epidemiology studies that address global needs will be very welcome to Annals of Oncology.

**balanced**

Publication and dissemination biases dramatically distort the field of medicine [3]. In order to overcome this issue, the Editorial Board will recommend acceptance of reviews and guidelines written by highly authoritative authors, with a pre-defined and transparent method for literature search and analysis.

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**Demystifying the role of tumor HPV status in recurrent and/or metastatic squamous cell carcinoma of the head and neck**

Progress in molecularly targeted therapeutics and genomic characterization has led to meaningful improvements in the outcome of selected advanced human malignancies [1]. The positive results of the pivotal, phase III EXTREME trial comprised one of the major breakthroughs in the treatment of patients with recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN). The addition of the epidermal growth factor receptor (EGFR) targeting monoclonal antibody cetuximab to cytotoxic chemotherapy was associated with benefit in clinical outcome in this population [2]. Despite this improvement, the median overall survival of R/M SCCHN remains <1 year, underscoring the continued need to seek therapeutic advances in this disease.

The identification of valid prognostic and predictive markers is a key step to unravel the biological complexity of cancer. Prognostic markers classify patients based on their expected outcomes regardless of therapy, including those with poor prognosis who are at the greatest need for intervention. Predictive markers form the basis of precision medicine by providing information related to effects of specific treatments. In the setting of locally or locoregionally advanced SCCHN, in addition to known clinical prognostic markers such as stage, the prognostic role of tumor human papillomavirus (HPV) status in oropharyngeal squamous cell cancers is established [3, 4]. In contrast, while various independent clinical and pathologic prognostic factors for overall survival have been reported in R/M SCCHN, including weight loss, Eastern Cooperative Oncology Group (ECOG) performance status, primary tumor location, prior radiation treatment and tumor cell differentiation [5], no prognostic and/or predictive molecular markers have yet been validated in this patient population. The prognostic impact of HPV status in early-stage disease makes this a biomarker of interest in R/M SCCHN, but its use in this setting remains speculative until sufficient evidence emerges.

In this issue of *Annals of Oncology*, Vermoken et al. carried out a retrospective analysis of the impact of tumor HPV status on outcome in R/M SCCHN, using archival formalin-fixed paraffin-embedded (FFPE) samples available from 416 of 442 patients enrolled in the EXTREME study [6]. Two methods were utilized to ascertain tumor HPV status, HPV deoxyribonucleic acid (DNA) testing by Cervista® oligonucleotide hybridization assay and p16 immunohistochemistry (IHC). In subgroup analyses, survival benefits of chemotherapy plus cetuximab were observed over chemotherapy alone independent of tumor HPV, p16 or combined HPV/p16 status. Within treatment arms, patients with HPV-positive or p16-positive disease had longer survival, although statistical significance was not reached and subgroup sample sizes were generally small. These findings support a prognostic role for tumor HPV status in R/M SCCHN, but do not suggest predictive ability for added efficacy by anti-EGFR antibodies.

These results should be evaluated in the context of other similar data. In addition to EXTREME, two other reports have carried out detailed retrospective analyses of tumor HPV status to evaluate its prognostic significance in patients with R/M SCCHN [7, 8]. In the phase III SPECTRUM study, patients were randomized to receive standard chemotherapy plus the anti-EGFR antibody panitumumab versus standard chemotherapy alone [9]. Tumor HPV status was determined using only p16 IHC staining in FFPE samples, available from 443 of 657 patients enrolled in the trial [7]. Mehra et al. measured both tumor HPV DNA by *in situ* hybridization (Dako) and p16 by
IHC in 65 and 66 patients, respectively, using FFPE specimens collected from two ECOG trials [8]; E1395 randomized 218 patients to cisplatin and paclitaxel versus cisplatin and 5-fluorouracil [10] and E3301 recruited 52 patients in a single-arm phase II study of docetaxel and irinotecan [11].

Pooling of data from these three studies [6–8] may help to more definitively evaluate the role of tumor HPV status in R/M SCCHN. For the assessment of prognostic value, only treatment arms containing cytotoxic chemotherapy alone were selected from the EXTREME, SPECTRUM and ECOG studies, to avoid any potential confounding effects due to the interaction between tumor HPV status and anti-EGFR therapy. Pooled data from the chemotherapy-only arms of these three reports showed that HPV DNA detection or p16 overexpression was associated with improved overall survival, with a reduction in the hazard of death of 30%–40% [hazard ratio (HR) for HPV = 0.61, 95% confidence intervals (CIs) 0.26–1.46; HR for p16 = 0.70, 95% CI 0.52–0.93; Figure 1A]. Both HPV DNA positivity and p16 overexpression demonstrated similar prognostic impact (P-value for difference = 0.78; Figure 1A). In addition, the predictive value of p16 overexpression for the effect of adding anti-EGFR antibody (cetuximab or panitumumab) to standard chemotherapy was evaluated using combined data from EXTREME and SPECTRUM studies only, since the ECOG studies did not investigate molecularly targeted therapy. HPV DNA data were not included to avoid duplication of patient data in this pooled analysis. Overall, the presence of p16 overexpression did not appear to predict for benefit from the addition of anti-EGFR antibodies to cytotoxic chemotherapy; both p16-positive and p16-negative patients appearing to benefit from targeted therapy. The addition of anti-EGFR antibody to chemotherapy had a numerically greater benefit in patients with p16-negative tumors (HR 0.77, 95% CI 0.66–0.91; Figure 1B) compared with those with p16-positive tumors (HR 0.87, 95% CI 0.58–1.32; Figure 1B). However, these differences were not statistically significant (P-value for difference = 0.59; Figure 1B).

Although our limited pooled analysis appears to corroborate the conclusions by Vermorken et al. based on their retrospective

Figure 1. Limited pooled data analysis to evaluate the prognostic (A) and predictive (B) roles of tumor HPV status using retrospective results from EXTREME, SPECTRUM and ECOG studies.
analysis of EXTREME [6], there remains no prospective validation of the prognostic and predictive roles of tumor HPV status in R/M SCCHN. The retrospective nature of subgroup analysis and the small number of HPV/p16-positive patients in the EXTREME, SPECTRUM and ECOG reports (7%–16% of the pooled dataset) limit appropriate multivariable analysis of clinical and molecular prognostic factors. Furthermore, many potentially important variables are heterogeneous across these studies, including distribution of primary tumor sites, geographical origin of patients (Asia-Pacific versus Europe versus North/South America) and treatment interventions (different cytotoxic agents and anti-EGFR antibodies). These may confound and complicate the assessment of the role of HPV/p16 status.

Technical factors may also play a critical part as there are different strategies to determine tumor HPV status [direct (HPV DNA) versus surrogate (p16 IHC) markers], heterogeneous laboratory assays (Cervista®, Dako platforms for in situ hybridization and different antibodies for p16 IHC), and variable p16 cutoffs (percentage of cells with strong staining ranges from 10% to 80% to define positivity) are noted across studies. Although tumor HPV status and p16 IHC positivity have previously been shown to be highly concordant in locally or locoregionally advanced oropharyngeal squamous cell cancers [12, 13], such comparative data have not been available in the R/M SCCHN setting. Since p16 is a cyclin-dependent kinase inhibitor that can be upregulated as a marker of cell cycle modulation and tumor suppression independent of tumor HPV status [14, 15], the significance of its overexpression in R/M SCCHN is less certain. In the EXTREME, SPECTRUM and ECOG studies, among patients who had sufficient tissue for evaluation, between 49% and 60% of patients with positive HPV/p16 status had oropharyngeal squamous cell cancers [6, 8, 9], suggesting that the remaining patients who had these positive markers were from other primary SCCHN sites. It is reassuring that tumor HPV DNA detection and p16 testing were consistent with high concordance rates of 94% among 303 of 416 samples evaluable by both tests in the EXTREME dataset [6], and 98% among 65 samples in the ECOG dataset [8].

The retrospective analyses described above raise the question of whether tumor HPV status should become a standard stratification factor in future randomized trials of R/M SCCHN. Previous studies have shown that inclusion of both HPV DNA and p16 testing can be complementary [16, 17]. This dual testing strategy may also be informative to better characterize patients whose tumors reveal discordant profiles (HPV-negative/p16-positive or HPV-positive/p16-negative). The retrospective analysis of tumor HPV status in the EXTREME trial [6], along with the additional results from the SPECTRUM and ECOG studies [7, 8], have provided the impetus to prospectively stratify patients in R/M SCCHN trials based on their HPV status and perform further validation with p16 IHC evaluations.

A. Spreafico, E. Amir & L. L. Siu*
Division of Medical Oncology and Hematology
Princess Margaret Cancer Centre, University of Toronto,
Toronto, Canada
(*E-mail: lillian.siu@uhn.ca)

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