Triplet therapy for prostate cancer

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The past 8 years have seen four agents shown to be superior to androgen deprivation therapy (ADT) alone in terms of overall survival when given as doublet therapy with ADT for metastatic castration-sensitive prostate cancer.[1–7] In *The Lancet*, Karim Fizazi and colleagues[8] report the findings from the PEACE-1 trial, which provides evidence in support of triplet therapy for metastatic castration-sensitive prostate cancer. The trial enrolled 1173 male patients (aged ≥18 years, across Belgium, France, Ireland, Italy, Romania, Spain, and Switzerland) with synchronous (de novo) metastatic hormone-sensitive prostate cancer who received ADT (plus docetaxel in 60% of patients) as standard of care alone, or standard of care with the addition of abiraterone plus prednisone (hereafter referred to as abiraterone), radiotherapy to the primary tumour, or abiraterone plus radiotherapy, in a randomised 2 × 2 factorial design.

The results of the PEACE-1 trial are striking. Addition of abiraterone to standard of care improved both coprimary endpoints of radiographic progression-free survival (hazard ratio 0·54, 99·9% CI 0·41–0·71; p<0·0001) and overall survival (0·82, 95·1% CI 0·69–0·98; p=0·030). Radiographic progression-free survival and overall survival were also improved when the analysis was restricted to the population who received ADT with docetaxel as standard of care. Further analysis by metastatic disease burden in the population who received ADT with docetaxel showed that radiographic progression-free survival was improved with the addition of abiraterone in patients with either high or low metastatic burden, but overall survival was shown to be improved only in patients with high-volume disease, probably due to insufficient events in patients with low-volume disease. More adverse events were observed with abiraterone, notably hypertension, but docetaxel toxicity did not appear to be increased by the addition of abiraterone. The results of the patient-reported outcome measures are yet to be reported. The improved outcomes were unlikely to be due to differences in uptake of subsequent life-prolonging therapies, which were used more often in the standard of care without abiraterone group. We await with interest the results of the remaining secondary outcomes.

PEACE-1 had a complex but efficient design, made more complex during its course by amendments to the protocol and planned statistical analysis. These amendments incorporated emerging information and changes in clinical practice, notably the use of docetaxel in addition to ADT as standard of care, and the investigators are to be commended for responding so effectively. This ensured that PEACE-1 maintained and grew its relevance, even as new information came to light and was adopted into practice.[1]

Basic clinical features can indicate fundamental differences in prostate cancer biology and how it responds to treatment. Burden or volume of disease, described in PEACE-1 using the CHAARTED criteria,[1] affects outcomes substantially.[9] The onset of metastatic disease can be synchronous with initial diagnosis (de novo) or metachronous (diagnosed after initial presentation with localised cancer), and is associated with prognosis and with what treatments might be most appropriate.[9] It is important to emphasise that PEACE-1 included only patients with synchronous metastatic hormone-sensitive prostate cancer, and that the findings from this trial cannot be extrapolated to those with metachronous metastatic disease. We now have evidence that patients with metastatic hormone-sensitive prostate cancer should be offered ADT, abiraterone, and docetaxel. Caveats to this recommendation include the assumption that the agents are available and that the patient is medically able to receive each agent and has synchronous metastatic disease. Overall survival benefits so far have only been shown in patients with high-volume metastatic burden.

There remain several other unanswered questions. Addition of abiraterone to ADT with docetaxel improves outcomes, but is docetaxel necessary? There has not yet been a direct comparison of doublet ADT plus abiraterone versus triplet ADT with docetaxel plus abiraterone. This question urgently needs an answer, but the relevant trial is unlikely to be done, due to the scope of the trial design and the very large sample size that is likely to be necessary. We might require real-world outcomes data to help us decide. Is abiraterone the best choice? Abiraterone and androgen receptor antagonists both reduce androgen receptor signalling, but by very different mechanisms. The ARASENS trial[10] tested the addition of darolutamide or placebo to ADT plus docetaxel and showed benefits in overall survival and multiple secondary endpoints,

but similarly did not address the question of whether docetaxel was required, included some patients with metachronous disease, and did not address outcomes by metastatic burden. The ENZAMET trial[6] included docetaxel concurrently with enzalutamide in 45% of patients, but was not designed to answer the question of whether docetaxel was necessary, and showed no overall survival benefit from triplet therapy at the first planned interim analysis, despite a strong signal for the secondary endpoints of prostate-specific antigen progression-free survival and clinical progression-free survival, as found in PEACE-1; updated results are expected this year.

Are there some patients who do not need such intensification of treatment, and might benefit similarly from ADT alone? Can we de-escalate or cease concurrent additional androgen-receptor-targeted therapy in the absence of progression after a good response? These questions require carefully designed clinical trials. Initiatives such as STOP-CaP, PIONEER, the PanProstate Cancer Group, and others are bringing together clinical and translational data from across multiple trials and are our best chance of answering these questions. Finally, another challenge is how best to integrate this information into clinical practice, especially since we have not yet done well in taking up even doublet therapy options. Clinicians, advocates, and regulatory and funding bodies all need to work together to advance clinical practice. To adapt Eleanor Roosevelt's comment—it is not enough to talk about PEACE-1. One must believe in it. And it is not enough to believe in it. One must work at it.

I am the unremunerated chair of the ANZUP Cancer Trials Group and global co-chair of the ENZAMET trial and an unremunerated member or chair of industry advisory boards for Astellas, AstraZeneca, Bayer, Eisai, Ipsen, Janssen, Merck/Pfizer, Merck Sharp & Dohme, and Roche; all honoraria are invoiced by and paid directly to the ANZUP Cancer Trials Group.

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For more on **STOP-CaP** see http://www.stopcapm1.org/

For more on **PIONEER** see https://prostate-pioneer.eu/

For more on the **PanProstate Cancer Group** see https://panprostate.org/

Preventing enterovirus A71 disease: another promising vaccine for children

Enterovirus A71 (EV71) is a cause of large outbreaks of hand, foot, and mouth disease (HFMD) in children and is associated with severe neurological manifestations, including brainstem encephalitis, which can lead to fatal non-cardiogenic pulmonary oedema and acute flaccid myelitis with potential permanent paralysis.[1] Sporadic outbreaks of EV71 have occurred worldwide since its discovery in 1969, while regular cyclical epidemics have plagued the Asia-Pacific region, including Japan, China, Malaysia, Taiwan, Singapore, South Korea, and Vietnam, over the past several decades.[1,2] Owing to the public health threat of EV71 in this region, three EV71 vaccines have been licensed in China for use in children.[3] Phase 3 trials of a two-dose series of these inactivated whole virus C4 subgenotype-based vaccines showed high efficacy rates (90·0–97·4%) against EV71 HFMD in children aged 6–35 months with 100% efficacy against severe disease in a phase 4 trial.[4–8]

In *The Lancet*, Trong Toan Nguyen and colleagues report the safety, efficacy, and immunogenicity of an inactivated aluminium phosphate-adjuvanted B4 subgenotype-based vaccine (EV71vac) from a

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