**Targeting PP2A to overcome enzalutamide resistance in AR+ breast tumors**

**Dear Editor,**

We have read with great interest the recent published manuscript by Caiazza et al. (2016), which provides novel exciting findings about the potential therapeutic value of enzalutamide in patients with androgen receptor (AR)-positive triple-negative breast cancer (TNBC). Some previous studies have shown promising antitumor effects of this drug in breast tumors. Thus, enzalutamide-mediated AR inhibition has been reported to reduce proliferation, anchorage-independent growth, migration and invasion and increases apoptosis of TNBC cells *in vitro* and decrease the viability of TNBC xenografts *in vivo* (Cochrane et al. 2014, Barton et al. 2015). In concordance with these data, Caiazza and coworkers found that enzalutamide reduced cell growth and clonogenic potential as well as migration and invasion capabilities of breast cancer cells. Moreover, the authors showed that enzalutamide exerts its antitumor effects through an AR-dependent manner and probably modulates the expression of the transcription factors AP-1 and SP-1. Of note, it has been recently described that targeting the PP2A/SET signaling axis is able to overcome the enzalutamide resistance in castration-resistant prostate cancer cells (Hu et al. 2015). Interestingly, PP2A is a largely reported tumor suppressor frequently inactivated in human cancer that regulates both AP-1 and SP-1 activation as well as AR expression (Al-Murrani et al. 1999, Huang et al. 2009). Our group has reported that PP2A is inhibited in breast cancer, with a particularly higher incidence in TNBC. In addition, this alteration represents a novel therapeutic target that defines a subgroup of breast cancer patients with very poor outcome (Rincón et al. 2015). Altogether, these data highlight the potential therapeutic value of targeting PP2A to prevent or overcome enzalutamide resistance in AR+ TNBC.

Furthermore, AR is known to be expressed in around 90% of estrogen receptor (ER)-positive breast tumors. The fact that AR is required for maximum ER genomic binding and activity determines the synergistic effect observed when anti-androgens such as enzalutamide are used in combination with traditional endocrine therapy with tamoxifen or fulvestrant. In fact, enzalutamide has been found effective even as a single agent in tumors resistant to these treatments (Cochrane et al. 2014, D’Amato et al. 2016). These findings are concordant with the work by Caiazza and coworkers, showing that antitumor effects of enzalutamide were similar in TN and non-TN cell lines but dependent on the AR expression. In this line of thinking, PP2A also has been found to directly regulate ER expression (Lu et al. 2003) and its pharmacologic reactivation using FTY720 serves to enhance the sensitivity of breast cancer cells to tamoxifen (Hait et al. 2015).

Altogether, these data would support the potential benefit derived from the use of enzalutamide in combination with PP2A-activating drugs also in the set of AR+/ER+ breast cancer tumors. In conclusion, the potential clinical usefulness of this novel therapeutic strategy based on the inclusion of enzalutamide in combination with PP2A activators for treating AR+ breast cancers should be further confirmed in the forthcoming studies.

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Declaration of interest
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