HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2020 January 15.

Published in final edited form as:

Clin Cancer Res. 2019 January 15; 25(2): 478–486. doi:10.1158/1078-0432.CCR-18-1325.

A Phase 1/2 Study of evofosfamide, A Hypoxia-Activated Prodrug with or without Bortezomib in Subjects with Relapsed/ Refractory Multiple Myeloma

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Abstract

Introduction.—The presence of hypoxia in the diseased bone marrow presents a new therapeutic target for multiple myeloma (MM). Evofosfamide (formerly TH-302) is a 2-nitroimidazole prodrug of the DNA alkylator bromo-isophosphoramide mustard that is selectively activated under hypoxia. A phase 1/2 study investigating evofosfamide in combination with dexamethasone

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Conflicts of interest: IMG is on the advisory board of Celgene, Takeda, BMS, Janssen, and Amgen and research support from Celgene, Takeda, BMS and Janssen. PGR: Research support from Takeda and Celgene; member of advisory committees for Takeda, Celgene, Janssen, and Amgen. All others have no conflict of interest.

(EvoD) and in combination with bortezomib and dexamethasone (EvoBorD) in relapsed/refractory MM.

Experimental Design: 59 patients initiated therapy, 31 received EvoD and 28 received EvoBorD. Pts were heavily pre-treated with a median number of prior therapies of 7 (range: 2–15). All had previously received bortezomib and immunomodulators. The maximum tolerated dose (MTD), treatment toxicity, and efficacy were determined.

Results: The MTD was established at 340 mg/m^2 Evo+D with dose limiting mucositis at higher doses. For EVOBorD, no patient had a dose limiting toxicity and the recommended phase 2 dose was established at 340 mg/m^2. The most common ≥ Gr 3 adverse events were thrombocytopenia (25 patients), anemia (24 patients), neutropenia (15 patients) and leukopenia (9 patients). Skin toxicity was reported in 42 (71%). Responses included 1 VGPR, 3 PR, 2 MR, 20 SD and 4 PD for EvoD and 1 CR, 2 PR, 1 MR, 18 SD and 5 PD for EvoBorD. Disease stabilization was observed in over 80% and this was reflective of the prolonged overall survival of 11.2 months.

Conclusions: Evofosfamide can be administered at 340 mg/m^2 twice a week with or without bortezomib. Clinical activity has been noted in patients with heavily pre-treated relapsed refractory MM.

Keywords

multiple myeloma; hypoxia-activated pro-drug; hypoxic bone marrow microenvironment

Introduction

Multiple Myeloma (MM) is a plasma cell malignancy characterized by clonal evolution and resistance to therapy at end stages of the disease(1). In recent years, combinations of therapy using the cornerstone classes of agents in MM including proteasome inhibitors (e.g., bortezomib and carfilzomib) and immunomodulatory agents (e.g., lenalidomide and pomalidomide), have significantly improved response rates and survival in MM(2). Despite significant advances in the treatment of MM, including the FDA approval of several novel agents (3–5), most patients with relapsed/refractory MM succumb to their disease. In fact, the median overall survival of patients refractory to immunomodulatory agents and proteasome inhibitors is estimated to be about 9 months, with a median event-free survival of 5 months (6). Therefore, there is an urgent need to develop therapeutic agents with new mechanisms of action that can overcome drug resistance in MM.

Alkylators and DNA targeting agents remain essential in the treatment of patients with MM. However, the use of melphalan, cyclophosphamide and benadmustine is associated with significant toxicities, especially at high doses(7–9). A novel method of delivering higher doses of alkylator therapy while eliminating the associated side effects could potentially optimize the effectiveness of these agents.

Tumors are more than insular masses of proliferating cancer cells (10). Instead, they are complex tissues composed of multiple distinct cell types that participate in heterotypic interactions with one another as previously described(11). Growing evidence supports a pivotal role of the microenvironment in tumorigenesis and tumor progression (12). Cancer

niches have been shown to promote tumor proliferation, metastasis, resistance to therapy and eventually recurrence/relapse in a number of cancers, including MM (13).

Hypoxia is an imbalance between oxygen supply and consumption that deprives cells or tissues of oxygen. Decreases in oxygen levels are observed in certain types of pathological situations, such as cancer. Hypoxic regions arise in tumors because of rapid cell division and aberrant blood vessel formation(14, 15). In solid tumors, it has been shown that the hypoxic microenvironment contributes to cancer progression by activating adaptive transcriptional programs, thereby promoting tumor-cell survival, motility, and metastasis leading to a worse prognosis(16–18). Specifically, it has been shown that the BM of MM mouse models and MM patients is hypoxic compared to healthy controls(19–21). Therefore, targeting hypoxia niches should be considered as a novel approach for the treatment of MM.

Evofosfamide is an investigational 2-nitroimidazole prodrug of the DNA alkylator bromo-isophosphoramide (Br-IPM) designed to be selectively activated under hypoxic conditions. Evofosfamide exhibited activity in both *in vitro* and *in vivo* preclinical MM models (20, 22). Additionally, *in vitro* synergism was seen when evofosfamide was combined with the proteasome inhibitor bortezomib (23). Therefore, targeting the hypoxic microenvironment in combination with other novel anti-MM agents, such as bortezomib, represents a novel anti-MM treatment strategy.

We conducted a Phase 1/2 study to determine the maximum tolerated dose (MTD), dose-limiting toxic effects (DLT), safety, tolerability, and clinical activity of evofosfamide plus low-dose dexamethasone with or without bortezomib in patients with relapsed and/or refractory multiple myeloma (NCT01522872).

Patients and Methods

Patients

Patients who had relapsed/refractory multiple myeloma for which no standard therapies were anticipated to result in a durable response and for whom therapy with a bortezomib-containing regimen and an iMID-containing regimen had failed. Eligible patients were required to have measurable disease as defined by the IMWG Criteria (24, 25) with the only exception being that measurable serum paraprotein was defined as ≥ 0.5 g/dL. Other eligibility criteria included age 18 years or older, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate hepatic and renal functions. Exclusion criteria included New York Heart Association class III or IV, POEMS syndrome, symptomatic brain metastases, severe chronic obstructive pulmonary disease, active uncontrolled infection, or a washout period of less than 3 weeks for cytotoxic agents and less than 2 weeks for non-cytotoxic agents from prior treatment to time of entry on study.

The study protocol was approved by the Institutional Review Boards at all sites. All patients gave written informed consent (NCT01522872).

Study design

Patients were assigned to a treatment arm and treatment dose in the order they were enrolled onto the study. Arm A was completed before initiating Arm B. On Arm A, evofosfamide was administered IV over 30 to 60 minutes with a fixed oral 40 mg dose of dexamethasone (EvoD) on Days 1, 4, 8 and 11 of a 21-day cycle. On Arm B, evofosfamide was administered IV over 30 to 60 minutes with a fixed oral 40 mg dose of dexamethasone and a fixed IV or SC administration of bortezomib (1.3 mg/m^2) (EvoBorD) on days 1, 4, 8, and 11 of a 21-day cycle.

A standard 3+3 dose escalation design was implemented in both arms. Three patients were enrolled at the initial dose level. Doses were increased to the next level in groups of 3 patients until the MTD was established. If one patient developed a DLT at a certain dose level, up to three additional patients were treated at that dose level. If two or more patients at a given dose level experienced a DLT during the first cycle, then the MTD was considered to have been exceeded and a total of six patients were enrolled at the next lower dose level. When fewer than two of those six patients experienced a DLT at this next lower dose level, this dose was declared the MTD. Enrollment at the MTD was conducted based on Simon two-stage designs as described below.

A DLT was defined as a clinically significant adverse event (AE) or an abnormal laboratory value assessed as attributed to evofosfamide or bortezomib and unrelated to disease progression, intercurrent illness, or concomitant medications and occurring during the first cycle of therapy. Additionally, the DLT had to meet one of the following criteria: (1) Hematologic toxicity defined as thrombocytopenia with platelets < 10,000 on more than one occasion within first cycle, despite transfusion. (2) Grade 4 neutropenia that lasted for more than 5 days and/or resulted in neutropenic fever with elevated temperature (defined as ≥ 101 degrees F). (3) Grade 3 or greater non-hematologic toxicity, excluding nausea, diarrhea, or vomiting that did not receive maximal supportive care. (4) Inability to receive Day 1 dose for Cycle 2 by more than 3 weeks due to prolonged recovery from a drug-related toxicity.

Dose modifications for attributable adverse events were permitted after the first cycle; bortezomib could be reduced from 1.3 mg/m. to 1.0 mg/m. to 0.7 mg/m., and evofosfamide could be reduced from 340 or 240 mg. No dose re-escalation was allowed. Patients received supportive treatment including bisphosphonates, erythropoietin, and granulocyte colony-stimulating factor (G-CSF) and blood or platelet transfusions as clinically indicated. All patients received monthly bisphosphonates (pamidronate or zoledronic acid) as a standard of care for multiple myeloma. If thrombocytopenia resolved to grade 2 or lower, that dose was held and treatment continued with the next planned dose, and both evofosfamide and bortezomib were resumed at the same dose. If thrombocytopenia resolved to less than grade 2 and any two or more doses were held because of adverse events (either consecutive or two or more in one cycle), then the doses of evofosfamide and bortezomib were reduced by one dose level. If there were adverse events on day 1 of the cycle, then the cycle was delayed by 1 week. Prophylactic acyclovir or valaciclovir were also recommended for all patients. Adverse events were monitored throughout the study and for up to 30 days after the last dose of study drug. Adverse events were graded according to the National Cancer Institute

Common Terminology Criteria for Adverse Events (version 3.0). Neuropathy symptoms were assessed with the FACT/GOG-Neuropathy questionnaire (version 4.0).

Response criteria

Response assessments were performed day 1 of each cycle. IMWG response criteria(26), including that of minimal response, was used to assess response. Patients with stable disease or responding disease could stay on study until progression. Patients discontinued the study because of progressive disease, unacceptable toxicity (at the discretion of the patient or physician), or because of patient or physician decision.

Statistical analysis

This Phase 1/2 study was designed to evaluate the safety and efficacy of evofosfamide. Descriptive statistics were used to define patient characteristics. A Simon two-stage design was utilized at the MTD of each cohort. At the MTD for Arm A, a Simon two-stage design was implemented to pursue a regimen with ≥ 25% response rate and discontinue if response rate was ≤ 5% (90% power, 10% alpha). Following the completion of Arm A, Arm B began at one dose level below the MTD established in Arm A.

Progression-free survival (PFS), duration of response, and overall survival (OS) including rates at points in time, medians and survival curves were estimated using Kaplan-Meier methodology. PFS was measured as either the first date of progression or the date of death. PFS included all deaths that occurred within 12 weeks of the last response assessment if not preceded by documented disease progression. For OS, patients alive at last contact were censored at date of last contact. Clinical laboratory test results, dosing day vital signs, and AEs were used to assess safety/tolerability and were summarized using descriptive statistics. The severity of AEs and clinically significant laboratory test results were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Results

Patient characteristics

From March 2012 to July 2015, 59 patients were recruited at 6 centers across the U.S., 31 in arm A and 28 in arm B. The baseline characteristics of patients in both arms are summarized in Table 1A. The median age for all patients enrolled in this study was 63 years (range, 45–86). The median time since the initial diagnosis of multiple myeloma to study entry was 4.7 years (range, 1.3–30.7).

Forty four of the 59 (75%) patients had relapsed/refractory disease. The median number of prior therapies received by patients in both arms was 7 (range, 2–15), with 33 (56%) patients having received ≥ 6 prior therapies. All had previously received bortezomib and lenalidomide or thalidomide. Prior therapies included: bortezomib-based therapy in 59 (100%) patients, IMiD-based therapy in 58 (98%) patients, and prior cyclophosphamide-combined therapy in 43 (73%) patients. There were 35 (59%) patients and 36 (61%) who received ≥ 3 prior lines of therapy with bortezomib or IMiDs, respectively. Furthermore, 47

(80%) and 42 (71%) of the patients in this trial were relapsed or refractory to bortezomib and IMiDs, respectively (Table 1).

Dose limiting toxicity and Maximum Tolerated Dose

Thirty-one patients received evofosfamide in Arm A (Evo alone), at doses ranging between 240 mg/m^2 and 480 mg/m^2; 28 patients received evofosfamide in Arm B (Evo in combination with Bortezomib) at doses ranging between 240 mg/m^2 and 340 mg/m^2. Table 1B lists the dose levels in the phase 1 study. Patients in the phase 1 study received a median of 4 treatment cycles (range 1–19) and patients in the phase 2 study received a median of 4 treatment cycles (range 2–19).

In Arm A, both patients treated with 480 mg/m^2 evofosfamide had DLTs, specifically, grade 3 stomatitis. The MTD in Arm A was established at 340 mg/m^2 as a 30–60 minute daily IV infusion. Overall 2 of 24 (8%) patients treated at 340 mg/m^2 in Arm A experienced DLTs; both were grade 3 cellulitis. In Arm B, no patients experienced a DLT and the recommended dose dose was established at 340 mg/m^2.

Treatment related adverse events

Table 2 shows the treatment-related adverse events. The most common hematological toxicities were cytopenias, specifically anemia and thrombocytopenia, while less neutropenia was observed. Grade 3 or 4 thrombocytopenia occurred in 11 (35%) patients in Arm A and 14 (50%) in Arm B; grade 3 or 4 anemia occurred in 13 (42%) in Arm A and 11 (39%) in Arm B. The most common non-hematological toxicities were skin and gastrointestinal toxicities. The skin toxicity was the well described skin toxicity of evofosfamide including a skin-burn like erythema. This occurred in 14 (45%) in Arm A and 16 (57%) in Arm B but there was only 1 case of Grade 3 or 4 toxicity related to the skin toxicity with a skin ulcer requiring admission to the hospital in Arm B. In Arm B, colitis and sepsis led to death in 2 patients. Sensory peripheral neuropathy was reported in one patient in Arm A and nine patients in Arm B (two of which were grade 2). No grade 3 or 4 sensory peripheral neuropathy was recorded.

In Arm A, planned dose delays occurred in 21 patients and unplanned dose delays occurred in eight patients. In Arm B, planned dose delays occurred in 18 patients and unplanned dose delays occurred in eight patients. Planned dose delays occurred primarily because of holidays and family reasons.

In Arm A, 31 patients discontinued treatment for the following reasons: progressive disease (19 patients), adverse events deemed unacceptable by the physician (4 patients), withdrawal of consent because of adverse events (4 patients), withdrawal of consent for reasons other than adverse events (1 patient), clinically significant deterioration (2 patients), and the need for other anti-tumor therapy (1 patient). In Arm B, 28 patients discontinued therapy for the following reasons: progressive disease (20 patients), unacceptable adverse event (3 patients), withdrawal of consent (1 patient), clinically significant deterioration (3 patients), and the need for other anti-tumor therapy (1 patient).

Efficacy

Table 3 and Figure 1 lists the treatment responses in Arms A and B. In Arm A, the reported partial or better response rate was 12.9% (95% CI 3.6–29.8%), including one patient that achieved a very good partial response (VGPR). The minimal-or-better response rate in Arm A was 19.4% (95% CI 7.5–37.5%). The disease control rate, stable disease (SD) or better, was 83.9% (95% CI 66.3–94.6%). In Arm B, the recorded PR or better response rate was 10.7% (95% CI 2.3–28.2%) and included one patient that achieved a complete response (CR). The minimal-or-better response rate in Arm B was 14.3% (95% CI 4.0–32.7%). The disease control rate (SD or better) was 78.6% (95% CI 59.1–91.7%).

The median time to minimal-or-better response for responding patients was 3.4 months (range 0.3–19.9) in Arm A, and was 2.0 months (range 0.8–14.2) in Arm B. Median time to PR or better response for all patients in Arm A was 3.7 months (range 0.3–19.9), and was 2.1 months (0.8–14.2) in patients in Arm B. The median duration of minimal-or-better response for the patients on Arm A was 7.2 months (range 1.0–11.6), and 7.0 months (range 1.7–12.6) for the patients on Arm B. The median duration of PR or better response for the patients on Arm A was 7.8 months (range 2.2–10.9) and 5.0 months (range 1.7–12.6) on Arm B.

Survival analysis

With a median follow-up of 9.9 months (range 0.3–19.9), 43 patients progressed (29 of whom subsequently died). An additional 10 patients died, but they did not have progressive disease. Of the 31 Arm A patients, 20 patients progressed (12 of whom subsequently died). Seven additional patients died without having shown progressive disease. Of the 28 patients in Arm B, 23 patients progressed (17 of whom subsequently died). An additional three patients died without having shown progressive disease. The total number of failures for the time-to-progression analysis was 43 for all patients, 20 for Arm A and 23 for Arm B. The total number of failures for the PFS analysis was 53 for all patients, 27 for Arm A and 26 for Arm B. At the time of our analysis, 39 patients had died (19 in Arm A and 20 in Arm B). 36 patients died due to disease, one patient died of colitis, one patient died from septic shock and one patient unknown. The median time to progression for all patients was 3.6 months (95% CI 2.2–5.8), median PFS was 3.4 months (95% CI 2.2–5.2) Figure 2, 19 of whom had a response beyond 6 months and median OS was 11.2 months (95% CI 8.3–15.3, Figure 3).

Cases of outstanding responses despite significant disease burden and aggressive disease

Although patients recruited on this study were heavily pretreated and refractory to multiple prior lines of therapy, and although agents such as daratumumab and ixazomib were not available at that time, there were some specific cases that attained a high response rate or achieved long remissions for over 6 months. For example, subject 217–026 was a 64-year-old male with IgG lambda multiple myeloma diagnosed in 2007. The subject had previously received 3 prior lines of therapy achieving various responses. He received 19 cycles of treatment and achieved a complete response. The time to CR was 5.5 months. The patients PFS was 13.4 months after participating in the trial. Subject 217–006 was a 78-year-old woman diagnosed with IgG Kappa multiple myeloma in 2006. The patient had previously

been treated with seven prior lines of therapy, with varying levels of response. She received 19 cycles of therapy and achieved a partial response. The patients PFS was 12.3 months after participating in the trial. Subject 217–031 was a 67-year-old female with IgG Kappa multiple myeloma diagnosed in 2002. The subject had previously received 15 prior lines of therapy achieving varying levels of response. While on trial, she received 14 cycles of therapy achieving a minimal response. The patients PFS was 9.2 months.

Discussion

This study was designed to evaluate the safety and efficacy of the combination of the hypoxia prodrug evofosfamide alone, or in combination with bortezomib, in myeloma patients with relapsed/refractory diseases. The rationale for this study is based on previous in vitro and in vivo studies, in which Evofosfamide showed significant activity in preclinical models indicating that targeting hypoxia in a myeloma bone marrow microenvironment may be an effective mechanism of action(19, 20). This trial demonstrates that the combination of evofosfamide and bortezomib was well tolerated in the majority of these heavily pre-treated patients and showed a modest degree efficacy in this patient population.

Evofosfamide is activated in the setting of hypoxia, whereby its 2-nitroimidazole component is reduced by intracellular reductases, releasing the alkylator DNA cross-linker bromo-isophosphoramide mustard (Br-IPM) (27). What is more, although it is originally released in hypoxic tissue, it is not confined to it; rather, through diffusion, Br-IPM acts as a cytotoxic agent in adjacent normoxic regions of the tumor, too (28).

In terms of efficacy, evofosfamide has shown preclinical and clinical activity in a variety of solid tumors, including pancreatic cancer (29–31). In a phase I/II clinical trial (NCT00743379) investigating the combination of evofosfamide/gemcitabine vs. gemcitabine alone in 214 patients with advanced pancreatic cancer, an overall response rate of up to 26% (depending on evofosfamide dose) and a superior median PFS time of 5.6 months (hazard ratio 0.61, p-value = 0.005) were achieved in the experimental arm(31).

In terms of toxicity, in an early-phase study of evofosfamide in patients with solid tumors, the most commonly reported adverse events (AEs) related to evofosfamide were skin/mucosal toxicity, and myelosuppression (32). However, these AEs were not associated with treatment discontinuation in the phase I/II trial mentioned above (30).

Evofosfamide is a prototype of a new class of compounds, the hypoxia-activated prodrugs, aimed at circumventing the side effects of typical chemotherapy. Although inactive under normal levels of oxygen, upon exposure to the hypoxic tumor environment, these agents release a diffusible alkylator, able to not only kill the hypoxic tumor cells, but also induce a so-called bystander effect, thereby killing neighboring cells with intermediate levels of hypoxia(33). Other agents, like Melflufen, have been developed with the same aim of overcoming the traditional cytotoxic agent side effects. However, Melflufen’s safety and efficacy profile, with 71% of patients exhibiting grade 3–4 hematological toxicities and a response rate of 4% (1/27) in a study (34), is significantly inferior to that of evofosfamide.

The bone-marrow niche includes areas of hypoxia, which can influence the behavior of both microenvironmental components and neoplastic cells via the hypoxia inducible factor 1 (HIF-1)–von Hippel–Lindau disease tumor suppressor (VHL) signaling pathway(33). Hypoxia promotes quiescence, and is accompanied by changes in oxidative metabolism that can result in oncogenic changes in epigenetic patterns, especially in the citric acid cycle. In addition, neoangiogenesis is a well-established hallmark of the bone-marrow microenvironment of MM (35, 36). The fact that the bone-marrow microenvironment is hypoxic relative to other tissues, resulting in expression of HIF-1 and VEGF, contributes to the increased neoangiogenesis in patients with MM (37). Hypoxia also drives epithelial-to-mesenchymal transition of MM cells, thereby promoting tumour dissemination (19). This mechanism is principally dependent on decreased expression of E-cadherin, limiting the adhesion of the malignant plasma cells to the bone-marrow stroma and consequently increasing egress of MM cells into the circulation (19). In addition, hypoxia leads to overexpression of C-X-C-motif chemokine receptor 4 (CXCR4) on the plasma cells, promoting the dissemination and homing of circulating MM cells to novel bone-marrow sites (19).

The MTD of evofosfamide was established at 340 mg/m^2 in combination with dexamethasone. The main toxicities were anemia and thrombocytopenia but interestingly not neutropenia. This is in contrast with many other alkylating agents that would cause significant cytopenias. This indicates that indeed activation of the prodrug in a bone marrow packed with myeloma cells and with a hypoxic microenvironment can have a differential effect on its effect on hematopoietic stem cells. The most common non-hematological toxicities were skin and gastrointestinal toxicities which are well-defined and known to be associated with evofosfamide. Prior studies in advanced pancreatic cancer have shown that most common non-hematologic AEs in treated patients were pain in extremities (25%), skin rash (21%), diarrhea (21%), fatigue (17%), constipation (17%), and stomatitis (17%) (38).

There was a trend for patients in Arm B (EvoBorD) to have a shorter PFS and OS compared to those in Arm A (EvoD), though it was not statistically significant. This was likely due to differences in patient characteristics including the enrollment of more patients with high risk cytogenetics and a higher number of prior lines of therapy in Arm B compared to Arm A

The longer remissions and PFS that were observed in a subgroup of patients highlight the concept of amazing responders to specific therapeutic agents even if those agents were not highly active in the majority of the patients enrolled on the clinical trial. Such amazing responders have been described in prior studies where large numbers of patients had no response, but single patients with specific mutations demonstrated exceptional responses (39). We attempted to perform correlative studies including next generation sequencing to further elaborate on the mechanisms for these responders but could not identify enough samples for these studies. One potential hypothesis could be that these patients had a higher hypoxia level in the bone marrow and therefore had a higher active drug concentration in the area of cancer cells. Another possibility is that these cells had mutations in the DNA repair genes and therefore were more susceptible to alkylating agents (38). We will attempt to prove this hypothesis in future studies with larger numbers of samples.

Although many agents have been approved for MM, there is an urgent need to develop ones that overcome resistance to proteasome inhibitors and immunomodulators, since most patients still succumb to the disease in the relapsed/refractory setting. At the time of this study accrual, daratumumab, elotuzumab and ixazomib were not approved and therefore not available for use in most of these patients unless through clinical trial participation. Most importantly, the patients in this study were heavily pretreated and may not have been eligible to many other clinical trials. Indeed, the median number of prior therapies received by patients in both arms was 7 (range, 2–15), with 33 (56%) patients having received ≥ 6 prior therapies. All had previously received bortezomib and lenalidomide or thalidomide. However, disease stabilization was observed in the majority of these patients (over 80%) indicating that in the setting of significantly advanced disease, stable disease might be of significant value. Indeed, this was reflective of the prolonged overall survival of 11.2 months observed in this end-stage myeloma population. In some cases, there was a significant response to therapy with prolonged time on therapy with over 1 year of response duration, indicating that this agent can have prolonged responses in a subset of a patient population. Unfortunately, bone marrow hypoxia levels were not systematically assessed on the study to determine whether the level of hypoxia correlated with response in these patients. There are few options in clinical trials for such advanced relapsed/refractory myeloma patients including BCMA-targeted CAR T-cell therapy and Selinexor (KPT-330), a small molecule inhibitor of XPO1. However, many of the patients enrolled on this study may not have been eligible for such trials and indeed, there is an urgent need to develop more agents with new mechanisms of action that can overcome drug resistance in MM.

In summary, this study demonstrates that evofosfamide alone or in combination with bortezomib is well tolerated and achieves stable disease and prolonged survival in a heavily pre-treated end- stage relapsed/refractory myeloma population. The specific role of this agent or other hypoxia-activated agents remains to be determined in patients who are less refractory to therapy. The concept of targeting a niche-dependent factor such as hypoxia of the bone marrow is novel and warrants further studies in the future.

Acknowledgments

Funding source: Threshold Pharmaceuticals funded the study in partnership with Merck KGaA, Darmstadt, Germany. This was partially supported by R01 CA181683-01A1 and the Leukemia and Lymphoma Society.

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Translational Relevance:

Evofosfamide is an investigational 2-itroimidazole prodrug of the DNA alkylator bromo-isophosphoramide (Br-IPM) designed to be selectively activated under hypoxic conditions. Evofosfamide exhibited activity in both in vitro and in vivo preclinical multiple myeloma (MM) models. Additionally, in vitro synergism was seen when evofosfamide was combined with the proteasome inhibitor bortezomib. Therefore, targeting the hypoxic microenvironment in combination with anti-MM agents, such as bortezomib, represents a novel anti-MM treatment strategy. We conducted a Phase 1/2 study to determine the maximum tolerated dose (MTD), dose-limiting toxic effects (DLT), safety, tolerability, and clinical activity of evofosfamide plus low-dose dexamethasone with or without bortezomib in patients with relapsed and/or refractory multiple myeloma. Clinical activity has been noted in these heavily treated patients.

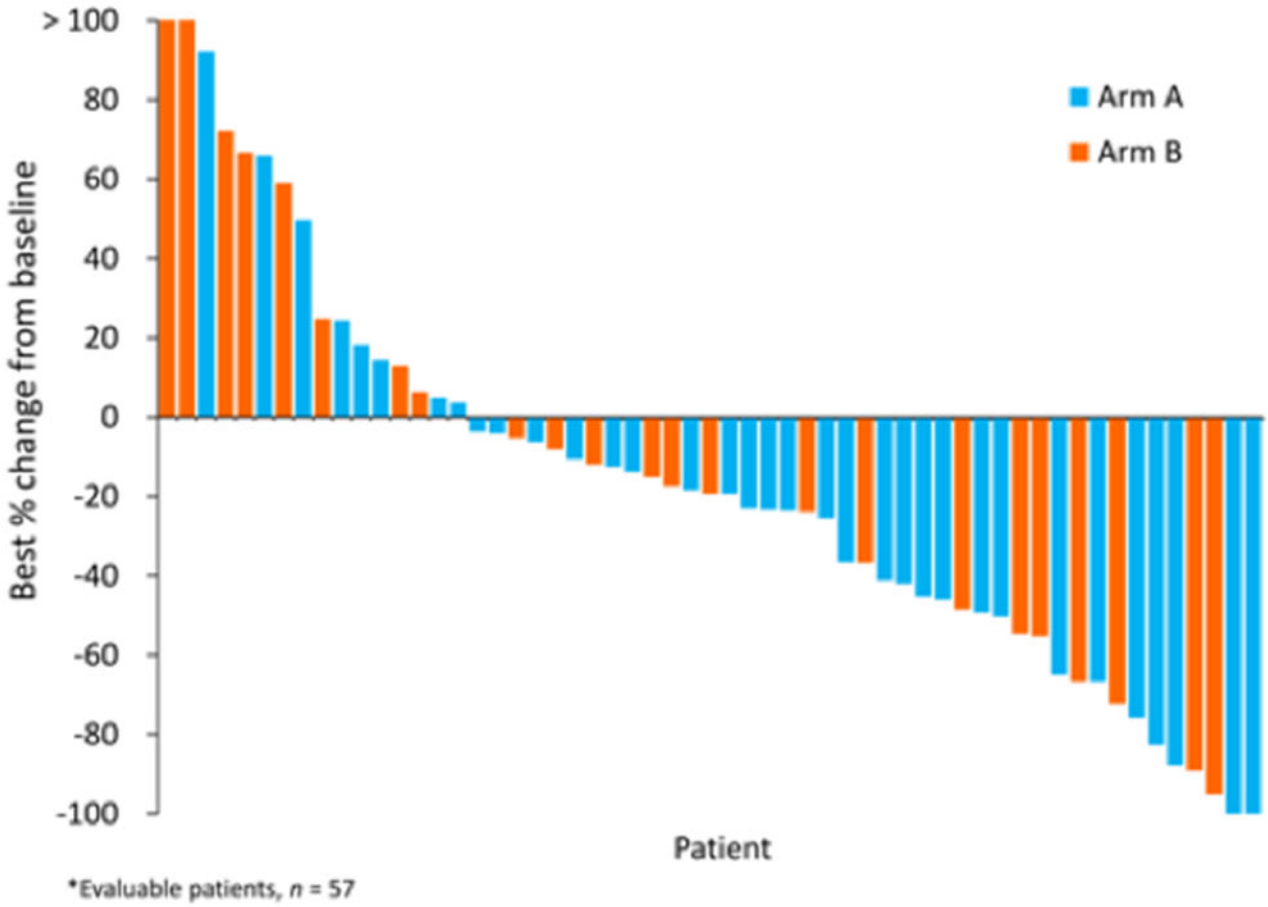

Figure 1. The maximum difference in M-protein from baseline.

The maximum change from baseline in the level of M-protein after treatment

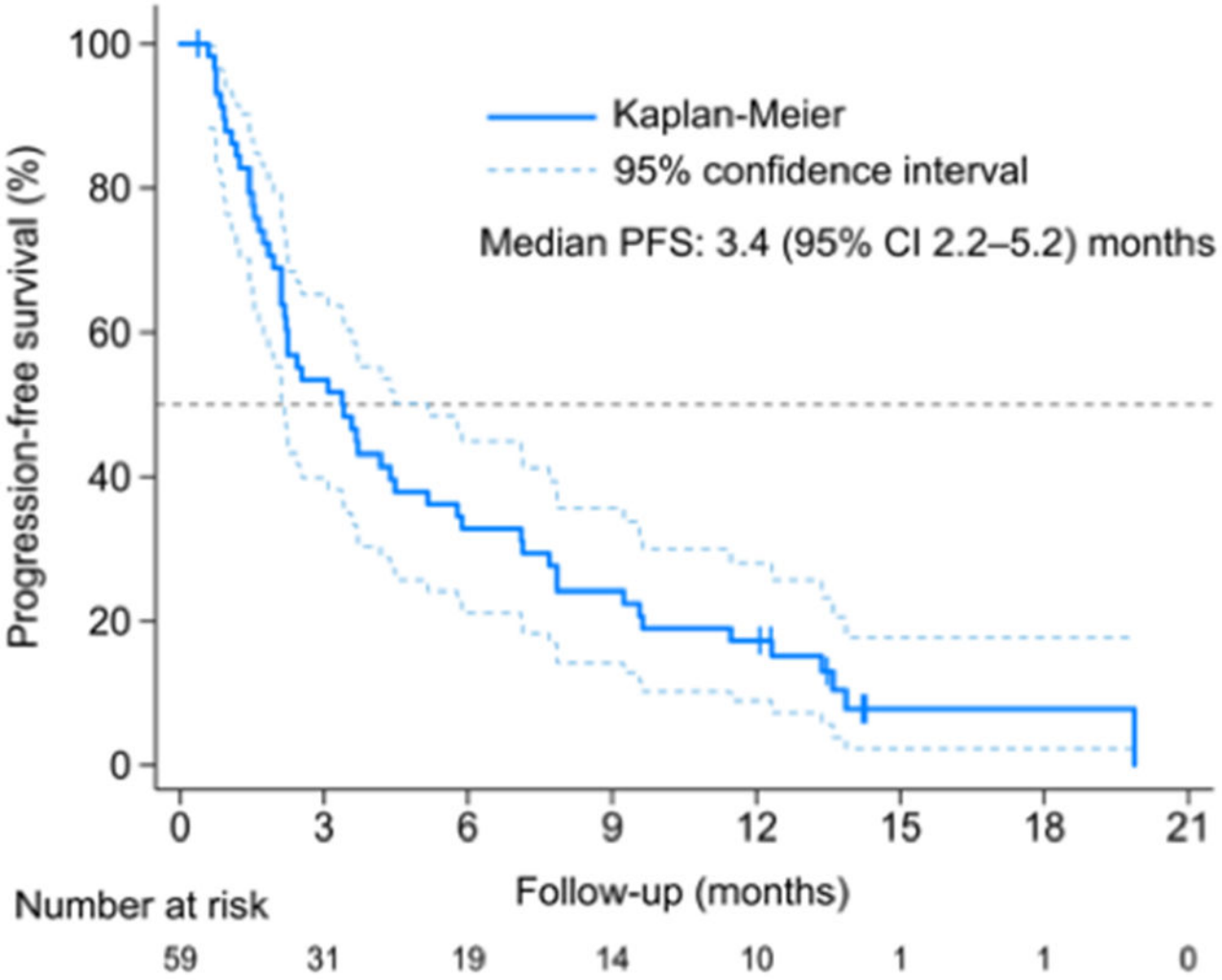

Figure 2. Progression-free survival among patients treated with Evofosfamide +/−bortezomib.

The Kaplan–Meier curve exhibits progression-free survival (PFS) among patients treated with Evofosfamide +/−bortezomib. The median progression-free survival was 3.4 months (95% CI 2.2–5.2).

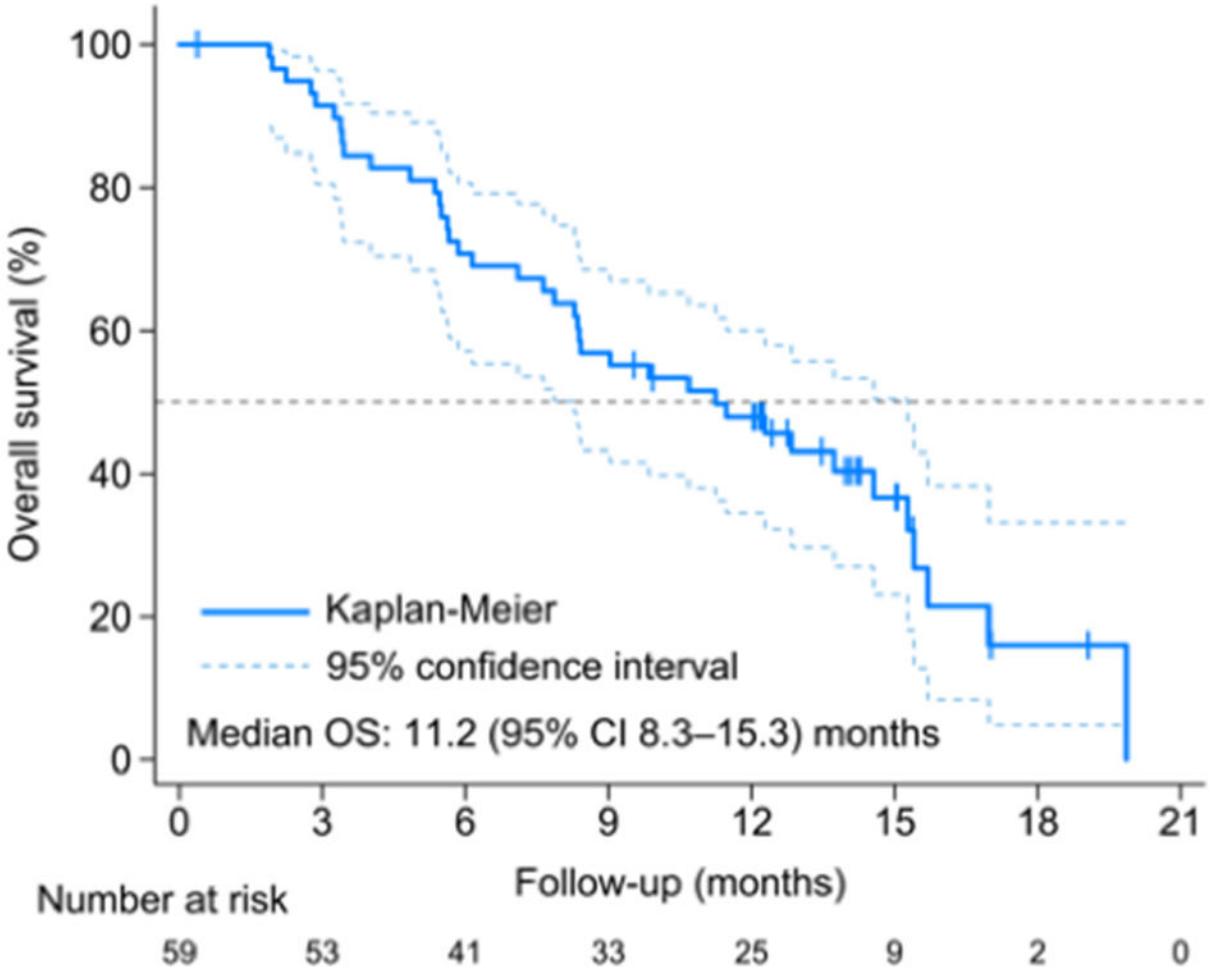

Figure 3. Overall survival among patients treated with Evofosfamide +/−bortezomib.

The Kaplan–Meier curve exhibits overall survival (OS) among patients treated with Evofosfamide +/−bortezomib. The median was 11.2 months (95% CI 8.3–15.3)

Table 1A.

Baseline patient, disease and treatment characteristics

	Evofosfamide + Dex (*n* = 31)	Evofosfamide + Bortezomib + Dex (*n* = 28)	Total (*n* = 59)
Median age (range), years	65 (53–86)	62 (45–83)	63 (45–86)
Male	23 (74.2)	16 (57.1)	39 (66.1)
International staging system (ISS)			
I	14 (45.2)	9 (32.1)	23 (39.0)
II	4 (12.9)	9 (32.1)	13 (22.0)
III	8 (25.8)	5 (17.9)	13 (22.0)
Unknown	5 (16.1)	5 (17.9)	10 (17.0)
ECOG performance status			
0	12 (38.7)	6 (21.4)	18 (30.5)
1	16 (51.6)	17 (60.7)	33 (55.9)
2	3 (9.7)	5 (17.9)	8 (13.6)
Cytogenetic profile - no. (%)			
Standard risk cytogenetics	24 (77.4)	16 (57.1)	40 (67.8)
High risk cytogenetics[a]	7 (22.6)	12 (42.9)	19 (32.2)
Median time since initial diagnosis of MM	54.7 (15.2–152.1)	66.3 (15.2–367.8)	56.8 (15.2–367.8)
Prior Therapy			
Prior Stem Cell Transplant	18 (58.1)	19 (67.9)	37 (62.7)
Median no. of prior therapies (range)	5 (2–12)	8 (3–15)	7 (2–15)
≥ 6 prior therapies	15 (48.4)	18 (64.3)	33 (55.9)
Prior use of bortezomib	31 (100.0)	28 (100.0)	59 (100.0)
Relapsed to bortezomib	16 (51.6)	20 (71.4)	36 (61.0)
Refractory to bortezomib	10 (32.3)	8 (28.6)	18 (30.5)
Relapsed or refractory to bortezomib	23 (74.2)	24 (85.7)	47 (79.7)
Median no. of prior bortezomib therapies (range)	3.0 (1.0–8.0)	3.0 (1.0–8.0)	3.5 (1.0–7.0)
≥ 3 prior therapies bortezomib therapies	16 (51.6)	19 (67.9)	35 (59.3)
Prior therapy with an IMiD	31 (100.0)	27 (96.4)	58 (98.3)
Relapsed to IMiD	14 (45.2)	15 (53.6)	29 (49.2)
Refractory to IMiD	10 (32.3)	18 (64.3)	28 (47.5)
Relapsed or refractory to IMiD	18 (58.1)	24 (85.7)	42 (71.2)
Median no. of prior proteasome and IMiDs therapies (range)	4.0 (1.0–8.0)	3.0 (1.0–8.0)	4.5 (1.0–8.0)
Prior radiotherapy	16 (51.6)	17 (60.7)	33 (55.9)

[a]High risk cytogenetics including Del 17p, t (4:14) and t (14:16) and 1q+

Table 1B.

Study drug exposure

Evofosfamide Dose	Arm A Evofosfamide + Dex (*n* = 31)	Arm B Evofosfamide + Bortezomib + Dex (*n* = 28)	Total (*n* = 59)
240 mg/m^2	5 (16)	4 (14)	9 (15)
340 mg/m^2	24 (77)	24 (86)	48 (81)
480 mg/m^2	2 (7)	0 (0)	2 (3)

Table 2.

Most frequent adverse events (≥ 15%)

Adverse events	Evofosfamide + Dex (*n* = 31)		Evofosfamide + Bortezomib + Dex (*n* = 28)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hematological toxicities				
Anemia	17 (54.8)	13 (41.9)	13 (46.4)	11 (39.3)
Thrombocytopenia	16 (51.6)	11 (35.5)	14 (50.0)	14 (50.0)
Neutropenia	16 (51.6)	8 (25.8)	8 (28.6)	7 (25.0)
Leukopenia	13 (41.9)	6 (19.4)	3 (10.7)	3 (10.7)
Gastrointestinal toxicities				
Nausea	8 (25.8)	0 (0.0)	10 (35.7)	0 (0.0)
Vomiting	5 (16.1)	0 (0.0)	8 (28.6)	0 (0.0)
Constipation	4 (12.9)	0 (0.0)	6 (21.4)	0 (0.0)
Diarrhea	5 (16.1)	1 (3.2)	4 (14.3)	0 (0.0)
Stomatitis	6 (19.4)	2 (6.5)	1 (3.6)	0 (0.0)
Skin and subcutaneous tissue disorders				
Skin erythema/rash	14 (45.2)	0 (0.0)	16 (57.1)	1 (3.6)
General disorders and administration site conditions				
Fatigue	14 (45.2)	2 (6.5)	13 (46.4)	1 (3.6)
Edema	4 (12.9)	0 (0.0)	6 (21.4)	0 (0.0)
Infusion site reactions	6 (19.4)	1 (3.2)	1 (3.6)	0 (0.0)
Pyrexia	5 (16.1)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders				
Hyperglycemia	11 (35.5)	1 (3.2)	1 (3.6)	0 (0.0)
Decreased appetite	6 (19.4)	0 (0.0)	2 (7.1)	0 (0.0)
Hypomagnesaemia	5 (16.1)	0 (0.0)	1 (3.6)	0 (0.0)
Nervous system disorders				
Peripheral neuropathy	1 (3.2)	0 (0.0)	9 (32.1)	0 (0.0)
Headache	5 (16.1)	1 (3.2)	4 (14.3)	1 (3.6)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	5 (16.1)	0 (0.0)	1 (3.6)	0 (0.0)

Table 3.

Efficacy summary

	Evofosfamide + Dex (*n* = 31)	Evofosfamide + Bortezomib + Dex (*n* = 28)
IMWG Response		
Complete response	0 (0.0)	1 (3.6)
Very good partial response	1 (3.2)	0 (0.0)
Partial response	3 (9.7)	2 (7.1)
Stable disease	20 (64.5)	18 (64.3)
Progressive disease	4 (12.9)	5 (17.9)
Unassessable	1 (3.2)	1 (3.6)
Partial or better response	4 (12.9)	3 (10.7)
Minimal or better response	6 (19.4)	4 (14.3)
Progression-free survival (PFS)		
Median PFS (95% CI) months	4.4 (2.2–7.9)	2.2 (1.6–3.6)
6-month PFS (95% CI) %	40.0 (22.8–56.7)	25.0 (11.1–41.8)
Overall survival (OS)		
Median OS (95% CI) months	12.8 (8.3–17.0)	9.0 (5.5–13.7)
12-month OS (95% CI) %	53.3 (34.3–69.1)	42.0 (23.5–59.4)