regional lymph nodes. T1 or T2.

Stage III-B T3-4 N1 M0 N1 : Metastasis to 1 to 3 regional lymph nodes. T3 or T4.

Stage III-C any T, N2 M0 N2: Metastasis to 4 or more regional lymph nodes. Any T.

Stage IV any T, any N, M1 : Distant metastases present. Any T, any N.

Specific embodiments of the invention

As described above the present invention relates to a dopamine receptor agonist for the treatment of a colorectal cancer.

5 In some embodiments of the invention the dopamine receptor agonist is a D2 and/or D3 dopamine receptor agonist.

In some embodiments of the invention the dopamine receptor agonist is an ergoline compound, such as a propylergoline compound, such as Pergolide.

In some embodiments of the invention the colorectal cancer is an adenocarcinoma.

In some embodiments of the invention the cancer is a stage II or III colorectal cancer.

10 In some embodiments of the invention the cancer is a stage IV colorectal cancer.

In some embodiments of the invention the dopamine receptor agonist is administered adjunctive to surgical resection of tissue comprising adenomatous polyps.

In some embodiments of the invention the dopamine receptor agonist is administered adjunctive to any other antitumor agent.

15

EXAMPLE 1

Resection colectomy material from patients undergoing surgery for treatment of colorectal cancer (stage I-III) was washed and tissue biopsies of morphologically normal epithelium from resection margins (5 x 5 mm) as well as tumour biopsies (3 x 3 x 3 mm) from the
20 macroscopically identified tumour mass were aseptically collected at the Herlev and Roskilde hospitals (Denmark). The study has been approved by the local bioethical committee and all samples were obtained from patients who provided informed consent before surgery. Biopsies were stored in Advanced DMEM/F12 (Life Technologies) medium at 4-8°C until processing (within 10h of the resection). After washing thoroughly with PBS, biopsies were
25 cut into small pieces of 1-3 mm in size and incubated in freshly prepared ice-cold chelation buffer (96 mM NaCl, 55 mM D-sorbitol, 44 mM Sucrose, 10 mM EDTA, 8 mM KH₂PO₄, 5.6

mM Na₂HPO₄, 1.6 mM KCl, 0.5 mM DTT) for 45 min. with agitation on ice. After decanting the chelation buffer and suspending tissue fragments in PBS, biopsies were manually shaken 3 x 10 s in order to detach epithelial cells. Tumour samples were subsequently further fragmented in a 10 cm Petri dish on ice using a scalpel blade, until a homogeneous cell mass was obtained (ca. 2 min.). Both normal epithelial crypts and dissociated tumours were then filtered using 300 µm nylon mesh filters (Great Lakes Filters), rinsed with PBS containing 1% BSA and centrifuged at 350 rcf for 3 min. Intestinal crypts and cancer cells were then suspended in ice cold Matrigel plated in 48-well plates in a gel-dome format (40 µl), solidified at 37°C for 30 min. and covered with 200-250 µl of organoid culture medium (Advanced DMEM/F12 (Life Technologies), 1x penicillin/streptomycin (Life Technologies), 10 mM HEPES (Life Technologies), 2 mM GlutaMAX (Life Technologies), 10 mM Nicotamide (Sigma), 1x N2 (Life Technologies), 1x B27 (Life Technologies), 1 mM N-acetylcysteine (Sigma), 10 µM Y-27632, 0.5 µM A-83-01 (Tocris), 10 µM SB202190 (Sigma), 100 ng/ml mWnt3a (Cell Guidance Systems), 500 ng/ml mRspodin-1 (R&D), 100 ng/ml mNoggin (R&D), 50 ng/ml hEGF . 2.5 µM PGE-2 (Sigma)). Organoid cultures were regularly inspected for any signs of possible infection using light microscopy and passaged every 1-4 weeks by mechanical disruption following removal of Matrigel by several washes using ice-cold PBS.

For chemosensitivity assays organoids were plated in 48-well plates and assayed using Presto Blue (Life Technologies). Baseline readout was performed 5-7 days after initial plating.

Subsequently cytotoxic drugs were added to the organoid culture medium (20 µM oxaliplatin, 50 µM 5-FU, 200 µM irinotecan, 25 µM Pergolide). Cytotoxic effects were measured in triplicate after 24h and 48 h using Presto Blue assay. Final results were calculated relative to vehicle-treated control after baseline normalisation for each individual well. Cytotoxicity screen was performed using an overall experimental outline modified from the above by using 96-well plates (10 µl Matrigel domes). In parallel to organoid cancer lines, the effects of compounds were also tested on respective normal epithelium organoids derived from same patients.

The results are represented by table 1 below.

Table 1. Effects of treatment with Pergolide on established cancer cell lines and organotypic primary cultures obtained from colorectal cancer patients.

Cell line	Efficiency of the drug at killing cancer cells
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HT29	69% (63%-74% 95% CI)
SW480	32% (25%-39% 95% CI)
SW620	51% (45%-57% 95% CI)
HCT116	38% (32%-44% 95% CI)
PATIENT 1	77% (70%-84% 95% CI)
PATIENT 2	54% (50%-58% 95% CI)
PATIENT 3	51% (47%-55% 95% CI)
PATIENT 4	73% (65%-81% 95% CI)
PATIENT 5	47% (44%-50% 95% CI)

CLAIMS

1. A dopamine receptor agonist for use in the treatment of a colorectal cancer.
2. The dopamine receptor agonist for use according to claim 1, which is a D2 and/or D3 dopamine receptor agonist.
- 5 3. The dopamine receptor agonist for use according to claims 1 or 2, which is an ergoline compound, such as a propylergoline compound, such as Pergolide.
4. The dopamine receptor agonist for use according to any one of claims 1-3, wherein said colorectal cancer is an adenocarcinoma.
- 5 5. The dopamine receptor agonist for use according to any one of claims 1-4, wherein
10 the cancer is a stage II or III colorectal cancer.
6. The dopamine receptor agonist for use according to any one of claims 1-5, wherein the cancer is a stage IV colorectal cancer.
7. The dopamine receptor agonist for use according to any one of claims 1-6, wherein
15 the dopamine receptor agonist is administered adjunctive to surgical resection of tissue comprising adenomatous polyps.
8. The dopamine receptor agonist for use according to any one of claims 1-7, wherein the dopamine receptor agonist is administered adjunctive to any other antitumor agent.
9. Use of dopamine receptor agonist for the treatment of a colorectal cancer.
- 10 10. Use according to claim 9, wherein the dopamine receptor agonist is as defined in any
20 one of claims 1-8.
11. A method of treating a patient suffering from colorectal cancer characterized by administration of effective amounts of a dopamine receptor agonist, or a pharmaceutically acceptable salt thereof, to a patient in need of such treatment.
12. The method according to claim 11, wherein the dopamine receptor agonist is as
25 defined in any one of claims 1-8.

INTERNATIONAL SEARCH REPORT

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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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/023047 A1 (UNIV SUNGKYUNKWAN RES & BUS [KR]) 9 February 2017 (2017-02-09) abstract figures 37-39	1-12
X	----- C. SARKAR ET AL: "Dopamine Increases the Efficacy of Anticancer Drugs in Breast and Colon Cancer Preclinical Models", CLINICAL CANCER RESEARCH, vol. 14, no. 8, April 2008 (2008-04), pages 2502-2510, XP055405494, US ISSN: 1078-0432, DOI: 10.1158/1078-0432.CCR-07-1778 abstract figures 1C,1D,4B,4D page 2506, column 2, paragraph 1 ----- -/-	1-12



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PERACHON S ET AL: "Functional potencies of new antiparkinsonian drugs at recombinant human dopamine D1, D2 and D3 receptors", EUROPEAN JOURNAL OF PHARMACOLOGY, ELSEVIER SCIENCE, NL, vol. 366, no. 2-3, 5 February 1999 (1999-02-05), pages 293-300, XP002238224, ISSN: 0014-2999, DOI: 10.1016/S0014-2999(98)00896-6 abstract -----	1-12
A	B. GLIMELIUS ET AL: "Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up", ANNALS OF ONCOLOGY., vol. 24, no. suppl 6, 27 September 2013 (2013-09-27), pages vi81-vi88, XP055405522, NL ISSN: 0923-7534, DOI: 10.1093/annonc/mdt240 the whole document -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2017023047	A1	09-02-2017	NONE
