

## **Dual EGFR/HER2 inhibition with post-operative chemoradiation in SCCHN: the verdict is in.**

**Kevin J. Harrington**

The Institute of Cancer Research, London, UK

**Jean Bourhis**

CHUV, Lausanne, Switzerland

In response to our recent publication<sup>1</sup>, Saba and Wong<sup>2</sup> make a number of important observations regarding the potential role for dual EGFR/HER2-targeted therapy as part of combined chemoradiotherapy in patients with SCCHN.

They question the potential influence of HPV-positive oropharyngeal SCC on the overall study results, pointing out the perceived lack of clarity regarding the importance of so-called high-risk features, such as extracapsular extension (ECE), in HPV-positive patients who receive post-operative chemoradiation. This matter is currently under evaluation in a number of clinical trials that use a graded, rather than a binary (ECE-positive or ECE-negative), approach to ECE as a risk factor. However, until the results of those studies are known, post-operative chemoradiotherapy remains the standard post-operative management of ECE-positive SCCHN (including oropharyngeal disease), irrespective of HPV status<sup>3</sup>. Even so, it is important to emphasise that our study included only 44 patients with HPV-positive disease – 38 of whom had oropharyngeal disease. Only 27 patients with HPV-positive disease had ECE (14 in placebo group, 13 in lapatinib group). Independently-assessed disease-free survival (DFS) results for subgroups defined by age, race, gender, primary tumor site, geographical region, ECOG performance status, EGFR status, nodal stage, HPV and p16 status and high-risk pathological status had no impact on the treatment effect: the hazard ratios between lapatinib and placebo varied between 0.70 and 1.36 in these subgroups and were not statistically significant. Therefore, it is impossible to conclude that our study findings were unduly influenced by the presence of a cohort of patients with HPV-positive disease.

In regard to the apparent discordance between the current definitively negative phase III results<sup>1</sup> and the encouraging data in HPV-negative disease from our previous phase II study<sup>4</sup>, it is important to avoid over-interpretation. One study included nearly 700 patients, albeit in the post-operative setting, and the other involved only 67 patients treated with definitive chemoradiotherapy. In the phase II study, data on HPV status were available for only 46 patients, of whom 39 were HPV-negative. Therefore, while we agree that the ongoing TRYHARD study of lapatinib in poor prognosis HPV-negative disease is an important test of the role of dual EGFR/HER2 blockade, we must recognize that the data supporting this trial are rather modest<sup>4</sup>. We entirely agree that biomarker-driven selection of high-risk patients would be the most rational manner in which to proceed with testing dual or pan-HER-targeted therapies but, like others, we remain disappointed by the lack of progress in defining useful predictive tools.

Finally, in relation to the fact that the control group in our study performed better than the chemoradiotherapy arm in RTOG 9501<sup>5</sup>, we agree with Saba and Wong's analysis of the factors that may have been associated with that finding. Having said that, as pointed out in our paper, it may have been more appropriate to base DFS and OS projections on data from the EORTC 22931 study<sup>6</sup> – in which case, the control arm in our study would be judged to have behaved as expected.

Therefore, in conclusion, there is no doubt about the verdict on the role of lapatinib in post-operative chemoradiotherapy in SCCHN – it plays no useful role. It remains to be seen if this agent will be successful in the context of definitive chemoradiotherapy in HPV-negative disease and, in that regard, we wish the patients and investigators every success.

## References

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