

# A second opportunity to come for anti-angiogenics in prostate cancer?

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*comment on:* Michaelson MD, Oudard S, Ou YC, et al. Randomized, placebo-controlled, phase III trial of sunitinib plus prednisone versus prednisone alone in progressive, metastatic, castration-resistant prostate cancer. *J Clin Oncol* 2014;32:76-82.

**Abstract:** Similar to the previous experience combining the anti-angiogenic agent bevacizumab with docetaxel, the use of sunitinib and prednisone (as compared to placebo and prednisone) did not result in prolongation of overall survival in patients with metastatic castration resistant prostate cancer (mCRPC) who had failed one previous docetaxel-based regimen. However, both progression-free survival (PFS) and response rate were significantly improved. Possible explanations to these findings and strategies to optimize the clinical application of anti-angiogenics in prostate cancer are discussed.

**Keywords:** Angiogenesis inhibitors; prostate cancer; sunitinib

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Better understanding of the biology of advanced prostate cancer has led to unprecedented progress in its therapy over the past few years. The androgen biosynthesis inhibitor abiraterone acetate, the androgen receptor (AR) antagonist enzalutamide, the cytotoxic chemotherapeutics docetaxel and cabazitaxel, the immunotherapeutic sipuleucel-T and the alpha particle-emitting radiopharmaceutical radium-223 have all been shown to extend survival (OS), and in some cases provide symptomatic improvement in phase III clinical trials in patients with metastatic castration resistant prostate cancer (mCRPC) (1-7). While androgen signaling inhibitors and chemotherapy primarily target tumor cells, the effects of radium-223 and particularly sipuleucel-T are likely mediated in part by modulation of the tumor microenvironment, including immune and other stromal cell constituents of the primary tumor and metastatic sites. Thus, targeting components of the microenvironment in prostate cancer can meaningfully affect the rate of cancer progression and survival outcomes.

Tumor growth is often critically dependent on its ability to sustain an adequate blood supply, which, to a different degree depending on cancer type and state, is facilitated

by newly developed blood vessels through the process known as tumor angiogenesis. Anti-angiogenic drugs were developed to “starve” tumors by primarily affecting tumor-associated blood vessels. These agents have been mostly designed to inhibit vascular endothelial growth factor (VEGF) signaling, a key mediator of tumor angiogenesis. Several VEGF-targeted drugs (the anti-VEGF monoclonal antibody bevacizumab, the synthetic VEGF trap aflibercept, and the multi-tyrosine kinase inhibitors (VEGFR TKI) sorafenib, sunitinib, pazopanib, axitinib, vandetanib, cabozantinib and regorafenib) have been approved as single agents for solid tumors such as some that respond poorly to conventional chemotherapy (e.g., advanced renal cell, pancreatic neuroendocrine, medullary thyroid and hepatocellular carcinomas), and also in combination with chemotherapy (8). However, the results of controlled clinical trials using anti-VEGF therapies in prostate cancer have so far been disappointing.

A few VEGF inhibitors have been tested in combination with standard first-line docetaxel-based chemotherapy in mCRPC. In phase II clinical trials, bevacizumab and sunitinib showed seemingly modest additional activity

when combined with docetaxel (9,10). Yet neither bevacizumab nor aflibercept in combination with docetaxel and prednisone led to improvement in OS as compared with docetaxel and prednisone alone in respectively the CALGB 90401 and VENICE phase III clinical trials, even though bevacizumab resulted in extension of progression-free survival (PFS) and a higher rate of objective responses (ORR) (11,12).

As single agents, sorafenib, sunitinib, and cediranib (a separate VEGFR TKI) showed noticeable but limited activity in phase II studies, both in chemotherapy-naïve patients and after progression to docetaxel (13-16). Interestingly, responses (in pain and scans) were frequently discordant with changes in PSA, which tended to increase during treatment (4 weeks on, 2 weeks off schedule) and drop off it (17). Some of those early trials were designed using PSA response as the primary endpoint, leading to early study closure. Bevacizumab monotherapy, however, did not show clinical activity in mCRPC (18).

Marc Dror Michaelson *et al.* recently published the results of the international phase III trial of sunitinib plus prednisone versus placebo plus prednisone in patients with progressive mCRPC (SUN 1120) (19). Different to the CALGB and VENICE studies above, sunitinib was used as mainstay treatment without chemotherapy, and following failure of one previous docetaxel-based regimen. Patients (n=873) were randomly assigned 2:1 to receive the study drug or placebo continuously in combination with oral prednisone. OS, the primary endpoint, did not differ significantly between treatment arms (13.1 *vs.* 11.8 months respectively for sunitinib and placebo,  $P=0.168$ ), leading to early termination of the trial after a second interim analysis on the basis of futility. Sunitinib was however comparatively better in secondary endpoints, such as PFS (5.6 *vs.* 4.1 months,  $P\leq 0.001$ ) and ORR in patients with measurable disease (6% *vs.* 2%,  $P=0.04$ ). Also to note, the rate of discontinuation of sunitinib before objective disease progression was an important 37%, mostly due to toxicity but also to a high censoring rate from patient termination before disease progression in relation to the early study closure. How the interpretation of PSA raises by the treating oncologists may have influenced their evaluation of response and thus the study results was not formally evaluated.

Together, the data from the sunitinib and the docetaxel and bevacizumab/aflibercept combination phase III trials strongly suggest that there is no general role for limited anti-VEGF therapies in patients with mCRPC, either alone

or in combination with docetaxel. The clinical experience suggests that the multi-targeted TKI, particularly sunitinib, are more active in mCRPC than the VEGF ligand blocking drugs as single agent, and that only subsets of individuals seem to obtain benefit. Important challenges therefore remain. What characterizes the disease of the responsive patients? And at what point in the natural history of the disease are anti-angiogenics most beneficial? In the current state of knowledge, the answer to neither question is obvious. In spite of the established relevance of angiogenesis in tumorigenesis, prostate cancer is characterized by a dominance of androgen signaling-related evolutionary and adaptive changes in its castration resistant progression. How each of those changes alters the balance of pro- and anti-angiogenic drivers in the microenvironment and the host, and in the end the relative contribution of tumor angiogenesis through prostate cancer progression remain poorly depicted in patients. Moreover, the consistent tropism of prostate cancer for bone and the inherent difficulty in reliably evaluating disease and treatment-related changes in the osseous environment make this characterization particularly challenging.

Still, it is speculative but probable that a subset of mCRPC patients exist in whom angiogenic mechanisms of progression are important, thus potentially rendering them more responsive to angiogenesis inhibition. For instance, an estimated 10-20% patients treated with sunitinib demonstrate sometimes dramatic bone scan responses, although the translation of these findings into survival outcomes is not available (20). Moreover, the biology of the disease in specific metastatic sites may rely heavily on angiogenesis. This could be the case of lymph nodes, which are the most frequent site of measurable metastasis in mCRPC patients. Both the CALGB 90401 and SUN 1120 studies demonstrated significant improvements in ORR compared to control (11,19).

Regarding timing for application, the limited existing data for bevacizumab and sunitinib in castration sensitive patients (mostly with high-risk prostate cancer) do not suggest that early introduction of VEGF-targeted therapy results in meaningfully better outcomes than in the castration resistant phase, at least in what concerns the primary disease site. However, even complete pathologic responses occur in rare cases (21), suggesting that angiogenesis inhibition can be useful in treating prostate cancer patients.

So what are the possible venues to improve the efficacy of these agents? An obvious one is the definition of

predictive molecular and/or genetic markers that enrich for microenvironmental dependence on angiogenesis. Years of research in the field of biomarkers have not yet resulted in the identification of any prospectively validated molecular or cellular surrogate of anti-angiogenic treatment benefit in prostate or any other cancer type. Because of the limited relevance of animal models in prostate cancer and the disease's inherent heterogeneity, information should originate from characterization of angiogenesis mediators in clinical specimens serially obtained from individual patients. Another comes from the development and application of multi-targeted drugs or combinations that block pathways complementary to VEGF in driving angiogenesis and metastatic progression, or mechanisms of adaptive resistance to angiogenesis inhibition. A very relevant even if *a priori* unexpected example of this comes from cabozantinib, which inhibits VEGFR and the hepatocyte growth factor (HGF) receptor potently and can result in striking radiologic and pain-relieving responses in mCRPC (22). HGF receptor has been shown to participate in escape from VEGFR inhibition (23) and mediate cross-talk signaling between prostate cancer and host cells in bone metastasis (24). Not surprisingly, cabozantinib is being evaluated as single agent in phase III clinical trials in mCRPC. Combinations of anti-angiogenics with immune and bone metastasis modulatory drugs may also prove useful.

Last is the issue of toxicity, which is quite relevant because mCRPC patients are generally older and more comorbid than those with other tumor types. In CALGB 90401, the number of treatment-related deaths (4% *vs.* 1.2%) was greater in the experimental bevacizumab arm (11). In SUN 1120, 27% patients abandoned sunitinib therapy because of toxicity before progression, probably affecting the OS results (19). Studies have shown that sudden discontinuation of anti-angiogenic treatment may result in "rebound" production of potentially tumor supportive pro-angiogenic factors. Therefore, it may be useful to sustain or even expand angiogenesis inhibition to other relevant targets beyond disease progression (8). Eight percent of the patients in SUN 1120 had their sunitinib dose escalated, resulting in no apparent effect on clinical outcome. Whether more conservative and thus less toxic doses and schedules than those used in cancers more dependent on angiogenesis would be sufficient to achieve anti-tumor effect in prostate cancer has not been formally tested and warrants consideration.

In spite of so far limited effectiveness and significant toxicity and cost, the available data suggests that angiogenesis

inhibition should still be considered a potentially useful strategy for the treatment of prostate cancer. Upcoming clinical trials should be based on rational combinations that include potent but narrow in spectrum (and thus likely less toxic) angiogenesis inhibitors, targeting only specific prostate cancer patient subsets and clinical states. The hope is that next generation profiling technologies soon result in better understanding of the driver genetic and molecular networks in prostate cancer, allowing for optimization of the use not only of angiogenesis inhibitors but of all other treatment options for the welfare of the patients.

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