

A Phase 2 Study of Coltuximab Ravtansine (SAR3419) Monotherapy in Patients with Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL)

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A Phase 2 Study of Coltuximab Ravtansine (SAR3419) Monotherapy in Patients with Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL)

Running title: Coltuximab ravtansine in adult ALL

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K.K. reports personal fees from Novartis Oncology and Pharmacyclics, outside the submitted work. S.K.K. reports personal fees from Seattle Genetics, Agensys, Bayer, and ImmunoGen, outside the submitted work. J.C. reports grants and personal fees from Sanofi, outside the submitted work. C.O. is an employee of, and stockholder in Sanofi. L.H. is an employee of Sanofi. H.M.K., B.L., E.A., T.L., J.P.M., M.E-B., X.G.T., E.J., S. O'B., P.B., and H.D. have nothing to disclose.

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Therapy options are limited for adult patients with relapsed or refractory acute lymphoblastic leukemia (ALL). In this phase 2 study, 36 patients with relapsed or refractory ALL were treated with the anti-CD19 antibody-drug conjugate, coltuximab ravtansine. Coltuximab ravtansine was well tolerated, but the clinical response rate was low (4/17 patients).

Background: Long-term disease-free survival in adult patients with acute lymphoblastic leukemia (ALL) remains unsatisfactory, and treatment options are limited for those patients who relapse or fail to respond following initial therapy. We conducted a dose-escalation/expansion phase 2, multicenter, single-arm study to determine the optimal dose of coltuximab ravtansine (SAR3419), an anti-CD19 antibody-drug conjugate, in this setting. **Patients and Methods:** The dose-escalation part of the study determined the selected dose of coltuximab ravtansine for evaluation of efficacy and safety in the dose-expansion phase. Patients received coltuximab ravtansine induction therapy (up to 8 weekly doses); responding patients were eligible for maintenance therapy (biweekly administrations for up to 24 weeks). Three dose levels of coltuximab ravtansine were examined: 55, 70, and 90 mg/m^2. The primary endpoint was objective response rate (ORR). Secondary endpoints included duration of response (DOR) and safety. **Results:** A total of 36 patients were treated: 19 during dose escalation; 17 during dose expansion. One dose-limiting toxicity was observed at 90 mg/m^2 (grade 3 peripheral motor neuropathy), and therefore 70 mg/m^2 was selected for the dose-expansion phase. Five patients discontinued therapy due to adverse events (AEs). The most common AEs were pyrexia, diarrhea, and nausea. Of 17 evaluable patients treated at the selected dose, 4 responded (estimated ORR using Bayesian methodology: 25.47% [80% confidence interval: 14.18-39.6%]); DOR was 1.94 (range: 1-5.6) months. Based on these results, the study was prematurely discontinued. **Conclusions:** Coltuximab ravtansine is well tolerated but is associated with a low clinical response rate in patients with relapsed/refractory ALL.

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Introduction

The long-term disease-free survival rates in adult patients with acute lymphoblastic leukemia (ALL) are low (approximately 40%).[1] Standard frontline therapy for ALL generally includes regimens consisting of vincristine, corticosteroids, and an anthracycline, with or without asparaginase.[2] Consolidation chemotherapy with or without allogeneic stem cell transplantation following frontline treatment is associated with long-term disease-free survival rates of approximately 60%.[3,4] Salvage regimens for patients with ALL recurrence include variations of the drug combinations used in induction protocols, but are associated with poor outcomes.[1] Therefore, newer agents are required to treat patients who do not respond to initial therapy.

Coltuximab ravtansine (SAR3419) is an anti-CD19 monoclonal antibody conjugated to a potent cytotoxic maytansinoid, DM4, via an optimized hindered disulfide bond.[5,6] The antibody selectively targets the CD19 antigen present on the surface of ALL cells in over 90% of patients.[7] Antibody binding results in the internalization of the CD19-SAR3419 complex, and release of DM4 (a potent inhibitor of tubulin polymerization and microtubule assembly) inside the tumor cell. This results in microtubule disruption and cell cycle arrest.[5,6] In xenograft tumor models, coltuximab ravtansine treatment significantly improved survival, with efficacy being directly related to CD19 expression levels.[8] Phase 1 studies in non-Hodgkin's lymphoma have determined an optimized dosing schedule, in which coltuximab ravtansine (55 mg/m^2) is administered weekly for 4 doses, followed by biweekly dosing.[9]

This phase 2, multicenter, single-arm study was conducted to determine the optimal dose of coltuximab ravtansine for patients with ALL, and to evaluate the efficacy of coltuximab ravtansine in patients with relapsed or refractory ALL.

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Methods

Eligibility

Patients with relapsed or primary refractory ALL of B-cell origin (including Burkitt's lymphoma), who had received up to 3 prior salvage therapies, and had CD19-positive disease (> 30% of cells), were enrolled. Patients with Ph+ ALL who had failed treatment with imatinib mesylate were also eligible. The main exclusion criteria were: Eastern Cooperative Oncology Group (ECOG) performance status > 2, age < 16 years, corneal abnormalities requiring local treatment at study entry, and abnormal organ functions. Refractory disease was defined as failure to achieve a complete response (CR) with the last line of therapy received. Relapsed disease was defined as achievement of a CR of any duration with the last line of therapy, followed by progression prior to entering the study.

Study Design

This was a phase 2, single-arm, open-label study, conducted at 14 sites in France and the United States.

The study consisted of 2 parts: part 1 was to determine the selected dose for administration of coltuximab ravtansine during part 2; part 2 was to evaluate safety and efficacy at the selected dose. Patients received coltuximab ravtansine induction therapy, once weekly for up to 8 weeks (1 or 2 $\times$ 4-week cycles, if no CR after first induction). Patients who achieved an objective response (CR, CR without recovery of counts [CRi], or partial response [PR]) could receive maintenance therapy, consisting of biweekly administrations of coltuximab ravtansine, until disease progression, unacceptable toxicity, or withdrawal of consent, for a maximum of 24 weeks (6 cycles).

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During part 1, escalating doses of coltuximab ravtansine were tested using a standard 3+3 protocol. The starting dose of coltuximab ravtansine was 55 mg/m^2. Under the assumption that tumor bulk of blast cells expressing CD19 in ALL patients is higher when compared with that seen in lymphoma patients, we anticipated that higher doses could be administered in this population. Based on the pharmacokinetic and safety results from the first cycle of treatment in the first 6 patients, the dose was increased to 70 mg/m^2 for the remaining patients. The decision to increase to 90 mg/m^2 was based on a modified Hunsberger's "Proportion [4/6]" design,[10] as required by protocol amendment 1 (August 6, 2012). The selected dose for part 2 of the study was determined following a review of both safety and efficacy (defined as an objective response). During part 2 (expansion cohort), patients were treated at the selected dose, and were monitored continuously for safety.

At the beginning of the study, premedication consisting of diphenhydramine (50 mg, intravenous administration) and acetaminophen (1000 mg, oral administration) was mandated for all patients, with dexamethasone (40 mg) also administered if deemed necessary. Following 2 cases of treatment-related anaphylaxis on the study, occurring during the expansion cohort at 70 mg/m², the protocol was amended (protocol amendment 5, January 22, 2014) to include dexamethasone in the premedication protocol for all patients (8-10 mg intravenous, 30 minutes prior to infusion, or 8 mg po twice daily for 3 days prior to infusion). Patients who failed to achieve an objective response during the induction period, or who experienced a grade 3/4 infusion-related reaction (IRR) during coltuximab ravtansine administration, were permanently discontinued from the study. Follow-up was every 2 months until disease progression, initiation of a new anti-cancer drug, death, or end of study (1 year after the first infusion in the last enrolled patient).

Signed written informed consent was obtained from all patients prior to enrolment. The study was conducted according to the Declaration of Helsinki. The study protocol was approved by the

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Institutional Review Boards and/or Ethics Committees at each study site. ClinicalTrials.gov identifier: NCT01440179.

Study Endpoints

The primary objective was to determine the recommended dose of coltuximab ravtansine, and to evaluate the efficacy of coltuximab ravtansine at the selected dose, in patients with relapsed or refractory ALL. The primary efficacy endpoint was objective response rate (ORR, the proportion of patients achieving an objective response) according to the Southwest Oncology Group (SWOG) clinical research associate manual (Chapter 11A, revised April 2010). Duration of response (DOR) and safety were secondary endpoints.

Assessments

Clinical responses were determined by performing blood cell counts (hemoglobin, white blood cells with differential, and platelets), at baseline, during treatment, at the end of the study, and every 2 months during follow-up. Response was categorized as CR (normalization of marrow and blood with marrow blast ≤ 5%, neutrophil count > 1.0×10^9/L, platelet count > 100×10^9/L), CRi (patients meeting the criteria for CR, but with incomplete recovery of counts [platelet < 100×10^9/L and/or neutrophils < 1×10^9/L]), or PR (peripheral blood count recovery as for CR/CRi, but with a decrease in marrow blasts of ≥ 50% versus baseline with ≤ 25% abnormal cells in the marrow) (SWOG clinical research associate manual, Chapter 11A, revised April 2010). Bone marrow aspirates were collected during cycle 1 to confirm a CR, and every 2 months thereafter.

Safety was assessed based on physical examination, vital signs, ECOG performance status, and laboratory evaluations. Treatment-emergent adverse events (TEAEs) were classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (Version 4.03). Eye disorders,

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neuropathy, and IRRs (occurring on the day of infusion) were assessed as pre-specified AEs of special interest. CD19 expression was analyzed locally at each study center using flow cytometry or immunohistochemistry. Anti-drug antibodies (ADAs) were measured using a validated bridge enzyme-linked immunosorbent assay.

Statistical Analyses

During part 1, up to 6 patients were planned at each dose level. During part 2, a maximum of 40 evaluable patients at the selected dose were planned. In this pretreated study population, an ORR of at least 20% would be considered clinically beneficial. With an observed ORR of 20%, a sample size of 40 evaluable patients provided a probability of 0.53 that the true response rate was ≥ 20%. With an observed ORR of 40%, this probability increased to 0.98. Safety was analyzed in all patients receiving at least 1 dose of study treatment (safety population). ORR and DOR were assessed in the per-protocol (PP) population (all treated patients who had an evaluable response after at least 2 coltuximab ravtansine infusions during the induction period, or who died from progressive disease during cycle 1). The primary efficacy analysis was performed on the PP population at the selected dose. The ORR was estimated using Bayesian methodology assuming a prior distribution of response rate following a beta(1,1). The ORR and its 80% credibility interval were estimated using the corresponding posterior binomial distribution. Statistical calculations were made using R software (Redmond, Washington, United States).

Results

A total of 37 patients were enrolled between October 10, 2011 and December 19, 2013. One patient was included but did not receive study treatment, leaving 36 treated patients in the safety population. Nineteen patients were treated in part 1 of the study: 7 at 55 mg/m^2; 4 at 70 mg/m^2; and 8

at 90 mg/m^2. The selected dose was determined as 70 mg/m^2 and was used in part 2 of the study. As detailed below, the 90 mg/m^2 dose was associated with no improvement in ORR, and an increased occurrence of AEs. An additional 17 patients were included and treated during part 2 of the study. All patients were due to receive treatment at 70 mg/m^2, but 2 of them received the reduced dose of 55 mg/m^2 due to infusion-related toxicities.

Overall, 25 patients (69%) received 1 cycle and 11 patients (31%) received 2 cycles of induction therapy. Most patients (32/36, 89%) discontinued treatment prior to receiving maintenance therapy, including all patients who received 90 mg/m^2 during induction; this was mainly due to disease progression. Of the remaining patients, 3 received 1 cycle and 1 received more than 1 cycle of maintenance therapy. Five patients had no evaluable response during the induction period (after ≥ 2 coltuximab ravtansine infusions), leaving 31 patients evaluable for efficacy in the PP population.

Table 1 summarizes the baseline patient characteristics. The median age was 49.5 years. One-third of patients were primary refractory to their prior therapy. More than half of the patients (58%) had received 2 or more prior regimens, and almost all (97%) had received prior vinca alkaloids. Cytogenetic abnormalities were analyzed in 27 patients: 9 patients displayed a normal karyotype and 6 carried the t(9;22) translocation.

All 36 treated patients discontinued study treatment. Reasons for discontinuation were disease progression (n = 23), lack of response (n = 6), TEAEs (n = 5), and other reasons (n = 2).

Safety

The median duration of treatment was 7.7 (range: 5-10), 5.0 (range: 5-31), and 5.0 (range: 5-10) weeks at the 55, 70, and 90 mg/m^2 dose levels, respectively. Of 36 patients treated, 35 (97%) experienced at least 1 TEAE (Table 2). Grade ≥ 3 AEs were observed in 4/9 (44%), 12/19 (63%), and 7/8

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(88%) patients at the 55, 70, and 90 mg/m^2 dose levels, respectively, while serious AEs (SAEs) were reported in 2/9 (22%), 14/19 (74%), and 7/8 (88%) patients, respectively. Overall, the most common SAEs of any grade were bacteremia, pneumonia, febrile neutropenia, disease progression, and IRR. Most of the SAEs were considered by the investigator to be unrelated to coltuximab ravtansine. Drug-related SAEs included anaphylactic shock, drug hypersensitivity, peripheral motor neuropathy, interstitial lung disease, and IRR.

At the selected dose (70 mg/m^2), the most common non-hematologic AEs were nausea, diarrhea, and pyrexia (Table 3). Non-hematologic AEs of grade ≥ 3 were rare. The most common hematologic laboratory abnormalities at the selected dose were thrombocytopenia, anemia, and lymphopenia. Grade 3/4 hematologic laboratory abnormalities were also frequently observed, the most common being thrombocytopenia (84%), neutropenia (68%), and leukopenia (68%). Hepatic and renal laboratory abnormalities were most frequent in the 90 mg/m^2 cohort, and included elevated levels of aspartate aminotransferase (n = 8; 100%), alanine aminotransferase (n = 7; 88%), and alkaline phosphatase (n = 7; 88%).

Regarding the AEs of special interest, 9 cases of ocular toxicity were observed, all of which were grade 1/2. These events included 1 corneal event (keratitis, in the 70 mg/m^2 cohort), 6 extracorneal events, and 2 lacrimal disorders. Neuropathy was observed in 3 patients. Grade 3 peripheral motor neuropathy was observed in 1 patient in the 90 mg/m^2 cohort, and was considered a dose-limiting toxicity (DLT), resulting in permanent discontinuation of treatment. Other neuropathy events included hypoesthesia and paresthesia, both grade 1/2 and both occurring in the 70 mg/m^2 cohort. IRRs occurred in 3/9 (33%), 10/19 (53%), and 2/8 (25%) patients at the 50, 70, and 90 mg/m^2 dose levels, respectively, 5 of which were grade 3/4 (2 at 50 mg/m^2, 2 at 70 mg/m^2, and 1 at 90 mg/m^2).

Dose interruptions were required in 5 patients (4 at 70 mg/m^2; 1 at 90 mg/m^2) mostly due to IRRs (grade 1-3). All patients subsequently recovered. Three patients required a dose delay as a result of pneumonia (grade 3), interstitial lung disease (grade 3), and ALT (grade 1). The pneumonia had stabilized, but not resolved at the time of data collection, while the other AEs resolved within 3 weeks.

In total, 5 patients discontinued treatment due to AEs, all of which were classified as serious (sepsis, pneumonia, peripheral motor neuropathy, IRRs, and febrile neutropenia). On-treatment death (within 42 days after the last dose of coltuximab ravtansine) occurred in 1/9 (11%), 4/17 (21%), and 4/8 patients (50%) at the 55, 70, and 90 mg/m^2 dose levels, respectively. Death was a result of disease progression in 5 patients. The remaining deaths were due to AEs, none of which were determined by the investigator to be related to coltuximab ravtansine.

Among 9 patients evaluable for immunogenicity, 3 patients were ADA negative; results were inconclusive in the other 6 patients.

Efficacy

For the primary efficacy endpoint, of the 17 patients in the PP population treated at the selected dose, 4 had an objective response, including 1 CR, 2 CRi, and 1 PR (Table 4). The ORR, estimated as the median of the posterior binomial distribution, was 25.47% (80% confidence interval: 14.18-39.60). In addition, 3/7 patients from the PP population treated at 55 mg/m^2 and 1/7 patients from the PP population treated at 90 mg/m^2 achieved an objective response.

Among 4 patients responding to coltuximab ravtansine at the selected dose, the median DOR was 1.94 (range: 1.0-5.6) months. Median DOR for the 3 patients responding to coltuximab ravtansine at 55 mg/m^2 was 1.35 (range: 1.2-1.5) months. The patient who responded to treatment at 90 mg/m^2 had a DOR of 0.43 months.

Discussion

The results of this phase 2 trial demonstrate that treatment with coltuximab ravtansine is well tolerated in patients with relapsed or refractory ALL. The treatment was associated with modest efficacy, with 25% of patients treated at the selected dose achieving an objective response. All 3 dose cohorts were associated with a short DOR (less than 2 months), and as a result the study was prematurely terminated.

The limited efficacy in this study may be partially attributed to the selected patient population. These patients were heavily pretreated, and almost half had refractory disease (including primary refractory disease in one-third of patients). However, the response rates reported herein are low in comparison to other compounds under investigation in a similar patient population, such as blinatumomab (ORR: 43-69%)[11,12] and inotuzumab ozogamycin (approximately 50%).[13]

The safety profile of coltuximab ravtansine was favorable, consisting primarily of gastrointestinal disorders (diarrhea, nausea, vomiting), as previously reported in patients with non-Hodgkin's lymphoma.[9,14] Grade 3/4 non-hematologic AEs were rare. Hematologic AEs were commonly observed across all dose levels, with grade 3/4 events showing an apparently higher frequency with increasing dose. Although no formal analysis was conducted, a per-patient review did not demonstrate any exacerbation of hematologic disorders during the short treatment period. The 90 mg/m^2 dose was associated with several grade ≥3 AEs, including 1 DLT (peripheral motor neuropathy). Other neuropathy and ocular toxicities occurred, but were of grade 1/2. IRRs were common, occurring in more than half of the patients at the selected dose, but were generally of low grade. There were no treatment-related deaths during the study, but SAEs led to treatment discontinuation in 5 patients.

Conclusion

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In conclusion, the results of this phase 2 study demonstrate that coltuximab ravtansine has a favorable safety profile, but limited efficacy in patients with ALL.

Clinical Practice Points

- Long-term disease-free survival rates in adult patients with acute lymphoblastic leukemia (ALL) are low. Although consolidation chemotherapy with or without allogeneic stem cell transplantation following frontline treatment is associated with some improvement in survival, the prognosis for patients with recurrent ALL is generally very poor. Newer agents are required to treat patients with relapsed and/or refractory ALL.
- CD19 is expressed by 90% of patients with ALL. This dose-escalation/expansion study examined the safety and preliminary efficacy of an anti-CD19 antibody drug conjugate, coltuximab ravtansine in patients with relapsed or refractory ALL. Coltuximab ravtansine was well tolerated at the selected dose (70 mg/m^2), with few non-hematologic AEs of grade ≥ 3 reported. Of 17 patients treated at the selected dose, 4 achieved a partial response or better. The median duration of response in these patients was 1.94 months (range 1-5.6).
- The results of this study indicate that CD19 may be a viable future target for therapeutic intervention in patients with relapsed or refractory ALL.

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critically reviewed the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

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Table 1 Baseline Characteristics (Safety Population)

Variable, n (%)	55 mg/m^2 (n = 9)	70 mg/m^2 (n = 19)	90 mg/m^2 (n = 8)	All (n = 36)
Median age (range), years	57 (26-73)	44 (18-68)	69 (21-78)	50 (18-78)
Age group, years				
65-75	2 (22)	3 (16)	1 (13)	6 (17)
> s75	0	0	3 (38)	3 (8)
Female gender	4 (44)	7 (37)	3 (38)	14 (39)
ECOG performance status				
0	0	7 (37)	0	7 (19)
1	7 (78)	7 (37)	4 (50)	18 (50)
2	2 (22)	4 (21)	4 (50)	10 (28)
> 2	0	1 (5)	0	1 (3)
Karyotype[a]				
Normal	4 (44)	2 (11)	3 (38)	9 (25)
t(v;11q23) MLL rearranged	0	1 (5)	0	1 (3)
Hyperdiploidy	0	0	1 (13)	1 (3)
Hypodiploidy	0	0	0	0
t(9;22)(q34;q11.2)BCR-ABL1	2 (22)	3 (16)	1 (13)	6 (17)
Ph+	2 (22)	3 (16)	0	5 (14)
Ph–	0	0	1 (13)	1 (3)
t(1;19)(q23;p13.3) TCF3-PBX1	0	1 (5)	0	1 (3)

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Other abnormality	1 (11)	8 (42)	1 (13)	10 (28)
Not performed	2 (22)	5 (26)	2 (25)	9 (25)
Disease status at study entry				
Primary refractory	3 (33)	4 (21)	5 (63)	12 (33)
Refractory to last therapy	1 (11)	4 (21)	0	5 (14)
Relapsed	5 (56)	11 (58)	3 (38)	19 (53)
Number of prior regimens				
1	5 (56)	5 (26)	5 (63)	15 (42)
≥2	4 (44)	14 (74)	3 (38)	21 (58)

Abbreviations: ECOG = European Cooperative Oncology Group; Ph = Philadelphia chromosome.

[a]Patients may have several cytogenetic abnormalities.

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Table 2 Overview of Adverse Events

	55 mg/m^2 (n = 9)	**70 mg/m^2 (n = 19)**	**90 mg/m^2 (n = 8)**
Any TEAE, n (%)	9 (100)	18 (95)	8 (100)
Any grade 3/4 TEAE, n (%)	4 (44)	12 (63)	7 (88)
Any grade 5 TEAE, n (%)	1 (11)	5 (26)	4 (50)
Serious AEs, n (%)	2 (22)	14 (74)	7 (88)
Related TEAE, n (%)	5 (56)	13 (68)	4 (50)
Related grade 5 TEAE, n (%)	0	1 (5)	0
TEAE leading to dose modification/interruption, n (%)	3 (33)	6 (32)	2 (25)
TEAE leading to discontinuation, n (%)	1 (11)	2 (11)	2 (25)

Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event.

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Table 3 Adverse Events Occurring in ≥ 10% of Patients by Cohort

	55 mg/m^2 (n = 9)			70 mg/m^2 (n = 19)			90 mg/m^2 (n = 8)		
	All grades	**Grade 3/4**	**Grade 5**	**All grades**	**Grade 3/4**	**Grade 5**	**All grades**	**Grade 3/4**	**Grade 5**
Non-hematologic, n (%)									
Pyrexia	4 (44)	0	0	4 (21)	0	0	2 (25)	0	
Diarrhea	2 (22)	0	0	5 (26)	1 (5)	0	1 (13)	0	0
Nausea	2 (22)	0	0	6 (32)	0	0	0	0	0
Fatigue	1 (11)	0	0	3 (16)	0	0	4 (50)	1 (13)	0
Vomiting	2 (22)	0	0	3 (16)	1 (5)	0	1 (13)	0	0
Headache	1 (11)	0	0	4 (21)	0	0	1 (13)	0	0
Peripheral edema	0	0	0	3 (16)	0	0	3 (38)	0	0
Dyspnea	0	0	0	5 (26)	1 (5)	0	0	0	0
Blurred vision	1 (11)	0	0	4 (21)	0	0	0	0	0
Back pain	1 (11)	0	0	2 (11)	0	0	2 (25)	1 (13)	0
Disease progression	1 (11)	0	1 (11)	2 (11)	0	2 (11)	2 (25)	0	2 (25)

Insomnia	1 (11)	0	0	2 (11)	0	0	2 (25)	0	0
Weight decrease	0	0	0	2 (11)	0	0	2 (25)	0	0
Hematologic, n (%)[a]									
Thrombocytopenia	9 (100)	5 (56)	-	19 (100)	16 (84)	-	8 (100)	7 (88)	-
Anemia	8 (89)	4 (44)	-	18 (95)	6 (32)	-	8 (100)	5 (63)	-
Lymphopenia	9 (100)	7 (78)	-	17 (90)	11 (58)	-	7 (88)	5 (63)	-
Neutropenia	8 (89)	7 (78)	-	16 (84)	13 (68)	-	8 (100)	7 (88)	-
Leukopenia	7 (78)	5 (56)	-	16 (84)	13 (68)	-	7 (88)	6 (75)	-
Hepatic and renal abnormalities, n (%)[a]									
AST	6 (67)	1 (11)	-	15 (79)	4 (21)	-	8 (100)	1 (13)	-
ALT	4 (44)	1 (11)	-	14 (74)	6 (32)	-	7 (88)	2 (25)	-
Alkaline phosphatase	6 (75)[b]	0	-	11 (61)[c]	1 (5)[c]	-	7 (88)	1 (13)	-

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.

[a]Laboratory abnormalities; [b]n = 8; [c]n = 18

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Table 4 Summary of Best Response by Cohort Based on the SWOG Criteria

	55 mg/m^2 (n = 7)	**70 mg/m^2 (n = 17)**	**90 mg/m^2 (n = 7)**
Responders, n (%)	3 (43)	4 (24)	1 (14)
Complete response	2 (29)	1 (6)	0
Complete response without recovery of counts	0	2 (12)	0
Partial response	1 (14)	1 (6)	1 (14)
Non-responders/progressive disease, n (%)	4 (57)	13 (76)	6 (86)

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