and address potential limitations of others. The comparative modeling analysis will inform decisions about the elimination threshold and the interim targets to be reached on the pathway to elimination, and to identify what are the most effective and cost-effective strategies that lead to elimination for different countries. The modelling work will have an integral role in the development of WHO's global strategy to accelerate cervical cancer elimination, which will be presented for consideration by the World Health Assembly in May, 2020.[6,9]

The key contribution of the study by Simms and colleagues[2] is that it provides the first evidence of the potential for global cervical cancer elimination as a public health problem. The Article also represents a strong example of the role mathematical modelling can have in informing policy decisions.

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MB is involved in the WHO-driven cervival cancer elimination modelling project, but had no role in the development of the Article by Simms and colleagues. MD declares no competing interests.

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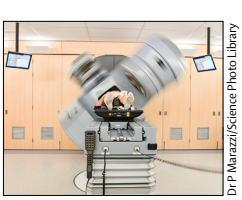
Combination therapies in prostate cancer: proceed with caution

In *The Lancet Oncology*, Matthew Smith and colleagues report the results of the phase 3 ERA 223 trial,[1] in which they investigated the effect of combining two therapies approved by the US Food and Drug Administration for the treatment of metastatic castration-resistant prostate cancer: radium-223 and abiraterone acetate plus prednisone or prednisolone. There is a biological rationale for this combination in view of the known cross-talk of DNA repair from ionising radiotherapy and androgen signalling.[2] Despite the rationale for this combination, the ERA 223 trial suggests that the combination of radium-223 with abiraterone acetate plus prednisone or prednisolone causes more harm than good. The trial, which included 806 patients (all of whom received abiraterone acetate plus prednisone or prednisolone), was unblinded prematurely after more fractures and deaths were noted in the radium-223 group than in the placebo group. Median symptomatic skeletal event-free survival did not differ between groups (hazard ratio [HR] 1·122 [95% CI 0·917–1·374]; p=0·2636). In the initial analysis,[3] which was done after 136 deaths occurred in the radium-223 group, overall survival was significantly worse in patients who received radium-223 than in those with received placebo (HR 1·35, 95% CI 1·05–1·73). In the current paper, which includes longer follow-up (155 deaths in the radium-223 group), overall survival no longer differs between groups (HR 1·195, 95% CI 0·950–1·505). Unexpectedly, fractures were more common in the radium-223 group than in the placebo group (112 [29%] of 392 patients *vs* 45 [11%] of 394 patients).

In ERA 223, the addition of radium-223 to abiraterone acetate plus prednisone or prednisolone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did not result in improvement in multiple exploratory endpoints for progression, including radiological progression-free survival and prostate-specific antigen response. Thus, radium-223 did not provide additive tumour control at a cohort level above and beyond that provided by abiraterone acetate plus prednisone or prednisolone. This lack of additive tumour control could be secondary to the effectiveness of abiraterone acetate plus prednisone or prednisolone in the initial treatment of predominately osseous (rather than visceral) androgen-receptor-driven prostate cancer. Furthermore, because death was usually preceded by disease progression, which was similar between groups, it is not surprising that overall survival would not be improved from the addition of radium-223 in the ERA 223 trial.

The main question is why was there an 18% absolute increase in fractures in the combination treatment group compared with the placebo group? First, the patients in ERA-223 presumably had years of luteinising-hormone-releasing hormone therapy, which can increase fracture risk, before they developed metastatic castration-resistant prostate cancer, and baseline bone densitometry was not done in this trial. Second, osteoblast function is regulated by the androgen receptor;[4] in COU-AA-301, further depletion of testosterone with the addition of abiraterone acetate to prednisone approximately doubled the risk of non-pathological fractures (5·9% *vs* 2·3%; data available online) and pathological fractures (15·3% *vs* 6·2%) compared with prednisone monotherapy.[5] Third, data from a randomised trial[6] have shown that 5 mg of prednisone per day can decrease indices of bone formation, and glucocorticoids can promote osteoclast activity and inhibit osteoblast function. These three points probably explain why 11% of patients in the placebo group of ERA 223 had fractures, and explain why the bone was potentially primed for further fracture from any additional insult.

To **access the data** see https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202379s024lbl.pdf

Ionising radiotherapy can also result in fractures, and the risk can exceed 10% with high-dose stereotactic-body radiotherapy. Fractures are hypothesised to be secondary to increased bone collagen crosslinks that restrict fibrillary sliding and suppress bone strength, activation of osteoclasts by low-dose radiotherapy, and cytotoxicity to osteoclasts, osteocytes, and osteoblasts with high-dose radiotherapy.[7,8] Because radium-223 is deposited throughout the osseous skeleton, it would be expected to lead not only to pathological fractures, but also to osteoporotic or insufficiency fractures if the bone was primed for fracture. Supporting this point, in ERA 223, 60 (79%) of the 76 fractures in the radium-223 group that were confirmed by independent assessment with conventional imaging occurred at sites without bone metastases (ie, non-pathological fractures). In patients not taking concurrent abiraterone acetate and prednisone or prednisolone, radium-223 monotherapy was associated with a low frequency of femoral neck and pathological fractures at 3-year follow-up in the ALSYMPCA trial.[9] Thus, it is plausible that the dual inhibitory effect on osteoblast function from abiraterone acetate and prednisone, combined with the osteoclastogenic effects of androgen deprivation, glucocorticoids, and radium-223 synergistically increased risk of fracture. Furthermore, analogous to tumour cell radiosensitisation from androgen-signalling inhibitors, it is unknown whether osteoblasts can similarly be radiosensitised by androgen-signalling inhibitors, or if abiraterone acetate plus prednisone or prednisolone can induce increased bone turnover to promote increased radium-223 deposition. In the context of multifactorial insult to bone health from chronic chemical castration, abiraterone, glucocorticoids, low use of bone health agents (approximately 40% in both groups in ERA 223), and unknown use of preventative bone health measures (eg, weight-bearing exercise), radium-223 was possibly the final factor that increased the frequency of fractures in ERA 223.

The ERA 223 trial is an important example of why randomised trials are necessary, and early-access or post-marketing data should not be the sole source of safety information about the combination of approved therapies already on the market.[10] The results of trials assessing the benefit of radium-223 in combination with other agents are eagerly awaited to clarify whether such combination therapy can be both effective and safe. At this time, radium-223 should not be combined with abiraterone acetate plus prednisone or prednisolone, and other second-generation androgen-signalling inhibitors should only be combined with radium-223 in the context of a clinical trial.

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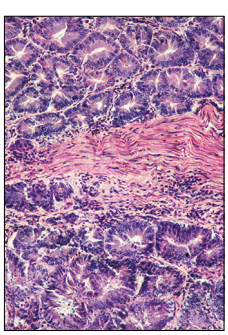
No clear role for angiogenesis inhibitors in first-line therapy for stomach cancer

In this century, anti-angiogenic therapy has played a part in the treatment of multiple solid cancers. Possible strategies to inhibit the angiogenic VEGF–VEGFR signalling axis include targeted therapy against VEGF ligand, VEGFR-2, and VEGFR tyrosine kinases. These approaches have identified ramucirumab, a recombinant, fully human IgG1 monoclonal antibody specific for VEGFR-2, as the most successful anti-angiogenic compound in gastric cancer treatment.[1,2] This finding has led to approval by the US Food and Drug Administration and European Medicines Agency of ramucirumab (in combination with paclitaxel or as monotherapy) for second-line treatment of patients with advanced gastric or gastro-oesophageal junction adenocarcinoma with disease progression after previous platinum and fluoropyrimidine chemotherapy.

In *The Lancet Oncology*, Charles Fuchs and colleagues[3] now report results of the placebo-controlled, phase 3 RAINFALL trial, investigating the role of ramucirumab in combination with standard first-line cisplatin and capecitabine (or 5-fluorouracil) chemotherapy. The primary endpoint was met: the addition of ramucirumab improved investigator-assessed progression-free survival, analysed by intention-to-treat in the first 508 eligible patients (HR 0·753, 95% CI 0·607–0·935). However, this finding was not accompanied by a clinically meaningful improvement in median progression-free survival: 5·7 months (95% CI 5·5–6·5) in the ramucirumab group versus 5·4 months (4·5–5·7) in the placebo group. Moreover, this difference in progression-free survival was not confirmed in a sensitivity analysis based on central independent review (0·961, 0·768–1·203, p=0·74). With a study population of 645 patients, the study was also powered to investigate overall survival as a secondary endpoint, but there was no difference between groups (HR 0·962, 95% CI 0·801–1·156), with median survival of 11·2 months (9·9–11·9) in the ramucirumab group versus 10·7 months (9·5–11·9) in the placebo group.

A clear question is why ramucirumab, as a single agent in the REGARD study[1] and in combination with paclitaxel in the RAINBOW study,[2] showed improved progression-free and overall survival in the second-line setting, but not as first-line therapy. Study populations and dose schedules vary slightly between the different studies and it is unclear whether this has influenced findings. For example, RAINFALL only included metastatic cancers, whereas RAINBOW also included locally advanced tumours. However, the proportion of locally advanced tumours in RAINBOW was probably low.[4,5] Furthermore, HER2-positive tumours were excluded from RAINFALL because anti-HER compounds are standard of care in patients with these tumours. In vitro, HER2 overexpression has been associated with increased angiogenesis and VEGF expression,[6] which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