ONO-4538

Multicenter, open-label, uncontrolled, Phase I study in solid tumor

Subtitle: A multicenter, open-label, uncontrolled Phase I study to evaluate the pharmacokinetics of ONO-4538 administered to Korean patients with advanced or recurrent solid tumors who are refractory or intolerant to standard therapy or for whom no appropriate treatment is available.

Protocol

Ono Pharmaceutical Co., Ltd.

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Contact Information for Adverse Event Reports

[redacted]

Confidentiality Statement

This protocol is to be disseminated to the principal investigator, sub investigators, clinical research coordinators, clinical trial pharmacist, medical laboratory technologist and institutional review boards etc. All information contained in this protocol should be treated as confidential and may not be disclosed to any third party.

Note

ONO-4538 is co-developed by Ono Pharmaceutical Co., Ltd. and Bristol-Myers Squibb (BMS) (BMS code: BMS-936558). ONO-4538 is described in this document as a compound code.

Ethics

This study will be conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki, the study protocol, standards stipulated under ICH Good Clinical Practice Guidelines (GCPs), the applicable local regulatory requirements and revised ordinances and relevant notifications.

This protocol will be amended when revision is needed to ensure the safety conduct of the study.

Protocol Synopsis

1. Study Objectives

The objective of the study is to investigate the pharmacokinetics of ONO-4538 administered to Korean patients with advanced or recurrent solid tumors who are refractory or intolerant to standard therapy or for whom no appropriate treatment is available.

2. Study Design

Multicenter, open label, uncontrolled study

3. Disease Studied

3.1 Disease

Advanced or recurrent solid tumors

3.1.1 Subject Inclusion Criteria

Patients satisfying all the following criteria will be included:

1. Male or female (Korean)
2. ≥ 20 years of age (at time of obtaining the Informed Consent)
3. Histologically or cytologically confirmed solid tumor
4. Patients with advanced or recurrent solid tumors who are refractory or intolerant to standard therapy or for whom no appropriate treatment is available
5. ECOG Performance Status (Appendix 2) is 0 to 1
6. Life expectancy is ≥ 90 days at time of patient enrollment
7. Women of childbearing potential (including women who are amenorrheic due to chemical menopause or for another medical reason) [*1] must agree to engage in contraception[*2] from the time of informed consent to at least 400 days after the final dose of the investigational product.
8. Men must agree to use a contraceptive from the start of study treatment until at least 400 days following the last dose of investigational product.
9. Most recently determined laboratory values, within 7 days before patient enrollment on this study, satisfy the criteria listed below. If all the laboratory values were obtained over 7 days before the ONO-4538 initial treatment, the laboratory test has to be performed within 7 days before the ONO-4538 initial treatment and the laboratory values have to meet the all criteria listed below.

Laboratory testing must be performed with no granulocyte colony stimulating factor (G-CSF) treatment or blood transfusion having taken place 14 or fewer days before testing.

- WBC count ≥ 2,000/mm^3 and neutrophil count ≥ 1,500/mm^3
- Platelet count ≥ 100,000/mm^3
- Hemoglobin ≥ 9.0 g/dL
- AST (GOT) and ALT (GPT) ≤ 3.0 times the upper limit of normal range of each institute
- Total bilirubin ≤ 2.0 times the upper limit of normal range of each institute
- Creatinine ≤ 1.5 mg/dL or creatinine clearance (raw or estimated using Cockcroft/Gault formula) > 45 mL/min

*1 The term "women of childbearing potential" includes all women who have experienced menarche but have not undergone a sterilization procedure (e.g., hysterectomy, bilateral tubal ligation, bilateral oophorectomy) or experienced menopause. Menopause is constituted by having been amenorrheic for at least 12 months without a notable reason. Women who use an oral contraceptive, an intrauterine device, the barrier method, or other mechanical method of contraception are considered to be of childbearing potential.

*2 The subject must consent to use any two of the following methods of contraception: vasectomy or condom for patients who are male or their partner and tubal ligation, contraceptive diaphragm, intrauterine device, or oral contraceptive for patients who are female or their partner.

3.1.2 Subject Exclusion Criteria

Patients satisfying any of the following criteria will be excluded:

1. Current or prior severe hypersensitivity to another antibody product
2. Adverse drug reactions due to prior treatments or remaining effects of surgical therapy that, in the principal or sub investigator's opinion, may interfere with the evaluation of the investigational product
3. Active autoimmune disease or history of chronic or recurring autoimmune disease (Appendix 3).
4. Current or prior interstitial lung disease or pulmonary fibrosis diagnosed based on diagnostic imaging or clinical findings.
5. Active diverticulitis or symptomatic gastrointestinal ulcerative disease

6. Multiple primary cancers (except for completely resected basal cell cancer, stage I squamous cell carcinoma, carcinoma in situ, intramucosal carcinoma, or superficial bladder cancer or any other cancer from which the patient has been recurrence-free for at least 5 years)
7. Original cancer or metastases to the brain or meninges (unless such lesions are asymptomatic and do not require treatment)
8. Pericardial effusion, pleural effusion, or ascites requiring treatment
9. Cancer pain not stable with a fixed regimen of an analgesic
10. History of transient ischemic attack, cerebrovascular accident, thrombosis, or thromboembolism (pulmonary arterial embolism or deep vein thrombosis) within 180 days of enrollment.
11. Any of the following cardiovascular diseases that are uncontrollable or severe:
    - Myocardial infarction within 180 days of enrollment
    - Uncontrollable angina pectoris within 180 days of enrollment
    - New York Heart Association (NYHA) Grade III or IV congestive cardiac failure
    - Hypertension (systolic blood pressure ≥ 150 mmHg or diastolic blood pressure ≥ 90 mmHg persisting for ≥ 24 hours) despite appropriate treatment
    - Arrhythmia requiring treatment
12. On anticoagulant therapy (other than antiplatelet therapy with low-dose aspirin) or having a disease requiring anticoagulant therapy.
13. A serious concomitant disease such as liver failure, renal failure or uncontrollable diabetes.
14. Patients requiring transplantation or with a history of transplantation except autotransplantation
15. Has received a systemic corticosteroid (unless temporarily for testing, prophylaxis, or a similar purpose unrelated to an autoimmune disease) or an immune suppressant 28 or fewer days before enrollment.
16. Has received an anti-cancer product (e.g., chemotherapy, molecular targeted therapy, and immunotherapy) 28 or fewer days before enrollment.
17. Has undergone surgery for pleural, pericardial, or similar adhesion 28 or fewer days before enrollment.
18. Has undergone surgical treatment accompanying general anesthesia 28 or fewer days before enrollment.
19. Has undergone surgical treatment accompanying local or surface anesthesia 14 or fewer days before enrollment.
20. Has received radiotherapy 28 or fewer days before enrollment or has received radiotherapy for relief of cancer symptoms 14 or fewer days before enrollment.

21. Has received a radiopharmaceutical agent (except when the radiopharmaceutical agent is used for testing or diagnostic purposes) 56 or fewer days before enrollment.
22. Has undergone gamma knife or CyberKnife treatment 14 or fewer days before enrollment.
23. Has a systemic infection that requires treatment.
24. Has tested positive for HIV-1 antibody, HIV-2 antibody, HTLV-1 antibody, HBs antigen, or HCV antibody.
25. Has tested positive for HBs antibody or HBc antibody and has a result of at least detectable in HBV-DNA assay despite testing negative for HBs antigen.
26. Is pregnant, nursing, or possibly pregnant.
27. Has received another investigational product 28 or fewer days before enrollment.
28. Has previously received ONO-4538 (MDX-1106 or BMS-936558), an anti-CTLA-4 antibody, or other antibody therapy or drug therapy intended to control T-cells.
29. Is found incapable of giving consent due to dementia or another such condition.
30. Patients otherwise found by the principal or sub investigator to be ineligible.

4. Study Schedule and Observations

The study consists of a screening phase, treatment phase, and follow-up phase (see Figure 4).

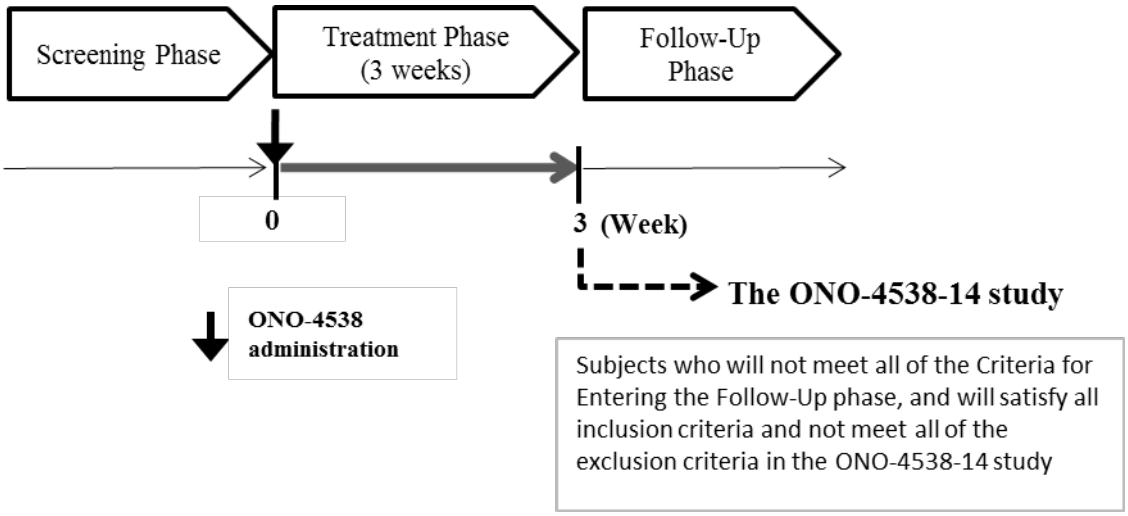

Figure 4 Summary of study design

4.1 Screening Phase

Patients who satisfy all of the subject inclusion criteria and none of the subject exclusion criteria and who are found eligible by the principal or sub investigator can be enrolled and then moved to the treatment phase.

4.2 Treatment Phase

ONO-4538 will be administered once. Subjects who will meet any of the Criteria for Entering the Follow-Up phase will move to the Follow-Up phase. The subjects who complete the treatment phase in this study and not meet all of the Criteria for Entering the Follow-Up phase, and will satisfy all inclusion criteria and not meet all of the exclusion criteria in the ONO-4538-14 study may move to the ONO-4538-14 study, otherwise the subjects will move to the Follow-Up phase.

4.3 Follow-up Phase

Those subjects receiving the investigational product who satisfy any of the Criteria for Entering the Follow-Up phase will proceed to the Follow-Up phase.

Table 4 Study schedule

Category	Screening Phase	Treatment Phase											Follow-Up phase
Study day		1				2	3	4	8	15	22	At discontinuation	28 days after the discontinuation or the Day 22 only if the subjects will not join the ONO-4538-14.
		Before administration	After the start of the administration	After the end of the administration									
			1 hr	2 hr	8 hr								
Allowable range (days)	-7 to -1	-							±2	±3		+3	±7
Written informed consent	○[1]												
Inclusion/exclusion criteria	○												
Virus tests	○[2]												
ONO-4538 administration		○											
Demographics	○												
Pregnancy test[3]	○											○	○
Vital signs/weight /percutaneous oxygen saturation	○	○[4]	○[4]	○[4]	○[4]	○[4]	○[4]	○[4]	○[4]	○[4]	○[4]	○	○
Performance Status	○										○	○	○
Chest X-ray[5]	○										○	○	○
12-lead ECG	○	○	○	○	○		○		○	○	○	○	○
Hematology tests/urinalysis /blood biochemistry tests	○								○		○	○	○
Immunology/hormone tests	○[6]								○		○	○	○
Serum drug concentration[7]		○	○	○	○	○	○	○	○	○	○	○	○
Anti-ONO-4538 antibody		○									○	○	○
[redacted]		■									■	■	
		■											
		■									■	■	
	■												■
Diagnostic imaging (e.g., CT, MRI)[9]	○[2]												●
Tumor marker[10]	●												
Concomitant drugs/adverse events	⟷												

○:essential, ●: optional

1. Begin administering the investigational product within 30 days of informed consent.
2. The data from virus tests performed within 1 year of enrollment, diagnostic imaging (e.g., CT, MRI) performed within 14 days of enrollment will be included.
3. Women of childbearing potential will undergo a serum pregnancy test in the screening phase and subsequently undergo urine pregnancy testing.
4. Other than weight.
5. Also perform at unscheduled visits as necessary if, during the study (from the time of informed consent to the end of the subjects' schedule), signs, subjective and objective symptoms, or test findings suggest respiratory disease.
6. SP-D and KL-6 will be measured in the screening phase and, as necessary, in the treatment phase.
7. Collect blood sample at 24, 48 and 72 hours after the completion of the administration on 2nd, 3rd and 4th day, respectively.
8. [redacted]
9. Check for brain metastases with head CT/MRI. Check for bone metastases with X-ray imaging, FDG-PET, or bone scintigraphy as required by the clinical symptoms.
10. Perform tumor marker assessment according to the cancer type of patient when required at Investigator's discretion.

5. Dose and Administration, and Duration of Treatment

Patients will be assigned any of the following groups in order of increasing dose and ONO-4538 is administered at a dose level of 1, 3 or 10 mg/kg (See Table 5)

Table 5. ONO-4538 Dose

Group	Treatment phase Dose (mg/kg)	Subjects number
A	1	6
B	3	6
C	10	6

ONO-4538 will be administered once in the treatment phase and each subject will be observed for 3 weeks. The appropriate dose of ONO-4538 will be diluted with physiological saline to a total amount of approximately not less than 60 mL before use (so that concentration of diluted solution of ONO-4538 is no less than 0.35 mg/mL). The entire dose of ONO-4538 will be administered as an intravenous infusion over approximately 60 minutes through a 0.20 or 0.22 μm in-line filter. The lower limit of the infusion time is 54 minutes. The target upper limit is 90 minutes. At the end of the infusion, the line will be flushed with a sufficient quantity of physiological saline. Regarding the calculation of the dosage amount, the dose can be rounded off to the nearest tenth.

6. Prior and Concomitant Therapies

6.1 Therapies Prohibited During the Study

The therapies listed below are prohibited during the study (from the time of informed consent to the end of the subjects' schedule).

1. Immunosuppressants and corticosteroids [*1]
2. Anti-cancer products (e.g., chemotherapy, molecular targeted therapy, immunotherapy[*2])
3. Surgical treatment for a malignant tumor
4. Radiotherapy
5. Radiopharmaceuticals[*3] and anti-androgen receptor therapy
6. Bisphosphonate products and anti-RANKL antibodies [*4]
7. Transplant therapy
8. Any other investigational product

[*1] Subjects are permitted to use a local corticosteroid such as topical, intra-articular, intranasal, ocular, inhalational administration, or otherwise temporal systemic corticosteroid for the treatment or prevention of a contrast media allergy or an adverse event.

[*2] This includes local therapies.

[*3] The use of a radiopharmaceutical for a testing or diagnostic purpose is permitted.

[*4] Bisphosphonate products and anti-RANKL antibodies may be used only when the dosage regimen used before study enrollment is maintained.

7. Criteria for Entering the Follow-Up phase

Subjects satisfying any of the following criteria in the treatment phase will proceed to the follow-up phase. Only when the subjects do not satisfy all of the following criteria in the treatment phase, the subjects may move to the ONO-4538-14 study.

1. The development of PD is identified by the principal or sub investigator according to the RECIST guideline (version 1.1) only in case in which the unplanned tumor assessment with diagnostic imaging is performed in the treatment phase.
2. It is determined that continuing the treatment is not appropriate because the worsening of clinical symptoms attributed to disease progression occurs.
3. The subject develops Grade 2 or higher interstitial lung disease, regardless of the causal relationship to the investigational product.
4. Grade 2 or greater eye pain, or visual acuity reduced occurs whose causal relationship with the investigational product cannot be ruled out and does not improve to Grade 1 severity with local treatment.
5. Grade 3 or greater bronchospasm, hypersensitivity reaction, infusion reaction (e.g., pyrexia, chills, nausea, pain, headache, cough, pruritus, and rash) or uveitis occurs whose causal relationship with the investigational product cannot be ruled out.
6. The investigator or sub-investigator otherwise determines that continuing to administer the investigational product is inappropriate.

8. Endpoints

8.1 Safety

1. Adverse events

2. Laboratory tests (hematology, blood biochemistry, qualitative urinalysis, immunology, hormone tests)
3. Vital signs (systolic blood pressure/diastolic blood pressure, pulse rate, and body temperature), body weight, percutaneous oxygen saturation (SpO_2)
4. 12-lead ECG
5. Chest X-ray
6. Performance Status (ECOG)

8.2 Pharmacokinetics

1. Serum ONO-4538 concentrations
2. Pharmacokinetic parameters such as Cmax, Tmax, AUC, T1/2

8.3 Anti-drug Antibodies

1. Anti-ONO-4538 antibody

9. Planned Number of Subjects

Total 18 subjects (6 subjects in each group)

10. Planned Study Period

July 2014 to December 2015