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Targeting androgen-independent pathways: new chances for patients with prostate cancer?

C. Cattrini[a,b,*], E. Zanardi[a,b], G. Vallome[a,b], A. Cavo[a,b], L. Cerbone[a,b], A. Di Meglio[a,b], C. Fabbroni[a,b], M.M. Latocca[a,b], F. Rizzo[a,b], C. Messina[a,b], A. Rubagotti[a,c], P. Barboro[a], F. Boccardo[a,b]

[a] Academic Unit of Medical Oncology, San Martino University Hospital – IST National Cancer Research Institute, L.go R. Benzi 10, 16132, Genoa, Italy
[b] Department of Internal Medicine and Medical Specialties (DIMI), School of Medicine, University of Genoa, V.le Benedetto XV 6, 16132, Genoa, Italy
[c] Department of Health Sciences (DISSAL), University of Genoa, Via A. Pastore 1, 16132, Genoa, Italy

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ABSTRACT

Androgen deprivation therapy (ADT) is the mainstay treatment for advanced prostate cancer (PC). Most patients eventually progress to a condition known as castration-resistant prostate cancer (CRPC), characterized by lack of response to ADT. Although new androgen receptor signaling (ARS) inhibitors and chemotherapeutic agents have been introduced to overcome resistance to ADT, many patients progress because of primary or acquired resistance to these agents. This comprehensive review aims at exploring the mechanisms of resistance and progression of PC, with specific focus on alterations which lead to the activation of androgen receptor (AR)-independent pathways of survival. Our work integrates available clinical and preclinical data on agents which target these pathways, assessing their potential clinical implication in specific settings of patients. Given the rising interest of the scientific community in cancer immunotherapy strategies, further attention is dedicated to the role of immune evasion in PC.

1. Introduction

Prostate cancer (PC) accounts for 1 in 5 new diagnoses of cancer in the United States of America and, despite the recent improvements, this neoplasm still causes more than 26,000 deaths per year (Siegel et al., 2016). The prostate gland is constituted both of basal and luminal epithelium arranged in a fibro-muscular stromal network (Packer and Maitland, 2016). Based on the observation that human PC are mostly luminal-like adenocarcinomas, the luminal origin of PC is supported by several studies (Wang et al., 2009; Wang et al., 2014). However, the basal cell transformation into tumorigenic luminal cells is also suggested as an alternative origin of PC (Packer and Maitland, 2016). Differently from basal cells, the luminal secretory cells of normal prostate require androgens for survival and undergo apoptosis upon androgen withdrawal (Long et al., 2005). Therefore, the androgen receptor (AR) has been historically considered the most relevant target to control the growth and dissemination of PC and this notion has guided the treatment of PC for several years (Watson et al., 2015). The time has probably come for this paradigm to be changed. First, not all hormone-naïve PC appear to be equally responsive to androgen deprivation therapy (ADT). Recently, Feng et al. segregated more than 3500 PC samples into luminal A, luminal B, and basal subtypes using the PAM50 classifier, which distinguishes basal and luminal breast cancers, and showed that only luminal B PC are significantly associated with post-operative response to ADT (Feng et al., 2017). Second, the high frequency of AR aberrations, found in highly pretreated patients with PC, suggests that AR probably acts as the main driver of proliferation and progression in some of these patients too, but this observation does not tell the whole story (Robinson et al., 2015). In fact, the poorly differentiated and aggressive PC cells show low levels of AR and prostate specific antigen (PSA) expression and sustain proliferation and invasion in a completely hormone-independent manner (Ellis and Loda, 2015; Miyamoto et al., 2015). Stemness signatures, self-renew capacity, resistance to immune-response, phenotypic plasticity and lack of contact inhibition are the main characteristics of these clones, which are refractory to therapies, exhibit high clonogenic potential, and show long-term tumor-propagating capacity (Boyd et al., 2012; Ellis and Loda, 2015; Mahal et al., 2016; Qin et al., 2012; Roubaud et al., 2016). These cells may be the result of multiple genetic and phenotypic alterations induced by treatments, but may also represent pre-existing

* Corresponding author at: Academic Unit of Medical Oncology, San Martino University Hospital – IST National Cancer Research Institute, L.go R. Benzi 10, 16132, Genoa, Italy. Tel.: +39 010 555 8930/8861; fax: +39 010 555 6385.
E-mail address: carlo.cattrini@gmail.com (C. Cattrini).

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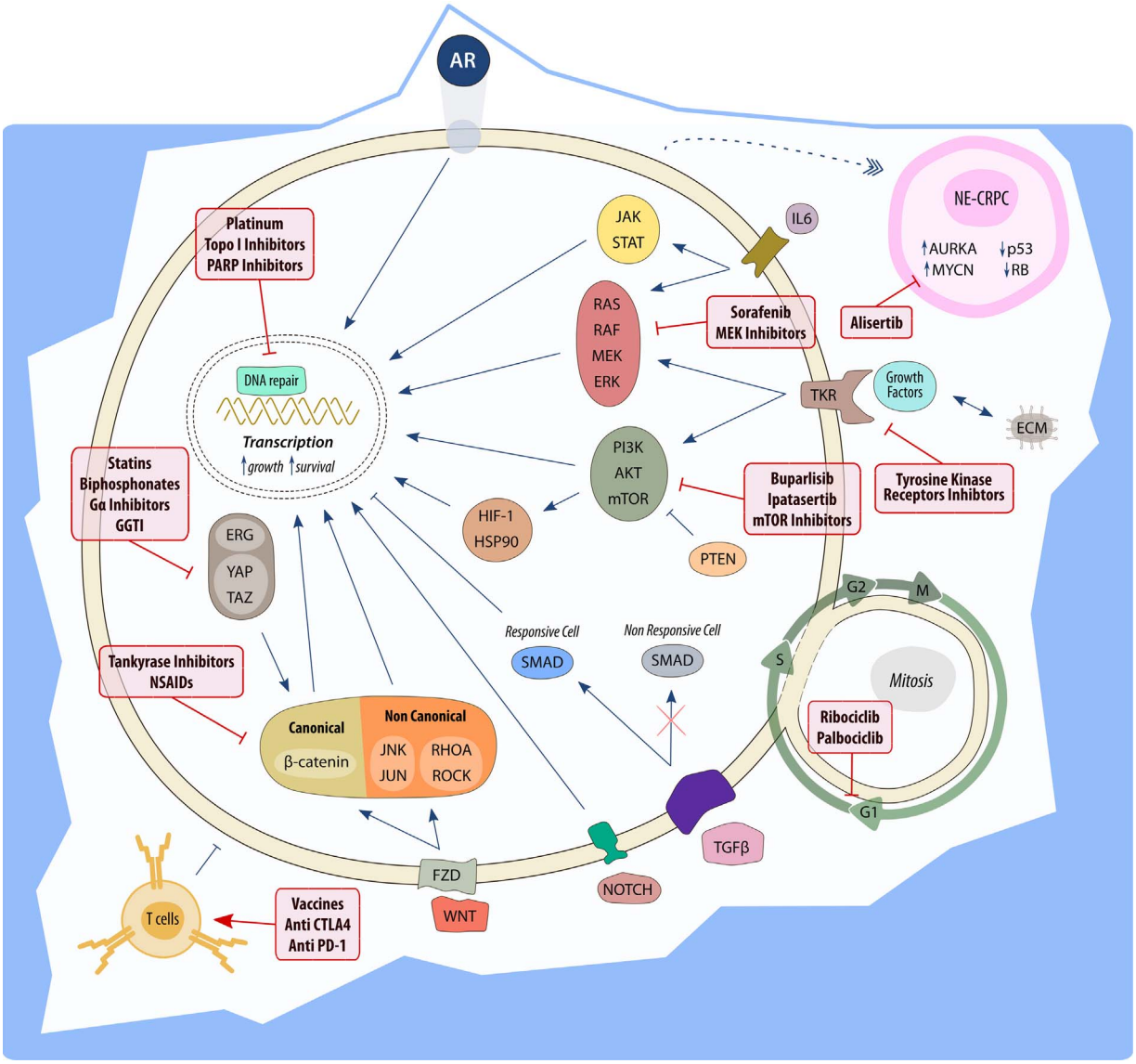

Fig. 1. The iceberg of resistance in PC. The AR alterations (i.e. mutations, amplifications, truncations) only represent the tip of the iceberg. Below we report a selection of AR-independent pathways potentially involved in the resistance of PC cells to treatments. Several drugs are currently available for inhibiting these pathways. Clockwise: (A) Divergent clonal evolution from CRPC adenocarcinoma cells is implicated in the development of NEPC; alisertib is effective in tumors which harbor amplifications of MYCN and AURKA. (B) IL-6 promotes PC cell proliferation and induces EMT through multiple signal pathways, including the JAK-STAT and the ERK-MAPK pathway. (C) Several components of the ECM influence the tumor microenvironment and activate the RAF-MEK-ERK kinase cascade and the PI3K-AKT-mTOR pathway. The hypoxia pathway is intimately connected with the PI3K-AKT-mTOR pathway. As shown, sorafenib, MEK inhibitors, buparlisib, ipatasertib and mTOR inhibitors are all potential modulators of these signaling pathways. (D) Palbociclib and ribociclib inhibit CDKs, inducing the blockade of cell cycle progression. (E) TGFβ exerts pleiotropic actions on immune cells and promote angiogenesis in PC; a models suggests that tumor cells may become resistant to TGFβ trough inactivation of TGFβ receptor or SMAD activity (Pickup et al., 2013). (F) Notch shows both tumor suppressive and oncogenic roles in PC, inducing the activation of several transcription factors. (G) Canonical (β-catenin-dependent) and non-canonical (RHOA, ROCK and JNK dependent) Wnt signaling exerts proliferative effects on tumor cells. ERG activates YAP transcriptional program and YAP/TAZ pathway acts on Wnt signaling. Tankyrase inhibitors, statins, NSAIDS, bisphosphonates, Gα inhibitors and GGTI potentially modulate these pathways. (H) Immunotherapy strategies block the inhibitors signals occurring on T-cells, thus reversing the inactivation of immune response against tumor cells. (I) PARP inhibitors block the repair of SSBs, induced by endogenous damages; cells with functional HR are able to repair more genotoxic DSBs produced by cytotoxic agents, but not BRCA 1 and 2 mutant cells, which undergo cell death. *AKT: protein kinase B; Anti-CTLA-4: anti-cytotoxic T-lymphocyte antigen 4; Anti-PD-1: anti-programmed cell death protein 1; AR: androgen receptor; AURKA: aurora kinase A; CRPC: castration-resistant prostate cancer; ECM: extracellular matrix; ERG: erythroblast transformation-specific related gene-1; ERK: extracellular signal-regulated kinase; GGTI: inhibitors of geranylgeranyl transferase-1; HIF1α: hypoxia-inducible factor 1-alpha; HSP90: heat shock protein 90; IL-6: interleukin-6; Fzd: frizzled; JAK: janus kinase; JNK: c-Jun N-terminal kinases; MAPK: mitogen-activated protein kinase; MEK: mitogen-activated protein kinase kinase; mTOR: mammalian target of rapamycin; MYCN: v-myc avian myelocytomatosis viral oncogene neuroblastoma derived; NEPC: neuroendocrine prostate cancer; NSAIDS: nonsteroidal anti-inflammatory drugs; p53: tumor protein p53; PARP: poly ADP-ribose polymerase; PC: prostate cancer; PI3K: phosphoinositide 3-kinase; PTEN: phosphatase and tensin homolog; Raf: rapidly accelerated fibrosarcoma; Ras: rat sarcoma; RB: retinoblastoma product; RHOA: ras homolog gene family, member A; ROCK: rho-associated protein kinase; SMAD: small mother against decapentaplegic; STAT: signal transducer and activator of transcription; TAZ: transcriptional coactivator with PDZ-binding motif; TKR: tyrosin kinase receptor; TGFβ: transforming growth factor-beta; VEGF: vascular endothelial growth factor; YAP: Yes-associated protein; Wnt: wingless-related integration site.*

subpopulations, which are selected based on their ability to survive in adverse conditions. Genomic rearrangements, rare mutations and epigenetic phenomena amplify transcriptomic diversity of PC, converging on specific cellular functions and AR-independent signaling pathways of survival and proliferation (Wyatt et al., 2013) (Fig. 1). Therefore, primary or acquired resistance to treatments is probably the result of the extensive genetic diversity and heterogeneity of PC rather than of a linear evolutionary process (Boyd et al., 2012; Liu et al., 2015). In addition to genetic or epigenetic events that occur in tumor cells, a favorable local microenvironment is an invariable prerequisite for the growth and the dissemination of this neoplasm (Barron and Rowley, 2012). Chemo-hormonal and mechanical signals modulate the behavior

Table 1
Promising agents targeting AR-independent pathways in patients with PC.

TARGET	DRUG	REFERENCES
AKT	Ipatasertib, AZD5363	(Crabb et al., 2017; De Bono, J. S. et al., 2016; Kolinsky et al., 2017)
AURKA	Alisertib	(Beltran et al., 2016a)
Hh	Itraconazole	(Antonarakis et al., 2013)
Hsp27	Apatorsen	(Chi et al., 2017)
mTOR	Everolimus	(Chow et al., 2016; Gross et al., 2015; Templeton et al., 2013)
PARP-1	Olaparib, veliparib	(Hussain et al., 2016; Mateo et al., 2015)
PD-1	Durvalumab, pembrolizumab	(Graff et al., 2016a; Hansen et al., 2016; Karzai et al., 2017)
RAF	Sorafenib	(Meyer et al., 2014)

of tumor, stromal and immune cells, affecting the progression of PC. Alterations in the cell structure, shape and polarity support the proliferation and migration of PC cells: several pathways activated during early stages of embryonic development also play key roles during tumorigenesis (Azzolin et al., 2012; Bissell and Hines, 2011; Taipale and Beachy, 2001; Zanconato et al., 2016b). Cell-surface molecules, growth and transcription factors are also frequently implicated in the activation of AR-independent pathways and in the process of epithelial–mesenchymal transition (EMT). Several studies have assessed drugs which target these AR-indipendent pathways of survival and have been focused on unselected, advanced, pluri-treated patients with castration-resistant prostate cancer (CRPC) (Table 1). However, specific molecular alterations, alternative to AR, are found in restricted subgroups of patients and in limited subsets of PC cells. Therefore, initial failures should not discourage further investigations on these drugs and new trials should be guided by the accurate identification of patients who might potentially benefit from these treatments. In addition, therapeutic interventions on these clones should be probably pursued as early as possible, in order to avoid the praecox selection of AR-indifferent cells, which gradually acquire more and more aggressive phenotypes.

2. Methods

This manuscript focuses on the results published by the Stand Up To Cancer – Prostate Cancer Foundation (SU2C-PCF) International Dream Team in 2015 (Robinson et al., 2015), which revealed the main alterations found in patients with metastatic castration-resistant prostate cancer (mCRPC). An analytical review of literature was implemented to confirm these findings and to assess the potential clinical implication of drugs that target these alterations. A systematic search of on-going, phase I, II and III clinical studies was performed in Feb 2017 on ClinicalTrial.gov, PubMed, American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) web-sites. Given the wide range of pathways explored, *in vitro* and *in vivo* studies were considered on the basis of their relevance to the topic. The search strategy included the terms metastatic prostate cancer (mPC), CRPC, molecular biology, AR, androgen receptor signaling (ARS), phosphoinositide 3-kinase (PI3K), protein kinase B (AKT), mammalian target of rapamycin (mTOR), poly ADP-ribose polymerase (PARP), wingless-related integration site (Wnt), mitogen-activated protein kinase (MAPK), rat sarcoma (RAS), rapidly accelerated fibrosarcoma (Raf), mitogen-activated protein kinase kinase (MEK), extracellular signal-regulated kinase (ERK), breast cancer-related gene (BRCA), cyclin-dependent protein kinases (CDK), androgen-regulated transmembrane protease serine 2 (TMPRSS2)/erythroblast transformation-specific related gene-1 (ERG) fusion, Yes-associated protein (YAP), transcriptional coactivator with PDZ-binding motif (TAZ), Notch, Hedgehog (Hh), neuroendrocrine prostate cancer (NEPC), aurora kinase A (AURKA), myc avian myelocytomatosis viral oncogene neuroblastoma derived (MYCN), immunotherapy, anti-cytotoxic T-lymphocyte antigen 4 (anti-CTLA-4), anti-programmed cell death protein 1 (anti-PD-1), vaccines.

3. Kinase-dependent pathways

More than 50% of patients with mCRPC harbor alterations in kinase-dependent signals, involving the PI3K-AKT-mTOR or the MAPK-ERK pathways (Robinson et al., 2015). Although many efforts have been carried out in recent years, the majority of tyrosine kinase (TK) inhibitors (i.e. cabozantinib, dasatinib, sunitinib) or growth factors inhibitors (i.e. bevacizumab), that were tested in unselected populations of patients with PC, proved ineffective (Lorente and De Bono, 2014; Messina et al., 2016). These failures may be attributed to the lack of absolute kinase dependency of CRPC and to the rare occurrence of TK genetic mutations (Grasso et al., 2012; Wyatt and Gleave, 2015). In addition, bypass signaling, epigenetic events or alterations in downstream effectors may also activate these pathways, independently of TK or growth factors inhibition (Lin and Shaw, 2016). Therefore, many attempts have been performed to inhibit the downstream checkpoints of these pathways, rather than the upstream elements.

3.1. PI3K-AKT-mTOR pathway

The PI3K-AKT-mTOR pathway is involved in cell survival, proliferation, differentiation and angiogenesis (Fruman and Rommel, 2014); however, its role in the anchorage-independent growth of tumor cells and oncogenic ECM remodeling is also well established (Hirsch et al., 2014). PI3K activation phosphorylates and activates AKT, which in turn activates mTOR; the phosphatase and tensin homolog (PTEN) is a tumor suppressor protein, that exerts an inhibitory effect on this signaling pathway (Luo et al., 2003). In addition, the activation of Twist induced by AKT represses the E-cadherin-mediated cell to cell adhesion, thus contributing to the EMT process (Xue et al., 2012). Preclinical data demonstrated a reciprocal regulation between PI3K and ARS during PC initiation and progression, pointing to a direct role of PTEN loss and PI3K/AKT activation in repressing AR expression and activation (Lee et al., 2015). PI3K-AKT-mTOR thus represents an interesting target to block a significant number of basic responses leading to PC cells proliferation and dissemination (Bitting and Armstrong, 2013; Hirsch et al., 2014). Buparlisib, an oral investigational pan PI3K inhibitor, either alone or when added to AR inhibition, did not improve PFS over historic control data in men with mCRPC progressing on enzalutamide (Armstrong et al., 2015). Also PX-866, a pan-isoform inhibitor of class I PI3K, showed modest activity in docetaxel-naïve CRPC patients (NCIC, 2013). Dactolisib, a novel small molecule, pan-class I PI3K and mTOR signaling inhibitor was recently tested in a phase I/II trial in combination with abiraterone acetate in chemo-naïve mCRPC; this trial was stopped during phase I, due to multiple toxicities (Siegel et al., 2014). Encouraging results were recently presented by De Bono et al. at the 2016 ESMO Annual Meeting (De Bono et al., 2016a,b). Ipatasertib, an AKT inhibitor, in combination with abiraterone was compared to abiraterone alone in a phase II study that enrolled 253 patients with mCRPC after docetaxel chemotherapy. This combination did not show statistically significant increased radiologic PFS in the unselected population of CRPC compared to abiraterone alone (median 8.2 vs 6.4 months; hazard ratio (HR) = 0.75; $p = 0.17$). However, a subgroup analysis revealed that patients with PTEN loss had superior radiologic PFS benefit when treated with ipatasertib 400 mg compared to those without PTEN loss (rPFS: 11.5 vs 7.5 months HR:0.39 [0.22–0.70] $p = 0.006$) (De Bono et al., 2016a,b). Also, the lowest dosage of ipatasertib (200 mg) in combination with abiraterone determined a rPFS advantage in patients with PTEN loss compared to those without PTEN alterations (rPFS: 11.1 vs 4.6 months HR:0.46 [0.22–0.70] $p = 0.028$). When PTEN is deleted, AKT regulates PC cells proliferation, while AR regulates their survival, thus offering a possible explanation of these results and supporting the rationale of combining AKT blockers with AR modulators (Sittadjody et al., 2016). This notion has guided a phase I

dose-escalation study of enzalutamide in combination with the AKT inhibitor AZD5363 in heavily pretreated patients with mCRPC (Kolinsky et al., 2017). AZD5363 at the dosage of 300 mg twice daily four days on – three days off combined with enzalutamide 160 mg once daily was well tolerated (only one patient experienced G3 maculopapular rash) and this dosage was recommended for the following phase II trials. Among ten patients who completed 12 weeks of treatment, three met at least one of the criteria for response; in addition, one patient who had previously progressed on enzalutamide exhibited partial response, suggesting that AZD5363 may be able to overcome resistance to enzalutamide. AZD5363 was also investigated in combination with docetaxel and prednisolone in the ProCAID trial, a phase I study, which enrolled ten patients with mCRPC (Crabb et al., 2017); even though this study was not designed to evaluate the efficacy of this combination, PSA reduction from baseline level to < 50% at 12 weeks of treatment was seen in seven (70%) of patients. Several compounds (i.e. temsirolimus, everolimus, ridaforolimus or sapanisertib) have been developed to specifically inhibit mTOR. Two phase II trials showed minimal activity of temsirolimus as a single agent both in chemo-naïve and in docetaxel-treated CRPC patients (Armstrong et al., 2013; Kruczek et al., 2013). This drug was also tested as maintenance treatment following successful docetaxel chemotherapy, and resulted in a median time to treatment failure of 24.3 weeks (Emmenegger et al., 2015). The activity of everolimus, either as monotherapy or in combination with other drugs, was tested in patients with mCRPC in several clinical trials (Roviello et al., 2016). A phase II trial assessed single-agent everolimus in 37 chemotherapy-naive patients with CRPC (Templeton et al., 2013). Though PTEN loss is correlated with an overall poor survival (Lotan et al., 2016), patients with PTEN-deficient tumors treated with this drug showed a trend towards longer PFS and increased likelihood of response. Given the reciprocal AR-mTOR crosstalk (Wu et al., 2010), everolimus was tested in combination with bicalutamide in two phase II trials that recruited patients with CRPC. In the first one, everolimus was given in combination with bicalutamide both in chemo-naïve and in docetaxel-treated patients (Nakabayashi et al., 2012); this trial showed minimal activity of this combination, but 31 out of 36 enrolled patients had already been treated with bicalutamide before trial enrollment, and might therefore suffer from acquired resistance to this antiandrogen drug. In a more recent trial, the combination of bicalutamide plus everolimus was tested in 24 patients with CRPC naïve to these drugs (Chow et al., 2016); the treatment arm with everolimus and bicalutamide was associated with significant toxicity (58.3% of patients experienced grade 3 or 4 adverse events, as mucositis, hyperglycemia and hematologic toxicity), but also with a decrease in PSA ≥30% in 75% of patients; this result is quite comparable to that observed with novel ARS inhibitors (Ryan et al., 2015). Everolimus was also tested in association with docetaxel (Courtney et al., 2015) and carboplatin (Vaishampayan et al., 2015), but showed modest activity in mCRPC. This drug was also evaluated in combination with docetaxel and bevacizumab in patients with CRPC chemo-naïve (Gross et al., 2015); this association demonstrated significant clinical activity (maximal PSA decline ≥50% achieved in 31 (74%) of patients), but was associated with several hematologic and non-hematologic grade ≥3 toxicities. A phase II trial also explored the efficacy of everolimus plus gefitinib, an epidermal growth factor receptor inhibitor, in patients with CRPC, but did not result in significant antitumor activity (Rathkopf et al., 2015). Ridaforolimus, another mTOR inhibitor, was tested as a single agent in 38 patients with taxane-treated mCRPC; this treatment did not produce objective responses, but stable disease was observed in 47.4% of patients (Amato et al., 2012). The safety and tolerability of the combination of ridaforolimus plus bicalutamide was assessed in a phase I trial (Meulenbeld et al., 2013); although there was no evidence of a clinically relevant pharmacological drug-drug interaction, the occurrence of dose-limiting toxicities in 3/11 evaluable patients discouraged further studies with this combination. Finally, sapanisertib (MLN0128), a dual mTOR blocker was tested in a phase II trial, which recruited nine heavily pretreated patients with mCRPC (Rathkopf et al., 2016). All patients enrolled had a rise in PSA on treatment with a median of 159% increase from baseline (range, 12-620%), while five patients (56%) showed an immediate PSA decline upon discontinuation of treatment. This observation suggests activation of the AR in response to dual mTOR inhibition, and confirms the reciprocal link between ARS and PI3K pathways. Recent studies also suggest that PI3K-AKT-mTOR pathway is intimately connected with HIF1α, regulating PC stem cells quiescence and metabolism via the hypoxic signaling (Marhold et al., 2015). Stressful conditions caused by treatments induce activity of the heat shock proteins (HSP) (i.e. HSP90 and HSP27); these chaperones promote the nuclear transport of the AR and are essential for the activation of HIF1α and hypoxia pathway (Minet et al., 1999; Wyatt and Gleave, 2015). HSP90 inhibitors showed limited activity when administered as monotherapy in patients with mCRPC (Thakur et al., 2016; Wyatt and Gleave, 2015). Conversely, apatorsen, an HSP27 inhibitor, showed good tolerability and encouraging activity in a phase I study (Chi et al., 2016) and the recent data presented at the 2017 Genitourinary Cancers Symposium (ASCO GU) suggest that apatorsen might overcome the resistance to abiraterone in patients with mCRPC (Chi et al., 2017). Given the dual blockade of ARS and hypoxia-inducible factor 1-alpha (HIF1α) by HSP inhibitors, the biological contribute of the hypoxia signaling to PC progression remains undefined; the exclusive activation of this pathway is probably relevant only in few PC clones, but these cells might represent the most undifferentiated and resistant populations. Anthracyclines effectively inhibit HIF1α (Masoud and Li, 2015); the use of these compounds in PC has been limited by toxicity and moderate activity, but some responses have been observed in patients with CRPC (Harris et al., 2002); these data might provide the rationale to renew interest in these chemotherapeutics. In conclusion, preclinical studies support the crucial role of the PI3K/AKT/mTOR pathway in mCRPC, but there is little evidence of clinical benefit with inhibition of this pathway in unselected population of mCRPC. The use of PTEN/AKT/mTOR inhibitors and/or HIF1α/HSP inhibitors and/or AR modulators may probably be required for efficient pharmaceutical targeting of the most resistant PC clones. Further combination strategies might improve the blockade of this complex pathway, which appears to sustain essential AR-independent metabolic processes (Qin et al., 2012; Robinson et al., 2015; Wyatt and Gleave, 2015). However, the identification of the best combinations of agents depending on the specific characteristics of patients (i.e. PTEN aberrations) is probably the current challenge to be faced.

3.2. MAPK-ERK pathway

The MAPK/ERK pathway (also known as the Ras-Raf-MEK-ERK pathway) is a complex system of signal transduction activated by a wide variety of growth factors. Though this pathway is found to be altered only in limited patients with mCRPC (Robinson et al., 2015), its activation generates extensive changes in gene expression, mediated by transcription factors that control tumor cells proliferation, differentiation, migration, and invasion as well as angiogenesis (Dhillon et al., 2007). Whereas activating somatic mutations in the Raf pathway are common in melanoma, Raf fusions (3% of mCPRC), rather than mutations, are suggested as a mechanism for Raf gene activation in PC (Palanisamy et al., 2010; Robinson et al., 2015). Several studies investigated the activity of sorafenib, a Raf inhibitor, both in chemotherapy-naïve (Chi et al., 2008; Safarinejad, 2010; Steinbild et al., 2007) and in pretreated unselected populations of patients with mCRPC (Aragon-Ching et al., 2009; Dahut et al., 2008; Nabhan et al., 2012), with discouraging results. Recently, Meyer et al. enrolled 21 patients whose disease had progressed during chemotherapy and added sorafenib to their last chemotherapy regimen (Meyer et al., 2014). They observed biochemical response in 10/21 patients and radiographic stability in 16/21, suggesting that sorafenib may overcome

chemotherapy-failure among patients with CRPC. Sorafenib combined with enzalutamide exerted a synergistic *in vivo* inhibitory effect both on AR and ERK pathways; therefore, clinical studies testing sorafenib in the prevention of resistance to enzalutamide are encouraged (Wu et al., 2017). Preclinical models showed that combination of MEK inhibitors with PI3K-AKT-mTOR blockers may exert synergistic activity and efficacy in enzalutamide-resistant CRPC (Park et al., 2015; Toren et al., 2016). A phase II trial is planned to assess the safety and efficacy of the MEK 1/2 inhibitor trametinib in men with progressive mCRPC Single-Arm, in press ,whereas a randomized phase II trial is comparing the effects of AR inhibition with and without MEK inhibition on the development of EMT in PC Randomized Open-label, 2017 Randomized Open-label, in press, In conclusion, though sorafenib showed limited activity in unselected populations of CRPC, further studies should probably clarify the role of Raf and MEK inhibition in overcoming resistance to standard therapies; in addition, selected patients presenting rearrangements of the Raf gene may benefit from pan-Raf or MEK inhibitors.

4. DNA-repair pathway

The accumulation of genetic and epigenetic aberrations characterizes prostate carcinogenesis; these molecular changes can be either inherited or be the result of altered AR transcriptional activity, changes in chromatin architecture, oncogenic replication, error-prone DNA repair, or defective cell division (Mateo et al., 2015). Deficient DNA repair response and defective apoptotic checkpoint control can lead to permanent incorporation of these genome abnormalities, conferring survival and growth advantage to the transformed cell. Deleterious germline or somatic aberrations in genes key to the DNA damage repair pathway (BRCA, CDK12, ATM) were found in 19% and 23% of primary PCs and mCRPC, respectively (Network, 2015; Robinson et al., 2015). Recently, Pritchard et al. confirmed that 82 (11.8%) of 692 men with mPC had at least one presumed pathogenic germline mutation in a gene involved in DNA-repair processes (Pritchard et al., 2016). Germline mutations in ataxia telangiectasia mutated (ATM) and BRCA1/2 are associated with earlier age at death, shorter survival time, and earlier relapse after local treatments in PC (Castro et al., 2015; Na et al., 2016). BRCA2 and BRCA1 also represent about 50% of all inherited mutations and these alterations are associated with higher risk of nodal involvement, distant metastasis, and poor survival outcomes (Castro et al., 2013). PARP are a family of enzymes involved in the recruitment of DNA repair effectors and modulate transcription processes (Deshmukh and Qiu, 2015). When DNA damage is repairable, PARP-1 recruits proteins involved in DNA repair, whereas when the damage is too severe, the same enzyme leads to cell death (Deshmukh and Qiu, 2015). PARP inhibitors are effective in cells with impairment of DNA repair genes (i.e. BRCA mutations) because of the so-called synthetic lethality. Single strand breaks induced by endogenous damages cannot be effectively repaired in the presence of PARP inhibitors (O'Connor et al., 2007); cells with functional homologous recombination are able to repair more genotoxic double strand breaks, but not BRCA 1 and 2 mutant cells, which undergo cell death (Mateo et al., 2015). Olaparib was the first PARP inhibitor tested in PC. The phase II study TOPARP-A assessed the antitumor activity of this drug in 49 patients who had received at least three lines of therapy for CRPC. Olaparib was well tolerated and led to response in 14 out of 16 patients who had defects in DNA-repair genes, included BRCA1/2, ATM, Fanconi's anemia genes, and CHEK2 (Mateo et al., 2015). Based on these results, the TOPARP-B study is ongoing to prospectively assess the activity of olaparib in patients with aberrations in DNA repair genes (Mateo et al., 2015;TOPARP, in press). PARP inhibition synergizes with AR targeted therapy in preclinical models (Brenner et al., 2011). This is the rationale of a phase II trial that was designed to evaluate the efficacy of veliparib, another PARP inhibitor, plus abiraterone acetate compared to abiraterone acetate alone in patients with mCRPC stratified basing on erythroblast transformation-specific (ETS) gene status; the preliminary results of this combination were presented at the 2016 ASCO Annual Congress (Hussain et al., 2016). Eighteen (27%) out of 153 randomized patients had homozygous deletions or deleterious mutations in genes involved in DNA repair, BRCA 1/2 and ATM included. The subgroup analysis revealed a better PFS in patients with DNA repair gene alterations as compared to those with an intact DNA-damage-repair system (13.5 months [95% CI: 8.2–NR] versus 5.8 months [95% CI: 4.2–8.2]). Other PARP inhibitors, as niraparib and rucaparib, are under investigation in two phase II (Galahad, TRITON 2) and one phase III (TRITON3) trials, respectively, which are enrolling patients with mCRPC with or without impairment of DNA repair genes An Efficacy, 2017 An Efficacy, in press A Study of Rucaparib, in press Study of Rucaparib, in press. DNA damaging agents, as carboplatin, satraplatin and topoisomerase inhibitors showed limited activity in unselected populations of patients with CRPC (Birtle et al., 2004; Buonerba et al., 2014; Klein et al., 2002; Sella et al., 2009; Sternberg et al., 2009). Nevertheless, retrospective analyses and spurious case reports support the notion that DNA defects might confer sensitivity to these treatments (Cheng et al., 2016; Kumar et al., 2016). For this reason, carboplatin monotherapy is considered an acceptable alternative for heavily pretreated CRPC patients, who harbor defects in DNA repair genes (Cheng et al., 2016). PARP inhibitors are suggested to enhance the antitumor activity of cytotoxic therapies and overcome acquired resistance to these drugs (O'Connor et al., 2007; Virag and Szabo, 2002). Veliparib was tested in association with temozolomide in a pilot study that enrolled pretreated patients with mCRPC. This combination was well tolerated, but showed limited activity in this unselected population (Hussain et al., 2014). Of note, dose-limiting hematological toxicity was reported when olaparib was combined with chemotherapy in patients with advanced solid tumors (Balmana et al., 2014; Rajan et al., 2012). Therefore, intermittent olaparib with reduced doses of cisplatin was suggested as an alternative combination to improve tolerability (Balmana et al., 2014). Further studies are warranted to assess the potential of PARP inhibitors in combination with cytotoxic agents. For example, olaparib enhanced the sensitivity of Ewing sarcoma bearing EWSR1-ETS fusions to trabectedin *in vivo* (Ordonez et al., 2015), and patients with CRPC who harbor ETS fusions might be suitable for this combination. EWSR1-ETS fusions mismatch repair (MMR) – deficient tumors appear to be more responsive to PD-1 blockade than MMR – proficient tumors (Le et al., 2015), therefore studies are also needed to assess the role of immunotherapy in the context of CRPCs with MMR alterations. Recently, the anti-PD-1 antibody durvalumab was investigated in combination with olaparib in a phase II trial which enrolled pretreated patients with mCRPC (Karzai et al., 2017). This combination was tolerable and led to PSA response in two out of six patients without BRCA mutation. In conclusion, many mCRPC patients harbor germline or somatic mutations in genes involved in DNA repair which might be predictive of response to DNA damaging agents or PARP inhibitors. Thus, DNA testing warrants clinical consideration in selected subsets of patients.

5. Cell-cycle pathway

Several signals (AR, PI3K-AKT, MAPK, Wnt) are integrated and processed by the cell-cycle regulatory machinery, which is responsible of cell division or quiescence (Balk and Knudsen, 2008; Cadoo et al., 2014). Four CDKs regulate the transitions from G2–M–G1–S phases, while the RB product is a critical inhibitor of transition from G1–S phase, preventing premature cell division (Weinberg, 2014). CDKs are responsible of retinoblastoma product (RB) phosphorylation and/or inactivation, allowing the cell to proceed or not with division. RB loss is reported in 21% of CRPCs and is also implicated in neuroendocrine differentiation of PC (Beltran et al., 2016b; Robinson et al., 2015; Tan et al., 2014). RB inactivation promotes the reprogramming of differentiated cells to a pluripotent state and this supports the notion that the selective pressure, induced by ARS inhibitors and chemotherapy, may

confer stemness-like features to PC cells (Ellis and Loda, 2015; Kareta et al., 2015). In addition, alterations in genes involved in CDKs regulation were reported in approximately 14% of CRPC samples (Robinson et al., 2015). All these alterations may be of clinical interest, because the use of CDK-inhibitors would prevent RB phosphorylation, repressing tumor cells proliferation and dedifferentiation (Knudsen and Wang, 2010). Palbociclib and ribociclib are CDK4/6 inhibitors effective in the treatment of advanced breast cancer (Finn et al., 2016; Hortobagyi et al., 2016; Turner et al., 2015). In PC, CDK4/6-specific inhibition reduced tumor proliferation both *in vivo* and in *ex vivo* primary human tumors (Comstock et al., 2013). Actually, a phase II study is evaluating the PSA response after treatment with palbociclib plus ADT, compared to ADT alone, in patients with RB-positive mPC REF: A Phase II Study of Androgen Deprivation, in press; a phase II study is also assessing the activity of this CDK inhibitor in an unselected population of CRPCs A Phase II Study of Palbociclib, in press. Ribociclib is under investigation in a phase Ib/II trial, that evaluates the PSA response of ribociclib plus enzalutamide compared to enzalutamide alone in chemotherapy-naïve mCRPC that retains RB expression Enzalutamide, in press.

6. Developmental pathways

Processes occurring during tumorigenesis are intimately connected with those observed during embryogenesis and organogenesis (Aiello and Stanger, 2016). Wnt, ERG, YAP/TAZ, Hh, and Notch are key regulators of early development and are also found to be deregulated in PC. These pathways might thus represent potential therapeutic targets for the treatment of this neoplasm.

6.1. Wnt pathway

The Wnt pathway is altered in 18% of patients with mCRPC (Robinson et al., 2015). The Wnt proteins direct cell proliferation and polarity as well as determine a wide range of embryonic patterning events (Sharma et al., 2015). Wnt pathway also promotes EMT-like changes and regulates the expression of factors that are relevant to metastatic progression, notably metalloproteinases and other regulators of the ECM (Anastas and Moon, 2013). In prostate, paracrine Wnt signaling is involved in the interactions between stromal and epithelial cells induced by transforming growth factor-beta (TGFβ), modulating androgen sensitivity of epithelial cells (Placencio et al., 2008). In the absence of Wnt ligands, β-catenin is recruited into a destruction complex, comprised of adenomatous polyposis coli (APC) and axin, which induces the phosphorylation of β-catenin by casein kinase 1 and glycogen synthase kinase 3. After activation of the Wnt canonical pathway, β-catenin escapes proteasomal degradation, accumulates in the cytoplasm and subsequently translocates to the nucleus, where it activates the transcription of Wnt target genes (Lai et al., 2009). R-spondins potentiate Wnt ligand activity as either coactivators or inhibitors of Wnt signaling receptor degradation (Jin and Yoon, 2012). Recurrent alterations of APC, β-catenin and R-spondin are observed in mCRPC patients (Robinson et al., 2015), supporting the role of this pathway in PC progression. The term non-canonical Wnt pathway has been used in the literature to refer to Wnt-activated signal transduction independent of β-catenin stabilization (Lai et al., 2009). β-Catenin-independent Wnt pathways have been proposed to regulate cell polarity and migration, including metastasis (Lai et al., 2009). The RNA-Seq of single prostate circulating tumor cells (CTCs) suggested the strong involvement of non-canonical Wnt signaling in antiandrogen resistance (Miyamoto et al., 2015) and the suppression of its key downstream components, such as Rho kinase, restored partial sensitivity to antiandrogen therapy *in vitro* (Rath and Olson, 2012). Ursolic acid, a Wnt inhibitor, exerted *in vitro* antitumor activity and has also been suggested as a chemotherapeutic agent in PC patients (Park et al., 2013). Other studies showed that Mesd, a LRP5/6 co-receptor inhibitor, effectively inhibits PC cells proliferation (Lu et al., 2010) and neutralizing antibodies to Wnt3a reversed PC cells tumorigenesis (Li et al., 2008). Some polyphenols, such as quercetin, epigallocatechin-3-gallat, curcumin and resveratrol, limited PC cell proliferation in *in vitro* models acting on Wnt signaling; however, their potential clinical implication is controversial (Jasinski et al., 2013). Non-steroidal anti-inflammatory drugs, such as sulindac and celecoxib block the Wnt signaling, decreasing nuclear compartmentalization or enhancing localization of β-catenin to the plasma membrane (Clapper et al., 2004; Lu et al., 2009). Clinical trials investigated the efficacy of celecoxib and sulindac in combination with chemotherapy in unselected populations of patients with CRPCs, but these drugs did not add any benefit to chemotherapy alone (Carles et al., 2007; Kattan et al., 2016; Ryan et al., 2005; Sinibaldi et al., 2006). Small-molecule therapeutics or even biologics that target the Wnt pathway are still in their infancy and therefore further studies are warranted to understand the potential anti-tumor activity of Wnt pathway inhibition (Kahn, 2014).

6.2. TMPRSS2/ERG and Hippo pathway

In 2005, Tomlins et al. reported a recurrent chromosome rearrangement in PC, involving the genes TMPRSS2, localized on chromosome 21q23.2, and ERG, an ETS-related gene localized on chromosome 21q22.2 (Tomlins et al., 2005). Subsequently, the SU2C-PCF International Dream Team confirmed that TMPRSS2/ERG fusion, resulting in ERG overexpression, is observed in about 40% of advanced PC (Robinson et al., 2015). ERG protein is involved in embryonic development, vascular integrity, cell proliferation, and apoptosis (Han et al., 2015). Several studies investigated the predictive and prognostic role of this aberration in PC. TMPRSS2/ERG fusion was found in peripheral blood mononuclear cells from patients with mCRPC and was associated with resistance to docetaxel and worse prognosis (Reig et al., 2016). Attard et al. suggested that the presence of TMPRSS2/ERG rearrangement in CTCs of mCRPC patients may be predictive of sensitivity to treatment with abiraterone (Attard et al., 2009); in contrast, Danila et al. did not find a correlation between TMPRSS2/ERG status in CTCs and response to abiraterone (Danila et al., 2011). PARP enzymes are necessary for ERG-mediated PC progression and ETS fusion-positive xenografts were shown sensitive to PARP inhibitors *in vitro* (Brenner et al., 2011). Upon this basis, a phase II trial is evaluating the efficacy of abiraterone plus veliparib compared to abiraterone alone in men with mCRPC stratified for the presence or absence of the TMPRSS2-ERG fusion Abiraterone, in press. Unfortunately, the preliminary results of this trial presented at the 2016 ASCO Annual Congress (Hussain et al., 2016) do not suggest that TMPRSS2-ERG fusion is predictive of response to this combination. Given the supposed sensitivity of TMPRSS2-ERG tumors to histone deacetylase inhibitors (Iljin et al., 2006), a phase II trial evaluated the efficacy of pracinostat in an unselected population of 32 CRPC patients (7/21 evaluable patients presented TMPRSS2/ERG fusion), but this drug showed limited activity in this setting of patients (Eigl et al., 2015). Celastrol, a NF-kB inhibitor, was effective in reducing the growth of TMPRSS2/ERG expressing PC *in vitro* and *in vivo* (Shao et al., 2013), but currently no clinical trial testing this drug is planned. Recently, Nguyen et al. demonstrated that ERG activates the YAP transcriptional program and induces the development of age-related prostate tumors in mouse models (Nguyen et al., 2015). This result provided direct genetic evidence of a causal role for ERG in PC and revealed a connection between ERG and the Hippo signaling pathway. YAP and TAZ, the main effectors of the Hippo pathway, can reprogram cancer cells into cancer stem cells and incite tumor initiation, progression and metastasis (Piccolo et al., 2014; Zanconato et al., 2016b). TAZ also serves as a downstream element of the Wnt pathway (Azzolin et al., 2012). These transcriptional regulators are transducers of cellular structural features, such as polarity, shape and cytoskeletal organization. In turn, these features are strictly connected to the cell's location in within the tridimensional architecture of tissues, including the

attachment to other cells and to the ECM (Zanconato et al., 2016b). First reports in 2007 showed that PC tissues have significant elevation of YAP protein levels and these data are confirmed by *in vitro* studies (Sheng et al., 2015; Zhang et al., 2015; Zhao et al., 2007). Tankyrase inhibitors, statins, bisphosphonates, geranylgeranyl transferase-1 and G-proteins inhibitors are suggested as modulators of YAP/TAZ pathway (Zanconato et al., 2016a); however, the pharmacological inhibition of this pathway remains challenging, as many interactions specifically involved in the control of YAP/TAZ activity may be difficult to target (Zanconato et al., 2016a).

6.3. Hh and Notch pathways

Hh signaling, as well as Wnt pathway, is suggested to modulate stem cells characteristics (Kalderon, 2002; Taipale and Beachy, 2001). In PC, Hh cascade regulates epithelial–mesenchymal interactions, cell survival, angiogenesis and metastatic potential of cells (Karhadkar et al., 2004). Antonarakis et al. evaluated the efficacy of high-dose itraconazole, an Hh pathway inhibitor, in men with metastatic chemotherapy-untreated CRPC; this drug showed modest clinical activity, as suggested by longer PFS times than in historical data (Antonarakis et al., 2013). TAK-441 and vismodegib are selective Smo antagonists and delayed progression of PC *in vivo* models, by disrupting paracrine hedgehog signaling (Ibuki et al., 2013; Karlou et al., 2012); some trials are ongoing to assess the efficacy of vismodegib in men with CRPC Leuprolide, in press A Study of Vismodegib, in press. Also, two small-molecule antagonists of Hh pathway inhibithed PC proliferation in *in vitro* and *in vivo* models, but no clinical application has yet been tested (Lauth et al., 2007). Notch signaling is another developmental pathway, which regulates organogenesis, cell death and tissue homeostasis (Su and Xin, 2016). Notch synergizes with several pathways, as AKT, Wnt, Ras/Raf/MAPK, and contributes to the development and progression of PC (Stoyanova et al., 2016). Both tumor suppressive and oncogenic roles of Notch have limited the investigation of Notch inhibitors for PC and probably more studies are needed to understand the therapeutic potential of this signaling pathway (Su and Xin, 2016; Yuan et al., 2015).

7. Neuroendrocrine differentiation

Neuroendocrine differentiation of PCs is estimated to drive approximately 25% of the nearly 34,000 cases of lethal PC in the United States per year (Jemal et al., 2011). Divergent clonal evolution from one or more CRPC adenocarcinoma cells has been suggested as the main mechanism of development of NEPC (Beltran et al., 2016b). With the growing clinical use of ARS inhibitors, a subset of resistant tumors shows reduced or absent AR expression and small-cell carcinoma or neuroendocrine features (chromogranin A, synaptophysin and neural cell adhesion molecule) on metastatic biopsy (Beltran et al., 2011; Palmgren et al., 2007; Watson et al., 2015). Molecular profiling of NEPC has revealed loss of RB1, PTEN and tumor protein p53 (p53) mutations as well as amplification of MYCN and AURKA (Beltran et al., 2011; Tan et al., 2014). Unfortunately, the development of NEPC is associated with a poor survival of patients due to lack of effective treatments available (Mosquera et al., 2013). Based on the clinical efficacy observed in neuroendocrine lung cancer, the use of platinum-based chemotherapy has been suggested in NEPC; however, this treatment strategy is characterized by a high response rate of short duration (Aparicio et al., 2013). Recently, Beltran et al. evaluated the activity and safety of alisertib, an AURKA inhibitor, in a phase II study, that enrolled 59 patients with metastatic NEPC (Beltran et al., 2016a). Based on the previously developed integrated 70-gene NEPC classifier (Beltran et al., 2016b), they showed high correlation of molecular alterations (AURKA/MYCN, AR signaling, RB1/TP53) with clinical-pathological features and exceptional responders. Although the trial did not meet its primary endpoint, which was PFS, the authors concluded that a specific subset of patients with clinical-pathologically defined NEPC may benefit from alisertib monotherapy. MYCN levels are regulated by bromodomain and extra-terminal proteins (BET) proteins and the BET inhibitors were effective in reducing the growth of CRPC *in vitro* and *in vivo* (Asangani et al., 2014; Wyce et al., 2013). In addition, BET inhibitors were recently shown to enhance the efficacy and disrupt resistance to AR antagonists in CRPCs, providing a compelling rationale to combine BET inhibitors with AR antagonists in clinical trials (Asangani et al., 2016).

8. Tumor microenvironment and immunotherapy

Normal tissue homeostasis and architecture physiologically inhibit cancer development and progression; therefore, tumor expansion and dissemination assumes an impaired control of all those transcriptional regulators that are modulated by a complex interchange of information among cells in the local microenvironment (Bissell and Hines, 2011). The ECM provides not only architectural support, but also chemical and mechanical cues to cells; several proteins (i.e. periostin, tenascin-C, versican), growth factors (i.e. TGFβ, epidermal growth factor, vascular endothelial growth factor, hepatocyte growth factor), interleukins as well as ECM stiffness influence the tumor microenvironment (Barron and Rowley, 2012; Bonnans et al., 2014; Nuzzo et al., 2014; Pickup et al., 2013). All these factors modulate PC cell proliferation and induce EMT through multiple signals, including the JAK-STAT, the SMAD, the MAPK and the PI3K pathway (Nguyen et al., 2014; Pickup et al., 2013). The serum levels of interleukin-6 and TGFβ are associated with PC progression, metastases and poor survival of patients (Shariat et al., 2004; Shariat et al., 2011). These markers are surrogated of chronic inflammation and a potential link between prostatitis, prostatic infections and the development of PC was suggested (Sfanos and De Marzo, 2012). Differently from melanoma and other neoplasms, which show high rates of somatic mutations and are considered good targets for immunotherapy, the mutational load of PC cells has been historically considered low (Schumacher and Schreiber, 2015). However, growing evidence suggests that mCRPC show higher mutational load compared with primary tumors (Drake, 2010; Robinson et al., 2015; Taylor et al., 2010). Many immunotherapy approaches share the common goal of inducing a specific T-cell response directed against the tumor cells and reversing their resistance to adaptive immunity (Drake, 2010; Ribas, 2015). The first successful achievement in PC immunotherapy was the development of Sipuleucel-T. This cell-based vaccine was approved in 2010 by the U.S. Food and Drug Administration for the treatment of mCRPC, given a 4-month OS improvement reported in the phase III trial IMPACT, which randomized 512 patients with mCRPC in a 2:1 ratio to receive either Sipuleucel-T or placebo (Kantoff et al., 2010). Based on this, Sipuleucel-T is widely included among the treatment options for patients with minimally symptomatic or asymptomatic mCRPC NCCN, 2017. Nevertheless, the Society for Immunotherapy of Cancer underscores that there is still no absolute consensus on the utilization of Sipuleucel-T regarding several aspects, including sequencing immunotherapy with other treatments and monitoring of response, and that recommendations still need to be improved (McNeel et al., 2016). In particular, in an era when several new ARS inhibitors are becoming increasingly available for the treatment of mCRPC, an interesting challenge will be to fit the use of Sipuleucel-T in the most appropriate temporal frame over the disease course, and to select the optimal subset of patients that may derive a greater benefit from it. Moreover, even though a direct cost comparison with other agents is difficult, especially over the complete course of treatment, Sipuleucel-T represents an expensive option. Some other vaccines achieved promising results in mCRPC patients in phase I/II trials, with mild side effects, and many others are currently under investigation (Cattrini et al., 2016). For example, the randomized, phase III trials VIABLE Phase III, in press and PROSPECT Randomized and Double-blind, in press are ongoing to evaluate the efficacy and safety of a dendritic-cell based vaccine

(DCVAC/PCa) and of a vector-based vaccine (PROSTVAC), respectively, in men with mCRPC eligible for first-line chemotherapy. Even though initial phase I/II trials showed promising results with the use of the anti-CTLA-4 antibody ipilimumab (Cha and Small, 2013), a randomized phase III trial failed to show an OS benefit when this agent was used alone for patients with mCRPC in the post-docetaxel setting (Kwon et al., 2014). Nevertheless, in a retrospective subgroup analysis of this study, OS was 22.7 months among a small cohort of ipilimumab-treated patients with favorable prognostic features (namely, patients with non-visceral disease, alkaline-phospatase < 1.5 times the upper limit of normal and hemoglobin of at least 11.5 g/dL) as compared to 15.8 months in the placebo group. Also, ipilimumab did not improve OS in patients with chemotherapy-naive mCRPC in a phase III trial that enrolled 598 patients to receive ipilimumab or placebo (2:1) (Beer et al., 2016). Two phase I trials evaluated the activity of the anti-PD-1 antibody nivolumab as a single agent in heavily pre-treated advanced malignancies, but failed to show objective responses in the PC cohort (Brahmer et al., 2010; Topalian et al., 2012). The Keynote-028 Study was designed to evaluate the safety and efficacy of the anti-PD-1 pembrolizumab monotherapy in PD-L1-positive advanced solid tumor cohorts (Hansen et al., 2016). The preliminary results from the PC cohort of this phase 1b study (23 patients) reported an ORR of 13%, but 45% of evaluable patients had a decrease from baseline in the sum of longest diameters of target lesions. Exploratory assessment of the relationship between gene expression profile score and clinical outcome revealed the putative T cell inflamed signature to be associated with better clinical outcome (Hansen et al., 2016). Bishop et al. observed that resistance to enzalutamide is associated with the strong expression of anti-PD-1 therapy targets in circulating immune cells both in mCRPC patients and in pre-clinical models (Bishop et al., 2015). On this basis, Graff et al. treated 20 mCRPC patients who progressed on enzalutamide with pembrolizumab 200 mg IV every 3 weeks for 4 doses (Graff et al., 2016a); of note, pembrolizumab was added to and did not replace the standard dose of enzalutamide. 20% of patients (4/20) showed remarkable long-lasting PSA responses and 35% (7/20) had stable disease ranging 9-50 weeks (Graff et al., 2016b). *In vitro* studies support that ADT may sensitize prostate cancer cells to T-cell killing through androgen receptor dependent modulation of the apoptotic pathway (Ardiani et al., 2014). These clinical data confirm that primary and secondary ADT may stimulate T cell infiltrates, synergizing with immunotherapeutics. In addition, the genetic analysis of two responders revealed markers of microsatellite instability in one patient, suggesting that patients with DNA repair genes alterations may also be candidates to these treatments (Graff et al., 2016b). Recent data also revealed that bone metastases from PC, with low AR expression and reduced metabolic activity, show high MHC class I expression and immune cell infiltration; this supports the rationale for treating specific PC patients with combinations of ADT and immunotherapy (Ylitalo et al., 2016). In conclusion, to date there are no prospective data to support monotherapy with either an anti-CTLA-4 or anti-PD-1 agents in patients with mCRPC. However, these immunotherapeutics appear to be effective in specific subgroups of patients; probably, the identification of synergies with ARS inhibitors or other drugs, as well as their correct implementation in the sequence of agents currently used in CRPC, may uncover unexpected potentialities of these new compounds. This notion is guiding the experimental design of new trials, such as the Keynote-199 study, which is recruiting 250 men with mCRPC to assess the activity of pembrolizumab in patients previously treated with chemotherapy Study of Pembrolizumab, in press; this study has three planned cohorts: participants with PD-L1-positive, measurable disease; participants with PD-L1 negative, measurable disease; participants with bone-metastases, non-measurable disease. The discovery of novel biomarkers of response may also help the selection of those cases candidates for immunotherapy.

9. Conclusions

The majority of treatments that are currently used in clinical practice to treat patients with PC modulate the ARS pathway. The increased heterogeneity, phenotypic plasticity, and genomic variability of PC cells in the setting of advanced disease are frequently responsible of resistance to treatment. Several studies suggest that AR is still activated after progression on AR-directed therapies and that it still plays a role in advanced and heavily pretreated CRPC. However, many pathways, both AR related and non-AR related, can contribute to progression of CRPC. In some cases, AR-independent pathways provide sustenance for the growth of aggressive tumor cells with high metastatic potential. Many non-AR-directed drugs have been tested in CRPC, mostly as monotherapy or in unselected populations of patients, and studies yielded conflicting results. Predictive markers of response are therefore needed to avoid the failure of future trials, and to properly select patients that would most likely benefit from non-AR-targeted therapies. For example, in the years to come, liquid biopsies might help identify these subsets of patients, offering new therapeutic opportunities for those with poor baseline prognostic features or primary as well as acquired resistance to hormone-therapies. In addition, studies evaluating combinations of ARS modulators or chemotherapy with compounds that target AR-independent pathways may provide new insight on the treatment options for both early and advanced PC.

Conflicts of interest statement

The authors declare no conflicts of interest.

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