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.

Bertrand Tombal
Service d'Urologie, Cliniques universitaires Saint Luc, Brussels B-1200, Belgium
Bertrand.tombal@uclouvain.be

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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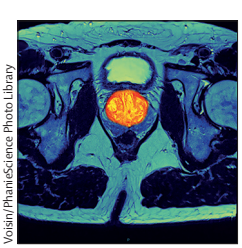
Post-operative salvage androgen deprivation and radiotherapy for prostate cancer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Published Online October 16, 2019 https://doi.org/10.1016/S1470-2045(19)30488-7
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In *The Lancet Oncology*, Christian 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

versus the radiotherapy alone group, but not in overall survival (0·93, 0·63–1·39; p=0·73).

Although the near halving of the risk of progression lends support to adding 6 months of an LHRHa to radiotherapy, the reduction in metastasis-free survival in the dual therapy group should be considered hypothesis-generating, since the study did not require annual or systematic scans during follow-up and since patients who reported pain could be scanned with a CT and bone scan. Without assurance of consistent scanning between the two randomised treatment groups, the metastasis-free survival endpoint is potentially subject to ascertainment bias.

Of 30 deaths from prostate cancer, 18 (4·8%) occurred in 373 patients in the radiotherapy alone group and 12 (3·3%) in 369 patients in the radiotherapy plus goserelin group in the GETUG-AFU 16 trial.[1,2] However, the reduced prostate cancer-related mortality was not significant. By contrast, the Radiation Therapy Oncology Group (RTOG) 9601 trial,[3] in which patients were randomly assigned to radiotherapy alone versus radiotherapy plus 2 years of androgen suppression, found the mortality values of 13·4% versus 5·8% to be significantly different (p<0·0001). These results showed a benefit in overall survival for patients receiving radiotherapy plus androgen suppression (HR 0·77, 95% CI 0·59–0·99; p=0·04).

The observation of an overall survival benefit in the RTOG 9601 trial,[3] but not in the GETUG-AFU 16 trial,[1,2] could be due to reduced competing risks in the the RTOG 9601 trial because of the patients' lower median age (65 years in the RTOG 9601 trial *vs* 67 years in the GETUG-AFU 16 trial), to a longer median follow-up (13 years in RTOG 9601 *vs* 9·33 years in GETUG-AFU 16), and to more patients with advanced prostate cancer in the the RTOG 9601 trial. Specifically, the median PSA concentration was 0·6 ng/mL in the RTOG 9601 trial[3] versus 0·3 ng/mL in the GETUG-AFU 16 trial[1,2] and the proportion of men with prostate cancer with a Gleason score of 8–10 was 17·3% versus 11% at randomisation, suggesting that some men with poor prognostic factors might benefit from adding 2 years, as opposed to 6 months, of androgen suppression to radiotherapy. Moreover, it is possible that some men with more favourable prognostic factors included in the GETUG-AFU 16 trial[1,2] might not have benefitted from the addition of any androgen suppression to radiotherapy. These uncertainties might be resolved by the ongoing RADICALS trial (NCT00541047).[4] This large randomised trial (n=2340) is designed to assess whether adding no, 6 months, or 2 years of treatment with a LHRHa to salvage radiotherapy will reduce death from prostate cancer. In addition, another trial (NCT03141671) aims to establish whether 6 months of treatment with an androgen synthesis inhibitor and an androgen receptor-targeted drug[5] plus a LHRHa compared with a LHRHa treatment and with a conventional androgen deprivation therapy will improve cancer control. Since these agents have been shown to prolong overall survival in men with metastatic castration-sensitive prostate cancer,[6,7] perhaps a treatment course of 6 months will be sufficient to improve overall survival in this earlier setting in which men do not have evidence of metastatic disease but just biochemical failure.

While awaiting the results of studies that will enable health-care providers who care for men with prostate cancer to personalise the use of androgen deprivation therapy in the salvage setting, on the basis of the results of the GETUG-AFU 16 trial,[1,2] it would be prudent to consider adding a 6 month course of an LHRHa to salvage radiotherapy in men with no or minimal comorbidity given the near halving of progression and the possible reduction in mortality due to prostate cancer.

Anthony V D'Amico
Brigham and Women's Hospital and Dana Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, USA
adamico@bwh.harvard.edu

I declare no competing interest.

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