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An international expanded-access programme of everolimus: Addressing safety and efficacy in patients with metastatic renal cell carcinoma who progress after initial vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapy

Viktor Grünwald [a,], Pierre I. Karakiewicz [b], Sevil E. Bavbek [c], Kurt Miller [d], Jean-Pascal Machiels [e], Se-Hoon Lee [f], James Larkin [g], Petri Bono [h], Sun Young Rha [i], Daniel Castellano [j], Christian U. Blank [k], Jennifer J. Knox [l], Robert Hawkins [m], Oezlem Anak [n], Marianne Rosamilia [o], Jocelyn Booth [o], Nicoletta Pirotta [n], István Bodrogi [p], on behalf of the REACT Study Group*

[a] *Clinic for Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Medical School Hannover, Hannover, Germany*
[b] *Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center, Montreal, Canada*
[c] *Istanbul University, Oncology Institute, Istanbul, Turkey*
[d] *Department of Urology, Charité-Universitätsmedizin, Berlin, Germany*
[e] *Cancer Center, Université Catholique de Louvain, Cliniques Universitaires Saint-Luc, Bruxelles, Belgium*
[f] *Department of Medicine, Seoul National University Hospital, Seoul, South Korea*
[g] *Urology Unit, Royal Marsden Hospital, London, UK*
[h] *Department of Oncology, Helsinki University Hospital, Helsinki, Finland*
[i] *Department of Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*
[j] *Hospital Universitario 12 de Octubre, Madrid, Spain*
[k] *NKI-AVL, The Netherlands Cancer Institute, Amsterdam, The Netherlands*
[l] *Princess Margaret Hospital, Toronto, Ontario, Canada*
[m] *Christie Hospital NHS Trust, Manchester, UK*
[n] *Novartis Oncology Global Development, Basel, Switzerland*
[o] *Novartis Oncology Global Development, Florham Park, NJ, USA*
[p] *National Institute of Oncology, Budapest, Hungary*

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ABSTRACT

Background and objectives: The RECORD-1 trial established the clinical benefit of everolimus in patients with metastatic renal cell carcinoma (mRCC) after failure of initial vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFr-TKI) therapy. The REACT (RAD001 Expanded Access Clinical Trial in RCC) study was initiated to address an unmet medical need by providing everolimus prior to commercial availability, and also to further assess the safety and efficacy of everolimus in patients with VEGFr-TKI-refractory mRCC.

* *Corresponding author:* Address: Clinic for Hematology, Hemostasis, Oncology, and Stem Cell Transplantation, Medical School Hannover, Carl Neuberg Str. 1, D-30627 Hannover, Germany. Tel.: +49 511 532 9196; fax: +49 511 532 8077.
E-mail address: gruenwald.viktor@mh-hannover.de (V. Grünwald).
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REACT
Safety
Second-line therapy

Patients and methods: REACT (Clinicaltrials.gov: NCT00655252) was a global, open-label, expanded-access programme in patients with mRCC who were intolerant of, or who had progressed on or after stopping treatment with, any available VEGFr-TKI therapy. Patients received everolimus 10 mg once daily, with dose and schedule modifications allowed for toxicity. Patients were closely monitored for the development of serious and grades 3/4 adverse events (AEs). Response was assessed by RECIST every 3 months for the first year and every 6 months thereafter.

Results: A total of 1367 patients were enroled. Safety findings and tumour responses were consistent with those observed in RECORD-1, with no new safety issues identified. The most commonly reported serious AEs were dyspnoea (5.0%), pneumonia (4.7%) and anaemia (4.1%), and the most commonly reported grades 3/4 AEs were anaemia (13.4%), fatigue (6.7%) and dyspnoea (6.5%). Best overall response was stable disease in 51.6% and partial response in 1.7% of patients. Median everolimus treatment duration was 14 weeks.

Conclusion: Everolimus is well tolerated in patients with mRCC and demonstrates a favourable risk–benefit ratio.

1. Introduction

The pivotal RECORD-1 phase 3 trial demonstrated the clinical efficacy of everolimus (RAD001) in patients with metastatic renal cell carcinoma (mRCC) who had progressed on, or were intolerant of, vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFr-TKIs) therapy.[1,2] In this randomised, placebo-controlled study, everolimus more than doubled median progression-free survival (PFS), from 1.9 months (placebo group; 95% confidence interval [CI] 1.8–1.9 months) to 4.9 months (everolimus group; 95% CI 4.0–5.5 months) (hazard ratio 0.33, 95% CI 0.25–0.43, $P < 0.001$) by independent central radiology review.[2] Best overall response of stable disease (SD), as defined by the Response Evaluation Criteria in Solid Tumours (RECIST),[3] was achieved in 66.8% and 32.4% of everolimus- and placebo-treated patients, respectively; 1.8% of everolimus-treated patients and 0% of placebo-treated patients achieved a partial response (PR). Clinical benefit of everolimus was maintained across subgroups regardless of age, gender, Memorial Sloan-Kettering Cancer Center (MSKCC) risk group,[4] prior treatment or geographic region.[1] Adverse events (AEs) associated with everolimus were mostly grades 1 or 2 in severity, medically manageable, and reversible, and quality of life was sustained during treatment.[1,2] The most common grades 3/4 AEs (reported in $\geqslant$5% of patients) included lymphopenia (18%), hyperglycaemia (16%), anaemia (13%), infection (10%), dyspnoea (7%), hypophosphatemia (6%) and fatigue (5%).[2]

Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, is approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with advanced RCC who have progressed after initial VEGFr-TKI therapy, and is the only approved category 1 treatment for these patients as supported by clinical practise guidelines released in the United States and the European Union.[5–10]

REACT (RAD001 Expanded-Access Clinical Trial in RCC) was designed to fulfil an unmet need by providing continuous everolimus therapy to patients with mRCC prior to regulatory approval. The primary objective of REACT was to evaluate the safety of everolimus in a large population of patients with mRCC who were intolerant of, or whose disease had progressed on, any available prior VEGFr-TKI therapy. The secondary objective was to determine the best overall response to everolimus treatment. Herein, we report the final results from this study.

2. Patients and methods

2.1. Study design

REACT was a global, open-label, expanded-access programme (EAP) that included patients from 34 participating countries (Clinicaltrials.gov: NCT00655252; EudraCT: 2007-005460-28). Enrolment commenced in July 2008 and ended in June 2010. The study was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonised Tripartite Guidelines for Good Clinical Practise, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and the Declaration of Helsinki. The protocol was reviewed and approved by each participating site's Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB). All patients provided written, IRB/IEC/REB-approved informed consent. At the time of this manuscript preparation, an amendment to the final study report was being prepared to address GCP audit findings concerning two patients in one centre. The study results presented are not impacted by this amendment.

2.2. Patients

Eligible patients were $\geqslant$18 years of age with clear cell mRCC and were intolerant of (i.e. discontinued therapy because of AEs), or had progressed on or after stopping treatment with, any available VEGFr-TKI therapy. An amendment to the protocol introduced on 22nd April, 2009 broadened the inclusion criteria to allow enrolment of patients with mRCC of any histology. Additional inclusion criteria included the presence of

measurable or non-measurable disease (as per RECIST 1.0),[3] Karnofsky performance status score $\geqslant$70% and adequate function of bone marrow (absolute neutrophil count $\geqslant 1.5 \times 10^9$/L, platelets $\geqslant 100 \times 10^9$/L, haemoglobin >9 g/dL), liver (serum bilirubin $\leqslant 1.5 \times$ upper limit of normal [ULN], alanine aminotransferase and aspartate aminotransferase $\leqslant 2.5 \times$ ULN [$\leqslant 5 \times$ ULN for patients with known liver metastases]) and kidney (serum creatinine $\leqslant 2 \times$ ULN). Prior treatment with vaccines or cytokines (interleukin-2, interferon) and/or VEGF–ligand inhibitors (bevacizumab) was permitted. Patients with a history of another distinguishable malignancy were eligible (if the disease was considered neither life-threatening nor required chemotherapy or radiation), as were patients with a history of brain metastases who were neurologically stable following definitive radiation or surgery and did not require corticosteroids.

Patients were ineligible if they had received chemotherapy, immunotherapy, radiation or any other investigational agent within 4 weeks, or a VEGFr-TKI (sunitinib or sorafenib) within 1 week, of study participation. Prior treatment with mTOR inhibitors was not allowed. Also excluded were patients with a known hypersensitivity to rapamycin analogues, those who required chronic immunosuppressive therapy and those who had an active bleeding diathesis or other serious medical condition that would preclude full study participation. Patients with risk factors for hepatitis B or who had lived in regions where prevalence of chronic hepatitis B virus infection is $\geqslant$2% (Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal and Greece)[11] were screened for hepatitis B during day −35 to day 0, and patients with detectable hepatitis B virus DNA or positive HBsAg at screening were excluded from the study. Patients with risk factors for hepatitis C were also screened and patients with detectable hepatitis C virus (HCV) RNA via polymerase chain reaction were excluded.

2.3. Treatment

Everolimus was administered continuously as a once-daily oral 10-mg dose. A treatment cycle was considered to be 28 d in duration. Treatment was continued until disease progression (as defined by RECIST 1.0),[3] unacceptable toxicity, death, discontinuation for any other reason (patient or physician discretion), commercial availability or 15th June 2010 (whichever came first). Dose reduction to 5 mg daily or 5 mg every other day and/or dose interruptions were permitted for toxicity. Treatment was discontinued in patients who required a dose delay $\geqslant$28 d or who were intolerant of the reduced dose.

2.4. Safety assessment

Serious adverse events (SAEs) and grades 3/4 AEs (including laboratory abnormalities) were assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) Version 3.0.[12] An AE was considered 'serious' if it was fatal or life-threatening, resulted in persistent or significant disability/incapacity, constituted a congenital anomaly/birth defect, or required inpatient hospitalisation or prolongation of existing hospitalisation. Grades 1/2 AEs were only captured if they resulted in a change in study drug administration (i.e. dose modification, temporary interruption or treatment discontinuation). Laboratory assessments were conducted and vital signs were measured at clinic visits on day 1 of every 28-d treatment cycle. Baseline assessments included physical examination, Karnofsky Performance Status, electrocardiogram and haematology, chemistry, lipid and coagulation profiles. Bone scan, chest X-ray and pulmonary function tests were performed as clinically indicated. Safety monitoring continued for a 28-d period following the last dose of study drug. Deaths were recorded during and up to 28 d following discontinuation of study treatment.

2.5. Efficacy assessment

Best overall tumour response, as determined by the investigator according to RECIST 1.0,[3] was captured for each patient. Assessments of measurable (by computed tomography [CT] scan or magnetic resonance imaging [MRI]) or non-measurable disease were conducted at baseline, every 3 months for the first year and every 6 months thereafter, and at study discontinuation. CT, MRI or bone scans obtained at baseline and during everolimus treatment were evaluated locally at each study centre.

2.6. Statistical analyses

The full analysis set (FAS) included all patients who received at least one dose of everolimus. The safety population included all patients who received at least one dose of everolimus and had at least 1 postbaseline assessment. The proposed sample size of 1000 patients was chosen based on the expected accrual rates and planned duration of the study. There was no formal calculation of sample size and no formal statistical tests were conducted. For the primary safety objective, the number and percentage of patients having any event that was recorded as a grades 3 or 4 AE, or as a SAE, was summarised by system organ class, Common Toxicity Criteria (CTC) grade, preferred term and relation to study drug. Supportive safety analyses were performed on all reported AEs of any grade and on AEs that caused modification in study drug administration (dose reduction/interruption or treatment discontinuation). Investigator-assessed best overall response achieved during the study was summarised for the FAS. A retrospective subanalysis was performed to determine best overall tumour response to everolimus according to best overall tumour response to prior sunitinib or sorafenib treatment in patients who received sunitinib or sorafenib as their last prior therapy.

3. Results

3.1. Patient characteristics and disposition

A total of 1367 patients were included in the FAS. Patients from 34 countries, representing North America, South America, Europe, Australia and Asia, participated in the study (Fig. 1). Baseline characteristics of evaluable patients are summarised in Table 1. Overall, clear cell histology was evident in 93.9% of patients. Nearly all patients (99.6%) had undergone

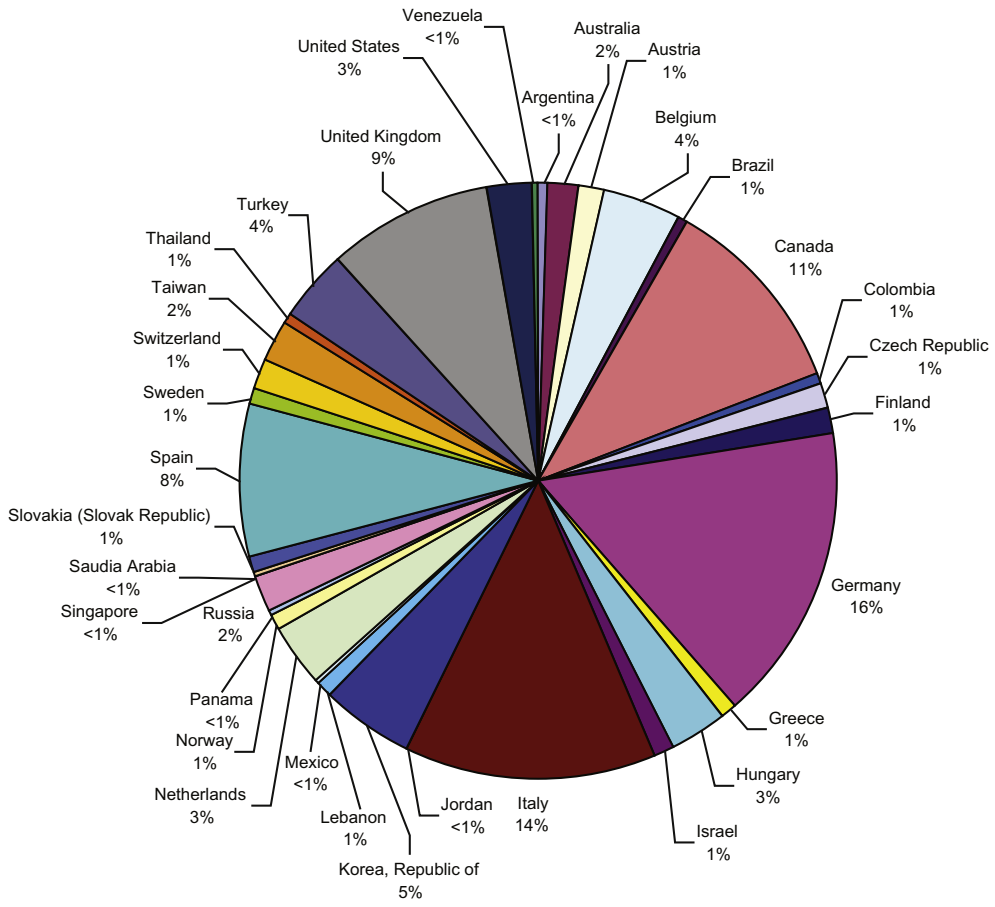

Fig. 1 – Geographic distribution of patients participating in the REACT expanded-access programme.

either partial or total nephrectomy, and 99.8% of patients had received prior targeted therapy (one or more VEGFr-TKIs). The majority of patients (65.5%) had received one prior VEGFr-TKI; however, only 38.5% of patients had received one prior VEGFr-TKI as their only prior anticancer therapy. Most patients (59.8%) had received more than one prior anticancer treatment and 24.9% were considered to be heavily pretreated (⩾3 prior regimens). Nearly all patients had progressed after VEGFr-TKI therapy (92.7%), 17.8% experienced both disease progression and VEGFr-TKI intolerance and 6.6% experienced only VEGFr-TKI intolerance.

At the end of the study, nearly 20% of patients had completed treatment, meaning that everolimus was commercially available in their respective countries (Table 2). Patients who were receiving study drug on 15th June 2010 (in countries where everolimus was not commercially accessible as of that date) were classified as 'discontinued due to administrative issues'. Of the patients who discontinued everolimus treatment prior to the data cut-off date, the majority discontinued due to disease progression (41.3%) or AEs (16.6%).

3.2. *Treatment administration and safety*

Patients received everolimus for a median duration of 14.0 weeks (range, 0.1–83.7 weeks), with the highest proportion (32.8%) treated for 8–16 weeks (Table 3). Median dose intensity was 10.0 mg/d (range, 2.2–10.0 mg/d). The majority of patients (68.9%) received study drug at a relative dose intensity of between 0.90 and 1.10 and mean relative dose intensity for all patients was 0.894, indicating that dose reductions and interruptions were infrequent.

Of the 1367 patients enroled, 170 died while on treatment. Most on-treatment deaths (120 patients) were due to disease progression; of the remaining 50 deaths, 10 were suspected to be related to everolimus (0.7% of the study population). Five deaths were due to respiratory causes (one respiratory distress, three pneumonitis, one respiratory failure), two were sudden deaths, one was related to myocardial infarction, one was due to acute renal failure and one was attributed to general physical health deterioration.

Overall, grades 3 and 4 AEs occurred in 48.8% and 12.8% of patients, respectively. Grades 3 and 4 haematologic AEs were reported in 11.8% and 3.1% of patients, respectively, and included anaemia (13.4%), the most frequently reported AE. Other grades 3/4 AEs occurring in ⩾2% of patients included fatigue (6.7%), dyspnoea (6.5%), hyperglycaemia (5.5%), stomatitis (5.4%), pneumonia (4.2%) and pneumonitis (2.7%) (Table 4). The overall occurrence of grades 3/4 infections was 9.8%. Grades 3/4 AEs in 530 patients (38.8%) were suspected to be study drug-related. SAEs were reported in 533 patients (39.0%); the most frequent SAEs were dyspnoea (5.0%), pneumonia (4.7%), anaemia (4.1%), pleural effusion (3.1%) and pneumonitis (2.3%) (Table 5). The combination of serious dyspnoea and serious pneumonia was observed

Table 1 – Baseline characteristics of everolimus-treated patients (*N* = 1367).

Age, median (range), years	63 (23–87)
⩾65 years, *n* (%)	592 (43.3)
Gender, *n* (%)	
Male	989 (72.3)
Female	378 (27.7)
Race, *n* (%)	
Caucasian	1220 (89.2)
Asian	114 (8.3)
Other	33 (2.4)
Tumour histology, *n* (%)	
Clear cell adenocarcinoma	1283 (93.9)
Other	75 (5.5)
Missing	9 (0.7)
Histologic grade, *n* (%)	
Well differentiated	76 (5.6)
Moderately differentiated	369 (27.0)
Poorly differentiated	351 (25.7)
Undifferentiated	106 (7.8)
Unknown	465 (34.0)
Months since initial diagnosis, *n* (%)	
⩽3	8 (0.6)
>3 to ⩽12	190 (13.9)
>12 to ⩽36	499 (36.5)
>36 to ⩽72	322 (23.6)
>72	348 (25.5)
Prior nephrectomy, *n* (%)	1361 (99.6)
Prior cancer treatments, *n* (%)	
Targeted therapy	1364 (99.8)
Immunotherapy	544 (39.8)
Chemotherapy	195 (14.3)
Hormonal therapy	17 (1.2)
Other	7 (0.5)
Number of prior cancer treatments[a], *n* (%)	
0	1 (0.1)
1	548 (40.1)
2	477 (34.9)
⩾3	341 (24.9)
Prior VEGFr-TKI therapy[b], *n* (%)	
None	40 (2.9)
One prior VEGFr-TKI	895 (65.5)
Two prior VEGFr-TKIs	432 (31.6)
One prior VEGFr-TKI as only prior therapy	526 (38.5)
Progression despite prior VEGFr-TKI, *n* (%)	
No	96 (7.0)
Yes	1267 (92.7)
Unknown	4 (0.3)
Intolerant to prior VEGFr-TKI, *n* (%)	
No	1030 (75.3)
Yes	333 (24.4)
Unknown	4 (0.3)

VEGFr-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

[a] Prior cancer treatments included chemotherapy, hormonal therapy, immunotherapy, targeted therapy or other.

[b] Prior VEGFr-TKI therapy reported includes sunitinib or sorafenib only. Prior pazopanib or investigational VEGFr-TKIs are not included.

Table 2 – Disposition of enroled patients treated with everolimus (*N* = 1367).

	n (%)
Completed[a]	269 (19.7)
Discontinued	1098 (80.3)
Primary reason for discontinuation	
Disease progression	565 (41.3)
Adverse events[b]	227 (16.6)
Administrative issues[c]	190 (13.9)
Patient withdrew consent	54 (4.0)
Death	45 (3.3)
Other[d]	17 (1.2)

[a] Patients still on study drug at the time that everolimus became commercially available in their respective countries (prior to 15th June 2010).

[b] Includes abnormal laboratory values.

[c] Includes patients still on study drug as of 15th June 2010 due to lack of commercial availability of everolimus.

[d] Includes patients lost to follow-up (9) and protocol deviation (8).

Table 3 – Exposure to everolimus (*N* = 1367).[a]

Duration of treatment, median (range), weeks	14.0 (0.1–83.7)
Duration of treatment, weeks, *n* (%)	
⩽4	118 (8.6)
>4 to ⩽8	188 (13.8)
>8 to ⩽16	448 (32.8)
>16 to ⩽24	199 (14.6)
>24 to ⩽32	160 (11.7)
>32 to ⩽52	199 (14.6)
>52	55 (4.0)
Cumulative dose of everolimus,[b] median (range) (mg)	885.0 (10.0–5310.0)
Dose intensity,[c] median (range) (mg/d)	10.0 (2.2–10.0)
Relative dose intensity,[d] *n* (%)	
0.00 to <0.50	50 (3.7)
0.50 to <0.70	173 (12.7)
0.70 to <0.90	195 (14.3)
0.90 to <1.10	942 (68.9)
Missing	7 (0.5)

[a] Patients with dose regimen specified as other (*n* = 7) are not accounted for in the cumulative dose and dose intensity analyses.

[b] Cumulative dose = total dose received.

[c] Dose intensity = cumulative dose/duration of exposure.

[d] Relative dose intensity = dose intensity/planned dose intensity.

in seven patients (0.5%), and three patients (0.2%) experienced both serious dyspnoea and serious pneumonitis. SAEs in 201 patients (14.7%) were suspected to be study drug-related.

AEs of any grade were reported in 1011 patients (74.0%). Overall, 230 patients (16.8%) experienced at least one AE leading to discontinuation of study drug. The most common AEs leading to discontinuation included dyspnoea (1.5% of the study population), pneumonitis (1.4%), pneumonia (1.3%), fatigue (1.2%) and decreased appetite (1.0%). Dose adjustment or interruption of study drug due to AEs was reported for 657 patients (48.1%).

Table 4 – Adverse events reported in ⩾5% of patients, regardless of relationship to study drug (*N* = 1367).[a]

	n (%)		
	CTC grade 3	CTC grade 4	All grades[b]
Anaemia	142 (10.4)	41 (3.0)	202 (14.8)
Stomatitis	72 (5.3)	2 (0.1)	138 (10.1)
Dyspnoea	75 (5.5)	13 (1.0)	116 (8.5)
Fatigue	89 (6.5)	3 (0.2)	116 (8.5)
Pneumonitis	33 (2.4)	4 (0.3)	83 (6.1)
Hyperglycaemia	67 (4.9)	8 (0.6)	78 (5.7)
Pneumonia[c]	50 (3.7)	7 (0.5)	71 (5.2)

[a] The event with maximum severity is counted for patients who experienced multiple episodes of an event. Laboratory values were not collected; data are based on adverse event (AE) reports. AEs occurring prior to start of study drug or more than 28 d after the discontinuation of treatment are not included.
[b] Includes grades 3 and 4 AEs, serious AEs and any AE that caused a change in study drug administration (i.e. change in the administered dose, temporary interruption and/or treatment discontinuation).
[c] The overall occurrence of grades 3/4 infections and infestations was 9.8%.

Table 5 – Serious adverse events (SAEs) occurring in ⩾2% patients, regardless of relationship to study drug[a] (*N* = 1367).

	n (%)
Dyspnoea	68 (5.0)
Pneumonia	64 (4.7)
Anaemia	56 (4.1)
Pleural effusion	42 (3.1)
Pneumonitis	32 (2.3)

[a] Multiple episodes of an event are counted only once per patient. SAEs occurring prior to the start of study drug or more than 28 d after the discontinuation of study drug are not included.

3.3. *Efficacy*

The best overall tumour response to everolimus by investigator assessment was SD in 705 patients (51.6%) and PR in 23 patients (1.7%) (Table 6). No complete responses were documented.

An analysis of best overall tumour response to everolimus by investigator assessment according to best overall tumour response to sunitinib or sorafenib as last prior regimen showed that among patients who had failed prior sunitinib treatment and who had progressive disease (PD) as their best overall tumour response ($n = 305$), 45.2% achieved disease control with everolimus (SD, 44.9%; PR, 0.3%) (Table 6). Similarly, among patients who had failed prior sorafenib treatment and who had PD as their best overall tumour response ($n = 171$), 50.3% achieved disease control with everolimus (SD, 45.0%; PR, 5.3%) (Table 6).

4. Discussion

VEGFr-TKIs have become the standard of care for first-line treatment of mRCC, but most patients will eventually exhibit disease progression.[13–15] The clinical benefit of everolimus has been established in patients with mRCC failing initial VEGFr-TKI treatment[1,2] and everolimus has been approved for this indication in 65 countries to date. The REACT EAP was initiated in 2008 to address an unmet medical need and offer everolimus to patients in countries where it was not yet commercially available.

In addition to providing a large number of patients with access to a promising new therapy, EAPs such as REACT enable the accumulation of safety and efficacy data in broader, more heterogenous patient populations than those typically eligible for clinical trials, and as such may more accurately reflect real-world clinical experience.[16–20] The REACT EAP enroled over 1300 patients with mRCC from a total of 34 countries. As in the RECORD-1 phase 3 trial, patients from all MSKCC risk categories were eligible, and the inclusion criteria were broadened to include patients with mRCC of any histology, measurable or non-measurable disease and brain metastases. It should be noted that although the protocol was amended to include patients with mRCC of any histology, this amendment was added relatively late in the course of patient enrolment (on 22nd April 2009). Thus, the majority (93.9%) of patients enroled had clear cell mRCC. Safety findings are consistent with those observed in the RECORD-1 trial and no new safety issues were identified. The percentage of patients in the REACT study requiring dose reduction or temporary interruption of everolimus treatment because of AEs was similar to that observed in the RECORD-1 trial (48.1% versus 45%[2]). Additionally, the relative dose intensity of everolimus in the majority of REACT patients was >0.90. These results confirm that everolimus is well tolerated by most patients.

The AE profile of everolimus is manageable and consistent with that of other mTOR inhibitors.[21,22] The toxicity profiles of mTOR inhibitors and VEGFr-TKIs are generally non-overlapping. AEs most commonly associated with VEGFr-TKIs include hypertension, cardiac events and hand-foot skin reaction;[23,24] these AEs are not typically observed with everolimus treatment.[2] Therefore, treatment with everolimus following initial VEGFr-TKI failure is unlikely to cause cumulative toxicity.

Non-infectious pneumonitis is a class effect of rapamycin-derived mTOR inhibitors.[21,25] Non-infectious pneumonitis has been observed in patients taking everolimus and some cases have been severe.[1,2,25] In this study, the overall incidence of pneumonitis of any grade was 6.1%. Grades 3 and 4 pneumonitis was reported in 33 patients (2.4%) and 4 patients (0.3%), respectively. Pneumonitis was reported as an SAE in 32 patients (2.3%). Guidelines for the management of pneumonitis

Table 6 – Best overall response[a] to everolimus by investigator assessment in the overall REACT population and by best overall response to last prior regimen.

Best overall response to everolimus,[b] *n* (%)		Overall REACT population				
		PR	SD	PD	Unknown[c]	TOTAL
		23 (1.7)	705 (51.6)	324 (23.7)	315 (23.0)	1367
Best overall response to last prior regimen,[d,e] *n* (%)		By last prior regimen				
Sunitinib	CR/PR	2 (1.2)	85 (51.8)	42 (25.6)	35 (21.3)	164
	SD	2 (0.7)	170 (57.0)	53 (17.8)	73 (24.5)	298
	PD	1 (0.3)	137 (44.9)	98 (32.1)	69 (22.6)	305
	Unknown/NA	1 (1.4)	38 (54.3)	12 (17.1)	19 (27.1)	70
	TOTAL	6 (0.7)	430 (51.4)	205 (24.5)	196 (23.4)	837
Sorafenib	CR/PR	0	19 (54.3)	9 (25.7)	7 (20.0)	35
	SD	2 (1.5)	76 (55.5)	25 (18.2)	34 (24.8)	137
	PD	9 (5.3)	77 (45.0)	46 (26.9)	39 (22.8)	171
	Unknown/NA	3 (5.5)	30 (54.5)	8 (14.5)	14 (25.5)	55
	TOTAL	14 (3.5)	202 (50.8)	88 (22.1)	94 (23.6)	398

CR, complete response; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease.
[a] Best overall tumour response according to RECIST 1.0.
[b] No CR were reported.
[c] All cases not qualifying for a confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks.
[d] Only patients who received sunitinib or sorafenib as last prior regimen are shown.
[e] Last prior regimens for remaining patients were: sunitinib in combination with another agent (*n* = 6), sorafenib in combination with another agent (*n* = 16), concomitant sunitinib and sorafenib (*n* = 1), other (*n* = 109).

were outlined in the study protocol and, depending on the severity of the event, included administration of corticosteroids and/or everolimus dose modification (i.e. reduction and/or interruption). In REACT patients, there did not appear to be a correlation between the development of respiratory AEs such as dyspnoea and the development of pneumonitis, as only 4% of patients who experienced serious dyspnoea also experienced serious pneumonitis.

Overall tumour response and treatment duration observed in REACT should be interpreted cautiously, given that nearly 20% of patients discontinued because of commercial availability of everolimus and prior to evidence of PD or study drug intolerance. This limitation, in conjunction with the fact that follow-up of patients ended 28 d after the end of study treatment, prevented meaningful assessment of patient survival. The observation of RECIST-defined SD as the best overall investigator-reported tumour response in the majority of patients (51.6%) is consistent with the advanced stage of mRCC, the history of progression at baseline and the known mechanism of action of targeted therapies (i.e. inhibition of angiogenesis). The overall response rates observed are similar to those reported in the RECORD-1 trial.[2] Median everolimus treatment duration was 14 weeks; though, notably, some patients (4%) remained on treatment without disease progression for over 1 year.

Interestingly, best overall response to prior sunitinib or sorafenib treatment did not predict best overall response to everolimus by investigator assessment. Substantial proportions of patients who had PD as their best overall response to prior treatment with sunitinib or sorafenib achieved disease control (best overall response of SD or better) with everolimus (45.2% and 50.3%, respectively).

In conclusion, the REACT study has provided everolimus in advance of regulatory approval and commercial availability to patients with mRCC who failed initial VEGFr-TKI therapy. The rapid enrolment rate of this EAP confirmed the unmet need in this patient population. Everolimus was well tolerated in this large group of heavily pretreated patients, with no new safety issues identified. Importantly, >50% of patients achieved disease stabilisation. Our results further support the use of everolimus as the standard of care in patients with VEGFr-TKI-refractory mRCC.

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This work was supported by Novartis Pharmaceuticals Corporation. Novartis-affiliated authors had a role in formulating the study concepts and design, coordinating data acquisition, performing quality control, data analysis and interpretation and statistical analysis, and editing and reviewing the manuscript. All authors participated in the decision to submit this manuscript for publication.

Conflict of interest statement

V. Grünwald has served as an advisor and received honoraria from GlaxoSmithKline, Novartis, Pfizer, and Roche. S.E. Bavbek serves on the CORE Group for Novartis and is on an advisory board for Novartis. K. Miller is a member of the speaker bureau for, and is an advisor to, Novartis. J. Larkin receives research funding, and has received consulting fees, from Novartis. P. Bono and R. Hawkins have received honoraria from Novartis. O. Anak, M. Rosamilia, J. Booth and N. Pirotta are employees of, and M. Rosamilia and J. Booth own stock in Novartis. P. Karakiewicz, J.P. Machiels, S.H. Lee, S.Y. Rha, D. Castellano, C. Blank, J.J. Knox and I. Bodrogi have nothing to declare.

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The REACT study group was composed of the following participating investigators and their clinical teams: *Argentina:* M. Romedi, S. Ferrandini, M. Rondinon; *Australia:* K. Pittman, D. Goldstein, J. Shapiro, S. Troon, D. Yip, P. Mainwaring; *Austria:* R. Zigeuner, W. Loidl, R.F. Greil, M. Schmidinger; *Belgium:* J. De Grève, S. Rottey, J. Vermorken, J. Machiels, T. Gil, C. Gennigens, T. Roumeguere; *Brazil:* C. Barrios, C. Mathias; *Canada:* H. Assi, S. Hotte, P. Karakiewicz, J. Knox, S. Spadafora, L. Wood, P. Zalewski, M. Mackensie, G. Bjarnason, A. Lalancette, A. Chan, B. Higgins, S. North, D. Soulieres, J. Asselah, C. Sperlich, W. Miller, S. Yadav, R. El-Maraghi; *Colombia*: J. Godoy; *Czech Republic:* J. Prausová, J. Katolicka, L. Petruzelka, I. Kiss; *Finland:* P. Bono, M. Lapela; *Germany:* K. Miller, V. Grünwald, L. Bergmann, J. Beck, E. Jäger, M. Kindler, F. Overkamp, M. Wirth, W. Hölzer, J. Gschwend, A. Stenzl, T. Gauler, D. Niederwieser, N. Marschner, A. Lück, H. Tessen, C. Eichelberg, T. Steiner, P. Goebell, E. Kettner, A. Bakhshandeh-Bath, M. Wilhelm, S. Schmitz, A. Jacob, S. Bierer, U. Kube, M. Staehler, E. Engel, M. Frambach, U. Schellenberger, P. Albers, J. Simon, M. Gleissler, T. Klotz, R. Repp, H. Kröning, J. Westermann, U. Rebmann, B. Brehmer, N. Niederle, C. Grund, K. Verpoort, P. Fonara, J. Rassweiler; *Greece:* A. Bamias, G. Fountzilas, E. Razis, D. Mouratidou, V. Georgoulias, E. Samantas; *Hungary:* I. Bodrogi, L. Mangel, J. Szanto; *Israel:* R. Berger, A. Pe'er, A. Sella, R. Ben-Yosef, H. Nechushtan; *Italy:* L. Crinò, S. Bracarda, L. Ciuffreda, C. Graiff, A. Falcone, M. Roselli, C. Sternberg, A. Santoro, E. Ruggeri, A. Bearz, M. Venturini, M. Aglietta, D. Amadori, F. Di Costanzo, M. Bari, N. Gebbia, P. Conte, A. Bonetti, R. Bordonaro, S. Cascinu, A. Contu, G. Cruciani, D. Gasparro, M. Nardi, G. Lelli, G. Lo Re, F. Boccardo, V. Lorusso, E. Maiello, P. Manente, R. Passalacqua, F. Piantedosi, C. Porta, C. Sacco, C. Tondini, S. De Placido, G. Carteni, L. Dogliotto, G. Rosti, M. Milella, F. Roila, D. Amoroso, G. Farina; *Jordan:* H. Al-Khatib; *Republic of Korea:* S. Lee, T. Kim, J. Ahn, H. Lim, S. Rha, I. Chung, J. Kim, J. Chung; *Lebanon:* M. Ghosn, A. Shameseddine; *Mexico:* R. Lugo, P. Cabrera; *Netherlands:* S. Osanto, G. Groenewegen, C. Blank, F. van den Eertwegh, C. van Herpen, S. Oosting, P. Soetekouw; *Norway:* W. Lilleby, O. Klepp, T. Guren; *Panama:* J. Alcedo; *Russia:* P. Karlov, D. Nosov, L. Roman, I. Rusakov; *Saudi Arabia:* S. Bazarbashi; *Singapore:* C. Toh; *Slovakia:* J. Mardiak; *Spain:* M. Constenla, F. Garcia del Muro Solans, J. Maroto Ray, J. Bellmunt Mollins, D. Castellano, I. Duran Martinez, B. Mellado Gonzalez, M. Domenech Santasusana, M. Lopez-Brea Piqueras, J. Campillo Fuentes, J. Gonzalez Larriba, R. Luque Caro, A. Meana Garcia, L. Aparicio, N. Batista Lopez, V. Calderero Aragon, C. Valverde Morales, M. Figueiras, J. Contreras Ibanez, E. Gonzalez Billalabeitia, E. Estrada, J. Arranz, J. Lambea Sorrosal, A. Lozano, M. Codes de Villena, E. Espinosa, R. Lopez, J. Perez Garcia; *Sweden:* A. Laurell, U. Stierner, M. Cwikiel; *Switzerland:* M. Borner, P.-Y. Dietrich, C. Rothermundt; *Taiwan:* Y. Pu, Y. Chang, Y. Ou, C. Chuang, Y. Liao; *Thailand:* V. Srimuninnimit, V. Sriuranpong; *Turkey:* S. Bavbek, S. Buyukberber, B. Yalcin, E. Goker, S. Yalcin; *United Kingdom:* T. Geldart, J. Wagstaff, S. Nicholson, S. Chowdhury, A. Bahl, R. Jones, A. Azzabi, D. Chao, K. Fife, R. Hawkins, J. Larkin, G. Mead, P. Nathan, H. Pandha; *USA:* J. Hajdenberg, N. Gabrail, N. Nimeh, T. Logan, T. Flaig, R. Schraeder, B. Rini, M. O'Rourke, C. Alemany, J. Beck, A. Kessinger, A. Amin; *Venezuela:* M. Arriaga, J. Rodriguez.

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