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Phase II Study of Mocetinostat (MGCD0103) In Patients with Relapsed and Refractory Classical Hodgkin Lymphoma

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Abstract

BACKGROUND—The prognosis of patients with relapsed Hodgkin lymphoma, especially those who relapsed after stem cell transplant, remains poor, and the development of new agents for this relatively young patient population represents an unmet medical need. In this study, we examined the safety and efficacy of mocetinostat, an oral isotype-selective histone deacetylase inhibitor, in patients with relapsed classical Hodgkin lymphoma

METHODS—Patients with relapsed or refractory classical Hodgkin lymphoma aged 18 years or older were treated with mocetinostat administered as an oral dose three-times weekly, in 28-day cycles. Two dose cohorts were evaluated (85 mg and 110 mg). Patients were treated until disease progression or prohibitive toxicity. The primary objective was to estimate the disease control rate induced by mocetinostat, defined as CR, PR or SD (for at least 6 cycles) analysed by intention to treat. This trial has been completed and is registered with ClinicalTrials.gov, number NCT00358982

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Contributors

AY, JB, RW, and REM were involved in the design of the study. AY, RGB, JK, MF, SN, AC, REM recruited and treated patients for this study. AY, DB, AG, ZL, LJM, and REM were involved in the design, conduct, and analysis of the biomarker studies, AY, MD, AC, TP, YO, and REM were involved in collecting and collating of the data. YJ, AY, JKP, ZL, DB, YO, and REM did statistical analysis. AY, YO, AC, and REM were involved in writing the draft of the report. All authors reviewed and approved the final draft of the report.

Conflict of interest

AY received consulting fees in relation to this study from Methylgene. He also provided consultancy to Celgene, Seattle Genetics, Novartis, Syndax, and Sanofi. JB, ZL, MD, and TP are employees of Methylgene. RW is an employee of Celgene. REM is a previous employee of Methylgene and has stock ownership in the company. YO, GB, JK, MF, SN, AC, DB, AG, YJ, JKP and LJM dclare that they have no conflict of interest

FINDINGS—A total of 51 patients were enrolled. Initially, 23 patients were enrolled in the 110 mg cohort. Subsequently, 28 additional patients were treated with a reduced dose of 85 mg to improve treatment tolerance. Based on intent to treat analysis, the overall disease control rate was 34.8% and 25% for the 110 mg and 85 mg groups, respectively. Thirty-four out of 42 (81%) patients who completed at least 2 cycles of therapy had a decrease in their tumor measurements. Forty-seven percent (24/51) discontinued therapy due to disease progression, 57% (16/28) in the 85 mg cohort and 34% in the 110 mg cohort. Twenty-four percent (12/51) discontinued due to adverse events, 32% (9/28) in the 85 mg cohort and 13% (3/23) in the 110 mg cohort. The most frequent treatment-related grade 3 and 4 adverse events included neutropenia, which was observed in 4 (17.4%) patients in the 110 mg group and in 3 (10.7%) patients in the 85 mg group; fatigue (in 5 (21.7%) of the 110 mg group vs 3 (10.7%) of the 85 mg group); and pneumonia (4 (17.4%) of the 110 mg group vs 2 (7.1% of the 85 mg group). Four patients, all in the 110 mg cohort, died during study, of whom two were considered possibly related to treatment.

INTERPRETATION—Mocetinostat 85 mg three-times weekly has promising single-agent clinical activity with manageable toxicity in patients with relapsed classical Hodgkin lymphoma.

FUNDING—MethylGene Inc., Montreal, Canada; Celgene Corporation, Summit, New Jersey; Tufts Medical Center, Boston, MA

INTRODUCTION

Classical Hodgkin Lymphoma (HL), is a B-cell lymphoid malignancy that is characterized by a relatively small number of malignant Hodgkin and Reed-Sternberg (HRS) cells that are surrounded by an overwhelming number of inflammatory and immune suppressive cells.[1–3] Over the past three decade, a substantial progress has been made in improving the cure rate of HL.[4,5] Unfortunately, up to 20% of the patients still require a second line therapy, including stem cell transplantation.[6,7] Patients whose disease relapses after stem cell transplantation have a dismal prognosis, and represent an unmet medical need for novel drug development.[8,9]

Histone deacetylases (HDACs) are considered potential targets for cancer therapy, as they regulate a variety of cell functions that are involved in survival, cell cycle progression, angiogenesis, and immunity.[10–13] Human HDACs are classified into four major classes: Class I includes HDAC 1, 2, 3, 8, and 11; Class II includes HDAC 4, 5, 6, 7, 9, and 10; Class III includes homologues of yeast SIRT 1–7, and Class IV, which currently includes only HDAC 11.[14] Most first generation HDAC inhibitors are unselective, as they inhibit several class I and II enzymes. The lack of selectivity of the currently available HDAC inhibitors may enhance their anti-tumor activity by modulating the acetylation and functional status of a wide range of protein targets, but they also cause undesirable toxic effects that may undermine their efficacy *in vivo*.[15,16] However, the optimal set of HDAC targets that are required to produce maximum clinical benefit with the least side effects remains unknown.

Mocetinostat (MGCD0103, MethylGene Inc., Montreal, Canada), is an oral isotype-selective non-hydroxamate HDAC inhibitor targeting HDAC isotypes 1, 2, 3 and 11.[17,18] Preclinical studies demonstrated that mocetinostat has a potent antiproliferative activity against a wide range of cancers.[18] We and others have recently reported that HDAC inhibitors, including

mocetinostat, have a potent antiproliferative activity against HL-derived cell lines by modulating several cellular mechanisms, including upregulation of p21, downregulation of STAT6, and activation of the caspase pathway. Furthermore, we have recently reported that mocetinostat may induce a favorable antitumor immune response in HL by down-regulating the expression and secretion of Thymus and activation-regulated chemokine (TARC/CCL17), and by upregulating OX40 ligand expression on HRS cells.[19–21] Those observations suggested that the clinical activity of HDAC inhibitors may be related to combined antiproliferative and immunomodulatory effects[8,22–24] With this background, we conducted a Phase II study of mocetinostat in patients with relapsed and refractory HL. The dose and schedule of this trial were based on date from recently reported phase I and early phase II studies in other malignancies.[25–27]

METHODS

Patients

This was an open-label, non-randomized, multi-centre Phase II trial of oral mocetinostat given as a three-times weekly in patients with relapsed or refractory classical HL. The primary endpoint of the trial was to estimate the disease control rate of this therapy as defined by complete and partial responses plus stable disease for at least 6 cycles. All patients provided a voluntary written IRB-approved informed consent to participate in this study. Inclusion criteria included pathologic confirmation of relapsed or refractory classical Hodgkin's lymphoma with at least one site of measurable disease (≥ 2.0 cm). Patients were required to have been ineligible for, or had previously undergone autologous stem cell transplant, irrespective of the number of prior treatment regimens. Patients who had prior allogeneic stem cell transplant, did not have evidence of active graft versus host disease and were not receiving immunosuppressive agents were eligible. Other eligibility criteria included an ECOG performance status of 0 or 1, age 18 years or older, total Bilirubin ≤ 1.5 × Upper Limit of Normal (ULN), ALT and AST <2.5 × ULN, serum creatinine ≤ 1.5 × ULN, absolute neutrophil count of ≥ 1,000/μL, and platelet count ≥ 25,000/μL. Patients were excluded if they had known human immunodeficiency virus (HIV), active Hepatitis B or C, central nervous system lymphoma, or were female and pregnant or lactating.

Procedure

This study required and received IRB approval at all sites. This was a 2-stage open label Phase 2 study, with expansion rules based on efficacy. The sample size was expected to be between 12 and 35 patients. However, after meeting the disease control rate criteria for dose expansion at the 110 mg starting dose it was decided to open enrolment to a second cohort of patients treated at a starting dose of 85 mg since many of the patients at 110 mg required dose reduction. Mocetinostat was administered as an oral dose three-times weekly (for example, Monday, Wednesday & Friday). One cycle was defined as 4 weeks (28 days). If after one cycle on study the patient had not experienced drug-related adverse events greater than grade 1, the dose of mocetinostat was allowed to be increased to 110 mg. Dose reductions to 60 mg and subsequently 40 mg were allowed in the setting of drug-related toxicities. Since mocetinostat is a weak inhibitor of isoform cytochrome P450 (CYP) – CYP3A4 and a strong inhibitor of isoform CYP2C9, caution was used when administering

mocetinostat to patients taking medications that are metabolized significantly by either of these enzymes.

In the case of drug-associated grade ≥ 3 non-hematologic toxicities, treatment was held until toxicity was resolved to ≤ grade 1 or to baseline, and treatment was resumed at the next lower dose level. If the toxicity could be managed by routine supportive care, such as anti-emetics or electrolyte supplementation, then a dose reduction was not required. Further dose reductions were allowed as necessary to achieve stable clinical status. In the event of a patient experiencing symptoms of cystitis (dysuria, pollakiuria, hematuria, urgency or bladder spasm) suspected to be mocetinostat related, patients were encouraged to have adequate hydration, and a urinalysis, urine culture, blood urea nitrogen (BUN), creatinine and complete blood count were examined. Treatment was held if clinically significant symptoms persist despite a negative work-up. In the case of drug-associated grade 4 hematologic toxicity lasting 7 or more days, treatment was held until toxicity had resolved to ≤ grade 1 or to baseline. If further treatment was desired, treatment would then be resumed at the next lower dose level. Anti-emetic prophylaxis and growth factor support were allowed. Medications that directly increase gastric pH such as short-acting antacids were avoided 4 hours before and 1 hour after administration of mocetinostat. Medications that affect gastric acid secretion, such as H2 antagonists or proton pump inhibitors were allowed.

Tumor assessments were performed at baseline by computed tomography scans (neck, thorax, abdomen, and pelvis), a PET CT scan, and bone marrow biopsy. Imaging studies were repeated every 2 months while on therapy. A repeat bone marrow biopsy was required to confirm a CR if the marrow had been involved with HL at baseline. Partial and complete responses were defined according to modified revised International Workshop Response Criteria.[28] Appearance of new lesions or increase by more than 25% in the sum of the products of perpendicular diameters of the lesions defined progressive disease PD. Stable disease (SD) did not meet criteria for CR, PR or PD. Durable SD required 6 month duration of SD. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 3.

Serum samples were collected from patients before starting therapy and one week (after 3 doses) after starting therapy using an IRB-approved consent. Sera were analyzed for changes in cytokines and chemokines levels, using commercially available ELISA kits (R&D Systems, Minneapolis, MN), and Multiplex Human cytokine 30-plex kits (Invitrogen Corporation, Carlsbad, CA) as previously published.[19,20]

Statistical analysis

The primary objective was to estimate the disease control rate induced by mocetinostat, defined as CR, PR or SD (for at least 6 cycles). Patients who were not evaluable for efficacy were to be replaced. Two dose cohorts were evaluated (85 mg and 110 mg). An optimal two-stage Phase II design according to Simon[29] was adopted for each dose cohort in this study. The null hypothesis was that the true success probability was less than or equal to 10% and the alternate hypothesis was that the true success probability was 30% or higher. A type I error of 10% and a power of 90% was assumed. The trial was to be stopped at the end of stage 1 if 1 or fewer successes in first 12 patients were observed. Otherwise enrollment was

to be continued to enroll another 23 patients in stage 2 for a total of 35 patients. If 5 or fewer successes were observed in these 35, then there would be less than 5% probability that the true disease control rate was 30% or higher.

Progression-free survival (PFS) was calculated from the date of the first dose of study medication to date of first recurrence (as documented on a Tumor Assessment Day) or death from any cause. Overall survival (OS) was calculated from the date of the first dose of study medication to date of death from any cause. Patients without a documented date of progression or date of death were censored at the last evaluable tumor response date. Kaplan-Meier survival analysis was used to compare overall- and progression-free survival time between the two dose cohorts. As a secondary analysis, Kaplan-Meier survival analysis was used to compare overall- and progression-free survival time among the three groups defined by a patient's best measured response. Eight patients were excluded from this analysis because their tumor response was "not evaluable" (patients came off study prior to on-study imaging without signs of clinical progression of disease). A best response was classified as Progressive Disease if there was any tumor growth, as Stable Disease if the best response was 0 change up to a <50% decrease, and a Partial (PR) or Complete Response (CR) with ≥50% reduction in tumor size. Given the expectation of early differences between survival curves, the generalized Wilcoxon procedure was used to test for differences between dose cohorts and best response groups. If the global Wilcoxon test was significant, pair-wise Wilcoxon tests were conducted between groups. Statistical significance was assumed at a p value < 0.05.

A non-parametric smoothing curve was used to depict the association between changes in TARC from baseline to Day 8 with tumor best response. Statistical analyses were conducted using the SAS statistical package, version 9.2 (SAS Institute, Cary, NC). This study is registered with ClinicalTrials.gov, number NCT00358982.

Role of the funding source

Representatives of the study sponsors were involved in the design of the study, the collection, analysis, and interpretation of the data, and the writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

RESULTS

A total of 51 patients were enrolled between August, 2006 and July 2008, 23 in the 110 mg cohort and 28 in the 85 mg cohort (Table 1). The median age of patients on study was 33 years (range 19–68). ECOG performance status was equally distributed between 1 and 0. Two thirds of patients received 4 or more prior treatment regimens, and 84% of patients had undergone one or more prior bone marrow/stem cell transplants. All patients had been previously treated with alkylating agents, antimetabolites, microtubule agents, topoisomerase inhibitors and anthracyclines, and all but one had also been exposed to platinum agents and bleomycin.

All patients received at least one dose of mocetinostat and were evaluable for toxicity. Forty-seven percent (24/51) discontinued therapy due to disease progression, 57% (16/28) in the 85mg cohort and 34% in the 110mg cohort. Twenty-four percent (12/51) discontinued due to adverse events, 32% (9/28) in the 85mg cohort and 13% (3/23) in the 110mg cohort. Patient request, investigator decision, death or patient non-compliance was the cause for discontinuation of 4% (1/28) and 35% (8/23) of patients in the 85 and 110mg groups respectively. Four patients, all in the 110mg cohort, died during study due to complications: 3 with neutropenic infection (1 considered related to study treatment and the other 2 considered unrelated), and one with an unexplained death at home (considered possibly related to study treatment). After implementation of an 85mg starting dose as well as guidelines for management of GI toxicity and dehydration there was improved tolerability and no treatment-related deaths. The most frequent treatment-related grade ≥ 3 adverse events included myelosuppression, fatigue and pneumonia (Table 2). Four subjects (3 in the 85mg cohort and 1 in the 110mg cohort) had serious adverse events where pericardial effusion was reported as one of the serious adverse events, three of which were at least grade 3. Two of the effusions were reported during the first cycle of treatment, one during the 2nd cycle and one during the 4th cycle. Presenting symptoms included chest pain, fever, syncope, shortness of breath and cough. Other signs included ST elevation, atrial fibrillation, hypotension and detection on scanning. Interventions included pericardiocentesis (N=2) and pericardial window (N=2). Three of the subjects had a prior history of pericardial effusion or pleural effusion related to disease. Of the 43 patients who completed at least 2 cycles (8 weeks) of therapy, 26 (60%) required dose reductions, 52% of the 85 mg cohort, and 70% in the 110 mg cohort.

All 51 patients who received at least one dose of mocetinostat were evaluated for treatment response based on intent to treat analysis. Forty-three patients completed at least 2 cycles of therapy and were included in the efficacy evaluable population. Two patients achieved CRs (110 mg cohort) and 12 patients achieved PRs (6 patients in each cohort), and one patient achieved a SD lasting for more than 6 months (85 mg cohort). Thus, the overall intent to treat response rate (PR + CR) was 35% (8/23) and 21% (6/28) in respectively in the 110mg and 85mg cohorts. The disease control rate in the efficacy evaluable patients, as defined by the study (CR + PR + durable SD) was 40% (8/20) and 30% (7/23) in 110mg and 85mg cohorts respectively (Table 3). Considering all treated patients, the disease control rate (CR + PR + SD>6m) was 25% (7/28) and 35% (8/23) for the 85mg and 110mg doses, respectively, which was not meaningfully different between dose levels. Using a waterfall plot of best responses, 34 out of 42 (81%) of the patients who completed at least 2 cycles of therapy had a decrease in their tumor measurements (Figure 1).

Kaplan Meier survival analysis revealed that the dose cohorts (110 mg and 85 mg) had a similar progression-free survival (PFS) (Figure 2 A, p value = 0.59) and overall survival (OS) (Figure 2 B, p value = 0.19). A secondary Kaplan Meier analysis indicated that those patients who had tumor reduction with no “objective response” (stable disease with tumor shrinkage) had a similar PFS as patients who achieved complete or partial response (p value = 0.61) (Supplementary Figure 1 A). Furthermore, the patients with stable disease with tumor shrinkage experienced significantly improved PFS as compared to those patients with

tumor growth or progressive disease (p value<0.0001). However, OS did not differ between these three groups (Supplementary Figure 1 B, p value = 0.27).

To determine the *in vivo* effect of MGCD0103 on serum cytokines, we measured the levels of 30 cytokines and chemokines at baseline and after one week (3 doses) of therapy with mocetinostat in a subset of patients (Figure 3). An increase in p40/p70, IP10, EGF, IL17, GCSF, VEGF, MIP1b, Eotaxin and MIG, and a decrease in IL8 and VEGF levels were observed in several patients (Fig 3A). However, no correlation between the changes in these cytokines and tumor response was observed. In contrast, approximately half of the subjects with data available (n=20) showed reduction in TARC levels by more than 40% from baseline following 8 days of treatment with mocetinostat (Fig 3B), and TARC reduction correlated with tumor response (Figure 3C). TARC reduction was of similar magnitude when comparing the 85mg dose with the 110mg dose (data not shown).

DISCUSSION

The results of this multicenter phase 2 study, showed for the first time the potential clinical therapeutic value of using isotype-specific HDAC inhibitors in HL. Results from a previous study using the pan HDAC inhibitor vorinostat were disappointing.[30] Twenty five patients were treated with 200 mg vorinostat given orally twice per day for 14 days every 21 day-cycle, but only one patient (4%) achieved a partial remission. In this study of mocetinostat, the overall response rate (CR + PR) was 27% (14/51). Remarkably, mocetinostat also induced reduction in tumor measurements in 81% of the patients who completed at least 2 cycles of therapy. It is important to note that patients who achieved minor tumor reductions had similar PFS compared with those who achieved partial remissions, suggesting that clinical benefit of mocetinostat spans well beyond the traditional measure of partial and complete responses.[31] Therefore, it is possible that response assessment of novel targeted agents in the relapsed setting, especially in patients who have no curative options may require different criteria compared with those used for frontline conventional chemotherapy to better reflect patients benefit.[31] For example, a decrease in tumor measurements by 40% may be as meaningful as a reduction by 50% in multiply relapsed patients, and data should be generated to determine the percent reduction in tumor measurements that represent patients benefit.

Most recently, the pan HDAC inhibitor panobinostat also demonstrated a promising clinical activity in patients with relapsed HL.[32] Collectively, these data indicate that HDAC inhibitors, as a class, have a promising clinical activity in patients with HL and warrants their further development for the treatment of this patients population. Future development of mocetinostat in HL should take into account its complex mechanisms of action, including the recently reported immunomodulatory anti-tumor activity.[19] Because of the 85 mg dose level demonstrated improved tolearance without loss of efficacy, this dose should be considered for future development of mocetinostat as a single agent. One strategy may be to explore mocetinostat effect as a maintenance strategy in patients who achieve remission after conventional therapy in order to prevent subsequent relapse. Because 81% of the patients had tumor reductions, a mocetinostat-based combination strategy with other biologic agents or conventional chemotherapy should be explored with the goal of achieving higher

complete remission rate and longer PFS. For example, recent studies demonstrated a significant clinical activity of the antibody-drug-conjugate brentuximab vedotin in patients with relapsed HL.[33] It is logical to explore the potential synergistic value of HDAC inhibitors and brentuximab vedotin.

Treatment side effects were challenging for some patients. However, as with many novel agents, there was a learning curve on how best to manage these. The implementation of proactive measures to avoid dehydration and dose modification improved tolerance. Although pericardial effusion was seen in several patients, the interpretation was confounded by other co-morbidities. Nevertheless, implementation of straight-forward monitoring, including echocardiograms, will allow early detection until future randomized data will elucidate whether or not this is a drug-related side-effect.

In this study we demonstrated that mocetinostat reduced serum TARC levels in the majority of patients, which correlated with clinical response. This in vivo biomarker study validated our previous in vitro data that demonstrated the ability of HDAC inhibitors to downregulate TARC expression in HL cell lines.[21,34] An early decline of serum TARC as a predictive marker for response should be further explored to select patients for continued therapy, and to explore its value in the design of future response-adapted clinical studies. If confirmed, its clinical utility should be compared to interim FDG-PET studies, which remain expensive and difficult to standardize across multicenter studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Panel: Research in context

Systematic review

At the time of protocol development and initiation of this phase II study, there was no clinical data on the activity of HDAC inhibitors in Hodgkin lymphoma (HL). The rationale for evaluating mocetinostat in patients with relapsed HL was based on early reports that aberrant epigenetic changes were involved in the observed loss of B-cell phenotype in the malignant Hodgkin and Reed-Sternberg (HRS) cells of HL. Furthermore, early preclinical work from our group which was recently published, also demonstrated promising antiproliferative activity of a variety of HDAC inhibitors against HL cell lines[21,34]. The rationale for the initially selected dose and schedule of mocetinostat in our study were based on safety data reported from a phase-I study in patiens with solid tumors.[26]

Interpretation

Mocetinostat is the first HDAC inhibitor to demonstrated promising clinical activity in heavily pretreated patients with relapsed HL. Although the overall PR+CR rate was modest, approximately 80% of patients who completed 2 cycles of therapy demonstrated tumor shrinkage. Our data suggest that the development of mocetinostat–based combination regimens for relapsed HL are warranted

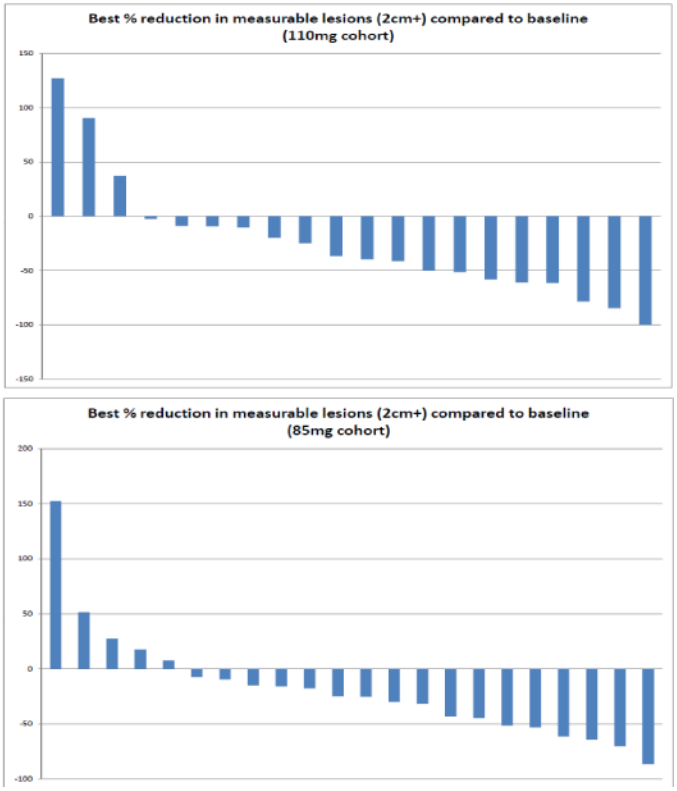
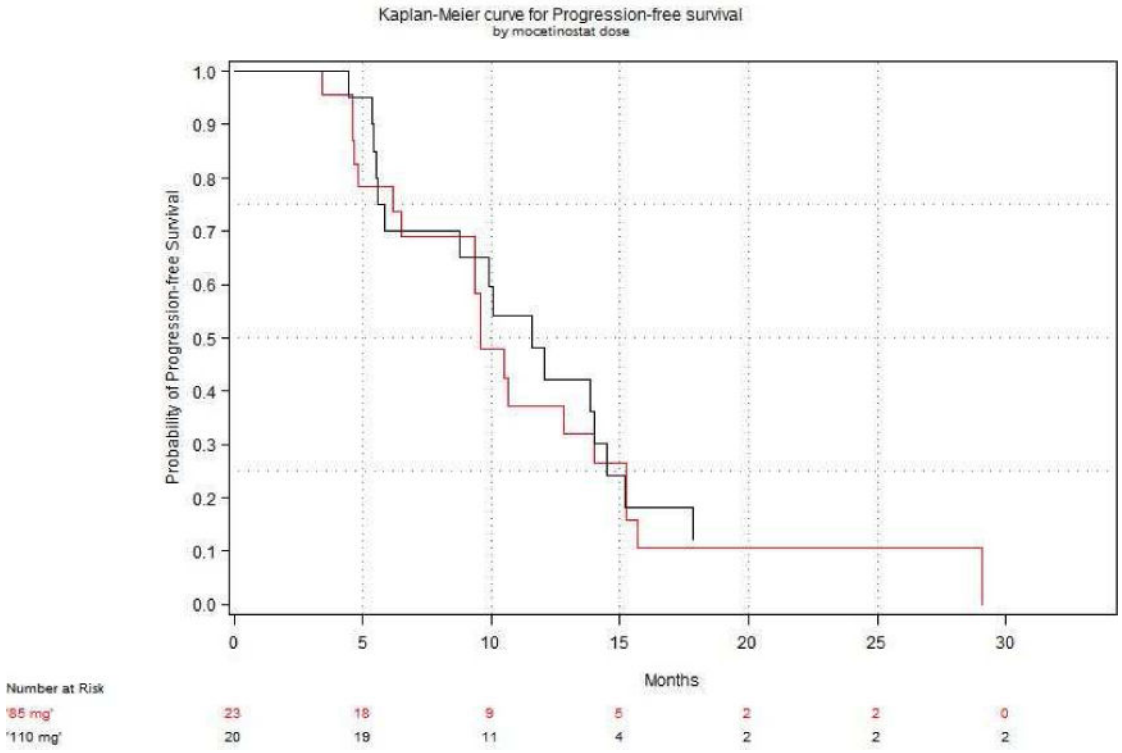


Figure 1.

A waterfall plot of best clinical responses. Top) patients treated with the 110 mg dose, B) patients treated with the 85 mg dose

A



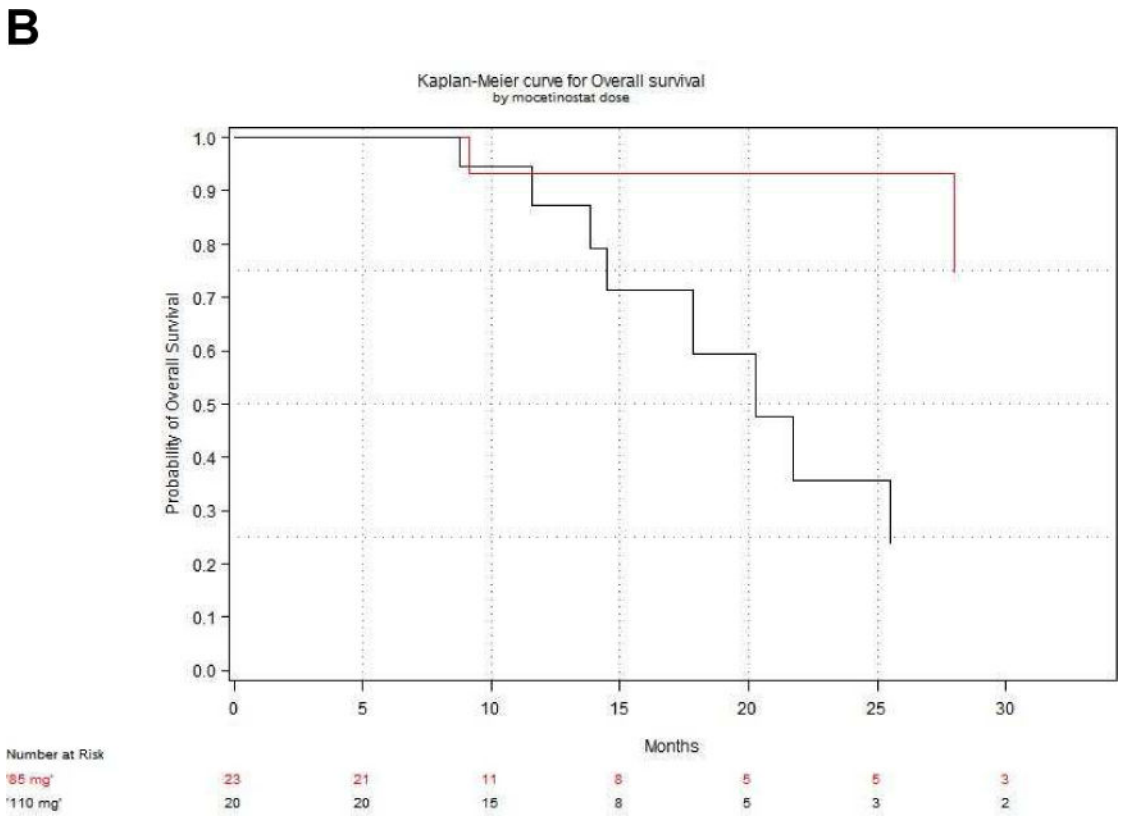


Figure 2.

A) Kaplan-Meier survival analysis for progression-free survival (PFS) as defined by the two dose cohorts (110 mg and 85 mg). PFS was not significantly different between the dose cohorts (*p* value = 0.59). B) Kaplan Meier survival analysis for overall survival by dose cohort (p value = 0.19).

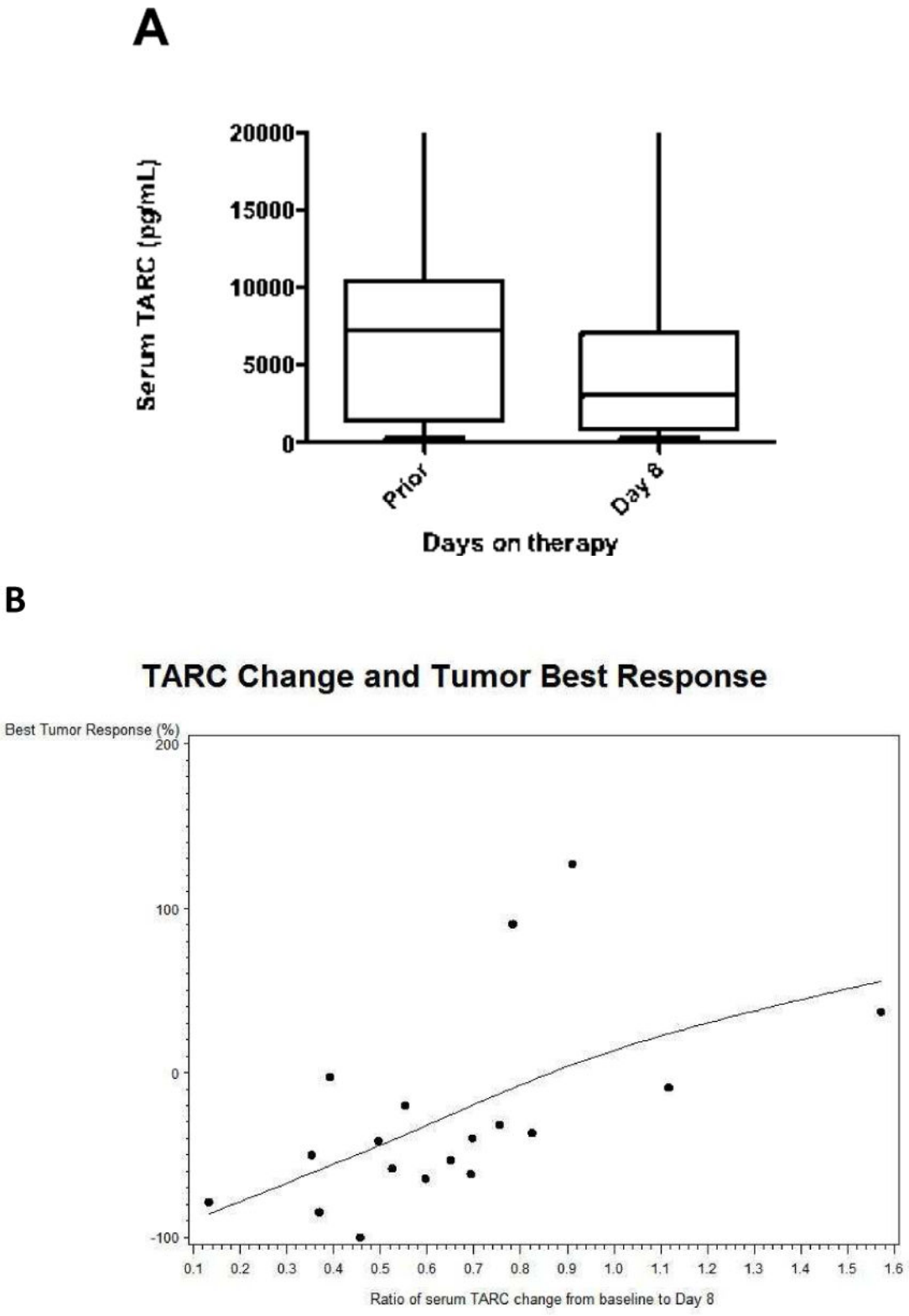


Figure 3.

A) Representative heatmap data of serum cytokine changes in 15 patients after 3 doses of MGCD0103. Green color indicates a decrease whereas a red color indicates an increase in cytokine levels compared to pretreatment values. White color indicates that the level was below the assay sensitivity. B) Box plot of serum TARC levels before and after 3 doses of MGCD0103 (day 8) ($P<0.05$) C) Non-parametric smoothing curve depicting changes in serum TARC and best tumor response measurement.

Table 1

Patient Characteristics

Category Statistics	Initial Dose 85mg (n=28)	Initial Dose 110 mg (n=23)	Total (n=51)
Age (years)			
Median	34.0	28.0	33.0
Min, Max	19, 68	20, 62	19, 68
Gender, n (%)			
Male	15 (53.6)	14 (60.9)	29 (56.9)
Female	13 (46.4)	9 (39.1)	22 (43.1)
Ethnicity, n (%)			
Caucasian	23 (82.1)	20 (87.0)	43 (84.3)
Black/African American	2 (7.1)	2 (8.7)	4 (7.8)
Latin American	1 (3.6)	1 (4.3)	2 (3.9)
Other	2 (7.1)	0	2 (3.9)
ECOG score, n (%)			
0	11 (39.3)	14 (60.9)	25 (49.0)
1	17 (60.7)	9 (39.1)	26 (51.0)
Best overall response to chemotherapy *			
CR	15 (53.6)	18 (78.3)	33 (64.7)
PR	10 (35.7)	3 (13.0)	13 (25.5)
SD	0	2 (8.7)	2 (3.9)
PD	3 (10.7)	0	3 (5.9)
Number of prior chemotherapy regimens			
Median (range)	5 (1–9)	4 (2–8)	5 (1–9)
≥ 4 Lines, n (%)	20 (71.4)	14 (60.9)	34 (66.7)
< 4 lines, n (%)	8 (28.6)	9 (39.1)	17 (33.3)
Number of patients who had a BMT/stem cell transplant *, n (%)	23 (82.1)	20 (87.0)	43 (84.3)
Radiation, n (%)	22 (78.6)	17 (73.9)	39 (76.5)

* All prior treatment for cancer records with unknown or missing responses were excluded

Table 2

Treatment-related grade 3 or 4 adverse events in ≥ 5% of Patients

Preferred Term n (%)	Initial Dose 85mg (n=28)	Initial Dose 110 mg (n=23)	Total (n=51)
Thrombocytopenia	7 (25.0)	4 (17.4)	11 (21.6)
Fatigue	3 (10.7)	5 (21.7)	8 (15.7)
Neutropenia	3 (10.7)	4 (17.4)	7 (13.7)
Pneumonia	2 (7.1)	4 (17.4)	6 (11.8)
Anemia	4 (14.3)	1 (4.3)	5 (9.8)
Pericardial effusion	1 (3.6)	2 (8.7)	3 (5.9)
Abnormal liver function test	1 (3.6)	2 (8.7)	3 (5.9)

Table 3

Treatment Response

Response by Initial Dosing Cohort	Efficacy Evaluable Population			Intent-to-Treat Population		
	85 mg (n=23) n (%)	110 mg (n=20) n (%)	Total (N=43) n (%)	85 mg (n=28) n (%)	110 mg (n=23) n (%)	Total (N=51) n (%)
CR	–	2 (10.0)	2 (4.7)	–	2 (8.7)	2 (3.9)
PR	6 (26.1)	6 (30.0)	12 (27.9)	6 (21.4)	6 (26.1)	12 (23.5)
Durable SD *	1 (4.3)	–	1 (2.3)	1 (3.6)	–	1 (2.0)
Disease control rate CR+PR+ SD *	7 (30.4)	8 (40.0)	15 (34.9)	7 (25)	8 (34.8)	15 (29.4)
SD	9 (39.1)	7 (35.0)	16 (37.2)	9 (32.1)	7 (30.4)	16 (31.4)
PD	7 (30.4)	5 (25.0)	12 (27.9)	7 (25.0)	5 (21.7)	12 (23.5)
Not evaluable	–	–	–	5 (17.9)	3 (13.0)	8 (15.7)

* Stable disease for at least 6 cycles