A Signal-Finding Study of Abemaciclib in Heavily Pretreated Patients with Metastatic Castration–Resistant Prostate Cancer: Results from CYCLONE 1

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ABSTRACT

Purpose: Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors radically changed the treatment paradigm for breast cancer. Similar to estrogen receptor in breast cancer, androgen receptor signaling activates cyclin D–CDK4/6, driving proliferation and resistance to hormonal manipulation in prostate cancer. This study was designed to detect signals of clinical activity for abemaciclib in treatment-refractory metastatic castration-resistant prostate cancer (mCRPC).

Patients and Methods: Eligible patients had progressive mCRPC, measurable disease, and previously received ≥1 novel hormonal agent(s) and 2 lines of taxane chemotherapy. Abemaciclib 200 mg twice daily was administered on a continuous dosing schedule. Primary endpoint was objective response rate (ORR) without concurrent bone progression. This study was designed to detect a minimum ORR of 12.5%.

Results: At trial entry, 40 (90.9%) of 44 patients had objective radiographic disease progression, 4 (9.1%) had prostate-specific antigen (PSA)–only progression, and 20 (46.5%) had visceral metastases (of these, 60% had liver metastases). Efficacy analyses are as follows: ORR without concurrent bone progression: 6.8%; disease control rate: 45.5%; median time to PSA progression: 6.5 months [95% confidence interval (CI), 3.2–NA]; median radiographic PFS; 2.7 months (95% CI, 1.9–3.7); and median OS, 8.4 months (95% CI, 5.6–12.7). Most frequent grade ≥3 treatment-emergent adverse events (AE) were neutropenia (25.0%), anemia, and fatigue (11.4% each). No grade 4 or 5 AEs were related to abemaciclib.

Conclusions: Abemaciclib monotherapy was well tolerated and showed clinical activity in this heavily pretreated population, nearly half with visceral metastases. This study is considered preliminary proof-of-concept and designates CDK4/6 as a valid therapeutic target in prostate cancer.

Introduction

Uncontrolled cellular proliferation is a hallmark of cancer and the cyclin D–CDK4/6 and Rb–E2F pathway plays a key role in controlling G_1–S transition of the cell cycle that irreversibly commits cells to division (1–3). Rb acts as a co-repressor that binds E2F transcription factors. When Rb becomes phosphorylated by cyclin D–CDK4/6, the Rb–E2F repressive complex is disrupted, enabling the expression of E2F target genes involved in S-phase entry and cell-cycle progression (4).

CDK4/6 inhibitors (abemaciclib, palbociclib, and ribociclib) have transformed the treatment paradigm for hormone receptor–positive (HR+), HER2− metastatic breast cancer. When combined with endocrine therapy, all three CDK4/6 inhibitors demonstrated significantly increased progression-free survival (PFS) over endocrine therapy alone, and overall survival (OS) was improved with abemaciclib and ribociclib (5–8). Mechanistically, CDK4/6 may also represent a promising therapeutic target in prostate cancer. Preclinical evidence indicates that androgen receptor (AR) signaling activates CDK4/6 to drive prostate cancer cell proliferation (1). In addition, increased expression of cyclin D, and subsequent activation of CDK4/6, has been proposed as a resistance mechanism to novel hormonal agents (NHA; ref. 9). Furthermore, pharmacological inhibition of CDK4/6 led to robust cell-cycle arrest and tumor growth inhibition in prostate cancer models (10).

Abemaciclib is a potent, orally administered inhibitor of CDK4/6 that is 14 times more potent against CDK 4/cyclin D1 than CDK 6/cyclin D3 in enzymatic assays (11, 12). It is approved as a single agent and in combination with endocrine therapy for patients with high-risk early stage or metastatic HR+, HER2− breast cancer. Distinct in its class due to hematologic toxicities not being dose limiting, abemaciclib is administered on a continuous dosing schedule (13).

Patients with metastatic castration-resistant prostate cancer (mCRPC) experiencing disease progression after failure of life-prolonging NHAs and taxanes have limited therapeutic options

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Translational Relevance

Persistent oncogenic addiction to androgen receptor (AR) signaling underlies the development and progression of castration-resistant prostate cancer (CRPC). Preclinical evidence suggests a key role for cyclin D–CDK4/6 in AR-induced mitogenic signaling and in resistance to hormonal agents. As evidence of the relationship between the cyclin D-CDK4/6 and AR pathways, cyclin D1 is a transcriptional regulator of AR, and conversely, AR elicits upregulation of cyclin D1 and downregulates CDK4/6 inhibitors p21 and p27. Abemaciclib is a potent oral inhibitor of CDK4/6 that significantly augments the efficacy of hormonal therapy in high-risk early-stage and metastatic breast cancer. In prostate cancer models, abemaciclib induces cell-cycle arrest and tumor growth inhibition. This study of abemaciclib in heavily pretreated patients with metastatic CRPC provides the first clinical proof-of-concept for targeting CDK4/6 in prostate cancer and supports further clinical investigations to leverage the expected synergy of CDK4/6 and AR dual inhibition.

and very poor prognoses (14). The pressing need for treatments with novel modes of action, and the biological rationale for CDK4/6 inhibition against prostate cancer prompted the design of CYCLONE 1, a single-arm, signal-finding, phase 2 study of abemaciclib monotherapy in heavily pretreated patients with refractory mCRPC.

Patients and Methods

Patient characteristics

Patient disposition and eligibility criteria are presented in Supplementary Fig. S1. Eligible patients had measurable disease and progressive mCRPC by at least two rising prostate-specific antigen (PSA) values and/or imaging per RECIST v1.1 for soft tissue and Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria for bone. Prior therapy with one or more NHA (abiraterone, apalutamide, darolutamide, or enzalutamide) and two taxane-based chemotherapy regimens (docetaxel and cabazitaxel) were required. Exceptions for not receiving the second taxane due to hypersensitivity/intolerance or contraindications to taxanes, or discontinuation of the first taxane due to adverse events (AE), required sponsor approval. Up to three prior systemic therapy regimens in the mCRPC setting were permitted [of note: luteinizing hormone-releasing hormone (LHRH) analogues, first-generation antiandrogens, diethylstilbestrol, or other estrogens, corticosteroids, ketoconazole, and bone loss prevention were not considered prior systemic therapies]. Metastatic tumor tissue collection was required before enrollment (fresh biopsy or ≤12-week-old archival formalin-fixed, paraffin-embedded block/slides).

The study was conducted in accordance with Good Clinical Practice Guidelines and in compliance with the Declaration of Helsinki. Written informed consent was provided from all patients before study enrollment. The study protocol was approved by all sites' ethical review boards and all patients gave written, informed consent.

Study design

CYCLONE 1 (NCT04408924) was a multicenter, single-arm, open-label, phase 2 study that evaluated the safety and efficacy of abemaciclib monotherapy in heavily pretreated patients with

mCRPC. Patients received study treatment until disease progression (symptomatic and/or radiographic), unacceptable treatment-related toxicity, or until another discontinuation criterion was met.

Procedures

Eligibility was assessed during a 28-day screening period. Abemaciclib 200 mg twice daily was administrated orally in a continuous dosing schedule on 28-day cycles. Standard androgen deprivation therapy with an LHRH analogue was continued for patients who had not undergone bilateral orchiectomy. Safety was evaluated using the National Cancer Institute Common Toxicity Criteria for AEs version 5 (NCI CTCAE v5.0). Contrast-enhanced CT of the chest, CT or MRI of the abdomen and pelvis, and whole-body bone scans were obtained at baseline and repeated every 8 weeks from cycle 1 day 1 until documented radiographic progression, start of new anticancer therapy, withdrawal of consent, death, or study completion. Tumor response was assessed according to RECIST v1.1 for soft tissue and PCWG3 criteria for bone.

Study endpoints

Definitions of primary and secondary endpoints are provided in Supplementary Table S1.

The primary endpoint was investigator-assessed objective response rate (ORR) defined as the proportion of all treated patients with a confirmed complete response (CR) or confirmed partial response (PR) in soft tissue per RECIST v1.1 without concurrent bone progression per PCWG3. Key secondary endpoints included radiographic PFS (rPFS), OS, time to PSA progression, time to symptomatic progression, pharmacokinetics, and safety. The nature and severity of AEs were assessed according to CTCAE v5.0.

Statistical analysis

All patients who received at least one dose of abemaciclib were included in the safety and efficacy analyses.

For the primary efficacy analysis, an ORR of ≥12.5% was considered promising in this highly treatment-refractory setting with no accepted standard of care. Patients with a non-evaluable tumor or unknown response were considered non-responders. Time-to-event efficacy endpoints such as rPFS, time to PSA progression, OS, and time to symptomatic progression were estimated using the Kaplan–Meier method and respective confidence intervals (CI) were reported with a 2-sided 95% level.

The primary analysis was planned to occur approximately 6 months after the last patient entered treatment. Because of sparse pharmacokinetic sampling, a population pharmacokinetic modeling approach matching CYCLONE 1 patient characteristics was used to simulate the pharmacokinetic parameters of interest based on a final population pharmacokinetic model previously developed (15).

Data availability

Eli Lilly and Company provides access, after anonymization, to all individual participant data collected during the trial, except for pharmacokinetic and genetic data. Data can be requested 6 months after the indication studied has been approved in the United States and European Union or after primary publication acceptance, whichever is later. No expiration date for data requests is set once the data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a

secure data-sharing environment. For details on submitting a request, see instructions at https://vivli.org.

Results

Patients

Between January and October 2021, 44 patients from France, Spain, and the United States were enrolled and received abemaciclib 200 mg twice daily on a continuous schedule (Supplementary Fig. S1). Representativeness of study participants is reflected in Supplementary Table S2.

The median age was 68 (range, 48–94) years and 75% of patients had an Eastern Cooperative Oncology Group performance status of 1. The Gleason score was ≥8 for 64.3% of the patients and 50.0% had metastatic disease at the initial diagnosis of prostate cancer. Median time from mCRPC diagnosis to study entry was 2.1 years (range, 0.7–6.6) and median PSA at study entry was 96.0 ng/mL. Most patients (40/44; 93.0%) had three or more metastatic lesions. All patients had measurable disease. Notably, nearly half of the patients (20/44; 46.5%) had visceral metastases, of whom 60.0% (12/20) had liver lesions. Patients predominantly experienced radiographic progression (RECIST/PCWG3) at study entry (40/44; 90.9%), whereas only four (9.1%) had PSA-only progression (**Table 1**). Baseline expression of the Ki-67 proliferation marker assessed by IHC was high (cutoff score ≥20%) for 74.2% (23/31) of the 31 patients with evaluable baseline metastatic tumor samples.

All patients were previously treated with at least one NHA, most commonly abiraterone and enzalutamide (54.5% each). Seven patients (15.9%) received two prior NHAs. In addition, all patients previously received docetaxel, and all but 4 (40/44; 90.9%) also received cabazitaxel. Other prior systemic therapies included radiopharmaceuticals (radium-223 and [177]Lutetium-PSMA-617, 2.3% each) and immune checkpoint inhibitors (pembrolizumab, 6.8%; atezolizumab, durvalumab, ipilimumab, and nivolumab, 2.3% each). The median number of prior lines of systemic treatments for mCRPC was 3 (range, 1–4; **Table 1**).

Efficacy

At the time of data cutoff on April 27, 2022, 3 of the 44 patients had a confirmed PR without concurrent bone progression for an ORR of 6.8% (95% CI, 0.0–14.3). **Figure 1** and Supplementary Table S3 summarize the best percentage of change in tumor size (waterfall plot) and best overall response by RECIST v1.1 criteria without concurrent bone progression. Notably, 17 (38.6%) patients experienced radiographic stabilization of their disease that was durable for ≥6 months for over a third (6/17; 35.3%) of these patients. The soft tissue disease control rate (CR+PR+stable disease) without concurrent bone progression was 45.5% (95% CI, 30.7–60.2). The clinical benefit rate (CR+PR+stable disease ≥6 months) without concurrent bone progression was 20.5% (95% CI, 8.5–32.4). The median time to PSA progression was 6.5 months (95% CI, 3.2–NA; **Fig. 2**). Two (4.6%) patients experienced ≥50% decline in PSA from baseline, confirmed with a second assessment conducted at least 3 weeks later. The median rPFS (soft tissue or bone progression, or death from any cause) was 2.7 months (95% CI, 1.9–3.7) and the 6-month rPFS rate was 24.9% (**Fig. 3**). The median time to symptomatic progression was 4.1 months (95% CI, 3.7–NA; Supplementary Fig. S2). Other secondary outcomes of duration of response, change in PSA, and PSA response are reported in Supplementary Table S4 and Supplementary Fig. S2. Because of the limited sample size, correlation between efficacy outcomes and baseline Ki-67 expression in the metastatic tumor samples could not be established.

Table 1. Patient characteristics.

| Characteristics	n (%)
Median age (range)	68 (48–94)
Gleason score (n = 42)	
≤7	15 (35.7)
8–10	27 (64.3)
Initial diagnosis (n = 42)	
Localized	21 (50.0)
Metastatic	21 (50.0)
ECOG PS (n = 44)	
0 (fully active)	11 (25.0)
1 (restricted)	33 (75.0)
Metastatic sites (n = 43)	
2	3 (7.0)
≥3	40 (93.0)
Site of disease (n = 43)	
Visceral[a]	20 (46.5)
Liver	12 (60.0)
Lung	9 (45.0)
Other	3 (15.0)
Non-visceral	23 (53.5)
Type of progression at trial entry (n = 44)	
PSA-only	4 (9.1)
Radiographic (by RECIST/PCWG3) ± PSA	40 (90.9)
Baseline Ki-67 expression by IHC (n = 31)	
Low (<20%)	8 (25.8)
High (≥20%)	23 (74.2)
Prior therapy	**n (%)**
Type of prior therapy[b] (n = 44)	
Chemotherapy	44 (100)
Docetaxel	44 (100)
Cabazitaxel	40 (90.9)
Carboplatin	2 (4.5)
Paclitaxel	1 (2.3)
Novel hormonal agent	44 (100)
1	37 (84.1)
2[c]	7 (15.9)
Abiraterone	24 (54.5)
Enzalutamide	24 (54.5)
Apalutamide	2 (4.5)
Darolutamide	1 (2.3)
Radiopharmaceuticals	2 (4.5)
Radium-223	1 (2.3)
^{177}Lu-PSMA	1 (2.3)
Immunotherapy	6 (13.6)
Pembrolizumab	3 (6.8)
Atezolizumab	1 (2.3)
Durvalumab	1 (2.3)
Ipilimumab	1 (2.3)
Nivolumab	1 (2.3)
Number of prior therapies for mCRPC (n = 44)	
≤2	19 (43.2)
≥3[d]	25 (56.8)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; mHSPC, metastatic hormone-sensitive prostate cancer; nmCRPC, nonmetastatic castration–resistant prostate cancer; PCWG3, Prostate Cancer Clinical Trials Working Group 3; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]Four patients had both liver and lung lesions.
[b]Patients may have received multiple prior therapies in any setting, including mHSPC, nmCRPC, or mCRPC.
[c]One patient received the two NHAs in combination.
[d]Three patients had four prior therapies for mCRPC.
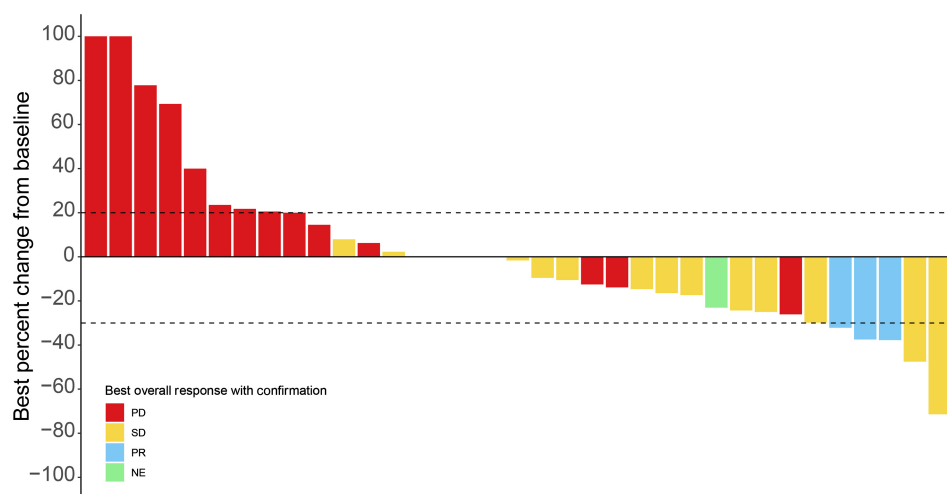
Figure 1.
Best percentage of change in tumor size. Two patients had a greater than 30% reduction in their target lesions but did not have their responses confirmed without concurrent bone progression.

Forty-one of the 44 patients (93.2%) discontinued abemaciclib study treatment: 30 (73.2%) due to progressive disease and 6 (14.6%) due to AEs (Supplementary Fig. S1). A total of 36 patients entered post-discontinuation follow-up, of whom 15 (41.7%) received subsequent treatment. Most common post-discontinuation treatments were palliative radiotherapy (4/15, 26.7%), radium-223 (3/15, 20%), and carboplatin (3/15, 20%; Supplementary Table S5).

At the primary outcome data cutoff, the median follow-up time was 8.5 months and OS was immature (19 events, median OS, 7.6 months; 95% CI, 5.6–not reached; **Fig. 4**). At the final OS analysis, the median follow-up was 21.1 months, there were 31 death events, and the median OS was 8.4 months (95% CI, 5.6–12.7).

Safety

All patients experienced ≥1 treatment-emergent AE (TEAE) that were mostly low grade (**Table 2**). The most frequently reported any-grade TEAEs were diarrhea (81.8%), fatigue (63.6%), decreased appetite (54.5%), nausea (47.7%), neutropenia (38.6%), anemia (36.4%), vomiting (36.4%), and constipation (20.5%). The most frequent grade ≥3 TEAEs were neutropenia (25.0%), anemia (11.4%), and fatigue (11.4%).

The most frequently reported any-grade treatment-related AEs (TRAE) occurring in >10% of patients were diarrhea (79.5%), decreased appetite (52.3%), fatigue (50.0%), nausea (43.2%), neutropenia (34.1%), vomiting (34.1%), anemia (29.5%), thrombocytopenia (15.9%), and blood creatinine increased (11.4%; **Table 2**). There were no grade 4 or 5 TRAEs.

Serious AEs (SAE) were reported for 16 patients (36.4%), with pyrexia (19%), renal failure (19%), anemia (13%), and serum creatinine increase (13%) being the most common. Two patients experienced SAEs deemed possibly related to abemaciclib: one patient had two SAEs (serum creatinine increase and renal failure) and discontinued study treatment; the second patient had a SAE of anemia.

The median relative dose intensity was 69.5% (Q1–Q3: 48.6%–92.6%). Thirty-four patients (34/44; 77.3%) had a dose suspension of abemaciclib due to an AE, most commonly diarrhea (11/34, 25.0%), neutropenia (7/34, 15.9%), and blood creatinine increased (4/34, 9.1%). Nineteen patients (19/44; 43.2%) required ≥1 dose
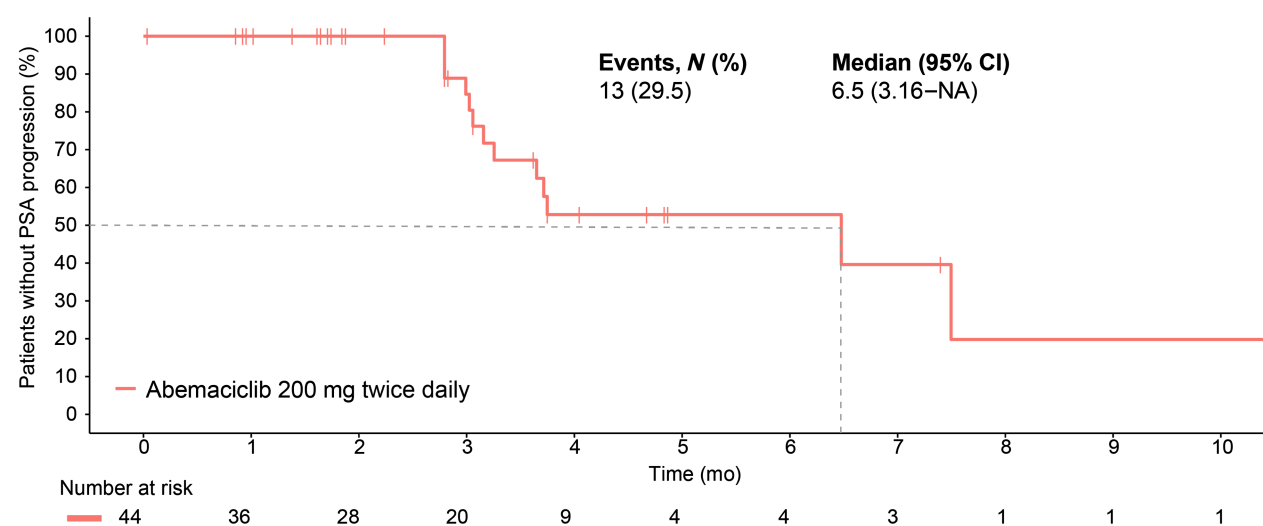
Figure 2.
Time to prostate-specific antigen progression.
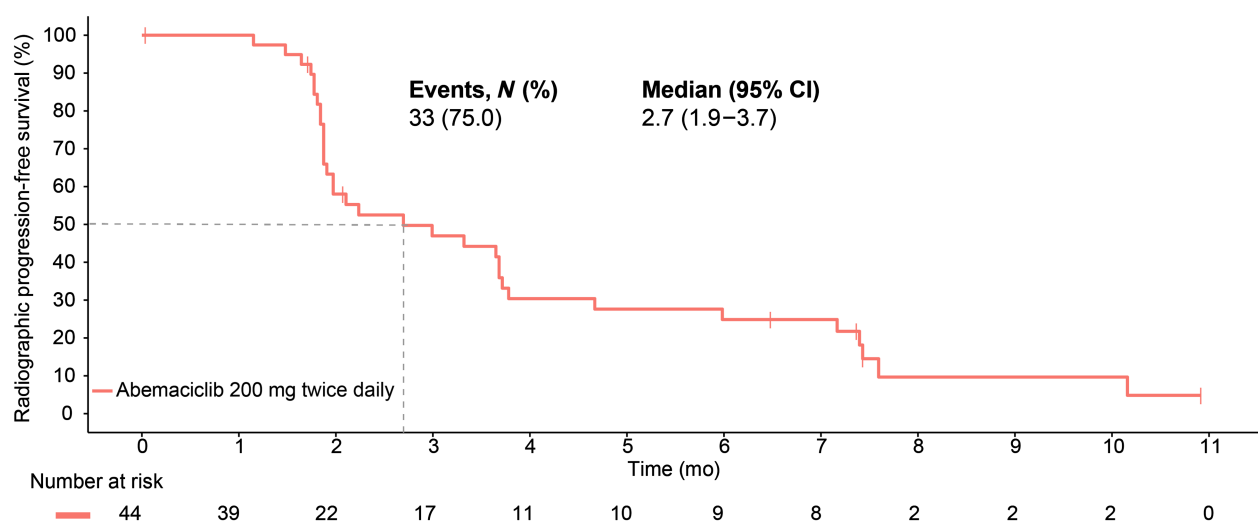
Figure 3.
Radiographic progression-free survival.

reduction of abemaciclib due to an AE. The most frequent AEs leading to dose reductions were diarrhea (7/19, 36.8%), blood creatinine increased (3/19, 15.8%), and neutropenia (3/19, 15.8%). Of the 44 patients, 6 (13.6%) discontinued treatment due to an AE/SAE (anemia, neutropenia, vomiting, or renal failure). AEs leading to treatment discontinuation were deemed possibly related to abemaciclib for 4 patients (4/44; 9.1%).

Pharmacokinetics

Plasma concentration-time data for abemaciclib were available for 43/44 patients (97.7%). In CYCLONE 1, the starting dose of abemaciclib was 200 mg twice daily, and sequential reductions by 50-mg dose levels were permitted. Summary exposures of 178 mg were calculated on the basis of the average dose received throughout the study and are consistent with previous studies in breast cancer (data on file; Supplementary Table S6).

Discussion

CYCLONE 1 enrolled a heavily pretreated population with no real treatment alternatives. Although the primary endpoint of a 12.5% ORR in soft tissue without concurrent bone progression was not met, results from this signal-finding study provided the first evidence of abemaciclib's clinical activity in a late and refractory mCRPC disease setting, after patients had progressed on NHA and taxanes. No new safety signals were identified in this study. Abemaciclib was well tolerated in this advanced patient population and demonstrated predictable toxicity, consistent with that previously observed in metastatic cancer (16, 17). Toxicities were generally low grade, manageable, and reversible with supportive care and dose adjustments. Altogether, the CYCLONE 1 findings are considered preliminary proof-of-concept and represent the first clinical validation of CDK4/6 as a therapeutic target in prostate cancer.
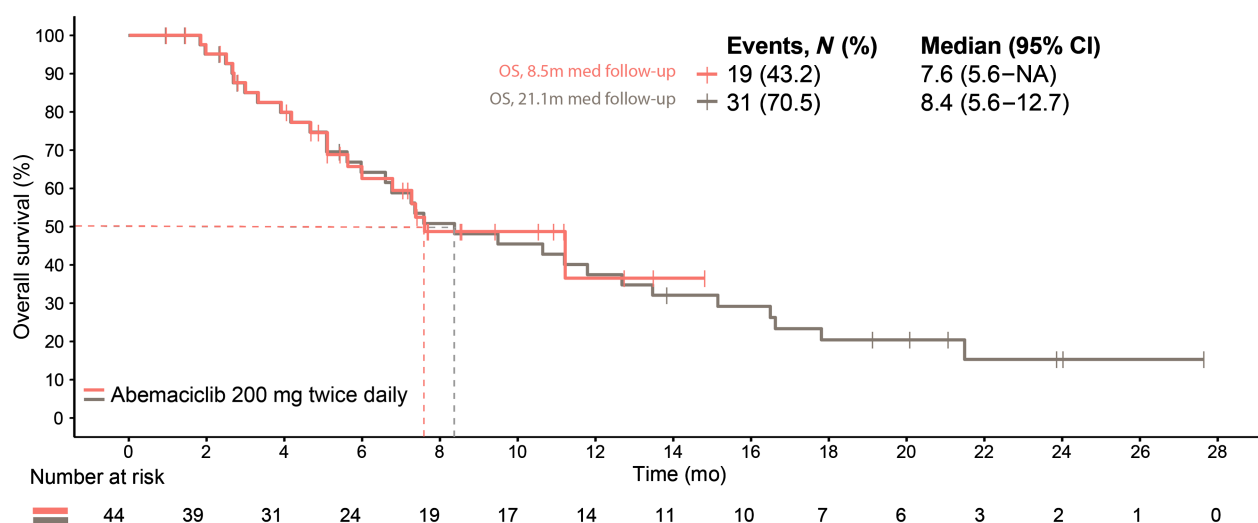
Figure 4.
Overall survival.

Table 2. Safety results.

TEAEs >10% of patients	$N = 44$	
	Any Grade	Grade ≥3
Diarrhea	36 (81.8)	4 (9.1)
Fatigue[a]	28 (63.6)	5 (11.4)
Decreased appetite	24 (54.5)	1 (2.3)
Nausea	21 (47.7)	0 (0.0)
Neutropenia[a]	17 (38.6)	11 (25.0)
Anemia	16 (36.4)	5 (11.4)
Vomiting	16 (36.4)	0 (0.0)
Constipation	9 (20.5)	0 (0.0)
Blood creatinine increased	8 (18.2)	0 (0.0)
Thrombocytopenia[a]	8 (18.2)	2 (4.5)
Back pain	7 (15.9)	0 (0.0)
Pyrexia	7 (15.9)	1 (2.3)
Edema peripheral	6 (13.6)	0 (0.0)
Arthralgia	5 (11.4)	0 (0.0)
TRAEs >10% of patients	**$N = 44$**	
	Any grade	Grade 3[b]
Diarrhea	35 (79.5)	3 (6.8)
Decreased appetite	23 (52.3)	1 (2.3)
Fatigue[a]	22 (50.0)	3 (6.8)
Nausea	19 (43.2)	0 (0.0)
Neutropenia[a]	15 (34.1)	10 (22.7)
Vomiting	15 (34.1)	0 (0.0)
Anemia	13 (29.5)	3 (6.8)
Thrombocytopenia[a]	7 (15.9)	1 (2.3)
Blood creatinine increased	5 (11.4)	0 (0.0)

[a]Consolidated terms: fatigue, fatigue and asthenia; neutropenia, neutropenia and neutrophil count decreased; thrombocytopenia, thrombocytopenia, and platelet count decreased.
[b]No Grade 4 or 5 TRAEs (as assessed by investigators) were reported.

CDK4/6 inhibitors have transformed outcomes for patients with early-stage and metastatic HR⁺, HER2⁻ breast cancer by significantly augmenting the clinical benefit of hormone therapy. Similar to the estrogen receptor in breast cancer, AR signaling, a key driver of mCRPC progression, elicits CDK4/6 activation to sustain prostate cancer cell uncontrolled proliferation and resistance to AR signaling directed therapies (1). Early attempts to evaluate the role for CDK4/6 inhibition in mCRPC were conducted with palbociclib monotherapy (NCT02905318) and ribociclib in combination with docetaxel (NCT02494921). These investigations demonstrated either no evidence of clinical activity or dose-limiting toxicities in the mCRPC setting. The phase 2 trial evaluating palbociclib monotherapy in previously treated mCRPC demonstrated a 0% ORR and no patients experienced any PSA decrease from baseline (18). The association of ribociclib and docetaxel in a similar mCRPC population demonstrated dose-limiting neutropenia and febrile neutropenia during the escalation portion, prompting a reduced and intermittent dosing schedule of the combination (17).

Abemaciclib is the only CDK4/6 inhibitor dosed continuously and approved as monotherapy based on its clinical activity in patients with heavily pretreated refractory HR⁺, HER2⁻ metastatic breast cancer. Uniquely, continuous inhibition of CDK4/6 may prevent cell-cycle rebound and development of resistance that may lead to durable responses, particularly in patients with aggressive disease features and rapidly growing tumors.

The clinical activity in this late mCRPC setting may have been hampered by the heavily pretreated and advanced nature of the disease population that often presents with significant morbidity. In addition, there was a relatively high proportion of patients with visceral metastases, including to the liver, and almost all patients had objective radiographic disease progression at study entry, a clinical scenario associated with a very poor prognosis and short survival. Consistently, about a fifth of the patients discontinued study treatment early, before the first scheduled post-baseline imaging assessment, mostly due to death before progressive disease and subject withdrawals. Because of differences in the measurement intervals and event definitions, as well as the high censoring rate for time to PSA progression driven by confirmation requirements, the median time to PSA progression was slightly greater than the median rPFS time. The small sample size of this non-randomized study in a heavily pretreated mCRPC population also limits broad interpretation of the clinical activity observed for abemaciclib.

Nonetheless, the tumor responses observed in this study provide rationale for further exploration of abemaciclib in earlier disease settings. The opportunity to leverage the potential compounding effect of dual inhibition of the AR axis and CDK4/6 to maximize the therapeutic benefit and delay hormonal resistance and progression served as the basis for CYCLONE 2 (NCT03706365), a randomized, placebo-controlled, adaptive, phase 2/3 study of abiraterone with abemaciclib in first-line mCRPC. CYCLONE 2 expanded from phase 2 to 3 based on an adaptive interim efficacy analysis and triggered further interest in evaluating this drug combination in patients with high-risk metastatic hormone-sensitive prostate cancer in CYCLONE 3, a randomized, placebo-controlled, phase 3 trial (NCT05288166). Primary results from CYCLONE 2 and CYCLONE 3 are awaited to confirm whether, similar to augmenting ER signaling inhibition in hormonally driven breast cancer, abemaciclib will meaningfully augment the clinical benefit of AR signaling pathway inhibition.

Authors' Disclosures

Authors' Contributions

N. Agarwal: Conceptualization, data curation, formal analysis, investigation, visualization, methodology, writing–review and editing. **D. Castellano:** Conceptualization, data curation, formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **T. Alonso-Gordoa:** Investigation, writing–review and editing. **J.A. Arranz Arija:** Investigation, writing–review and editing. **E. Colomba:** Data curation, investigation, writing–review and editing. **G. Gravis:** Data curation, investigation, writing–review and editing. **L. Mourey:** Data curation, writing–review and editing. **S. Oudard:** Data curation, formal analysis, investigation, writing–review and editing. **A. Fléchon:** Data curation, formal analysis, investigation, writing–review and editing. **M. González:** Data curation, writing–review and editing. **P.M. Rey:** Data curation, writing–review and editing. **M.T. Schweizer:** Data curation, investigation, writing–review and editing. **E. Gallardo:** Data curation, writing–review and editing. **E. Johnston:** Conceptualization, formal analysis, investigation, methodology, writing–review and editing. **A. Balar:** Formal analysis, investigation, writing–original draft, writing–review and editing. **N. Haddad:** Writing–original draft, writing–review and editing, interpretation of data for the work. **A.K. Appiah:** Formal analysis, writing–original draft, interpretation of data for the work. **K. Nacerddine:** Formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **J.M. Piulats:** Investigation, 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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