PTL 2: WO2015/025936A1

Non-patent Literature

[0005] NPL 1: Nat. Rev. Cancer, vol. 6, pp. 803-812 (2006)

NPL 2: Nature Medicine, vol. 19, pp. 1389-1400 (2013)

NPL 3: Nat. Rev. Cancer, vol. 7, pp. 169-181 (2007)

NPL 4: Clin. Cancer Res., vol. 24, pp. 3097-3107 (2018)

Summary

[0005a] In one aspect, the present disclosure refers to use of (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof in the manufacture of a pharmaceutical composition for treating a malignant tumor expressing EGFR having at least one mutation selected from the group consisting of L718X mutation in exon 18 and L792X mutation in exon 20, wherein the EGFR further has at least one mutation selected from the group consisting of exon 19 deletion mutation~~,~~ and L858R~~, L861Q, G719X, E709X, and exon 20 insertion mutation~~.

[0005b] In another aspect, the present disclosure refers to an *in vitro* method for predicting therapeutic effects of chemotherapy using an antitumor agent comprising, as an active ingredient, (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4- b]indolizin-8-yl)acrylamide or a salt thereof in a malignant tumor patient, the method comprising steps (1) and (2) below:

(1) a step of detecting the presence or absence of mutation of EGFR gene contained in a biological sample obtained from the patient; and

(2) a step of predicting that the chemotherapy is highly likely to exhibit sufficient therapeutic effects with respect to the patient when the results of the detection in step (1) find that the EGFR gene has at least one mutation selected from the group consisting of L718X mutation in exon 18 and L792X mutation in exon 20, wherein X represents an arbitrary amino-acid residue, and wherein the EGFR further has at least one mutation selected from the group consisting of exon 19 deletion mutation and L858R.

Technical Problem

[0006] Treatments using EGFR inhibitors are in the process of being established for lung cancer patients having major EGFR mutations. In contrast, the presence of patients who are resistant to osimertinib treatment has also been known. It is reported that some of the causes thereof are EGFR gene mutations (NPL 4). It has been confirmed that, for example, lung cancer having, in addition to exon 19 deletion mutation or L858R mutation, both of which are de novo mutations, and T790M mutation, which is acquired resistance mutation, point mutation in which leucine encoded by codon 718 in

exon 18 is substituted with an arbitrary amino acid (hereinafter also referred to as "L718X mutation") or point mutation in which leucine encoded by codon 792 in exon 20 is substituted with an arbitrary amino acid (hereinafter also referred to as "L792X mutation"), is resistant to osimertinib treatment. It is proposed that amino acid substitution caused by L718X mutation or L792X mutation induces steric hindrance and decrease in hydrophobic binding, thereby preventing EGFR binding to osimertinib (NPL 4). Accordingly, there is a demand for the development of inhibitors having high inhibitory activity against EGFR having composite mutation of de novo active mutation, T790M acquired resistance mutation, and L718X mutation or L792X mutation.

[0007] Therefore, the development of drugs having high inhibitory activity against EGFR having composite mutation containing L718X or L792X is assumed to make it possible to exhibit antitumor effects against lung cancer that is resistant to osimertinib treatment, and is expected to contribute to the life prolongation and QOL improvement of mutant EGFR-positive cancer patients for whom no therapy has been established. Further, a drug having high inhibitory activity with respect to T790M, which is acquired resistance mutation against treatments using EGFR inhibitors, is expected to reduce expression frequency of acquired resistance during the treatments using EGFR inhibitors against exon 19 or exon 21 mutant EGFR, which is de novo mutation; and is therefore expected to contribute to the life prolongation of cancer patients.

[0008] Under such circumstances, an object of the present invention is to provide an inhibitor that has high inhibitory activity against L718 and L792 mutant EGFR, which

[CLAIMS]

[Claim 1]
Use of (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof in the manufacture of a pharmaceutical composition for treating a malignant tumor expressing EGFR having at least one mutation selected from the group consisting of L718X mutation in exon 18 and L792X mutation in exon 20, wherein the EGFR further has at least one mutation selected from the group consisting of exon 19 deletion mutation and L858R.

[Claim 2]
The use according to claim 1, wherein the EGFR further has T790M mutation.

[Claim 3]
The use according to claim 1 or 2, wherein the L718X mutation is L718Q mutation.

[Claim 4]
The use according to any one of claims 1 to 3, wherein the L792X mutation is L792H, L792F, or L792Y.

[Claim 5]
The use according to any one of claims 1 to 4, wherein the pharmaceutical composition comprises a pharmaceutically acceptable carrier.

[Claim 6]
An *in vitro* method for predicting therapeutic effects of chemotherapy using an antitumor agent comprising, as an active ingredient, (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof in a malignant tumor patient, the method comprising steps (1) and (2) below:
(1) a step of detecting the presence or absence of mutation of EGFR gene contained in a biological sample obtained from the patient; and
(2) a step of predicting that the chemotherapy is highly likely to exhibit sufficient therapeutic effects with respect to the patient when the results of the detection in step (1) find that the EGFR gene has at least one mutation selected from the group consisting of L718X mutation in exon 18 and L792X mutation in exon 20, wherein X represents an arbitrary amino-acid residue, and wherein the EGFR further has at least one mutation selected

from the group consisting of exon 19 deletion mutation and L858R.

[Claim 7]
The method according to claim 6, wherein the EGFR further has T790M mutation.

[Claim 8]
The method according to claim 6 or 7, wherein the L718X mutation is L718Q mutation.

[Claim 9]
The method according to any one of claims 6 to 8, wherein the L792X mutation is L792H, L792F, or L792Y.

[Claim 10]
The use of any one of claims 1-5 comprising steps (1) to (3) below:
(1) a step of detecting the presence or absence of mutation of EGFR gene contained in a biological sample obtained from the patient;
(2) a step of predicting that chemotherapy using an antitumor agent comprising, as an active ingredient, (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof is highly likely to exhibit sufficient therapeutic effects with respect to the patient when the results of the detection in step (1) find that the EGFR gene has at least one mutation selected from the group consisting of L718X mutation in exon 18 and L792X mutation in exon 20, wherein X represents an arbitrary amino-acid residue, and wherein the EGFR further has at least one mutation selected from the group consisting of exon 19 deletion mutation and L858R; and
(3) wherein (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof is to be administered to a malignant tumor patient who has been predicted highly likely to sufficiently respond to the chemotherapy using an antitumor agent comprising, as an active ingredient, (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide or a salt thereof, in step (2).