August 18, 2025
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 12, Apparatus for Physical therapy
Term Name	Alternating electric field tumor treating system
Brand Name	Optune Lua
Applicant	NovoCure GmbH
Designated Marketing Authorization Holder	NovoCure K.K.
Date of Application	December 27, 2023 (Application for marketing approval of a medical device produced by a foreign manufacturer)

Results of Deliberation

In its meeting held on August 18, 2025, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product is not designated as a medical device subject to a use-results survey for approval. The product is not classified as a biological product or a specified biological product.

The product should be approved with the following condition.

Approval Condition

1. The applicant is required to ensure that the product is used for eligible patients selected by physicians who are adequately knowledgeable and experienced in the treatment of non-small cell lung cancer and familiar with how to use and treatment-associated complications, and at medical institutions with established treatment systems. To this end, dissemination of the proper use guidelines compiled jointly with relevant academic societies, provision of a training program, and other measures must be taken as necessary.

Review Report

August 7, 2025
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Classification	Instrument & Apparatus 12, Apparatus for Physical therapy
Term Name	Alternating electric field tumor treating system
Brand Name	Optune Lua
Applicant	NovoCure GmbH
Designated Marketing Authorization Holder	NovoCure K.K.
Date of Application	December 27, 2023 (Application for marketing approval of a medical device produced by a foreign manufacturer)
Reviewing Office	Office of Medical Devices II

Review Results

August 7, 2025

Classification	Instrument & Apparatus 12, Apparatus for Physical therapy
Term Name	Alternating electric field tumor treating system
Brand Name	Optune Lua
Applicant	NovoCure GmbH
Designated Marketing Authorization Holder	NovoCure K.K.
Date of Application	December 27, 2023 (Application for marketing approval of a medical device produced by a foreign manufacturer)

Results of Review

"Optune Lua" (or "the product") is a tumor treatment system with alternating tumor treating fields to be used in combination with programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors to treat adult patients diagnosed with unresectable advanced or recurrent non-small cell lung cancer (NSCLC) progressing after platinum-based chemotherapy. The product consists of a generator that produces tumor treating fields (TTFields) to treat NSCLC, transducer arrays that deliver TTFields to the thoracic cavity, cables, power supply, etc. TTFields inhibits cancer cell replication by preventing proper formation of mitotic spindles and cytoplasmic bands during the anaphase stage of mitotic cell division cycle, inducing intracellular translocation of macromolecules and organelles by dielectrophoresis during the telophase.

The applicant submitted the non-clinical data of Optune Lua including physical and chemical characterization, electrical safety, electromagnetic compatibility, biological safety, stability, durability, and performance, demonstrating no particular problem.

Also submitted were data of Optune Lua from a foreign LUNAR trial (hereinafter referred to as "the clinical study"), which evaluated the efficacy and safety of Optune Lua combination therapy against the control standard-of-care alone in patients with stage 4 NSCLC progressing during or after treatment with platinum-based antineoplastics.

The primary efficacy endpoint was overall survival (OS) at the data cutoff (median follow-up period, 10.0 months [range, 0.03-64.5]). The median OS was 13.2 months (95% confidence interval [CI], 10.3-15.5) in the Optune Lua group (n = 145) and 9.9 months (95% CI, 8.2-12.2) in the control group (n = 146). The hazard ratio for death was 0.76 (95% CI, 0.58-0.99), which achieved the primary endpoint of the clinical study and demonstrated significant prolongation of OS in the Optune Lua group ($P = 0.0413$, based on log-rank test).

The OS in the standard of care therapy (immune checkpoint inhibitor [ICI]) or docetaxel hydrate (docetaxel) was compared as secondary endpoint. The median OS was 19.0 months (95% CI, 10.6-28.2 months) in the Optune Lua + ICI group (n = 70) and 10.8 months (95% CI, 8.3-17.6 months) in the ICI alone group (n = 71), with a hazard ratio for death of 0.63 (95% CI, 0.42-0.95) ($P = 0.024$[1] based on log-rank test). The median OS was 11.1 months (95% CI, 8.2-13.9) in the Optune Lua + docetaxel group (n = 75) and 8.9 months (95% CI, 6.5-11.3) in the docetaxel alone group (n = 75), with a hazard ratio for death of 0.88 (95% CI, 0.61-1.26) ($P = 0.469$[2] based on log-rank test).

The safety analyses revealed no difference in the incidences of serious adverse events between the study groups. Device-related adverse events occurred in 97 patients (68.8%), mostly Grade 1 or Grade 2 in severity, and Grade 3 adverse events occurred in 8 patients (5.7%). Of the 97 patients, 90 experienced known adverse events classified as “skin and subcutaneous tissue disorders” due to application of the transducer arrays on the skin.

While the clinical study achieved the primary efficacy endpoint, the OS analysis of each standard of care for the secondary endpoint showed the add-on effect of Optune Lua only in the Optune Lua + ICI group. There was no clear difference in the Optune Lua + docetaxel group, and this may be attributable to the primary mechanisms of action of Optune Lua and docetaxel with some overlap, i.e., acting on microtubules and thereby inhibiting cell division. Because the present data have failed to show the efficacy of Optune Lua in combination with docetaxel, PMDA has concluded that Optune Lua’s clinically significant efficacy is demonstrated when used with ICI.

The safety evaluation revealed device-related adverse events that were mostly known cutaneous events due to the application of the transducer arrays, which were treatable and manageable by medication, etc. Therefore, these events were considered acceptable.

NSCLC is a malignant tumor with a poor prognosis accounting for approximately 90% of all lung cancers. Optune Lua is intended for use in patients with unresectable advanced or recurrent NSCLC who have previously received platinum-based chemotherapy regimens. Currently, the second-line standard therapies have not shown favorable results in this patient population. Optune Lua has been shown to improve OS when used in combination with ICI, and PMDA has concluded that the product is highly useful and that it is clinically meaningful to introduce Optune Lua in Japan as a new therapy for NSCLC.

In NSCLC treatment, Optune Lua will be Japan’s first tumor treatment system employing alternating tumor treating fields. For its effective and safe introduction, it is crucial that eligible patients be selected by physicians and at medical institutions with adequate knowledge and experience in lung cancer treatment after obtaining product knowledge including how to use it, in view of the characteristics of Optune Lua as local treatment. In addition, medical institutions providing Optune Lua treatment should be able to appropriately follow up patients with product-associated cutaneous disorders and those who

[1] Corrected after the deliberation by the Committee on Medical Devices and In-vitro Diagnostics (Note: The text herein has been corrected in accordance with the errata sheet of the Japanese review report.)

[2] Corrected after the deliberation by the Committee on Medical Devices and In-vitro Diagnostics (Note: The text herein has been corrected in accordance with the errata sheet of the Japanese review report.)

use it at home. To this end, adherence to the guidelines for proper use, which will be prepared by related academic societies, is important.

As a result of its regulatory review, PMDA has concluded that Optune Lua may be approved for the intended use shown below, with the following approval condition, and that the application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

Intended Use

Optune Lua is intended for use in combination therapy with PD-1/PD-L1 inhibitors for adult patients with a diagnosis of unresectable advanced or recurrent non-small cell lung cancer progressing after platinum-based chemotherapy regimens.

Approval Condition

The applicant is required to ensure that the product is used for eligible patients selected by physicians who are adequately knowledgeable and experienced in the treatment of non-small cell lung cancer and familiar with how to use and treatment-associated complications, and at medical institutions with established treatment systems. To this end, dissemination of the proper use guidelines compiled jointly with relevant academic societies, provision of a training program, and other measures must be taken as necessary.

Review Report

August 7, 2025

Product for Review

Classification	Instrument & Apparatus 12, Apparatus for Physical therapy
Term Name	Alternating electric field tumor treating system
Brand Name	Optune Lua
Applicant	NovoCure GmbH
Designated Marketing Authorization Holder	NovoCure K.K.
Date of Application	December 27, 2023 (Application for marketing approval of a medical device produced by a foreign manufacturer)
Proposed Intended Use	Optune Lua is intended for use for adult patients with a diagnosis of unresectable advanced or recurrent non-small cell lung cancer progressing after cancer chemotherapy.

Table of Contents

List of Abbreviations

BMI	Body Mass Index
BOR	Best Overall Response
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
ICI	Immune Checkpoint Inhibitor
IEC	International Electrotechnical Committee
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent To Treat
MRI	Magnetic Resonance Imaging
NE	Not Evaluable
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
ORR	overall response rate
OS	Overall Survival
PD	progressive disease
PD-1	Programmed cell death 1
PD-L1	programmed cell death ligand 1
PFS	Progression Free Survival
PR	partial response
PS	Performance Status
QOL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable Disease
SOC	Standard of Care
TPS	Tumor Proportion Score
ULN	Upper Limit of Normal

I. Product Overview

"Optune Lua" (or the product) is a tumor treatment system with alternating tumor treating fields to be used in combination with programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors to treat adult patients diagnosed with unresectable advanced or recurrent non-small cell lung cancer (NSCLC) progressing after platinum-based chemotherapy. The product consists of a generator that produces tumor treating fields (TTFields) to treat NSCLC, transducer arrays that deliver TTFields to the thoracic cavity, and other components (cables, power supply, etc.) (Figure 1).

TTFields inhibits cancer cell replication by preventing proper formation of mitotic spindles and cytoplasmic bands during the anaphase stage of the mitotic phase of the cell cycle and inducing intracellular translocation of macromolecules and organelles by dielectrophoresis during the telophase. The applicant's "NovoTTF-100A System," a device employing TTFields technology to treat glioblastoma multiforme, was approved (Approval number, 22700BZI00010000, hereinafter referred to as "Optune Gio") in 2015. Optune Lua is a device to treat NSCLC, sharing the same principle as Optune Gio.

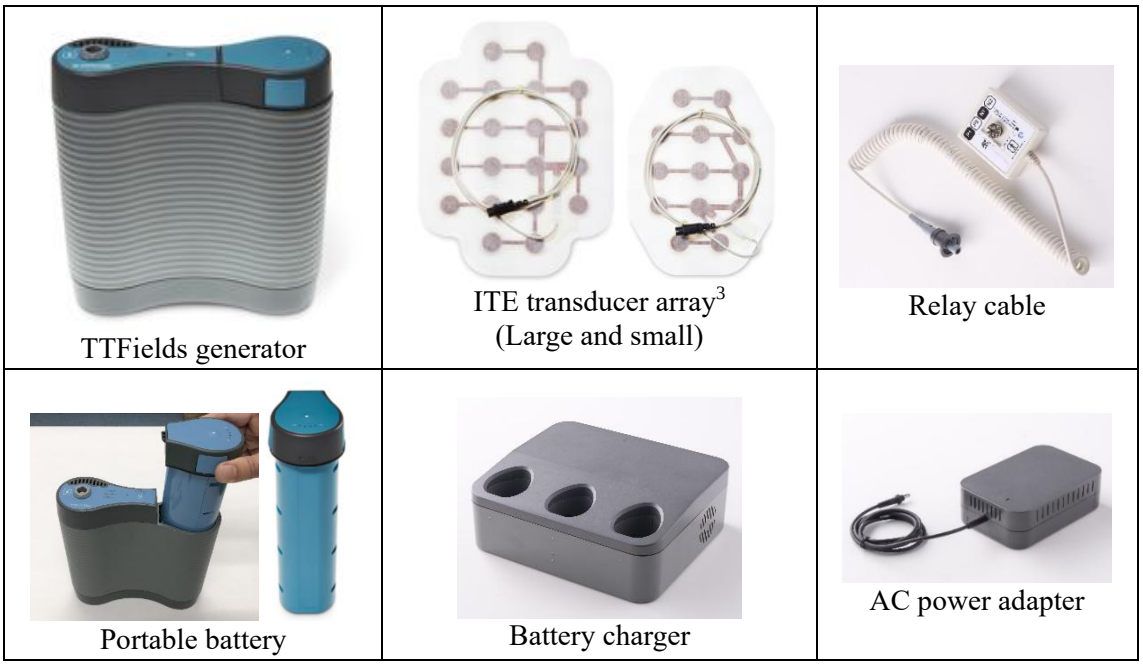


Figure 1. Main constituent parts of Optune Lua

TTFields therapy is non-invasive. Two pairs (4 in total) of electrically insulated transducer arrays are placed directly around the patient's chest or torso (Figure 2). The TTFields generator applies alternating current to the paired transducer arrays alternately to produce TTFields alternately. The transducer arrays are comprised of multiple ceramic disks (20 per large transducer array and 13 per small transducer array). The TTFields generator applies alternating current to the ceramic disks (150 kHz and 200 mA per ceramic disk).

[3] The application data includes the former model "ILE transducer array" which may be distributed as a backup. The "ITE transducer array" has a better fit than the "ILE transducer array," but there is no difference in the components that affect the treatment performance.

During the use of Optune Lua, the TTFields generator needs to be connected to the AC power adapter or the portable battery. The portable battery can be carried in the special bag or knapsack so that patients are treated during everyday life. The recommended treatment duration with Optune Lua is 18 hours a day. The transducer arrays need to be changed at least twice a week.

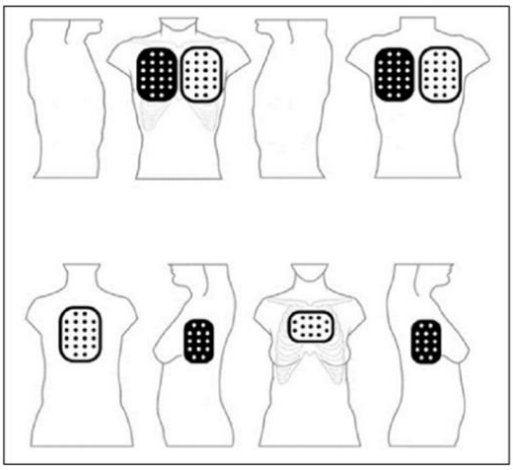


Figure 2. Typical locations of placement of the transducer arrays (Top, examples for men; Bottom, examples for women)

II. Summary of the Data Submitted and Outline of the Review Conducted by the Pharmaceuticals and Medical Devices Agency

The following outlines the data submitted by the applicant in support of the present application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA).

The expert advisors present during the Expert Discussion on Optune Lua declared that they did not fall under the Item 5 in Chapter 3 of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

According to the latest cancer statistics from the National Cancer Center Japan, the probability of death from lung cancer (cumulative risk of death) in Japanese people in recent years is 26.2% in men and 17.7% in women (based on data in 2021). The number of deaths from lung cancer is highest in men and second highest in women. The 5-year relative survival rates (2009-2011) is as low as 34.9% (29.5% in men and 46.8% in women), indicating that lung cancer treatment has been a critical issue.[i]

NSCLC is a malignant tumor accounting for approximately 90% of all lung cancers.[ii] NSCLC leads to significantly decreased quality of life (QOL), severe symptoms, and poor prognosis. For patients with advanced metastatic lesions, chemotherapy, molecular targeted therapy, cancer immunotherapy, and other supportive therapies are expected to improve survival and alleviate symptoms.[iii] However, these treatments have so far shown only limited efficacy particularly in patients on the second-line or subsequent chemotherapy. New therapeutic options are in great demand.

Optune Lua is a tumor treatment system generating TTFields specially intended for NSCLC utilizing the TTFields technology of Optune Gio.

Previous studies on TTFields evaluated the effects of 72-hour exposure to TTFields in cancer cell lines of major tumor types including NSCLC, glioma, breast tumor, pancreas tumor, and melanoma. The optimal frequency of TTFields depends on tumor types. The optimal frequency of TTFields for NSCLC was found to be 150 kHz, and thus the output frequency of Optune Lua was determined as 150 kHz.[iv]

After design verification based on basic studies, a multicenter, open-label, randomized study (EF-24, LUNAR study) started in 2016 in the US, Europe, Canada, Serbia, and China to compare the combination of Optune Lua with the standard of care (immune checkpoint inhibitor [ICI] or docetaxel hydrate [docetaxel]) against the standard of care, aiming to verify the efficacy and safety of Optune Lua in patients with stage 4 NSCLC who did not respond to platinum-based agents.

During the clinical study, a new TTFields generator, lighter but harmless to the performance, was developed for Optune Lua, and it was used in the study. After the completion of the clinical study, improved ITE transducer arrays of Optune Lua were developed for a better fit.

1.A.(2) Use in foreign countries

The product's approval status in foreign countries is shown in Table 1. Optune Lua has been approved for the same intended use in the US and Europe (as of July 11, 2025).

Table 1. Use in foreign countries

Region	Intended Use	Date of approval	Quantity used
US	Optune Lua concurrent with PD-1/PD-L1 inhibitors or docetaxel is indicated for adult patients with metastatic NSCLC who have progressed on or after a platinum-based regimen.	October 15, 2024	[redacted] cases
Europe	Optune Lua concurrent with an immune checkpoint inhibitor or docetaxel is indicated for adult patients with metastatic NSCLC who have progressed on or after a platinum-based regimen.	April 17, 2025	[redacted] cases

1.A.(3) Malfunctions in foreign countries

As of July 11, 2025 in the US, adverse events of hypersensitivity and skin reaction occurred in [redacted] of [redacted] cases (1.1%) and [redacted] of [redacted] cases (0.6%), respectively. All were known and serious events. No malfunctions occurred.

2. Design and Development

2.(1) Performance and safety specifications

2.(1).A Summary of the data submitted

The proposed performance and safety specifications of Optune Lua included accuracy of the measurement circuit in the TTFields generator, output current of the TTFields generator, signal frequency of electric current applied to the transducer arrays through the TTFields generator, measurement accuracy and recording of the thermistor temperatures of the transducer arrays, leakage current of the transducer arrays, cover tape adhesion of the transducer arrays, ceramic disk capacitance

of the transducer arrays, impedance of the transducer arrays, biological safety, sterility assurance, electrical safety, and electromagnetic compatibility.

2.(1).B Outline of the review conducted by PMDA

PMDA reviewed justifications of the performance and safety specifications, test methods, and acceptance criteria and concluded that there was no particular problem with these specifications.

2.(2) Physical and chemical characterization

2.(2).A Summary of the data submitted

The applicant submitted test results on impedance and leakage current of the transducer arrays, ceramic disk conductance and capacitance, and adhesive strength of the cover tape as data supporting the physical and chemical characterization of Optune Lua. The acceptance criteria were met in all tests.

2.(2).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the physical and chemical characterization and concluded that there was no particular problem.

2.(3) Electrical safety and electromagnetic compatibility

2.(3).A Summary of the data submitted

The applicant submitted data on the electrical safety and electromagnetic compatibility of Optune Lua. The data have demonstrated that Optune Lua meets standards that define the general requirements for the basic safety and essential performance of medical electrical equipment (International Electrotechnical Committee [IEC] 60601-1:2005 + AMD1:2012 + AMD2:2020) and standards that define electromagnetic compatibility of medical electrical equipment (IEC 60601-1-2:2014 + AMD1:2020). The electrical safety study of the battery charger was conducted in accordance with IEC62368-1:2014, and the applicant submitted data showing conformity to the standard.

2.(3).B Outline of the review conducted by PMDA

PMDA reviewed the electrical safety and electromagnetic compatibility and concluded that there was no particular problem.

2.(4) Biological safety

2.(4).A Summary of the data submitted

The applicant submitted test results on cytotoxicity, sensitization, and skin irritation as data supporting biological safety of Optune Lua. There were no problematic findings.

2.(4).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the biological safety and concluded that there was no particular problem.

2.(5) Stability and durability

2.(5).A Summary of the data submitted

The applicant omitted the submission of test results supporting the stability of Optune Lua, and submitted a self-declaration stating that its shelf life was determined based on the results of necessary stability studies in accordance with the "Handling of stability studies related to the determination of the shelf life in the application for marketing approvals (certifications) of medical devices (in Japanese)" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012). The applicant also omitted the submission of the data on material deterioration of the transducer arrays due to gamma radiation sterilization in accordance with the "Partial revision of 'Points to Consider in Preparing Summary Technical Documentation (STED) for Medical Devices'" (PSEHB/MDED Notification No. 0228-7, dated February 28, 2018). Material deterioration was tested using appropriate test samples, taking into consideration the maximum possible dose estimated from the dose distribution shown in manufacturing process data. The applicant submitted a declaration assuring the product performance of Optune Lua against material degradation and its 9-month shelf life.

2.(5).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the stability and durability of Optune Lua and concluded that there was no particular problem.

2.(6) Performance

The applicant submitted results of the design verification, *in vivo* safety test at TTFields, and simulation test of TTFields distribution as data supporting the performance of Optune Lua.

2.(6).A Summary of the data submitted

The applicant submitted results of design verification tests for generator current, voltage, and signal frequency generation, measurement accuracy of temperatures inside the generator hardware, system error detection in the generator software, temperature measurement accuracy and operational temperature rise of the transducer arrays, and the performance of the portable battery. All test results met the acceptance criteria.

To support the *in vivo* safety of TTFields, the applicant submitted results of safety studies in rats with TTFields applied to the torso. TTFields was applied to rats' torso at a frequency of 150 kHz for comparative evaluation between the sham and TTFields groups. The rats were treated for 2 weeks. Based on the similarities in blood cell count, biochemical markers, and the histopathology between the 2 groups, the safety of TTFields was confirmed. Also submitted were results of a long-term follow-up study in rabbits on the safety of TTFields when used in combination with chemotherapy compared with that in chemotherapy alone. The rats were treated for 4 weeks and followed for 4 weeks. Based on the similarities in blood cell count, biochemical markers, and histopathology between the 2 groups, the safety of TTFields was confirmed.

The applicant submitted results of TTFields distribution simulation studies including simulations of TTFields in animals and TTFields intensity distribution in animal body and TTFields distribution in the human chest and upper abdomen. The distributions of the TTFields in 3 human models were confirmed

after assessing the justification for the simulation models based on evaluation in animal organs. The models simulated women, men, and obese men, all demonstrating sufficiently intense TTFields of >0.7 V_{RMS}/cm applied to ≥75% of the lung volume.

2.(6).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the performance of Optune Lua and concluded that there was no particular problem.

2.(7) Electrical safety and electromagnetic compatibility in conformity to IEC62304

2.(7).A Summary of the data submitted

The applicant submitted data demonstrating that Optune Lua meets the international standards (IEC 62304:2006+Amd. 1:2015) which define the software life cycle processes of medical device software.

2.(7).B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the conformity to IEC 62304 and concluded that there was no particular problem.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that Optune Lua meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Public Notice No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of Optune Lua to the Essential Principles.

(1) PMDA's view on the conformity of Optune Lua to Article 1, which defines preconditions, etc. for designing medical devices (particularly requirements for users, such as the expected level of technical knowledge and experience, and the expected level of education and training for users):
As described later in Section "6.B Outline of the review conducted by PMDA," the selection of eligible patients, users, and medical institutions, users training, adherence to the guidelines for proper use, etc. are important to maintain the risk-benefit balance of Optune Lua. To ensure this, an approval condition should be attached so that necessary measures will be taken.

(2) PMDA's view on the conformity of Optune Lua to Article 3, which defines requirements for the performance and functions of medical devices, and to Article 6, which defines the efficacy of medical devices:
As described earlier in Section "2.(6).B Outline of the review conducted by PMDA," the performance of Optune Lua has been confirmed. In addition, as described later in Section "6.B Outline of the review conducted by PMDA," Effective and safe use of Optune Lua can be assured by proper patient selection. Optune Lua conforms to Articles 3 and 6.

(3) PMDA's view on the conformity of Optune Lua to Article 4, which defines the shelf life or durability of medical devices:
As described earlier in Section "2.(5).B Outline of the review conducted by PMDA," the stability and durability of Optune Lua have been confirmed. Optune Lua conforms to Article 4.

(4) PMDA's view on the conformity of Optune Lua to Article 7, which defines the chemical properties, biological safety, and other aspects of medical devices:
As described earlier in Sections "2.(2).B Outline of the review conducted by PMDA" and "2.(4).B Outline of the review conducted by PMDA," the biological safety and other aspects of Optune Lua have been justified. Optune Lua conforms to Article 7.

(5) PMDA's view on the conformity of Optune Lua to Article 8, which defines the prevention of microbial contamination of medical devices:
As described later in Section "5.B Outline of the review conducted by PMDA," the prevention of microbial contamination of Optune Lua has been justified. Optune Lua conforms to Article 8.

(6) PMDA's view on the conformity of Optune Lua to Article 13, which defines requirements for active medical devices, to Article 14, which defines requirements for mechanical risks of medical devices, and to Article 15, which defines requirements for medical devices supplying energy:
As described earlier in Sections "2.(3).B Outline of the review conducted by PMDA" and "4.B. Outline of the review conducted by PMDA," the requirements for active medical devices, mechanical risks of medical devices, and medical devices supplying energy of Optune Lua have been justified. Optune Lua conforms to Articles 13, 14, and 15.

(7) PMDA's view on the conformity of Optune Lua to Article 17, which defines requirements for publicizing information including precautionary advice or the communication of information to users via instructions for use, etc. (the Information on Precautions etc.):
As described later in Section "6.B Outline of the review conducted by PMDA," to maintain the risk-benefit balance of Optune Lua, it is crucial that users appropriately select eligible patients and use the product with the understanding of the product-associated risks, and that information is disseminated through the Information on Precautions, etc., guidelines for proper use, training, or other measures. Accordingly, PMDA instructed the applicant to advise strict adherence to the guidelines for proper use, which specify requirements for eligible patients, users, medical institutions, and training, for the use of Optune Lua, via the Information on Precautions, etc.

Based on the above, PMDA concluded that there was no problem with the conformity of Optune Lua to the Essential Principles.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, the risk management system, and its progress in accordance with ISO 14971: 2019 “Medical devices − Application of risk management to medical devices.”

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management taking into account the discussion presented in Section “3.B Outline of the review conducted by PMDA” and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted a declaration of sterilization conditions to assure the sterility assurance level as data on the sterilization process of Optune Lua.

5.B Outline of the review conducted by PMDA

PMDA reviewed the data supporting the manufacturing process and has concluded that there is no particular problem.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

6.A Summary of the data submitted

The applicant submitted the clinical study data in the form of results from the LUNAR study, a pivotal clinical study conducted overseas (NCT number, NCT02973789; study period, December 2016 to October 2024; hereinafter referred to as “the clinical study”).

6.A.(1) Study design

The clinical study is an open-label, multicenter, randomized study conducted at 79 study sites in 14 foreign countries in patients with unresectable, advanced, or recurrent NSCLC who have previously received chemotherapy with platinum-based antineoplastics to assess efficacy and safety of combination therapy with Optune Lua plus ICI or docetaxel. Table 2 outlines the clinical study.

Table 2. Summary of the clinical study

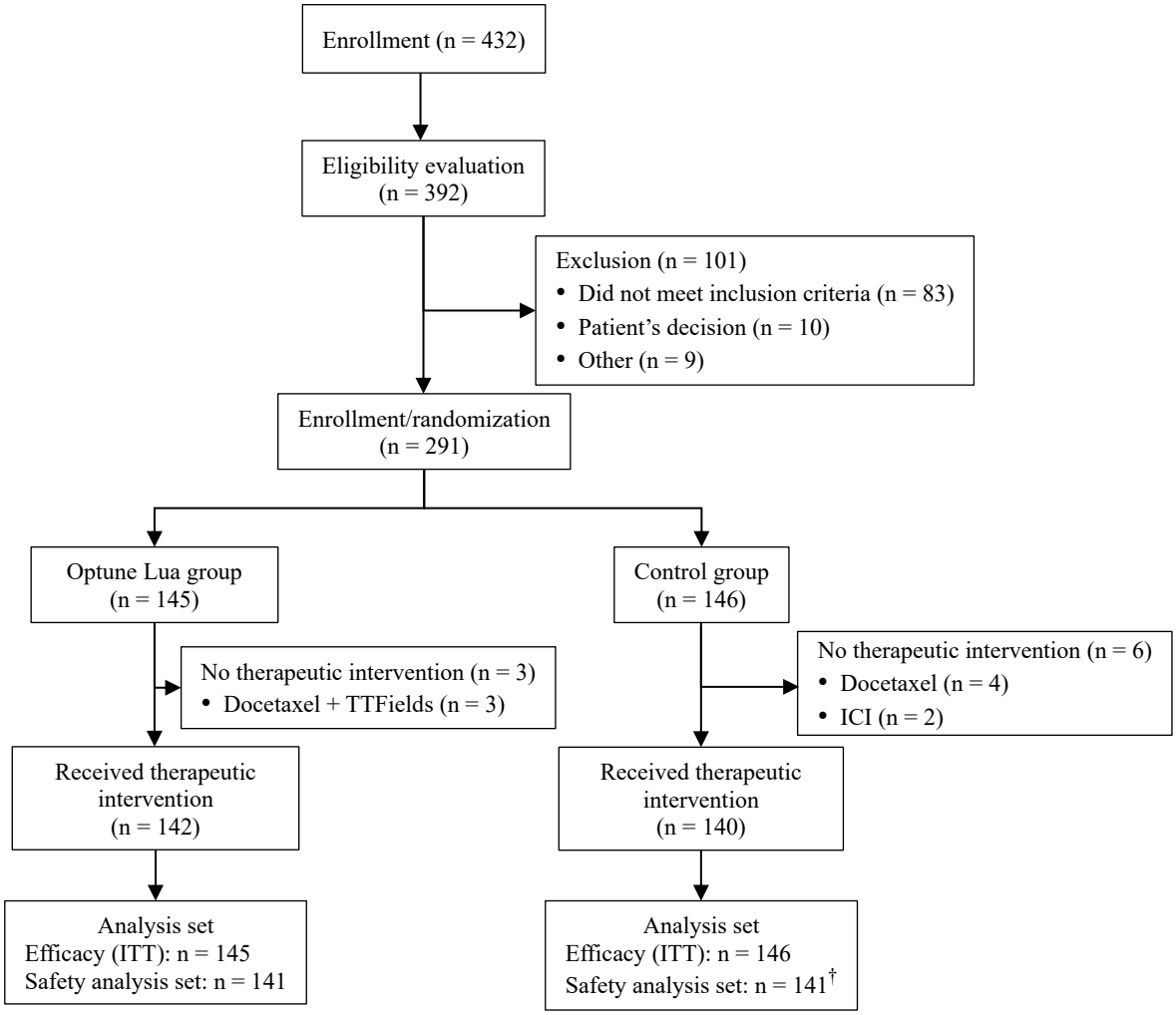
Item	Outline
Objectives	To evaluate the efficacy and safety of Optune Lua used in combination with docetaxel or ICI in patients with unresectable advanced or recurrent NSCLC who have previously received chemotherapy with platinum-based antineoplastics
Study design	A prospective, open-label, multicenter, pivotal, randomized study
Main endpoints	Primary endpoint: The superiority of overall survival (OS) "Optune Lua + standard of care group" vs. "standard of care group" Secondary endpoint: The superiority of the OS (1) "Optune Lua + ICI group" vs. "ICI alone group" (2) "Optune Lua + docetaxel group" vs. "Docetaxel alone group" Other key secondary endpoints: • Progression free survival (PFS) • QOL • OS and PFS in the Optune Lua + ICI group analyzed by ICI type
Sample size	291 patients (Of 392 enrolled patients, 101 patients were excluded due to screen failures, etc.) Final analysis Arm 1: Optune Lua +standard of care group Efficacy analysis set, 145 patients; Safety analysis set, 141 patients Arm 2: Standard of care group Efficacy analysis set, 146 patients; Safety analysis set, 141 patients
Treatment period	Until disease progression (according to irRECIST or RECIST criteria) or unacceptable toxicity
Observation period	Until the end of follow-up at 12 months after the start of treatment
Data cut-off date	October 3, 2023
Main inclusion criteria	• ≥22 years of age (≥18 years in Europe) • Life expectancy of ≥3 months • Histologically or cytologically confirmed squamous or non-squamous, inoperable, metastatic non-small cell lung cancer • Confirmed disease progression during or after the first systemic treatment with platinum-based antineoplastics for advanced or metastatic disease a. Including patients with metastatic lesions developing within 6 months after the completion of platinum-based chemotherapy as neoadjuvant or adjuvant therapy or combination therapy with radical thoracic irradiation. b. Including patients who had metastatic disease of ≥6 months after completion of a platinum-based chemotherapy combined with neoadjuvant or adjuvant therapy, and had progression during or after another platinum-based chemotherapy regimen to treat the advanced or metastatic disease. c. Prior to enrollment in the clinical study, patients were not allowed to receive systemic therapy after failure of platinum-based antineoplastics. Maintenance therapy following treatment with platinum-based antineoplastics and prior to disease progression was allowed. • Eastern Cooperative Oncology Group (ECOG) PS of 0 to 2 • Treatment with docetaxel or ICI was advised by a physician. • Ability to operate Optune Lua independently or with the help of a caregiver

Main exclusion criteria	• Metastasis to central nervous system (CNS) with confirmed clinical symptoms or no evidence of new metastasis to CNS during screening. Patients were allowed to enroll in the study if they were previously treated for CNS metastases, had stable metastatic lesion and clinical symptoms, and met the following criteria: a. Neurological symptoms have recovered to baseline (excluding residual signs or symptoms related to CNS treatment). b. No treatment for CNS metastases during screening c. No progression of CNS lesions identified by MRI within 14 days prior to randomization d. No meningeal metastasis or spinal cord compression • Contraindication to ICI or docetaxel • Severe complications a. Clinically significant (as determined by the investigator) hematologic, hepatic, or renal impairment defined as: Neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, bilirubin >1.5 × upper limit of normal (ULN), aspartate aminotransferase and/or alanine transaminase >2.5 × ULN or 5 × ULN in patients with confirmed metastases to liver, serum creatinine >1.5 × ULN b. History of significant cardiovascular disease unless it is well controlled. Significant cardiovascular disease includes second/third degree atrioventricular block, serious ischemic cardiac disease, poorly controlled hypertension, and New York Heart Association (NYHA) Class II or greater congestive cardiac failure (slight restriction of physical activities; fatigue, palpitation, or dyspnea after ordinary activities; comfortable at rest). c. History of arrhythmia that is symptomatic or requires treatment. Patients with atrial fibrillation or atrial flutter controlled by drug therapy were not excluded from the clinical study. d. History of pericarditis e. History of interstitial lung disease f. History of cerebrovascular disorder within 6 months prior to randomization or that with unstable symptoms g. Active infection or serious underlying disease that may interfere with the protocol treatment h. History of psychiatric illness that may impair the ability to understand, comply with, and provide a consent to the requirements of the clinical study i. Any other malignant tumors requiring antitumor treatment within the past 3 years (excluding stage I prostate cancer, cervical cancer, breast cancer, and non-melanoma skin cancer that have already been treated) • Ongoing Concurrent therapy with other experimental therapies for NSCLC while in the study • Implantable electronic medical devices (pacemaker, defibrillator, etc.) in the upper torso • Known allergy to medical adhesives or hydrogels • Pregnancy or breastfeeding (patients with reproductive potential must use effective methods of birth control throughout the study period according to the decision by investigator/gynecologist).

The primary endpoint of the clinical study was overall survival (OS). The superiority of the standard of care therapy (ICI or docetaxel) in combination with TTFields (the Optune Lua group) was evaluated over the standard of care group (the control group). Based on the initial plan to enroll 240 subjects per group (480 subjects in total) taking into account a lost to follow-up of 10%, the target sample size was 534 subjects (267 subjects per group) to achieve a power of 80% with a two-sided test at an alpha of 0.05. After the start of the study, a pre-specified interim analysis[4] was conducted when 432 patients were enrolled. The patient enrollment rate in the clinical study was lower than expected. Moreover, the enrollment process delayed amid the COVID-19 pandemic. Since the number of enrolled subjects at the time of the interim analysis was statistically adequate, and due to the ethical issue with control patients that they would not be treated with Optune Lua, further enrollment was deemed unnecessary by the Independent Data Monitoring Committee. Assuming that a total sample size of 276 would be required to evaluate the proposed endpoints while maintaining the statistical power of the clinical study, and the initially proposed 18 months follow-up period was changed to 12 months to obtain proper efficacy and safety data.

[4] The alpha levels at the interim and final analyses were calculated according to the Lan-DeMets method using O'Brien and Fleming spending function (approximately 0.00306 for the interim analysis and 0.04694 for the final analysis).

Figure 3 is the flow from the subject enrollment to the establishment of analysis sets. Of the enrolled patients, 392 patients were screened and assessed for eligibility. Those who did not meet the inclusion criteria were excluded. The remaining 291 patients (intent to treat [ITT] population) were included in the efficacy analysis set, and 145 subjects were randomly assigned to the Optune Lua group, and 146 subjects to the control groups. Of these, 142 and 140 subjects who received therapeutic interventions in the Optune Lua and control groups, respectively, were included in the safety analysis set.



† One patient randomized to the standard of care + TTFields therapy group received only the standard of care (ICI). In the ICI treatment population, 1 patient was treated with docetaxel.

Figure 3. Subject composition

6.A.(2) Patient characteristics

Table 3 shows patient characteristics of the ITT population in the clinical study.

Table 3. Patient characteristics (ITT population)

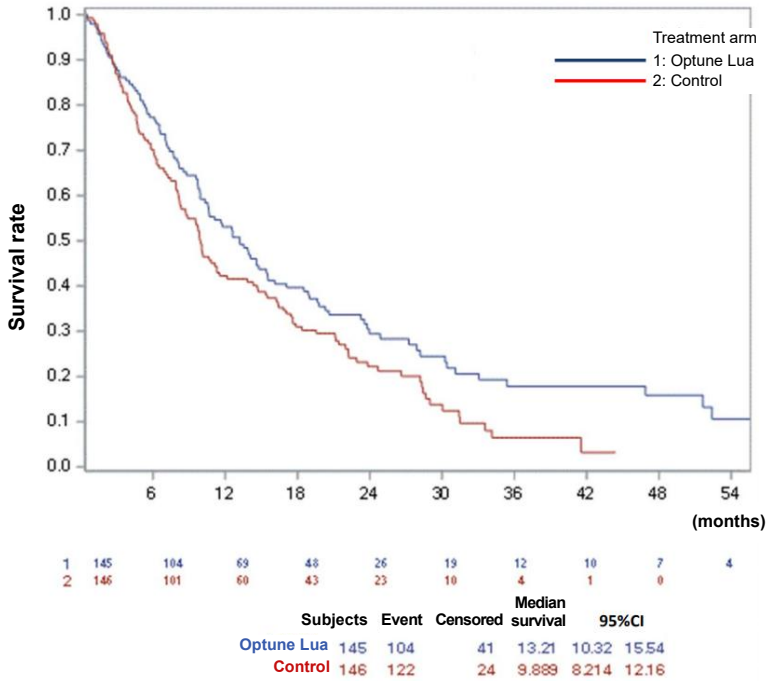
Item	Optune Lua			Control			Sum total (n = 291)
	Docetaxel (n = 75)	ICI (n = 70)	Total (n = 145)	Docetaxel (n = 75)	ICI (n = 71)	Total (n = 146)	
Age (years)							
Median (min, max)	63.0 (43, 81)	64.5 (36, 85)	64.0 (36, 85)	65.0 (22, 81)	65.0 (23, 86)	65.0 (22, 86)	65.0 (22, 86)
Sex (n [%])							
Men	51 (68.0)	48 (68.6)	99 (68.3)	46 (61.3)	46 (64.8)	92 (63.0)	191 (65.6)
Women	24 (32.0)	22 (31.4)	46 (31.7)	29 (38.7)	25 (35.2)	54 (37.0)	100 (34.4)
Race (n [%])							
Native Americans or Alaskan Native	0	0	0	1 (1.3)	1 (1.4)	2 (1.4)	2 (0.7)
Asian	12 (16.0)	7 (10.0)	19 (13.1)	10 (13.3)	7 (9.9)	17 (11.6)	36 (12.4)
Black or African American	3 (4.0)	1 (1.4)	4 (2.8)	1 (1.3)	2 (2.8)	3 (2.1)	7 (2.4)
Pacific Islander	0	1 (1.4)	1 (0.7)	0	0	0	1 (0.3)
Caucasian	57 (76.0)	58 (82.9)	115 (79.3)	59 (78.7)	54 (76.1)	113 (77.4)	228 (78.4)
Other	2 (2.7)	3 (4.3)	5 (3.4)	4 (5.3)	4 (5.6)	8 (5.5)	13 (4.5)
Unknown	1 (1.3)	1 (1.4)	2 (1.4)	0	4 (5.6)	4 (2.7)	6 (2.1)
ECOG PS (n (%))							
0	19 (25.3)	22 (31.4)	41 (28.3)	19 (25.3)	22 (31.0)	41 (28.1)	82 (28.2)
1	51 (68.0)	46 (65.7)	97 (66.9)	52 (69.3)	49 (69.0)	101 (69.2)	198 (68.0)
2	5 (6.7)	2 (2.9)	7 (4.8)	4 (5.3)	0	4 (2.7)	11 (3.8)
Smoking history (n [%])							
Never-smoker	10 (13.3)	10 (14.3)	20 (13.8)	11 (14.7)	13 (18.3)	24 (16.4)	44 (15.1)
Current smoker	16 (21.3)	20 (28.6)	36 (24.8)	13 (17.3)	17 (23.9)	30 (20.5)	66 (22.7)
Ex-smoker	48 (64.0)	40 (57.1)	88 (60.7)	51 (68.0)	41 (57.7)	92 (63.0)	180 (61.9)
Unknown	1 (1.3)	0	1 (0.7)	0	0	0	1 (0.3)
Tumor histology (n [%])							
Non-squamous cell carcinoma	44 (58.7)	39 (55.7)	83 (57.2)	43 (57.3)	39 (54.9)	82 (56.2)	165 (56.7)
Squamous cell carcinoma	31 (41.3)	31 (44.3)	62 (42.8)	32 (42.7)	32 (45.1)	64 (43.8)	126 (43.3)
Prior treatment for non-small cell lung cancer (n [%])							
Yes	75 (100)	70 (100)	145 (100)	75 (100)	71 (100)	146 (100)	291 (100)
No	0	0	0	0	0	0	0
PD-L1 TPS (n (%))							
<1%	12 (16.0)	12 (17.1)	24 (16.6)	7 (9.3)	16 (22.5)	23 (15.8)	47 (16.2)
≥1% and <50%	21 (28.0)	19 (27.1)	40 (27.6)	22 (29.3)	18 (25.4)	40 (27.4)	80 (27.5)
≥50%	5 (6.7)	5 (7.1)	10 (6.9)	11 (14.7)	8 (11.3)	19 (13.0)	29 (10.0)
Unknown	37 (49.3)	34 (48.6)	71 (49.0)	35 (46.7)	29 (40.8)	64 (43.8)	135 (46.4)

6.A.(3) Study results

6.A.(3).1) Results of efficacy evaluation

(a) Primary endpoint: OS (Optune Lua group vs. control group)

Figure 4 shows the OS final analysis results, the primary endpoint. At the data cut-off (follow-up period, median 10.0 months [range, 0.03-64.5]), the median OS in the Optune Lua group (n = 145) and control group (n = 146) were 13.2 months (95% confidence interval [CI], 10.3-15.5) and 9.9 months (95% CI, 8.2-12.2), respectively. The hazard ratio of the Optune Lua group relative to the control group was 0.76 (95% CI, 0.58-0.99), which demonstrated statistically significant prolongation in the Optune Lua group (P = 0.0413, based on log-rank test).



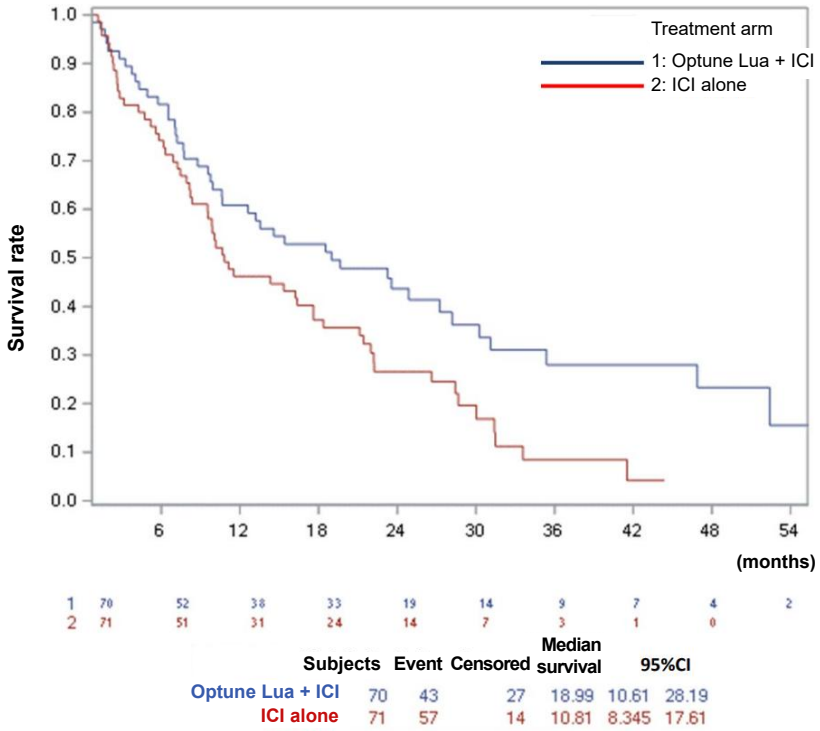
	Optune Lua (n = 145)	Control (n = 146)
Median OS, months	13.2	9.9
95% CI, months	10.3; 15.5	8.2; 12.2
P value based on log rank test	*P* = 0.0413	
Hazard ratio (95% CI)	0.76 (0.58; 0.99)	

Figure 4. OS in the Optune Lua group vs. the control group (ITT) (Kaplan-Meier curve)

The standard of care therapy includes both ICI and docetaxel. For this reason, the secondary endpoints were OS in the subgroups of patients treated with ICI and docetaxel, respectively, compared between combination with Optune Lua and monotherapy. To avoid multiplicity, the secondary endpoints were assessed hierarchically after achievement of the primary endpoint was confirmed.

(b) Secondary endpoint: OS (Optune Lua + ICI group vs. ICI alone group)

The OS times in the Optune Lua + ICI group (n = 70) and the ICI alone group (n = 71) were compared for evaluation (Figure 5). The median OS was 19.0 months (95% CI, 10.6-28.2 months) in the Optune Lua + ICI group and 10.8 months (95% CI, 8.3-17.6 months) in the ICI alone group, with a hazard ratio of the Optune Lua + ICI group relative to the ICI alone group of 0.63 (95 %CI, 0.42-0.95, *P* = 0.024).

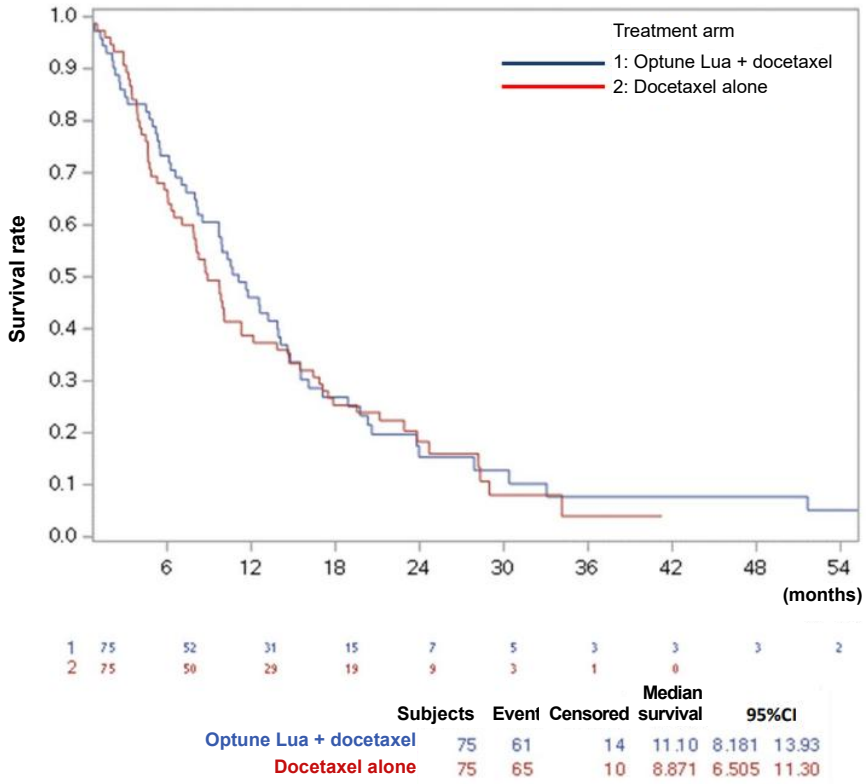


	Optune Lua + ICI (n = 70)	ICI alone (n = 71)
Median OS, months	19.0	10.8
95% CI, months	10.6, 28.2	8.3, 17.6
P value based on log rank test	*P* = 0.024	
Hazard ratio (95% CI)	0.63 (0.42; 0.95)	

Figure 5. OS in the Optune Lua + ICI group vs. the ICI alone group (ITT) (Kaplan-Meier curve)

(c) Secondary endpoint: OS (Optune Lua + docetaxel group vs. docetaxel alone group)

The OS times in the Optune Lua + docetaxel group (n = 75) and the docetaxel alone group (n = 75) were compared for evaluation (Figure 6). The median OS was 11.1 months (95% CI, 8.2-13.9 months) in the Optune Lua + docetaxel group and 8.9 months (95% CI, 6.5-11.3 months) in the docetaxel alone group, with a hazard ratio of the Optune Lua + docetaxel group relative to the docetaxel alone group of 0.88 (95% CI, 0.61-1.26, *P* = 0.469).

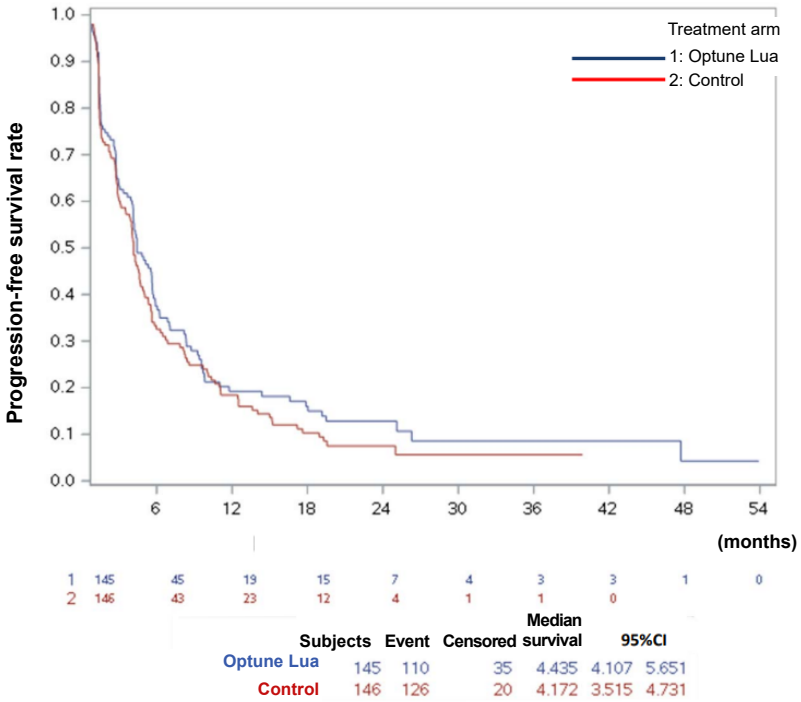


	Optune Lua + docetaxel (n = 75)	Docetaxel alone (n = 75)
Median OS, months	11.1	8.9
95% CI, months	8.2; 13.9	6.5; 11.3
P value based on log rank test	*P* = 0.469	
Hazard ratio (95% CI)	0.88 (0.61; 1.26)	

Figure 6. Optune Lua + docetaxel group vs. docetaxel alone group (ITT) (Kaplan-Meier curve)

(d) Secondary endpoint: PFS (Optune Lua group vs. control group)

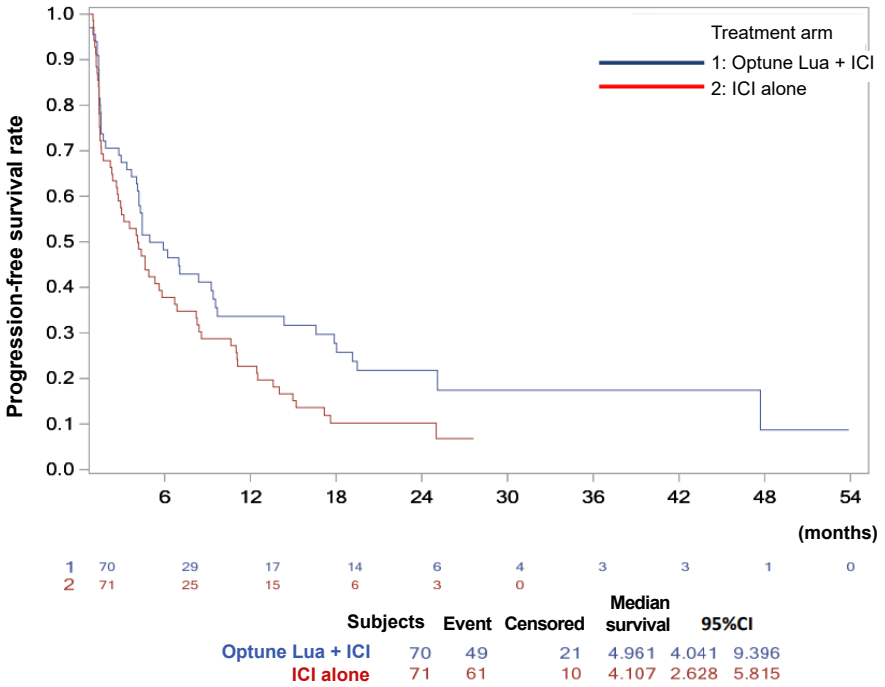
Figure 7 shows progression free survival (PFS) in the ITT analysis set. The median PFS was 4.4 months (95% CI, 4.1-5.7 months) in the Optune Lua group and 4.2 months (95% CI, 3.1-4.7 months) in the control group, with a hazard ratio of the Optune Lua group relative to the control group of 0.91 (95 % CI, 0.70-1.18, *P* = 0.458).



	Optune Lua (n = 145)	Control (n = 146)
Median PFS, months	4.4	4.2
95% CI, months	4.1; 5.7	3.5; 4.7
P value based on log rank test	*P* = 0.458	
Hazard ratio (95% CI)	0.91 (0.70; 1.18)	

Figure 7. PFS in the Optune Lua group vs. the control group (ITT) (Kaplan-Meier curve)

As a related exploratory analysis, a subgroup analysis of PFS was conducted in patients treated with ICI. The results are shown in Figure 8.



Hazard ratio = 0.703 (0.481; 1.027), *P* = 0.066 based on log-rank test

Figure 8. PFS in the Optune Lua + ICI group vs. the ICI alone group (Kaplan-Meier curve)

(e) Secondary endpoint: Response rate

Overall response rate (ORR) was analyzed in 128 of 145 patients (88%) in the Optune Lua group and 134 of 146 patients (92%) in the control group who underwent at least 1 CT scan after baseline (Table 4). The ORR was 19.3% (28 of 128 patients; 95% CI, 13.2-26.7) in the Optune Lua group and 18.5% (27 of 134 patients; 95% CI, 12.6-25.8) in the control group. Patients with complete response (4 in the Optune Lua group and 1 in the control group) were all treated with ICI.

Table 4. ORR (ITT population)

	Optune Lua (n = 128)	**Control (n = 134)**
Best overall response (BOR), n (%)		
Complete response (CR)	4 (2.8)	1 (0.7)
Partial response (PR)	24 (16.6)	26 (17.8)
Stable disease (SD)	71 (49.0)	68 (46.6)
Progressive disease (PD)	26 (17.9)	37 (25.3)
Not evaluable (NE)	3 (2.1)	2 (1.4)
Number of responders (ORR: CR + PR)	28	27
Overall response rate (%) (95% CI)	19.3 (13.2, 26.7)	18.5 (12.6, 25.8)
Difference in ORR (%) (95% CI)	0.82 (-8.38, 10.09)	
Two-sided *P*-value	0.859	

As a related exploratory analysis, a subgroup analysis of ORR was conducted in patients treated with ICI. The ORR was 22.9% (95% CI, 13.7-34.4) in the Optune Lua + ICI group and 21.1% (95% CI, 12.3-32.4) in the ICI alone group. Complete response was confirmed in 4 patients in the Optune Lua + ICI group and only 1 in the ICI alone group (Table 5).

Table 5. ORR in the ICI combination therapy group (ITT population)

	ICI + TTFields (n = 70)	ICI alone (n = 71)
Best overall response (BOR), n (%)		
Complete response (CR)	4 (5.7)	1 (1.4)
Partial response (PR)	12 (17.1)	14 (19.7)
Stable disease (SD)	28 (40.0)	30 (42.3)
Progressive disease (PD)	17 (24.3)	21 (29.6)
Not evaluable (NE)	2 (2.9)	0
Missing	7 (10.0)	5 (7.0)
Number of responders (ORR: CR + PR)	16	15
Overall response rate (%) (95% CI)	22.9 (13.7, 34.4)	21.1 (12.3, 32.4)
Difference in ORR (%) (95% CI)	1.73 (-12.2, 15.87)	
Two-sided P-value	0.804	

(f) Secondary endpoint: QOL

The mean value, standard deviation, and change (%) from baseline of each QOL measure were calculated using a modular supplement to LC13 (lung cancer) and EORTC QLQ-C30 questionnaire for comparison up to Week 54. QOL score changes of <10 points were defined as stable, and changes of ≥10 points were defined as reduced or improved, depending on the measures. There were no clear differences between the Optune Lua and control groups across all measures.

There were no differences between the groups in any of the general measures, including physical and social functions that could potentially be affected by carrying the device. There were no differences between the groups in any of the systemic symptom scales as well. Most of the symptoms observed in the systemic symptom scale were considered known adverse drug reactions of treatment with ICI or docetaxel. Moreover, there were no differences between the groups in lung symptom scales. These symptoms were most likely related to primary lung cancer, and the relationship to the treatment with ICI, docetaxel or Optune Lua was ruled out.

Scores of the role functioning (both groups), social functioning (both groups), QLQ C-30 dyspnoea (Optune Lua group), and cough (control group) showed 10 to 15-point decreases from baseline during the 54-week evaluation period in a small number of patients. However, the scores in other scales changed by <10 points from baseline, and the QOL was stable. There were no clear differences between the 2 groups in all of the scales.

(g) Secondary endpoint: OS and PFS in the Optune Lua + ICI group analyzed separately by ICI type

In the clinical study, the investigator selected one of the ICIs including nivolumab, atezolizumab, and pembrolizumab. Table 6 shows the type of ICIs used in the clinical study.

Table 6. Type of ICIs used in patients

Treatment arm	Type of ICIs*			
	Nivolumab	Atezolizumab	Pembrolizumab	Total
Optune Lua + ICI	68% (48/71)	20% (14/71)	13% (9/71)	71
ICI alone	55% (38/69)	29% (20/69)	16% (11/69)	69
Total	61% (86/140)	24% (34/140)	14% (20/140)	140

* Two patients randomized to the docetaxel + Optune Lua group received ICI, 1 patient received nivolumab and the other received pembrolizumab. One patient in the ICI alone group received docetaxel.

The OS and PFS in Optune Lua when used in combination with each ICI (nivolumab, pembrolizumab, or atezolizumab) were additionally analyzed for each treatment group. There were no clear differences between the Optune Lua + ICI group and the ICI alone group in any of the following subgroups:

- Optune Lua + nivolumab group vs. nivolumab alone group
- Optune Lua + pembrolizumab group vs. pembrolizumab alone group
- Optune Lua + atezolizumab group vs. atezolizumab alone group

6.A.(3).2) Results of safety evaluation

In the safety analysis set, 265 of 282 patients (94%) experienced at least 1 adverse event, and 141 of 282 patients (50%) experienced Grade 3 or 4 adverse events. There were no clear differences in the incidence of Grade 3 to 4 adverse events among the study groups.

Table 7 shows commonly reported (≥10% of patients) adverse events in the clinical study.

Table 7. Commonly reported adverse events* (n [%])

	Optune Lua			Control			Total of both groups (n = 282)
Adverse event	**Optune Lua + docetaxel (n = 70)**	**Optune Lua + ICI (n = 71)**	**Total (n = 141)**	**Docetaxel (n = 72)**	**ICI (n = 69)**	**Total (n= 141)**	
Fatigue	21 (30.0)	17 (23.9)	38 (27.0)	30 (41.7)	25 (36.2)	55 (39.0)	93 (33.0)
Musculoskeletal pain	25 (35.7)	24 (33.8)	49 (34.8)	23 (31.9)	16 (23.2)	39 (27.7)	88 (31.2)
Anaemia	16 (22.9)	17 (23.9)	33 (23.4)	23 (31.9)	11 (15.9)	34 (24.1)	67 (23.8)
Dyspnoea	15 (21.4)	12 (16.9)	27 (19.1)	21 (29.2)	14 (20.3)	35 (24.8)	62 (22.0)
Dermatitis	26 (37.1)	32 (45.1)	58 (41.1)	2 (2.8)	1 (1.4)	3 (2.1)	61 (21.6)
Cough	13 (18.6)	12 (16.9)	25 (17.7)	14 (19.4)	18 (26.1)	32 (22.7)	57 (20.2)
Diarrhoea	13 (18.6)	12 (16.9)	25 (17.7)	12 (16.7)	14 (20.3)	26 (18.4)	51 (18.1)
Nausea	17 (24.3)	10 (14.1)	27 (19.1)	10 (13.9)	13 (18.8)	23 (16.3)	50 (17.7)
Leukopenia	19 (27.1)	3 (4.2)	22 (15.6)	21 (29.2)	5 (7.2)	26 (18.4)	48 (17.0)
Anorexia	11 (15.7)	12 (16.9)	23 (16.3)	13 (18.1)	10 (14.5)	23 (16.3)	46 (16.3)
Pneumonia	12 (17.1)	9 (12.7)	21 (14.9)	13 (18.1)	12 (17.4)	25 (17.7)	46 (16.3)
Local oedema	14 (20.0)	6 (8.5)	20 (14.2)	15 (20.8)	9 (13.0)	24 (17.0)	44 (15.6)
Respiratory infection	7 (10.0)	14 (19.7)	21 (14.9)	5 (6.9)	18 (26.1)	23 (16.3)	44 (15.6)
Alopecia	13 (18.6)	0	13 (9.2)	24 (33.3)	2 (2.9)	26 (18.4)	39 (13.8)
Pain	9 (12.9)	9 (12.7)	18 (12.8)	16 (22.2)	4 (5.8)	20 (14.2)	38 (13.5)
Constipation	12 (17.1)	4 (5.6)	16 (11.3)	12 (16.7)	6 (8.7)	18 (12.8)	34 (12.1)
Pruritus	12 (17.1)	11 (15.5)	23 (16.3)	1 (1.4)	8 (11.6)	9 (6.4)	32 (11.3)
Hepatic enzyme increased	4 (5.7)	9 (12.7)	13 (9.2)	6 (8.3)	11 (15.9)	17 (12.1)	30 (10.6)
Hypoalbuminaemia	7 (10.0)	4 (5.6)	11 (7.8)	9 (12.5)	10 (14.5)	19 (13.5)	30 (10.6)
Vomiting	8 (11.4)	6 (8.5)	14 (9.9)	7 (9.7)	9 (13.0)	16 (11.3)	30 (10.6)
Hypokalaemia	11 (15.7)	5 (7.0)	16 (11.3)	9 (12.5)	4 (5.8)	13 (9.2)	29 (10.3)
Hyponatraemia	7 (10.0)	5 (7.0)	12 (8.5)	7 (9.7)	10 (14.5)	17 (12.1)	29 (10.3)

* Commonly reported (≥10% of patients) adverse events in the clinical study according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (safety population)

Of the 141 patients who used Optune Lua, 97 patients (68.8%) reported device-related adverse events (Table 8). Among these, 90 patients had skin-related known events attributed to the application of the transducer arrays on the skin. Non-skin-related Grade 3 and serious adverse events included “pain” and “bronchopleural fistula” in 1 patient each.

Table 8. Adverse events likely to be related to Optune Lua (n [%])

	Optune Lua + ICI (n = 71)			Optune Lua + docetaxel (n = 70)		
CTCAE grade	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Device-related adverse event	25 (35.2)	21 (29.6)	3 (4.2)	20 (28.6)	23 (32.9)	5 (7.1)
Device-related skin adverse event	24 (33.8)	21 (29.6)	1 (1.4)	18 (25.7)	21 (30.0)	5 (7.1)
Device-related serious adverse event	0	0	1 (1.4)	0	2 (2.8)	1 (1.4)
Device-related adverse event resulting in death	0	0	0	0	0	0
(System organ class)						
General disorders and administration site conditions						
• Pain	0	1 (1.4)	1 (1.4)	0	1 (1.4)	0
Infections and infestations						
• Skin infection	0	0	0	1 (1.4)	1 (1.4)	1 (1.4)
Respiratory, thoracic and mediastinal disorders						
• Bronchopleural fistula	0	0	1 (1.4)	0	0	0
Skin and subcutaneous tissue disorders						
• Blister	0	0	0	1 (1.4)	1 (1.4)	0
• Dermatitis	18 (25.4)	12 (16.9)	1 (1.4)	12 (17.1)	11 (15.7)	2 (2.9)
• Dermatitis bullous	0	0	0	1 (1.4)	0	0
• Erythema	1 (1.4)	1 (1.4)	0	3 (4.3)	2 (2.9)	0
• Pruritus	7 (9.9)	3 (4.2)	0	5 (7.1)	2 (2.9)	1 (1.4)
• Rash	6 (8.5)	2 (2.8)	0	1 (1.4)	3 (4.3)	0
• Rash maculo-papular	1 (1.4)	1 (1.4)	0	2 (2.9)	5 (7.1)	0
• Skin reaction	2 (2.8)	0	0	0	1 (1.4)	0
• Skin ulcer	4 (5.6)	3 (4.2)	0	0	4 (5.7)	1 (1.4)

6.A.(3).3) Effects of use of TTFields therapy on outcomes

The average daily use time for Optune Lua was specified as ≥ 18 hours (average monthly use rate of 75%) based on the results from previous clinical studies on Optune Gio in patients with glioblastoma. However, this was fulfilled by 19.7% of patients in the Optune Lua + ICI group and 25.7% of patients in the Optune Lua + docetaxel group. Use of the transducer arrays on the chest is assumed to be a greater obstacle to treatment compliance than on the head.

In 71 patients in the Optune Lua + ICI group, the distribution of the average monthly use rates of TTFields varied from 0.4% to 94.7%, with an average of 52.3% (equivalent to an average of 12.5 hours per day). In 70 patients in the Optune Lua + docetaxel group, the average monthly use rates of TTFields varied from 4.0% to 92.7%, with an average of 56.8% (equivalent to an average of 13.6 hours per day). Accordingly, an additional analysis was conducted with a cut-off value of 50% (equivalent to an average of 12 hours per day) (Figure 9).

In the Optune Lua group, median OS in patients with average monthly use rates of ≥50% and <50% was 14.1 and 12.6 months, respectively, showing a tendency of longer OS in patients with average monthly use rates of ≥50% compared with patients with average monthly use rates of <50%.

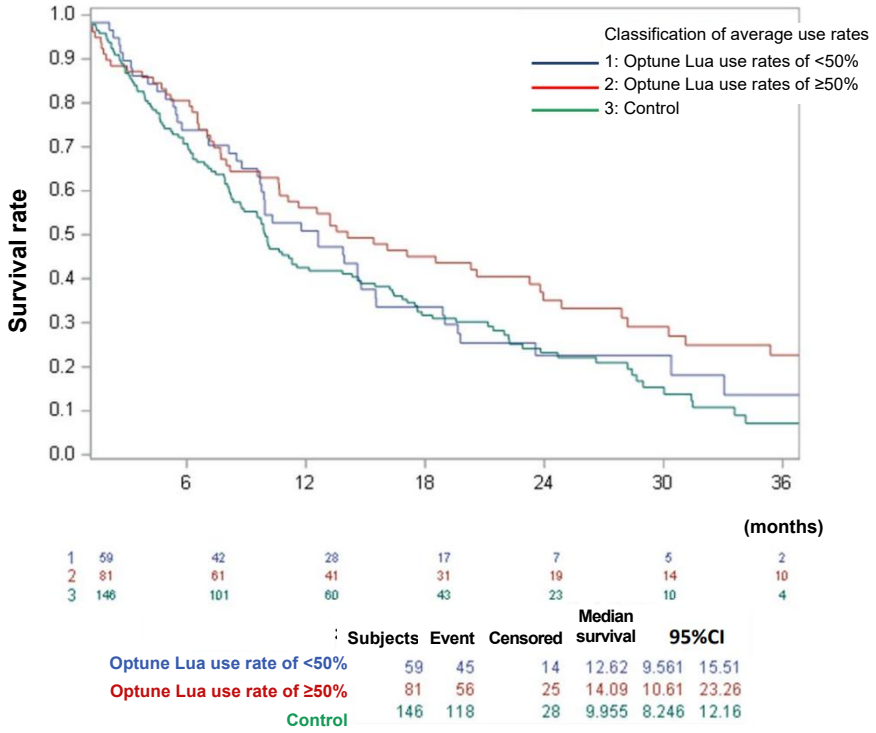


Figure 9. Analysis results of OS in patients with average Optune Lua use rates of ≥50% and <50% in the Optune Lua group

The safety in the Optune Lua group was examined in the subgroups with "average monthly use rates of <50%" and "average monthly use rates of ≥50%." Standardized[5] incidences of serious adverse events were 2.5% in the subgroup with "average monthly use rates of <50%" and 1.93% in the subgroup with "average monthly use rates of ≥50%." The standardized incidences of Grade 3 to 4 adverse events were 2.9% in the subgroup with "average monthly use rates of <50%" and 2.17% in the subgroup with "average monthly use rates of ≥50%." In conclusion, there was no tendency towards a higher incidence of adverse events with longer use periods.

6.B Outline of the review conducted by PMDA

6.B.(1) Extrapolability of foreign clinical studies to Japan

The applicant's explanation about the extrapolability of the foreign clinical study to Japan:

Although the clinical study was conducted in foreign countries, the results of the clinical study can be extrapolated to Japan for the following reasons:

- Based on the following analysis, physical size difference by race is considered to have little impact on efficacy and safety.
  - ➢ The mean body mass index (BMI) by age group in Japanese patients is 22.9 to 24.7 in men and 21.0 to 23.1 in women,[v] which are lower than the baseline BMI of 24.7 in patients (Optune Lua group) of the clinical study.
  - ➢ The OS, PFS, and incidence of adverse events in the Optune Lua group in the clinical study were stratified by BMI (<25 and ≥25), which showed no significant difference.
- There was no substantial difference in the treatment system for NSCLC between Japan and overseas.

[5] Standardized incidences of adverse events are those divided by the mean treatment period in each subgroup.

- There were no safety concerns specific to Japanese patients for TTFields therapy in glioblastoma treatment using the approved Optune Gio.

PMDA conclusion:
The applicant's view that there was no problem for extrapolation of the results of the foreign clinical study to Japan is acceptable, taking into account the results of investigation on physical size differences among races, the equivalence of the treatment system for NSCLC in Japan and overseas, and the safety information of the approved product.

6.B.(2) Efficacy and safety

6.B.(2).1) Results of efficacy evaluation

(a) Concomitant standard of care therapy

The primary endpoint of the clinical study was achieved. However, the conclusion on the efficacy of Optune Lua should be carefully reached in light of the 2 types of drugs used as standard of care therapy, ICI and docetaxel showing different tendencies in the efficacy assessed as secondary endpoints.

The applicant's explanation about the efficacy of Optune Lua by concomitant standard of care therapy:
The results of OS by standard of care therapy as secondary endpoints of the clinical study showed significant differences in OS with Optune Lua + ICI. Optune Lua + docetaxel showed no significant difference in the median OS but prolonged OS for 2.2 months. Therefore, the combined use of Optune Lua and docetaxel is of clinical significance.

In response, PMDA requested additional PFS analysis results from the docetaxel subgroup and asked to explain the cause of the difference in efficacy results between the subgroups of ICI and docetaxel used with Optune Lua.

The applicant's explanation:
In the subgroups treated with docetaxel, the median PFS was 4.2 months (95% CI, 2.8-5.6 months) with Optune Lua + docetaxel and 4.2 months (95% CI, 3.1-5.0 months) with docetaxel alone. The hazard ratio of the Optune Lua + docetaxel relative to the docetaxel alone was 1.15 (95% CI, 0.78-1.65, P = 0.45) (Figure 10).

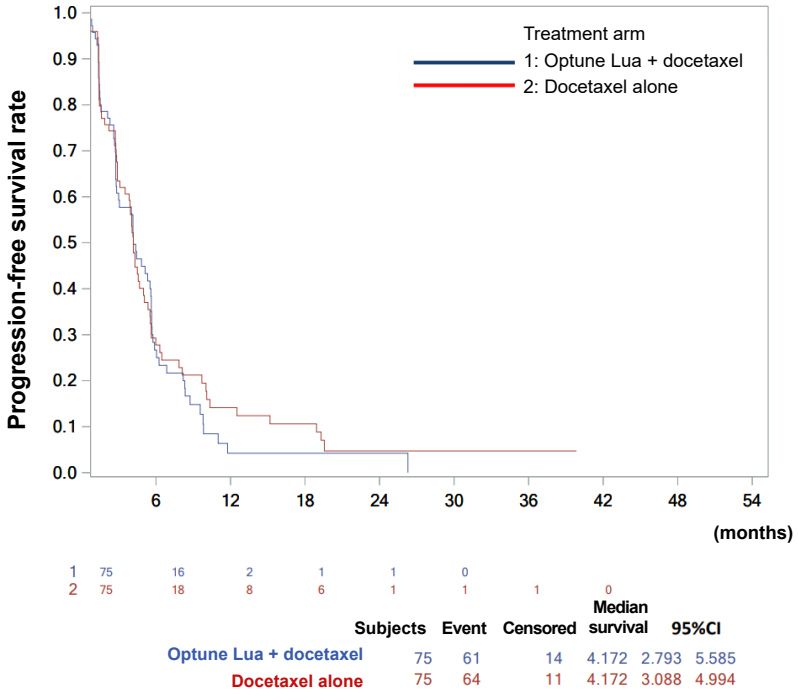


Figure 10. PFS in the docetaxel + TTFields group vs. the docetaxel alone group (Kaplan-Meier curve)

The observed inconsistency in efficacy results of Optune Lua between the ICI and docetaxel subgroups are possibly due to the primary action mechanisms of Optune Lua and docetaxel, i.e., acting on microtubule activity to inhibit cell division, have some overlap.

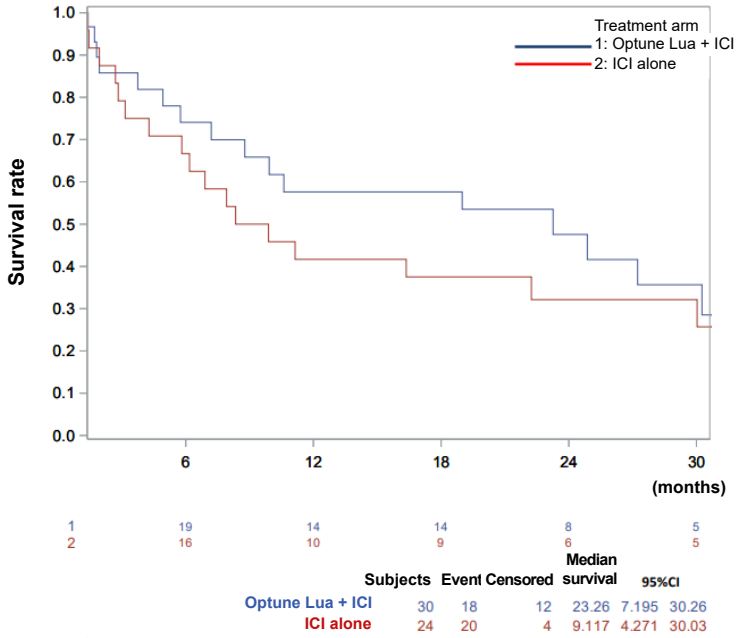
PMDA's view based on the clinical study results and the discussion on the mechanism of action:
The median OS, one of the secondary endpoints, was 19.0 months (95% CI, 10.6-28.2 months) in the Optune Lua + ICI group and 10.8 months (95% CI, 8.3-17.6 months) in the ICI alone group, with a hazard ratio of Optune Lua + ICI relative to ICI alone of 0.63 (95% CI, 0.42-0.95, P = 0.024), demonstrating add-on effects of Optune Lua + ICI. Meanwhile, the median OS was 11.1 months (95% CI, 8.2-13.9 months) in the Optune Lua + docetaxel group and 8.9 months (95% CI, 6.5-11.3 months) in the docetaxel alone group, with a hazard ratio of the Optune Lua + docetaxel relative to the docetaxel alone of 0.88 (95% CI, 0.61-1.26, P = 0.469). Based on the hazard ratio of 0.75 in the hypothesis test, there was no clear difference. The results of additional subgroup PFS analyses also suggested no add-on effects in Optune Lua + docetaxel. As explained by the applicant, both Optune Lua and docetaxel act on microtubules to inhibit cell division, and this overlap may have affected the efficacy of Optune Lua used with docetaxel. Based on the comments from the Expert Discussion, PMDA has concluded that the currently available data do not adequately demonstrate the efficacy of combined use of Optune Lua with docetaxel.

(b) Clinical significance of local treatment for patients with metastasis

While Optune Lua is a device primarily intended for metastatic NSCLC, the product treats the thoracic region locally. PMDA asked the applicant to explain the clinical significance of providing local treatment in the thoracic region for metastatic NSCLC.

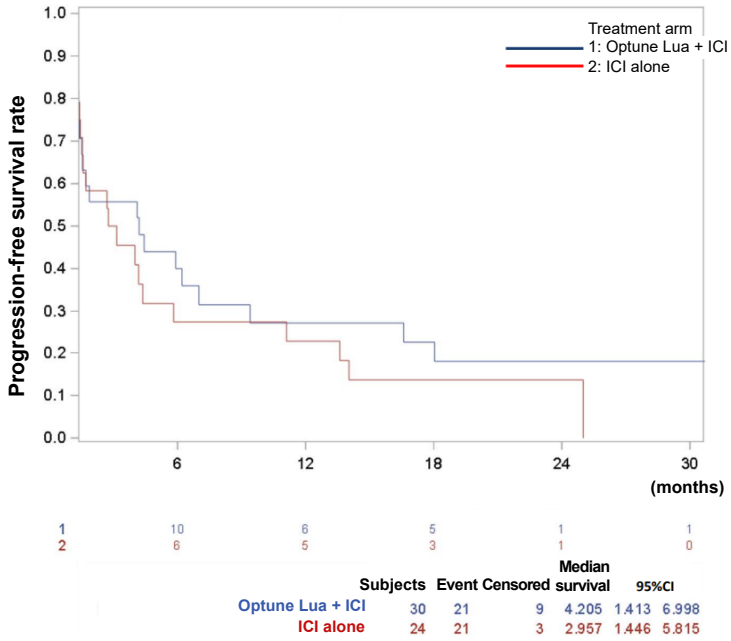
The applicant's explanation:

Figure 11 and Figure 12 respectively show the results of additional OS and PFS analyses in the Optune Lua + ICI group and the ICI alone group in patients who had metastasis at enrollment in the clinical study.



Hazard ratio = 0.785 (0.392; 1.573), *P* = 0.3699 based on log-rank test

Figure 11. OS in patients with metastases in non-treatment regions (Optune Lua + ICI group vs. ICI alone group) (Kaplan-Meier curve)



Hazard ratio = 0.821 (0.438; 1.538), *P* = 0.5237 based on log-rank test

Figure 12. PFS in patients with metastases in non-treatment regions (Optune Lua + ICI group vs. ICI alone group) (Kaplan-Meier curve)

The additional analyses included patients who had metastases in at least 1 organ (lymph nodes, bones, adrenal glands, kidneys, pancreas, greater omentum/peritoneum, rectum, and other organs) in non-

treatment regions at enrollment. Median OS and PFS were both longer in the Optune Lua + ICI group, albeit in the limited number of patients (n = 54), demonstrating its therapeutic effect in the Optune Lua + ICI group.

PMDA's view on the clinical significance of Optune Lua used in patients with metastatic NSCLC, based on the comments from the Expert Discussion:
Optune Lua does not deliver TTFields to the primary or metastatic cancer lesions outside the thoracic region, and therefore its antiproliferative effect does not act directly on cancer cells in the non-treatment regions. However, Optune Lua has promising therapeutic potential in patients with eligible NSCLC lesions that are considered likely to affect prognosis significantly. As explained by the applicant, the efficacy of Optune Lua was also shown in patients who have metastasis outside the treatment area of Optune Lua. Thus, the product is of clinical significance.[6]

6.B.(2).2 Results of safety evaluation

The applicant's explanation:
As shown in Table 8, major device-related adverse events were known skin-related events. Grade 3 or serious device-related but non-skin-related adverse events were pain and bronchopleural fistula in 1 patient each.

PMDA asked for detailed information about pain and bronchopleural fistula reported. In light of the possibility that skin-related events may affect the continuity of Optune Lua treatment, PMDA requested detailed explanation on the countermeasures planned against skin troubles.

The applicant's explanation about pain and bronchopleural fistula:
Optune Lua treatment began in 1 patient with pain on October 23, 2020. On the same day, non-serious Grade 3 pain occurred in the thoracic region. The event resolved. The investigator assessed it as study device-related event. The applicant viewed that the event was attributable to prior treatments of NSCLC and the previous surgery for NSCLC performed around the thoracic region, and ruled out its relationship to the study device.

Optune Lua treatment began in 1 patient with bronchopleural fistula on November 19, 2018. A serious Grade 3 bronchopleural fistula occurred on January 4, 2019 and resolved. The reporting physician assessed the event as possibly related to Optune Lua. The applicant had the following view: fistula formation is a known complication of malignant thoracic tumors, and nivolumab is known to be involved in immune-mediated events and increased intratumoral inflammation. Such mechanism of action has not been reported in the treatment with Optune Lua, and the adverse event is thus unlikely to be related to Optune Lua. It is clear that the event is related to the history of NSCLC and prior surgery for NSCLC complications in the thoracic region.

The applicant presented the following plan to take measures against skin-related adverse events, noting that these events would be controllable.

[6] Corrected after the deliberation by the Committee on Medical Devices and In-vitro Diagnostics (Note: The text herein has been corrected in accordance with the errata sheet of the Japanese review report.)

- Development of a skin care protocol: The package insert and operating instructions will provide information including guidelines for preparation for skin care and management.
- Training and education: Patients and healthcare professionals will attend training on transducer array placement, skin monitoring, and early management of skin reactions. The training will be provided by qualified personnel.
- Post-marketing monitoring: The applicant will implement post-marketing monitoring of cutaneous adverse events and of treatment regimen adherence on a regular basis as part of pharmacovigilance practice.

PMDA asked the applicant to explain the possibility that Optune Lua intensifies adverse drug reactions of pharmaceutical products, in view of the adverse events in the Optune Lua + ICI group reported with higher incidences than in the ICI alone group.

The applicant's explanation:
Table 9 lists adverse events in the Optune Lua + ICI group reported with higher incidences than in the ICI alone group.

Table 9. Adverse events with higher incidence in the ICI + Optune Lua group (n [%])

Adverse event	ICI + Optune Lua (n = 71)	ICI alone (n = 69)
Musculoskeletal pain	24 (33.8)	16 (23.2)
Anaemia	17 (23.9)	11 (15.9)
Anorexia	12 (16.9)	10 (14.5)
Pain	9 (12.7)	4 (5.8)
Hypokalaemia	5 (7.0)	4 (5.8)
Headache	8 (11.3)	7 (10.1)
Sleep disorder	3 (4.2)	2 (2.9)
Infection	5 (7.0)	1 (1.4)
COVID-19	5 (7.0)	4 (5.8)
Pleural effusion	4 (5.6)	2 (2.9)
Dysphagia	4 (5.6)	1 (1.4)
Hyperglycaemia	4 (5.6)	3 (4.3)
Paraesthesia	4 (5.6)	2 (2.9)
Thrombocytopenia	3 (4.2)	1 (1.4)

These adverse events are consistent with those reported in the US and European labeling of the ICIs used in the clinical study, and are within the scope of the known adverse event profile.
- Highly frequent (≥10%): musculoskeletal pain, anemia, anorexia, and headache
- Common (≥1% and <10%): hypokalemia, dysphagia, hyperglycemia, thrombocytopenia, paresthesia, and pleural effusion

Taking account of the comments from the Expert Discussion, PMDA concluded that the applicant's explanation on the safety of Optune Lua was acceptable.

6.B.(2).3) Efficacy and safety of Optune Lua

In the clinical study, the primary efficacy endpoint of OS was significantly prolonged in the Optune Lua group compared to the control group. The add-on effects of Optune Lua, one of secondary endpoints, was demonstrated in the Optune Lua + ICI regimen. In contrast, Optune Lua + docetaxel showed no clear difference in OS. PFS also indicated no add-on effects of Optune Lua in the combination regimen,

failing to demonstrate acceptable efficacy of Optune Lua. In terms of safety, the device-associated adverse events were known cutaneous events and were manageable. Optune Lua + ICI indicated no tendency of enhanced adverse reactions of ICI. Therefore, the safety of Optune Lua is considered clinically acceptable.

Currently, chemotherapies for patients with unresectable advanced or recurrent NSCLC previously treated with platinum-based antineoplastic chemotherapy, the target population of Optune Lua in the clinical study, have shown only limited effects. Given this situation, PMDA has concluded that it is meaningful to introduce Optune Lua in the clinical practice in Japan as a new therapy for NSCLC, in view of its usefulness shown with add-on effects on OS when combined with ICI and no serious safety concerns observed during the clinical study.

6.B.(3) Use duration of Optune Lua

The applicant's explanation about the use duration of Optune Lua:

The secondary endpoints were analyzed using the average monthly use rate of 50% (equivalent to an average of 12 hours per day) as threshold. The results suggested a positive correlation between the average monthly use rates and the efficacy results. In 71 patients in the Optune Lua + ICI group, the average monthly use rate was 52.3% (equivalent to an average of 12.5 hours per day). Based on this, the recommended use duration was determined as 12 hours a day.

PMDA advised the applicant to select the recommended use duration of 18 hours a day due to the following reasons:

- The clinical study was conducted as per the protocol stipulating that "Optune Lua treatment should be continued for at least 18 hours a day on average."
- In view of its mechanism of action, longer use of Optune Lua produces greater effects. Optune Gio demonstrated a positive correlation between OS/PFS and the use duration of the device.[vi, vii]
- During the clinical study, in which Optune Lua was supposed to be used for 18 hours per day, nearly half of patients used the product for only approximately 12 hours a day. There is a concern about starting clinical use of the product with recommendation of 12-hour, as it may turn out to be even shorter in reality.
- Safety analyses revealed no tendency toward higher incidences of adverse events with longer use.

The applicant's explanation:

Taking account of the PMDA's view, the recommended use duration will be defined as follows: "As a rule, Optune Lua should be used for at least 18 hours a day. If daily use duration can occasionally be shorter than 18 hours, the average of at least 18 hours must be ensured." Taking account of the comments from the Expert Discussion, PMDA concluded that the applicant's explanation is acceptable.

6.B.(4) Intended patients of Optune Lua based on clinical practice guidelines

The present standard of care therapies for NSCLC differ from those in 2016 when the clinical study was planned. PMDA asked the applicant to explain intended patients of Optune Lua in Japan, in light of the efficacy of Optune Lua demonstrated in the Optune Lua + ICI group as mentioned in Section "6.B.(2).1).(a) Concomitant standard of care therapy."

The applicant's explanation:
In 2016 when the clinical study was planned, the standard first-line treatment for stage 4 NSCLC with driver gene mutations/translocation negative was combination therapy with platinum-based antineoplastics, and ICI or docetaxel was used as the standard second-line therapy. The clinical study was designed to evaluate add-on effects of Optune Lua on the standard second-line therapy at that time (ICI or docetaxel). After that, however, ICI began to gain recognition as useful first-line therapy, causing changes in positioning among standard therapies. ICI is currently used as the standard second-line therapy for patients with performance status (PS) scores of 2.

There are some cases when ICI monotherapy is performed as second-line therapy not only by the Guidelines for Diagnosis and Treatment of Lung Cancer (2024 Edition)[viii] (Figure 13) but also for patients whose first-line treatment include only platinum-based antineoplastic combination therapy without ICIs for some reason (e.g., patient's wish [concerns over immune-related adverse drug reactions, long-term hospital visit, economic problem, etc.] or due to medical condition [poor general condition, suspected interstitial pneumonia, comorbid autoimmune disease, etc.]) regardless of PS scores. The use of Optune Lua is a possible treatment option in such future cases.

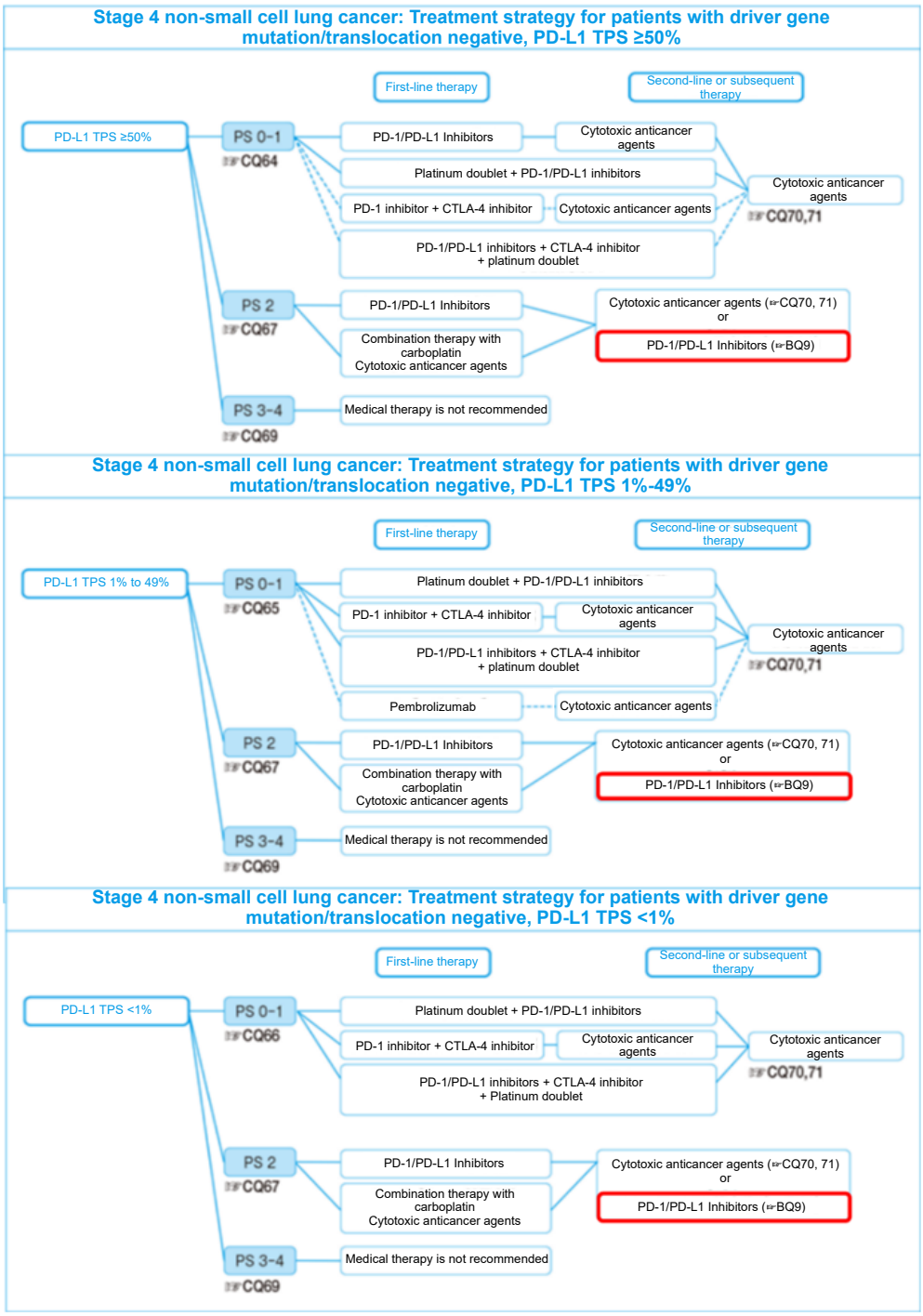


Figure 13. Treatment strategy for stage 4 NSCLC with driver gene mutation/translocation negative

PMDA's view:

Currently, the use of ICIs as second-line therapy is less frequent for stage 4 NSCLC, as compared to 2016 according to the guidelines. Even so, there should be a certain number of patients eligible for Optune Lua treatment, in light of possible cases untreated with ICIs in their first-line therapy due to PS2 or any other individual reasons regardless of PS scores.

6.B.(5) Intended use or indications

The proposed intended use of Optune Lua was "Optune Lua is intended for use in adult patients with a diagnosis of unresectable advanced or recurrent non-small cell lung cancer progressing after cancer

chemotherapy." PMDA asked for some modification to make clearer the product's target population, taking account of the discussions on the target population of the clinical study, as in Sections "6.B.(2).1).(a) Concomitant standard of care therapy" and "6.B.(4) Intended patients of Optune Lua based on clinical practice guidelines."

By referring to the descriptions of the target patients of the clinical study and intended use of Optune Lua in the US, the applicant modified the intended use of Optune Lua as follows. Taking account of the comments from the Expert Discussion, PMDA concluded that the applicant's explanation was acceptable.

Intended Use or Indications (Underlines denote major changes.)
Optune Lua is intended for use in combination therapy with PD-1/PD-L1 inhibitors for adult patients with a diagnosis of unresectable advanced or recurrent non-small cell lung cancer progressing after platinum-based chemotherapy regimens.

6.B.(6) Post-marketing safety measures

PMDA's view:
Optune Lua will be the first alternating TTFields system for NSCLC treatment in Japan. While no particular problems were identified in the safety evaluation results and the procedure, it is critical to select appropriate NSCLC patients with possible metastasis who are expected to respond to Optune Lua treatment. In addition, follow-up care including the standard of care therapy for NSCLC and treatment for Optune Lua-associated skin disorders should be provided appropriately by physicians and at medical institutions with adequate knowledge and experience in lung cancer treatment. Patient selection is subject to further review based on future treatment outcomes.[7] To ensure effective and safe introduction of Optune Lua in Japan, the product's proper use guidelines are essential as measures to ensure the following:

(a) Eligible patients, in whom risk-benefit balance will be maintained with Optune Lua treatment, are selected appropriately by knowledgeable and experienced physicians specialized in lung cancer treatment.
(b) Treatment is provided by physicians and at medical institutions with adequate knowledge, skill, and experience to fulfill accurate diagnosis, guidance on effective and safe treatment with Optune Lua, and follow-up.

Taking account of the comments from the Expert Discussion, these requirements should be attached as approval condition, in light of the importance of adherence to the guidelines for proper use that will be compiled by the relevant academic societies (The Japanese Respiratory Society, The Japanese Association for Chest Surgery, The Japan Lung Cancer Society, and Japanese Society of Medical Oncology) and the provision of training on Optune Lua. Table 10 shows the proposed requirements for physicians and medical institutions written in the guidelines for proper use. Table 11 shows the planned Optune Lua training program.

[7] Corrected after the deliberation by the Committee on Medical Devices and In-vitro Diagnostics (Note: The text herein has been corrected in accordance with the errata sheet of the Japanese review report.)

Table 10. Guidelines for proper use (draft)

Relevant academic societies	The Japanese Respiratory Society, The Japanese Association for Chest Surgery, The Japan Lung Cancer Society, and Japanese Society of Medical Oncology
Requirements for physicians	• Experience in treatment with PD-1/PD-L1 inhibitors for NSCLC in ≥5 patients annually • Completion of the Optune Lua training program
Requirements for medical institutions	• Specializing in pulmonary medicine, pulmonary surgery, or medical oncology • Treating physicians meeting the criteria • Experience in treatment with PD-1/PD-L1 inhibitors for NSCLC in ≥10 patients annually • Capability for specialized treatment for skin-related adverse events on site or at affiliated facilities

Table 11. Training program plan (draft)

- Face-to-face or web-based training
- NovoCure global standard training, and hands-on training which meets the requirements for regulatory approval in Japan
  - ✓ Lecture: Mechanism of action of TTFields, non-clinical data, layout of transducer arrays, clinical study results, management of cutaneous adverse events, etc.
  - ✓ Hands-on training: How to apply transducer arrays, how to handle the main unit, etc.
- Registration in the NovoCure internal system as certified attendees, i.e., physicians who have acquired knowledge from the training and signed the "Optune Lua Information Provision Confirmation" form

7. Plan for Post-marketing Surveillance, etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

The applicant explained that the use-results survey is unnecessary due to the following reasons:

The clinical study revealed no safety concerns other than skin reactions. Optune Gio, which operates by the same mechanism as Optune Lua's, has been used so far in approximately 2,000 Japanese patients with glioblastoma. Mild to moderate non-serious skin reactions are the most common device-related adverse events while no new safety concerns have been identified. The safety profile of Optune Lua used in combination with chemotherapy was consistent between Japanese and non-Japanese patients with glioblastoma, while revealing no clear ethnic difference in the TTFields therapy. Thus, the use-results survey needs not be conducted.

7.B Outline of the review conducted by PMDA

As shown by the safety assessment in the clinical study, many of the adverse events were known skin disorders with no particular concerns, and there have been no unknown adverse events or adverse events specific to Japanese patients reported from the domestic or foreign data on the approved product for glioblastoma, which shares the same operating principle with Optune Lua. It is unlikely that Optune Lua-associated new safety concerns is identified through the use-results survey. PMDA has concluded that the use-results survey is unnecessary, with comments from the Expert Discussion taken into account.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The medical device application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment,

PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

The review of Optune Lua focused on (1) the efficacy and safety of Optune Lua and (2) post-marketing safety measures. PMDA has reached the following conclusions, taking account of discussion at the Expert Discussion.

(1) Efficacy and safety of Optune Lua

The clinical study investigated the efficacy and safety of Optune Lua used in combination with the standard of care therapy compared to the standard of care therapy alone as a control in patients with stage 4 NSCLC progressing during or after the treatment with platinum-based antineoplastics. OS was the primary efficacy endpoint of the clinical study. The median OS was 13.2 months (95% CI, 10.3-15.5) in the Optune Lua group and 9.9 months (95% CI, 8.2-12.2) in the control group, with a hazard ratio for death of 0.76 (95% CI, 0.58-0.99), achieving the primary endpoint (P = 0.0413 based on log-rank test).

Safety evaluation with a focus on serious adverse events revealed no difference in incidence between the study groups. Device-related adverse events occurred in 97 patients (68.8%), the majority of which were Grade 1 or 2 events, while Grade 3 events occurred only in 8 patients (5.7%). Of 97, 90 patients had cutaneous disorders that were known adverse events due to the application of the transducer arrays on the skin, and were treatable and manageable with medication, etc. Therefore, the events are clinically acceptable.

The primary endpoint was achieved. However, the OS analyses by standard of care group as secondary endpoints demonstrated the add-on effects of Optune Lua in Optune Lua + ICI but no clear inter-group difference in Optune Lua + docetaxel. Therefore, Optune Lua shows its efficacy when used in with ICI.

Optune Lua is intended for patients with unresectable advanced or recurrent NSCLC who were previously treated with platinum-based chemotherapy. In light of the unfavorable outcomes of the current standard second-line therapy in this population, PMDA has concluded that Optune Lua is highly useful as shown by improved OS in its use with ICI, and it is of clinical significance to introduce Optune Lua in Japan as a new therapy for NSCLC.

(2) Post-marketing safety measures

For effective and safe introduction of Optune Lua in Japan as its first alternating TTFields system for NSCLC, it is important that adequately knowledgeable and experienced physicians and medical institutions specializing in lung cancer treatment should learn about the product including how to use, and select appropriate patient based on the product's characteristics as a local treatment device. Also, Optune Lua treatment should be provided at medical institutions that can manage Optune Lua-associated skin issues and follow-up of patients using the product at home. PMDA has concluded that these requirements should be attached as approval condition, as it is crucial to use Optune Lua in adherence to the guidelines for proper use that will be compiled by related academic societies.

The use-results survey is unnecessary based on the results from the clinical study and actual use data of the approved product for glioblastoma, which indicate no likeliness of any new safety concerns emerged through the survey.

Based on the results above, PMDA has concluded that Optune Lua may be approved for the intended use below.

Intended Use

Optune Lua is intended for use in combination therapy with PD-1/PD-L1 inhibitors for adult patients with a diagnosis of unresectable advanced or recurrent non-small cell lung cancer progressing after platinum-based chemotherapy regimens.

Approval Condition

The applicant is required to ensure that the product is used for eligible patients selected by physicians who are adequately knowledgeable and experienced in the treatment of non-small cell lung cancer and familiar with how to use and treatment-associated complications, and at medical institutions with established treatment systems. To this end, dissemination of the proper use guidelines compiled jointly with relevant academic societies, provision of a training program, and other measures must be taken as necessary.

The product is not classified as a biological product or a specified biological product.

PMDA has concluded that the application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

References

[i] National Cancer Center Japan, Cancer Statistics Update (https://ganjoho.jp/reg_stat/statistics/stat/cancer/12_lung.html)

[ii] Cancer Information Service, National Cancer Center Japan, “Annual Report of Hospital-Based Cancer Registries” (https://jhcr-cs.ganjoho.jp/hbcrtables/)

[iii] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209-49. doi:10.3322/caac.21660.

[iv] Kirson ED, Gurvich Z, Schneiderman RS, Dekel E, Itzhaki A, Wasserman Y, et al. Alternating electric fields (Tumor-Treating Fields therapy) can improve chemotherapy treatment efficacy in non-small cell lung cancer both in vitro and in vivo. *Semin Oncol.* 2014;41 Suppl 5:S35-41. doi:10.1053/j.seminoncol.2014.09.007.

[v] National Health and Nutrition Survey 2019; Means and standard deviations for Body Mass Index (BMI) - by age group, number of people, mean, and standard deviation - men and women aged ≥15 years (excluding pregnant women) (in Japanese) (https://www.e-stat.go.jp/dbview?sid=0003224178)

[vi] Stupp R, Taillibert S, Kanner A, et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma. *JAMA.* 2017;318(23):2306. doi:10.1001/jama.2017.18718

[vii] Toms SA, Kim CY, Nicholas G, Ram Z. Increased compliance with tumor treating fields therapy is prognostic for improved survival in the treatment of glioblastoma: a subgroup analysis of the EF-14 phase III trial. *J Neurooncol.* 2019;141(2):467-473.

[viii] The Japan Lung Cancer Society. Guidelines for Diagnosis and Treatment of the Lung Cancer 2024 Edition (https://www.haigan.gr.jp/publication/guideline/examination/2024/)