Clinical Cancer Research

HER2 and HER3 in HPV$^+$ and HPV$^-$ HNSCC—Letter

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The nice experiments performed by Pollock and colleagues showed that Human papillomavirus (HPV) infection coincided with overexpression of HER2 (ERBB2), HER3 (ERBB3), and the associated HER2:HER3 heterodimer and that this may contribute to EGFR therapy resistance. The authors concluded that pan-HER inhibitors could have significant activity in HPV-positive or cetuximab-resistant head and neck squamous cell carcinoma (HNSCC) cell lines (1).

Although not fully published when Pollock submitted her paper, the LUX Head and Neck 1 trial results can help to put her findings into perspective (2). HNSCC patients with recurrent and/or metastatic HNSCC were randomized between afatinib (a pan-HER inhibitor) and methotrexate. Afatinib significantly improved progression-free survival (PFS) versus methotrexate: median PFS 2·6 versus 1.7 months ($P = 0.03$). Importantly, this study allowed the inclusion of patients with p16-positive tumors or pretreated with cetuximab. In the p16-positive subgroup, median PFS with afatinib and methotrexate were 1.5 versus 2.3 months, respectively (HR 0.95, $P = 0.87$). In patients with p16-negative tumor, median PFS for afatinib and methotrexate were 2.7 versus 1.6 months, respectively (HR 0.69, $P = 0.022$). Objective response rates with afatinib in p16-negative and positive patients were 13.5% and 0%, respectively. Similarly, the benefit of afatinib was higher for patients not previously treated with anti-EGFR mAb with limited activity (if any) in cetuximab pretreated patients. Taken together, these clinical data do not support the preclinical observations of Pollock and colleagues and show that patients with p16-positive tumors or that progress after anti-EGFR therapy derive less benefit from afatinib.

One plausible reason for the observed discrepancy could be that work performed with cell lines only partially recapitulates the features of tumors originating from individuals. Better models such as patient-derived tumor xenografts that have been shown to maintain better the morphologic and molecular markers of the source tumors over time could be relevant to confirm or infirm the hypotheses generated by cell line experiments.

Besides the HER2:HER3 hypothesis, Pollock and colleagues also investigated afatinib in a cell line with EGFR variant III (EGFRvIII). The presence and significance of EGFRvIII in HNSCC is controversial. Whereas some investigators found low expression of EGFRvIII in 10%–40% of HNSCC, others, including us, were not able to detect EGFRvIII by qRT-PCR or immunochemistry (3–5). EGFRvIII mutations were identified in less than 0.5% of HNSCC samples from The Cancer Genome Atlas project. Therefore, it is likely that other mechanisms than EGFRvIII can contribute to anti-EGFR therapy resistance in HNSCC.

Disclosure of Potential Conflicts of Interest

J.-P. Machiels is a consultant/advisory board member for Boerhinger Ingelheim, MSD, and Debio. No potential conflicts of interest were disclosed by the other authors.

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References

1. Pollock NI, Wang L, Wallweber G, Gooding WE, Huang W, Chenna A, et al. Increased expression of HER2, HER3, and HER2:HER3 heterodimers in HPV-positive HNSCC using a novel proximity-based assay: implications for targeted therapies. Clin Cancer Res 2015;21:4597–606.
2. Machiels JP, Haddad RI, Fayette J, Licitra LF, Tahara M, Vermorken JB, et al. LUX-H&N 1 investigators Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. Lancet Oncol 2015;16:583–94.
3. Wheeler SE, Egloff AM, Wang L, James CD, Hammerman PS, Grandis JR. Challenges in EGFRvIII detection in head and neck squamous cell carcinoma. PLoS One 2015;10:e0117781.
4. Khattri A, Zuo Z, Brägelmann J, Keck MK, El Dinali M, Brown CD, et al. Rare occurrence of EGFRvIII deletion in head and neck squamous cell carcinoma. Oral Oncol 2015;51:53–8.
5. Machiels JP, Specenier P, Krauß J, Dietz A, Kaminsky MC, Lalami Y, et al. A proof of concept trial of the anti-EGFR antibody mixture Sym004 in patients with squamous cell carcinoma of the head and neck. Cancer Chemother Pharmacol 2015;76:13–20.

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