and/or a C-terminus are selectively cleaved.

The pharmaceutical composition according to the present disclosure may further include one or more selected from pharmaceutically acceptable additives, particularly a buffer, a stabilizer, and a surfactant.

The pharmaceutical composition according to the present disclosure may be used in the form of an injection formulation for subcutaneous injection.

[Summary]

In one aspect, the present disclosure refers to a pharmaceutical composition comprising:

(a) pembrolizumab;

(b) a hyaluronidase PH20 variant, wherein the amino acid sequence of the PH20 variant consists of the amino acid sequence of SEQ ID NO 44, 5, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 22, 23, 24, 25, 27, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 45, 46, 47, 48, 49, or 50; and

(c) one or more pharmaceutically acceptable additives.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising:

(a) pembrolizumab;

(b) a hyaluronidase PH20 variant, wherein the amino

acid sequence of the PH20 variant consists of the amino acid sequence of SEQ ID NO: 44, 9, 16, 22, 23, 24, 32, 38, or 39; and; and

(c) one or more pharmaceutically acceptable additives.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising:

(a) pembrolizumab;

(b) a hyaluronidase PH20 variant comprising the amino acid sequence of SEQ ID NO: 44; and

(c) one or more pharmaceutically acceptable additives.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising:

(a) pembrolizumab;

(b) a hyaluronidase PH20 variant, wherein the amino acid sequence of the PH20 variant consists of the amino acid sequence set forth in SEQ ID NO:44; and

(c) one or more pharmaceutically acceptable additives.

In another aspect, the present disclosure refers to a composition comprising:

(a) pembrolizumab; and

(b) a hyaluronidase PH20 variant comprising the amino acid sequence of SEQ ID NO: 44.

In another aspect, the present disclosure refers to a composition comprising:

(a) pembrolizumab; and

(b) a hyaluronidase PH20 variant, wherein the amino acid sequence of the PH20 variant consists of the amino acid sequence set forth in SEQ ID NO: 44.

In another aspect, the present disclosure refers to the pharmaceutical composition as disclosed herein for use in therapy.

In yet another aspect, the present disclosure refers to a use of the pharmaceutical composition as disclosed herein in the preparation of a medicament for treating cancer in a subject in need thereof.

In yet another aspect, the present disclosure refers to a use of pembrolizumab in the manufacture of a medicament for use in combinatorial therapy for treating cancer, wherein the medicament is to be subcutaneously administered in combination with a PH20 variant as provided herein.

【Description of Drawings】

The above and other objects, features and other advantages of the present disclosure will be more clearly understood from the following detailed description taken in conjunction with the accompanying drawings, in which:

FIG. 1A illustrates size-exclusion chromatography chromatograms of trastuzumab in a stability test under harsh conditions at 45°C, and FIG. 1B illustrates a change in the purity of a trastuzumab monomeric protein according to formulation in a stability test under harsh conditions at 45°C;

FIG. 2 illustrates the results of measuring the protein aggregation temperatures of formulations including trastuzumab and a novel PH20 variant HP46;

FIG. 3A is a weak cation exchange (WCX) chromatogram of trastuzumab in a stability test under harsh conditions at

【CLAIMS】

1. A pharmaceutical composition comprising:

(a) pembrolizumab;

(b) a hyaluronidase PH20 variant, wherein the amino acid sequence of the PH20 variant consists of the amino acid sequence of SEQ ID NO: 44, 5, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 22, 23, 24, 25, 27, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 45, 46, 47, 48, 49, or 50; and

(c) one or more pharmaceutically acceptable additives.

2. A pharmaceutical composition comprising:

(a) pembrolizumab;

(b) a hyaluronidase PH20 variant, wherein the amino acid sequence of the PH20 variant consists of the amino acid sequence of SEQ ID NO: 44, 9, 16, 22, 23, 24, 32, 38, or 39; and

(c) one or more pharmaceutically acceptable additives.

3. A pharmaceutical composition comprising:

(a) pembrolizumab;

(b) a hyaluronidase PH20 variant comprising the amino acid sequence of SEQ ID NO: 44; and

(c) one or more pharmaceutically acceptable additives.

4. A pharmaceutical composition comprising:

(a) pembrolizumab;

(b) a hyaluronidase PH20 variant, wherein the amino acid sequence of the PH20 variant consists of the amino acid sequence set forth in SEQ ID NO:44; and

(c) one or more pharmaceutically acceptable additives.

5. The pharmaceutical composition of any one of claims 1 to 4, wherein the one or more pharmaceutically acceptable additives is or are a buffer, and optionally a stabilizer or a surfactant.

6. The pharmaceutical composition of any one of claims 1 to 4, wherein the one or more pharmaceutically acceptable additives are a buffer, a stabilizer, and a surfactant.

7. The pharmaceutical composition of claim 5 or 6, wherein the stabilizer is a sugar, a sugar alcohol, or an amino acid, and the surfactant is a non-ionic surfactant.

8. The pharmaceutical composition of any one of claims 1 to 4, wherein the one or more pharmaceutically acceptable additives is or are a histidine buffer and optionally one or more of any one of sucrose, trehalose, methionine, polysorbate 20, and polysorbate 80.

9. The pharmaceutical composition of any one of claims 1 to 4, wherein the one or more pharmaceutically acceptable additives consist of a histidine buffer, sucrose, methionine, and polysorbate 80.

10. A composition comprising:

(a) pembrolizumab; and

(b) a hyaluronidase PH20 variant comprising the amino acid sequence of SEQ ID NO: 44.

11. A composition comprising:

(a) pembrolizumab; and

(b) a hyaluronidase PH20 variant, wherein the amino acid sequence of the PH20 variant consists of the amino acid sequence set forth in SEQ ID NO: 44.

12. The composition of any one of claims 1 to 11, which is for subcutaneous injection to a subject.

13. The composition of any one of claims 1 to 11, which is a subcutaneous injection formulation.

14. The composition of any one of claims 1 to 11 for use in therapy.

15. The composition for use of claim 14, wherein the composition is formulated for subcutaneous injection.

16. Use of the composition of any one of claims 1 to 13, in the preparation of a medicament for treating cancer in a subject in need thereof.

17. The use of claim 16, wherein the cancer is skin cancer, liver cancer, hepatocellular carcinoma, gastric cancer, breast cancer, lung cancer, ovarian cancer, bronchial cancer, nasopharyngeal cancer, laryngeal cancer, pancreatic cancer, bladder

cancer, colorectal cancer, colon cancer, brain cancer, prostate cancer, bone cancer, thyroid cancer, parathyroid cancer, kidney cancer, esophageal cancer, biliary tract cancer, testicular cancer, rectal cancer, head and neck cancer, cervical cancer, ureteral cancer, osteosarcoma, neuroblastoma, fibrosarcoma, rhabdomyosarcoma, astrocytoma, or glioma.

18. The use of claim 16, wherein the cancer is melanoma, hepatocellular carcinoma, gastric cancer, breast cancer, lung cancer, bladder cancer, colorectal cancer, colon cancer, cervical cancer, kidney cancer, esophageal cancer, or head and neck cancer.

19. Use of pembrolizumab in the manufacture of a medicament for use in combinatorial therapy for treating cancer, wherein said medicament is to be subcutaneously administered in combination with a PH20 variant defined in claim 2.

20. Use of pembrolizumab in the manufacture of a medicament for use in combinatorial therapy for treating cancer, wherein the medicament is to be subcutaneously administered in combination with a PH20 variant defined in claim 3.

21. Use of pembrolizumab in the manufacture of a medicament for use in combinatorial therapy for treating cancer, wherein the medicament is to be subcutaneously administered in combination with a PH20 variant defined in claim 4.

22. The use of any one of claims 19 to 21, wherein the cancer is skin cancer, liver cancer, hepatocellular carcinoma, gastric cancer, breast cancer, lung cancer, ovarian cancer, bronchial cancer, nasopharyngeal cancer, laryngeal cancer, pancreatic cancer, bladder cancer, colorectal cancer, colon cancer, brain cancer, prostate cancer, bone cancer, thyroid cancer, parathyroid cancer, kidney cancer, esophageal cancer, biliary tract cancer, testicular cancer, rectal cancer, head and neck cancer, cervical cancer, ureteral cancer, osteosarcoma, neuroblastoma, fibrosarcoma, rhabdomyosarcoma, astrocytoma, or glioma.

23. The use of any one of claims 19 to 21, wherein the cancer is melanoma hepatocellular carcinoma, gastric cancer, breast cancer, lung cancer, bladder cancer, colorectal cancer, colon cancer, cervical cancer, kidney cancer, esophageal cancer, or head and neck cancer.