Title

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Journal

Journal of Urologic Oncology, 22(3)

ISSN

2951-603X

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Publication Date

2024-11-30

DOI

10.22465/juo.244800520026

https://doi.org/10.22465/juo.244800520026
pISSN: 2951-603X eISSN: 2982-7043
Journal of Urologic Oncology 2024;22(3):211-223

ORIGINAL ARTICLE

JUO
JOURNAL OF UROLOGIC ONCOLOGY

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Assessing Patient Risk, Benefit, and Outcomes in Drug Development: A Decade of Abiraterone Clinical Trials

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Received July 12, 2024
Revised October 17, 2024
Accepted October 23, 2024

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Purpose: Our study aimed to evaluate the risk and benefit profiles of clinical trials using abiraterone in cancer treatment.

Materials and Methods: A comprehensive search was conducted on May 24, 2023, using databases such as PubMed, Embase, Cochrane CENTRAL, and ClinicalTrials.gov. We extracted data on adverse events, progression-free survival, overall survival, objective response rate (ORR), and prostate-specific antigen response rate (PSA-RR). The Common Terminology Criteria for Adverse Events were used to assess risks, while ORR and PSA-RR were used to assess benefits. Trials were categorized as positive, negative, or indeterminate based on their safety profiles and efficacy outcomes.

Results: Nearly all clinical trials testing abiraterone in prostate cancer showed promising outcomes with 89% of studies meeting their endpoint. Our study supports abiraterone's use in prostate cancer, its only U.S. Food and Drug Administration-approved indication to treat, with a median ORR of 20.0% and a median PSA-RR of 42.0%. However, when looking at the 3 novel indications tested, the risk-to-benefit profile was similar to that of its original approval. Even though most novel indications failed to meet their primary endpoint, the overall toxicity profile was similar to that found in prostate cancer.

Conclusion: Abiraterone showed an overall risk-to-benefit portfolio that supports the use of its treatment in prostate cancer. Although the primary endpoints in ovarian and breast cancer trials were not met, the use was appropriate when assessing how the mechanism of action for abiraterone could be beneficial in patients with these types of cancers.

Key Words: Prostatic neoplasms, Abiraterone, Clinical trials, Risk assessment, Off-label use, United States Food and Drug Administration

- **Grant/Fund Support:** This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
- **Research Ethics:** The Oklahoma State University Center for Health Sciences reviewed our protocol and determined that this research qualifies as non-human subjects research as defined in regulation 45 CFR 46.102(d) and (f).
- **Conflicts of Interest:** VP reports research funding from Arnold Ventures; royalties from Johns Hopkins Press, Medscape, and MedPage; honoraria from GrandRounds/lectures from universities, medical centers, non-profits, professional societies, YouTube, and Substack; consulting from UnitedHealthcare and OptumRX; speaking fees from Evicore. Plenary Session podcast has Patreon backers. MV reports receipt of funding from the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, the U.S. Office of Research Integrity, Oklahoma Center for Advancement of Science and Technology, and internal grants from Oklahoma State University Center for Health Sciences — all outside of the present work. All other authors have nothing to report.

INTRODUCTION

Prostate cancer remains one of the most common cancers in men, accounting for nearly 15% of all new cancer diagnoses in 2023 [1]. Among these, high-risk cases—defined by a Gleason score of 8–10—comprise 15%, while metastatic disease represents 7% of diagnoses [2,3]. These cases typically require antiandrogen therapy when treatments like androgen deprivation therapy (ADT), prostatectomy, or radiation are insufficient [2]. Abiraterone—an oral antiandrogen—was approved by the U.S. Food and Drug Administration (FDA) and made first-line for the treatment of castration-resistant prostate cancer (CRPC) in 2011 and for high-risk castration-sensitive prostate cancer in 2018 [4]. Further, abiraterone is used off-label for the treatment of very high-risk nonmetastatic prostate cancer. As of June 2023, abiraterone is currently used in clinical trials for the treatment of adrenocortical tumors, breast cancer, and congenital adrenal hyperplasia [5].

In a 2020 study, Carlisle et al. [6] demonstrated that once an antineoplastic agent is found to be effective for one indication, it is often trialed on other cancers or conditions. These trials are likely conducted in a good-faith effort to reduce morbidity and to help pharmaceutical companies recoup their losses from drug development. The development of a novel chemotherapy cost an average of 2.7 billion dollars [7] and could take up to 15 years [8] to receive approval; but when using an existing chemotherapy for a new indication, approval takes approximately half the time, cost 60% less, and is 3 times more likely to be approved by the FDA [9]. In order to repurpose a medication, another clinical trial must take place. Thus, more patients are asked to risk their time, resources, and health for a potential improvement in their cancer. In addition to the strain on patients, repeat trials have been shown to drain financial and clinical resources [6]. Therefore, to limit harm to patients and research waste, systematic assessments of all on and off-label uses of antineoplastic agents—drug portfolios—must be developed.

Complete drug development profiles are paramount for assessing the true safety and efficacy of chemotherapies, yet few studies have done so. The 2020 catalog of imatinib's clinical trials found that when tried on novel histologies, imatinib showed no clinical benefit [6]. In a similar analysis, Carlisle et al. [10] discovered a worsening risk/benefit balance and slow response when sunitinib was tried for new indications. Due to the number of men affected by prostate cancer, we believe it is imperative that a drug development profile for abiraterone be performed. Thus, we aim to create a complete catalog of abiraterone's clinical trials with the goal of better understanding patients' risk/benefit balance. Further, we believe the findings of this study will provide healthcare providers, patients, and policymakers with valuable insight into the implications of cancer treatment.

MATERIALS AND METHODS

1. Study Design/Open-Science

This study was conducted as a systematic review aimed at analyzing the risk and benefit profiles of clinical trials involving abiraterone (Zytiga, Janssen Biotech, Horsham, PA, USA) across its development and applications for indications beyond its initial FDA approval. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and comprehensive reporting. To enhance quality, reproducibility, and transparency, we shared a protocol prior to this investigation. Upon completion, we made the raw data, statistical analysis scripts, and extraction forms available on Open Science Framework (OSF), a publicly accessible data repository [11]. Our data will remain accessible for as long as OSF is active or upon request.

2. Research Objective, Definitions, and Hypothesis

Considering that clinical trials are costly and potentially harmful, this study aimed to analyze the risk/benefit profile of clinical trials assessing the efficacy of abiraterone. The primary objective was to evaluate if the combined risk profiles represented an overall excessive risk to the patients. This study defined a clinical trial *profile* as the overall risk and benefit encountered by participants during a single trial as measured by selected tools mentioned in the *Data Extraction* section. Additionally, a drug's portfolio was defined as the total collection of trial profiles for a given intervention. We hypothesized that the expansion of abiraterone clinical trials

https://doi.org/10.22465/juo.244800520026

in off-label indications would lead to an increase in negative trials with higher patient risk, resulting in an overall negative drug portfolio.

3. Training

All authors were trained in clinical trial design, reporting, and outcomes by author VP, an experienced clinical oncologist and expert in evidence-based medicine. The training included both the Common Terminology Criteria for Adverse Events [12] and Response Evaluation Criteria in Solid Tumors (RECIST) [13]. The screening authors were trained how to use Rayyan (https://www.rayyan.ai/) [14]. Data extraction was carried out using a pilot-tested Google form. Authors began by extracting data from 5 example studies for training proposes before proceeding to extract the included sample of trials.

4. Literature Search

We performed a literature search on May 24, 2023 of PubMed/MEDLINE, Embase (Elsevier), Cochrane CENTRAL, and ClinicalTrials.gov for clinical trials using abiraterone as monotherapy or in combination with other interventions for cancer treatment. We standardized our search strings across these databases using the PolyGlot Search Translator (https://sr-accelerator.com/#/polyglot) developed by Bond University and the Institute for Evidence Based Healthcare [14]. Our search strings, including date of search and initial returns, were uploaded to OSF and are available as supplementary data in the final manuscript submission.

5. PRISMA Adherence

We followed the PRISMA guidelines throughout the systematic review process, including database searches, screening, data extraction, and synthesis. A detailed flowchart of study selection is provided in Fig. 1.

6. Selection Process

We uploaded search returns into Rayyan for literature screening. Two authors (MR and EO) screened titles and abstracts, in a masked duplicated fashion, for potential inclusions. Upon finishing screening, author AP resolved any discrepancies. We recorded reasons for exclusion during the screening process to create a flowchart for study exclusions.

7. Inclusion and Exclusion Criteria

Studies that qualify for inclusion must: (1) be a clinical trial of adult, human subjects, (2) assess efficacy of abiraterone as monotherapy or in combination as an intervention to treat solid cancers, (3) assess the benefit of abiraterone using prostate-specific antigen response rate (PSA-RR) or objective response rate (ORR) as defined by the RECIST criteria and (4) be published in English. We excluded non-oncological studies, biosimilar studies, pharmacology studies on healthy participants, and exclusively pediatric studies. Additionally, we excluded other publication types including: secondary reports, interim results, clinical trial updates and follow-ups, preclinical studies, literature reviews, systematic reviews, meta-analyses, human tissue studies, laboratory studies, case reports, letters to the editor, editorials, opinion pieces, conference abstracts, and corrections or redactions.

8. Data Extraction

Following data screening, the final study sample underwent data extraction in a masked, duplicate fashion by 2 authors (MR and EO) with a third author (AP) available to resolve discrepancies. The following were extracted by the authors: published trial title, PubMed ID, clinical trial registry number, country of first author's affiliation, date of publication, number of participants, mean or median age of participants, number of male participants, number of female participants, indication(s) of the trial, metastatic or nonmetastatic stage, whether the trial was controlled, if the trial assessed monotherapy or combination therapies, phase of the trial, number of centers, blinding of trial participants, randomization ratio, and study sponsor, including funding and conflicts of interest statements.

For risk and benefit outcomes, the following variables were extracted for treatment arms: the name of the arm, adverse events grade, median progression-free survival (PFS) in months, median overall survival (OS) in months, partial

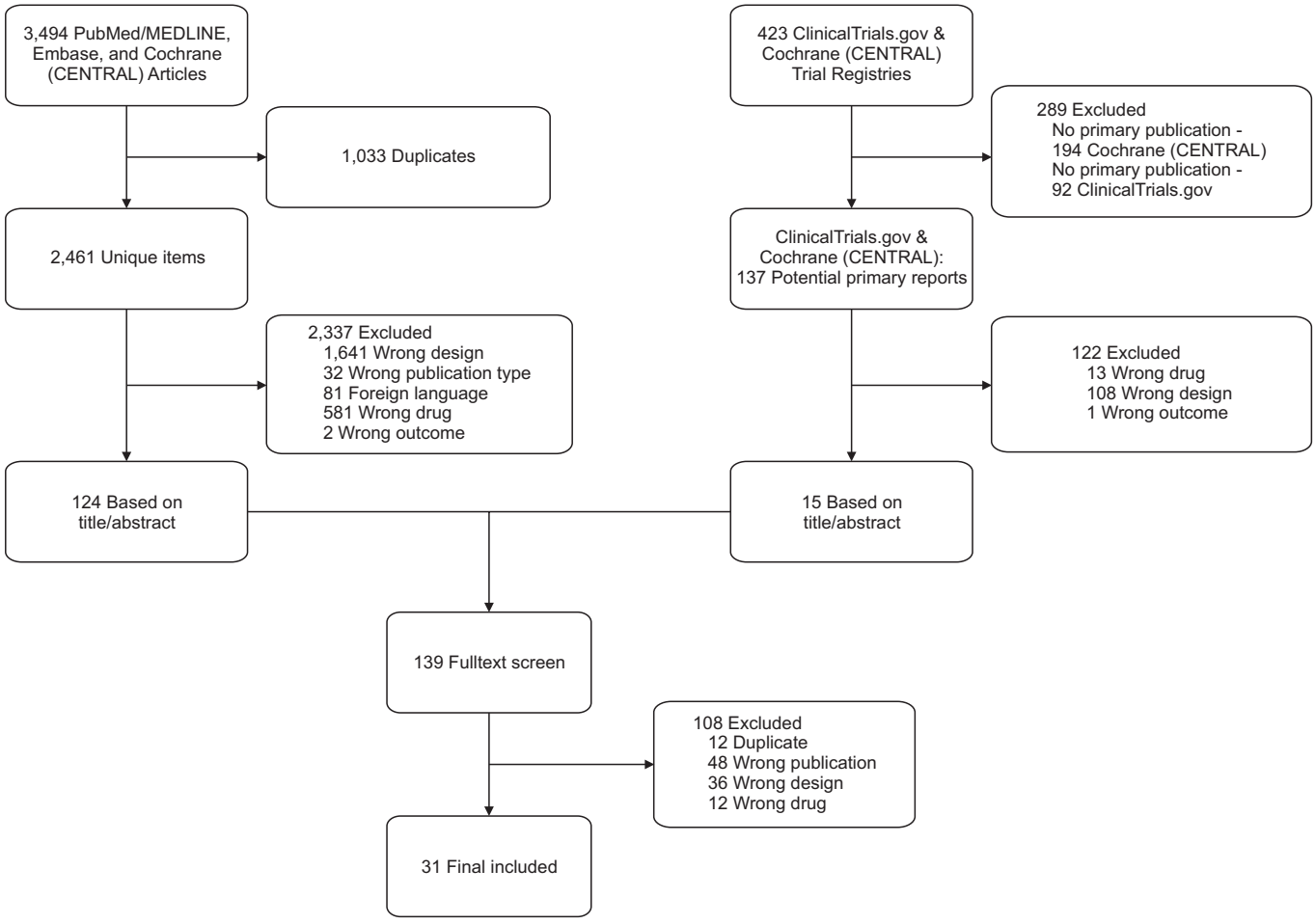

Fig. 1. Flow diagram of screening and exclusion criteria.

response, complete response, ORR as defined in the RECIST criteria, number of grade 3–5 adverse events and if the trial was positive, indeterminate, or negative. Measurements of outcomes and adverse events, covering all trial participants in a prespecified indication, were extracted. A trial was deemed positive if it achieved the prespecified endpoints accompanied with a tolerable regimen. A trial was deemed indeterminate if prespecified endpoints were not established and was using a tolerable regimen. A trial was deemed negative if prespecified endpoints were not met or the trial was using a nontolerable regimen. The tolerability of a regimen was determined by the authors of the clinical trial in question [10].

We made a number of design decisions for trial specific characteristics. The higher phase was extracted if a trial reported multiple phases. If a trial reported a response rate without specifying the proportions of partial or complete responses, it was assumed that only partial response was measured. If trialists specified responses as confirmed or unconfirmed, the confirmed responses were extracted. If trialists specified that measurement confirmation was conducted by independent investigators, we extracted the independently confirmed measurements. We pooled dose-escalation and dose expansion treatment and indications into individual summary arms. We extracted variables of interest from the pre-crossover allocation group to control for carryover effects that affected the response rate in crossover trials. Trials that included 4 or more different indication types were reported as "multiple indications" with a supplement available for the clarification of reported indications. Lastly, ORRs were calculated for all participants of a specific arm unless the trialist specified evaluable patients.

9. Statistical Analysis

We will conduct descriptive statistics in R ver. 4.2.1 (R

https://doi.org/10.22465/juo.244800520026

Foundation for Statistical Computing, Vienna, Austria) and RStudio.

RESULTS

1. General Characteristics

Our systematic search identified 3,393 studies from various bibliographic databases, along with an additional 423 studies from clinical trial registries. After screening titles and abstracts, we selected 139 publications for full-text review. Following this process, 108 studies were excluded, leaving a final sample of 31 publications.

The most common indication for abiraterone was prostate cancer (27 of 31, 87.1%), followed by breast cancer (2 of 31, 6.5%), ovarian cancer (1 of 31, 3.2%), and salivary gland cancer (1 of 31, 3.2%). The total number of participants was 5,499. Of the 31 studies included in our sample, 23 (74.2%) were monotherapy, while 8 (25.8%) were combination therapy. Twenty-five (80.6%) yielded positive results, while 6 (19.4%) yielded negative results. Three trials (9.7%) were phase I, 22 (71.0%) were phase II, and 6 (19.4%) were phase III. Twenty-six (83.9%) were nonblinded, and 5 (16.1%) were double-blinded. Of the 31 publications, 25 (80.7%) were randomized and 6 (19.4%) were nonrandomized. Additional trial characteristics can be found in Table 1.

Table 1. Trial characteristics

Characteristic	Monotherapy (N=23)	Combination (N=8)	Overall (N=31)
Phase			
Phase 1	2 (8.7)	1 (12.5)	3 (9.7)
Phase 2	16 (69.6)	6 (75.0)	22 (71.0)
Phase 3	5 (21.7)	1 (12.5)	6 (19.4)
Stage			
Metastatic	21 (91.3)	7 (87.5)	28 (90.3)
Nonmetastatic	2 (8.7)	1 (12.5)	3 (9.7)
Response criteria used			
RECIST	15 (65.2)	5 (62.5)	20 (64.5)
mRECIST	4 (17.4)	1 (12.5)	5 (16.1)
Other	4 (17.4)	2 (25.0)	6 (19.4)
Results			
Positive	19 (82.6)	6 (75.0)	25 (80.7)
Negative	4 (17.4)	2 (25.0)	6 (19.4)
Randomized			
Nonrandomized	19 (82.6)	6 (75.0)	25 (80.7)
Randomized	4 (17.4)	2 (25.0)	6 (19.4)
Randomization ratio			
1:1	2 (50.0)	1 (50.0)	3 (50.0)
1:1:1	0 (0)	1 (50.0)	1 (16.7)
2:1	2 (50.0)	0 (0)	2 (33.3)
Unknown/nonrandomized	19 (82.6)	6 (75.0)	25 (80.6)
Blinding			
Nonblinded	19 (82.6)	7 (87.5)	26 (83.9)
Double	4 (17.4)	1 (12.5)	5 (16.1)
Centers			
Multicenter	20 (87.0)	7 (87.5)	27 (87.1)
Single-center	3 (13.0)	1 (12.5)	4 (12.9)
Sponsorship/funding			
Industry	10 (43.5)	4 (50.0)	14 (45.2)
Industry, government	7 (30.4)	1 (12.5)	8 (25.8)
Industry, government, nonindustry	4 (17.4)	1 (12.5)	5 (16.1)
Industry, nonindustry	1 (4.4)	1 (12.5)	2 (6.5)
Government	0 (0)	1 (12.5)	1 (3.2)
Not stated	1 (4.4)	0 (0)	1 (3.2)

(continued)

Table 1. Trial characteristics (continued)

Characteristic	Monotherapy (N=23)	Combination (N=8)	Overall (N=31)
Country			
United States	9 (39.1)	5 (62.5)	14 (45.2)
United Kingdom	4 (17.4)	0 (0.0)	4 (12.9)
France	3 (13.0)	1 (12.5)	4 (12.9)
Canada	1 (4.4)	1 (12.5)	2 (6.4)
China	2 (8.7)	0 (0)	2 (6.5)
Italy	1 (4.4)	0 (0)	1 (3.2)
Japan	1 (4.4)	1 (12.5)	2 (6.5)
South Korea	1 (4.4)	0 (0)	1 (3.2)
Taiwan	1 (4.4)	0 (0)	1 (3.2)
Conflict of interest/disclosure statement			
Reports conflicts of interest	19 (82.6)	8 (100.0)	27 (87.1)
Not reported	2 (8.7)	0 (0)	2 (6.5)
Reports no conflicts of interest	2 (8.7)	0 (0)	2 (6.5)
Journals			
Annals of Oncology	4 (12.9)	2 (25.0)	6 (19.4)
Asian Journal of Urology	1 (4.4)	0 (0)	1 (3.2)
Cancer	1 (4.4)	0 (0)	1 (3.2)
Clinical Cancer Research	3 (13)	1 (12.5)	4 (12.9)
Clinical Genitourinary Cancer	2 (8.7)	1 (12.5)	3 (9.7)
European Urology Oncology	1 (4.4)	1 (12.5)	2 (6.5)
International Journal of Radiation Oncology, Biology, Physics	1 (4.4)	1 (12.5)	2 (6.5)
International Journal of Urology	2 (8.7)	0 (0)	2 (6.5)
JAMA Oncology	1 (4.4)	0 (0)	1 (3.2)
Japanese Journal of Clinical Oncology	1 (4.4)	0 (0)	1 (3.2)
Journal of Clinical Oncology	6 (26.1)	0 (0)	6 (19.4)
Journal of Urology	1 (4.4)	0 (0)	1 (3.2)
Lancet Oncology	3 (13.0)	1 (12.5)	4 (12.9)
The Journal of Clinical Pharmacology	1 (4.4)	1 (12.5)	2 (6.5)
The New England Journal of Medicine	1 (4.4)	0 (0)	1 (3.2)
Therapeutic Advances in Medical Oncology	1 (4.4)	0 (0)	1 (3.2)
Urological Science	1 (4.4)	0 (0)	1 (3.2)

Values are presented as number (%).

2. Endpoints

Prostate cancer had the highest reported median PFS (8 months), median ORR (21.9%), and OS (22.5 months). In contrast, ovarian cancer had the lowest median PFS (2.5 months), median ORR (2.4%), and OS (11.8 months). PSA-RR was the most common primary endpoint used in prostate cancer and the most common primary endpoint in our samples. The mean PSA-RR was 42.0%, and the mean ORR was 20.0%. ORR was used in all nonprostate histologies. CRPC had the largest OS (22.5 months), while ovarian cancer had the lowest (11.8 months). The total number of partial response rates was 526 (18.5%), and the total number of complete response rates was 43 (1.5%). Table 2 contains additional information.

3. ΔPFS and ΔOS

Only 4 randomized controlled trials for abiraterone measured PFS and OS. These trials were indicated in prostate cancer and compared abiraterone to a placebo with and without apalutamide, a drug used in ADT. Abiraterone consistently outperformed the placebo in all trials, with a median ΔPFS of 4.4 months. The largest recorded difference was 8.2 months, and the lowest was 2.0 months. Additionally, the median ΔOS was 3.0 months, with the largest recorded difference being 4.6 months and the lowest being 2.5 months. These results indicate that treatment with abiraterone consistently led to an increase in both ΔPFS and ΔOS, and the multiple significant p-values (<0.05) substantiate 3 findings. Additional information can be found in Table 3.

https://doi.org/10.22465/juo.244800520026

Table 2. Overall trial characteristics and outcomes by indication

Indication	No. of trials	No. of randomized trials, n (%)	No. of participants	No. of males	No. of females	No. of grade 3–5 events	Median PFS (mo)	Median age (yr)	Total evaluable for ORR	Partial response rates, n (%)	Complete response rates, n (%)	Median ORR	Median OS (mo)	PSA response rate
Prostate cancer	27	5 (18.5)	4,995	4,993	0	2,465	8.0	69.6	2,508	508 (20.3)	42 (1.7)	21.9%	22.5	42.0%
Breast cancer	2	1 (50)	438	0	438	85	3.7	62.8	211	12 (5.7)	1 (0.5)	6.2%	-*	-
Ovarian cancer	1	-	42	0	42	41	2.5	64.6	42	1 (2.4)	0 (0)	2.4%	11.8	-
Salivary gland cancer	1	-	24	23	1	4	3.7	65.8	77	5 (6.5)	0 (0)	6.5%	22.5	-
Totals/ median	31	6 (19.4)	5,499	5,016	481	2,595	5.6	69.0	2,838	526 (18.5)	43 (1.5)	20.0%	21.7	42.0%

PFS, progression-free survival; ORR, objective response rate; OS, overall survival; PSA, prostate-specific antigen.
*Did not measure outcome, failed to report outcomes, or faulted to report outcome measure for all enrolled patients.

Table 3. ΔPFS and ΔOS measurements for randomized controlled trials of abiraterone (monotherapy or combination therapy) vs. placebo

Trial	Phase	Result	Date	Indication	Abiraterone group	Comparison group	ΔPFS	ΔPFS	ΔOS	ΔOS
NCT02257736	3	Positive	2021-09-30	CRPC	Apalutamide and abiraterone and prednisone	Abiraterone and prednisone	6.0	p<0.001*	2.5	p<0.001*
NCT01695135	3	Positive	2016-02-15	CRPC	Abiraterone and prednisone	Placebo and prednisone	2.7	p<0.001*	-	p=0.060
NCT00091442	3	Positive	2012-09-18	CRPC	Abiraterone and prednisone	Placebo and prednisone	2.0	p<0.001*	4.6	p<0.001*
NCT00887198	3	Positive	2012-12-10	CRPC	Abirateron and prednisone	Placebo and prednisone	8.2	p<0.001*	-	p=0.009*
							Median, 4.4		Median,3.6	

Δ, xfinal–xinitial; PFS, progression-free survival; OS, overall survival; CRPC, castration-resistant prostate cancer.
*p<0.05, statistically significant differences.

4. Risk Assessment

Of the 5,152 participants evaluated for adverse events, there were a total of 2,595 grade 3–5 adverse events. As seen in Fig. 2, adverse events peaked in 2011–2012, and this can be attributed to the COU-AA-301 and 302 trials, which were the phase III flagship studies used for FDA approval. These trials evaluated a substantial number of participants (n=1,195 and n=1,088, respectively), explaining the spike in adverse events. The ratio of adverse events to the number of participants has declined as clinical trials have continued for abiraterone.

As demonstrated in Fig. 3, adverse event rates (AERs) peaked in 2011–2012 which is consistent with the COU-AA trials as mentioned previously. The highest cumulative ORR occurred in 2009 because abiraterone was only used for prostate cancer and no other indications. Prostate cancer maintained the highest ORR at 21.9%, while ovarian cancer had the lowest ORR at 2.4%. The cumulative AER decreased minimally after 2012 while the cumulative ORR also decreased minimally since 2009, indicating that there has not been an increased risk of adverse events in clinical trials since the initial FDA approval of abiraterone.

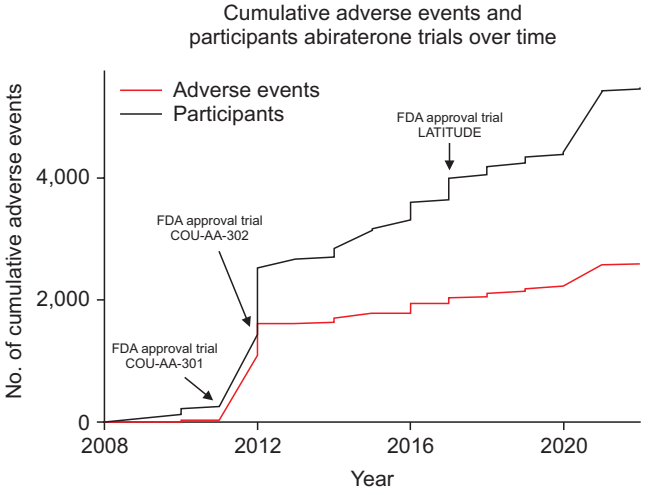

Fig. 2. Cumulative adverse events and cumulative participants over time. FDA, U.S. Food and Drug Administration.

5. Accumulating Evidence and Research Organization Diagram

Fig. 4 displays the growth and development of abiraterone's clinical trial portfolio, exhibiting its various phases and indications. Abiraterone consistently demonstrated positive results when used for its FDA-approved indication, prostate cancer. The subsequent FDA approvals for abiraterone did not significantly alter the interpretation of our results since they were also for prostate cancer. Prostate cancer trials reached their primary endpoint in 88.9% of studies. However, the 3 prostate cancer clinical trials that did not reach their primary endpoint tested participants that had previously shown resistance to abiraterone treatment. Clinical trials were also performed for breast, ovarian, and salivary gland cancer. Of these novel indications, salivary gland cancer was the only one that reached its endpoint, but it has yet to receive FDA approval since its trial in 2021. There was no notable trend of increasing off-label use following FDA approvals.

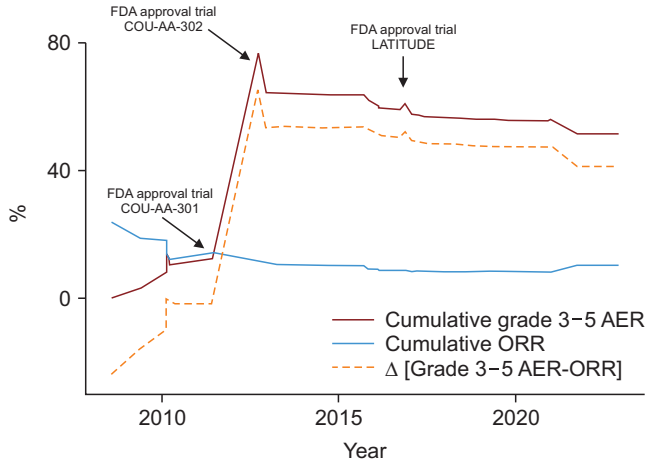

Fig. 3. Cumulative grade 3–5 adverse event rate (AER) per trial date, cumulative object response rate (ORR) per trial date, and difference between cumulative grade 3–5 AER and cumulative ORR per trial date. Δ[AER-ORR] indicates the absolute difference between cumulative AER and the cumulative ORR. FDA, U.S. Food and Drug Administration.

DISCUSSION

Abiraterone initially received FDA approval in 2011 for the treatment of CRPC that had progressed on docetaxel. In 2018, it was also approved for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC). As of 2023, these remain the primary FDA-approved indications for abiraterone [15]. Our study was conducted to better understand the clinical trial landscape of abiraterone. Our findings indicate that abiraterone has been assessed in 4 different cancers and is approved by the FDA for 1 (25%). The early trials specifically targeted prostate cancer, and a large majority of these trials yielded positive results. These findings are inconsistent with previous works, as discussed below. The following discussion offers a first look at the trial portfolio of abiraterone.

Our results indicate that abiraterone achieved its primary endpoints in 25 of 31 trials (80.65%). Among the 3 clinical trials with negative results that targeted CRPC, all of the enrolled patients were resistant to abiraterone therapy which

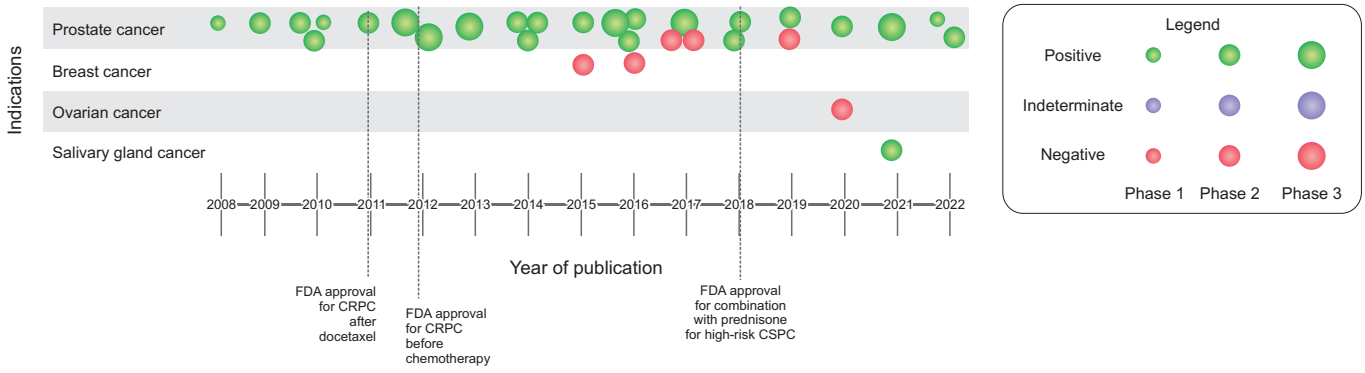

Fig. 4. Accumulating Evidence and Research Organization graph for abiraterone therapy, showing clinical trials' indications, date of publication, FDA approval dates, outcomes, and phases. Clinical trials are arranged horizontally according to publication date and are stratified by indication. Green circles indicate positive clinical trial results, and red are negative. The small circles are phase 1, medium circles are phase 2, and the large circles are phase 3. FDA, U.S. Food and Drug Administration; CRPC, castration-resistant prostate cancer; CSPC, castration-sensitive prostate cancer.

https://doi.org/10.22465/juo.244800520026

prompted the exploration of combination therapy or dose adjustments in an attempt to overcome their resistance. Furthermore, our study reveals that abiraterone has been investigated in cancers beyond its original indication, including breast cancer, ovarian cancer, and salivary cancer. There were no notable trends that supported our hypothesis that there would be increased off-label clinical trials with increased negative results after abiraterone's FDA approval.

Although researchers reported positive results for abiraterone in salivary gland cancer, the drug has yet to receive FDA approval for any indication beyond prostate cancer [15]. Notably, only 3 novel cancer types were trialed, which contrasts with other cancer drugs that have undergone extensive testing across a wider range of conditions [6,10].

Abiraterone, an androgen biosynthesis inhibitor, works by inhibiting the enzyme 17α-hydroxylase/C17,20-lyase (CYP17), which is key in androgen production. This mechanism has been well-established in the treatment of CRPC and mHSPC. However, abiraterone has also been tested off-label in other cancers, such as breast, ovarian, and salivary gland cancers, where androgen pathways may still play a role. In ovarian cancer, some studies have suggested that certain subtypes of ovarian tumors express androgen receptors (ARs), making the inhibition of androgen production through CYP17 blockade a potential therapeutic strategy. However, results have been mixed, as not all ovarian cancers are androgen-driven. In breast cancer, particularly in postmenopausal women, the role of AR expression has been linked to disease progression [16-18].

In breast cancer, abiraterone inhibits the CYP17A1 enzyme, reducing androgen and estrogen production. This mechanism aims to slow the growth of hormone-driven cancers, particularly those expressing estrogen (ER) and/or ARs. However, clinical trials have shown mixed efficacy. The phase II BCA2001 trial found no improvement in PFS when abiraterone was added to exemestane in ER+ HER2- postmenopausal patients. A phase I/II trial noted some benefit, with 22% of AR+ and ER+ patients achieving stable disease for ≥24 weeks [18-21]. These results highlight the need for better biomarkers to identify patients who might benefit from abiraterone therapy. Salivary gland cancers have also been explored as a target for androgen deprivation therapies due to AR expression in some subtypes, although more research is needed to confirm its utility in this setting. These off-label uses highlight the potential for abiraterone to target androgen-driven pathways beyond prostate cancer, but also underscore the need for better biomarkers to identify which patients are most likely to benefit from such therapies [2,16-20].

Abiraterone's mechanism involves inhibiting the CYP17A1 enzyme, which reduces the production of androgens and estrogens. This is especially effective in prostate cancer, where androgen signaling plays a central role. However, other cancers, like certain subtypes of breast and ovarian cancers, may also express ARs, suggesting potential benefits from abiraterone. The variability in AR expression across different tumor types has contributed to mixed results in clinical trials, underscoring the need for molecular profiling to better select patients who might benefit from abiraterone therapy [2,16-20].

Understanding the mechanism of abiraterone has been instrumental in expanding its therapeutic applications. Abiraterone works by inhibiting the CYP17A1 enzyme, which is crucial to produce androgens and estrogens [2]. This mechanism has made abiraterone particularly effective in treating prostate cancers that rely heavily on androgen signaling for growth, leading to its initial FDA approval for CRPC in 2011 and subsequent approval for mHSPC in 2018 [21]. In mHSPC, the ability of abiraterone to reduce androgen levels significantly delays disease progression and improves survival outcomes. Beyond prostate cancer, abiraterone has also been investigated for its potential use in other cancers that may be driven by hormonal pathways, such as AR+ (AR-positive) breast cancers [19].

The rationale is that abiraterone's suppression of androgen production could benefit patients whose breast cancer cells express AR, a similar mechanism to its use in prostate cancer. However, the results have been mixed. For example, the phase II BCA2001 trial assessed the addition of abiraterone to exemestane in postmenopausal women with ER+ HER2- breast cancer who had progressed on nonsteroidal aromatase inhibitors. This trial found that adding abiraterone did not significantly improve PFS compared to exemestane alone [19]. Nevertheless, some antitumor activity has been observed in specific subgroups. In a phase I/II study involving AR+ and ER+ breast cancer patients resistant to endocrine

therapy, 22% of ER+ patients achieved stable disease for ≥24 weeks while on abiraterone [20]. This suggests that abiraterone may offer benefits to a carefully selected subset of patients with AR+ breast cancer, although further research is needed to confirm these findings and to identify biomarkers that can predict response.

Moving forward, biomarkers will play a pivotal role in guiding abiraterone's clinical applications. By identifying patients whose tumors exhibit high AR expression or are more dependent on CYP17A1 pathways, abiraterone can be directed towards those most likely to benefit [10]. This targeted approach could improve therapeutic outcomes while minimizing adverse effects in patients unlikely to respond, ultimately refining the risk-benefit profile of abiraterone [16].

However, Kensler et al. [22]'s systematic review of the link between androgens and breast cancer indicates that ADT was not considered suitable. It is important to note that this understanding was not yet established during the time of the breast cancer trials for abiraterone [22]. Because of ineffective clinical trials like the one for breast cancer, Guerrera et al. [23] argues that clinical trials should only be conducted for thoroughly tested indications to limit the number of patients exposed to toxic chemotherapy.

Our findings diverge from the current literature on cancer drug portfolios in several aspects. Firstly, we observed a higher number of successfully achieved endpoints compared to what is commonly reported. There is also a lack of clinical trials performed on drugs outside of abiraterone's original indication. Lastly, our study suggests that the number of adverse events are within a reasonable range. The existing literature suggests that clinical trials for cancer drugs are often conducted in a liberal and ineffective manner, aiming to discover new uses outside of the original indication [6,10].

For example, imatinib, demonstrated effectiveness in chronic myeloid leukemia, but its success rate in novel indications was only 14% [6]. A similar trend was observed for sunitinib, where the risk-to-benefit ratio worsened when the drug was used outside of its original indication [10]. While exploring the use of drugs beyond their intended purpose can offer novel and beneficial treatment approaches for different cancers, it is crucial to exercise caution and consider their mechanisms, as patients may be exposed to potentially life-threatening adverse events without careful evaluation.

Our data shows that out of the 27 prostate cancer clinical trials conducted for abiraterone, 18 trials (66.7%) used PSA-RR as a primary endpoint, in contrast to OS. While OS is widely recognized as a direct measure of patient benefit, PSA-RR is considered a surrogate endpoint [24]. Surrogate endpoints, despite their limited predictive power in terms of potential clinical advantages, persist in usage due to their ability to yield faster results. For instance, obtaining OS data may take up to 15 years, whereas PSA-RR can be measured in 12 weeks [9]. Given that CRPC exhibits a relatively higher survival rate compared to other cancers, OS as an endpoint may be impractical, leading to the preference for measuring PSA-RR [25].

A review in 2012 by Colloca [24] suggested that PSA kinetics, a collaboration of various PSA measurements, may be a better predictor of OS and should be explored as a primary endpoint. Colloca et al. [21] went on to do a systematic review of endpoints for CRPC in 2014 that suggested that PSA-RR was the most reliable primary endpoint for measuring CRPC but also suggested that PSA kinetics could prove better if more evidence were produced. As of 2020, recommendations that PSA kinetics should be used as a primary endpoint instead of PSA-RR have continued [26]. The discussion concerning these changes is important because if measurements obtained in a clinical trial are not accurate, it could subject patients to inappropriate treatment, potentially leading to adverse events. If PSA kinetics can more accurately direct a patient's treatment, it is worth considering standardizing the use of PSA kinetics over PSA-RR as a primary endpoint for the wellbeing of future patients with CRPC.

Our results showed that 50.4% of the adverse events were grade 3–5 events while taking abiraterone for CRPC. Grade 3 and 4 are considered severe, oftentimes interfering with day-to-day activities and potentially becoming life-threatening, while grade 5 events directly lead to the patients' deaths [12]. It has been recorded that the most common and most distressful adverse event while taking abiraterone is fatigue [27,28]. While these adverse events are a concern, it is important to consider the overall risk-to-benefit ratio of abiraterone for CRPC. Previous literature has shown this ratio to be favorable, demonstrating that the median OS after CRPC onset is 23.2 months, whereas it increases to 53.3

https://doi.org/10.22465/juo.244800520026

months with abiraterone when taken for CRPC treatment [29]. Our results support these claims, showing an increase in both PFS and OS in the abiraterone groups versus placebo groups.

Furthermore, Sternberg et al. [27]'s review of abiraterone's effect on fatigue in CRPC patients showed that patients taking abiraterone experienced a notable improvement in fatigue intensity and fatigue interference when compared to patients with clinically significant baseline fatigue. The increased OS and potential ability to decrease disease-related fatigue suggests that abiraterone demonstrates a promising risk-to-benefit ratio for CRPC. The only novel indication that showed an abnormal number of adverse events when taking abiraterone was ovarian cancer. However, upon further analysis of the ovarian cancer clinical trial, it was noted that the clinical trial administrators did not differentiate abiraterone-related adverse events from disease-related adverse events, presumably inflating our recorded number.

Our analysis has various strengths and limitations. The core strength is that our study used reproducible, robust methodologies including: (1) systematically searching databases, such as PubMed/MEDLINE, Embase, Cochrane CENTRAL, and ClinicalTrials.gov for clinical trials using abiraterone for cancer treatment, (2) implementing a masked, duplicate data extraction method, and (3) using Rayyan, a systematic review search platform, to perform our abstract and title screening. We have also provided our protocol, raw data, analysis scripts, and Google extraction form to aid in the reproducibility of our study. In terms of limitations, we only assessed abiraterone's use in oncology clinical trials; thus, we did not include indications, such as adrenocortical tumors, Cushing syndrome, and congenital adrenal hyperplasia. It is also possible that our systematic search did not capture all studies, which is a common limitation in research synthesis methodologies [30].

CONCLUSIONS

Abiraterone's drug portfolio has been positively maintained in respect to the data obtained in our study. Abiraterone was primarily tested in prostate cancers, but it was also appropriately tested in breast, ovarian, and salivary gland cancers. Abiraterone demonstrated consistently positive results in prostate cancer treatment, with significant improvements in OS and PFS. Our study is the first to provide a holistic evaluation of the drug's clinical development, examining both its FDA-approved and off-label applications. This comprehensive assessment not only highlights the effectiveness of abiraterone in prostate cancer but also offers valuable long-term safety data from a longitudinal analysis of adverse events. Although off-label indications showed limited success, the detailed insights into clinical trial design and endpoints, particularly the use of PSA response rate, contribute to a deeper understanding of abiraterone's clinical utility. The number of adverse events reported fell within the expected range for abiraterone, including the adverse events from clinical trials for novel indications. Overall, this study contributed to the understanding of abiraterone risk/benefit profile and the importance of researching novel indications, prior to trials, to improve patient outcomes in the field of oncology.

NOTES

- **Author Contribution:** Conceptualization: MR, VP, EO, MV; Data curation: MR, EO, GKH; Formal analysis: MR, EO; Funding acquisition: NA; Methodology: MV, GKH, BJ, AP, CL, RM, BG, AH, JT; Project administration: JT, GKH, AH, VP; Visualization: VP, MV; Writing - original draft: MR, EO; Writing - review & editing: MR, EO, GKH, AMP, CL, BG, RM, BJ, JT, AH, VP, MV.
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