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Phase I, multicenter, dose-escalation study of avadomide in adult Japanese patients with advanced malignancies

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Abstract

Non-Hodgkin lymphoma (NHL) treated with chemoimmunotherapy has limited efficacy in some patients, resulting in relapsed or refractory disease. Avadomide (CC-122) is a novel cereblon-binding agent that exhibits antilymphoma and immunemodulation activities with a biological profile distinct from similar agents, such as lenalidomide. This phase I multicenter study evaluated avadomide in Japanese patients with advanced solid tumors or NHL. Fourteen patients with NHL and one with a solid tumor (esophageal carcinoma), were enrolled in four dose-escalation cohorts using a 3 + 3 design. Primary endpoints included safety, dose-limiting toxicities (DLT), maximum-tolerated dose and/or recommended phase II dose (RP2D), and pharmacokinetics. Secondary endpoints included overall response rate (ORR) and duration of response. One patient with NHL experienced DLT, which included face edema, pharyngeal edema, and tumor flare (all grade 1) that led to a dose reduction. Eleven patients had grade ≥3 treatment-emergent adverse events, most frequently decreased neutrophil count (33%) and decreased lymphocyte count (20%). The ORR in patients with NHL (n = 13) was 54%, including four complete and three partial responses. The best response for the solid tumor patient was progressive disease. Avadomide dose intensity was consistent across cohorts, and the 3-mg dose given five consecutive days/week was established as the RP2D. This phase I study identified a tolerable dose

Abbreviations: ABC, activated B cell; AE, adverse event; AIC, active ingredient in capsule; AITL, angioimmunoblastic T-cell lymphoma; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the plasma concentration time curve; CL/F, apparent clearance; C_{max}, peak plasma concentration; CNS, central nervous system; CR, complete response; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; DOR, duration of response; F6, formulated capsule; FL, follicular lymphoma; GCB, germinal center B cell; HCl, hydrochloride; IL-2, interleukin; LDH, lactate dehydrogenase; MedDRA, Medical Dictionary for Regulatory Activities; MTD, maximum tolerated dose; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NE, not estimable; NHL, non-Hodgkin lymphoma; NK, natural killer; NTD, non-tolerated dose; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; PTCL NOS, peripheral T-cell lymphoma not otherwise specified; R/R, relapsed/refractory; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RP2D, recommended phase 2 dose; SAE, serious adverse events; SD, stable disease; SRC, safety review committee; $t_{1/2}$, terminal half-life; TEAE, treatment-emergent adverse events; T_{max}, time to maximum plasma concentration; ULN, upper limit of normal; Vz/F, volume of distribution.

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of avadomide, with an acceptable toxicity profile and clinically meaningful efficacy in Japanese patients with previously treated NHL.

KEYWORDS
avadomide, CC-122, cereblon, dose-escalation, non-Hodgkin lymphoma, phase I

1 | INTRODUCTION

Non-Hodgkin lymphoma includes multiple clinical-pathological subtypes, primarily of B-cell origin, including DLBCL and FL.[1] Treatment for NHL often includes chemoimmunotherapy, using the anti-CD20 monoclonal antibody rituximab in combination with cytotoxic agents, such as R-CHOP. Efficacy is often limited, and some patients will relapse or develop refractory disease.[2] In patients with DLBCL treated with R-CHOP, primary refractory disease (no response or relapse within 3 months) occurs in 10%–15% of patients. Of those who do respond initially, 20%–25% relapse, with most relapses occurring within 3 years.[3]

Avadomide (CC-122) is a novel agent that binds to cereblon, a substrate receptor of the Cullin-RING E3 ubiquitin ligase complex.[4-7] This binding results in selective ubiquitination and proteasomal degradation of the hematopoietic transcription factors Ikaros (IKZF1) and Aiolos (IKZF3) in vitro.[6] In a single-arm, phase I clinical trial of avadomide (CC-122-ST-001; NCT01421524), lymph node biopsies from patients with R/R DLBCL who were treated with avadomide showed reduced expression of Ikaros and Aiolos compared with baseline levels.[6]

Degradation of Aiolos and Ikaros by avadomide and other cereblon-binding agents, such as lenalidomide, has been identified as a key mechanism in their antitumor and immunomodulation activities.[8,9] In preclinical studies, avadomide decreased tumor growth in xenograft models and also inhibited proliferation and induced apoptosis in ABC and GCB DLBCL cell lines.[6] Activity in both ABC- and GCB-cell lines indicates that avadomide has broad cytotoxic activity across cell-of-origin-based DLBCL subtypes. In contrast, lenalidomide has been reported to have preferential activity in ABC-subtype cell lines and in patients with ABC-subtype DLBCL.[6,10] In conjunction with antilymphoma activity, avadomide has immunomodulatory effects. Ex vivo studies showed that avadomide significantly activated T cells, as measured by a dramatic increase in IL-2 secretion upon stimulation.[6,11] Avadomide also decreased $CD19^+$ B cells and expanded cytotoxic memory T cells in patients with NHL.[12,13] Furthermore, paired biopsies from DLBCL patients showed increased infiltration of T cells and macrophages upon treatment with avadomide.[11] Avadomide has also been shown to activate NK cells that mediate antibody-dependent, cell-mediated cytotoxicity.[14] Additionally, avadomide has demonstrated antiangiogenic activity that may make it effective against solid tumors.[14]

An ongoing phase I study of avadomide (CC-122-ST-001; NCT01421524) has determined the NTD and MTD, respectively, to be 3.5 and 3 mg once daily with continuous treatment.[13] Preliminary results from the study showed that the 3-mg dose resulted in an ORR of 23% in patients with R/R NHL but was associated with neutropenia-related dose reductions.[15] Further exploration of dosing schedules determined that 3 mg given on an intermittent dosing schedule of 5 continuous days per week mitigated neutropenia-related dose reductions while maintaining the clinical activity of avadomide.[15] We report here the safety and efficacy results from a phase I study of avadomide in Japanese patients with advanced solid tumors or NHL.

2 | MATERIALS AND METHODS

2.1 | Study objectives

CC-122-ST-002 is an ongoing multicenter, open-label, phase I study to assess the safety, tolerability, and PK of avadomide in adult Japanese patients with advanced solid tumors or NHL (NCT02509039). The findings presented here are as of the 30 March 2017 data cutoff date. Primary objectives were to evaluate safety and tolerability of avadomide, determine the MTD or RP2D, and measure PK parameters. Secondary endpoint was antitumor efficacy, based on response rates and DOR. Exploratory endpoints included defining the relationship between biomarkers and clinical endpoints, and elucidating differences in PK and DLT profiles among different doses and formulations: avadomide AIC and the avadomide F6.

2.2 | Patients

The study was designed and conducted in adherence to Good Clinical Practice per the International Conference for Harmonisation Guideline E6 and in accordance with the Declaration of Helsinki. The study was approved by the Institutional Review Boards of the participating sites (Aichi Cancer Center Hospital, National Cancer Center Hospital East, Niigata Cancer Center Hospital, The Cancer Institute Hospital of Japanese Foundation for Cancer Research). All patients provided written informed consent before any study-related procedures were carried out. Patients were ≥ 20 years old and had histological or cytological confirmation of advanced solid tumors or NHL. Patients who had progressed on, or were unable to tolerate, standard anticancer therapy were included, as well as those for whom no other conventional therapy existed. ECOG PS was ≤ 2 for all patients. Required initial laboratory values included

absolute neutrophil count ≥ 1.5 × 10^9/L, hemoglobin ≥ 9 g/dL, platelets ≥ 100 × 10^9/L, AST and ALT ≤ 3 × ULN or ≤ 5.0 × ULN if liver tumors were present, serum bilirubin ≤ 1.5 × ULN, and serum creatinine ≤ ULN or 24-hour clearance ≥ 50 mL/min. Key exclusion criteria included primary CNS malignancies or symptomatic CNS metastases (patients with previously treated brain metastases and were stable for 6 weeks were allowed); acute or chronic pancreatitis; peripheral neuropathy grade ≥ 2 according to NCI CTCAE version 4.03; persistent diarrhea or malabsorption NCI CTCAE grade ≥ 2; impaired cardiac function or clinically significant cardiac diseases; prior systemic cancer–directed treatments or investigational modalities ≤ 5 half-lives or 4 weeks (whichever was shorter), prior to starting avadomide, or continued side effects of such therapy; and major surgery ≤ 2 weeks prior to starting avadomide or continued postoperative side effects.

2.3 | Treatment

Four treatment cohorts were used in a standard 3 + 3 study design with sequential enrollment to establish the MTD/RP2D and evaluate toxicity.[16] Patients in cohorts 1, 2, and 3 received avadomide AIC at 2 mg/d, 3 mg/d, and 4 mg/d, respectively. Patients in cohort 4 received avadomide F6 at 3 mg/d. Avadomide F6 has a different base-free amount and higher total and peak plasma exposures compared with AIC. Avadomide AIC 0.5-, 1-, and 3-mg strengths were based on avadomide HCl and are equivalent to 0.44, 0.88, and 2.64 mg avadomide free base, respectively. Avadomide F6 1-, 3-, 3.5-, and 4-mg strengths are based on avadomide free base and are equivalent to 1.13-, 3.38-, 3.95, and 4.51-mg avadomide HCl, respectively.

Patients with solid tumors or NHL were enrolled in cohort 1, but only those with NHL were enrolled in cohorts 2-4. All avadomide doses were given orally once daily on an intermittent dosing schedule of five continuous days out of 7 days per week. Doses were given in an escalating method, beginning with cohort 1. All patients were treated and observed for at least 28 days (Cycle 1) after the first dose of avadomide (DLT evaluation period) before the dose level was escalated in another cohort. A SRC evaluated the safety and available PK data at the end of the DLT evaluation period for each cohort to determine whether dose escalation could occur, to confirm the dose level to be used in the subsequent cohort, and to determine the MTD/RP2D. No dose reduction was allowed during the DLT evaluation period, except in patients who experienced DLT. Patients who experienced DLT during the DLT evaluation period could resume avadomide at a reduced dose once their toxicity recovered to grade 1 or baseline, provided recovery occurred within 28 days of treatment interruption. Dose reductions for non-DLT were allowed after the DLT evaluation period and in consultation with the sponsor. Intrapatient dose escalation was not permitted during the DLT evaluation period. Patients who continued treatment with avadomide beyond Cycle 1, and who had not experienced grade ≥ 3 toxicities at their assigned dose level, were allowed a dose level increase following approval by the SRC, provided the alternative dose level had been shown to be well tolerated in at least one cohort of other patients. Treatment was given until disease progression, unacceptable toxicity, or voluntary withdrawal.

2.4 | Safety, PK, and response assessments

Adverse events were assessed according to the NCI CTCAE, version 4.03. AE were classified using the MedDRA classification system. NTD was defined as the dose level at which ≥ 2 of six evaluable patients in a cohort experienced a drug-related DLT during the DLT evaluation period. MTD was defined as the last dose level below the NTD at which ≤ 1 of six evaluable patients had a DLT during the DLT evaluation period. DLT were defined as TEAE related to avadomide that were first observed during the DLT evaluation period and that necessitated a dose reduction during the DLT evaluation irrespective of grade level, based on the following criteria: (i) a clinically relevant nonhematologic TEAE grade ≥ 3 (except for grade 3 acneiform or maculopapular rash lasting ≤ 4 days or grade 3 diarrhea or vomiting lasting < 72 hours); (ii) a clinically relevant grade ≥ 3 laboratory abnormality; (iii) any febrile neutropenia; (iv) grade 4 neutropenia lasting > 7 days; (v) grade 4 thrombocytopenia lasting > 24 hours or of any grade requiring platelet transfusions; (vi) any grade 3/4 thrombocytopenia with clinically significant bleeding; (vii) grade 4 liver function tests or grade 3 ALT with grade ≥ 2 bilirubin; or (viii) any TEAE necessitating a dose reduction.

One predose and seven postdose (range, 0.5-8 hours postdose) PK samples were collected during Cycle 1 on Day 1 and on Day 10, 11, or 12. Samples were also collected 24 hours postdose during Cycle 1 on Day 2 and on Day 11, 12, or 13. PK measurements included AUC, C_{max}, $t_{1/2}$, T_{max}, CL/F, and apparent Vz/F.

Patients were evaluated for tumor response on Day 15 of Cycles 2, 4, and 6 and every three cycles thereafter. Tumors were assessed by imaging studies, including CT and/or MRI of the chest, abdomen, and pelvis (including other sites as appropriate). Tumor response was based on investigator assessment using the Response Evaluation Criteria in Solid Tumors, version 1.1, for solid tumors, and the International Working Group Revised Response Criteria for NHL.[17,18]

2.5 | Statistical analysis

The enrolled population included all patients who were assigned an enrollment number, the treated population was composed of all enrolled patients who received ≥ 1 dose of avadomide, and the efficacy-evaluable population consisted of all patients who completed ≥ 1 cycle of their assigned treatment regimen and had a baseline and ≥ 1 postbaseline efficacy assessment. Descriptive statistics were provided for all PK data.

3 | RESULTS

3.1 | Patients

As of the 30 March 2017 data cutoff date, 15 patients had participated in the study, including 14 with NHL (5 DLBCL, 5 FL, 3 PTCL NOS, and 1 AITL) and one with a solid tumor (esophageal carcinoma). Key baseline characteristics for all study participants are listed in Table 1. Median age was 64 years (range, 48-78), 53% were ≤ 65 years of age, and 60% were male. Most patients (93%) had an ECOG PS 0-1, and the median number of prior systemic anticancer therapies was three (range, 1-10). Eight patients were still on treatment at the cutoff date.

TABLE 1 Baseline patient demographics and clinical characteristics

Characteristic	N = 15
Median (range) age, y	64 (48-78)
Age distribution, n (%)	
≤65 y	8 (53)
>65 y	7 (47)
Gender, n (%)	
Male	9 (60)
Female	6 (40)
Tumor type, n (%)	
NHL	14 (93)
FL	5 (33)
DLBCL	5 (33)
PTCL-NOS	2 (13)
PTCL	1 (7)
AITL	1 (7)
Solid tumor	1 (7)
ECOG PS, n (%)[a]	
0	10 (67)
1	4 (27)
2	1 (7)
Prior systemic anticancer therapies, n (%)	
1	4 (27)
2	2 (13)
3	4 (27)
4	3 (20)
7	1 (7)
10	1 (7)

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified.

[a]Sum exceeds 100% due to rounding.

TABLE 2 Treatment-emergent adverse events

	N = 15		
Adverse event, n (%)[a]	Any grade	Grade 3	Grade 4
Rash maculopapular	8 (53)	2 (13)	0
Lymphocyte count decreased	7 (47)	2 (13)	1 (7)
Constipation	6 (40)	0	0
Neutrophil count decreased	6 (40)	3 (20)	2 (13)
Upper respiratory tract infection	6 (40)	0	0
Platelet count decreased	5 (33)	0	0
White blood cell count decreased	5 (33)	0	0
Diarrhea	4 (27)	0	0
Hepatic function abnormal	4 (27)	1 (7)	0
Malaise	4 (27)	1 (7)	0
Proteinuria	3 (20)	0	0
Pyrexia	3 (20)	0	0
Stomatitis	3 (20)	0	0
Viral upper respiratory tract infection	3 (20)	0	0
Abdominal pain	2 (13)	0	0
Back pain	2 (13)	1 (7)	0
Neutropenia	2 (13)	2 (13)	0
Cataract	2 (13)	0	0
Erythema	2 (13)	0	0
Muscle spasms	2 (13)	0	0
Musculoskeletal pain	2 (13)	0	0
Nausea	2 (13)	1 (7)	0
Vomiting	2 (13)	1 (7)	0
Decreased appetite	2 (13)	0	0
Pruritus	2 (13)	0	0
Sinus bradycardia	2 (13)	0	0
Insomnia	2 (13)	0	0
General physical health deterioration	2 (13)	0	0
Lipase increased	1 (7)	1 (7)	0

[a]Adverse events occurring in ≥10% of patients and all grade 3/4 adverse events are reported.

3.2 | Safety and treatment exposure

Median duration of avadomide treatment was 29 weeks (range, 4-82), and median relative dose intensity was 84% (range, 31-100). DLT were reported in one patient (cohort 4) in Cycle 1 and included face edema, pharyngeal edema, and tumor flare (all grade 1) that led to dose reductions. This patient discontinued from treatment after 32 days and was not included in the efficacy-evaluable population. Seven patients discontinued the study, all due to PD. After the DLT evaluation period, one patient (cohort 1) had their dose escalated from 2 to 3 mg based on the intrasubject dose-escalation allowance.

All 15 patients evaluable for toxicity experienced AE. Grade ≥ 3 TEAE occurred in 11 patients (73%), most frequently decreased neutrophil count (33%) and decreased lymphocyte count (20%). The most common TEAE (≥30%) of any grade were maculopapular rash (53%), decreased lymphocyte count (47%), decreased neutrophil count (40%), constipation (40%), upper respiratory tract infection (40%), decreased platelet count (33%), and decreased white blood cell count (33%; Table 2). No TEAE leading to dose discontinuation were reported. TEAE leading to dose reduction and interruption were reported in eight patients (53%) and 10 patients (67%), respectively; all were resolved (Table S1). Among patients with TEAE (observed in > 1 patient) that led to dose reductions, neutrophil count decreased/neutropenia was the most frequently reported AE, occurring in five patients. Of those with TEAE leading to dose interruptions, neutrophil count decreased/neutropenia occurred in seven patients, upper respiratory tract infection in three patients, and rash maculopapular in two patients. SAE occurred in three patients (20%); one SAE of pulmonary eosinophilia was suspected to be related to avadomide. Two patients died within 30 days of the last dose of avadomide; both deaths were due to progressive disease.

Based on these data, the 3-mg dose of avadomide F6 given daily for five consecutive days per week was considered safe and tolerable and was determined to be the RP2D.

3.3 | Efficacy

Table 3 summarizes response rates and survival data for the efficacy-evaluable population, which consisted of 13 patients with NHL and one patient with a solid tumor. ORR in the efficacy-evaluable population of patients with NHL was 54% (95% CI, 25.1-80.8) with four patients (31%) achieving a CR (Table 3). Subgroup analyses showed that response rates were similar regardless of the number of prior therapies (Table S2). One patient in cohort one with transformed FL who received five prior therapies achieved a CR, and one patient in cohort 2 with heavily treated FL who received 10 prior therapies achieved a PR. The single patient with a solid tumor did not achieve an objective response and had PD. Changes in absolute lymphocyte counts, percentage of lymphocytes, weight, and LDH levels were similar in patients who responded (CR or PR) and those who did not respond (SD, PD, or NE) through Cycle 8, with a slight increasing trend in lymphocyte counts and weight over time (data not shown).

Among all responders, median time to response was 6.3 weeks (range, 5.9-22.0), which corresponds roughly with the first efficacy assessment, on Cycle 2, Day 15. Individual PFS data for all 15 patients including outcome, response, and tumor histology are shown in Figure 1A. In patients with NHL, median DOR had not been reached (Table 3, Figure S1), and median PFS was 46.1 weeks (95% CI, 13.86–NE) (Table 3, Figure 1B).

TABLE 3 Response rates and progression-free survival

Outcome	NHL (N = 13)	Solid tumor (N = 1)
ORR, n (%)	7 (54)	0
CR, n (%)	4 (31)	0
PR, n (%)	3 (23)	0
SD, n (%)	4 (31)	0
PD, n (%)	2 (15)	1 (100)
mPFS, wk (95% CI)	46.1 (13.86–NE)	NE
mDOR, wk (95% CI)	NE (24.29–NE)	NE
mTTR, wk (range)	6.29 (5.9-22.0)	NE

Abbreviations: CR, complete response; mDOR, median duration of response; mPFS, median progression-free survival; mTTR, median time to response; NE, not estimable; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

3.4 | Pharmacokinetics

Avadomide plasma concentrations were measured after a single dose (Figure 2A) and multiple doses (Figure 2B). The plasma concentration versus time profiles of avadomide were characterized by a rapid absorption phase at all dose levels tested, and median T_{max} was generally similar at each dose level. Following the attainment of C_{max}, avadomide plasma concentration appeared to decline in a monophasic manner at all dose levels tested. In all four dose levels tested, mild-to-moderate accumulation of avadomide plasma exposure was observed on Day 10, 11, or 12 versus Day 1. It was noted that the time profile curves after multiple doses of 4 mg AIC and 3 mg F6 were very similar. After a single dose on Cycle 1, Day 1, geometric mean C_{max} levels of avadomide were 52.78 ng/mL for 2 mg AIC, 55.26 ng/mL for 3 mg AIC, 73.80 ng/mL for 4 mg AIC, and 107.72 ng/mL for 3 mg F6 (Table S3).

4 | DISCUSSION

We report here the results of a phase I, multicenter, open-label, dose-escalation study of avadomide in 15 Japanese patients with NHL or solid tumors. A safe and tolerable dose of avadomide was identified that generated a clinically meaningful response in previously treated patients with NHL. The most common TEAE were maculopapular rash and reduced lymphocyte count. The most frequently reported grade 3 or 4 TEAE were reduced neutrophil and lymphocyte counts. Most of the TEAE were manageable with dose interruptions or reductions, or with the use of appropriate supportive care, and the safety profile of avadomide was considered acceptable. Overall, the safety results of this study were consistent with the known safety profile of avadomide from global studies.[12,13,15,19,20]

One of the primary objectives of this study was to determine the MTD/RP2D of avadomide in Japanese patients. Only one patient experienced DLT. The dose could not be further escalated because, per study design, doses could not exceed the MTD obtained in global studies; therefore, the MTD could not be determined. However, the

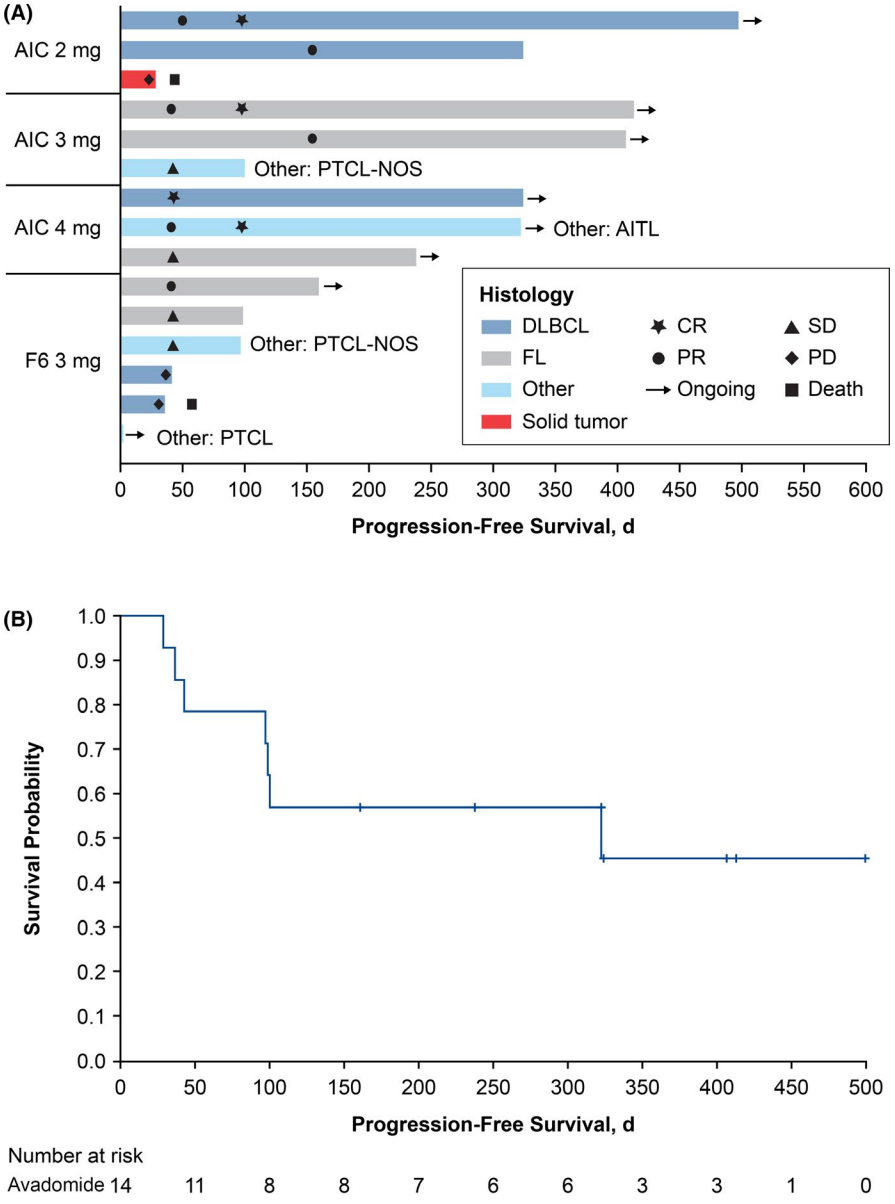

FIGURE 1 Progression-free survival by patient (A) and among all evaluable patients (B). Abbreviations: AIC, active ingredient in capsule; AITL, angioimmunoblastic T-cell lymphoma; CR, complete response; DLBCL, diffuse large B-cell lymphoma; F6, formulated capsule; FL, follicular lymphoma; PD, progressive disease; PFS, progression-free survival; PR, partial response; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; SD, stable disease

3-mg F6 dose, which is the RP2D in other global studies, was considered safe and tolerable. Dose intensity was relatively consistent across cohorts and, after a single dose, avadomide 3 mg F6 had similar exposure to 4 mg AIC. At steady state, avadomide at 4 mg AIC had the highest exposure followed by 3 mg F6, 2 mg AIC, and 3 mg AIC (Figure 2A). However, as a result of the high interpatient variability, the observed difference may not be clinically meaningful. The PK parameters in Japanese patients appeared similar to those previously reported in other populations.[13,15]

Although the number of patients in this study was small, responses (≥PR) were observed in seven of 13 NHL patients (54%; CR, 4 patients [31%]; PR, 3 patients [23%]). Responses were observed even in patients with heavily treated or transformed lymphoma. Median PFS was 46.1 weeks, and median DOR had not been reached. At the cutoff date, response was still ongoing in six of 15 patients.

The focus of the present study was to evaluate avadomide monotherapy in patients with NHL and solid tumors; however, its use in other malignancies and in combination with anti-CD20 antibodies is also being explored based on encouraging results seen with other agents in this class, such as lenalidomide.[21-24] Preclinical studies have shown that combining avadomide and obinutuzumab, an anti-CD20 antibody, resulted in synergistic enhancement of apoptosis in FL cell lines, and additive apoptosis effects in DLBCL cell lines as well as in mouse models.[25] Notably, in vitro studies combining avadomide with rituximab or obinutuzumab resulted in greater levels of apoptosis compared with combinations of lenalidomide and either antibody.[26] These combinations are being investigated in ongoing studies of patients with R/R DLBCL (NCT02031419) and indolent NHL (NCT02406742, NCT02031419, and NCT02417285), with promising response rates observed in these populations that will be reported separately.[19,20] Based on the tolerability of avadomide and its mechanism of action, more effective uses of avadomide will likely involve combination with other agents, such as immunotherapeutic drugs, that can further augment anticancer response.

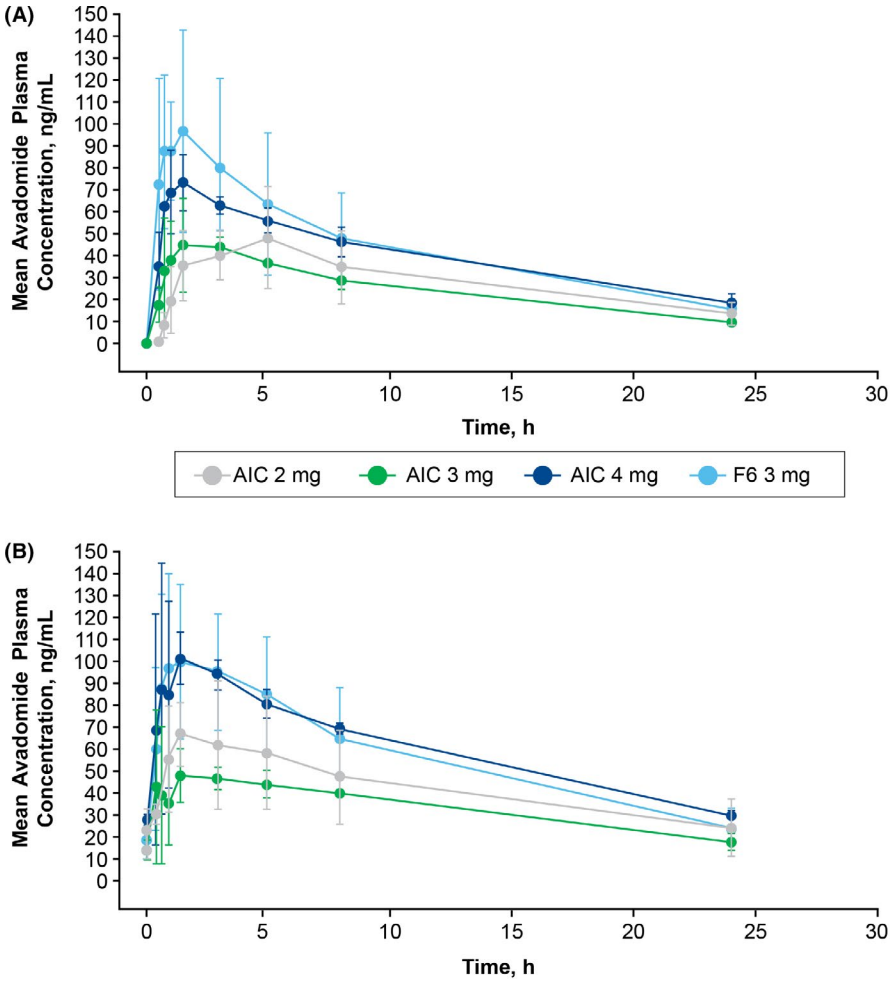

FIGURE 2 Mean (±SD) Avadomide plasma concentration by dose level after a single dose (Cycle 1, Day 1) (A) and after multiple doses (Cycle 1, Day 10, 11, or 12) (B). Abbreviations: AIC, active ingredient in complex; F6, formulated capsule; SD, standard deviation

Avadomide is also currently undergoing a phase II trial for melanoma (NCT03834623).

In conclusion, the safety and reasonable PK results observed in this study are consistent with global studies and the known profile of avadomide, with the 3-mg F6 dose considered safe and tolerable. Additionally, the preliminary efficacy with avadomide in Japanese patients with previously treated NHL provides the rationale for further investigation of avadomide monotherapy.

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DISCLOSURE

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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