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Pilot Phase II Study of Metronomic Chemotherapy in Combination with Bevacizumab in Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer

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Abstract

Introduction—The goal of this study was to explore the efficacy and tolerability of metronomic chemotherapy, a novel anti-angiogenic treatment strategy, in combination with bevacizumab in patients with advanced non-small cell lung cancer (NSCLC)

Methods—Subjects with newly diagnosed stage IV NSCLC were treated with 4-week cycles of paclitaxel 80 mg/m² and gemcitabine 300 mg/m² weekly for three weeks, plus bevacizumab 10 mg/kg every two weeks. Radiologic assessments were performed every 8 weeks. The primary endpoint was progression free survival (PFS). An exploratory objective was to correlate plasma levels of angiogenic biomarkers with treatment response.

Results—Thirty-nine subjects were included in the intent to treat (ITT) analysis. The objective response rate (ORR) was 56%, the median PFS was 8.5 months, and median overall survival (OS) was 25.5 months. The PFS rate at 6, 12, and 24 months was 61%, 21%, and 11% respectively. The OS rate at 12 and 24 months was 74% and 53% respectively. Treatment was well tolerated, without significant myelosuppressive, gastrointestinal, or neurologic events. Subjects with less than median baseline values of angiopoietin-2 and IL-8 experienced significantly longer PFS. Longer OS was associated with subjects with less than the median baseline values for PLGF and angiopoietin-2. There were statistically significant differences in median values of several biomarkers between cycles 1 and 3 in subjects with objective responses.

Conclusions—The combination of paclitaxel and gemcitabine, delivered in a metronomic schedule, in combination with bevacizumab, appears to be an effective and tolerable treatment strategy in patients with advanced NSCLC.

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1. Introduction

Most lung cancers (87%) are of non-small cell histology (NSCLC), and most patients with NSCLC have advanced disease on presentation [1]. These patients have historically been treated in the first line setting with platinum-based doublet chemotherapy which has resulted in an overall median survival of 8–10 months, and 1-year and 2-year survival rates of 33% and 11%, respectively [2–6]. Chemotherapy has historically been administered every three weeks at maximum tolerated doses (MTD) in order to achieve optimal cell kill; this strategy often results in significant normal tissue toxicity limiting further therapy.

One of the most important clinical breakthroughs in the treatment of advanced NSCLC has been the recognition of the critical role of angiogenesis in tumor development. Overexpression of vascular endothelial growth factor (VEGF) and its receptors (VEGFR) is common in lung cancer, and there is a close correlation between the expression of VEGF/VEGFR, degree of neoangiogenesis, and survival in patients with advanced NSCLC [7, 8]. In 2006, Sandler, et al. published the results of a phase III trial which demonstrated an overall survival advantage with the addition of the monoclonal antibody to VEGF-A, bevacizumab, to doublet chemotherapy for patients with advanced NSCLC [9]. This landmark achievement represented the first agent to show a survival advantage versus standard chemotherapy and underscored the importance of targeting angiogenesis in lung cancer. However, despite this important advancement, the median survival for patients with advanced NSCLC remains only minimally improved at approximately 12 months.

A reappraisal of the optimal treatment strategy for advanced NSCLC is needed. Rather than continuing the traditional paradigm of MTD chemotherapy in which drug delivery is often limited by normal tissue toxicity, emerging data support the use of more compressed or accelerated scheduled of drug administration using much small individual doses than the MTD [10–12]. *Metronomic* chemotherapy (MC) refers to the frequent administration of cytotoxic chemotherapeutic agents at doses significantly below the MTD, without prolonged drug-free breaks. Unlike MTD chemotherapy, MC compromises the repair mechanisms in the endothelial cells of the growing tumor vasculature and is expected to lead to delay in tumor progression [11]. In contrast to MTD which has been shown to increase expression of VEGF and other pro-angiogenic growth factors in a rebound response to treatment, MC results in sustained and potent anti-angiogenic effects by targeting endothelial cells of newly forming blood vessels [13]. The combination of cytotoxic chemotherapy with bevacizumab, delivered in a metronomic schedule, could result in enhanced anti-angiogenic effect and clinical benefit for patients with advanced NSCLC. Here we report results of a single institution phase II pilot study of patients with advanced NSCLC treated with MC in combination with bevacizumab.

2. Materials and Methods

2.1 Patient eligibility

Patients were required to be over 18 years of age; have stage IV, histologically proven non-squamous NSCLC; have Eastern Cooperative Oncology Group (ECOG) performance status

(PS) 0–1; to have received no prior systemic therapy for cancer; and have adequate organ function.

Patients were excluded for life expectancy less than 12 weeks, other active malignancy, poorly controlled hypertension, radiation therapy less than three weeks prior to study initiation, pregnancy, lack of effective contraception, New York Heart Association (NYHA) grade II or greater congestive heart failure, history of myocardial infarction or unstable angina within six months of study initiation, history of stroke within six months of study initiation, known CNS disease (except treated brain metastases), major surgical procedure within 28 days of study initiation, or intra-thoracic lung carcinoma of squamous histology.

2.2 Treatment design

In this single arm, phase II pilot study, subjects were treated with MC as paclitaxel plus gemcitabine weekly for three out of four weeks, and bevacizumab 10 mg/kg every two weeks. Paclitaxel was administered at a dose of 80 mg/m² weekly. Gemcitabine was administered at 200 mg/m² weekly for the first cycle and dose escalations to 300 mg/m² were allowed if no significant toxicities were experienced. One treatment cycle consisted of four weeks of therapy. Treatment with MC was continued for six cycles in the absence of disease progression or intolerable toxicity. Maintenance therapy with bevacizumab was then continued until disease progression or intolerable toxicity.

2.3 Response and Safety Evaluation

Patients were evaluated with computed tomography (CT) imaging at baseline and after every two cycles (eight weeks). Treatment response was assessed using response evaluation criteria in solid tumors (RECIST) version 1.0. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 3.0.[14]

2.4 Serum Biomarker Analysis

To identify potential serologic markers predictive of treatment response to metronomic chemotherapy, plasma biomarkers from 21 study subjects were collected at baseline and the day prior to the start of cycle 3. Biomarkers analyzed included VEGF- α , VEGFR-2, ICAM-1, thrombospondin-1, human stromal-cell derived factor 1 α (SDF-1 α), β -fibroblast growth factor (β FGF), fibroblast growth factor-2 (FGF-2), placenta growth factor (PLGF), platelet-derived growth factor- α (PDGF- α), e-selectin, transforming growth factor β -1 (TGF β -1), angiopoietin-1 (angio-1), angiopoietin-2 (angio-2), interleukin 8 (IL-8), and endocan. Fifty milliliters of whole blood was collected in anti-coagulant tubes and centrifuged for 15 minutes at 1000G within 30 minutes of collection. The plasma component was stored at –20 degrees centigrade. Before analysis, plasma samples were thawed slowly to room temperature. Two methods of quantitation were employed. Enzyme-linked immuno-absorbent assay (ELISA) uses a spectrophotometer to measure the absorbance of an antibody-analyte conjugate in solution. ELISA (R&D Systems, Minneapolis, MN) was used to quantify levels of PDGF- α , thrombospondin-1, SDF-1 α , and endocan. The remaining biomarkers were quantified using electrochemiluminescence (MesoScale Discovery, Gaithersburg, MD), which utilizes similar antibody-analyte technology but quantitates conjugate levels based on electrochemical stimulation instead of light absorbance.

2.5 Statistical Considerations

The goal of this pilot phase II open label study was to explore the efficacy of MC in combination with bevacizumab in treatment naïve subjects with stage IV non-squamous NSCLC. The primary efficacy endpoint was progression free survival (PFS) assessed as a median of the total study population and as a percentage of patients without progression at 6, 12, and 24 months. Secondary endpoints included objective response rate (ORR), overall survival (OS) expressed as a median of the total study population and as a percentage of patients alive at 12 and 24 months. Additionally an exploratory analysis of plasma levels of angiogenic biomarkers at baseline and after two cycles of treatment was planned.

This feasibility/pilot study was not powered with enough number of patients to ascertain statistical power. Nevertheless, our goal was to determine if the metronomic chemotherapy with bevacizumab will provide a 30% improvement in the PFS (8.3 months), representing a 1.9 month difference from the experimental arm of ECOG 4599 [9]. Based on a sample size 35–40 subjects, the 80% lower bound of the expected PFS of 8.3 months is 6.6 months. Descriptive statistics were generated for the 39 subjects in the intent to treat (ITT) population. We estimated medians and interquartile ranges (IQR) for continuous variables, and frequency and percentages for categorical variables. For the ITT and response-evaluable (RE) populations, median survival time and their corresponding 95% confidence limits (CL) were estimated using the Kaplan-Meier curves. Moreover, PFS and OS expressed as the proportion of subjects without progression or alive at the corresponding time points were estimated using 95% Clopper-Pearson confidence limits. For the exploratory biomarker analysis, we dichotomized subject's baseline biomarker levels based on the median, and examined the associations with the clinical response parameters dichotomized at median PFS and OS survival times using chi-square tests. In addition, we examined the differences between cycles 1 and 3 and compared the median within-subject differences between complete/partial responders and those with stable disease using Mann-Whitney U-Test. Statistical significance was assessed based on p-values less than 0.05.

3. Results

3.1 Patient characteristics

Patient characteristics are listed in Table 1. From July 16, 2008 until August 15, 2013, 39 patients with advanced NSCLC were included in the ITT analysis including 16 men and 23 women. 36 patients were evaluable for response. 3 patients were excluded from efficacy analysis because they either withdrew consent (1) or expired before first imaging evaluation (2). Of the 2 subjects who expired before the first imaging evaluation, 1 died of complications related to colonoscopy-induced colon perforation, and 1 suffered progressive global deterioration. Median age was 59 years and most patients had adenocarcinoma by histologic analysis. Four patients had controlled brain metastases at time of study initiation. Six patients had epidermal growth factor receptor (EGFR) exon 19 or 21 mutations. The median number of induction cycles was 6 (range 1–7) and the average number of cycles of maintenance bevacizumab was 3 (range 0–28). Nearly half of the patients in the ITT population (19/39 = 49%) were treated with at least one subsequent line of systemic therapy on disease progression.

3.2 Outcome

Table 2 shows negligible differences in efficacy parameters between the ITT and RE populations. In the ITT population, the ORR was 56% and disease control rate (DCR) (defined as CR, PR, or SD) was 85%. The median PFS was 8.5 months and median overall survival was 25.5 months. The PFS rate at 6, 12, and 24 months was 61%, 21%, and 11% respectively. The OS rate at 12 and 24 months was 74% and 53% respectively. Figure 1 shows the Kaplan-Meier estimates of median PFS and OS for the ITT and RE populations.

Six patients in the study were positive for EGFR mutation. Of those patients, 4 achieved objective response and 1 achieved stable disease. Kaplan-Meier estimates (not shown) of the median PFS for these patients were 10.5 months (95% CI 2–25 months), while median OS was 42 months (95% CI 10–84 months).

Of the 35 patients without brain metastases at the beginning of study, 2 developed brain metastases as site of initial progression on trial. None of the four patients with known brain metastases experienced intra-cranial progression during treatment.

3.3 Exploratory biomarker analysis

Results of our exploratory correlative analysis can be found in Table 3. Previous work has demonstrated prognostic significance of selected elevated or depressed angiogenic plasma biomarkers relative to median values [15]. In our study, patients with baseline measurements greater than the median for VEGFR-2, endocan, IL-8, TGF β -1, thrombospondin-1, and angiopoietin-1 were found to have significantly higher objective response rates than patients with values lower than the median. By contrast, subjects whose baseline neuropilin-1 values were below the median were found to have significantly higher response rates. Patients with less than median baseline values of angiopoietin-2 and IL-8 experienced significantly longer PFS. Longer overall survival was associated with subjects who had less than the median baseline values for PLGF and angiopoietin-2. There were statistically significant reductions of median values of VEGF, TGF β -1, angiopoietin-1, PDGF-2, and thrombospondin between cycles 1 and 3 in patients with objective responses.

4. Safety

Selected adverse events are listed in Table 4. MC plus bevacizumab was well tolerated in this study. Hematologic toxicities during induction were relatively mild with only 6 subjects (15.4%) experiencing neutropenia of grade 3 or higher. There were no observed grade 3–4 anemia or thrombocytopenia events. Fatigue was the most commonly reported non-hematologic toxicity (82.1%) followed by diarrhea (51.3%), neuropathy (48.7%), and nausea/vomiting (43.6%). There were 4 non-hematological toxicities grade 3: one for nausea/vomiting, one for fatigue. Two patients developed grade 4 gemcitabine-induced pneumonitis resulting in treatment delays. The incidence of any-grade hypertension was 67% at the end of cycle 1 and 82% at the end of induction. Hypertension was easily managing using standard anti-hypertensive medications. Rates of proteinuria were similar in both the induction and maintenance phases for all grades (35%) and for grades 3 (10.3%).

4. Discussion

This study demonstrates that the combination of metronomic chemotherapy and bevacizumab is an active first-line treatment strategy for patients with advanced non-squamous NSCLC. Compared to historical controls, patients in this study achieved longer time to progression (8.5 vs 6.2 months) and over twice as many months of survival (25.5 vs 12.3 months)[9]. The regimen was well tolerated with hypertension emerging as the most common adverse event.

The efficacy of MC, to a very limited extent, depends on direct cytotoxic activity, and a major role is played by antiangiogenic and immunomodulatory effects. Several possibilities exist for the improved progression free and overall survival results in this study. In contrast to MTD chemotherapy, the MC strategy allows for targeting of not only the tumor cells, but also the non-malignant endothelial cells crucial for metastatic spread. The critical nature of angiogenesis to the survival and spread of the NSCLC is underscored by the fact that multiple pathways exist to recruit new blood supply to the tumor. In addition to the VEGF pathways, tumor cells recruit new blood vessels via multiple salvage pathways such as PDGF, FGF, TGF- β , and angiopoietins. While bevacizumab effectively inhibits neovascularization via the VEGF pathway, tumor cells eventually exploit alternative pathways of angiogenesis and the disease advances.

MC chemotherapy can delay the progression of metastases by causing growth arrest of activated endothelial cells in tumor neo-vasculature in addition to the cytotoxic effects on the tumor cells [16]. Additionally, while MTD chemotherapy has been shown to upregulate both the expression of VEGF and other endothelial cell pro-survival growth factors and to increase mobilization of circulating endothelial precursor cells from the bone marrow, MC chemotherapy results in suppression of these pro-angiogenic drivers [17, 18]. By causing apoptosis of activated endothelial cells and preventing mobilization of endothelial precursor cells, MC leads to decrease in tumor neovascularization. The down-regulation of pro-angiogenic proteins helps delay the adaptive resistance to bevacizumab.

It is also possible that the antiangiogenic effect of paclitaxel has a significant contribution to the MC approach in our study. In the last decade, a number of studies have shown that paclitaxel has antiangiogenic activity that could be ascribed to the inhibition of either tubule formation or cell migration, and to an anti-proliferative effect toward activated endothelial cells [19, 20]. Furthermore, paclitaxel at low-protracted doses has shown to downregulate VEGF and Ang-1 expression in tumor cells and to increase the secretion of TSP-1 in the tumor microenvironment [19, 20].

Although the anticancer activity of cytotoxic drugs is based on their direct influence on cancer cells, they are also able to modulate immune system functions. MC could enhance the immunomodulatory effect with minimal immunosuppression. Among the mechanisms responsible for such effects are induction of immune-dependent apoptosis, increased antigen presentation by dendritic cells, intensification of cancer cell immunogenicity, and decreasing regulatory T-cell numbers [21, 22].

In addition, because of the relative tolerability of MC compared with MTD chemotherapy, nearly half (49%) of the patients on this study retained adequate performance status to accommodate subsequent lines of systemic therapy. The major toxicities observed were hypertension, fatigue, and diarrhea, but there were very few safety events reported as grade 3 or above.

Another possible explanation for the improved survival outcomes relative to historical controls is the widespread use of targeted therapies which began during the time of our study. Six patients in this trial had detectable EGFR mutations and were treated with erlotinib at time of progression. The median PFS and OS in the EGFR mutated patients was 10.5 months and 42 months, which positively influenced the total study population's survival. However, treatment with erlotinib alone does not explain the favorable outcomes in the ITT population as the PFS and OS in the remaining 33 patients (EGFR wild-type or unknown) was 7.5 months and 21 months (data not shown), which are both longer than expected for patients treated with MTD chemotherapy.

The selection of optimal systemic treatment for elderly patients with advanced NSCLC is a real challenge. Oral vinorelbine could be an attractive option. Recently, the efficacy and safety of metronomic oral vinorelbine has been tested in this patient population, resulting in significant clinical benefits coupled with an optimal patient compliance [22–24]. In the MOVE trial [24], non-responder patients showed low baseline VEGF serum levels with respect to responders. Interestingly, in non-responders, there was a rapid increase in VEGF levels until disease progression, while in responders, VEGF levels were unchanged.

Proof of the concept of metronomic scheduling requires the development of appropriate intermediate surrogate markers. Although angiogenesis is known to be a critical component of tumor spread in NSCLC, validated predictive biomarkers to identify patients who might benefit from anti-angiogenic therapy are not available. We hypothesized that targeting angiogenesis with both bevacizumab and MC would preferentially impact those patients with higher than average levels of pro-angiogenic biomarkers in plasma. Our results suggest that patients with elevated baseline values of pro-angiogenic factors VEGF-2, endocan, IL-8, TGF β -1, and anti-angiogenic factors thrombospondin-1 and angiopoietin-1 were more likely to have an objective response to MC as compared to patients with low levels of these biomarkers. Perhaps more importantly, positive associations in PFS and OS were seen with elevated baseline levels of pro-angiogenic factors, PLGF and angiopoietin-2. While these results require validation in subsequent studies, they may provide preliminary guidance for future studies aiming to validate angiogenic biomarkers to prognosticate treatment response.

Our study has several strengths. This represents the first time that metronomic chemotherapy, a novel strategy for delivering chemotherapy has been used in combination with bevacizumab in the first line metastatic setting in patients with non-small cell lung cancer. Also, we identified several plasma biomarkers which could potentially prognosticate responders to the MC treatment strategy. Our study was limited by relatively few patients from a single academic center and our results require validation in larger multi-center studies.

In summary, the combination of paclitaxel and gemcitabine, delivered in a metronomic schedule, in combination with bevacizumab, appears to be a tolerable and effective treatment strategy in patients with advanced NSCLC. The PFS and OS in patients treated on this study exceeded historical expectations, and there were no significant myelosuppressive, gastrointestinal, or neurologic adverse events. The results of this study can be added to the growing bank of evidence supporting the usefulness of metronomic treatment strategy, and merit further investigation.

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Highlights

- Metronomic chemotherapy appears tolerable and effective treatment strategy
- Improved PFS and OS
- Plasma biomarkers could potentially prognosticate responders to MC treatment

Figure 1.

- A: Kaplan-Meier Plot for PFS in ITT population
- B: Kaplan-Meier Plot for OS in ITT population
- C: Kaplan-Meier Plot for PFS in RE population
- D: Kaplan-Meier Plot for OS in RE population.

Table 1 Baseline Patient Demographics and Clinical Characteristics^a

Characteristic		n=39	%
Age (years)	Median	59.5	
Gender	Female	23	59.0
	Male	16	41.0
Race	Black	8	20.5
	White	31	79.5
Smoking	Light/Never	9	23.1
	Former/Active	30	76.9
ECOG Performance			
Status	0	14	35.9
	1	25	64.1
Brain Mets	NO	35	89.7
	YES	4	10.3
Liver Mets	NO	33	84.6
	YES	6	15.4
Weight Loss	NO	21	53.9
	YES	18	46.2
LDH LEVEL ^b	HIGH	5	13.9
	NORMAL	31	86.1
ALBUMIN LEVEL	<3	3	7.7
	3	36	92.3
EGFR STATUS ^c	POSITIVE	6	33.3
	WILD	12	66.7
KRAS STATUS ^d	POSITIVE	0	0.0
	WILD	12	57.1
ADENOCARCINOM			
HISTOLOGY	A	31	79.5
	NSCLC	8	20.5

SD-Standard Deviation; IQR-Interquartile Range; EGFR-Epidermal Growth Factor Receptor; KRAS- ; NSCLC-Non small cell lung cancer

^a Intent-to-treat population,^b 36 patients were assessed for LDH level,^c 18 patients were assessed for EGFR,

d_{12} patients were assessed for KRAS

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Table 2
Efficacy parameters for the Intent to Treat and the Response Evaluable population

	Intent-to-Treat			Response Evaluable		
	N=39	%	95% CI	N=35	%	95% CI
Objective Response Rate ^a	22	56.4	(39.6, 72.2)	22	62.9	(44.9, 78.5)
Disease Control Rate ^b	33	84.6	(69.5, 94.1)	33	94.3	(80.8, 99.3)
6 months PFS	23	60.5	(43.4, 75.9)	23	65.7	(47.8, 80.9)
12 Months PFS	8	21.1	(9.6, 37.3)	8	22.9	(10.4, 40.1)
24 Months PFS	4	10.5	(2.9, 24.8)	4	11.4	(3.2, 26.7)
PFS Months, Median(CI) ^c		8.5	(5, 10)		9	(6, 10)
12 Months OS	28	73.7	(56.9, 86.6)	26	74.3	(56.7, 87.5)
24 Months OS	20	52.6	(35.8, 69.0)	19	54.3	(36.7, 71.1)
OS Months, Median(CI) ^d		25.5	(15, 35)		26	(15, 35)

PFS-Progression Free Survival; OS-Overall Survival; CI-95% confidence interval

^aDefined as PR or CR;

^bDefined as PR, CR, or SD;

^cKaplan Meier estimates

Table 3

Correlative analysis of potential biomarkers of angiogenesis: Baseline Values vs Clinical Response Parameters

	Median Values	Response Rate (p values)	Progression Free Survival (p values)	Overall Survival (p values)
Proangiogenic Factors				
VEGF	> vs < 160 pg/ml	0.475	0.407	0.397
VEGFR-2	> vs < 8,454 pg/ml	0.049 ^{a,d}	0.467	0.426
Neuropilin-1 ^d	> 2+ vs <2+	0.0647 ^{b,e}	0.453	0.771
BFGF-2	> vs < 27 pg/ml	0.475	0.207	0.252
PLGF	> vs < 15 pg/ml	0.271	0.186	0.041 ^{b,e}
PDGFa	> vs < 348 pg/ml	0.475	0.608	0.485
Angiopoietin-2	> vs < 3,038 pg/ml	0.185	0.0009 ^{b,e}	0.001 ^{b,e}
Endocan	> vs < 2.14 ng/ml	0.038 ^{a,d}	0.449	0.956
SDF-1a	> vs < 1,855 pg/ml	0.407	0.117	0.99
IL-8	> vs < 6.15 pg/ml	0.049 ^{a,d}	0.045 ^{b,e}	0.338
E-Selectin	> vs < 12.9 ng/ml	0.718	0.542	0.308
ICAM-1	> vs < 261 ng/ml	0.475	0.962	0.25
TGFb-1	> vs < 8,033 pg/ml	0.049 ^{a,d}	0.467	0.809
Anti-angiogenic factors				
Thrombospondin-1	> vs < 1,485 ng/ml	0.004 ^{a,d}	0.687	0.986
Angiopoietin-1	> vs < 3,381 pg/ml	0.049 ^{a,d}	0.366	0.326

^aHigher classification has better outcome;^blower classification has better outcome^cTumor neuropilin-1 expression by IHC in 13 subjects (0–2 vs 2–3+ cytoplasmic score)^dValues greater than the median were associated with improved clinical response parameter outcomes^eValues below the median were associated with improved clinical response parameter outcomes

Table 4

Selected Adverse Events among study participants during induction and maintenance therapy

N = 39 evaluable patients

Adverse Event	All grades	Grade 3
Neutropenia ^a Induction	14 (35.9%)	6 (15.4%)
Thrombocytopenia ^a Induction	17 (43.6%)	0 (0.0%)
Anemia ^a Induction	27 (69.2%)	0 (0%)
Nausea Vomiting: Induction	17 (43.6%)	1 (2.6%)
Diarrhea: Induction	20 (51.3%)	0 (0.0%)
Fatigue: Induction	32 (82.1%)	1 (2.6%)
Neuropathy: Induction	19 (48.7%)	0 (0.0%)
Hypertension grade: end of Cycle 1	26 (66.7%)	1 (2.6%)
Hypertension grade: end of induction	32 (82.1%)	5 (12.8%)
Hypertension grade: maintenance	17 (43.6%)	4 (10.3%)
Proteinuria: Induction	14 (35.9%)	4 (10.3%)
Proteinuria: Maintenance	14 (35.9%)	4 (10.3%)

^aBased on Cycles 1–6