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Targeting DNA repair with combination veliparib (ABT-888) and temozolomide in patients with metastatic castration-resistant prostate cancer

Maha Hussain,
Comprehensive Cancer Center, University of Michigan, Ann Arbor, MI, USA

Division of Hematology/Oncology, University of Michigan, 1500 E Medical Center Dr., 7314 Cancer Center, Ann Arbor, MI 48109-0946, USA

Michael A. Carducci,
Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins, Baltimore, MD, USA

Susan Slovin,
Genitourinary Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Jeremy Cetnar,
Department of Medicine, Carbone Cancer Center, University of Wisconsin, Madison, WI, USA

Jiang Qian,
AbbVie Inc, North Chicago, IL, USA

Evelyn M. McKeegan,
AbbVie Inc, North Chicago, IL, USA

Marion Refici-Buhr,
AbbVie Inc, North Chicago, IL, USA

Brenda Chyla,
AbbVie Inc, North Chicago, IL, USA

Stacie P. Shepherd,
AbbVie Inc, North Chicago, IL, USA

Vincent L. Giranda, and
AbbVie Inc, North Chicago, IL, USA

Joshi J. Alumkal
Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA

Maha Hussain: mahahuss@med.umich.edu

Correspondence to: Maha Hussain, mahahuss@med.umich.edu.

Present Address: J. Cetnar, Oregon Health & Science University, Knight Cancer Institute, Portland, OR, USA

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Conflict of interest Jiang Qian, Evelyn McKeegan, Marion Refici-Buhr, Brenda Chyla. Stacie Shepherd and Vincent Giranda are employees and stock owners of AbbVie. Maha Hussain, Michael Carducci, Susan Slovin, Jeremy Cetnar, and Joshi Alumkal have no conflicts to disclose.

Summary

Androgen receptor-mediated transcription is directly coupled with the induction of DNA damage, and castration-resistant tumor cells exhibit increased activity of poly (ADP-ribose) polymerase (PARP)-1, a DNA repair enzyme. This study assessed the efficacy and safety of low dose oral PARP inhibitor veliparib (ABT-888) and temozolomide (TMZ) in docetaxel-pretreated patients with metastatic castration-resistant prostate cancer (mCRPC) in a single-arm, open-label, pilot study. Patients with mCRPC progressing on at least one docetaxel-based therapy and prostate specific antigen (PSA) ≥2 ng/mL were treated with veliparib 40 mg twice daily on days 1–7 and TMZ once daily (150 mg/m^2/day cycle 1; if well tolerated then 200 mg/m^2/day cycle 2 onwards) on days 1–5 q28 days. Patients received 2 (median) treatment cycles (range, 1–9). The primary end-point was confirmed PSA response rate (decline≥30 %). Twenty-six eligible patients were enrolled, 25 evaluable for PSA response. Median baseline PSA was 170 ng/mL. Two patients had a confirmed PSA response (8.0 %; 95 % CI: 1.0– 26.0), 13 stable PSA, and 10 PSA progression. The median progression-free survival was 9 weeks (95 % CI: 7.9–17) and median overall survival 39.6 weeks (95 % CI: 26.6–not estimable). The most frequent treatment-emergent adverse events (AEs) were thrombocytopenia (77 %), anemia (69 %), fatigue (50 %), neutropenia (42 %), nausea (38 %), and constipation (23 %). Grade 3/4 AEs occurring in >10 % of patients were thrombocytopenia (23 %) and anemia (15 %). Veliparib and TMZ combination was well tolerated but with modest activity. Biomarker analysis supported the proof of concept that this combination has some antitumor activity in mCRPC.

Keywords

Pilotstudy; Metastatic castration-resistant prostate cancer; Veliparib; Temozolomide; Combination therapy

Introduction

The anticancer effect of many cancer therapeutics is mediated through DNA damage, leading to cell cycle arrest and apoptosis. Agents that inhibit DNA repair proteins are of significant clinical interest, primarily to potentiate the effects of cytotoxic therapies and other DNA damaging agents as well as monotherapy in tumors with defects in DNA repair. Of the poly (ADP-ribose) polymerase (PARP) family of proteins, PARP-1 and −2 play a role in DNA repair of single-strand DNA breaks via the base-excision repair mechanism [1–3]. PARP activity appears to be increased in some tumors [4, 5] and therefore represent a potential therapeutic target. Continuous inhibition of PARP-1 results in conversion of single-strand to double-strand breaks during DNA replication, thus stalling the process of replication [3]. PARP knockout mice are hypersensitive to alkylating agents and ionizing radiation [6–8]. Furthermore, clinical evidence indicates that PARP inhibitors have antitumor activity as monotherapy in DNA repair-deficient tumors due to mutations in *BRCA1* and *BRCA2* [9–12], and there is evidence of increased antitumor effect when added to cytotoxic chemotherapy [13, 14]. PARP-1 has been implicated at the chromatin level in androgen receptor-mediated cell proliferation in early- and late-stage prostate cancer models [15], with suppression of PARP-1 resulting in reduced cell proliferation.

Veliparib (ABT-888) is an orally bioavailable, well-tolerated, potent PARP inhibitor with a favorable pharmacokinetic profile [14, 16–18]. In *in vitro* and *in vivo* models, veliparib increased the sensitivity of prostate cancer cells to radiation therapy and chemotherapy, including the oral alkylating agent, temozolomide (TMZ) [19–23]. Veliparib also reversed resistance to TMZ in a mouse model of prostate cancer and resulted in improved survival [21]. The maximum tolerated oral dose of veliparib and TMZ 150–200 mg/m^2/day in a phase 1 dose-escalation study in patients with solid tumors (NCT00526617) was 40 mg BID. Human pharmacokinetics indicated that an oral dose of 40 mg BID would achieve exposures consistent with the preclinically maximally efficacious dose [24]. Based on these data, it was hypothesized that combination veliparib and TMZ will have antitumor activity in patients with metastatic castration-resistant prostate cancer (mCRPC).

Patients and methods

Study design

This multicenter, open-label, single-arm, pilot study was carried out between April 21, 2010 and July 6, 2011 at 5 sites in the US according to the regulations and guidelines of the International Conference on Harmonization for Good Clinical Practice and the US Food and Drug Administration, the ethical principles of the Declaration of Helsinki, and all applicable local regulations (ClinicalTrials.gov trial registration ID: NCT01085422). The protocol and all study-related information for participants were reviewed by an independent ethics committee or review board at each site.

Patient eligibility

Eligible patients had mCRPC with measurable and/or bony disease that had progressed despite androgen deprivation therapy and at least 1, but no more than 2, prior systemic non-hormonal therapies (at least 1 including docetaxel). Additional inclusion criteria were prostate specific antigen (PSA) progression (defined as a rising trend in PSA that was confirmed by another assessment at a minimum interval of 1 week), a minimum PSA of 2 ng/mL, and testosterone <50 ng/dL. Patients were required to continue androgen deprivation therapy with a luteinizing hormone-releasing hormone analog if they had not undergone orchiectomy. Subjects were also required to have adequate bone marrow, renal and hepatic function, evaluated within 2 weeks prior to treatment initiation: absolute neutrophil count (ANC) ≥1,500/μL, platelets ≥ 100,000/μL, hemoglobin ≥9.0 g/dL; serum creatinine ≤1.5× upper limit of normal (ULN) or creatinine clearance ≥50 mL/min/1.73 m^2; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5×ULN. For subjects with liver metastases, the required values were AST and ALT <5×ULN and bilirubin ≤1.5×ULN. All patients underwent baseline disease evaluation with a chest X-ray or chest computed tomography (CT), a CT scan of the abdomen and pelvis, and a bone scan.

Exclusion criteria included: cord compression or a history of uncontrolled central nervous system metastases or leptomeningeal disease; prior therapy with dacarbazine, or TMZ, or a PARP inhibitor; prior therapy with an investigational agent or any anticancer therapy within 28 days prior to study drug administration (subjects receiving bisphosphonate therapy were eligible); another active malignancy within the past year with the exception of definitely

treated carcinomas *in situ*, superficial bladder cancer, and non-melanoma carcinoma of the skin; clinically significant and uncontrolled major medical condition(s) or any medical condition that in the opinion of the investigator placed the subject at an unacceptably high risk for toxicity.

All participants provided institutional review board-approved written informed consent prior to initiation of any study-related procedures.

Treatment

Patients were treated with oral veliparib 40 mg twice daily (BID) on days 1 through 7 (all cycles) and oral TMZ once daily (QD) on days 1 through 5 in 28-day cycles. TMZ was given at a dose of 150 mg/m^2/day in cycle 1. If this dose was well tolerated (platelets ≥100,000/μL; ANC ≥1,500/μL; no grade 3/4 non-hematological toxicities per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 4.0), the dose could be escalated to 200 mg/m^2/day in cycle 2 onward. If the TMZ dose was not escalated in cycle 2, then the dose was not escalated in later cycles. Treatment could be taken for up to 24 cycles and was continued per protocol until disease progression (based on radiographic assessment and Response Evaluation Criteria in Solid Tumors [RECIST Version 1.0], clinical assessment, or pain), unacceptable toxicity, or subject/physician decision.

Dose reductions

Dose reductions or delays were permitted if required. If grade 3/4 toxicity was experienced that was not attributable to TMZ or the underlying disease, treatment was held until resolution to grade ≤1. For grade 3/4 toxicities attributed to veliparib, veliparib was reduced to 20 mg BID then 10 mg BID. If toxicity persisted at 10 mg BID, treatment was discontinued. If grade 3/4 toxicities attributable to TMZ were experienced, treatment was held until resolution, and the dose was reduced by 50 mg/m^2/day in the next cycle. Treatment was discontinued if this dose reduction was not sufficient. The next cycle was not started until the ANC was ≥1,500/μL and the platelet count was ≥100,000/μL. Discontinuation of TMZ or veliparib automatically resulted in discontinuation of the other study drug.

Efficacy assessments

The primary endpoint was confirmed PSA response rate (proportion of patients with a complete or partial PSA response). A complete response was defined as undetectable PSA (≤ 0.2 ng/mL) that was confirmed at least 4 weeks later and a partial response as a PSA decline of ≥30 % that was confirmed at least 4 weeks later. The choice for this endpoint was based on data indicating a 3-month PSA decline of at least 30 % was a surrogate for survival [25].

PSA was assessed at baseline, day 1 of each cycle, final visit, and the 30-day follow-up visit. Stable PSA was defined as PSA not meeting complete or partial response criteria but with no progression. PSA progression was defined as an increase in PSA of ≥25 % from baseline or nadir and an absolute increase of ≥2 ng/mL that was confirmed at least 4 weeks later.

Secondary endpoints included safety and tolerability of veliparib in combination with TMZ, ORR, PSA response rate at 12 weeks following first dose of study drug, TTP, PFS, and OS.

Tumor assessment was performed at baseline, every 8 weeks, and final visit (unless performed within 4 weeks of the final visit), and comprised a diagnostic chest X-ray or chest CT scan, CT scans of the abdomen and pelvis, and bone scans in subjects with known bone metastasis. Radiographic response was assessed according to RECIST [26]. The objective response rate was defined as the proportion of subjects with measurable disease with a complete or partial objective response according to RECIST.

Time to progression (TTP) was defined as the time from first dose to the earliest date of disease progression, regardless of whether this occurred during treatment or following discontinuation. If a subject did not experience disease progression, data were censored at the date of last assessment. Disease progression was based on pain, radiographic, or clinical assessment but not PSA elevation alone without radiographic or clinical evidence.

Survival information was collected approximately every 3 months after the final visit for a period of up to 18 months. Progression-free survival (PFS) was defined as the time from first dose to the earliest date of disease progression, or death within 56 days of last disease progression assessment if progression did not occur. If there was no progression or death within 56 days of last assessment, the data were censored at the date of last assessment. Overall survival (OS) was defined as time from first dose to death (all causes). For surviving subjects, data were censored at the last known alive date.

Safety assessments

Complete history and physical examination was carried out on days 1 and 15 of cycles 1 and 2, then on day 1 of subsequent cycles. Clinical laboratory tests (chemistry and hematology) were carried out at screening, days 1, 15, and 22 during cycles 1 and 2, then day 1 of subsequent cycles.

Adverse events (AEs) were monitored throughout the study and summarized using the Medical Dictionary for Regulatory Activities Version 14.0. Severity was rated according to the NCI-CTCAE Version 4.0. The relationship of AEs to study drug was also assessed by the investigator as ‘probably related’, ‘possibly related’, ‘probably not related’, or ‘not related’.

Pharmacodynamic correlates

Several exploratory biomarker analyses were performed to assess treatment effect and identify tumor-specific alterations in cellular proteins and/or circulating tumor cells. Blood samples for the exploratory assessment of biomarkers were collected prior to dosing on days 1 and 15 of cycle 1, on day 1 of every other cycle, and at final visit. Plasma samples were stored at −70 °C or lower until analysis for quantitative assessment of tumor markers.

Detection of the most common ETS transcription factor genomic rearrangement in prostate cancer, the ETS-related oncogenic transcription factor ERG and the androgen-regulated gene TMPRSS2 gene fusion (ERG: TMPRSS2), was assessed. Analysis was carried out by

fluorescence *in-situ* hybridization (FISH), performed using a breakaway probe on circulating tumor cells (CTCs) using the CymoGen Dx ERG/TMPRSS2 translocation probe set (CymoGen Dx, LLC, Irvine, CA), as previously described [27].

CTCs were measured at baseline and on therapy to provide further information on response to treatment. CTC detection was performed as previously described using the CellSearch® system (Veridex LLC, Raritan, NJ) [28–30].

Levels of the glycoprotein tumor marker, carcinoembryonic antigen (CEA), were measured using automated ARCHITECT enzyme-linked immunosorbent assays (ELISAs; Abbott Diagnostics, Abbott Park, IL).

The relationship between specific changes in these bio-markers and PFS was also assessed. For CTCs, the comparison was decrease versus increase/no change in CTC concentration. For CEA, the comparison was low (<5 ng/mL) vs. high (≥5 ng/mL) concentration at baseline, based on the diagnostic threshold for colorectal cancer. The presence or absence of the common ERG: TMPRSS2 translocations was examined for a correlation with response to combination of TMZ and PARP-1 inhibition by veliparib.

Statistical analysis

The primary objective of this study was PSA response rate in patients with mCRPC treated with veliparib and TMZ. Secondary objectives included assessment of safety and tolerability, tumor response rates, survival data, and exploratory analysis of biomarkers, including CTCs.

Based on the assumption that a PSA response rate of 20 % would be of clinical interest and a PSA response rate of 5 % indicates no benefit, a sample size of 25 subjects would provide 76 % power, with a one-sided type I error rate of 0.1.

All efficacy and safety analyses included all patients who received at least one dose of veliparib.

For overall and 12 week PSA response rate, and objective response rate, the proportion of subjects meeting the pre-specified criteria was estimated, and the 95 % confidence interval (CI) calculated based on exact binomial distribution. TTP, PFS and OS were estimated by the Kaplan-Meier method; median times and corresponding 95 % CI are presented.

For the exploratory biomarker analysis, survival curves based on subgroups of circulating tumor cells and CEA were compared using the log-rank test at a significance level of $P \leq 0.05$.

Results

A total of 26 patients were enrolled between April 21, 2010 and July 6, 2011. Baseline demographics are summarized in Table 1. Of the 25 subjects evaluable for response, 23 had received prior therapy with docetaxel, with 18 considered refractory to docetaxel (docetaxel discontinued due to progression). One of these subjects had also received prior therapy with

abiraterone, and one had received therapy with enzalutamide. The non-evaluable subject was also considered refractory to docetaxel.

Treatment summary

The median number of cycles was 2 (range, 1–9). Six subjects took less than 80 % of the assigned dose of veliparib during 1 cycle of treatment. Exposure to treatment is detailed in Table 2. The reasons for treatment discontinuation were: AE related to PSA, clinical or radiographic disease progression (*n*=27); AE not related to disease progression (*n*=4); withdrew consent (*n*=1); and other reason (*n*=2). Many subjects had >1 reason for discontinuation.

Dose reductions were required in 5 patients: reduction of both agents due to platelet count decrease (*n*=1); reduction of TMZ due to thrombocytopenia/platelet count decrease (*n*=3) or neutropenia (*n*=1).

Efficacy

The PSA response rate was 8.0 % (95 % CI: 1.0–26.0), based on 2 of 25 patients achieving a confirmed PSA decline of ≥ 30 %. In the remaining 23 patients, 13 patients had stable PSA, and 10 had PSA progression. The best percentage PSA reduction from baseline for each patient is shown in Fig. 1. Overall, 3 of 25 patients achieved a maximum PSA decline of ≥30 % at any time during the first 12 weeks of treatment.

None of the 16 patients with measurable disease for whom data were available achieved an objective response according to RECIST. The median TTP and the median PFS were both 9 weeks (95 % CI: 8–17) (Fig. 2a). The median OS was 39.6 weeks (95 % CI: 27-could not be estimated) (Fig. 2b); 15 deaths were reported in 26 patients (57.7 %). Mean changes from baseline in ECOG performance status scores were minimal.

Safety

Overall, 25 of 26 patients reported at least 1 treatment-emergent AE. The most common are summarized in Table 3. The majority of AEs were NCI-CTCAE grade 1/2. Grade 3/4 AEs occurring in more than 1 patient were: colitis (7.7 %), fatigue (7.7 %), neutropenia (7.7 %), anemia (15.4 %), and thrombocytopenia (23.1 %). The most common AEs (≥20 % of subjects) that were considered by the investigator at least ‘possibly related’ to treatment were: nausea (veliparib 34.6 % and TMZ 38.5 %), fatigue (34.6 % and 34.6 %, respectively), and thrombocytopenia (23.1 % and 34.6 %, respectively).

Treatment-emergent serious AEs were reported for 7 subjects (26.9 %): colitis (*n*=2), hepatorenal syndrome, hyperglycemia, bone pain, mental status change, hematuria, urinary tract obstruction, epistaxis, and deep vein thrombosis (all *n*=1). Discontinuation due to treatment-emergent AEs occurred in 3 of 26 subjects (11.5 %). One patient had fatal hepatorenal syndrome due to disease progression starting 29 days after the last dose (considered ‘probably not related’ to study drug).

Exploratory biomarkers

Several exploratory correlative biomarkers were included in this study, including both CTC enumeration and plasma protein markers potentially associated with mCRPC.

At baseline, 15 samples were evaluable for CTC and 14 of 15 patients assessed had detectable CTCs (range: 0–592 CTC/7.5 mL blood). A CTC value of ≥5 CTC has been shown to be a poor prognostic indicator in mCRPC [31]. In this study 13/15 patients had CTC values >5. However, for patients who provided samples both at baseline and cycle 2 day 1, there was a negative correlation between change from baseline in CTCs and PFS. Patients with a decrease in CTCs (from 86.9 to 9.6 CTC/7.5 mL blood) had a PFS of 116 vs. 51.5 days in those with no change/increase (from 238.0 to 372.7 CTC/7.5 mL blood) (P=0.0266) (Fig. 3a).

We also examined a set of tumor markers to determine if the baseline levels for any of these markers correlated with patient response. Of interest was the marker CEA which is commonly used to monitor colorectal cancer. Baseline values of CEA ≥ 5 ng/mL (considererd elevated in colorectal cancer) [32] were correlated with a shorter PFS of 51 vs. 116 days in patients with low baseline CEA concentrations (P<0.0001) (Fig. 3b). Notable, CEA levels did not correlate with the absolute number of CTCs detected at baseline, but 8 of the 16 patients with low baseline CEA also demonstrated a reduction in CTC levels after 1 cycle of therapy.

Approximately 50 % of prostate cancer tissue samples harbor the ERG:TMPRSS2 gene fusion [33, 34], and there is evidence for DNA-independent interaction between ERG: TMPRSS2, PARP-1, and DNA protein kinase [35] Consequently, FISH analysis of CTCs for the ERG:TMPRSS2 gene fusion was performed and was successful in 8 baseline samples; only 1 patient demonstrated clear translocations and 2 patients had no translocation but had large amplifications of the entire region in some CTCs but not in nearby peripheral blood mononuclear cells. The remaining 5 evaluable patients had no translocations or noted amplifications. As only 1 patient tested had the gene fusion, no meaningful correlation with response to treatment could be made; however, this patient achieved stable disease, with a PFS of 70 days and an OS of 277 days.

Discussion

The rationale for combining veliparib and TMZ for the treatment of mCRPC was based on several lines of evidence. First, PARP-1 has been implicated in androgen receptor-dependent cell proliferation in models of both early- and late-stage prostate cancer, with suppression of PARP-1 shown to reduce cell proliferation in these models [15], suggesting that PARP inhibition has the potential to be an effective therapeutic strategy in prostate cancer. Second, veliparib was shown to enhance the activity of chemotherapy in preclinical models of breast cancer and melanoma [16, 22, 23] and to significantly increase the sensitivity of prostate cancer cells to TMZ in an animal model [21], including reversing resistance to TMZ in this animal model, which translated to improved survival [21]. Third, approximately 50 % of prostate cancer samples harbor the ERG:TMPRSS2 gene fusion [33, 34], and there is evidence for DNA-independent interaction between ERG:TMPRSS2, PARP-1, and DNA

protein kinase [35]. PARP-1 blockade has been shown to inhibit the growth of ERG:TMPRSS2-positive prostate cancer xenografts in mice [35], and in another study, inhibition of PARP-1 reduced the number of prostate cancer cells in culture harboring the ERG:TMPRSS2 gene fusion [36].

This study tested the combination of veliparib and TMZ in chemotherapy-pretreated mCRPC patients. This combination was feasible, well tolerated, and the observed AEs were similar to those expected with TMZ monotherapy. Although there was evidence of some antitumor activity, this effect was modest, with 12 % of patients achieving a PSA decline of ≥ 30 % within 3 months, with a median PFS of 9 weeks and median OS of 39.6 weeks.

The overall limited clinical efficacy observed in this study is likely the result of several factors including the chosen relatively lower dose of veliparib maybe a limiting factor; a higher dose might be required for maximum efficacy in this patient population. The veliparib dose used in this trial (40 mg BID) was based on a phase I study of veliparib and TMZ. At this dose, veliparib had no dose-limiting toxicities and achieved a steady-state exposure (area under the plasma concentration-time curve [AUC]) that was effective in murine efficacy models, with no indication of a pharmacokinetic interaction between veliparib and TMZ.

There are other potential reasons for the limited efficacy in this study. If DNA damage is insufficient either due to moderate chemosensitivity of the underlying tumor and/or low DNA damage potential of the chemotherapy, the addition of veliparib may not lead to clinically significant efficacy. Similarly, despite the theoretical rationale and observed preclinical data, the lack of clinical efficacy of single-agent TMZ in patients with mCRPC [37] has likely played a significant role in the observed modest antitumor effect of the combination.

Limitations of the study include the small sample size, and the small number of subjects for whom biomarkers are available, all inherent limitations to a pilot study. The limitations of sample size may have been even more pronounced in the specific sub-populations whom data suggest are uniquely sensitive to PARP-inhibitor therapy, such as BRCA-mutated tumors or tumors with ETS gene fusion.

Current evidence supports a negative association between an on-therapy reduction in CTC levels and progression/survival in prostate cancer [38, 39]. In the present study, the majority of assessable patients had a decrease in CTCs with treatment, which was associated with longer PFS compared with no change or an increase in CTCs. Elevated CEA has been linked with castration resistant prostate cancer and with soft tissue metastatic lesions [40]. Here, longer PFS was observed in patients with low baseline CEA concentrations versus those with high baseline CEA. This is in contrast to a previous study, which found no association between CEA and survival in this disease setting [40]. As only 1 of 8 patients tested had the ERG:TMPRSS2 gene fusion, the hypothesis of better response in this population could not be assessed in this study.

This study is one of the first to evaluate the role of combination therapy targeting PARP-1 in patients with mCRPC. Based on the facts that androgen signaling in prostate cancer cells is

directly coupled with the induction of DNA damage [41], CRPC tumor cells exhibit increased PARP-1 activity [15], veliparib improves the response to hormone therapy in preclinical prostate cancer models [15], PARP-1 is required for ERG-associated function and ERG:TMPRSS2-positive xenografts are sensitive to PARP inhibition [35], an ongoing clinical trial is currently assessing abiraterone acetate and prednisone with and without veliparib (administered at 300 mg BID days 1–28, a much higher dose than the present study) in patients with mCRPC. The primary objectives of the trial are to assess the role of ETS gene fusion as a predictive biomarker for response to hormone therapy alone or in combination with PARP-1 targeted therapy using veliparib, and whether the addition of PARP-1 targeted therapy is superior to hormone therapy alone based on ETS gene fusion status (ClinicalTrials.gov trial registration ID: NCT01576172).

Conclusion

This pilot study in chemotherapy-treated patients with mCRPC indicates that the combination of veliparib and TMZ is well tolerated, with evidence of modest antitumor activity. Low baseline concentrations of CEA and on-treatment decreases in CTC were associated with longer PFS. Evaluation of other combination therapies with higher doses of veliparib is warranted in this patient population.

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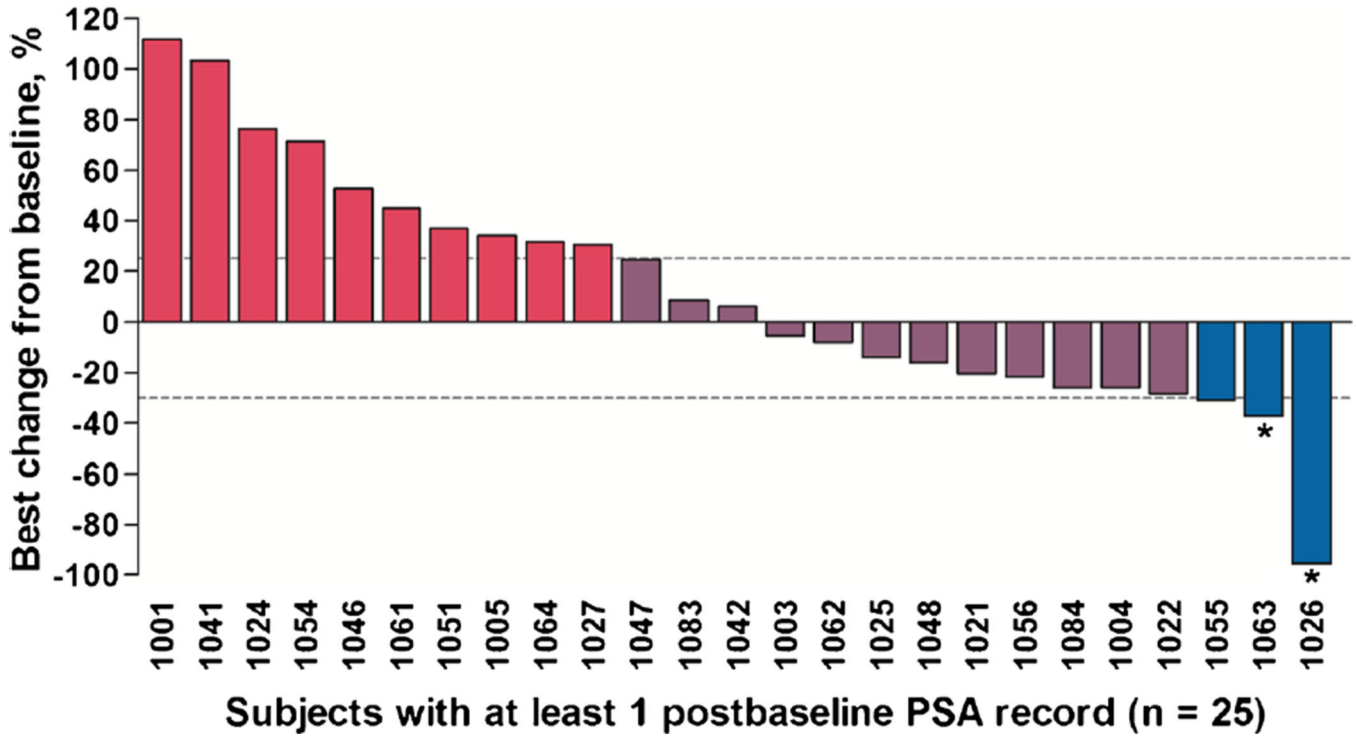

Fig. 1.

Best percentage reduction in PSA from baseline at 12 weeks (maximum reduction orminimum increase for subjects with no reduction). One patient was not included due to missing post-baseline assessment. *upper horizontal line*=25 % increase in PSA (disease progression). *lower horizontal line*=30 % decline in PSA (partial response) *Confirmed partial response

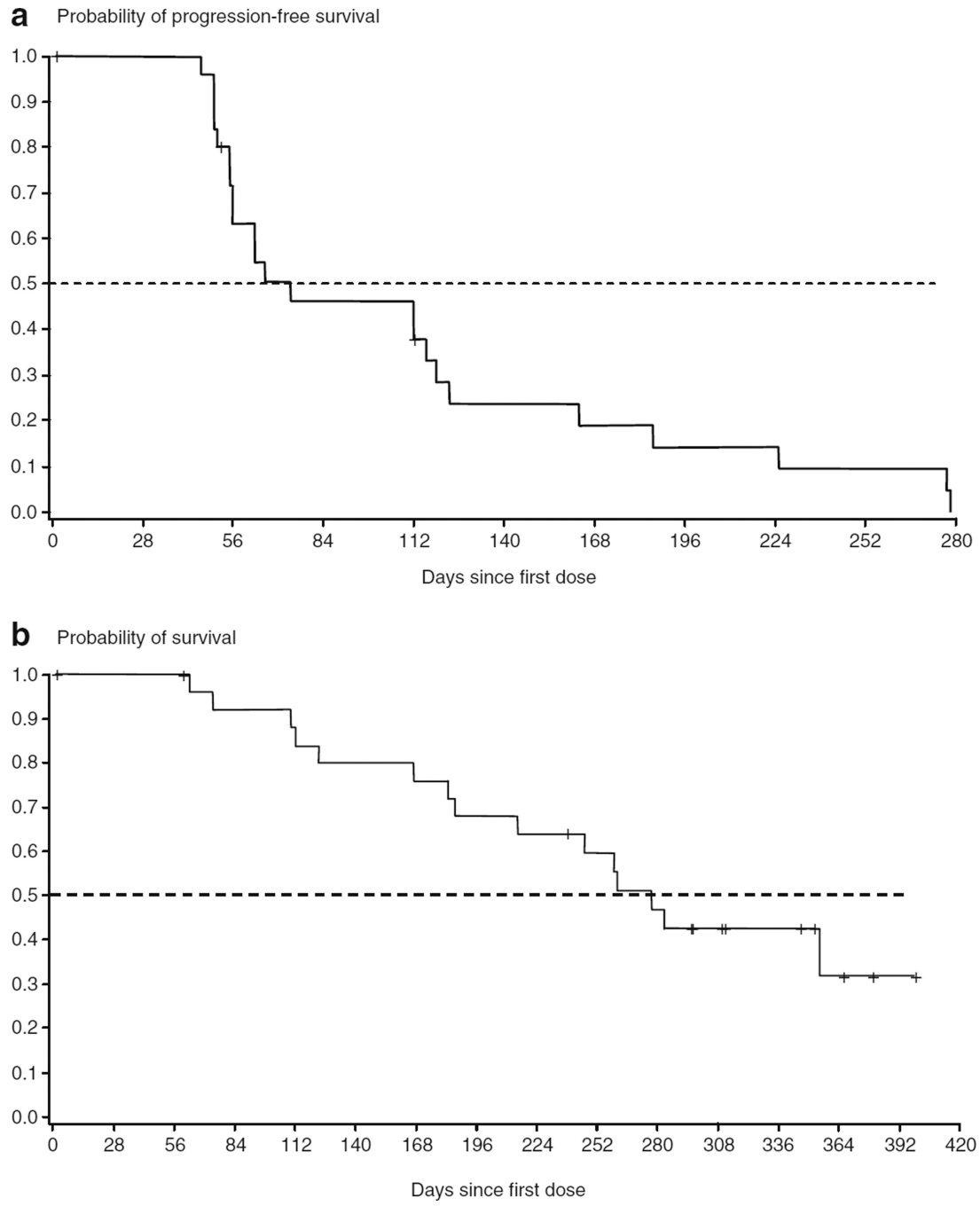

Fig. 2.

Kaplan-Meier plots. **a** progression-free survival (radiographic progression and all deaths). **b** overall survival (all deaths)

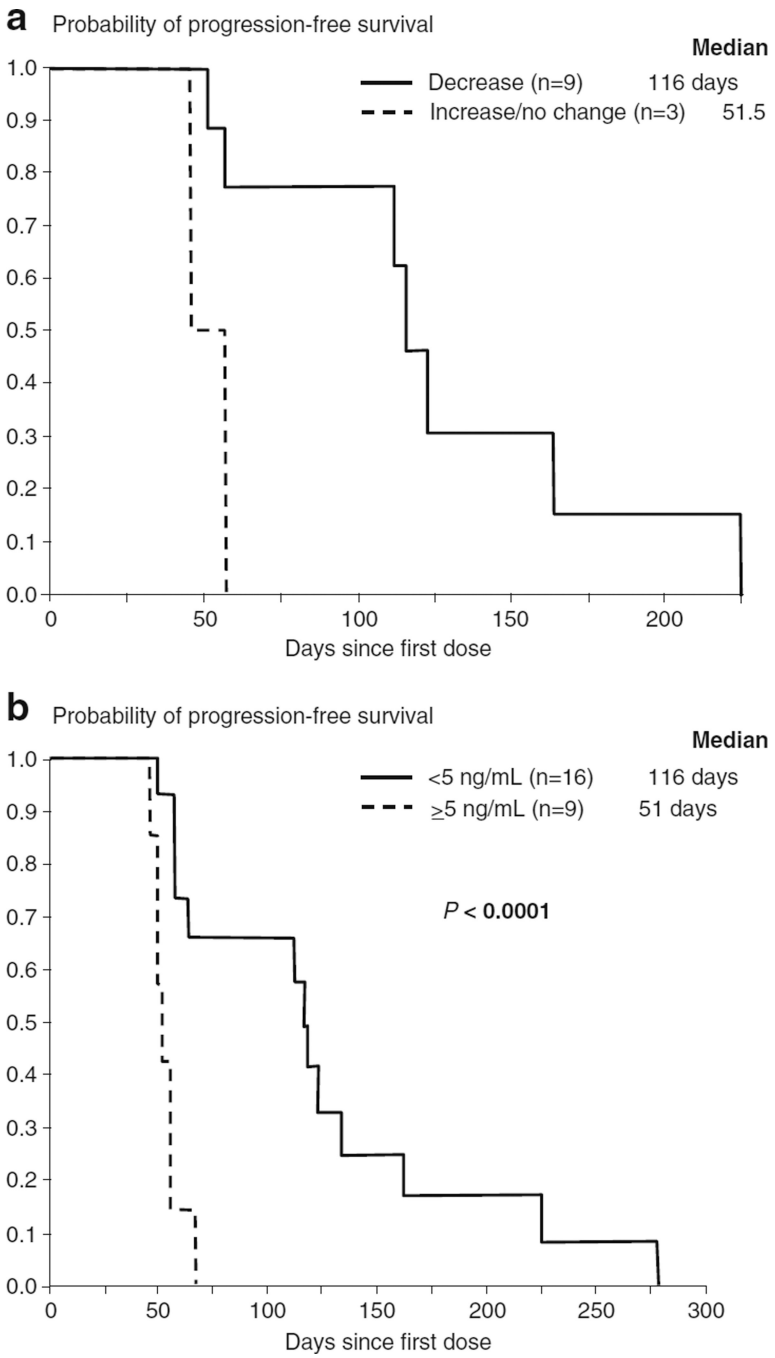

Fig. 3.
Exploratory biomarkers. **a**, circulating tumor cells. **b** carcinoembryonic antigen (CEA)

Table 1

Baseline demographics

	***N*=26**
Age in years, median (range)	67.0 (55–81)
Race, *n* (%)	
White	21 (80.8)
Black	5 (19.2)
PSA at study entry in ng/mL, median (range)	170.2 (6.9–4,584.4)
Prior chemotherapy, *n* (%)	
1	19 (73.1)
2	7(26.9)
Gleason score[a], *n* (%)	
0	1(4.0)
6–7	9(36.0)
8–10	15 (60.0)
ECOG PS, *n* (%)	
0	5(19.2)
1	15 (57.7)
2	6(23.1)
Measurable disease, *n* (%)	20 (76.9)
Bone disease, *n* (%)	22 (84.6)

[a] *n*=25; data missing for 1 subject

Table 2

Treatment exposure

	***N*=26**
Overall number of cycles, median (min/max)	2 (1/9)
Number of cycles received, *n* (%)	
1	3 (11.5)
2	12 (46.2)
3	3 (11.5)
4	5 (19.2)
5	0
6	1 (3.8)
7	1 (3.8)
8	0
9	1 (3.8)

Table 3

Treatment-emergent adverse events occurring in ≥10 % of subjects

		***N*=26**	
		Grade 1/2	**Grade 3/4**
General	Fatigue	11 (42.3)	2 (7.7)
Gastrointestinal	Nausea	10 (38.5)	0
	Constipation	6 (23.1)	0
	Dysphagia	3 (11.5)	0
	Vomiting	3 (11.5)	0
Hematologic	Thrombocytopenia[a]	14 (53.8)	6 (23.1)
	Anemia[a]	14 (53.8)	4 (15.4)
	Neutropenia[a]	9 (34.6)	2 (7.7)
Musculoskeletal and connective tissue	Pain in extremity	4 (15.4)	0
	Arthralgia	3 (11.5)	0
	Back pain	3 (11.5)	0
	Muscular weakness	3 (11.5)	0
Other	Hypoasthesia	3 (11.5)	0
	Weight decreased	5 (19.2)	0
	Decreased appetite	4 (15.4)	0
	Upper respiratory tract infection	4 (15.4)	0

[a]Includes related blood chemistry and laboratory adverse events