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, 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.

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-

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, wherein the KRAS inhibitor is a KRAS G12C 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, wherein the KRAS inhibitor is a KRAS G12C 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.

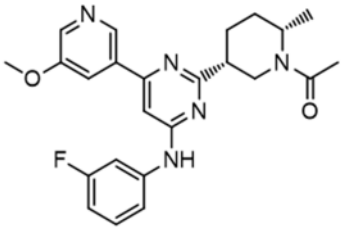
In a fifth example, the present disclosure is directed to a method of extending the duration of the therapeutic effect of a KRAS inhibitor in a patient in need thereof, said method comprising administering to the patient an effective amount of (i) a CBP/p300 bromodomain inhibitor and an effective amount 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-

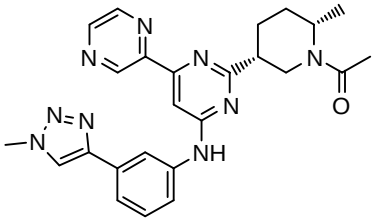
**Claims**

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, 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.

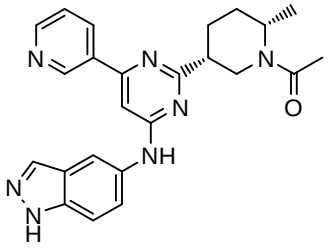
2. The use of a combination according to claim 1, wherein the oncogenic alteration in the KRAS results in overactivation of KRAS signalling.

3. The use of a combination according to claim 1 or 2, wherein the CBP/p300 bromodomain inhibitor is selected from the group consisting of

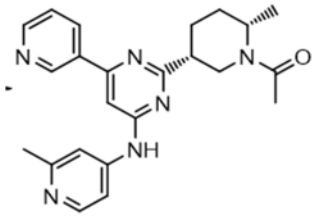




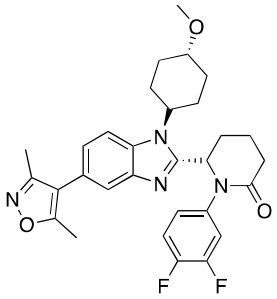
(Compound A),



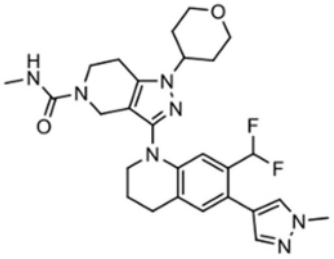
(Compound C),



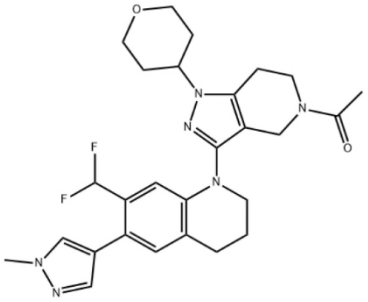
(Compound 00030),



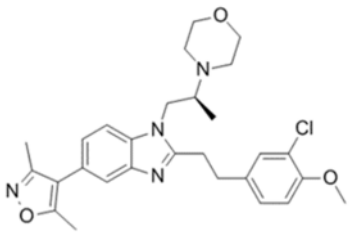
(Compound 00071),



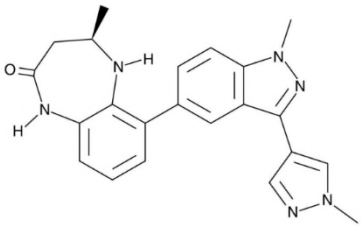
(CCS1477),

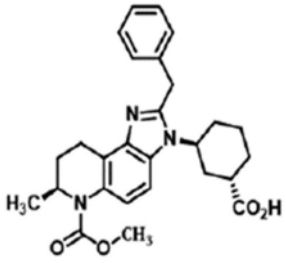


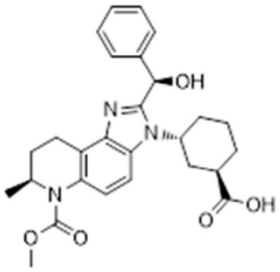
(GNE-781),

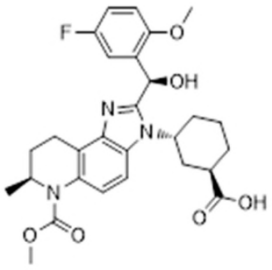


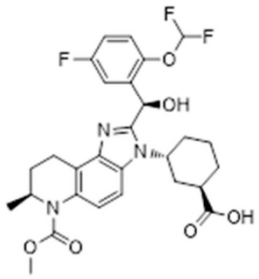
(GNE-049), (SGC-CBP30),



(CPI-637),  (FT-6876),

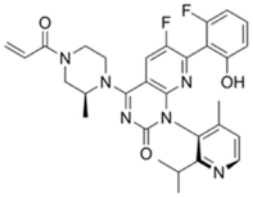


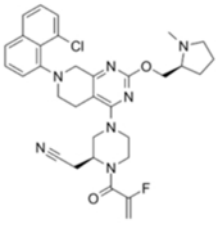
(Compound 462),  (Compound 424) and



(Compound 515).

4. 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), and (MRTX849) and combinations thereof.

5. 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.

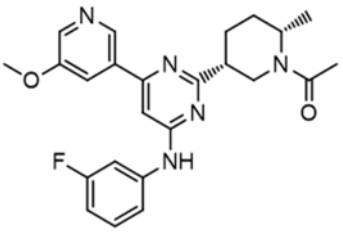
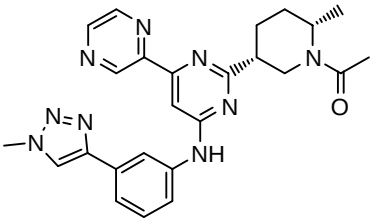
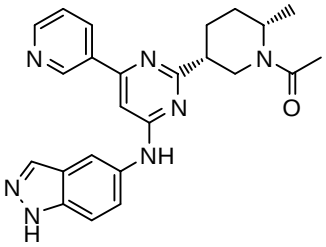
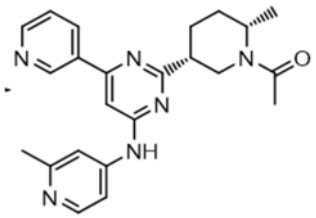
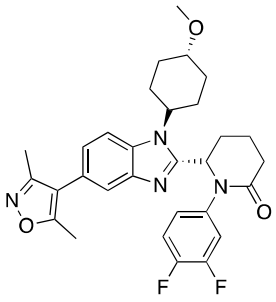
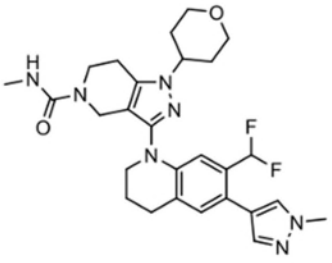
6. The use of a combination according to any one of the preceding claims, wherein the combination is to be administered to the patient during each treatment cycle.

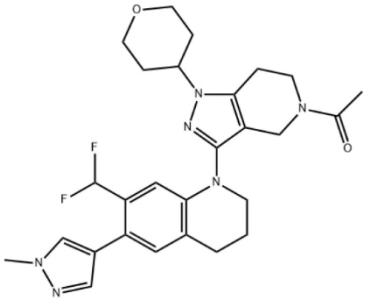
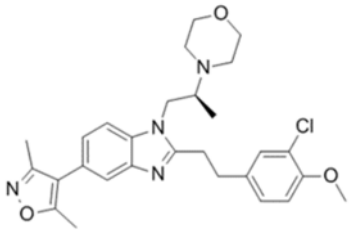
7. The use of a combination according to any one of the preceding claims, wherein (i) and (ii) are to be administered as separate dosage forms or comprised in a single dosage form.

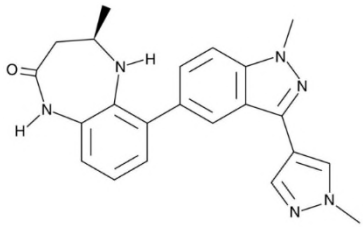
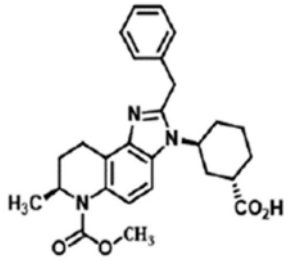
8. The use of a combination according to claim 6, wherein if (i) and (ii) are to be administered as separate dosage forms, they are to be administered during each treatment cycle concomitantly or sequentially.

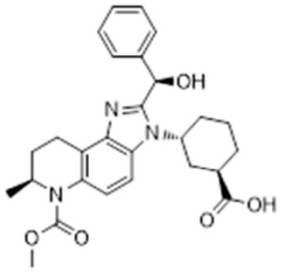
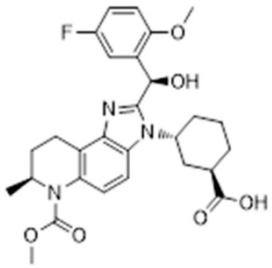
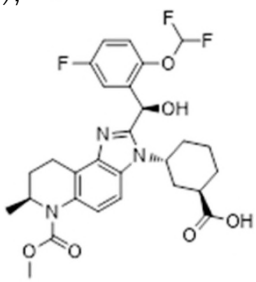
9. A kit comprising (i) a pharmaceutical dosage form comprising a CBP/p300 bromodomain inhibitor and (ii) a pharmaceutical dosage form comprising a KRAS inhibitor, wherein the KRAS inhibitor is a KRAS G12C inhibitor.

10. A pharmaceutical dosage form comprising (i) a CBP/p300 bromodomain inhibitor and (ii) a KRAS inhibitor, wherein the KRAS inhibitor is a KRAS G12C inhibitor.

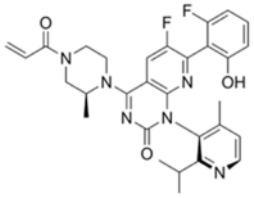
11. The kit according to claim 9 or the pharmaceutical dosage form according to claim 10, wherein the CBP/p300 bromodomain inhibitor is selected from the group consisting of  (Compound A),  (Compound C),  (Compound 00030),  (Compound 00071),  (CCS1477), 

(GNE-781),  (GNE-049), 

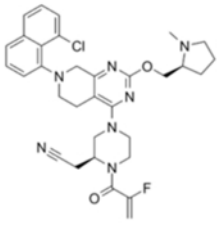
(SGC-CBP30),  (CPI-637), 

(FT-6876),  (Compound 462),  (Compound 424) and  (Compound 515).

12. The kit according to claim 9 or 11, or the pharmaceutical dosage form according to claim 10 or 11, wherein the KRAS inhibitor is selected from the group consisting of



the KRAS inhibitor is selected from the group consisting of



(AMG510), and (MRTX849) and combinations thereof.