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Original Research

Vismodegib in patients with advanced basal cell carcinoma: Primary analysis of STEVIE, an international, open-label trial☆

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Abstract ***Background:*** The SafeTy Events in VIsmodEgib study (STEVIE, ClinicalTrials.gov, NCT01367665), assessed safety and efficacy of vismodegib—a first-in-class Hedgehog pathway inhibitor demonstrating clinical benefit in advanced basal cell carcinoma (BCC)—in a patient population representative of clinical practice. Primary analysis data are presented.
Patients and methods: Patients with locally advanced or metastatic BCC received oral vismodegib 150 mg/d until progressive disease, unacceptable toxicity, or withdrawal. Primary objective was safety. Efficacy variables were assessed as secondary end-points.
Results: Evaluable adult patients ($N = 1215$, 1119 locally advanced; 96 metastatic BCC) from 36 countries were treated; 147 patients (12%) remained on study at time of reporting. Median (range) treatment duration was 8.6 (0–44) months. Most patients (98%) had ≥1 treatment-emergent adverse event (TEAE). The incidence of the most common TEAEs was consistent with reports in previous analyses. No association between creatine phosphokinase (CPK) abnormalities and muscle spasm was observed. Serious TEAEs occurred in 289 patients (23.8%). Exposure ≥12 months did not lead to increased incidence or severity of new TEAEs. The majority of the most common TEAEs ongoing at time of treatment discontinuation resolved by 12 months afterwards, regardless of Gorlin syndrome status. Response rates (investigator-assessed) in patients with histologically confirmed measurable baseline disease were 68.5% (95% confidence interval (CI) 65.7–71.3) in patients with locally advanced BCC and 36.9% (95% CI 26.6–48.1) in patients with metastatic BCC.
Conclusions: The primary analysis of STEVIE demonstrates that vismodegib is tolerable in typical patients in clinical practice; safety profile is consistent with that in previous reports. Long-term exposure was not associated with worsening severity/frequency of TEAEs. Investigator-assessed response rates showed high rate of tumour control.
ClinicalTrials.gov: NCT01367665.

1. Introduction

Basal cell carcinoma (BCC) constitutes approximately 80% of non-melanoma skin cancers and is the most commonly diagnosed cancer worldwide [1,2]. Although most BCCs are curable by surgery, disease may progress to advanced BCC (locally advanced/metastatic BCC), for which radiotherapy and surgery are inappropriate because cure is unlikely and/or because surgery might result in substantial deformity [3,4].

The key molecular driver in the development of BCC is abnormal Hedgehog pathway signalling, exhibited in >90% of BCCs [5]. Vismodegib is a first-in-class inhibitor of the Hedgehog signalling pathway.

Vismodegib is approved (by the US Food and Drug Administration [FDA] and the European Medicines Agency [EMA]) [6,7] for the treatment of adults with metastatic BCC or with locally advanced BCC that is inappropriate for surgery or radiotherapy. The pivotal phase II study ERIVANCE BCC demonstrated vismodegib response rates of 43% and 30% in patients with locally advanced and metastatic BCC, respectively, by independent review [8]. Subsequent analyses from ERIVANCE BCC demonstrated durable responses and a consistent efficacy/safety profile [9,10]. The SafeTy Events in VIsmodEgib study (STEVIE, ClinicalTrials.gov, NCT01367665) assesses safety and efficacy of vismodegib in a setting representative of clinical practice,

and it is the largest study ever conducted in patients with BCC [11]. We report results from the primary analysis of the total evaluable population ($N = 1215$, data cut-off March 16, 2015).

2. Methods

2.1. Study design and patients

STEVIE is a single-arm, multicentre, open-label study involving 167 sites in 36 countries. The study design was previously published [11]. Eligible patients (≥18 years old) had a histologically confirmed diagnosis of locally advanced/metastatic BCC, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate organ function. For patients with locally advanced BCC, the lesion was deemed inoperable/inappropriate for surgery, and radiotherapy must have been previously administered, unless inappropriate. Patients with measurable and/or non-measurable disease, as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, were eligible for enrolment. Patients with Gorlin syndrome who met inclusion criteria were also enrolled.

The study protocol was approved by the institutional review boards or independent ethics committees of participating centres, and the study was undertaken in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. Patient safety was monitored by an independent data safety monitoring board (DSMB) that reviewed all aspects of safety, including death. All patients provided written informed consent.

Enrolled patients received oral vismodegib 150 mg/d continuously until disease progression, unacceptable toxicity, withdrawal of consent, death or other reasons for discontinuation. Dose reductions were not allowed; however, treatment interruption of up to 8 weeks was permitted for management of toxicity or temporary inability to swallow capsules.

Primary end-point was safety. Assessments included treatment-emergent adverse events (TEAEs, defined as occurring between the first administration and 30 days after the last administration of study drug [inclusive] and assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 4.0), limited physical examination, vital signs, ECOG performance status and laboratory parameters. Patients enrolled after approval of study protocol version 2 had five safety follow-up visits at 1, 3, 6, 9 and 12 months after the last dose of vismodegib to assess resolution of TEAEs ongoing at the time of treatment discontinuation and progression-free survival (PFS). Secondary end-points included investigator-assessed objective response according to RECIST v1.1, duration of response (DOR, time from date of earliest response to date of progressive disease [PD] or death), time to response (TTR, time from date of first treatment to date of first documentation of confirmed complete response [CR] or partial response [PR]), PFS (time from date of first therapy to date of progression or death) and overall survival (OS, time from date of first treatment to date of death). Information on quality of life, assessed by Skindex-16 and impact of treatment on disease symptoms in patients with metastatic BCC assessed by MD Anderson Symptom Inventory (MDASI), will be published separately.

Tumour assessment by physical examination was performed every 4–8 weeks. When necessary, computed tomography (CT) and magnetic resonance imaging (MRI) were performed every 8–16 weeks.

2.2. Statistical analysis

The sample size was selected to allow the adverse event (AE) incidence rate to be estimated within 1.6% and 1.8% of the true AE rate, assuming an observed incidence of 10% (i.e. within a 95% Clopper-Pearson confidence interval [CI] of 8.4–11.8) and with a precision to estimate an AE of 1% frequency to within 0.5% and 1% of the true AE rate.

The efficacy-evaluable population included all patients who received at least one dose of study drug and had histologically confirmed disease at baseline (used for PFS and OS analysis). Patients who also had measurable disease at baseline were included in best overall response rate (BORR) and TTR assessments. All time-to-event end-points were analysed using the Kaplan–Meier method; 95% CIs were calculated using the Brookmeyer and Crowley method.

3. Results

3.1. Patient demographics and characteristics

Between June 2011 and September 2014, 1232 patients were enrolled in STEVIE at 167 sites in 36 countries. Seventeen patients were excluded from the safety and efficacy analysis (no documented exposure based on return of drug dispensed), leaving 1215 evaluable patients (1119 locally advanced, 96 metastatic BCC; Supplementary Fig. S1). Table 1 shows baseline characteristics. At the time of clinical cut-off, 147 patients (12%) were receiving treatment with vismodegib. TEAEs were the main reason for treatment discontinuation ($n = 349$).

3.2. Safety

Most patients (1192 [98%]) had ≥1 TEAE on study; the most common (>20% incidence) TEAEs were muscle spasms (807 [66%]), alopecia (747 [62%]), dysgeusia (663 [55%]), decreased weight (493 [41%]), decreased appetite (303 [25%]) and asthenia (291 [24%]) (Supplementary

Table 1
Baseline characteristics and demographics of all patients given study drug.

	Locally advanced BCC $n = 1119$	Metastatic BCC $n = 96$	All patients $n = 1215$
Men, *n* (%)	634 (56.7)	60 (62.5)	694 (57.1)
Women, *n* (%)	485 (43.3)	36 (37.5)	521 (42.9)
Women of childbearing potential, *n* (%)	57 (11.8)	5 (13.9)	62 (11.9)
Age, mean (SD), years	69.7 (16.1)	66.6 (13.0)	69.5 (15.9)
Age, median (range), years	72.0 (18–101)	67.0 (34–95)	72.0 (18–101)
Age group <65 years, *n* (%)	382 (34.1)	43 (44.8)	425 (35.0)
Age group ≥65 years, *n* (%)	737 (65.9)	53 (55.2)	790 (65.0)
Baseline ECOG performance status, *n* (%)			
Grade 0	662 (59.2)	39 (40.6)	701 (57.7)
Grade 1	316 (28.3)	42 (43.8)	358 (29.5)
Grade 2	138 (12.3)	15 (15.6)	153 (12.6)
Gorlin syndrome, *n* (%)			
Yes	214 (19.2)	5 (5.2)	219 (18.1)
No	899 (80.8)	91 (94.8)	990 (81.9)
Median time since first diagnosis, years	8.35	7.82	8.31
Diagnosis histologically confirmed, *n* (%)			
Yes	1111 (99.3)	89 (92.7)	1200 (98.8)
No	8 (0.7)	7 (7.3)	15 (1.2)
Ineligibility for surgery, *n* (%)			
Inoperable	433 (38.7)	–	433 (35.6)
Surgery contraindicated	686 (61.3)	–	686 (56.5)
Substantial morbidity and/or deformity anticipated	385 (34.4)	–	385 (31.7)
Unlikely to be curatively resected, *n* (%)	328 (29.3)	–	328 (27.0)
Other,[a] *n* (%)	88 (7.9)	–	88 (7.2)
Previous radiotherapy, *n* (%)			
Yes	312 (27.9)	59 (61.5)	371 (30.5)
No	806 (72.0)	37 (38.5)	843 (69.4)
Contraindicated	340 (30.4)	11 (11.5)	351 (28.9)
Inappropriate	466 (41.6)	26 (27.1)	492 (40.5)
Sites of disease, *n* (%)			
Skin	1102 (98.5)	32 (33.3)	1134 (93.3)
Extremity	141 (12.6)	5 (5.2)	146 (12.0)
Head	838 (74.9)	12 (12.5)	850 (70.0)
Neck	125 (11.2)	9 (9.4)	134 (11.0)
Trunk	245 (21.9)	10 (10.4)	255 (21.0)
Other skin	194 (17.3)	8 (8.3)	202 (16.6)
Bone	–	31 (32.3)	31 (2.6)
Liver	–	8 (8.3)	8 (0.7)
Lung	–	63 (65.6)	63 (5.2)
Lymph nodes	–	30 (31.3)	30 (2.5)
Lymph nodes local regional	5 (0.4)	–	5 (0.4)
Other site	28 (2.5)	13 (13.5)	41 (3.4)
Disease status, *n* (%)			
Measurable	1085 (97.0)	91 (94.8)	1176 (96.8)
Non-measurable	26 (2.3)	5 (5.2)	31 (2.6)
Total number of target lesions at baseline (median, range)	2216 (2, 1–12)	221 (2, 1–6)	2437 (2, 1–12)

BCC = basal cell carcinoma; ECOG = Eastern Cooperative Oncology Group.
[a] Patients who refused surgery or had other contraindications for medical or surgical reasons.

Table S1). A similar safety profile was observed regardless of Gorlin syndrome status (Supplementary Table S2). To address the impact of treatment exposure, rate of occurrence of TEAEs per 100 patient–years of exposure was calculated (Table 2). The higher rates observed during the first 12 months suggest that there is no trend towards increased number of new TEAEs or grade ≥3 TEAEs with increased time on treatment. Serious TEAEs were reported in 289 patients (23.8%; 260 locally advanced; 29 metastatic BCC) (Supplementary Table S3).

A summary of deaths on study is included in Supplementary Table S4. Grade 5 (fatal) TEAEs occurred in 46 patients (3.8%); seven were considered related to vismodegib by the investigator but showed presence of comorbidities/risk factors in each case (Supplementary Table S5). The DSMB determined these cases to be unrelated to vismodegib ($n = 6$) or not assessable because of insufficient clinical data ($n = 1$).

The TEAEs leading to treatment discontinuation reported in 380 patients (31%) were primarily grade 1/2. The most frequently reported TEAEs were muscle

Table 2
TEAEs by length of exposure.

TEAE by preferred term	Number of events (events per 100 patient–years)	
	Occurring <12 months' treatment (808.9 patient–years)	Occurring ≥12 months' treatment (288.1 patient–years)
Any grade	8578 (1060.5)	1128 (391.6)
Muscle spasm	793 (98.0)	14 (4.9)
Alopecia	732 (90.5)	15 (5.2)
Dysgeusia	647 (80.0)	16 (5.6)
Weight decreased	454 (56.1)	39 (13.5)
Decreased appetite	281 (34.7)	22 (7.6)
Asthenia	269 (33.3)	22 (7.6)
Ageusia	209 (25.8)	4 (1.4)
Nausea	208 (25.7)	10 (3.5)
Fatigue	190 (23.5)	11 (3.8)
Diarrhoea	160 (19.8)	37 (12.8)
Arthralgia	110 (13.6)	14 (4.9)
Constipation	105 (13.0)	11 (3.8)
Headache	87 (10.8)	5 (1.7)
Vomiting	90 (11.1)	12 (4.2)
Anaemia	60 (7.4)	29 (10.1)

CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; TEAE = treatment-emergent adverse event.
For each preferred term, the total number of TEAEs occurring at a rate of at least 10 events per 100 patient–years is displayed. No grade ≥3 TEAEs occurred at ≥10 events per 100 patient–years. The most common grade ≥3 TEAEs in either time period were muscle spasm, weight decreased, GGT increased, hypertension, dysgeusia, asthenia, fatigue and blood CPK level increased. A patient can be counted in both exposure categories if their total duration is 12 months or more. TEAEs were defined as occurring between the first administration of study drug and 30 days after the last administration of study drug, inclusive.

spasm (85 [7%]), dysgeusia (55 [5%]), weight decreased (47 [4%]), alopecia (39 [3%]), decreased appetite (37 [3%]), asthenia (35 [3%]), fatigue (27 [2%]), ageusia (23 [2%]) and nausea (13 [1%]).

Further evaluation of STEVIE showed that 51 patients (4%) with advanced BCC experienced cutaneous squamous cell carcinoma (SCC). Most patients were aged >75 years with lesions located in sun-exposed areas; 18 patients (35%) had a history of cutaneous SCC, three patients (6%) had a history of Bowen disease, and two patients (4%) had a history of actinic keratosis.

Due to the prevalence of muscle spasm in patients taking Hedgehog pathway inhibitors (HPIs), additional assessment of blood creatine phosphokinase (CPK) levels was performed. The TEAE of increased blood CPK was reported in 60 patients (4.9%) (Supplementary Table S1). The exploratory analysis used quantitative laboratory data from patients for whom ≥1 CPK measurement was available during the treatment period and showed CPK elevations in 36.4% of patients who did not experience muscle spasm and 33.9% of patients who did experience muscle spasm (Supplementary Fig. S2 and Supplementary Table S6).

An exploratory analysis of AE reversibility after treatment discontinuation included 266 patients who completed their 12-month follow-up. At the time of treatment discontinuation, 97% of patients had ≥1 ongoing AE. This decreased during the post-treatment phase, with 92.5%, 74.8%, 59.0%, 48.9% and 45.5% of patients having ongoing AEs at 1, 3, 6, 9 and 12 months after treatment, respectively (Supplementary Fig. S3). Analysis of the five most common TEAEs associated with vismodegib treatment—muscle spasm, alopecia, ageusia, dysgeusia and decreased weight—in Gorlin syndrome and non-Gorlin syndrome patient subgroups also showed a reduction in the proportion of patients with ongoing AEs during the post-treatment period (Supplementary Table S7). Most instances of muscle spasm resolved 1–3 months after treatment, and most occurrences of ageusia, dysgeusia and alopecia resolved by 6 months after treatment. Events of weight decreased took slightly longer to resolve; most patients experienced resolution by 12 months after treatment. There were no differences in TEAE resolution between patients with Gorlin syndrome and those without, and the pattern of resolution over time in the two subgroups was similar to that seen in the overall population. A number of patients began receiving commercial vismodegib at the 12-month follow-up visit (four patients with muscle spasms; six patients with alopecia; two patients with ageusia, five patients with dysgeusia and seven patients with weight decreased), confounding interpretability. After patients taking commercial vismodegib were excluded, the prevalence of ongoing AEs was 3.4% for muscle spasm, 8.1% for alopecia, 1.5% for ageusia, 3.4% for dysgeusia and 5.4% for weight decreased. Additional medical review of these ongoing cases showed that most were grade 1 and many of the patients with grade 2/3 AEs also had medical history/risk factors in addition to age that confounded the assessment of the AEs and attribution of the AEs to vismodegib treatment.

3.3. Efficacy

Median follow-up was 17.9 months, and 1161 patients in the efficacy-evaluable population had histologically confirmed measurable disease. Response rates were 68.5% (95% CI 65.7–71.3) in patients with locally advanced BCC and 36.9% (95% CI 26.6–48.1) in patients with metastatic BCC (Table 3), including CR in 33.4% and 4.8% of patients with locally advanced and metastatic BCC, respectively. Other end-points are described in Table 3 and Supplementary Fig. S4. OS data for patients in the efficacy-evaluable population (both cohorts) are immature; therefore, median OS was not estimable. Response rates in patients with Gorlin

Table 3
Best confirmed overall response rate in patients with histologically confirmed and measurable disease.

Efficacy parameter	Locally advanced BCC	Metastatic BCC	Total
Patients with measurable disease at baseline, *n*	1077	84	1161
Best overall response rate			
Responder, *n* (%)	738 (68.5)	31 (36.9)	769 (66.2)
95% CI	(65.66–71.29)	(26.63–48.13)	(63.43–68.96)
Complete response, *n* (%)	360 (33.4)	4 (4.8)	364 (31.4)
Partial response, *n* (%)	378 (35.1)	27 (32.1)	405 (34.9)
Stable disease, *n* (%)	270 (25.1)	39 (46.4)	309 (26.6)
Progressive disease, *n* (%)	21 (1.9)	9 (10.7)	30 (2.6)
Missing or not evaluable, *n* (%)	48 (4.5)	5 (6.0)	53 (4.6)
Median time to response, n	1077	84	1161
months (95% CI)	3.7 (2.9–3.7)	NE (5.5–NE)	3.7 (3.5–3.7)
Median duration of response, n	738	31	175
months (95% CI)	23.0 (20.4–26.7)	13.9 (9.2–NE)	22.7 (20.3–24.8)
Median progression-free survival, n	1103	89	1192
months (95% CI)	23.2 (21.4–26.0)	13.1 (12.0–17.7)	22.1 (20.3–24.7)

BCC = basal cell carcinoma; CI = confidence interval; NE = not estimable.
Data are *n* (%) based on the number of patients with measurable disease at baseline.

Table 4
Best confirmed overall response rate in patients with histologically confirmed and measurable disease by Gorlin syndrome status.

Efficacy parameter	Locally advanced BCC		Metastatic BCC		Total	
	With Gorlin *n* = 213	Without Gorlin *n* = 884	With Gorlin *n* = 5	Without Gorlin *n* = 84	With Gorlin *n* = 218	Without Gorlin *n* = 968
Patients with measurable disease at baseline, *n*	208	863	5	79	213	942
Best overall response rate						
Responder, *n* (%)	170 (81.7)	566 (65.6)	4 (80.0)	27 (34.2)	174 (81.7)	593 (63.0)
95% CI	75.8–86.7	62.3–68.8	28.4–99.5	23.9–45.7	75.8–86.6	59.8–66.0
Complete response, *n* (%)	95 (45.7)	263 (30.5)	1 (20.0)	3 (3.8)	96 (45.1)	266 (28.2)
Partial response, *n* (%)	75 (36.1)	303 (35.1)	3 (60.0)	24 (30.4)	78 (36.6)	327 (34.7)
Stable disease, *n* (%)	31 (14.9)	236 (27.3)	1 (20.0)	38 (48.1)	32 (15.0)	274 (29.1)
Progressive disease, *n* (%)	1 (0.5)	20 (2.3)	–	9 (11.4)	1 (0.5)	29 (3.1)
Missing or not evaluable, *n* (%)	6 (2.9)	41 (4.8)	–	5 (6.3)	6 (2.8)	46 (4.9)
Median time to response, (95% CI), months	2.9 (2.8–3.7)	3.7 (3.0–3.7)	2.0 (1.0–NE)	NE (6.5–NE)	2.9 (2.8–3.7)	3.7 (3.7–3.8)
Median duration of response,[a] (95% CI), months	28.8 (24.8–NE)	18.7 (16.8–21.1)	15.1 (13.9–16.2)	11.0 (8.3–NE)	28.8 (24.8–NE)	18.5 (16.4–20.8)

BCC = basal cell carcinoma; CI = confidence interval; NE = not estimable.
Data are *n* (%) based on the number of patients with measurable disease at baseline.
[a] Analysis based on responders only.

syndrome and histologically confirmed measurable disease were 81.7% (95% CI 75.8–86.7) and 80.0% (95% CI 28.4–99.5) in patients with locally advanced and metastatic BCC, respectively (Table 4).

4. Discussion

The STEVIE patient population is analogous to the real-world setting of advanced BCC because patients were elderly (median 72.0 years in locally advanced BCC) with a high level of comorbidities (91.7%) at baseline. A disease registry evaluating real-world practice in the United States (RegiSONIC study) supports similarities between the STEVIE population and patients treated in routine medical practice, reporting a median age of newly diagnosed patients with locally advanced BCC of 68 years [12]. Epidemiology studies in metastatic BCC have demonstrated a higher predominance of metastatic BCC in males (69%) similar to that in STEVIE (63%) and a similar pattern of disease spread; the most common sites are lymph nodes, lung and bone [13]. The primary analysis results demonstrate a consistent safety profile with that previously reported for vismodegib in patients with advanced BCC [8–11].

Commonly occurring AEs are similar to those seen with other HPIs; most patients experience muscle spasm, alopecia and taste disturbances (ageusia/dysgeusia) [11,14]. Although muscle-related AEs such as muscle spasm are seen with all HPIs, increases in CPK level in

patients taking vismodegib in STEVIE were mostly mild and asymptomatic. TEAEs of increased CPK level were reported in 5% of patients in STEVIE (mainly grade 1/2), with increased CPK level in 64 of 432 patients (14.8%) with available laboratory samples included in the exploratory analysis. TEAEs of increased blood CPK level occurred in ≥30% of patients treated with sonidegib despite the exclusion of patients treated with drugs that might cause muscle damage [14]. There were no reports of rhabdomyolysis in STEVIE. Exploratory analysis did not demonstrate any association between CPK abnormalities and muscle spasm or any clinically relevant sequelae, including renal insufficiency.

As experience with HPIs has increased, questions have arisen regarding the development of cutaneous SCC after exposure to vismodegib and the persistence of AEs after drug discontinuation [15,16]. Data from this large patient population with advanced BCC provide further understanding regarding these events, such as prevalence and risk factors.

The causality assessment in SCC is challenging because the observation occurred in a single-arm study and there is a known increased risk for developing new SCCs in patients with a history of BCC [17,18]. However, the incidence of cutaneous SCC in STEVIE was 4.2%, in contrast with the 12.5% observed in ERIVANCE BCC and consistent with the expected incidence based on literature in a similar population [19]. A recent meta-analysis estimating the risk for subsequent SCC in patients with a history of BCC reported a pooled estimate proportion of 4.3% (95% CI 1.7–10.1%) [18]. Nevertheless, the current analysis is limited by the lack of histological data and a control arm in STEVIE.

Case reports of persistent AEs have been described with vismodegib treatment [19]. STEVIE showed that the majority of common AEs associated with vismodegib treatment (muscle spasm, alopecia, ageusia, dysgeusia and decreased weight) that were ongoing at the time of treatment discontinuation resolved by 12 months after treatment discontinuation. The remaining cases were mostly mild, and confounding factors were present in all cases. The presence of ongoing AEs >6 months after treatment discontinuation might be related to the persistent blood levels of vismodegib due to the long half-life of this protein-bound drug, or it may be related to the physiological process associated with the AE (e.g. the kinetics of the hair growth cycle).

In the current study, most TEAEs that led to treatment discontinuation were grade 1/2, and 147 patients remain on treatment at the time of this report, demonstrating that the chronicity of AEs rather than the severity can lead to discontinuation. Management of TEAEs is essential to optimise treatment benefit; educating patients on what to expect and possible management options is important. Management recommendations that provide guidance for healthcare professionals have been published [20–23], and physicians should consult their local prescribing information for guidance on management of TEAEs.

Efficacy in this analysis was consistent with the previously reported efficacy profile of vismodegib in advanced BCC [10,11]. Response rates of 68.5% and 36.9% in patients with locally advanced and metastatic BCC, respectively, in STEVIE are consistent with those reported by investigators in ERIVANCE BCC at the final (30-month) analysis (60.3% and 48.5%), respectively [10]; DOR and PFS were also consistent with those of the final analysis of ERIVANCE BCC. The Gorlin subgroup analysis indicates that patients with Gorlin syndrome responded better to treatment, with a considerably higher rate of CR (45.1%) than patients without Gorlin syndrome (28.2%), which might be a result of these patients being younger and having a better ECOG performance status than patients without Gorlin syndrome. However, it is clear that response rates in the whole study population were not influenced by the inclusion of patients with Gorlin syndrome because they were similar to response rates in the subgroup of patients without Gorlin syndrome.

Limitations of STEVIE include the absence of a control arm and the lack of independent central review [8]; however, the STEVIE population is reflective of real-world patients seen in everyday practice. A multidisciplinary approach is essential to the decision to treat patients with advanced BCC with use of HPIs. Close follow-up of patients after treatment initiation is necessary to manage TEAEs and assess continued benefit of treatment.

Results from the primary analysis of STEVIE show that vismodegib has a manageable and consistent safety profile in a population representative of patients treated in routine clinical practice. Treatment with vismodegib led to tumour response and control and should be considered for this difficult-to-treat patient group.

Funding support and role of the sponsor

Funding for this study was provided by F. Hoffmann-La Roche, Ltd. (no grant number). This study was designed by the investigators and representatives of the funder. Funder representatives participated in study design; study steering committee meetings; the gathering, analysis or interpretation of the data; and writing of the report and had access to the raw data. The funder was responsible for data gathering and analysis. All authors contributed to the interpretation of the data and subsequent writing, reviewing and amendment of the manuscript. The funder financed writing and editorial support. All authors vouch for the accuracy and completeness of the reported data and attest that the study conformed to the protocol and statistical analysis plan. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest statement

The authors declare the following: Nicole Basset-Séguin: employee of Genentch/F. Hoffmann-La Roche, Ltd.; honoraria from Galderma, Leo, Pierre Fabre, Novartis and Roche; consulting or advisory role for Galderma, Leo, Pierre Fabre, Novartis, Roche; patents, royalties, or other intellectual property from Genentech/F. Hoffmann-La Roche, Ltd.; travel, accommodations, or expenses from Galderma, Leo and Roche. Natalie Dimier: employee of F. Hoffmann-La Roche, Ltd., and holds stock or other ownership. Alberto Fittipaldo: employee of F. Hoffmann-La Roche, Ltd., and holds stock or other ownership. IoannisXynos: employee of F. Hoffmann-La Roche, Ltd., and holds stock or other ownership. Reinhard Dummer: honoraria from Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis and Roche; consulting or advisory role for Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis and Roche; research funding from Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis and Roche. Kate Fife: honoraria from GlaxoSmithKline, Pfizer and Roche; consulting or advisory role for Pfizer and Roche; research funding from AstraZeneca and Roche; travel, accommodations or expenses from Novartis and Roche. Jean-Jacques Grob: honoraria from Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis and Roche; consulting or advisory role Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis and Roche; speaker's bureau for GlaxoSmithKline and Roche; research funding from Bristol-Myers Squibb and Roche; travel, accommodations or expenses from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme and Roche. Axel Hauschild: honoraria from Amgen, Bristol-Myers Squibb, Celgene, Eisai, GlaxoSmithKline, MedImmune, MELA Sciences, Merck Serono, Merck Sharp & Dohme/Merck, Novartis, Oncosec and Roche; consulting or advisory role for Amgen, Bristol-Myers Squibb, Celgene, Eisai, GlaxoSmithKline, MedImmune, MELA Sciences, Merck Serono, Merck Sharp & Dohme, Novartis, Oncosec and Roche; research funding from Amgen, Bristol-Myers Squibb, Celgene, Eisai, GlaxoSmithKline, MedImmune, MELA Sciences, Merck Serono, Merck Sharp & Dohme, Novartis, Oncosec and Roche; travel, accommodations, or expenses from Amgen, Bristol-Myers Squibb, Celgene, Eisai, GlaxoSmithKline, MedImmune, MELA Sciences, Merck Serono, Merck Sharp & Dohme, Novartis, Oncosec and Roche. Rainer Kunstfeld: honoraria from Meda, Menarini, Novartis and Roche; consulting or advisory role for Leo, Meda, Menarini, Novartis, Roche and Sprig. Nicolas Meyer: honoraria from Amgen, Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Pierre Fabre and Roche; consulting or advisory role for Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis and Roche; expert testimony for Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis and Roche; travel, accommodations or expenses from Bristol-Myers Squibb and Roche. Paulo A. Ascierto: consulting or advisory role for Amgen, Array, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Genentech/Roche and Ventana; research funding from Bristol-Myers Squibb, Genentech/Roche and Ventana. Brigitte Dreno: consulting or advisory role for Bristol-Myers Squibb, GlaxoSmithKline, Novartis and Roche; speaker's bureau for Bristol-Myers Squibb, GlaxoSmithKline and Roche; research funding from Bristol-Myers Squibb, GlaxoSmithKline and Roche; travel, accommodations or expenses from Amgen, Bristol-Myers Squibb and Roche. Johan Hansson: consulting or advisory role for Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme, Novartis and Roche; research funding from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis and Roche. Lisa Licitra: consulting or advisory role for AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, Merck Serono, Merck Sharp & Dohme, Novartis, Roche and Sobi. Laurent Mortier: consulting or advisory role for Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharpe & Dohme and Roche; research funding from Bristol-Myers Squibb, CSO Pharma (institution), GlaxoSmithKline, Novartis and Roche; travel, accommodations or expenses from Bristol-Myers Squibb, GlaxoSmithKline, Merck Sharp & Dohme and Roche. Ana Raimundo: consulting or advisory role for Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis and Roche; speaker's bureau for Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme and Roche; travel, accommodations or expenses from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme and Roche. Petr Arenberger, Emi Dika, Caroline Dutriaux, Bernard Guillot, Luc Thomas: no conflicts of interest.

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Appendix 1. List of investigators, sites and patients enrolled

Investigator	Centre	Patients enrolled
Rainer Kunstfeld	AKH Wien; Klinische Abteilung für allgemeine Dermatologie	61
Jean-Jacques Grob	Hopital Timone Adultes; Dermatologie	61
Brigitte Dreno	Hopital Hotel Dieu Et Hme; Clinique Dermatologique	50
Laurent Mortier	Centre Oscar Lambret; Hopital De Jour	41
Paulo Ascierto	Istituto Nazionale Tumori Fondazione G. Pascale	37
Lisa Licitra	Fondazione IRCCS Istituto Nazionale dei Tumori; S.S. Trattamento MedicoTumori dellaTesta e delCollo	33
Caroline Dutriaux	Hopital Saint Andre CHU De Bordeaux; Dermatologie	29
Luc Thomas	Centre Hospitalier Lyon Sud; Dermatologie	27
Nicolas Meyer	Hôpital Larrey Université Paul Sabatier; Service Dermatologie	25
Bernard Guillot	Hopital Saint Eloi; CHU de Montpellier; Svc de Dermatologie	24
Reinhard Dummer	Universitätsspital Zürich; Dermatologische Klinik	23
Nicole Basset-Seguin	Hopital Saint Louis; Dermatologie 1	23
Pertr Arenberger	Fakultni nemocnice Kralovske Vinohrady	20
Kate Fife	Addenbrookes Hospital; Cambridge Cancer Trials Centre, S4 Box 279	19
Johan Hansson	Karolinska Universitetssjukhuset, Solna	18
Ana Raimundo	IPO do Porto; Servico de Oncologia Medica	17
Annalisa Patrizi	Policlinico Sant'Orsola Malpighi; U.O. Dermatologia	16
Eric Winquist	London Regional Cancer Centre, London, Ontario, Canada	15
Verónica Ruiz Soles	Hospital de la Santa Creu i Sant Pau; Servicio de Dermatologia	15
Carlos Guillen Barona	Instituto Valenciano Oncologia; Oncologia Medica	13
Caroline Robert	Institut Gustave Roussy; Comite 5	13
Alfonso Berrocal Jaime	Hospital General Universitario de Valencia; Servicio de oncologia	12
Ekaterina Peycheva	National Specialized Hospital for Active Oncology Treatment; Dermatology Clinic	12
Pablo Fernandez-Penas	Skin and Cancer Foundation Australia	11
Pierre vabres	Chu Site Du Bocage; Dermatologie	11
Sergio Chimenti	Fondazione PTV Policlinico Tor Vergata; Dermatologia	11
Ralf Gutzmer	Medizinische Hochschule Hannover; Klinik für Dermatologie, Allergologie und Venerologie	11
Georgy Moiseevich Manikhas	Saint-Petersburg City Clinical Oncology Dispensary	11
Piergiacomo Calzavara Pinton	Università di Brescia; Dipartimento di Dermatologia	11
Claus Garbe	Universitaets-Hautklinik Tuebingen	10
Nowell Solish	Dr. Nowell Solish Cosmetic Dermatology	10
Maria Concetta Fargnoli	Ospedale San Salvatore (ASL-01); Dip. di Dermatologia U.O.S. di Dermatologia Oncol	10
Ellen de Haas	Erasmus MC; Dermatology	10
Evgeny Levchenko	FSBI Research Oncology Institute n.a. N.N. Petrov of Ministry of Health and Social Development	10
Peter Foley	Skin & Cancer Foundation	9
Franz Trautinger	Landesklinikum St. Pölten	9
Alessandro Testori	Irccs Istituto Europeo Di Oncologia (IEO); Oncologia Medica	9
Yves Poulin	Centre de Recherche Dermatologique du Quebec Metropolitain (CRDQ)	9
Santora Armando	IRCCS Istituto Clinico Humanitas; Farmacia	8
Alexander Stratigos	Andreas Syggros Hospital; 1st University Dermatology Clinic; Oncology Department	8
Dirk Schadendorf	Universitätsklinikum Essen, Klinik für Dermatologie	8
Patrick Schöffski	U.Z. Gasthuisberg; Gezwelziekten – Medische Oncologie	8
Carola Berking	Klinikum der LMU München; Klinik und Poliklinik für Dermatologie und Allergologie	8
Francesco De Rosa	I.R.S.T. Srl – Meldola – FC; Day Hospital Oncologico	8
Dedee Murrell	Premier Specialists	8
Ioannis Bassukas	University General Hospital of loannina; Dermatology and Venereal Diseases Clinic	7
Eva Brun	Skånes Onkologiska Klinik Universitetssjukhusest	7
Robert Herd	Western Infirmary; Division of Cardiovascular and Medical Sciences	7
Martin Leverkus	Klinikum Mannheim Klinik fuer Dermatologie, Venerologie und Allergologie	7
Luis De La Cruz Merino	Hospital Universitario Virgen Macarena; Servicio de Oncologia	7
Vincenzo De Giorgi	Ospedale IOT-Palagi Dermatologia 2	7
Roland Kaufmann	Klinikum Johann-Wolfgang-Goethe-Uni.; Klinik für Dermatologie, Venerologie und Allergologie	7
Susana Puig Sardá	Hospital Clinic i Provincial; Servicio de dermatología	7
Gilberto Castro Junior	Instituto do Cancer do Estado de Sao Paulo – ICESP	6
Suayib Yalcin	Hacettepe Uni Medical Faculty Hospital; Oncology Department	6
Mariusz Sapijaszko	Western Canada Dermatology Institute	6
Janja Ocvirk	Institute of Oncology Ljubljana	6

(*continued*)

Investigator	Centre	Patients enrolled
Lev Demidov	Russian Cancer Research Center	6
Lidija Kandolf Sekulovic	Military Medical Academy	6
Marni Wiseman	Cancer Care Manitoba	6
Zygmunt Adamski	Centrum Diagnostyki Znamion	6
Paola Queirolo	IRCCS Istituto Nazionale Per La Ricerca Sul Cancro (IST); Oncologia Medica A	6
Gabriella Liszkay	Orszagos Onkologiai Intezet; Borgyogyaszati Osztaly	6
Sari Pitkänen	Helsinki University Central Hospital; Skin & Allergy Hospital	6
Jessica Hassel	Universitaetsklinikum Heidelberg	6
Yvetta Vantuchová	Fakultní nemocnice Ostrava; Kožní oddělení	5
Ivana Krajsová	Vseobecna fakultni nemocnice v Praze	5
Elkin Peñaranda	Riesgo De Fractura; Rheumatology	5
Mirna Situm	Clinical Hospital Sisters of Mercy	5
Sergio Azevedo	Hospital das Clinicas − UFRGS	5
Michele Maio	A.O.U. Senese Policlinico Santa Maria Alle Scotte	5
Massimo Aglietta	Fondazione Del Piemonte Per L'oncologia Ircc Di Candiolo; Dipartimento Oncologico	5
Laima Plesniene	National Cancer Institute	5
Slavomir Urbancek	Facultna Nemocnica Roosevelta	5
Ricardo Fernández de Misa	Complejo Hospitalario Nuestra Señora de la Candelaria; Servicio de Dermato	5
Teresa Guerrero Urbano	St Thomas Hospital	5
Rudolf Herbst	HELIOS Klinikum Erfurt, Klinik für Hautkrankheiten und Allergologie	5
Uwe Martens	Klinikum am Gesundbrunnen; Tumorzentrum	5
Klara Mosterd	Maastricht University Medical Centre; Dermatologie	5
Javier Medina Martinez	Complejo Hospitalario de Toledo-H. Virgen de la Salud; Servicio de Dermatologia	5
Gregorio Carretero Hernández	Hospital de Gran Canaria Dr. Negrin; Servicio de Dermatologia	5
Julie Gehl	Herlev Hospital; Onkologisk afdeling	5
Roxana Del Aguila	Inst. De Oncologia Angel H. Roffo; Servicio De Oncologia	4
Patrizio Mulas	Ospedale Armando Businco; Dermatologia	4
Ruth Plummer	Freeman Hospital; Northern Centre for Cancer Care	4
John Lear	Salford Royal NHS Foundation Trust	4
Tudor Eliade Ciuleanu	Prof. Dr. I. Chiricuta Institutul Oncologic	4
Luciano Viana	Hospital de Cancer de Barretos	4
Ingrid Wolf	LKH Graz; Abteilung für allgemeine Dermatologie	4
Axel Hauschild	UNI-Klinikum Campus Kiel Klinik f.Dermatologie Tagesklinik f.Dermatologie	4
Anja Gesierich	Universitätsklinikum Würzburg Klinik und Poliklinik für Dermatologie Venerologie u. Allergologie	4
Laura Eibenschutz	Istituto Dermatologico San Gallicano IRCCS; Dermatologia Oncolgica	4
Steven Bernstein	Victoria Park MediSpa	4
Jose Luis López Estebaranz	Fundacion Hospital de Alcorcon; Servicio de Dermatologia	4
Erwin Schultz	Klinikum Nürnberg Nord; Hautklinik	4
Saverio Cinieri	Ospedale Antonio Perrino; Oncologia Medica	4
Remco van Doorn	LUMC; Dermatologie	4
Richard Martin	Waitemata District Health; General Surgery	4
Michelle Murphy	Cork University Hospital; Dermatology Dept	3
Giuseppe Gullo	St Vincent's Uni Hospital; Medical Oncology	3
Sarolta Karpati	Semmelweis Egyetem; Bor-, Nemikortani es Boronkologiai Klinika	3
Jens Ulrich	Klinikum Dorothea Ch.Erxleben; Klinik für Dermatologie und Allergologie	3
Peter Mohr	Elbe Kliniken Buxtehude Dermatologisches Zentrum	3
Martin Kaatz	SRH Wald-Klinikum Gera; Klinik für Hautkrankheiten und Allergologie	3
Danil Stroyakovskiy	Moscow city oncology hospital #62 of Moscow Healthcare Department	3
Stefano Calvieri	Azienda Ospedaliera Umberto I; Clinica Dermatologica	3
Sebnem Ozkan	Dokuz Eylul University Medicine Faculty; Dermatology	3
Isil Somali	Dokuz Eylul University Medicine Faculty; Dermatology	3
Maria Luisa Zubiri Ara	Hospital Universitario Miguel Servet; Servicio Dermatologia	3
Andrzej Kaszuba	DERMED Centrum Medyczne; Sp zoo	3
Cornelia Toganel	Spital Clinic Judetean Mures; Oncologie	3
Åse Bratland	Oslo Universitetssykehus HF; Radiumhospitalet	3
Josef Koller	LKH Salzburg; Universitätsklinik für Dermatologie	3
Gergana Shalamanova-Deleva	District Oncology Dispensary; Department for Oncology and Dermatology	3
Cornelia Mauch	Klinik der Uni zu Köln; Klinik & Poliklinik fuer Dermatologie & Venerologie	3
Jose Antonio Lopez Martin Jose	Hospital Universitario 12 de Octubre; Servicio de Oncologia	3
Philippe Saiag	Hopital Ambroise Pare; SCE Dermatologie	3
Maria Agustina Segurado	Hospital Universitario del Sureste; Servicio de Dermatologia	3

(*continued on next page*)

(*continued*)

Investigator	Centre	Patients enrolled
Rodriguez		
Jacob Schachter	Sheba Medical Center; Tel Hashomer	3
Eyal Fenig	Rabin Medical Center-Beilinson Campus	3
Armin Bender	Universitätsklinikum Marburg Klinik f. Dermatologie	3
Pedro Mercader Garcia	Hospital General Universitario J.M Morales Meseguer; Servicio de Dermatologia	3
Alvaro Acosta	Inst. Nacional de Cancerologia; Clinica de Seno	2
Natalia Jaimes	Hospital Pablo Tobin Uribe	2
Shireen Sidhu	CMAX A division of IDT Australia Limited	2
Predrag Nikolic	University Hospital Clinical Center Banja Luka	2
Guillermo Jimenez	Reumalab Sas; Rheumatology	2
Jitka Abrahamova	Facultni Thomayerova Nemocnice; Onkologicke Oddeleni	2
Rauno Harvima	Kuopion yliopistollinen sairaala	2
Wolfgang Harth	Vivantes Klinikum Spandau	2
Patrick Terheyden	Universitätsklinikum Schleswig-Holstein; Klinik für Dermatologie, Allergologie und Venerologie	2
Carsten Weishaupt	Universitätsklinikum Münster; Klinik fuer Hautkrankheiten	2
Dorothée Nashan	Klinikum Dortmund gGmbH Klinikzentrum Mitte	2
Vanna Chiarion Sileni	IRCCS Istituto Oncologico Veneto (IOV); Oncologia Medica Seconda	2
Roxolyana Adbah-Bortnyak	Rambam Medical Center	2
Andrzej Cichocki	Centrum Onkologii – Instytut im. Marii Sklodowskiej-Curie; Klinika Onkologiczna	2
Salvatore Siena	Asst Grande Ospedale Metropolitano Niguarda; Dipartimento Di Ematologia Ed Oncologia	2
Paolo Marchetti	Istituto Dermopatico dell'Immacolata (IDI)-IRCCS; IV Divisione Oncologica e Dermatologia Oncologica	2
Jacek Jassem	Uniwersyteckie Centrum Kliniczne, Klinika Onkologii i Radioterapii	2
Rodica Anghel	Institutul Oncologic Prof. Dr. Al. Trestioreanu Bucuresti	2
Jorge Frank	Universitätsklinikum Düsseldorf; Hautklinik	2
Ivan Marquez Rodas	Hospital General Universitario Gregorio Marañon; Servicio de Oncologia	2
Martin Gore	Royal Marsden Hospital	2
Pablo Coto Segura	Hospital Univ. Central de Asturias; Servicio de Dermatologia	2
Rafael Salido Vallejo	Hospital Reina Sofia; Servicio de dermatología	2
José Carlos Moreno Gimenez	Hospital Reina Sofia; Servicio de dermatología	2
Claas Ulrich	Campus Charité Mitte CharitéCentrum 12 Klinik für Dermatologie Venerologie und Allergologie	1
Ana Francisca Ramirez	Hemato Oncologos S.A.	1
Eva Remenyik	Debreceni Egyetem OEC; Borgyogyaszati Klinika	1
Zita Battyani	Kaposi Mor Teaching Hospital	1
Sidika Kurul	Istanbul Uni of Medicine Faculty; Oncology Department	1
Esther De Eusebio	Hospital General Universitario de Guadalajara; Servicio de Dermatologia	1
Andres Garcia-Paolomo Perez	Complejo Asistencial Universitario de Leon; Servicio de Onc	1
Javier Martin Broto	Hospital Universitario Son Espases; Servicio de Oncologia	1
Guillermo Lopez Vivanco	Hospital de Cruces; Servicio de Oncologia	1
Nada Babovic	Institute for Oncology and Radiology of Serbia; Medical Oncology	1
Geke Hospers	Academ Ziekenhuis Groningen; Medical Oncology	1
Lajos Kemeny	Szegedi Tudomanyegyetem; Borgyogyaszati es Allergologiai Klinika	1
Vassilis Georgoulias	Univ General Hosp Heraklion; Medical Oncology	1
Konstantinos Paparzisis	Euromedical General Clinic of Thessaloniki; Oncology Department	1
Helen Gogas	Laiko General Hospital; 1st Pathological Clinic	1
Hans-Robert Metelmann	Universitätsmedizin Greifswald; Klinik für MKG-Chirurgie und Plastische Operationen	1
Rüdiger Hein	Klinikum rechts der Isar der TU München; Klinik & Poliklinik für Dermatologie und Allergologie	1
Maja Banjin	Clinic of Oncology – Clinical Center University of Sarajevo	1
Harald Gollnick	Universitätsklinikum Magdeburg Klinik für Dermatologie und Venerologie	1
Friedegund Meier	Universitätsklinikum 'Carl Gustav Carus'; Klinik und Poliklinik für Dermatologie	1
Annette Stein	Universitätsklinikum 'Carl Gustav Carus'; Klinik und Poliklinik für Dermatologie	1
Mark Berneburg	Universitätsklinikum Regensburg; Klinik und Poliklinik für Dermatologie	1
Edgar Dippel	Klinikum d.Stadt Ludwigshafen Hautklinik	1
Jiri Horazdovsky	Nemocnice Ceske Budejovice	0

Appendix 2. List of ethics committees/institutional review boards

Country	Ethics committee/institutional review board
Argentina	Comite de Docencia e Investigacion del Roffo Av. San martin 5481 C1417DTB Buenos Aires
Australia	Bellberry Human Research Ethics Committee Bellberry Limited 229 Greenhill Road 5065 Dulwich
Austria	Ethikkommission d. Landes Niederösterreich Landhausplatz 1 3109 St. Pölten
Austria	Ethikommission des Land Salzburg Sebastian-Stief-Gasse 2 5010 Salzburg
Austria	EK Graz Med. Fakultaet Universitaet Graz 8036 Graz
Austria	Ethikkommission der Universität Wien /AKH Borschkegasse 8b/E 06 1090 Wien
Belgium	UZ Leuven – Ethisch comite Herestraat, 49 3000 Leuven
Bosnia and Herzegovina	EC Clinical Center University of Sarajevo Bolnicka 25 71 000 Sarajevo
Bosnia and Herzegovina	EC Clinical Center Banja Luka Dvanaest beba bb 78 000 Banja Luka
Brazil	CEP para Analise de Projetos de Pesquisa do HCFMUSP e da FMUSP;Hospital da Universidade de São Paulo Rua Doutor Arnaldo, 455–01246-903 05403-010 São Paulo
Brazil	CEP da Fundacao Pio XII – Hospital de Cancer de Barretos Rua Antenor Duarte Vilela 1331 14784-400 Barretos
Brazil	Comitê de Ética em Pesquisa do Hospital de Clínicas de Porto Alegre Hospital de Clínicas de Porto Alegre Rua Ramiro Barcelos, 2350 90035-003 Porto Alegre
Bulgaria	Local Ethics Committee Specialized Hospital For Active Treatment in Oncology 6 Plovdivsko pole Street 1756 Sofia
Bulgaria	Local Ethics Committee Complex Oncology Center – Plovdiv 2A, Alexander Stamboliisky Str 4004 Plovdiv
Canada	Quorum Review IRB 1501 Fourth Ave. Suite 800 98101 Seattle
Canada	Health Research Ethics Board University of Alberta 308 Campus Tower 8625-112 Street T6G 1K8 Edmonton
Canada	University of Western Ontario Office of Research Ethics Support Services Building, 1393 Western Road N6A 3K7 London
Canada	Biomedical Research Ethics Board Univeristy Of Manitoba – Faculty Of Medicine P126 R3E 0W3 Winnipeg
Colombia	Comité de Etica CAYRE Carrera 12 No. 98-38 Bogotá
Colombia	Comité de Ética en Investigación del Instituto Nacional de Cancerologia Empresa social del Estado Bogotá
Colombia	Comité de Investigaciones y ética en Investigaciones CALLE 78 B NO. 69-240 0 MEDELLIN
Colombia	CREIMED. Comite de Estudios Medicos S.A.S Carrera 43 A # 34 – 155 Piso 6 Medellin
Colombia	Comité de Etica en Investigacion IDYCIC SAS Carrera 21 # 14 – 80 Casa G 8 Chia
Croatia	Central Ethics Committee Agency for Medicinal Products and Medical Devices, Ksaverska cesta 4 10000 Zagreb
Czech Republic	Eticka Komise Vseobecne fakultni nemocnice Na Bojisti 1 128 08 Praha 2
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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2017.08.022.

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