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A PHASE 1 STUDY OF ACAPATAMAB, A HALF-LIFE EXTENDED, PSMA-TARGETING BISPECIFIC T-CELL ENGAGER FOR METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

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Abstract

Purpose: Safety and efficacy of acapatamab, a prostate-specific membrane antigen (PSMA) × CD3 bispecific T-cell engager were evaluated in a first-in-human study in metastatic castration-resistant prostate cancer (mCRPC).

Patients and Methods: Patients with mCRPC refractory to androgen receptor pathway inhibitor therapy and taxane-based chemotherapy received target acapatamab doses ranging from 0.003 mg–0.9 mg in dose exploration (7 dose levels) and 0.3 mg (recommended phase 2 dose) in dose expansion intravenously Q2W. Safety (primary objective), pharmacokinetics, and antitumor activity (secondary objectives) were assessed.

Results: In all, 133 patients (dose exploration, n=77; dose expansion, n=56) received acapatamab. Cytokine release syndrome (CRS) was the most common treatment-emergent adverse event seen in 97.4% and 98.2% of patients in dose exploration and dose expansion respectively; grade ≥ 3 was seen in 23.4% and 16.1%, respectively. Most CRS events were seen in treatment cycle 1; incidence and severity decreased at/beyond cycle 2. In dose expansion, confirmed prostate-specific antigen responses (PSA50) were seen in 30.4% of patients and radiographic partial responses in 7.4% (RECIST 1.1). Median PSA progression-free survival (PFS) was 3.3 months (95% CI, 3.0–4.9), radiographic PFS per PCWG3 was 3.7 months (95% CI, 2.0–5.4). Acapatamab induced T-cell activation and increased cytokine production several-fold within 24h of initiation. Treatment-emergent antidrug antibodies were detected in 55% and impacted serum exposures in 36% of patients in dose expansion.

Conclusions: Acapatamab was safe and tolerated and had a manageable CRS profile. Preliminary signs of efficacy with limited durable antitumor activity were observed. Acapatamab demonstrated pharmacokinetic and pharmacodynamic activity.

Keywords

acapatamab; PSMA; T cell engager; TCE; AMG 160; bispecific antibody; first-in-human; HLE BiTE; mCRPC; metastatic castration-resistant prostate cancer

INTRODUCTION

Globally, prostate cancer (PCa) accounted for 1.4 million new cancer diagnoses (7.3% of all new cases of cancer) and 375,304 deaths (3.8% of all cancer-related deaths) in 2020 (1). PCa was the leading cause of cancer and the second leading cause of cancer-related deaths among US men in 2022 (2). Approximately 10%–20% of patients with PCa develop castration-resistant PCa (CRPC) within 5 years of follow-up (3). Most patients with CRPC either present with metastatic disease at diagnosis (> 80%) or progress to metastatic CRPC (mCRPC) within 2 years (3). Patients with mCRPC have a poor prognosis and differential rates of overall survival (OS) depending on organ involvement. Patients with non-visceral bone metastasis have a better prognosis (median OS: 21.3 months) than those with lung (median OS: 19.4 months) or liver metastasis (median OS: 13.5 months) (4).

mCRPC remains incurable, with a median survival of less than 2 years (5) despite the introduction of life prolonging therapies in the past 20 years. In 2004, docetaxel became the first chemotherapeutic agent to improve survival of patients with mCRPC. Results from the phase 3 TAX 327 study demonstrated that docetaxel in combination with prednisone improved survival and quality of life of patients with advanced, hormone-refractory PCa compared with mitoxantrone-prednisone (6). Since abiraterone in combination with prednisone became the new standard-of-care for patients with metastatic disease in 2011 (7), several other treatment options have become available, including enzalutamide (8,9), sipuleucel-T (10), radium-223 (11), cabazitaxel (12), and olaparib (13). Despite these advances, resistance to these therapies ultimately develops, leaving patients, particularly post treatment with taxane-based chemotherapy, with limited therapeutic options. Thus, novel therapies are urgently needed (14).

Prostate-specific membrane antigen (PSMA) is a cell surface protein that is highly overexpressed on the surface of prostate epithelial cells in PCa, and its expression is directly correlated with advanced disease stage and the presence of distant metastases (15,16). PSMA is also a clinically validated target for the imaging and treatment of mCRPC (17,18). The PSMA-targeting radiolabeled agent, ^{177}Lu-PSMA-617, is a small molecule that binds to cell surface PSMA and delivers a high dose of ionizing radiation to PCa cells (19). In the phase 3 VISION trial, ^{177}Lu-PSMA-617 significantly improved radiographic progression-free survival (rPFS) and OS in patients with PSMA-positive mCRPC progressing on androgen receptor pathway inhibitor therapy and taxane-based chemotherapy, thereby confirming the rationale for targeting PSMA in mCRPC (20). Based on these results, ^{177}Lu-PSMA-617 was approved by the FDA for the treatment of patients with mCRPC in 2022.

Bispecific T-cell engagers (BiTE®) are immuno-oncology therapies designed to engage autologous T cells with tumor cells by simultaneously binding the tumor-associated antigen and the CD3 antigen on the T cell. This binding activates the cytotoxic potential of T cells, resulting in apoptosis of the tumor cell, as well as T-cell activation and T-cell proliferation (21–24). BiTE molecules amplify the antitumor activity by facilitating the binding of a single T cell to multiple tumor cells leading to serial lysis of tumor cells (21). Pasotuxizumab and JNJ-63898081 (JNJ-081) are two PSMA × CD3 bispecific

immunotherapies whose clinical development was discontinued following phase 1 clinical trials (25) (26). Acapatamab (formerly AMG 160) is a half-life extended (HLE) BiTE® immuno-oncology therapy that binds to PSMA on PCa cells and CD3 on T cells (23). Acapatamab's structure contains an immunoglobulin G (IgG) single chain fragment crystallizable (scFc) region that interacts with the neonatal, cell surface Fc receptor; this interaction protects acapatamab from lysosomal degradation and causes it to be recycled to the extracellular space resulting in a significant prolongation of the molecule's half-life (27,28). In preclinical studies, acapatamab demonstrated potent antitumor activity in PSMA-expressing PCa cell lines and CRPC xenograft models (29). The encouraging antitumor activity of acapatamab in preclinical studies served as the rationale for the conduct of this first-in-human study. Here, we report the safety and preliminary efficacy results from a phase 1 study of acapatamab monotherapy in patients with mCRPC.

MATERIAL AND METHODS

Study design and patients

This was an open-label, multi-center, phase 1, dose-exploration/dose-expansion study in patients with mCRPC from North America, Europe, Asia, and Australia (NCT03792841). The trial commenced in February 2019. The data cutoff date for this analysis was May 31, 2022.

The target dose of acapatamab was administered as a short-term intravenous (IV) infusion over approximately 1 h every 2 weeks (Q2W) in a 28-day cycle. Step dosing was implemented to achieve a higher target dose without exacerbating the risk of cytokine release syndrome (CRS). The step dosing protocol involved starting with lower doses on cycle 1 day 1 (1-step), escalating on day 8 (2-step) and day 15 (3-step) followed by the target dose 7 days after the last step dose. Separately, a strategy utilizing an extended IV (eIV) infusion (ranging over 2 to 5 days) for the first dose (or C1D1 dose) followed by the target dose on cycle 1 day 8 (1 h infusion) was used (Supplementary Table S1). Once the target dose was reached, acapatamab was administered Q2W as a 1-h infusion. Patients were categorized based on the target dose (the highest dose after either eIV infusion or step dose[s] that the patient received for the duration of treatment)

Following the dose exploration phase, a dose expansion study was conducted to confirm the safety, pharmacokinetics, and pharmacodynamics of acapatamab at the recommended phase 2 dose (RP2D), obtain further safety and efficacy data, and to conduct exploratory correlative biomarker analysis. The RP2D evaluated in the dose expansion phase was a 3-day eIV infusion of 0.09 mg acapatamab starting on cycle 1 day 1 followed by 0.3 mg of acapatamab (target dose), administered over 1 h Q2W starting on cycle 1 day 8. To mitigate the risk of CRS, prophylactic oral dexamethasone (8 mg or equivalent dose of other corticosteroids) was administered 6–16 h before all doses of acapatamab in cycle 1. Additionally, IV dexamethasone (8 mg or equivalent dose of other corticosteroids) was administered within 1 h before all doses of acapatamab were administered in cycle 1. Prophylactic IV hydration was administered at the investigator's discretion either immediately after short-term (60-min) acapatamab infusions in cycle 1 or at the beginning of the eIV infusion in cycle 1. Patients were hospitalized during the eIV infusion and for

48 h after each short-term infusion in cycle 1 and for 24 h after each infusion in cycle 2 to monitor for the development of adverse events (AEs), particularly CRS. The study schema is shown in Supplementary Fig. S1.

The primary objectives of this study were to determine the maximum tolerated dose or RP2D and evaluate the safety and tolerability of acapatamab. The secondary objectives were to evaluate the preliminary antitumor activity and characterize the pharmacokinetics of acapatamab. Exploratory objectives were to study pharmacodynamic biomarkers and the immunogenicity of acapatamab.

Men aged ≥18 years were included if they had histologically or cytologically confirmed mCRPC that was refractory to at least one androgen receptor pathway inhibitor therapy, had failed one or two taxane-based regimens (or were unsuitable for or had refused treatment with a taxane regimen), and had evidence of progressive disease (PD) as defined by the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) guidelines (30). Eligible patients were also required to have undergone bilateral orchiectomy or be on continuous androgen deprivation therapy with a gonadotropin-releasing hormone agonist or antagonist, with adequate organ function, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and a life expectancy of ≥ 6 months. Patients were not tested for tumor PSMA expression to determine eligibility. Patients were excluded if they had active autoimmune disease; required immunosuppressive therapy; had received prior PSMA–targeted therapy (patients treated with PSMA radionuclide therapy were considered eligible at the discretion of the Amgen medical monitor); or had evidence of central nervous system metastases, leptomeningeal disease, or spinal cord compression. Patients on a stable bisphosphonate or denosumab regimen for ≥ 30 days prior to randomization were not excluded.

The study was conducted in accordance with the ethical principles derived from international guidelines, including the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, and applicable International Conference on Harmonisation guidelines, laws, and regulations. The study protocol was approved by the Institutional Review Board/Independent Ethics Committee at each study site, and written informed consent was obtained from all patients.

Assessments

Primary endpoints included dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs), changes in vital signs, electrocardiogram, and clinical laboratory tests. Secondary endpoints included characterization of acapatamab pharmacokinetics, objective response (OR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 prostate-specific antigen (PSA) response, duration of response (DoR) per RECIST 1.1, PSA DoR based on PSA50 response, time to progression (radiographic and PSA), progression-free survival (PFS) (radiographic and PSA), and OS.

AEs were assessed continuously and graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, except for CRS, which was graded using the Lee et al

2014 criteria (31). The DLT evaluation period was the first 28 days following the first dose of acapatamab. Dose-limiting toxicities were defined as any adverse event with an onset within the first 28 days following the first dose of acapatamab monotherapy with any of the following criteria unless clearly attributable to causes other than acapatamab treatment: (1) grade 5 toxicity, (2) a grade 3 adverse event lasting more than 3 days (with the exception of fatigue), (3) grade 4 adverse event regardless of duration, (4) grade 3 nausea, vomiting, or diarrhea that did not improve to grade ≤ 1 within 72 hours despite maximum supportive care, (4) grade ≥3 neurologic events that did not improve to grade ≤ 1 within 7 days with treatment interruption and routine medical management, and (5) grade 3 febrile neutropenia that could not be attributed to CRS.

Efficacy analysis included the assessment of PSA response, OR, and DoR per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (30), PSA and radiographic progression-free survival (rPFS), and OS. A PSA response was defined as a 50% reduction in the PSA level from baseline that was confirmed by a second test value obtained at least 3 weeks later. PSA30/50/70/90 responses were defined as a ≥ 30%, ≥ 50%, ≥ 70%, and ≥ 90% reduction in PSA levels from baseline, respectively. Patients with measurable disease at baseline on imaging assessments were evaluated for OR using RECIST 1.1 (32) by investigator assessment. Responses were confirmed by a repeat consecutive assessment at least 4 weeks after the first detection of a radiographical response.

Radiological imaging (MRI/CT), bone scans, and tumor burden assessments were performed at screening, at week 8 (defined as the baseline scan), every 8 weeks during weeks 1–24, every 12 weeks thereafter, and at the end of treatment and safety follow-up visits.

Local laboratory assessments were reported for all safety and efficacy outcome measures.

To assess tumor PSMA expression and tumor volume, PSMA-positron emission tomography/ computed tomography (PET/CT) and fluorodeoxyglucose (FDG)-PET/CT were performed at baseline.

The protocols used for blood collection and staining for flow cytometry, as well as the antibodies used for biomarker analysis are described in Supplementary Methods. Levels of IFN-γ, interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13 and TNF-α were measured in patient sera using a multiplex electrochemiluminescence assay (V Plex; Meso Scale Discovery, Rockville, MD, USA).

Statistical analyses

A Bayesian logistic regression model was employed during the dose-exploration phase of the study to guide dose escalation or de-escalation decisions (33). Approximately 70–90 patients were expected to be enrolled in the dose exploration cohorts and approximately 50 additional patients in the dose expansion cohort, resulting in a total of 120–140 patients. In the dose expansion cohort, 50 patients provided a 92% probability of observing ≥1 AE with a 5% incidence rate. With approximately 50 patients in the dose expansion cohort, a 2-sided 95% confidence interval (CI) of objective response rate (ORR) per RECIST 1.1 extended ≤23% in length from the observed ORR (ie, if the estimated ORR was 50%, the

estimated 95% CI of ORR would be within 27%–73%). The true ORR was assumed to be approximately 50%; the proportion of patients with RECIST measurable disease was assumed to be approximately 40%.

The analysis of all endpoints, unless noted otherwise, was conducted on the safety analysis set, which included all enrolled patients who received ≥ 1 dose of acapatamab.

Supplementary Table S2 shows the representativeness of the study participants.

Descriptive statistics were provided for selected demographics, safety, pharmacodynamic, and biomarker data by treatment, dose, dose schedule, and time, as appropriate. Descriptive statistics for continuous data included the estimation of means, medians, standard deviations, and ranges. Categorical data were summarized using frequency counts and percentages.

DATA AVAILABILITY

Qualified researchers may request data from Amgen clinical studies. Complete details are available at http://www.amgen.com/datasharing

RESULTS

Patients and treatment

As of May 31, 2022, a total of 133 patients had received ≥ 1 dose of acapatamab as part of the dose exploration and dose expansion regimens. Most (63.2%) patients were White and 93.2% had received ≥ 3 lines of therapies before study entry (Table 1, Supplementary Table S3). The median patient age was 67 years (range, 45–85) and the median baseline PSA level was 112.2 ng/mL (range, 0.1–8196.0). At baseline, 16.5% of patients had visceral metastases (Table 1).

Initially, 77 patients received acapatamab monotherapy with target doses ranging from 0.003 mg to 0.9 mg as part of the dose exploration phase. Administration of target doses between 0.03 mg and 0.9 mg was preceded by either step-dosing or eIV infusions of acapatamab. The totality of safety, tolerability, pharmacokinetics, and preliminary activity data from the dose exploration phase informed the selection of the RP2D: 0.3 mg target dose with an initial dose of 0.09 mg as a 3-day eIV infusion. At data cut off, 56 patients were enrolled in the dose expansion part of the study that received the RP2D regimen.

Patient disposition

Overall, 75/77 (97.4%) patients in dose exploration and 53/56 (94.6%) in dose expansion had discontinued treatment with acapatamab at data cutoff. The primary reason for acapatamab discontinuation in both parts was disease progression (99/133 [74.4%]); 16/133 (12.0%) discontinued due to patient request, and 7/133 (5.3%) due to AEs.

Safety

All patients in dose exploration and dose expansion experienced TEAEs. Grade 3 TEAEs were reported in 58.4% and 67.9% of patients and grade 4 TEAEs in 19.5% and 12.5% of patients in the dose exploration and expansion parts, respectively.

CRS was the most common TEAE (any grade) in both parts: 97.4% and 98.2% of patients developed CRS in dose exploration and dose expansion, respectively (Table 2A and Table 2B). CRS was also the most commonly observed treatment-related AE (TRAEs) (97.7%). A complete list of TRAEs occurring in ≥ 5% of patients is shown in Supplementary Table S4.

The most common grade ≥ 3 TEAEs in dose exploration were CRS (23.4%), increased aspartate aminotransferase (18.2%), and increased alanine aminotransferase (18.2%) in the context of CRS (Table 2A). The most common grade ≥ 3 TEAEs in dose expansion were anemia (19.6%), CRS (16.1%), and hypophosphatemia (16.1%; Table 2B). Grade 4 TEAEs observed in the two parts are listed in Supplementary Tables S5A and S5B.

In dose exploration, with target doses of 0.09 mg, 0.3 mg and 0.9 mg, grade 3 CRS events developed in 6.3%, 17.9% and 55.6% of patients respectively. Overall, 18/77 (23.4%) patients in dose exploration and 8/56 (14.3%) patients in dose expansion developed grade 3 CRS (Table 3A). A single grade 4 CRS event was noted on cycle 1 day 1 in dose expansion due to a grade 4 acute kidney injury in a patient with a solitary kidney (Table 3B). Of note, there was a progressive decline in the incidence and severity of CRS with increasing treatment cycles (Table 3B). Most CRS events occurred in cycles 1–2 and grade ≥ 3 CRS events were not noted after the first treatment cycle (Table 3B).

There were no permanent treatment discontinuations or fatalities due to CRS in in either part. CRS events were managed using oral or intravenous corticosteroids and IL-6 pathway inhibitors (tocilizumab or siltuximab). A minority of patients required vasopressors and oxygen (Supplementary Table S6). Overall, a lower proportion of patients in dose expansion required corticosteroids or vasopressors for CRS management. Specifically, 35.7% and 8.9% of patients in dose expansion received corticosteroids or vasopressors, respectively, while 44.2% and 15.6% of patients in dose exploration received these medications. The frequency of use of IL-6 pathway inhibitors (tocilizumab/siltuximab) or oxygen administration was similar between dose expansion vs. dose exploration s (41.1% vs. 39.0% and 32.1% vs. 31.2%). There was no difference in the median duration of CRS between patients who received at least one dose of tocilizumab (n = 47/133; median duration of CRS: 3.0 days [median IQR, 2.0–4.0]) and in those who did not receive tocilizumab (n = 83/133; median duration of CRS: 3.0 days [median IQR, 2.0–3.0]).

Other notable TEAEs included eye disorders in 54/133 (40.6%) patients. Of these, blurred vision was noted in 19/133 (14.3%) patients (grade 3 in two patients) and visual impairment in 9/133 (6.8%) patients (grade 4 in one patient). Dry mouth in 52/133 (39.1%) patients (grade ≥3 events were not observed), and deafness in 7/133 (5.3%) patients (grade 3 in two patients) were the other TEAE’s of note.

DLTs were observed in 15 patients (Supplementary Table S7 and Supplementary Table S8). DLTs led to hospitalization in 11 patients, treatment discontinuation in two patients, and treatment interruption in one patient. None of the DLTs were fatal. Three grade 4 DLTs were observed (acute kidney injury, hypertransaminasaemia [both at the 0.3 mg target dose level], and conjunctival oedema [0.6 mg target dose level]).

Efficacy

In dose exploration, confirmed PSA responses were observed in the 0.03–0.9 mg target dose ranges (5 dose levels); PSA responses were not observed in patients who received the 0.003 or 0.01 mg target dose (Table 4, Supplementary Fig. S2). PSA waterfall plots for dose exploration showed deepening maximum (unconfirmed) PSA declines with increasing target dose levels (Supplementary Fig. S2). While only 3 of 6 patients had a PSA decline from baseline at the two lowest target dose levels (0.003 mg and 0.01 mg), all four patients in the 0.6 mg target dose level and 17 of 18 patients in the 0.9 mg target dose level achieved PSA declines. The (confirmed) PSA50 response rate was higher in the 0.3 and 0.6 mg target dose levels (42.9% and 75.0%, respectively) than in the 0.9 mg target dose level (33.3%).

In dose expansion, 30.4% of patients achieved a PSA50 response while 39.3%, 21.4%, and 5.4% of patients achieved a PSA30, PSA70, and PSA90 response, respectively (Table 4, Figure 1A). In dose expansion and exploration, 17/26 (65.4%) and 25/32 (78.1%) of patients with a maximum PSA decline of > 50% achieved PSA50 response confirmation at least 3 weeks later, respectively (Table 4, Figure 1A, Supplementary Fig. S2, Supplementary Fig. S3). At 12 weeks of treatment, a PSA decline of > 50% from baseline was still noted in six patients in dose expansion (Figure 1B). The median PSA PFS ranged between 2.8 and 3.6 months in dose exploration and was 3.3 months (95% CI: 3.0–4.9) in dose expansion (Table 4).

At baseline, patients were tested for tumor volume and tumor expression of PSMA by FDG-PET/CT and PSMA-PET/CT, respectively. While tumor volume was comparable between patients with and without a PSA50 response, patients with a PSA50 response had a higher baseline tumor PSMA expression as indicated by a higher maximum standardized uptake (SUV_{max}) value (Figure 2A). Six patients in the dose expansion group had received prior PSMA-targeting radioligand therapy (Lutetium-177 PSMA therapy) before starting acapatamab; 4/6 patients experienced a PSA decline with acapatamab and one patient experienced a >50% decline in PSA levels (Supplementary Fig. S4).

Outcomes were assessed in the RECIST 1.1-evaluable analysis set for a total of 66 patients (39 patients in dose exploration, 27 patients in dose expansion). In dose exploration, 5/39 (12.8%) patients achieved a partial response (PR) as their best response—1 each in the 0.03, 0.09, and 0.6 mg dose levels, and two patients in the 0.3 mg dose level. Stable disease was noted in 13/39 (33.3%) patients and PD in 15 patients (38.5%). The ORR was 12.8% across all dose exploration groups.

In the dose expansion part, 2 (7.4%) patients achieved a PR; 12 (44.4%) patients had stable disease, and 10 (37.0%) patients had PD as their best response. No patient achieved a complete response (CR) resulting in an ORR of 7.4% in the dose expansion part (Table 4).

The median OS ranged between 7.3 and 19.0 months (median follow-up time: not estimable to 29.5 months) in dose exploration and was estimated to be 10.0 months (95% CI: 8.1–13.5; median follow-up time: 11.1 months) in dose expansion. The median radiographic PFS (rPFS) ranged between 1.7 and 11.4 months (median follow-up time: not estimable to 5.6 months) in dose exploration and 3.7 months (95% CI: 2.0–5.4; median follow-up time: 5.6 months) in dose expansion (Table 4). When rPFS was analyzed by baseline PSMA expression levels, patients with higher tumor PSMA expression (SUV_{max} > 5.06) had longer rPFS compared with those with lower levels of PSMA expression (SUV_{max} < 5.06) (5.4 vs. 2.0 months) (Supplementary Table S9).

In dose expansion, 3 (5.4%) patients continued to be on treatment at data cutoff for this analysis (May 31, 2022). The median duration of exposure to acapatamab in dose expansion was 11.3 weeks (range, 0.3–75.3 weeks). Overall, 7/56 (12.5%) patients received acapatamab for ≥ 24 weeks.

Pharmacokinetics and immunogenicity

The mean (SD) serum concentration-time profile of acapatamab following administration of the RP2D (0.09 mg 3-day eIV infusion; 0.3 mg target dose) in 54 patients who tested negative for anti-acapatamab antibodies in dose exploration and dose expansion is shown in Supplementary Fig S5. Acapatamab demonstrated dose-proportional increases in serum exposure within the evaluated target dose range of 0.003–0.9 mg. Steady-state serum concentrations were achieved within two weeks following the Q2W regimen, with minimal accumulation. With the RP2D regimen, the mean terminal elimination half-life, peak serum concentration (C_{max}), and area under the concentration vs time curve during a 14-day dosing interval (AUC_{14day}) at steady state were estimated to be 105 h (coefficient of variation [CoV]: 25%), 66.9 ng/mL (CoV: 27%) and 5240 h·ng/mL (CoV: 37%), respectively.

As of December 7, 2022, baseline and post-baseline antidrug antibody (ADA) values were available for 81 patients in dose exploration and for 53 patients in dose expansion. Pre-existing ADAs were not observed in any of the tested patients. In dose exploration, 30 of 81 (37%) patients developed treatment-emergent ADAs (TE-ADAs). Patients with detectable ADAs were not tested further for the presence of neutralizing antibodies. In dose expansion, 29 of 53 (55%) patients developed TE-ADAs, of whom 24 developed neutralizing antibodies (24/29, 83%). Nineteen of the 29 TE-ADA-positive (66%) patients had a significant reduction in exposure (as defined by a ≥ 50% decrease in C_{max} or C_{trough}). In dose exploration and dose expansion, the median time to development of TE-ADAs was cycle 3 day 1 (day 56) and cycle 4 day 1 (day 84) respectively. ADA development was not associated with any AEs in both parts.

In dose expansion, 3 subjects maintained their PSA response despite the development of neutralizing and exposure-impacting ADAs; 8 patients had exposure-impacting ADA contemporaneous with PSA reversal. However, many patients had a reversal in PSA decline in the absence of ADAs.

Pharmacodynamics

Acapatamab treatment induced T-cell activation and an increase in proinflammatory cytokine levels. There was a rapid increase in the percentage of activated CD69+ CD4+ and CD69+ CD8+ T cells from baseline with average peak activation levels observed around 24 h for both CD4+ T cells and CD8+ T cells after the first acapatamab infusion with CD8+ T cells maintaining their activation levels for up to 48 h. Activation levels returned to within 10% of baseline levels before the second infusion on cycle 1 day 8 (Figure 2B). Acapatamab induced the production of the proinflammatory cytokines: IFN-γ, TNF-α, IL-10, IL-6, IL-2, and IL-8 the levels of which peaked, in most instances, 24 h after infusion (Figure 2C).

To investigate whether acapatamab induced an increase in the number of activated memory cytotoxic T cells, changes in the frequencies of CD8+ T-cell subsets, including memory and terminally differentiated cells were evaluated for their association with PSA decline at cycle 2, day 1, relative to their frequencies on cycle 1 day 1. Following one cycle of acapatamab treatment, a trend towards the expansion of effector memory CD8+ T cells (CD3+CD8+CD45RA-CD197-), terminally differentiated CD8+ T cells (CD3+CD8+CD45RA+CD197-), and central memory CD8+T cells (CD3+CD8+CD45RA-CD197+) from baseline was observed in patients with a PSA50 response compared with those in patients who did not register a PSA50 response (Figure 2D).

DISCUSSION

Although recently approved therapies have improved survival for patients with mCRPC, the development of drug resistance often complicates the disease course and contributes to relapse and mortality (34). Consequently, there is an urgent need for newer therapies with novel mechanisms of action for PCa that has become resistant to currently available androgen receptor pathway inhibitors, chemotherapies or radioligand therapies. The first BiTE immuno-oncology molecule to demonstrate clinical antitumor activity was blinatumomab, which has shown notable and durable efficacy in the treatment of patients with B-cell acute lymphoblastic leukemia, resulting in accelerated FDA approval in 2014 (35–37). More recently, tarlatamab, a DLL3-targeted BiTE immuno-oncology therapy has shown encouraging results in a phase 1 study of heavily pretreated patients with small-cell lung cancer with an ORR of 23.4% and an impressive median DoR of 12.3 months (38). These findings emphasize the therapeutic potential of BiTE molecules in the treatment of hematological malignancies as well as solid tumors.

In this first-in-human study, acapatamab demonstrated an acceptable safety profile. The most common TEAE in all parts was CRS, which was manageable and reversible with corticosteroids and/or IL-6 pathway inhibitors. In addition, 8.9% of patients in dose expansion received vasopressors for the treatment of CRS-induced hypotension. CRS was most severe in cycle 1 and developed infrequently in later cycles, with less than 20% of patients developing CRS (mostly grade 1) after cycle 3. CRS did not lead to treatment discontinuation in any patient. While the need for management of hypotension with vasopressors in a minority of patients is a concern due to the predominantly elderly patient population, the risks associated with this CRS event were mitigated by increased monitoring in cycle 1. CRS occurring in later cycles was less severe and infrequent,

obviating the need for extended post-infusion observation (≤4 h). In some patients, CRS was accompanied by transient and reversible elevation of alanine and aspartate aminotransferases. Anemia or worsening of pre-existing anemia and thrombocytopenia, associated with CRS, were the other noteworthy TEAEs. Importantly, only 5.3% of all TEAEs led to acapatamab discontinuation. This compares favorably with other non-radioligand PSMA-targeting therapies with distinct mechanisms of action. For example, treatment with MEDI3726, a PSMA-targeting antibody-drug conjugate, resulted in AEs that led to treatment discontinuation in 33.3% of patients in a phase 1 study (39). In the VISION trial, TEAEs led to discontinuation of ^{177}Lu-PSMA-617 in 11.9% of patients in the treatment arm (20).

Dry mouth was a common TEAE noted in 39.1% of the patients in this trial and this frequency was similar to that reported in patients in the VISION trial (38.8%) (20). The association of dry mouth and eye disorders with PSMA-targeting therapies is possibly related to the high levels of PSMA expression reported in the salivary and lacrimal glands (40). Another clinical TEAE of interest was deafness reported in 7/133 (5.3%) patients in this trial. Interestingly, sensorineural deafness was reported in 2/38 (5.3%) patients in a trial of ^{225}Ac-PSMA-617 in patients with mCRPC (41). The etiology could not be identified in either trial.

Overall, acapatamab's safety profile is in line with the expectations for a solid tumor T-cell engager (TCE). CRS was identified as the key safety risk associated with acapatamab therapy and also reported to develop in the majority of patients treated with other PSMA-targeting TCEs such as JNJ-63898081 (26). Similarly, PSMA-targeting CAR T-cell therapy is also known to be associated with high grade CRS development. Two phase 1 studies reported grade ≥ 3 CRS in 2/14 and 3/13 patients who received PSMA-targeting CAR T-cell infusions (42,43). In both studies, one patient died after an initial grade ≥ 3 CRS event occurred (42,43). Although first generation TCEs such as acapatamab are associated with high rates of CRS, they tend to be more manageable and of a lower grade than the CRS associated with CAR T cells.

Early signs of the antitumor activity of acapatamab based on PSA responses were encouraging. Almost half of the patients in dose expansion (26/54, 48%) had an initial PSA decrease from baseline of ≥50%, but only about a third had their PSA50 confirmed at least 3 weeks later (PSA50 response rate in dose expansion: 30.4%). Furthermore, only 7.4% of RECIST-evaluable patients had a confirmed response (PR), suggesting that the initial antitumor activity — based on PSA decline — was not sustained, likely due to secondary resistance mechanisms and/or ADA development with or without loss of exposure. In line with this observation, the median PSA PFS was 3.3 months and the median rPFS was 3.7 months with acapatamab treatment in dose expansion. The PSA50 response rate observed in this study was similar or higher than that reported in mCRPC clinical trials investigating PSMA-targeting CAR T-cells (35.7% PSA50 response rate) (43), the PSMA-targeting antibody-drug conjugate MEDI3726 (1/10, [10.0%] PSA50 response rate in dose exploration) (39), checkpoint inhibitor combination studies with nivolumab plus ipilimumab (10.0% - 17.6% PSA50 response rate) (44), or atezolizumab plus cabozantinib (23% PSA50 response rate) (45). Thus, acapatamab demonstrated preliminary signs of antitumor activity

based on the PSA response rate, particularly in comparison with checkpoint inhibitors. However, the response rate was lower than that reported in the VISION trial in which 46.0% of patients treated with ^{177}Lu-PSMA-617 achieved a PSA50 response (20). A factor contributing to this difference in responses may have been the enrollment of patients independent of PSMA expression status in this study in contrast to the VISION trial, which excluded patients with PSMA-negative lesions. In line with observations from trials of PSMA-targeting radioligand therapies (46), we too observed a higher likelihood of antitumor activity (as measured by a PSA50 response and rPFS) in patients with higher baseline tumor PSMA expression.

The median rPFS of 3.7 months observed with acapatamab treatment was similar to that observed with the post-chemotherapy cohort of the CheckMate 650 trial (3.8 months), in which patients were treated with nivolumab and ipilimumab (44). In the VISION trial, almost all patients (97.5%) had received prior chemotherapy with docetaxel and approximately 40% had received cabazitaxel (20). In this heavily pretreated patient population, the rPFS was 8.7 months in the ^{177}Lu-PSMA-617 plus standard care treatment arm versus 3.4 months in the standard care arm. Therefore, acapatamab monotherapy is expected to have limited potential for exerting a clinically meaningful benefit compared with PSMA-targeting ^{177}Lu-PSMA-617 in this pretreated patient population.

Acapatamab induced a rapid increase in the number of activated CD4+ and CD8+ T cells and increased the levels of inflammatory and other cytokines, consistent with the proposed mechanism of action of TCE molecules. Effector memory T cells are thought to constitute the major population of proliferating T cells following TCE binding and are the primary drivers of antitumor activity in single-agent bispecific TCE therapy (47,48). In keeping with these findings, responders demonstrated a higher expansion in the numbers of effector memory T cells following acapatamab treatment. Overall, the pharmacodynamic analyses confirmed the biological activity of acapatamab in this first-in-human study.

Treatment-emergent ADAs were detected in 37%–55% of patients treated with acapatamab. ADA development was associated with a significant reduction in drug exposure in a majority of ADA-positive patients. ADA development occurring in parallel with other resistance mechanisms may have accounted for the reversal of PSA declines. However, in some patients the PSA response was maintained despite ADA development. Therefore, a clear relationship between ADA development and any observed loss in PSA response could not be conclusively determined in this study. Pasotuxizumab reduced PSA levels (relative to baseline) in 88% of patients who received the drug as a continuous IV infusion (25). ADAs were not detected in patients receiving continuous IV infusion. However, all patients who were administered pasotuxizumab subcutaneously developed ADAs. ADAs also developed in patients treated with JNJ-63898081; 63.0% of patients who received JNJ-63898081 subcutaneously and 17.0% of those who received JNJ-63898081 intravenously at the highest dose level developed ADAs; ADAs were associated with decreasing serum concentrations of JNJ-63898081 in patients who received subcutaneous doses of the drug (26). In contrast to these studies, the current study included a dose expansion phase in which 56 patients were treated at the RP2D, allowing for a more comprehensive evaluation of the safety and preliminary efficacy of acapatamab.

Although the first generation of PSMA-targeting T cell engagers such as pasotuxizumab and acapatamab demonstrated early signs of antitumor activity, lack of response durability coupled with the CRS profile make future development challenging. CRS is of particular concern given the elderly patient population in which PCa typically develops and the challenges associated with hypotension and/or hypoxia in such patients. The next generation of molecules are being developed to overcome these obstacles. AMG 340 demonstrated preclinical efficacy in vivo models with markedly attenuated levels of cytokine production following T-cell activation, possibly improving the clinical CRS profile (49). JANX007 aims to decrease the frequency and severity of CRS through conditional activation within the tumor. Both these (NCT04740034 and NCT05519449, respectively) and other TCEs for the treatment of mCRPC are currently in phase 1 clinical development and interim results are eagerly anticipated. Other strategies to improve efficacy include combining TCE therapy with blockade of the programmed death-1 pathway to overcome the immunosuppressive microenvironment that characterizes many solid tumors (50). Structural modifications to increase efficacy are currently mostly in the development stage and include improvements in the antigen-binding valency of TCEs and development of multi-specific TCEs that target multiple molecules involved in anti-tumor immunity (51). Recently, xaluritamig, a 2+1 TCE with dual binding domains for the tumor-associated antigen, six-transmembrane epithelial antigen of the prostate 1 (STEAP1), and an anti-CD3 domain achieved encouraging PSA50 (49%–59%) and ORR (24%–41%) responses in a first-in-human study of patients with mCRPC pretreated with taxane (52) (53).

In conclusion, the results of this phase 1 study indicate that acapatamab monotherapy was associated with a manageable safety profile dominated by CRS and showed early signs of antitumor activity but with limited durability in this group of heavily pretreated patients with mCRPC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. International Agency for Research on Cancer: World Health Organization. Cancer Fact Sheets. [cited 2022 Oct 5]. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/27-Prostate-fact-sheet.pdf.
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022;72(1):7–33. doi 10.3322/caac.21708. [PubMed: 35020204]
3. Kirby M, Hirst C, Crawford ED. Characterising the castration-resistant prostate cancer population: a systematic review. Int J Clin Pract 2011;65(11):1180–92. doi 10.1111/j.1742-1241.2011.02799.x. [PubMed: 21995694]
4. Halabi S, Kelly WK, Ma H, Zhou H, Solomon NC, Fizazi K, et al. Meta-Analysis evaluating the impact of site of metastasis on overall survival in men with castration-resistant prostate cancer. J Clin Oncol 2016;34(14):1652–9. doi 10.1200/jco.2015.65.7270. [PubMed: 26951312]
5. Moreira DM, Howard LE, Sourbeer KN, Amarasekara HS, Chow LC, Cockrell DC, et al. Predicting time from metastasis to overall survival in castration-resistant prostate cancer: Results from SEARCH. Clin Genitourin Cancer 2017;15(1):60–6. e2. doi 10.1016/j.clgc.2016.08.018. [PubMed: 27692812]
6. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351(15):1502–12. doi 10.1056/NEJMoa040720. [PubMed: 15470213]
7. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364(21):1995–2005. doi 10.1056/NEJMoa1014618. [PubMed: 21612468]
8. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371(5):424–33. doi 10.1056/NEJMoa1405095. [PubMed: 24881730]
9. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367(13):1187–97. doi 10.1056/NEJMoa1207506. [PubMed: 22894553]
10. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363(5):411–22. doi 10.1056/NEJMoa1001294. [PubMed: 20818862]
11. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fosså SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med 2013;369(3):213–23. doi 10.1056/NEJMoa1213755. [PubMed: 23863050]
12. de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376(9747):1147–54. doi 10.1016/s0140-6736(10)61389-x. [PubMed: 20888992]

13. de Bono J, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 2020;382(22):2091–102. doi 10.1056/NEJMoa1911440. [PubMed: 32343890]

14. Gillessen S, Bossi A, Davis ID, de Bono J, Fizazi K, James ND, et al. Management of patients with advanced prostate cancer-metastatic and/or castration-resistant prostate cancer: Report of the Advanced Prostate Cancer Consensus Conference (APCCC) 2022. Eur J Cancer 2023;185:178–215. doi 10.1016/j.ejca.2023.02.018. [PubMed: 37003085]

15. Bostwick DG, Pacelli A, Blute M, Roche P, Murphy GP. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer 1998;82(11):2256–61. doi 10.1002/(sici)1097-0142(19980601)82:11<2256::aid-cncr22>3.0.co;2-s. [PubMed: 9610707]

16. Cimadamore A, Cheng M, Santoni M, Lopez-Beltran A, Battelli N, Massari F, et al. New prostate cancer targets for diagnosis, imaging, and therapy: Focus on prostate-specific membrane antigen. Front Oncol 2018;8:653. doi 10.3389/fonc.2018.00653. [PubMed: 30622933]

17. Fendler WP, Eiber M, Beheshti M, Bomanji J, Calais J, Ceci F, et al. PSMA PET/CT: joint EANM procedure guideline/SNMMI procedure standard for prostate cancer imaging 2.0. Eur J Nucl Med Mol Imaging 2023;50(5):1466–86. doi 10.1007/s00259-022-06089-w. [PubMed: 36604326]

18. Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, et al. [(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol 2018;19(6):825–33. doi 10.1016/s1470-2045(18)30198-0. [PubMed: 29752180]

19. Hofman MS, Emmett L, Sandhu S, Iravani A, Joshua AM, Goh JC, et al. [(177)Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. Lancet 2021;397(10276):797–804. doi 10.1016/s0140-6736(21)00237-3. [PubMed: 33581798]

20. Sartor O, de Bono J, Chi KN, Fizazi K, Herrmann K, Rahbar K, et al. Lutetium-177–PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 2021;385(12):1091–103. doi 10.1056/NEJMoa2107322. [PubMed: 34161051]

21. Arvedson T, Bailis JM, Britten CD, Klinger M, Nagorsen D, Coxon A, et al. Targeting solid tumors with bispecific T cell engager immune therapy. Annual Review of Cancer Biology 2022;6(1):17–34. doi 10.1146/annurev-cancerbio-070620-104325.

22. Baeuerle PA, Reinhardt C. Bispecific T-cell engaging antibodies for cancer therapy. Cancer Res 2009;69(12):4941–4. doi 10.1158/0008-5472.Can-09-0547. [PubMed: 19509221]

23. Bailis J, Deegen P, Thomas O, Bogner P, Wahl J, Liao M, et al. Preclinical evaluation of AMG 160, a next-generation bispecific T cell engager (BiTE) targeting the prostate-specific membrane antigen PSMA for metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2019;37(7_suppl):301. doi 10.1200/JCO.2019.37.7_suppl.301.

24. Klinger M, Benjamin J, Kischel R, Stienen S, Zugmaier G. Harnessing T cells to fight cancer with BiTE® antibody constructs--past developments and future directions. Immunol Rev 2016;270(1):193–208. doi 10.1111/imr.12393. [PubMed: 26864113]

25. Hummel HD, Kufer P, Grüllich C, Seggewiss-Bernhardt R, Deschler-Baier B, Chatterjee M, et al. Pasotuxizumab, a BiTE(®) immune therapy for castration-resistant prostate cancer: Phase I, dose-escalation study findings. Immunotherapy 2021;13(2):125–41. doi 10.2217/imt-2020-0256. [PubMed: 33172323]

26. Lim EA, Schweizer MT, Chi KN, Aggarwal R, Agarwal N, Gulley J, et al. Phase 1 study of safety and preliminary clinical activity of JNJ-63898081, a PSMA and CD3 bispecific antibody, for metastatic castration-resistant prostate cancer. Clin Genitourin Cancer 2023;21(3):366–75. doi 10.1016/j.clgc.2023.02.010. [PubMed: 36948922]

27. Rath T, Baker K, Dumont JA, Peters RT, Jiang H, Qiao SW, et al. Fc-fusion proteins and FcRn: structural insights for longer-lasting and more effective therapeutics. Crit Rev Biotechnol 2015;35(2):235–54. doi 10.3109/07388551.2013.834293. [PubMed: 24156398]

28. Tang Y, Cao Y. Modeling pharmacokinetics and pharmacodynamics of therapeutic antibodies: Progress, challenges, and future directions. Pharmaceutics 2021;13(3):422. doi 10.3390/pharmaceutics13030422. [PubMed: 33800976]

29. Deegen P, Thomas O, Nolan-Stevaux O, Li S, Wahl J, Bogner P, et al. The PSMA-targeting half-life extended BiTE therapy AMG 160 has potent antitumor activity in preclinical models of metastatic castration-resistant prostate cancer. Clin Cancer Res 2021;27(10):2928–37. doi 10.1158/1078-0432.CCR-20-3725. [PubMed: 33504551]
30. Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, et al. Trial design and objectives for castration-resistant prostate cancer: Updated recommendations from the prostate cancer Clinical Trials Working Group 3. J Clin Oncol 2016;34(12):1402–18. doi 10.1200/JCO.2015.64.2702. [PubMed: 26903579]
31. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood 2014;124(2):188–95. doi 10.1182/blood-2014-05-552729. [PubMed: 24876563]
32. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47. doi 10.1016/j.ejca.2008.10.026. [PubMed: 19097774]
33. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med 2008;27(13):2420–39. doi 10.1002/sim.3230. [PubMed: 18344187]
34. Buttigliero C, Tucci M, Bertaglia V, Vignani F, Bironzo P, Di Maio M, et al. Understanding and overcoming the mechanisms of primary and acquired resistance to abiraterone and enzalutamide in castration resistant prostate cancer. Cancer Treat Rev 2015;41(10):884–92. doi 10.1016/j.ctrv.2015.08.002. [PubMed: 26342718]
35. von Stackelberg A, Locatelli F, Zugmaier G, Handgretinger R, Trippett TM, Rizzari C, et al. Phase I/Phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. J Clin Oncol 2016;34(36):4381–9. doi 10.1200/JCO.2016.67.3301. [PubMed: 27998223]
36. Kantarjian H, Stein A, Gokbuget N, Fielding AK, Schuh AC, Ribera JM, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med 2017;376(9):836–47. doi 10.1056/NEJMoa1609783. [PubMed: 28249141]
37. Gokbuget N, Dombret H, Bonifacio M, Reichle A, Graux C, Faul C, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. Blood 2018;131(14):1522–31. doi 10.1182/blood-2017-08-798322. [PubMed: 29358182]
38. Paz-Ares L, Champiat S, Lai WV, Izumi H, Govindan R, Boyer M, et al. Tarlatamab, a First-in-Class DLL3-Targeted Bispecific T-Cell Engager, in Recurrent Small-Cell Lung Cancer: An Open-Label, Phase I Study. J Clin Oncol 2023;41(16):2893–903. doi 10.1200/JCO.22.02823. [PubMed: 36689692]
39. de Bono JS, Fleming MT, Wang JS, Cathomas R, Miralles MS, Bothos J, et al. Phase I study of MEDI3726: A prostate-specific membrane antigen-targeted antibody-drug conjugate, in patients with mCRPC after failure of abiraterone or enzalutamide. Clin Cancer Res 2021;27(13):3602–9. doi 10.1158/1078-0432.CCR-20-4528. [PubMed: 33795255]
40. Klein Nulent TJW, Valstar MH, de Keizer B, Willems SM, Smit LA, Al-Mamgani A, et al. Physiologic distribution of PSMA-ligand in salivary glands and seromucous glands of the head and neck on PET/CT. Oral Surg Oral Med Oral Pathol Oral Radiol 2018;125(5):478–86. doi 10.1016/j.oooo.2018.01.011. [PubMed: 29523427]
41. Sen I, Thakral P, Tiwari P, Pant V, Das SS, Manda D, et al. Therapeutic efficacy of (225)Ac-PSMA-617 targeted alpha therapy in patients of metastatic castrate resistant prostate cancer after taxane-based chemotherapy. Ann Nucl Med 2021;35(7):794–810. doi 10.1007/s12149-021-01617-4. [PubMed: 34059998]
42. Narayan V, Barber-Rotenberg JS, Jung IY, Lacey SF, Rech AJ, Davis MM, et al. PSMA-targeting TGFbeta-insensitive armored CAR T cells in metastatic castration-resistant prostate cancer: a phase 1 trial. Nat Med 2022;28(4):724–34. doi 10.1038/s41591-022-01726-1. [PubMed: 35314843]
43. Slovin S, Dorff T, Falchook G, Wei X, Gao X, McKay RR, et al. Phase 1 study of P-PSMA-101 CAR-T cells in patients with metastatic castration resistant prostate cancer (mCRPC). Poster presented at: American Society for Clinical Oncology Genitourinary Cancer Symposium; Feb 17–19, 2022; San Francisco, CA.

44. Sharma P, Pachynski RK, Narayan V, Flechon A, Gravis G, Galsky MD, et al. Nivolumab Plus ipilimumab for metastatic castration-resistant prostate cancer: Preliminary analysis of patients in the CheckMate 650 trial. Cancer Cell 2020;38(4):489–99.e3. doi 10.1016/j.ccell.2020.08.007. [PubMed: 32916128]
45. Agarwal N, McGregor B, Maughan BL, Dorff TB, Kelly W, Fang B, et al. Cabozantinib in combination with atezolizumab in patients with metastatic castration-resistant prostate cancer: results from an expansion cohort of a multicentre, open-label, phase 1b trial (COSMIC-021). Lancet Oncol 2022;23(7):899–909. doi 10.1016/S1470-2045(22)00278-9. [PubMed: 35690072]
46. Emmett L, Crumbaker M, Ho B, Willowson K, Eu P, Ratnayake L, et al. Results of a Prospective Phase 2 Pilot Trial of (177)Lu-PSMA-617 Therapy for Metastatic Castration-Resistant Prostate Cancer Including Imaging Predictors of Treatment Response and Patterns of Progression. Clin Genitourin Cancer 2019;17(1):15–22. doi 10.1016/j.clgc.2018.09.014. [PubMed: 30425003]
47. Huo Y, Sheng Z, Lu DR, Ellwanger DC, Li CM, Homann O, et al. Blinatumomab-induced T cell activation at single cell transcriptome resolution. BMC Genomics 2021;22(1):145. doi 10.1186/s12864-021-07435-2. [PubMed: 33648458]
48. Baeuerle PA, Wesche H. T-cell-engaging antibodies for the treatment of solid tumors: challenges and opportunities. Curr Opin Oncol 2022;34(5):552–8. doi 10.1097/CCO.0000000000000869. [PubMed: 35880455]
49. Dang K, Castello G, Clarke SC, Li Y, Balasubramani A, Boudreau A, et al. Attenuating CD3 affinity in a PSMAxCD3 bispecific antibody enables killing of prostate tumor cells with reduced cytokine release. J Immunother Cancer 2021;9:e002488.(6). doi 10.1136/jitc-2021-002488. [PubMed: 34088740]
50. Krupka C, Kufer P, Kischel R, Zugmaier G, Lichtenegger FS, Kohnke T, et al. Blockade of the PD-1/PD-L1 axis augments lysis of AML cells by the CD33/CD3 BiTE antibody construct AMG 330: reversing a T-cell-induced immune escape mechanism. Leukemia 2016;30(2):484–91. doi 10.1038/leu.2015.214. [PubMed: 26239198]
51. Zhou S, Liu M, Ren F, Meng X, Yu J. The landscape of bispecific T cell engager in cancer treatment. Biomark Res 2021;9(1):38. doi 10.1186/s40364-021-00294-9. [PubMed: 34039409]
52. Nolan-Stevaux O, Li C, Liang L, Zhan J, Estrada J, Osgood T, et al. AMG 509 (Xaluritamig), an Anti-STEAP1 XmAb 2+1 T-cell Redirecting Immune Therapy with Avidity-Dependent Activity Against Prostate Cancer. Cancer Discov 2023. doi 10.1158/2159-8290.CD-23-0984.
53. Kelly WK, Danila DC, Lin CC, Lee JL, Matsubara N, Ward PJ, et al. Xaluritamig, a STEAP1 × CD3 XmAb 2+1 Immune Therapy for Metastatic Castration-Resistant Prostate Cancer: Results from Dose Exploration in a First-in-Human Study. Cancer Discov 2023:OF1–OF14. doi 10.1158/2159-8290.CD-23-0964.

TRANSLATIONAL RELEVANCE

Prostate-specific membrane antigen (PSMA) is a diagnostically and therapeutically validated target for prostate cancer. In 2022, the PSMA-targeting radioligand ^{177}Lu-PSMA-617 was approved by the Food and Drug Administration (FDA) for the treatment of patients with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) previously treated with androgen receptor pathway inhibitors and taxane-based chemotherapy. Acapatamab is a half-life extended, PSMA-targeting, T-cell engager (TCE) that was evaluated in a similar, heavily pretreated mCRPC patient population in this first-in-human study. As expected, the most common treatment-related adverse event was cytokine release syndrome which was manageable and reversible. Early antitumor activity, as demonstrated by prostate-specific antigen declines, was not sustained in the majority of dose expansion patients, possibly, in part, due to the development of antidrug antibodies that reduced systemic drug exposure. Nonetheless, these early signs of antitumor activity provide clinical validation for the potential of TCEs to treat mCRPC.

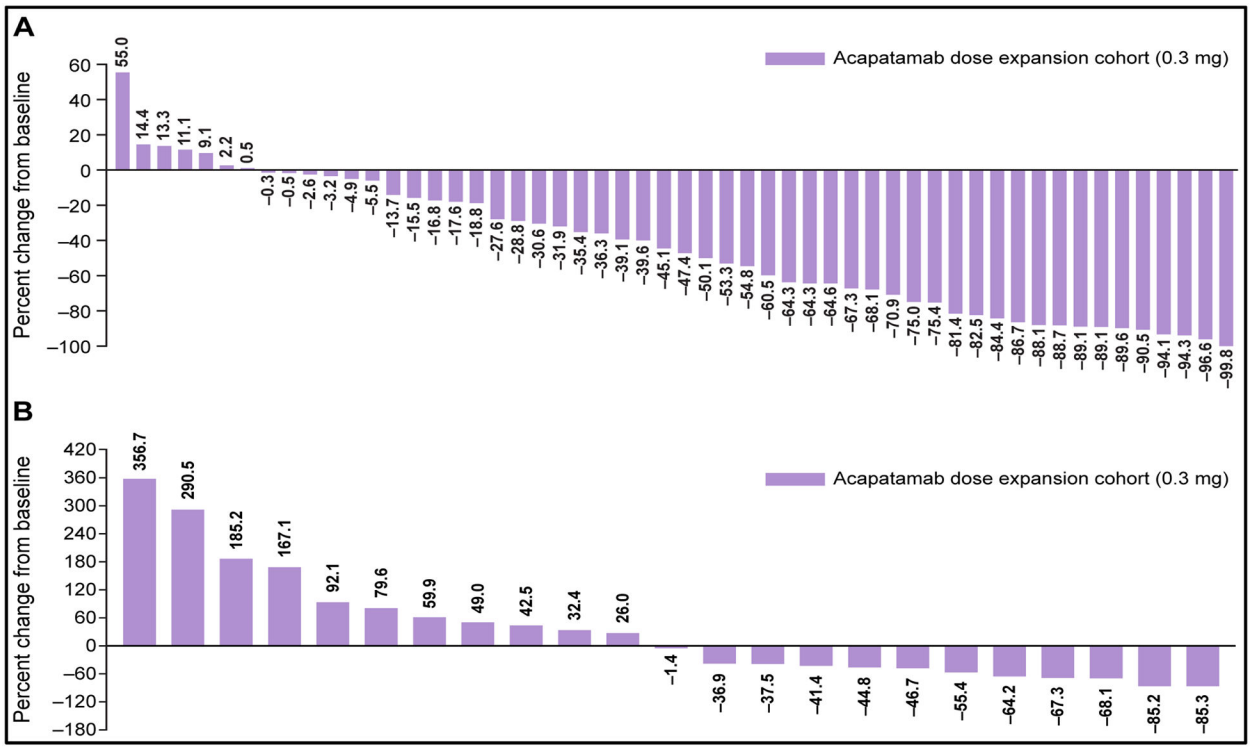

Figure 1.

Prostate-specific antigen response with acapatamab in dose expansion

Figure 1A. Best (unconfirmed) PSA response after treatment initiation, shown as percentage change from baseline for each of the 54 patients with post-baseline PSA measurements.

Figure 1B. Prostate-specific antigen response 12 weeks after acapatamab initiation shown as percentage change from baseline for patients (n = 23) in the PSA response evaluable set in dose expansion. The PSA response evaluable set included all subjects that enrolled and received at least one dose of acapatamab, had measurable (>0) baseline PSA levels and had the opportunity to be followed for at least 9 weeks starting from study day 1 and included patients who discontinued treatment prior to the 9-week time point as long as the data cut-off date was at least 9 weeks after cycle 1 day 1 of acapatamab treatment.

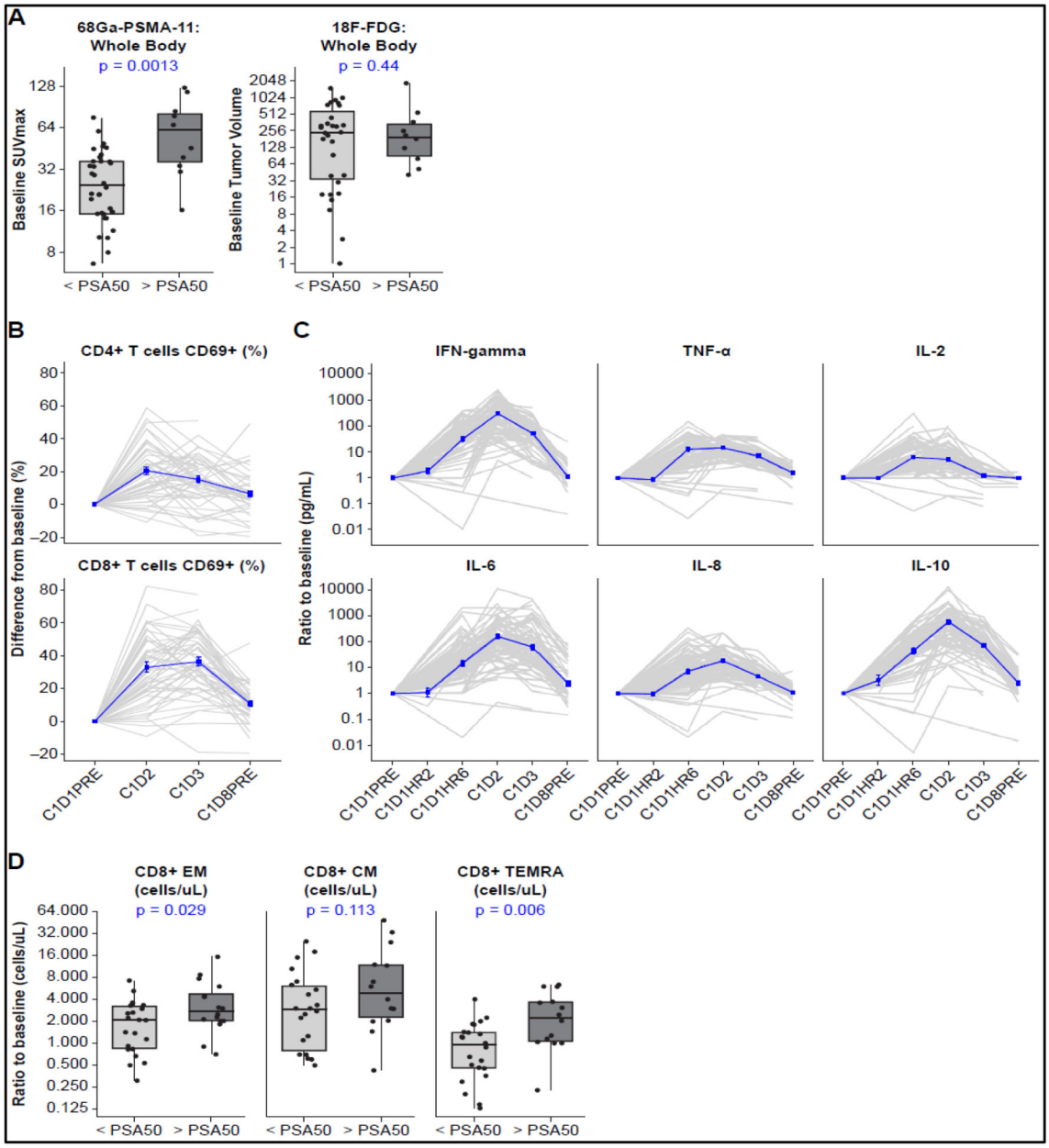

Figure 2.

Association of baseline tumor volume with prostate-specific antigen response and pharmacodynamics associated with acapatamab therapy

Figure 2. Panel A: Higher baseline tumor PSMA expression was associated with PSA50 responses. Panels 2B, 2C, and 2D: Acapatamab induces T-cell activation in patients and higher levels of T cell differentiation in responders.

Panel A shows the baseline PSMA maximum standardized uptake value (SUVmax) and baseline tumor volume as measured by PSMA-PET/CT and FDG-PET/CT in patients with and without a PSA50 response. Number of patients assessed by PSMA-PET/CT = 45; < PSA50 = 34; > PSA50 = 11; the number of patients assessed by FDG-PET/CT = 41; < PSA50 = 31; > PSA50 = 10. Patients in Panel B, C, and D received a 3-day eIV infusion

of 0.09 mg acapatamab in week 1, followed by 0.3 mg of IV acapatamab (target dose), administered over 1h every 2 weeks starting in week 2. **Panel B** shows the changes from baseline in the percentage of activated (CD69+) CD4+ T cells and CD8+ T cells (n = 62). The blue line represents mean ± standard error. Grey lines represent data from individual patients. **Panel C** shows cytokine induction following acapatamab infusion within the first infusion period (n = 63). Data are shown as fold change from baseline. Blue lines represent mean ± standard error. Grey lines represent data from individual patients. **Panel D** shows the ratio of change in the number of different T cell subsets by PSA50 response from baseline at cycle 2, day 1 prior to next acapatamab infusion (< PSA50, n = 11; > PSA50, n = 26) for flow cytometry analysis. Changes in T cell numbers are shown relative to baseline. Abbreviations: C: cycle; CM: central memory; D: day; EM: effector memory; HR: hour; pre: pre-acapatamab infusion; PSA: prostate-specific antigen; TEMRA: effector memory T cells re-expressing CD45RA

Table 1.

Baseline demographics and clinical characteristics of study patients

	Dose exploration[a] (N = 77)							Dose expansion (N = 56)	Total
	Target dose levels								
	0.003 mg (n = 3)	0.01 mg (n = 4)	0.03 mg (n = 4)	0.09 mg (n = 16)	0.3 mg (n = 28)	0.6 mg (n = 4)	0.9 mg (n = 18)	0.3 mg	(N =133)
Age, median (range), years	69.0 (56–70)	69.0 (66–73)	60.5 (49–62)	65.0 (45–76)	69.0 (51–79)	63.5 (51–77)	63.5 (52–78)	67.5 (51–85)	**67.0 (45–85)**
Race, n (%)									
White	2 (66.7)	4 (100.0)	4 (100.0)	11 (68.8)	13 (46.4)	4 (100.0)	13 (72.2)	33 (58.9)	**84 (63.2)**
Asian	1 (33.3)	0 (0.0)	0 (0.0)	4 (25.0)	9 (32.1)	0 (0.0)	1 (5.6)	10 (17.9)	**25 (18.8)**
Black/African American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.7)	0 (0.0)	1 (5.6)	1 (1.8)	**5 (3.8)**
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	3 (10.7)	0 (0.0)	3 (16.7)	12 (21.4)	**19 (14.3)**
ECOG PS, n (%)									
0	1 (33.3)	1 (25.0)	3 (75.0)	11 (68.8)	14 (50.0)	4 (100.0)	8 (44.4)	26 (46.4)	**68 (51.1)**
1	2 (66.7)	3 (75.0)	1 (25.0)	5 (31.3)	14 (50.0)	0 (0.0)	9 (50.0)	30 (53.6)	**64 (48.1)**
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)	0 (0.0)	**1 (0.8)**
Number of prior systemic therapies, n (%)									
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)	1 (5.6)	6 (10.7)	**8 (6.0)**
3	2 (66.7)	1 (25.0)	1 (25.0)	1 (6.3)	3 (10.7)	1 (25.0)	7 (38.9)	9 (16.1)	**25 (18.8)**
4	1 (33.3)	1 (25.0)	1 (25.0)	6 (37.5)	9 (32.1)	1 (25.0)	4 (22.2)	10 (17.9)	**33 (24.8)**
5	0 (0.0)	0 (0.0)	1 (25.0)	3 (18.8)	1 (3.6)	1 (25.0)	3 (16.7)	12 (21.4)	**21 (15.8)**
6	0 (0.0)	1 (25.0)	0 (0.0)	5 (31.3)	7 (25.0)	1 (25.0)	3 (16.7)	9 (16.1)	**26 (19.5)**
7	0 (0.0)	1 (25.0)	1 (25.0)	1 (6.3)	7 (25.0)	0 (0.0)	0 (0.0)	9 (16.1)	**19 (14.3)**
Number of subjects reporting prior use of taxane chemotherapy	3 (100.0)	4 (100.0)	4 (100.0)	16 (100.0)	28 (100.0)	4 (100.0)	17 (94.4)	52 (92.9)	**128 (96.2)**
Number of subjects reporting prior use of ARPI	3 (100.0)	4 (100.0)	4 (100.0)	16 (100.0)	28 (100.0)	4 (100.0)	18 (100.0)	55 (98.2)	**132 (99.2)**
PSA level at baseline (local laboratory reading)									
Median (range), ng/mL	36.6 (3.5–130.0)	100.4 (50.8–1056.0)	302.0 (79.2–1887.9)	32.8 (6.4–1514.0)	171.6 (4.2–4862.0)	198.9 (84.7–2713.0)	114.0 (0.1–4035.0)	107.0 (0.5–8196.0)	**112.2 (0.1–8196.0)**

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	Dose exploration[a] (N = 77)							Dose expansion (N = 56)	Total
	Target dose levels								
	0.003 mg (n = 3)	0.01 mg (n = 4)	0.03 mg (n = 4)	0.09 mg (n = 16)	0.3 mg (n = 28)	0.6 mg (n = 4)	0.9 mg (n = 18)	0.3 mg	(N =133)
No. of patients with visceral metastases [b], n %)	0 (0.0)	0 (0.0)	0 (0.0)	4 (25.0)	6 (21.4)	1 (25.0)	2 (11.1)	9 (16.1)	**22 (16.5)**

[a] Patients received acapatamab (target doses: 0.003–0.9 mg) intravenously Q2W. Administration of target doses between 0.03 mg and 0.9 mg was preceded by either step-dosing or extended IV infusions.

[b] Sites considered for visceral metastases were the abdomen, brain, breast, eye, gastrointestinal tract, heart, kidney, liver, lung, pleura, retroperitoneum, skin, spleen, bladder, and the colon. Patients with visceral metastases in more than one site were counted once.

Abbreviations: ARPI = androgen receptor pathway inhibitors

Table 2A.

Worst grade ≥ 3 treatment-emergent adverse events noted in greater than 5% of patients in dose exploration

	Dose exploration (N = 77)	
TEAE	**Any grade n (%)**	**Grade ≥ 3 n (%)**
Cytokine release syndrome	75 (97.4)	18 (23.4)
Fatigue	41 (53.2)	6 (7.8)
Aspartate aminotransferase increased	26 (33.8)	14 (18.2)[a]
Hypophosphatemia	24 (31.2)	7 (9.1)
Alanine aminotransferase increased	22 (28.6)	14 (18.2)[b]
Anemia	21 (27.3)	13 (16.9)
Bone pain	10 (13.0)	4 (5.2)
Hypertension	10 (13.0)	9 (11.7)
Atrial fibrillation	9 (11.7)	4 (5.2)
Platelet count decreased	9 (11.7)	4 (5.2)[b]
Lymphopenia	5 (6.5)	4 (5.2)[c]

[a] Includes 6 patients who experienced grade 4 TEAEs

[b] Includes 2 patients who experienced grade 4 TEAEs

[c] All 4 patients experienced grade 4 TEAEs

TEAEs were coded using MedDRA version 25.0 and graded using CTCAE version 5.0 criteria.

Table 2B.

Worst grade ≥ 3 treatment-emergent adverse events noted in greater than 5% of patients in dose expansion

TEAE	Dose expansion (N = 56)	
	Any grade n (%)	Grade ≥ 3 n (%)
Cytokine release syndrome	55 (98.2)	9 (16.1)[a]
Anemia	20 (35.7)	11 (19.6)
Hypophosphatemia	20 (35.7)	9 (16.1)
Alanine aminotransferase increased	12 (21.4)	3 (5.4)
Aspartate aminotransferase increased	11 (19.6)	3 (5.4)
Platelet count decreased	8 (14.3)	3 (5.4)[a]
Hypertension	4 (7.1)	3 (5.4)
Neutropenia	4 (7.1)	4 (7.1)[a]

[a]Includes 1 patient who experienced a grade 4 event.

TEAEs were coded using MedDRA version 25.0 and graded using CTCAE version 5.0 criteria.

Table 3A.

Incidence of treatment-emergent cytokine release syndrome

	Dose exploration (N = 77)							Dose expansion	Total
	Target dose levels								
	0.003 mg (n = 3) n (%)	**0.01 mg (n = 4) n (%)**	**0.03 mg (n = 4) n (%)**	**0.09 mg (n = 16) n (%)**	**0.3 mg (n = 28) n (%)**	**0.6 mg (n = 4) n (%)**	**0.9 mg (n = 18) n (%)**	**0.3 mg (N = 56) n (%)**	**N = 133 n (%)**
Number of patients reporting treatment-emergent CRS adverse events	2 (66.7)	4 (100.0)	3 (75.0)	16 (100.0)	28 (100.0)	4 (100.0)	18 (100.0)	55 (98.2)	**130 (97.7)**
Worst grade ≥3 CRS[a]	0 (0.0)	1 (25.0)	1 (25.0)	1 (6.3)	5 (17.9)	0 (0.0)	10 (55.6)	9 (16.1)[b]	**27 (20.3)**
Serious adverse events	0 (0.0)	2 (50.0)	1 (25.0)	4 (25.0)	4 (14.3)	0 (0.0)	7 (38.9)	18 (32.1)	**36 (27.1)**
Leading to treatment interruption	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (14.3)	0 (0.0)	1 (5.6)	10 (17.9)	**15 (11.3)**
Leading to treatment discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**

[a] No grade 5 CRS event was observed.

[b] Includes 1 patient who experienced a grade 4 CRS event

Table 3B.

Incidence of treatment-emergent cytokine release syndrome by treatment cycle in dose expansion

	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Dose expansion 0.3 mg (N = 56)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Cycle 1 Day 1	53 (94.6)	21 (37.5)	28 (50.0)	3 (5.4)	1 (1.8)
Cycle 1 Day 8	42 (75.0)	19 (33.9)	20 (35.7)	3 (5.4)	0 (0.0)
Cycle 1 Day 22	30 (53.6)	19 (33.9)	9 (16.1)	2 (3.6)	0 (0.0)
Cycle 2 Day 1	26 (46.4)	17 (30.4)	9 (16.1)	0 (0.0)	0 (0.0)
Cycle 2 Day 15	26 (46.4)	13 (23.2)	13 (23.2)	0 (0.0)	0 (0.0)
Cycle 3 Day 1	10 (17.9)	9 (16.1)	1 (1.8)	0 (0.0)	0 (0.0)
Cycle 3 Day 15	8 (14.3)	4 (7.1)	4 (7.1)	0 (0.0)	0 (0.0)
Cycle 4 Day 1	4 (7.1)	4 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 4 Day 15	3 (5.4)	3 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cycle 5+	4 (7.1)	3 (5.4)	1 (1.8)	0 (0.0)	0 (0.0)

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Table 4.

Prostate-specific antigen response, best overall response, and radiographic progression-free survival response

	Dose exploration (N = 77)							Dose expansion (N = 56)	Total
	Target dose levels								
	0.003 mg (N = 3) n (%)	**0.01 mg (N = 4) n (%)**	**0.03 mg (N = 4) n (%)**	**0.09 mg (N = 16) n (%)**	**0.3 mg (N = 28) n (%)**	**0.6 mg (N = 4) n (%)**	**0.9 mg (N = 18) n (%)**	**0.3 mg n (%)**	**(N = 133) n (%)**
PSA Response[a,b,c]									
PSA30	0 (0.0)	0 (0.0)	2 (50.0)	4 (25.0)	14 (50.0)	4 (100.0)	8 (44.4)	22 (39.3)	**54 (40.6)**
PSA50	0 (0.0)	0 (0.0)	1 (25.0)	3 (18.8)	12 (42.9)	3 (75.0)	6 (33.3)	17 (30.4)	**42 (31.6)**
PSA70	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	7 (25.0)	3 (75.0)	5 (27.8)	12 (21.4)	**29 (21.8)**
PSA90	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	4 (14.3)	2 (50.0)	3 (16.7)	3 (5.4)	**13 (9.8)**
PSA PFS[d] **(in months)**									
Median (95% CI)	2.8 (1.4, NE)	3.6 (2.5, NE)	2.9 (1.5, NE)	3.8 (2.1, 6.2)	3.0 (2.4, 3.5)	3.6 (2.1, NE)	3.0 (2.1, 5.6)	3.3 (3.0, 4.9)	**3.1** (3.0, 3.7)
RECIST 1.1 response[e,f]									
RECIST 1.1-evaluable	2	2	1	10	13	1	10	27	66
No. of patients for whom BOR assessment was done	1 (50.0)	2 (100.0)	1 (100.0)	10 (100.0)[g]	10 (76.9)	1 (100.0)	9 (90.0)	25 (92.6)[h]	59 (89.4)
Complete response (CR)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**
Partial response (PR)	0 (0.0)	0 (0.0)	1 (100.0)	1 (10.0)	2 (15.4)	1 (100.0)	0 (0.0)	2 (7.4)	**7 (10.6)**
Stable disease (SD)	1 (50.0)	1 (50.0)	0 (0.0)	2 (20.0)	7 (53.8)	0 (0.0)	2 (20.0)	12 (44.4)	**25 (37.9)**
Progressive disease (PD)	0 (0.0)	1 (50.0)	0 (0.0)	6 (60.0)	1 (7.7)	0 (0.0)	7 (70.0)	10 (37.0)	**25 (37.9)**
rPFS[i] **(in months)**									
Median (95% CI)	1.7 (1.4, NE)	5.0 (1.6, NE)	11.4 (1.5, NE)	3.8 (0.9,10.4)	4.9 (3.5, 6.9)	8.3 (NE, NE)	2.1 (1.8, 3.8)	3.7 (2.0, 5.4)	**3.8 (3.5, 4.9)**
Median follow-up time (95% CI)	1.8 (NE, NE)	NE (1.9, NE)	NE (8.1, NE)	5.4 (3.7, NE)	5.6 (2.9, NE)	4.1 (0.03, NE)	NE (5.4, NE)	5.6 (2.0, 7.9)	5.6 (5.4, 8.1)

[a]PSA response evaluable analysis set is defined as all patients who were enrolled; received ≥ 1 dose of acapatamab; and had a measurable (i.e., > 0) baseline PSA, as measured at a local laboratory, and had the opportunity to be followed for ≥ 9 weeks starting from study day 1. Patients who stopped disease assessment prior to 9 weeks were included in this analysis set if the data cutoff was ≥ 9 weeks after their first study dose date.

[b] All PSA responses shown here were confirmed by a second value ≥ 3 weeks later.

[c] A PSA30/50/70/90 response is defined as a ≥ 30%/ ≥ 50%/ ≥ 70%/ ≥ 90% reduction from the baseline PSA level to the PSA level during any post-baseline visit (maximum reduction), respectively.

[d] PSA PFS is defined as the interval from study day 1 to the earlier of either PSA progression or death from any cause; otherwise, PSA PFS was censored on the date of the last PSA measurement. If a patient had no post-baseline PSA measurement and a vital status of alive or unknown, PSA PFS was censored on study day 1.

[e] RECIST 1.1 evaluable analysis set includes all patients who are enrolled; received at least 1 dose of acapatamab; had measurable baseline disease per RECIST 1.1 with PCWG3 modifications per protocol; and had the opportunity to be followed for at least 9 weeks starting from study day 1. Patients who stopped disease assessment prior to 9 weeks were included in this analysis set if the data cutoff was at least 9 weeks after their first study dose date.

[g] Includes 1 patient with a non-CR/non-PD response.

[h] Includes 1 patient whose response was not evaluable.

[i] Radiographic progression-free survival (rPFS) was defined as the interval from study day 1 to the earlier of a radiographic progression or death from any cause; otherwise, rPFS was censored at the last evaluable tumor assessment date. If a patient had no post-baseline radiographic tumor assessment and a vital status of alive or unknown, rPFS was censored at study day 1.

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