The current and future impact of human papillomavirus on treatment of squamous cell carcinoma of the head and neck

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Background: Squamous cell carcinoma of the head and neck (SCCHN) was traditionally associated with smoking and alcohol use; however, human papillomavirus (HPV) infection has recently been implicated as a novel risk factor for oropharyngeal tumors. Furthermore, HPV-associated oropharyngeal carcinoma (OPC) appears to be a distinct entity with different epidemiology, biology, and clinical outcomes.

Methods: Here, we comprehensively review the existing data regarding HPV status and prognostic or predictive outcomes in both the locoregionally advanced (LA) and recurrent/metastatic (RM) disease setting and discuss ongoing trials that may eventually impact the treatment of patients with HPV-positive (HPV+) SCCHN.

Results: A body of retrospective and prospective data established an association between HPV+ OPC and better survival, particularly for LA disease. Current data on RM disease are limited, but they also suggest prognostic significance for HPV.

Conclusions: Better outcomes in HPV+ LA disease may allow for less aggressive treatment in the future, and several trials are evaluating deintensified regimens in patients with HPV+, LA OPC; it should be emphasized that deintensification strategies are appropriate only in a clinical research setting and only for selected subgroups of HPV+ patients. In addition, HPV-targeted strategies, such as vaccines, are currently undergoing clinical evaluation. On the other hand, the prognostic impact of HPV in RM disease requires further validation before any modifications in treatment can be made. Likewise, the predictive significance of HPV status in both disease settings remains to be defined.

Clinical Trial Numbers: NCT00226239, NCT00301028, NCT00387127, NCT00410826, NCT00503997, NCT00514943, NCT00544414, NCT00768664, NCT00939627, NCT01084083, NCT01302834, NCT01687413, NCT01706939.

Key words: human papillomavirus, squamous cell carcinoma of the head and neck, oropharyngeal cancer, cetuximab, panitumumab

introduction: human papillomavirus and head and neck cancer

An estimated 53,640 new cases of and 11,520 deaths due to squamous cell carcinoma of the head and neck (SCCHN) are expected to occur in the United States in 2013 [1]. In Europe, 139,000 new cases of SCCHN occur yearly, with mortality rates of 18 and 3 per 100,000 males and females, respectively [2].

More than 90% of head and neck cancers have a squamous histological subtype and originate in the lip/oral cavity, nasopharynx, oropharynx, hypopharynx, or larynx [3]. Locoregionally advanced (LA) SCCHN includes stage III or IV tumors that may have invaded underlying anatomical structures or spread to the cervical lymph nodes. A multimodal regimen of chemotheraphy, radiotherapy (RT), and/or surgery is used to treat LA-SCCHN, with increased intensity depending on clinical risk features. Recurrent/metastatic (RM) SCCHN includes tumors that recur locally, regionally, or at distant sites after treatment or present with distant metastases at primary diagnosis and have a poor prognosis [3].

SCCHN risk factors include tobacco use, alcohol use, and poor oral health [4, 5]. Recently, human papillomavirus (HPV) infection has emerged as a novel risk factor, and its prevalence in oropharyngeal carcinomas (OPCs) is growing in the United
States, Canada, Western Europe, and Australia [6–10]. HPV infection has been reported in 45%–90% of OPCs, and the high-risk HPV16 subtype is the most prevalent [7].

**HPV-associated OPC is a distinct disease entity**

Although HPV is found in SCCHN tumors at many anatomical sites, HPV-induced carcinogenesis usually occurs in the oropharynx [11, 12], which contains multiple structures that promote HPV-induced transformation. Mucosal linings of the tonsils, tonsillar crypts with reticulated, netlike, squamous epithelial lining, and a porous basement membrane allow direct passage of immune cells but also expose the tonsil to pathogens, including HPV [13].

HPV infection promotes tumorigenesis through a complex process. Briefly, HPV encodes E6 and E7 oncoproteins, which deregulate host cellular processes [14]. E6 promotes genomic instability by recruiting E6-associated protein, a ubiquitin ligase, to trigger p53 degradation [15]. p53 abrogation deregulates the G1/S and G2/M checkpoints that are usually induced after DNA damage and cytotoxic stress [13, 16]. E7 degrades retinoblastoma (Rb) protein, disrupting its inhibition of E2F transcription factor and stimulating E2F target transactivation and prematurity entry into S phase [17–19]. Rb degradation also induces expression of p16INK4a (p16)—a hallmark of HPV-associated (HPV+) OPC [20]. Consequently, E6- and E7-mediated gene expression produces a distinct signature compared with non-HPV-associated (HPV−) OPC [21, 22]. In particular, HPV− OPC accumulates approximately twofold more mutations than HPV+ OPC and usually harbors mutated p53, whereas p53 is usually wild type in HPV+ OPC [14, 20]. The molecular profile of HPV+ OPC thus establishes it as a distinct biological entity [23].

Patients with HPV+ OPC tend to be younger, white, and male, although these characteristics do not predict HPV positivity [24]. HPV+ OPC is associated with novel risk factors, including a high lifetime number of oral and/or vaginal sex partners and exposure to marijuana, rather than alcohol and/or tobacco use [12, 25]. Therefore, HPV+ OPC is a separate disease epidemiologically and is potentially characterized by novel risk factors.

HPV+ OPC also appears to be distinct clinically, with tumors that typically present at an early T stage with extensive nodal involvement. Consequently, distant metastasis may be a concern during management of HPV+ OPC [26, 27]. Despite this, the prognosis for HPV+ OPC appears to be better than that for HPV− OPC, particularly in LA disease.

**HPV is associated with improved outcomes in LA-OPC**

Many studies (Table 1) have indicated that HPV+ LA-OPC is associated with better outcomes than is HPV− LA-OPC. Among the most impactful of these studies, the TROG 02.02/HeadSTART phase III study evaluated the addition of tirapazamine, a hypoxia-activated cytotoxin, to concurrent cisplatin + radiotherapy (cisRT). Tirapazamine did not improve the primary end point of overall survival (OS) compared with cisRT alone [29]. However, the relationship between HPV and outcome was determined in a subanalysis of patients with OPC [28]. Of 185 analyzed patients, 106 had p16-positive (p16+) tumors, whereas 79 had p16-negative (p16−) tumors. Patients with p16+ disease had a lower T stage, a higher N stage, and a better performance status (PS) and were less likely to be current smokers. In patients from both arms, 2-year OS was superior in p16+ versus p16− tumors, and p16 status was independently associated with OS [hazard ratio (HR), 0.43; 95% confidence interval (CI) 0.20–0.93; P = 0.031]. Two-year failure-free survival was significantly improved in the p16+ subgroup, whereas the 2-year time to locoregional failure was numerically improved. The rate of distant failures appeared similar in both p16 groups despite advanced nodal status in the p16+ cohort. Although there was no interaction for OS between p16 status and study arm (P = 0.95), a trend for improved locoregional control (LRC) with tirapazamine existed in the p16− cohort: the 2-year time to locoregional failure rate was numerically improved. Of note, interpretation of many retrospective studies—including TROG 02.02/HeadSTART—is complicated by the fact that HPV or p16 status is often available for only a subset of patients.

The phase III RTOG 0129 trial compared accelerated fractionation (AFX) RT + cisplatin and standard fractionation RT + cisplatin and showed no significant difference in OS [30]. In a post hoc analysis of patients from both arms, patients with HPV+ OPC (n = 206) had better OS and progression-free survival (PFS) than patients with HPV− OPC (n = 117). HPV positivity was independently associated with a reduced risk of death (HR, 0.42; 95% CI, 0.27–0.66) and risk of relapse or death (HR, 0.49; 95% CI, 0.33–0.74). The locoregional failure rate, but not the distant failure rate, was lower for HPV+ OPC than for HPV− OPC. In this study, a recursive partitioning analysis was used to separate patients into risk groups associated with survival on the basis of HPV status, smoking, tumor stage, and nodal stage. Most patients with HPV+ OPC were considered to be at low risk of death, although smokers with HPV+, N2-N3 tumors were considered to be at intermediate risk. Nonsmokers with HPV−, T2-T3 tumors were also considered to be at intermediate risk, whereas all other patients with HPV− tumors were considered to be at high risk [30]. Of note, a recent retrospective analysis of patients enrolled in RTOG 0129 and RTOG 0522 demonstrated that patients with HPV+ OPC had superior OS after disease progression compared with patients with HPV− OPC. Furthermore, while advanced tumor stage and high cumulative tobacco exposure at diagnosis and distant metastases were adverse prognostic factors, salvage surgery was reported to significantly improve prognosis [32].

Recently, a retrospective analysis of the phase III IMCL-9815 Bonner trial [53, 54] assessed the role of HPV status in patients with LA-SCCHN treated with either RT or RT + cetuximab [31]. HPV status was determined via p16 immunohistochemistry, with p16 positivity defined as strong and diffuse nuclear staining in >70% of tumor cells. In this subanalysis, p16 was confirmed as a strong prognostic factor for patients with OPC. Moreover, the addition of cetuximab to RT improved LRC, OS, and PFS in both p16+ and p16− patients. Although univariate analyses demonstrated a more dramatic treatment effect stemming from the addition of cetuximab in p16+ patients for all end points in both the intent-to-treat (ITT) and OPC
<table>
<thead>
<tr>
<th>Trial/regimen</th>
<th>N</th>
<th>Prognostic outcomes</th>
<th>Predictive outcomes</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>HPV/p16+ versus HPV/p16−</td>
<td>2-year time to LRF (tirapazamine versus control), p16− group: 92% versus 81%; HR, 0.33; 95% CI, 0.09–1.24, P = 0.13</td>
</tr>
<tr>
<td>TROG 02.02/ HeadSTART [28, 29]</td>
<td>Total: 861</td>
<td>p16+ versus p16− (as assayed by p16 IHC):</td>
<td>–</td>
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<tr>
<td>Phase III</td>
<td>OPC: 465</td>
<td>2-year OS (overall evaluable population): 91% versus 74%; HR, 0.36; 95% CI, 0.17–0.74; P = 0.004</td>
<td>–</td>
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<tr>
<td>Cisplatin + RT ± tirapazamine</td>
<td>Evaluable: 185</td>
<td>2-year FFS (overall evaluable population): 87% versus 72%; HR, 0.39; 95% CI, 0.20–0.74; P = 0.003</td>
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<tr>
<td></td>
<td>p16+: 106</td>
<td>2-year time to LRF (overall evaluable population): 93% versus 86%; HR, 0.43; 95% CI, 0.17–1.11; P = 0.091</td>
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<tr>
<td></td>
<td>p16−: 79</td>
<td>2-year OS (control arm): 89% versus 68%; HR, 0.34; 95% CI, 0.14–0.86; P = 0.021</td>
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<td></td>
<td></td>
<td>2-year OS (tirapazamine arm): 94% versus 80%; HR, 0.36; 95% CI, 0.11–1.18; P = 0.094</td>
<td>–</td>
</tr>
<tr>
<td>Phase III</td>
<td>OPC: 433</td>
<td>3-year OS (overall evaluable population): 82.4% versus 57.1%; HR, 0.38; 95% CI, 0.26–0.55; P &lt; 0.001</td>
<td>–</td>
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<tr>
<td>AFX-CB + cisplatin versus conventional RT + cisplatin</td>
<td>Evaluable: 323</td>
<td>3-year PFS (overall evaluable population): 73.3% and 43.4%; HR, 0.40; 95% CI, 0.29–0.57; P &lt; 0.001</td>
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<tr>
<td></td>
<td>HPV+: 206</td>
<td>p16+ versus p16− (as assayed by p16 IHC):</td>
<td>–</td>
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<tr>
<td></td>
<td>HPV−: 117</td>
<td>3-year OS (overall evaluable population): 83.6% versus 51.3%; HR, 0.29; 95% CI, 0.20–0.43</td>
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<tr>
<td></td>
<td></td>
<td>3-year PFS (overall evaluable population): 74.4% versus 38.4%; HR, 0.33; 95% CI, 0.24–0.46</td>
<td>–</td>
</tr>
<tr>
<td>IMCL-9815 Bonner trial p16 analysis [31]</td>
<td>Total: 424</td>
<td>OS: HR, 0.27; 95% CI, 0.15–0.51</td>
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<tr>
<td>Phase III</td>
<td>OPC: 253</td>
<td>LRC (p16+, RT + cetuximab versus RT): HR = 0.31; 95% CI, 0.11–0.88</td>
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<tr>
<td>RT versus. RT + cetuximab</td>
<td>OPC evaluable: 182</td>
<td>LRC (p16−, RT + cetuximab versus RT): HR = 0.78; 95% CI, 0.49–1.25</td>
<td>–</td>
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<tr>
<td></td>
<td>p16+: 75</td>
<td>OS: (p16+, RT + cetuximab versus RT): HR = 0.38; 95% CI, 0.15–0.94</td>
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<td>OPC evaluable p16−: 107</td>
<td>OS: (p16−, RT + cetuximab versus RT): HR = 0.85; 95% CI, 0.61–1.19</td>
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<td>Interaction tests for both LRC and OS did not demonstrate a significant interaction between p16 status and treatment effect</td>
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<table>
<thead>
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<tr>
<td><strong>RTOG 9003 [32, 33]</strong></td>
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<tr>
<td>Phase III</td>
<td>Total: 1073</td>
<td>HPV/p16+ versus HPV/p16− (as assayed by p16 IHC):</td>
<td>TPF versus control</td>
</tr>
<tr>
<td>Standard FX RT versus hyper-FX RT versus AFX with split versus AFX-CB</td>
<td>OPC: 646</td>
<td>5-year OS (overall evaluable population): 49.0% versus 19.6%; HR: 0.43; 95% CI: 0.31–0.61; P &lt; 0.0001</td>
<td>HPV−: no significant difference in OS due to small sample size and loss of statistical power</td>
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<td></td>
<td>Evaluable: 190</td>
<td>5-year PFS (overall evaluable population): 43.6% versus 19.0%; HR: 0.45; 95% CI: 0.32–0.63; P &lt; 0.0001</td>
<td>HPV+: no significant difference in OS due to small sample size and loss of statistical power</td>
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<td>p16+: 39%</td>
<td>5-year LRF (overall evaluable population): 30.5% versus 54.9%; P &lt; 0.001</td>
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<td>5-year distant metastasis (overall evaluable population): 11.1% versus 13.0%; P = 0.71</td>
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<td>5-year rate of second primary tumor (overall evaluable population): 13.8% versus 11.4%; P = 0.40</td>
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<tr>
<td>TAX 324 [34, 35]</td>
<td>Total: 501</td>
<td>HPV+ versus HPV− (as assayed by E6 and E7 PCR):</td>
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<tr>
<td>Phase III</td>
<td>OPC: 264</td>
<td>OS* (overall evaluable population): 79% versus 31%; HR: 0.2; 95% CI: 0.10–0.38; P &lt; 0.0001</td>
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<tr>
<td>TPF versus PF ICT (both followed by carboplatin/RT)</td>
<td>Evaluable: 111</td>
<td>Median OS (overall evaluable population): NR @ FUP versus 21 months</td>
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<tr>
<td></td>
<td>HPV+: 56</td>
<td>5-year OS (overall evaluable population): 82% versus 35%; P &lt; 0.0001</td>
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<td>HPV−: 55</td>
<td>PFS* (overall evaluable population): 73% versus 29%; P &lt; 0.0001</td>
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<td>5-year PFS (overall evaluable population): 78% versus 28%; P &lt; 0.0001</td>
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<td>LRF (overall evaluable population): 13% versus 42%; P = 0.0006</td>
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<td>Distant failure (overall evaluable population): 5% versus 11%; P = NS</td>
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<td>Total failure (overall evaluable population): 16% versus 49%; P = 0.0002</td>
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<tr>
<td>Phase III</td>
<td>Evaluable (prognostic): 156</td>
<td>5-year LRC (control arm): 58% versus 28%; OR: 0.26; 95% CI: 0.12–0.57; P = 0.0005</td>
<td>p16+: 42% versus 28%; HR: 0.69; 95% CI: 0.50–0.95; P = 0.02</td>
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<tr>
<td>RT ± nimorazole</td>
<td>p16+: 35</td>
<td>5-year DSS (control arm): 72% versus 34%; OR: 0.30; 95% CI: 0.14–0.66; P = 0.0006</td>
<td>p16+: 63% versus 58%; HR: 0.93; 95% CI: 0.45–1.91; P = 0.8</td>
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<td>p16−: 121</td>
<td>5-year OS (control arm): 62% versus 26%; OR: 0.22; 95% CI: 0.08–0.56; P = 0.0003</td>
<td>5-year DSS (nimorazole versus control):</td>
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<td>Evaluable (predictive): 331</td>
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<td>p16+: 46% versus 34%; HR: 0.79; 95% CI: 0.57–1.10</td>
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<td>p16+: 72% versus 69%; HR: 0.84; 95% CI: 0.40–1.77</td>
</tr>
</tbody>
</table>
**RTOG 0522 [39]**

**Phase III**

Cisplatin/RT ± cetuximab

- Total: 895
- OPC: 628
- No specimens available for p16 analysis: 307
- Evaluable: 321
- p16+: 235
- p16−: 86

**ECOG 2399 [40]**

**Phase II prospective trial (HPV− versus HPV+)**

Induction paclitaxel + carboplatin followed by paclitaxel + RT

- Total: 105
- Evaluable: 96
- HPV+: 38 (all were OPC)
- HPV−: 58 (OPC and laryngeal SCC)

**NCT00410826 [41]**

Cisplatin + RT ± erlotinib

- Phase II

- Total: 204
- Evaluable: 84
- p16+ versus p16− (as assayed by p16 IHC):

**CONCERT-1 [42]**

**Phase II**

Cisplatin + RT ± panitumumab

- Total: 150
- Evaluable: 99
- p16+: 42%
- p16−: 58%

**CONCERT-2 [43]**

**Phase II**

Panitumumab + AFX RT versus cisplatin + AFX RT

- Total: 151
- Evaluable: 99
- p16+: 24%
- p16−: 75%

**ECOG 3303 [44]**

**Phase II**

Cetuximab + cisplatin + RT

- Total: 69
- Evaluable: 29
- HPV+: 10
- HPV−: 19

**NCT00387127P [45]**

**Phase II**

Cisplatin + RT ± lopatinib (with maintenance lopatinib or placebo)

- Total: 67
- Evaluable: 46
- p16+: 7
- p16−: 39

**PFS (cetuximab versus control):**

- p16−: no difference between treatment arms
- p16+: nonsignificant trend favoring control arm

**Cohort with no specimens available: no difference between treatment arms**

**OS (cetuximab versus control):**

- p16−: no difference between treatment arms
- p16+: no difference between treatment arms

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Table 1. Continued

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<th>N</th>
<th>Prognostic outcomes HPV/p16+ versus HPV/p16−</th>
<th>Predictive outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-CAIR [46]</td>
<td>Total: 279</td>
<td>HPV+ versus HPV− (as assayed by qPCR for HPVk):</td>
<td>5-year LRC (5 versus 7 days)</td>
</tr>
<tr>
<td>5 days a week versus 7 days a week adjuvant RT</td>
<td>Evaluable: 131</td>
<td>5-year LRC (overall evaluable population): 100% versus 58%; P = 0.02</td>
<td>HPV+: 50.3% versus 65.2%; P = 0.37</td>
</tr>
<tr>
<td></td>
<td>HPV+: 9</td>
<td>5-year distant metastasis-free survival (overall evaluable population): 100% versus 82%; Second primary (overall evaluable population): 2/9 (22.2%) versus 10/122 (8.2%)</td>
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<td></td>
<td>HPV−: 122</td>
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<tr>
<td>NCT00503997 [47]</td>
<td>Total: 42</td>
<td>HPV/p16+ versus HPV/p16− (as assayed by PCR for HPV and p16 IHC):</td>
<td>-</td>
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<tr>
<td>Phase II</td>
<td>Evaluable: 24</td>
<td>HPV+: 17</td>
<td></td>
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<tr>
<td>Pemetrexed + oxaliplatin ICT followed by surgery or CRT</td>
<td>HPV+: 17</td>
<td>ORR: 56.3% versus 14.3%; P = 0.051</td>
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<tr>
<td></td>
<td>HPV−: 7</td>
<td>RFS: 33.7 versus 19.3 months; P = 0.032</td>
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<tr>
<td></td>
<td></td>
<td>OS: 34.1 versus 20.3 months; P = 0.039</td>
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<tr>
<td>NCT00544414 [48]</td>
<td>Total: 31</td>
<td>HPV+ versus HPV− (as assayed by PCR for HPVm):</td>
<td>-</td>
</tr>
<tr>
<td>Phase II</td>
<td>Evaluable: 24</td>
<td>HPV+: 14</td>
<td></td>
</tr>
<tr>
<td>TPF + leucovorin ICT followed by surgery+ RT</td>
<td>HPV+: 14</td>
<td>ORR: 85.7% versus 90.0%; P &gt; 0.05</td>
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<td></td>
<td>HPV−: 10</td>
<td>pCR: 38.5% versus 42.9%; P &gt; 0.05</td>
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<tr>
<td></td>
<td></td>
<td>PFS: better in HPV+ group; HR, 0.15; 95% CI, 0.002–1.25; P = .06</td>
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<tr>
<td></td>
<td></td>
<td>OS: better in HPV+ group; HR, 0.14; 95% CI, 0.001–1.41; P = .10</td>
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<tr>
<td></td>
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<td>Death from cancer: 7% versus 40%; P = 0.17</td>
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<tr>
<td>NCT00301028 [49]</td>
<td>Total: 47</td>
<td>HPV+ versus HPV− (as assayed by HPV ISH):</td>
<td>-</td>
</tr>
<tr>
<td>Phase II</td>
<td>Evaluable: 26</td>
<td>HPV+: 12</td>
<td></td>
</tr>
<tr>
<td>Induction paclitaxel, cetuximab + cisplatin followed by surgery, RT or CRT</td>
<td>HPV+: 12</td>
<td>CR after ICT: 25% versus 21%; P = 1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HPV−: 14</td>
<td>PFS: superior in HPV+ group; P = 0.012 (0/12 events versus 6/14 events (median FUP 33 months))</td>
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<tr>
<td></td>
<td></td>
<td>OS: superior in HPV+ group; P = 0.046 (0/12 events versus 4/14 events)</td>
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</tr>
</tbody>
</table>
Phase II
Cetuximab, docetaxel, and cisplatin ICT followed by cetuximab, cisplatin, and RT with maintenance cetuximab

Total: 39
Evaluable: 28
HPV+: 18
HPV−: 9

HPV+ versus HPV− (as assayed by HPV ISH):
OS: not significantly different; HR, 0.55; 95% CI, 0.13–2.23
PFS: not significantly different; HR, 0.75; 95% CI, 0.19–2.90; P = 0.57
LRF (n): 1/18 versus 3/9
Distant metastasis (n): 3/18 versus 0/9

*p16 IHC was scored by a pathologist for intensity of nuclear and cytoplasmic staining. 2+ (moderate staining) and 3+ (strong) scores were determined to be positive while 0 and 1+ (weak) scores were negative. HPV viral subtypes were also assessed by in situ hybridization and PCR to determine the concordance with p16.

bHPV status was determined by in situ hybridization with probes specific for HPV16 and 12 additional oncogenic types. Tumor p16 expression was evaluated, and positivity was defined as strong and diffuse nuclear and cytoplasmic staining in 70% of more of tumor cells.

*p16 IHC was used as a surrogate marker, with ≥70% expression considered to be a positive signal.

dHPV status was determined by PCR for the E6 and E7 viral oncoproteins.

*After median follow-up of 83 months in the HPV+ cohort and 82 months in the HPV− cohort.

*p16 IHC with strong and diffuse nuclear and cytoplasmic staining in >10% of carcinoma cells.

#HPV status determined by p16 IHC.

The presence of HPV subtypes was identified using a multiplexed PCR/array-hybridization assay. Positive tumors were reassayed using FISH for HPV16 and in situ hybridization for other subtypes.

fHPV status was assayed using a pan-specific DNA probe and bright field in situ hybridization.

HPV status was determined by p16 IHC; p16 IHC was scored as positive if strong and diffuse nuclear and cytoplasmic staining in 70% or more of the malignant cells.

#The presence of HPV was determined using multiplex qPCR for different subtypes of HPV.

PCR and p16 IHC were used to identify HPV+ tumors.

PCR followed by sequencing was used to identify HPV+ tumors.

*As determined by positive nuclear signal from in situ hybridization using probes for high-risk HPV genotypes.

*xThe presence of HPV subtypes was identified using in situ hybridization with a pan-selective probe set.

#Phase III data indicate no significant differences in disease-free survival upon the addition of lapatinib for any of the prespecified subgroups, including HPV [51].

AFX, accelerated fractionation; CB, concomitant boost; CR, complete response; CRR, complete response rate; CRT, chemoradiotherapy; DSS, disease-specific survival; FFS, failure-free survival; FISH, fluorescence in situ hybridization; FX, fractionation; FUP, follow-up; HPV, human papillomavirus; HR, hazard ratio; ICT, induction chemotherapy; IHC, immunohistochemistry; LRC, locoregional control; LRF, locoregional failure; NR, not reached; NS, not significant; OPC, oropharyngeal carcinoma; OR, odds ratio; ORR, overall response rate; OS, overall survival; pCR, pathological complete response; PCR, polymerase chain reaction; PF, cisplatin + 5-fluorouracil; PFS, progression-free survival; qPCR, quantitative PCR; RT, radiotherapy; SCC, squamous cell carcinoma; TPF, paclitaxel + cisplatin/5-fluorouracil.
populations, interaction tests for LRC, OS, and PFS in both the ITT and OPC populations did not demonstrate a statistically significant interaction between p16 status and treatment effect [31]. Thus, these data suggest that the addition of cetuximab confers improved clinical outcome irrespective of p16 status.

Another retrospective analysis to determine the association between HPV and clinical outcomes was conducted in the RTOG 9003 study—a 4-arm, phase III trial [32]. RTOG 9003 compared different RT protocols, of which hyperfractionation and AFX with concomitant boost improved LRC [33]. In a sub-analysis of 190 patients with OPC, p16 positivity was associated with better PS, absence of anemia, T1 stage, and less tobacco use. Regardless of assigned treatment, the p16+ OPC group had superior 5-year OS compared with the p16− group, and PFS was improved. The p16+ cohort had lower 5-year rates of locoregional failure but similar 5-year rates of distant metastases compared with the p16− group [32].

TAX 324, a phase III trial of sequential therapy, investigated the addition of docetaxel to cisplatin + 5-fluorouracil (PF) induction chemotherapy (ICT) versus ICT with PF alone [35]. Both ICT regimens were followed by carboplatin + RT. The addition of docetaxel to PF ICT significantly improved OS—the primary end point. A retrospective analysis of HPV status was conducted in 111 patients with OPC from both treatment arms [34]. In this cohort, patients with HPV+ tumors were more likely to be nonblack, younger, and fitter and had less advanced T-stage tumors. Patients with HPV+ tumors had significantly higher OS and PFS and experienced significantly fewer total failures and locoregional failures and slightly fewer distant failures.

The phase III DAHANCA5 trial added the hypoxic radiosensitizer nimorazole to RT, which improved LRC (the primary end point) compared with RT + placebo [38]. A retrospective analysis of 156 placebo-treated patients was conducted to determine the relationship between HPV and outcome [36]. Of 156 tumors tested, 35 were p16+; of those, 24 were oropharyngeal. Despite including nonoropharyngeal tumors, a significant improvement in LRC was observed for the p16+ subgroup. p16 status also correlated with 5-year disease-specific survival (DSS) and 5-year OS. p16 status was independently associated with locoregional failure (HR, 0.35; 95% CI, 0.19–0.64), cancer-specific mortality (HR, 0.36; 95% CI, 0.20–0.64), and overall mortality (HR, 0.44; 95% CI, 0.28–0.68). In a subsequent predictive analysis including both treatment arms [37], those with p16− disease who received RT + placebo had poorer LRC than did those who received RT + nimorazole. In the p16+ group, LRC was not associated with treatment.

NCT00387127, a phase II study comparing cisplatin + RT ± lapatinib (with maintenance lapatinib or placebo), reported that the difference between study arms was greatest in patients with p16− disease [45]. However, a recent phase III trial in which patients were randomized to concurrent chemotherapy and RT with either lapatinib or placebo found that lapatinib did not extend disease-free survival (DFS)—the primary end point of the study—and that no significant differences in DFS were observed for any of the prespecified subgroups, including HPV+ patients [51].

These analyses were largely retrospective and thus had limitations. For example HPV+ and HPV− groups were not stratified by patient demographics. In addition, different methods of HPV diagnosis were used, adding variability. Moreover, short follow-up in some studies may not have fully captured failure patterns in HPV+ OPC, in which distant metastasis may occur after a longer interval [55]. However, Eastern Cooperative Oncology Group (ECOG) 2399, a phase II study, prospectively separated patients by HPV+ and HPV− disease and included a 5-year follow-up [40]. The HPV+ cohort included only patients with OPC, whereas the HPV− cohort included both patients with OPC and patients with laryngeal carcinoma. Patients received an induction regimen of paclitaxel + carboplatin followed by definitive therapy with paclitaxel + RT. Those with HPV+ disease had higher rates of response after both ICT and paclitaxel + RT. In addition, 1- and 2-year rates of PFS and OS were improved. One potential weakness of the ECOG 2399 study is the relatively low number of patients that were evaluated.

Together, the existing data suggest that HPV is a prognostic factor in LA-OPC. Indeed, among currently available prognostic factors for SCCHN, HPV status in OPC is perhaps the strongest yet identified [30]. HPV positivity appears to be associated with improved LRC but not necessarily improved distant control, suggesting that improved LRC is a major determinant of survival in HPV+ OPC. The optimal test for determination of HPV status has not been identified yet. At present, p16 protein status followed by HPV DNA detection by polymerase chain reaction (PCR) appears to be the most reliable diagnostic algorithm for determination of HPV-associated OPC [20, 56]. However, alternative diagnostic methodologies—including in situ hybridization for HPV—are also routinely used. Demonstration of a single diagnostic algorithm that unequivocally displays optimal sensitivity and specificity awaits future research and represents a topic of significant clinical importance.

The impact of HPV status on treatment response is less established. As mentioned previously, nimorazole and tirapazamine both improved LRC in the HPV− subgroups [28, 37]. A planned subanalysis of the phase III RTOG 0522 trial, which evaluated the addition of the epidermal growth factor receptor (EGFR) immunoglobulin (Ig) G1 monoclonal antibody cetuximab to cisRT, investigated the predictive significance of HPV status [39]. The addition of cetuximab to cisRT did not improve PFS or OS in the overall population. Likewise, the addition of cetuximab did not improve outcomes in the p16− OPC subgroup (n = 86) or in the OPC subgroup without specimens available for analysis (n = 307). A trend existed for worse outcome with the addition of cetuximab in patients with p16+ OPC (n = 235), but was not observed in the subgroup without available specimens, in which ~75% of tumors would be predicted to harbor HPV. Because these outcomes do not align, the observations in the p16+ OPC group may be a random event. Consequently, the predictive significance of HPV status needs further study.

The role of HPV in recurrent/metastatic SCCHN

Only recently was the relationship between HPV and outcomes in RM-SCCHN evaluated in large trials (Table 2). The phase III EXTREME trial randomized patients with RM-SCCHN to
### Table 2. Prognostic and predictive outcomes by HPV or surrogate p16 status in recurrent or metastatic head and neck squamous cell carcinoma

<table>
<thead>
<tr>
<th>Trial/regimen</th>
<th>N</th>
<th>Prognostic outcomes</th>
<th>Predictive outcomes (experimental arm versus control arm)</th>
</tr>
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<tbody>
<tr>
<td><strong>EXTREME [57–60]</strong></td>
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<tr>
<td>Phase III</td>
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<tr>
<td>Platinum + 5-FU ± cetuximab</td>
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<tr>
<td>Total: 442</td>
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<tr>
<td>Evaluable: 381</td>
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<tr>
<td>p16+ = 41</td>
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<tr>
<td>p16− = 340</td>
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<tr>
<td>p16+ versus p16− (as assayed by p16 IHC):</td>
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<tr>
<td>Cetuximab arm:</td>
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<tr>
<td>OS: 12.6 versus 9.7 months; HR, 0.59; 95% CI, 0.32–1.10; $P = 0.0925$</td>
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<tr>
<td>Chemotherapy-alone arm:</td>
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<tr>
<td>OS: 9.6 versus 7.3 months; HR, 0.83; 95% CI, 0.50–1.36; $P = 0.4492$</td>
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<tr>
<td>p16+ cohort:</td>
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<tr>
<td>OS: 12.6 versus 9.6 months; HR, 0.63; 95% CI, 0.30–1.34; $P = 0.2241$</td>
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<tr>
<td>PFS: 5.6 versus 3.6 months; HR, 0.73; 95% CI, 0.36–1.47; $P = 0.3761$</td>
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<tr>
<td>ORR: 50% versus 22%; OR, 3.60; 95% CI, 0.93–13.96; $P = 0.0614$</td>
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<tr>
<td>SPECTRUM [61]</td>
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<tr>
<td>Phase III</td>
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<tr>
<td>Cisplatin + 5-FU ± panitumumab</td>
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<tr>
<td>Total: 657</td>
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<tr>
<td>Evaluable: 443</td>
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<tr>
<td>p16+ = 99</td>
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<tr>
<td>p16− = 344</td>
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<tr>
<td>p16+ versus p16− (as assayed by p16 IHC):</td>
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<tr>
<td>IHC:</td>
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<tr>
<td>Chemotherapy-alone arm:</td>
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<tr>
<td>OS: 12.6 versus 8.6 months (HR, 0.70; 95% CI, 0.47–1.04)</td>
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<tr>
<td>p16+ cohort:</td>
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<tr>
<td>OS: 11.0 versus 12.6 months; HR, 1.00; 95% CI, 0.62–1.61; $P = 0.998$</td>
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<tr>
<td>PFS: 5.6 versus 5.5 months; HR, 1.08; 95% CI, 0.71–1.63; $P = 0.73$</td>
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<tr>
<td>ORR: 37% versus 17%; OR, 2.75; 95% CI, 1.66–4.58; $P &lt; 0.0001$</td>
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<tr>
<td>Pooled analysis of patients from E1395 (cisplatin + 5-FU versus cisplatin + paclitaxel) and E3301 (irinotecan + docetaxel) [62]</td>
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<tr>
<td>Total: 218 (E1395) and 52 (E3301)</td>
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<tr>
<td>Evaluable: 65 (HPV ISH) and 66 (p16 IHC):</td>
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<tr>
<td>HPV+: 11</td>
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<tr>
<td>p16+: 12</td>
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<tr>
<td>HPV/p16−: 54</td>
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<tr>
<td>HPV+ versus HPV− (as assayed by HPV ISH):</td>
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<tr>
<td>OS: 2.66; 95% CI, 1.16–6.09; $P = 0.021$</td>
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<tr>
<td>PFS: 1.63; 95% CI, 0.80–3.32; $P = 0.18$</td>
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<tr>
<td>ORR: 54.5% versus 18.5%; $P = 0.020$</td>
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<tr>
<td>HPV− versus HPV− (as assayed by p16 IHC):</td>
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<tr>
<td>OS: 2.27; 95% CI, 1.04–4.98; $P = 0.04$</td>
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<tr>
<td>PFS: 1.45; 95% CI, 0.73–2.88; $P = 0.29$</td>
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<tr>
<td>ORR: 50% versus 18.5%; $P = 0.048$</td>
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</table>

Continued
<table>
<thead>
<tr>
<th>Trial/regimen</th>
<th>N</th>
<th>Prognostic outcomes</th>
<th>Predictive outcomes (experimental arm versus control arm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00514943 [63]</td>
<td></td>
<td></td>
<td>p16− cohort:</td>
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<tr>
<td>Phase II</td>
<td></td>
<td></td>
<td>ORR: 20.0% (5/25) with afatinib and 8.7% (2/23) with cetuximab</td>
</tr>
<tr>
<td>Afatinib versus cetuximab with crossover after disease progression</td>
<td>Total: 124</td>
<td>HPV/p16+ versus HPV/p16−</td>
<td>p16+ cohort:</td>
</tr>
<tr>
<td></td>
<td>Evaluable: 65</td>
<td></td>
<td>ORR: 11.1% (1/9) with afatinib and 0% (0/8) with cetuximab</td>
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<tr>
<td></td>
<td>p16+: 17</td>
<td></td>
<td>These results may indicate that EGFR inhibitors are more effective in p16− disease</td>
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<tr>
<td></td>
<td>p16−: 48</td>
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<tr>
<td>PARTNER</td>
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<td>p16− cohort:</td>
</tr>
<tr>
<td>Phase II</td>
<td></td>
<td>p16+ versus p16− (as assayed by p16 IHC)</td>
<td>ORR: 20.0% (5/25) with afatinib and 8.7% (2/23) with cetuximab</td>
</tr>
<tr>
<td>Cisplatin + docetaxel ± panitumumab [64]</td>
<td>Total: 103</td>
<td>Panitumumab arm:</td>
<td>p16+ cohort:</td>
</tr>
<tr>
<td></td>
<td>Evaluable: 66</td>
<td>PFS: 8.1 versus 7.3 months</td>
<td>ORR: 11.1% (1/9) with afatinib and 0% (0/8) with cetuximab</td>
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<tr>
<td></td>
<td>p16+: 19</td>
<td>ORR: 67% versus 52%</td>
<td>These results may indicate that EGFR inhibitors are more effective in p16− disease</td>
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<tr>
<td></td>
<td>p16−: 47</td>
<td>Chemotherapy-alone arm:</td>
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<tr>
<td></td>
<td></td>
<td>PFS: 5.7 versus 3.3 months</td>
<td>p16+ cohort:</td>
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<tr>
<td></td>
<td></td>
<td>ORR: 54% versus 27%</td>
<td>ORR: 20.0% (5/25) with afatinib and 8.7% (2/23) with cetuximab</td>
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<tr>
<td>NCT00939627</td>
<td></td>
<td>p16+ versus p16− (as assayed by p16 IHC)</td>
<td>p16+ cohort:</td>
</tr>
<tr>
<td>Phase II</td>
<td>Total: 56</td>
<td>Regardless of treatment arm:</td>
<td>ORR: 20.0% (5/25) with afatinib and 8.7% (2/23) with cetuximab</td>
</tr>
<tr>
<td>Cetuximab ± sorafenib [65]</td>
<td>Evaluable: 38</td>
<td>PFS: 1.6 versus 3.5 months</td>
<td>p16+ cohort:</td>
</tr>
<tr>
<td></td>
<td>p16+: 7</td>
<td>ORR: 52% versus 27%</td>
<td>ORR: 20.0% (5/25) with afatinib and 8.7% (2/23) with cetuximab</td>
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<tr>
<td></td>
<td>p16−: 31</td>
<td>Chemotherapy-alone arm:</td>
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<td></td>
<td></td>
<td>PFS: 3.5 versus 1.6 months</td>
<td>p16+ cohort:</td>
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<tr>
<td></td>
<td></td>
<td>ORR: 54% versus 27%</td>
<td>ORR: 20.0% (5/25) with afatinib and 8.7% (2/23) with cetuximab</td>
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<tr>
<td>NCT00768664</td>
<td></td>
<td>p16+ versus p16− (as assayed by p16 IHC)</td>
<td>p16+ cohort:</td>
</tr>
<tr>
<td>Phase II</td>
<td>Total: 69</td>
<td>HPV/p16+ versus HPV/p16− (as assayed</td>
<td>ORR: 20.0% (5/25) with afatinib and 8.7% (2/23) with cetuximab</td>
</tr>
<tr>
<td>Dacomitinib [66]</td>
<td>Evaluable: 41</td>
<td>by HPV genotyping and p16 IHC):</td>
<td>p16+ cohort:</td>
</tr>
<tr>
<td></td>
<td>HPV+: 13</td>
<td>OS: 59.9 versus 32.7 weeks; HR, 0.47;</td>
<td>ORR: 20.0% (5/25) with afatinib and 8.7% (2/23) with cetuximab</td>
</tr>
<tr>
<td></td>
<td>HPV−: 28</td>
<td>95% CI, 0.21–1.07; P = 0.068</td>
<td>p16+ cohort:</td>
</tr>
</tbody>
</table>

*aAs determined by p16 IHC status with ≥70% expression.

*bAs determined by p16 IHC status with a cutoff of ≥10% tumor cells having strong and diffuse nuclear and cytoplasmic staining.

'As determined using p16 IHC. Positive samples had strong and diffuse staining in ≥80% of tumor cells.

'As determined by p16 IHC. Positive samples had strong and diffuse nuclear and cytoplasmic staining.

'As determined by p16 IHC. Positive samples had strong and diffuse nuclear and cytoplasmic staining.

'As determined using p16 IHC with a cutoff of >10% uniformly staining cells.

'As determined using p16 IHC.

'HPV genotyping and p16 IHC were conducted. p16 IHC was positive if strong and diffuse nuclear and cytoplasmic staining was observed.

'S-FU, 5-fluorouracil; CI, confidence interval; EGFR, epidermal growth factor receptor; HPV, human papillomavirus; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
receive platinum + 5-fluorouracil (5-FU) with or without cetuximab as first-line therapy [57]. Addition of cetuximab to chemotherapy improved OS—the primary end point—as well as PFS, the overall response rate (ORR), disease control rate, and time-to-treatment failure. Recently, a retrospective analysis of HPV status and outcomes was conducted [58, 59]. Paired tissue samples were assessed for p16 expression by immunohistochemistry and HPV using oligonucleotide hybridization assays. Altogether, 416 of 442 patients had samples available for p16 and HPV analysis; 10% of tumors were p16+ and 5% were HPV+ [60]. In the cetuximab arm, 196 of 222 patients had samples available for p16 analysis; 18 were p16+ using a 70% expression cutoff. In the control arm, 185 of 220 patients had samples available for evaluation, and 23 were p16+. Overall, p16 positivity was associated with longer survival than was p16 negativity in both the cetuximab and control arms [58], as was HPV positivity versus HPV negativity. Analysis of assessable patients with OPC demonstrated a similar pattern [60]. In predictive analyses, the p16− subgroup that received cetuximab had longer OS and PFS than did the chemotherapy-alone subgroup [58]. In the p16+ cohort, OS and PFS also favored cetuximab. This pattern remained in a combined analysis of p16 and HPV status. Because adding cetuximab to chemotherapy improved survival regardless of tumor p16 or HPV status, these biomarkers were not predictive of treatment efficacy. Although the number of HPV+ patients in this analysis was low, the results suggested that HPV has prognostic but not predictive significance in RM-SCCHN.

The phase III SPECTRUM trial randomized patients to receive first-line PF with or without the anti-EGFR IgG2 monoclonal antibody panitumumab for RM-SCCHN [61]. The addition of panitumumab to PF significantly improved PFS, but not OS—the primary end point. A prespecified HPV analysis was conducted in 443 of 657 patients. Of these, 99 (22%) had p16+ tumors and 344 (78%) had p16− tumors. In this study, the cutoff for HPV positivity was 10% p16 expression, notably different from the EXTREME analysis parameters. However, analyses using alternative cutoffs (between 10% and 70%) demonstrated consistent outcomes [61]. An analysis for prognostic significance was restricted to the control arm because p16 status was associated with panitumumab efficacy (discussed subsequently). The p16+ subgroup had nonsignificantly longer OS than the p16− subgroup. Analyses of predictive significance for panitumumab efficacy in the p16+ cohort did not reveal differences in OS or PFS. However, in the p16− cohort, OS and PFS favored the panitumumab arm. These results suggest that p16 negativity predicts panitumumab efficacy in RM-SCCHN. However, it is unclear why results with panitumumab + chemotherapy differed from those obtained with cetuximab + chemotherapy in p16+ subgroups. One possible explanation is that cetuximab-induced antibody-dependent cell-mediated cytotoxicity increases antitumor activity against HPV+ OPC—an immunologic cancer; however, this hypothesis requires clinical validation. Nonetheless, SPECTRUM was a negative study overall, and panitumumab is not approved for the treatment of patients with SCCHN.

The ECOG conducted a pooled study of patients with RM-SCCHN from E1395, a phase III trial comparing PF versus cisplatin + paclitaxel, and E3301, a phase II trial of irinotecan + docetaxel [62]. Tumors were analyzed for HPV (65 samples) and p16 (66 samples). Of these, 11 were HPV+ (12 were p16+), and 54 were HPV−/p16−. OS favored patients with HPV+/p16+ disease. No association existed between PFS and HPV/p16 status. Despite this, the ORR was significantly higher in HPV+/p16+ disease. Furthermore, HPV status was independently associated with ORR (OR, 4.01; 95% CI, 1.06–16.85; P = 0.0048). The results of this relatively small study of patients with RM-SCCHN who received cytotoxic chemotherapy without anti-EGFR medication are aligned with the prognostic OS outcomes from EXTREME and SPECTRUM.

Taken together, these three studies are congruent regarding the relationship between HPV positivity and improved survival. What remains unclear is the impact of anti-EGFR antibodies on outcome in HPV+ and HPV− subgroups. A further complication is the inclusion of non-OPC tumors in these studies because p16 is unvalidated as an HPV marker at other sites [67, 68]. Unfortunately, the other studies listed in Table 2 are too small to resolve any of these issues. Thus, further investigation is needed in RM-SCCHN.

**treatment of HPV+ OPC**

Currently, patients with HPV+ OPC are treated similarly to age- and stage-matched HPV− counterparts, although HPV testing of OPC is recommended for prognostic purposes [3]. Yet, because HPV+ OPC is associated with a distinct patient profile, treatment goals and selection of therapy may differ in these patients. Because patients with HPV+ LA-OPC are expected to live longer after treatment, avoiding late toxicity and maintaining quality of life (QoL) are particularly important. These goals may be met by using less aggressive therapy, i.e. treatment deintensification. Because HPV+ LA-OPC responds well to RT-based therapy, deintensification may maintain efficacy while reducing treatment-related morbidity and preserving patient QoL, and investigations are ongoing. Treatment strategies for HPV+ RM-SCCHN have not yet emerged because the significance of HPV in this setting is less clear. Moreover, long-term survivors with RM-SCCHN (still not identifiable) are rather exceptional, regardless of HPV status.

Deintensification strategies for HPV+ LA-OPC include reducing the RT dose, using RT alone rather than chemoradiotherapy (CRT), and replacing chemotherapy with targeted agents [69]. Importantly, in the Bonner study, which established the efficacy of cetuximab + RT (cetRT) in LA-SCCHN [53], subgroups that benefitted the most with cetuximab were consistent with an HPV+ profile including OPC, advanced N stage, good PS, and younger age [54]. In addition, a small hypothesis-generating, retrospective analysis suggested that patients with p16+ tumors treated with RT and an EGFR inhibitor had better survival than those treated with CRT [70]. Together, these results provide a rationale for evaluating targeted therapy as a deintensification strategy.

Despite the overall good prognosis for HPV+ OPC, an aggressive subtype exists that is characterized by distant spread and early death [27, 55, 71]. Furthermore, smoking and advanced nodal stage remain associated with worse prognosis in HPV+ disease [30, 72]. Thus, some patients with HPV+ OPC remain at risk of poor outcomes, complicating deintensification efforts. Risk-stratification models incorporating tobacco use and nodal
ongoing trials in HPV+ OPC

HPV+ OPC is a distinct disease associated with different patients and outcomes. Thus, future clinical trials in LA-SCCHN should at the very least stratify by HPV status. Ideally, HPV+ and HPV– groups should be evaluated in separate trials.

Ongoing trials in HPV+ LA-OPC are primarily evaluating treatment deintensification. ECOG 1308 (NCT01084083), a phase II trial, examined a deintensification strategy of RT dose reduction, and preliminary data were recently released [74]. In ECOG 1308, patients with HPV+ OPC received paclitaxel, cisplatin, and cetuximab ICT. Candidates for deintensification were selected on the basis of their response to ICT. Patients with a complete response (CR) received low-dose intensity-modulated RT (54 Gy in 27 fractions) + cetuximab. Patients with a partial response (PR) or stable disease received standard-dose intensity-modulated RT (69.3 Gy in 33 fractions) + cetuximab. Of 80 assessable patients, 62 received the low-dose regimen, 15 received the standard-dose regimen, and 3 withdrew after ICT. After ICT, clinical response at the primary site was 71.3% CR and 8.8% PR. After completion of therapy, the clinical ORR at the primary site was 94%. One-year PFS rates were 91 and 87% in the low- and standard-dose arms, respectively. Subanalyses of high-risk cohorts, including T4 stage, N2c stage, and smoking history of >10 pack-years, indicated promising efficacy with low-dose RT, with 1-year PFS rates of 86, 88, and 84%, respectively. Toxicities during ICT included rash (21% grade 3, 4% grade 4) and neutropenia (9% grade 3, 2% grade 4). Toxicities during CRT included mucositis (31% grade 3), dysphagia (17% grade 3), rash (13% grade 3), lymphopenia (13% grade 3, 1% grade 4), and radiation dermatitis (8% grade 3). Although the primary end point of 2-year PFS is not mature, preliminary results suggest good tolerability, low toxicity, and efficacy, even in high-risk patients. However, because distant relapses may occur beyond 3 years in HPV+ OPC [55], longer follow-up may be needed to determine the promise of this deintensification approach. Nonetheless, final results are eagerly awaited.

The phase III RTOG 1016 trial (NCT01302834) is evaluating a deintensification strategy that replaces cisplatin with cetuximab [75]. Patients with p16+ OPC are randomized to receive cetuximab + intensity-modulated RT or cisplatin + intensity-modulated RT. The goal is to determine whether cetRT has efficacy that is noninferior to cisRT and produces less toxicity to yield better QoL. The primary end point is 5-year OS. Secondary end points include PFS, failure patterns, acute and late toxicity, and QoL. The planned enrollment is 1000 patients. RTOG 1016 was expected to conclude in June 2020 but is nearing its target accrual as of May 2014 (889 patients enrolled as of 1 May 2014) [76].

DeESCALaTE HPV (EudraCT 2011–005165-21) is a phase III European trial that is also comparing cetRT with cisRT in 304 patients with low-risk [30] p16+ LA-OPC [77]. The primary end point is severe toxicity. Secondary end points include OS, failure patterns, acute and late toxicity, and QoL. The anticipated study completion date is February 2015 [78].

The phase III Quarterback trial (NCT01706939) is investigating a deintensification scheme of low-dose RT plus targeted therapy [79]. Patients with HPV16– and p16+ disease receive TPF ICT with paclitaxel + PF; those who respond are randomized to low-dose RT + carboplatin + cetuximab or standard-dose RT + carboplatin. Nonresponders receive standard-dose CRT. The primary noninferiority end point is 3-year PFS. Secondary end points include OS, LRC, and toxicity. The estimated enrollment is 365 patients, and the estimated study completion date is June 2021.

ADEPT (NCT01687413) is a phase III trial exploring adjuvant RT without chemotherapy [80]. Eligible patients have extracapsular lymph node spread and a negative tumor margin after transoral resection. Patients are randomized to receive intensity-modulated RT + cisplatin or intensity-modulated RT alone. Primary end points are DFS and LRC. Secondary end points include distant failure, DSS, toxicity, and QoL. Estimated enrollment is 496 patients, and the anticipated study completion date is October 2021.

These trials are evaluating the feasibility of deintensified therapy. It should be highlighted that not all patients with HPV+ OPCs are candidates for treatment deintensification. RTOG 0129 [39] demonstrated that heavy smokers (>10 pack-years) with advanced nodal stage (N2b, N3) HPV+ OPC have a 3-year OS rate of 70.8%. These results were validated by an Italian study [82], which reported that patients who were classified as ‘intermediate’ risk are not good candidates for deintensification studies. In addition, O’Sullivan et al. [27] showed that patients with HPV+ OPC and advanced nodal (N3) or T stage (T4) have 3-year distant control rates of 72% and 78%, respectively. Therefore, distant pattern of recurrence is not uncommon in HPV OPC, and late relapses (beyond 3 years) may occur. These results have implications for clinical trial design, follow-up, and surveillance of HPV+ OPC.

Another treatment alternative for HPV+ OPC targets the oncogenic driver [69]. The European Organisation for Research and Treatment of Cancer is planning a randomized phase IIb, placebo-controlled trial of TG4001—an HPV16 cancer vaccine [83]. TG4001 will be administered during and after concurrent CRT and will be compared with CRT plus placebo (AP, MD, PhD, unpublished data, August 2013). Patients with intermediate-risk (N2b or N3 with a tobacco history of >10 pack-years) HPV16+ LA-OPC will be eligible. Planned enrollment is 390 patients, and the primary end point is 2-year PFS.

conclusions

The aforementioned studies have established the impact of HPV on prognosis in LA-OPC, although limited data exist regarding
its predictive significance. In RM-SCCHN, data from EXTREME and SPECTRUM and a subanalysis of E1395 and E3301 demonstrated improved prognosis for p16+ subgroups treated with cytotoxic chemotherapy alone. The predictive analyses of EXTREME stratified improved prognosis for p16+ subgroups treated with cytotoxic chemotherapy and SPECTRUM and a subanalysis of E1395 and E3301 demonstrated improved prognosis for p16+ subgroups treated with cytotoxic chemotherapy alone. The predictive analyses of EXTREME and SPECTRUM with cetuximab and panitumumab, respectively, yielded contradictory findings. Further prospective studies in patients with RM-SCCHN, including in both the OPC and non-OPC subgroups, are required. Ongoing trials in HPV+ LA-OPC aim to identify deintensified regimens that can lead to cure without debilitating toxicity. Preliminary results from E1308 suggest that this approach is promising, and the results from RTOG 1016 and other trials are highly anticipated. However, candidates for deintensification should be selected very carefully because patients with intermediate risk have a suboptimal 3-year survival; it should again be noted that deintensification strategies are only appropriate in a clinical research setting. In addition, HPV-targeted approaches appear promising and may become another therapeutic option. It is hoped that these investigations will personalize and ultimately improve care for patients with HPV+ OPC.

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disclosure

AP has a consultant/advisory role with Merck Serono, Genentech, Vaccinogen, and SMS-Oncology and has received honoraria for giving lectures at satellite meetings of Merck Serono.

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Best practices in the management of the psycho-oncologic aspects of head and neck cancer patients: recommendations from the European Head and Neck Cancer Society Make Sense Campaign

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Squamous cell carcinoma of the head and neck (SCCHN) is considered a worldwide health care problem. The majority of patients have a history of alcohol abuse and high-level tobacco consumption; however, SCCHN is also associated with exposure to viruses including human papillomavirus (HPV) and Epstein–Barr virus. A major problem facing SCCHN patients is that their disease is often diagnosed at an advanced stage where treatment options may not be curative, or can have severe post-treatment consequences. Confronted with their diagnosis and treatment options, the patient can express a range of emotional reactions which may lead to maladaptive coping. During the SCCHN patient journey, there are a number of stages where emotional support could be offered. A point of contact should be allocated to help patients navigate these stages and deliver practical emotive support (such as encouraging attendance at hospital appointments, ...