Original Research

Association of human papillomavirus and p16 status with mucositis and dysphagia for head and neck cancer patients treated with radiotherapy with or without cetuximab: Assessment from a phase 3 registration trial

James A. Bonner a,*, Jordi Giralt b, Paul M. Harari c, Jose Baselga d, Sharon Spencer e, Diana Bell f, David Raben g, Joyce Liu h, Jeltje Schulten i, Kian K. Ang f, David I. Rosenthal f

a University of Alabama at Birmingham Comprehensive Cancer Center, Department of Radiation Oncology, 619 19th Street South, Birmingham, AL 35233, USA
b Servei d’Oncologia Radioteràpica, Hospital Universitari Vall d’Hebron, 08035 Barcelona, Spain
c Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, 600 Highland Avenue K41 336, Madison, WI 53792, USA
d Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
e University of Alabama, Hazelrig-Salter Radiation Oncology Center, 1700 6th Avenue South, Birmingham, AL 35233, USA
f MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA
g Department of Radiation Oncology at the Anschutz Medical Campus, 1665 Aurora Court, Suite 1032, Aurora, CO 80045, USA
h Merck Serono, Beijing, China
i Merck KGaA, Frankfurter Str 250, 135001, Darmstadt, Germany

Received 21 January 2016; received in revised form 28 April 2016; accepted 6 May 2016
Available online 17 June 2016

KEYWORDS
Cetuximab; IMCL-9815; Mucositis; Dysphagia; p16; HPV; SCCHN

Abstract
Background: Mucositis and dysphagia are common adverse effects of radiotherapy (RT) treatment of locally advanced squamous cell cancer of the head and neck (LA-SCCHN). Chemotherapy added to RT increases survival rates but causes worse mucositis and dysphagia. The aim of this analysis was to assess the impact of p16 status on mucositis, dysphagia, and feeding tube use in LA-SCCHN among patients treated with RT ± cetuximab in the phase 3 IMCL-9815 trial.

Methods: Patients received RT plus weekly cetuximab or RT alone. Subgroup analyses were conducted on patients with p16-positive (n = 75) or p16-negative (n = 106) oropharyngeal cancer (OPC), as determined by immunohistochemical analysis. The onset and duration of
Radiotherapy (RT) for locally advanced head and neck squamous cell carcinoma (LA-SCCHN) can induce mucositis, pain, dysphagia, and diminished quality of life [1,2]. Severe mucositis contributes to the need for narcotic analgesics, intravenous fluids, and gastrostomy feeding and may lead to unplanned RT interruptions, thereby compromising outcomes [3,4]. Concurrent chemotherapy improves survival rates for patients with SCCHN compared with RT alone, but often at the expense of increased mucositis and dysphagia. In contrast, the phase 3 IMCL-9815 trial, which investigated addition of the anti-epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab to RT, showed that cetuximab did not appear to worsen these toxicities when added to RT.

These findings and the recent availability of p16 analyses of the IMCL-9815 trial prompted us to re-evaluate these toxicities by characterizing onset, duration, and incidence in both p16-positive and p16-negative oropharyngeal cancer (OPC). Analysis of the IMCL-9815 trial recently showed that patients with either p16-positive or p16-negative OPC benefitted from the addition of cetuximab to RT [5]. An interaction analysis did not indicate that there was an association between p16 status and the efficacy of cetuximab [5]. We believe that it is important to further examine the toxicity profiles of the p16-positive and p16-negative groups. Our rationale for this belief is further underscored by the vast differences in prognosis between p16-positive and p16-negative OPC: for patients with p16-positive disease, their long life expectancy highlights the need for efficacious therapies that incur fewer long-term adverse effects (e.g. feeding tube use); in contrast, for patients with poorer-prognosis p16-negative disease, their increased fragility necessitates the avoidance of potentially severe adverse effects (e.g. mucositis).

This study is the first to examine the rate of onset and duration of radiation-induced mucositis and dysphagia for patients receiving RT alone or RT and cetuximab. In addition, the role of p16 status was evaluated in the incidence, onset, and duration of mucositis and dysphagia, as well as feeding tube use, in patients with OPC receiving RT plus cetuximab compared with those receiving RT alone in the IMCL-9815 trial.

2. Methods

2.1. Study design

The design of the phase 3, randomized IMCL-9815 cetuximab registration trial has previously been reported in detail [6,7]. Patients with LA-SCCHN were randomized to receive cetuximab plus RT once daily (2.0 Gy/fraction; 5 fractions/week for 7 weeks), twice daily (1.2 Gy/fraction; 10 fractions/week for 6.0–6.5 weeks), or concomitant boost (72 Gy in 6 weeks, using twice-daily fractionation for the final 2.4 weeks) or RT alone. The trial protocol was approved by the ethics committees of all participating centres. The primary end-point of the study was the duration of locoregional control. Secondary end-points included overall survival, progression-free survival, and response rate. Quality of life and incidence of adverse events were also evaluated. In this retrospective subgroup analysis, feeding tube use and the incidence of mucositis and dysphagia were evaluated in the overall safety population (n = 181), as well as subpopulations of patients with p16-positive and
p16-negative OPC subgroups; by definition (see the later discussion), for evaluation of the onset and duration of mucositis and dysphagia, only those patients in the overall safety population who received at least one dose of RT were included (n = 180).

2.2. Safety assessment

Toxicity was assessed using the Radiation Therapy Oncology Group (RTOG) criteria [8]. Assessments of acute toxicity were carried out during weekly RT and through the eighth week after treatment. Late radiation effects were assessed thereafter using RTOG toxicity scales. Mucositis was defined as aphthous stomatitis, gingivitis, glossitis, mouth ulceration, mucous membrane disorder, stomatitis, or ulcerative stomatitis. The onset of mucositis and dysphagia was calculated from the date of the first RT until the first day of mucositis/dysphagia. Duration was calculated from the day of the first onset until resolution to grade 0 or end date. Feeding tube use was derived from a subset of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Head and Neck Cancer (QLQ–H&N35) questionnaire. Scoring was carried out as defined by the EORTC scoring manual. All scores were derived from mutually exclusive sets of items, with scale scores ranging from 0 to 100 after a linear transformation. Data for feeding tube use were reported as the percent of patients with a feeding tube placed; in our study, feeding tubes were inserted on a patient-needed basis (pre-emptive use was not pre-specified in the protocol, nor was it forbidden).

2.3. p16 Assessment

The effect of human papillomavirus (HPV) status on the incidence, onset, and duration of mucositis and dysphagia in patients with OPC was evaluated by determining the presence of p16 as a surrogate marker of HPV in the 181 evaluable patients that comprised the safety population (Fig. 1). p16 Protein expression status was evaluated by means of immunohistochemical analysis using the CINtec histology kit (Ventana Medical Systems Inc, Tucson, AZ, USA). Positive p16 expression was defined as strong and diffuse nuclear and cytoplasmic staining in ≥70% of the tumour cells [9].

2.4. Statistical analysis

The Fisher exact test was used to evaluate differences in baseline characteristics between treatment arms and to calculate \( P \) values for the incidence of mucositis and dysphagia. The onset and duration of toxicities were estimated using the Kaplan–Meier method. Log-rank tests were used to compare the time courses. When durations of mucositis and dysphagia were evaluated, patients were censored if their end date was not available or if their outcome was listed as ongoing.

3. Results

3.1. Baseline characteristics and study populations

The baseline characteristics of the patients in the intent-to-treat population (n = 424), the OPC population
(n = 253), and the p16-evaluable population (n = 182) are presented in Table 1. Characteristics of the total OPC and p16-evaluable OPC populations were similar. Patients with p16-positive OPC had higher Karnofsky scores and were more likely to have stage T1–T3 cancer and be from the United States. Patients with p16-positive OPC were more likely to have received concomitant boost RT. Treatment arms were well balanced with respect to RT regimen. Baseline characteristics of patients receiving RT plus cetuximab or RT alone were well balanced within the p16-positive (n = 75) and p16-negative (n = 106) OPC subsets (Table 1).

The majority of the findings presented in the current analysis were derived from the safety data set; this includes analysis of the overall safety population and the p16 subgroups (Fig. 1). Of the 420 patients in the safety population, 208 were randomized to receive RT plus cetuximab and 212 received RT alone (Table 2).

### 3.2. Mucositis and dysphagia in the safety population

There was no difference in the incidence of all-grade or grade 3/4 mucositis and dysphagia in patients treated with RT plus cetuximab or RT alone (Table 2). Because the treatment arms were well balanced with respect to RT regimen, RT regimens were pooled to assess the onset and duration of mucositis and dysphagia. There was no difference in the onset or duration of grade 3/4 mucositis in patients receiving RT plus cetuximab or RT alone (Fig. 2A and B). Similarly, the onset and duration of grade 3/4 dysphagia were not significantly different in patients who received RT plus cetuximab or RT alone (Fig. 2C and D). These findings remained consistent when all grades of mucositis and dysphagia were considered (Supplementary Table 1). When all RT regimens were considered, the addition of cetuximab did not significantly impact the onset or duration of all-grade or grade 3/4 mucositis and dysphagia (Supplementary Tables 1 and 2).

In contrast, the type of RT regimen had an effect on the incidence of mucositis and dysphagia. Patients who received altered-fractionation RT experienced significantly more events compared with patients who received once-daily RT, regardless of whether cetuximab was included in the regimen (Table 3). However, with the exception of a significantly later onset of dysphagia in patients who received twice-daily RT compared with those who received twice-daily RT plus cetuximab, there was no significant effect of the addition of cetuximab on the onset or duration of all-grade or grade 3/4 mucositis and dysphagia in patients receiving once-daily, twice-daily, or concomitant boost RT regimens (Supplementary Tables 1 and 2).

### 3.3. p16 Subset analysis of mucositis and dysphagia

In the p16-positive and p16-negative OPC populations, the incidence of all-grade and grade 3/4 mucositis and dysphagia was not significantly different between treatments arms (Table 2). Within the p16-positive population, the addition of cetuximab showed a trend toward more cases of grade 3/4 mucositis, all-grade dysphagia, and grade 3/4 dysphagia compared with treatment with RT alone. In the p16-negative population, there was a trend toward more cases of grade 3/4 mucositis but

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OPC a</th>
<th>p16-Positive b</th>
<th>p16-Negative b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex Male</td>
<td>81 (79)</td>
<td>83 (82)</td>
<td>77 (77)</td>
</tr>
<tr>
<td>Age &lt;65 Years</td>
<td>77 (75)</td>
<td>81 (74)</td>
<td>81 (81)</td>
</tr>
<tr>
<td>Site of primary tumour</td>
<td>Oropharynx</td>
<td>100 (100)</td>
<td>100 (100)</td>
</tr>
<tr>
<td>Karnofsky score &gt;80</td>
<td>73 (76)</td>
<td>90 (82)</td>
<td>70 (70)</td>
</tr>
<tr>
<td>Nodal stage N0</td>
<td>11 (13)</td>
<td>7 (9)</td>
<td>17 (17)</td>
</tr>
<tr>
<td>Tumour stage T1–T3</td>
<td>72 (71)</td>
<td>83 (88)</td>
<td>69 (69)</td>
</tr>
<tr>
<td>EGFR expression: % positive cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50%</td>
<td>46 (59)</td>
<td>71 (62)</td>
<td>55 (55)</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>32 (40)</td>
<td>27 (38)</td>
<td>44 (44)</td>
</tr>
<tr>
<td>EGFR expression: Unknown</td>
<td>22 (1)</td>
<td>2 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Radiation fractionation</td>
<td>Concomitant boost</td>
<td>58 (65)</td>
<td>78 (71)</td>
</tr>
<tr>
<td>Once daily</td>
<td>23 (21)</td>
<td>2 (9)</td>
<td>30 (30)</td>
</tr>
<tr>
<td>Twice daily</td>
<td>17 (13)</td>
<td>17 (21)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Region United States</td>
<td>64 (64)</td>
<td>95 (91)</td>
<td>41 (41)</td>
</tr>
</tbody>
</table>

EGFR, epidermal growth factor receptor; OPC, oropharyngeal cancer; RT, radiotherapy.

a Demography analysis was performed on the intent-to-treat population.

b The Fisher exact test did not reveal a significant difference between treatment arms.
In those with p16-positive or p16-negative tumours, the time to onset and duration of grade 3/4 mucositis were not altered by the addition of cetuximab to RT (Fig. 3). When all grades of mucositis were considered, there was a nonsignificant trend toward a later onset of mucositis in p16-negative patients who received RT alone (Supplementary Table 3). The duration of all mucositis grades was not altered by the addition of cetuximab to RT in those with p16-positive or p16-negative tumours.

Table 2
Incidence of adverse events by treatment arm in the overall safety population.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade</th>
<th>Overall safety population</th>
<th>OPC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RT (n = 212 (%))</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT (n = 40 (%))</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT (n = 63 (%))</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>All grades</td>
<td>93</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Grades 3–4</td>
<td>56</td>
<td>78</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>All grades</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Grades 3–4</td>
<td>26</td>
<td>45</td>
</tr>
</tbody>
</table>

OPC, oropharyngeal cancer; RT, radiotherapy.

a Rates of mucositis and dysphagia within the overall safety population were previously published in the study by Bonner et al. [6].

b The Fisher exact test determined that there was no P < 0.05 when treatment arms were compared.

Fig. 2. Kaplan–Meier estimates of onset and duration of grade 3/4 mucositis and dysphagia in the applicable safety population. Onset (A and C) and duration (B and D) of grade 3/4 mucositis (A and B) and dysphagia (C and D) in the applicable safety population (by definition, only those patients in the overall safety population who received at least one dose of RT were included). All RT regimens were combined. RT, radiotherapy.
grades of mucositis in p16-negative patients who received RT plus cetuximab appeared to be numerically longer compared with that of patients who received RT alone (Supplementary Table 3). Although not significant, there was a numerical increase in the duration of all grades of dysphagia in patients with p16-negative disease who received cetuximab plus RT (Supplementary Table 3).

Table 3
Rates of mucositis and dysphagia in the overall safety population by RT regimen.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade</th>
<th>RT + cetuximab</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Once-daily</td>
<td>Altered fractionation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fractionation</td>
<td>(n = 155) (%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>All grades</td>
<td>81.8</td>
<td>94.9</td>
</tr>
<tr>
<td></td>
<td>Grades 3–4</td>
<td>25.5</td>
<td>65</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>All grades</td>
<td>50.9</td>
<td>68.8</td>
</tr>
<tr>
<td></td>
<td>Grades 3–4</td>
<td>16.3</td>
<td>28.6</td>
</tr>
</tbody>
</table>

RT, radiotherapy.

a Twice daily or concomitant-boost RT.

b The Fisher exact test was used to determine the P value.

Fig. 3. Kaplan–Meier estimates of onset and duration of grade 3/4 mucositis in the applicable p16-evaluable OPC subgroups. Onset (A and B) and duration (C and D) of grade 3/4 mucositis in the p16-positive (A and C) and p16-negative (B and D) OPC subgroups (by definition, only those patients in the overall safety population who received at least one dose of RT were included). All RT regimens were combined. OPC, oropharyngeal cancer; RT, radiotherapy.
Overall, the incidence, time to onset, and duration of all-grade and grade 3/4 mucositis did not appear to be different in patients with p16-positive tumours versus those with p16-negative tumours (Table 2, Figs. 3 and 4, and Supplementary Table 3). Patients with p16-positive OPC had a numerically higher incidence of grade 3/4 mucositis and dysphagia compared with those with p16-negative OPC (Table 2), and the onset of dysphagia in patients with p16-negative OPC occurred later compared with patients with p16-positive disease in both treatment arms (Supplementary Table 3).

### 3.4. Feeding tube use

The use of feeding tubes as assessed by responses to the EORTC QLQ-H&N35 questionnaire during and after RT was evaluated in the overall population and the p16-positive and p16-negative OPC subgroups. In the overall population, there was no difference between feeding tube use at 2 months after RT for patients receiving RT plus cetuximab (n = 175) compared with RT alone (n = 159) (Fig. 5). This remained consistent 12 months after RT. In both the p16-positive and the p16-negative subgroups, the rate of placement of feeding tubes at 2 and 12 months after RT was similar for patients who received RT in combination with cetuximab or RT alone (Fig. 5B and C). Compared with patients with p16-positive OPC, the reported use of feeding tubes at 12 months appeared to be numerically greater in patients with p16-negative OPC (Fig. 5B and C).
4. Discussion

Although some investigations of single-institution experiences have suggested that the addition of cetuximab to RT may result in increased rates of grade ≥3 mucositis, compared with radiation alone [10–12], this is the only prospectively randomized trial of these treatments, and these results demonstrated no treatment-related differences in rates of this toxicity. In addition, this is the first report showing that the addition of cetuximab did not alter the rate of onset or duration of grade ≥3 mucositis or dysphagia. Our results have been supported by other single-institution studies [13,14]. Other reviews have suggested that mucosal toxicities occur less frequently with cetuximab and RT treatment compared with cisplatin and RT treatment [15]. The studies that have suggested increased rates of mucositis for the addition of cetuximab to RT have generally been small studies (14–34 patients) and their processes for treatment selection were not well defined. The finding that the incidence, onset, and duration of grade ≥3 mucositis and dysphagia were comparable for RT ± cetuximab is important information for physicians who are selecting treatments and consulting with patients regarding potential side-effects. Furthermore, this study included a retrospective analysis of HPV status and revealed that rates of mucositis and dysphagia were not increased with the addition of cetuximab to RT in either the HPV-positive or HPV-negative population.

We found that for patients enrolled in the prospective IMCL-9815 trial for LA-SCCHN, the addition of cetuximab to RT did not alter the incidence, time to onset, severity, or duration of mucositis and dysphagia, specifically including grade 3 dysphagia defined as requiring gastrostomy feeding tubes. We recently published the efficacy analysis showing that both the p16-positive and p16-negative subgroups had higher locoregional control and overall survival with the addition of cetuximab, although the difference is much greater for the p16-positive group.

Patients in this study were treated with standard-fractionation, altered-fractionation, concomitant boost, or hyperfractionation RT. It is well known that altered-fractionation RT can increase the severity of mucositis. However, in both the standard- and altered-fractionation groups, the severity of mucositis peaked during the last week of treatment. At 12 weeks after the start of treatment, fewer than 10% of patients in both groups had grade 3/4 mucositis; by week 16, almost all patients had healed. Most patients in our study received concomitant boost RT. Although both altered-fractionation RT regimens resulted in a slightly higher incidence of mucositis and dysphagia, the onset and duration of these events did not appear to be affected by RT regimen in the overall or the p16-evaluable OPC populations.

In addition, it is important to note that this trial was conducted in the era of three-dimensional conformal RT and not the more current standard of intensity-modulated radiotherapy (IMRT) for SCCHN. Studies comparing three-dimensional conformal RT and IMRT have shown that IMRT does not reduce the peak incidence of mucositis but may decrease its volume and allow for dose reduction to the pharyngeal constrictors [16]. Therefore, the use of a systemic agent such as cetuximab that does not appear to enhance radiation-induced mucositis remains highly relevant in the IMRT era.

In the overall safety population and p16-evaluable subgroups, we found no significant difference in the rate of feeding tube use during the first year after RT in patients receiving RT plus cetuximab or RT alone. However, there appeared to be a numerically greater incidence of feeding tube usage in patients with p16-negative disease at 12 months after RT. This may be due to underlying differences in patient demographics, including tumour status, performance status, and United States/non–United States origin. Furthermore, HPV-negative patients were more likely to have greater tobacco exposure and more comorbidities than their HPV-positive counterparts [17], which may have contributed to the need for feeding tubes. Although no background characteristics could be confirmed as predictors of feeding tube use in the present trial, this is an interesting hypothesis that could be explored in larger, ongoing studies. Indeed, a limitation of our study is the relatively modest number of patients with feeding tube information available beyond 8 weeks after RT and we cannot exclude the possibility that this patient subgroup is not representative of the entire study patient population at risk; nevertheless, our data do not suggest a difference in feeding tube use between treatment arms.

Given our prior finding that patients with p16-positive or p16-negative OPC benefitted from the addition of cetuximab to RT [5], the present study suggests that cetuximab did not increase mucositis and dysphagia rates in either of these populations. Some observed minor differences in the incidence and kinetics of mucositis and dysphagia in the p16-positive and p16-negative populations may be attributable to the differences between smoking-related and HPV-related disease. The data from this study suggest that cetuximab does not increase acute toxicities in HPV-positive patients while still benefiting overall outcome. However, small sample size is a
limitation of these analyses, and our findings should be regarded as hypothesis generating.

Several ongoing and recently completed trials are investigating the treatment of HPV-positive OPC with RT and cetuximab. The RTOG recently enrolled 987 patients to RTOG 1016, a phase 3 randomized study to compare the treatment of HPV-positive OPC with RT in combination with either cisplatin or cetuximab [18]. The results of this study, which examines treatment efficacy, treatment-related toxicity, and quality of life, are eagerly anticipated. The Eastern Cooperative Oncology Group has completed a phase 2 study (ECOG 1308), in which patients with HPV-positive OPC received three cycles of induction chemotherapy (ICT) consisting of cisplatin, paclitaxel, and cetuximab [19]. Patients who demonstrated a complete response to ICT received a reduced dose of RT with weekly cetuximab. Those who did not achieve a complete response underwent standard RT with weekly cetuximab. Early findings from this study demonstrated a 2-year overall survival rate of 95% in patients who received reduced-dose RT plus cetuximab, which increased to 97% when only patients with fewer than 10 pack-years of smoking were considered. This study suggests that the combination of low-dose RT with cetuximab following ICT may be a worthy alternative regimen for further study.

Cetuximab is a valuable addition to the SCCHN treatment paradigm. Over the last decade, HPV status has emerged as a significant factor in disease aetiology and treatment outcome. The present study suggests that regardless of p16 status, when added to RT, cetuximab does not appear to increase the incidence, onset, or duration of severe mucositis and dysphagia. Furthermore, the addition of cetuximab to RT does not appear to increase the use of feeding tubes during the first year after RT. Given the growing incidence of OPC affecting younger, healthier patients—who have a high expected cure rate—compared with those with tobacco-driven cancers, it is important to find the most effective therapeutic regimen that produces the lowest rates of acute mucositis and dysphagia because these acute toxicities are associated with an increased risk for long-term dysphagia, aspiration, and feeding tube requirement. The results of this study support the use of cetuximab for both p16-positive and p16-negative patients with OPC. The maturing RTOG 1016 trial will give further prospective comparison on the efficacy and toxicity profile for cetuximab versus cisplatin for the p16-positive population.

Acknowledgements

Funding for cetuximab treatment and collection of data for the original registration trial was provided by ImClone Systems, Eli Lilly and Company, Bristol-Myers Squibb, and Merck KGaA, Darmstadt, Germany. The statistical analysis, production of figures, and editorial support for the preparation of this manuscript were provided by Merck KGaA, Darmstadt, Germany, and Merck Serono, Beijing, China. Medical writing assistance was provided by ClinicalThinking (Hamilton, NJ, USA) and funded by Merck KGaA, Darmstadt, Germany.

Author contributions


Conflict of interest statement

J.A.B. receives honorarium from Merck Serono, Eli Lilly, and Bristol-Myers Squibb. J.B. is a consultant for Merck and in the advisory boards for Eli Lilly. J.L. is an employee of Merck Serono, Beijing, China. J.S. is an employee of Merck KGaA, Darmstadt, Germany. D.I.R. receives research funding (grant) from Merck Serono and is in the advisory boards for Merck Serono and Bristol-Myers Squibb. All other authors have no conflicts to report.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.05.008.

References


