4-month overall survival advantage over EXTREME.[4] Within the larger subpopulation of patients with tumour combined positive score of more than 1%, pembrolizumab monotherapy conferred a 2-month overall survival advantage over EXTREME.[4] The proportions of patients achieving an objective response were even lower in this subpopulation (pembrolizumab 19% *vs* EXTREME 35%), but the median duration of response was 17 months longer with pembrolizumab than EXTREME.[4] Finally, in the entire study population, substituting pembrolizumab for cetuximab in the EXTREME regimen increased overall survival by 2 months, with equal proportions of patients achieving objective responses (36%) and a longer duration of response with pembrolizumab (pembrolizumab 7 months *vs* EXTREME 4 months).[4] These data led the US Food and Drug Administration to approve pembrolizumab as first-line treatment in recurrent and metastatic HNSCC.

For more on the **US FDA approval** see https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-first-line-treatment-head-and-neck-squamous-cell-carcinoma

Sensing a signal in palbociclib and possibly anticipating a marked change in the treatment of recurrent and metastatic HNSCC because of the arrival of immunotherapy, Adkins and colleagues[5] begin to reframe CDK4/6 inhibition as an immunotherapy adjunct. The combination strategy of CDK4/6 inhibitor and immunotherapy agent is rational: all three approved CDK4/6 inhibitors can increase antigen presentation and tumour-infiltrating lymphocyte fractions in preclinical systems.[10] A retrospective series of patients from the trial who went on to receive immunotherapy after failure of cetuximab and palbociclib will be of interest, because it might help to assess whether palbociclib sensitised recurrent and metastatic HNSCC to immunotherapy. Postcetuximab, postpalbociclib, and preimmunotherapy biopsies to assess tumour lymphocyte infiltration might also be informative.

Together, the in-vitro and in-vivo evidence supports further investigation of palbociclib in recurrent and metastatic HNSCC, even with the lack of activity of the combination of cetuximab and palbociclib in the randomised study.[6] However, we should be circumspect about the prospect of CDK4/6 inhibitors as standardised, cost-effective therapies in recurrent and metastatic HNSCC. Bringing this class of drugs to head and neck oncology clinics, as either monotherapies or immunotherapy partners, will require appropriately controlled studies linked to biomarker evaluation with both overall survival and cost-effectiveness endpoints.

*Garth W Strohbehn, *Everett E Vokes*
Section of Hematology/Oncology, Department of Medicine and Comprehensive Cancer Center, The University of Chicago, Chicago, IL 60637, USA (GWS, EEV)
evokes@medicine.bsd.uchicago.edu

EEV is a consultant or advisor with AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, EMD Serono, Genentech, Merck, Novartis, and Regeneron. GWS declares no competing interests.

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Combining PARP inhibition with PD-1 inhibitors

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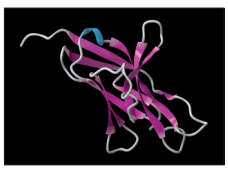
In *The Lancet Oncology*, Michael Friedlander and colleagues[1] report the findings of a phase 1a/b trial of the combination of poly (ADP-ribose) polymerase (PARP) inhibition and checkpoint inhibitors in patients with previously treated, advanced solid tumours. The authors hypothesise that tumours responding to PARP inhibition might have enhanced sensitivity to the combination of PARP inhibition and anti-PD-1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therapy. There is a strong rationale for combining PARP inhibitors with checkpoint inhibitors. Genomic instability and DNA damage repair pathway mutations have been shown to induce neoantigens[2] and DNA damage upregulates PD-L1 via multiple mechanisms, including interferon expression and activation of the innate immune pathway by the stimulator of interferon genes molecule (STING).[3,4] Furthermore, DNA damage repair pathway deficiency in at least one gene other than the classic mismatch repair genes (*MLH1*, *MLH3*, *MSH2*, *MSH3*, *MSH6*, *PMS1*, and *PMS2*) has been shown to result in better response to checkpoint inhibitors compared with patients with normal DNA damage repair pathway (80% *vs* 19%).[5]

The primary outcomes of the study by Friedlander and colleagues were safety and to establish the recommended dose for further evaluation. It is very encouraging that the safety and pharmacokinetic profiles of the combination in general were similar to the profiles of each drug when given as monotherapy and similar to other PARP inhibitors and checkpoint inhibitors.

Overall, 49 patients were included in the study, the results of which demonstrated that pamiparib plus tislelizumab was generally well tolerated with most adverse events being of low grade and reversible. Only four patients had dose-limiting toxicities (two with tiselizumab 200 mg plus pamiparib 40 mg, and two with tiselizumab 200 mg/kg plus pamiparib 60 mg), and the recommended phase 2 dose was established as tislelizumab 200 mg every 3 weeks plus pamiparib 40 mg twice daily. Immune-related adverse events, including elevated alanine and aspartate transaminase concentrations, hepatitis, and diarrhoea, were observed in 23 (49%) of the 49 enrolled patients and grade 3–4 hepatic immune-related adverse events were reported in nine (39%) of these 23 patients (across all cohorts), all of whom were successfully treated with corticosteroids. The clinical significance of immune-related hepatitis is unknown and needs to be explored. The proportion of patients with liver enzyme elevation in monotherapy studies were less than 5% for pamiparib and less than 6% for tislelizumab, respectively.[6,7]

The combination of pamiparib plus tislelizumab was associated with an objective response in ten (20%) of 49 patients, with no differences observed between patients with *BRCA*-wild-type and *BRCA*-mutated ovarian cancer. However, the number of patients included is too small to establish any meaningful conclusions, and further studies are required to investigate the efficacy of this combination, especially in patients with homologous recombination deficiency. For example, one patient with pancreatic cancer and one with bile duct cancer achieved stable disease, both of whom had unknown *BRCA* status.

Several ongoing clinical trials are exploring combinations of PARP inhibitors and checkpoint inhibitors. Safety data have been presented at the 2018 American Society of Clinical Oncology Annual Meeting for the combination of veliparib and nivolumab (NCT02944396) and niraparib and pembrolizumab (NCT02657889). At least nine other clinical trials are exploring the combination of PARP inhibitors and checkpoint inhibitors, including several different PARP inhibitors and both PD-1 and PD-L1-inhibitors (NCT03964532, NCT03834519, NCT03639935, NCT03602859, NCT03330405, NCT02953457, NCT02849496, NCT02734004, and NCT02484404). An optimum study design should include both baseline and on-study tumour samples, and patients with progression after PARP inhibition or checkpoint inhibitors should be included in such studies, to investigate synergistic effects. Furthermore, data on germline *BRCA* mutations and germline mutations in other homologous recombination deficiency genes such as *RAD51C*, *ATM*, and *BARD1* are important. For safety and based on the results of the present study, close monitoring of liver function should be mandatory in patients with solid tumours treated with this type of combination therapy.

Ulrik Lassen
Department of Oncology, Rigshospitalet,
2100 Copenhagen, Denmark
ulrik.lassen@regionh.dk

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Radical surgery for cervical cancer

Jessica Bordeau/ BSIP/ Science Photo Library

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In *The Lancet Oncology*, Michael Höckel and colleagues[1] report the long-term results of a prospective cohort study assessing the role of cancer field resection in cervical cancer. Mesometrial resection is aimed at removing the embryologically defined uterovaginal (ie, Müllerian) compartment consisting of the Fallopian tubes, uterus, and proximal and middle vagina enveloped by topographically complex peritoneal and retroperitoneal mesometrium. The study cohort included 523 patients with 2009 FIGO stage IB1–IIB cervical cancer who underwent total or extended mesometrial resection plus lymphadenectomy without adjuvant radiotherapy. The median follow-up was 61·8 months (IQR 49·3–94·8). The study population, of which 150 (29%) of 523 patients had positive lymph nodes and 160 (31%) had stage IIB disease, had a 5-year overall survival of 87·9% (95% CI 84·8–91·1).[1] This survival estimate, albeit a secondary outcome of the study, exceeded those reported elsewhere. For instance, available data from the Surveillance, Epidemiology, and End Results programme suggested that 5-year overall survival is about 55–60% for patients with lymph node metastasis and in patients with locally advanced cervical cancer.[2] Similarly, the Cancer Research UK estimated that the 5-year overall survival for stage II cervical cancer is about 55%.[3] These differences lead to the hypothesis, although indirectly, that mesometrial resection is associated with improved local control and survival. However, it is unlikely that modifying the surgical approach resulted in a greater than 30% improvement in survival. Patient selection might have a role in explaining these results.

The study included a very heterogeneous group of patients with cervical cancer, including those receiving neoadjuvant chemotherapy and those with stage IIIB cancer, making it difficult to estimate the effects of mesometrial resection across patients with various types of cervical cancer. Moreover, about half of the study population comprised patients with stage IB1 cancer. It is questionable to offer this radical procedure to this group of early-stage patients. Published data show that 5-year overall survival is more than 90% in patients with stage IB1 disease, with negative nodes, after type B radical hysterectomy; thus, mesometrial resection might represent overtreatment in these patients, possibly increasing morbidity without improving oncological outcomes.[4] A fair evaluation of the effects of mesometrial resection plus lymphadenectomy on oncological outcome can only be achieved in a study comparing this approach with other types of radical hysterectomy.

Another point deserving attention is the use of radiotherapy. The adoption of radiotherapy for cervical cancer is a source of concern, because it might increase the risk of long-term morbidity, especially when delivered after radical surgery. However, the data reported by Höckel and colleagues[1] do not rule out the possibility that radiotherapy adds to mesometrial resection in terms of local tumour control. A large randomised trial[5] enrolling more than 1800 patients with rectal cancer and comparing total mesorectal excision with total mesorectal excision plus radiotherapy showed that the addition of radiotherapy almost doubled tumour local control (5·6% *vs* 11%). These data suggest that a study evaluating the effectiveness of radiotherapy in patients with cervical cancer after mesometrial resection is needed.

The authors made a substantial clinical effort to improve patient outcomes without jeopardising their survival. However, until now, this technique is the preserve of a single institution and has been tested