for transcription of different genes (see Dyson and Wright, JBC Vo. 291, no. 13, pp. 6714-6722, Figure 2).

One of the multiple domains of CBP/p300 is the bromodomain. The bromodomain as such was first identified in *Drosophila* in 1992 and described to be a binding module to acetyl-lysine about 10 years later. In humans, there are many bromodomain-containing proteins that may be classified into eight groups based on sequence and structural similarities. It seems that all bromodomain-containing proteins are involved in the regulation of transcriptional programs. Oncogenic rearrangements suggest that targeting bromodomain-containing proteins and more particularly their bromodomains might be beneficial in particular in the treatment of cancer.

For this reason, several drug candidates have been developed that are presently undergoing clinical testing, which target so-called “bromodomain and extra-terminal motif” proteins, typically referred to as BET-proteins, which constitute one group of bromodomain-containing proteins. Examples of BET-protein targeting drugs are INCB054329 (Incyte Corporation), ABBV-075 (AbbVie) and I-BET762 (GlaxoSmithKline). There are also drugs that selectively target the bromodomain of CBP and p300, which are part of a separate group of bromodomain-containing proteins. Such inhibitors include e.g. CCS1477 (CellCentric) which is presently undergoing clinical studies for the treatment of metastatic castration resistant prostate cancer and haematological malignancies or FT-7051 (Forma Therapeutics Inc.) which is presently undergoing studies for the treatment of metastatic castration resistant prostate cancer.

In view of the results by Hou et al. discussed above, there is the need to further elucidate the role of p300 and in particular its different domains in NSCLC in order to provide an effective NSCLC treatment.

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 NSCLC exhibiting an oncogenic alteration in the EGFR if administered in combination with an EGFR inhibitor, while the CBP/p300 bromodomain inhibitor does not affect the cell proliferation of NSCLC cells if administered alone. In other words, the inventors have surprisingly found that the combination of a CBP/p300 bromodomain inhibitor and an EGFR inhibitor is more effective in treating NSCLC exhibiting an oncogenic alteration in the EGFR compared to the effect that either of the two actives exhibits on its own on the NSCLC exhibiting an oncogenic alteration in the EGFR. 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 EGFR inhibitor when given alone decreases over time, likely due to the development of resistance against the EGFR inhibitor.

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

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

In a preferred example of the first example, the oncogenic alteration in the EGFR results in overactivation of the EGFR. The oncogenic alteration in the EGFR may even result in constitutively active EGFR (in the meaning that the enzymatic activity of the EGFR, namely the protein-kinase activity, is constitutively active).

In a further preferred example of the first example, the oncogenic alteration in the EGFR is caused by a deletion and/or insertion in exon 18 or in exon 19 or in exon 20 of the EGFR gene; a kinase domain duplication in the EGFR gene; an amplification of the EGFR gene; at least one base mutation in the EGFR gene resulting in an amino acid substitution in the EGFR selected from the group consisting of L858R, G719S, G719A, G719C, V765A, T783A, S768I, S768V, L861Q, E709X, L819Q, A750P and combinations thereof; and combinations of any of the foregoing. It can be preferred that the oncogenic alteration is caused by a deletion in exon 19 of the EGFR gene; an insertion in exon 20 of the EGFR gene; at least one base mutation in the EGFR gene resulting in an amino acid substitution in the EGFR selected from the group consisting of L858R, G719S, G719A, G719C, V765A, T783A, S768I, S768V, L861Q, E709X, L819Q, A750P and combinations thereof; and combinations of any of the foregoing. It can also be preferred that the oncogenic alteration is caused by a deletion in exon 19 of the EGFR gene; at least one base mutation in the EGFR gene resulting in the amino acid substitution L858R in the EGFR; and combinations thereof. A deletion and insertion in exon 18 of the EGFR gene is in particular a deletion resulting in the deletion of E709-T710 in the EGFR and an insertion of D at this position in the EGFR. A deletion in exon 19 of the EGFR gene is in particular a deletion resulting in the deletion of E746-A750 or L747-E749 in the EGFR. A deletion and insertion in exon 19 of the EGFR is in particular a deletion resulting in the deletion of L747-A750 in the EGFR and an insertion of P at this position in the EGFR or a deletion resulting in the deletion of L747-T751 in the EGFR and an insertion of S at this position in the EGFR. An insertion in exon 20 of the EGFR gene is in particular an insertion resulting in the insertion of an amino acid (in the meaning of any amino acid or X) at a position in the EGFR between two amino acids selected from the group consisting of D761-E762, A763-Y764, Y764-V765, A767-S768, S768-V769, V769-D770, D770-N771, N771-P772, P772-H773, H773-V774, V774-C775, V765-M766, and combinations thereof. It can be most preferred that the oncogenic alteration is caused by a deletion in exon 19 of the EGFR gene (in particular a deletion resulting in the deletion of E746-A750 or L747-

E749 in the EGFR); at least one base mutation in the EGFR gene resulting in the amino acid substitution L858R or A750P in the EGFR; and combinations thereof. It can also be very preferred that the oncogenic alteration is caused by a deletion in exon 19 of the EGFR gene or at least one base mutation in the EGFR gene resulting in the amino

acid substitution L858R in the EGFR. When reference is made herein to “X” as an amino acid, “X” indicates any amino acid (but of course an amino acid differing from the wild-type amino acid at the respective position, if applicable, e.g. for E709X).

In an example of the first example, the NSCLC does not additionally exhibit a resistance alteration in the EGFR. Accordingly, the combination for use of the present disclosure would be used as first-line treatment, and the EGFR inhibitor in the combination may be any EGFR inhibitor that is administered (or indicated) for treating NSCLC exhibiting an oncogenic alteration in the EGFR.

In another example of the first example, the NSCLC additionally exhibits a resistance alteration in the EGFR. The resistance alteration in the EGFR may in particular be caused by at least one base mutation in the EGFR gene resulting in an amino acid substitution in the EGFR selected from the group consisting of T790M, C797X (mainly C797S), L792X, G796X, L718Q, L718V, G724S, D761Y, V834L, T854A, and combinations thereof. It can be preferred that the resistance alteration in the EGFR is caused by at least one base mutation in the EGFR gene resulting in an amino acid substitution in the EGFR selected from the group consisting of T790M, C797X (mainly C797S), L718Q, L718V, T854A, and combinations thereof. Most preferred is that the resistance alteration in the EGFR is caused by at least one base mutation in the EGFR gene resulting in the amino acid substitution T790M in the EGFR. When reference is made herein to “X” as an amino acid, “X” indicates any amino acid (but of course an amino acid differing from the wild-type amino acid at the respective position, if applicable, e.g. for C797X).

When the NSCLC additionally exhibits a resistance alteration in the EGFR, the patient was previously treated with a (first) EGFR inhibitor that was effective initially and then became ineffective due to the development of resistance, in particular due to development of an EGFR resistance alteration. It is important to understand that in the combination for use of the present disclosure, the EGFR inhibitor in such a scenario is not the (first) EGFR inhibitor administered previously, but a (second or third) EGFR inhibitor that is initially therapeutically effective despite the at least one resistance alteration when administered alone. We refer to an “initial therapeutic effectiveness” here as it is a common observation that yet a further resistance towards this (second or third) EGFR inhibitor develops, rendering this (second or third) EGFR inhibitor ultimately also ineffective. In such a scenario, the combination for use of the present disclosure would be used as second-line or third-line treatment. To give an example, gefitinib may have been administered (alone as first-line treatment) previously to a patient suffering from NSCLC exhibiting an oncogenic alteration, with the gefitinib treatment becoming ineffective over time (typically after a period of about 10 to about 12 months) and with the finding (e.g. via a biopsy and a corresponding test in order to detect EGFR mutations) that the EGFR T790M resistance alteration developed in the tumor during the gefitinib-treatment. In such a situation, gefitinib would not be used in the combination for use of the present disclosure, but in particular osimertinib that has been shown (and is indicated) to be effective in the treatment of patients with EGFR T790M mutation-positive NSCLC, whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

Taking the above into account, the present disclosure in an example relates to the combination of (i) a CBP/p300 bromodomain inhibitor and (ii) an EGFR inhibitor for use in the treatment of a patient suffering from NSCLC, wherein the NSCLC exhibits an oncogenic alteration in the EGFR, with the proviso that, if the NSCLC additionally exhibits a resistance alteration in the EGFR due to previous administration of an EGFR inhibitor, the EGFR inhibitor of the combination is not the EGFR inhibitor previously administered but in particular an EGFR inhibitor, which is therapeutically effective despite the resistance alteration in the EGFR (namely the resistance alteration that rendered the previously administered EGFR inhibitor therapeutically ineffective). One may also refer to the combination for use according to the first example of the present disclosure with the proviso that, if the NSCLC additionally exhibits a resistance alteration in the EGFR due to previous administration of an EGFR inhibitor, the EGFR inhibitor of the combination is not the EGFR inhibitor previously administered but an EGFR inhibitor which is therapeutically effective during the first treatment cycles if administered alone despite the resistance alteration or with the proviso that, if the NSCLC additionally exhibits a resistance alteration in the EGFR due to previous administration of an EGFR inhibitor, the EGFR inhibitor of the combination is not the EGFR inhibitor previously administered but an EGFR inhibitor that is indicated for treatment of NSCLC additionally exhibiting the resistance alteration in the EGFR.

To give examples when considering two specific EGFR inhibitors (namely “X” and “the EGFR inhibitor of the combination”), the above paragraph is understood to refer in an example to the combination of (i) a CBP/p300 bromodomain inhibitor and (ii) an EGFR inhibitor for use in the treatment of a patient suffering from NSCLC, wherein the NSCLC exhibits an oncogenic alteration in the EGFR, with the proviso that, if the NSCLC additionally exhibits a resistance alteration in the EGFR due to previous administration of EGFR inhibitor X, the EGFR inhibitor of the combination is not EGFR inhibitor X. It is noted that the EGFR inhibitor of the combination is therapeutically effective despite the resistance alteration in the EGFR (namely the resistance alteration that rendered the previously administered EGFR inhibitor X therapeutically ineffective).

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 EGFR inhibitor is a small molecule inhibitor or an antibody. Thus, in such an example, the EGFR inhibitor is not a nucleic acid-based inhibitor, such as e.g. a shRNA or RNAi directed to EGFR. In yet another example of the first example, the EGFR inhibitor is a small molecule inhibitor. In a further example of the first example, the EGFR inhibitor inhibits the tyrosine kinase activity of the EGFR.

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 EGFR inhibitor may be selected from the group consisting of ABBV-321, abivertinib, afatinib, alflutinib, almonertinib, apatinib, AZD3759, brigatinib, D 0316, D 0317, D 0318, dacomitinib, DZD9008, erlotinib, FCN-411, gefitinib, icotinib, lapatinib, lazertinib, mobocertinib, nazartinib, neratinib, olafertinib, osimertinib, poziotinib, pyrotinib, rezivertinib, TAS6417, vandetanib, varlitinib, XZP-5809, amivantamab, CDP1, cetuximab, GC1118, HLX07, JMT101, M1231, necitumumab, nimotuzumab, matuzumab, panitumumab, SCT200, SI-B001, SYN004, zalutumumab, and combinations thereof. The EGFR inhibitor may also be selected from the group consisting of cetuximab, panitumumab, zalutumumab, nimotuzumab, matuzumab, gefitinib, erlotinib, lapatinib, neratinib, vandetanib, necitumumab, osimertinib, afatinib, dacomitinib, brigatinib, poziotinib, and combinations thereof. In a preferred example, the EGFR inhibitor is selected from the group consisting of abivertinib, afatinib, alflutinib, almonertinib, apatinib, AZD3759, brigatinib, D 0316, D 0317, D 0318, dacomitinib, DZD9008, erlotinib, FCN-411, gefitinib, icotinib, lapatinib, lazertinib, mobocertinib, nazartinib, neratinib, olafertinib, osimertinib, poziotinib, pyrotinib, rezivertinib, TAS6417, vandetanib, varlitinib, XZP-5809, and combinations thereof. In a more preferred example, the EGFR inhibitor is gefitinib or osimertinib. It can be most preferred that the EGFR inhibitor is osimertinib.

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

In still another example of the first example, the EGFR inhibitor is administered as sole active agent during the first treatment cycle, followed by the additional administration of the CBP/p300 bromodomain inhibitor during the later treatment cycle, wherein a resistance alteration in the EGFR has not yet developed in response to the administration of the EGFR inhibitor alone during the first treatment cycle (i.e. prior to the administration of the combination of the present disclosure). As noted above, the development of a resistance alteration can be assessed e.g. via a biopsy and a corresponding test in order to detect EGFR mutations. Since the development of a resistance may be prevented when using the combination for use according to the present disclosure, the administration of the combination during each treatment cycle is preferred.

In another example of the first example, the CBP/p300 bromodomain inhibitor and the EGFR inhibitor are administered as separate dosage forms or comprised in a single dosage form. If the CBP/p300 bromodomain inhibitor and the EGFR 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 EGFR inhibitor.

In yet another example of the first example, the treatment results in an extended duration of the therapeutic effect of the EGFR inhibitor compared to the duration of the therapeutic effect of

the EGFR inhibitor when administered as the sole active agent. In still another example, the treatment results in an increased therapeutic efficacy of the EGFR inhibitor compared to the therapeutic efficacy of the EGFR inhibitor when administered as the sole active agent. In another example, the treatment results in the prevention of resistance to the EGFR 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 EGFR 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 EGFR inhibitor in the label, if available) if the EGFR inhibitor is administered as the sole active agent. The typical daily amount (or the indicated daily amount, if available) depends on the specific EGFR inhibitor that will be used. Thus, gefitinib may e.g. be administered in the combination for use of the present disclosure at a daily amount of between about 50 and about 300 mg, preferably of between about 100 mg and about 250 mg, and most preferably of between about 150 mg and about 250 mg. Osimertinib may e.g. be administered in the combination for use of the present disclosure at a daily amount of between about 5 and about 1500 mg, preferably of between about 10 mg and about 100 mg, and most preferably of between about 50 mg and about 80 mg. Erlotinib may e.g. be administered in the combination for use of the present disclosure at a daily amount of between about 10 mg and about 300 mg, preferably of between about 25 mg and about 200 mg, and most preferably of between about 100 mg and about 150 mg. Afatinib may e.g. be administered in the combination for use of the present disclosure at a daily amount of between about 5 mg and about 100 mg, preferably of between about 10 mg and about 80 mg, and most preferably of between about 20 mg and about 40 mg. Dacomitinib may e.g. be administered in the combination for use of the present disclosure at a daily amount of between about 5 mg and about 100 mg, preferably of between about 10 mg and about 80 mg, and most preferably of between about 15 mg and about 50 mg.

In another example of the first example, the EGFR inhibitor is administered at a daily amount that is lower than the above-mentioned typical daily amount if the EGFR inhibitor is administered as the sole active agent. In other words, if an EGFR inhibitor is not administered as the sole active agent but in the combination for use according to the present disclosure, the EGFR inhibitor may be administered at a lower amount than the amount used when the EGFR 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 a further example of the first example, the present disclosure is directed to a combination of (i) Compound A and (ii) an EGFR inhibitor for use in the treatment of a patient suffering from non-small cell lung cancer (NSCLC), wherein the NSCLC exhibits an oncogenic alteration in the EGFR. It can be preferred in this exmaple that the EGFR inhibitor is osimertinib and that the oncogenic alteration is caused by a deletion in exon 19 of the EGFR gene (in particular a deletion resulting in the deletion of E746-A750 or L747-E749 in the EGFR); at least one base mutation in the EGFR gene resulting in the amino acid substitution L858R or A750P in the EGFR; and combinations thereof. The at least one base mutation in the EGFR gene resulting in the amino acid substitution T790M in the EGFR corresponding to a resistance alteration in the EGFR may or may not be present in the example where the EGFR inhibitor is osimertinib.

In yet a further example of the first example, the present disclosure is directed to a combination of (i) Compound A or Compound C and (ii) an EGFR inhibitor for use in the treatment of a patient suffering from non-small cell lung cancer (NSCLC), wherein the NSCLC exhibits an oncogenic alteration in the EGFR. It can be preferred in this example that the EGFR inhibitor is osimertinib and that the oncogenic alteration is caused by a deletion in exon 19 of the EGFR gene (in particular a deletion resulting in the deletion of E746-A750 or L747-E749 in the EGFR); at least one base mutation in the EGFR gene resulting in the amino acid substitution L858R or A750P in the EGFR; and combinations thereof. The at least one base mutation in the EGFR gene resulting in the amino acid substitution T790M in the EGFR corresponding to a resistance alteration in the EGFR may or may not be present in the example where the EGFR inhibitor is osimertinib.

In yet a further example of the first example, the present disclosure is directed to a combination of (i) CCS1477 and (ii) an EGFR inhibitor for use in the treatment of a patient suffering from non-small cell lung cancer (NSCLC), wherein the NSCLC exhibits an oncogenic alteration in the EGFR. It can be preferred in this exmaple that the EGFR inhibitor is osimertinib and that the oncogenic alteration is caused by a deletion in exon 19 of the EGFR gene (in particular a deletion resulting in the deletion of E746-A750 or L747-E749 in the EGFR); at least one base mutation in the EGFR gene resulting in the amino acid substitution L858R or A750P in the EGFR; and combinations thereof. The at least one base mutation in the EGFR gene resulting in the amino acid substitution T790M in the EGFR corresponding to a resistance alteration in the EGFR may or may not be present in the example where the EGFR inhibitor is osimertinib.

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) an EGFR inhibitor for use in the treatment of a patient suffering from non-small cell lung cancer (NSCLC), wherein the NSCLC exhibits an oncogenic alteration in the EGFR. It can be preferred in this example that the EGFR inhibitor is osimertinib and that the oncogenic alteration is caused by a deletion in exon 19 of the EGFR gene (in particular a deletion resulting in the deletion of E746-A750 or L747-E749 in the EGFR); at least one base mutation in the EGFR gene resulting in the amino acid substitution L858R or A750P in the EGFR; and combinations thereof. The at least one base mutation in the EGFR gene resulting in the amino

acid substitution T790M in the EGFR corresponding to a resistance alteration in the EGFR may or may not be present in the example where the EGFR inhibitor is osimertinib.

In yet a further example of the first example, the present disclosure is directed to a combination of (i) CPI-637 and (ii) an EGFR inhibitor for use in the treatment of a patient suffering from non-small cell lung cancer (NSCLC), wherein the NSCLC exhibits an oncogenic alteration in the EGFR. It can be preferred in this example that the EGFR inhibitor is osimertinib and that the oncogenic alteration is caused by a deletion in exon 19 of the EGFR gene (in particular a deletion resulting in the deletion of E746-A750 or L747-E749 in the EGFR); at least one base mutation in the EGFR gene resulting in the amino acid substitution L858R or A750P in the EGFR; and combinations thereof. The at least one base mutation in the EGFR gene resulting in the amino acid substitution T790M in the EGFR corresponding to a resistance alteration in the EGFR may or may not be present in the example where the EGFR inhibitor is osimertinib.

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) an EGFR inhibitor for use in the treatment of a patient suffering from non-small cell lung cancer (NSCLC), wherein the NSCLC exhibits an oncogenic alteration in the EGFR. It can be preferred in this example that the EGFR inhibitor is osimertinib and that the oncogenic alteration is caused by a deletion in exon 19 of the EGFR gene (in particular a deletion resulting in the deletion of E746-A750 or L747-E749 in the EGFR); at least one base mutation in the EGFR gene resulting in the amino acid substitution L858R or A750P in the EGFR; and combinations thereof. The at least one base mutation in the EGFR gene resulting in the amino acid substitution T790M in the EGFR corresponding to a resistance alteration in the EGFR may or may not be present in the example where the EGFR inhibitor is osimertinib.

In a second example, the present disclosure is directed to a method of treating NSCLC 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) an EGFR inhibitor, wherein the NSCLC exhibits an oncogenic alteration in the EGFR.

In a third example, the present disclosure is directed to a method of extending the duration of the therapeutic effect of an EGFR 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 EGFR inhibitor, wherein the NSCLC exhibits an oncogenic alteration in the EGFR. In other words, the duration of the therapeutic effect of the EGFR inhibitor (when administered in the combination) is extended compared to the duration of the therapeutic effect of the EGFR inhibitior when administered as the sole active agent in NSCLC treatment.

In a fourth example, the present disclosure is directed to a method of increasing the therapeutic efficacy of an EGFR 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 EGFR inhibitor, wherein the NSCLC exhibits an oncogenic alteration in the

EGFR. In other words, the therapeutic efficacy of the EGFR inhibitor (when administered in the combination) is increased compared to the therapeutic efficacy of the EGFR inhibitor when administered as the sole active agent in NSCLC treatment.

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

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

The examples outlined above for the first example equally apply for the methods of the second to sixth examples.

DESCRIPTION OF THE FIGURES

FIG. 1: Only CBP/p300 inhibitors that bind to the bromodomain (Compound A, CCS1477) or the HAT domain (A485) blunt EGFR inhibitor-induced gene expression in EGFR-mutated non-small cell lung cancer cells (NSCLC), but not inhibitors that prevent the interaction of CBP with β-catenin (ICG001). Two different EGFR inhibitors are used in cell lines that carry the resistance-causing gatekeeper mutation T790M or not. Examples of regulated genes shown are ALPP (Alkaline phosphatase, placental type; A and C) and HOPX (Homeodomain-only protein; B and D). Data from 2 independent experiments with qPCRs in duplicate (mean ± SD).

FIG. 2: Only the enantiomer that binds the bromodomain (BRD) of CBP/p300 (Compound A) but not the enantiomer that does not bind the bromodomain of CBP/p300 (Compound B) potentiates EGFR inhibitor-mediated NSCLC cell proliferation inhibition in a concentration-dependent manner. Cell numbers of EGFR-mutated HCC827 cells were monitored over time. (A) Cells were treated with DMSO alone (filled circles), with 20 nM EGFR inhibitor alone (Gefitinib; 1st generation EGFR inhibitor, open circles) or in combination with the bromodomain-binding enantiomer of the CBP/p300 BRD inhibitor (Compound A). (B) HCC827 cells were exposed to Compound A & B in absence of EGFR inhibitor. In the absence of an EGFR inhibitor Compound A loses its effect on proliferation of EGFR-mutated NSCLC cells and behaves like Compound B that does not bind the bromodomain of CBP/p300. Presented graphs are from one experiment with triplicates for each time-point and condition (mean ± SD).

FIG. 3: Only inhibitors that bind to the bromodomain of CBP/p300 (Compound A, CCS1477) potentiate the effect of an EGFR inhibitor without affecting cell growth in the absence of the EGFR inhibitor. CBP/p300 inhibitors that inhibit the histone acetyl transferase (HAT) domain of CBP/p300 inhibitors (A485) affect cell proliferation of EGFR-mutated NSCLC cells even in the ab-

Claims

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

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

3. The use of a combination according to claim 1 or 2, wherein the oncogenic alteration is caused by a deletion and/or insertion in exon 18 or in exon 19 or in exon 20 of the EGFR gene; a kinase domain duplication in the EGFR gene; an amplification of the EGFR gene; at least one base mutation in the EGFR gene resulting in an amino acid substitution in the EGFR selected from the group consisting of L858R, G719S, G719A, G719C, V765A, T783A, S768I, S768V, L861Q, E709X, L819Q, A750P and combinations thereof, wherein X indicates any amino acid; and combinations of any of the foregoing.

4. The use of a combination according to any one of claims 1 to 3, wherein the oncogenic alteration is caused by a deletion in exon 19 of the EGFR gene, preferably a deletion resulting in the deletion of E746-A750 or L747-E749 in the EGFR; at least one base mutation in the EGFR gene resulting in the amino acid substitution L858R or A750P in the EGFR; and combinations thereof.

5. The use of a combination according to any one of the preceding claims with the proviso that, if the NSCLC additionally exhibits a resistance alteration in the EGFR due to previous administration of an EGFR inhibitor, the EGFR inhibitor of the combination is not the EGFR inhibitor previously administered.

6. The use of a combination according to claim 5, wherein the resistance alteration in the EGFR is caused by at least one base mutation in the EGFR gene resulting in an amino acid substitution in the EGFR selected from the group consisting of T790M, C797X, L792X, G796X, L718Q, L718V, G724S, D761Y, V834L, T854A, and combinations thereof, wherein X indicates any amino acid.

7. The use of a combination according to claim 5 or 6, wherein the resistance alteration in the EGFR is caused by at least one base mutation in the EGFR gene resulting in the amino acid substitution T790M in the EGFR.

8. 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.

9. The use of a combination according to any one of the preceding claims, wherein the EGFR inhibitor is selected from the group consisting of ABBV-321, abivertinib, afatinib, alflutinib, almonertinib, apatinib, AZD3759, brigatinib, D 0316, D 0317, D 0318, dacomitinib, DZD9008, erlotinib, FCN-411, gefitinib, icotinib, lapatinib, lazertinib, mobocertinib, nazartinib, neratinib, olafertinib, osimertinib, poziotinib, pyrotinib, rezivertinib, TAS6417, vandetanib, varlitinib, XZP-5809, amivantamab, CDP1, cetuximab, GC1118, HLX07, JMT101, M1231, necitumumab, nimotuzumab, matuzumab, panitumumab, SCT200, SI-B001, SYN004, zalutumumab, and combinations thereof.

10. 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.

11. 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.

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

13. 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 EGFR inhibitor when administered as the sole active agent.

14. The use of a combination according to any one of claims 1 to 12, wherein the treatment results in an increased therapeutic efficacy compared to the therapeutic efficacy of the EGFR inhibitor when administered as the sole active agent.

15. The use of a combination according to any one of claims 1 to 12, wherein the treatment results in the prevention of resistance to the EGFR inhibitor.