Appeal Decision

Appeal No. 2020-8197

Appellant Bristol Myers Squibb Company

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The case of appeal against the examiner's decision of refusal of Japanese Patent Application No. 2016-567719, entitled "TREATMENT OF LUNG CANCER USING A COMBINATION OF AN ANTI-PD-1 ANTIBODY AND ANOTHER ANTI-CANCER AGENT" (International Publication No. WO 2015/176033 published on November 19, 2015, National Publication of International Patent Application No. 2017-515859 published on June 15, 2017) has resulted in the following appeal decision.

Conclusion

The appeal of the case was groundless.

Reason

No. 1 History of the procedures

The present application was filed on May 15, 2015 as an international filing date (the priority claims under the Paris Convention were received by the foreign receiving office on May 15, 2014 in the US, May 30, 2014 in the US, and April 24, 2015 in the US), and the history of the procedures is as follows:

June 28, 2019 : Notification of reasons for refusal
January 8, 2020 : Submission of a written opinion and a written amendment
January 31, 2020 : An examiner's decision of refusal
June 12, 2020 : Submission of a request for appeal

July 28, 2020 : Submission of a written amendment (formality)
(Amendment of the reasons of the request in the request for appeal)

No. 2 The Invention

The inventions according to the claims of the present application are specified by the matters recited in Claims 1 to 14 according to the scope of claims amended by the written amendment submitted on January 8, 2020. The invention according to Claim 1 of the present application (hereinafter referred to as "the Invention") is as follows:

"[Claim 1]

A composition for treating a subject afflicted with non-small cell lung cancer (NSCLC) in combination with a platinum-based doublet chemotherapy (PT-DC), comprising an antibody or an antigen-binding portion thereof ("anti-PD-1 antibody") that binds specifically to a programmed cell death-1 (PD-1) receptor and inhibits PD-1 activity; wherein the PT-DC is a combination of (i) gemcitabine at a dose of 1250 mg/m^2 and cisplatin at a dose of 75 mg/m^2, (ii) pemetrexed at a dose of 500 mg/m^2 and cisplatin at a dose of 75 mg/m^2, or (iii) paclitaxel at a dose of 200 mg/m^2 and carboplatin at a target area under the curve of 6 mg × minute/ml (AUC6)."

No. 3 Reasons for refusal stated in the examiner's decision

The reasons for refusal stated in the examiner's decision is as follows: the inventions according to Claims 1 to 14 of the present application would have been easily made by a person having ordinary skill in the art pertaining to the invention before the date of the priority claim of the present application (hereinafter referred to as "the priority date of the present application"), based on inventions described in Cited Documents 1 to 3 below which had been distributed or had become available to the public through electric communication lines within Japan or in a foreign country before the priority date of the present application, and accordingly, the Appellant should not be granted a patent under the provisions of Article 29(2) of the Patent Act.

Cited Document 1: Clin. Pharmacol. Ther., August 2014, 96(2), pp. 214-223, Epub 2014 Apr. 1
Cited Document 2: J. Clin. Oncol., July 20, 2008, 26(21), pp. 3543-3551
Cited Document 3: Oncology Letters, 2013, 5, pp. 761-767

No. 4 Described matters in the Cited Documents and Cited Invention

1. Cited Document 1

(1) Clin. Pharmacol. Ther., August 2014, 96(2), pp. 214-223, Epub 2014 Apr. 1 (hereinafter referred to as "Cited Document 1"), which was cited in the reasons for refusal stated in the examiner's decision, and is electronic technical information having been available to the public through electric communication lines before the priority date of the present application, describes the following matters. (The underlines have been added by the body. The same applies hereafter.) Note that since the original text is in English, the translation by the body is shown below.

1a (page 214, left column, lines 1 to 4)
"BACKGROUND

First-line therapy for advanced non-small cell lung cancer (NSCLC), which accounts for ~85% of all lung cancers, is platinum-based chemotherapy."

1b (page 216, right column, line 8 from the bottom to page 217, right column, line 3 from the bottom)
"Nivolumab, a fully human IgG4 PD-1 immune checkpoint inhibitor antibody, has undergone the most extensive clinical evaluation in lung cancer among the PD-1 pathway inhibitors. Evidence of activity both as a monotherapy in squamous and nonsquamous NSCLC and in combination with conventional chemotherapy has been demonstrated in patients with NSCLC (Table 3).[50,51] In pretreated advanced NSCLC patients, nivolumab monotherapy had an overall response rate of 17% (22/129), not including 6 patients with immune-related responses.[50] ... The estimated median response duration was 74.0 weeks (range: >6.1 to >133.9 weeks), and responses were ongoing in 45% of patients at the time of analysis. Overall survival was 42% at 1 year and 24% at 2 years.

Nivolumab has nine active clinical trials in NSCLC at the time of writing, including trials in patients with advanced or metastatic solid tumors that include NSCLC.[40] Phase I and I/II trials combine nivolumab with various other therapies including chemotherapies, targeted agents (bevacizumab or erlotinib), or other immunotherapies: IL-21, ipilimumab, anti-lymphocyte activation gene 3, or lirilumab, which targets a key inhibitory receptor on NK cells (...)."

1c (page 218, left column, line 7 from the bottom to right column, line 4)
"There is initial evidence that combination strategies that involve immune checkpoint blockade may also have additive effects in the clinic. In patients with advanced melanoma, combination therapy with nivolumab and ipilimumab showed preliminary

activity much greater than that seen in previous experience with either agent alone: 40% of patients on a concurrent regimen had an objective response, and 65% had evidence of clinical activity.[52] Results of the ongoing trials of checkpoint inhibitors in lung cancer will provide further insight into new therapeutic targets and inform approaches for checkpoint inhibitor use in patients who currently have limited treatment options."

1d (page 219, Table 3)

"

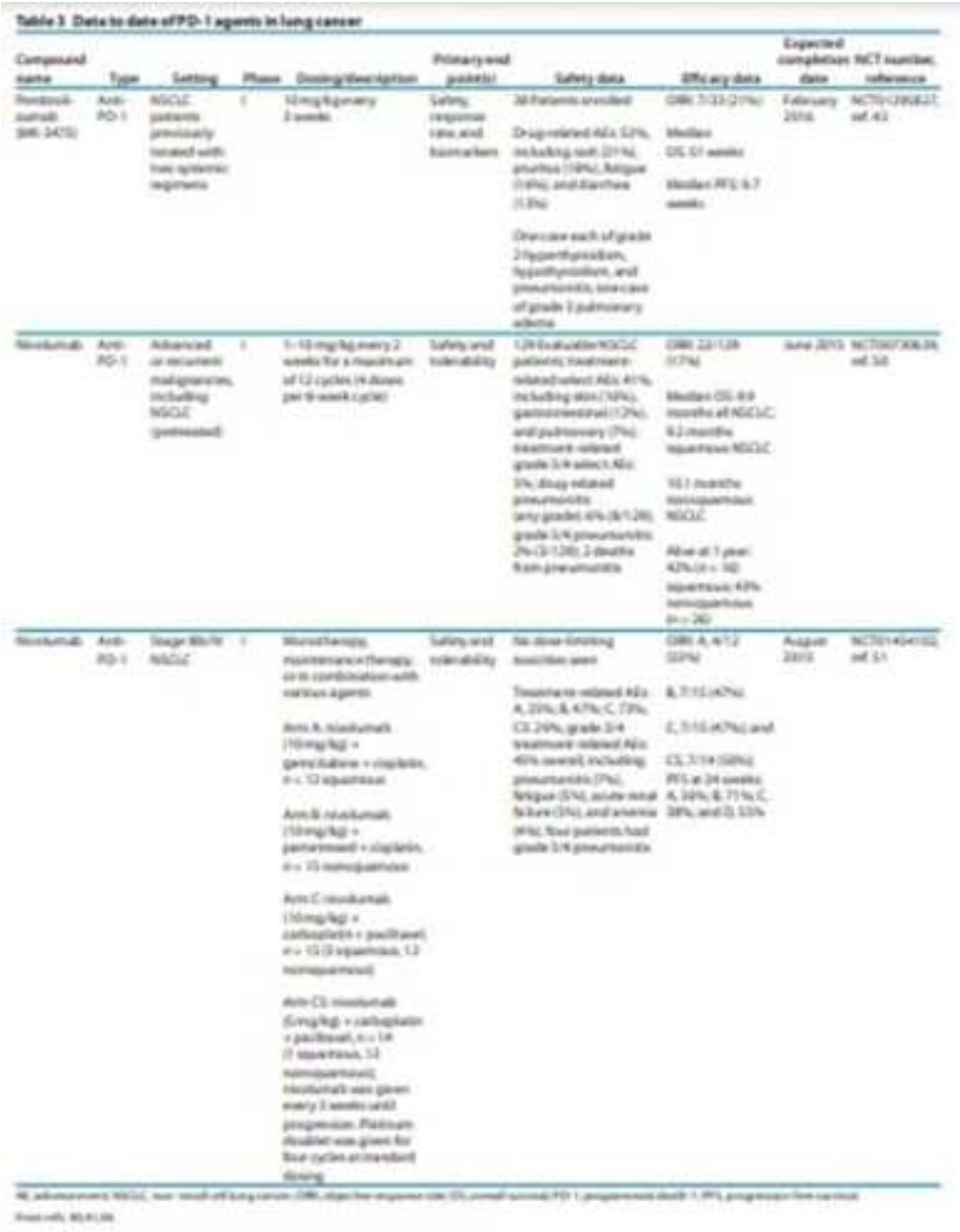

Table 3 Data to date of PD-1 agents in lung cancer

Compound name	Type	Setting	Phase	Dosing/description	Primary end point(s)	Safety data	Efficacy data	Expected completion date	NCT number, reference
Pembrolizumab (MK-3475)	Anti-PD-1	NSCLC patients previously treated with two systemic regimens	I	10 mg/kg every 2 weeks	Safety, response rate, and biomarkers	38 Patients enrolled Drug-related AEs: 52%, including rash (21%), pruritus (18%), fatigue (16%), and diarrhea (13%) One case each of grade 2 hyperthyroidism, hypothyroidism, and pneumonitis; one case of grade 3 pulmonary edema	ORR: 7/33 (21%) Median OS: 51 weeks Median PFS: 3.7 weeks	February 2016	NCT01295827; ref. 43
Nivolumab	Anti-PD-1	Advanced or recurrent malignancies, including NSCLC (pretreated)	I	1–10 mg/kg every 2 weeks for a maximum of 12 cycles (4 doses per 8-week cycle)	Safety and tolerability	129 Evaluable NSCLC patients; treatment-related select AEs: 41%, including skin (14%), gastrointestinal (12%), and pulmonary (7%); treatment-related grade 3/4 select AEs: 5%; drug-related pneumonitis (any grade): 6% (8/129), grade 3/4 pneumonitis: 2% (3/129); 2 deaths from pneumonitis	ORR: 22/129 (17%) Median OS: 9.9 months all NSCLC, 8.2 months squamous NSCLC 10.1 months nonsquamous NSCLC Alive at 1 year: 42% (n = 16) squamous; 43% nonsquamous (n = 26)	June 2015	NCT00730639; ref. 50
Nivolumab	Anti-PD-1	Stage IIIb/IV NSCLC	I	Monotherapy, maintenance therapy, or in combination with various agents Arm A: nivolumab (10 mg/kg) + gemcitabine + cisplatin, n = 12 squamous Arm B: nivolumab (10 mg/kg) + pemetrexed + cisplatin, n = 15 nonsquamous Arm C: nivolumab (10 mg/kg) + carboplatin + paclitaxel, n = 15 (3 squamous, 12 nonsquamous) Arm D1: nivolumab (3 mg/kg) + carboplatin + paclitaxel, n = 14 (1 squamous, 13 nonsquamous); nivolumab was given every 3 weeks until progression. Platinum doublet was given for four cycles or intended dosing	Safety and tolerability	No dose-limiting toxicities seen Treatment-related AEs: A, 25%; B, 47%; C, 73%; D1, 29%; grade 3/4 treatment-related AEs: 40% overall, including pneumonitis (7%), fatigue (5%), acute renal failure (5%), and anemia (4%); four patients had grade 5/4 pneumonitis	ORR: A, 4/12 (33%) B, 7/15 (47%) C, 7/15 (47%); and D1, 3/14 (50%) PFS at 24 weeks: A, 16%; B, 71%; C, 38%; and D1, 55%	August 2015	NCT01454102; ref. 51

AE, adverse event; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed death 1; PFS, progression-free survival

"

表３の標題「肺癌におけるＰＤ－１剤のこれまでのデータ」　Title of Table 3 "Data to date of PD-1 agents in lung cancer"

表３の第３段の左側から順に　From the left to the right side in the third column of Table 3

化合物名　Compound name

ニボルマブ　Nivolumab

タイプ　Type

抗ＰＤ－１　Anti-PD-1

背景　Setting

ステージＩＩＩｂ／ＩＶのＮＳＣＬＣ　Stage IIIb/IV NSCLC

フェーズ　Phase

Ｉ　　I

投薬／記述　Dosing/description

単剤療法、維持療法、又は様々な薬剤との組み合わせ

アームＡ：ニボルマブ（１０ｍｇ／ｋｇ）＋ゲムシタビン＋シスプラチン、ｎ＝１２扁平上皮、

アームＢ：ニボルマブ（１０ｍｇ／ｋｇ）＋ペメトレキセド＋シスプラチン、ｎ＝１５非扁平上皮、

アームＣ：ニボルマブ（１０ｍｇ／ｋｇ）＋カルボプラチン＋パクリタキセル、ｎ＝１５（３人が扁平上皮、１２人が非扁平上皮）、

アームＣ５：ニボルマブ（５ｍｇ／ｋｇ）＋カルボプラチン＋パクリタキセル、ｎ＝１４（１人が扁平上皮、１３人が非扁平上皮）；

ニボルマブは進行まで３週間毎に投与し、プラチナダブレット化学療法は通常の投薬で４サイクル投与　Monotherapy, maintenance therapy, or in combination with various agents

Arm A: nivolumab (10 mg/kg) + gemcitabine + cisplatin, n = 12 squamous

Arm B: nivolumab (10 mg/kg) + pemetrexed + cisplatin, n = 15 nonsquamous

Arm C: nivolumab (10 mg/kg) + carboplatin + paclitaxel, n = 15 (3 squamous, 12 nonsquamous)

Arm C5: nivolumab (5 mg/kg) + carboplatin + paclitaxel, n = 14 (1 squamous, 13 nonsquamous);

nivolumab was given every 3 weeks until progression. Platinum doublet chemotherapy was given for four cycles at standard dosing"

主要エンドポイント　Primary end point(s)

安全及び忍容性　Safety and tolerability

安全データ　Safety data

投薬を制限する毒性はみられない。治療に関連した有害事象；Ａ、２５％；Ｂ、４７％；Ｃ、７３％；Ｃ５：２５％；グレード３／４

治療に関連した有害事象：肺炎（７％）、疲労（５％）、急性腎不全（５％）、貧血（４％）；４患者は、グレード３／４の肺炎を含む全体で４５％

No dose-limiting toxicities seen

Treatment-related AEs: A, 25%; B, 47%; C, 73%; C5: 25%; grade 3/4

Treatment-related AEs: 45% overall, including pneumonitis (7%), fatigue (5%), acute renal failure (5%), and anemia (4%); four patients had grade 3/4 pneumonitis

有効性データ　Efficacy data

ＯＲＲ．Ａ、４／１２（３３％）、Ｂ、７／１５（４７％）、Ｃ、７／１５（４７％）；及びＣ５、７／１４（５０％）；２４週でのＰＦＳ：Ａ、３６％；Ｂ、７１％；Ｃ、３８％；及びＤ、５５％

ORR: A, 4/12 (33%); B, 7/15 (47%); C, 7/15 (47%); and C5, 7/14 (50%); PFS at 24 weeks: A, 36%; B, 71%; C, 38%; and D, 55%

予想完了日　Expected completion date

２０１５年８月　August 2015

ＮＣＴナンバー、参照文献　NCT number, reference

ＮＣＴ０１４５４１０２、参照文献５１　NCT01454102, ref. 51

(2) From the above description, regarding the matters described in Cited Document 1, the following is recognized.

· In Described matter 1d, Table 3 describes in column "Setting" that the subject of treatment is stage IIIb/IV NSCLC, and according to Described matter 1a, NSCLC refers to non-small cell lung cancer. That is, Cited Document 1 describes that patients with stage IIIb/IV non-small cell lung cancer have been selected as the subject of treatment.

· In Described matter 1d, Table 3 describes in column "Dosing/description" that Arm A is given nivolumab, gemcitabine, and cisplatin; Arm B is given nivolumab, pemetrexed, and cisplatin; and Arms C and C5 are given nivolumab, carboplatin, and paclitaxel.

· In Described matter 1d, Table 3 describes in column "Dosing/description" that nivolumab was given every three weeks, followed by the description that platinum doublet therapy was given at standard dosing. Thus, the platinum doublet therapy refers to a therapy with a combination of drugs other than nivolumab; i.e., a combination of gemcitabine and cisplatin in Arm A; a combination of pemetrexed and cisplatin in Arm B; and a combination of paclitaxel and carboplatin in Arms C and C5.

(3) In light of (2) above, it is recognized that Cited Document 1 describes the following invention (hereinafter referred to as "Cited Invention 1"):
"A composition for treating a subject afflicted with non-small cell lung cancer in combination with a platinum doublet therapy, comprising nivolumab; wherein the platinum doublet therapy is a combination of (i) gemcitabine and cisplatin, (ii) pemetrexed and cisplatin, or (iii) paclitaxel and carboplatin, and the platinum doublet therapy is one which is administered at standard dosing."

2. Cited Document 2
(1) J. Clin. Oncol., July 20, 2008, 26(21), pp. 3543-3551 (hereinafter referred to as "Cited Document 2"), which was also cited in the reasons for refusal stated in the examiner's decision, and is a publication distributed before the priority date of the present application, describes the following matters. Note that since the original text is in English, the translation by the body is shown below.

2a (page 3543, section "ABSTRACT")
"Purpose
Cisplatin plus gemcitabine is a standard regimen for first-line treatment of advanced non-small-cell lung cancer (NSCLC). Phase II studies of pemetrexed plus platinum compounds have also shown activity in this setting.

Patients and Methods
This noninferiority, phase III, randomized study compared the overall survival between treatment arms using a fixed margin method (hazard ratio [HR] < 1.176) in 1,725 chemotherapy-naive patients with stage IIIB or IV NSCLC and an Eastern Cooperative Oncology Group performance status of 0 to 1. Patients received 75 mg/m^2 cisplatin on day 1 and 1,250 mg/m^2 gemcitabine on days 1 and 8 (n = 863) or 75 mg/m^2 cisplatin and 500 mg/m^2 pemetrexed on day 1 every 3 weeks for up to six cycles.

Results
Overall survival for cisplatin/pemetrexed was noninferior to cisplatin/gemcitabine (median survival, 10.3 v 10.3 months, respectively; HR = 0.94; 95% CI, 0.84 to 1.05). Overall survival was statistically superior for cisplatin/pemetrexed versus cisplatin/gemcitabine in patients with adenocarcinoma (n = 847; 12.6 v 10.9 months, respectively) and large-cell carcinoma histology (n = 153; 10.4 v 6.7 months, respectively). In contrast, in patients with squamous cell histology, there was a

significant improvement in survival with cisplatin/gemcitabine versus cisplatin/pemetrexed (n = 473; 10.8 v 9.4 months, respectively). For cisplatin/pemetrexed, rates of grade 3 or 4 neutropenia, anemia, and thrombocytopenia ($P \leq .001$); febrile neutropenia ($P = .002$); and alopecia ($P < .001$) were significantly lower, whereas grade 3 or 4 nausea ($P = .004$) was more common.

Conclusion
In advanced NSCLC, cisplatin/pemetrexed provides similar efficacy with better tolerability and more convenient administration than cisplatin/gemcitabine. This is the first prospective phase III study in NSCLC to show survival differences based on histologic type."

(2) From the above description, it is recognized that Cited Document 2 describes that:
· a combination of gemcitabine at a dose of 1250 mg/m^2 and cisplatin at a dose of 75 mg/m^2; or
· a combination of pemetrexed at a dose of 500 mg/m^2 and cisplatin at a dose of 75 mg/m^2,
is administered in order to treat a subject afflicted with non-small cell lung cancer.

3. Cited Document 3
(1) Oncology Letters, 2013, 5, pp. 761-767 (hereinafter referred to as "Cited Document 3"), which was also cited in the reasons for refusal stated in the examiner's decision and is a publication distributed before the priority date of the present application, describes the following matters. Note that since the original text is in English, the translation by the body is shown below.

3a (page 761, section "Abstract")
"The combination of carboplatin and paclitaxel is one of the most commonly used regimens for the treatment of non-small cell lung cancer (NSCLC). We aimed to compare the standard tri-weekly and weekly schedules of this treatment, while considering treatment-related hematological toxicities. We retrospectively analyzed the weekly [paclitaxel, 70 mg/m^2/week on days 1, 8, and 15, and carboplatin, area under the curve (AUC) = 6, every 4 weeks] and standard tri-weekly (200 mg/m^2 paclitaxel, and AUC = 6 carboplatin, on day 1 every 3 weeks] schedules in patients with previously untreated advanced NSCLC. A total of 167 patients were enrolled in this study. The median age of the patients was 65 years (range, 31-79 years). The weekly and

standard arms included 73 and 94 patients, respectively. The incidence of grade 3 or 4 neutropenia and neuropathy was significantly decreased in the weekly arm compared with the standard arm (37.0 vs. 70.2%). The median survival and progression-free survival times were 11.8 and 4.2 months, respectively, in the weekly arm and 11.6 and 3.1 months, respectively, in the standard arm. The results of the multivariate analysis indicated that the weekly schedule [hazard ratio (HR) = 0.634, P = 0.0262] and grade 3 or 4 neutropenia (HR = 0.372, P = 0.0007) were independent favorable prognostic factors for overall survival time. In conclusion, the weekly schedule of carboplatin and paclitaxel was less toxic than and potentially superior to the standard tri-weekly schedule. However, further optimization of the dose and schedule is warranted."

(2) From the above description, it is recognized that Cited Document 3 describes that:
· a combination of paclitaxel at a dose of 200 mg/m^2 and carboplatin at AUC6
is administered in order to treat a subject afflicted with non-small cell lung cancer.

No. 5 Comparison
1. The Invention and Cited Invention 1 are compared.

The "platinum doublet therapy" of Cited Invention 1 is a chemotherapy because it refers to a therapy with chemotherapeutic agents such as a combination of: gemcitabine and cisplatin; pemetrexed and cisplatin; or paclitaxel and carboplatin. Thus, the "platinum doublet therapy" of Cited Invention 1 corresponds to the "platinum-based doublet chemotherapy" of the Invention.

Further, according to Described matter 1b, "nivolumab" of Cited Invention 1 is a "fully human IgG4 PD-1 immune checkpoint inhibitor antibody" and a "PD-1 pathway inhibitor"; that is, it refers to an "antibody that binds specifically to a PD-1 receptor and inhibits PD-1 activity." Thus, the "nivolumab" of Cited Invention 1 corresponds to "an antibody or an antigen-binding portion thereof ("anti-PD-1 antibody") that binds specifically to a programmed cell death-1 (PD-1) receptor and inhibits PD-1 activity" of the Invention.

2. From the above, the corresponding feature and the different feature between the Invention and Cited Invention 1 are as follows.
[Corresponding Feature]
"A composition for treating a subject afflicted with non-small cell lung cancer (NSCLC) in combination with a platinum-based doublet chemotherapy (PT-DC), comprising an antibody or an antigen-binding portion thereof ("anti-PD-1 antibody") that binds

specifically to a programmed cell death-1 (PD-1) receptor and inhibits PD-1 activity; wherein the PT-DC is a combination of (i) gemcitabine and cisplatin, (ii) pemetrexed and cisplatin, or (iii) paclitaxel and carboplatin."

[Different Feature]

In the Invention, the platinum-based doublet chemotherapy is "a combination of (i) gemcitabine at a dose of 1250 mg/m^2 and cisplatin at a dose of 75 mg/m^2, (ii) pemetrexed at a dose of 500 mg/m^2 and cisplatin at a dose of 75 mg/m^2, or (iii) paclitaxel at a dose of 200 mg/m^2 and carboplatin at a target area under the curve of 6 mg × minute/ml (AUC6)." In contrast, in Cited Invention 1, the combination of drugs defined in (i) to (iii) of the Invention is described, but the doses are only described as "standard dosing."

No. 6 Judgment

The different feature will now be discussed below.

1. Different Feature

According to No. 4, 2.(2) above, Cited Document 2 describes that:

· a combination of gemcitabine at a dose of 1250 mg/m^2 and cisplatin at a dose of 75 mg/m^2; or

· a combination of pemetrexed at a dose of 500 mg/m^2 and cisplatin at a dose of 75 mg/m^2

is administered in order to treat a subject afflicted with non-small cell lung cancer. These are none other than the combinations of "(i) gemcitabine at a dose of 1250 mg/m^2 and cisplatin at a dose of 75 mg/m^2" and "(ii) pemetrexed at a dose of 500 mg/m^2 and cisplatin at a dose of 75 mg/m^2" as defined in the Invention, respectively.

In addition, according to No. 4, 3.(2) above, Cited Document 3 describes that:

· a combination of paclitaxel at a dose of 200 mg/m^2 and carboplatin at AUC6

is administered in order to treat a subject afflicted with non-small cell lung cancer. This is none other than the combination of "(iii) paclitaxel at a dose of 200 mg/m^2 and carboplatin at a target area under the curve of 6 mg × minute/ml (AUC6)" as defined in the Invention.

Further, Cited Invention 1 and the technology described in Cited Document 2 or 3 are common in the point that both are technology for administering a combination of (i) gemcitabine and cisplatin, (ii) pemetrexed and cisplatin, or (iii) paclitaxel and

carboplatin in order to treat a subject afflicted with non-small cell lung cancer (NSCLC). Therefore, as the "standard dosing" in platinum-based doublet chemotherapy that is "a combination of (i) gemcitabine and cisplatin, (ii) pemetrexed and cisplatin, or (iii) paclitaxel and carboplatin" as described in Cited Invention 1, a person skilled in the art would have easily conceived of using "a combination of (i) gemcitabine at a dose of 1250 mg/m^2 and cisplatin at a dose of 75 mg/m^2, (ii) pemetrexed at a dose of 500 mg/m^2 and cisplatin at a dose of 75 mg/m^2, or (iii) paclitaxel at a dose of 200 mg/m^2 and carboplatin at a target area under the curve of 6 mg × minute/ml (AUC6)" by adopting the exemplary doses described in Cited Document 2 or 3.

2. Effects

(1) Objective response rate (ORR)

The objective response rate (ORR) is discussed below.

The specification of the Invention describes that the objective response rates (ORRs) resulting from the composition according to the Invention are 33% of 4/12, 47% of 7/15, 45% of 7/15, and 43% of 6/14 in the order of "nivolumab 10 mg/kg and a combination of gemcitabine at a dose of 1250 mg/m^2 and cisplatin at a dose of 75 mg/m^2", "nivolumab 10 mg/kg and a combination of pemetrexed at a dose of 500 mg/m^2 and cisplatin at a dose of 75 mg/m^2," "nivolumab 10 mg/kg and a combination of paclitaxel at a dose of 200 mg/m^2 and carboplatin at a target area under the curve of 6 mg × minute/ml (AUC6)," and "nivolumab 5 mg/kg and a combination of paclitaxel at a dose of 200 mg/m^2 and carboplatin at a target area under the curve of 6 mg × minute/ml (AUC6)" (Table 2).

On the other hand, Cited Document 1 describes that the ORRs are 33% of 4/12, 47% of 7/15, 47% of 7/15, and 50% of 7/14 in the order of "nivolumab 10 mg/kg and a combination of gemcitabine and cisplatin," "nivolumab 10 mg/kg and a combination of pemetrexed and cisplatin," "nivolumab 10 mg/kg and a combination of paclitaxel and carboplatin," and "nivolumab 5 mg/kg and a combination of paclitaxel and carboplatin" (Described matter 1d). Of these four combinations, the first three combinations are exactly the same as the ORRs described in the specification of the Invention, including the number of patients, and the fourth combination results in an objective response rate (43%) described in the specification of the Invention, which is rather worse than 50% in Cited Invention 1.

In light of the above, regarding the ORR, it is not deemed that the Invention exerts a prominent effect as compared to Cited Invention 1.

(2) Duration of progression-free survival (PFS)

The duration of progression-free survival (PFS) is discussed below. The specification of the Invention describes in [0123] that "PFS rates at 24 weeks ranged from 38 - 71% ... across treatment arms." This range almost overlaps with the range of 36% to 71% that is PFS rate at 24 weeks described in Cited Document 1 (Described matter 1d). Therefore, regarding the PFS rate at 24 weeks, it is not deemed that the Invention exerts a prominent effect as compared to Cited Invention 1.

(3) Adverse event (AE)

The adverse event (AE) is discussed below.

The specification of the Invention describes that the proportions of patients with any adverse event resulting from the composition according to the Invention are 25%, 47%, 73%, and 29% in the order of "nivolumab 10 mg/kg and a combination of gemcitabine at a dose of 1250 mg/m^2 and cisplatin at a dose of 75 mg/m^2," "nivolumab 10 mg/kg and a combination of pemetrexed at a dose of 500 mg/m^2 and cisplatin at a dose of 75 mg/m^2," "nivolumab 10 mg/kg and a combination of paclitaxel at a dose of 200 mg/m^2 and carboplatin at a target area under the curve of 6 mg × minute/ml (AUC6)," and "nivolumab 5 mg/kg and a combination of paclitaxel at a dose of 200 mg/m^2 and carboplatin at a target area under the curve of 6 mg × minute/ml (AUC6)" (Table 5).

On the other hand, Cited Document 1 describes that no dose-limiting toxicities have been seen and that the proportions of treatment-related adverse events are 25%, 47%, 73%, and 29% in the order of "nivolumab 10 mg/kg and a combination of gemcitabine and cisplatin," "nivolumab 10 mg/kg and a combination of pemetrexed and cisplatin," "nivolumab 10 mg/kg and a combination of paclitaxel and carboplatin," and "nivolumab 5 mg/kg and a combination of paclitaxel and carboplatin." These four values exactly correspond to the proportions of patients with any adverse event described in the specification of the Invention.

In light of the above, regarding the adverse event (AE), it is not deemed that the Invention exerts a prominent effect as compared to Cited Invention 1.

(4) Duration of overall survival (OS)

Cited Document 1 does not describe any specific data of results on the duration of overall survival (OS). However, as mentioned in (1) to (3) above, the various effects on ORR, PFS, and AE exerted by Cited Invention 1 are similar to the trial results of Example 1 in the specification of the Invention. Therefore, it is expected that Cited

Invention 1 has a similar effect on OS to that shown in Example 1 of the specification of the Invention.

3. Appellant's allegation
(1) The Appellant alleges the following matters in the request for appeal which was amended by the written amendment submitted on July 28, 2020.

(A) Regardless of whether Cited Document 2 and/or Cited Document 3 describe dosage regimens for various PT-DCs, a person skilled in the art cannot assume from the descriptions of Cited Document 1, Cited Document 2, and/or Cited Document 3 that the same dose is safe and effective when combined with anti-PD-1 antibody therapy as recited in Claim 1 of the present application.
(B) The specification of the Invention provides data showing that the combination therapy recited in the claims of the present application has improved properties as compared to the PT-DC therapy disclosed in Cited Document 2 and Cited Document 3. In particular, Example 1 of the present application provides that patients treated with the combination therapy of nivolumab and PT-DC had improved progression-free survival (PFS) and objective response rate (OS) (Note added by the appeal decision: So in original) as compared to PT-DC alone.
(C) Cited Document 3 describes that 70 mg/m^2 paclitaxel and AUC6 carboplatin in the weekly schedule was "less toxic and potentially superior" to 200 mg/m^2 paclitaxel and AUC6 carboplatin in the tri-weekly schedule (page 766, last paragraph and Abstract). Therefore, taking Cited Document 3 into consideration, a person skilled in the art would not have easily selected paclitaxel at a dose of 200 mg/m^2 and carboplatin at a target area under the curve of 6 mg × minute/ml (AUC6) in combination with anti-PD-1 antibody.

(2) The above allegations are discussed below.
Regarding (A) and (B)

The Appellant alleges that the platinum-based doublet chemotherapy described in Cited Document 2 or Cited Document 3 is safe and effective at the same dose when combined with anti-PD-1 antibody therapy, and that in particular, regarding efficacy, the combined therapy has improved progression-free survival (PFS), objective response rate (ORR), and duration of overall survival (OS).

However, regarding efficacy, as mentioned in 2 above, it is not deemed that the Invention exerts prominent effects on objective response rate (ORR), progression-free

survival (PFS) rate at 24 weeks, and duration of overall survival (OS) as compared to Cited Invention 1.

In addition, regarding safety, as mentioned in 2 above, the Invention does not exert a prominent effect on adverse event (AE) as compared to Cited Invention 1.

Further, the NCT number for the Phase I clinical trial described in Example 1 of the Invention is "NCT01454102" ([0117]). On the other hand, in Described matter 1d of Cited Document 1, regarding the data in the third column from the top of Table 3, the column for "NCT Number" is described as "NCT01454102". That is, the two are the same NCT number, which is the identification number assigned to the clinical trial. Thus, the clinical trial described in Example 1 of the specification of the Invention and the clinical trial described in Cited Document 1 are actually the same trial. Furthermore, in light of this point as well, it is not considered that the various effects on (1) ORR, (2) PFS, (3) AE, and (4) OS exerted by the Invention shown in Example 1 of the specification of the Invention provide any difference in prominent effects as compared to the above-mentioned various effects which can be exerted by Cited Invention 1.

Regarding (C)

Cited Document 3 aimed to compare the tri-weekly dosage schedule, which is the standard treatment schedule of combination therapy with paclitaxel and carboplatin, with the weekly dosage schedule (Described matter 3a), and describes that "the weekly schedule ... was less toxic than and potentially superior to the standard tri-weekly schedule" (Described matter 3a). However, Cited Document 3 describes "a combination of paclitaxel at a dose of 200 mg/m^2 and carboplatin at AUC6" as standard dosing. Thus, in the invention according to the case where a combination of paclitaxel and carboplatin is selected as the platinum-based doublet therapy of Cited Invention 1, as the "standard dosing", a person skilled in the art could have easily conceived of adopting "a combination of (iii) paclitaxel at a dose of 200 mg/m^2 and carboplatin at a target area under the curve of 6 mg × minute/ml (AUC6)" described as the standard dosing in Cited Document 3.

Therefore, the Appellant's allegations (A) to (C) above cannot be accepted.

4. Summary

Therefore, the Invention would have been easily made by a person skilled in the art based on Cited Invention 1 and the matters described in Cited Documents 2 and 3, and the Appellant should not be granted a patent for the Invention under the provisions

of Article 29(2) of the Patent Act.

No. 7 Closing

As described above, since the Appellant should not be granted a patent for the Invention under the provisions of Article 29(2) of the Patent Act, the present application shall be rejected even without examining the inventions relating to other claims.

Therefore, the appeal decision shall be made as described in the conclusion.

May 24, 2021

Chief administrative judge: OKAZAKI, Miho
Administrative judge: TOMINAGA, Midori
Administrative judge: OKUBO, Motohiro