A Phase I/II Study for Dose-finding, and to Investigate the Safety, Pharmacokinetics and Preliminary Efficacy of NK012, an SN-38-Incorporating Macromolecular Polymeric Micelle, in Patients with Multiple Myeloma

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Abstract:

Objective	Multiple myeloma (MM) is the second most common hematological cancer. An attempt to treat MM using a topoisomerase I inhibitor was made based on our previous non-clinical studies suggesting the usefulness of an SN-38 derivative. Our aim was to conduct a phase I/II study of NK012, a micelle-forming SN-38 conjugate, in patients with relapsed/refractory multiple myeloma (RRMM).

Methods	NK012 was administered at doses of 12-24 mg/m^2 and the safety, pharmacokinetics and preliminary efficacy were evaluated.

Results	Neutropenia was the most common grade 3 or 4 adverse drug reaction. Grade 4 neutropenia accounted for the majority of dose-limiting toxicities (DLTs) and only appeared at a dose of 24 mg/m^2. The maximum concentrations (Cmax) and the area under the concentration-time curves from time zero to infinity (AUCinf) for both NK012 and its active metabolite SN-38 increased in a dose-dependent manner. The best overall response was stable disease (SD), which was achieved in 12 out of 16 patients.

Conclusion	The recommended dose of NK012 monotherapy for RRMM patients was concluded to be 20 mg/m^2. However, this phase I/II study was terminated at the end of the phase I stage because no patients showed an objective response. Additional clinical studies of combination therapy with NK012 and other agents are warranted.

Key words: multiple myeloma, micelle, SN-38, bone marrow, extramedullary lesions

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Introduction

Multiple myeloma (MM), which is the second most common form of hematological cancer, is formed by malignant plasma cells. Nearly 230,000 people have this condition worldwide. In 2012, approximately 114,000 new cases were diagnosed and 80,000 patients died (1). MM is characterized by the overproduction of monoclonal proteins, with unique clinical symptoms. During disease progression, it is often accompanied by several unfavorable complications (2), including extramedullary lesions and leukemic changes. The main treatment regimens that are preferred for relapsed or refractory multiple myeloma (RRMM) include proteasome inhibitors (PIs) (3-5) and/or immunomodulatory drugs (IMiDs) (5-7). However, most patients with MM develop resistance to PIs and/or IMiDs during treatment, which makes RRMM incurable. In the search for better treatments, several novel agents are under investigation (7), including new types of PIs, IMiDs, histone deacetylase (HDAC) inhibitors,

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The constitutive expression of topoisomerase I (Topo I), a target molecule of SN-38, and high expression levels of carboxylesterase-2, which metabolizes CPT-11 to SN-38, were previously reported in human MM cells (8). CPT-11 monotherapy significantly reduced the tumor volume in a mouse xenograft model of subcutaneously transplanted human MM cells, and its combination with bortezomib completely eradicated the tumor masses in all mice (n=5) (8). These results suggested that CPT-11 or SN-38 could be candidate drugs that can be used in the treatment of MM.

NK012 is a micelle-forming macromolecular prodrug that is prepared by the conjugation of SN-38 (7-ethyl-10-hydroxycamptothecin) with amphiphilic block copolymers (9-11). Unlike CPT-11, the release of SN-38 from NK012 is non-enzymatic, and is therefore expected to exhibit a stable therapeutic effect, independent of the carboxylesterase enzymatic activity, which varies among patients. In addition, the frequency and the severity associated with NK012 are expected to be lower in comparison to patients with MM in comparison with CPT-11 because the cholinergic mechanism that was suggested to be associated with CPT-11 was not found in NK012. The antitumor activity of NK012 was examined in a mouse model of orthotopic MM using CD138-positive U2661B1 cells. The intravenous administration of NK012 was found to suppress the plasma M protein concentration and the proliferation of infiltrating myeloma cells in the bone marrow in a dosedependent manner (11).

The results from these CPT-11 and NK012 studies indicated there was sufficient value in the further clinical evaluation of NK012. Phase I studies of NK012 in patients with solid tumors have already been conducted in Japan (12) and the US (13), respectively. Conversely, a patient continued NK012 treatment for more than 10 cycles at 9 mg/m² in the phase I study in the US (13). Thus, the dose escalation plan was set as 12, 16, 20, 24, and 28 mg/m². The dose was selected because grade 3 and 2 neutropenia first occurred at this dose in phase I studies in Japan (12) and the US (13), respectively. Conversely, a patient continued NK012 treatment for more than 10 cycles at 9 mg/m² in the phase I study in the US (13). Thus, the dose escalation plan was set as 12, 16, 20, 24, and 28 mg/m².

Patients

Patients with symptomatic RRMM and a history of treatment with at least two standard regimens, at least one of which contained bortezomib, lenalidomide, or thalidomide, were eligible. The further inclusion criteria were as follows: 20-79 years of age; the estimation or measurement of the disease state with serum M-protein values of IgG ≥1.0 g/dL, IgA ≥0.5 g/dL, or IgD ≥0.2 g/dL, and a urine M-protein value of ≥0.2 g/24 hours; in patients in whom the functions of the main organs were well maintained (shown by a neutrophil count of ≥1,500/μL, a platelet count of ≥7.5×10⁴/μL, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of ≤3 times the upper limit of normal, a serum creatinine level of ≤2.0 mg/dL; a performance status (PS) of 0-2 on the East Cooperative Oncology Group (ECOG)/Zubrod scale. Additionally, patients with a PS of 3 due to an osteolytic lesion were eligible for inclusion. Patients with homozygous UGT1A1*28 or UGT1A1*6 or both heterozygous UGT1A1*28 and UGT1A1*6, in a UGT1A1 genetic polymorphism assay were excluded to improve the precision of the study.

The administration of the study drug

NK012 was intravenously administered over 30 min on the first day of a 4-week cycle. Dexamethasone (6.6 mg/body) was administered intravenously prior to the administration of NK012 as a prophylactic measure against nausea and vomiting. The maximum number of cycles was defined as eight. However, the continuation of treatment beyond the eighth cycle was permitted based on the patient’s benefit and was determined by the study sponsor and the investigator in charge.
Assessment

Safety assessments, including the observation of adverse events, vital signs, and laboratory tests, were initially performed every week. However, beyond the third cycle, investigators were permitted to reduce the frequency of observation to every other week if the patient’s safety status was considered stable based on the observation of past cycles. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. DLT was defined as any of the following adverse events (AEs) in the first cycle: grade 4 neutropenia persisting for at least 8 days, grade 4 thrombocytopenia requiring blood transfusion, and grade 3 or 4 non-hematologic adverse events (blood chemistry, urinalysis, signs and symptoms). If the severity of nausea, vomiting, and diarrhea decreased to grade ≤2 with appropriate treatment, they were not recognized as DLTs. Additionally, grade 3 hypersensitivity, grade 3 decreased appetite, and a grade ≥3 increase in alkaline phosphatase (ALP) were likely to be associated with new bone formation, grade ≥3 electrolyte level abnormalities or abnormal chemistry parameters associated with tumor lysis syndrome were not considered to be DLTs.

The QT/QTc interval was assessed by electrocardiography (ECG) in the first phase of the I stage according to the following schedule and procedure: 1) the baseline was measured at three time points on the day before treatment (the planned pretreatment time, 1 hour, and 6 hours); 2) on the first day of treatment, at the same time points as on the previous day; and 3) at 24 hours and 4 weeks after the first treatment.

The blood samples for the pharmacokinetics (PK) analysis were obtained from each patient in the first cycle at the following time points: before, just after the start of the infusion, and a further 1, 6, 24, and 72 hours, and 7, 14, and 28 days after the end of the NK012 infusion. The drug concentration in the bone marrow aspirate was measured at 7 days after the administration in patients who gave their consent. In parallel, a smear was prepared to investigate the percentage of plasma cells.

The efficacy of NK012 was evaluated according to the International Myeloma Working Group (IMWG) Uniform Response Criteria and Bladé criteria/European Group for Blood and Marrow Transplant (EBMT) criteria. The serum M-protein levels were measured at 2 and 4 weeks after each cycle of NK012 administration, at the central laboratory (SRL, Inc., Tokyo, Japan).

The PK analysis

Blood samples (2 mL) were collected with heparin as an anticoagulant, and were cooled immediately on ice. The samples were centrifuged and plasma was obtained. Bone marrow aspirate (0.5 mL to 1 mL) was collected and part of the fluid was used to prepare the smear. The remaining fluid was transferred into a heparin-containing tube placed on ice. Ice-cold 0.1 mol/L hydrochloric acid was added all biological samples to prevent the hydrolysis of NK012.

The concentrations of free SN-38 (polymer-unbound SN-38) and SN-38-glucuronide were measured by reversed-phase high-performance liquid chromatography (HPLC) with fluorescence detection (15). The total concentration of SN-38 (polymer-bound and unbound) was measured by analyzing hydrolyzed samples (16).

The pharmacokinetic parameters were calculated using the WinNonlin software program (Pharsight Corporation, version 6.1) with a non-compartmental analysis.

Statistical Analysis

The sample size in the phase II stage was set at 41 patients, based on the number that was required to meet the threshold and expected overall response rate (10% and 25%, respectively) with 80% power and a type I error of 0.05.

A two-sided confidence interval with a confidence level of 95%, and a two-tailed test with a significance level of 0.05 were used for the statistical analyses. The safety analysis was conducted in the safety analysis cohort, which included patients who received at least one dose of the study drug. The efficacy endpoints of this study were the overall response rate according to the IMWG criteria (stringent complete response [sCR], complete response [CR], very good partial response [VGPR] and partial response [PR]), progression-free survival (PFS) and overall survival (OS). The median values and 95% confidence intervals for the PFS, and OS curves were estimated using the Kaplan-Meier method.

Results

Phase I stage

Patient characteristics

This trial, which was sponsored by Nippon Kayaku Co., Ltd (Tokyo, Japan), started in November 2011, and was terminated in February 2014 at the completion of the eighth cycle of treatment by the last enrolled patient. All 16 patients enrolled received NK012 treatment. The patient characteristics are shown in Table 1. All of the 16 patients had previously received bortezomib, and 11 patients (69%) had previously received IMiDs, including lenalidomide and thalidomide. High-risk cytogenetic abnormalities, t(4;14), t(14;16), and/or del(17p), were found in five patients (31%). Three patients enrolled in the 24 mg/m² cohort had extramedullary lesions.

Dose escalation

Three patients each were enrolled in the level 1 (12 mg/m²), 2 (16 mg/m²), and 3 (20 mg/m²) cohorts. No DLTs were observed at these levels. In the level 4 (24 mg/m²) cohort, one of the first three patients experienced grade 4 neutropenia (which persisted for at least 8 days), and grade 3 anemia, as DLTs. We therefore planned to add three patients to the cohort. Actually, four patients were enrolled because the fourth patient gave their consent prior to the administra-
nomodulation was observed in 1 of the 3 patients (33.3%) in the 20 mg/m² group. A causal relationship with NK012 could not be excluded for six SAEs in three patients, including two cases of decreased appetite and one case each of leukopenia, anemia, pneumonia, and tremor. No patients died during the study period.

The evaluation of QT/QTc prolongation following NK012 treatment showed slight prolongation in comparison to the serum polymer-unbound SN-38 level (data not shown).

Safety

All 16 patients who were treated with NK012 were included in the safety analysis. Hematologic or non-hematologic adverse drug reactions (ADRs) occurred in more than 10% of the patients; the grade ≥3 ADRs that occurred in at least one patient are shown in Table 2. All patients experienced at least one ADR. The most commonly observed ADRs were hematologic toxicities; neutropenia was the most common grade ≥3 ADR. Grade 4 neutropenia was observed in 1 of the 3 patients (33.3%) in the 20 mg/m² group and in 6 of the 7 patients (85.7%) in the 24 mg/m² group.

A total of seven serious adverse events (SAEs) occurred in three patients: one patient in the 20 mg/m² group and two patients in the 24 mg/m² group. A causal relationship with NK012 could not be excluded for six SAEs in three patients, including two cases of decreased appetite and one case each of leukopenia, anemia, pneumonia, and tremor. No patients died during the study period.

Pharmacokinetics

The time profiles of the mean plasma concentration of polymer-bound SN-38, polymer-unbound SN-38, and SN-38-glucuronide are shown in Table 3. The pharmacokinetic profiles of NK012 in MM patients were similar to those in patients with solid tumors. Eventually, four of the seven patients in the in the level 4 group experienced six DLTs (grade 4 neutropenia persisting for at least 8 days, n=3; grade 3 anemia, n=1; grade 3 hyponatremia, n=1; and grade 4 thrombocytopenia requiring blood transfusion, n=1). Thus, the recommended dose for the phase II stage was determined to be 20 mg/m² every 4 weeks.

Table 1. Demographics and Other Baseline Characteristics.

| Factor               | Category | 12 mg/m²  | 16 mg/m²  | 20 mg/m²  | 24 mg/m²  | Total       |
|----------------------|----------|-----------|-----------|-----------|-----------|-------------|
|                      |          | n=3, (%)  | n=3, (%)  | n=3, (%)  | n=7, (%)  | n=16, (%)  |
| Gender               | Male     | 2 (66.7)  | 2 (66.7)  | 2 (66.7)  | 6 (85.7)  | 12 (75.0)  |
|                      | Female   | 1 (33.3)  | 1 (33.3)  | 1 (33.3)  | 1 (14.3)  | 4 (25.0)   |
| Age                  | Median   | 59.0      | 62.0      | 62.0      | 67.0      | 62.0       |
|                      | Range    | 46-71     | 51-77     | 51-65     | 56-72     | 46-77      |
| Performance status   | 0        | 3 (100)   | 1 (33.3)  | 2 (66.7)  | 3 (42.9)  | 9 (56.3)   |
|                      | 1        | 2 (66.7)  | 1 (33.3)  | 2 (28.6)  | 5 (31.3)  | 2 (12.5)   |
|                      | ≥2       |           |           |           |           |            |
| Cytogenetic abnormalities | t(4;14) | 3 (100)   | 1 (33.3)  | 1 (14.3)  | 4 (25.0)  | 2 (12.5)   |
|                      | 17p      |           |           |           |           |            |
|                      | t(14;16) |           |           |           |           |            |
|                      | 13q      | 1 (33.3)  | 1 (33.3)  | 1 (6.3)   | 1 (6.3)   |             |
| Serum                | IgG      | 2 (66.7)  | 2 (100)   | 3 (100)   | 4 (66.7)  | 11 (78.6)  |
| M-protein            | IgA      | 1 (33.3)  | 1 (33.3)  | 1 (6.3)   | 1 (6.3)   |             |
| Urine                | κ        |           |           |           |           |            |
|                      |         |           |           |           |           |            |
|                      | μ        | 1 (100)   | 1 (100)   | 1 (100)   | 3 (100)   | 7 (43.8)   |
|                      | Λ        |           |           |           |           |            |
| Prior therapy        | Radiation therapy | 1 (33.3) | 1 (33.3) | 2 (66.7) | 2 (28.6) | 6 (37.5) |
|                      | ASCT     | 1 (33.3)  | 2 (66.7)  | 4 (57.1)  | 7 (43.8)  |             |
|                      | Bortezomib alone | 1 (33.3) | 1 (33.3) | 1 (33.3) | 2 (28.6) | 5 (31.3) |
|                      | Bortezomib and IMiDs | 2 (66.7) | 2 (66.7) | 2 (66.7) | 5 (31.3) | 11 (68.8) |

ASCT: autologous stem cell transplantation, IMiDs: immunomodulatory drugs

Table 2. Adverse Drug Reactions Following NK012 Administration (more than 10% and at Least of Grade 3 severity in One Patient).

| Adverse drug reactions | Number of patients (n=16) Any grade (%) | ≥Grade 3 (%) |
|------------------------|----------------------------------------|-------------|
| Hematologic Toxicities |                                        |             |
| Neutropenia            | 15 (93.8)                              | 13 (81.3)   |
| Leukopenia             | 15 (93.8)                              | 12 (75.0)   |
| Hb decrease            | 15 (93.8)                              | 4 (25.0)    |
| Lymphopenia            | 14 (87.5)                              | 8 (50.0)    |
| Red blood cell decrease| 10 (62.5)                              | 4 (25.0)    |
| Ht decrease            | 10 (62.5)                              | 4 (25.0)    |
| Thrombocytopenia       | 7 (43.8)                               | 2 (12.5)    |
| Non-Hematologic Toxicities |                                              |             |
| Anorexia               | 10 (62.5)                              | 3 (18.8)    |
| Potassium decrease     | 4 (25.0)                               | 2 (12.5)    |
| CRP increase           | 4 (25.0)                               | 1 (6.3)     |
| Anemia                 | 2 (12.5)                               | 2 (12.5)    |
| Sodium decrease        | 2 (12.5)                               | 1 (6.3)     |

Hb: hemoglobin, Ht: hematocrit, CRP: C-reactive protein
Figure 1. The plasma concentration-time profiles of polymer-bound (left) and polymer-unbound (right) SN-38 in patients with MM after an intravenous infusion of NK012 at 20 mg/m². Error bars show the standard deviation.

Table 3. Pharmacokinetic Parameters of Polymer-bound SN-38, Polymer-unbound SN-38, and SN-38-glucuronide.

| Dose (mg/m²) | Polymer-bound SN-38 | Polymer-unbound SN-38 | SN-38-G |
|-------------|---------------------|-----------------------|---------|
|             | C_{max} (μg/mL)     | T_{1/2ε} (h)          | AUC_{inf} (μg·h/mL) | C_{max} (μg/mL) | T_{1/2ε} (h) | AUC_{inf} (μg·h/mL) | C_{max} (μg/mL) | T_{1/2ε} (h) | AUC_{inf} (μg·h/mL) |
| 12 Mean     | 5.69                | 124                   | 88.6     | 0.0425              | 89.9           | 0.677          | 0.0281              | 138           | 1.04              |
| SD          | 0.23                | 27                    | 1.9      | 0.0143              | 47.7           | 0.095          | 0.0132              | 53            | 0.54              |
| 16 Mean     | 7.82                | 142                   | 139      | 0.0829              | 83.1           | 1.27           | 0.0588              | 127           | 2.30              |
| SD          | -                   | -                     | -        | -                   | -              | -              | -                   | -             | -                 |
| 20 Mean     | 9.15                | 143                   | 152      | 0.0859              | 121            | 1.35           | 0.0461              | 195           | 2.05              |
| SD          | 1.01                | 9                     | 17       | 0.0093              | 23             | 0.17           | 0.0254              | 63            | 0.97              |
| 24 Mean     | 11.0                | 148                   | 185      | 0.137               | 222            | 2.01           | 0.0746              | 210           | 3.32              |
| SD          | 2.6                 | 10                    | 39       | 0.045               | 101            | 0.43           | 0.0328              | 86            | 1.41              |

C_{max}: maximum concentration, T_{1/2ε}: terminal-phase half-life, AUC_{inf}: area under the concentration-time curve from time zero to infinity.
The time course of the serum and urine M-protein levels until the confirmation of disease progression in 16 individual patients. The serum (closed circle) or urine (open circle) M-protein levels were measured at the baseline and every two weeks, after the administration of the study drug in each cycle.

The median PFS (min-max) of all enrolled patients, according to IMWG criteria, was 135 days (14-812 days). One patient each in the 16 mg/m$^2$ 20 mg/m$^2$ groups displayed no disease progression for more than 1 year. The time course of the serum or urine M-protein levels from the initiation of treatment with the study drug to the confirmation of disease progression in each patient is shown in Fig. 2. The median OS (min-max) of all of the enrolled patients was 443 days (140-843 days).

Three in the 24 mg/m$^2$ group had extramedullary lesions (soft tissue masses). None of the extramedullary lesions progressed during the study period. In particular, the extramedullary lesion of one patient was found to have completely disappeared by the end of the second cycle (Fig. 3).

The disappearance of an extramedullary lesion following treatment with NK012. A 70-year-old man with an extramedullary lesion in the basal part of the right lung (indicated by the arrow in the left CT image) was treated with NK012 at a dose of 24 mg/m$^2$. The lesion was observed to have disappeared on the CT image obtained 59 days after the initiation of NK012 treatment (right).

Phase II stage

After the completion of the phase I stage, the initiation of the phase II stage was evaluated by the Independent Efficacy/Safety Data Review Committee. The committee did not recommend the initiation of the phase II stage because the results of the phase I stage suggested that it was unlikely
that an objective response would be achieved at the initially expected level. The study sponsor accepted the recommendation, and terminated the study without initiating the phase II stage.

Discussion

This study was conducted to evaluate the safety and tolerability, as well as pharmacokinetics and preliminary efficacy, of NK012 in patients with RRMM. The safety analysis revealed that neutropenia was the most common DLT to occur in association with the administration of NK012. This was similar to observations in previous phase I studies involving patients with solid tumors (12, 13). Six DLTs were observed in four of the seven patients in the 24 mg/m² group, but no DLTs were observed in the 20 mg/m² group. Thus, it was concluded that the recommended dose for patients with MM should be 20 mg/m². The recommended dose determined in this study was lower than that in previous phase I studies involving solid tumors (28 mg/m²) (12, 13). The suspected reason for this was that the hematopoietic functions in patients with MM differed from those in patients with solid tumors.

The major grade ≥3 drug reactions included myelosuppression (neutropenia [13/16; 81.3%], leukopenia [12/16; 75.0%], and lymphopenia [8/16; 50%]). However, these toxicities were manageable with adequate supportive care, such as the prophylactic or therapeutic administration of G-CSF and/or antibiotics. The careful monitoring of myelosuppression would be important during NK012 treatment. Among the non-hematological toxicities, the severe diarrhea that was a clinical problem with CPT-11, was not observed. This result was consistent with the results of previous phase I studies involving patients with solid tumors (12, 13).

The plasma concentrations of polymer-bound SN-38 and polymer-unbound SN-38 showed a decline within one week and accumulation was not considered to be significant in the weekly dosing schedule. The plasma concentrations increased in a dose-dependent manner no differences were evident among the 16, 20 and 24 mg/m² groups, which reflected the small increment in the dosage.

As NK012 was observed to be highly distributed in the bone marrow of rats (data not shown), the concentration of polymer-bound or unbound SN-38 in bone marrow, one of the target tissues of nanoparticle distribution, was measured for exploratory purposes. The existence of NK012 (polymer-bound SN-38) and its active form (polymer-unbound SN-38) in bone marrow was confirmed (Supplemental Fig. 1). As the NK012 concentration in bone marrow was not less than the SN-38 concentration at 168 hours after administration, it is possible that the NK012 was distributed to the bone marrow and released SN-38 there. Further investigations are necessary to understand the dynamics of NK012 in plasma and bone marrow.

None of the patients in the present study showed a PR following NK012 treatment. The best response—SD—was achieved in 12 of the 16 patients. These results indicated that the objective tumor response in patients receiving NK012 monotherapy—measured according to the serum or urine M-protein level—was insufficient. With regard to the patients who showed a limited objective tumor response, three patients continued to receive NK012 treatment without progression for more than 1 year; in some cases, long-term disease control was observed at a lower dose. Three patients with extramedullary lesions were enrolled in this study. Interestingly, in two cases, the extramedullary lesions showed no progression during the study period; in the third case, the lesion rapidly disappeared. Varettoni et al. reported that the prevalence of extramedullary involvement had increased in recent years (2000-2007) in comparison to previous reports (1971-1999), and that the overall survival and progression-free survival times in patients with extramedullary disease were shorter in comparison to patients without extramedullary disease (17). An effective treatment strategy for extramedullary disease is desired, and this remarkable response of the extramedullary lesions represents another area in which NK012 may be clinically effective.

In conclusion, the recommended dose of NK012 monotherapy for UGT1A1 wt/wt and wt/*28 genotype patients with RRMM was concluded to be 20 mg/m². This phase I/II study was terminated at the end of the phase I stage because no patients showed an objective response. The further clinical development of NK012 as a monotherapy for RRMM was not recommended because of its low efficacy. In the future, NK012 should be considered for the treatment of RRMM as a combination therapy with other agents, including PIs. This is supported by a mice model of orthotopic MM, in which bortezomib/NK012 prolonged the median survival time in comparison to bortezomib alone (11).

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