There is a need for further combination strategies that also result in deeper and longer-lasting responses, ideally for a combination strategy that overcomes a decrease in effect of the KRAS inhibitor over time when administered as single agent (or when administered in combination with other anti-cancer therapies).

OBJECTS AND SUMMARY OF THE DISCLOSURE

The inventors of the present disclosure have surprisingly found that a CBP/p300 bromodomain inhibitor, i.e. a bromodomain inhibitor selectively binding to the bromodomain of CBP/p300, provides an effective treatment of cancer exhibiting an oncogenic alteration in the KRAS if administered in combination with a KRAS inhibitor, while the CBP/p300 bromodomain inhibitor does not affect the cell proliferation of the cancer cells if administered alone. In other words, the inventors have surprisingly found that the combination of a CBP/p300 bromodomain inhibitor and a KRAS inhibitor is more effective in treating cancer exhibiting an oncogenic alteration in the KRAS compared to the effect that either of the two actives exhibits on its own on the cancer exhibiting an oncogenic alteration in the KRAS. Thus, as noted above, the CBP/p300 bromodomain inhibitor has no effect when given alone (where “no effect” in particular means that there are no objective responses as defined by the RECIST 1.1 response criteria for target lesions or non-target lesions in a subject) while the effect of the KRAS inhibitor when given alone decreases over time, likely due to the development of resistance against the KRAS inhibitor.

In one aspect, there is provided a use of a combination of (i) a CBP/p300 bromodomain inhibitor and (ii) a KRAS inhibitor for the manufacture of a medicament for the treatment of a patient suffering from cancer, wherein the cancer exhibits an oncogenic alteration in the KRAS.

In the first example, the present disclosure is directed to a combination of (i) a CBP/p300 bromodomain inhibitor and (ii) a KRAS inhibitor for use in the treatment of a patient suffering from cancer, wherein the cancer exhibits an oncogenic alteration in the KRAS. The first example may also be referred to as a combination of (i) a CBP/p300 bromodomain inhibitor and (ii) a KRAS inhibitor for use in the treatment of a patient suffering from cancer, wherein the cancer is characterized by the KRAS-mutational profile given in the one or more indications of the label of the KRAS inhibitor used in the combination (such as e.g. KRAS G12C) or wherein the cancer is characterized by the KRAS-mutational profile targeted in the clinical trial setting by the KRAS inhibitor used in the combination (such as e.g. KRAS G12C).

In a preferred example of the first example, the oncogenic alteration in the KRAS results in overactivation of KRAS signalling. The oncogenic alteration in the KRAS may even result in constitutively active KRAS signalling (in the meaning that the signaling activity of the GTP-bound KRAS is constitutively active).

In a further preferred example of the first example, the oncogenic alteration in the KRAS is caused by at least one base mutation in the KRAS gene resulting in an amino acid substitution in the KRAS selected from the group consisting of G12C, G12V, G12D, G13D,

Q61H, Q61L, Q61R, K117N and combinations thereof. It can be preferred that the oncogenic alteration is caused by at least one base mutation in the KRAS gene resulting in an amino acid substitution in the KRAS selected from the group consisting of G12C, G12V and G12D. It is most preferred that the onco-

genic alteration in the KRAS is caused by at least one base mutation in the KRAS gene resulting in the amino acid substitution G12C in the KRAS.

In another example of the first example, the cancer is selected from the group consisting of lung cancer, colorectal cancer and pancreatic cancer. The lung cancer is preferably non-small cell lung cancer (NSCLC) and may be locally advanced or metastatic NSCLC, most preferably KRAS G12C-mutated locally advanced or metastatic NSCLC (which may, in the language as used herein, be alternatively formulated as the treatment of a patient suffering from NSCLC, optionally locally advanced or metastatic NSCLC, wherein the NSCLC exhibits the oncogenic alteration G12C in the KRAS).

In another example of the first example, the CBP/p300 bromodomain inhibitor is a small molecule inhibitor. Thus, in such an example, the CBP/p300 bromodomain inhibitor is not a nucleic acid-based inhibitor, such as e.g. a shRNA or RNAi directed to CBP and/or p300.

In another example of the first example, the KRAS inhibitor is a small molecule inhibitor. Thus, in such an example, the KRAS inhibitor is not a nucleic acid-based inhibitor, such as e.g. a shRNA or RNAi directed to KRAS. In a further example of the first example, the KRAS inhibitor is targeted to KRAS G12C, i.e. targeted to treat a cancer that exhibits the oncogenic alteration G12C in the KRAS. Such an inhibitor may in particular be a covalent inhibitor, which targets the cysteine at position 12 present in the G12C KRAS through covalent interactions.

The CBP/p300 bromodomain inhibitor may be selected from the group consisting of Compound A, Compound C, Compound 00030, Compound 00071, CCS1477, GNE-781, GNE-049, SGC-CBP30, CPI-637, FT-6876, Compound 462, Compound 424 and Compound 515. These compounds are either commercially available or publicly disclosed as outlined further below, or their synthesis and structures are shown in the examples of the present application. It can be preferred that the CBP/p300 bromodomain inhibitor is selected from the group consisting of Compound A, Compound C, CCS1477, GNE-781, GNE-049, CPI-637, Compound 462, Compound 424 and Compound 515.

The KRAS inhibitor may be selected from the group consisting of AMG510, MRTX849, JNJ-74699157/ARS-3248, BI 1701963, BI 1823911, BAY-293, GDC-6036, MRTX1133, a RAS(ON) inhibitor (wherein the RAS(ON) inhibitor is preferably RMC-6291 or RMC-6236), and combinations thereof. In a more preferred example, the KRAS inhibitor is AMG510 or MRTX849. It can be most preferred that the KRAS inhibitor is AMG510.

It needs to be understood that the combination of (i) and (ii) as referred to herein can be an open or a closed combination. Thus, the present combination of (i) and (ii) may be for use in the treatment of a patient suffering from cancer, wherein the cancer exhibits an oncogenic alteration in the KRAS, and wherein (i) and (ii) are the sole active agents (a “closed” combination). How

ever, the combination of (i) and (ii) may alternatively be for use in the treatment of a patient suffering from cancer, wherein the cancer exhibits an oncogenic alteration in the KRAS, and wherein at

least one additional active agent (iii) may be administered, such as e.g. an active agent (iii) selected from the group consisting of a PD1 inhibitor, a MEK inhibitor, an SHP2 allosteric inhibitor, a Pan-ErbB tyrosine kinase inhibitor, a PD-L1 inhibitor, an EGFR inhibitor, a chemotherapeutic regimen drug, an mTOR inhibitor, a CDK inhibitor, a VEGF inhibitor, pembrolizumab, cetuximab, atezolizumab, bevacizumab, and combinations of any of the foregoing (an “open” combination).

In a preferred example of the first example, the combination is administered to the patient during each treatment cycle.

In another example of the first example, the CBP/p300 bromodomain inhibitor and the KRAS inhibitor are administered as separate dosage forms or comprised in a single dosage form. If the CBP/p300 bromodomain inhibitor and the KRAS inhibitor are administered as separate dosage forms, the administration during each treatment cycle may be concomitantly or sequentially. This includes the option that the CBP/p300 bromodomain inhibitor is administered first, followed by the administration of the KRAS inhibitor.

In yet another example of the first example, the treatment results in an extended duration of the therapeutic effect of the KRAS inhibitor compared to the duration of the therapeutic effect of the KRAS inhibitor when administered as the sole active agent. In still another example, the treatment results in an increased therapeutic efficacy of the KRAS inhibitor compared to the therapeutic efficacy of the KRAS inhibitor when administered as the sole active agent. In another example, the treatment results in the prevention of resistance to the KRAS inhibitor.

In another example of the first example, the CBP/p300 bromodomain inhibitor is administered at a daily amount of between about 1 mg and about 3000 mg, preferably of between about 10 mg and about 2000 mg, more preferably of between about 15 mg and about 1000 mg. It can be preferred to administer the CBP/p300 bromodomain inhibitor at a daily amount of about 10 mg, about 15 mg, about 20 mg, about 50 mg, about 100 mg, about 250 mg, about 500 mg, about 1000 mg, about 1500 mg, about 2000 mg, about 2500 mg, or about 3000 mg. The administration may take place intermittently, i.e. not every day, but on a day the administration takes place, the afore-mentioned daily amount may be administered. If CCS1477, Compound 462, Compound 424 or Compound 515 is used as CBP/p300 bromodomain inhibitor, the respective compound may be administered at a daily amount of between about 10 mg and about 600 mg.

In another example of the first example, the KRAS inhibitor is administered at a daily amount that is in the range of a typical daily amount (in particular the daily amount mentioned for the KRAS inhibitor in the label, if available) if the KRAS inhibitor is administered as the sole active agent. The typical daily amount (or the indicated daily amount, if available) depends on the specific KRAS inhibitor that will be used. Typically, a KRAS inhibitor will be administered at a daily amount of between about 10 mg and about 2000 mg. Thus, AMG510 may e.g. be administered in the combination for use of the present disclosure at a daily amount of between about 240 mg and about 1200 mg, about 480 mg and about 1200 mg, or

about 600 mg to about 1200 mg, preferably of between about 720 mg to about 1080 mg, more preferably of between about 840

mg and about 960 mg or about 960 mg. MRTX849 may e.g. be administered in the combination for use of the present disclosure at a daily amount of between about 200 mg and about 1400 mg, or about 400 mg and about 1300 mg, preferably of between about 600 mg and about 1200 mg, most preferably at about 1200 mg.

In another example of the first example, the KRAS inhibitor is administered at a daily amount that is lower than the above-mentioned typical daily amount if the KRAS inhibitor is administered as the sole active agent. In other words, if a KRAS inhibitor is not administered as the sole active agent but in the combination for use according to the present disclosure, the KRAS inhibitor may be administered at a lower amount than the amount used when the KRAS inhibitor is administered as the sole active agent. This e.g. means for the examples given above that the daily amount would be at the lower ends of the ranges given or even below these ranges.

In yet another example of the first example, the present disclosure is directed to a combination of (i) a CBP/p300 bromodomain inhibitor and (ii) a KRAS G12D inhibitor (preferably MRTX1133) for use in the treatment of a patient suffering from cancer, wherein the cancer exhibits the oncogenic alteration G12D in the KRAS. It can further be preferred in this example that the cancer is selected from the group consisting of lung cancer, preferably NSCLC, colorectal cancer and pancreatic cancer.

In a highly preferred example of the first example, the present disclosure is directed to a combination of (i) a CBP/p300 bromodomain inhibitor and (ii) a KRAS G12C inhibitor for use in the treatment of a patient suffering from cancer, wherein the cancer exhibits the oncogenic alteration G12C in the KRAS. It can further be preferred in this example that the cancer is selected from the group consisting of lung cancer, preferably NSCLC, colorectal cancer and pancreatic cancer. Lung cancer may be preferred. It can also be preferred that the KRAS G12C inhibitor is selected from the group consisting of AMG510, MRTX849, JNJ-74699157/ARS-3248, BI 1823911, GDC-6036, a RAS^{G12C}(ON) inhibitor (wherein the RAS^{G12C}(ON) inhibitor is preferably RMC-6291), and combinations thereof; preferably wherein the KRAS G12C inhibitor is AMG510 or MRTX849.

In another preferred example of the first example, the present disclosure is directed to a combination of (i) a CBP/p300 bromodomain inhibitor and (ii) a KRAS G12C inhibitor, preferably AMG510 or MRTX849, for use in the treatment of a patient suffering from locally advanced or metastatic NSCLC, who has received at least one prior systemic therapy, wherein the NSCLC exhibits the oncogenic alteration G12C in the KRAS.

In yet a further example of the first example, the present disclosure is directed to a combination of (i) Compound A and (ii) a KRAS inhibitor for use in the treatment of a patient suffering from cancer, wherein the cancer exhibits an oncogenic alteration in the KRAS. It can be preferred in this example that the KRAS inhibitor is a KRAS G12C inhibitor, preferably AMG510 or MRTX849, and that the cancer exhibits the oncogenic al

teration G12C in the KRAS. It can further be preferred in this example that the cancer is selected from the group consisting of lung cancer, preferably NSCLC, colorectal cancer and pancreatic cancer.

In yet a further example of the first example, the present disclosure is directed to a combination of (i) Compound C and (ii) a KRAS inhibitor for use in the treatment of a patient suffering from cancer, wherein the cancer exhibits an oncogenic alteration in the KRAS. It can be preferred in this example that the KRAS inhibitor is a KRAS G12C inhibitor, preferably AMG510 or MRTX849, and that the cancer exhibits the oncogenic alteration G12C in the KRAS. It can further be preferred in this example that the cancer is selected from the group consisting of lung cancer, preferably NSCLC, colorectal cancer and pancreatic cancer.

In yet a further example of the first example, the present disclosure is directed to a combination of (i) CCS1477 and (ii) a KRAS inhibitor for use in the treatment of a patient suffering from cancer, wherein the cancer exhibits an oncogenic alteration in the KRAS. It can be preferred in this example that the KRAS inhibitor is a KRAS G12C inhibitor, preferably AMG510 or MRTX849, and that the cancer exhibits the oncogenic alteration G12C in the KRAS. It can further be preferred in this example that the cancer is selected from the group consisting of lung cancer, preferably NSCLC, colorectal cancer and pancreatic cancer.

In yet a further example of the first example, the present disclosure is directed to a combination of (i) GNE-781 or GNE-049 and (ii) a KRAS inhibitor for use in the treatment of a patient suffering from cancer, wherein the cancer exhibits an oncogenic alteration in the KRAS. It can be preferred in this example that the KRAS inhibitor is a KRAS G12C inhibitor, preferably AMG510 or MRTX849, and that the cancer exhibits the oncogenic alteration G12C in the KRAS. It can further be preferred in this example that the cancer is selected from the group consisting of lung cancer, preferably NSCLC, colorectal cancer and pancreatic cancer.

In yet a further example of the first example, the present disclosure is directed to a combination of (i) CPI-637 and (ii) a KRAS inhibitor for use in the treatment of a patient suffering from cancer, wherein the cancer exhibits an oncogenic alteration in the KRAS. It can be preferred in this example that the KRAS inhibitor is a KRAS G12C inhibitor, preferably AMG510 or MRTX849, and that the cancer exhibits the oncogenic alteration G12C in the KRAS. It can further be preferred in this example that the cancer is selected from the group consisting of lung cancer, preferably NSCLC, colorectal cancer and pancreatic cancer.

In yet a further example of the first example, the present disclosure is directed to a combination of (i) Compound 462 or Compound 424 or Compound 515 and (ii) a KRAS inhibitor for use in the treatment of a patient suffering from cancer, wherein the cancer exhibits an oncogenic alteration in the KRAS. It can be preferred in this example that the KRAS inhibitor is a KRAS G12C inhibitor, preferably AMG510 or MRTX849, and that the cancer exhibits the oncogenic alteration G12C in the KRAS. It can further be preferred in this example that the cancer is selected from the group consisting of lung cancer, preferably NSCLC, colorectal cancer and pancreatic cancer.

In an especially preferred example of the first example, the present disclosure is directed to a combination of (i) a CBP/p300 bromodomain inhibitor, wherein the CBP/p300 bromodomain in-

hibitor is a small molecule inhibitor, and (ii) a KRAS inhibitor, wherein the KRAS inhibitor is a KRAS G12C small molecule inhibitor (preferably selected from the group consisting of AMG510, MRTX849, JNJ-74699157/ARS-3248, BI 1823911, GDC-6036, a RAS^{G12C}(ON) inhibitor [preferably RMC-6291] and combinations thereof, most preferably AMG510 or MRTX849), for use in the treatment of a patient suffering from cancer, wherein the cancer exhibits the oncogenic alteration G12C in the KRAS. It can further be preferred in this example that the cancer is selected from the group consisting of lung cancer, preferably NSCLC, colorectal cancer and pancreatic cancer.

In another aspect, the present disclosure is concerned with a kit comprising (i) a pharmaceutical dosage form comprising a CBP/p300 bromodomain inhibitor and (ii) a pharmaceutical dosage form comprising a KRAS inhibitor.

The pharmaceutical dosage forms (i) and (ii) may be oral dosage forms, such as e.g. tablets. The amount of the CBP/p300 bromodomain inhibitor comprised in the dosage form preferably fits with the daily amount to be administered as stated above in the first example. Thus, the amount of the CBP/p300 bromodomain inhibitor in the dosage form may be the complete daily amount if administered once daily. However, it may also be less than the daily amount, e.g. half the daily amount, if administered twice daily or administered once daily via two tables. The amount of the KRAS inhibitor comprised in the dosage form preferably fits with the daily amount to be administered as stated above in the first example. Thus, the amount of the KRAS inhibitor in the dosage form may be the complete daily amount if administered once daily. However, it may also be less than the daily amount, e.g. half the daily amount, if administered twice daily or administered once daily via two tables. For AMG510, the amount can in particular be 120 mg, wherein the dosage form preferably corresponds to a tablet.

Each pharmaceutical dosage form typically contains at least one pharmaceutically acceptable excipient as defined in section 3 below.

In a preferred example of the second example, the CBP/p300 bromodomain inhibitor is selected from the group consisting of Compound A, Compound C, Compound 00030, Compound 00071, CCS1477, GNE-781, GNE-049, SGC-CBP30, CPI-637, FT-6876, Compound 462, Compound 424 and Compound 515.

In another preferred example of the second example, the KRAS inhibitor is selected from the group consisting of AMG510, MRTX849, JNJ-74699157/ARS-3248, BI 1701963, BI 1823911, BAY-293, GDC-6036, MRTX1133, a RAS(ON) inhibitor (preferably RMC-6291 or RMC-6236), and combinations thereof.

In yet another preferred example of the second example, the kit comprises (i) a pharmaceutical dosage form comprising a CBP/p300 bromodomain inhibitor and (ii) a pharmaceutical dosage form comprising AMG510 or MRTX849.

In another aspect, the present disclosure is concerned with a pharmaceutical dosage form comprising (i) a CBP/p300 bromodomain inhibitor and (ii) a KRAS inhibitor.

The pharmaceutical dosage form may be an oral dosage form, such as e.g. a tablet. The amount of the CBP/p300 bromodomain inhibitor comprised in the dosage form preferably fits with the daily amount to be administered as stated above in the first example. Thus, the amount of the CBP/p300 bromodomain inhibitor in the dosage form may be the complete daily amount if administered once daily. However, it may also be less than the daily amount, e.g. half the daily amount, if administered twice daily or administered once daily via two tables. The amount of the KRAS inhibitor comprised in the dosage form preferably fits with the daily amount to be administered as stated above in the first example. Thus, the amount of the KRAS inhibitor in the dosage form may be the complete daily amount if administered once daily. However, it may also be less than the daily amount, e.g. half the daily amount, if administered twice daily or administered once daily via two tables. For AMG510, the amount can in particular be 120 mg, wherein the dosage form preferably corresponds to a tablet.

The pharmaceutical dosage form typically contains at least one pharmaceutically acceptable excipient as defined in section 3 below.

In a preferred example of the third example, the CBP/p300 bromodomain inhibitor is selected from the group consisting of Compound A, Compound C, Compound 00030, Compound 00071, CCS1477, GNE-781, GNE-049, SGC-CBP30, CPI-637, FT-6876, Compound 462, Compound 424 and Compound 515.

In another preferred example of the third example, the KRAS inhibitor is selected from the group consisting of AMG510, MRTX849, JNJ-74699157/ARS-3248, BI 1701963, BI 1823911, BAY-293, GDC-6036, MRTX1133, a RAS(ON) inhibitor (preferably RMC-6291 or RMC-6236), and combinations thereof.

In yet another preferred example of the third example, the pharmaceutical dosage form comprises (i) a CBP/p300 bromodomain inhibitor and (ii) AMG510 or MRTX849.

In a fourth example, the present disclosure is directed to a method of treating cancer in a patient in need thereof, said method comprising administering to the patient an effective amount of (i) a CBP/p300 bromodomain inhibitor and an effective amount of (ii) a KRAS inhibitor, wherein the cancer exhibits an oncogenic alteration in the KRAS.

In a fifth example, the present disclosure is directed to a method of extending the duration of the therapeutic effect of a KRAS inhibitor in a patient in need thereof, said method comprising administering to the patient an effective amount of (i) a CBP/p300 bromodomain inhibitor and an effective amount of (ii) the KRAS inhibitor, wherein the cancer exhibits an oncogenic alteration in the KRAS. In other words, the duration of the therapeutic effect of the KRAS inhibitor (when ad-

ministered in the combination) is extended compared to the duration of the therapeutic effect of the KRAS inhibitior when administered as the sole active agent in cancer treatment.

In a sixth example, the present disclosure is directed to a method of increasing the therapeutic efficacy of a KRAS inhibitor in a patient in need thereof, said method comprising administering to the patient an effective amount of (i) a CBP/p300 bromodomain inhibitor and an effective amount of (ii) the KRAS inhibitor, wherein the cancer exhibits an oncogenic alteration in the KRAS. In other words, the therapeutic efficacy of the KRAS inhibitor (when administered in the combination) is increased compared to the therapeutic efficacy of the KRAS inhibitor when administered as the sole active agent in cancer treatment.

In a seventh example, the present disclosure is directed to a method of blocking proliferation of a cancer cell, said method comprising administering to the cell an effective amount of (i) a CBP/p300 bromodomain inhibitor and an effective amount of (ii) a KRAS inhibitor, wherein the cancer cell exhibits an oncogenic alteration in the KRAS.

In an eight example, the present disclosure is directed to a method of retarding the proliferation of a cancer cell, said method comprising administering to the cell an effective amount of (i) a CBP/p300 bromodomain inhibitor and an effective amount of (ii) a KRAS inhibitor, wherein the cancer cell exhibits an oncogenic alteration in the KRAS.

The examples outlined above for the first example equally apply for the methods of the fourth to eight examples.

DESCRIPTION OF THE FIGURES

FIG. 1: The initial Fo-Fc difference electron density map of the model (contoured at 4.0 σ) resulting from refinement of the initial model prior to modelling of the compound with REFMAC5, in the determination of the crystal structure of the bromodomain of human CREBBP in complex with compound 00004.

FIG. 2A-E: SNU-1411 confluency over 32 days, wherein the cells were treated as indicated, namely either with DMSO (control), or AMG510 alone or any of the different CBP/p300 bromodomain inhibitors alone, or with a combination of (i) AMG510 and (ii) any of the different CBP/p300 bromodomain inhibitors. Details can be found in example 6.

FIG. 3A-E: SNU-1411 confluency over 32 days, wherein the cells were treated as indicated, namely either with DMSO (control), or MRTX849 alone or any of the different CBP/p300 bromodomain inhibitors alone, or with a combination of (i) MRTX849 and (ii) any of the different CBP/p300 bromodomain inhibitors. Details can be found in example 7.

FIG 4A-E: SW837 confluency over 49 days, wherein the cells were treated as indicated, namely either with DMSO (control), or AMG510 alone or any of the different CBP/p300 bromodomain in-

Claims

1. Use of a combination of (i) a CBP/p300 bromodomain inhibitor and (ii) a KRAS inhibitor for the manufacture of a medicament for the treatment of a patient suffering from cancer, wherein the cancer exhibits an oncogenic alteration in the KRAS.

2. The use of a combination according to claim 1, wherein the oncogenic alteration in the KRAS results in overactivation of KRAS signalling.

3. The use of a combination according to claim 1 or 2, wherein the oncogenic alteration is caused by at least one base mutation in the KRAS gene resulting in an amino acid substitution in the KRAS selected from the group consisting of G12C, G12V, G12D, G13D, Q61H, Q61L, Q61R, K117N and combinations thereof.

4. The use of a combination according to any one of the preceding claims, wherein the CBP/p300 bromodomain inhibitor is selected from the group consisting of Compound A, Compound C, Compound 00030, Compound 00071, CCS1477, GNE-781, GNE-049, SGC-CBP30, CPI-637, FT-6876, Compound 462, Compound 424 and Compound 515.

5. The use of a combination according to any one of the preceding claims, wherein the KRAS inhibitor is selected from the group consisting of AMG510, MRTX849, JNJ-74699157/ARS-3248, BI 1701963, BI 1823911, BAY-293, GDC-6036, MRTX1133, a RAS(ON) inhibitor, and combinations thereof.

6. The use of a combination according to any one of claims 1 to 4, wherein the oncogenic alteration is caused by at least one base mutation in the KRAS gene resulting in the amino acid substitution G12C in the KRAS.

7. The use of a combination according to any one of claims 1 to 4, wherein the oncogenic alteration is caused by at least one base mutation in the KRAS gene resulting in the amino acid substitution G12C in the KRAS and the KRAS inhibitor is a KRAS G12C inhibitor.

8. The use of a combination according to any one of the preceding claims, wherein the cancer is selected from the group consisting of lung cancer, colorectal cancer and pancreatic cancer.

9. The use of a combination according to any one of the preceding claims, wherein the combination is to be administered to the patient during each treatment cycle.

10. The use of a combination according to any one of the preceding claims, wherein (i) and (ii) are to be administered as separate dosage forms or comprised in a single dosage form.

11. The use of a combination according to claim 10, wherein if (i) and (ii) are to be administered as separate dosage forms, they are to be administered during each treatment cycle concomitantly or sequentially.

12. The use of a combination according to any one of the preceding claims, wherein the treatment results in an extended duration of the therapeutic effect compared to the duration of the therapeutic effect of the KRAS inhibitor when administered as the sole active agent.

13. The use of a combination according to any one of claims 1 to 11, wherein the treatment results in an increased therapeutic efficacy compared to the therapeutic efficacy of the KRAS inhibitor when administered as the sole active agent.

14. The use of a combination according to any one of claims 1 to 11, wherein the treatment results in the prevention of resistance to the KRAS inhibitor.

15. A kit comprising (i) a pharmaceutical dosage form comprising a CBP/p300 bromodomain inhibitor and (ii) a pharmaceutical dosage form comprising a KRAS inhibitor.

16. A pharmaceutical dosage form comprising (i) a CBP/p300 bromodomain inhibitor and (ii) a KRAS inhibitor.

17. The kit according to claim 15 or the pharmaceutical dosage form according to claim 16, wherein the CBP/p300 bromodomain inhibitor is selected from the group consisting of Compound A, Compound C, Compound 00030, Compound 00071, CCS1477, GNE-781, GNE-049, SGC-CBP30, CPI-637, FT-6876, Compound 462, Compound 424 and Compound 515.

18. The kit according to claim 15 or 17, or the pharmaceutical dosage form according to claim 16 or 17, wherein the KRAS inhibitor is selected from the group consisting of the KRAS inhibitor is selected from the group consisting of AMG510, MRTX849, JNJ-74699157/ARS-3248, BI 1701963, BI 1823911, BAY-293, GDC-6036, MRTX1133, a RAS(ON) inhibitor, and combinations thereof.