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ОЦАЛЮК ТА ПАРТНЕРИ
ПАТЕНТНО-ПРАВОВЕ БЮРО

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TO THE UKRAINIAN NATIONAL INTELLECTUAL PROPERTY OFFICE

AND INNOVATION"

Regarding the application for invention No. **a 2020 05849**
Submission date: **08.02.2019**
Date of entry into the national phase: **11.09.2020**
Applicant: **MERCK SHARP & DOME ELECTRONICS, (US)**
Patent Attorney Case Number: **OVM-1375**

15.12.2025

REMARKS REGARDING THE COMPLIANCE OF THE CLAIMED INVENTION WITH THE CONDITIONS

PROVISION OF LEGAL PROTECTION

In accordance with part eighteen of Article 16 of the Law of Ukraine “On Protection rights to inventions and utility models" (hereinafter referred to as the Law), after publication of information about the application Any person may submit to the NOIP comments on the conformity of an invention of the claimed invention to the conditions for granting legal protection specified by the Law.

On behalf of the charitable organization "All-Ukrainian Network of People Living with HIV/AIDS" (BO "100 PERCENT OF LIFE"), we ask the Expertise to accept the comments, the basis for which is **the non-compliance of the technical solution for this application the patentability condition "inventive step",** and please take into account the comments when the next consideration of the application.

The objects of the invention under application a202005849 are:

- a method of treating cancer in a patient, comprising administering to the patient about 400 mg antibodies against PD-1 or its antigen-binding fragment, approximately every six weeks, where the anti-PD-1 antibody or antigen-binding fragment thereof is Pemprolizumab (independent claim 1 of the claims (hereinafter referred to as the “Claim”) and dependent claims 2-37 FV);

- a composition containing approximately 400 mg of Pembrolizumab and pharmaceutically acceptable medium (independent item 38 of the FV and dependent item 39 of the FV);

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- a kit for treating a patient with cancer, wherein the kit contains 400 mg of an antibody against PD-1 or its antigen-binding fragment and instructions for its use (independent item 40 FV and dependent item 41 FV);

- use of the composition according to items 38-39 and the kit according to items 40-41 for the treatment a patient suffering from cancer (independent item 42 of the FV and dependent item 43 of the FV).

The objective of the invention under application No. a202005849 was to develop an alternative, less frequent dosing (administration) regimen for treating a cancer patient with an antibody against PD-1 or its antigen-binding fragment, in which the dosing regimen is expected to be will provide a safe and effective dose of an antibody against PD-1 or its antigen-binding fragment. In particular, the claimed invention provides a method of treating cancer in a patient-human, which involves administering to the patient approximately 400 mg of an anti-PD-1 antibody or its antigen-binding fragment every six weeks, where the antibody against PD-1 or its the antigen-binding fragment is Pembrolizumab.

The task was solved by administering Pembrolizumab in an amount of 400 mg every 6 weeks.

During the conducted patent search, the following relevant patents were identified: documents that, in our opinion, constitute the state of the art of this invention:

1. WO 2008/156712 (hereinafter referred to as D1);

2. US 2016022814 (hereinafter referred to as D2);

3. WO 2017/210624 (hereinafter referred to as D3);

4. J. Elassaiss-Schaap et al., Using Model-Based “Learn and Confirm” to Reveal the Pharmacokinetics-Pharmacodynamics Relationship of Pembrolizumab in the KEYNOTE-001 Trial, CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 21–28 (hereinafter – D4);

5. Alexander M. Castellino, Pembrolizumab Flat Dosing Wastes Nearly $1 Billion, Annually American Society of Clinical Oncology (ASCO) 2017 Annual Meeting. Abstract 9013. Presented June 3, 2017 (https://www.medscape.com/viewarticle/882104#vp_4?form=fpf) (hereinafter referred to as D5).

Below is a brief description of the contents of these documents for better understanding. justification of the remark.

D1 describes antibodies that block the binding of the human programmed cell receptor death of PD-1 and its ligands. In particular, D1 describes Pembrolizumab for the treatment of various types of cancer, administered to a patient who needs such treatment.

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D2 proposes a method of treating cancer in humans, which involves administering to a human fixed dose of 100 to 500 mg of PD-1 antagonist at intervals of 14, 21 or 30 (+ 2 days) days (see para. [0267]). MK-3475 is proposed as a PD-1 antagonist (see para. [0271]), also known as Pembrolizumab. The method described herein also provides for administering a booster dose to a subject, wherein the booster dose is administered after initial dose of the drug, where the period between the initial and booster doses immunogenic composition is 1 week, in another embodiment - 2 weeks, in in another implementation option – 3 weeks, in another implementation option – 4 weeks, in another implementation option – 5 weeks, **in another implementation option – 6-8 weeks,** and in another In one implementation, the booster dose is administered 8-10 weeks after the primary dose. immunogenic composition (see paragraph [0249]). **D2** also describes a composition containing MK-3475 (Pembrolizumab), 7% sucrose, 0.02 Polysorbate 80 in 10 mM histidine buffer pH 5.5 and this composition is intended for intravenous administration (see paragraph [0271]).

D3 **states** that a treatment regimen using an anti-PD-1 antibody involves administering it about once a week, about once every 2 weeks, about once every 3 weeks, about once every 4 weeks, **about once once a month, approximately once every 3-6 months or longer.** The dosage regimen is usually designed to achieve exposure that results in sustained receptor occupancy (RO) based on typical pharmacokinetic properties of the antibody (see para. [0172]).

Document **D4** describes a study evaluating pharmacokinetic/pharmacodynamic (PK/PD) properties of the clinical development of Pembrolizumab. Modeling of the obtained Data showed that the PK of pembrolizumab is nonlinear at <0.3 mg/kg every 3 weeks, but linear in the clinical dose range. Saturation of interaction with the target ex vivo in blood started at ‡1 mg/kg every 3 weeks, and to achieve 95% binding to the target was a steady-state dose of **2 mg/kg** every 3 weeks is required, as confirmed by a dose 2 study mg/kg every 3 weeks in ongoing studies in melanoma and other cancers.

Document **D5** reviews studies using a fixed dose pembrolizumab (Keytruda, Merck &Co) for first-line treatment of lung cancer instead of personalized doses according to the patient's body weight, leading to an increase in doses of the drug by 25%, and therefore to an increase in the cost of the drug by 25%, as the group claims oncologists. They estimated that this surplus could reach almost $1 billion annually in the United States.

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The closest in essence is document **D2,** which describes the introduction of a fixed dose into a person. doses of 100 to 500 mg of PD-1 antagonist at intervals of 14, 21, or 30 days, where the antagonist PD-1 is Pembrolizumab. Also in **D2** it is noted that the interval of administration of the booster dose The duration of the effect on the subject after the initial dose of the drug may be up **to 6-8 weeks.** This administration regimen is common practice for administering antibodies of this class (see D3), which also includes Pembrolizumab, and can be established based on typical pharmacokinetic properties of the antibody. This administration regimen may be determined experimentally on the basis of conventional routine studies that allow establish high values, at least 95%, of target site blocking ex vivo, using commonly accepted dosages of Pembrolizumab that have been studied and described in **D4.** Also, a reduction in the frequency of administration of Pembrolizumab may be prompted by optimization of treatment costs, which is described in document **D5,** in which a more rational personalized administration of Pembrolizumab may reduce the cost of overall treatment costs treatment by 25%. Even better results can be achieved by increasing the intervals between with Pembrolizumab injections, but provided that the necessary therapeutic effect is maintained, which is quite simply established experimentally on the basis of well-known techniques used in this field.

Therefore, the proposed solution to the technical problem outlined in application a202005849 clearly follows from the prior art documents and the claimed invention under application a202005849 **is not meets the patentability condition "inventive step",** since it is obvious to specialist in this field of technology (clause 4, chapter 2, section II of the Rules for the preparation, submission and examination of an application for an invention and an application for a utility model), and is routine a solution that does not require any invention.

For a specialist in the field, it is quite obvious to search for new modes of administration of drugs. means that will reduce the frequency of drug administration, the cost of treatment, better perceived by patients, etc., and at the same time will ensure the proper effect of treatment. This search for new administration regimens is a routine process that is widely used in this industry.

In addition to the arguments regarding the non-compliance of the claimed invention with the condition patentability "inventive step" we want to draw the attention of the Examination to ethical and socially significant risks of granting a patent for this application.

Protection of primary patents for Pembrolizumab - a drug that used to treat a wide range of malignant neoplasms, including cancer

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cervical, melanoma, lung cancer, renal cell carcinoma, endometrial carcinomas, esophageal cancer, stomach cancer and a number of other cancers - in most countries is completed in 2028 - 2030. Today the cost of this drug remains extremely high. In particular, in Ukraine its price in pharmacy chains is on average is $1,864 per package. Thus, the annual course of treatment (depending on depending on the therapeutic protocol used) requires from 9 to 17 packages, which corresponds to 16,776 - 31,688 USD. Full recommended course of treatment lasting up to two years involves 18 to 34 packages, i.e. $33,552 - $63,376 USA. For most Ukrainian patients, this cost of the drug makes it virtually impossible access to it.

According to the National Cancer Registry, the number of people diagnosed with oncological diseases in 2020-2024 and which were at the end of 2024 registered in oncology institutions is 393,651 people.1

At the same time, it should be noted that the appearance of generics on the pharmaceutical market medicines and biosimilars, and thus increased competition, provides significant savings both during procurements from the state budget and in the costs of private households on healthcare. Let's give an example with the drug trastuzumab (a medicine used to treat breast cancer, as well as cancer stomach). The entry into the Ukrainian market of a biosimilar of trastuzumab caused a significant reducing its cost: in 2023, the price for 60,000 units of trastuzumab during public The procurement cost turned out to be lower than even the expected cost of UAH 144,043,800. The drug Pfizer TRAZIMERA was more than ten times cheaper than HERCEPTIN produced Roche. Total savings exceeded UAH 892,775,600.2 Further purchases, carried out by the State Enterprise "Medical Procurement of Ukraine" also showed a trend towards a decrease in prices on trastuzumab.

[1] http://www.ncru.inf.ua/publications/BULL_26/PDF/str-5ykont.pdf

[2] https://prozorro.gov.ua/uk/tender/UA-2023-05-08-007180-a

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Реєстр пропозицій

Друкувати реєстр отриманих тендерних пропозицій PDF ● HTML

Дата і час розкриття: 19 травня 2023 • 10:00

Учасник	Первинна пропозиція	Остаточна пропозиція	Відповідність критеріям	Документи
Pfizer Export B.V.	94 180 000,00 UAH	94 180 000,00 UAH	Відповіді учасника	Документи
ТОВ "ДОЙЧ-ФАРМ"	97 063 200,00 UAH	97 063 200,00 UAH	Відповіді учасника	Документи
Органон Сентрал Іст ГмбХ	136 035 192,00 UAH	136 035 192,00 UAH	Відповіді учасника	Документи
ТОВ "РОШ УКРАЇНА"	986 955 600,00 UAH	986 955 600,00 UAH	Відповіді учасника	Документи

Taking into account the above, the issuance of a patent under application No. a202005849, the invention under which does not meet the patentability condition "inventive step", for a long time will block competition in the Ukrainian pharmaceutical market and further restrict access of Ukrainian patients to this drug.

Patent attorney Otsalyuk V.M.

Appendix: Documents cited above