



Neoadjuvant androgen deprivation therapy through intense inhibition of the androgen target: “*Midsummer Night’s Dream*” or “*Much Ado About Nothing*”?

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In the last two decades, the risk profile of patients treated with radical prostatectomy (RP) shifted away from the most favorable disease towards intermediate and high-risk diseases (1). These patients are at increased risk of recurrence and prostate cancer (PCa) mortality (2,3). From this perspective, the development of novel multimodality strategies to improve outcomes of surgically-treated PCa patients are needed.

Adjuvant hormone therapy after RP failed to demonstrate a survival advantage (4) and it is not recommended by current guidelines in patients without lymph-node involvement (5). Enzalutamide and Abiraterone, two intense androgen receptor (AR) axis-targeting molecules, demonstrated to be more efficacious than luteinizing hormone-releasing hormone agonist (LHRH-A) in prolonging survival of metastatic PCa patients with castration sensitive disease (6,7).

The greater efficacy of enzalutamide or abiraterone in the management of metastatic disease provides the rationale of testing these drugs in neoadjuvant setting (8-10). Both drugs target the AR-axis in different way and this provides the rationale for their association. Current guidelines do not recommend androgen deprivation therapy (ADT) as neoadjuvant approach before RP (5,11). Nonetheless, this treatment modality offers the unique opportunity to study the effect of drugs on tumor size and biology *in vivo* and represents a useful tool to obtain precious information on the possible efficacy of new therapies. Indeed, neoadjuvant

ADT may affect PCa biology on different pathways (12). For example, ADT with LHRH-A may reduce proliferation and induce apoptosis of PCa tumor cells, as well as it may stimulate the immune response. However, pathologic variables that characterize response of prostate carcinoma to neoadjuvant therapy have not been characterized in detail. On the basis of the results of large randomized neoadjuvant trials in breast cancer, pathological complete remission (pCR) was found to be an independent predictor of improved disease-free survival and overall survival (13). Therefore, a similar clinical significance of pCR in PCa patients receiving neoadjuvant therapy may be expected. While pCR was almost never observed after neoadjuvant therapy with LHRH-A alone (12), the addition of abiraterone (8) or enzalutamide (9) to LHRH-A resulted in a pCR rate of about 10%. These results are encouraging. Whether more pronounced inhibition of the AR-axis by the combination of both drugs could lead to a greater proportion of pCR or not, is a plausible question.

In their recently published phase II trial, McKay *et al.* (14) tested the effect of neoadjuvant Enzalutamide and Leuprolide with or without abiraterone acetate and Prednisone before RP in a cohort of intermediate or high risk PCa patients. The rationale of this study stems on their previous findings, where combination arms achieved better pathological responses (8,9). Seventy-five

intermediate or high-risk PCa patients were enrolled and randomly assigned 2:1 to receive enzalutamide, leuprolide, abiraterone acetate and prednisone *vs.* enzalutamide and leuprolide alone for 24 weeks before undergoing RP. The majority of patients enrolled (86.7%) had high-risk disease. The primary endpoint of the study was presence of either pCR or minimal residual disease (MRD), defined as largest cross-sectional dimension of residual tumor measuring 5 mm or less. The results showed a superimposable pCR rate in both arms (8% *vs.* 8%, respectively). Conversely, MRD was more frequent after the combination of enzalutamide, leuprolide, abiraterone acetate and prednisone (20%) than enzalutamide and leuprolide (8%), although the difference did not attain the statistical significance. Additionally, immunohistochemistry analyses on 60 RP specimens revealed a similar expression of erythroblast transformation-specific related gene (ERG), phosphatase and tensin homolog (PTEN), AR prostate specific antigen (PSA), glucocorticoid receptor (GR) and Ki-67 in the residual PCa cells in both arms. Nonetheless, the authors found that ERG positivity or PTEN loss were significantly associated with larger residual tumors, as well as with lower AR expression and lower baseline PSA values. Additionally, ERG-positive or PTEN-loss tumors did not experience MRD. As regards as toxicity profile, the Enzalutamide, Leuprolide, Abiraterone Acetate and Prednisone arm showed an increase of any-grade and grade 3 hypertension and alanine aminotransferase (ALT) and aspartate transaminase (AST) elevation. No grade 4 and 5 adverse events were reported in both treatment arms.

The authors concluded that neoadjuvant ADT followed by RP resulted in favorable pathological response in selected patients with intermediate- and high-risk PCa, with improved outcomes in the enzalutamide, leuprolide, abiraterone acetate and prednisone arm. However, this improvement trend in the combination arms was based on a not statistically significant greater proportion of MRD and a similar proportion of pCR between the two treatment regimens. The role of pCR as surrogate endpoint of treatment efficacy of neoadjuvant systemic therapy in breast cancer or survival is still debatable (15,16). Along this line, differences in pCR and MRD among neoadjuvant treatment arms in PCa patients could not translate in a real difference in terms of patient outcomes. It is worth mentioning that the results of the Alliance A031201 trial (17), a phase III study which compared the efficacy of enzalutamide alone versus combination of enzalutamide plus abiraterone in patients with metastatic castration resistant PCa, failed to

demonstrate a superiority of the combination over single agent enzalutamide in terms of progression free survival and overall survival.

As regard as the authors observation that ERG positivity and/or PTEN loss were significantly associated with poorer response and larger residual tumors, no multivariable adjustments were performed. Therefore, whether both are independent predictive factors or only one of them is the true predictor is uncertain. Noteworthy, a previous study (18) reported that the TMPRSS2: ERG expression might favor the development of neuroendocrine differentiation in neoadjuvant ADT-treated PCa patients. These findings may at least partially explain the association between ERG positivity and poorer response outcomes. However, McKay *et al.* (14) did not investigate neuroendocrine phenotype in their cohort. This may be an important issue, since neuroendocrine differentiation may lead to androgen independent growth and, therefore, to early development of castration-resistant disease.

With respect to tolerability, although no grade 4 or 5 adverse events were reported, treatment-related adverse events should not be ignored. Indeed, grade 3 adverse events proportion was not negligible in all these neoadjuvant ADT studies. Efforts should also be made to decrease the adverse effects of ADT, especially in the absence of long-term outcomes. For example, whether increased grade 3 hypertension rate may translate into increase cardiovascular mortality rate in PCa patients should not be ascertained with the current knowledge in the neoadjuvant setting. Finally, quality of life and medical cost are also important issues that should be addressed in decision making.

In conclusion, the McKay *et al.* study (14) confirm the activity of enzalutamide as neoadjuvant approach in PCa patients but the addition of abiraterone substantially failed to improve the disease response. Further study with longer follow-up data is needed to better understand the potential role of biological marker assessed before and after neoadjuvant ADT in predicting the patient outcome and the development of a castrate resistant state.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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