Phase I Trial of 2-Methoxyestradiol NanoCrystal Dispersion in Advanced Solid Malignancies

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Abstract

Purpose: 2-Methoxyestradiol (2ME2; Panzem) is an endogenous, estradiol-17β metabolite that at pharmacologic doses exerts antimitotic and antiangiogenic activities. Studies with a 2ME2 capsule formulation showed limited oral bioavailability. We report the results of a phase I study using a NanoCrystal Dispersion formulation of 2ME2 (2ME2 NCD).

Experimental Design: Patients with refractory solid tumors received 2ME2 NCD orally. Patients received drug either every 6 hours (part A) or every 8 hours (part B). Doses were escalated in successive cohorts until the maximum tolerated dose (MTD) was identified. The primary objective was identifying the MTD. Secondary objectives were to evaluate the plasma pharmacokinetics of 2ME2 and efficacy.

Results: In part A, 16 patients received a median of 4 cycles of 2ME2 NCD. Dose-limiting toxicities (DLT) included fatigue (2), hypophosphatemia (2), increased alanine aminotransferase (1), and muscle weakness (1). Trough levels at steady-state reached the minimum effective concentration in all cohorts. The MTD was determined to be 1,000 mg orally every 6 hours. In part B, 10 patients received a median of 1 cycle. DLTs included elevated γ-glutamyltransferase (1), hyponatremia (1), fatigue (1), and anorexia (1). An MTD could not be defined for part B because 4 of 10 patients had DLTs at the initial dose level and dose reduction was not pursued. Thirteen patients had stable disease (A, 11; B, 2); there were no confirmed responses.

Conclusion: For 2ME2 NCD, the MTD and recommended phase II regimen is 1,000 mg orally every 6 hours. Treatment was generally well-tolerated.

2-Methoxyestradiol (2ME2; EntreMed, Inc.) is a naturally occurring estrogen metabolite found at low levels in human plasma. Under physiologic conditions, plasma 2ME2 levels are in the picomolar range; however, during late pregnancy, these levels may increase to the tens of nanomolar (1). Initially felt to be an inactive estrogen metabolite, the last decade has revealed the potential of 2ME2 as an agent for cancer treatment. Preclinical studies in multiple cell lines show antiproliferative and antiangiogenic properties of 2ME2. The antiproliferative effects may result from the induction of apoptosis through the activation of p53 (2, 3) and/or through effects on tubulin polymerization (4, 5). The antiangiogenic properties are potentially mediated via direct antimitotic effects on endothelial cells, or via inhibition of hypoxia-inducible factor-1α, a key angiogenic transcription factor (6, 7).

Previous phase I studies with a capsule formulation showed low oral bioavailability of 2ME2. Dahut et al. (8) noted a lack of dose proportionality with increasing doses of drug. Other studies also noted a high interpatient and intrapatient variability in the pharmacokinetic (PK) variables (3, 9–11). Previous studies suggest that 2ME2 is metabolized by CYP 450 enzymes into four major metabolites, including 2ME1 (12). 2ME1 may also be formed from 2ME2 via oxidation by the enzyme β-hydroxysteroid dehydrogenase, as is the case for formation of estrone from estradiol. Low aqueous solubility and extensive “first pass” hepatic metabolism likely account for the poor bioavailability and large interpatient and intrapatient variability of 2ME2. Therefore, several approaches to increasing oral bioavailability were evaluated, including suspensions and solubilization with cyclodextrins. Preclinical studies showed that a nanoparticulate dispersion of 2ME2 lead to higher and more consistent plasma levels of 2ME2, suggesting that therapeutic levels in humans could be achieved using this drug delivery approach.

Nanocrystal dispersion (NCD) is a novel drug delivery approach for poorly water-soluble drug. It involves reduction of drug substance particle size into nanometer-sized drug particles to enhance dissolution (13). There are various approaches for production of nanoparticle drug formulations, but the one used in this study involves a technique known as NanoCrystal technology developed by Elan Drug Delivery, Inc. Poorly water-soluble drugs are milled to submicron size particles, and formulated as nanoparticle drug crystals (14). The
formulation known as 2ME2 NCD (Panzem NCD; EntreMed, Inc.) uses this technology.

Based on the preclinical efficacy of 2ME2 NCD, the University of Wisconsin conducted a phase I study in patients with advanced, treatment-resistant solid malignancies. The primary objective of this study was to define the maximum tolerated dose (MTD) and recommended phase II regimen for 2ME2 NCD. Secondary objectives were to determine the plasma pharmacokinetics of 2ME2 NCD and to assess efficacy.

Materials and Methods

Patient accrual. A phase I, single center, open-label design was used to assess the safety, PK characteristics, and efficacy of 2ME2. This study was conducted at the University of Wisconsin Paul P. Carbone Comprehensive Cancer Center after institutional review board approval. Patients ages >18 y, with biopsy-proven disease, a life expectancy of >3 mo, Karnofsky performance status of >80%, and unresectable or metastatic solid malignancy were eligible. Patients were required to have either progressed on a previous therapy or to lack effective treatment options. Inclusion criteria included at least one measurable lesion as defined by the Response Evaluation Criteria in Solid Tumors (15) or, in the case of patients with prostate cancer, an increasing serum level of prostate-specific antigen.

Exclusion criteria included hematopoietic (Hgb, <10 g/dL; platelets, <75,000/mm³), hepatic (aspartate aminotransferase or ALT of >2.5 times the upper limit of normal) or renal (Cr of >1.5 times upper limit of normal) dysfunction. Patients were also excluded for current active brain metastases, use of other anticancer agents, radiotherapy, or surgery within the previous 4 wk or baseline sensory neuropathy of more than grade 2 per the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 (NCI CTC). All patients provided written informed consent before enrollment.

Study design. This study was conducted in two parts. The study initially called for patients to receive drug every 6-h (part A). The protocol was later amended to obtain further MTD data using an 8-h dosing schedule (part B). The rationale for exploring the every 8-h dosing schedule was ease of administration and the potential for improved patient convenience. When the study drug was administered every 6 h, it was noted to interfere with patient sleep. For example, if an evening dose was taken at 10 p.m., patients had to awaken at 4 a.m. for the next dose.

For part A, cohorts A1 (initial accrual level), A2, A3, and A4 corresponded to 1,000, 2,000, 4,000, and 6,000 mg/d of 2ME2 NCD. This total daily dose was to be given in equal divisions every 6 h. Each cohort consisted of three patients. Advancement to the next dose occurred when three patients in the previous cohort completed the 28-d treatment period and 7-d observation period with no evidence of dose-limiting toxicity (DLT). If none of the three patients in a cohort experienced a DLT, three patients were enrolled in the next higher cohort. Three additional patients were added to a cohort if one of three patients experienced a DLT. If two of three patients experienced a DLT, the MTD was exceeded and additional patients would be enrolled at the next lower dose level.

For part B, cohorts B1 (initial accrual level), B2, and B3 corresponded to 3,000, 3,750, and 4,500 mg/d of 2ME2 NCD. This total daily dose was to be given in equal divisions every 8 h. The initial cohort was to consist of four patients. Dose cohorts were to be expanded to include an additional two patients in the event of DLT or to replace patients who discontinued early for reasons other than DLT.

DLT was defined as grade 3 or greater nonhematologic, or grade 4 hematologic, treatment-related toxicity, not returning to baseline within 2 wk of onset, or an event that made continued treatment unsafe in the opinion of the investigator. For practical purposes, given that 2ME2 NCD is an oral medication dosed continuously, the investigators did not emphasize the 2-wk criteria for duration of DLT. Toxicity was graded according to according to NCI CTC. Patients not completing the initial 28-d treatment period for reasons other than DLT were deemed un evaluable for toxicity and were replaced.

Treatment plan and patient follow-up. 2ME2 NCD was provided by the study sponsor, EntreMed, Inc. Drug was supplied as 50 or 100 mg/mL dispersion in 8-ounce bottles. Patients received the study drug in four (part A) or three (part B) divided daily doses continually throughout a 28-d cycle. Patients who completed the initial 35-d treatment cycle (a 28-d treatment period followed by a 7-d period of observation) without evidence of DLT or symptomatic disease progression were eligible for additional cycles. Patients were assessed on day 1, 2, 8, 15, and 28 for the first 4 wk and then on day 1 of each subsequent cycle with clinical exam, chemistries, and complete blood counts. Patients enrolled in part B also had an 8-d initial treatment period to evaluate the pharmacokinetics (PK) of 2ME2 in the fed versus fasting state. On day -7, patients received a single oral dose of 2ME2 NCD with food. On day 0, patients received a single oral dose of 2ME2 NCD after fasting overnight. Patients who discontinued study drug were followed for 30 d subsequently, or until the resolution of any toxicity.

Dose modifications. Development of a DLT that did not resolve within 14 d mandated that patients discontinue 2ME2 NCD. If the toxicity resolved in 14 d, the patient resumed therapy at the next lower dose level, or with a 50% dose reduction. Treatment otherwise continued until withdrawal of consent or progressive disease.

PK analyses. PK variables of 2ME2 and a principal metabolite 2-methoxyestrone (2ME1) were assessed during cycle 1. For part A patients, blood samples were drawn on day 1, at baseline, at 30 and 60 min, 2, 4, 6, 12, 18, 18.5, 19, 20, 22, and 24 h after the first dose of 2ME2. Blood samples were also drawn immediately before the first dose on days 15, 22, and 28. In addition, blood samples were drawn at 30 and 60 min, 2, 4, and 6 h after the initial dose on day 28. For part B patients, blood samples for PK analysis were drawn on day -7 (fed) and day 0 (fasted), at baseline, at 30 and 60 min, and 2, 4, 6, 8, 12, 18, and 24 h after the initial dose. Blood samples were also drawn immediately before the first dose on days 15, 22, and 28. In addition, on day 28, blood samples were drawn for PK analysis at 30 and 60 min, and 2, 4, 6, 8, and 12 h after the last dose of 2ME2 NCD before the observation period. On subsequent cycles for both part A and B patients, samples were drawn immediately before the first dose on day 28.

The plasma concentration-time data were analyzed by standard noncompartmental methods using Kinetica, Version 4.2 (Thermo-Fisher). Area under the concentration-time curves was calculated using linear trapezoidal method.

Tumor response. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (15) after the first cycle and then every other cycle. Patients with prostate cancer and nonmeasurable disease were followed with tumor markers (prostate-specific antigen) using prostate-specific antigen consensus criteria (16).
Statistical analyses. Data were summarized in tables listing the mean, SD, minimum, median, maximum, and number of patients for continuous data, or in tables listing count and percentage for categorical data, where appropriate. Statistical analyses were done and data appendices were created by using the SAS system, Version 9.1.3.

Results

Baseline patient characteristics
A total of 26 patients were enrolled. For part A, 3 patients were treated in cohort A1, 7 in cohort A2, 3 each in cohort A3 and A4, for a total of 16 patients. For part B, 10 patients were treated in cohort B1 (the planned cohort size was increased for reasons discussed later). No patients were enrolled in the planned cohorts B2 or B3. Table 1 summarizes their baseline characteristics.

Treatment
Part A. Thirteen patients (81%) completed at least 1 cycle and 10 (63%) received multiple cycles (range, 3-20 cycles). Duration on study ranged from 9 to 574 days. Reasons for discontinuation included disease progression (n = 11), toxicity (n = 3), and withdrawn consent (n = 2). Of note, 1 patient with renal cell carcinoma received 2ME2 NCD therapy for 20 cycles before discontinuing therapy due to disease progression.

Part B. Five patients (50%) completed at least 1 cycle, and 2 (20%) received multiple cycles (3, 5 cycles). Duration on study ranged from 1 to 145 days. Reasons for discontinuation before completing one cycle included disease progression (n = 2) and toxicity (n = 3); reasons for discontinuation after completing 1 cycle included disease progression (n = 4) and investigator discretion (n = 1). No patients were treated at the planned B2 or B3 dose cohorts (3,750 and 4,500 mg/d) because toxicity in cohort B1 was significantly higher than expected. A dose de-escalation was not done for cohort B.

Toxicity
Part A. The most frequent toxicities were fatigue (n = 10), nausea (6), hypophosphatemia (5), and cough (5). The most common treatment-related toxicities were fatigue (n = 6, grades 1-3), nausea (2, grade 1), increased ALT (2, grade 2-3), abdominal bloating (2, grade 1), hypophosphatemia (2, grade 3), and dysgeusia (2, grade 1).

None of the three patients in Cohort A1 experienced a DLT. DLTs in Cohort A2 included grade 3 hematuria (cycle 2) and grade 3 hypophosphatemia (cycles 1 and 3). Cohort A2 was therefore expanded to include three additional patients. No further DLTs were observed in Cohorts A2, or in the three patients enrolled in Cohort A3. However, all three patients enrolled in Cohort A4 experienced DLTs during cycle 1 (see Table 2). For part A, the MTD and recommended phase II dose for 2ME2 NCD was therefore considered to be 1,000 mg orally every 6 hours (4,000 mg/d).

Part B. The most frequent toxicities were fatigue (n = 7), abdominal pain (5), hyperglycemia (3), and hypophosphatemia (3). The most common treatment-related toxicities were fatigue (n = 4, grades 1-3) and nausea (n = 2, grades 1-2).

Four patients were initially enrolled in Cohort B1. One patient with liver metastases developed a grade 3 elevation in GGT levels; one patient on furosemide developed grade 3 hyponatremia, with associated grade 3 confusion. These were considered DLTs. However, controversy surrounded these attributions, given that GGT can increase because of liver metastases and furosemide can cause hyponatremia. Therefore, the investigators recommended expanding Cohort B1 to 10 patients total. Two additional patients enrolled in Cohort B1 experienced DLTs: grade 3 fatigue (n = 1) and grade 3 anorexia.

Table 1. Patient baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Part A (n = 16)</th>
<th>Part B (n = 10)</th>
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<tbody>
<tr>
<td>Sex, no</td>
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<tr>
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<td>Age, y</td>
<td>64.4 (51-81)</td>
<td>64.3 (52-72)</td>
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<td>PS, median (Karnofsky)</td>
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<td>90</td>
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<td>Number prior therapies, median (range)*</td>
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<td>6 (2-8)</td>
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<td>Dose cohort, no</td>
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<tr>
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<td>Renal (2), pancreatic (1)</td>
<td>Colorectal (5), bile duct (1), prostate (1), endometrial (1), pancreatic (2)</td>
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<tr>
<td>2</td>
<td>Esophageal (1), renal (3), ovarian (1), prostate (2)</td>
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</tr>
<tr>
<td>3</td>
<td>Renal (2), bile duct (1)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>GI stromal tumor (1), prostate (2)</td>
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</table>

Abbreviation: GI, gastrointestinal.
*Angiogenesis inhibitors and biologics were counted as a prior therapy, however, hormonal therapies for prostate or breast cancer were not.
(\(n = 1\)). Dose escalation was stopped per protocol. No patients were treated at the planned B2 or B3 cohort doses (3,750 and 4,500 mg/d). For part B, the recommended phase II dose for 2ME2 NCD dosed orally every 8 hours was therefore not determined.

Table 2 includes a summary of all grade 3 or 4 toxicities related to 2ME2 NCD, for both dosing schedules. All patients reported one or more toxicities. No deaths were observed during treatment; 1 patient died within 30 days of treatment due to disease progression.

### Pharmacokinetics variables

**Part A.** PK variables were determined for all patients who received at least one dose of study drug. After oral administration of 2ME2 NCD, quantifiable levels of 2ME2 were observed at 30 minutes postdosing in all patients. Dose-related increases in systemic exposures were observed when the dose in part A was increased from 250 to 1,000 mg, but no additional increase was observed when the dose was increased from 1,000 to 1,500 mg. Large interpatient variability in plasma concentrations of 2ME2 was observed at all four dose levels. Steady state conditions for 2ME2 seemed to be reached by day 15. The area under the concentration-time curve during a dosing interval (AUC\(_{\text{tau}}\)) on day 28 was 2 to 3.5 times greater than AUC\(_{\text{tau}}\) on day 1, indicating significant accumulation of 2ME2 with multiple doses. Based on these data, the accumulation half-life of 2ME2 was calculated to be 6 to 12 hours. This accumulation occurred because the dosing interval was shorter than the amount of time required to eliminate the drug after each dose from the body. Therefore, plasma levels increase after each dose until steady-state is reached. The accumulation seen is therefore not due to reduction in metabolism but is a desired result of the chosen divided daily dosing strategy. At steady-state, 2ME2 trough levels were above the target minimum effective concentration of 3.3 ng/mL (10 nmol/L) in all dose cohorts (17).

2ME1, a known metabolite of 2ME2, is formed by enzymatic oxidation of 2ME2. In preclinical trials, 2ME1 is roughly 1/10th as active as 2ME2 (12). Here, 2ME1 was formed rapidly from 2ME2 NCD. A maximum concentration (C\(_{\text{max}}\)) of 2ME1 occurred roughly 1.5 hours after drug administration. Dose-related increases in C\(_{\text{max}}\) and AUC\(_{\text{tau}}\) for 2ME1 were observed over the dose range of 250 to 1,500 mg on day 1. At steady-state, systemic exposures of 2ME1 were 10 to 20 times greater than 2ME2. Significant accumulation of 2ME1 was also observed after multiple doses of 2ME2 NCD.

**Part B.** The average plasma concentrations of 2ME2 in part B were higher than in part A after single dose and multiple doses of 2ME2 NCD. In contrast, the average plasma concentrations of 2ME1 were lower. The observed differences in systemic exposure of 2ME2 and 2ME1 between part A and B may due the large interpatient variability and small number of patients in part A (\(n = 3\)). Plasma levels of 2ME1 significantly exceeded levels of 2ME2. Food had minimal or no effect on the pharmacokinetics of 2ME2 and 2ME1.

### Tumor response evaluation

All enrolled patients had measurable disease; all patients receiving two or more cycles of 2ME2 NCD were evaluated for tumor response (Table 3). There were no confirmed complete or partial responses.

**Part A.** The median number of cycles was 4, range 1 to 20 cycles. The best confirmed response was stable disease for 11 (69%) patients. One patient with cholangiocarcinoma did have a 33% decrease, although this could not be confirmed on subsequent scans. One patient with renal cell cancer also had prolonged disease stabilization (20 cycles). Overall time to progression analysis using the Kaplan-Meier method was 141 days (95% confidence interval, 92-210 days).

**Part B.** The median number of cycles was 4, range 1 to 5 cycles. The best confirmed response was stable disease for 2 (20%) patients. However, 1 patient with pancreatic adenocarcinoma did have a 46% decrease, although this could not be confirmed on subsequent scans. Time to progression analysis was 48 days (95% confidence interval, 42-96 days).

### Discussion

2ME2 is an endogenous estradiol-17\(\beta\) metabolite. When dosed in animal models at pharmacologic levels, 2ME2 treatment has been associated with antimitotic and antiangiogenic effects.
activities (6, 18–20). A previous 2ME2 capsule formulation showed limited oral bioavailability in phase I studies (8). Therefore, 2ME2 was reformulated as a NCD. Preclinical data indicated that 2ME2 NCD had increased oral bioavailability. Anticancer activity in animal models was enhanced when there was reasonably constant plasma exposure to 2ME2, i.e., when the 2ME2 was delivered either by implanted osmotic pumps or when multiple daily oral doses were given (17). Furthermore, this work also identified a target minimum effective concentration of 3.3 ng/mL. Achieving continuous plasma levels over multiple dosing cycles can be problematic in patients; therefore, it was decided to explore several dosing strategies using divided daily oral continuous dosing to achieve constant exposure above the target plasma level. Two different dosing schedules were explored—every 6 hours (part A) and every 8 hours (part B). This report describes the significant discrepancies identified between these dosing schedules.

The MTD and recommended phase II dose for part A was 1,000 mg every 6 hours. The most common treatment-related toxicities were fatigue, nausea, mild transaminitis, and dysgeusia. DLTs included fatigue, hypophosphatemia, elevated ALT, and muscle weakness. Elevated liver enzymes were an anticipated toxicity on the basis of preclinical and prior clinical data. Toxicology studies in rats showed evidence of slight to mild hepatotoxicity indicated by increases in ALT, AST, GGT, total bile acids, total protein, low density lipoprotein, and globulin levels. In addition, treatment-related elevations in liver enzymes of grades 1 to 4, responsive to dose interruption and/or dose reduction, had been noted in two previous clinical studies (9, 10).

The DLTs of fatigue and muscle weakness were attributed to 2ME2 NCD. However, these symptoms were also consistent with patient age and advanced malignancies. Fatigue is not a DLT seen previously with other 2ME2 formulations (9), and a parallel phase I study of 2ME2 NCD done at Indiana University did not encounter significant fatigue (21). Investigators felt that the every 6-hour schedule might have contributed to patient fatigue, as patients typically awakened at 3 or 4 a.m. for a dose. When fatigue was encountered as a DLT in part A, we attempted to explore every 8-hour dosing schedule (part B), which was predicted to be an easier schedule for patients to follow, with less likelihood of sleep interruption. In September 2006, we amended the study to identify the MTD on this modified schedule. We deemed 1,000 mg every 8 hours a reasonable starting dose, given that the MTD for part A was 1,000 mg every 6 hours. Previous studies have used much higher total doses, albeit with capsule formulations having lower oral bioavailability (8).

Escalating the dose of 2ME2 NCD proved difficult on the every 8-hour dosing schedule. Patients enrolled in part B were not able to tolerate 1,000 mg every 8 hours, with DLTs including elevated GGT, fatigue, and anorexia. These DLTs are nonspecific, and might well have been partly or even substantially related to underlying disease rather than 2ME2 NCD. Given that we had already defined an MTD for part A, we choose not to de-escalate the doses for part B. Therefore, a recommended phase II dose for 2ME2 NCD was not determined for the every 8-hour dosing schedule used in this study.

Given the surprising discrepancy between the two dosing schedules, we retrospectively examined the performance status, number of prior therapies, tumor type, presence of liver metastases, and concomitant medications for patients on part B compared with part A. No significant trend could be found to explain why patients on part A tolerated a higher overall dose than those on part B. These findings highlight the potentially capricious findings of dose escalation using a traditional 3+3 design. Less traditional study designs, such as a time-to-event continual reassessment method (22), may avoid some of the limitations of 3+3 design. These alternative study designs are especially attractive when a drug has already been well-characterized. However, in this case, we believe that the difficulties in part B were not related to drug exposure, but rather to the patient selection and subjective nature of some toxicities, and probably could not have been ameliorated even with an alternate study design.

Using the 2ME2 NCD dosage form, we were able to achieve the targeted steady-state concentration identified from preclinical evaluations. PK analyses suggest that the MTD may not accurately reflect the toxicity of orally administered 2ME2 NCD. An increase in 2ME2 plasma levels occurred when the dose was increased from 250 to 1,000 mg. However, minimal additional increases in 2ME2 were observed when the dose was increased from 1,000 to 1,500 mg on day 1 and on day 28 in part A. The increased severity and frequency of toxicities observed in cohort A4 did not correlate to an increased systemic drug exposure of 2ME2 compared with cohort A3. Although tumor response was not a primary end point of this study, we noted stable disease in one patient with renal cell cancer, who remained on 2ME2 NCD for 20 cycles. This patient eventually progressed with central nervous system

<table>
<thead>
<tr>
<th>Table 3. Summary of best confirmed overall tumor response</th>
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<tbody>
<tr>
<td>Category of response</td>
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<tr>
<td>-----------------------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Complete response</td>
</tr>
<tr>
<td>Partial response</td>
</tr>
<tr>
<td>Stable disease</td>
</tr>
<tr>
<td>Progressive disease</td>
</tr>
<tr>
<td>Not evaluable</td>
</tr>
</tbody>
</table>

NOTE: Best overall tumor response: target, nontarget, new lesions, and prostate-specific antigen levels.
metastasis. Treatment was withheld during radiotherapy, and subsequent imaging showed progression of lung and nodal metastasis. Although the numbers are too small to allow a definitive conclusion, it is interesting that with increasing 2ME2 concentration, fewer patients discontinued treatment due to disease progression. Solid tumors for consideration in the phase II setting are renal and prostate cancer based on our findings. Further trials of 2ME2 NCD in breast and ovarian cancer are currently under way, based on previous studies of 2ME2, suggesting possible activity for these malignancies (8, 11). A trial with 2ME2 NCD is being considered in rheumatoid arthritis, another disease where proliferation and angiogenesis play a role in disease progression. Additionally, analogues of 2ME2 are in development, which have reduced metabolic liabilities.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Acknowledgments**

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**References**

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