Safety and Clinical Activity of Atezolizumab in Patients with Metastatic Castration-Resistant Prostate Cancer: A Phase I Study

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ABSTRACT

Purpose: Atezolizumab [anti–programmed death-ligand 1 (anti-PD-L1)] is well tolerated and efficacious in multiple cancers, but has not been previously evaluated in metastatic castration-resistant prostate cancer (mCRPC). This study examined the safety, efficacy, and biomarkers of atezolizumab monotherapy for mCRPC.

Patients and Methods: This phase Ia, open-label, dose-escalation and dose-expansion study (PCD4989g) enrolled patients with mCRPC who had progressed on sipuleucel-T or enzalutamide. Atezolizumab was given intravenously every 3 weeks until confirmed disease progression or loss of clinical benefit. Prespecified endpoints included safety, efficacy, biomarker analyses, and radiographic assessments.

Results: All 35 evaluable patients [median age, 68 years (range, 45–83 years)] received atezolizumab after ≥1 prior line of therapy; 62.9% of patients had received ≥3 prior lines. Treatment-related adverse events occurred in 21 patients (60.0%), with no deaths. One patient had a confirmed partial response (PR) per RECIST 1.1, and 1 patient had a PR per immune-related response criteria. The confirmed 50% PSA response rate was 8.6% (3 patients). Median overall survival (OS) was 14.7 months [95% confidence interval (CI): 5.9–not evaluable], with a 1-year OS rate of 52.3% (95% CI: 34–70); 2-year OS was 35.9% (95% CI: 13–59). Median follow-up was 13.0 months (range, 1.2–28.1 months). Biomarker analyses showed that atezolizumab activated immune responses; however, a composite biomarker failed to reveal consistent correlations with efficacy.

Conclusions: Atezolizumab was generally well tolerated in patients with mCRPC, with a safety profile consistent with other tumor types. In heavily pretreated patients, atezolizumab monotherapy demonstrated evidence of disease control; however, its limited efficacy suggests a combination approach may be needed.

Introduction

Prostate cancer is the second leading cause of cancer-related deaths in men in the United States (1). Castration-resistant prostate cancer (CRPC) is defined by disease progression, as assessed by PSA levels or radiographic imaging, despite adequate suppression of testosterone levels (2). Overall, patients with metastatic CRPC (mCRPC) have a poor prognosis (3) and a high unmet need despite several therapies being approved in the past decade. These therapies include a chemotherapeutic agent (cabazitaxel), a radiotherapeutic that targets the bone (radium-233), agents targeting the androgen receptor–signaling pathway (enzalutamide) or androgen synthesis (abiraterone acetate), PARP inhibitors that interfere with repair of DNA single-strand breaks in tumor cells (olaparib and rucaparib), and the autologous cell–based cancer vaccine, sipuleucel-T. Despite these advances, progressive disease and treatment resistance still develop. Patients with mCRPC have a median life expectancy of <3 years, and it is <1 year for those who have received two prior lines of therapy for mCRPC (4–6).

The immune checkpoint protein programmed death-ligand 1 (PD-L1) is expressed on tumor cells (TC) and tumor-infiltrating immune cells (IC) in many cancers (7). Binding of PD-L1 to its receptors, programmed cell death-1 (PD-1) and B7.1 (CD80), on activated T cells can suppress the T-cell immune response and inhibit anticancer immunity (8, 9). Atezolizumab is a humanized engineered IgG1 mAb that selectively targets PD-L1, blocking its receptor interactions, which can enhance T-cell responses and improve antitumor activity (7, 8, 10). Atezolizumab has demonstrated safety and durable long-term clinical benefit in patients with various advanced malignancies (11–20).

Although patients with mCRPC typically have low PD-L1 expression on both immune cells and tumor cells (21, 22), early-phase clinical trials have shown preliminary efficacy in patients treated with a PD-L1/PD-1 pathway inhibitor (23–26). Previous data suggested that sipuleucel-T or enzalutamide may activate the immune system. Suppression of androgen receptor activity has several immunomodulatory effects, including promotion of thymopoiesis, increase in prostate immune infiltrates, and inhibition of tolerance to prostatic antigens (27). Furthermore, patients with mCRPC who progress while

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Clin Cancer Res 2021;27:3360–9

doi: 10.1158/1078-0432.CCR-20-1981

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Translational Relevance

This phase I trial cohort of 35 patients with mCRPC treated with the immune checkpoint inhibitor atezolizumab [anti–programmed death-ligand 1 (PD-L1)] as monotherapy demonstrated safety consistent with that seen for other tumor types. While clinical activity was observed in these heavily pretreated patients (median follow-up >1 year), the overall limited efficacy suggests that a combination approach to treating these patients may be needed. Furthermore, as the biomarkers tested here did not consistently correlate with efficacy, additional biomarkers will need to be tested to identify genomic profiles that may help inform treatment selection in this patient population.

receiving enzalutamide have more circulating PD-L1/PD-L2–positive dendritic cells than enzalutamide-naïve patients or patients still responding to treatment (28). Finally, PD-L1 expression is increased on circulating tumor cells following sipuleucel-T vaccination (29). Therefore, we explored the safety and tolerability of atezolizumab in patients with mCRPC who had received prior treatment with sipuleucel-T or enzalutamide.

Patients and Methods

Study design and treatment

PCD4989g (ClinicalTrials.gov ID NCT01375842) is an ongoing phase Ia study of atezolizumab in patients with advanced or metastatic solid tumors and hematologic malignancies. The overall study design, comprising dose-escalation and dose-expansion cohorts, has been described previously (7). Patients with mCRPC were only included in a tumor-specific expansion cohort. This study was approved by local Institutional Review Boards at all study sites and was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent. The protocol is available in the Supplementary Data.

The primary objective was to evaluate the safety and tolerability of atezolizumab. Additional key objectives specific to mCRPC included PSA complete response, PSA response rate (<50% and <30% by week 12), PSA progression, radiographic progression per Prostate Cancer Working Group 2 criteria and soft-tissue response per RECIST 1.1, and immune-related response criteria (irRC; refs. 30–32). Progression-free survival (PFS), overall survival (OS), and biomarker analyses were exploratory objectives. Atezolizumab was administered intravenously at 1,200 mg every 3 weeks. Tumor assessments (CT with or without bone scan) were performed every 6 weeks for 24 weeks and then every 12 weeks (or every 6 weeks if treating beyond progression). PSA was assessed every 6 weeks for 24 weeks and every 12 weeks thereafter until disease progression. Adverse events (AE) were graded using NCI Common Terminology Criteria for Adverse Events v4.0. Atezolizumab was continued until disease progression, unacceptable toxicity, or symptomatic deterioration. Patients could continue to receive atezolizumab after disease progression if there was still clinical benefit.

Patients

Key eligibility criteria included prior treatment with sipuleucel-T or enzalutamide for mCRPC, PSA, or radiological disease progression in soft tissue or bone prior to enrollment, as well as Eastern Cooperative Oncology Group performance status of 0 to 1, no history of autoimmune disease, and amenability to metastatic biopsy at screening (pretreatment) and during treatment. Biopsies were collected during treatment approximately 2 weeks after the first atezolizumab dose and at additional timepoints per investigator discretion. Patients were not excluded from enrollment if the tissue provided during screening was not evaluable for biomarker assessments. A complete listing of the inclusion and exclusion criteria is available in the protocol (Supplementary Data).

Statistical analyses

Separate cohort analyses were conducted for certain endpoints due to different lengths of follow-up for the initial and expansion cohorts. Objective response rate and corresponding 95% confidence intervals (CI) were calculated using the Clopper–Pearson method. The first CT scan to determine response occurred at 6 weeks. Objective response is a complete response or partial response (PR), as determined by investigator assessment and confirmed by repeat assessment ≥4 weeks after initial documentation. Patients with missing or no response assessments at <6 weeks from baseline were considered nonresponders.

PSA response was defined as a PSA concentration <50% of the PSA reference value occurring at any time after treatment initiation. The PSA reference value was the PSA concentration measured immediately prior to treatment. PSA progression was assessed as described in Prostate Cancer Working Group 2 criteria (32).

The duration of response (time from first occurrence of documented response to disease progression or death from any cause), PFS, and OS were assessed using the Kaplan–Meier method. The OS, radiographic PFS, and PSA PFS were calculated from the first atezolizumab dose. For OS, patients who were alive or lost to follow-up as of the clinical cut-off date were censored at the last known date they were alive. The 95% CIs for the median OS were estimated using the Brookmeyer–Crowley method. Milestone rates for OS, radiographic PFS, and PSA PFS were estimated using the Kaplan–Meier method, with 95% CIs calculated using the Greenwood formula.

Exploratory biomarkers

IHC was conducted for PD-L1 (centrally evaluated per SP142 assay; Ventana) and CD8 (clone C8/144B; Dako). IC0, 1, 2, or 3 refers to <1%, ≥1% and <5%, ≥5% and <10%, or ≥10% PD-L1–expressing immune cells, respectively. TC0, 1, 2, or 3 refers to <1%, ≥1% and <5%, ≥5% and <50%, or ≥50% PD-L1–expressing tumor cells, respectively.

Tumor RNA expression analyses were evaluated using RNA sequencing (RNA-seq) and Fluidigm technologies. Mutation analyses, including tumor mutational burden (TMB) and DNA damage repair (DDR) alternations, were conducted using the FoundationOne assay T7 baitset [Foundation Medicine Inc (FMI)]. *DDR* genes were defined as the subset of the gene set curated by Richard Wood (https://www.mdanderson.org/documents/Labs/Wood-Laboratory/human-dna-repair-genes.html) and are available on the T7 baitset (33). T-cell receptor repertoire sequencing was conducted on the ImmunoSEQ platform (centrally evaluated per Adaptive Biotechnologies).

Case report 1 (patient 31) did not have sufficient tissue for central biomarker testing; therefore, whole-exome sequencing (WES) analyses were completed locally. Sequence capture, enrichment, and elution of genomic DNA samples from the tumor and control biopsies were performed by IntegraGen. Agilent in-solution enrichment was used with the manufacturer's biotinylated oligonucleotide probe library SureSelect human all-exon kit v5 + UTRs per manufacturer's instructions. The eluted enriched DNA sample was sequenced on an Illumina NextSeq500 as paired-end 75 bp reads. MuTect2 was used to call somatic mutations from WES data by comparing each tumor sample

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with its matched nontumor counterpart. R Package Sequenza was used to reconstruct copy-number profiles from WES data.

Results

Patients

Fifteen patients with mCRPC were enrolled in an initial cohort from January to December 2015 with a median follow-up of 25.3 months (range, 2.3–28.1 months). An expansion phase enrolled 20 additional patients from March to September 2016, with a median follow-up of 11.3 months (range, 1.2–13.2 months). Baseline characteristics are shown in **Table 1**. Twenty-two patients (62.9%) had received ≥3 prior lines of therapy, 32 (91.4%) had received enzalutamide as a prior metastatic therapy, and 13 (37.1%) had received sipuleucel-T as a prior metastatic therapy. As expected for mCRPC, most patients had low PD-L1 expression, with 33 patients (94.3%) exhibiting a PD-L1 immune cell or tumor cell IHC score of 0/1 (<5% PD-L1 expression). Median follow-up for all 35 patients was 13.0 months (range, 1.2–28.1 months). Median follow-up was 25.3 months (range, 2.3–28.1 months) for the initial cohort ($n = 15$) and 11.3 months (range, 1.2–13.2 months) for the expanded cohort ($n = 20$). Patients received atezolizumab for a median of 2.1 months (upper range, 27.9 months) and a median of four doses (range, 1–41 doses). As of the data cutoff of June 30, 2017, 4 patients (11.4%) were continuing treatment and 14 (40.0%) remained on the study.

Table 1. Baseline characteristics.

Status	Total ($N = 35$)	Initial cohort ($n = 15$)	Expansion cohort ($n = 20$)
Median age (range), years	68 (45–83)	69 (45–82)	68 (55–83)
Race, *n* (%)			
White	23 (65.7)	10 (66.7)	13 (65.0)
Black or African American	3 (8.6)	2 (13.3)	1 (5.0)
Asian	1 (2.9)	0	1 (5.0)
Other	8 (22.9)	3 (20.0)	5 (25.0)
ECOG PS, *n* (%)			
0	12 (34.3)	6 (40.0)	6 (30.0)
1	23 (65.7)	9 (60.0)	14 (70.0)
Stage at initial diagnosis, *n* (%)			
I	1 (2.9)	0	1 (5.0)
II	6 (17.1)	2 (13.3)	4 (20.0)
III	3 (8.6)	2 (13.3)	1 (5.0)
IV	23 (65.7)	9 (60.0)	14 (70.0)
Unknown	2 (5.7)	2 (13.3)	0
Prior lines of therapy, *n* (%)			
1	5 (14.3)	2 (13.3)	3 (15.0)
2	8 (22.9)	2 (13.3)	6 (30.0)
≥3	22 (62.9)	11 (73.3)	11 (55.0)
Selected prior metastatic prostate cancer therapy, *n* (%)			
Enzalutamide	32 (91.4)	14 (93.3)	18 (90.0)
Abiraterone acetate	25 (71.4)	12 (80.0)	13 (65.0)
Taxane	22 (62.9)	9 (60.0)	13 (65.0)
Sipuleucel-T	13 (37.1)	7 (46.7)	6 (30.0)
Type of progression at enrollment, *n* (%)			
PSA only	8 (22.9)	5 (33.3)	3 (15.0)
Radiographic only	4 (11.4)	0	4 (20.0)
Radiographic progression + PSA	23 (65.7)	10 (66.7)	13 (65.0)
Gleason score at diagnosis, *n* (%)	$n = 34$	$n = 15$	$n = 19$
2–7	12 (35.3)	6 (40.0)	6 (31.6)
8–10	17 (50.0)	4 (26.7)	13 (68.4)
Not done	5 (14.7)	5 (33.3)	0
Median PSA	121.4	79.0	171.7
Range	5.6–26,810.0	5.6–4,113.0	12.5–26,810.0
Bone disease, *n* (%)	27 (77.1)	9 (60.0)	18 (90.0)
Lymph node disease, *n* (%)	26 (74.3)	12 (80.0)	14 (70.0)
Visceral disease, *n* (%)	13 (37.1)	4 (26.7)	9 (45.0)
PD-L1 IHC IC score, *n* (%)[a]			
IC0/1	33 (94.3)	14 (93.3)	19 (95.0)
Unknown	2 (5.7)	1 (6.7)	1 (5.0)
PD-L1 IHC TC score, *n* (%)			
IC0/1	33 (94.3)	14 (93.3)	19 (95.0)
Unknown	2 (5.7)	1 (6.7)	1 (5.0)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; IC, immune cell; IHC, immunohistochemistry; TC, tumor cell.
[a]No baseline samples had a PD-L1 score of 2/3.

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Safety

Treatment-related AEs (TRAE) occurred in 21 patients (60%; **Table 2**). The any-grade TRAEs occurring in ≥3 patients were fatigue, nausea, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood alkaline phosphatase, decreased appetite, dry mouth, and pruritus. Four patients (11.4%) had a grade 3/4 TRAE. Each of the following grade 3/4 TRAEs occurred once: hypertension, lethargy, anemia, bone marrow infiltration, hypercalcemia, hypokalemia, hyponatremia, hypophosphatemia, and spinal cord compression. Only 1 patient had a TRAE leading to treatment withdrawal (Supplementary Table S1). There were nine AEs of special interest, of which only one was grade 3/4 (increased alanine aminotransferase; Supplementary Table S1). There were no grade 5 AEs.

Efficacy

Of 25 patients with measurable disease at baseline, 1 (4%) had a confirmed PR per RECIST 1.1 and irRC (median duration of response was 7.2 months; time to initial response was 37 days; **Figs. 1** and **2A**; Supplementary Table S2). One patient (4%) showed response by irRC only (**Fig. 2A**; Supplementary Table S2). Five (20%) had stable disease for ≥24 weeks (**Fig. 1**; Supplementary Table S2). Three of 35 patients (8.6%) had a confirmed PSA response (50% decrease from baseline); median time to PSA progression was 3.8 months [95% CI: 2.8–not evaluable (NE)] and 1-year PSA PFS rate was 35.1% (**Fig. 2B**).

Confirmed PFS per investigator-assessed RECIST 1.1 for the combined cohort was 2.7 months (95% CI: 1.4–4.6) with 6- and 12-month landmark PFS rates of 20.7% and 3.5%, respectively (**Fig. 2C**; Supplementary Fig. S1). Median OS ($n = 35$) was 14.7 months (95% CI: 5.9–NE), with a 1-year OS rate of 52.3% (95% CI: 34–70) and a 2-year OS rate of 35.9% (95% CI: 13–59; **Fig. 2D**). The initial cohort ($n = 15$) had a median OS of 18.6 months (95% CI: 5.5–NE) with a 1-year OS rate of 58% and a 2-year OS rate of 40% (Supplementary Fig. S2A). The expansion cohort ($n = 20$) had a median OS of 11.1 months (95% CI: 5.5–NE) and a 1-year OS rate of 49.7% (95% CI: 26–73; Supplementary Fig. S2B).

Biomarker analyses

The biomarker-evaluable population (BEP) by RNA-seq was 20 patients (**Figs. 1** and **3**). Because relatively few responses were observed with atezolizumab, the BEP was analyzed as short (≤6 months, $n = 9$) versus long (>6 months, $n = 11$) time on study, defined by time from first atezolizumab treatment to date of study discontinuation due to death ($n = 10$), loss to follow-up ($n = 3$), or last known date alive ($n = 7$). Patient samples were evaluated by FMI for known/likely gene alterations (defined as identical or similar alterations that have been reported in cancer, including *BRCA2* alterations and positive homologous recombination deficiency status; Supplementary Fig. S3; Supplementary Table S3). Baseline FMI samples were available for 14 patients (10 were DDR positive) and 11 had known/likely gene alterations; 3 patient samples contained no known/likely gene alterations. Overall, known/likely gene alterations did not correlate with OS.

Sorting patients by time on study in this small BEP did not reveal distinct biological differences in tumor immune infiltrate or tumor microenvironment (TME), as shown by TMB, DDR status, PD-L1 status, CD8 infiltration, or TME signature expression by RNA-seq (**Fig. 3A**). One of 14 patients was centrally confirmed as having microsatellite instability–high (MSI-H) with a TMB of 18 mut/Mb, but this patient did not have a response to atezolizumab, and he experienced a short survival time on study of <6 months (**Figs. 1** and **3A**). This patient had a number of known/likely alterations, including MSH2 loss. In addition, known/likely alterations were observed in *PTEN, AR, TP53, SPOP, TET2, APC, SPEN, BRCA2, BCORL1, CIC, ARID2, MAP3K13*, and *TSC2*, as well as a frameshift mutation in *JAK1*. Conversely, 1 patient who had a PR (irRC) and whose biomarkers were evaluated separately harbored deletions for *MSH2* and *MHS6*, thereby having MMR deficiency. Ten of 14 patients had centrally confirmed alterations in DDR pathway genes, but there

Table 2. TRAEs.

	Safety-evaluable population ($N = 35$)	
	Any grade	**Grade 3/4**
Any TRAE, *n* (%)	21 (60.0)	4 (11.4)
Fatigue	7 (20.0)	0
Nausea	4 (11.4)	0
ALT increased	3 (8.6)	0
AST increased	3 (8.6)	0
Blood alkaline phosphatase increased	3 (8.6)	0
Decreased appetite	3 (8.6)	0
Dry mouth	3 (8.6)	0
Pruritus	3 (8.6)	0
Hypertension	2 (5.7)	1 (2.9)
Lethargy	2 (5.7)	1 (2.9)
Chills	2 (5.7)	0
Diarrhea	2 (5.7)	0
Dyspnea	2 (5.7)	0
Headache	2 (5.7)	0
Hypothyroidism	2 (5.7)	0
Infusion-related reaction	2 (5.7)	0
Rash	2 (5.7)	0
Tumor flare	2 (5.7)	0
Anemia	1 (2.9)	1 (2.9)
Bone marrow infiltration	1 (2.9)	1 (2.9)
Hypercalcemia	1 (2.9)	1 (2.9)
Hypokalemia	1 (2.9)	1 (2.9)
Hyponatremia	1 (2.9)	1 (2.9)
Hypophosphatemia	1 (2.9)	1 (2.9)
Spinal cord compression	1 (2.9)	1 (2.9)
Abdominal pain lower	1 (2.9)	0
Arthralgia	1 (2.9)	0
Blood bilirubin increased	1 (2.9)	0
Constipation	1 (2.9)	0
Dysphagia	1 (2.9)	0
Eczema	1 (2.9)	0
Eosinophilia	1 (2.9)	0
Eosinophil count increased	1 (2.9)	0
Gastritis	1 (2.9)	0
Hyperhidrosis	1 (2.9)	0
Hypocalcemia	1 (2.9)	0
Hypomagnesemia	1 (2.9)	0
Leukopenia	1 (2.9)	0
Myalgia	1 (2.9)	0
Night sweats	1 (2.9)	0
Palmar-plantar erythrodysesthesia	1 (2.9)	0
Pancytopenia	1 (2.9)	0
Platelet count decreased	1 (2.9)	0
Pyrexia	1 (2.9)	0
Rash generalized	1 (2.9)	0
Rhinitis allergic	1 (2.9)	0
Uveitis	1 (2.9)	0
Vomiting	1 (2.9)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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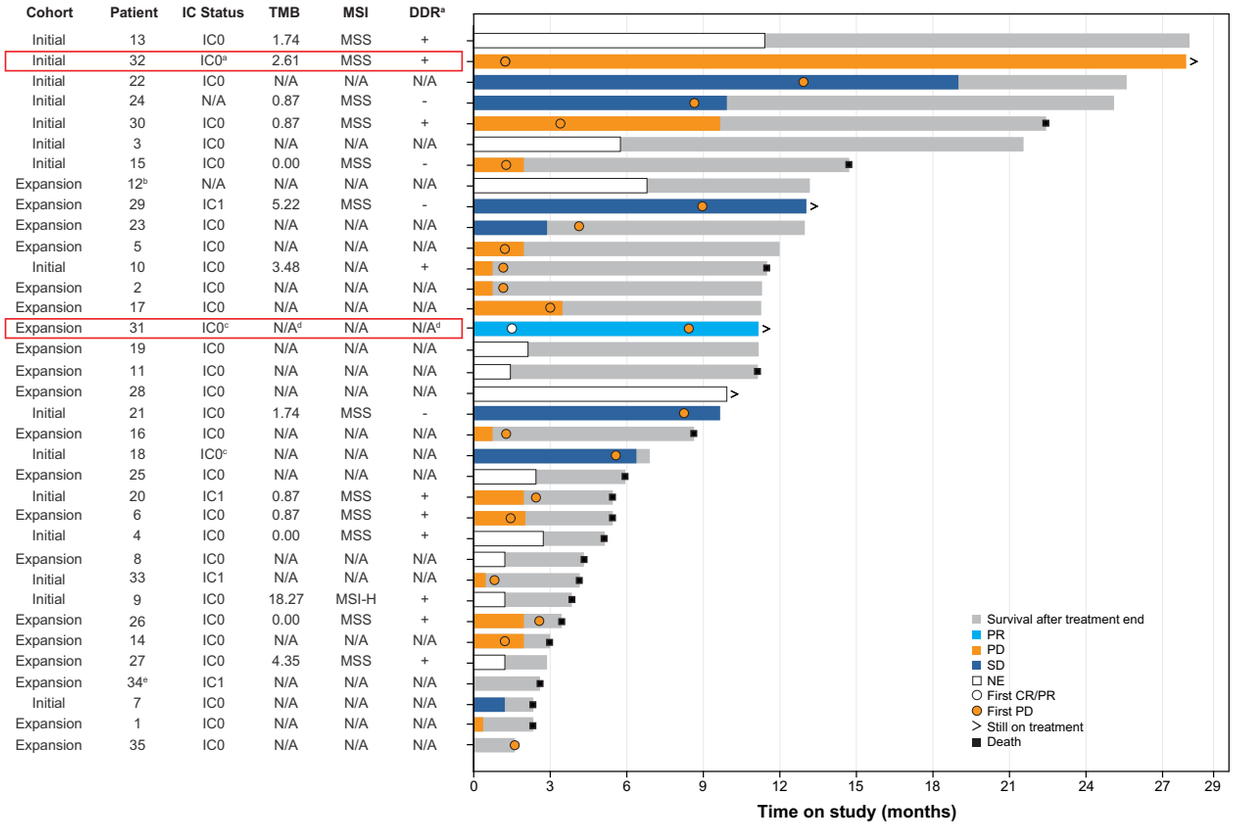

Figure 1.

Duration of treatment, time on study, and response. Time on treatment and time on study are plotted for patients with confirmed investigator-assessed RECIST 1.1 and irRC responses. Bar color and symbols indicate response assessments. CR, complete response; MSS, microsatellite stable; N/A, not applicable; PD, progressive disease; SD, stable disease. Red boxes denote patients discussed in case studies. [a]On-treatment samples from patient 32 showed a change in PD-L1 staining from IC0 to IC1. [b]Patient 12 did not have a biomarker sample available. [c]On-treatment samples from patients 18 and 31 showed a change in PD-L1 staining from IC0 to IC3. [d]Baseline TMB and DDR status for patient 31 was provided locally; this patient had high TMB and deletions in *MSH2* and *MSH6*. [e]Patient 34 did not have postbaseline tumor assessments.

was no correlation with time on study, and only 1 of these patients had a tumor response per irRC (**Fig. 1**).

A composite score was derived from biomarkers previously shown to be associated with response to checkpoint inhibitors [TMB-high ≥10 mut/Mb, DDR positive, MSI-H, PD-L1 high (IC2/3); **Fig. 3B**] in a BEP of only 14 patients. Ten of 14 BEP patients were positive for ≥1 of the four assessed biomarkers, and Kaplan–Meier analyses of OS by presence or absence of biomarkers were conducted.

Case studies

Two patients with confirmed PRs per irRC but different biomarker profiles are described further as case studies (Supplementary Figs. S4 and S5).

A 63-year-old man previously treated with enzalutamide for mCRPC had a confirmed PR per RECIST 1.1 and irRC after treatment with atezolizumab and showed associated dramatic changes in the TME (case report 1; patient 31; Supplementary Fig. S4). This patient was not included in the FMI BEP but was determined locally to have screening tissue with high TMB, DDR mutations, and MMR deficiency due to loss of *MSH2* and *MSH6*. In contrast, a 56-year-old man more heavily pretreated for mCRPC with prior treatments, including sipuleucel-T, docetaxel, abiraterone, and enzalutamide, had a confirmed irRC PR after atezolizumab treatment per investigator. This patient showed an activated immune response despite having archival tissue from a lymph node metastasis with a low TMB and being microsatellite stable (case report 2; patient 32; Supplementary Fig. S5). Both patients remained on treatment as of the clinical cut-off date. Of note, both patients had increased CD8 infiltration, expansion of novel T-cell receptor clones, and increased clonality in the periphery during atezolizumab treatment. Case 2 also had expansion of baseline and novel clones in the tumor. Interestingly, this patient had PSA response, but experienced progressive disease while on treatment. The patient's tumor was MSS with a TMB of 0.87 mut/Mb, but was DDR positive, including carrying a *BRCA2* alteration. Both PFS and OS for this patient were 166 days.

Discussion

Despite recent advances, mCRPC treatment is still challenging. This study is the first report on the long-term safety, clinical activity, and biomarker analyses associated with single-agent atezolizumab in patients with mCRPC. Atezolizumab was generally well tolerated with a safety profile consistent with that of other tumor types; there were no treatment-related deaths.

In these heavily pretreated patients with mCRPC, atezolizumab monotherapy demonstrated clinical activity with a median OS of

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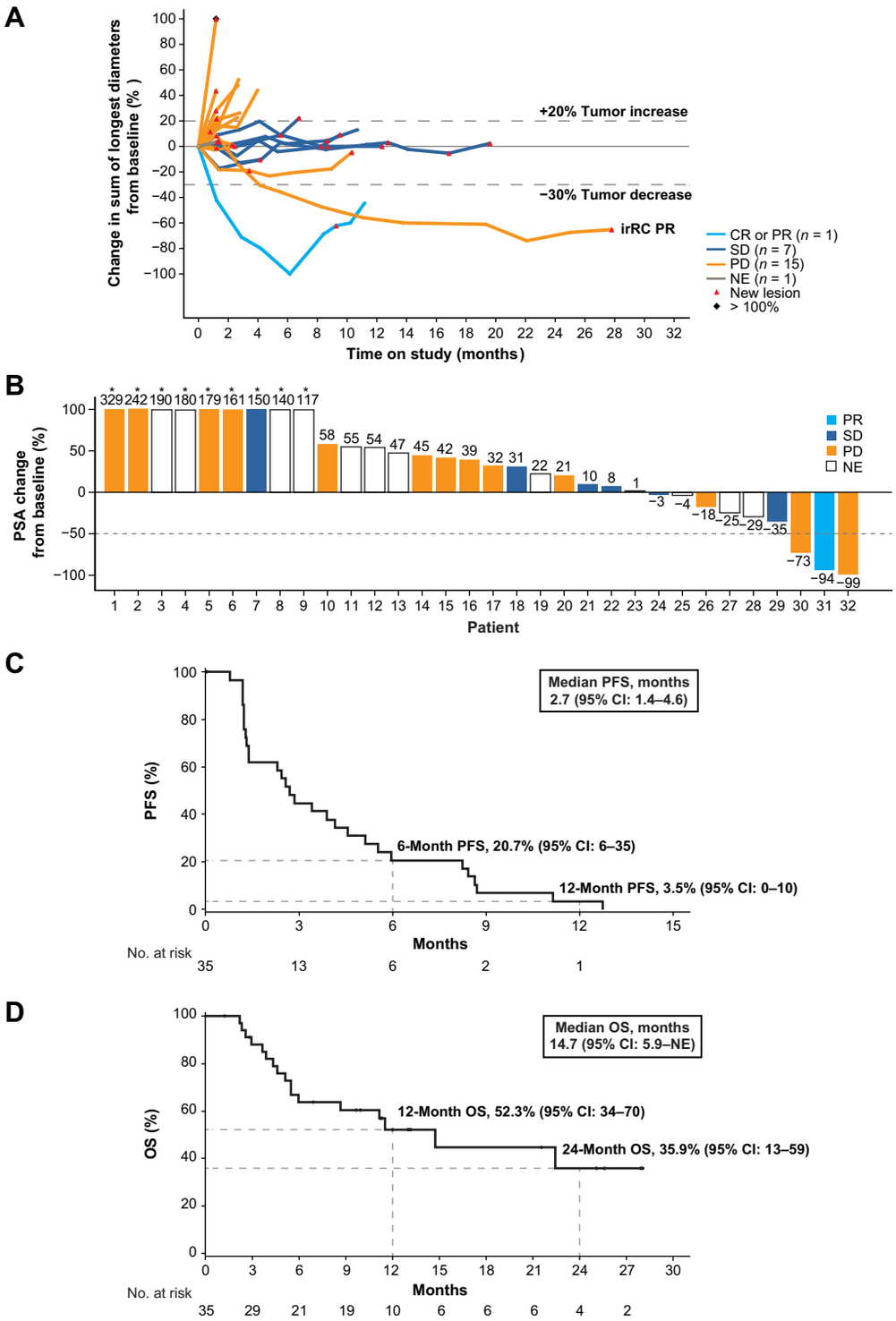

Figure 2.

Clinical activity of atezolizumab in mCRPC. **A,** Change in tumor burden over time, measured as the SLD, in patients with mCRPC receiving atezolizumab. Confirmed investigator-assessed RECIST 1.1 and irRC responses are included for patients with postbaseline tumor measurements. **B,** Maximum percent decrease in PSA from baseline. Confirmed PSA response rate (50% decrease from baseline): 3 patients (8.6%). Median time to PSA progression: 3.8 months (95% CI: 2.8–NE). Bar colors are per RECIST 1.1 criteria. Asterisks indicates patients whose percent PSA change from baseline is >100. **C,** Kaplan–Meier estimates of PFS in all patients ($N = 35$); 6-month and 12-month landmarks are shown. One-year PSA PFS rate: 35.1%. **D,** Kaplan–Meier estimates of OS in all patients ($N = 35$); 12-month and 24-month landmarks are shown. CR, complete response; PD, progressive disease; SD, stable disease; SLD, sum of longest diameters. Censor marks are indicated by a plus (+) symbol.

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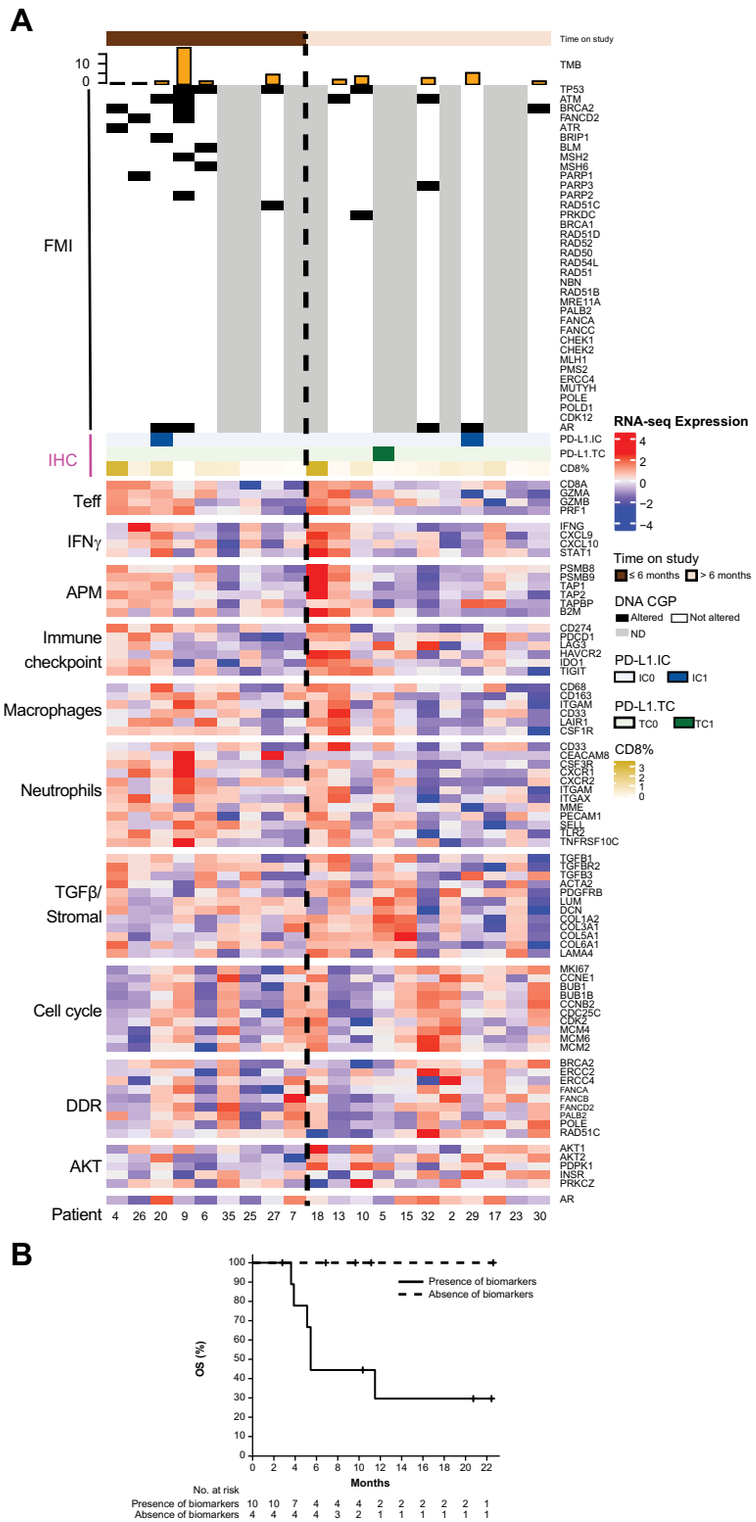

Figure 3.

Immune-related biomarker landscape **A,** RNA-seq analysis of biomarker-eligible patients analyzed by short (≤6 months) versus long (>6 months) time on study, comprehensive genomic profiling, and IHC (PD-L1, CD8). **B,** Kaplan–Meier estimates of OS by presence or absence of ≥1 composite of four biomarkers previously associated with response to CPI [TMB-high (≥10 mut/Mb), DDR positive, MSI-H, PD-L1 high (IC2/3)]. CGP, comprehensive genomic profile; IFNγ, interferon γ; IHC, immunohistochemistry; TGFβ, transforming growth factor β.

14.7 months for patients not selected by PD-L1. Consistent with previous immune therapy studies, this work did not identify a surrogate marker for OS (34). Of note, the median OS reported in this study is similar to that of other third-line agents (35).

Recent studies suggest an association between tumor MSI-H status and efficacy of PD-L1/PD-1 inhibitors in a range of solid tumors, including small numbers of prostate cancers (36, 37). In studies examining patients with prostate cancer receiving checkpoint

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inhibitors as monotherapy or combination therapy, approximately half of patients with MSI-H tumors have shown PSA reductions of 50% (38), with variable response rates (39, 40). In this study, 1 patient with MMR deficiency by local testing experienced a response on atezolizumab, but another patient with centrally confirmed MSI-H status did not benefit from treatment.

In addition, findings from this study suggest that the efficacy of atezolizumab in mCRPC is not limited to PD-L1–positive patients. These results are consistent with previous pembrolizumab studies suggesting that only modest increases in objective response rate and OS can be achieved by restricting treatment to PD-L1–positive patients. However, due to the use of different diagnostic assays and definitions of PD-L1 positivity, cross-study comparisons are difficult (23, 25, 26).

Given that most patients with DDR-positive tumors did not have a tumor response and there was no correlation between DDR status and duration on study, DDR status was not found to be a strong predictor of clinical benefit in this study. This is in contrast to results from combination studies with ipilimumab (anti-CTLA-4) plus nivolumab (anti-PD-1) and durvalumab (anti-PD-L1) plus olaparib (PARP inhibitor; refs. 41–43). One possible explanation for the lack of correlation in the current monotherapy study is that a biologic pathway–specific combination therapy may be needed in mCRPC.

Biomarker analyses from the 2 patients who experienced PR per irRC suggest that atezolizumab treatment altered and activated an antitumor immune response. Although these patients had similar clinical responses, their initial biomarker profile, prostate cancer history, and prior treatment regimens differed. Analysis of the BEP for TMB, DDR status, PD-L1 status, CD8 infiltration, or TME signature expression did not reveal biomarker correlations with efficacy. Further analyses are not possible given the limited amount of sample obtained. Taken together, these case studies highlight the diversity of possible biomarker profiles among patients with prostate cancer who have different disease sites and who had received distinct prior therapies.

Across the studies of checkpoint blockade in prostate cancer, there is inconsistency in findings on the association between tissue biomarkers and efficacy, which could help predict which patients are likely to respond to atezolizumab. This study's analyses of baseline biopsies underscore that biomarker profiles may not be a definitive patient selection tool for atezolizumab treatment in mCRPC and serve as a caution for clinical interpretations based solely on biomarker profiles. These distinctions can only be resolved in randomized trials aimed at differentiating between the predictive and prognostic effects of biomarkers. Because preliminary efficacy was observed with atezolizumab monotherapy in this study, investigation of combination approaches will be important in the future. The phase III IMbassador250 trial adding atezolizumab to enzalutamide, while not identifying any new safety signals, did not demonstrate improved OS compared with enzalutamide alone (44). The role of checkpoint inhibitors in prostate cancer is being evaluated in multiple combinations and in different settings. For example, a study evaluating atezolizumab in combination with ipatasertib and docetaxel in mCRPC (ClinicalTrials.gov ID NCT04404140) is ongoing.

Limitations of this study include its single-arm design and small sample size, including that only 14 patients were evaluated for MSI status. In addition, patients were heavily pretreated; therefore, biomarker expression in archival tumor specimens may not have been representative of the current disease. Furthermore, all enrolled patients had PD-L1 immune cell expression of IC0/1 (if known). This report is also limited by the use of two distinct cohorts, each with different follow-up times, and the need to keep them separate for certain analyses.

In conclusion, with a median follow-up of >1 year, atezolizumab was well tolerated in patients with mCRPC, and safety concerns were minimal. Preliminary clinical activity suggests a potential therapeutic benefit with atezolizumab in some heavily pretreated patients with mCRPC. Contrary to our hypothesis, the composite biomarker was associated with lack of response; given the small dataset, no definitive biomarker conclusions can be made from this study. However, combination approaches are likely to yield the best chance at improved efficacy and survival and are being explored.

Data sharing

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Authors' Disclosures

D.P. Petrylak reports personal fees from Ada Cap (Advanced Accelerator Applications), Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Clovis Oncology, Eli Lilly, Exelixis, Incyte, Janssen, Pfizer, Pharmacyclics, Roche, Seattle Genetics, and Urogen; grants from Ada Cap (Advanced Accelerator Applications), Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Clovis Oncology, Eli Lilly, Endocyte, Genentech, Innocrin, MedImmune, Medivation, Merck, Novartis, Pfizer, Progenics, Roche, Sanofi Aventis, and Seattle Genetics; and other from Bellicum and Tyme during the conduct of the study. Y. Loriot reports personal fees from Roche during the conduct of the study; personal fees from Bristol Myers Squibb, AstraZeneca, and Astellas; grants and personal fees from MSD and Janssen; and personal fees from Pfizer, Seattle Genetics, and Immunomedics outside the submitted work. F. Braiteh reports reports grants and nonfinancial support from F. Hoffmann-La Roche, as well as personal fees from Lilly and Novartis during the conduct of the study. F. Braiteh also reports personal fees and nonfinancial support from Genentech, BMS, AstraZeneca, Daiichi Sankyo, Celgene, Amgen, Ipsen, Incyte, Eisai, Boehringer Ingelheim, Exelexis, Lilly, Novartis, Pfizer, Merck, and Regeneron oustide the submitted work. J. Powderly reports other from Genentech during the conduct of the study, as well as other from AstraZeneca, Bristol Myers Squibb, Merck, EMD Serono, Macrogenics, Incyte, Alkermes, Tempest, Curis, Corvus, Top Alliance BioSciences, Precision for Medicine, MT Group, StemCell, Sequenom, Carolina BioOncology Institute, PLLC, AbbVie, Arcus Biosciences, Dendreon, FLX Bio, Lilly/ImClone, Seattle Genetics, and BioCytics outside the submitted work; Carolina BioOncology Institute PLLC and BioCytics are both developing intellectual property for personalized autologous immune cell therapies. L.C. Harshman reports previous employment at Dana-Farber Cancer Institute; grants to institution from Bayer, Sotio, Bristol Myers Squibb, Merck, Takeda, Dendreon/Valient, Janssen, Medivation/Astellas, Genentech, Pfizer, and Endocyte (Novartis); and advisory or consulting services for Bayer, Genentech, Pfizer, Medivation/Astellas, Corvus, Merck, Exelixis, Novartis, Advanced Accelerator Applications, Jounce, Bristol Myers Squibb, EMD Serrano, Michael J Hennessy Associates (Healthcare Communications Company and several brands such as OncLive and PER), ASIM CME, and Ology Medical Education during the conduct of the study. L.C. Harshman also reports current employment (including stock options) at Surface Oncology and travel support from Bayer and Genentech outside the submitted work. P. Conkling reports other support from Genentech during the conduct of the study, as well as other support from Pfizer, Bristol Myers Squibb, Arcus, Aptose, Janssen, and USOncology Research outside the submitted work. J.-P. Delord reports grants from Genentech during the conduct of the study. M. Gordon reports grants from Genentech/Roche, Tracon, BeiGene, Endocyte, Arcus, Merck, Bristol Myers Squibb, Tesaro, AbbVie, Calithera, Corcept, Plexxicon, Daiichi Sankyo, and Serono during the conduct of the study. M. Gordon also reports institutional support from Amgen, Aeglea, Astex, BluePrint, CellDex, Clovis, Eli Lilly, FivePrime, Genocea, Neon, Revolution Medicine, Seattle Genetics, SynDevRx, and

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Toleron, as well as personal fees from Tracon, Imaging Endpoints, Agenus, Daiichi Sankyo, Salarius, and Deciphera outside the submitted work. K. Yuen reports personal fees from Genentech during the conduct of the study. E.E. Kadel III is an employee of Genentech, owner of this molecule, and sponsor for the study. S. Mariathasan reports personal fees and other from Genentech/Roche outside the submitted work. The study was supported by F. Hoffmann-La Roche Ltd./Genentech, Inc., a member of the Roche Group. C. O'Hear reports personal fees from Genentech during the conduct of the study. M. Fassò reports personal fees from Genentech during the conduct of the study, as well as personal fees from Genentech outside the submitted work. S. Carroll reports personal fees from Calithera Biosciences outside the submitted work. T. Powles reports personal fees from Bristol Myers Squibb, MSD, and Seattle Genetics; grants and personal fees from Roche, AstraZeneca, Pfizer, and Merck Serono; and honoraria for advisory boards from Exelixis, Incyte, Ipsen, and Novartis during the conduct of the study. Editorial support, funded by the F. Hoffmann-La Roche Ltd., was provided by an independent medical writer under the guidance of the authors. No disclosures were reported by the other authors.

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Acknowledgments

This study was sponsored by F. Hoffmann-La Roche, Ltd/Genentech, Inc, a member of the Roche Group. We thank the patients participating in this trial and their families, the nurses, research coordinators, data managers, and clinical study site investigators. The authors would like to acknowledge Christina Schiff and Jennifer Doss for critical reviews and insights. Medical writing assistance for this article was provided by Paige S. Davies of Health Interactions and funded by F. Hoffmann-La Roche, Ltd.

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Received May 27, 2020; revised December 15, 2020; accepted February 5, 2021; published first February 10, 2021.

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