(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 June 2015 (11.06.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/084804 Al

(51) International Patent Classification:
A61K 31/00 (2006.01) *A61K 31/472* (2006.01)
A61K 31/4188 (2006.01) *A61K 31/4725* (2006.01)
A61K 31/437 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/US20 14/068091

(22) International Filing Date:
2 December 2014 (02.12.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/91 1,174 3 December 2013 (03. 12.2013) US

(71) Applicant *(for all designated States except US):* **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and
(71) Applicants *(for US only):* **EMERSON, Erling** [US/US]; c/o Novartis Institutes for BioMedical Research, Inc., 250 Massachusetts Avenue, Cambridge, Massachusetts 021 39 (US). **HALILOVIC, Ensar** [US/US]; c/o Novartis Institutes for BioMedical Research, Inc., 250 Massachusetts Avenue, Cambridge, Massachusetts 02139 (US). **WANG, Hui-Qin** [US/US]; c/o Novartis Institutes for BioMedical Research, Inc., 250 Massachusetts Avenue, Cambridge, Massachusetts 02139 (US). **ZUBROWSKI, Matthew** [US/US]; c/o Novartis Institutes for BioMedical Research, Inc., 250 Massachusetts Avenue, Cambridge, Massachusetts 02139 (US).

(74) Agent: **FERRARO, Gregory;** Novartis Pharmaceuticals Corporation, Patent Department, One Health Plaza, Bldg. 433, East Hanover, New Jersey 07936 (US).

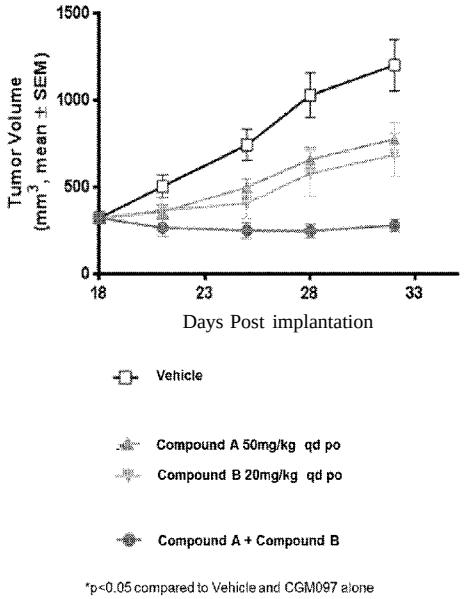
(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,

[Continued on next page]

(54) Title: COMBINATION OF MDM2 INHIBITOR AND BRAF INHIBITOR AND THEIR USE

Fig. 3



(57) Abstract: The present disclosure relates to a pharmaceutical combination, e.g. a product, comprising a combination of (i) a Mdm2 inhibitor and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, respectively, which are jointly active in the treatment of proliferative diseases. The disclosure also relates to corresponding pharmaceutical formulations, uses, methods, combinations, data carrier and related disclosure embodiments. In addition, the disclosure relates to the use of Mdm2 inhibitor in the treatment of colorectal cancer.

WO 2015/084804 A1

LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(Hi))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

Combination of Mdm2 inhibitor and BRAF inhibitor and their Use

Field of the disclosure

The present disclosure relates to a pharmaceutical combination, e.g. a product, comprising a combination of (i) a Mdm2 inhibitor and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, respectively, which are jointly active in the treatment of proliferative diseases. In addition, the disclosure relates to a Mdm2 inhibitor alone or a BRAF inhibitor alone for use in the treatment. The disclosure also relates to corresponding pharmaceutical formulations, uses, methods, combinations, data carrier and related disclosure embodiments.

Background of the Disclosure

Mitogen-activated protein kinase (MAPK) hyper-activation is a common property of human cancers and is often due to activating mutations in the BRAF and RAS genes. BRAF kinase domain mutations result in the production of a constitutively activated form of the protein and occur in approximately 8% of human tumours (Davies et al., 2002; Wan et al., 2004). BRAF mutation stimulates extracellular signal-regulated kinase (ERK) signalling, induces proliferation and is capable of promoting transformation. Given the frequent occurrence of BRAF mutations in human cancer and the continued requirement for BRAF activity in tumours in which it is mutated, efforts are underway to develop targeted inhibitors of BRAF and its downstream effectors. RAF kinase inhibitors have shown substantial therapeutic effects in patients with BRAF-mutant melanoma. However, despite impressive initial responses, therapeutic effects are often temporary due to acquired resistance.

The protein p53 is a transcription factor that controls the expression of a multitude of target genes involved in DNA damage repair, apoptosis and cell cycle arrest, which are all important phenomena counteracting the malignant growth of tumours. p53 is thus critical for maintaining genetic stability and preventing tumour development. The TP53 gene is one of the most frequently mutated genes in human cancers. It is reported that approximately half of all cancers have inactivated p53, caused by direct mutation. In cancers in which the p53 gene is not mutated, functional inactivation at the protein level has been demonstrated. One of the mechanisms of p53 inactivation described is through its interaction with human homolog of MDM2 (Mouse double minute 2). Mdm2 is therefore an important negative regulator of the p53 tumour suppressor. Mdm2 protein functions both as an E3 ubiquitin ligase, that leads to proteasomal degradation of p53, and an inhibitor of p53 transcriptional activation. This inhibitory mechanism is thought to be reversible provided p53 remains wild-type. Mdm2 inhibitors can limit the interaction between Mdm2 and p53 and thus allow the protein to exert again its effector functions.

US 2013/0245039 A1 discloses a combination of vemurafenib and an mdm2 inhibitor.

Summary of the disclosure

The acquired resistance in BRAF mutant cancers highlights the need to identify effective alternative therapeutic approaches to improve the durability of responses to RAF inhibitors. It was surprisingly found that specific set of active mdm2 inhibitors, combined with particular BRAF inhibitors, causes much more pronounced reduction in cancer proliferation, viability and volume. Combined inhibition of Mdm2 by using specific inhibitors of formula I or II, particularly (S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1,4-dihydro-2H-isoquinolin-3-one, and BRAF using potent inhibitors, particularly (S)-methyl-1-(4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1 H-pyrazol-4-yl)pyrimidin-2-ylamino)propan-2-ylcarbamate or vemurafenib, inhibited the viability of BRAF mutant cells in vitro and tumour growth in vivo. Together they induce a complementary set of anti-proliferative and apoptosis stimulating molecules, which result in strong antitumor effects. In one embodiment, the antitumor effects are even synergistic. Therefore, combined inhibition of Mdm2 and BRAF by using specific inhibitors as disclosed herein provides an effective therapeutic modality capable of overcoming the resistance observed with the BRAF inhibitor monotherapy and thus can lead to improved antitumor activity or more durable responses in the clinic.

Specifically, the present disclosure provides the following aspects, advantageous features and specific embodiments, respectively alone or in combination, as listed in the following items:

1. A pharmaceutical combination comprising (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof.
2. The pharmaceutical combination according to item 1, wherein the pharmaceutical combination comprises (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, separately or together.
3. The pharmaceutical combination according to item 1 or 2 for simultaneous or sequential use of the (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof.
4. The pharmaceutical combination according to any one of items 1 to 3, further comprising at least one pharmaceutically acceptable carrier.
5. The pharmaceutical combination according to any one of items 1 to 4 in the form of a fixed combination.
6. The pharmaceutical combination according to any one of items 1 to 5 in the form or a kit of parts for the combined administration where the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and the BRAF inhibitor, or a pharmaceutically acceptable salt thereof may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners are jointly active.
7. The pharmaceutical combination according to any one of items 1 to 6 for use in the treatment of cancer, wherein (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically accept-

able salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, are in a quantity which is jointly therapeutically effective.

8. The pharmaceutical combination according to item 7, wherein the cancer is melanoma, colorectal cancer, sarcoma, thyroid cancer, lung cancer or leukemia.

9. The pharmaceutical combination according to item 7 or 8, wherein the cancer is melanoma.

10. The pharmaceutical combination according to item 7 or 8, wherein the cancer is colorectal cancer.

11. The pharmaceutical combination according to any one of items 7 to 10, wherein the cancer comprises BRAF having the V600E mutation.

12. The pharmaceutical combination according to any one of items 7 to 11, wherein the cancer comprises functional p53 or p53 wt.

13. A Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament, wherein the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, is to be administered simultaneously or sequentially to a BRAF inhibitor, or a pharmaceutically acceptable salt thereof.

14. A Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, is to be administered simultaneously or sequentially to a BRAF inhibitor, or a pharmaceutically acceptable salt thereof.

15. The Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, according to item 14, wherein the cancer is melanoma, colorectal cancer, sarcoma, thyroid cancer, lung cancer or leukemia.

16. The Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, according to item 14 or 15, wherein the cancer is melanoma.

17. The Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to item 14 or 15, wherein the cancer is colorectal cancer.

18. The Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, according to any one of items 14 to 17, wherein the cancer comprises BRAF having the V600E mutation.

19. The Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, according to any one of items 14 to 18, wherein the cancer comprises functional p53 or p53 wt.

20. Use of a data carrier comprising information about using (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, simultaneously or sequentially, to instruct to administer (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, simultaneously or sequentially for the treatment of cancer.

21. A method of treating a patient suffering from cancer comprising administering to the patient, either simultaneously or sequentially: (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, wherein the amount of said Mdm2 inhibitor and BRAF inhibitor being such that the combination thereof is therapeutically effective in the treatment of the cancer.

22. The method of treating a patient suffering from cancer according to item 21, wherein the cancer is melanoma, colorectal cancer, sarcoma, thyroid cancer, lung cancer or leukemia.
23. The method of treating a patient suffering from cancer according to item 21 or 22, wherein the cancer is melanoma.
24. The method of treating a patient suffering from cancer according to item 21 or 22, wherein the cancer is colorectal cancer.
25. The method of treating a patient suffering from cancer according to any one of items 21 to 24, wherein the cancer comprises BRAF having the V600E mutation.
26. The method of treating a patient suffering from cancer according to any one of items 21 to 25, wherein the cancer comprises functional p53 or p53 wt.
27. The pharmaceutical combination according to any one of items 1 to 12 in the form of a combination product.
28. A pharmaceutical combination comprising (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer.
29. The pharmaceutical combination according to item 28, wherein the cancer is melanoma, colorectal cancer, sarcoma, thyroid cancer, lung cancer or leukemia.
30. The pharmaceutical combination according to item 28 or 29, wherein the cancer is melanoma.
31. The pharmaceutical combination according to item 28 or 29, wherein the cancer is colorectal cancer.
32. The pharmaceutical combination according to any one of items 28 to 31, wherein the cancer comprises BRAF having the V600E mutation.
33. The pharmaceutical combination according to any one of items 28 to 32, wherein the cancer comprises functional p53 or p53 wt.
34. A Mdm2 inhibitor of formula I or formula II or a pharmaceutically acceptable salt thereof and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine.
35. The pharmaceutical combination according to any one of items 1 to 12, or 27, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to item 13, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of items 14 to 19, the method of treating a patient suffering from cancer according to any one of items 21 to 26, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of items 28 to 33, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to item 34, wherein an amount of the BRAF inhibitor, or a pharmaceutically acceptable salt thereof, is lower than the amount administered when the BRAF inhibitor, or a pharmaceutically acceptable salt thereof, is used alone.
36. The pharmaceutical combination according to any one of items 1 to 12, or 27, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to item 13, the Mdm2 inhibitor of formula I or formula II, or a

pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of items 14 to 19, the method of treating a patient suffering from cancer according to any one of items 21 to 26, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of items 28 to 33, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to item 34, wherein an amount of the BRAF inhibitor, or a pharmaceutically acceptable salt thereof, is a subtherapeutic amount.

37. The pharmaceutical combination according to any one of items 1 to 12, or 27, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to item 13, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of items 14 to 19, the method of treating a patient suffering from cancer according to any one of items 21 to 26, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of items 28 to 33, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to item 34, wherein an amount of the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, is lower than the amount administered when the Mdm2 inhibitor is used alone.

38. The pharmaceutical combination according to any one of items 1 to 12, or 27, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to item 13, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of items 14 to 19, the method of treating a patient suffering from cancer according to any one of items 21 to 26, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of items 28 to 33, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to item 34, wherein an amount of the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, is a subtherapeutic amount.

39. A Mdm2 inhibitor of formula I or formula II for use in the treatment of colorectal cancer.

40. The Mdm2 inhibitor of formula I or formula II for use in the treatment according to item 39, wherein the colorectal cancer comprises BRAF having the V600E mutation.

41. The Mdm2 inhibitor of formula I or formula II for use in the treatment according to items 39 or 40, wherein the cancer comprises functional p53 or p53 wt.

42. A pharmaceutical composition comprising Mdm2 inhibitor of formula I or formula II for use in the treatment of colorectal cancer.

43. The pharmaceutical composition comprising Mdm2 inhibitor of formula I or formula II for use in the treatment according to item 42, wherein the colorectal cancer comprises BRAF having the V600E mutation.

44. The pharmaceutical composition comprising Mdm2 inhibitor of formula I or formula II for use in the treatment according to items 42 or 43, wherein the cancer comprises functional p53 or p53 wt.

45. The pharmaceutical combination according to any one of items 1 to 12, 27 or 35 to 38, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to any one of items 13 or 35 to 38, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of items 14 to 19 or 35 to 38, the method of treating a patient suffering from cancer according to any one of items 21 to 26 or 35 to 38, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of items 28 to 33 or 35 to 38, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to any one of items 34 to 38, or the Mdm2 inhibitor of formula I or formula II for use in the treatment according to any one of items 39 to 41, or the pharmaceutical composition comprising Mdm2 inhibitor of formula I or formula II for use in the treatment according to any one of items 42 to 44, wherein the Mdm2 inhibitor of formula I or formula II is selected from the group consisting of:
(S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1 ,4-dihydro-2H-isoquinolin-3-one
(S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1 ,4-dihydro-2H-isoquinolin-3-one
(S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(6-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-pyridin-3-yl)-1 ,4-dihydro-2H-isoquinolin-3-one
(S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(6-{methyl-[4-(3-methyl-4-oxo-imidazolidin-1-yl)-trans-cyclohexylmethyl]-amino}-pyridin-3-yl)-1 ,4-dihydro-2H-isoquinolin-3-one
(S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(5-{methyl-[4-(3-methyl-4-oxo-imidazolidin-1-yl)-trans-cyclohexylmethyl]-amino}-pyrazin-2-yl)-1,4-dihydro-2H-isoquinolin-3-one
1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1 ,4-dihydro-2H-isoquinolin-3-one,
(S)-5-(5-Chloro-1-methyl-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(4-chloro-phenyl)-2-(2,4-dimethoxy-pyrimidin-5-yl)-1-isopropyl-5,6-dihydro-1 H-pyrrolo[3,4-d]imidazol-4-one
4-[(S)-5-(3-Chloro-2-fluoro-phenyl)-2-(2,4-dimethoxy-pyrimidin-5-yl)-3-isopropyl-6-oxo-3,4,5,6-tetrahydro-pyrrolo[3,4-d]imidazol-4-yl]-benzonitrile
(S)-5-(5-Chloro-2-oxo-1 ,2-dihydro-pyridin-3-yl)-6-(4-chloro-phenyl)-2-(2,4-dimethoxy-pyrimidin-5-yl)-1 -isopropyl-5,6-dihydro-1 H-pyrrolo[3,4-d]imidazol-4-one
(S)-5-(3-chloro-4-fluorophenyl)-6-(4-chlorophenyl)-2-(2,4-dimethoxypyrimidin-5-yl)-1-((R)-1-methoxypropan-2-yl)-5,6-dihydropyrrolo[3,4-d]imidazol-4(1 H)-one, and
(S)-5-(5-chloro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-chlorophenyl)-2-(2,4-dimethoxy-d6-pyrimidin-5-yl)-1-((R)-1-methoxypropan-2-yl)-5,6-dihydropyrrolo[3,4-d]imidazol-4(1 H)-one.

46. The pharmaceutical combination according to any one of items 1 to 12, 27 or 35 to 38, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to any one of items 13 or 35 to 38, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of items 14 to 19 or 35 to 38, the method of treating a patient suffering from cancer according to any one of items 21 to 26 or 35 to 38, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of items 28 to 33 or 35 to 38, or the Mdm2 inhibitor of formula I or formula

II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to any one of items 34 to 38, or the Mdm2 inhibitor of formula I or formula II for use in the treatment according to any one of items 39 to 41, or the pharmaceutical composition comprising Mdm2 inhibitor of formula I or formula II for use in the treatment according to any one of items 42 to 44, wherein the Mdm2 inhibitor is (S)-5-(5-Chloro-1-methyl-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(4-chloro-phenyl)-2-(2,4-dimethoxy-pyrimidin-5-yl)-1-isopropyl-5,6-dihydro-1 H-pyrrolo[3,4-d]imidazol-4-one.

47. The pharmaceutical combination according to any one of items 1 to 12, 27 or 35 to 38, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to any one of items 13 or 35 to 38, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of items 14 to 19 or 35 to 38, the method of treating a patient suffering from cancer according to any one of items 21 to 26 or 35 to 38, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of items 28 to 33 or 35 to 38, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to any one of items 34 to 38, or the Mdm2 inhibitor of formula I or formula II for use in the treatment according to any one of items 39 to 41, or the pharmaceutical composition comprising Mdm2 inhibitor of formula I or formula II for use in the treatment according to any one of items 42 to 44, wherein the Mdm2 inhibitor is (S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1 ,4-dihydro-2H-isoquinolin-3-one.

48. The pharmaceutical combination according to any one of items 1 to 12, 27, 35 to 38 or 45 to 47, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to any one of items 13, 35 to 38 or 45 to 47, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of items 14 to 19, 35 to 38 or 45 to 47, the method of treating a patient suffering from cancer according to any one of items 21 to 26, 35 to 38 or 45 to 47, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of items 28 to 33, 35 to 38 or 45 to 47, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to any one of items 34 to 38 or 45 to 47, wherein the BRAF inhibitor is selected from the group consisting of: (S)-methyl-1-(4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1 H-pyrazol-4-yl)pyrimidin-2-ylamino)propan-2-ylcarbamate;

methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;

methyl N-[(2S)-1-({4-[3-(2,5-difluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;

methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-ethyl-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;

methyl N-[(2S)-1-({4-[3-(2-fluoro-3-methanesulfonamido-5-methylphenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;

methyl N-[(2S)-1-({4-[3-(2-chloro-3-methanesulfonamido-5-methylphenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;
methyl N-[(2S)-1-({4-[3-(2-chloro-5-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;
methyl N-[(2R)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;
methyl N-[(2S)-1-({4-[3-(2,5-dichloro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate; and
vemurafenib.

49. The pharmaceutical combination according to any one of items 1 to 12, 27, 35 to 38 or 45 to 47, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to any one of items 13, 35 to 38 or 45 to 47, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of items 14 to 19, 35 to 38 or 45 to 47, the method of treating a patient suffering from cancer according to any one of items 21 to 26, 35 to 38 or 45 to 47, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of items 28 to 33, 35 to 38 or 45 to 47, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to any one of items 34 to 38 or 45 to 47, wherein the BRAF inhibitor is (S)-methyl-1-(4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)propan-2-ylcarbamate, methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate or vemurafenib.

50. The pharmaceutical combination according to any one of items 1 to 12, 27, 35 to 38 or 45 to 47, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to any one of items 13, 35 to 38 or 45 to 47, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of items 14 to 19, 35 to 38 or 45 to 47, the method of treating a patient suffering from cancer according to any one of items 21 to 26, 35 to 38 or 45 to 47, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of items 28 to 33, 35 to 38 or 45 to 47, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to any one of items 34 to 38 or 45 to 47, wherein the BRAF inhibitor is (S)-methyl-1-(4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)propan-2-ylcarbamate.

51. The pharmaceutical combination according to any one of items 1 to 12, 27, 35 to 38 or 45 to 50, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to any one of items 13, 35 to 38 or 45 to 50, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of items 14 to 19, 35 to 38 or 45 to 50, the method of treating a patient suffering from cancer according to any one of items 21 to 26, 35 to 38 or 45 to 50, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical

product for the treatment of cancer according to any one of items 28 to 33, 35 to 38 or 45 to 50, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to any one of items 34 to 38 or 45 to 50, further comprising another therapeutically active agent.

52. The pharmaceutical combination according to any one of items 1 to 12, 27, 35 to 38 or 45 to 51, in a form of a pharmaceutical composition or a product.

Description of Figures

Fig. 1. Graphic representation of the in vitro effect on proliferation of a combination of the BRAF inhibitor compound B with the Mdm2 inhibitor compound A in the melanoma derived cell lines (WM2664, SkMel24 and C32). Shown here are matrices for inhibition of growth and Loewe (ADD) excess inhibition for compound B combinations with compound A in the melanoma cell lines. The combination resulted in strong synergistic antiproliferative effects.

Fig. 2. Graphic representation of the in vitro effect on proliferation of a combination of the BRAF inhibitor compound B with the Mdm2 inhibitor compound A in the melanoma derived cell lines, and comparison to combination of the vemurafenib with the compound A. The synergistic effects of the combination of compound A with compound B start to occur at concentrations 55 times lower than that of vemurafenib.

Fig 3. Graphic representation of the in vivo effect of the combination of compound B with compound A. In the WM266-4 model the combination resulted in stronger anti-tumour effects compared to either single agent alone.

Fig 4. Graphic representation of the in vivo effect of the combination of compound B with compound A. In the WM266-4 model the combination resulted in prolonged survival compared to either single agent alone.

Fig 5. Graphic representation of the in vivo effect of the combination of compound B with compound A. The combination is tolerated well in nude mice.

Fig. 6. Graphic representation of the in vitro effect on proliferation of a combination of the BRAF inhibitor compound B with the Mdm2 inhibitor compound C in the melanoma derived cell lines (A-375, SKMEL5). Synergy score indicates synergy.

Fig. 7. Graphic representation of the in vitro effect on proliferation of a combination of the BRAF inhibitor compound B with the Mdm2 inhibitor compound A in the colorectal cancer derived cell lines (RKO). The combination resulted in strong synergistic antiproliferative effects.

Fig. 8. shows matrices for inhibition of growth (top row) and Loewe (ADD) excess inhibition (bottom row) for Compound B combinations with Compound C in the colorectal cell lines.

Fig 9. Anti-tumour effects of Compound C, Compound B and combination of Compounds C + B in human colorectal xenograft model.

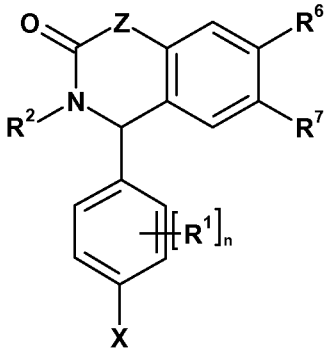
Fig 10. Anti-tumour effects of Compound C, Compound B and combination of Compounds C + B in human colorectal xenograft model.

Fig 11. Body weight changes in Compound C, Compound B and combination of Compounds C + B treated HCOX2145 and HCOX1329 models.

Detailed Description of the disclosure

In one embodiment, the present disclosure provides a pharmaceutical combination comprising (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof. It was unexpectedly found that a compound of formula I or formula II, or a pharmaceutically acceptable salt thereof, can have its antitumor effects significantly potentiated when combined with a BRAF inhibitor. The combination induces a complementary set of anti-proliferative and apoptosis stimulating molecules, which result in strong increase of antineoplastic effect. Combination partners, when administered simultaneously or sequentially, achieve sustained tumour regression and marked prolonged survival relative to either single agent. In one embodiment, the combination results in the synergistic effects. Such pronounced effect can for example be observed in vitro when a Mdm2 inhibitor of formula I or formula II, for example (S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1,4-dihydro-2H-isoquinolin-3-one (compound A), or (S)-5-(5-Chloro-1-methyl-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(4-chloro-phenyl)-2-(2,4-dimethoxy-pyrimidin-5-yl)-1-isopropyl-5,6-dihydro-1 H-pyrrolo[3,4-d]imidazol-4-one (compound C), is combined with as low concentration as 0.001 8μM of (S)-methyl-1-(4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)propan-2-ylcarbamate (compound B). The increase in effect is seen at about 55 times lower concentration of BRAF inhibitor when for example the same mdmd2 inhibitor is combined with vemurafenib. A remarkable observation was also made, unexpectedly, during the in vivo studies with combination of compounds A and B. The combination caused more profound tumour regressions compared to the combination of the mdm2 inhibitor with vemurafenib. Vemurafenib, in combination with the mdm2 inhibitor, still allowed tumours to grow from 146.39 to 400.67 mm^3 (270% tumour growth compared to starting volume; ref. US 2013/0245039 A 1), whereas the combination of the present disclosure can lead to tumour shrinkage (13.2% regression) from the starting tumour volume. The results also show that the two compounds alone show an effect in melanoma. Also, the same was observed for Mdm2 inhibitor or BRAF inhibitor, when used alone in colorectal cancer. Clearly, Mdm2 inhibitor alone, particularly compounds A or C, can be used for the treatment of colorectal cancer.

According to the present disclosure, the Mdm2 inhibitor can also include Mdm4 inhibitor or Mdm2/4 inhibitor. The Mdm2 inhibitor as used herein can be for example a compound of formula I:



formula (I)

wherein

Z is CH_2 or N-R^4;

X is halogen;

R^4 is selected from the group consisting of

H-

C_1-C_7-alkyl-;

R^6 is independently selected from the group consisting of

H-

R'O-

$(R')_2N$-;

R^7 is independently selected from the group consisting of

R'O-

$(R')_2N$-;

each R' is independently selected from the group consisting of

H-

Ci-C_7-alkyl-

Ci-C_7-alkenyl-

halo-Ci-C_7-alkyl-

halo-CrC_7-alkenyl-

C_3-C_{12}-cycloalkyl-

heterocyclyl-

aryl-

hydroxy-CrC_7-alkyl-

C_1-C_7-alkoxy-Ci-C_7-alkyl-

amino-C_1-C_7-alkyl-

N-Ci-C_7-alkyl-amino-Ci-C_7-alkyl-

N,N-di-Ci-C_7-alkyl-amino-Ci-C_7-alkyl-

C_3-Ci2-cycloalkyl-CrC_7-alkyl-

heterocyclyl-Ci-C_7-alkyl-

aryl-CrC_7-alkyl-

Ci-C_7-alkyl-carbonyl-

halo-CrC_7-alkyl-carbonyl-

hydroxy-C_1-C_7-alkyl-carbonyl-

CrC_7-alkoxy-Ci-C_7-alkyl-carbonyl-

amino-C_1-C_7-alkyl-carbonyl-

N-**Ci-C**$_7$-alkyl-amino-**Ci-C**$_7$-alkyl-carbonyl-
N,N-di-**CrC**$_7$-alkyl-amino-**Ci-C**$_7$-alkyl-carbonyl-
C$_3$-Ci$_2$-cycloalkyl-carbonyl-
heterocyclyl-C$_1$-C$_7$-alkyl-carbonyl-
aryl-**Ci-C**$_7$-alkyl-carbonyl-
C$_3$-Ci$_2$-cycloalkyl-**CrC**$_7$-alkyl-carbonyl-
heterocyclyl-carbonyl-
aryl-carbonyl-
Ci-C$_7$-alkyl-carbonyl-**CrC**$_7$-alkyl-
halo-**CrC**$_7$-alkyl-carbonyl-**Ci-C**$_7$-alkyl-
hydroxy-**CrC**$_7$-alkyl-carbonyl-**Ci-C**$_7$-alkyl-
CrC$_7$-alkoxy-**Ci-C**$_7$-alkyl-carbonyl-d-**C**$_7$-alkyl-
amino-**Ci-C**$_7$-alkyl-carbonyl-**CrC**$_7$-alkyl-
N-**Ci-C**$_7$-alkyl-amino-**Ci-C**$_7$-alkyl-carbonyl-**CrC**$_7$-alkyl-
N,N-di-**Ci-C**$_7$-alkyl-amino-**Ci-C**$_7$-alkyl-carbonyl-**CrC**$_7$-alkyl-
C$_3$-Ci$_2$-cycloalkyl-carbonyl-**CrC**$_7$-alkyl-
heterocyclyl-carbonyl-C$_1$-C$_7$-alkyl-
aryl-carbonyl-**Ci-C**$_7$-alkyl-
carbonyl-**Ci-C**$_7$-alkyl-
hydroxy-carbonyl-**Ci-C**$_7$-alkyl-
Ci-C$_7$-alkoxy-carbonyl-**CrC**$_7$-alkyl-
amino-carbonyl-C$_1$-C$_7$-alkyl-
N-**Ci-C**$_7$-alkyl-amino-carbonyl-**CrC**$_7$-alkyl-
N,N-di-**Ci-C**$_7$-alkyl-amino-carbonyl-**CrC**$_7$-alkyl-
C$_3$-Ci$_2$-cycloalkyl-carbonyl-**Ci-C**$_7$-alkyl-
heterocyclyl-carbonyl-**CrC**$_7$-alkyl-
aryl-carbonyl-C$_1$-C$_7$-alkyl-
Ci-C$_7$-alkyl-carbonyl-amino-**CrC**$_7$-alkyl-
Ci-C$_7$-alkyl-carbonyl-N-**Ci-C**$_7$-alkyl-amino-**CrC**$_7$-alkyl-
halo-C$_1$-C$_7$-alkyl-carbonyl-amino-C$_1$-C$_7$-alkyl-
halo-**Ci-C**$_7$-alkyl-carbonyl-N-**Ci-C**$_7$-alkyl-amino-**CrC**$_7$-alkyl-

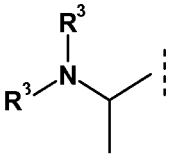
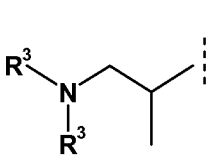
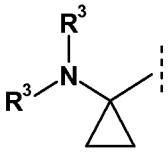
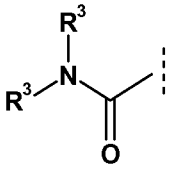
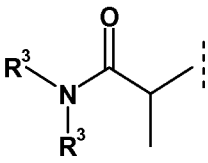
wherein aryl, heterocyclyl and **C$_3$-Ci$_2$**-cycloalkyl are unsubstituted or substituted by 1-4 substituents selected from **Ci-C**$_7$-alkyl, halo-**Ci-C**$_7$-alkyl, halogen, hydroxy, **Ci-C**$_7$-alkoxy, amino, nitro or cyano;

each R^1 is independently selected from the group consisting of
halogen-
cyano-
nitro-
Ci-C$_7$-alkyl-
Ci-C$_7$-alkenyl-
halo-**Ci-C**$_7$-alkyl-
hydroxy-

CrC $_7$-alkoxy-
amino-
N-Ci-C $_7$-alkyl-amino-
N^-di-CrC $_7$-alkyl-amino-
amino-carbonyl-amino-
N-Ci-C $_7$-alkyl-amino-carbonyl-amino-
N,N-di-C_1-C_7-alkyl-amino-carbonyl-amino-
CrC $_7$-alkyl-carbonyl-amino-
amino-carbonyl-
N-Ci-C $_7$-alkyl-amino-carbonyl-
N,N-di-CrC $_7$-alkyl-amino-carbonyl-
hydroxy-C_1-C_7-alkyl-
amino-CrC $_7$-alkyl-
N-Ci-C $_7$-alkyl-amino-Ci-C $_7$-alkyl-
N,N-di-CrC $_7$-alkyl-amino-Ci-C $_7$-alkyl-
Ci-C_7-alkyl-carbonyl-amino-CrC $_7$-alkyl-
C_1-C_7-alkyl-carbonyl-N-C $_1$-C_7-alkyl-amino-C $_1$-C_7-alkyl-;
n is 0 to 2;

R^2 is selected from

(A) phenyl, 2-pyridyl and 3-pyridyl
substituted in the para-position relative to the isoquinolinone or quinazolinone, by
$(R^3)_2$N-Y-
wherein Y is absent (a bond) or
$(R^3)_2$N-Y- is selected from

and wherein said phenyl, 2-pyridyl or 3-pyridyl is optionally substituted by 1-2 additional substituents selected from
halogen-
cyano-
C_1-C_7-alkyl-
halo-Ci-C $_7$-alkyl-
hydroxy-
Ci-C_7-alkoxy- and
hydroxy-Ci-C $_7$-alkyl-;
or

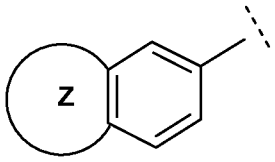
(B) phenyl, 2-pyridyl or 3-pyridyl
substituted in para-position relative to the isoquinolinone or quinazolinone by a substituent selected from

cyano-
halogen-
nitro-
C_1-C_7-alkyl-
halo-Ci-C_7-alkyl-
hydroxy-Ci-C_7-alkyl-
hydroxy-carbonyl-
Ci-C_7-alkoxy-carbonyl-
Ci-C_7-alkyl-carbonyl-
Ci-C_7-alkoxy-
(C-bound)-heterocyclyl-
wherein (C-bound)-heterocyclyl is unsubstituted or substituted by 1-4 substituents selected from Ci-C_7-alkyl, halo-Ci-C_7-alkyl, halogen, hydroxy, Ci-C_7-alkoxy, amino, nitro or cyano;
and optionally substituted by 1-2 additional substituents selected from
halogen-
cyano-
Ci-C_7-alkyl-
halo-Ci-C_7-alkyl-
hydroxy-
Ci-C_7-alkoxy-
(C-bound or N-bound)heterocyclyl- C_1-C_4-alkyl-
hydroxy- Ci-C_7-alkyl-;

or

(C) phenyl,
substituted in ortho-position relative to the isoquinolinone or quinazolinone by
R^30-
and substituted in para- or meta-position by a substituent selected from methyl, chloro, Ci-C_7-alkyl-carbonyl- or Ci-C_7-alkoxy-carbonyl- ;

(D) (C-bound)-heterocycle selected from

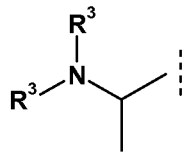


,

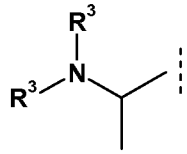
wherein Z is a 4-6 membered heterocyclic ring, annulated to phenyl in para and meta position, containing 1-3 heteroatoms selected from N,0 or S,
which is optionally substituted by 1-2 additional substituents selected from
halogen-
cyano-
Ci-C_7-alkyl-
halo-Ci-C_7-alkyl-
hydroxy-

CrC $_7$-alkoxy-
hydroxy-Ci-C $_7$-alkyl-;

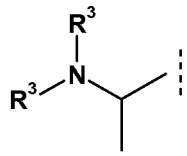
(E) pyrazin-2-yl,
substituted at the 5 position by:



(F) pyridazin-3-yl, substituted at the 6 position by:



or
(G) pyrimidin-2-yl, substituted at the 5 position by:



.

wherein each R^3 is independently selected from
H-
C_1-C_7-alkyl-
hydroxy-Ci-C $_7$-alkyl-
C_3-Ci $_2$-cycloalkyl-
Ci-C_7-alkoxy- d-d-alkyl-carbonyl-
amino- CrC $_7$-alkyl-carbonyl
N-C_1-C_7-alkyl -amino- C_1-C_7-alkyl-carbonyl
N, N-di CrC $_7$-alkyl -amino- CrC $_7$-alkyl-carbonyl
$(R^5)_2$N-C_3-Ci $_2$-cycloalkyl-
$(R^5)_2$N-CrC $_7$-alkyl-
$(R^5)_2$N-C_3-Ci $_2$-cycloalkyl-Ci-C $_7$-alkyl-
$(R^5)_2$N-C_3-C_{12}-cycloalkyl-carbonyl-
$R^5$0-C $_3$-Ci $_2$-cycloalkyl-
$R^5$0-Ci-C $_7$-alkyl-
$R^5$0-C $_3$-C_{12}-cycloalkyl-C $_1$-C_7-alkyl-
$R^5$0-(C $_1$-C_7-alkyl)-C $_3$-Ci $_2$-cycloalkyl-Ci-C $_7$-alkyl-
R^-ihydroxy-d-C^alkyO-Cs-dz-cycloalkyl-d-C^alkyl-
$(R^5)_2$N-CO-d-Ci $_2$-cycloalkyl- d-d-alkyl-

Ci-C$_7$-alkoxycarbonyl **-C$_3$-Ci$_2$**-cycloalkyl **-Ci-C$_7$**-alkyl-
hydroxycarbonyl **-C$_3$-Ci$_2$**-cycloalkyl **-CrC$_7$**-alkyl-
amino-carbonyl **-C$_3$-Ci$_2$**-cycloalkyl **-Ci-C$_7$**-alkyl-
R^{5}0-C$_3$-C$_{12}$-cycloalkyl-carbonyl-
(R^5)$_2$N-carbonyl-C$_1$-C$_7$-alkyl-
R^{5}0-carbonyl **-Ci-C$_7$**-alkyl-
aryl **-CrC$_7$**-alkyl-
heterocyclyl **-Ci-C$_7$**-alkyl-
Ci-C$_7$-alkyl-carbonyl-
halo**-CrC$_7$**-alkyl-carbonyl-
heterocyclyl-carbonyl-
aryl-carbonyl-
C$_3$**-Ci$_2$**-cycloalkyl-carbonyl-
C$_3$-Ci$_2$-cycloalkyl **-Ci-C$_7$**-alkyl-
heterocyclyl-
aryl-

wherein aryl, heterocyclyl and C$_3$-C$_{12}$-cycloalkyl are unsubstituted or substituted by 1-4 substituents selected from
halogen-
Ci-C$_7$-alkyl-
halo**-Ci-C$_7$**-alkyl-
CrC$_7$-alkyl-carbonyl-
C$_3$**-Ci$_2$**-cycloalkyl-carbonyl-
Ci-C$_7$-alkyl-sulfonyl-
amino-sulfonyl-
N**-Ci-C$_7$**-alkyl-amino-sulfonyl-
N,N-di-C$_1$-C$_7$-alkyl-amino-sulfonyl-
amino-carbonyl-
N**-Ci-C$_7$**-alkyl-amino-carbonyl-
N,N-di-C$_1$-C$_7$-alkyl-amino-carbonyl-
0X0=

or

two R^3, together with the N to which they are attached my form a 3-9 membered heterocyclic ring, optionally containing 1-4 additional heteroatoms selected from N, O or S, said heterocyclic ring is unsubstituted or substituted by 1-3 substituents selected from:
halogen-
hydroxy- **CrC$_7$**-alkyl-
Ci-C$_7$-alkyl-
halo-C$_1$-C$_7$-alkyl-
oxo=
hydroxy-
Ci-C$_7$-alkoxy-
amino-

N-**Ci-C**$_7$-alkyl-amino-
N,N-di-**CrC** $_7$-alkyl-amino-
hydroxy-carbonyl-
CrC $_7$-alkoxy-carbonyl-
amino-carbonyl-
N-**CrC** $_7$-alkyl-amino-carbonyl-
N,N-di-C_1-C_7-alkyl-amino-carbonyl-
Ci-C$_7$-alkyl-carbonyl-
Ci-C$_7$-alkyl-sulphonyl-
heterocyclyl-
CrC $_7$-alkyl-carbonyl-amino-
C_1-C_7-alkyl-carbonyl-N-C $_1$-C_7-alkyl-amino-;
and

each R^5 is independently selected from:
H-
C_1-C_7-alkyl-
hydroxy-**Ci-C**$_7$-alkyl-
Ci-C$_7$-alkyl-carbonyl-
Ci-C$_7$-alkoxy-carbonyl **-CrC** $_7$-alkyl-
amino-carbonyl **-Ci-C**$_7$-alkyl-
N-C_1-C_7-alkyl-amino-carbonyl-C $_1$-C_7-alkyl-
N,N-di-**Ci-C**$_7$-alkyl-amino-carbonyl **-Ci-C**$_7$-alkyl-
Ci-C$_7$-alkyl-sulfonyl-
amino-sulfonyl-
N-**Ci-C**$_7$-alkyl-amino-sulfonyl-
N,N-di-C_1-C_7-alkyl-amino-sulfonyl-
heterocyclyl-carbonyl-
amino-carbonyl-
N-C_1-C_7-alkyl-amino-carbonyl-
N,N-di-**Ci-C**$_7$-alkyl-amino-carbonyl-
C_3-**Ci** $_2$-cycloalkyl-carbonyl-
Ci-C$_7$-alkoxy-carbonyl-amino **-Ci-C**$_7$-alkyl-
Ci-C$_7$-alkoxy-carbonyl-N **-Ci-C**$_7$-alkyl-amino **-Ci-C**$_7$-alkyl-
CrC $_7$-alkoxy-carbonyl-
C_3-**Ci** $_2$-cycloalkyl-
hydroxy-C_3-**Ci** $_2$-cycloalkyl-
or
two R^5, together with the N to which they are attached my form a 3-9 membered heterocyclic ring, optionally containing from 1-4 additional heteroatoms selected from N, O or S, said heterocyclic ring is unsubstituted or substituted by from 1 to 3 substituents selected from
Ci-C$_7$-alkyl-
oxo=,

CrC_7-alkyl-carbonyl,
Ci-C_7-alkyl-sulphonyl,
hydroxy- Ci-C_7-alkyl;

with the proviso that if Z is CH_2, n is 0 or 1, and when present, R^1 is ortho-chloro, and R^2 is selected from

para-CrC_8-alkyl-phenyl-
para-(halo-CrC_3-alkyl)-phenyl-
para-CrC_3-alkoxy-phenyl-
para-halo-phenyl-
para-nitro-phenyl-
para-iCrCs-alkoxy-carbonyO-phenyl-
para-(hydroxy-carbonyl)-phenyl-
wherein the phenyl is optionally substituted by 1-2 additional substituents, said substituents being independently selected from halo and methyl,

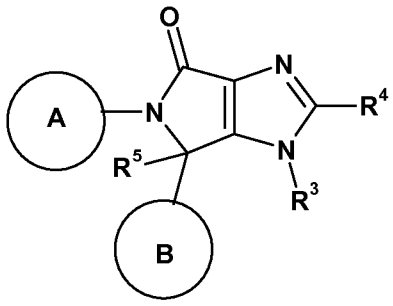
then R^6 and R^7 are not both ethoxy or methoxy,

aryl means phenyl or naphthyl,

and

heterocyclyl means an unsaturated, saturated, or partially saturated ring or ring system comprising 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 ring atoms, and containing at least one heteroatom selected from N, O and S, where the N and S can also optionally be oxidized, and wherein, unless otherwise stated, the heterocyclic group can be attached at a heteroatom or a carbon atom. The compounds can be synthetized as explained in WO 201 1/076786. The reference also includes specific examples of possible compounds.

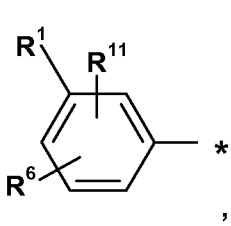
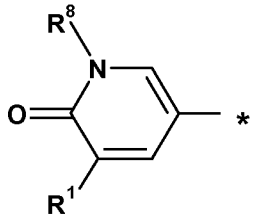
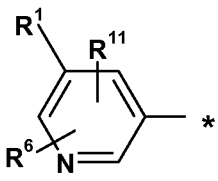
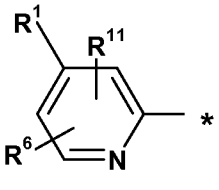
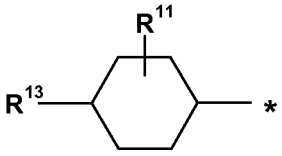
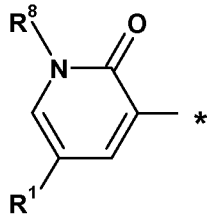
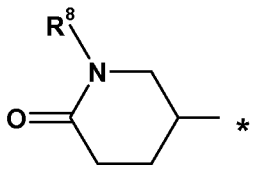
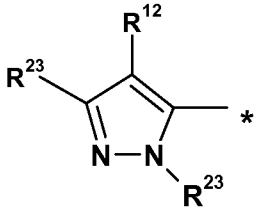
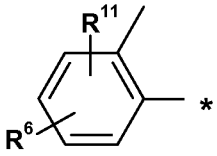
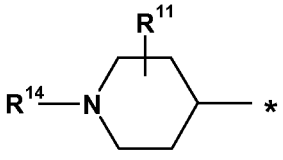
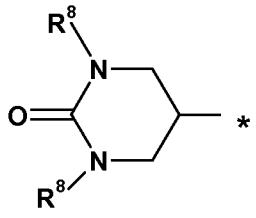
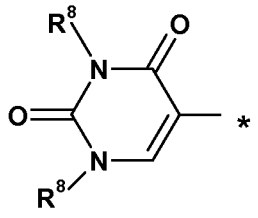
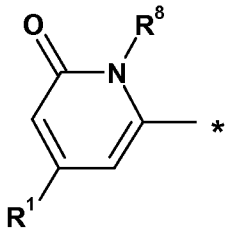
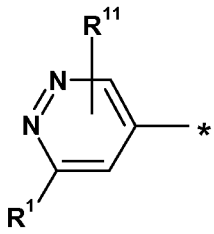
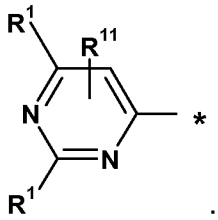
The Mdm2 inhibitor can also be a compound of formula II:

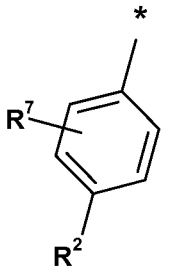
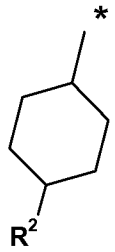
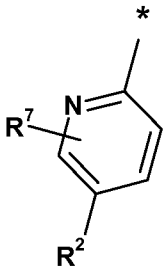


formula (II)

wherein

A is selected from:

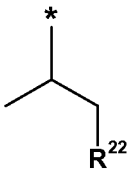














and

;

B is selected from:

,

and

;

each R^1 is independently selected from halo and methyl;

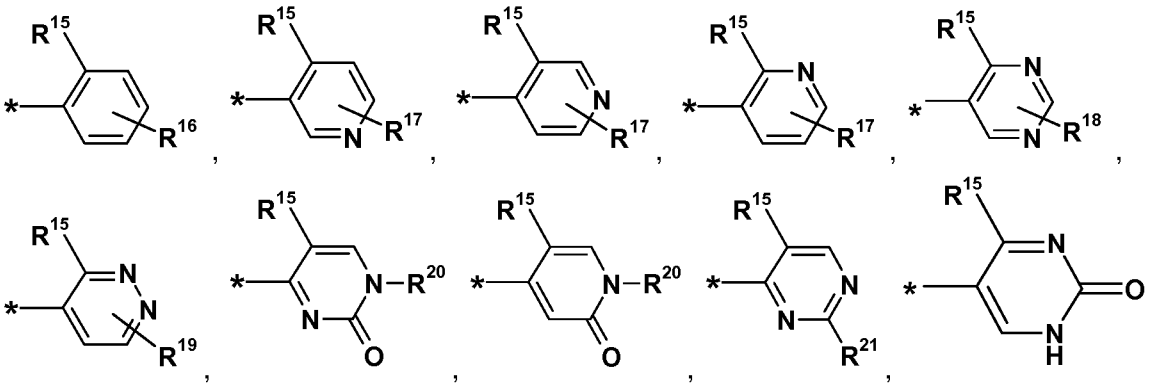
R^2 is selected from chloro, fluoro, trifluoromethyl, methyl and cyano;

R^3 is selected from isopropyl, cyclopropyl, isobutyl, cyclobutyl and cyclopentyl, or R^3 is:

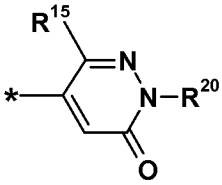


wherein R^{22} is selected from OH, OCH_3, NH_2, NHMe, NMe_2, NHCOMe and NHCOH;

R^4 is selected from:



and



wherein

R^{15} is independently selected from OCH_3, CH_2CH_3, OH, OCF_3 and H;

R^{16} is selected from H, -0-(d-C_4)alkyl, halo, OCF_3, CN, -C(0)NR^9R^{10}, -C(0)-morpholinyl-4-yl, hydroxy-azetidin-1-yl-carbonyl, -$CH_2NR^9R^{10}$, -CH_2NR^9-C(0)R^{10}, CH_2CN, methyl-imidazolyl-, -$CH_2C(0)NR^9R^{10}$, -$CH_2C(0)OH$, -C(0)OH, -$CH_2C(0)0$-(C_1-C_4)alkyl, -$N(R^9)$-C(0)-(C_1-C_4)alkyl, -NR^9R^{10} and (d-d)alkyl optionally substituted by 1 or 2 OH;

R^{17} is selected from H, 0 (C_1-C_4)alkyl, -$CH_2C(0)NR^9R^{10}$, -$CH_2C(0)0$-(d-d)alkyl, -$CH_2C(0)OH$, -NR^9R^{10}, -C(0)NR^9R^{10}, -$CH_2NR^9R^{10}$, -C(0)OCH_3 and -CH_2CN;

R^{18} is selected from H, 0(d-C_4)alkyl, OH, $CH_2NR^9R^{10}$, -NR^9R^{10} and azetidin-1-yl, said azetidin-1-yl being substituted with OH or both CH_3 and OH,

R^{19} is selected from H, 0(d-d)alkyl, (d-d)alkyl, -NR^9R^{10}, -$N(R^9)$-C(0)-(d-C_4)alkyl and -C(0)NR^9R^{10};

R^{20} is selected from H, CH_3 and -CH_2CH_3;

R^{2} is selected from $-NR^{9}R^{10}$, $-CH_2NR^{9}R^{10}$, $C(0)NR^{9}R^{10}$ and CN;

R^5 is selected from:

- H,
- heterocyclyl ^{1}-C(0)-$(CH_2)_n$-,
- $(C_1$-$C_4)$alkyl-, said $(C_1$-$C_4)$alkyl- being optionally substituted with 1 or 2 substituents independently selected from OH, =0,
- heterocyclyl ^{1}-(CrC_4)alkyl-, wherein said alkyl of heterocyclyl ^{1}-$(Ci$-$C_4)$alkyl- is optionally substituted by 1 or 2 OH, and said heterocyclyl ^{1} can be optionally substituted by methyl or ethyl,
- $(Ci$-$C_4)$alkyl-0-C(0)-$(CH_2)_m$-, and
- cyano;

R^6 is selected from:

- H,
- $(Ci$-$C_4)$alkyl-, optionally substituted with $(Ci$-$C_4)$alkoxy,
- $(Ci$-$C_4)$alkoxy, optionally substituted with $(Ci$-$C_4)$alkoxy,
- $(C_1$-$C_4)$alkoxy$(C_1$-$C_4)$alkoxy$(C_1$-$C_4)$alkyl-,
- halo,
- $R^9(R^{10})$N-C(O)-$(CH_2)_m$-,
- cyano,
- $R^9(R^{10})$N-$(CH_2)_m$-,
- $R^9(R^{10})$N-$(CH_2)_n$-O-$(CH_2)_m$-,
- $(C_1$-$C_4)$alkyl-C(O)-(R^{10})N-$(CH_2)_m$-,
- -0-$(CH_2)_p$-heteroaryl ^{2};

R^7 is selected from:

- H,
- halo, and
- $(C_1$-$C_4)$alkyl-, optionally substituted with $(Ci$-$C_4)$alkoxy;

each R^8 is independently selected from H, methyl, ethyl, hydroxyethyl and methoxyethyl-, wherein said methyl or ethyl is optionally substituted with 1, 2 or 3 fluoro substituents;

each R^9 is independently selected from H, methyl or ethyl;

each R^{10} is independently selected from H and $(Ci$-$C_4)$ alkyl wherein said $(Ci$-$C_4)$ alkyl is optionally substituted by 1 or 2 substituents independently selected from methoxy, ethoxy, hydroxy and halo;

or R^9 and R^{10}, together with the N atom to which they are attached, can join to form a saturated 5 or 6 membered heterocyclic ring further comprising ring carbon atoms and optionally one ring

heteroatom independently selected from N, O and S, and wherein when the ring contains a S atom, said S is optionally substituted with one or two oxo substituents;

R^{11} is H, (C_1-C_4)alkyl, (C_1-C_4) alkoxy or halo;

R^{12} is H or halo;

R^{13} is selected from NH_2, -C(0)OH, -NH(C(0)-CH_3) and -C(O)- $NH(CH_3)$;

R^{14} is selected from -C(O)- $NR^9(R^{10})$, (C_1-C_4)alkyl, -C(0)(Ci-C_4)alkyl,-C(0)0(C_1-C_4)alkyl;

each R^{23} is independently selected from H, halo, cyclopropyl and (CrC_4)alkyl;

n is 1, 2 or 3;
p is 0, 1, 2 or 3;

heterocyclyl[1] is a 3, 4, 5 or 6 membered fully saturated or partially unsaturated monocyclic group comprising ring carbon atoms and 1 or 2 ring heteroatoms independently selected from N, O and S;

heteroaryl[2] is 5 or 6 membered fully unsaturated monocyclic group comprising ring carbon atoms and 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, wherein the total number of ring S atoms does not exceed 1, and the total number of ring O atoms does not exceed 1;

and

m is 0, 1 or 2.

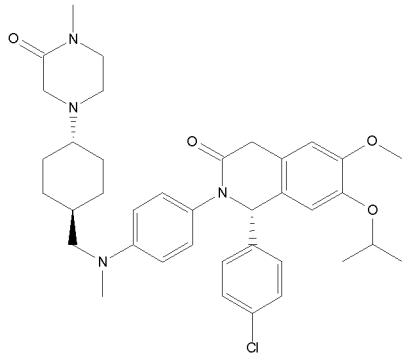
* indicates the point of attachment to the remainder of the molecule.

Mdm2 inhibitor can be selected from the group consisting of:
(S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1 ,4-dihydro-2H-isoquinolin-3-one;
(S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1,4-dihydro-2H-isoquinolin-3-one;
(S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(6-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-pyridin-3-yl)-1 ,4-dihydro-2H-isoquinolin-3-one;
(S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(6-{methyl-[4-(3-methyl-4-oxo-imidazolidin-1-yl)-trans-cyclohexylmethyl]-amino}-pyridin-3-yl)-1 ,4-dihydro-2H-isoquinolin-3-one;
(S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(5-{methyl-[4-(3-methyl-4-oxo-imidazolidin-1-yl)-trans-cyclohexylmethyl]-amino}-pyrazin-2-yl)-1,4-dihydro-2H-isoquinolin-3-one;
1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1 ,4-dihydro-2H-isoquinolin-3-one;

(S)-5-(5-Chloro-1-methyl-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(4-chloro-phenyl)-2-(^ ,4-dimethoxy-pyrimidin-5-yl)-1-isopropyl-5,6-dihydro-1 H-pyrrolo[3,4-d]imidazol-4-one;
4-[(S)-5-(3-Chloro-2-fluoro-phenyl)-2-(2,4-dimethoxy-pyrimidin-5-yl)-3-isopropyl-6-oxo-^ ,4,5,6-tetrahydro-pyrrolo[3,4-d]imidazol-4-yl]-benzonitrile;
(S)-5-(5-Chloro-2-oxo-1 ,2-dihydro-pyridin-3-yl)-6-(4-chloro-phenyl)-2-(2,4-dimethoxy-pyri midin-5-yl)-1-isopropyl-5,6-dihydro-1 H-pyrrolo[3,4-d]imidazol-4-one;
(S)-5-(3-chloro-4-fluorophenyl)-6-(4-chlorophenyl)-2-(2,4-dimethoxypyrimidin-^ -yl)-1-((R)-1-methoxypropan-2-yl)-5,6-dihydropyrrolo[3,4-d]imidazol-4(1 H)-one; and
(S)-5-(5-chloro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-chlorophenyl)-2-(2,4-dimethoxy-d6-pyrimidin-5-yl)-1-((R)-1-methoxypropan-2-yl)-5,6-dihydropyrrolo[3,4-d]imidazol-4(1 H)-one.

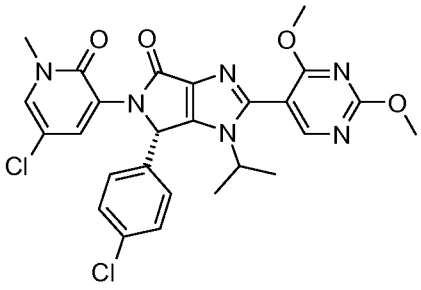
The compounds can be in the form of pharmaceutically acceptable salts thereof. The compounds of formula (I) can be prepared by using processes described in international patent application WO 201 1/076786. The compounds of formula (II) can be prepared by using processes described in the international patent application WO2013/1 11105. Further specific examples of the Mdm2 inhibitors are presented therein.

In one embodiment the Mdm2 inhibitor is selected from the list of compounds as provided in the claims or items, and is (S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1,4-dihydro-2H-isoquinolin-3-one of formula (III) (compound A). The compound A can be prepared by the process disclosed in Example 106 of the international patent application WO 201 1/076786.



formula (III)

In another embodiment, the Mdm2 inhibitor is (S)-5-(5-Chloro-1-methyl-2-oxo-1 ,2-dihydro-pyridin-3-yl)-6-(4-chloro-phenyl)-2-(2,4-dimethoxy-pyrimidin-5-yl)-1-isopropyl-5,6-dihydro-1 H-pyrrolo[3,4-d]imidazol-4-one (compound C) of formula (V):

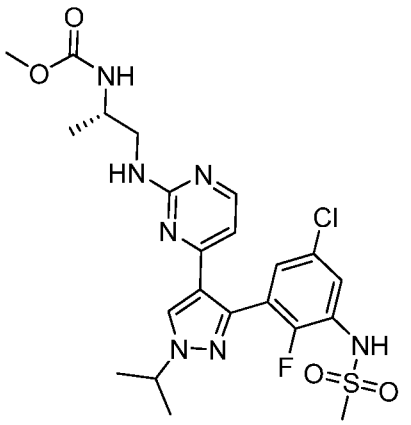


formula (V)

The compound C can be synthetized as explained in the international patent application WO2013/1 11105.

BRAF inhibitor can be for example selected from the group consisting of:
(S)-methyl-1-(4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1 H-pyrazol-4-yl)pyrimidin-2-ylamino)propan-2-ylcarbamate;
methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;
methyl N-[(2S)-1-({4-[3-(2,5-difluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;
methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-ethyl-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;
methyl N-[(2S)-1-({4-[3-(2-fluoro-3-methanesulfonamido-5-methylphenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;
methyl N-[(2S)-1-({4-[3-(2-chloro-3-methanesulfonamido-5-methylphenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;
methyl N-[(2S)-1-({4-[3-(2-chloro-5-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;
methyl N-[(2R)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;
methyl N-[(2S)-1-({4-[3-(2,5-dichloro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate; and
vemurafenib.

In one embodiment, the BRAF inhibitor is (S)-methyl 1-(4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1 H-pyrazol-4-yl)pyrimidin-2-ylamino)propan-2-ylcarbamate of formula (IV) (compound B).



formula (IV)

The BRAF inhibitors can be obtained by the processes disclosed in WO201 1/025927.

The Ras-Raf-MEK-ERK signalling pathway transmits signals from cell surface receptors to the nucleus and is essential, for example, in cell proliferation and survival. The regulation of this signalling cascade is further enriched by the multiple isoforms of Ras (including K-Ras, N-Ras and H-Ras), Raf (A-Raf, B-Raf, C-Raf/Raf-1), MEK (MEK-1 and MEK-2) and ERK (ERK-1 and ERK-2). Since 10-20% of human cancers harbour oncogenic Ras mutations and many human cancers have activated growth factor receptors, this pathway can lead to disturbed cell proliferation and rise of cancer. Recent findings suggest that Raf may have a prominent role in the formation of certain tumours with no requirement of an oncogenic Ras allele. In particular, activating alleles of B-Raf and N-Ras have been identified in -70% of melanomas, 40% of papillary thyroid carcinoma, 30% of ovarian low-grade carcinoma, and 10% of colorectal cancers. Mutations in K-Ras occur in approximately 90% of pancreatic cancers. Most B-Raf mutations are found within the kinase domain, with a single substitution (V600E) accounting for at least 80%. The mutated B-Raf proteins activate the Raf-MEK-ERK pathway either via elevated kinase activity towards MEK or via activating C-Raf. Therefore, it is expected that the pharmaceutical combination, use, administration, composition, method, product or formulation of the present disclosure can achieve the best response in treating a disease in an animal in which kinase activity, particularly B-Raf activity, particularly mutant B-raf (for example V600E), contributes to the pathology and/or symptomology of the disease.

Similarly, dysregulation of the MDM2/p53 ratio, e.g. due to mutations, polymorphisms or molecular defects in the affected cells, can be found in many proliferative diseases. MDM2 is capable to inhibit the activity of the tumour suppressor protein p53, thus leading to loss of p53's tumour suppressor activity and inhibiting regulatory mechanisms that impede cells from uncontrolled proliferation. As a consequence, uncontrolled proliferation can take place, leading to tumours, leukemias or other proliferative diseases. Administering the Mdm2 inhibitor tilts the ratio back towards the functional p53, which in turn can act as a tumour suppressor protein and help to control cellular integrity and prevents the proliferation of permanently damaged cells by initiating, among other responses, growth arrest or apoptosis (controlled cell death). The combination of the present disclosure can thus be most effective in the event that p53 is functional p53 or p53 wild type (wt).

The present disclosure embodiments also include pharmaceutically acceptable salts of the compounds useful according to the disclosure described herein. As used herein, "pharmaceutically acceptable salt" refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and *Journal of Pharmaceutical Science,* 66, 2 (1977), each of which is incorporated herein by reference in its entirety. For example, the salt is sulphate salt, or bisulphate salt.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The compounds useful according to the disclosure (= being included in a combination, especially a pharmaceutical combination, according to the disclosure, respectively, or being used according to the disclosure, optionally also including further co-agents as defined below, that is, all active ingredients), as well as their pharmaceutically acceptable salts, can also be present as tautomers, N-oxides or solvates, e.g. hydrates. All these variants, as well as any single one thereof or combination of two or more to less than all such variants, are encompassed and to be read herein where a compound included in the inventive combination products, e.g. a Mdm2 inhibitor and/or a BRAF inhibitor, is mentioned. The same also applies if the respective compound is used alone in a specific indication.

The present disclosure, according to a first embodiment mentioned above and below, relates to a pharmaceutical combination, especially a pharmaceutical combination product, comprising the mentioned combination partners and at least one pharmaceutically acceptable carrier.

"Pharmaceutical combination" refers to use, application or formulations of the separate partners with or without instructions for combined use or to combination products. The combination partners may thus administered entirely separately or be entirely separate pharmaceutical dosage forms. The combination partners may be pharmaceutical compositions that are also sold independently of each other and where just instructions for their combined use are provided in the package equipment, e.g. leaflet or the like, or in other information e.g. provided

to physicians and medical staff (e.g. oral communications, communications in writing or the like), for simultaneous or sequential use for being jointly active, especially as defined below. It can refer to either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where an Mdm2 inhibitor and a BRAF inhibitor (and optionally yet a further combination partner (e.g. another drug as explained below, also referred to as "co-agent") may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative (= joint) effect. In one embodiment the effect is synergistic. The terms "co-administration" or "combined administration" or "combined use" or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (e.g. a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration and/or at the same time.

The term "pharmaceutical combination" as used herein thus means a pharmaceutical product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients (which may also be combined).

The term "fixed combination" means that the active ingredients, e.g. an Mdm2 inhibitor and a BRAF inhibitor, are both administered to a patient simultaneously in the form of a single entity or dosage. In other terms: the active ingredients are present in one dosage form, e.g. in one tablet or in one capsule.

The term "non-fixed combination" means that the active ingredients are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients. The term "non-fixed combination" thus defines especially administration, use, composition or formulation in the sense that the combination partners (i) Mdm2 inhibitor and (ii) BRAF inhibitor (and if present further one or more co-agents) as defined herein can be dosed independently of each other or by use of different fixed combinations with distinguished amounts of the combination partners, i.e. simultaneously or at different time points, where the combination partners may also be used as entirely separate pharmaceutical dosage forms or pharmaceutical formulations that are also sold independently of each other and just instructions of the possibility of their combined use is or are provided in the package equipment, e.g. leaflet or the like, or in other information e.g. provided to physicians and medical staff. The independent formulations or the parts of the formulation, product, or composition, can then, e.g. be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Particularly, the time intervals are chosen such that the effect on the treated disease in the combined use of the parts is larger than the effect which would be obtained by use of only any one of the combination partners (i) and (ii), thus being jointly active. The ratio of the total amounts of the combination partner (i) to the combination partner (ii) to be administered in the combined preparation can be varied, e.g. in order to cope with the needs of a patient sub-

population to be treated or the needs of the single patient which different needs can be due to age, sex, body weight, etc. of the patients.

Because the combination of BRAF inhibitor, particularly the one selected from the list of compounds disclosed herein, potentiates the effects of the Mdm2 inhibitor of formula I or II, particularly from the selected ones, already at minute doses, the dose of one of the combination partner can be lower than the amount administered when the compound is used alone (e.g., not in a combination). It is also contemplated to be able to reduce the dose of both compounds in the pharmaceutical combination. This has the benefit of limiting or reducing side effects and improved flexibility in deciding on a treatment plan. The advantage of reducing the dose is even better when a further co-agent is involved.

In another embodiment, either one or both of the compounds of the present pharmaceutical combination can be used in subtherapeutic dose. For example, since it was observed in *in vitro* experiments that BRAF inhibitor can almost double the antiproliferative effect of the Mdm2 inhibitor already at very low amounts, it is expected that doses of the BRAF inhibitor that otherwise would not be sufficient to elicit full therapeutic effect, could be in fact used for the treatment of the cancer disease when combined with the Mdm2 inhibitor of the present disclosure. The same may be true also for the Mdm2 inhibitor.

The combination partners (i) and (ii) in any disclosure embodiment are preferably formulated or used to be jointly (prophylactically or especially therapeutically) active. This means in particular that there is at least one beneficial effect, e.g. a mutual enhancing of the effect of the combination partners (i) and (ii), in particular a synergism, e.g. a more than additive effect, additional advantageous effects (e.g. a further therapeutic effect not found for any of the single compounds), less side effects, a combined therapeutic effect in a non-effective dosage of one or both of the combination partners (i) and (ii), and very preferably a clear synergism of the combination partners (i) and (ii).

For example, the term "jointly (therapeutically) active" may mean that the compounds may be given separately or sequentially (in a chronically staggered manner, especially a sequence-specific manner) in such time intervals that they preferably, in the warm-blooded animal, especially human, to be treated, and still show a (preferably synergistic) interaction (joint therapeutic effect). A joint therapeutic effect can, inter alia, be determined by following the blood levels, showing that both compounds are present in the blood of the human to be treated at least during certain time intervals, but this is not to exclude the case where the compounds are jointly active although they are not present in blood simultaneously.

The present disclosure thus pertains to a combination product for simultaneous or sequential use, such as a combined preparation or a pharmaceutical fixed combination, or a combination of such preparation and combination.

In the combination therapies of the disclosure, the compounds useful according to the disclosure may be manufactured and/or formulated by the same or different manufacturers. Moreover, the combination partners may be brought together into a combination therapy: (i) prior to release of the combination product to physicians *(e.g.* in the case of a kit comprising the

compound of the disclosure and the other therapeutic agent); (ii) by the physician themselves (or under the guidance of a physician) shortly before administration; (iii) in the patient themselves, *e.g.* during sequential administration of the compound of the disclosure and the other therapeutic agent.

In one embodiment, a data carrier comprising information about using (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, simultaneously or sequentially, is provided. The data carrier, for example in a form of a product information leaflet or a label, packaging, brochure or web page instruction can be used to instruct to administer (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, simultaneously or sequentially for the treatment of cancer. The data carrier is particularly useful in the event the two partners of the combination are not formulated together, and supplied or sold separately. Each of the partners can be supplied with the data carrier, or even have the data carrier detached or provided separately, that informs or instructs about the possibility to use the combination partner in a pharmaceutical combination of the present disclosure. The data carrier can be used for the same purpose also in fixed combinations or situations, where both partners are supplied or sold together.

In certain embodiment, any of the above pharmaceutical combination, use, administration, composition, method, product or formulation involve further administering one or more other (e.g. third) co-agents, especially a chemotherapeutic agent.

Thus, the disclosure relates in a further embodiment to a pharmaceutical combination, particularly a pharmaceutical composition or a product comprising a therapeutically effective amount of (i) a Mdm2 inhibitor and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, respectively, and at least one third therapeutically active agent (co-agent), e.g. another compound (i) and/or (ii) or a different co-agent. The additional co-agent is preferably selected from the group consisting of an anti-cancer agent and an anti-inflammatory agent, particularly is an anti-cancer agent.

Also in this case, the combination partners forming a corresponding combination according to the disclosure may be mixed to form a fixed pharmaceutical composition or they may be administered separately or pairwise (i.e. before, simultaneously with or after the other drug substance(s)).

A combination product according to the disclosure can besides or in addition be administered especially for cancer therapy in combination with chemotherapy, radiotherapy, immunotherapy, surgical intervention, or a combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumour regression, or even chemo preventive therapy, for example in patients at risk.

Possible anti-cancer agents (e.g. for chemotherapy) as co-agents include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds

which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity; anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine amino peptidase inhibitors; bisphosphonates; biological response modifiers; anti-proliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors; kinesin spindle protein inhibitors; MEK inhibitors; leucovorin; EDG binders; antileukemia compounds; ribonucleotide reductase inhibitors; S-adenosylmethionine decarboxylase inhibitors; angiostatic steroids; corticosteroids; other chemotherapeutic compounds (as defined below); photosensitizing compounds.

Further, alternatively or in addition combination products according to the disclosure may be used in combination with other tumour treatment approaches, including surgery, ionizing radiation, photodynamic therapy, implants, e.g. with corticosteroids, hormones, or they may be used as radio sensitizers.

The term "aromatase inhibitor" as used herein relates to a compound which inhibits the estrogen production, i.e. the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole.

The term "antiestrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride.

The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (CASODEX), which can be formulated, e.g. as disclosed in US 4,636,505.

The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate. The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, gimatecan, irinotecan, camptothecian and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in W099/17804).

The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin (including liposomal formulation, e.g. CAELYX), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide.

The term "microtubule active compound" relates to microtubule stabilizing, microtubule destabilizing compounds and microtublin polymerization inhibitors including, but not limited to taxanes,

e.g. paclitaxel and docetaxel, vinca alkaloids, e.g., vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolides, cochicine and epothilones and derivatives thereof, e.g. epothilone B or D or derivatives thereof.

The term "alkylating compound" as used herein includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel).

The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes compounds disclosed in WO 02/22577, especially N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1 H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2£-2-propenamide and pharmaceutically acceptable salts thereof. It further especially includes Suberoylanilide hydroxamic acid (SAHA). Compounds which target, decrease or inhibit activity of histone deacetylase (HDAC) inhibitors such as sodium butyrate and suberoylanilide hydroxamic acid (SAHA) inhibit the activity of the enzymes known as histone deacetylases. Specific HDAC inhibitors include MS275, SAHA, FK228 (formerly FR901228), Trichostatin A and compounds disclosed in US 6,552,065, in particular, /V-hydroxy-3-[4-[[[2-(2-methyl-1 H-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof and /V-hydroxy-3-[4-[(2-hydroxyethyl){2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2£-2-propenamide, or a pharmaceutically acceptable salt thereof, especially the lactate salt.

The term "antineoplastic antimetabolite" includes, but is not limited to, 5-Fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists such as pemetrexed.

The term "platin compound" as used herein includes, but is not limited to, carboplatin, cis-platin, cisplatinum and oxaliplatin.

The term "compounds targeting/decreasing a protein or lipid kinase activity"; or a "protein or lipid phosphatase activity"; or "further anti-angiogenic compounds" as used herein includes, but is not limited to, c-Met tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, e.g.,

a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib, SU101 , SU6668 and GFB-1 11;

b) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the kinase activity of IGF-I receptor, such as those compounds disclosed in WO 02/092599, or antibodies that target the extracellular domain of IGF-I receptor or its growth factors;

c) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin kinase family inhibitors;

d) compounds targeting, decreasing or inhibiting the activity of the Axl receptor tyrosine kinase family;

e) compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase;

f) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, e.g. imatinib;

g) compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases - (part of the PDGFR family), such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, e.g. imatinib;

h) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. BCR-Abl kinase) and mutants, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib or nilotinib (AMN107); PD1 80970; AG957; NSC 680410; PD1 73955 from ParkeDavis; or dasatinib (BMS-354825)

i) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK1 , PKB/Akt, and Ras/MAPK family members, and/or members of the cyclin-dependent kinase family (CDK) and are especially those staurosporine derivatives disclosed in US 5,093,330, e.g. midostaurin; examples of further compounds include e.g. UCN-01 , safingol, BAY 43-9006, Bryostatin 1, Perifosine; llmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds such as those disclosed in WO 00/09495; FTIs; PD1 84352 or QAN697 (a P13K inhibitor) or AT7519 (CDK inhibitor);

j) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (GLEEVEC) or tyrphostin. A tyrphostin is preferably a low molecular weight (Mr < 1500) compound, or a pharmaceutically acceptable salt thereof, especially a compound selected from the benzylidenemalonitrile class or the S-arylbenzenemalonirile or bisubstrate quinoline class of compounds, more especially any compound selected from the group consisting of Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin);

k) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, e.g. EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 97/02266, e.g. the com-

pound of ex. 39, or in EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US 5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and, especially, WO 96/30347 (e.g. compound known as CP 358774), WO 96/33980 (e.g. compound ZD 1839) and WO 95/03283 (e.g. compound ZM105180); e.g. trastuzumab (Herceptin™), cetuximab (Erbitux™), Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.1 1, E6.3 or E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives which are disclosed in WO 03/013541; and

l) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor, such as compounds which target, decrease or inhibit the activity of c-Met, especially compounds which inhibit the kinase activity of c-Met receptor, or antibodies that target the extracellular domain of c-Met or bind to HGF;

m) compounds targeting, decreasing or inhibiting the activity of the Ron receptor tyrosine kinase.

Further anti-angiogenic compounds include compounds having another mechanism for their activity, e.g. unrelated to protein or lipid kinase inhibition e.g. thalidomide (THALOMID) and TNP-470.

The term "Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase" includes, but is not limited to inhibitors of phosphatase 1, phosphatase 2A, or CDC25, e.g. okadaic acid or a derivative thereof.

The term "Compounds which induce cell differentiation processes" includes, but is not limited to e.g. retinoic acid, α- γ- or δ-tocopherol or a- γ- or δ-tocotrienol.

The term "cyclooxygenase inhibitor" as used herein includes, but is not limited to, e.g. Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib (CELEBREX), rofecoxib (VIOXX), etoricoxib, valdecoxib or a 5-alkyl-2-arylaminophenylacetic acid, e.g. 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib.

The term "bisphosphonates" as used herein includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid.

The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (Rapamune®), everolimus (Certican™), CCI-779 and ABT578.

The term "heparanase inhibitor" as used herein refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88.

The term "biological response modifier" as used herein refers to a lymphokine or interferons, e.g. interferon γ.

The term "inhibitor of Ras oncogenic isoforms", e.g. H-Ras, K-Ras, or N-Ras, as used herein refers to compounds which target, decrease or inhibit the oncogenic activity of Ras e.g. a "farnesyl transferase inhibitor" e.g. L-744832, DK8G557 or R115777 (Zarnestra).

The term "telomerase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, e.g. telomestatin.

The term "methionine aminopeptidase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase are e.g. bengamide or a derivative thereof.

The term "proteasome inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include e.g. Bortezomid (Velcade™)and MLN 341 .

The term "matrix metalloproteinase inhibitor" or ("MMP" inhibitor) as used herein includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, e.g. hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA21 1, MMI270B or AAJ996.

The term "compounds used in the treatment of hematologic malignancies" as used herein includes, but is not limited to, FMS-like tyrosine kinase inhibitors e.g. compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1-b-D-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors e.g. compounds which target, decrease or inhibit anaplastic lymphoma kinase.

The term "Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R)" are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, e.g. PKC412, midostaurin, a staurosporine derivative, SU1 1248 and MLN518.

The term "HSP90 inhibitors" as used herein includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90 e.g., 17-allylamino,17-demethoxygeldanamycin (17AAG, 17-DMAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors;IPI-504, CNF1010, CNF2024, CNF1010 from Conforma Therapeutics; temozolomide, AUY922 from Novartis.

The term "antiproliferative antibodies" as used herein includes, but is not limited to erbitux, bevacizumab, rituximab, PR064553 (anti-CD40) and 2C4 Antibody. By antibodies is meant e.g. intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least

2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

The term "antileukemic compounds" includes, for example, Ara-C, a pyrimidine analog, which is the 2'-alpha-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is the purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate. For the treatment of acute myeloid leukemia (AML), compounds of formula (I) can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of formula (I) can be administered in combination with, e.g., farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

"Somatostatin receptor antagonists" as used herein refers to compounds which target, treat or inhibit the somatostatin receptor such as octreotide, and SOM230.

"Tumor cell damaging approaches" refer to approaches such as ionizing radiation. The term "ionizing radiation" referred to above and hereinafter means ionizing radiation that occurs as either electromagnetic rays (such as X-rays and gamma rays) or particles (such as alpha and beta particles). Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. See Hellman, Principles of Radiation Therapy, Cancer, in *Principles and Practice of Oncology,* Devita et al., Eds., 4th Edition, Vol. 1, pp. 248-275 (1993).

The term "EDG binders" as used herein refers a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720.

The term "kinesin spindle protein inhibitors" is known in the field and includes SB715992 or SB743921 from GlaxoSmithKline, pentamidine/chlorpromazine from CombinatoRx.

The term "MEK inhibitors" is known in the field and includes ARRY1 42886 from Array PioPharma, AZD6244 from AstraZeneca, PD181461 from Pfizer, leucovorin.

The term "ribonucleotide reductase inhibitors" includes, but is not limited to pyrimidine or purine nucleoside analogues including, but not limited to, fludarabine and/or cytosine arabinoside (ara-C), 6-thioguanine, 5-fluorouracil, cladribine, 6-mercaptopurine (especially in combination with ara-C against ALL) and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1H-isoindole-1,3-dione derivatives, such as PL-1, PL-2, PL-3, PL-4, PL-5, PL-6, PL-7 or PL-8 mentioned in Nandy et al., *Acta Oncologica,* Vol. 33, No. 8, pp. 953-961 (1994).

The term "S-adenosylmethionine decarboxylase inhibitors" as used herein includes, but is not limited to the compounds disclosed in US 5,461,076.

Also included are in particular those compounds, proteins or monoclonal antibodies of VEGF / VEGFR disclosed in WO 98/35958, e.g. 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, e.g. the succinate, or in WO 00/09495, WO 00/27820, WO 00/59509, WO 98/1 1223, WO 00/27819 and EP 0 769 947; those as described by Prewett

et al, *Cancer Res,* Vol. 59, pp. 5209-5218 (1999); Yuan et al., *Proc Natl Acad Sci U SA,* Vol. 93, pp. 14765-14770 (1996); Zhu et al., *Cancer Res,* Vol. 58, pp. 3209-3214 (1998); and Mordenti et al., *Toxicol Pathol,* Vol. 27, No. 1, pp. 14-21 (1999); in WO 00/37502 and WO 94/10202; ANGIOSTATIN, described by O'Reilly et al., *Cell,* Vol. 79, pp. 315-328 (1994); ENDOSTATIN, described by O'Reilly et al., *Cell,* Vol. 88, pp. 277-285 (1997); anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor antibodies, e.g. rhuMAb and RHUFab, VEGF aptamer e.g. Macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 lgG1 antibody, Angiozyme (RPI 4610) and Bevacizumab.

"Photodynamic therapy" as used herein refers to therapy which uses certain chemicals known as photosensitizing compounds to treat or prevent cancers. Examples of photodynamic therapy includes treatment with compounds, such as e.g. VISUDYNE and porfimer sodium.

"Angiostatic steroids" as used herein refers to compounds which block or inhibit angiogenesis, such as, e.g., anecortave, triamcinolone. hydrocortisone, 11-a-epihydrocotisol, cortexolone, 17a-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

"Corticosteroids" as used herein includes, but is not limited to compounds, such as e.g. fluocinolone, dexamethasone; in particular in the form of implants.

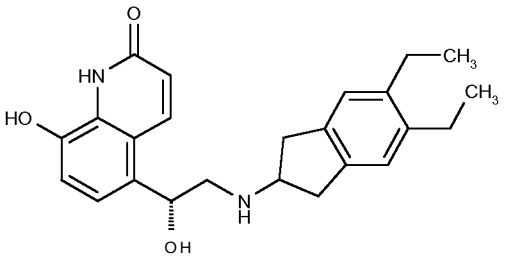
Other chemotherapeutic compounds include, but are not limited to, plant alkaloids, hormonal compounds and antagonists; biological response modifiers, preferably lymphokines or interferons; antisense oligonucleotides or oligonucleotide derivatives; shRNA or siRNA; or miscellaneous compounds or compounds with other or unknown mechanism of action.

A combination product according to the disclosure may also be used in combination with or comprise one or more further drug substances selected from the group of anti-inflammatory drug substances; antihistamine drug substances; bronchodilatatory drug substances, NSAID; antagonists of chemokine receptors.

Suitable anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone dipropionate, fluticasone propionate, ciclesonide or mometasone furoate, or steroids described in WO 02/88167, WO 02/12266, WO 02/100879, WO 02/00679 (especially those of Examples 3, 11, 14, 17, 19, 26, 34, 37, 39, 51, 60, 67, 72, 73, 90, 99 and 101), WO 03/035668, WO 03/048181, WO 03/062259, WO 03/064445, WO 03/072592, non-steroidal glucocorticoid receptor agonists such as those described in WO 00/00531 , WO 02/10143, WO 03/082280, WO 03/082787, WO 03/104195, WO 04/005229;

LTB4 antagonists such LY2931 1 1, CGS025019C, CP-195543, SC-53228, BIIL 284, ONO 4057, SB 209247 and those described in US 5451700; LTD4 antagonists such as montelukast and zafirlukast; PDE4 inhibitors such as cilomilast, Roflumilast (Byk Gulden), V-1 1294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 / PD168787 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo), and those disclosed in WO 92/19594, WO 93/19749, WO 93/19750,

WO 93/19751 , WO 98/18796, WO 99/16766, WO 01/13953, WO 03/104204, WO 03/104205, WO 03/39544, WO 04/000814, WO 04/000839, WO 04/005258, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/ 018431 , WO 04/018449, WO 04/018450, WO 04/018451 , WO 04/018457, WO 04/018465, WO 04/019944, WO 04/019945, WO 04/045607 and WO 04/037805; A2a agonists such as those disclosed in EP 409595A2, EP 1052264, EP 1241 176, WO 94/17090, WO 96/02543, WO 96/02553, WO 98/28319, WO 99/24449, WO 99/24450, WO 99/24451, WO 99/38877, WO 99/41267, WO 99/67263, WO 99/67264, WO 99/67265, WO 99/67266, WO 00/23457, WO 00/77018, WO 00/78774, WO 01/23399, WO 01/27130, WO 01/27131 , WO 01/60835, WO 01/94368, WO 02/00676, WO 02/22630, WO 02/96462, WO 03/086408, WO 04/ 039762, WO 04/039766, WO 04/045618 and WO 04/046083; A2b antagonists such as those described in WO 02/42298; and beta-2 adrenoceptor agonists such as albuterol (salbutamol), metaproterenol, terbutaline, salmeterol fenoterol, procaterol, and especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of WO 00751 14, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof, as well as compounds (in free or salt or solvate form) of formula I of WO 04/16601, and also compounds of WO 04/033412.

Suitable bronchodilatory drugs include anticholinergic or antimuscarinic compounds, in particular ipratropium bromide, oxitropium bromide, tiotropium salts and CHF 4226 (Chiesi), and glycopyrrolate, but also those described in WO 01/041 18, WO 02/51841 , WO 02/53564, WO 03/00840, WO 03/87094, WO 04/05285, WO 02/00652, WO 03/53966, EP 424021, US 5171744, US 3714357, WO 03/33495 and WO 04/018422.

Suitable chemokine receptors include, e.g. CCR-1 , CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists such as Schering-Plough antagonists SC-351 125, SCH-55700 and SCH-D, Takeda antagonists such as N-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5H-benzo-cyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-N,N-dimethyl-2H-pyran-4-amin-ium chloride (TAK-770), and CCR-5 antagonists described in US 6166037 (particularly claims 18 and 19), WO 00/66558 (particularly claim 8), WO 00/66559 (particularly claim 9), WO 04/018425 and WO 04/026873.

Suitable antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine

hydrochloride, activastine, astemizole, azelastine, ebastine, epinastine, mizolastine and tefenadine as well as those disclosed in WO 03/099807, WO 04/026841 and JP 2004107299.

The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference.

The term "pharmaceutically effective" preferably relates to an amount that is effective against the progression of a disease or disorder as disclosed herein.

The pharmaceutical combination is useful in the treatment of one or more of the diseases which respond to an inhibition of Mdm2 or BRAF activity, especially a neoplastic or tumour disease, especially solid tumour, more especially those cancers in which Mdm2 or BRAF are implicated, such as benign or malignant tumors, a sarcoma, such as liposarcoma, rhabdomyosarcoma or bone cancer, e.g. osteosarcomas, a carcinoma, such as of the brain, kidney, liver, adrenal gland, bladder, breast, gastric, ovary, colon, rectum, pro-state, pancreas, lung, vagina or thyroid, a glioblastoma, a multiple myeloma, a gastrointestinal cancer, especially colon carcinoma or colorectal adenoma, a tumour of the head and neck, a melanoma, a prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, a leukemia or a lymphoma, such as of B- or T-cell origin, and metastases in other organs), viral infections (e.g. herpes, papilloma, HIV, Kaposi's, viral hepatitis).

The combination product of the present disclosure is especially appropriate for treatment a patient suffering from a proliferative disorder, in particular a solid tumour, for example, melanoma, colorectal cancer, sarcoma, lung cancer, thyroid cancer and leukemia. In one embodiment the cancer that can be treated by the pharmaceutical combination is melanoma. In another embodiment, the tumour is colorectal cancer. In further embodiment, the cancer comprises BRAF having the V600E mutation. In yet another embodiment, the cancer comprises functional p53 or p53 wt. In a further embodiments, respective compounds are used in the treatment of colorectal cancer alone. Particularly, Mdm2 inhibitor when used alone can be administered to a patient in order to treat colorectal cancer. In a specific embodiment, the Mdm2 inhibitor is compound A or compound C.

The term "a therapeutically effective amount" of a compound of the present disclosure refers to an amount of the compound of the present disclosure that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the present disclosure that, when administered to a subject, is effective to (1) at least partially alleviating, inhibiting, preventing and/or ameliorating a condition, or a disorder or a disease (i) mediated by Mdm2 and/or mediated by BRAF activity, or (ii) characterized by activity (normal or abnormal) of Mdm2 and/or BRAF; or (2) reducing or inhibiting the activity of Mdm2 and/or of BRAF; or (3) reducing or inhibiting the expression of Mdm2 and/or BRAF. A "subtherapeutic" dose as used herein describes the dose that does not lead to clinically satisfactory effect.

As used herein, the term "subject" refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

Mdm2 inhibitor of formula I or II of the pharmaceutical combination can be administered in unit dosage of about 1-5000 mg of active ingredient(s) for a subject of about 50-70 kg, or about 1mg - 3g or about 1-250 mg or about 1-150 mg or about 0.5-100 mg, or about 1-50 mg of active ingredients. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

BRAF inhibitor of the present disclosure can be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 30mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5mg to about 2000mg, conveniently administered, e.g. in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from about 1 to 500mg active ingredient.

In general, the dosage of the active ingredient to be applied to a warm-blooded animal depends upon a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound employed. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

As used herein, the term "carrier" or "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavouring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The pharmaceutical combination product according to the disclosure (as fixed combination, or as kit, e.g. as combination of a fixed combination and individual formulations for one or both combination partners or as kit of individual formulations of the combination partners) comprises the combination of the present disclosure and one or more pharmaceutically acceptable carrier materials (carriers, excipients). In the same way the Mdm2 inhibitor alone can be mixed with one or more pharmaceutically acceptable carrier materials (carriers, excipients) before it is to be administered for the treatment. The pharmaceutical combination or the combination partners constituting it can be formulated for particular routes of administration such as oral administration, parenteral administration, and rectal administration, etc. In addition, the combination products of the present disclosure can be made up in a solid form (including without limitation capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including without limitation solutions, suspensions or emulsions). The combination products and/or their combination partners can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers and buffers, etc. The same can be applied when preparing Mdm2 inhibitor alone.

In one embodiment, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with one or more commonly known carriers, e.g. one or more carriers selected from the group consisting of

a) diluents, *e.g.,* lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, *e.g.,* silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, *e.g.,* magnesium aluminium silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

d) disintegrants, *e.g.,* starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and

e) absorbents, colorants, flavours and sweeteners.

Tablets may be either film coated or enteric coated according to methods known in the art. Similarly as the combination, the pharmaceutical compositions comprising Mdm2 inhibitor alone or BRAF inhibitor alone can be formulated in the final dosage form.

Suitable compositions for oral administration especially include an effective amount of one or more or in case of fixed combination formulations each of the combination partners (active ingredients) in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may

contain the active ingredient(s) in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets are uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

Parenteral compositions, transdermal, topical compositions and other can be prepared by known methods in the art.

The following Examples illustrate the disclosure and provide specific embodiments, however without limiting the scope of the disclosure.

Examples:

Compound A: (S)-1 -(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1 ,4-dihydro-2H-isoquinolin-3-one

Compound B: (S)-methyl 1-(4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1H-pyrazol-4-yl)pyrimidin-2-ylamino)propan-2-ylcarbamate

Compound C: (S)-5-(5-Chloro-1-methyl-2-oxo-1 ,2-dihydro-pyridin-3-yl)-6-(4-chloro-phenyl)-2-(2,4-dimethoxy-pyrimidin-5-yl)-1-isopropyl-5,6-dihydro-1 H-pyrrolo[3,4-d]imidazol-4-one;

Example 1. The in vitro effect on proliferation of combining the BRAF inhibitor Compound B or vemurafenib with the Mdm2 inhibitor Compound A in cell lines (WM2664, SkMel24 and C32).

Both compounds were dissolved in 100% DMSO (Cellgro, catalogue number 25-290-CQC) at concentrations of 10mM and stored at -20°C until use. Compounds were arrayed in 2ml deep 96-well plates (Greiner bio-one, catalog number 780271) serially diluted 3-fold. COMPOUND A was used over a concentration range of 0.0 - 4uM. COMPOUND B was used over a concentration range of 0.0 - 1.3uM in WM2664 and C-32 cells and over a concentration range of 0.0 - 4uM in SkMel24

Synergy Score
SS ~ 0 → Dose Additive
SS >2 → Synergy

SS >1 → Weak Synergy

All cell lines were purchased from ATTC (WM2664, SkMel24 and C32). Cells were cultured in Eagle's Minimum Essential Medium (ATCC, Catalog number 30-2003) supplemented with 10% FBS (GIBCO, Catalog number 10099-141) according to vendor recommendations.

Cell lines were cultured in 37°C and 5% C02 incubator and expanded in T-75 flasks. In all cases cells were thawed from frozen stocks, expanded through ≥1 passage using 1:3 dilutions, counted and assessed for viability using a ViCell counter (Beckman-Coulter), prior to plating in 96-well. To split and expand cell lines, cells were dislodged from flasks using 0.25% Trypsin-EDTA (GIBCO, Catalog number 25200). All cell lines were determined to be free of mycoplasma contamination as determined by a PCR detection methodology performed at Idexx Radii (Columbia, MO, USA) and correctly identified by detection of a panel of SNPs.

Cell proliferation was measured in 72hr CellTiter-Glo™ (CTG) assays and all results shown are the result of at least triplicate measurements. For CellTiter-Glo™ assays, cells were dispensed into tissue culture treated 96-well plates (Costar, catalog number 3904) with a final volume of 80 µl of medium and at density of 3000 cells per well. 12 to 24 hrs after plating, 20 µl of each compound dilution series were transferred to plates containing the cells, resulting in compound concentration ranges stated above and a final DMSO concentration of 0.16%. Plates were incubated for 72 hrs and the effects of compounds on cell proliferation was determined using the CellTiter-Glo™ Luminescent Cell Viability Assay (Promega) and a Victor™ X4 plate reader (Perkin Elmer).

The CellTiter-Glo® Luminescent Cell Viability Assay is a homogeneous method to determine the number of viable cells in culture based on quantitation of the ATP present, which signals the presence of metabolically active cells. The method is described in detail in the Technical Bulletin, TB288 Promega. Briefly, cells were plated in Opaque-walled multiwell plates in culture medium as described above. Control wells containing medium without cells were also prepared to obtain a value for background luminescence. After 72 hrs of incubation as described above the plate and its contents are allowed to equilibrate at room temperature for approximately 30 minutes. A volume of CellTiter-Glo® Reagent equal to the volume of cell culture medium present in each well was then added and contents mixed for 2 minutes on an orbital shaker to induce cell lysis. The plate was then incubated at room temperature for 10 minutes after which luminescence was recorded.

The percent growth inhibition and excess inhibition were analysed using the Chalice software (CombinatoRx, Cambridge MA). The percentage of growth inhibition relative to DMSO is displayed in the panel labelled inhibition, and the amount of inhibition in excess of the expected amount in the panel (labelled ADD Excess Inhibition). Concentrations of COMPOUND B are shown along the bottom row from left to right and increasing concentrations of COMPOUND A along the leftmost column from bottom to top. All remaining points in the grids display results from a combination of the two inhibitors that correspond to the single agent concentrations denoted on the two axes. Data analysis of cell proliferation was performed using Chalice Analyser as described in (Lehar et al. 2009). Excess inhibition was calculated using the Loewe synergy model which measures the effect on growth relative to what would be expected if two drugs behave in a dose additive manner. Positive numbers represent areas of increasing synergy.

IC50 is the compound concentration which inhibits 50% of the CTG signal by 50%. IC50 calculations were made using model number 203 from the XLfit Microsoft Excel™ add-In

version 5.2.0.0 (IDBS Enabling Science). Synergy scores and IC50 calculations were determined as described in (Lehar et al. 2009).

Fig. 1 shows matrices for inhibition of growth and Loewe (ADD) excess inhibition for COMPOUND B combinations with COMPOUND A in the melanoma cell lines.

Fig. 2 shows matrices for inhibition of growth and Loewe (ADD) excess inhibition for vemurafenib combinations with COMPOUND A compared to combination with COMPOUND B in the melanoma cell line.

The table below shown single agent IC50 values for each compound and synergy score measurements for the combination of COMPOUND A-COMPOUND B combination (described in Lehar J, Krueger AS, A very W, et al (2009). Synergistic drug combinations tend to improve therapeutically relevant selectivity. Nat Biotechnol27, 659-666). Interactions were deemed synergistic when scores ≥ 2.0 where observed.

Cell Line	**Compound A** IC50 (nM)	**Compound B** IC50 (nM)	Synergy Score
WM-266-4	930	1	5
LOX IMVI	830	40	4.72
SK-MEL-24	2740	200	4.58
C32	Insensitive	30	4.16

In vitro, the effects of combination with vemurafenib start to occur at concentrations of 1uM of vemurafenib. The synergistic effects with Compound B start to occur at it concentration of 0.0018uM.

Example 2. In vivo WM266-4 xenografts with combination of compounds A and B

WM266-4 cells were cultured in EMEM containing 10% heat-inactivated fetal bovine serum without antibiotics until the time of implantation. WM266-4 harboured B-RAF V600E mutation and CDKN2A loss. WM266-4 Melanoma Xenograft Model in Female Nude Mice was prepared. WM266-4 cells were harvested in exponential growth. Two million cells in 200 µl PBS were subcutaneously implanted into the upper right flank of female nude mice. In general, a total of 8 animals per group were enrolled in efficacy study. For single-agent and combination studies, animals were dosed via oral gavage for both Compound B and Compound A. Compound B was formulated in 0.5% CMC/0.5% Tween 80, and Compound A was formulated in 0.5% HPMC at 50 mg/kg as free base (equivalent to 65 mg/kg Compound A, bisulphate salt). The tumors reached approximately 320 mm^3 at day 18 post cell implantation. On Day 18, tumour-bearing mice were randomized into treatment groups. Treatments were maintained through the study, once the tumour reached 1000 mm3, the mouse was considered as reaching end point and euthanized.

The design of the study including dose schedule for all treatment groups are summarized in the table below. Animals were weighed at dosing day(s) and dose was body weight adjusted, dosing volume was 10 ml/kg. Tumour dimensions and body weights were collected at the time of randomization and twice weekly thereafter for the study duration. The following data was provided after each day of data collection: incidence of mortality, individual and group average body weights, and individual and group average tumour volume.

Groups	Treatment	Dose	Schedule	Number of mice
1	Vehicle	0.5%HPMC 0.5% CMC/0.5% Tween 80	PO QD PO QD	8
2	Compound A	50 mg/kg	QD, PO	8
3	Compound B	20 mg/kg	QD, PO	8
4	Compound B Compound A	20 mg/kg 50 mg/kg	QD, PO QD PO	8

For the study, treatments were initiated on day 18 following tumour cell implantation of two million WM266-4 cells, when the average tumour volume was 320 mm^3.

Data Analysis

(a) Body Weight

The % change in body weight was calculated as $(BW_{current} - BW_{initial})/(BW_{initial}) \times 100$. Data is presented as percent body weight change from the day of treatment initiation.

(b) Tumour Volume and percent mice remaining on the study

Percent treatment/control (T/C) values were calculated using the following formula:

% T/C = 100 **x** AT/AC if $\Delta T > 0$

% Regression = 100 χ $\Delta T/T_0$ if $\Delta T < 0$

where:

T = mean tumour volume of the drug-treated group on the final day of the study;

ΔT = mean tumour volume of the drug-treated group on the final day of the study - mean tumour volume of the drug-treated group on initial day of dosing;

T_0 = mean tumour volume of the drug-treated group on the day of cohort;

C = mean tumour volume of the control group on the final day of the study; and

AC = mean tumour volume of the control group on the final day of the study - mean tumour volume of the control group on initial day of dosing.

Percent mice remaining on the study = 8- number of mice reaching end point/8* 100

(c) Statistical Analysis

All data were expressed as mean ± standard error of the mean (SEM). Delta tumour volume and percent body weight changes were used for statistical analysis. Between group comparisons were carried out using the Kruskal-Wallis ANOVA followed by a post hoc Dunn's test. For all statistical evaluations, the level of significance was set at $p < 0.05$. Significance compared to the vehicle control group is reported unless otherwise stated.

d) Results

Treatment	T/C% at day 32	T/T0% at day 32
Vehicle	100	
Compound A	52	
Compound B	40	
Compound A Compound B		-13.21

Compound B at 20 mg/kg produced statistically non-significant anti-tumour effects with 40% T/C. Compound A at 50 mg/kg resulted in non-significant anti-tumour effects with 52% T/C. Combination Compound B + Compound A led to tumour regression with -13.2% T/T0.

In vivo, the combination treatment resulted in sustained tumour regressions and markedly prolonged survival relative to either single agent (Fig. 3 and Fig. 4). Collectively, these data show that activation of p53, through inhibition of Mdm2, leads to antitumor effects in melanoma. Furthermore, the data show that simultaneous activation of tumour suppressor p53 and inhibition of BRAF synergistically suppresses melanoma growth. Therefore, combined inhibition of Mdm2 and BRAF in melanoma may provide an effective therapeutic modality capable of overcoming the resistance observed with the BRAF inhibitor monotherapy and thus lead to more durable responses in the clinic.

In addition, the mean body weight change at day 32 is shown in Fig. 5. Since WM266-4 xenograft tumour is a cachexia model, growing tumour induces mouse body weight loss. The body weight loss of -10.5% in vehicle treated group is related to tumour size. Treatment of mice with compounds B or A exhibit less body weight loss (-3.9% and -5.7% respectively). The combination group showed the least body weight loss (-0.5%). No other signs of adverse events were observed in this study.

Example 3. The in vitro effect on proliferation of combining the BRAF inhibitor Compound B with the Mdm2 inhibitor Compound C in A-375 and SKMEL5 melanoma cell lines

The protocol of example 1 was repeated for a combination of compound B and an mdm2 inhibitor, which was in this case the compound C, a representative compound of formula II. The experiments were done with A-375 and SKMEL5 melanoma cell lines. The potentiating antiproliferative effect of the combination is depicted in Fig. 6. The data indicates synergy.

Example 4. The in vitro effect on proliferation of combining the BRAF inhibitor Compound B with the Mdm2 inhibitor Compound A in RKO colorectal cancer cell line

The protocol of example 1 was repeated for a combination of compound B and an mdm2 inhibitor Compound A. The experiments were done RKO colorectal cancer cell line. The synergistic antiproliferative effect of the combination is depicted in Fig. 7.

Example 5. The in vitro effect on proliferation of combining the BRAF inhibitor Compound B with the Mdm2 inhibitor Compound C in cell lines (LIM2405, and RKO).

Both compounds were dissolved in 100% DMSO (Sigma, Catalog number D2650) at concentrations of 10mM and stored at -20°C until use. Compounds were arrayed in 300ul deep 384-well plates (BrandTech, catalog number 701355) serially diluted 3-fold at 4X concentration. Then, 10uL of the 4X compound plate was stamped onto 30uL of cells resulting in a final 1X concentration. Compound C was used over a concentration range of 0.0 - 3uM. Compound B was used over a concentration range of 0.0 - 1uM.

Synergy Score
SS ~ 0 → Dose Additive
SS >2 → Synergy
SS >1 → Weak Synergy

The RKO cell line was purchased from ATTC and the LIM2405 cell line was purchased from CellBank Australia. Cells were cultured in RPMI1640 (ATCC, Catalog number 30-21 10) supplemented with 10% FBS (HyClone, Catalog number SH30071 .03) according to vendor recommendations. The two cell lines carry the BRAF V600E mutation and are wild type for TP53.

Cell lines were cultured in 37°C and 5% C02 incubator and expanded in T-75 flasks. In all cases cells were thawed from frozen stocks, expanded through ≥1 passage using 1:3 dilutions, counted and assessed for viability using a ViCell counter (Beckman-Coulter), prior to plating in 384-well. To split and expand cell lines, cells were dislodged from flasks using 0.25% Trypsin-EDTA (GIBCO, Catalog number 25200). All cell lines were determined to be free of mycoplasma contamination as determined by a PCR detection methodology performed at Idexx Radii (Columbia, MO, USA) and correctly identified by detection of a panel of SNPs.

Cell proliferation was measured in 72hr CellTiter-Glo™ (CTG) assays and all results shown are the result of at least triplicate measurements. For CellTiter-Glo™ assays, cells were dispensed into tissue culture treated 384-well plates (Costar, catalog number 3707) with a final volume of 30 µl of medium and at density of 1000 cells per well. 12 to 24 hrs after plating, 10 µl of each compound dilution series were transferred to plates containing the cells, resulting in compound concentration ranges stated above and a final DMSO concentration of 0.16%. Plates were incubated for 72 hrs and the effects of compounds on cell proliferation was determined using the CellTiter-Glo™ Luminescent Cell Viability Assay (Promega) and a Victor™ X4 plate reader (Perkin Elmer).

The CellTiter-Glo® Luminescent Cell Viability Assay is a homogeneous method to determine the number of viable cells in culture based on quantitation of the ATP present, which signals the presence of metabolically active cells. The method is described in detail in the Technical Bulletin, TB288 Promega. Briefly, cells were plated in Opaque-walled multiwell plates in culture medium as described above. Control wells containing medium without cells were also prepared to obtain a value for background luminescence. A volume of CellTiter-Glo® Reagent equal to the volume of cell culture medium present in each well was then added and contents mixed for 60 minutes on an orbital shaker to induce cell lysis. Next, luminescence was recorded using the plate reader.

The percent growth inhibition and excess inhibition were analysed using the Chalice software (CombinatoRx, Cambridge MA). The percentage of growth inhibition relative to DMSO is displayed in the panel labelled inhibition, and the amount of inhibition in excess of the expected amount in the panel (labelled ADD Excess Inhibition). Concentrations of Compound B are shown along the bottom row from left to right and increasing concentrations of Compound C along the leftmost column from bottom to top. All remaining points in the grids display results from a combination of the two inhibitors that correspond to the single agent concentrations denoted on the two axes. Data analysis of cell proliferation was performed using Chalice Analyser as described in (Lehar et al. 2009). Excess inhibition was calculated using the Loewe synergy model which measures the effect on growth relative to what would be expected if two drugs behave in a dose additive manner. Positive numbers represent areas of increasing synergy.

IC50 is the compound concentration which inhibits 50% of the CTG signal by 50%. IC50 calculations were made using model number 203 from the XLfit Microsoft Excel™ add-In version 5.2.0.0 (IDBS Enabling Science). Synergy scores and IC50 calculations were determined as described in (Lehar et al. 2009).

The table below shows single agent IC50 values for each compound and synergy score measurements for the combination of Compound B with Compound C (described in Lehar J, Krueger AS, A very W, et al (2009). Interactions were deemed synergistic when scores ≥ 2.0 where observed.

Cell Line	**Compound C** IC50 (uM)	**Compound B** IC50 (uM)	Synergy Score
LIM2405	0.573	0.0189	4.19
RKO	1.75	>1	4.31

Compound C as single agent strongly inhibited the growth of both cell lines (Figure 8) evident by nanomolar IC50 values. Compound B as single agent strongly inhibited the growth of LIM2405 cells and weakly inhibited the growth of RKO cells (Figure 8), evident by IC50 values (see table). In combination, Compound C and Compound B treatment caused strong synergistic growth inhibition in both cell lines. Synergy was calculated using the Loewe model as described in (Lehar et al. 200S).

Example 6. In vivo HCOX2145 and HCOX1329 human primary tumour colorectal xenografts with combination of compounds C and B

The xenograft models were established by direct subcutaneous (sc) implantation of minced surgical material into the subcutaneous area of nude mice. The tumors were then serially passaged in mice. All surgeries were carried out using aseptic technique. The mice were anesthetized during the entire period of the procedure. HCOX2145 and HCOX1329 harboured B-RAF V600E mutation and p53 wild type.

In general, a total of 5 animals per group were enrolled in efficacy study. For single-agent and combination studies, animals were dosed via oral gavage for both Compound B and Compound C. Compound B was formulated in 0.5% CMC/0.5% Tween 80, and Compound C was formulated in Methylcellulose 0.5% w/V in pH 6.8 50 mM phosphate buffer at 20 mg/kg as free base. For model HCOX2145, the tumors reached approximately 200 mm^3 at day 29 post fragment implantation. On Day 29, tumour-bearing mice were randomized into treatment groups. For model HCOX1329, tumors reached approximately -236 to 288 mm^3 at day 14 post fragment implantation. On Day 14, tumour-bearing mice were randomized into treatment groups.

The design of the study including dose schedule for all treatment groups are summarized in the table below. Animals were weighed at dosing day(s) and dose was body weight adjusted, dosing volume was 10 ml/kg. Tumour dimensions and body weights were collected at the time of randomization and twice weekly thereafter for the study duration. The following data was provided after each day of data collection: incidence of mortality, individual and group average body weights, and individual and group average tumour volume.

Treatment and doses:

Groups	Treatment	Dose	Schedule	Number of mice
1	Vehicle	0.5% MC in phosphate buffer 0.5% CMC/0.5% Tween 80	QD, PO QD, PO	5
2	Compound C	20 mg/kg	QD, PO	5
3	Compound B	20 mg/kg	QD, PO	5
4	Compound B Compound C	20 mg/kg 20 mg/kg	QD, PO QD PO	5

Data Analysis

(d) Body Weight

The % change in body weight was calculated as $(BW_{current} - BW_{initial})/(BW_{initial}) \times 100$. Data is presented as percent body weight change from the day of treatment initiation.

(e) Tumour Volume and percent mice remaining on the study

Percent treatment/control (T/C) values were calculated using the following formula:

% T/C = 100 **x** $\Delta T/AC$ if $\Delta T > 0$

% Regression = 100 χ $\Delta T/T_0$ if $\Delta T < 0$

where:

T = mean tumour volume of the drug-treated group on the final day of the study;

ΔT = mean tumour volume of the drug-treated group on the final day of the study - mean tumour volume of the drug-treated group on initial day of dosing;

T_0 = mean tumour volume of the drug-treated group on the day of cohort;

C = mean tumour volume of the control group on the final day of the study; and

AC = mean tumour volume of the control group on the final day of the study - mean tumour volume of the control group on initial day of dosing.

Percent mice remaining on the study = 8- number of mice reaching end point/8* 100

(f) Statistical Analysis

All data were expressed as mean ± standard error of the mean (SEM). Delta tumour volume and percent body weight changes were used for statistical analysis. Between group comparisons were carried out using the One way ANOVA followed by a post hoc Tukey test. For all statistical evaluations, the level of significance was set at $p < 0.05$. Significance compared to the vehicle control group is reported unless otherwise stated.

d) Results

Model	HCOX2145
Treatment	T/C% at day 58
Vehicle	100
Compound C	67
Compound B	53
Compound C Compound B	4

Model	HCOX1329
Treatment	T/C% at day 28
Vehicle	100
Compound C	94
Compound B	32
Compound C Compound B	17

In HCOX2145 model (Fig. 9), Compound B at 20 mg/kg produced statistically non-significant anti-tumour effects with 53% T/C. Compound C at 20 mg/kg resulted in non-significant anti-tumour effects with 67% T/C. Combination of Compound B + Compound C led to tumour stasis

with 4% T/C, which is statistically significant compared to Vehicle and Compound C treated tumors.

In HCOX1329 model (Fig. 10), Compound B at 20 mg/kg produced statistically non-significant anti-tumour effects with 32% T/C. Compound C at 20 mg/kg did not have any anti-tumour effects (94% T/C). Combination of Compound B + Compound C resulted in anti-tumour effects with 17% T/C, which is statistically significant compared to Vehicle and Compound C treated tumors.

Collectively, these data show that activation of p53, through inhibition of Mdm2, as monotherapy did not have antitumor effects in CRC models. However, the data show that simultaneous activation of tumour suppressor p53 and inhibition of BRAF potently suppresses CRC tumour growth. Therefore, combined inhibition of Mdm2 and BRAF in CRC may provide an effective therapeutic modality capable of overcoming the primary resistance observed with the BRAF inhibitor monotherapy and thus lead to more durable responses in the clinic.

In addition, the mean body weight change for HCOX2145 and HCOX1329 are shown in Fig. 11. Since both xenograft tumours are cachexia model, growing tumour induces mouse body weight loss of -3.9% for HCOX2145, and -4.75% for HCOX1329. Treatment of mice with compound C exhibit body weight loss (-8.1% and -7.4% respectively). The combination group showed less body weight loss compared to Compound B group. Compound B treated group has the least body weight changes. No other signs of adverse events were observed.

Claims:

1. A pharmaceutical combination comprising (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof.

2. The pharmaceutical combination according to claim 1, wherein the pharmaceutical combination comprises (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, separately or together.

3. The pharmaceutical combination according to claim 1 or 2 for simultaneous or sequential use of the (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof.

4. The pharmaceutical combination according to any one of claims 1 to 3, further comprising at least one pharmaceutically acceptable carrier.

5. The pharmaceutical combination according to any one of claims 1 to 4 in the form of a fixed combination.

6. The pharmaceutical combination according to any one of claims 1 to 5 in the form or a kit of parts for the combined administration where the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and the BRAF inhibitor, or a pharmaceutically acceptable salt thereof may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners are jointly active.

7. The pharmaceutical combination according to any one of claims 1 to 6 for use in the treatment of cancer, wherein (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, are in a quantity which is jointly therapeutically effective.

8. The pharmaceutical combination according to claim 7, wherein the cancer is melanoma, colorectal cancer, sarcoma, thyroid cancer, lung cancer or leukemia.

9. The pharmaceutical combination according to claim 7 or 8, wherein the cancer is melanoma.

10. The pharmaceutical combination according to claim 7 or 8, wherein the cancer is colorectal cancer.

11. The pharmaceutical combination according to any one of claims 7 to 10, wherein the cancer comprises BRAF having the V600E mutation.

12. The pharmaceutical combination according to any one of claims 7 to 11, wherein the cancer comprises functional p53 or p53 wt.

13. A Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament, wherein the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, is to be administered simultaneously or sequentially to a BRAF inhibitor, or a pharmaceutically acceptable salt thereof.

14. A Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, wherein the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, is to be administered simultaneously or sequentially to a BRAF inhibitor, or a pharmaceutically acceptable salt thereof.

15. The Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, according to claim 14, wherein the cancer is melanoma, colorectal cancer, sarcoma, thyroid cancer, lung cancer or leukemia.

16. The Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, according to claim 14 or 15, wherein the cancer is melanoma.

17. The Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to claim 14 or 15, wherein the cancer is colorectal cancer.

18. The Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, according to any one of claims 14 to 17, wherein the cancer comprises BRAF having the V600E mutation.

19. The Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer, according to any one of claims 14 to 18, wherein the cancer comprises functional p53 or p53 wt.

20. Use of a data carrier comprising information about using (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, simultaneously or sequentially, to instruct to administer (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, simultaneously or sequentially for the treatment of cancer.

21. A method of treating a patient suffering from cancer comprising administering to the patient, either simultaneously or sequentially: (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, wherein the amount of said Mdm2 inhibitor and BRAF inhibitor being such that the combination thereof is therapeutically effective in the treatment of the cancer.

22. The method of treating a patient suffering from cancer according to claim 21, wherein the cancer is melanoma, colorectal cancer, sarcoma, thyroid cancer, lung cancer or leukemia.

23. The method of treating a patient suffering from cancer according to claim 21 or 22, wherein the cancer is melanoma.

24. The method of treating a patient suffering from cancer according to claim 21 or 22, wherein the cancer is colorectal cancer.

25. The method of treating a patient suffering from cancer according to any one of claims 21 to 24, wherein the cancer comprises BRAF having the V600E mutation.

26. The method of treating a patient suffering from cancer according to any one of claims 21 to 25, wherein the cancer comprises functional p53 or p53 wt.

27. The pharmaceutical combination according to any one of claims 1 to 12 in the form of a combination product.

28. A pharmaceutical combination comprising (i) a Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer.

29. The pharmaceutical combination according to claim 28, wherein the cancer is melanoma, colorectal cancer, sarcoma, thyroid cancer, lung cancer or leukemia.

30. The pharmaceutical combination according to claim 28 or 29, wherein the cancer is melanoma.

31. The pharmaceutical combination according to claim 28 or 29, wherein the cancer is colorectal cancer.

32. The pharmaceutical combination according to any one of claims 28 to 31, wherein the cancer comprises BRAF having the V600E mutation.

33. The pharmaceutical combination according to any one of claims 28 to 32, wherein the cancer comprises functional p53 or p53 wt.

34. A Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine.

35. The pharmaceutical combination according to any one of claims 1 to 12, or 27, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to claim 13, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of claims 14 to 19, the method of treating a patient suffering from cancer according to any one of claims 21 to 26, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of claims 28 to 33, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to claim 34, wherein an amount of the BRAF inhibitor, or a pharmaceutically acceptable salt thereof, is lower than the amount administered when the BRAF inhibitor, or a pharmaceutically acceptable salt thereof, is used alone.

36. The pharmaceutical combination according to any one of claims 1 to 12, or 27, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to claim 13, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of claims 14 to 19, the method of treating a patient suffering from cancer according to any one of claims 21 to 26, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of claims 28 to 33, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to claim 34, wherein an amount of the BRAF inhibitor, or a pharmaceutically acceptable salt thereof, is a subtherapeutic amount.

37. The pharmaceutical combination according to any one of claims 1 to 12, or 27, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to claim 13, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of claims 14 to 19, the method of treating a patient suffering from cancer according to any one of claims 21 to 26, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of claims 28 to 33, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to claim 34, wherein an amount of the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, is lower than the amount administered when the Mdm2 inhibitor is used alone.

38. The pharmaceutical combination according to any one of claims 1 to 12, or 27, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to claim 13, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of claims 14 to 19, the method of treating a patient suffering from cancer according to any one of claims 21 to 26, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of claims 28 to 33, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to claim 34, wherein an amount of the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, is a subtherapeutic amount.

39. A Mdm2 inhibitor of formula I or formula II for use in the treatment of colorectal cancer.

40. The Mdm2 inhibitor of formula I or formula II for use in the treatment according to claim 39, wherein the colorectal cancer comprises BRAF having the V600E mutation.

41. The Mdm2 inhibitor of formula I or formula II for use in the treatment according to claims 39 or 40, wherein the cancer comprises functional p53 or p53 wt.

42. A pharmaceutical composition comprising Mdm2 inhibitor of formula I or formula II for use in the treatment of colorectal cancer.

43. The pharmaceutical composition comprising Mdm2 inhibitor of formula I or formula II for use in the treatment according to claim 42, wherein the colorectal cancer comprises BRAF having the V600E mutation.

44. The pharmaceutical composition comprising Mdm2 inhibitor of formula I or formula II for use in the treatment according to claims 42 or 43, wherein the cancer comprises functional p53 or p53 wt.

45. The pharmaceutical combination according to any one of claims 1 to 12, 27 or 35 to 38, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to any one of claims 13 or 35 to 38, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of claims 14 to 19 or 35 to 38, the method of treating a patient suffering from cancer according to any one of claims 21 to 26 or 35 to 38, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of claims 28 to 33 or 35 to 38, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to any one of claims 34 to 38, or the Mdm2 inhibitor of formula I or formula II for use in the treatment according to any one of claims 39 to 41, or the pharmaceutical composition comprising Mdm2 inhibitor of formula I or formula II for use in the treatment according to any one of claims 42 to 44, wherein the Mdm2 inhibitor of formula I or formula II is selected from the group consisting of:

(S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1 ,4-dihydro-2H-isoquinolin-3-one

(S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1 ,4-dihydro-2H-isoquinolin-3-one

(S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(6-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-pyridin-3-yl)-1 ,4-dihydro-2H-isoquinolin-3-one

(S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(6-{methyl-[4-(3-methyl-4-oxo-imidazolidin-1-yl)-trans-cyclohexylmethyl]-amino}-pyridin-3-yl)-1 ,4-dihydro-2H-isoquinolin-3-one

(S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(5-{methyl-[4-(3-methyl-4-oxo-imidazolidin-1-yl)-trans-cyclohexylmethyl]-amino}-pyrazin-2-yl)-1,4-dihydro-2H-isoquinolin-3-one

1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1 ,4-dihydro-2H-isoquinolin-3-one,

(S)-5-(5-Chloro-1-methyl-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(4-chloro-phenyl)-2-(2,4-dimethoxy-pyrimidin-5-yl)-1-isopropyl-5,6-dihydro-1 H-pyrrolo[3,4-d]imidazol-4-one

4-[(S)-5-(3-Chloro-2-fluoro-phenyl)-2-(2,4-dimethoxy-pyrimidin-5-yl)-3-isoprop yl-6-oxo-3,4,5,6-tetrahydro-pyrrolo[3,4-d]imidazol-4-yl]-benzonitrile

(S)-5-(5-Chloro-2-oxo-1 ,2-dihydro-pyridin-3-yl)-6-(4-chloro-phenyl)-2-(2,4-dimethoxy-pyri midin-5-yl)-1 -isopropyl-5,6-dihydro-1 H-pyrrolo[3,4-d]imidazol-4-one

(S)-5-(3-chloro-4-fluorophenyl)-6-(4-chlorophenyl)-2-(2,4-dimethoxypyrimidin-5 -yl)-1-((R)-1-methoxypropan-2-yl)-5,6-dihydropyrrolo[3,4-d]imidazol-4(1 H)-one, and

(S)-5-(5-chloro-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-6-(4-chlorophenyl)-2-(2,4-dimethoxy-d6-pyrimidin-5-yl)-1-((R)-1-methoxypropan-2-yl)-5,6-dihydropyrrolo[3,4-d]imidazol-4(1 H)-one.

46. The pharmaceutical combination according to any one of claims 1 to 12, 27 or 35 to 38, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to any one of claims 13 or 35 to 38, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of claims 14 to 19 or 35 to 38, the method of treating a patient suffering from cancer according to any one of claims 2 1 to 26 or 35 to 38, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of claims 28 to 33 or 35 to 38, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to any one of claims 34 to 38, or the Mdm2 inhibitor of formula I or formula II for use in the treatment according to any one of claims 39 to 4 1, or the pharmaceutical composition comprising Mdm2 inhibitor of formula I or formula II for use in the treatment according to any one of claims 42 to 44, wherein the Mdm2 inhibitor is (S)-5-(5-Chloro-1-methyl-2-oxo-1,2-dihydro-pyridin-3-yl)-6-(4-chloro-phenyl)-2-(2,4-dimethoxy-pyrimidin-5-yl)-1-isopropyl-5,6-dihydro-1 H-pyrrolo[3,4-d]imidazol-4-one.

47. The pharmaceutical combination according to any one of claims 1 to 12, 27 or 35 to 38, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to any one of claims 13 or 35 to 38, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of claims 14 to 19 or 35 to 38, the method of treating a patient suffering from cancer according to any one of claims 2 1 to 26 or 35 to 38, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of claims 28 to 33 or 35 to 38, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to any one of claims 34 to 38, or the Mdm2 inhibitor of formula I or formula II for use in the treatment according to any one of claims 39 to 4 1, or the pharmaceutical composition comprising Mdm2 inhibitor of formula I or formula II for use in the treatment according to any one of claims 42 to 44, wherein the Mdm2 inhibitor is (S)-1-(4-Chloro-phenyl)-7-isopropoxy-6-methoxy-2-(4-{methyl-[4-(4-methyl-3-oxo-piperazin-1-yl)-trans-cyclohexylmethyl]-amino}-phenyl)-1 ,4-dihydro-2H-isoquinolin-3-one.

48. The pharmaceutical combination according to any one of claims 1 to 12, 27, 35 to 38 or 45 to 47, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to any one of claims 13, 35 to 38 or 45 to 47, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of claims 14 to 19, 35 to 38 or 45 to 47, the method of treating a patient suffering from cancer according to any one of claims 21 to 26, 35 to 38 or 45 to 47, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of claims 28 to 33, 35 to 38 or 45 to 47, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to any one of claims 34 to 38 or 45 to 47, wherein the BRAF inhibitor is selected from the group consisting of: (S)-methyl-1-(4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1 H-pyrazol-4-yl)pyrimidin-2-ylamino)propan-2-ylcarbamate;

methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;

methyl N-[(2S)-1-({4-[3-(2,5-difluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;

methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-ethyl-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;

methyl N-[(2S)-1-({4-[3-(2-fluoro-3-methanesulfonamido-5-methylphenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;

methyl N-[(2S)-1-({4-[3-(2-chloro-3-methanesulfonamido-5-methylphenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;

methyl N-[(2S)-1-({4-[3-(2-chloro-5-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;

methyl N-[(2R)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate;

methyl N-[(2S)-1-({4-[3-(2,5-dichloro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate; and

vemurafenib.

49. The pharmaceutical combination according to any one of claims 1 to 12, 27, 35 to 38 or 45 to 47, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to any one of claims 13, 35 to 38 or 45 to 47, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of claims 14 to 19, 35 to 38 or 45 to 47, the method of treating a patient suffering from cancer according to any one of claims 21 to 26, 35 to

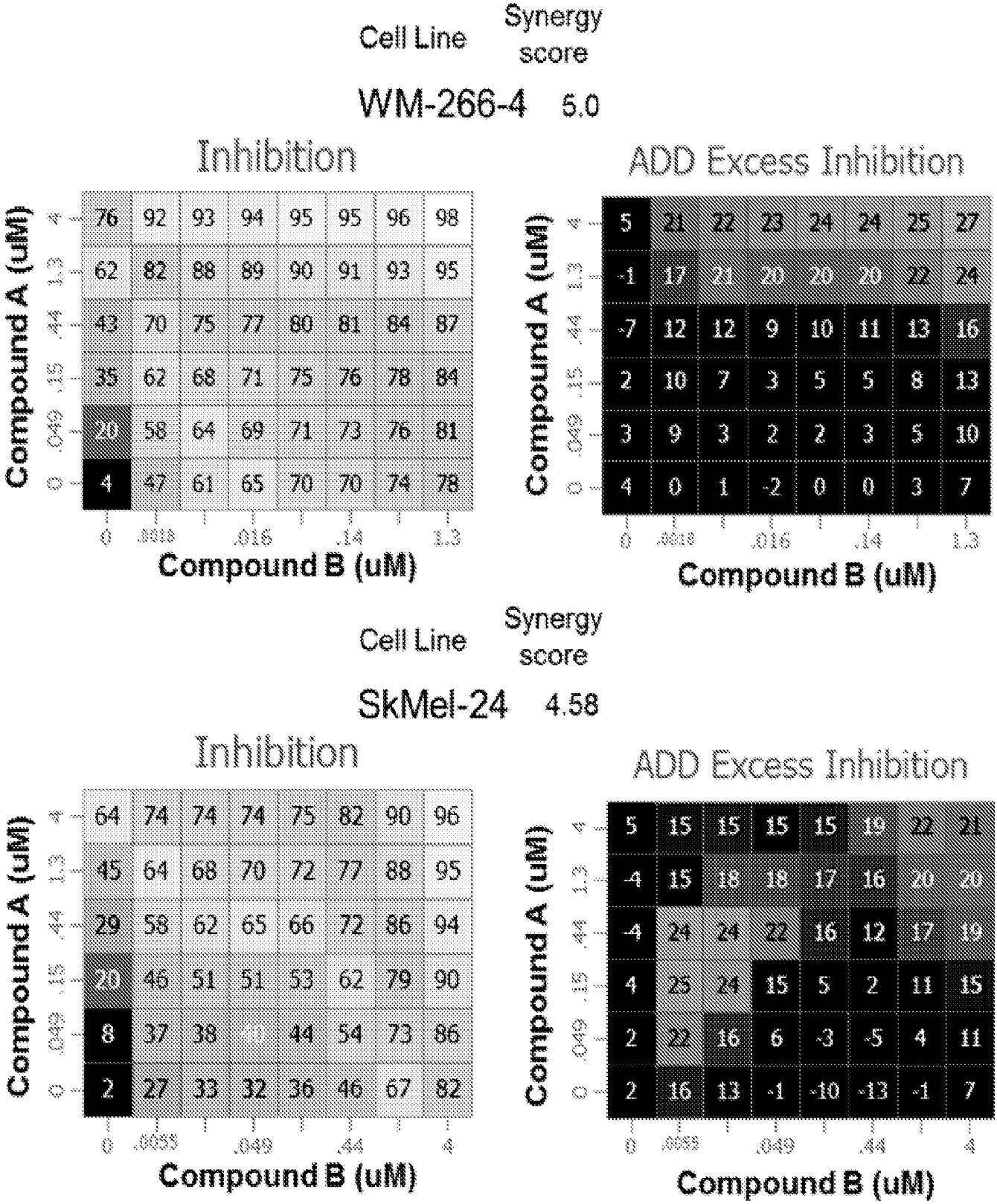
38 or 45 to 47, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of claims 28 to 33, 35 to 38 or 45 to 47, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to any one of claims 34 to 38 or 45 to 47, wherein the BRAF inhibitor is (S)-methyl-1-(4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1 H-pyrazol-4-yl)pyrimidin-2-ylamino)propan-2-ylcarbamate, methyl N-[(2S)-1-({4-[3-(5-chloro-2-fluoro-3-methanesulfonamidophenyl)-1-(propan-2-yl)-1 H-pyrazol-4-yl]pyrimidin-2-yl}amino)propan-2-yl]carbamate or vemurafenib.

50. The pharmaceutical combination according to any one of claims 1 to 12, 27, 35 to 38 or 45 to 47, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to any one of claims 13, 35 to 38 or 45 to 47, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of claims 14 to 19, 35 to 38 or 45 to 47, the method of treating a patient suffering from cancer according to any one of claims 21 to 26, 35 to 38 or 45 to 47, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of claims 28 to 33, 35 to 38 or 45 to 47, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to any one of claims 34 to 38 or 45 to 47, wherein the BRAF inhibitor is (S)-methyl-1-(4-(3-(5-chloro-2-fluoro-3-(methylsulfonamido)phenyl)-1-isopropyl-1 H-pyrazol-4-yl)pyrimidin-2-ylamino)propan-2-ylcarbamate.

51. The pharmaceutical combination according to any one of claims 1 to 12, 27, 35 to 38 or 45 to 50, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use as a medicament according to any one of claims 13, 35 to 38 or 45 to 50, the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer according to any one of claims 14 to 19, 35 to 38 or 45 to 50, the method of treating a patient suffering from cancer according to any one of claims 21 to 26, 35 to 38 or 45 to 50, the pharmaceutical combination for the manufacture of a medicament or a pharmaceutical product for the treatment of cancer according to any one of claims 28 to 33, 35 to 38 or 45 to 50, or the Mdm2 inhibitor of formula I or formula II, or a pharmaceutically acceptable salt thereof, and (ii) a BRAF inhibitor, or a pharmaceutically acceptable salt thereof, for combined use as a medicine according to any one of claims 34 to 38 or 45 to 50, further comprising another therapeutically active agent.

52. The pharmaceutical combination according to any one of claims 1 to 12, 27, 35 to 38 or 45 to 51, in a form of a pharmaceutical composition or a product.

Fig. 1


Cell Line
Synergy score
WM-266-4 5.0
Inhibition
ADD Excess Inhibition
Compound A (uM)
Compound B (uM)
0 .0018 .016 .14 1.3
76 92 93 94 95 95 96 98
62 82 88 89 90 91 93 95
43 70 75 77 80 81 84 87
35 62 68 71 75 76 78 84
20 58 64 69 71 73 76 81
4 47 61 65 70 70 74 78
5 21 22 23 24 24 25 27
-1 17 21 20 20 20 22 24
-7 12 12 9 10 11 13 16
2 10 7 3 5 5 8 13
3 9 3 2 2 3 5 10
4 0 1 -2 0 0 3 7
Cell Line
Synergy score
SkMel-24 4.58
Inhibition
ADD Excess Inhibition
Compound A (uM)
Compound B (uM)
0 .0055 .049 .44 4
64 74 74 74 75 82 90 96
45 64 68 70 72 77 88 95
29 58 62 65 66 72 86 94
20 46 51 51 53 62 79 90
8 37 38 44 54 73 86
2 27 33 32 36 46 67 82
5 15 15 15 15 19 22 21
-4 15 18 18 17 16 20 20
-4 24 24 22 16 12 17 19
4 25 24 15 5 2 11 15
2 22 16 6 -3 -5 4 11
2 16 13 -1 -10 -13 -1 7

cont. Fig. 1

Cell Line	Synergy score
C-32	4.16

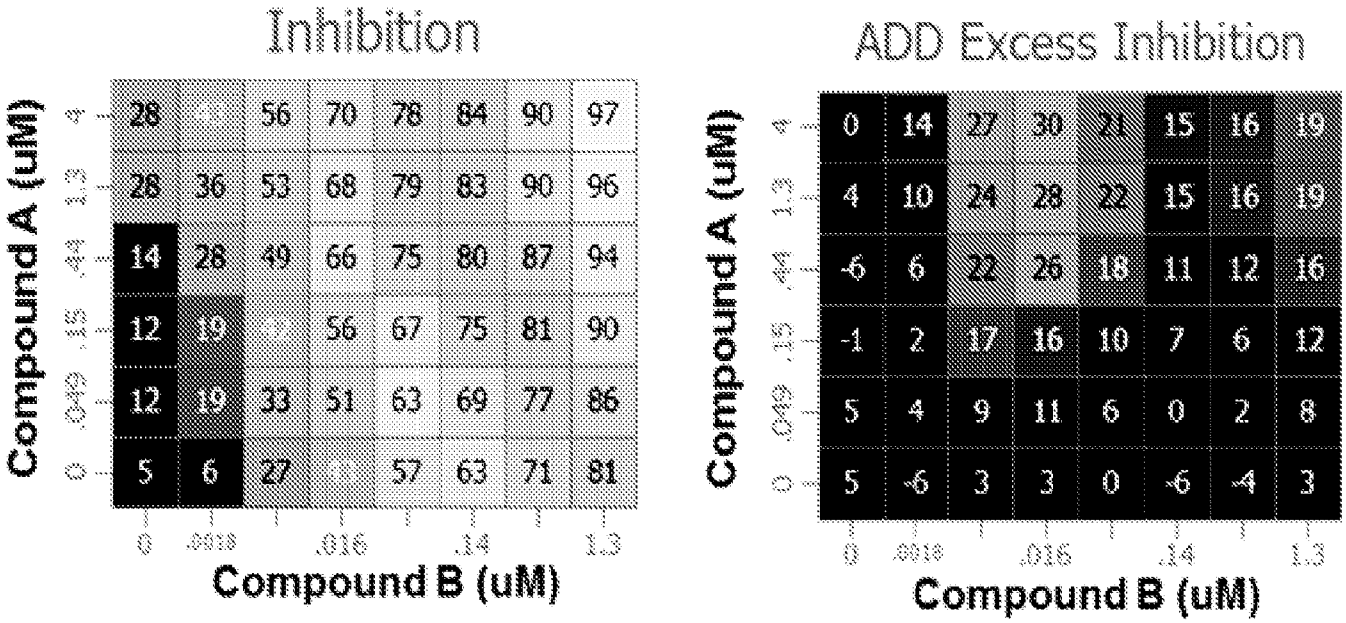


Fig. 2

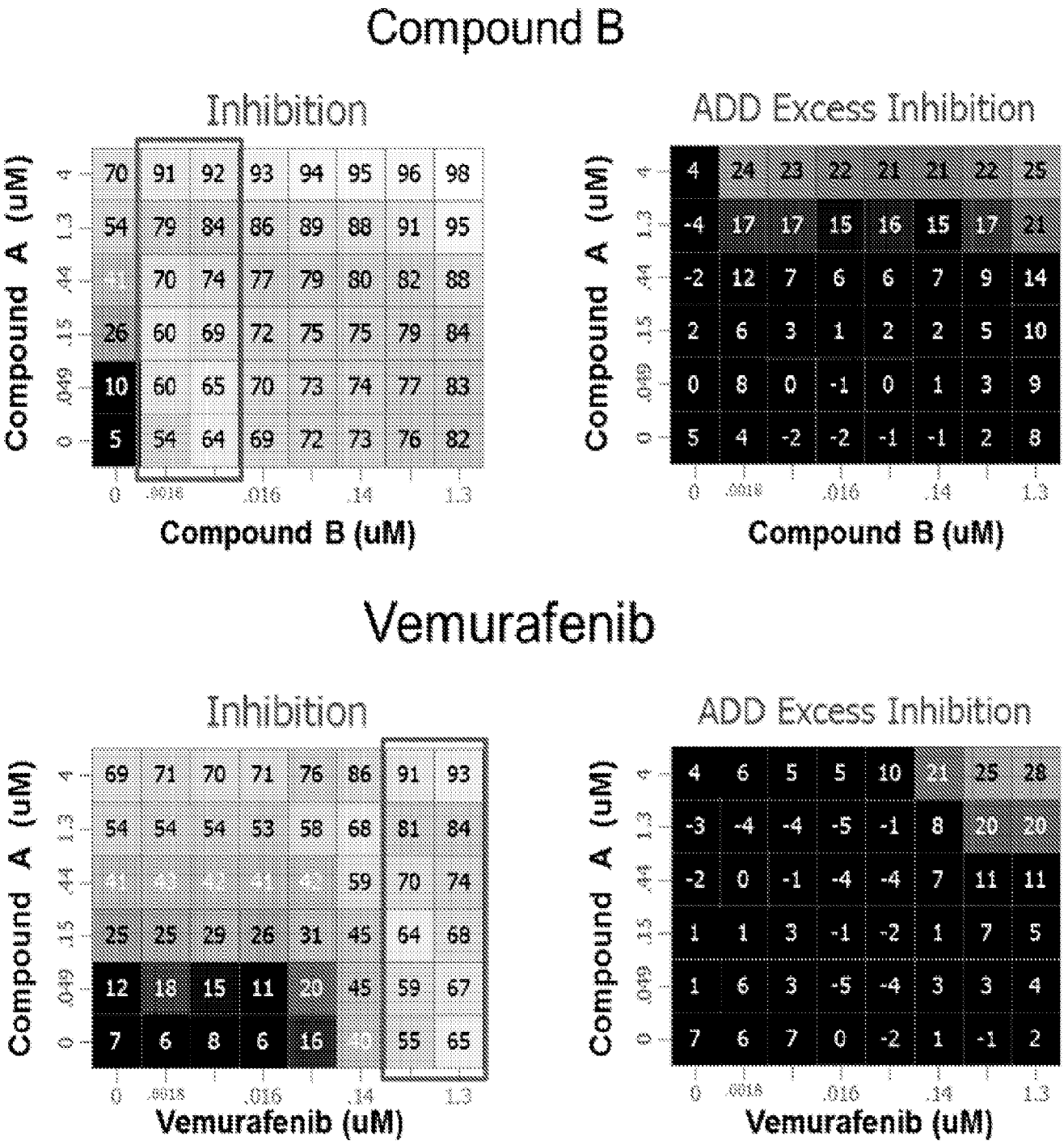
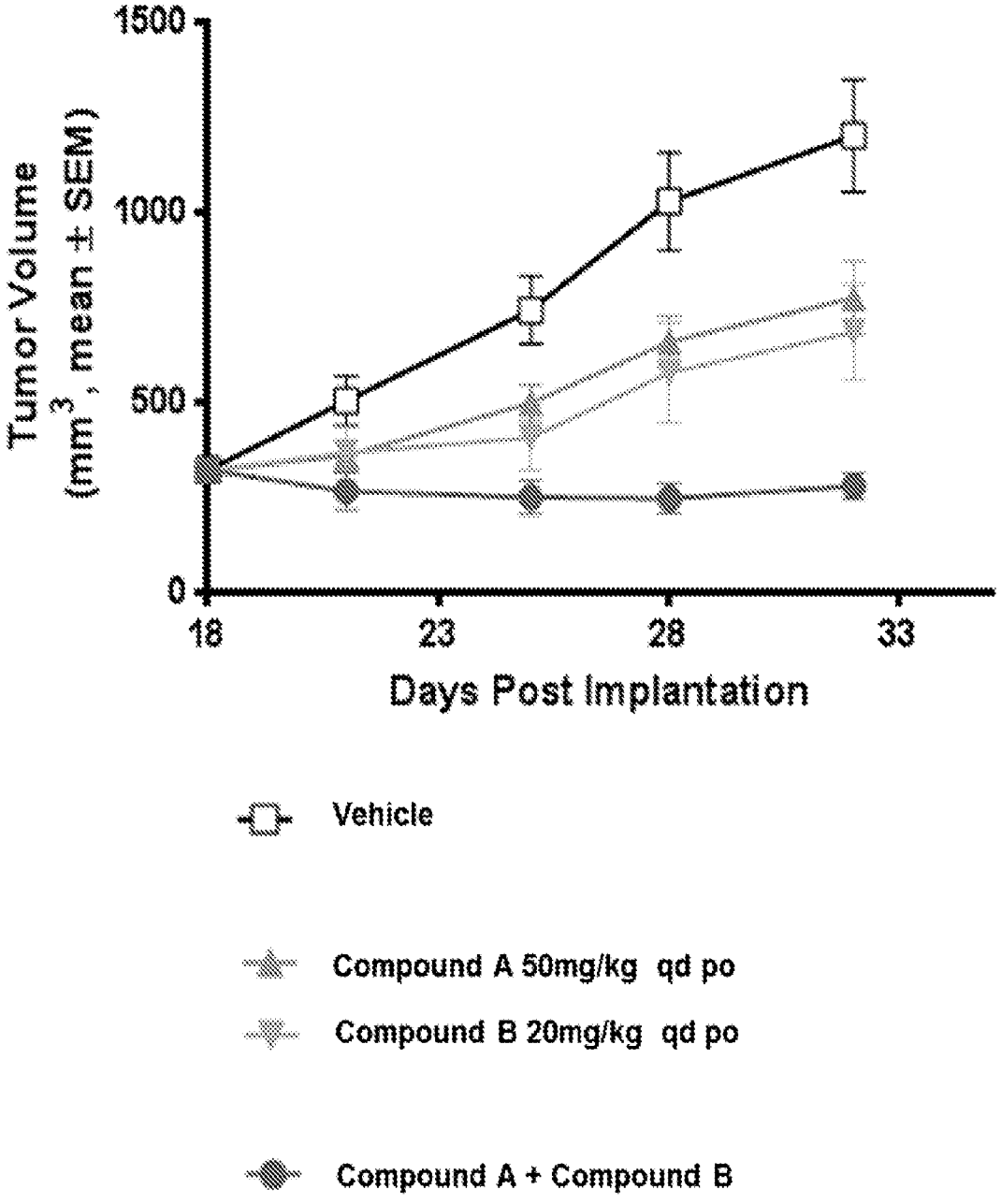

Compound B
Inhibition
Compound A (uM)
4 70 91 92 93 94 95 96 98
1.3 54 79 84 86 89 88 91 95
.44 70 74 77 79 80 82 88
.15 26 60 69 72 75 75 79 84
.049 10 60 65 70 73 74 77 83
0 5 54 64 69 72 73 76 82
0 .0018 .016 .14 1.3
Compound B (uM)
ADD Excess Inhibition
Compound A (uM)
4 4 24 23 22 21 21 22 25
1.3 -4 17 17 15 16 15 17 21
.44 -2 12 7 6 6 7 9 14
.15 2 6 3 1 2 2 5 10
.049 0 8 0 -1 0 1 3 9
0 5 4 -2 -2 -1 -1 2 8
0 .0018 .016 .14 1.3
Compound B (uM)
Vemurafenib
Inhibition
Compound A (uM)
4 69 71 70 71 76 86 91 93
1.3 54 54 54 53 58 68 81 84
.44 59 70 74
.15 25 25 29 26 31 45 64 68
.049 12 18 15 11 20 45 59 67
0 7 6 8 6 16 55 65
0 .0018 .016 .14 1.3
Vemurafenib (uM)
ADD Excess Inhibition
Compound A (uM)
4 4 6 5 5 10 21 25 28
1.3 -3 -4 -4 -5 -1 8 20 20
.44 -2 0 -1 -4 -4 7 11 11
.15 1 1 3 -1 -2 1 7 5
.049 1 6 3 -5 -4 3 3 4
0 7 6 7 0 -2 1 -1 2
0 .0018 .016 .14 1.3
Vemurafenib (uM)

Fig. 3



*p<0.05 compared to Vehicle and CGM097 alone

Fig. 4

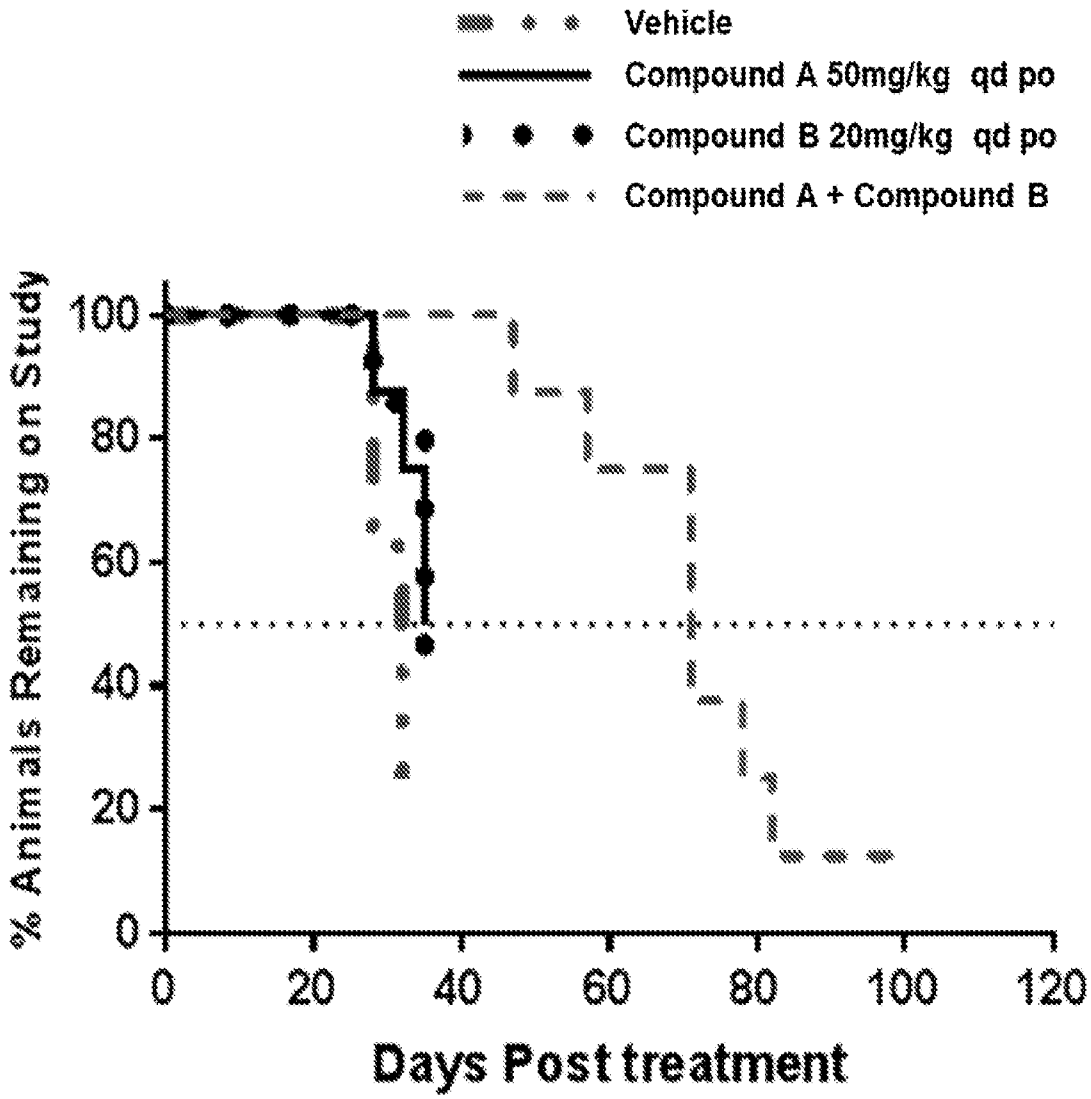

Vehicle
Compound A 50mg/kg qd po
Compound B 20mg/kg qd po
Compound A + Compound B
% Animals Remaining on Study
100
80
60
40
20
0
0
20
40
60
80
100
120
Days Post treatment

Fig. 5

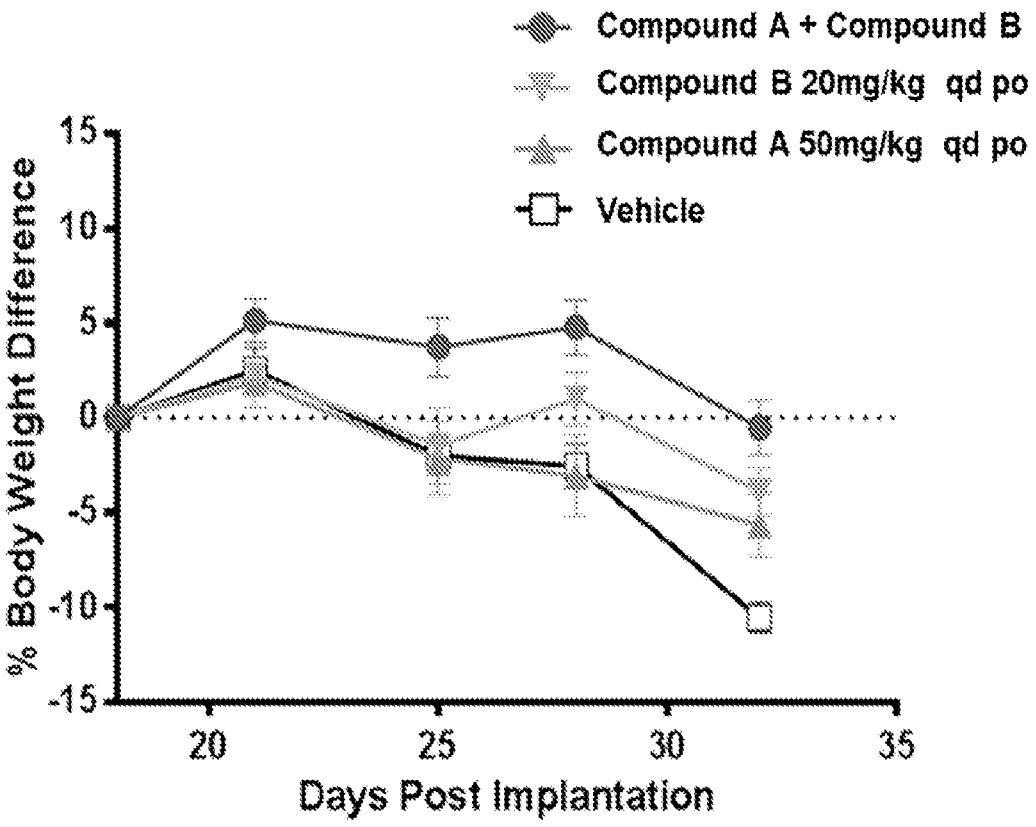
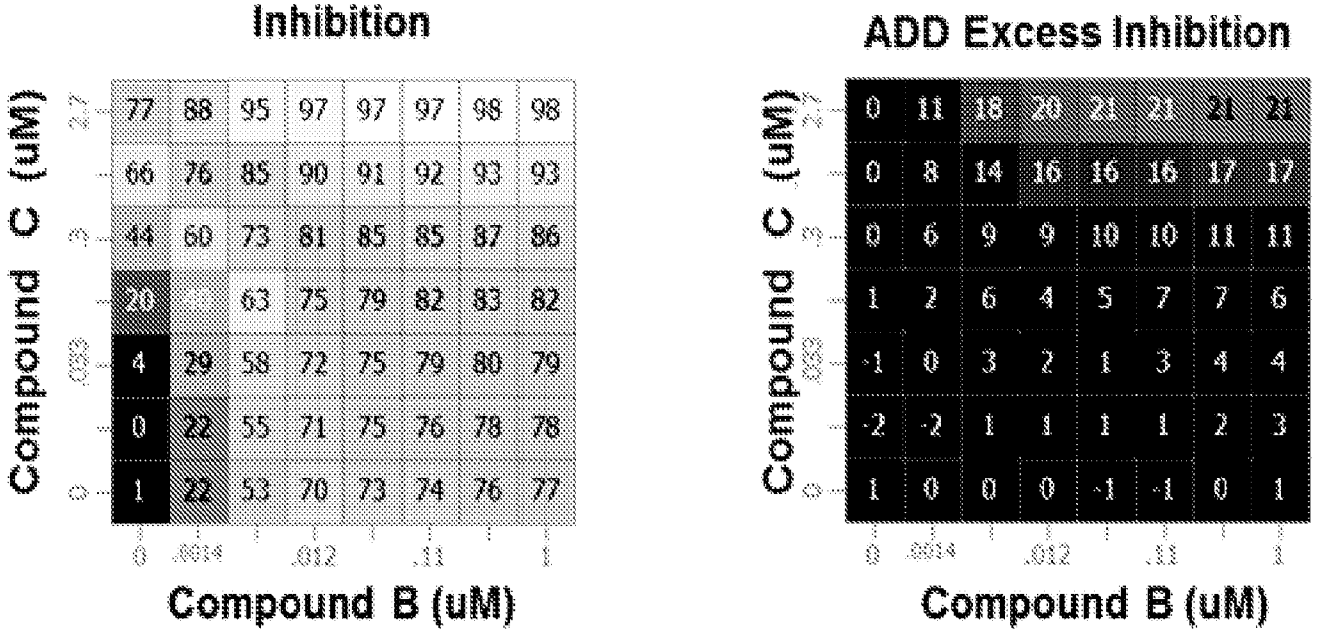

Compound A + Compound B
Compound B 20mg/kg qd po
Compound A 50mg/kg qd po
Vehicle
% Body Weight Difference
15
10
5
0
-5
-10
-15
20
25
30
35
Days Post Implantation

Fig. 6

A-375
Synergy Score: 3.85



SKMEL5
Synergy Score: 3.88

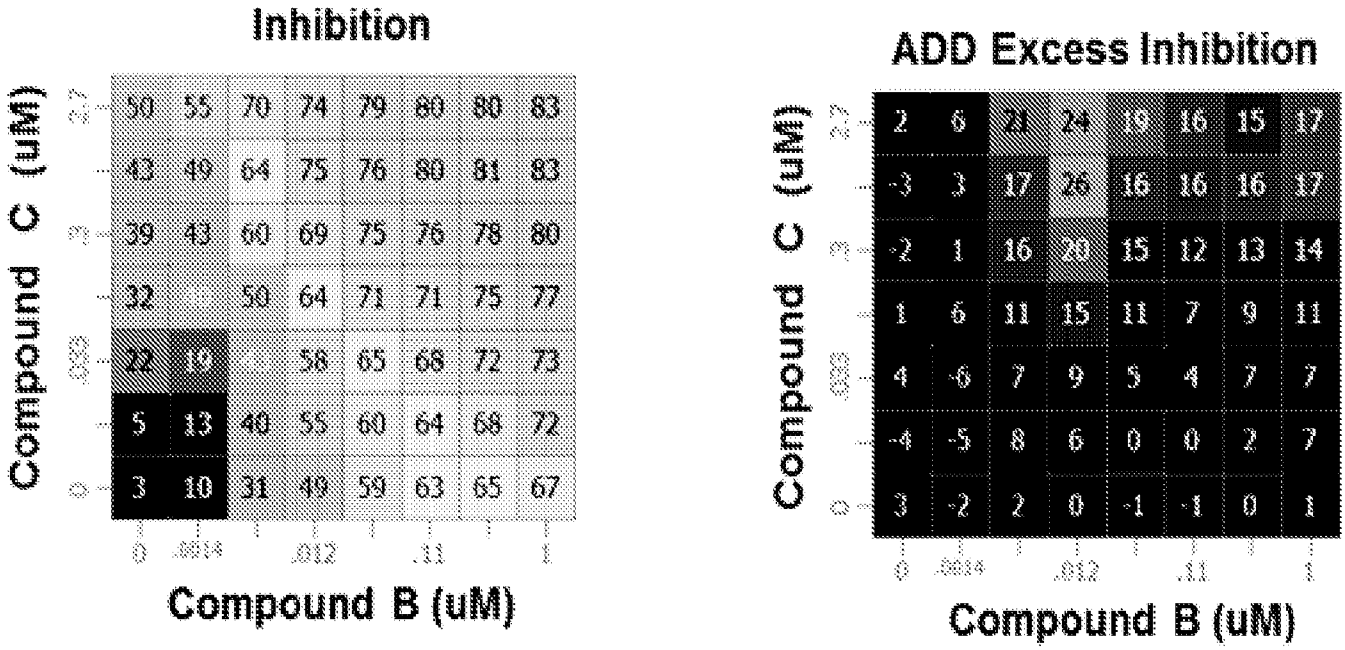


Fig. 7

RKO
Synergy Score: 2.86

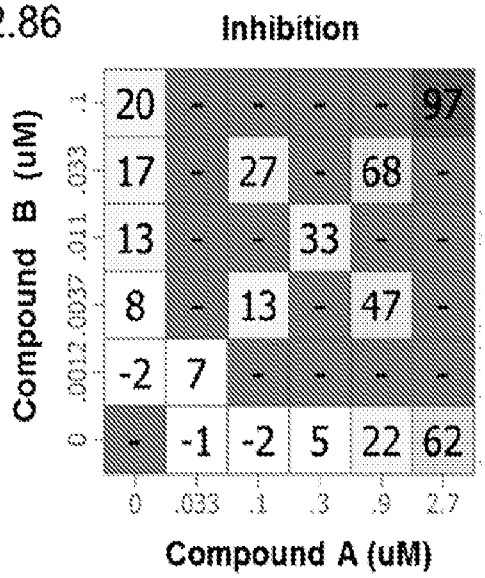


Fig. 8

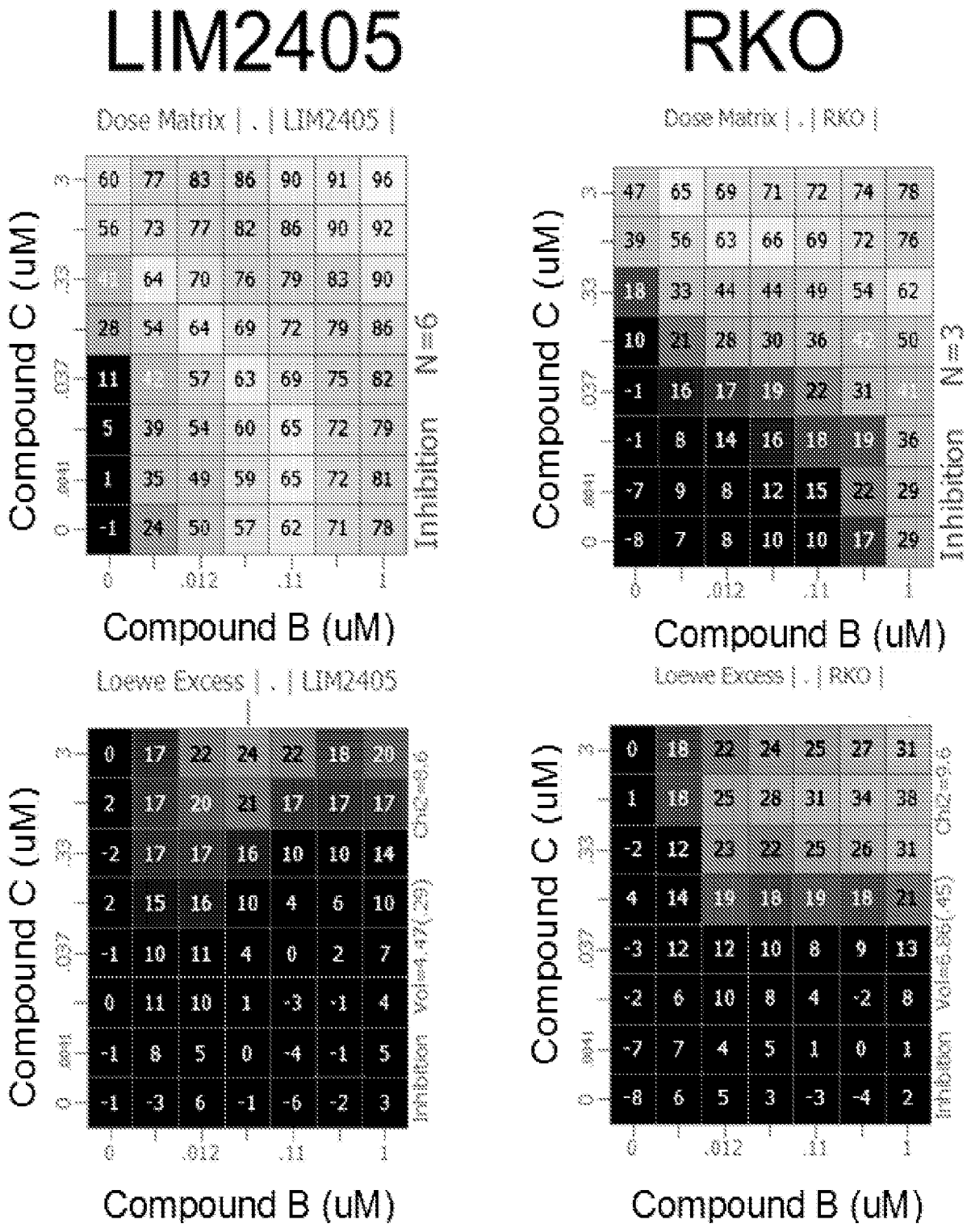

LIM2405
RKO
Dose Matrix | . | LIM2405 |
Dose Matrix | . | RKO |
Compound C (uM)
Compound B (uM)
Inhibition
N=6
N=3
Loewe Excess | . | LIM2405
Loewe Excess | . | RKO
Chi2=9.6
Vol=4.4X(.29)
Vol=9.8X(.45)
0
.012
.11
1
.037
.33
3

Fig. 9

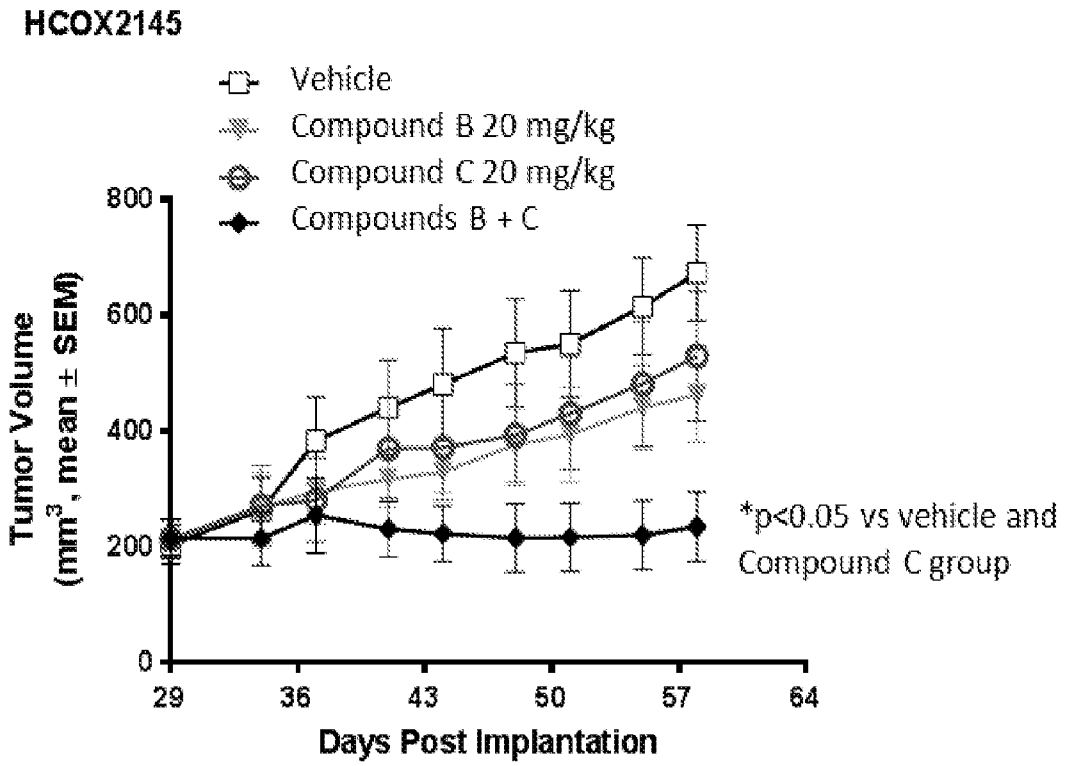

HCOX2145
Vehicle
Compound B 20 mg/kg
Compound C 20 mg/kg
Compounds B + C
Tumor Volume
(mm3, mean ± SEM)
800
600
400
200
0
29
36
43
50
57
64
Days Post Implantation
*p<0.05 vs vehicle and
Compound C group

Fig.10

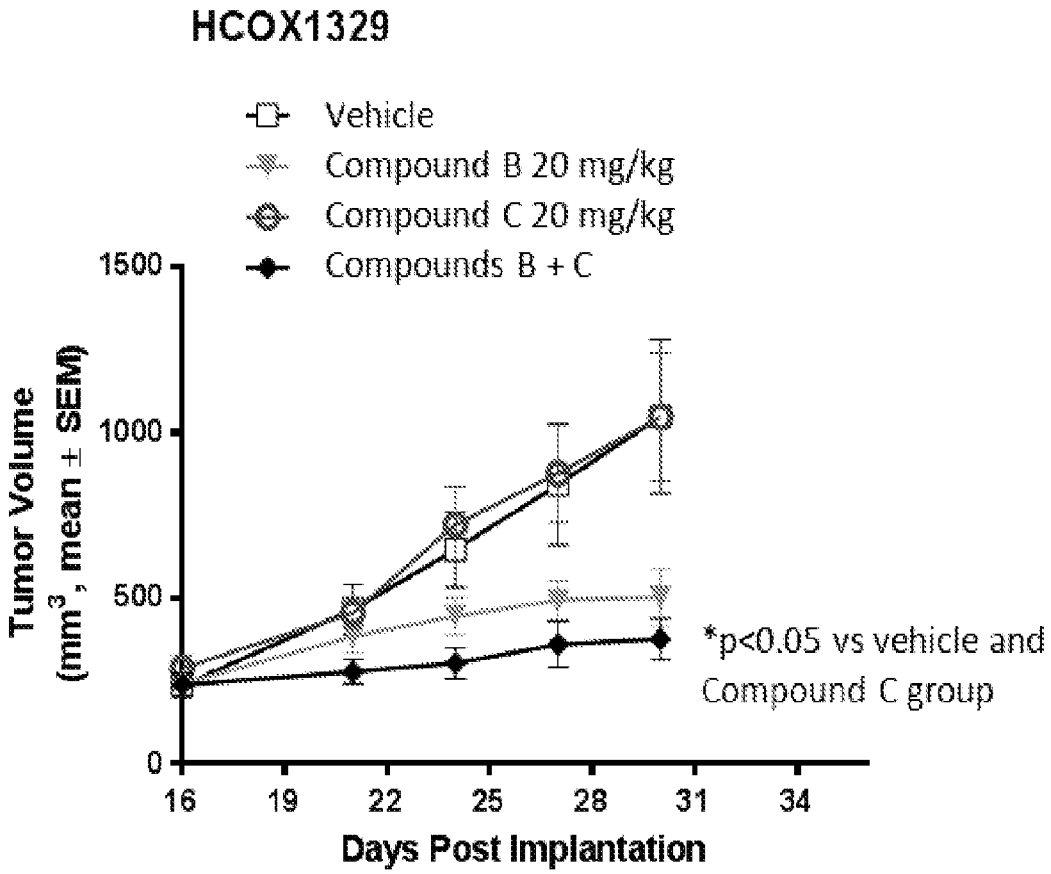
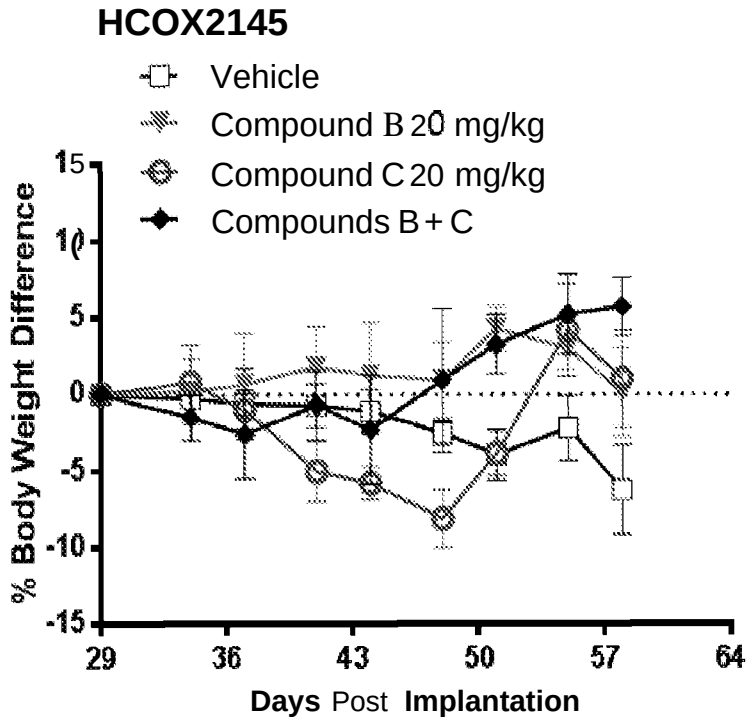
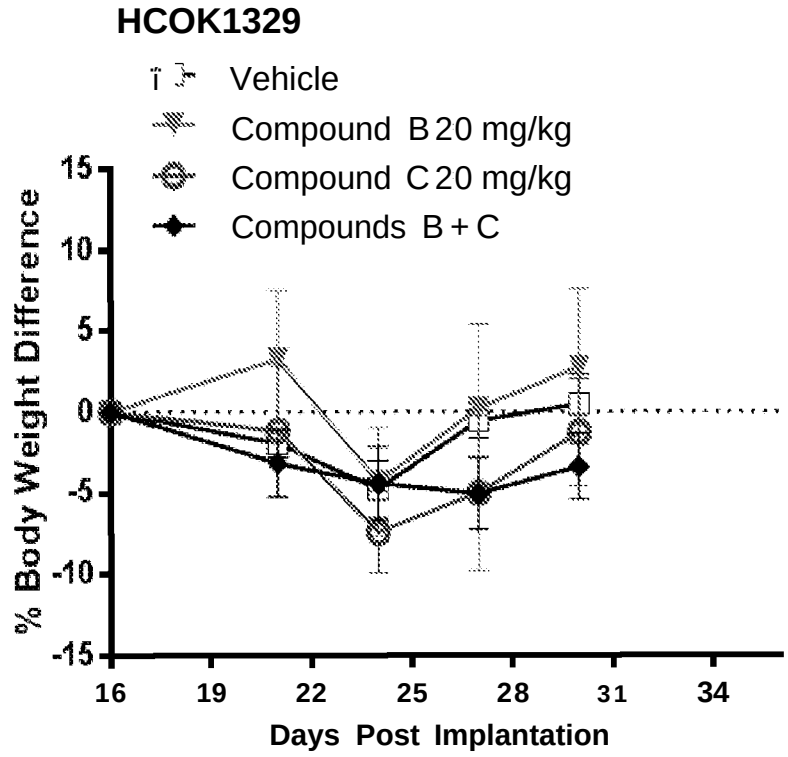

HCOX1329
Vehicle
Compound B 20 mg/kg
Compound C 20 mg/kg
Compounds B + C
Tumor Volume
(mm3, mean ± SEM)
1500
1000
500
0
16
19
22
25
28
31
34
Days Post Implantation
*p<0.05 vs vehicle and
Compound C group

Fig. 11


HCOX2145
Vehicle
Compound B 20 mg/kg
Compound C 20 mg/kg
Compounds B + C
% Body Weight Difference
15
10
5
0
-5
-10
-15
29
36
43
50
57
64
Days Post Implantation


HCOK1329
Vehicle
Compound B 20 mg/kg
Compound C 20 mg/kg
Compounds B + C
% Body Weight Difference
15
10
5
0
-5
-10
-15
16
19
22
25
28
31
34
Days Post Implantation

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/068091

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/00 A61K31/4188 A61K31/437 A61K31/472 A61K31/4725
ADD. A61P35/00

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2013/281473 Al (BERGHAUSEN JOERG [DE] ET AL) 24 October 2013 (2013-10-24) tabl e 2 (2100) ; 0001 ; 0006; cl aims 1 and 20; 0954	1-52
Y	W0 2013/111105 Al (N0VARTIS AG [CH]) 1 August 2013 (2013-08-01) cited in the appl i cati on claims 1, 18; p. 83, first	1-52
Y	US 2013/245039 Al (HIGGINS BRIAN [US] ET AL) 19 September 2013 (2013-09-19) cited in the appl i cati on 0007 ; 0016- 0017 ; cl aims	1-38, 45-49 , 51,52

-/- ·

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" documentwhich may throw doubts on priority claim(s) orwhich is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 Apri l 2015	06/05/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Dahse, Thomas

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/068091

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LU MIN ET AL: "Restoring p53 Function in Human Melanoma Cells by Inhibiting MDM2 and Cyclin Bl/CDKl-Phosphorylated Nuclear iASPP", CANCER CELL, CELL PRESS, US, vol. 23, no. 5, 25 April 2013 (2013-04-25), pages 618-633, XP028539938, ISSN: 1535-6108, DOI: 10.1016/J.CCR.2013.03.013 title, abstract; Fig. 8e	1-52
A	Anonymous: "The essenTials of life science ReseaRch Globally DeliveReD(TM)", , 1 August 2013 (2013-08-01), XP055182988, Internet Retrieved from the Internet: URL: http://web.archive.org/web/20130818191850/http://atcc.org/"/media/PDFs/Culture Guides/Cell_Lines_by_Gene_Mutation.ashx [retrieved on 2015-04-14] p. 3, cell line CRL-2577	1-52
Y	US 2006/211757 Al (WANG SHA0MENG [US] ET AL) 21 September 2006 (2006-09-21) examples 136, 137; claims	39-44
Y, P	Anne Y Saiki ET AL: "MDM2 antagonists synergize broadly and robustly with compounds targeting fundamental oncogenic signaling pathways", Oncotarget, 30 April 2014 (2014-04-30), page 2030, XP055168601, United States Retrieved from the Internet: URL: http://www.ncbi.nlm.nih.gov/pubmed/24810962 title, abstract; Fig. 2B	1-52

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/068091

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/068091

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2013281473 Al	24-10-2013	AR 079663 Al	08-02-2012
		AU 2010334890 Al	12-07-2012
		CA 2785340 Al	30-06-2011
		CO 6561772 A2	15-11-2012
		CR 20120333 A	20-07-2012
		DK 2516009 T3	05-01-2015
		DO P2012000172 A	31-08-2012
		EA 201200920 Al	30-01-2013
		EC SP12011990 A	28-09-2012
		EP 2516009 Al	31-10-2012
		ES 2527001 T3	19-01-2015
		GT 201200208 A	03-12-2013
		HK 1170972 Al	30-01-2015
		HR P20141259 TI	27-02-2015
		JP 5542962 B2	09-07-2014
		JP 2013515038 A	02-05-2013
		KR 20120112618 A	11-10-2012
		KR 20140140602 A	09-12-2014
		MA 33832 Bl	03-12-2012
		NZ 600716 A	25-10-2013
		PE 15102012 Al	22-11-2012
		PT 2516009 E	08-01-2015
		SG 181734 Al	30-07-2012
		SI 2516009 TI	30-01-2015
		SM T201400193 B	15-01-2015
		TW 201130801 A	16-09-2011
		US 2011230457 Al	22-09-2011
		US 2013281473 Al	24-10-2013
		WO 2011076786 Al	30-06-2011
WO 2013111105 Al	01-08-2013	AR 089807 Al	17-09-2014
		AU 2013213260 Al	14-08-2014
		CA 2860951 Al	01-08-2013
		CO 7010838 A2	31-07-2014
		CR 20140354 A	09-09-2014
		DO P2014000170 A	15-09-2014
		EA 201491423 Al	28-11-2014
		EP 2807164 Al	03-12-2014
		JP 2015509103 A	26-03-2015
		KR 20140121851 A	16-10-2014
		PE 16552014 Al	14-11-2014
		PH 12014501702 Al	13-10-2014
		TW 201333012 A	16-08-2013
		US 2014011798 Al	09-01-2014
		US 2014343084 Al	20-11-2014
		UY 34591 A	02-09-2013
		WO 2013111105 Al	01-08-2013
US 2013245039 Al	19-09-2013	AR 090349 Al	05-11-2014
		AU 2013203637 Al	03-10-2013
		CA 2861056 Al	26-09-2013
		CN 104114168 A	22-10-2014
		EP 2827859 Al	28-01-2015
		JP 2015510908 A	13-04-2015
		KR 20140130179 A	07-11-2014
		US 2013245039 Al	19-09-2013
		WO 2013139724 Al	26-09-2013

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/068091

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2006211757 Al	21-09-2006	NZ 561215 A	24-12-2010
		SG 176463 Al	29-12-2011
		US 2006211757 Al	21-09-2006
		US 2010273799 Al	28-10-2010
		US 2012101092 Al	26-04-2012
		US 2013030173 Al	31-01-2013

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-38, 45-52

   directed to combinations of formula I or II with a BRAF inhibitor, uses thereof or a data carrier comprising information about the combination

   ---

2. claims: 39-44

   directed to formula I or II or compositions comprising the same, for use in the treatment of colorectal cancer

   ---