evidence of activity was seen in heavily pretreated patients with several cancers, particularly bladder cancer (four responses in 15 patients) and cervical cancer (nine in 34). Most responses were relatively short-lived (median duration 5·7 months), although further follow-up will be needed to assess duration of responses. The most common treatment-emergent adverse events included fatigue, nausea, alopecia, decreased appetite, constipation, diarrhoea, and vomiting, which are common with other antibody–drug conjugates. However, other common adverse events in this study—such as epistaxis, conjunctivitis, and dry eye—have not often been described in other antibody–drug conjugates studies.

The incidence of epistaxis (69%) and ocular adverse events (60%) merits further exploration. Epistaxis was the most common treatment-emergent adverse event, although most events (98%) were grade 1 and thus did not require intervention. Ocular symptoms, particularly conjunctivitis, were noted early on in the study's enrolment, and a mitigation strategy was enacted. After this intervention, the incidence of conjunctivitis decreased from 56% to 29%. However, the incidence of other ocular toxicities increased, such as dry eye (from 17% to 27%), conjunctival ulcer (from 1% to 7%), and conjunctival hyperaemia (from 0% to 6%). Notably, high concentrations of tissue factor have been shown in the nasal mucosa,[8] and are hypothesised to be present in the eye as well, given that it is a highly vascular mucosal site.

Correlative studies are needed to determine the most appropriate patients for therapy. Although the tumour types studied by de Bono and colleagues are known to have tissue factor expression in at least some cases, it was not reported how many patients had tissue factor-expressing tumours in this study. Conceivably, only tumours with moderate or high expression of tissue factor would benefit from this agent. It also remains to be seen whether tisotumab vedotin will be tolerable in combination with other agents, given its toxicity profile.

In summary, de Bono and colleagues provide preliminary evidence of the activity of tisotumab vedotin in patients with advanced solid tumours. Tisotumab vedotin has a novel mechanism of action accompanied by somewhat unusual side-effects. Translational studies to define the most appropriate patients and understand the mechanisms of toxicities will be important next steps.

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Global elimination of cervical cancer as a public health problem

In May 2018, the WHO Director-General made a global call for action to eliminate cervical cancer as a public health problem.[1] Before embarking on the pathway to eliminate cervical cancer, which will require immense resources and a global concerted effort, an essential initial step is to understand whether

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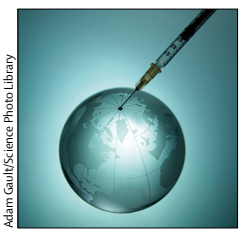

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achieving elimination is possible, and to understand the potential effects of different screening and human papillomavirus (HPV) vaccination strategies. Such questions can only be examined using mathematical modelling, which can provide projections on the basis of our understanding of the epidemiology of HPV infection and cervical cancer, and the efficacy of HPV vaccines and cervical cancer screening and treatment.

In their Article in *The Lancet Oncology*, Kate Simms and colleagues[2] provide the first global modelling estimates of the potential for elimination of cervical cancer through HPV vaccination and cervical screening. The authors predict that HPV vaccination of girls only with 80–100% coverage and a perfect nine-valent vaccine combined with HPV-based screening twice per lifetime with 70% uptake could reduce the worldwide mean age-adjusted cervical cancer incidence from about 16 per 100 000 to less than four per 100 000 women-years between 2020 and 2080.[2] However, even under this optimistic scenario, many countries with a low Human Development Index (HDI) are not predicted to reach incidences of less than four per 100 000 women-years in the same timeframe. The results also suggest that high HPV vaccination coverage is necessary to reach elimination of cervical cancer, whereas the main role of screening is to increase the number of cervical cancers averted on the path to elimination (projected to be about 6 million cases over 50 years).[2]

To understand the implications of these results, it is important to note that the call for action is to eliminate cervical cancer as a public health problem and that there is no agreed definition of cervical cancer elimination.[3] Contrary to the terminology used in infectious diseases, in which elimination is the interruption of transmission (zero incidence of infection), elimination as a public health problem is the control of disease at a very low incidence. WHO has used such a definition in the past and stressed that it requires a clear and well defined threshold. The interim definition of elimination is cervical cancer incidence of less than four per 100 000 women-years, which was proposed during various WHO Technical Experts Group meetings and Global Stakeholder consultations (between March and September, 2018).[3,4] However, alternatives, such as a higher incidence threshold or a 90% reduction in incidence, have also been discussed.[3,4] There are many remaining questions related to the definition of cervical cancer elimination, such as should mortality be used as an outcome instead of incidence to capture progress in treatment, should the same definition be used across all countries independently of the effort required or underlying burden, and should the definition be pragmatic or optimistic? The final definition will most probably have the greatest effect on the feasibility of low-HDI countries reaching elimination.

The results from Simms and colleagues[2] should be interpreted with consideration of their strengths and limitations. The main strengths of the Article are that the predictions are based on a transmission-dynamic model that captures herd effects and includes projections of underlying trends in cervical cancer incidence based on registry data available for the 2012 GLOBOCAN cancer estimates.[5] As with any modelling paper, there are potential limitations to the analysis that are related to simplifying model assumptions and availability of data. First, the model does not capture the stark differences in sexual behaviour between countries and regions (eg, number of partners and age gap between partners), does not include core groups (eg, female sex workers) that are known to have an important role in transmission dynamics and elimination of infectious diseases, and does not include the potential effects of cofactors such as HIV. The effects of these simplifying choices on predictions are unclear, but will probably vary by country and region. Second, the projected increase in cervical cancer in low-HDI countries, and thus predicted difficulty in reaching elimination in these countries, is based on only a few cancer registries in sub-Saharan Africa that might not be representative of the entire region. The sparsity of population-based cancer registries will be a limitation for any modelling analyses of global elimination of cervical cancer. Investment in cancer registries will be crucial to better assess the true baseline cervical cancer incidence in countries and to monitor the progress towards elimination.

WHO commissioned different academic groups (including Simms and colleagues)[2] to do comparative modelling analyses of cervical cancer elimination.[6] The aim is to use different HPV and cervical cancer models,[2,7,8] which contribute their own strengths

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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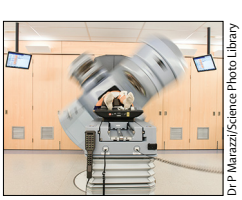
Combination therapies in prostate cancer: proceed with caution

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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