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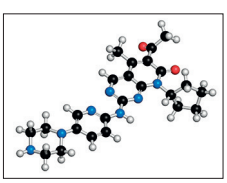
Palbociclib: a new partner for cetuximab?

Recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) remains a substantial health problem. The EGFR-inhibitory monoclonal antibody cetuximab is regularly used in recurrent and metastatic HNSCC, either as monotherapy or in combination with chemotherapy, as part of the EXTREME (platinum-containing agent, fluorouracil, and cetuximab) or TPEx (cisplatin, docetaxel, and cetuximab) regimens, resulting in approximately 13%, 36%, and 46%, of patients achieving objective responses, respectively.[1–3] Unfortunately, these responses are of short duration and median overall survival times have ranged from 10 to 14 months.[1–4] The discovery of adjunctive EGFR-sensitising therapies has therefore become one of the major goals in head and neck oncology research.

In *The Lancet Oncology*, Douglas Adkins and colleagues[5] report the combined results of two of three groups of a non-randomised, phase 2 study evaluating the cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor palbociclib with cetuximab in recurrent and metastatic HNSCC. This combination was supported by HNSCC gene expression array analysis implicating the retinoblastoma gene (*Rb*) pathway as a compensatory mechanism to EGFR inhibition and by subsequent studies in p16-negative HNSCC cell cultures showing synergy between palbociclib and the EGFR inhibitors afatinib and lapatinib. Adkins and colleagues assessed cetuximab and palbociclib in two groups of patients with recurrent and metastatic HNSCC: cetuximab-naive, platinum-refractory patients (group 1) and cetuximab-resistant patients in whom palbociclib was an attempt to rescue cetuximab sensitivity (group 2).[5] Although the proportions of patients achieving an objective response in the two groups were encouraging (group 1: 39% [95% CI 22–59], group 2: 19% [6–38]) and higher than proportions historically seen for cetuximab monotherapy, duration of response remained short (group 1: 4·0 months [IQR 1·8–5·6], group 2: 6·0 months [2·0–15·5]).[1,5]

Although this uncontrolled study provides a possible signal, limitations remain. Cohort sizes were small, and relevant biomarkers are still scarce. Furthermore, a randomised, placebo-controlled study (PALATINUS), presented in 2019, evaluating the cetuximab and palbociclib combination against single-agent cetuximab in the recurrent and metastatic setting did not produce statistically significant gains in either progression-free survival or overall survival.[6] Two mechanistic points about the combination should also be raised. First, although afatinib and lapatinib both inhibit EGFR, they are not purely EGFR inhibitors and do have off-target effects. These off-target effects can lead to overestimation of the effect size of EGFR-targeted therapy in preclinical systems, falsely attribute the synergy with CDK4/6 inhibitors to an EGFR-specific mechanism, and help to explain discrepancies between expectation derived from the laboratory and clinical reality. Second, in CDK4/6-dysregulated HNSCC patient-derived xenograft models, the CDK4/6 inhibitor abemaciclib shows single-agent activity.[7]

The treatment of recurrent and metastatic HNSCC has not been without progress, and immunotherapy has begun to make inroads.[4,8,9] Most recently, in 2019, KEYNOTE-048[4] compared pembrolizumab monotherapy and pembrolizumab plus chemotherapy with the EXTREME regimen in the first-line setting. Within the subpopulation of patients with recurrent and metastatic HNSCC with a PD-L1 combined positive score of more than 20%, pembrolizumab monotherapy conferred a



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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.

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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