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"REAL-LIFE" EFFECTIVENESS STUDIES IN MCRPC PATIENTS: SYSTEMATIC REVIEW."

C. DELLA PEPA[1], C. D'ANIELLO[2], S. ROSSETTI[1], G. IOVANE[1], S. PISCONTI[2], R. FISICHELLA[3], G. FACCHINI[1], C. CAVALIERE[2]

[1]Division of Medical Oncology, Department of Uro-Gynaecological Oncology, Istituto Nazionale Tumori "Fondazione G. Pascale", IRCCS, Naples, Italy
[2]Department of Onco-Ematology Medical Oncology, S.G. Moscati Hospital of Taranto, Taranto, Italy
[3]Department of Surgery, University of Catania, Catania, Italy

ABSTRACT – *Docetaxel is considered the standard of care in first line for metastatic Castration Resistant Prostate Cancer however over the last decade 5 new agents have demonstrated to prolong survival in the same setting (Cabazitaxel, Sipuleucel-T, Abiraterone Acetate, Enzalutamide, Radium 223), the introduction of such therapeutic options into the routine clinical practice has significantly improved patients prognosis and has totally changed the management of the disease. Currently there are not prospective data about the best sequential strategy hence the oncologist has to choose on the basis of patients characteristics and his own experience with the drug; furthermore the patients, we routinely see in our clinics, significantly differ from the clinical trials population that is typically compliant and in good clinical condition. In this context the 'real life' studies, which offer a realistic scenario of our daily practice, have become more and more valuable, we tried to summarize the data emerged from these studies, available only for some of the above mentioned new agents, to identify a potential, 'ideal' sequence of treatment for patients with mCRPC. There are not enough evidences to define an exact sequence but this paper highlight several aspects which may help the clinician to decide the best therapeutic approach.*

KEY WORDS: *Prostate cancer, Docetaxel, Castration, Abiraterone, Enzalutamide.*

NEW ISSUES AND CHALLENGES IN MCRPC

For more than ten years, since the publication of two large clinical trials[1-3], Docetaxel, given intravenously every three weeks together with prednisone 10 mg orally, represented the only effective therapy for mCRPC (metastatic Castration Resistant Prostate Cancer) and such schedule is still considered the standard of care.

Nevertheless, over the last decade 5 new agents have demonstrated to prolong survival in patients with mCRPC: 1. The Cabazitaxel, a new generation chemotherapy belonging to the taxane family,[4]; 2. the Sipuleucel-T, an anticancer vaccine[5]; 3. The Abiraterone Acetate, AA, an inhibitor of the androgens synthesis[6,7]; 4. The Enzalutamide, a second-generation-antiandrogen[8]; 5. The Radium 223, an alpha-emitting radionuclide, targeting cancer cells[9].

The introduction of such therapeutic options into the routine clinical practice has significantly improved patients prognosis but has notably complicated the management of the disease. There are not prospective data about the best sequential strategy neither head-to-head comparative ran-

Corresponding Author: Gaetano Facchini, MD; e-mail: gafacchi@libero.it

domized studies hence the oncologist has to choose on the basis of patients characteristics such as comorbidities, general condition, age, tolerability profile for prior treatments and his own experience with the drug.

Furthermore the patients, we routinely see in our clinics, significantly differ from the clinical trials population that is typically compliant, healthy, in good clinical condition.

For these reasons the 'real life' or 'real world' studies acquire every day more credibility and value; such studies, despite the limit of their retrospective nature, offer a more realistic scenario of the routine clinical practice.

'Real life' data are currently available only for some of the above mentioned therapeutic agents, our paper aims to review these findings and to identify a potential, 'ideal' sequence of treatment for patients with mCRPC.

'HYPERCASTRATION'

For a long time the tumoral growth in the CRPC has been thought to be an androgen-independent process however the last data have clearly demonstrated that the Androgen-Receptors, ARs, maintain a key role in the biology of prostate cancer also when 'castration resistance' occurs. Many works recognize the re-activation of the androgen-receptor axis as an essential driver of the progression to the hormone refractory disease[10]; this hypothesis explains the high intratumoral levels of testosterone observed in mCRPC, that are similar, if not superior, to the ones detected in the normal prostate tissue[11,12].

The resistance to the ADT, Androgen Deprivation Therapy, is due to an up-regulation of the ARs which happens after a variable time of castration, such up-regulation may be mediated by different mechanisms:

Stronger affinity for the dihydrotestosterone (DHT) through gene amplification[13,14].

Mutations leading to ARs activation through ligands other than androgens, such as adrenal steroids or even antiandrogens like bicalutamide[15-18].

Mutations leading to constitutive activation of the ARs[19,20].

The most important effect of the recent findings about the ARs role in the mCRPC has been the development of the so-called 'new antiandrogens', AA and Enzalutamide, both currently used in the post ADT setting.

AA and Enzalutamide are defined 'hypercastration agents' because they block the androgen-receptor axis also in the CRPC; the AA inhibits the CYP17 (Cytochrome P17) which is involved in the synthesis of the steroids while the Enzalutamide binds with very high affinity to the ARs and keeps its activity even in patients with prostate cancer resistant to bicalutamide, with ARs mutated or overexpressed[21].

ABIRATERONE

At AA has demonstrated to prolong survival in patients with mCRPC in second line, in subjects already trated with Docetaxel[6], then the efficacy has been confirmed in the pre-Docetaxel setting[7]. In both trials the experimental arm was associated with improved OS, Overall Survival, and PFS, Progression Free Survival, compared to the placebo group.

Given the different population it is not surprising that the outcome parameters significantly vary between the two studies: mOS (median OS) 15.8 *vs.* 11.2 months and mPFS (median PFS) 5.6 months in the former; mOS 35.3 *vs.* 30.1 months and mPFS 16.5 months in the latter.

On note in the post-Docetaxel setting a PSA, Prostate Specific Antigen, decrease ≥ 50% was observed in the 38% of the patients compared to the 62% in the post-Docetaxel population, such finding suggests that the AA may be more active before Docetaxel rather than after chemotherapy; however it must be highlighted that the two trial populations were notably different as patients enrolled in the pre-Docetaxel trial were asymptomatic or oligosymptomatic, had no visceral metastases and presented low-volume disease[13].

Recently many groups have published their experience with AA in the post-Docetaxel setting, all these 'real life' studies confirm the value of the drug, both in terms of activity and safety.

In the Italian paper by Caffo et al[22], 255 patients treated with AA after Docetaxel were included, the authors reported a favorable tolerability profile (most common adverse events: anemia, fatigue, bone pain) and outcome parameters even superior to the pivotal study: mOS 17 months, mPFS 7 months.

In the 'real world' European study published by Dearden et al[23], involving 553 patients treated in France and Netherlands, the reported outcome has been approximately the same: mOS 18.2 months, mPFS 12.7 months, no new concerns have been raised about safety.

In another Italian work[24], presented at the ECCO (European Cancer COnference) 2015, the efficacy data have met the expectations once again, in that retrospective analysis, including 189 patients, mOS resulted 26 months and mPFS 10 months, an interesting aspect was the correlation

between the outcome and the prior hormone therapy: more favorable OS and PFS were observed in subjects who received hormone treatment for at least 12 months before Docetaxel.

The 'real life' studies have confirmed the activity of the AA in the treatment of mCRPC progressing during or after Docetaxel and they have also reassured the clinicians about the potential side effects not only of the drug itself but also of the prednisone, which needs to be given together with AA to prevent the 'abiraterone-induced mineralocorticoid excess' (5 mg orally twice a day). A good tolerability profile has been observed in the general population[25,26] as well as in a cohort with cardiovascular risk factors[27]. Hepatic and cardiac functions must be closely monitored but there are no patients categories that should be precluded a priori from receiving AA.

Finally, the results of the 'early access protocol trial' have been recently reported on Lancet; this protocol recruited 2314 patients receiving AA after chemotherapy in 23 countries; the primary endpoint of the study was to verify the safety in a large patients sample in order to accelerate the procedures for the approval by the different drug control agencies. The goal has been fully met, no unexpected toxicities occurred: the 25% of the patients had a grade 3-4 toxicity, mainly liver function alterations (8%); hypertension (4%); cardiovascular abnormalities (2%). The mPFS was a secondary endpoint, mPFS resulted 8.5 months, according to PSA criteria, and 12.7 months, considering clinical progression[28].

While we already have strong 'real life' data about the AA in the post-Docetaxel setting, deriving from analyses in large cohorts, we still have few literature in regards to the pre-Docetaxel use; 2 retrospective studies, in very small populations, have raised the doubt of a potential decrease of the activity of Docetaxel when given after AA, suggesting a cross-resistance among the two drugs.

The work by Menzynski et al[29] involved 35 patients and reported a mOS of 12.5 months and a PSA decrease ≥ 50% only in the 26% of the enrolled subjects; Aggarwal et al[30] in a retrospective analysis on 14 patients highlighted a mPFS of 4.2 months, these data are considerably inferior to the ones observed in first line for Docetaxel[1].

ENZALUTAMIDE

As happened for the AA also for the Enzalutamide the efficacy has been proved at first in the post-Docetaxel setting and then in the pre-Docetaxel one. In the chemo-naïve patients, who received Enzalutamide or placebo in the AFFIRM trial[8], the drug demonstrated to improve survival (mOS 18.4 *vs.* 13.6 months, $p < 0.001$) and PFS (mPFS 8.3 *vs.* 3 months, $p < 0.001$); more recently, thanks to the results of the PREVAIL trial[31], the activity has been confirmed in the post-Docetaxel setting: after 12 months of follow up PFS 65% *vs.* 14%, survival 72% *vs.* 63%, with a death-risk reduction of the 29% (compared to placebo).

The most important 'real world' study about Enzalutamide is a retrospective American study which recruited 310 patients, the population was not homogeneous; of the total 310 subjects, 36 (12%) were naïve for Docetaxel and AA; 79 (25%) had already received AA; 30 (10%) had already received Docetaxel and 165 (53%) had already received both Docetaxel and AA[32].

The median treatment duration resulted understandably different among the four groups, in particular, in the group receiving Enzalutamide in first line (naïve for both Docetaxel and AA) it was 9.1 months and in the group already treated with both Docetaxel and AA 3.9 months; in the middle there were the population exposed only to Docetaxel, 5.4 months, and the one exposed only to AA, 4.7 months.

In that work the mOS has been reached only for the cohort with the poorest prognosis (receiving Enzalutamide after Docetaxel and AA, hence in third line) and was 12.2 months; the tolerability profile has been confirmed very favorable without new safety issues.

The Enzalutamide appears less active when administered following treatment with AA, this finding is congruent with the data reported in several retrospective studies, involving patients who were given Enzalutamide after AA[33-37].

However such effect is observed not only for the Enzalutamide after AA but also for the AA in the reverse sequence, though the available date regard very small patients sample[38-40]. Furthermore the low Response Rate, RR, to Enzalutamide in the subjects who failed to respond to AA, allows to speculate that some subsets of patients have a primary resistance to both the agents[32].

CABAZITAXEL

The Cabazitaxel is a chemotherapeutic agent belonging to the Taxane family, in the TROPIC trial it was administered every three weeks intravenously at the dose of 25 mg/m^2 together with prednisone 10 mg/die orally and compared to Mitoxantrone[4]. 755 patients already treated with Docetaxel were enrolled: the experimental arm was significantly superior to the control arm for mPFS (2.8 *vs.* 1.4 months) and mOS (15.1 *vs.* 12.7 months). The most

common side effects were neutropenia, 82%, febrile neutropenia, 8%, and diarrhea, 6%.

The data of the Italian 'early access program', which involved 218 patients, who were given Cabazitaxel from January 2011 to December 2012, have been recently published[41]; this was mainly a safety study: the neutropenia has been confirmed as the most frequent adverse event but with a significantly lower incidence compared to the pivotal trial (34% vs 82%), though such gap is probably due, as suggested by the authors themselves, to a larger use of the G-CSFs (Granulocyte Colony Stimulating Factors), as consequence of the concerning results of the TROPIC.

Further positive data about the tolerability of the Cabazitaxel in a European cohort have been reported also by Heidenreich et al[42,43].

PURSUING THE OPTIMAL SEQUENCING

In a short time the scenario of the prostate cancer care has dramatically changed due to the availability of a number of options that anyone could have imagined a few years ago; we are still learning how to use such treatments and further elements emerge continuously.

On the one hand we are every day more familiar with the new hormone therapies, AA and Enzalutamide, thanks to their manageability, the favorable toxicity profile and all the reassuring 'real life' reports recently published; on the other hand the Cabazitaxel, after some initial concern about the high risk of mielotoxicity, is gaining popularity because the 'real world' analyses have demonstrated that the side effects can be well controlled by using the adequate supportive therapy (prophylactic G-CSFs).

In Italy we have no experience with the Sipuleucel-T[5], which has never been approved in Europe; the radio-metabolic therapy is still not prescribed in routine clinical practice but its use may increase significantly in the light of the results of the ALSYMPCA trial[9].

A standard treatment sequencing for mCRPC currently does not exist and the clinician has to choose the therapeutic strategy according to the patients characteristics and the results achieved with the prior lines of treatment. Docetaxel remains the standard of care in first line though the AA represents a valid option in case of PSA DT (PSA Doubling Time) $\geq$ 6 months, 'frail' patient, long duration of the hormone-sensitive phase, lack of visceral metastases, low-volume disease.

There are a lot of open questions about the third line and the chances of responding to Enzalutamide after AA and viceversa; the CARD trial is trying to address these doubts by comparing Cabazitaxel with AA/Enzalutamide in the patients who received the one or the other following progression during or after Docetaxel (ClinicalTrials.gov identifier: NCT02485691).

CONCLUSIONS

There are not enough evidences to define a clear and universally-accepted sequence for mCRPC and the scenario could be complicated further by anticipating Docetaxel in the newly diagnosed metastatic patients (hormone therapy naïve) as successfully suggested in several clinical trials[44,45].

All the treatments that have demonstrated to improve the survival in the post-ADT setting have to be considered as options.

More clinical studies are required to find the best strategy by comparing the alternative sequences and further translational research is needed to define biomarkers which may help to recognize the different patients subgroups.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

REFERENCES

1. Tannock IF, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Théodore C, James ND, Turesson I, Rosenthal MA, Eisenberger MA; TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351: 1502-1512.
2. Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 2008; 26: 242-245.
3. Petrylak D, Tangen CM, Hussain MH, Lara PN Jr, Jones JA, Taplin ME, Burch PA, Berry D, Moinpour C, Kohli M, Benson MC, Small EJ, Raghavan D, Crawford ED. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004; 351: 1513–1520.
4. De Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, Gravis G, Bodrogi I, Mackenzie MJ, Shen L, Roessner M, Gupta S, Sartor AO; TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010; 376: 1147-1154
5. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, Ferrari AC, Dreicer R, Sims RB, Xu Y, Frohlich MW, Schellhammer PF; IMPACT Study. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010; 363: 411–422.

6. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB Jr, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Fléchon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011; 364: 1995-2005.
7. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, Fizazi K, Mainwaring P, Piulats JM, Ng S, Carles J, Mulders PF, Basch E, Small EJ, Saad F, Schrijvers D, Van Poppel H, Mukherjee SD, Suttmann H, Gerritsen WR, Flaig TW, George DJ, Yu EY, Efstathiou E, Pantuck A, Winquist E, Higano CS, Taplin ME, Park Y, Kheoh T, Griffin T, Scher HI, Rathkopf DE; COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med 2013; 368: 138-148.
8. Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Fléchon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367: 1187-1197.
9. Parker C, Heinrich D, O'Sullivan J, Fossa S, Chodacki A, Wiechno P, et al. Updated analysis of the phase III, double-blind, randomized, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSYMPCA). J Clin Oncol 2012; 30: LBA4512.
10. Sweeney C, Chen YH, Carducci MA, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): an ECOG-led phase III randomized trial. J Clin Oncol 2014; 32: 5s (suppl; abstr LBA2).
11. Ferraldeschi R, Welti J, Luo J, Attard G, de Bono JS. Targeting the androgen receptor pathway in castration-resistant prostate cancer: progresses and prospects. Oncogene 2015; 34: 1745-1757.
12. Mostaghel EA, Page ST, Lin DW, Fazli L, Coleman IM, True LD, Knudsen B, Hess DL, Nelson CC, Matsumoto AM, Bremner WJ, Gleave ME, Nelson PS. Intraprostatic androgens and androgen-regulated gene expression persist after testosterone suppression: therapeutic implications for castration-resistant prostate cancer. Cancer Res 2007; 67: 5033-5041.
13. Page ST, Lin DW, Mostaghel EA, Hess DL, True LD, Amory JK, Nelson PS, Matsumoto AM, Bremner WJ. Persistentintraprostatic androgen concentrations after medical castration in healthy men. J Clin Endocrinol Metab 2006; 91: 3850-3856.
14. Bubendorf L, Kononen J, Koivisto P, Schraml P, Moch H, Gasser TC, Willi N, Mihatsch MJ, Sauter G, Kallioniemi OP. Survey of gene amplifications during prostate cancer progression by high-throughout fluorescence in situ hybridization on tissue microarrays. Cancer Res 1999; 59: 803-806.
15. Franco R, Caraglia M, Facchini G, Abbruzzese A, Botti G. The role of tissue microarray in the era of target-based agents. Expert Rev Anticancer Ther 2011; 11: 859-869.
16. Caraglia M, Giuberti G, Marra M, Di Gennaro E, Facchini G, Caponigro F, Iaffaioli RV, Budillon A, Abruzzese A. Docetaxel induces p53-dependent apoptosis and synergizes with farnesyl transefrase inhibitor r115777 in human epithelial cancer cells. Front Biosci 2005; 10: 2566-2575.
17. Haapala K, Kuukasjärvi T, Hyytinen E, Rantala I, Helin HJ, Koivisto PA. Androgen receptor amplification is associated with increased cell proliferation in prostate cancer. Hum Pathol 2007; 38: 474-478.
18. Brooke GN, Bevan CL. The role of androgen receptor mutations in prostate cancer progression.Curr Genomics 2009; 10: 18-25.
19. Taplin ME, Bubley GJ, Shuster TD, Frantz ME, Spooner AE, Ogata GK, Keer HN, Balk SP. Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. N Engl J Med 1995; 332: 1393-1398.
20. Taplin ME1, Bubley GJ, Ko YJ, Small EJ, Upton M, Rajeshkumar B, Balk SP. Selection for androgen receptor mutations in prostate cancers treated with androgen antagonist. Cancer Res 1999; 59: 2511-2515.
21. Chi K, Hotte SJ, Joshua AM, North S, Wyatt AW, Collins LL, Saad F. Treatment of mCRPC in the AR axis-targeted therapy resistant state. Ann Oncol 2015 Jun 22. pii: mdv267.
22. Caffo O, De Giorgi U, Fratino L, Lo Re G, Basso U, D'Angelo A, Donini M, Verderame F, RattaR, Procopio G, Campadelli E, Massari F, Gasparro D, Macrini S,Messina C, Giordano M, Alesini D, Zustovich F, Fraccon AP, Vicario G, Conteduca V, Maines F, Galligioni E. Safety and clinical outcomes of patients treated with abiraterone acetate after docetaxel: results of the Italian Named Patient Programme. BJU Int 2015; 115: 764-771.
23. Dearden L, Musingarimi P, Shalet N, Demuth D, Garcia Alvarez L, Muthutantri A, Venerus A, Lasry R, Hankins M, Maher T. A description of real-world treatment with abiraterone acetate in metastatic castration-resistant prostate cancer patients in the post-chemotherapy setting in France and The Netherlands. Value Health 2015; 18: A435.
24. Fabbri MA, Cortesi E, Marchetti P, Santini D, Gamucci T, Angelini F, Longo F, Milano A, Mancini ML, Giuli A, Quadrini S, Sperduti I, Pellegrino A, Ratta R, Primi F, Chilelli MG, Ruggeri EM. Abiraterone acetate in metastatic castration-resistant prostate cancer after chemotherapy. A retrospective "Real Life" analysis of activity and safety. ECCO 2015, abstract number: 2544.
25. Karim Fizazi, Kim N. Chi, Johann Sebastian De Bono, Leonard G. Gomella, Kurt Miller, Dana E. Rathkopf, Charles J. Ryan, Howard I. Scher, Neal D. Shore, Peter De Porre, Anil Londhe, Tracy McGowan, Nonko Pehlivanov, Robert Louis Charnas, Mary Beth Todd and Robert B. Montgomery. Assessment of corticosteroid (CS)-associated adverse events (AEs) with long-term (LT) exposure to low-dose prednisone (P) given with abiraterone acetate (AA) to metastatic castration-resistant prostate cancer (mCRPC) patients (Pts). Journal of Clinical Oncology, 2015 Genitourinary Cancers Symposium (February 26-28, 2015). Vol 33, No 7 suppl (March 1 Supplement), 2015: 169.
26. Miller K, Chi K, De Bono JS, Fizazi K, Gomella LG, Rathkopf DE, Ryan CJ, Scher HI, Shore N, De Porre P, Londhe A, McGowan T, Pelhivanov N, Charnas R, Todd MB, Montgomery B. Assessment of corticosteroid (CS)-associated adverse events (AEs) with long-term (LT) exposure to low-dose prednisone (P) given with abiraterone acetate (AA) to metastatic castration-resistant prostate cancer (mCRPC) patients (pts). EAU 2015 Abstract number: 564.

27. Procopio G, Grassi P, Testa I, Verzoni E, Torri V, Salvioni R, Valdagni R, de Braud F. Safety of abiraterone acetate in castration-resistant prostate cancer patients with concomitant cardiovascular risk factors. Am J Clin Oncol 2015; 38: 479-482.
28. Sternberg CN, Castellano D, Daugaard G, Géczi L, Hotte SJ, Mainwaring PN, Saad F, Souza C, Tay MH, Garrido JM, Galli L, Londhe A, De Porre P, Goon B, Lee E, McGowan T, Naini V, Todd MB, Molina A, George DJ; Abiraterone Global EAP Investigators. Abiraterone acetate for patients with metastatic castration-resistant prostate cancer progressing after chemotherapy: final analysis of a multicentre, open-label, early-access protocol trial. Lancet Oncol 2014; 15: 1263-1268.
29. Mezynski J, Pezaro C, Bianchini D, Zivi A, Sandhu S, Thompson E, Hunt J, Sheridan E, Baikady B, Sarvadikar A, Maier G, Reid AH, Mulick Cassidy A, Olmos D, Attard G, de Bono J. Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? Ann Oncol 2012; 23: 2943-2947.
30. Aggarwal R, Formaker C, Small E, Molina A, Ryan C. Response to ketoconazole (keto) or docetaxel (D) following clinical progression on abiraterone acetate (AA) in castrate-resistant prostate cancer (CRPC). J Clin Oncol 2012; 30(Suppl): abstract 4664.
31. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, Iversen P, Bhattacharya S, Carles J, Chowdhury S, Davis ID, de Bono JS, Evans CP, Fizazi K, Joshua AM, Kim CS, Kimura G, Mainwaring P, Mansbach H, Miller K, Noonberg SB, Perabo F, Phung D, Saad F, Scher HI, Taplin ME, Venner PM, Tombal B; PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371: 424-433.
32. Cheng HH, Gulati R, Azad A, Nadal R, Twardowski P, Vaishampayan UN, Agarwal N, Heath EI, Pal SK, Rehman HT, Leiter A, Batten JA, Montgomery RB, Galsky MD, Antonarakis ES, Chi KN, Yu EY. Activity of enzalutamide in men with metastatic castration-resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel Prostate Cancer Prostatic Dis 2015; 18: 122-127.
33. Bianchini D, Lorente D, Rodriguez-Vida A, Omlin A, Pezaro C, Ferraldeschi R, Zivi A, Attard G, Chowdhury S, de Bono JS. Antitumour activity of enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer (CRPC) pre-treated with docetaxel and abiraterone. Eur J Cancer 2014; 50: 78-84.
34. Badrising S, van der Noort V, van Oort IM, van den Berg HP, Los M, Hamberg P, Coenen JL, van den Eertwegh AJ, de Jong IJ, Kerver ED, van Tinteren H, Bergman AM. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. Cancer 2013; 120: 968-975.
35. Thomson D, Charnley N, Parikh O. Enzalutamide after failure of docetaxel and abiraterone in metastatic castrate-resistant prostate cancer. Eur J Cancer 2014; 50: 1040-1041.
36. Schmid SC, Geith A, Boker A, Tauber R, Seitz AK, Kuczyk M, von Klot C, Gschwend JE, Merseburger AS, Retz M. Enzalutamide after docetaxel and abiraterone therapy in metastatic castration-resistant prostate cancer. Advances Ther 2014; 31: 234-241.
37. Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer patients. Eur Urol 2015; 67: 23-29.
38. Ileana E, Loriot Y, Albiges L, Massard C, Blesius A, Di Palma M, et al. Abiraterone in patients with metastatic castration-resistant prostate cancer progressing after docetaxel and MDV3100. J Clin Oncol 2012; 30 (suppl.): abstr 4554.
39. Loriot Y, Bianchini D, Ileana E, Sandhu S, Patrikidou A, Pezaro C, Albiges L, Attard G, Fizazi K, De Bono JS, Massard C. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). Ann Oncol 2013; 24: 1807-1812.
40. Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. Ann Oncol 2013; 24: 1802–1807
41. Bracarda S, Gernone A, Gasparro D, Marchetti P, Ronzoni M, Bortolus R, Fratino L, Basso U, Mazzanti R, Messina C, Tucci M, Boccardo F, Cartenì G, Pinto C, Fornarini G, Mattioli R, Procopio G, Chiuri V, Scotto T, Dondi D, Di Lorenzo G. Real-world cabazitaxel safety: the Italian early-access program in metastatic castration-resistant prostate cancer. Future Oncol 2014; 10: 975-983
42. Heidenreich A, Bracarda S, Mason M, Ozen H, Sengelov L, Van Oort I, Papandreou C, Fossa S, Hitier S, Climent MA; European investigators. Safety of cabazitaxel in senior adults with metastatic castration-resistant prostate cancer: results of the European compassionate-use programme. Eur J Cancer 2014; 50: 1090-1099.
43. Heidenreich A, Scholz HJ, Rogenhofer S, Arsov C, Retz M, Müller SC, Albers P, Gschwend J, Wirth M, Steiner U, Miller K, Heinrich E, Trojan L, Volkmer B, Honecker F, Bokemeyer C, Keck B, Otremba B, Ecstein-Fraisse E, Pfister D. Cabazitaxel plus prednisone for metastatic castration-resistant prostate cancer progressing after docetaxel: results from the German compassionate-use programme. Eur Urol 2013; 63: 977-982
44. Gravis G, Fizazi K, Joly F, Oudard S, Priou F, Esterni B, Latorzeff I, Delva R, Krakowski I, Laguerre B, Rolland F, Théodore C, Deplanque G, Ferrero JM,Pouessel D, Mourey L, Beuzeboc P, Zanetta S, Habibian M, Berdah JF, Dauba J, Baciuchka M, Platini C, Linassier C, Labourey JL, Machiels JP, El Kouri C,Ravaud A, Suc E, Eymard JC, Hasbini A, Bousquet G, Soulie M. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol 2013; 14: 149-158.
45. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, Wong YN, Hahn N, Kohli M, Cooney MM, Dreicer R, Vogelzang NJ, Picus J, Shevrin D,Hussain M, Garcia JA, DiPaola RS. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med 2015; 373: 737-746.