PTL 2: WO2015/025936A1

Non-Patent Literature

[0008]

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: Lancet Oncol. Vol. 13, e. 23-31 (2012)

NPL 5: Lancet Oncol. Vol. 16, pp. 830-838 (2015)

Summary

[0008a] In one aspect, there is provided an antitumor agent for use in the treatment of a malignant tumor in a patient expressing EGFR having exon 20 insertion mutation, the antitumor agent comprising a compound selected from the group consisting of:

(S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide;

(S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)acrylamide;

(S,E)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-3-chloroacrylamide; and

(R)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)-N-methylacrylamide,

or a salt thereof.

[0008b] In another aspect, there is provided a compound selected from the group consisting of:

(S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide;

(S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)acrylamide;

(S,E)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-3-chloroacrylamide; and

(R)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)-N-methylacrylamide,

or a salt thereof, for use in the treatment of a malignant

tumor in a patient expressing EGFR having exon 20 insertion mutation.

[0008c] In another aspect, there is provided use of a compound selected from the group consisting of:

(S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide;

(S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)acrylamide; and

(S,E)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-3-chloroacrylamide; and

(R)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)-N-methylacrylamide,

or a salt thereof for the production of a pharmaceutical agent for treating a malignant tumor patient expressing EGFR having exon 20 insertion mutation.

[0008d] In another aspect, there is provided use of an antitumor agent comprising a compound selected from the group consisting of:

(S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide;

(S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)acrylamide;

(S,E)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-3-chloroacrylamide; and

(R)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)-N-methylacrylamide,

or a salt thereof

in the manufacture of a medicament for treating a malignant tumor in a patient expressing EGFR having exon 20 insertion mutation.

Technical Problem

[0009]

An object of the present invention is to provide an antitumor agent with reduced side effects derived from the inhibition of wild-type EGFR, the antitumor agent serving as an inhibitor that can ensure high selectivity with respect to exon 20 insertion mutant EGFR for which the therapeutic effects of the previously known EGFR

inhibitors are insufficient.

Solution to Problem

[0010]

The inventors of the present invention conducted extensive research, and found that exon 20 insertion mutant EGFR is an appropriate target in treating cancers, and that EGFR inhibitors conventionally used for the treatments have inferior selectivity between wild-type EGFR and exon 20 insertion mutant EGFR. Further, the inventors also confirmed that a specific compound exerts selectivity with respect to exon 20 insertion mutant EGFR and tumor growth inhibitory effects, and is thus regarded as superior to afatinib, which is a typical EGFR mutation-positive cancer-treating agent. With this finding, the inventors accomplished the present invention.

[0011]

Accordingly, the present invention encompasses the following embodiments.

CLAIMS

[Claim 1]

An antitumor agent for use in the treatment of a malignant tumor in a patient expressing EGFR having exon 20 insertion mutation, the antitumor agent comprising a compound selected from the group consisting of:

(S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide;

(S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)acrylamide;

(S,E)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-3-chloroacrylamide; and

(R)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)-N-methylacrylamide,

or a salt thereof.

[Claim 2]

The antitumor agent for use according to claim 1, wherein the compound is (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide.

[Claim 3]

The antitumor agent for use according to claim 1 or 2, wherein the patient expressing EGFR having exon 20 insertion mutation is a patient with lung cancer, breast cancer, head and neck cancer, brain tumor, uterine cancer, hematopoietic tumor, or skin cancer.

[Claim 4]

The antitumor agent for use according to any one of claims 1 to 3, wherein the patient expressing EGFR having exon 20 insertion mutation is a lung cancer patient.

[Claim 5]

The antitumor agent for use according to any one of claims 1 to 4, wherein the exon 20 insertion mutation is a mutation in which

one or more amino acids are inserted in the exon 20 region.

[Claim 6]

The antitumor agent for use according to any one of claims 1 to 5, wherein the exon 20 insertion mutation is a mutation in which 1 to 7 amino acids are inserted in the exon 20 region.

[Claim 7]

The antitumor agent for use according to any one of claims 1 to 6, wherein the exon 20 insertion mutation is a mutation in which 1 to 4 amino acids are inserted in the exon 20 region.

[Claim 8]

The antitumor agent for use according to any one of claims 1 to 7, wherein the exon 20 insertion mutation is V769_D770insASV, D770_N771insSVD, D770_N771insG, H773_V774insNPH, or H773_V774insPH.

[Claim 9]

A compound selected from the group consisting of:

(S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide;

(S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)acrylamide;

(S,E)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-3-chloroacrylamide; and

(R)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)-N-methylacrylamide,

or a salt thereof, for use in the treatment of a malignant tumor in a patient expressing EGFR having exon 20 insertion mutation.

[Claim 10]

Use of a compound selected from the group consisting of:

(S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide;

(S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)acrylamide; and

(S,E)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-3-chloroacrylamide; and

(R)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)-N-methylacrylamide,

or a salt thereof for the production of a pharmaceutical agent for treating a malignant tumor patient expressing EGFR having exon 20 insertion mutation.

[Claim 11]

Use of an antitumor agent comprising a compound selected from the group consisting of:

(S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide;

(S)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)acrylamide;

(S,E)-N-(4-amino-6-methylene-5-(quinolin-3-yl)-7,8-dihydro-6H-pyrimido[5,4-b]pyrrolizin-7-yl)-3-chloroacrylamide; and

(R)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)-N-methylacrylamide,

or a salt thereof

in the manufacture of a medicament for treating a malignant tumor in a patient expressing EGFR having exon 20 insertion mutation.

[Claim 12]

The use according to claim 11, wherein the compound is (S)-N-(4-amino-6-methyl-5-(quinolin-3-yl)-8,9-dihydropyrimido[5,4-b]indolizin-8-yl)acrylamide.

[Claim 13]

The use according to claim 11 or 12, wherein the patient expressing EGFR having exon 20 insertion mutation is a patient with lung cancer, breast cancer, head and neck cancer, brain tumor, uterine cancer, hematopoietic tumor, or skin cancer.

[Claim 14]

The use according to any one of claims 11 to 13, wherein the patient expressing EGFR having exon 20 insertion mutation is a lung cancer patient.

[Claim 15]

The use according to any one of claims 11 to 14, wherein the exon 20 insertion mutation is a mutation in which one or more amino acids are inserted in the exon 20 region.

[Claim 16]

The use according to any one of claims 11 to 15, wherein the exon 20 insertion mutation is a mutation in which 1 to 7 amino acids are inserted in the exon 20 region.

[Claim 17]

The use according to any one of claims 11 to 16, wherein the exon 20 insertion mutation is a mutation in which 1 to 4 amino acids are inserted in the exon 20 region.

[Claim 18]

The use according to any one of claims 11 to 17, wherein the exon 20 insertion mutation is V769_D770insASV, D770_N771insSVD, D770_N771insG, H773_V774insNPH, or H773_V774insPH.