sarcomatous transformation because the investigators believed they had been misdiagnosed with giant cell tumour of bone at baseline. This unplanned adjudication eliminated three-quarters of the cancers in which the drug was either associated with sarcoma development or should never have been used. This fact is sobering. Even a small increase in the frequency of this complication alters the risk-benefit ratio of denosumab and changes the preferred treatment from drug therapy to surgery. Thorough genetic testing of tumour samples is essential to characterise these controversial cases, and ongoing post-marketing surveillance is needed to fully understand the phenomenon of sarcomatous transformation.

Worryingly high incidences of local recurrence have been reported for intralesional surgery after preoperative denosumab therapy. In difficult-to-treat cases, such as pelvic and sacral giant cell tumour, recurrence rates as high as 62% have been reported.[3] Notably, these results were from the Rizzoli Orthopedic Institute (Bologna, Italy) and the Royal National Orthopaedic Hospital (Birmingham, UK): both centres that contributed patients to the Chawla and colleagues trial.[1] These results raise questions about how effective the drug will be when used outside the structure of a clinical trial.[6]

Important questions remain unanswered regarding the disease and its treatment. What is the origin of the disease? What is its natural pathophysiology and method of control? How does the immune response modify the tumour's behaviour? What is the best way to assess response to treatment (Response Evaluation Criteria in Solid Tumours [RECIST], Choi criteria, or the Rizzoli CT system)? What is the true likelihood of local recurrence? Is there more frequent recurrence after denosumab treatment, as uncontrolled reports suggest?[6] Should the drug be used postoperatively, and for how long? What dose modification is acceptable and effective? Does combined drug therapy help, and what is the optimal method for a drug such as preliminary use of denosumab for 3 months then use bisphosphonates. Is there an increased risk of malignant transformation associated with denosumab? How should patients be monitored on long-term therapy?

Chawla and colleagues[1] show that we can now use denosumab with confidence and start to address these remaining unanswered questions. Hopefully, enough investigator, corporate, and scientific community support exists to obtain clinical answers for patients. Therapies targeting the spindle cell perpetrators of disease and not just the accompanying monocytic or giant cells might be even more effective than treatment with denosumab.

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This work is supported in part by institutional core grant support from NIH P30 CA008748. I declare no competing interests.

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Androgen receptor-targeted agents in the management of advanced prostate cancer

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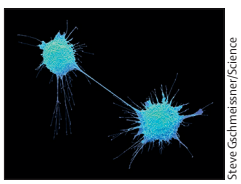
Since 2010, the prostate cancer treatment landscape has been profoundly modified by the introduction of eight agents: four hormone treatments (abiraterone acetate, apalutamide, enzalutamide, and darolutamide), two chemotherapy drugs (docetaxel and cabazitaxel), the α-emitter radionuclide radium, and sipuleucel-T (a vaccine available only in the USA). These molecules were all approved within a few years of each other in parallel trials, creating a complicated conundrum: when should patients be given these drugs, in what sequence, and—most importantly—can we ascertain that their efficacy remains unchanged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when used after another agent that improves overall survival?

Because they are well tolerated and orally available agents, enzalutamide and abiraterone have become the cornerstone first-line treatment for early asymptomatic metastatic castration-resistant prostate cancer (mCRPC).[1] There has been an intense commercial battle between pharmaceutical companies about which drug should be used for first-line treatment and which one is the most effective and most well tolerated.

Although four other different class of agents are available, switching between enzalutamide and abiraterone, or the opposite sequence, has become a standard second-line treatment strategy.[2] Although the molecules both target the androgen receptor axis, they do so in a slightly different manner, such that the combination of abiraterone and enzalutamide was initially even postulated to have a synergistic effect.[3] To test this theory, several combinations trials were done, but instead of confirming any synergistic effect, the trials showed a very high level of cross resistance between abiraterone and enzalutamide.[4] However, despite compelling evidence for cross resistance, sequencing drugs targeted at androgen receptors remains very popular.

In *The Lancet Oncology*, Daniel F Khalaf and colleagues[5] provide important insights into the best second-line hormone treatment for the management of advanced prostate cancer and the added value of a back-to-back hormone sequence. The authors randomly assigned 202 patients who had never previously been treated with androgen receptor-targeted agents to receive either abiraterone plus prednisone until prostate-specific antigen progression followed by crossover to enzalutamide (group A; n=101), or the opposite sequence (group B; n=101).

Time to second prostate-specific antigen progression, was longer in group A than group B (median 19·3 months [95% CI 16·0–30·5] *vs* 15·2 months [11·9–19·8]; hazard ratio 0·66, 95% CI 0·45–0·97, p=0·036). Additionally, prostate-specific antigen responses were almost nine times more frequent in the abiraterone followed by enzalutamide group than in the enzalutamide followed by abiraterone group (26 [36%] of 73 patients in group A *vs* three [4%] of 75 in group B). Do these data definitively consecrate the abiraterone followed by enzalutamide sequence as the new standard of care for patients with early metastatic castration-resistant prostate cancer, under the assumption that patients have no contraindication to either of the two drugs?

Unfortunately, such a conclusion cannot be drawn. First, although time to second prostate-specific antigen progression was longer in group A than group B, overall survival was not significantly different between the groups. Moreover, the choice of whether to give abiraterone or enzalutamide as the first drug in the treatment sequence is mainly influenced by relative contraindication, as suggested during the 2017 Advanced Prostate Cancer consensus conference.[1] Abiraterone was recommended by experts for patients with stable brain metastases, history of falls, baseline-significant fatigue, or neurocognitive impairment; whereas enzalutamide was recommended in case of diabetes requiring prescription drug therapy, cardiac ejection fraction below 45–50%, or active liver dysfunction.

Khalaf and colleagues' results[5] confirm that the benefit of second-line treatment with either hormone is somewhat trivial in terms of prolonging time to second prostate-specific antigen progression, with the time difference benefit ranging from a few weeks to a few months. Therefore, the question remains of whether or not it is worth giving abiraterone after enzalutamide (or vis versa), in view of the high price of the drugs and, more importantly, the availability of other drugs.

The study[5] should be read in the context of two other trials. In the CARD trial,[6] patients progressing on abiraterone or enzalutamide received the alternative agent or cabazitaxel. Second-line treatment with cabazitaxel plus prednisone improved progression-free survival by 4·3 months and overall survival by 2·6 months compared with second-line abiraterone or enzalutamide treatment (depending on which one patient received first) in patients who had progressed after previous docetaxel treatment and within 10 months of first-line biraterone or enzalutamide treatment.[6] In CARD, most patients ultimately received the two remaining alternative treatments, the second adrogen receptor pathway inhibitor or cabazitaxel. A third of the patients received cabazitaxel at progression in the hormone group, thus suggesting that the timing of chemotherapy is important. In the Profound trial,[7] the poly (ADP-ribose) polymerase

inhibitor olaparib improved median progression-free survival by 3·84 months and median overall survival, at interim analysis, by 3·39 months versus a second hormone (abiraterone or enzalutamide) in patients with selected DNA repair mutations whose prostate cancer had progressed after treatment with a first hormone.[7]

Although the trial by Khalaf and colleaugus[5] showed that a second-line inhibitor can be beneficial, the results from the trial should encourage physicians to switch between different agents such hormone and chemotherapy at least in selected patients, and avoid prescribing back-to-back hormones in a sequence in the metastatic castration-resistant prostate cancer setting.

The question of what sequence to give the drugs in is becoming even more important now that androgen receptor-targeted agents are used early on in treatment for newly diagnosed metastatic prostate cancer and in non-metastatic, castration-resistant prostate cancer. Many of these patients will receive first-line therapy with an androgen receptor-targeted agent before progressing. Although speculation is difficult, it is highly plausible that back-to-back hormonal treatment will soon be shown to have limited benefit in this setting and more effective alternative treatments will be needed. An urgent need exists to gather more data for other drugs that are less dependent on the androgen receptor pathway than enzalutamide and abiraterone.

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BT reports grants from Astellas, Bayer, and Janssen, during the conduct of the study; personal fees from Astellas, Sanofi-Genzyle, Bayer, and Janssen, during the conduct of the study; grants from Ferring, outside the submitted work; and personal fees from Ferring and Amgen, outside the submitted work.

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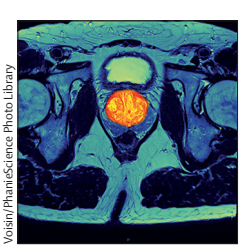
Post-operative salvage androgen deprivation and radiotherapy for prostate cancer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Published Online October 16, 2019 https://doi.org/10.1016/S1470-2045(19)30488-7
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In *The Lancet Oncology*, Christian Carrie and colleagues[1] provide updated data, at a median follow-up of 9·33 years (as compared to 5·25 years for the first analysis[2]) of the randomised GETUG-AFU 16 trial. This trial evaluated the effect on progression-free survival of adding 6 months of androgen deprivation therapy (consisting of the administration of goserelin, a luteinizing hormone-releasing hormone agonist [LHRHa]) to salvage radiotherapy in men with initially undetectable concentrations of post-operative prostate-specific antigen (PSA), then increasing to between 0·2 ng/mL and 2 ng/mL. Progression was defined as biochemical (PSA concentration 0·5 ng/mL above nadir); local (within the prostatic bed), regional (in pelvic lymph nodes), or distant (lymph nodes beyond the pelvis, bone, or viscera); or death from any cause measured from the date of randomisation. Secondary prespecified outcomes included metastasis-free survival and overall survival. Time to metastasis was defined as time from randomisation to documentation of disease outside the prostatic bed, including pelvic nodal recurrence or death from any cause. Importantly, annual or systematic scans were not required during follow-up to assess for and document metastasis, and patients with biochemical relapse or who reported pain, or both, could be scanned using CT and bone scan at the discretion of the treating physician. The authors found significant improvements in both progression-free survival (hazard ratio [HR] 0·54, 95% CI 0·43–0·68; p<0·0001) and metastasis-free survival (0·73, 0·54–0·98; p=0·0339) in the radiotherapy plus goserelin group