Phase Ib Study of the BET Inhibitor GS-5829 as Monotherapy and Combined with Enzalutamide in Patients with Metastatic Castration-Resistant Prostate Cancer

Rahul Aggarwal[1], Alexander N. Starodub[2], Brian D. Koh[3], Guan Xing[3], Andrew J. Armstrong[4], and Michael A. Carducci[5]

ABSTRACT

Purpose: A phase Ib study (1604) was conducted to evaluate the safety and efficacy of GS-5829, an oral bromodomain and extraterminal inhibitor, alone and in combination with enzalutamide in metastatic castration-resistant prostate cancer (mCRPC). A phase I study (1599) in solid tumors/lymphoma was also conducted.

Patients and Methods: Men with confirmed mCRPC and disease progression despite abiraterone and/or enzalutamide treatment were enrolled in a 3 + 3 dose escalation paradigm starting at 2 mg daily with GS-5829 alone and in combination with 160 mg daily enzalutamide. The primary efficacy endpoint was nonprogression rate at week 24; secondary endpoints included prostate-specific antigen reduction from baseline, progression-free survival, and GS-5829 pharmacokinetics (PK). PK and safety were also evaluated in Study 1599.

Results: Thirty-one men, with a median of five prior regimens, received at least 1 dose of study drug in Study 1604. Treatment-emergent adverse events (TEAE) were reported in 94% of patients; 16% discontinued for TEAEs. There were no dose-dependent increases in the AUC_{tau} or C_{max} after once-daily administration of GS-5829 2 to 9 mg, and biomarkers *CCR2* inhibition and *HEXIM1* induction were increased only at higher doses of monotherapy. A high degree of interpatient variability existed across all doses in PK and pharmacodynamic parameters. The proportion with nonprogression at week 24, estimated by Kaplan–Meier model, was 25% (95% confidence interval, 10–42) for all treated patients.

Conclusions: GS-5829 was generally tolerated but demonstrated limited efficacy and lack of dose proportional increases in plasma concentrations in patients with mCRPC.

Introduction

Androgen deprivation therapy for prostate cancer using surgical or chemical approaches aims to decrease androgen receptor (AR) signaling (1) upon which the growing tumor depends (2, 3). Unfortunately, while initial responses are good, these therapies eventually fail in nearly all patients (4). Second-generation antiandrogen therapies abiraterone and enzalutamide have improved outcomes in patients with castration-resistant prostate cancer (CRPC) including metastatic disease (5–11); however, resistance to all antiandrogens invariably develops (11). Mechanisms of resistance include *AR* mutations (12), *AR* amplification (13), and development of AR variants that confer resistance to therapies targeting the AR ligand–binding domain (AR-LBD; refs. 14, 15). AR variant 7 (AR-V7) is known to lack the AR-LBD but facilitates ligand-independent AR signaling (14).

Bromodomain and extraterminal (BET) is a family of proteins known to regulate gene transcription in diverse cell types, including prostate (16). BET protein BRD4 levels increase significantly with castration resistance, and other BET proteins correlate with increased expression of AR-V7 (17). BET inhibitors have antitumor activity in CRPC models, including enzalutamide-resistant models, and have also been shown to decrease AR-V7 expression (17, 18) and regulate full-length AR signaling (17). One particular BRD4 inhibitor (NEO2734) overcomes speckle-type POZ protein (SPOP; responsible for the ubiquitination and degradation of BET proteins) resistance and disrupts the activity of ARs in maintaining tumor survival in SPOP-mutated prostate cancer (19). These preclinical studies have provided the rationale to explore BET inhibition as a therapeutic strategy to overcome persistent AR signaling independent of AR-LBD in CRPC. Several orally administered BET inhibitors have also been evaluated in early-stage clinical development for the treatment of solid tumors or hematologic malignancies (20, 21). Initial evidence of clinical activity at tolerated doses was reported for the BET inhibitor ZEN-3694, in combination with enzalutamide, which demonstrated acceptable tolerability and potential efficacy in patients with androgen-signaling inhibitor-resistant metastatic CRPC (mCRPC; ref. 22).

GS-5829 is an oral small-molecule investigational BET inhibitor conceptualized for the treatment of solid tumors and hematologic malignancies. GS-5829 inhibits the transcription of AR target genes by binding to the bromodomains of BET proteins and blocking the recruitment of positive transcription elongation factor b to AR target genes. This prevents the phosphorylation of RNA polymerase II and subsequent transcription of AR targets, including kallikrein-related

[1]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California. [2]The Christ Hospital Cancer Center, Cincinnati, Ohio. [3]Gilead Sciences, Inc., Foster City, California. [4]Duke Cancer Institute Center for Prostate and Urologic Cancer, Duke University, Durham, North Carolina. [5]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland.

R. Aggarwal and A.N. Starodub contributed equally to this article.

Corresponding Author: Rahul Aggarwal, UCSF Helen Diller Family Comprehensive Cancer Center, 550 16th Street, San Francisco, CA 94158. Phone: 415-476-4616; E-mail: Rahul.Aggarwal@ucsf.edu

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Translational Relevance

Resistance to antiandrogens in castration-resistant prostate cancer (CRPC) emerges through several mechanisms, including enhanced androgen receptor (AR) activity through amplification, structural rearrangements, and variants of the AR that facilitate signaling independent of the AR ligand-binding domain. Expression of full-length AR and AR variant 7 (AR-V7) is modulated by bromodomain and extra-terminal (BET) proteins. In preclinical studies, BET inhibitors decrease both AR and AR-V7 expression and inhibit CRPC tumor growth. The BET inhibitor GS-5829 was evaluated as a single agent and in combination with enzalutamide in patients with metastatic CRPC in a phase Ib study. GS-5829 was generally well tolerated but had limited clinical efficacy. Drug exposure was not dose proportional, and interpatient variability was high across doses. BET target gene *CCR2* inhibition and *HEXIM1* induction were observed at higher doses. This study suggests that alternative epigenetic modulators with more favorable efficacy and pharmacokinetic characteristics are needed.

peptidase 3 that encodes prostate-specific antigen (PSA). In nonclinical studies, GS-5829 inhibited cell growth and induced apoptosis of solid tumor and hematologic cancer cells by inhibiting BET protein-dependent transcription of *MYC* (21, 23, 24). GS-5829 also inhibited other oncogenic pathways, including transcription mediated by the AR in prostate cancer cells. Preclinical studies also suggest an additive effect of GS-5829 and enzalutamide, which with the strong AR-binding affinity of enzalutamide (25) and the observation that patients with CRPC and AR-V7 express higher levels of full-length *AR* mRNA (15), led to a hypothesis that combining GS-5829 with enzalutamide may increase clinical efficacy in patients with mCRPC.

Study GS-US-350–1604 (Study 1604) was designed to evaluate the safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of GS-5829 as a single agent and in combination with enzalutamide in patients with mCRPC (NCT02607228). Results from Group 1 of the phase I study GS-US-350–1599 (Study 1599) to determine the safety and PK of GS-5829 monotherapy in patients with advanced solid tumors and lymphoma (NCT02392611) provided guidance on an initial dose for Study 1604. Results of both studies are reported.

Patients and Methods

Study population

Study 1599

Group 1 enrolled male or female patients, age ≥18 years with histologically or cytologically confirmed advanced malignant solid tumor or lymphoma (any subtype) that was refractory to or intolerant of standard therapy or for which no standard therapy was available. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤1, life expectancy ≥3 months, adequate organ function, and coagulation meeting International Normalized Ratio (INR) ≤1.2 were required. Patients with known brain metastasis or leptomeningeal disease were excluded. Group 2 enrolled patients with locally advanced or metastatic breast cancer to receive GS-5829 in combination with exemestane or fulvestrant (see Supplementary Methods).

Study 1604

Male patients age ≥18 years with histologically or cytologically confirmed mCRPC who had documented disease progression were enrolled. Progressive disease was defined as meeting at least 1 of the Prostate Cancer Working Group 2 (PCWG2) criteria despite treatment with abiraterone and/or enzalutamide (for monotherapy) or despite treatment with abiraterone and no prior treatment for mCRPC with enzalutamide or chemotherapy (for combination therapy). Patients who did not have a bilateral orchiectomy were required to maintain effective gonadotropin-releasing hormone-analogue therapy for the duration of the trial. ECOG performance status of ≤1, life expectancy ≥3 months, adequate organ function, and coagulation meeting INR ≤1.2 were also required. Patients with primary neuroendocrine carcinoma of prostate and those whose disease spread was limited to regional pelvic lymph nodes were excluded.

Studies 1599 and 1604 were conducted in compliance with international scientific and ethical standards, including but not limited to the International Council for Harmonization guideline for Good Clinical Practice, and the ethical principles embodied in the Declaration of Helsinki. All patients gave written informed consent.

Study design

Study 1599 (Group 1)

This was a phase I, open-label, sequential dose escalation study of GS-5829 monotherapy given orally once daily (0.6, 1.4, 2, 3, 4, 6, 9, and 12 mg). One patient was enrolled at each dose level until a grade ≥2 treatment-related toxicity was observed, at which point enrollment was expanded to 3 patients and the study followed a standard 3 + 3 dose escalation design (see Supplementary Methods). Primary objectives were to characterize the safety and tolerability of GS-5829 monotherapy and determine the maximum tolerated dose (MTD) or recommended dose for phase II studies.

Study 1604

Study 1604 was a phase Ib open-label, multicenter, sequential dose escalation study followed by a phase II expansion study. Patients in the monotherapy and combination therapy cohorts received oral GS-5829 daily for the duration of the study. Patients in the combination therapy cohort also received 160-mg oral enzalutamide daily beginning approximately 2 weeks before the first dose of GS-5829 to minimize effects of enzalutamide, a potent CYP3A4 inducer, on the PK of GS-5829 in cycle 1. Dose escalation followed a standard 3 + 3 design with GS-5829 monotherapy initiated at 2 mg, a dose demonstrated in Study 1599 to be safe and tolerable. Patients were sequentially enrolled to receive progressively higher dose levels of GS-5829 as a single agent daily (2, 3, 4, 6, and 9 mg). Planned doses of GS-5829 in the combination therapy cohorts were the same as the single-agent doses. Dose escalations were based on safety, tolerability, and PK data results. Treatment continued in the absence of disease progression, unacceptable toxicity, withdrawal of consent, or other reasons specified in the protocol.

The primary objectives of the study were to characterize the safety and tolerability of GS-5829, and to determine the MTD as a single agent and in combination with enzalutamide in patients with mCRPC. Secondary objectives were to evaluate the PK and efficacy of GS-5829 as a single agent and in combination with enzalutamide in patients with mCRPC as measured by the PCWG2 criteria.

Assessments

Safety

Safety and tolerability were evaluated in both studies by assessment of adverse events (AE), clinical laboratory tests, physical examinations, 12-lead electrocardiograms, and vital sign measurements.

Clinical and laboratory AEs were coded using the Medical Dictionary for Regulatory Activities, versions 20.1 (Study 1599) and 22.0 (Study 1604). AEs of interest, defined by the medical search term provided by Gilead Pharmacovigilance and Epidemiology, included decreased platelets, diarrhea, and hemorrhage. The MTD was the highest dose level with a patient incidence of 0 dose-limiting toxicities (DLT) for 3 to 4 patients or <2 DLTs for 6 patients during the first 28 days of study drug dosing.

Pharmacokinetics and pharmacodynamics

Study 1604 detailed PK sampling was performed on day 8 of cycle 1 and day 1 of cycle 2 for cohorts receiving GS-5829 alone, or day 15 of cycle 1 for cohorts receiving GS-5829 in combination with enzalutamide. Study treatments were administered under fasted conditions except for day 1 of cycle 2, when GS-5829 was administered under fed conditions to conduct a preliminary assessment of food on PK exposures. PK parameters were estimated using Phoenix WinNonlin (Certara) software applying standard noncompartmental methods. The linear/log trapezoidal rule was used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real-time values, based on drug dosing times whenever possible. PK parameters calculated included maximum plasma concentration (C_{max}), area under the plasma concentration–time curve from time 0 to the last measurable concentration (AUC_{last}), area under the plasma concentration-time curve for a dosing interval (AUC_{tau}), plasma trough concentration (C_{tau}), and time to maximal GS-5829 concentration (T_{max}). For Study 1599 PK assessments, see Supplementary Methods.

Expression of BET target genes C-C motif chemokine receptor 2 (*CCR2*; ref. 26) and hexamethylene bisacetamide inducible 1 (*HEXIM1*; ref. 27) in peripheral blood were assessed as validated pharmacodynamic (PD) markers in patients dosed with 2 mg to 9 mg of GS-5829 in Study 1604. Samples for PD data analysis were collected on days 1 and 8 of cycle 1 in the monotherapy cohorts, and on days 1 and 15 in the combination cohorts. Additional samples were taken for all groups on day 1 of cycles 2–6. Derived endpoints were percent baseline at each post-baseline visit, defined as 100% × (post-baseline count/baseline count), where baseline is the predose of study day 1. Inhibition is defined as 100% minus percent baseline. Induction is defined as percent baseline minus 100%. For further details, see Study 1599 PD assessments in Supplementary Methods.

Efficacy

Study 1604

The primary efficacy endpoint was the proportion of patients who did not have disease progression by week 24 as determined by investigators according to PCWG2 criteria. Efficacy criteria included PSA response as determined by a decline from baseline, soft-tissue change using RECIST criteria, and appearance of lesions as confirmed by bone scan. The nonprogression rate at week 24 and 95% confidence interval (CI) were estimated using the Kaplan–Meier (KM) method through progression-free survival (PFS) analysis.

Secondary efficacy endpoints were PSA response defined as a ≥30% confirmed decline in PSA from baseline at week 12 (≥50% PSA reduction from baseline at 12 weeks was also assessed), PFS, and overall survival (OS). For Study 1599 efficacy assessments, see Supplementary Methods.

Statistical analyses

All data summaries for both studies were designed to be descriptive in nature. For continuous variables, sample size, mean, median, SD, minimum, and maximum were determined. Sample size and proportion were determined for categorical variables. Baseline values were the last recorded value prior to the administration of the first dose of study treatment.

Study 1604

The analyses of PFS and OS were performed using the KM method for the Full Analysis Set (FAS). Medians, first quartile (Q1), third quartile (Q3), and the proportion of patients who had no events at 24 and 48 weeks from the first dosing date were determined along with corresponding 95% CIs. KM curves for PFS and OS were determined by treatment group. The sample size of the phase Ib part of Study 1604 was determined based on the number of dose levels evaluated and emerging GS-5829–related toxicities, with up to 72 patients to be enrolled. Sample size of the phase II expansion portion was based on the assumption that the 24-week nonprogression rate would be >30% with GS-5829 monotherapy and/or with GS-5829 combined with enzalutamide. If the true nonprogression rate is above 50%, and >10 nonprogression patients are observed from 20 treated patients per group, a lower bound of the 90% CI of the estimated rate will be guaranteed to be >30%. For Study 1599 statistical analyses, see Supplementary Methods.

Data availability

Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Science's discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

Results

Baseline demographics, characteristics, and disposition

Study 1599

A total of 33 patients were enrolled in Study 1599, 23 with solid tumors/lymphomas in Group 1 (monotherapy) and 10 with breast cancer in Group 2 (combination therapy with exemestane or fulvestrant). Group 2 will not be discussed further in this report. Patient disposition is shown in Supplementary Fig. S1. Seven patients (33.3%) prematurely discontinued the study: 3 (14.3%) due to progressive disease, 1 (4.8%) due to AEs, 2 (9.5%) due to death, and 1 (4.8%) withdrew consent. Baseline demographic and disease characteristics are shown in Supplementary Table S1.

Study 1604

A total of 31 patients, median age 67 years (range, 50–81 years), were enrolled in the dose escalation portion of the study; 23 received monotherapy and 8 received combination therapy (Supplementary Fig. S2). The phase II expansion portion was not conducted. Patients received GS-5829 monotherapy at doses of 2 mg ($n = 5$), 3 mg ($n = 4$), 4 mg ($n = 3$), 6 mg ($n = 6$), or 9 mg ($n = 5$). Patients received combination therapy with 3 mg ($n = 6$) or 6 mg ($n = 2$) GS-5829 plus enzalutamide. All 31 patients prematurely discontinued the study, the majority due to progressive disease (67.7%) or AEs (16.1%).

Most patients (87%) were Caucasian and not of Hispanic or Latino ethnicity, and the mean age was 66.7 years. The median number of prior therapies was 5.0 (range, 1–11); 97% had received at least 2 prior regimens, 77% at least 4 prior regimens, and 32% had previously been

Table 1. Study 1604 Patient Demographics and Baseline Characteristics.

	GS-5829							
Parameter	**2 mg (*N* = 5)**	**3 mg (*N* = 4)**	**4 mg (*N* = 3)**	**6 mg (*N* = 6)**	**9 mg (*N* = 5)**	**3 mg + Enza (*N* = 6)**	**6 mg + Enza (*N* = 2)**	**Total (*N* = 31)**
Age, mean (SD)	68.2 (9.3)	67.3 (10.7)	67.7 (5.7)	66.8 (9.4)	69.2 (6.6)	62.5 (10.2)	67.0 (0.00)	66.7 (8.3)
Race, *n* (%)								
Black or African American	1 (20)	0	1 (33.3)	0	0	1 (16.7)	0	3 (9.7)
White	4 (80)	4 (100)	2 (66.7)	6 (100)	4 (80)	5 (83.3)	2 (100)	27 (87.1)
Other	0	0	0	0	1 (20)	0	0	1 (3.2)
Ethnicity, *n* (%)								
Hispanic or Latino	0	0	0	0	1 (20)	1 (16.7)	0	2 (6.5)
Not Hispanic or Latino	5 (100)	4 (100)	3 (100)	6 (100)	3 (60.0)	5 (83.3)	2 (100)	28 (90.3)
Unknown	0	0	0	0	1 (20.0)	0	0	1 (3.2)
Baseline BMI (kg/m^2),								
mean (SD)	29.2 (3.6)	23.9 (6.0)	30.4 (5.1)	25.7 (2.3)	29.0 (5.8)	35.2 (3.8)	28.7 (1.4)	29.0 (4.9)
(*n*)	(5)	(2)	(3)	(6)	(5)	(4)	(2)	(27)
Alkaline phosphatase (U/L),	92.0	118.5	141.0	75.0	147.0	182.0	89.0	96.0
median (range)	(38.0, 325.0)	(52.0, 184.0)	(71.0, 252.0)	(40.0, 164.0)	(74.0, 383.0)	(57.0, 331.0)	(69.0, 109.0)	(38.0, 383.0)
Hemoglobin (g/dL),	11.2	12.25	12.0	13.2	12.4	12.65	12.9	12.4
median (range)	(9.2, 14.10)	(9.6, 13.9)	(11.9, 12.1)	(11.1, 13.8)	(12.1, 12.9)	(11.9, 15.7)	(12.3, 13.5)	(9.2, 15.7)
TNM Classification								
Primary Tumor, *n* (%)								
T0	0	1 (25)	0	0	0	0	0	1 (3.2)
T1	1 (20)	0	0	0	0	0	0	1 (3.2)
T2	1 (20)	1 (25)	0	1 (16.7)	1 (20)	0	0	4 (12.9)
T3	1 (20)	0	0	1 (16.7)	2 (40)	3 (50)	0	7 (22.6)
T4	1 (20)	0	0	0	0	0	1 (50)	2 (6.5)
TX	1 (20)	2 (50)	1 (33.3)	3 (50)	2 (40)	3 (50)	1 (50)	13 (42)
Missing	0	0	2 (66.7)	1 (16.7)	0	0	0	3 (9.7)
Lymph Nodes, *n* (%)								
N0	2 (40)	2 (50)	0	2 (33.3)	0	3 (50)	1 (50)	10 (32)
N1	2 (40)	1 (25)	0	0	4 (80)	3 (50)	0	10 (32)
NX	1 (20)	1 (25)	1 (33.3)	3 (50)	1 (20)	0	1 (50)	8 (25.8)
Missing	0	0	2 (66.7)	1 (16.7)	0	0	0	3 (9.7)
Metastasis, *n* (%)								
M0	1 (20)	1 (25)	0	1 (16.7)	0	1 (16.7)	0	4 (12.9)
M1	3 (60)	3 (75)	1 (33.3)	4 (66.7)	5 (100)	5 (83.3)	2 (100)	23 (74)
MX	1 (20)	0	0	0	0	0	0	1 (3.2)
Missing	0	0	2 (66.7)	1 (16.7)	0	0	0	3 (9.7)
Number of prior regimens								
median (range)	6.0 (3, 11)	5.5 (5, 8)	3.0 (2, 4)	5.0 (4, 7)	6.0 (4, 7)	4.0 (1, 5)	3.0 (3, 3)	5.0 (1, 11)
(*n*)	(5)	(4)	(3)	(6)	(5)	(6)	(2)	(31)
Number of prior therapies, *n* (%)								
≥1 prior regimen	5 (100)	4 (100)	3 (100)	6 (100)	5 (100)	6 (100)	2 (100)	31 (100)
≥2 prior regimens	5 (100)	4 (100)	3 (100)	6 (100)	5 (100)	5 (83.3)	2 (100)	30 (96.8)
≥3 prior regimens	5 (100)	4 (100)	2 (66.7)	6 (100)	5 (100)	5 (83.3)	2 (100)	29 (93.5)
≥4 prior regimens	4 (80.0)	4 (100)	1 (33.3)	6 (100)	5 (100)	4 (66.7)	0	24 (77.4)
Treated by enzalutamide	3 (60.0)	3 (75.0)	2 (66.7)	2 (33.3)	2 (40.0)	0	0	13 (41.9)
Treated by abiraterone	5 (100)	4 (100)	1 (33.3)	5 (83.3)	5 (100)	6 (100)	2 (100)	28 (90.3)
Treated by chemotherapy	4 (80.0)	3 (75.0)	2 (66.7)	1 (16.7)	3 (60.0)	1 (16.7)[a]	1 (50.0)[a]	15 (48.4)

Note: Chemotherapy included cabazitaxel, carboplatin, docetaxel, paclitaxel. Other prior therapies included GnRH agonists, antiandrogens, corticosteroids, immunotherapy, investigational therapies, and alternative medicine/herbal supplements.

Abbreviations: BMI, body mass index; Enza, enzalutamide; TNM, primary tumor, lymph nodes, metastasis.

[a]The patient in the 3 mg + enzalutamide group received docetaxel for prostate cancer in the adjuvant setting 420 days prior to the first dose of study drug, and the patient in the 6 mg + enzalutamide group received docetaxel for metastatic prostate cancer in the adjuvant setting 288 days prior to the first dose of study drug.

treated with enzalutamide (**Table 1**; note that lactate dehydrogenase was assessed at baseline in Study 1599 but not in Study 1604).

Safety and tolerability

Study 1599

Twenty-one of 23 enrolled patients in Group 1 received treatment of GS-5829. The median time on monotherapy treatment in Study 1599 was 8.9 weeks with a range of 0.9 to 56.3 weeks (**Table 2**), and median adherence to GS-5829 during the treatment period was 100% (minimum 89.1%). All patients had at least 1 treatment-emergent AE (TEAE) and 11 patients (52.4%) had a Grade ≥3 TEAE. Three patients (14.3%) discontinued treatment due to TEAEs, and 8 (38.1%) experienced serious TEAEs. Twelve patients (57.1%) experienced at least 1 TEAE assessed by the investigator as related to GS-5829. There were no

Table 2. Study 1599 GS-5829 Exposure and Adverse Events.

Parameter	GS-5829						
	0.6 mg (*N* = 2)	1.4 mg (*N* = 1)	2 mg (*N* = 1)	3 mg (*N* = 7)	4 mg (*N* = 6)	6 mg (*N* = 4)	Total (*N* = 21)
Exposure to GS-5829							
Duration of exposure, Weeks							
Mean (SD)	14.4 (3.94)	10.0	8.9	15.7 (19.53)	9.9 (6.01)	6.0 (6.81)	11.5 (12.06)
Median	14.4	10.0	8.9	6.0	8.7	3.2	8.9
Min, Max	11.6, 17.1	10.0, 10.0	8.9, 8.9	1.4, 56.3	0.9, 17.3	1.6, 16.1	0.9, 56.3
Adverse events overall summary							
TEAEs, *n* (%)	2 (100)	1 (100)	1 (100)	7 (100)	6 (100)	4 (100)	21 (100)
TEAE Grade ≥3	1 (50.0)	1 (100)	0	4 (57.1)	2 (33.3)	3 (75.0)	11 (52.4)
TEAE Related to GS-5829	1 (50.0)	1 (100)	0	5 (71.4)	3 (50.0)	2 (50.0)	12 (57.1)
TEAE Related to GS-5829 Grade ≥3	0	0	0	2 (28.6)	1 (16.7)	2 (50.0)	5 (23.8)
TE SAE	1 (50.0)	1 (100)	0	3 (42.9)	2 (33.3)	1 (25.0)	8 (38.1)
TE SAEs Related to GS-5829	0	0	0	0	1 (16.7)	0	1 (4.8)
TEAE Leading to Discontinuation	0	0	0	1 (14.3)	2 (33.3)	0	3 (14.3)
TEAE Leading to Death	0	0	0	0	0	0	0
Adverse events of interest							
Any TEAE of interest, *n* (%)	1 (50.0)	1 (100)	0	3 (42.9)	2 (33.3)	3 (75.0)	10 (47.6)
Decreased Platelets, *n* (%)	0	1 (100)	0	2 (28.6)	0	3 (75.0)	6 (28.6)
Thrombocytopenia	0	1 (100)	0	1 (14.3)	0	3 (75.0)	5 (23.8)
Platelet count decreased	0	0	0	1 (14.3)	0	0	1 (4.8)
Diarrhea, *n* (%)	0	0	0	0	1 (16.7)	0	1 (4.8)
Hemorrhage, *n* (%)	1 (50.0)	0	0	1 (14.3)	1 (16.7)	1 (25.0)	4 (19.0)
Epistaxis	0	0	0	1 (14.3)	0	1 (25.0)	2 (9.5)
Adrenal hemorrhage	0	0	0	0	1 (16.7)	0	1 (4.8)
Hematuria	0	0	0	1 (14.3)	0	0	1 (4.8)
Stoma site hemorrhage	1 (50.0)	0	0	0	0	0	1 (4.8)

Abbreviations: SAE, serious adverse events; TE, treatment-emergent; TEAE, treatment-emergent adverse events.

TEAEs leading to death. Three patients died of disease progression within 30 days of the last dose of GS-5829. Four patients had DLTs: 1 of 7 (14%) in the 3-mg group had Grade 3 thrombocytopenia; 1 of 6 (17%) in the 4-mg group had Grade 3 adrenal hemorrhage (platelets and coagulation tests were normal); and in the 6-mg group of 4 patients, 1 (25%) had Grade 3 thrombocytopenia and 1 (25%) had Grade 3 aspartate aminotransferase increased. Therefore, the MTD for GS-5829 monotherapy was 4 mg daily in Study 1599.

Study 1604

The median time on treatment was 12.1 weeks with a range of 0.9 to 130.9 weeks (**Table 3**), and median adherence to medication during the treatment period was 100% (minimum 88.2%). TEAEs in Study 1604 were reported in 29 patients (93.5%). Grade 3 or higher TEAEs occurred in 12 patients (38.7%). Twenty-two patients (71.0%) had TEAEs considered related to GS-5829, with 5 patients (16.1%) experiencing grade 3 or higher TEAEs related to GS-5829. Nine patients (29.0%) had serious TEAEs. Five patients (16.1%) had TEAEs leading to premature discontinuation of GS-5829. One patient in the 3 mg + enzalutamide group had DLTs (asthenia, fatigue, and fall) that led to permanent study discontinuation. Two deaths were reported in Study 1604; a patient in the 3-mg monotherapy group, and a patient in the 3 mg + enzalutamide group. Both deaths occurred after the patients had discontinued study treatment. One death was caused by progressive disease and another by AE (embolic stroke). Neither one was considered to be related to study drug.

The most common AEs were fatigue, diarrhea, and decreased appetite, respectively, in 16 (51.6%), 10 (32.3%), and 7 (22.6%) patients. Back pain and nausea were seen in 6 (19.4%) patients, and anemia and constipation were each seen in 5 (16.1%) patients.

AEs of interest (diarrhea, decreased platelet count, and hemorrhage) were seen in 15 (48.4%) patients; the majority, 8 (25.8%) patients, were grade 1 in severity (**Table 3**). Five patients (16.1%) had at least an AE that involved decreased platelets: 1 patient in the 6-mg group had grade 2 thrombocytopenia, and 4 patients had decreased platelet counts (1 patient in the 3-mg group with grade 1, 1 patient each in the 4-mg and 9-mg groups with grade 2, and 1 patient in the 9-mg group with grade 3). All AEs of interest related to decreased platelets were considered related to study drug. Five patients (16.1%) also had an AE of hemorrhage; 2 of these were considered related to study drug. Ten (32.3%) patients had diarrhea. Nine (29.0%) patients had grade 1 diarrhea that was considered related to study drug in 4 patients, and to enzalutamide specifically in 1 patient.

Pharmacokinetics

Study 1604

A high degree of interpatient variability was observed across all doses and PK parameters, as can be seen in the plasma concentration over time curves for the monotherapy and combination therapy groups (**Fig. 1**). The median (Q1, Q3) T_{max} ranged from 0.50 (0.50–1.02) to 1.42 (0.60–3.00) hours in cohorts receiving GS-5829 alone. There was no dose-dependent increase in GS-5829 AUC_{tau}, C_{max}, or C_{tau} following daily administration of GS-5829 at doses between 2 and 9 mg in either the monotherapy or combination group, and GS-5829 exposures were lower in the enzalutamide combination group compared to corresponding dose cohorts in the monotherapy group. Enzalutamide is a strong cytochrome P450 3A4 inducer, which was expected to decrease the exposure of GS-5829; therefore, higher doses of GS-5829 were anticipated to achieve target coverage compared with GS-5829 monotherapy. As expected, the drug–drug interaction between

Table 3. Study 1604 GS-5829 Exposure and Adverse Events.

Parameter	GS-5829 2 mg (*N* = 5)	3 mg (*N* = 4)	4 mg (*N* = 3)	6 mg (*N* = 6)	9 mg (*N* = 5)	3 mg + Enza (*N* = 6)	6 mg + Enza (*N* = 2)	Total (*N* = 31)
Exposure to GS-5829								
Total duration of exposure to study drug, Weeks, Mean (SD)	15.9 (12.48)	10.2 (2.02)	24.9 (15.66)	53.7 (42.37)	19.4 (23.98)	23.1 (34.00)	19.9 (11.11)	25.6 (28.73)
Median	12.0	10.4	24.0	47.7	12.1	11.6	19.9	12.1
Min, Max	7.1, 37.9	8.0, 12.0	9.7, 41.0	12.1, 130.9	0.9, 59.4	1.6, 92.0	12.0, 27.7	0.9, 130.9
Adverse Events Overall Summary								
TEAEs, *n* (%)	5 (100)	3 (75.0)	3 (100)	6 (100)	5 (100)	5 (83.3)	2 (100)	29 (93.5)
TEAE Grade ≥3	3 (60.0)	2 (50.0)	1 (33.3)	1 (16.7)	2 (40.0)	2 (33.3)	1 (50.0)	12 (38.7)
TEAE Related to GS-5829	4 (80.0)	2 (50.0)	3 (100)	4 (66.7)	4 (80.0)	3 (50.0)	2 (100)	22 (71.0)
TEAE Leading to GS-5829 Discontinuation	1 (20.0)	0	1 (33.3)	0	1 (20.0)	1 (16.7)	1 (50.0)	5 (16.1)
TEAE Leading to Death[a]	0	0	0	0	0	1 (16.7)	0	1 (3.2)
SAEs *n* (%)	2 (40.0)	0	1 (33.3)	1 (16.7)	2 (40.0)	2 (33.3)	1 (50.0)	9 (29.0)
SAEs Related to GS-5829	0	0	0	0	0	2 (33.3)	0	2 (6.5)
Adverse Events of Interest								
Any TEAE of interest, *n* (%)	2 (40.0)	2 (50.0)	2 (66.7)	3 (50.0)	3 (60.0)	2 (33.3)	1 (50.0)	15 (48.4)
Decreased Platelets	0	1 (25.0)	1 (33.3)	1 (16.7)	2 (40%)	0	0	5 (16.1)
Thrombocytopenia	0	0	0	1 (16.7)	0	0	0	1 (3.2)
Platelet count decreased, *n* (%)	0	1 (25.0)	1 (33.3)	0	2 (40.0)	0	0	4 (12.9)
Diarrhea, *n* (%)	1 (20.0)	1 (25.0)	1 (33.3)	3 (50.0)	2 (40.0)	1 (16.7)	1 (50.0)	10 (32.3)
Hemorrhage, *n* (%)	1 (20.0)	1 (25.0)	0	1 (16.7)	1 (20.0)	1 (16.7)	0	5 (16.1)
Contusion	0	0	0	1 (16.7)	1 (20.0)	0	0	2 (6.5)
Epistaxis	1 (20.0)	0	0	0	0	0	0	1 (3.2)
Hematuria	0	1 (25.0)	0	0	0	0	0	1 (3.2)
Wound hemorrhage	0	0	0	0	0	1 (16.7)	0	1 (3.2)

Abbreviations: SAE, serious adverse events; TEAE, treatment-emergent adverse events.
[a]Death due to embolic stroke considered not related to study drug.

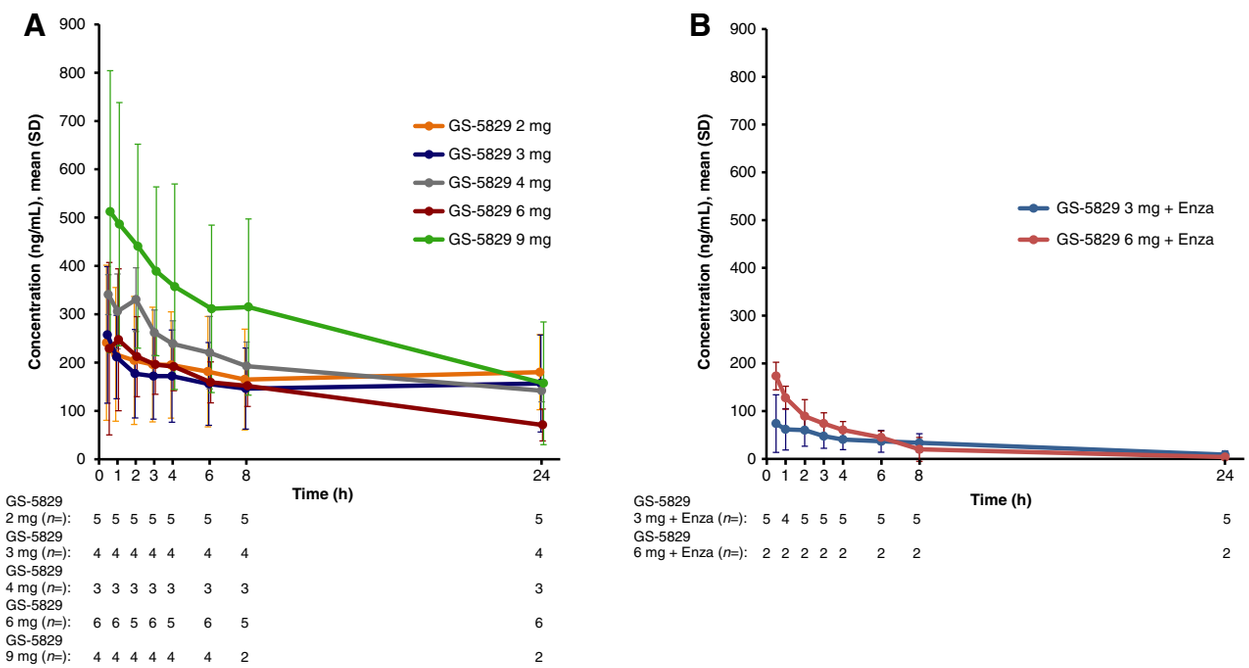

Figure 1.
GS-5829 plasma concentration over time by dose under fasted conditions. **A,** Data for GS-5829 monotherapy are shown for Cycle 1, Day 8. **B,** Data for GS-5829 + enzalutamide are shown for Cycle 1, Day 15. Enza, enzalutamide.

GS-5829 and enzalutamide dramatically decreased mean exposure (AUC_{tau}) to GS-5829 by nearly 80% as compared with the similar monotherapy dose (**Fig. 1**; Supplementary Fig. S3). PK parameters C_{max}, AUC_{tau}, AUC_{last}, C_{tau}, and T_{max} by dose are shown in Supplementary Table S2. PK parameters for Study 1599 are shown in Supplementary Table S3. *Post hoc* analyses showed no correlation between PK parameters and toxicity (Supplementary Fig. S4) or PSA response (Supplementary Fig. S5).

Pharmacodynamics

Study 1599

The biomarker evaluable population consisted of 20 patients distributed across 6 monotherapy dose cohorts. Maximum inhibition of *CCR2* ranged from 22.5% to 43.3% at cycle 1 day 1 and from 34.5% to 57.5% at cycle 1 day 8 in the different dose cohorts. Maximum induction of *HEXIM1* ranged from 3.7% to 61.4% at cycle 1 day 1 and from 12.5% to 94.0% at cycle 1 day 8 (Supplementary Table S4). Average inhibition of *CCR2* and induction of *HEXIM1* in all cohorts was stronger at cycle 1 day 8 than cycle 1 day 1, consistent with drug accumulation. Maximum inhibition for *CCR2* and induction for *HEXIM1* were seen at 1 to 4 hours and 2 to 4 hours postdose, respectively.

Study 1604

The biomarker evaluable population was 31 patients distributed across 5 monotherapy dose cohorts and 2 combination cohorts. In the monotherapy cohorts, maximum inhibition of BET target gene *CCR2* expression ranged from –8% (an increase of expression) to 40% at cycle 1 day 1 and from 16% to 73% at cycle 1 day 8 (Supplementary Table S5). Inhibition generally increased with dose at both time points, except in the 3-mg cohort ($n = 2$), and average inhibition in all cohorts was stronger at cycle 1 day 8 than cycle 1 day 1. Maximum induction of BET target gene *HEXIM1* ranged from 3% to 54% at cycle 1 day 1 and from 30% to 109% at cycle 1 day 8 (Supplementary Table S5). Induction also increased by dose (except in the 4-mg cohort) and was stronger at cycle 1 day 8 than cycle 1 day 1. Maximum inhibition of *CCR2* occurred at 2 to 3 hours postdose, and maximum induction of *HEXIM1* occurred at 2 to 4 hours postdose. Inhibition of *CCR2* and induction of *HEXIM1* was similar in the combination cohorts.

Efficacy

Study 1604

Among the 31 patients in the FAS, the KM estimate of nonprogression at week 24, the primary endpoint, was 25% (95% CI, 10–42; **Table 4**). The KM-estimated median PFS based on investigator assessment for all patients ($n = 31$) was 2.79 months (95% CI, 2.60–3.29; **Table 4**). The KM curve of PFS is shown in **Fig. 2A**. All but 2 patients discontinued the study without death; therefore, OS was not evaluable.

One patient (33.3%) in the 4-mg group and 1 patient in the 3 mg + enzalutamide group had a confirmed ≥30% reduction in PSA from baseline by week 12, and 1 patient (20.0%) in the 9-mg group had a confirmed ≥30% reduction from baseline during the study (**Table 4**). The patient in the 3 mg + enzalutamide group had a ≥50% reduction in PSA from baseline by week 12 (3.92 ng/mL at baseline, <0.2 ng/mL at nadir) and stable disease per RECIST. Individual best PSA response and target lesion change from baseline are shown by waterfall plots in **Figs. 2B** and **C**, respectively. No patient experienced a complete response, and 1 patient in the 9-mg group had a confirmed partial response (lymph node disease, with 34% PSA reduction). Most patients experienced stable disease [14 patients (45.2%)] or progressive disease [11 patients (35.5%)] during the study. Biomarker findings did not show a relationship to treatment response.

Table 4. Study 1604 efficacy results.

	GS-5829							
Parameter	**2 mg (*N* = 5)**	**3 mg (*N* = 4)**	**4 mg (*N* = 3)**	**6 mg (*N* = 6)**	**9 mg (*N* = 5)**	**3 mg + Enza (*N* = 6)**	**6 mg + Enza (*N* = 2)**	**Total (*N* = 31)**
Primary endpoint								
Nonprogression at Week 24, %	25	0	50	17	25	17	100	25
95% CI	1, 67	NE, NE	1, 91	1, 52	1, 67	1, 52	NE, NE	10, 42
Secondary endpoints								
PSA Reduction by Week 12, *n* (%)								1 (3.2)
≥30% from baseline	0	0	1 (33.3)	0	0	0	0	0
≥50% from baseline	0	0	0	0	0	0	0	
PSA Reduction any time during treatment, *n* (%)								
≥30% from baseline	0	0	1 (33.3)	0	1 (20)	0	0	2 (6.5)
≥50% from baseline	0	0	0	0	0	0	0	0
PFS (months)								
Median	2.61	2.10	4.17	2.78	2.69	3.25	5.98	2.79
95% CI	1.58, 8.61	1.97, 2.60	2.79, 5.55	2.69, 11.07	0.53, 14.00	1.15, 21.59	NE, NE	2.60, 3.25
Overall survival at week 24, %	100	NE	100	100	100	83	100	92
95% CI	NE, NE	NE, NE	NE, NE	NE, NE	NE, NE	27, 97	NE, NE	72, 98
Best overall response by lesion scan, *n* (%)								
Complete response	0	0	0	0	0	0	0	0
Partial response	0	0	0	0	1 (20)	0	0	1 (3.2)
Stable disease	1 (20)	1 (25)	2 (66.7)	5 (83.3)	1 (20)	2 (33.3)	2 (100)	14 (45.2)
Progressive disease	3 (60)	3 (75)	0	0	2 (40)	3 (50)	0	11 (35.5)

Abbreviations: CI, confidence interval; Enza, enzalutamide; NE, non-evaluable; PFS, progression-free survival; PSA, prostate-specific antigen; Q1, first quartile; Q3, third quartile.

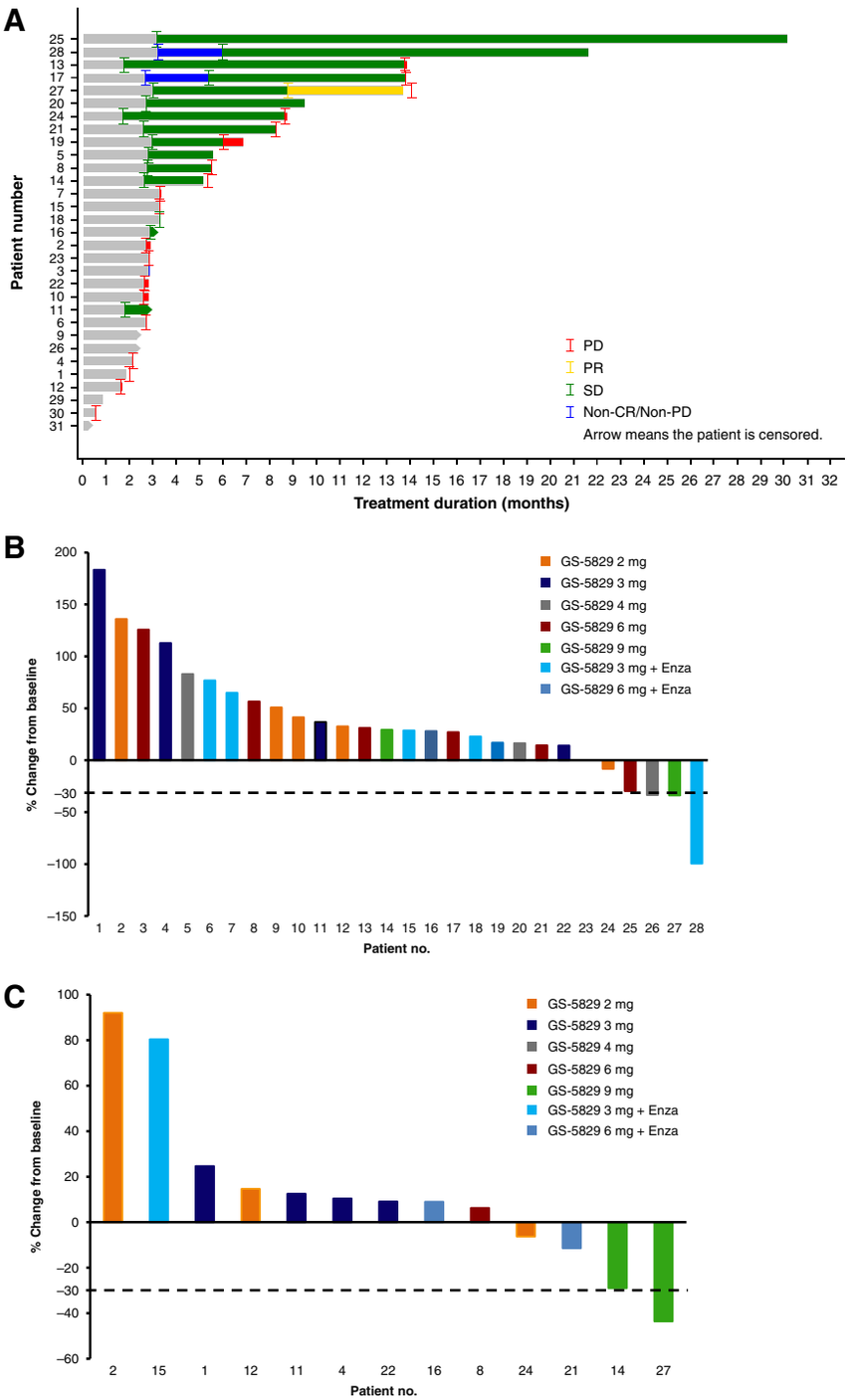

Figure 2.

Efficacy of GS-5829 monotherapy or combined with enzalutamide in mCRPC. Individual patients are identified by patient number in each graph. **A,** Swimmer plot of progression-free survival (full analysis set) with GS-5829 monotherapy treatment or combination therapy treatment. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. **B,** Waterfall plot of individual patient best prostate-specific antigen (PSA) response with GS-5829 treatment. Dashed line represents a 30% decrease in PSA. **C,** Waterfall plot of individual patient lowest target lesion by diameter by RECIST 1.1 post-therapy change from baseline (at any time point). Dashed line represents a 30% decrease in sum of target lesion diameters per RECIST 1.1. Five patients (1 in each group except the GS-5829 3 mg and GS-5829 6 mg + enzalutamide) were not assessed. Enza, enzalutamide.

Study 1599

Exploratory efficacy endpoints for patients with solid tumors and lymphomas treated with GS-5829 monotherapy are shown in Supplementary Table S6. Patients with prostate cancer were excluded from efficacy analyses. The overall response rate (ORR) based on investigator assessment was 0%, and the median PFS was 1.9 months (range, 0.3–3.8 months).

Discussion

BET proteins are a family of epigenetic molecules involved in transcription that are amplified and overexpressed in a variety of cancer types. BET inhibitors downregulate the expression of genes involved in pathways of tumorigenesis, offering a promising target for cancer therapy (20). The mechanisms by which BET modulates cellular proliferation have been described in detail elsewhere (28, 29).

Preclinical and early-stage clinical studies are beginning to provide evidence for the potential of BET inhibitors in the treatment of several advanced solid and hematologic cancers that currently have limited options in the metastatic setting (20–22).

GS-5829 is an oral small-molecule BET inhibitor that has been in development for the treatment of solid tumors, including CRPC, ER-positive advanced-stage breast cancer, and hematologic malignancies. Inhibition of cell growth and induction of apoptosis of solid and hematologic cancer in preclinical studies of GS-5829 (21), high potency and selectivity for BRD4 bromodomains (23), and favorable PK properties in preclinical models (23, 24) provided rationale for further clinical exploration in advanced cancers.

The early-phase studies reported here provide the first clinical experience with GS-5829 in patients with cancer. The phase I study, Study 1599, determined the starting dose for Study 1604, finding that 2-mg GS-5829 was safe and tolerable in patients with advanced tumors. Study 1604 was a dose escalation study of GS-5829 in 31 heavily pretreated patients with mCRPC as a single daily oral agent (2–9 mg) or as two doses (3 and 6 mg) in combination with 160-mg daily oral enzalutamide.

The development of BET inhibitors has provided important insights into the potential of BET proteins as therapeutic targets. Antiproliferative activity of BET inhibitors against tumors has been promising in pre-clinical studies (30), although clinical progress has been limited, perhaps due in part to a lack of biomarkers predicting sensitivity to BET inhibitors (31) or the presence of DLTs in trial patients. In earlier studies of BET inhibitors, the rates of toxicities, primarily thrombocytopenia and gastrointestinal toxicities, were relatively high (32–36), and impacted medication adherence (34) and the ability to escalate dosing sufficient to inhibit tumor BET and provide clinical efficacy. A recent clinical trial using the novel BET inhibitor BAY1238097 was terminated due to unexpected toxicities including thrombocytopenia (35). In contrast, BET inhibitors have also been shown to increase the expansion and maturation of megakaryocytes from human stem cells isolated from cord blood, suggesting a potential benefit of BET inhibition for platelet production (37), which is discordant with the thrombocytopenia findings and leaves open the question of BET inhibitor effects on megakaryocytes and platelets in circulating human blood and potential mechanisms of thrombocytopenia. In the current studies, GS-5829 was generally well tolerated. DLTs were observed in 4 patients receiving monotherapy in Study 1599, and 1 patient in Study 1604 experienced DLTs that led to permanent study discontinuation. The treatment-related AEs were primarily grades 1 and 2 and did not impact treatment adherence. However, platelet decreases were recorded as AEs in 23.8% (thrombocytopenia) and 4.8% (platelet count decreased) of patients in Study 1599, and 12.9% (platelet count decreased) and 3.2% (thrombocytopenia) of patients in Study 1604; 5 patients across these 2 studies had grade 3 thrombocytopenia. The rate of discontinuation due to TEAEs was low; 3 patients (14.3%) in Group 1 discontinued Study 1599 and 5 patients (16.1%) discontinued Study 1604 due to AEs. The similarity in tolerability between the 2 studies, comprising patients with a mix of solid and hematologic cancers, suggest that GS-5829 is well tolerated across different tumor types.

The efficacy of GS-5829 was lacking across the primary and secondary endpoints evaluated: the primary efficacy endpoint of nonprogression rate at week 24 was 25%. Indeed, most of the 31 patients treated experienced stable disease or disease progression. Only 1 patient had a 50% or greater reduction in PSA response (PSA50) from baseline during the study. No unique features were identified in the 3 PSA responders that could help predict a PSA response in future BET inhibitor studies. In a similar phase Ib/II study of ZEN-3694, a BET inhibitor evaluated in combination with enzalutamide in 75 patients with mCRPC, the PSA50 rate was less than 10%, and median PSA PFS was less than 4 months (22). The authors of that study speculated that a decline in serum PSA may not be the best metric for gauging BET inhibitor efficacy. A study of the BET inhibitor mivebresib also showed stable disease as the best tumor response in solid tumors and no changes in PSA consistent with efficacy in an mCRPC expansion cohort (38). Although exploratory, ORR and PFS in Study 1599 support a lack of antitumor efficacy for GS-5829.

PK analyses showed no dose-dependent increases in GS-5829 AUC_{tau}, C_{max}, or C_{tau} with daily administration of GS-5829. A high degree of variability was observed across all doses and parameters evaluated. In Study 1599, the plasma exposures to GS-5829 generally increased with increasing doses and showed moderate accumulation at steady state but were also highly variable between patients at a given dose. Patients were instructed to take GS-5829 at least 1 hour before or 2 hours after a meal, but adherence to this schedule was not documented and diet was not restricted. Consequently, there may have been an unanticipated food effect (this was not formally studied given the small number of patients). Drug–drug interactions with other concomitant medications cannot be ruled out. Preclinical studies suggest a half-maximal effective concentration (EC_{50}) of approximately 176 ng/mL (plasma corrected; 23), and mean C_{max} here exceeded the EC_{50} in Study 1604 monotherapy cohorts [ranging from 263.0 ng/mL (GS-5829 2.0 mg) to 526.0 ng/mL (GS-5829 9 mg)] and at the higher doses in Study 1599 [ranging from 64.0 ng/mL (GS-5829 0.6 mg) to 711.5 ng/mL (GS-6.0 mg)], although mean C_{tau} generally did not [ranging from 14.7 ng/mL (GS-5829 0.6 mg daily) to 237.1 ng/mL (GS-5829 6.0 mg) in Study 1599; and from 70.9 (GS-5829 6 mg daily) to 180.0 (GS-5829 2 mg daily) in Study 1604]. Combination therapy did not achieve this level. Given the high variability in PK parameters, it is possible that adequate concentrations were not sustained sufficiently to provide a clinically meaningful effect in individual patients. The lack of dose proportionality in GS-5829 exposure indicates that exploration of higher GS-5829 doses to achieve greater efficacy will not be fruitful.

GS-5829 showed appropriate PD effects in Studies 1599 and 1604, indicating that BET inhibition was achieved. The inhibition of *CCR2* and the induction of *HEXIM1* as PD biomarkers were similar for Studies 1599 and 1604. These biomarkers have been validated for BET inhibition in tumor models (26, 27) and have been used in recent BET inhibitor trials (38, 39). In Study 1599, inhibition of *CCR2* was observed at the lowest dose tested. In cohorts with more than 1 patient, induction of *HEXIM1* was observed at doses above 3 mg. In Study 1604, inhibition of *CCR2* and induction of *HEXIM1* both increased moderately with dose. Unexpectedly, inhibition of *CCR2* and induction of *HEXIM1* in the combination cohorts were similar to those in the monotherapy cohorts even though GS-5829 itself is reduced in combination with enzalutamide. In both studies, biomarker modulation increased following higher doses of GS-5829, particularly for *CCR2*, reflecting compound accumulation documented by the PK data. *HEXIM1* has a greater degree of induction than *CCR2* does inhibition, and maximum *CCR2* inhibition was <50% in Study 1604, although it is unclear how much inhibition is required for clinical efficacy. Interestingly, patients with PSA or target lesion responses did not show biomarker responses differing from others in their treatment group. Inhibition of *CCR2* and induction of *HEXIM1* reached a maximum at 2 to 4 hours following GS-5829 administration, then decreased thereafter and returned to

baseline, suggesting that these effects may not have been sustained long enough for clinical improvement.

Several clinical trials are in progress that utilize BET inhibitor ZEN-3694 in different types of cancer (ovarian cancer, NCT04840589; triple-negative breast cancer, NCT03901469; and prostate cancer, NCT04471974), which will provide more information on the utility of small-molecule BET inhibitors. BET inhibitors may have potential in suppressing tumor oncogenic networks particularly as a part of rational combination therapy. Overexpression of phosphatidylinositol 3-kinase (PI3K), for example, induces BET inhibitor resistance *in vitro* that may be mitigated through the combined use of BET inhibitors and PI3K inhibitors (40). A combination of BET inhibitors and mitogen-activated protein kinase inhibitor PD901 also showed promise in mouse models: synergy between the 2 agents resulted in the inhibition of cell proliferation (41). BET inhibitor ZEN-3694 was also tested in combination with enzalutamide in patients with mCRPC, with preliminarily promising results (22). Other approaches to BET inhibition may provide results where small-molecule BET inhibitors have not. For example, the use of proteolysis-targeting chimera technology to degrade BET family proteins is an exciting approach that is being explored in a number of tumor types, including CRPC (42, 43).

It is important to recognize the limitations of this phase Ib study. A total of 31 patients were enrolled, and each treatment cohort included only 2 to 6 patients. Patients entered the study having received a variety of prior therapies, and some patients were more heavily pretreated than others. It is not clear whether prior therapeutic regimen may impact clinical response to GS-5829.

In conclusion, GS-5829 was generally well tolerated, but inhibition of disease progression was lacking. Drug exposure was not dose proportional and was highly variable. Although the clinical development of GS-5829 has been terminated based on these findings, the attractiveness of the target warrants exploration of other BET inhibitors in CRPC and other cancers.

Authors' Disclosures

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Authors' Contributions

R. Aggarwal: Conceptualization, supervision, investigation, methodology, writing–original draft, writing–review and editing. **A.N. Starodub:** Investigation, writing–review and editing. **B.D. Koh:** Investigation, writing–review and editing. **G. Xing:** Software, validation, methodology, writing–review and editing. **A.J. Armstrong:** Resources, data curation, supervision, investigation, writing–original draft, writing–review and editing. **M.A. Carducci:** Conceptualization, formal analysis, supervision, investigation, writing–original draft, writing–review and editing.

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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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