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A dose escalation feasibility study of lenalidomide for treatment of symptomatic, relapsed chronic lymphocytic leukemia[☆]

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Abstract

Adequate dosing of lenalidomide in Chronic Lymphocytic Leukemia (CLL) remains unclear. This study determined maximum tolerated dose (MTD) in relapsed CLL patients (Cohort A) and patients achieving a partial response (PR) or better to recent therapy (Cohort B). Thirty-seven patients were enrolled. MTD was 2.5 mg followed by 5.0 mg continuous. In Cohort A, tumor flare grade 1–2 occurred in 15 patients (50%) and grade 3 in 1 patient (3%). Cohort A had 19 of 23 evaluable (83%) patients, 4 PR (17%) and 15 (65%) stable disease (SD), Cohort B had 6 of 7 patients (86%) with SD. Despite overall response rate not being high, many patients remained on therapy several months with SD.

Keywords

Chronic Lymphocytic Leukemia; Relapse; Lenalidomide; Tumor flare; Maintenance

1. Introduction

Chronic Lymphocytic Leukemia (CLL) is a common adult leukemia characterized by humoral and cellular immune defects, with patients having increased risk of infections,

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Conflict of interest statement

None declared.

secondary malignancies, and autoimmune complications. Despite high initial response rates to frontline standard chemoimmunotherapy agents, patients will eventually relapse from their disease requiring other therapies, many of which contribute to increased immunosuppression and infectious toxicities. Patients eventually become refractory to therapy over time and CLL remains an incurable disease with chemoimmunotherapy. Identifying new therapies for CLL represents a high research priority.

Lenalidomide, a derivative of thalidomide, is an oral therapeutic immunomodulatory drug with FDA approval for treatment of 5q-myelodysplastic syndrome [1,2], multiple myeloma [3,4], and mantle cell lymphoma [5–8] and has been shown to have activity in hematologic malignancies including acute myeloid leukemia [9], diffuse large B-cell lymphoma, follicular lymphoma [10] and CLL [11,12]. The precise mechanism of action of lenalidomide in CLL remains unknown but appears to be indirect as lenalidomide does not promote direct cytotoxicity toward CLL cells. Lenalidomide has the ability to promote cellular and innate immune activation, alters the tumor microenvironment via activation of T-cell and natural killer cells [13–15], and down-regulates critical pro-survival cytokines [16,17]. In addition, lenalidomide also activates CLL cells similar to CD154 gene therapy, promoting tumor surface antigen expression of CD40, CD80, CD86, HLADR as well as cellular up-regulation of p73 and BID. Based upon this, it is currently hypothesized that this tumor and immune cell interaction contributes to the eventual observed disease reduction in CLL.

Early trials with lenalidomide using the NCI 1996 response criteria have shown single agent activity in relapsed/refractory chronic lymphocytic leukemia with overall response rates ranging from 30 to 50% with some complete responses noted [11,12]. In patients with CLL, lenalidomide has demonstrated the unique toxicity of tumor flare which may be clinically indistinguishable from disease progression [18,19] and has also been associated with tumor lysis and significant hematologic toxicities.

Although two prior phase II studies in patients with relapsed/refractory CLL have shown clinical activity in relapsed/refractory CLL patients, the appropriate dose and schedule of lenalidomide in this population of patients remains unclear. Responses have been seen in patients at dosing as low as 5 mg orally daily while other patients have received up to 25 mg orally daily; however, increased toxicity has been seen at the higher dosing regimens including a significant number of patients with grade 3 or 4 hematologic toxicity and 30–60% of patients experiencing a tumor flare reaction[11,12]. A phase II/III study was planned to address the question of optimal dose and schedule for lenalidomide in this population comparing lenalidomide 10 mg daily versus 25 mg daily for 21 of 28 days, however four cases of serious tumor lysis and/or flare in the first 18 patients enrolled prompted an amendment to a phase 1 trial with intra-patient-dose escalation with lenalidomide given at 2.5 mg initially, increasing to 5 mg after 28 days with subsequent 5 mg incremental increases to 10 mg, 15 mg, or 20 mg. In that study, one-third of the patients could not escalate beyond 2.5 mg and the response rate, 11.5%, was much lower than previously seen [20].

We previously reported preliminary results of a phase I clinical trial evaluating the safety and tolerability of lenalidomide at a starting dose of 25 mg orally daily [18]. This study was amended to include a lower starting dose and increased tumor flare and tumor lysis prophylaxis. In addition to the relapsed/refractory population, this study included a cohort of patients that had attained a partial response or better to initial therapy to determine the safety of lenalidomide treatment in these patients. Here we report the final results of the amended phase I dose escalation study of lenalidomide in these patients.

2. Materials and methods

All patients were enrolled and treated at the Ohio State University (OSU) Medical Center (Columbus, OH) on an institutional review board-approved phase I study of lenalidomide for previously treated CLL (OSU-06003, NCT00466895). Informed written consent approved by the OSU Human Studies Committee was obtained for all patients prior to study entry.

2.1. Eligibility criteria

Adult patients, ≥ 18 years of age with CLL were enrolled on one of two cohorts (A or B) between May 2007 and July 2010. Cohort A included relapsed and refractory CLL patients, whereas Cohort B also included relapsed and refractory CLL patients having achieved a complete or partial response (CR/PR) to therapy and not considered candidates for stem cell transplantation. Patients had to be within 12 months of achieving a CR or PR and at least 60 days from the last dose of chemotherapy, with those patients in CR required to have minimal residual disease by flow cytometry. Other criteria for both cohorts included an absolute lymphocyte count less than $200,000 \times 10^9 \text{ L}^{-1}$, a platelet count of at least $50 \times 10^9 \text{ L}^{-1}$ or $100,000 \times 10^9 \text{ L}^{-1}$ for Cohorts A and B respectively, an absolute neutrophil count of at least $1 \times 10^9 \text{ L}^{-1}$, total bilirubin $\leq 2 \times$ upper limit of normal, serum creatinine $\leq 2.0 \text{ mg/dL}$, ALT/AST $\leq 5 \times$ the upper limit of normal, and absence of infection. Only patients with an Eastern Cooperative Oncology Group performance status ≤ 2 were included.

2.2. Treatment plan

This phase I trial was a nonrandomized, dose-escalation study to determine the maximum tolerated dose (MTD) for single-agent lenalidomide. On this study, each of the two cohorts of patients with relapsed or refractory CLL followed independent dose escalation regimens, conducted in parallel. Dose escalation proceeded according to a standard 3 + 3 design with each cohort enrolling 3–6 patients at each dose level. Initially, 3 patients in Cohort A were to be treated with one cycle of oral lenalidomide 25 mg/d for 21 days and with a 7-day rest period. However, 2 patients experienced significant tumor flare and the third patient developed grade 3 sepsis with anemia and neutropenia, as has been previously described [17]. Subsequently, the protocol was amended to reduce the starting dose of oral lenalidomide for each cohort to 2.5 mg daily, allowing for intra-patient dose escalation as shown in Table 1. All patients received dexamethasone for tumor flare prophylaxis at a dose of 4 mg per day on days 3–14 during cycle 1. If tumor flare was observed at a particular dose level, then the dose of dexamethasone was escalated to 12 mg/day for as long as clinically indicated.

2.3. Assessment of toxicity and response

Adverse events were defined and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0; Bethesda, MD). Response assessment occurred after cycles 1, 3, 6, and beyond as indicated. Responses were defined according to the International Working Group criteria for CLL [21]. Interphase cytogenetics were performed using methods previously reported [22] and prioritized according to the Dohner classification [23].

2.4. Dose-limiting toxicity

Patients in each cohort were independently evaluated for dose limiting toxicity (DLT) during the first cycle of lenalidomide. DLT included adverse events that could be attributable to lenalidomide and (1) any grade 3–4 non-hematologic toxicity with the exception of manageable tumor lysis syndrome, tumor flare, or electrolyte abnormality, (2) uncontrolled or intolerable grade 2 non-hematologic toxicities, (3) hematologic toxicities including grade 4 thrombocytopenia, grade 4 neutropenia, and grade 3 neutropenia with fever and or infection, or (4) any toxicity that inhibited the ability to initiate cycle 2 of therapy.

2.5. Statistical considerations

This phase I study used a standard 3 + 3 dose escalation design to determine the MTD of lenalidomide in two independent cohorts of CLL patients: Cohort A with treatment of relapsed and refractory patients and Cohort B with consolidation/maintenance treatment of relapsed and refractory patients. The MTD was defined as that dose beneath the one at which 2 or more of 6 patients experienced DLT. Expansion cohorts with up to 12 patients were planned at the MTD for both Cohorts A and B to provide additional data regarding toxicity and preliminary data on efficacy. Descriptive statistics are provided for the primary end points of safety and tolerability. Other secondary end points including response (CR/PR) and overall response (CR/PR/SD) rate were calculated among evaluable patients treated at the MTD and are presented with exact 90% confidence intervals. Time to next treatment (TTNT) was calculated from the date on-study until the date of first non-protocol treatment off-study or date of death, where patients who were alive and had not started another treatment were censored at the date of last contact. Progression-free survival (PFS) was calculated from the date on-study until the date of progression or death, censoring patients who were alive and progression-free at last contact; patients who had not progressed but had started another treatment were also censored at the date of their next treatment. Overall survival (OS) was calculated from the date on-study until date of death, censoring patients on the date last known alive. Due to the limited number of patients treated in Cohort B, Kaplan–Meier estimates of TTNT, PFS, and OS are only provided for the group of patients in Cohort A and who were treated at the MTD.

3. Results

3.1. Patient characteristics

A total of 37 patients with CLL were enrolled on this study in two cohorts: Cohort A with 30 relapsed and refractory patients treated with lenalidomide and Cohort B with 7 relapsed and refractory patients treated with lenalidomide, specifically as consolidation/maintenance therapy. Baseline characteristics of patients enrolled in each cohort are presented in Table 2. In Cohort A, 47% of patients were female and the median age was 61 years (range 37–79). All patients had an ECOG performance status less than 2, 47% had high-risk Rai disease (i.e. stage III/IV), and 47% had del(17p)/del(11q) abnormalities with median number of prior therapies equal to 2.5 (range 1–11). Among the 7 patients enrolled on Cohort B, 3 were female and the median age was 61 years (range: 42–64). Two patients had an ECOG performance status of 2, one with del(17p) and one with del(11q). Two additional patients harbored a del(11q) abnormality and 3 patients had high-risk Rai disease. The median number of previous treatments was 2 (range 1–6).

3.2. Cohort A: dose escalation scheme

The initial starting dose of oral lenalidomide was 25 mg daily. As previously reported, in the first cohort of three, significant tumor flare was observed in two of the patients, 1 patient with grade 2 and 1 patient with grade 3 tumor flare. Given the significance of tumor flare seen at the 25 mg dosing, the protocol was amended with a new dosing scheme. The starting dose under the amendment was 2.5 mg of oral lenalidomide daily in week 1, followed by 5.0 mg daily in weeks 2 and 3 with continuous dosing thereafter. In the first 6 patients treated at this dose level, one DLT was observed (grade 2 tumor flare). This was manageable but required the patient to be admitted for corticosteroid therapy given respiratory complications. Due to concerns regarding tumor flare, an additional 3 patients were enrolled at this dose level to ensure safety. None of these additional patients experienced tumor flare or DLTs, and hence the dosing was escalated to dose level 2. At dose level 2, patients received 2.5 mg of oral lenalidomide daily in week 1, 5.0 mg daily in week 2, and 7.5 mg daily in week 3, with continuous dosing thereafter. Of the first 6 patients enrolled at this dose level, 1 patient experienced both grade 4 thrombocytopenia (ITP) and grade 4 neutropenia, which was considered a DLT event. Another patient had grade 4 neutropenia that resolved and its relation to treatment was uncertain. Toxicity concerns were strengthened by 2 additional patients enrolled at this dose level where one experienced intolerable grade 2 muscle weakness with neutropenia while the other underwent dose reductions due to dizziness during the course of therapy. The combination of these toxicities and others observed in the first cohort of 6 patients raised enough questions regarding safety that the previous dose level (dose level 1) was declared the maximally tolerated dose that should be pursued in subsequent studies. An expansion cohort of 10 patients was then enrolled at this dose level to collect additional data on safety and efficacy.

3.3. Cohort A: toxicity

A comprehensive summary of grade > 3 toxicities that were related to lenalidomide treatment are summarized for all patients enrolled in Cohort A as well as for those patients treated at the MTD ($n = 19$) in Table 3. The incidence of grade 3/4 adverse events observed

at dose level 1, the MTD, was similar to that observed for all patients treated in this cohort. Of all patients treated in Cohort A ($n = 30$), the majority (70%) experienced adverse events that were grade 3/4 hematologic toxicities, with the most common being neutropenia (6 grade 3 and 12 grade 4). After the first cycle of therapy to assess for DLT, patients that had absolute neutrophil counts (ANC) < 500 for ≥ 7 days had their lenalidomide held and it was resumed once ANC was ≥ 1000 at a one level dose reduction. Half of the patients experienced at least a grade 3 non-hematologic toxicity, including one grade 4 adverse event. The most common on-hematologic adverse events included documented infections (17%), electrolyte abnormalities (20%), and fatigue (13%). Only one patient experienced grade 3 tumor flare and this was not in a patient enrolled at the MTD. Lesser grades of tumor flare occurred in 15 patients (50%), 10 with grade 1 and 5 with grade 2 (data not shown).

Seven patients had a total of 13 dose reductions, with the most common reason for dose reduction due to neutropenia (57%). Most of these dose reductions occurred in patients treated at dose levels that were not deemed safe or tolerable; 1 patient each required a dose reduction to 5.0 or 2.5 mg every other day, 2 patients required dose reductions to 5 mg daily, and 1 patient to 2.5 mg daily. Only 2 patients treated at the MTD (11%) required dose reductions, 1–2.5 mg daily and 1–2.5 mg every other day.

The median number of cycles completed for the 19 patients enrolled at the MTD was 3 (range: 0–14) and median treatment duration was 2.6 months. Eight patients (42%) discontinued treatment due to adverse events. Two patients developed autoimmune complications, including one with Immune Thrombocytopenic Purpura (ITP) and 1 patient with Autoimmune Hemolytic Anemia (AIHA); 1 patient experienced tumor flare; 1 patient experienced a transient ischemic attack (TIA); 1 patient neutropenia; 1 patient pancytopenia; 1 patient dyspnea and there was one death due to sepsis occurring in the setting of neutropenia and pneumonia that was not considered to be drug-related. Nine patients (47%) came off study due to progressive disease and 2 (11%) patients withdrew from study, both with stable disease where one was in the second cycle of treatment and the other had completed 14 cycles of treatment.

3.4. Cohort A: efficacy

Clinical response was seen in 19 of 23 evaluable patients. Four patients achieved a partial response and 15 had stable disease. The number of cycles of therapy patients received ranged from < 1 to 14 (Table 4). At the MTD of 5 mg daily, clinical response was observed in 13 of 17 evaluable patients (76%, 90% CI: 0.54–0.92). Two patients achieved a partial response and 11 had stable disease. The two patients achieving PR and treated at the MTD completed 7 cycles of therapy each. The two patients achieving PR treated at a higher dose level had been dose reduced to the 5 mg daily in cycles 2 and 3 (defined as the MTD) and completed 11 and 12 cycles of therapy, respectively. Among the 19 patients treated at the MTD, 14 went on to begin another treatment, 4 died before beginning another treatment and one is currently still alive. The median time to next treatment or death was 9.9 months (95% CI: 4.3–14.7) and the median progression-free survival was 6.5 months (95% CI: 2.6–12.8).

Eleven of the 19 patients have expired with a median overall survival of 18.3 months (95% CI: 14.6–not reached).

3.5. Cohort B: dose escalation scheme

A total of 7 patients were enrolled in Cohort B. The first cohort of 3 patients was treated at dose level 1 with dosing of 2.5 mg of oral lenalidomide daily in week 1, 5.0 mg daily in weeks 2 and 3, with continuous dosing thereafter. None of the first 3 patients experienced DLT and the dose was escalated to dose level 2 with dosing of 2.5 of oral lenalidomide daily in week 1, 5.0 mg daily in week 2, and 7.5 mg daily in week 3, with continuous dosing thereafter. Here, DLT occurred in the first 2 patients treated, one with grade 3 ALT and one with grade 3 headache. Dosing was de-escalated to dose level 1, where a second cohort of 3 patients was to be enrolled. Even though only 2 of the 3 patients were treated for a total of 5 at this dose level, no DLTs were observed and dose level 1 was declared the MTD.

3.6. Cohort B: toxicity

A comprehensive summary of grade > 3 toxicities that were related to lenalidomide treatment are summarized for all patients enrolled in Cohort B and is provided in Table 3. Among the 7 patients treated in this cohort, grade 3/4 hematologic adverse events occurred in 4 patients, all treated at dose level 1. Three patients had grade 3 non-hematologic adverse events, one with AIHI treated at dose level one, one with headache and one with transaminitis, both treated at dose level 2. No one experienced a grade 4 non-hematologic toxicity related to treatment.

Two of the 7 patients had dose reductions, including one who was treated at dose level 2 and had dose reductions to 5 mg daily due to the grade 3 transaminitis but went on to receive 12 cycles of treatment. The other patient continues to be treated at dose level 1 and has currently completed 41 cycles of therapy 2.5 mg daily. Two patients (29%) discontinued treatment due to adverse events, grade 3 AIHA and grade 3 headache, respectively. One patient (14%) withdrew from study after completing 5 cycles of therapy due to low grade fever and fatigue. Three patients (43%) completed one year of therapy and one (14%) continues on therapy at 41 months as stated above. The median treatment duration was 10.9 months.

3.7. Cohort B: efficacy

Clinical response was achieved in 6 of 7 evaluable patients treated in Cohort B, all of whom maintained stable disease (Table 4). Three patients went on to receive other treatment prior to progression, including 1 patient who subsequently died at 24 months, 1 patient died after having a year of treatment but without a documented progression at 18 months and the remaining patients are alive and progression-free (supplemental table).

4. Discussion

In this phase I dose-escalation trial of lenalidomide in CLL, the maximum tolerated dose in the relapsed/refractory population (Cohort A) and in the maintenance population (Cohort B) was 2.5 mg of oral lenalidomide taken daily in week 1, 5.0 mg taken daily in weeks 2 and 3,

with continuous dosing thereafter. Even at these lower doses of lenalidomide treatment, a substantial number of patients experienced grade 1 or grade 2 tumor flare (50%) in the relapsed population; the one patient (3%) who experienced grade 3 tumor flare was treated at the 25 mg dose prior to the protocol amendment. Among the 7 patients treated in the maintenance population, only one (14%) experienced grade 1 tumor flare during the first cycle of treatment.

While only 2 of 17 relapsed or refractory patients treated at the MTD in Cohort A and evaluable for response achieved a PR, an additional 11 patients (65%) maintained stable disease, with treatment benefiting 76% of patients. Both patients who achieved a PR remained on therapy for at least 6 months as did 3 patients with stable disease. In this trial, lower PR rates were seen than in the previous phase II trials [11,12], although similar PR and SD rates as previously seen in a multicenter phase I [20]. The lower rates of PR may related to the higher starting doses used in the phase II trials, 10 mg and 25 mg of lenalidomide, as compared to the starting dose of 2.5 mg used in both phase I trials. Patients were able to dose escalate to 5 mg, but were unable to continue to escalate regardless of tolerability. The lower response rates also need to be considered in the context of the high-risk population of patients included in this study, in which 50% had bulky disease and 47% had high-risk cytogenetic abnormalities.

In Cohort B, 6 of the 7 patients enrolled achieved stable disease, allowing four to remain on treatment for at least 10 months, including the 1 patient who has been on lenalidomide for over 41 cycles spanning 3 years.

Adverse events were primarily hematologic toxicity, electrolyte abnormalities, infections and fatigue. The common toxicities observed were similar to those previously shown with lenalidomide therapy in CLL and other hematologic malignancies. Of interest, 3 patients had autoimmune complications requiring them to discontinue therapy, one with ITP and two with AIHA.

In summary, this phase I dose escalation study demonstrates that oral lenalidomide is feasible in both heavily pretreated patients at a dose of 5.0 mg continuous dosing and as maintenance therapy at a dose of 5.0 mg continuous dosing. Even at lower doses, tumor flare was observed but was manageable with concomitant administration of dexamethasone. While overall response rate was not particularly high, a number of patients were able to remain on the drug for several months with stable disease. Based on this durability of treatment, further investigation with lenalidomide as maintenance therapy or as combination therapy should be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Amended dosing schema for Cohorts A and B.

Dose level	Week 1 dose	Week 2 dose	Week 3 dose and all subsequent doses using continuous dosing
<i>Cohort A</i>			
-2	2.5 mg QOD	2.5 mg/QD	2.5 mg/QD
-1	2.5 mg/QD	2.5 mg/QD	2.5 mg/QD
1	2.5 mg/QD	5.0 mg/QD	5.0 mg/QD
2	2.5 mg/QD	5.0 mg/QD	7.5 mg/QD
3	2.5 mg/QD	5.0 mg/QD	10.0 mg/QD
4	2.5 mg/QD	7.5 mg/QD	12.5 mg/QD
5	2.5 mg/QD	7.5 mg/QD	15 mg/QD
<i>Cohort B</i>			
-2	2.5 mg QOD	2.5 mg/QD	2.5 mg/QD
-1	2.5 mg/QD	2.5 mg/QD	2.5 mg/QD
1	2.5 mg/QD	5.0 mg/QD	5.0 mg/QD
2	2.5 mg/QD	5.0 mg/QD	7.5 mg/QD
3	2.5 mg/QD	5.0 mg/QD	10.0 mg/QD

QOD: every other day; QD: every day.

Table 2

Baseline characteristics.

Characteristic	Cohort A All patients (n = 30)	Cohort B All patients (n = 7)
<i>Age, years</i>		
Median (range)	61 (37–79)	61 (42–64)
Female, no. (%)	13 (43)	3 (43)
<i>ECOG Performance Status, no. (%)</i>		
0	12 (40)	5 (71)
1	17 (57)	0 (0)
2	1 (3)	2 (29)
<i>Rai stage, no. (%)</i>		
0	6 (20)	3 (43)
I	9 (30)	1 (14)
II	0 (0)	0 (0)
III	7 (23)	2 (29)
IV	8 (27)	1 (14)
Bulky adenopathy > 5 cm, no. (%)	15 (50)	1 (14)
<i>WBC, K/ul</i>		
Median (range)	9.9 (2.6–330.8)	3.1 (2.2–3.5)
<i>ALC, cells/ul</i>		
Median (range)	5.98 (0.80–317.57)	0.70 (0.20–1.00)
<i>LDH, U/L</i>		
Median (range)	190 (94–537)	136 (80–169)
<i>Number of previous treatments</i>		
Median (range)	2.5 (1–11)	2 (1–6)
<i>Dohner classification, no. (%)</i>		
Del(17p)	9 (30)	1 (14)
Del(11q)	7 (23)	3 (43)
Trisomy 12	2 (7)	0 (0)
Normal	5 (17)	2 (29)
Del(13q)	7 (23)	1 (14)

Table 3

Summary of grade 3/4 related toxicities.

Toxicity, n (%)	Cohort A Dose level 1 n = 19	Cohort A All patients n = 30	Cohort B All patients n = 7
<i>Hematologic</i>			
Neutropenia	11 (58)	18 (60)	3 (43)
Lymphopenia	1 (5)	3 (10)	1 (14)
Anemia	3 (16)	5 (17)	2 (29)
Thrombocytopenia	3 (16)	4 (13)	0 (0)
<i>Non-hematologic</i>			
Autoimmune haemolytic anemia	0 (0)	1 (3)	1 (14)
Immune thrombocytopenia	0 (0)	1 (3)	0 (0)
Documented infection	3 (16)	5 (17)	0 (0)
Electrolyte abnormality	5 (26)	6 (20)	0 (0)
Transaminitis	0 (0)	0 (0)	1 (14)
Tumor flare	0 (0)	1 (3)	0 (0)
Anorexia	1 (5)	1 (3)	0 (0)
Diarrhea	1 (5)	1 (3)	0 (0)
Cough	1 (5)	1 (3)	0 (0)
Dyspnea	1 (5)	2 (7)	0 (0)
Fatigue	3 (16)	4 (13)	0 (0)
Headache	0 (0)	0 (0)	1 (14)
Pain	1 (5)	1 (3)	0 (0)
Transient ischemic attack	1 (5)	1 (3)	0 (0)

Table 4

Best response by dose level and cohort.

Dose level	Dose level	Best response
<i>Cohort A</i>		
1A	Initial cohort ($n = 3$)	PR, SD, NE
25 mg		
1	Initial cohort ($n = 6$)	PR (1), SD (3), PD (1), NE (1)
2.5/5.0/5.0 mg	Additional patients ($n = 3$)	PR, SD, PD
	Expansion ($n = 10$)	SD (7), PD (2), NE (1)
2	Initial cohort ($n = 6$)	PR (1), SD (3), NE (2)
2.5/5.0/7.5 mg	Additional patients ($n = 2$)	PR, SD
<i>Cohort B</i>		
1	Initial cohort ($n = 5$)	SD (5)
2.5/5.0/5.0 mg		
2	Initial cohort ($n = 2$)	SD (1), NE (1)
2.5/5.0/7.5 mg		