Competing interests
The authors declare no competing interests.

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COMBINATION THERAPY

Abiraterone prolongs survival in metastatic prostate cancer

Oliver Sartor

Abiraterone plus prednisone prolongs overall survival relative to prednisone alone in patients with metastatic castration-resistant prostate cancer who have disease progression after treatment with docetaxel. The survival gain observed in this pivotal trial is accomplished with few adverse events and conclusively demonstrates that patients with castration levels of serum testosterone remain sensitive to additional hormonal manipulation.

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The recent article by de Bono and colleagues[1] describing an improvement in overall survival for patients treated in the phase III trial (COU-AA-301) with abiraterone plus prednisone, dramatically alters our view of hormonal treatment in advanced-stage prostate cancer. This trial enrolled 1,195 men with metastatic castration-resistant prostate cancer (CRPC) with disease progression despite previous therapy with docetaxel. Patients were randomly assigned to receive abiraterone plus prednisone or placebo plus prednisone; the primary end point was overall survival. The trial was terminated early by the data-monitoring committee as a consequence of a pre-planned interim efficacy analysis. At the time the trial was stopped, the median overall survival was 14.8 months in the abiraterone group versus 10.9 months in the control group (hazard ratio [HR] = 0.65, P <0.0001). The therapy was well tolerated and now, as a consequence, approved by the FDA in the post-docetaxel metastatic CRPC setting.

Practice point

Abiraterone is the first hormonal agent to prolong survival in metastatic castration-resistant prostate cancer and it achieves this goal with a moderate adverse-event profile

Since the Nobel Prize-winning work of Huggins and Hodges published in 1941,[2] it has been well accepted that lowering testosterone to castration levels by orchiectomy or treatment with estrogens was effective in the treatment of metastatic prostate cancer. Since then, advances in hormonal therapy for this disease have been important but limited. In the 1980s, luteinizing hormone-releasing hormone (LHRH) agonists—which dramatically lower testosterone to levels equivalent to those obtained with orchiectomy—were both the psychological issues of surgical orchiectomy and the side effects of estrogens (such as deep vein thrombosis and pulmonary embolism, and other thromboembolic complications). Later, some—but not all—trials with antiandrogens demonstrated a modest advantage in overall survival when used in combination with medical or surgical castration. Until 2004, however, no trial had demonstrated an increase in overall survival in patients with castration levels of testosterone. In that year, docetaxel plus prednisone and docetaxel plus estramustine were shown to prolong overall survival compared with mitoxantrone plus prednisone in patients with metastatic 'hormone-refractory' prostate cancer.[4,5]

The past 2 years have seen an increasing activity in the development of therapies that target metastatic prostate cancer recurring after initial androgen deprivation. After docetaxel, Sipuleucel-T was the second agent shown to prolong overall survival,[6] followed by cabazitaxel.[7] Abiraterone was the fourth agent,[1] and now a fifth agent (alpharadin)[8] has joined the group (Table 1). After many years of futile effort, the recent progress in prolonging survival is stunning for those long involved in the field.

The evidence that castrated patients can have a second-line hormonal treatment—abiraterone—that prolongs overall survival disrupts the long-standing dogma that these patients are 'hormone-refractory'. In fact, on the contrary, it seems that patients relapsing after initial androgen deprivation are extremely sensitive to concentrations of androgens previously thought insignificant. In light of this observation, the term 'hormone-refractory' is no longer justified and 'castration-resistant' is now confirmed as the appropriate term because CRPC does not imply sensitivity or resistance to hormonal therapy, only that the prostate cancer has progressed after castration.

Discarding the 'hormone-refractory' concept is a conceptual breakthrough that has far-reaching implications. First and foremost, the androgen–androgen receptor (AR) axis remains a validated target in CRPC, even when serum levels of testosterone are in the castration range. This paves the way for a variety of new strategies, some of which (blocking AR with the antagonist MDV3100, and inhibiting androgen synthesis with the inhibitor TAK-700) are now in phase III trials. More therapies targeting the androgen–AR axis are on their way, with particularly interesting

Table 1 | Phase III trials with a prolongation of OS (primary end point) in metastatic CRPC

Trial	Year	Regimen	Median OS (months)	HR
TAX327[5]*	2004	Docetaxel + prednisone vs mitoxantrone + prednisone	18.9 vs 16.5	0.76
SWOG 9916[4]*	2004	Docetaxel + estramustine vs mitoxantrone + prednisone	17.5 vs 15.6	0.80
IMPACT[6]‡	2010	Sipuleucel-T and 'unactivated' antigen-presenting cells	25.8 vs 21.7	0.78
TROPIC[7]	2010	Cabazitaxel + prednisone vs mitoxantrone + prednisone	15.1 vs 12.7	0.70
COU-AA-301[1]§	2011	Abiraterone + prednisone vs placebo + prednisone	14.8 vs 10.9	0.65
ALSYMPCA[8]§	Unpublished	Radium-223 + best supportive care vs placebo + best supportive care	14.0 vs 11.2	0.70

*SWOG 9916 and TAX327 trials used first-line chemotherapy. ‡IMPACT trial was carried out in asymptomatic or minimally symptomatic patients without visceral metastases. §TROPIC and COU-AA-301 trials were conducted in patients who had received docetaxel. The Radium-223 trial was conducted in patients considered 'unsuitable' for chemotherapy without visceral metastases. Abbreviations: CRPC, castration-resistant prostate cancer; HR, hazard ratio; OS, overall survival.

and more-selective inhibitors of steroid 17-α-hydroxylase/17,20 lyase (CYP17) such as VT-464 (Viamet Pharmaceuticals, NC, USA). The trial led by de Bono *et al.*[1] was conducted in a post-docetaxel metastatic CRPC setting. However, there is no reason to believe that activity of abiraterone will be restricted to these patients, and a current trial of abiraterone in a pre-docetaxel metastatic CRPC setting is expected to be reported later this year.

Recent updates of the abiraterone trial have revealed important new information that was not included in the original article. First, reported pain was markedly reduced in the abiraterone plus prednisone arm.[9] Second, preliminary reports indicate that circulating tumors cells (CTCs)—a novel biomarker indicative of poor prognosis—were reduced in the experimental arm and that a combination of levels of lactate dehydrogenase (LDH) and CTCs at baseline and changes in these levels after treatment may predict survival, independently of therapy, in patients with an elevated baseline CTC count. These data have important potential implications for the use of biomarkers and patient reported outcomes in future trials that attempt to meet regulatory standards. Given the current multiplicity of agents shown to be effective in metastatic CRPC, it will be challenging to approve new drugs if overall survival persists as the primary end point.

Before the post-abiraterone enthusiasm becomes irrational, it is important to note that time to radiographic progression in the trial by de Bono *et al.*[1] was relatively modest. Median time to radiographic progression was 5.6 months in the abiraterone arm. The time to progression measured by prostate-specific antigen (PSA), seems artificially long in both arms of the study, perhaps as a consequence of the relatively prolonged PSA testing interval (every 3 months). We note that the median time to PSA progression was 6.6 months in the prednisone arm whereas, in another trial conducted in patients with metastatic CRPC with disease progression after treatment with docetaxel (TROPIC), the combination of prednisone and mitoxantrone yielded a time to PSA progression of 3.1 months.[7] In conclusion, although abiraterone is an effective and relatively well tolerated agent, further progress is needed to optimize treatments for patients with metastatic CRPC. The next step is test this agent in earlier stages of the disease and to combine it with other agents that have demonstrated activity. I suspect that only combination therapy will result in the truly dramatic results that clinicians expect for patients with advanced-stage prostate cancer.

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Competing interests
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REVIEWS

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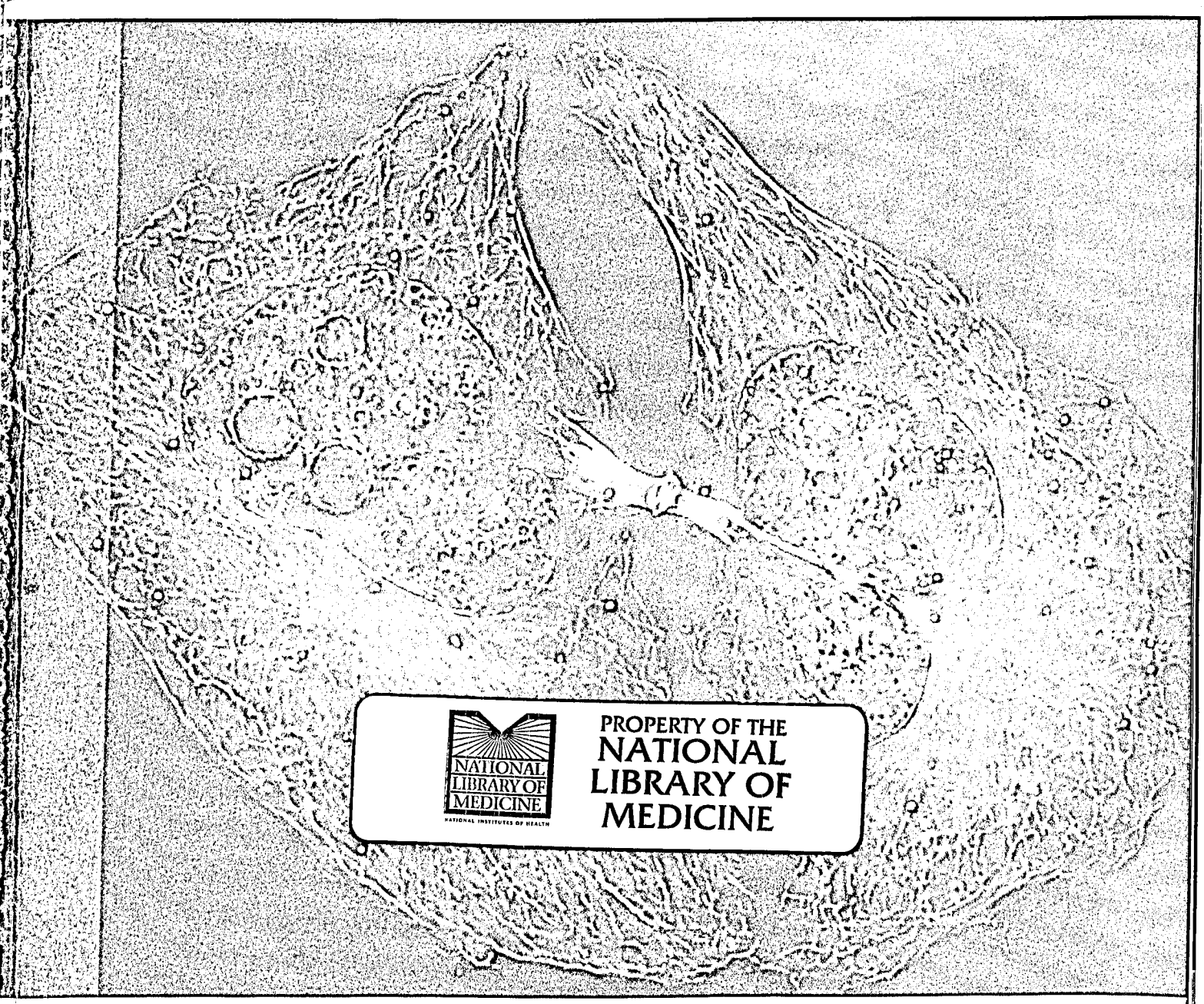


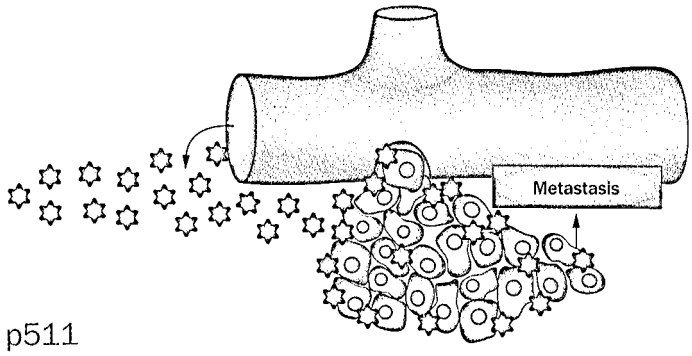
AUTOPHAGY: FRIEND OR FOE?
Exploring the role of autophagy as a novel therapeutic target

Imaging methods used in clinical trials
Opportunities and pitfalls

RESEARCH HIGHLIGHTS

NEWS & VIEWS

PERSPECTIVES



p511

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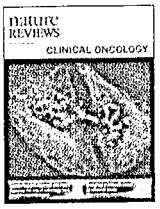

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