density or alter bone quality such as AI or glucocorticoids. Bone density is a risk factor for osteoporotic fracture and half of the fracture occurs in subjects with T-score ≥−2.5. The decision to treat patients should be tailored on an individual basis taking into account all the risk factors.

Finally, in our study, oral bisphosphonates avoided bone density loss but did not avoid all fractures which were more frequent in older women. Considering the poor gastric absorption, the constraints of pills intake and the poor adherence of oral bisphosphonates, i.v. bisphosphonates represent a valid therapeutic option.

The efficacy of i.v. bisphosphonates in the prevention of AI-induced bone loss has been already published. There is some evidence of the benefit effects of zoledronic acid in survival in postmenopausal early breast cancer patients but data are scarce and need to be improved.

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Controversies and role of HPV16 in recurrent/metastatic squamous cell cancers of the head and neck

Human papillomavirus 16 (HPV16) is etiologically responsible for a distinct subset of squamous cell cancers of the head and neck (SCCHN) of oropharynx (OPX). HPV16 has been shown to be the single strongest prognostic factor for SCCHN but its role in recurrent/metastatic (R/M) SCCHN is not well understood [1]. Recently, presented data from the Extreme and Spectrum study showed conflicting outcomes in overall survival (OS) and progression-free survival based on a HPV16 status [2, 3]. The Extreme study also suggested that the survival benefit of cetuximab treatment was independent of tumor p16 or HPV status and the Spectrum study concluded that p16 status could be a prognostic and predictive marker in patients treated with panitumumab and chemotherapy. Significant differences in HPV16 positivity testing between those studies emphasized again a concern for accuracy when p16 is used as a standalone HPV16 test [4]. In both the Spectrum and Extreme studies, p16 immunohistochemistry was used as a surrogate marker for HPV16 infection with a strong and diffuse nuclear and cytoplasmic staining cutoff at ≥10% of the tumor in the Spectrum, and at ≥70% in the Extreme study. Although the validity of empirically defined p16 cutoff is still questionable, in most clinical trials, ≥70% positivity of the tumor is required for p16 positivity. It is widely known that p16 overexpression occurs independently of HPV infection [5]. For non-OPX SCCHN, p16 alone has a low positive predictive value. Combined analysis of three major clinical trials reported false positives for oral cavity, hypopharynx and larynx at 62%, 66% and 61%, respectively, suggesting that p16 alone in non-OPX SCCHN would plausibly misclassify the tumor [6]. Not in the Spectrum, but in the Extreme study in addition to p16, HPV DNA was detected using the Cervista® HPV 16/18 and Cervista® HPV HR assays; approved by the Food and Drug Administration for cervical specimen. In our opinion, p16 alone, as used in the Spectrum study, is not a prognostic or predictive marker that can be used in clinical trials, especially in those testing HPV16-targeted therapy. As reported in the Extreme study, only 19 of 41 (46%) p16-positive patients tested positive with HPV DNA assay. In the Extreme study, only 24 of 41(58%) p16-positive patients originated in OPX, in HPV DNA-positive group 18 of 24 (75%) (Table 1). In the Spectrum trial, of 99 patients diagnosed as having a HPV16-positive carcinoma, only 47 of those cancers originated in the OPX. The trial resulted in an unusually large sample size of enrolled HPV16-positive patients in an R/M SCCHN clinical trial, where more than half (52 of 99) originated in a non-OPX area [7]. In both studies, the actual HPV16-positive number remains unknown. Prognosis of p16-positive, but HPV DNA-negative, locally advanced OPX SCCHN is significantly different from that for truly HPV-positive patients [8, 9]. Furthermore, since the OPX p16-positive population may be very heterogeneous, other variables may contaminate the data, such as smoking history, low rate of recurrence among HPV-positive cancers, p53 mutations [10]. Overall, we can conclude that, in

Table 1 Distribution of p16-positive and HPV-positive patients in the Extreme study

<table>
<thead>
<tr>
<th>Site</th>
<th>Percentage out of all p16-positive patients (N = 41)</th>
<th>Percentage out of all HPV-positive patients (N = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cetuximab arm (n = 18)</td>
<td>Control arm (n = 23)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>20% (8/41)</td>
<td>39% (16/41)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>10% (4/41)</td>
<td>5% (2/41)</td>
</tr>
<tr>
<td>Larynx</td>
<td>7% (3/41)</td>
<td>5% (2/41)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>7% (3/41)</td>
<td>2% (1/41)</td>
</tr>
<tr>
<td>Other</td>
<td>0% (0/41)</td>
<td>5% (2/41)</td>
</tr>
</tbody>
</table>
both studies, there is a data contamination by inappropriate HPV16 classification, enrichment of HPV-negative patients in the OPX population and unknown smoking status of HPV16-positive patients, which all lead to inaccurate conclusions. Although there are not enough data to recommend any HPV16 testing algorithm, the combination of p16 with a 70% cutoff and HPV DNA testing by polymerase chain reaction (PCR) is a well-accepted standard that offers high sensitivity and specificity. Since the combination of p16 and HPV PCR provides significantly higher sensitivity and specificity for HPV16 positivity, current clinical trials should not rely on a single surrogate biomarker.

Appropriate HPV classification is absolutely necessary and warrants accurate testing. A low rate of enrollment of R/M SCCHN HPV16-positive patients into clinical trials may pose as an accrual challenge, but premature conclusions may lead to an elimination of potentially efficacious drugs from clinical practice.

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‘Pre-cachexia’: a non-existing phenomenon in cancer?

We read with great interest the article by Blum et al. [1] who reported an important validation study on the diagnostic framework of cancer cachexia. For patients with cancer, cachexia is a major problem associated with reduced physical functioning [2], tolerance to anti-cancer therapy [3] and survival [2]. Despite the growing knowledge on the pathophysiology of cachexia, assessment in clinical practice is limited due to lack of adequate diagnostic criteria. The past years, experts developed a diagnostic framework [4] but validation studies were still awaited. Blum et al. reported that differentiation of cachexia from no cachexia using the proposed framework worked out successfully with significant and clinically relevant differences in laboratory values, food intake, performance status and survival [1].

With limited treatment options for cancer cachexia, focus has been shifting to pre-cachexia, a potential early stage of cachexia, in which (multi-modal) interventions may slow down the process of cachexia [4]. Blum et al. defined pre-cachexia as weight loss >1 kg but <5% of usual body weight/6 months [1] and found that, by using these criteria, survival rates were not different from those of patients without cachexia. The authors state that ‘the pre-cachexia stage might be better defined by additional factors representing the cachexia domain, for instance CRP and appetite loss’ [1].

In our cancer centre, we assessed these additional factors and weight loss in 200 patients before start of treatment with (combination) chemotherapy in a prospective study. Pre-cachexia was defined as:

1) Weight loss of >1.0 kg, but <5%;
2) C-Reactive protein ≥8.0 mmol/l, the upper limit of normality in our hospital;
3) Appetite loss: the section AC/S-12 of the FAACT questionnaire ≤24 points [5].

We recruited 85 females and 115 males with a mean age of 64 years (±10 years). The patients were diagnosed with lung cancer (stages II–IV, n = 83, 41.5%), stage IV colorectal cancer (n = 54, 27.0%), prostate cancer (n = 40, 20.0%) or breast cancer (n = 23, 11.5%).

Weight loss was present in 40 patients (20%); inflammation in 107 patients (64%) and anorexia in 16 patients (8.5%), but the combination of the three was only found in one patient, resulting in a pre-cachexia prevalence of 0.5%.

Extending the cut-off value for anorexia measured by FAACT to ≤30, as has been suggested by the Special Interest Group ‘Cachexia-Anorexia in Chronic Wasting Diseases’ from ESPEN, increased the prevalence of pre-cachexia from one to four patients (2%).

Based on these preliminary data, we conclude that the clinical relevance of pre-cachexia in patients with cancer seems to be