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Review

# Role of the novel generation of androgen receptor pathway targeted agents in the management of castration-resistant prostate cancer: A literature based meta-analysis of randomized trials

Giandomenico Roviello [a,b,*], Sandra Sigala [a], Shahneen Sandhu [c], Alberto Bonetta [d], Maria Rosa Cappelletti [b], Laura Zanotti [b], Alberto Bottini [b], Cora N. Sternberg [f], Stephen B. Fox [e], Daniele Generali [b,g]

[a] *Department of Molecular and Translational Medicine, University of Brescia, 25123, Brescia, Italy*
[b] *Molecular Therapy and Pharmacogenomic Unit, ASST di Cremona, Viale Concordia 1, 26100, Cremona, Italy*
[c] *Department of Cancer Medicine, Peter MacCallum Cancer Centre, East Melbourne, Australia*
[d] *Radiotherapy Department, Azienda Ospedaliera "Istituti Ospitalieri di Cremona", Cremona, Italy*
[e] *Department of Pathology, Peter Mac Callum Cancer Centre, and Department of Pathology, University of Melbourne, Australia*
[f] *Medical Oncology Department, San Camillo and Forlanini Hospitals, Rome, Italy*
[g] *Department of Medical, Surgery and Health Sciences, University of Trieste, Piazza Ospitale 1, 34129, Trieste, Italy*

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**Abstract** ***Background:*** Several novel androgen receptor pathway targeted agents have recently entered on to therapeutic landscape for metastatic castration-resistant prostate cancer (CRPC). We performed a meta-analysis to assess the effect of these novel androgen receptor pathway targeted agents in improving outcome of CRPC patients.
***Methods:*** A literature-based meta-analysis of randomized controlled trials (RCTs) in accordance with the preferences for reported items in systematic reviews and meta-analyses guidelines was undertaken. Relevant publications from PubMed, the Cochrane Library, and abstracts from American Society of Clinical Oncology meetings were searched. The primary outcome was overall survival. The secondary end-points were time to the first symptomatic skeletal event, progression-free survival, prostatic antigen specific (PSA) response rate, time to PSA progression and safety.
***Results:*** Pooled analysis from RCTs of novel androgen receptor pathway targeted agents

* *Corresponding author*: Department of Molecular and Translational Medicine, University of Brescia, Viale Europa, 11, 25123, Brescia, Italy.
*E-mail address:* giandomenicoroviello@gmail.com (G. Roviello).

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revealed significantly increased overall survival compared with placebo or prednisone (hazard ratio [HR] for death: 0.79, 95% confidence interval [CI]: 0.71–0.87; P < 0.00001). All secondary end-points favoured the androgen receptor pathway targeted agents, although heterogeneity was high in some cases. The pooled analysis revealed that the androgen receptor pathway targeted agents significantly improved time to the first skeletal event (HR = 0.69, 95% CI: 0.63–0.75; P < 0.00001), progression-free survival (HR = 0.48, 95% CI: 0.37–0.62; P < 0.00001), time to PSA progression (HR = 0.37, 95% CI: 0.24–0.59; P < 0.0001) and PSA response rate (relative risk [RR] = 4.46, 95% CI: 2.63–7.55; P < 0.00001). The incidence of grade ≥3 adverse events was moderately higher with androgen receptor pathway targeted agents as compared with the control arms (RR = 1.11, 95% CI: 0.98–1.25; P = 0.09).

***Conclusion:*** This study confirmed the efficacy and safety of the novel androgen receptor pathway targeted agents.



## 1. Introduction

Prostate cancer is the second leading cause of cancer-related deaths in men in Western countries. Advanced and metastatic prostate adenocarcinoma have been traditionally managed with androgen-deprivation therapy (ADT) [1]. Despite initial responses elicited by ADT, patients invariably relapse due to the development of treatment resistance, a condition previously considered to be 'hormone-refractory'. The term 'hormone resistance' is now widely recognized as a misnomer and has been replaced with 'castration-resistant prostate cancer' (CRPC), as most prostate cancers maintain androgen receptor (AR) signalling and hormone sensitivity despite low levels of serum testosterone. Indeed, men with advanced CRPC who have progressed during ADT continue to benefit from novel AR–targeted agents such as abiraterone and enzalutamide. In the last few years, five new agents have been approved for the treatment of metastatic CRPC [2]. Enzalutamide, a second generation AR antagonist and abiraterone, an irreversible P450c17 (CYP17) inhibitor that blocks androgen biosynthesis, which has resulted in a significant survival advantage for men with metastatic CRPC [3–6]. Orteronel (TAK-700), a nonsteroidal, reversible, selective 17,20-lyase inhibitor also demonstrated antitumour activity in patients with CRPC but did not meet its primary end-point of improved overall survival (OS) [7,8]. The next generation of AR pathway targeted agents such as ARN-509, Galeterone and ODM-201 are in advanced stages of clinical development. The collective success of these AR pathway targeted agents reinforces the persistent dependence of AR signalling in CRPC [9–11]. In this meta-analysis, the efficacy and safety from randomized controlled trials (RCTs) of these new AR pathway targeted agents in patients with metastatic CRPC have been analysed and reported.

## 2. Materials and methods

### 2.1. Data retrieval strategies

We conducted a meta-analysis of RCTs in accordance with the preferences for reported items in systematic reviews and meta-analyses guidelines [12]. Relevant publications from PubMed, the Cochrane Library, and the American Society of Clinical Oncology (ASCO) Meeting were identified using the following search terms: prostate cancer, castration-resistant prostate cancer, CRPC, abiraterone, enzalutamide, orteronel, ARN-509, Galeterone, and ODM-201. Publications available in these databases up to 31st January 2016 were analysed. The search criteria were limited to articles of phase III or phase II RTCs. The computer search was supplemented with a manual search of the primary studies referenced in all of the retrieved review articles. When the results of a study were reported in subsequent analysis, only the most recent and complete version was included in this meta-analysis.

### 2.2. Inclusion criteria

Two independent reviewers screened the studies according to specific selection and exclusion criteria. The inclusion/exclusion decisions regarding contentious studies were made in consultation with a third reviewer. The studies were identified according to the following inclusion criteria: (1) participants with metastatic CRPC; (2) an AR pathway targeted agents as the experimental drug; (3) the presence of a control arm for comparison (placebo or not), (4) a primary outcome of OS expressed as the hazard ratio (HR) and secondary outcomes of progression-free survival (PFS) expressed as the HR, time to prostatic antigen specific (PSA) progression expressed as the HR, time to the first symptomatic skeletal event (SSE) expressed as the HR, PSA response rate expressed as relative risk (RR) and