Critical Reviews in Oncology / Hematology 120 (2017) 227–233

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Review

The effects of enzalutamide and abiraterone on skeletal related events and bone radiological progression free survival in castration resistant prostate cancer patients: An indirect comparison of randomized controlled trials

Sergio Rizzo[a,1], Antonio Galvano[a,1], Francesco Pantano[b], Michele Iuliani[b], Bruno Vincenzi[b], Francesco Passiglia[a], Silvia Spoto[c], Giuseppe Tonini[b], Viviana Bazan[a], Antonio Russo[a,2,*], Daniele Santini[b,2]

[a] Medical Oncology, Department of Surgical, Oncological and Stomatological Sciences, University of Palermo, Palermo, Italy
[b] Medical Oncology, Campus Biomedico University, Roma, Italy
[c] Internal Medicine Department, University Hospital Campus Bio-Medico, Rome, Italy

ARTICLE INFO

Keywords:
mCRPC
tSRE
rPFS
Abiraterone
Enzalutamide

ABSTRACT

Two new drugs, the CYP17 inhibitor abiraterone acetate and the androgen receptor (AR) antagonist enzalutamide, have recently shown to prolong OS prior chemotherapy or in docetaxel treated mCRPC patients, using steroidal therapy or placebo as control group. Updated analyses underlined the role of these new agents on two prostate-specific endpoints as radiographic progression-free survival (rPFS) and time to first skeletal-related event (tSRE). On the basis of these reports, we made an indirect comparison between abiraterone and enzalutamide. We obtained a clinically but not significant difference favouring enzalutamide over abiraterone in terms of rPFS (HR 0.48, 95% CI 0.22–1.02). No significant difference was shown in term of tSRE (HR 0.99, 95% CI 0.83–1.17). In conclusion, abiraterone and enzalutamide have both demonstrated to significantly delay the bone progression resulting in similar improvements in bone-related endpoints in patients with mCRPC.

1. Introduction

Prostate cancer (PCa) is currently the second leading cause of cancer-related deaths in men in the United States and the most common cancer in elderly males in Europe (Arnold et al., 2015; Siegel et al., 2017). Androgen deprivation therapies (ADT) represents the standard first line therapy for advanced prostate cancer. This treatment drives to prostate-specific antigen (PSA) decrease and clinical improvements in more than 90% of patients (Damber, 2005). Nevertheless, this therapeutic approach is not curative and the majority of patients often develop castration resistance. In the last years, the introduction of highly effective novel treatments has significantly changed the management of metastatic castration resistant prostate cancer (mCRPC) patients with an improved overall survival (OS) advantage. In particular, two new drugs the CYP17 inhibitor abiraterone acetate and the potent androgen receptor (AR) antagonist enzalutamide were recently shown to prolong OS prior chemotherapy or in docetaxel treated mCRPC patients (de Bono et al., 2011; Ryan et al., 2015, 2013; Scher et al., 2012; Beer et al., 2014).

Abiraterone acetate is an orally administered steroidal antiandrogen derived from the structure of pregnenolone. It inhibits androgen biosynthesis blocking the hydroxylase and lyase activities of CYP17A with 10–30 fold stronger than ketoconazole (Rowlands et al., 1995) resulting in virtually undetectable serum and intratumoral androgens production in the adrenals, testes and prostate cancer cells (O'Donnell et al., 2004; Barrie et al., 1994). Abiraterone is usually administered with prednisone to ameliorate the secondary increase of the adrenocorticotropic hormone that can lead to excess mineralocorticoid synthesis (Attard et al., 2012). Two randomized clinical Phase III trials (RCTs) demonstrated that abiraterone improved OS compared with placebo. In the COU-AA-301 trial (de Bono et al., 2011), 1195 patients previously treated with docetaxel were randomized to abiraterone plus prednisone or placebo plus prednisone. The primary endpoint of OS was met with an improvement in OS of 3.9 months compared with placebo and a

* Corresponding author at: Department of Oncology – A.O.U.P. "P. Giaccone" University Hospital, 2013 ESMO Designated Centres of Integrated Oncology and Palliative Care, Via del Vespro 129, 90127 Palermo, Italy.
E-mail address: antonio.russo@usa.net (A. Russo).
[1] These authors contributed equally to this work.
[2] Co-last authors.

http://dx.doi.org/10.1016/j.critrevonc.2017.09.008
Received 27 April 2017; Received in revised form 4 August 2017; Accepted 7 September 2017

longer radiographic progression free survival (rPFS) (5.6 vs. 3.6 months) was also observed. In the COU-AA-302 trial, 1088 chemotherapy-naïve patients were randomized to abiraterone plus prednisone or to placebo plus prednisone. The results showed a significantly longer OS in the abiraterone group (34.7 months vs 30.3 months) (Ryan et al., 2015) and a 8.2 month improvement in radiographic progression free survival (rPFS). Abiraterone treatment was also associated with better pain control from skeletal metastases, a delay in development of SREs, and delayed radiological skeletal progression (Ryan et al., 2013).

Recently, in the placebo-controlled phase 3 trial LATITUDE, the addition of abiraterone and prednisone to ADT significantly increased OS and rPFS in men with metastatic, castration-sensitive prostate cancer. In particular, the median OS was significantly longer in the abiraterone group than in the placebo group (not reached vs. 34.7 months) while the median length of rPFS was 33.0 months in the abiraterone arm and 14.8 months in the placebo arm (Higgins et al., 2011). Similar results were obtained in STAMPEDE trial that showed an improvement in overall and failure-free survival in locally advanced or metastatic prostate cancer patients treated with ADT plus abiraterone than those who received ADT alone. Data demonstrated that when abiraterone (with prednisone) was added to ADT it improved the 3 year survival rate to 83%, compared to 76% with ADT alone and, additionally, the 3 year failure-free survival rate was of 75% in the treatment arm vs 45% with standard therapy (Jüni et al., 2001).

Enzalutamide is an oral AR inhibitor that targets multiple steps in the AR signaling pathway. In the randomized phase III AFFIRM study, significant improvements in survival versus placebo were observed when enzalutamide was used as a treatment for patients with mCRPC following prior treatment with docetaxel. Additional benefits included an increase in rPFS (8.3 vs. 2.9 months), a significant delay in time to first SREs and improvement in several measures of pain and health-related quality of life (Scher et al., 2012). Furthermore, in the phase III PREVAIL study evaluating enzalutamide versus placebo in patients with mCRPC, who had not received chemotherapy, the anti-androgen significantly decreased the risk of radiographic progression and death (Beer et al., 2014). There were also significant improvements in all secondary and prespecified exploratory endpoints, including delayed initiation of chemotherapy, reduction in risk of first skeletal-related event and a high percentage of patients with objective response compared with placebo (Beer et al., 2014).

These RCTs that led to regulatory approval of abiraterone and enzalutamide in mCRPC have demonstrated that both drugs seems to have benefits on bone disease in terms of rPFS and time to SRE (tSRE) onset (Table 1).

The aim of this systematic review was to conduct a meta-analysis of RCTs to assess the impact of these two drugs on bone specific endpoints (rPFS and tSRE) in mCRPC.

2. Methods

We have searched for RCTs including men with histologically or cytologically proven metastatic castration resistant prostate cancer (mCRPC). We include in our analysis trials in which prostate cancer (PCa) were treated with Abiraterone, a steroidal CYP17A1 inhibitor, or Enzalutamide, an androgen-receptor inhibitor regardless of prior chemotherapy or chemotherapy naive. Abiraterone or Enzalutamide trials were both compared to placebo. The outcomes are radiographic progression free survival (rPFS) and time to skeletal-related event (tSRE). We excluded trials in which data were unavailable, ongoing studies and studies with small sample size (less than 10 patients for arm). To minimize the risk of bias, we excluded observational trials. For the articles with multiple follow-up over time, we decided to choose the most updated and methodically valid. Data extraction and assessment was made independently by two different authors (D.S, A.G.) and disagreement were solved by discussion with another author (G.T). We include article with cross-over between treatments, managing data according to the arm where patients were originally randomized to. We searched for RCTs using Medline (PubMed), Embase-databases and Cochrane-Library up to December 2016, with no language restrictions. The inclusion of relevant abstract from the American Society of Clinical Oncology(ASCO), European Society of Medical Oncology (ESMO) or SIUrO (Italian Society of Oncological Urology) was made. Other unpublished data were explored through the ClinicalTrials.gov site (www.clinicaltrials.gov), the reference lists of selected RCTs and all the previous meta-analysis about abiraterone and/or enzalutamide (see supplement 1). We made a quality analysis of selected trials following the criteria reported in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2011) including: allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; sequence generation; elective outcome reporting; other sources of bias. For each study we defined “Yes” as at low risk of bias and as “No” at high risk of bias. We define also “unclear” if there were insufficient data for a precise judgement. The risk of selective outcome reporting bias was also evaluated by two independent reviewers (D.S. and A.G.) and disagreement were solved by consensus.

Outcomes (rPFS and tSRE) were analysed using Hazard Ratio (HR), with a 95% of confidence interval (CI). For each study we first computed the logarithm of HR (logHR) and its logarithm of standard error (logSE) to perform meta-analysis. Subsequently, in case of more than one RCT for a comparison (abiraterone vs placebo or enzalutamide vs placebo), first we perform a standard meta-analysis to obtain the pooled estimates (Jüni et al., 2001). An indirect meta-analysis is able to maintain the randomization within a RCT and to compare outcomes between different treatments (Bucher et al., 1997; Glenny et al., 2005). Since all studies evaluating enzalutamide or abiraterone use placebo as control arm, we can use indirect meta-analysis to provide pooled

Table 1
Characteristics of the 6 clinical trials included in the meta-analysis.

Trial	Setting	Endpoint	Hormone	Control arm	Patients (HT arm/ Control arm)	rPFS mo (HR)	tSRE mo (HR)	Time to pain deterioration mo (HR)
Beer et al. (2014)	PRE-CT	rPFS, tSRE	Enzalutamide	Placebo	1717 (872/845)	NR vs 3,9 (0,19)	31,1 vs 31.3 (0,72)	NA
de Bono et al. (2011)	POST-CT	rPFS	Abiraterone	Placebo/ Prednisone	1195 (797/398)	5,6 vs 3,6 (0,67)	NA	NA
Fizazi et al. (2014)	POST-CT	tSRE	Enzalutamide	Placebo	1199 (800/399)	NA	16,7 vs 13,3 (0,69)	NR vs 13,8 (0,56)
Logothetis et al. (2012)	POST-CT	tSRE	Abiraterone	Placebo/ Prednione	1195 (797/398)	NA	25,0 vs 20,3 (0,61)	NA
Rathkopf et al. (2014)	PRE-CT	rPFS	Abiraterone	Placebo/ Prednione	1088 (546/542)	16,5 vs 8.2 (0,52)	NA	NR – 23,7 (0,71)
Scheret al. (2012)	POST-CT	rPFS	Enzalutamide	Placebo	1199 (800/399)	8,3 vs 2.9 (0,40)	NA	NA

rPFS: Radiographic progression-free survival; tSRE: Time to skeletal event; NR: Not yet reached; NA: Not applicable.

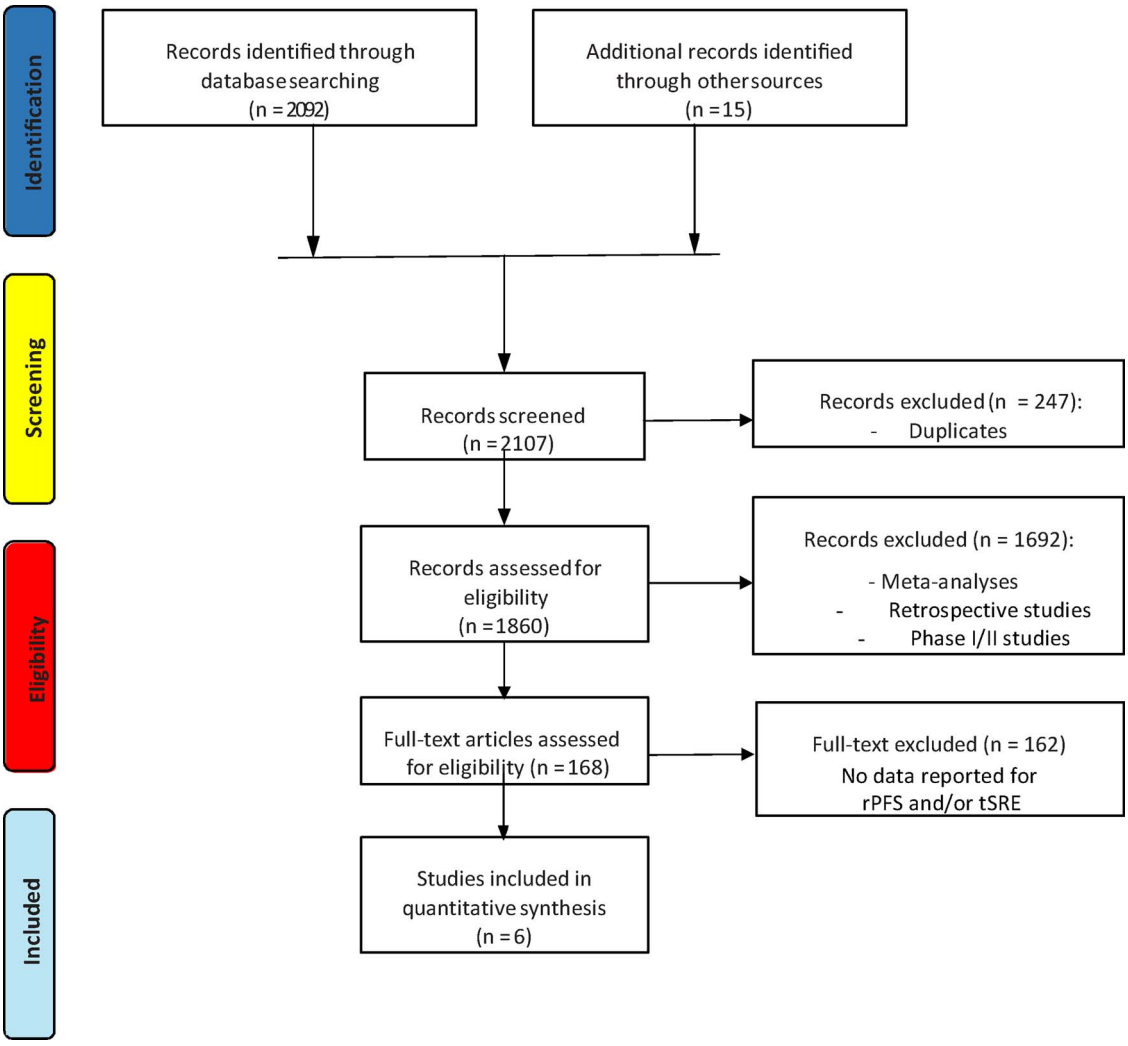

Fig. 1. Flow diagram (CONSORT) for the meta–analysis included studies (according to the PRISMA statement).

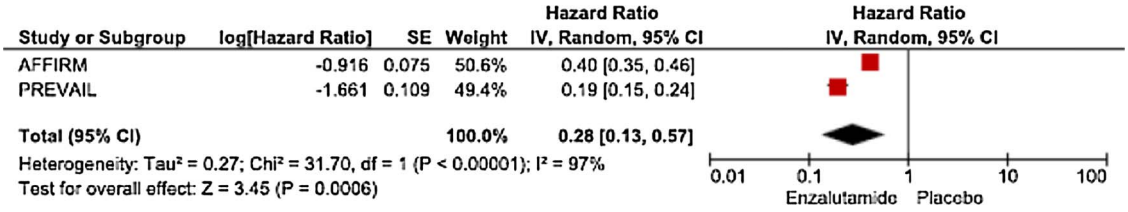

Fig. 2. Forest plot Enzalutamide versus Placebo (rPFS).

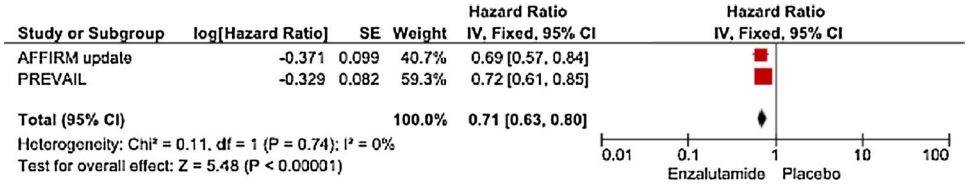

Fig. 3. Forest plot Enzalutamide versus Placebo (tSRE).

estimates of HRs (rPFS and tSRE) for the indirect comparison between abiraterone and enzalutamide. As regard the above mentioned indirect comparison, if we assume ABIes as the estimate of the direct comparison between abiraterone (pre and post CT setting) versus placebo and ENZAes as the estimates of the direct comparison between Enzalutamide (pre and post CT setting) versus placebo, we performed the indirect comparison of enzalutamide versus placebo as follow: ENZA/ABI_indirect (logHR) = ENZAes(logHR) – ABIes(logHR). If we consider that variances are from different studies, the indirect comparison variance was computed as follow: Var (log ENZA/ABI_indirect) = (Var log ENZAes) + (Var log ABIes) (Bucher et al., 1997; Glenny et al., 2005; Lumley, 2002).

Heterogeneity between studies was explored using I-square and Chi-square tests. If I-square value was higher than 75% it was considered as at high risk of heterogeneity and meta-analysis was performed using random effect-based model of Der Simonian and Laird. If not, we used

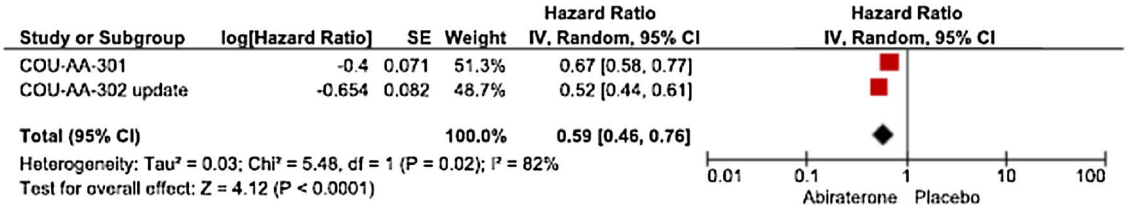

Fig. 4. Forest plot Abiraterone versus Placebo (rPFS).

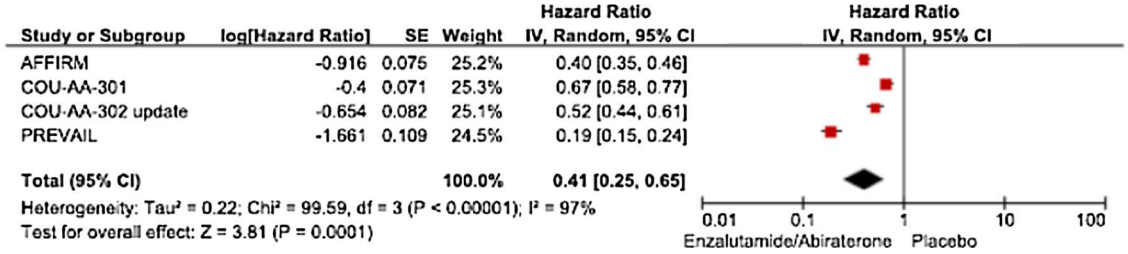

Fig. 5. Forest plot Enzalutamide + Abiraterone (rPFS) versus Placebo.

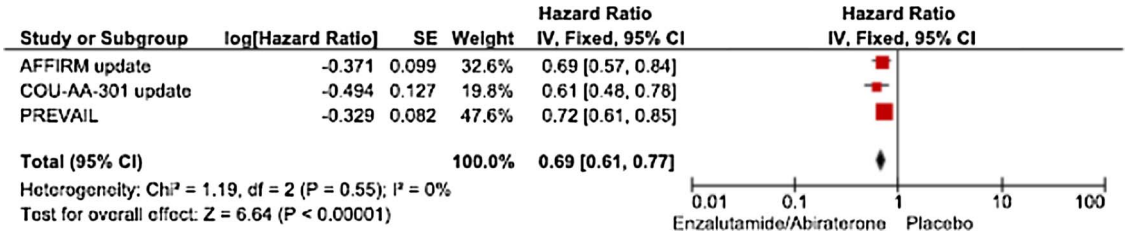

Fig. 6. Forest plot Enza + Abi (tSRE) versus Placebo.

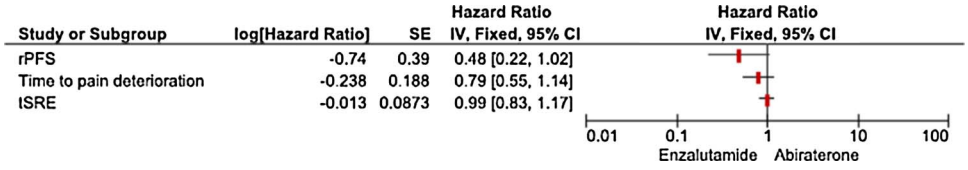

Fig. 7. Indirect comparisons between enzalutamide and abiraterone.

Table 2
Summary of indirect comparison results.

Overall results (pooled)	rPFS HR (95% CI)	tSRE HR (95% CI)	Time to pain deterioration HR (95% CI)
Abiraterone vs Placebo	0,59 (0,46–0,76)	0,61 (0,48–0,79)	0,71 (0,59–0,85)
Enzalutamide vs Placebo	0,28 (0,13– 0,57)	0,71 (0,63–0,80)	0,56 (0,41–0,78)
Enzalutamide + Abiraterone vs Placebo	0,41 (0,25–0,65)	0,69 (0,61– 0,77)	0,67 (0,57–0,79)
Enzalutamide vs Abiraterone	0,48 (0,22– 1,02)	0,99 (0,83–1,17)	0,79 (0,55–1,14)

rPFS: Radiographic progression-free survival; SRE: Time to skeletal event.

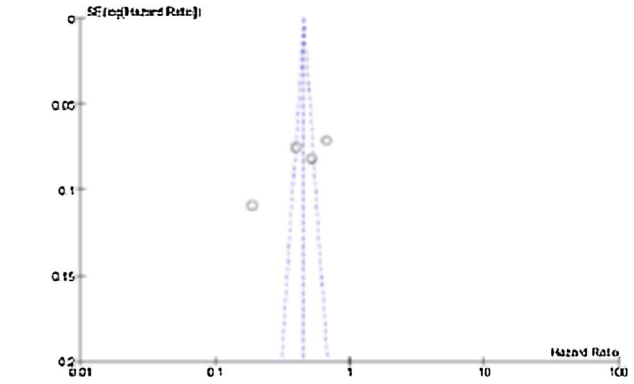

Fig. 8. Funnel plot for rPFS trials of the comparison abiraterone/enzalutamide versus placebo.

the fixed effect-based Mantel-Haenszel model (Borenstein et al., 2008; Higgins and Green, 2011). As regards the risk of bias across studies, we performed a publication bias analysis using Egger's test and a Funnel Plot. All the p-values were considered as statistically significant if $p < 0,05$. The meta-analysis was performed according to the PRISMA – guidelines for reporting of systematic reviews (Moher et al., 2010), using Cochrane RevMan ver. 5.3 statistical software and Comprehensive Meta – Analysis ver. 2.0 to assess the risk of publication bias (Egger's Test).

3. Results

The search for literature identified in a total of 2107 records, of which 247 were excluded because duplicates; 1692 records were excluded because meta-analyses, retrospective or phase I/II studies. A total of 168 trials were assessed for eligibility and 162 were excluded

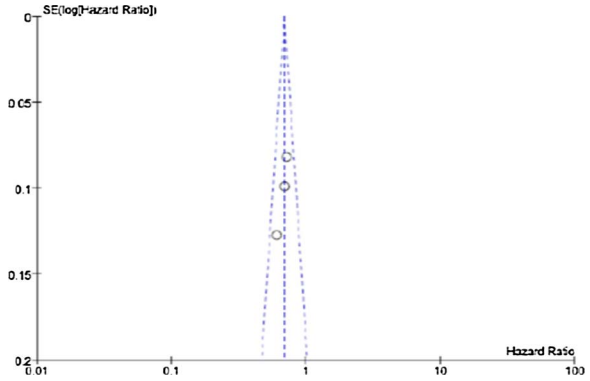

Fig. 9. Funnel plot for tSRE trials of the comparison abiraterone/enzalutamide versus placebo.

because no data about the principal outcomes of our meta – analysis (rPFS and tSRE) were reported. Finally, a total of six studies met all the inclusion/exclusion criteria and were included in the meta–analysis (Fig. 1)

3.1. Direct comparisons

3.1.1. Enzalutamide vs placebo

Two RCTs enrolling 2916 patients evaluated enzalutamide vs placebo in mCRPC settings. Pooled results showed statistically significant differences in terms of rPFS (HR 0.28, 95% CI 0.13–0.57) (Fig. 2) and tSRE (HR 0.71, 95% CI 0.63–0.80) (Fig. 3) favouring enzalutamide. A trial evaluated the time to pain deterioration (HR 0.56, 95% CI 0.41–0.78).

3.1.2. Abiraterone vs placebo

Two RCTs enrolling 2283 patients investigated also abiraterone versus placebo in the same PCa settings (pre and post CT). Pooled results showed a statistically significant result in terms of rPFS (HR 0.59, 95% CI 0.46–0.76) (Fig. 4). As regard tSRE, only one RCT investigated abiraterone versus placebo showing a statistically significant advantage favouring abiraterone (HR 0.61, 95% CI 0.48–0.79). Time to pain deterioration was also explored in one trial (HR 0.71, 95% CI 0.59–0.85).

3.1.3. Abiraterone/enzalutamide vs placebo

Since RCTs evaluating Enzalutamide and Abiraterone were compared to Placebo and studies were consistent each other (similar inclusion criteria), we decided to perform a pooled comparison to underline the global effect of both new generation hormonal therapies (enzalutamide and abiraterone) versus placebo. We showed pooled significant results both in term of rPFS (HR 0.41, 95% CI 0.25–0.65) (Fig. 5) and tSRE (HR 0.69, 95% CI 0.61–0.77) (Fig. 6). Even in terms of time to pain deterioration, both drugs showed to be superior if compared to placebo (HR 0.67, 95% CI 0.57–0.79).

3.2. Indirect comparisons

3.2.1. Enzalutamide vs abiraterone

We use the meta – analytic technique to do an indirect comparison between enzalutamide and abiraterone pooled results on rPFS and tSRE. We obtained a clinically but not formally significant difference favouring enzalutamide over abiraterone in terms of rPFS (HR 0.48, 95% CI 0.22–1.02). No significant difference was shown both in term of tSRE (HR 0.99, 95% CI 0.83–1.17) and of time to pain deterioration (HR 0.79, 95% CI 0.55–1.14) (Fig. 7; Table 2).

3.2.2. Risk of bias assessment

Publication bias test is required in a meta-analysis including at least 3 studies. In our analysis, Egger's test was calculated only for the enzalutamide/abiraterone vs placebo comparisons (rPFS–4 trials, tSRE 3 trials) showing no statistical significance ($p = 0.16$ and $p = 0.1$ respectively) (Funnel Plots Figs. 8 and 9). The overall quality of included trials was also investigated following the CONSORT checklist statement. We reported an average good quality of all trials. In particular, only two trials (Logothetis and Rathkopf) did not specify the randomization procedures, but it is probably partially due to the fact that trial by Logothetis is an updated report from de Bono original article including the randomization information. The same would be for the allocation concealment and for the blinding of patients and personnel involved in the study. For the outcome blinding, Logothetis, Rathkopf and Fizazi did not report any evaluation probably for the above mentioned reasons, with a higher likelihood of bias due to the type of outcomes (quality of life area) considered in these trials. For incomplete outcome data, only Fizazi reported high risk of bias due to 35% of dropouters. No significant risk of bias detected for selecting reporting (Figs. 10 and 11).

4. Discussion

This meta-analysis shows that, relative to placebo, enzalutamide significantly improves rPFS and delays occurrence of first SRE in men with mCRPC (pre and post CT). Similarly, abiraterone prolongs rPFS in both chemo-naïve and post docetaxel treated patients and increases tSRE in chemo-treated setting compared to placebo. Data regarding the effects of abiraterone in pre-docetaxel setting on the SRE events are lacking. Furthermore, pooled analysis evaluating the impact of both agents on skeletal endpoints still demonstrated a significant advantage in treated population vs placebo in terms of rPFS and tSRE.

These results demonstrate that the role of abiraterone and enzalutamide are evolving.

The results from LATITUDE and STAMPEDE are certainly impressive and unambiguous and reshape treatment algorithms for prostate cancer. Indeed, abiraterone with conventional hormone therapy should become a new standard of care for men with high-risk, metastatic disease. In addition to being associated with survival benefits in patients with mCRPC, abiraterone and enzalutamide has shown

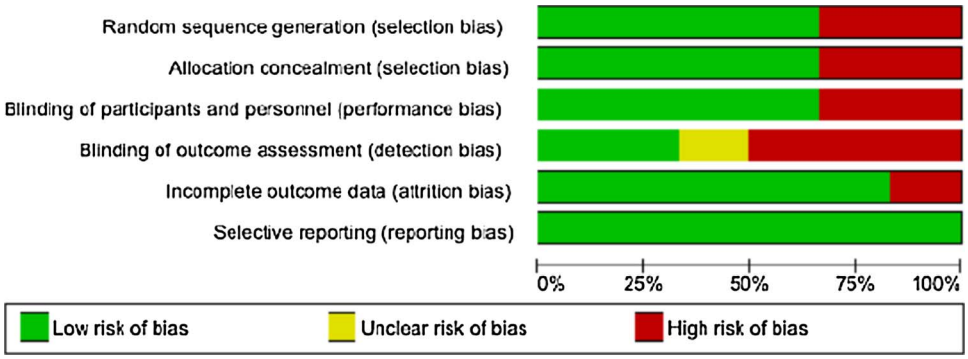

Fig. 10. Risk of bias graph according to review authors' judgements.

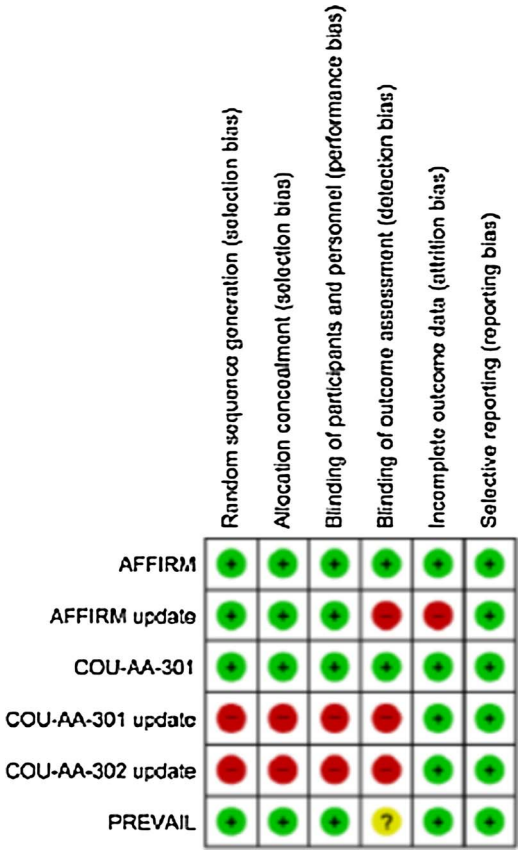

Fig. 11. Risk of bias summary according to review authors' judgements.

consistent efficacy benefits in bone metastatic disease, further supporting its broad use in this indication. It is unsurprising that treatments that are globally active in prostate cancer are similarly active in skeletal outcomes, but it is unclear if these effects on bone-related endpoints may be secondary to a systemic control of the disease, or direct on bone microenvironment. In this regard, a direct bone anabolic and an anti-resorptive effect of abiraterone has been previously demonstrated both *in vitro* and in mCRPC patients (Iuliani et al., 2015). In particular, our group found that abiraterone have a significant inhibitory effect on human primary osteoclasts function and promoted osteoblast differentiation and bone matrix deposition (Iuliani et al., 2015). Such evidence aquired a particular interest given results from LATITUDE and STAMPEDE that in near future will lead to an significant extention of the patient's life under androgen deprivation treatment. From this perspective abiraterone treatment could exert additional positive effect on limiting Cancer Treatment Induced Bone Loss (CTIBL) due to hormonal deprivation.

No data about the direct effect of enzalutamide treatment on bone microenvironment are reported, but it could be interesting to evaluate its potential specific action on bone cells.

Despite these evidences, the indirect comparison between enzalutamide and abiraterone have shown an advantage favoring enzalutamide only in term of rPFS very close to the statistical significance.

A possible explanation of this result is that abiraterone is co-administrated with prednisone, an active agent in the treatment of advanced prostate cancer. The activity of prednisone as a single agent has been well characterized, even if the mechanism by which it exerts its effect on prostate cancer is at least partially understood. Prednisone was effective, for example, in the control arm of the pre-chemotherapy COU-AA-302 study of abiraterone/prednisone versus prednisone-alone. In that study, 24% of patients receiving prednisone 10 mg daily achieved a > 50% PSA response rate, with a PFS of 8.1 months (Ryan et al., 2013). Conversely, in enzalutamide trials pre (PREVAIL) and post CT (AFFIRM), only 3% and 2% of the control group (placebo) had a > 50% PSA decline respectively. In our opinion, the different control group for abiraterone (prednisone) and enzalutamide (placebo) may represent an explanation of this difference in term of rPFS. Moreover, this indirect comparison has other additional limitations. Firstly, the inclusion of patients with visceral disease in the PREVAIL trial (11,2% in enzalutamide arm and 12,5% in placebo group) were excluded from the COU-AA-302 trial. Moreover, differences in PSA and number of bone metastases at baseline in AFFIRM/PREVAIL trials compared to COU-AA 301/302 could have generated some potential bias. Finally, the impact of co-administration of bone target therapies may potentially have influenced the final results of our analyses but, unfortunately, the percentage of the patients treated with these agents are available only for enzalutamide trials. To date, there is no strong literature data able to establish which would be the optimal management of mCRPC. Probably factors such as the availability and costs must be added to the tumor and individual patient characteristics. A new possibility may come from some promising biomarkers and the consolidated use of liquid biopsies that could play a significant role in mCRPC decision-making. Liquid biopsies could be a promising tool, thanks to its manageability and mini-invasiveness, to study several blood parameters such as circulating tumor cells, circulating tumor DNA, or exosomes. In addition to prognosis (for example LDH/CTCs combination) evaluation, from the study of these components researchers could identify other negative predictive biomarkers of response to the new generation hormone treatments, such as TMPRSS2: ERG rearrangements, which would seem associated with Abiraterone activity (Danila et al., 2011).

In conclusion, abiraterone and enzalutamide have both demonstrated to significantly delay the bone progression of the disease in patients with mCRPC and to obtain similar improvements in bone-related endpoints confirming the key role of these two agents in bone mCRPC patients.

Conflict of interest

All authors have no potential conflict of interest to disclose.

Funding

This manuscript has been produced without funding.

Acknowledgement

All authors thank to Dr. Chiara Drago for the English revision.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.critrevonc.2017.09.008.

References

Arnold, M., et al., 2015. Recent trends in incidence of five common cancers in 26 European countries since 1988: analysis of the European cancer observatory. Eur. J. Cancer 51 (9), 1164–1187.

Attard, G., et al., 2012. Clinical and biochemical consequences of CYP17A1 inhibition with abiraterone given with and without exogenous glucocorticoids in castrate men with advanced prostate cancer. J. Clin. Endocrinol. Metab. 97 (2), 507–516.

Barrie, S.E., et al., 1994. Pharmacology of novel steroidal inhibitors of cytochrome P450(17) alpha (17 alpha-hydroxylase/C17-20 lyase). J. Steroid Biochem. Mol. Biol. 50 (5–6), 267–273.

Beer, T.M., et al., 2014. Enzalutamide in metastatic prostate cancer before chemotherapy. N. Engl. J. Med. 371 (5), 424–433.

Borenstein, M.H.L., Higgins, J.P.T., Rothstein, H.R., 2008. Introduction to Meta-Analysis. Wiley March.

Bucher, H.C., et al., 1997. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J. Clin. Epidemiol. 50 (6), 683–691.

de Bono, J.S., et al., 2011. Abiraterone and increased survival in metastatic prostate

cancer. N. Engl. J. Med. 364 (21), 1995–2005.
Damber, J.E., 2005. Endocrine therapy for prostate cancer. Acta Oncol. 44 (6), 605–609.
Danila, D.C., et al., 2011. TMPRSS2-ERG status in circulating tumor cells as a predictive biomarker of sensitivity in castration-resistant prostate cancer patients treated with abiraterone acetate. Eur. Urol. 60 (5), 897–904.
Fizazi, K., et al., 2014. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial. Lancet Oncol. 15 (10), 1147–1156.
Glenny, A.M., et al., 2005. Indirect comparisons of competing interventions. Health Technol. Assess. 9 (26), 1–134 iii–iv.
Higgins, J.P.T., Green, S. (Eds.), 2011. Cochrane Handbook for Systematic Reviews of Interventions. Wiley-Blackwell.
Higgins, J.P., et al., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 343 p. d5928.
Iuliani, M., et al., 2015. Biological and clinical effects of abiraterone on anti-resorptive and anabolic activity in bone microenvironment. Oncotarget 6 (14), 12520–12528.
Jüni, P., Altman, D.G., Egger, M., 2001. Systematic reviews in health care: assessing the quality of controlled clinical trials. BMJ 323 (7303), 42–46.
Logothetis, C.J., et al., 2012. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised trial. Lancet Oncol. 13 (12), 1210–1217.
Lumley, T., 2002. Network meta-analysis for indirect treatment comparisons. Stat. Med. 21 (16), 2313–2324.
Moher, D., et al., 2010. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int. J. Surg. 8 (5), 336–341.
O'Donnell, A., et al., 2004. Hormonal impact of the 17alpha-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. Br. J. Cancer 90 (12), 2317–2325.
Rathkopf, D.E., et al., 2014. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). Eur. Urol. 66 (5), 815–825.
Rowlands, M.G., et al., 1995. Esters of 3-pyridylacetic acid that combine potent inhibition of 17 alpha-hydroxylase/C17,20-lyase (cytochrome P45017 alpha) with resistance to esterase hydrolysis. J. Med. Chem. 38 (21), 4191–4197.
Ryan, C.J., et al., 2013. Abiraterone in metastatic prostate cancer without previous chemotherapy. N. Engl. J. Med. 368 (2), 138–148.
Ryan, C.J., et al., 2015. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 16 (2), 152–160.
Scher, H.I., et al., 2012. Increased survival with enzalutamide in prostate cancer after chemotherapy. N. Engl. J. Med. 367 (13), 1187–1197.
Siegel, R.L., et al., 2017. Cancer Statistics, 2017. CA Cancer J. Clin. 67 (1), 7–30.