Published in final edited form as:

Lancet Oncol. 2015 March ; 16(3): 247–249. doi:10.1016/S1470-2045(15)70071-9.

Moving the goal posts in prostate cancer trials

Ravi A Madan and James L Gulley

National Cancer Institute, National Institutes of Health, Center Drive, Bethesda, MD 20892, USA

In *The Lancet Oncology*, Fred Saad and colleagues¹ present final data from ELM-PC 4, a phase 3 trial of orteronel plus prednisone versus placebo plus prednisone in patients with chemotherapy-naïve, metastatic castration-resistant prostate cancer. Orteronel was developed to inhibit CYP17-mediated secondary androgen production via selective blocking of 17,20-lyase. Although abiraterone acetate has similar biological effects and is already approved for metastatic castration-resistant prostate cancer, orteronel represented another candidate androgen biosynthesis inhibitor. This study¹ enrolled 1560 patients, randomly assigning 781 patients to receive orteronel plus prednisone and 779 to receive placebo plus prednisone. The co-primary endpoints were radiographic progression-free survival and overall survival. Despite a benefit in radiographic progression-free survival (median 13.8 months with orteronel plus prednisone vs 8.7 months with placebo plus prednisone; hazard ratio [HR] 0.71; 95% CI 0.63–0.80; $p < 0.0001$) as well as improvements in PSA response and circulating tumour cells, orteronel plus prednisone did not improve overall survival (median 31.4 months with orteronel plus prednisone vs 29.5 months with placebo plus prednisone; HR 0.92; 95% CI 0.79–1.08; $p = 0.31$). Of note, EML-PC 5, a study in docetaxel-treated metastatic castration-resistant prostate cancer, also failed to show an overall survival advantage for orteronel and prednisone versus placebo and prednisone, despite a benefit in radiographic progression-free survival.²

The results of this study raise important questions about therapeutic development in the suddenly crowded treatment landscape of metastatic castration-resistant prostate cancer, in which six drugs have a confirmed effect in overall survival.³ In recent years, overall survival has been the principal endpoint for regulatory agencies in the assessment of emerging anti-tumour drugs in prostate cancer. The results of this trial provide an opportunity to assess whether other benchmarks could be used to definitively assess efficacy. It is possible that the difference in radiographic progression-free survival noted in this trial was clinically meaningful. Additionally, the benefit in overall survival of orteronel might have been diminished by other newly approved drugs that target the androgen-receptor pathway. This concern is somewhat supported by data suggesting that sequentially targeting the androgen receptor with androgen biosynthesis inhibitors (ie, orteronel and abiraterone) and androgen-receptor antagonists (ie, enzalutamide) results in a reduction in clinical benefits due to common mechanisms of resistance.⁴ Therefore, patients receiving prednisone alone could benefit from subsequent treatment with enzalutamide or abiraterone, whereas androgen-receptor or androgen biosynthesis inhibitors following orteronel may have less effect,

gulleyj@mail.nih.gov.

We declare that we have no competing interests.

potentially minimising orteronel's effect on overall survival. The authors also suggest that patients were prone to discontinue this study to get an approved therapy, thereby underestimating the treatment effect of orteronel. It should be noted, however, that enzalutamide and abiraterone showed a benefit in overall survival despite substantial crossover.^{5,6} Ultimately, the absence of effect on time to pain progression and a treatment discontinuation rate of 30% due to toxic effects (slightly higher than discontinuation due to radiographic progression) with orteronel substantially differ from the effects of enzalutamide and abiraterone, challenging the potential clinical benefit of orteronel.

Nonetheless, the question remains: should the goal posts be moved in trials of metastatic castration-resistant prostate cancer since the number of approved treatments might confound overall survival endpoints? Our colleagues treating breast cancer have dealt with this conundrum for some time. The hazards of approving a treatment based on progression-free survival alone have been well described, including the absence of clear data confirming that changing progression-free survival has implications for clinical benefit.⁷ Indeed, a 4.2-month delay in the development of bone metastasis in earlier stages of prostate cancer was insufficient to get a labelled indication for denosumab.⁸ Further challenges for progression-free survival as a registration endpoint include difficulties in achieving effective masking, having consistent approaches to disease assessments, vagaries of assessing responses in bone lesions, reducing contamination of patients with non-study assessments or treatments, and acquiring requisite follow-up data.⁷ Perhaps most concerning are the difficulties and stigma associated with rescinding approval on the basis of new data, as evidenced by the Food and Drug Administration's repeal of bevacizumab's preliminary indication in breast cancer after several trials suggested an absence of benefit.^{9,10}

Despite these obstacles, in view of the growing therapeutic options in metastatic castration-resistant prostate cancer, the recalibration of measurements of success in this disease should receive serious consideration, and not simply by regulators. Trial designs must be updated to ensure that progression-free survival is given due significance and is associated with robust data. One strategy could include selection of appropriate patient populations, such as those who are refractory to drugs targeting the androgen-receptor pathway. Such data provide a more compelling platform for emerging treatments to demonstrate clinical benefit. Although prednisone can affect PSA and disease symptoms, we must acknowledge that it is no longer the ideal control for studies in chemotherapy-naïve metastatic castration-resistant prostate cancer if progression-free survival is a desired registration endpoint; comparator groups would be more meaningful if they consisted of other approved treatments such as enzalutamide or abiraterone. These considerations would provide a more meaningful context for changes in correlative biomarkers such as circulating tumour cells and PSA. Additionally, comprehensive trial designs that incorporate assessments of quality of life and pain progression could provide valuable corroborating data validating the effect of progression-free survival. Incorporating novel but validated imaging techniques would further strengthen analyses of progression-free survival. As we move forward, we must acknowledge that the proliferation of treatments for metastatic castration-resistant prostate cancer has created new opportunities for patients and new realities for clinical trial design.

References

1. Saad F, Fizazi K, Jinga V, et al., for the ELM-PC 4 investigators. Orteronel plus prednisone in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (ELM-PC 4): a double-blind, multicentre, phase 3, randomised, placebo-controlled trial. *Lancet Oncol* 2015; published online Feb 18. 10.1016/S1470-2045(15)70027-6.
2. Fizazi K, Jones R, Oudard S, et al. Phase III, randomized, double-blind, multicenter trial comparing orteronel (TAK-700) plus prednisone with placebo plus prednisone in patients with metastatic castration-resistant prostate cancer that has progressed during or after docetaxel-based therapy: ELM-PC 5. *J Clin Oncol* 2015; 10.1200/JCO.2014.56.5119.
3. Basch E, Loblaw DA, Oliver TK, et al. Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. *J Clin Oncol* 2014; 32: 3436–48. [PubMed: 25199761]
4. Antonarakis ES, Lu C, Wang H, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. *N Engl J Med* 2014; 371: 1028–38. [PubMed: 25184630]
5. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014; 371: 424–33. [PubMed: 24881730]
6. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2015; 16: 152–60. [PubMed: 25601341]
7. D'Agostino RB Sr. Changing end points in breast-cancer drug approval—the Avastin story. *N Engl J Med* 2011; 365: e2. [PubMed: 21707384]
8. Smith MR, Saad F, Coleman R, et al. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet* 2012; 379: 39–46. [PubMed: 22093187]
9. Robert NJ, Dieras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J Clin Oncol* 2011; 29: 1252–60. [PubMed: 21383283]
10. Pivot X, Schneeweiss A, Verma S, et al. Efficacy and safety of bevacizumab in combination with docetaxel for the first-line treatment of elderly patients with locally recurrent or metastatic breast cancer: results from AVADO. *Eur J Cancer* 2011; 47: 2387–95. [PubMed: 21757334]